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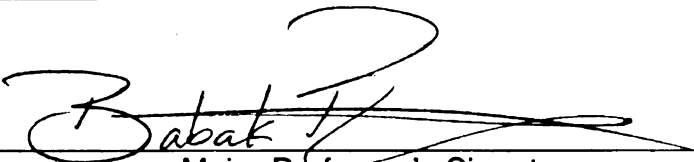
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**PORPHYRIN TWEEZERS FOR THE ABSOLUTE STEREOCHEMICAL
DETERMINATION OF SMALL MOLECULES THROUGH ECCD**

Volume I

By

Marina Tanasova

A DISSERTATION

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PORPHYRIN TWEEZERS FOR THE ABSOLUTE STEREOCHEMICAL DETERMINATION OF SMALL MOLECULES THROUGH ECCD

By

Marina Tanasova

The Exciton Coupled Circular Dichroism (ECCD) is a non-empirical method allowing for the determination of the absolute stereochemistry of chiral compounds. The ECCD phenomenon is based on the ability of two or more chromophores to interact through space and, when helically disposed, produce a bisignate spectrum reflecting their relative orientation. The chromophores necessary for the exciton coupling are introduced through chemical derivatization or non-covalent binding. The latter is achieved by use of bis-porphyrin tweezers, where the aromatic porphyrins provide excitonic interaction and a metal incorporated into the porphyrin core serves as a major site for coordination to the chiral molecule. For binding to a porphyrin tweezer, a chiral guest must possess two coordination sites, which led to the use of the “carriers” - achiral molecules providing necessary coordination sites and allow formation of a 1:1 tweezer/guest complex. After designing and studying various “carriers” the 1,4-phenylenediamine was found to be a reliable tool for use with carboxylic acids; the tweezer-substrate complexes of carrier conjugates exhibited consistent ECCD spectra, which were easily correlated with the absolute stereochemistry of the bound guest. While the sets of chiral α -alkyl, α -alkoxy and α -aryl carboxylic acids exhibited a consistent ECCD that led to a functional mnemonic, introduction of a halide on the asymmetric center changed the mode of stereodifferentiation with the porphyrin tweezer. After thorough investigation, the

observed phenomenon was contributed to the secondary interaction, presumably C-X-- π (X= halide), occurring between the aromatic system of the porphyrin and a halide of the chiral substrate. This led to devising anew mnemonic for 1,4-phenylenediamine derivatized α -halo carboxylic acids.

In a separate study factors such as longer length and steric bulk of porphyrin tweezer were studied. As a result, bulking of the tweezer by introduction of *t*-butyl substituents on the periphery of the porphyrin allowed the first application of the porphyrin tweezer method for the absolute stereochemical determination of remote chirality. After complexation with the bulky porphyrin, β - and γ -chiral amides tweezer produced prominent and consistent ECCD spectra, which were easily correlated with the absolute stereochemistry of the substrates and summarized in a working mnemonic. Interestingly, by changing the size and rigidity of the linker connecting the two porphyrins in a tweezer the conformational preference and ultimately the sign of ECCD was affected. Moreover, shortening of the linker allowed stabilization of one common conformation for α -chiral amides, regardless the type of the substituent at the asymmetric center.

Induction of chirality into bis-porphyrin systems was further extended to the formation of porphyrin aggregates with controlled helicity. For these purposes, porphyrins were derivatized with a hydrophilic "tail", and complexation of such aggregate with chiral diamines yielded prominent ECCD spectra that easily correlated with the helicity of the chiral guest.

“Perhaps, looking-glass milk isn’t good to drink,” Alice said to her cat.

Lewis Carroll

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LIST OF ABBREVIATIONS

α	angle of rotation
$[\alpha]$	specific rotation
A	CD amplitude
Ar	aromatic
$\text{BF}_3 \cdot \text{Et}_2\text{O}$	boron trifluoride diethyl ether
Bn	benzyl
BnBr	benzylbromide
BnOH	benzyl alcohol
Boc	<i>tert</i> -butoxycarbonyl
<i>n</i> -BuLi	butyl lithium
BuOOH	<i>tert</i> -butylhydroperoxide
Bu_3P	tributylphosphine
CD	circular dichroism
CE	Cotton Effect
<i>p</i> -chloranil	tetrachloro-1,4-benzoquinone
cm	centimeter
d	doublet
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEGMME	diethyleneglycol monomethyl ether
L-DET	L-diethyl tartrate
DIAD	diisopropylazodicarboxylate

DMAP	4-diaminopyridine
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodane
DMSO	dimethyl sulfoxides
Et ₃ N	triethylamine
ϵ	molar absorption coefficient
ECCD	Exciton Coupled Circular Dichroism
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EtOAc	ethyl acetate
equiv	equivalents
FAB-MS	fast atom bombardment mass spectroscopy
g	gram
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
h	hour
IR	infrared
<i>J</i>	NMR coupling constant
KI	potassium iodide
LDA	lithium diisopropylamine
LAH	lithium aluminum hydride
<i>m</i>	magnetic dipole transition moment
m	multiplet
min	minute

mg	milligram
MHz	megahertz
M	molar
μM	micromolar
MS	mass spectrometry
n	refractive index
NaBH_4	sodium borohydrate
NaH	sodium hydride
NaHMDS	sodium hexamethyldisilazane
NaIO_4	sodium periodate
NaI	sodium iodate
NaNO_2	sodium nitrite
NBS	N-bromosuccinimide
nm	nanometer
NMR	nuclear magnetic resonance
ORD	optical rotatory dispersion
PPh_3	triphenylphosphine
$i\text{-Pr}_2\text{NEt}$	diisopropylethylamine
Ph	phenyl
q	quartet
s	singlet
R	rotational strength
rt	room temperature

SOCl ₂	thionylchloride
t	triplet
TBS	<i>tert</i> -butyldimethylsilyl
TBAI	tetrabutylammonium iodide
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TBP-acid	5-(4-carboxyphenyl)-10,15,20-tri-3,5-di- <i>t</i> -butylphenylporphyrin
TBP-ester	5-(4-methylcarboxyphenyl)-10,15,20-tri-3,5-di- <i>t</i> -butylphenylporphyrin
TMP-acid	5-(4-carboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenylporphyrin
TMP-ester	5-(4-methylcarboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenylporphyrin
TMsP-acid	5-(4-carboxyphenyl)-10,15,20-tri-2,4,6-trimethylphenylporphyrin
TMsP-ester	5-(4-methylmethylcarboxyphenyl)-10,15,20-tri-2,4,6- trimethylyphenylporphyrin
TNP-ester	5-(4-methylcarboxyphenyl)-10,15,20-trinaphthylporphyrin
TNP-acid	5-(4-carboxyphenyl)-10,15,20-trinaphthylporphyrin
TPP-acid	5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin
TPP-ester	5-(4-methylcarboxyphenyl)-10,15,20-triphenylporphyrin
TBP-tz	5-(4-carboxyphenyl)-10,15,20-tri-3,5-di- <i>t</i> -butylphenylporphyrin tweezer
TMP-tz	5-(4-carboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenylporphyrin
TMsP-tz	5-(4-carboxyphenyl)-10,15,20-tri-2,4,6-trimethylphenylporphyrin tweezer
TNP-tz	5-(4-carboxyphenyl)-10,15,20-trinaphthylporphyrin tweezer
TPP-tz	5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin tweezer

UV-vis	ultraviolet-visible spectroscopy
ZnTPP	zinc tetraphenylporphyrin
ZnTBP-tz	zinc 5-(4-carboxyphenyl)-10,15,20-tri-3,5-di- <i>t</i> -butylphenylporphyrin tweezer
ZnTMP-tz	zinc 5-(4-carboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenylporphyrin
ZnTMsP-tz	zinc 5-(4-carboxyphenyl)-10,15,20-tri-2,4,6-trimethylphenylporphyrin tweezer
ZnTNP-tz	zinc 5-(4-carboxyphenyl)-10,15,20-trinaphthylporphyrin tweezer
ZnTPP-tz	zinc 5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin tweezer

Chapter I

Introduction

I.1. Chirality or Handedness in Nature and Chemistry

Although the term “chirality” or “handedness” might sound as a word from a “chemical” dictionary, is actually the preference for right or left “handedness” manifests itself in many ways in everyday life. Rotation of our galaxy, solar system and then the movement of our planet traces a certain circular direction. Most humans are right-handed and the arrangement of the heart and liver is universally left sided and right sided respectively, with a few rare individual exceptions.¹ And, it is not a characteristic of the human race alone to display definite trends with regards to handedness. The animal kingdom and plants are also found to exhibit handedness. For instance the common vineyard snail exists in both right-handed and left-handed forms with the ratio 20000:1 (Figure I-1).¹ In contrast to them, the lightning-whelk of the Atlantic coast are predominantly left-handed (Figure I-1). In plants, the honeysuckle winds around its support in a left-handed helix, while the bindweed prefers winding from right to left.¹

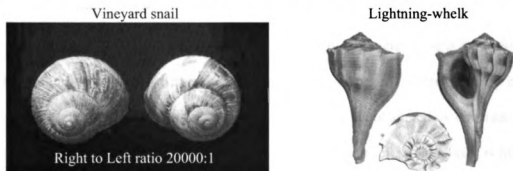


Figure I-1: Chirality in Nature. [http://www.ento.csiro.au/aicn/name_c/a_4531.htm]

Even in bacteria, some of their right-spiral colonies were found to change the spiral direction to left-handed turns with increase of temperature.² If we plunge into the micro-world, the first example of the preferred handedness is the DNA backbone twist followed by the helicity of the proteins governed by the asymmetry of the amino acids. Such preference of one “handedness” over the other in different organisms gave fertile soil for philosophical theories and debates about the origins of chirality on Earth. Numerous scientists have focused on finding the answers to the oldest philosophical questions in the history of human kind - what is the origin of life - but now with consideration of *chirality*.

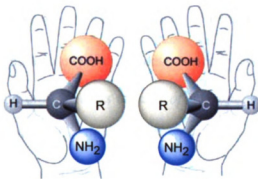


Figure I-2: Two hands and two amino acids represent the non-superimposable system in the macro- and micro-world respectively.

[<http://www.answersingenesis.org/tj/v12/i3/chirality.asp>]

For our part the questions to which we turn our attention are: what is handedness and what significance does it possess. If we are moving in circles whether we take a turn from right to left, or left to right, the net result of the motion is not altered by direction. If we pick up an object with our right hand or pick it up with our left, so long as it is lifted the question of right or left loses significance. The question of handedness or chirality becomes significant when it is applied to the physical characteristics of the object or molecule. Many molecules required for life exist in two forms. These two forms are

non-superimposable mirror images of each other, i.e. they are related like our left and right hands. For instance, Figure I-2 presents two amino acids that are mirror images, or so called enantiomers (from Greek word for opposite). Such molecules are called “chiral” from Greek $\chi\epsilon\iota\rho$ (*kheir*) for *hand*, and the phenomenon is known as “*chirality*”.

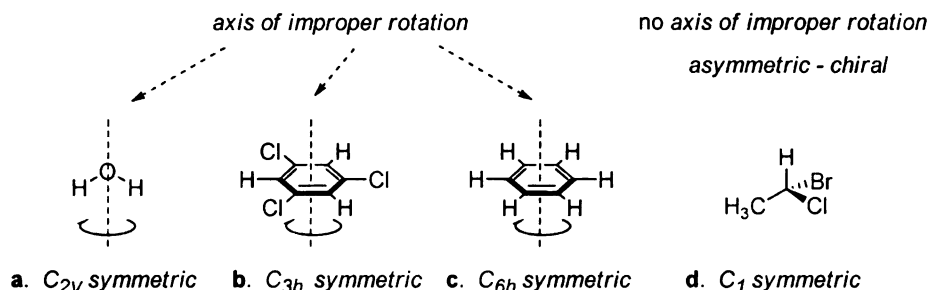


Figure I-3: Symmetry and asymmetry in organic molecules.

Whether or not a molecule is chiral is determined by its *symmetry*. A molecule is *achiral* (non-chiral) if and only if it has an *axis of improper rotation*, that is, an n -fold rotation (rotation by $360^\circ/n$) followed by a reflection in the plane perpendicular to this axis maps the molecule on to itself. For instance, water and benzenes presented in Figure I-3a-c have an axis of improper rotation. Water is defined to be C_2 -symmetric, since 360° rotation maps the molecule on to itself twice ($n = 2$). 1,3,5-Trichlorobenzene supporting $n = 3$ rotations, is C_3 symmetric. Non-substituted benzene supports 6-fold rotation around the axis and is C_6 symmetric. The geometry of the halogenated alkane depicted in Figure I-3d, however, does not support any rotations that could map the molecule on to itself and, subsequently, does not possess the axis of improper rotation. These types of structures are known as C_1 symmetric or asymmetric (chiral). Thus a molecule is chiral if and only if it *lacks* an axis of improper rotation. Because chiral molecules lack this type of symmetry, they are called dissymmetric. Thus, all amino

acids (except glycine) and many sugars, as well as a wide variety of other organic molecules, are indeed asymmetric as well as dissymmetric.

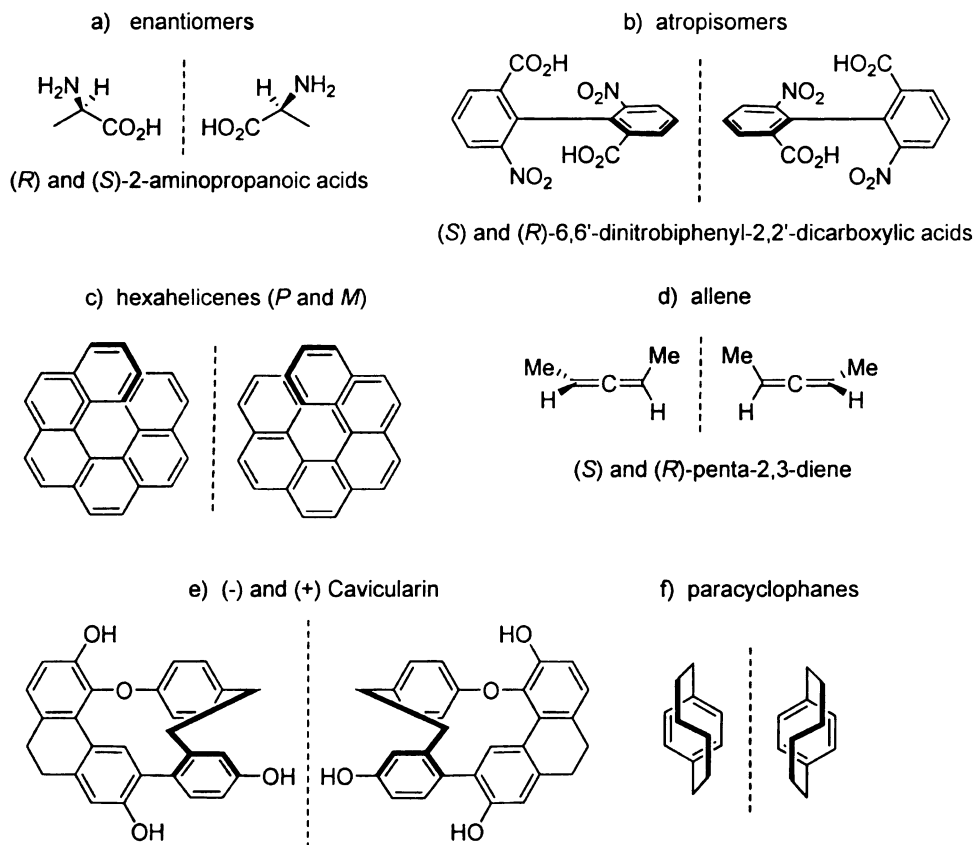


Figure I-4: The types of chirality: a) chiral carboxylic acids represent the point chirality and b) atropisomers, c) helicenes and d) allenes represent an axial chirality, e) Cavicularin and f) paracyclophanes represent a planar chirality.

Molecules can be chiral by asymmetrically arranging atoms in space around a center, axis, or plane. These arrangements are classified as point, axial, and planar chirality respectively (Figure I-4 represents the types of chirality in organic molecules).

Point chirality is often considered as the most fundamental form of chirality. Originating from different substituents bonded three-dimensionally to a central atom that results in C_1 symmetry for a whole molecule. A classic case of this type of chirality is an

sp^3 hybridized carbon (chiral carbon or stereocenter), bearing four different substituents (amino acids on Figure I-2 and chiral carboxylic acids on Figure I-4a). Existence of point chirality requires use of additional nomenclature for differentiation of the two enantiomers and a general rule for assigning the relative spatial orientation of substituents, or, in other words assignment of absolute configuration (stereochemistry).

Assignment of the absolute configuration of the substrates possessing point chirality is performed according to the Cahn-Ingold-Prelog priority rule system. The groups at the chiral center are compared first by atomic mass (or atomic number) of the atom directly attached to the stereocenter. The group having the atom of higher atomic number receives higher priority. If there is a tie, a list is made for each group of the atoms bonded to the one directly attached to the stereocenter, i.e., the atom at distance 2 from the asymmetric carbon. Each list is arranged in order of decreasing atomic number, and the lists are compared atom by atom. At the first difference, the group containing the atom of higher atomic number receives higher priority. After assigning the priorities for the substituents of a chiral carbon, the molecule is oriented in space in a way that would point the group with the lowest priority away from the observer. The substituents can be numbered from 1 to 4, assigning the lowest priority and the highest priority respectively. The direction of rotation of a curve starting from the highest priority substituent 4, through 3 and 2 will assign whether the absolute stereochemistry is *R* or *S*. Namely, a chiral center with distribution of the substituents that follows a clockwise rotation is an *R* (*rectus*) center and a center with a counterclockwise sense of rotation is an *S* (*sinister*) center. The names are derived from the Latin words for right and left, respectively.^{3, 4}

Molecules without a chiral center may also possess a sense of chirality. The example is axial chirality. Axially chiral molecules do not possess a stereogenic center, but an axis of chirality - an axis about which a set of substituents is held in a spatial arrangement, which is non-superimposable on its mirror image. Axial chirality is most commonly observed in atropisomeric biaryl compounds where the rotation about the aryl-aryl bond is restricted, for example (*S*)- and (*R*)-6,6'-dinitrobiphenyl-2,2'-dicarboxylic acids (Figure I-4b).^{5, 6} Certain allene compounds also display axial chirality and are also labeled with *R* and *S* such as the enantiomeric penta-2,3-dienes depicted in Figure I-4d.⁶ The assignment of axial chirality, *R* and *S*, also follows the Cahn-Ingold-Prelog priority rule.

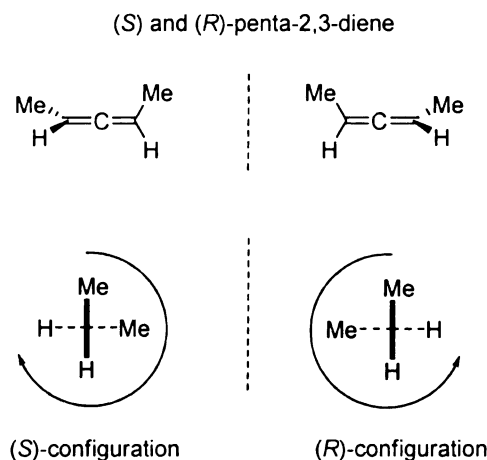


Figure I-5: Absolute stereochemical assignment of axial chirality

When looking through the axis of symmetry the four σ bonds of the two sp^2 carbons are oriented perpendicular to one another. For the stereochemical assignment only substituents of higher priority need to be considered. The rotation from the substituent of higher priority at the front carbon towards the higher priority substituent at

the back carbon (the priorities are assigned by the Cahn-Ingold-Prelog rule) leads to the configurational assignment of substrates with axial chirality. For instance the rotation from the front methyl group to the methyl substituent at the back carbon for the allenes depicted in Figure I-5 results in the absolute stereochemistry assigned as *S* for the enantiomer on the left, and *R* for the enantiomer at the right.

The plus (*P*) and minus (*M*) notation is employed for the third representatives of axial chirality – helices (Figure I-4c).⁶ Here, chirality arises from a unidirectional twist propagated along the long axis of the molecule. The convention is that, on looking from either end downward along the helical axis, clockwise rotation is termed *P* helicity and counterclockwise rotation is termed *M* helicity.

Planar chirality is the special case of chirality in two dimensions. This classification is applied to molecules that do not possess an asymmetric chiral carbon atom but have the perpendicular dissymmetric planes due to restricted rotation around a chemical bond in the molecule. Planar chirality is most commonly found in compounds like (E)-cyclooctene, some di-substituted ferrocenes, and certain monosubstituted paracyclophanes (Figure I-4f).⁷ Caviculatin⁸ – a rare example of a natural product exhibiting planar chirality is presented in the Figure I-4e.

I.2. History of Chirality

It is only a little more than 150 years since the evidence of chirality in nature came to light. In early 1800, studies performed by crystallographer Just Haüy (1743-1822), and then continued by Gabriel Delafosse (1796-1878) and John Herschel (1792-1871) revealed that, quartz crystals can be separated into two *enantiomorphous* sets, one

with left-handed and the other with a right-handed screw sequence of the facets. Although the two *enantiomorphous* forms possess similar physical properties, they rotated the plane polarized light in opposite directions. Further it was noticed, that the left-handed morphological set rotated the plane of the light counterclockwise and were called *levorotatory*, while those of a right-handed morphology induced a clockwise rotation and were named *dextrorotatory*. The property of compounds to rotate a polarization plane was referred to as *optical activity* and the molecules causing this phenomenon - *optically active*. Later, in 1824, Augustin Fresnel (1788-1827) showed that optically active substances transmit two components of light with different speed or decompose a ray of light into two components: left and right. This phenomenon was called a circular *birefringence* or *double refraction*. Birefringence ($n_L - n_R$) was found to be positive - (+) - for dextrorotatory and negative - (-) - for levorotatory media, where n_L and n_R refer to the refractive indices for left and for right circularly polarized light, respectively.

The *isomorphysm* theory was completed by Louis Pasteur (1822-1895) in 1848. During his early work, he resolved a problem concerning the nature of tartaric acid. Earlier, in 1830, Berzelius (1779-1848) discovered the chemical isomerism of a dextrorotatory tartaric acid and optically inactive or *para*-tartaric acid (*racemic* tartaric acid). It was observed that, unlike the isomorphism of quartz crystals discussed above, the crystals of various salts of the two tartaric acids (in particular crystals of sodium ammonium tartrate) were identical in all aspects except for the optical activity. Thomas Graham (1805-1869) remarked in his textbook, *Elements of Chemistry* (1842), that optical isomerism “defeated every attempt at explanation”, since these tartrate salts “not

only coincide in the proportion of their water and other constituents and in the composition of their acids, but also in their external form, having been observed by Mitscherlich to be isomorphous” (Eilhard Mitscherlich (1794-1863)).⁹

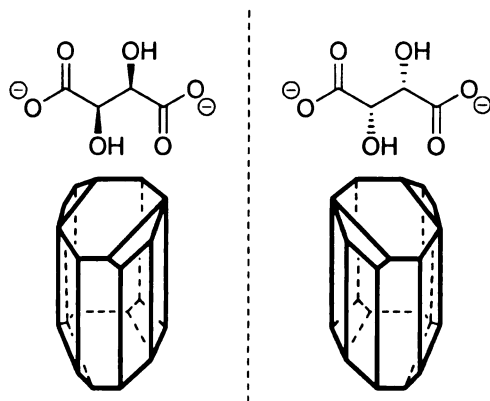


Figure I-6: Enantiomeric crystals of sodium tartrate isolated by Louis Pasteur

Studying a solution of the same salts, Louis Pasteur noticed that a solution of tartaric acid derived from living things (specifically, wine lees) rotated the plane of polarized light passing through it. The analysis of the tartrate salt derived by chemical synthesis, however, did not show any optical activity. Upon examination of the crystals of chemically derived sodium ammonium tartrate, Pasteur noticed that the crystals came in two asymmetric forms that were mirror images of one another. The sorted by hand crystals gave two forms of the tartrate: solutions that rotated light counterclockwise, while the other form rotated polarized light clockwise. An equal mix of the two, i.e., a *racemic* mixture, had no polarizing effect on light. Pasteur concluded that the individual molecules of (-) and (+) tartrate, while being identical in chemical reactions and its elemental composition, were asymmetric and represented two different *enantiomerically* related forms.¹⁰ The compound obtained from a living source consisted purely of the one

type – i.e., in enantiomerically pure form, while synthesized tartrate represented a racemic mixture of (-) and (+) form.¹¹ This was the first time anyone had demonstrated chirality in molecules (Figure I-6) and the first method used to resolve chiral molecules.¹² However, the term “chirality” was introduced much later (in 1884) by Lord Kelvin (William Thomson, 1824-1907), Professor of Natural Philosophy in the University of Glasgow.¹³

The second important discovery in the field of “chirality” was identification of diastereomers (chiral substrates containing two or more nonequivalent chiral centers) made by Louis Pasteur in 1853. He noticed that presence of a second stereocenter in a molecule or addition of “another active substance” diminishes the similarity between enantiomers.¹⁴ This discovery in the field of chirality not only potentially gave the method for separation of enantiomers, but more importantly, opened the way towards enantioselective synthesis. In his experiment with the enzymes “emulsin” and “invertin” Pasteur noticed that both enzymes catalyzed hydrolysis of D-glucoside with formation of one product, and that both enzymes were inactive to the L-form of the sugar as well as to the other hemiacetal sugar derivatives. At the same time, treatment of D-glucose with methyl alcohol and acetic acid led to formation of both α - and β -methyl-D-glucoside. This, and other experiments led Pasteur to propose that in order to interact, enzyme and substrate must have a complementary structures like a “key and lock”. He also observed that synthetic reactions starting with a single enantiomer or enantiomerically enriched mixture led to a prevalent formation of one diastereomeric product: “I have found that, once a molecule is asymmetric, its extension proceeds also in an asymmetric sense.”¹⁵

All these findings opened a new area in chemistry which now is known as stereoselective synthesis.

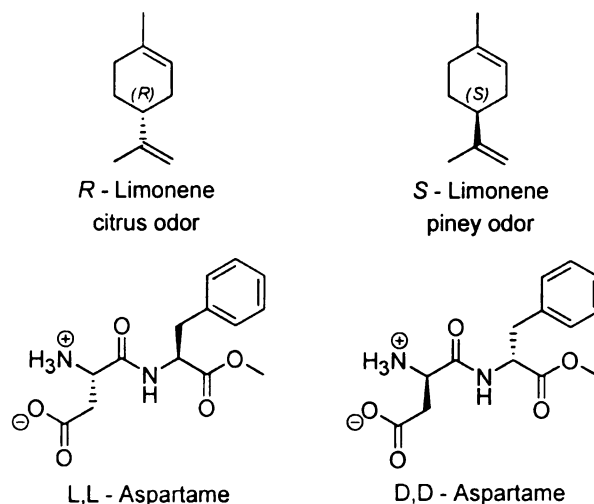


Figure I-7: Enantiomers of limonene and aspartame (artificial sweetener) possess different physical properties.

Although in most of the cases, the specific rotation of the plane of polarized light is the only distinguishable characteristic of enantiomeric substrates, there are examples, when chirality has altered the physical and biological properties of isomers. For instance, limonene – a hydrocarbon classed as a terpene – is found in both lemons and oranges. It is a colorless liquid at room temperature, which is responsible for their citrus smell. It takes its name from the lemon, since the rind of the lemon, like other citrus fruits, contains considerable amounts of this compound. Similarly to a wide variety of substrates produced by biological sources, limonene is produced in one enantiomeric form - D-limonene ((+)-limonene). In contrast to the citrus scent of D-limonene, the enantiomer L-limonene has a piney, turpentine-like odor. Another example, L,L-aspartame – synthesized from two natural amino acids: phenylalanine and aspartic acid -

is a sweetening agent more than a hundred times sweeter than sucrose. And yet, its mirror image molecule is bitter (Figure I-7).

Another example of chirality influencing the biological activity of a chemical compound relates to enantiomers of thalidomide (Figure I-8). Racemic thalidomide was introduced in 1963 as a treatment for morning sickness in pregnant women. However, some mothers treated by the drug gave birth to babies with congenital defects. A subsequent intensive research revealed that two enantiomers of the compound have different biological properties. While one enantiomer cured morning sickness, the other produced a negative effect on the embryo. The most profound side-effect was the deformities of the lower limbs among the infants born under its influence.

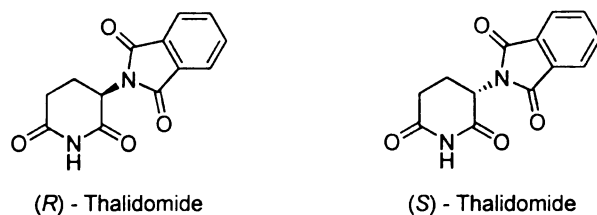


Figure I-8: The structures of (R)- and (S)-thalidomide.

Analyzing the scope of natural products reported in literature, it becomes evident that chiral substances occur in nature as one enantiomer and biological activity of the substrate is often related to its absolute chirality. Few natural products are represented in nature by both enantiomers, and few also exist as mixtures with equal proportions of enantiomers. On the other hand, synthesis of chiral substances in the laboratory in the absence of chiral agents or conditions results in racemates, which exhibit no measurable optical activity, since the activity of one enantiomer cancels that of the other. The emphasis on obtaining enantiomerically pure pharmaceuticals and chemicals resulted in a

rapid growth of fields such as asymmetric synthesis and asymmetric catalysis. Production of chiral organic compounds and the fact that chirality is able to change physical, biological and pharmaceutical characteristics of organic compounds, and sometimes their chemical properties necessitates of simple and reliable methods for the determination of enantiomeric purity and absolute configuration of chiral substrates.

I.3. Methods for stereochemical determination of chiral organic molecules

Several instrumental methods exist for the determination of the absolute configuration of chiral organic molecules. The most widely known are X-ray crystallography, followed by NMR (Mosher ester analysis¹⁶) and chiroptical methods (e.g., circular dichroism^{17, 18} (CD), and optical rotatory dispersion (ORD)). Other methods include specific rotation,¹⁹ infrared (IR) vibrational CD,²⁰ and vibrational Raman optical activity.²¹

I.3-1: X-ray Crystallography

The most unambiguous method applied for the determination of absolute stereochemistry is X-ray crystallography. Although the crystal structure can provide a full stereochemical analysis of chiral compounds in a single experiment, there are some drawbacks that are hard to overcome. The major limitation of the applicability of the method towards the absolute stereochemical determination is the necessity of the heavy atom present in the analyzed molecule, limiting the scope of the potential targets. Another drawback is the difficulty of growing crystals of X-ray quality. Not all organic compounds can be crystallized, and even fewer provide a single crystal suitable for X-ray

analysis. This requirement limits the application of the X-ray crystallography for absolute stereochemical determinations. The quality of crystals can be improved through derivatization of the target organic molecule with certain functionalities or formation of co-crystallants,²² but the preparation of the sample still represents a tedious and time consuming process. Hence, development of new methods for the stereochemical determination of organic molecules remains an important and active area of research.

I.3-2: Characterization of diastereomers by NMR

Among techniques that are used for absolute stereochemical determination of organic molecules, Mosher's method is one of the most commonly used. It is based on the NMR nonequivalence of internal or external diastereotopic groups, i.e., while enantiomeric compounds are indistinguishable with NMR spectroscopy, diastereotopic compounds exhibit characteristic spectra.

The Mosher's method¹⁶ is based on derivatization of a chiral substrate with the (*R*)- and (*S*)-enantiomers of a chiral auxiliary, usually an α -chiral carboxylic acid containing an aryl ring, that selectively directs its anisotropic cone toward one of the substituents (L_1/L_2) of the asymmetric center of a substrate (Figure I-9). The chemical shifts observed for substituents L_1 and L_2 of the substrate under investigation (alcohols or amines) reflect their spatial relationship with respect to the aromatic group of the auxiliary, and therefore, an absolute configuration at the chiral center of the substrate can be correlated to that of the auxiliary by means of NMR.²³⁻²⁶

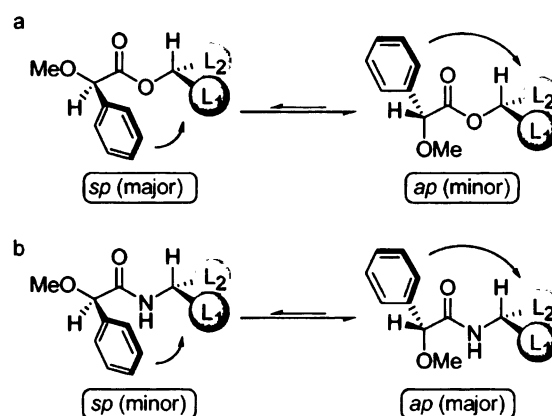


Figure I-9: Absolute stereochemical determination of a) chiral alcohols and b) amines through Mosher ester NMR analysis.

This phenomenon depends on the existence of a preferred conformation in the ester or amide derivatives (the same for the *R* and the *S* derivative), where the aryl ring is oriented to produce selective shielding on only one substituent (L_1/L_2) of the amine/alcohol. The conformational characteristics and the role of the aryl ring (ring current and orientation) are well understood in the case of the arylmethoxyacetic acids AMMA (*O*-methylmandelic acid (MMA))²³ and methoxy(trifluoromethyl) phenylacetic (MTPA)²⁷ acids derivatives of secondary alcohols^{28, 29} and primary α -substituted amines.^{30, 31} The esters of AMAAs with secondary alcohols are dominated by two main conformers - *ap* and *sp*, where the *sp* and *ap* conformers are defined by the synperiplanar and antiperiplanar arrangement of the C_α -OMe and C=O groups, respectively (Figure 1-9a). In each conformation the aryl group selectively shields one substituent (L_1 or L_2) of the alcohol. The average spectra relates to the structure of the predominant *sp* conformer, and the assignment of the *R/S* stereochemistry can be obtained from the difference in the chemical shifts of L_1/L_2 measured as $\Delta\delta^{RS}$ for two diastereomers. Similar analysis of

primary and secondary amines proceeds with consideration of the *ap* conformation being a predominant one (Figure 1-9b).

Further, the method was utilized for the stereochemical determination of carboxylic acids, cyanohydrins, diols, thiols and amino alcohols.²⁴ Determination of secondary thiols was approached with application of two enantiomers of 2-tert-butoxy-2-(2-naphthyl)acetic acid (2-NTBA) (an analog of Mosher acid (Figure I-10))³² and the NMR spectra of the two obtained diastereomers were analyzed as it was discussed above. Application of the Mosher ester method towards the absolute stereochemical determination of diols/amino alcohols and triols requires a detailed analysis of a combinatorial anisotropic effect produced by the aromatic groups of the auxiliaries and consideration of the effect of each auxiliary on the closest stereocenter.³³

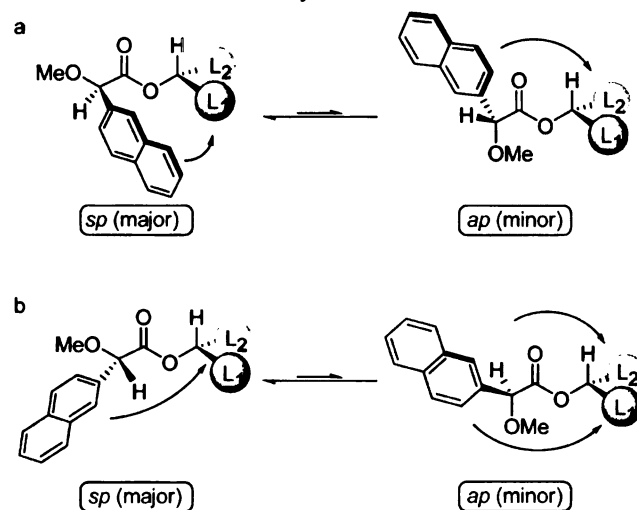


Figure I-10: Absolute stereochemical determination of chiral alcohols through Mosher ester NMR analysis with application of two enantiomers of 2-tert-butoxy-2-(2-naphthyl)acetic acid (2-NTBA).

Despite the necessity of tedious analysis, and more importantly, the dependence of the assigned stereochemistry on the geometry of the auxiliary, the Mosher ester

analysis is one of the most utilized methods in organic synthesis. Although, it has to be pointed out that since the correct assignment of the absolute chirality of derivatized stereocenter depends on the conformational stability of the auxiliary, the analysis of the preferred rotamer of the latter must be carried out with extreme caution.

A few additional methods address the stereochemical determination of polyols using NMR analysis of diastereomeric lanthanide complexes^{34, 35} or measurements in chiral NMR solvents.^{36, 37} With the data obtained from the application of chemical shifts of diols, triols and polyols observed in chiral solvents in ¹H-NMR and ¹³C-NMR analysis, an attempt has been made to derive a universal database for their absolute stereochemical determination.³⁸⁻⁴⁴ Large number of acyclic diols and polyols characterized by ¹H-NMR and ¹³C-NMR led to the following: (1) the spectroscopic profile of the stereo clusters that can be found in natural products is characteristic for the specific stereochemical arrangement and is independent from the rest of the molecule, and (2) the stereochemical arrangement is influenced only by structural clusters separated by one methylene. These observations advanced the logic of universal NMR database for assignment of the relative and absolute stereochemistry on acyclic contiguous polyols.⁴⁰

I.4: Chiroptical methods for stereochemical determination of chiral organic molecules: Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD)

Chiroptical methods for stereochemical determination are based on the ability of chiral media to interact with polarized light. Light in the form of a plane wave in space is defined as linearly polarized. It can also be presented as a transverse electromagnetic

wave, where fluctuating electromagnetic and electric field are mutually perpendicular. Natural white light is made up of the electric and corresponding magnetic waves that oscillate at all possible angles. Linearly polarized light contains only waves that fluctuate in one specific plane, i.e., only one electric and perpendicular to it magnetic components are present. Thus, as is depicted in Figure 10, the electric component of the linearly polarized light transverses only plane z . The corresponding magnetic field fluctuates in the y plane (Figure I-11). The property of the resulting electromagnetic wave depends on the intensity and phase difference of the component waves. Traditionally only the electric component is considered for plain polarization, since the magnetic wave is essentially the same.

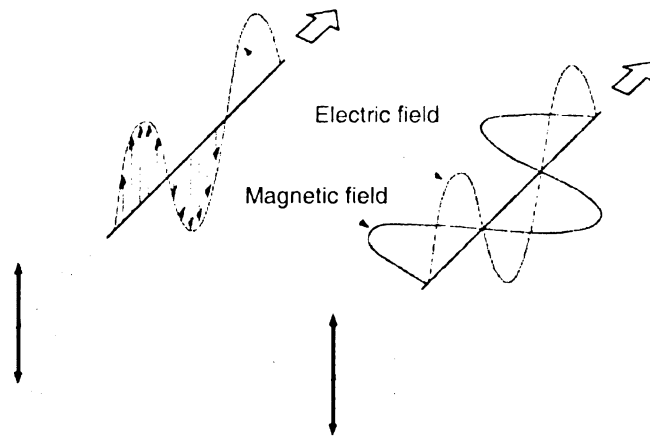


Figure I-11: Plane-polarized light.

The transverse electric field wave is accompanied by a magnetic field wave as illustrated.
<http://hyperphysics.phy-astr.gsu.edu/hbase/phyopt/polclas.html>

When two waves that are plane polarized in two perpendicular planes meet out of phase, then the wave resulting from the superposition of the two waves will no longer be plane-polarized. The result of the superposition of the plain-polarized waves is a special

electromagnetic wave that traces a circle while its length remains constant. Such waves are called *circularly polarized waves*.

In case that the two plane-polarized waves oscillate with a phase difference of 90 degrees the resultant circularly polarized wave (electric field vector) rotates clockwise when looked at from the direction of propagation. If the two waves are added with a phase difference of -90 degree, then the resultant electric field of the circularly polarized light rotates counterclockwise, rather than clockwise, when looked at from the direction of propagation. Since both interactions are equally populated, the plane-polarized light contains both a left-handed and a right-handed circularly polarized component (Figure I-12).

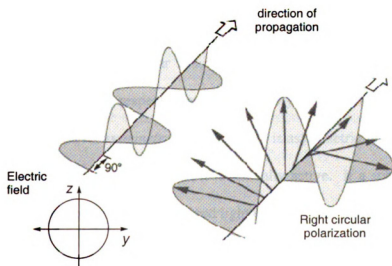


Figure I-12: Circularly polarized light consists of two perpendicular electromagnetic plane waves of equal amplitude with 90° difference in phase. The illustrated system is right- circularly polarized. <http://hyperphysics.phy-str.gsu.edu/hbase/phyopt/polclas.html>

When light interacts with matter, its properties may change.⁴⁵ Namely, its intensity (amplitude), polarization, velocity (c), wavelength (λ), etc. may alter. The two basic phenomena of the interaction of light and matter, *absorption* (or *extinction* (ϵ)) and

a *decrease in velocity* (c), are caused by the interaction of the electric (E) vector of the propagating wave with the electrons of the component atoms. This interaction has the effect of reducing the velocity of propagation (also called *retarding* the light) and in decreasing the amplitude of the E vector. Reducing the velocity of propagation is called *refraction* and is described by the *index of refraction*, n (first described by Fresnel in 1825), and decreasing the amplitude of the E vector is called *absorption* and is described by the *molar absorption coefficient*, ϵ .

For most substances, simple refraction and absorption are the only detectable results of such an interaction even if the light is polarized. However, the behavior of some molecules is sensitive to the plane of polarization of the incident light. Such a molecule is called *optically active* and is characterized by having distinct indices of refraction, n_L and n_R , and molar absorption coefficients, ϵ_L and ϵ_R , for left and right circularly polarized light, respectively. The property that determines whether a molecule is optically active is its *asymmetry*. If a molecule is asymmetric in the sense that it cannot be superimposed on its mirror image, it is optically active. If a substance retards both L and R components of circularly polarized light equally (i.e., if the indices of refraction for L and R circularly polarized light, n_L and n_R , are the same), the transmitted L and R waves will recombine to form plane-polarized light, with the plane of the transmitted beam E being the same as that of the incident beam (Figure I-13a).

However, if n_L and n_R are not equal, the transmitted L and R components of circularly polarized light are each retarded to a different extent so that on leaving the material the phases of the two sine waves differ and the medium is said to be *circularly birefringent*, and can be described by equation (I-1).

$$\Delta n = n_L - n_R \neq 0 \quad (\text{I-1})$$

Since the two circularly polarized components do not travel with the same velocity, the E vectors of the L and R waves combine to form a beam of plane-polarized light whose angle differs from that of the plane of polarization of the incident wave. The amount of rotation caused by the asymmetry of the sample is determined as the angle α and is called *optical rotation* (Figure I-13).

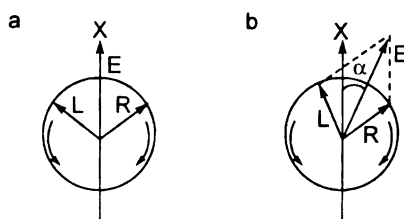


Figure I-13: a) Left (L) and Right (R) circular components of the plain polarized light are equally retarded by the medium and the electric vector E propagates in the linear direction X; b) difference in refractive indices for L and R components causes a rotation of the plane of linearly-polarized light on the angle α .

Hence, one of the methods that enables characterization of chiroptical properties of a chiral substrate can be obtained by measuring the difference of *refractive indexes* ($\Delta n = n_L - n_R \neq 0$),⁴⁶ which is referred to as *optical rotation*.

Optical rotation is the oldest of chiroptical methods. Nevertheless, it can be used for determining the absolute stereochemistry of a compound or as a criterion for enantiomeric purity, only if optical rotation data of a compound had been previously identified.

The measured rotation α depends on the number of chiral molecules in the cell and can be presented with the following equation:

$$\alpha = \kappa \rho l \quad (\text{I-2})$$

Thus, rotation α is linearly proportional to the length of the cell l , which is measured for historical reasons in decimeters (dm) and to the density ρ of the substance (if liquid). If ρ is expressed in g cm^{-3} , then the proportionality factor is called $[\alpha]$, *specific rotation*, and must be reported in $10^{-1} \text{deg cm}^2 \text{g}^{-1}$:

$$[\alpha] = \alpha / (\rho l) \quad (\text{I-3})$$

More commonly optical rotation cites the concentration in percent (i.e., g/100 cm^3). This leads to a different definition of *specific rotation*:

$$[\alpha] = 100 \alpha / (c_p l) \quad (\text{I-4})$$

It was observed that specific rotation $[\alpha]$ depends on some external factors, and is very characteristic for the wavelength, λ , and the solvent used for sample preparation, and, hence, is usually reported in the form that specifies temperature, wavelength, concentration and solvent used for measurements.

When optical rotation $[\alpha]$ is plotted as a function of wavelength the Optical Rotatory Dispersion (ORD) spectrum is generated (Figure I-14, blue curve) and ORD spectroscopy is used for absolute stereochemical determinations.⁴⁷

The difference in refractive indices for left and right circularly polarized light is related to the angle of rotation, α , and is represented by equation I-5:⁴⁶

$$\alpha = (n_L - n_R) 1800 l / \lambda_0 \quad (\text{I-5})$$

where α is the angle of rotation, in degree, n_L and n_R are the refractive indices for left and right circularly polarized light, l is the path length in decimeters, and λ_0 is the wavelength in vacuum of the light beams, in centimeters.

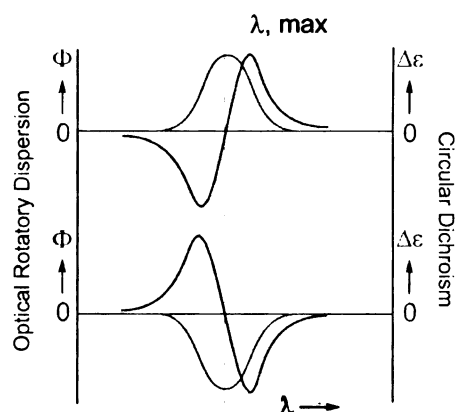


Figure I-14: Positive and negative Circular Dichroism (CD) and Optical Rotatory Dispersion (ORD) spectra.

Thus, up to this point we have focused on rotation of the plane of linearly-polarized light through an angle α relative to the initial direction of polarization that occurs in optically active matter due to the difference in refractive indices of the two circularly polarized components. In addition to the circular birefringence, the left and the right circular components might be also absorbed to a different extent (it is noteworthy that absorption of the light implies presence of a chromophore). In other words, the optically active medium has a different molar absorptivity coefficient ϵ for right and left circularly polarized light: $\epsilon_L \neq \epsilon_R$. The difference in molar absorptivity (eq. I-6) is called *circular dichroism* and a plot of its wavelength (or frequency) dependence is referred to as a circular dichroism (CD) curve (Figure I-14, red curve).⁴⁶

$$\Delta\epsilon = \epsilon_L - \epsilon_R \neq 0 \quad (\text{I-6})$$

Both ORD and CD effects are also referred as a Cotton Effect (CE), in honor of French physicist Aimé Cotton who first observed both phenomena in 1896.

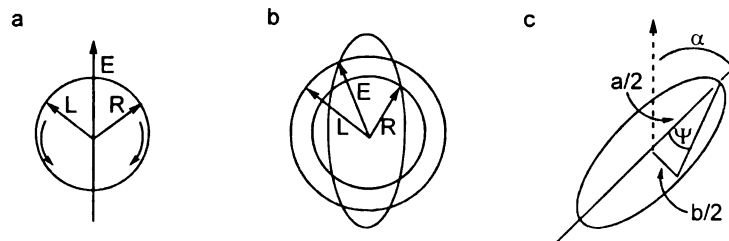


Figure I-15: Generation of elliptically polarized light: a) Left (L) and Right (R) circular components of the plain polarized light; b) difference in absorption of right and left components by a chiral medium causes the resultant vector (E) to follow an elliptical path; c) the angle Ψ formed between the semi axes of the ellipse (the ellipticity) is proportional to the circular dichroism.

The rotation α corresponds to the optical rotation

Nonequivalent absorption of the two circular components results in the change of a geometry of the wave. Upon emerging from the optically active medium, the two circularly polarized components are not only out of phase, but also of unequal amplitude. As it is depicted in Figure I-15b, the superposition of the two components is no longer a linearly polarized wave: the resulting field vector E does not oscillate along a straight line but rotates along an ellipsoid path and produces an *elliptically polarized light* (Figure I-15b).

The quantitative description of circular dichroism can be obtained from the Beer-Lambert-Bouguer law. If I_0 is the intensity of light entering the cell and I is that when leaving, the absorbance can be described by the following equation:

$$A = \log_{10}(I_0 / I) = \epsilon c \quad (\text{I-7})$$

That is, the recorded absorbance A is proportional to the concentration c of the sample in the cell and l is the path length. If c is given in mol liter^{-1} and l is in centimeters, then ϵ is called the *molar (decadic) absorption coefficient* or *molar absorptivity*.

In a chiral medium, since the two circular components of the plane polarized light travel with different speed and are absorbed differently, we can record two such absorptions, one for the left and one for the right circularly polarized light:

$$A_L = \log_{10}(I_{0L}/I_L) \quad \text{and} \quad A_R = \log_{10}(I_{0R}/I_R) \quad (\text{I-8})$$

Since upon entrance into the chiral medium the initial intensity of both left (I_{0L}) and right (I_{0R}) components are equal, we can omit the index L and R . Then the *circular dichroism* can be presented as a difference in the absorption of the two circularly polarized lights by the chiral medium as follows:

$$\Delta A = A_L - A_R = \log_{10}(I_0/I_L) - \log_{10}(I_0/I_R) = \log_{10}(I_R/I_L) \quad (\text{I-9})$$

If derived from Beer-Lambert-Bouguer law, *circular dichroism* can be viewed as a difference in the molar absorptivity according to the following equation:

$$A = \epsilon c l \quad \Rightarrow \quad \Delta \epsilon = (l/c l) \Delta A \quad (\text{I-10})$$

Since a CD spectrum reflects the difference between ϵ_L and ϵ_R (or A_L and A_R) the sign of the spectrum might be positive or negative (Figure I-14). The sign of the spectrum is governed by the direction of a momentary dipole called electric dipole transition moment (edtm), $\vec{\mu}$, which is created upon absorption of light by the molecule, i.e. excitation of the electrons from the ground state to an excited state. The direction of $\vec{\mu}$ is the same as the transition polarization – i.e., the direction in which the electrons are pushed during the transition.

In contrast to the linear effect of the electric field, the magnetic field induces a circular arrangement of electron density. The net direction of charge is the magnetic dipole transition moment (mdtm), $\vec{m} = \vec{I}$.⁵ The direction of the magnetic dipole transition moment $\vec{m}$ can be determined by the application of the “right hand rule” to the

rotation of circular current. As is depicted in Figure I-16, if four fingers of right hand are curved in the direction of the rotation of the charge in the magnetic field $\vec{B}$, then the thumb points in the direction of the magnetic dipole transition moment (mdtm) $\vec{m}$.

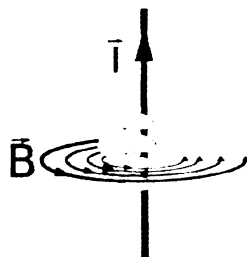


Figure I-16: Pictorial description of “right hand rule”.

In an achiral molecule the net electron redistribution is planar. It is either linear, having $\vec{\mu} \neq 0$, $\vec{m} = 0$, or circular - having $\vec{\mu} = 0$, $\vec{m} \neq 0$. In a chiral molecule the rearrangement of electrons is always helical. The latter represents the case when chiral perturbation of the electric charge creates a magnetic transition dipole moment $\vec{m}$ that is polarized relative to $\vec{\mu}$ and combines with it to force a helix of electron redistribution.

If the helix of electron motion is right-handed then it is induced by left circularly polarized light and a positive *CD* is observed, and *vice versa*. The fact that left-handed circularly polarized light induces a right-handed transition better than a left handed one follows from the interaction of the electric vector of the light with $\vec{\mu}$ (edtm) and the simultaneous interaction of the complex component of the magnetic field with $\vec{m}$ (mdtm). The equation that summarizes this interaction is the Rosenfeld equation I-11. Thus, CD intensity or rotation strength *R* is a correlation of $\vec{\mu}$ and $\vec{m}$ of randomly oriented molecules:

$$R = \text{Im}[\vec{\mu} \times \vec{m}] = \vec{\mu} \bullet \vec{m} = |\vec{\mu}| |\vec{m}| \cos\beta \quad (\text{I-11})$$

where ‘Im’ denotes ‘imaginary part of’, $\bar{\mu}$ is the edtm for the transition from the final to the initial state, $\bar{m}$ is the mdtm for the reverse transition and β is an angle between these transitions. The sign of CD is positive when the angle is acute ($0 < \beta < 90^\circ$) or, in the limited case parallel, and it is negative when the angle is obtuse ($90 < \beta < 180^\circ$) or, in the limiting case, antiparallel.

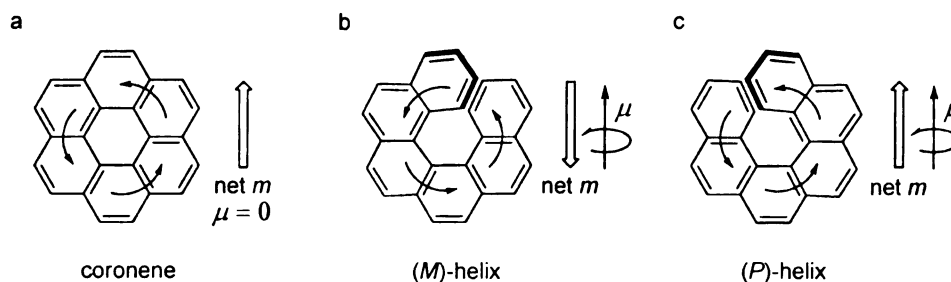


Figure I-17: The electric dipole transition moment and the magnetic transition dipole moment in an achiral coronene and chiral hexahelicenes.

The helical motion of electrons in chiral compounds upon excitation can be demonstrated with helicenes. Achiral coronene (Figure I-17a) provides circular perturbation of electrons and, hence, has the net electric dipole transition moment $\bar{\mu} = 0$. Although the mdtm is present the product of the two vectors is equal to zero and no CD can be observed. Unlike coronene, the net electron perturbation in *M* and *P* hexahelicenes is linear, and, hence induces a definite electric dipole transition moment. Since edtm oscillates along the direction of electron flow, the two hexahelicenes have $\bar{m}$ oriented in a same direction. Following the “right hand rule” the magnetic dipole transition moment in *M*-helicene will be oriented antiparallel to the edtm (Figure I-17b), while the orientation of $\bar{m}$ in *P*-hexahelicene is parallel to that of $\bar{\mu}$ (Figure I-17c). Thus, *M*-helicene represent the case with antiparallel alignment of the two transition

moments and according to equation I-11 must lead to negative Cotton effect, while P-helicene supports parallel alignment of the two dipole transition moments and leads to positive CD.

Both ORD and CD spectroscopy can be recorded by Circular Dichrometers (spectropolarimeters). The essential features of CD spectropolarimeter are a source of monochromatic left and right circularly polarized light and a detector of the difference in absorbance of the two polarized beams.

Since ORD and CD are the manifestations of the chirality in the medium they can be used for detection and characterization of optical activity of previously analyzed and established samples, but do not allow the determination of absolute chirality of an unknown sample. Since the first application of CD and ORD several empirical⁴⁸ and semi-empirical⁴⁹ methods have been developed to relate the observed CD or ORD data with the absolute chirality of the substrate. However, these methods and rules must be applied with great caution and only toward specific structures, since they are based on empirical observations. Recent developments in the field offer reliable quantum mechanical calculations of the rotation angle of a chiral molecule that could be used for further empirical establishment of absolute stereochemistry.⁵⁰⁻⁵³ The computation of the specific rotation angle is based on the calculation of the electric-dipole magnetic-dipole polarization (G'),⁵⁴⁻⁵⁶ a measure of the overlap of the electronic polarization induced by the electric and the magnetic field of the incident light, which can be calculated using the couple-perturbed Hartree-Fock method⁵⁷ on standard desktop workstation.

I.5: Octant rule – Stereochemical determination of chiral ketones

The sector rules mostly focus on chromophores and correlate the CD Cotton effect detected for the chiral sample with the chirality of the molecule. One of the most important applications of the empirical sector rules is the stereochemical determination of chiral saturated alkyl ketones and aldehydes. The method is known as Octant rule and was first introduced by Djerassi in 1960.⁵⁸ The relevant transition for the Octant rule is the $n \rightarrow \pi^*$ transition around 300 nm characteristic for carbonyl group. The rotation of charge caused by UV irradiation induces perturbation of electrons that for carbonyls in achiral environment (similar to the case of helicenes presented in the previous paragraph) creates a strong magnetic dipole transition moment $\vec{m}$, but does not induce electric dipole transition $\vec{\mu}$. However, when the carbonyl group is located in a chiral environment, dissymmetric perturbations of the $n \rightarrow \pi^*$ transition leads to nonzero rotatory strength $R = \vec{m} \bullet \vec{\mu}$.

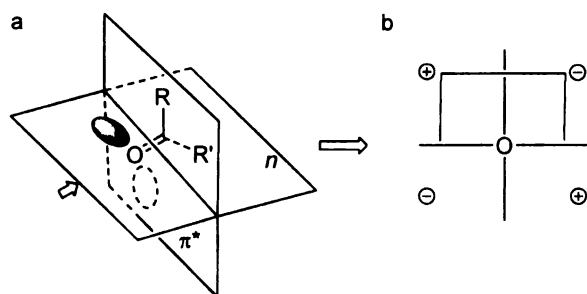


Figure I-18: Octant for saturated ketones: a) Nodal planes of carbonyl, b) Signs of four rear octants viewed along the carbonyl bond axis from oxygen atom.

The Octant rule states that substituents lying in the nodal planes do not contribute to the $n \rightarrow \pi^*$ transition, and consequently, to the sign of the CD. Thus, in order to interpret the sign of the obtained CD on the basis of Octant rule it is necessary to

establish the nodal planes of the carbonyl. The nodal plane of n orbital of oxygen atom bisects the R-C-R' bond angle and is perpendicular to the C=O plane. The nodal plane of π^* is in the plane of the C=O bond that dissects the bond between C and O (Figure I-18a). Since most of the substituents that are in the plane of the nodal surface do not contribute to the CD sign, only the substituents that are off the nodal planes will be considered, and the view of the nodal modes is simplified to the view on Figure I-18b. The ketone of question has to be virtually placed into the octant and the sector that will be occupied by the substituents of the asymmetric center will determine the sign of the CD couplet. For instance, the stereochemistry of chiral 3-methylcyclohexanone which exhibits positive Cotton effect is deduced with Octant rule in the way presented on Figure I-19.

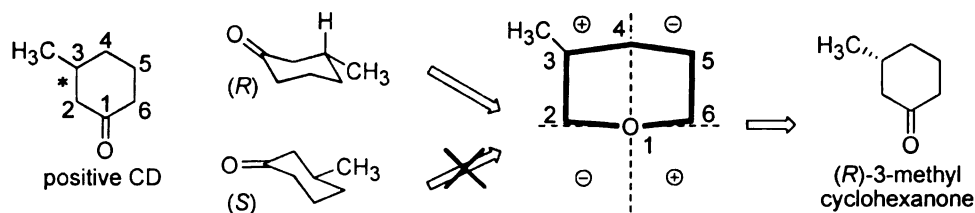


Figure I-19: Determination of absolute stereochemistry of 3-methylcyclohexanone through the Octant rule.

The substrate is placed into the octant in such a way that the two α -carbons occupy the n nodal plane (Figure I-19). Considering that the substituent (CH_3 group) prefers to occupy an equatorial position in the cyclohexanone two cases are possible: the carbons 3 and 5 can occupy either a lower segment of vertical node if the chirality is (*S*), or the top segment of the vertical plane if the chirality is (*R*). Since the observed sign of CD is positive, the first approach is not valid since the methyl group of the asymmetric

carbon will occupy a negative octant and, hence, lead to negative sign of Cotton effect. The (*R*) stereoisomer will place the methyl group into the positive octant of the top segment and, therefore, explain the observed sign of Cotton effect.

The Octant rule remains one of the most applied methods for absolute stereochemical determination of chiral ketones and aldehydes, although similarly to the CD and ORD, it has limited application^{48, 59-65} and, in some cases provides incorrect correlation⁶⁶ between sign of CD and absolute chirality of the substrate of question.

I.6: Raman optical activity (ROA) and Vibrational circular dichroism (VCD)

The traditional chiroptical methods described in previous paragraphs focus on studies of *electronic* optical activity through measurement of optical rotation and circular dichroism of visible and ultraviolet radiation. However, over the last two decades, new achievements in the field of vibrational spectrometry have led to the application of both Infra Red (IR) and Raman spectrometry towards determination of absolute stereochemistry of organic molecules and inorganic metal complexes. The methods that are based on vibrational optical activity are Raman Optical Activity technique (ROA)⁶⁷⁻⁷¹ and Vibrational Circular Dichroism (VCD).⁷²⁻⁷⁴ Vibrational optical activity measures a small difference in the Raman-scattered intensity of left and right circularly polarized light, i.e., it senses the chirality in the molecule directly, while CD spectroscopy relies on the “vision through chromophore”.⁶⁷

Raman Optical activity was first observed by Barron, Bogaard and Buckingham in 1973.^{67, 70, 75, 76} While at the beginning the method was limited to small chiral

molecules, the latest modification of the method has made the technique applicable to determination proteins.⁷⁷ Nevertheless, the sensitivity of ROA restricts its application to neat liquid or concentrated solutions.^{70, 77} Vibrational Circular Dichroism (VCD)^{73, 78} is based on differential absorption of left and right circularly polarized infrared light (IR) by vibrating molecules and was found to be more sensitive and more reliable as compared to ROA. The basic measurements for both ROA and VCD are associated with a vibrational transition of angular frequency $\omega_v = I^R - I^L$, where I^R and I^L are the Raman scattered intensities at the angular frequency $(\omega - \omega_v)$.⁷⁸ The availability of quantum mechanical programs that provide reliable predictions of VCD using density functional theory and the development of commercial VCD instruments facilitated the predictions of absolute configurations using VCD. Numerous examples are now available where VCD has been successfully used in confirming known absolute configurations, or resolving the ambiguous literature assignments or unambiguous determination of absolute configuration, in addition to determining the predominant conformations in the solution phase.^{20, 79}

I.7. Circular Dichroism of bis-chromophoric systems – Exciton Coupled Circular Dichroism (ECCD)

The CD and ORD phenomena described in section I.4 represent the chiroptical methods that are based on excitation of a single chromophoric system. The excitation of systems containing two or more non-conjugated chromophores with polarized light induces a through space interaction of the chromophores that is detected as a bisignate CD curve. The phenomenon is called *exciton coupling*. The method was developed from

the couplet oscillator theory^{80, 81} and group polarizability theory^{82, 83} and the CD curve observed is named as an *ECCD* (*exciton coupled circular dichroic*) *spectrum*. Since its discovery by Harada and Nakanishi¹⁸ the ECCD method has shown to be a reliable, and, in contrast to the other methods described above, a non-empirical methodology for establishment of absolute stereochemistry of chiral organic molecules.

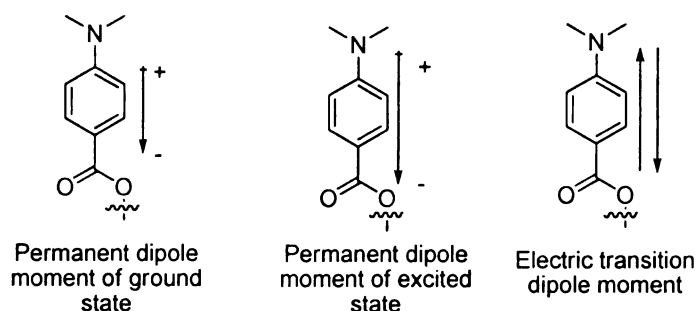


Figure I-20: Permanent electric dipole and electric dipole transition moment in the chromophore.

The method is based on detection of excitonic interaction between two or more chromophores that are chirally oriented relative to one another in space. The exciton interaction is originated between the electric dipole transition moments of the chromophores. To start from the beginning, it is known that chromophores exhibit a dipole moment. As it is shown in Figure I-20, a permanent dipole moment in *p*-amino benzoate is directed from the amino group to the ester group. In the course of a π - π^* intramolecular charge transfer transition (excitation), electrons migrate from the amino to the ester group via the benzene ring. Therefore, the permanent dipole of the excited state is much more polarized, and is expressed by a single arrow as the polarization from the electron-donating group to the electron-withdrawing group. The electric dipole transition moment is represented by two arrows, which indicate oscillation. The rotational strength

of exciton coupling depends only on the edtm and is independent of the permanent dipole moment.

Thus, in excited state the chromophore retains the direction of its dipole moment, but acquires a new electric dipole transition moment, which has two directions for oscillation. When there are two chromophores in the system, they both gain an electric dipole transition moment that interact through space. The resultant excitation is delocalized between the chromophores and the excited state (exciton).⁸⁴ Most significant interaction of the two edtm of chromophore i and chromophore j is the transition occurring at the same energy E . Since the transition moment in chromophore i oscillates, its interaction with the transition moment of the chromophore j might be either in-phase or out-of-phase and each of this interaction will be of different energy. In fact the two phase interaction of edtm causes a split of the excited state into two energy levels α and β . The energy gap between the two states can be quantitatively expressed as $2V_{ij}$ and is called *Davydov split* (Figure I-21) for the theoretical physicist Davydov A.S. who first observed the split excited state in the electronic spectra on molecular crystals in 1942.⁸⁵

⁸⁶ Thus, appearance of the split excited state results from the out-of-phase stabilizing dipole-dipole interaction (low energy interaction, α -state) and in-phase destabilizing dipole-dipole interaction (high energy interaction, β -state) of electric dipole transition moments of two chromophores. The two transitions lead to two absorptions that are differentiated by the absorption wavelength: the out-of-phase transition is detected at higher wavelength, while in-phase transition, being higher in energy, appears at lower wavelength. Thus, in the UV-vis spectrum the interaction of the bis-chromophoric system is detected as two component spectra of the same sign, which usually appear as a

single absorption with double intensity (Figure I-21). However, when the energy gap $2V_{ij}$ between the two energy levels is substantial the two transitions might be observed separately.⁸⁴

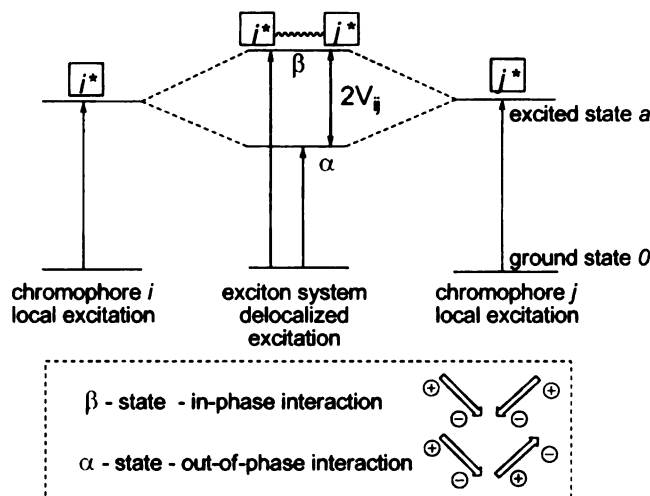


Figure I-21: Origins of Exciton Coupling. Interaction of the edtms of chromophore i and chromophore j splits the excited state into two energy levels. The energy $2V_{ij}$ is called Davidov splitting. Split of the excited state of the bis-chromophoric system is due to in-phase and out-of-phase interaction of electric dipole transition moments.

The Exciton interaction of edtm of the bis-chromophoric system can also be detected in the CD spectrum. Unlike in the UV-vis, the existence of the CD detectable transition depends on the relative spatial orientation of the chromophores. Since CD spectroscopy is based on the differential absorption of the left and right circularly polarized light ($\Delta\epsilon = \epsilon_L - \epsilon_R \neq 0$) the chiral orientation of chromophores is a must. In other words, when the relative orientation of the edtm is non-chiral (either they are oriented parallel to each other, or both chiral orientations present at the same time) the interactions are equivalent and cancel out. In this case no CD can be detected.

The chiral orientation of the chromophores results in a chiral exciton interaction of their electric dipole transition moments and gives origin only to the CD active transitions. This transition is detected as a bisignate CD curve, or ECCD spectrum (Figure I-22b). Thus, the appearance of the ECCD curve depends on the angular arrangement of edmt, and, therefore on rotational strength R . It is also noteworthy, that ECCD activity depends on the interaction of the electron dipole transition moments and does not depend on the permanent dipole of the chromophore.^{18, 87}

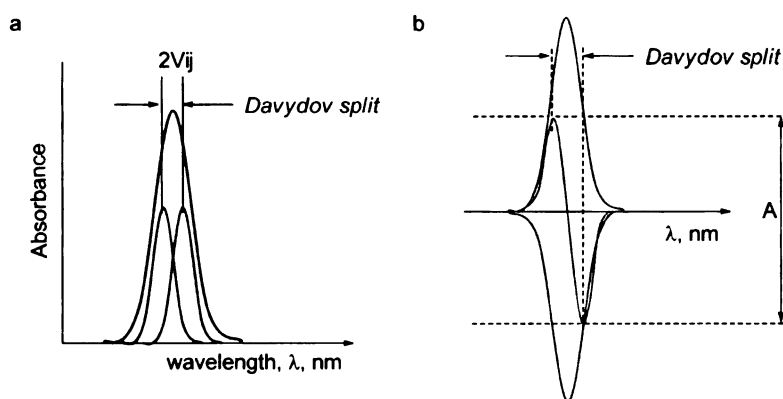


Figure I-22: Origins of Cotton Effect (CE). The interaction of edtms leads to two absorptions at different wavelength: a) absorption of the two interactions in α and β -states with energy difference of $2V_{ij}$ and UV-vis absorption as a summation of the two curves; b) Manifestation of the same effect detected as bisignate CD curve.

There are two possible chiral orientations of the chromophores, clockwise (positive) and counterclockwise (negative), and, hence two chiral orientations of their electric dipole transition moments. Considering that each interaction of edtm involves symmetric (in-phase) and asymmetric (out-of-phase) exciton coupling then every helical arrangement of two chromophores has two sets of exciton couplings.

Figure I-23 presents detailed analysis of exciton coupling interaction of transition dipole moments leading to rise of bisignate CD spectrum for clockwise and counterclockwise orientation of chromophores. As it was mentioned above there are two possible orientations of chromophores: clockwise and counterclockwise. Each orientation gives rise to two possible interactions of edtm: clockwise in-phase and clockwise out-of-phase, or counterclockwise in-phase and counterclockwise out-of phase (Figure I-23 dashed boxes).

The oscillation of charge (from minus to plus) in each transition follows either clockwise (positive) or counterclockwise (negative) direction. For instance, a clockwise in-phase interaction induces positive oscillation of charge and, hence, leads to a positive Cotton effect.

The out of phase interaction in the same system results in negative rotation of charge and gives rise to negative CD couplet. The energies of two transitions differ due to the symmetry of interaction. The symmetric in-phase interaction is of higher energy due to repulsion between similar charges and will appear at lower wavelength, while the stabilized out-of-phase exciton will appear at higher wavelength. Thus, the combination of the interaction taking place between the chromophores that are oriented clockwise will lead to the positive ECCD spectrum with a positive Cotton effect (CE) of lower energy, followed by a negative CD of higher energy. Similar analysis of counterclockwise orientation of two chromophores and excitonic interaction of edtm will lead to a negative ECCD spectrum, where lower energy transition is negative CE, followed by positive CE at lower wavelength.

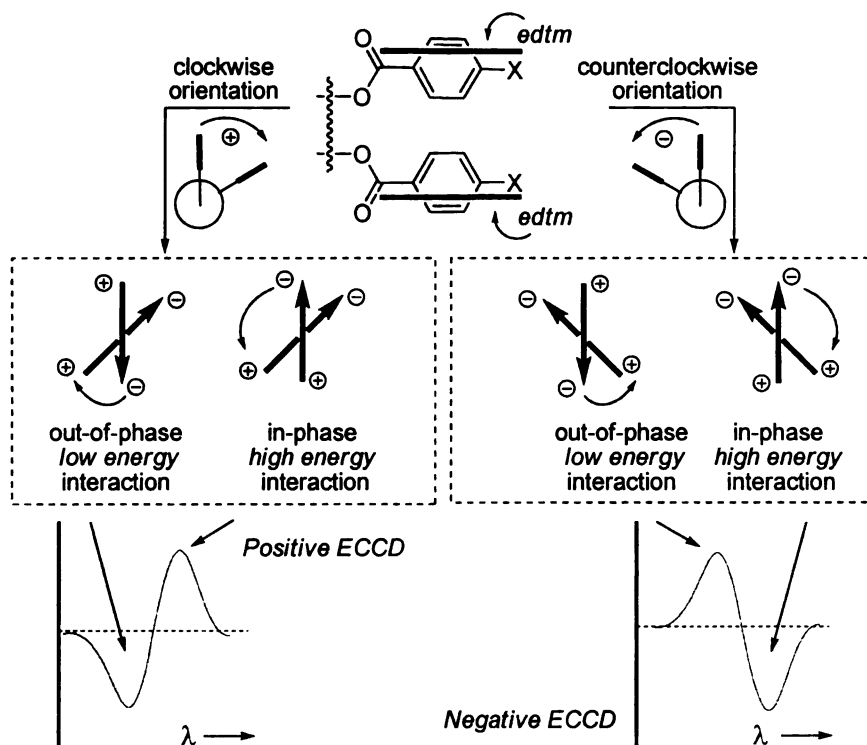


Figure I-23: Origins of bisignate CD: Excitonic interaction of edtm of two non-conjugated chromophores (in-phase and out-of-phase) result in a bisignate CD curve.

The appearance and the sign of bisignate CD can be also expressed through quantum mechanical theories and can be quantitatively expressed as rotational strength R with equation I-12:¹⁸

$$R_{\alpha,\beta} = \pm (1/2) \pi \sigma_o R_{ij} \cdot (\mu_{ioa} \times \mu_{ioa}) \quad (\text{I-12})$$

where the positive and negative sign correspond to the states α and β , respectively, R_{ij} is the distance vector from chromophore i to j , μ_{ioa} and μ_{ioa} are electric dipole transition moments for excitation $0 \rightarrow a$ (ground state to excited state) of group i and j , respectively, and σ_o is the excitation number of transition from ground state 0 to excited state a , which can be expressed as: $\sigma_o = \nu_o / c = (E_a - E_o) / (hc)$, h is the Planck constant and c is the speed of light in vacuum. The equation indicates that the Cotton effects of α - and β -state have identical rotational strength, but differ in sign. As is shown in Figure I-22, this

leads to a bisignate CD spectrum with Cotton effect (CE) peaks of opposite sign, which are separated by the energy gap $\Delta\lambda = 2V_{ij}$ (Davydov split).

Another approach to theoretical definition of the sign of ECCD spectrum is presented in equation I-13:

$$R_{ij} \bullet (\mu_{ioa} \times \mu_{joa}) V_{ij} \quad (I-13)$$

where the positive and negative sign correspond to the states α and β , R_{ij} is the distance vector from chromophore i to j, μ_{ioa} and μ_{joa} are electric dipole transition moments for excitation $0 \rightarrow a$ (ground state to excited state) of group i and j, respectively, and V_{ij} is the interaction energy between the two groups. As can be seen from the equation, the sign of the ECCD spectrum completely depends on the relative orientation of the two transition moments. For dihedral angle $0^\circ < \tau < 180^\circ$, the rotational strength R_{ij} is greater than zero, while for angles $180^\circ < \tau < 360^\circ$ the rotational strength R_{ij} is less than zero. Thus, the sign derived from the equation defines the sign of the expected ECCD spectrum.

A direct correlation of dihedral angles between chromophores and sign of ECCD spectrum is possible through equation I-14:

$$R^\pm = \pm \frac{\epsilon \mu^2 R_{ij}}{4\hbar} \sin\alpha \sin\gamma \sin\tau \quad (I-14)$$

where R_{ij} – is a vector from chromophore i to chromophore j, α and γ – are the angles between the edtm μ_{ioa} and μ_{joa} of the chromophores i and j respectively, and τ – is the dihedral angle between the two chromophores. Equation I-14 is simplest when $\alpha = \gamma = 0^\circ$ or $\alpha = \gamma = 90^\circ$, i.e. when transitions are polarized either parallel or perpendicular to the line connecting the chromophore origins (R_{ij}). If two degenerate transition are oriented with $\alpha = \gamma = 0^\circ$ then these transitions are coplanar and form an achiral system and have

no ECCD arising from this coupling. If, however, two degenerate transition interact with $\alpha = \gamma = 90^\circ$, then the resulting coupling depends on the dihedral angle τ . The classical example of such system – biphenyl – is presented in Figure I-24.

When $\tau = 0^\circ$ the CD strength is zero and when $\tau = 90^\circ$ or 270° (i.e. perpendicular), there is no energy split between the two bands, so no CD can be observed. For the values of dihedral angle between the chromophores within a range of $0^\circ < \tau \neq 90^\circ < 180^\circ$ equation I-14 gives a positive a CD, and if the dihedral angle varies within $180^\circ < \tau \neq 270^\circ < 360^\circ$ a negative CD is observed.

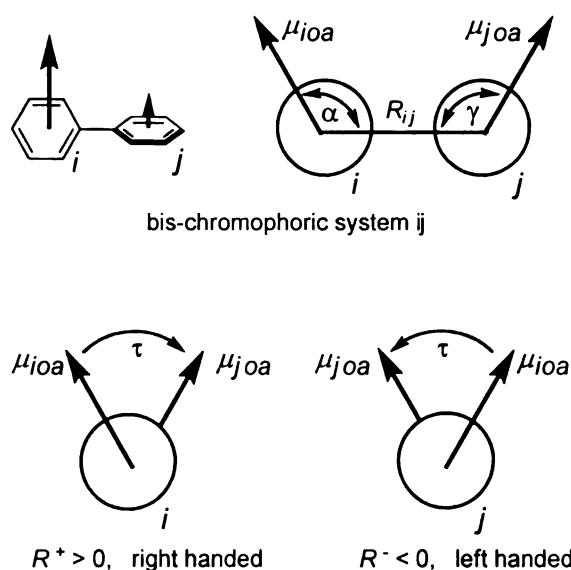


Figure I-24: Schematic illustration of the coupling of two edtms in a chiral biphenyl system. The coupling of the two dipoles produces a net helical - right handed or left handed - motion of electrons giving rise to positive or negative ECCD, respectively.

However, in most of the systems the arrangement of chromophores varies from $\alpha = \gamma = 90^\circ$ and can be represented as $\alpha = \gamma \neq 90^\circ$, i.e. the transitions are neither parallel nor perpendicular to R_{ij} . For this system, the expected sign of the CD couplet also depends on the handedness between the chromophores. The amplitude of ECCD spectrum

depends on the values for α and γ . Statistically, it was detected that the highest magnitude of CD spectrum can be observed at $\alpha = \gamma = 73^\circ$ and $\tau = 112^\circ$.

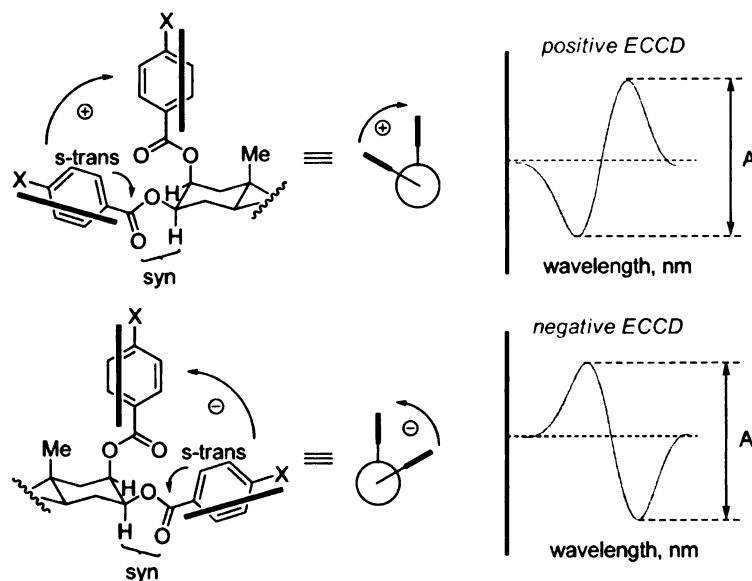


Figure I-25: Two enantiomeric diols, derivatized with chromophores lead to Exciton Coupled CD spectra of opposite sign: (*R*, *S*) stereoisomer induced positive helicity within the bis-chromophoric system and results in positive CD bisignate, while (*S*, *R*) enantiomer gives rise to positive ECCD indicating a counterclockwise orientation of the chromophores.

The ease of the analysis and correlation of the sign of the observed ECCD spectrum and the relative orientation of chromophores in space lead to the wide application of the Exciton Coupled Circular Dichroism method for the absolute stereochemical determination of a variety of chiral substrates. Figure I-25 depicts the classical case where the absolute stereochemistry of enantiomeric steroidal diols is determined through the exciton coupling method. Since the excitonic interaction occurs between chromophores, the two alcohols were derivatized with aromatic moieties as benzoates.⁸⁸

The through space exciton interaction between the two benzoates is detected as a bisignate CD curve, different for each enantiomer. Thus, the (*R*, *S*) stereoisomer induces a positive CD bisignate, i.e. the bisignate spectrum with the positive Cotton effect (CE) at higher wavelength, followed by a negative CE at lower wavelength, while the (*S*, *R*) enantiomer results in negative ECCD spectrum (the spectrum has a negative CE at higher wavelength).^{17, 18} The sign of the CD bisignate is in direct correlation with the relative orientation of chromophores, or, to be more precise, with the orientation of their electric dipole transition moments. The clockwise orientation of edtms induces positive ECCD spectrum, while counterclockwise orientation leads to negative bisignate Cotton effect. There is no exception in the sign of bisignate CD curves, positive and negative chirality always lead to positive and negative couplets, respectively.^{87, 89, 90}

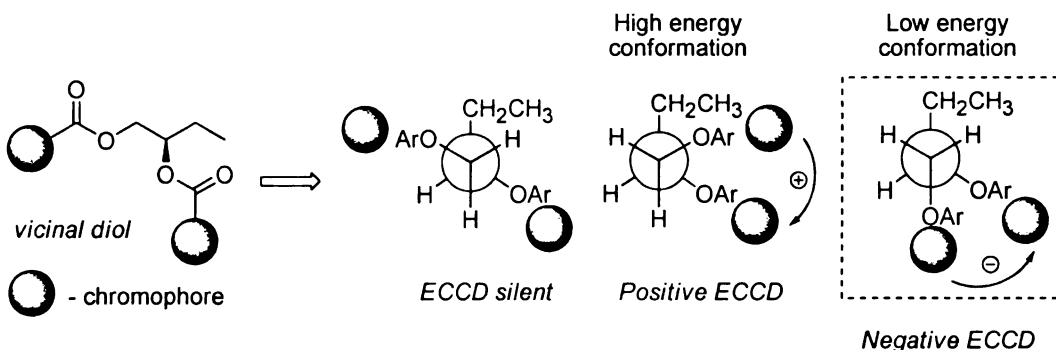


Figure I-26: Stereochemical determination of 1,2-diol after derivatization with dibenzoate.

Ease of interpretation of the observed bisignate CD spectrum and straightforward correlation of the sign of ECCD to the relative orientation of the chromophores, and, hence to the absolute chirality of the substrate has led to the application of this method for establishing the absolute chirality of a variety of mono-alcohols and diols, polyols and aminopolyols,⁹¹⁻⁹⁵ carbohydrates,⁹⁵ quinuclidines⁹⁶ and hydroxyl acids,^{31, 97} etc.

Figure I-26 depicts conformational analysis of (*R*)-1,2-diol resulting in a negative CD bisignate. The three gauche conformations are the low energy conformations expected for the substrate. The first conformation places the two chromophores antiperiplanar to each other, hence diminishing the ECCD signal. The second conformation would induce a clockwise orientation of the chromophores, although being of higher energy would be less populated. The highly populated lower energy conformation orients the chromophores counterclockwise and, hence, gives rise to a negative ECCD spectrum. Thus, determining the major ECCD active conformation is the key for the interpretation of the spectrum.

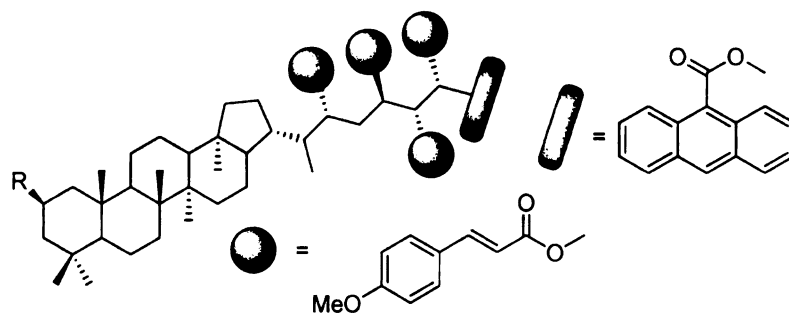


Figure I-27: Stereochemical determination of polyols after derivatization with chromophores.

Application of this method to polyols represents the example where more than two chromophores can be incorporated into the ECCD analysis. In this case the observed ECCD spectrum results from summation of all the component CD couplets (Figure I-27).^{95, 98}

to exciton coupling with endocyclic double bond. The minor dibenzoate product showed no split CD due to the coplanarity of both benzoate groups.

The exciton chirality method can also be applied to systems that possess one or both chromophores as a structural element(s). The former case will require introduction of a second chromophore, while the latter can use the preexisting chromophores for exciton coupling. The examples of these systems are in Figure I-29, where bisignate CE is detected due to the exciton interaction of two chromophoric structural units. The method was successfully applied to such simple acyclic systems as 1,2-diarylethane and α -pyridyl-arylcarbinols.¹⁰⁶⁻¹⁰⁹

I.8. Chromophores for ECCD measurements

Along with a sign (positive or negative), the intensity or the *amplitude* *A* of the ECCD spectrum is also important. The amplitude *A* is the vertical distance between the peaks of the split CD curve and is either positive or negative depending on the sign of the first CE. Although, as it was discussed above, correlation of the ECCD sign to the absolute chirality of a stereocenter is straightforward, the absorption maxima at 230-310 nm characteristic for commonly introduced chromophores (i.e., functionalized benzoates) frequently overlaps with those of substrates containing carbonyl groups and isolated or conjugated double bonds. Such overlap of absorption maxima leads to complex CD spectra and complicates their interpretation. When the chromophores used for detection of ECCD spectrum are the structural units of the analyzable molecules, the complications arising from interaction with other chromophores that could be present in the molecule are unavoidable. However, when chromophores are introduced through chemical

derivatization an undesired secondary interaction can be overcome. A possible solution for this problem would be to enhance the signal provided by the chromophores over the background noise signal originated from a secondary exciton coupling between the chromophore and other π electron containing functional group that could potentially occur in the system. For these reasons a set of physical parameters that affect the sensitivity (or amplitude) of the exciton coupling has been investigated:¹¹⁰

- (1) **Interchromophoric distance (R):** A is inversely proportional to the square of interchromophoric distance (R) between two interacting chromophores;^{84, 111}
- (2) **Projection angle between transition moments** (i.e. dihedral angle between two chromophores): A depends on the angle between the vectors representing the coupled electric dipole transitions of the chromophores. The magnitude of the two bands can be derived from equation I-14:

$$R^{\pm} = \pm \frac{\epsilon \mu^2 R_{ij}^2}{4\hbar} \sin\alpha \sin\gamma \sin\tau \quad (\text{I-14})$$

α and γ are the angles between the edtm μ_{ioa} and μ_{joa} of the chromophores i and j respectively, and τ is the dihedral angle between the two chromophores. From the equation above, the highest magnitude of ECCD for bis-chromophoric systems is expected for dihedral angles when $\alpha = \gamma = \pm 73^\circ$ and no ECCD can be detected for angles 0° , 90° and 180° .^{84, 111}

- (3) **Number of interacting chromophores:** based on experimental results and theoretical calculations the amplitude A of the signal for the overall system was found to be a summation of the A value induced by every pair chromophore in the

system.^{112, 113} Thus for the systems that contains chromophores X, Y and Z the total amplitude would be: $A_{total} = A_{xy} + A_{xz} + A_{zy}$.

- (4) **Molar absorptivity of the chromophore (ϵ , $M^{-1}cm^{-1}$):** The ECCD amplitude defined as $A = \Delta\epsilon_1$ (first Cotton effect) - $\Delta\epsilon_2$ (second Cotton effect), where $\Delta\epsilon = \epsilon_L - \epsilon_R$, increases as the molecular extinction coefficient value ϵ_{max} increases. It was found to be proportional to the ϵ^2 .^{112, 114-116}

Considering that the interchromophoric distance, dihedral angle and number of chromophores are specific for each molecule and in most of the cases cannot be altered, a general enhancement of the amplitude of CD bisignate using these three parameters is not an easy task. Molar absorptivity, however, is the characteristic of a chromophore that can be improved by extended conjugation or introduction of electron rich substituents. In such case, due to the direct relationship between the amplitude and extinction coefficient of the chromophore, increase of ϵ could positively contribute to the intensity of the ECCD signal. On the other hand, extended conjugation and electron rich systems are characterized by red-shifted absorption maximum. Hence, an improved absorption of chromophores could be used for both improvement of the amplitude of the ECCD spectrum and shift of the exciton coupling towards higher wavelength. Use of the red-shifted chromophores would limit the transitions to the region solely due to the exciton coupling between the target chromophores.

For the latter reasons new chromophores with improved spectroscopic characteristics (red-shifted λ_{max} and high ϵ) have been devised.^{99, 117-119} Figure I-30 depicts several chromophores designed to provide higher absorption maximum and extinction coefficient.¹¹⁹ As can be seen, all depicted chromophores have absorption

maxima significantly red-shifted as compared to benzoate (UV: $\lambda = 280$ nm, $\epsilon = 32,000$ $M^{-1}cm^{-1}$) and are characterized by higher molar coefficient ϵ .

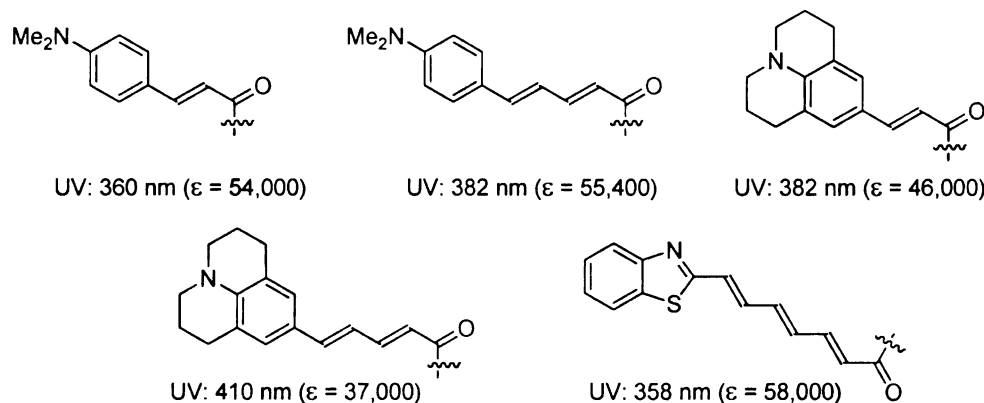


Figure I-30: Alternative chromophores for ECCD determination with improved spectroscopic characteristics.

The ongoing search for the universal chromophore drew attention to the highly chromophoric molecules – porphyrins (Figure I-31). Porphyrins have been wide used due to several unique features:

- (1) Porphyrins are good chromophores with a sharp absorption maximum around 418 nm for the main absorption band (Soret band) avoiding an overlap of the signal with any other absorption generated by chromophores such as carbonyls and alkenes or any aromatic rings that may preexist in the system (a typical chromophore absorbs at 300 nm and below).
- (2) The molar absorptivity coefficient ϵ of $>350,000$ $M^{-1}cm^{-1}$ and higher makes porphyrins highly chromophoric. Intensities of Cotton Effects depend on the extinction coefficient of the chromophores, and hence the intense absorption of the porphyrins greatly enhances the sensitivity of CD. High ϵ not only ensures a

significant increase of the amplitude of the ECCD spectrum, but also allows reduction of the amount of sample necessary for the analysis.

- (3) The intense absorption of porphyrins leads to a through space interaction over a distance of nearly 50 Å.¹²⁰
- (4) Spectroscopic ($\lambda_{\max}$, ϵ) and physical properties (hydrophilicity and hydrophobicity) of porphyrins can be tuned by alteration of substituents at *meso* position and β -positions of the pyrrole rings.
- (5) Incorporation of a metal into the porphyrin ring allows non-covalent complexation of porphyrins with suitable Lewis base binding sites.

From the time of the first discovery of porphyrins in early 1920, the chromophores have been accessed both chemically and enzymatically.¹²¹⁻¹³⁰ First report using chemical condensation of pyrrolymethanes for construction of porphyrins was published by Fisher and coworkers in 1937 and gave the chromophore in ~0.03% yield.¹³¹ An attempt to improve the yield of the condensation reaction made in 1957 by Sugihara and McGee gave 0.5% of porphyrin.¹³² The subsequent work by Rapoport and coworkers in 1968 resulted in a significant improvement of the condensation reaction and gave porphyrin in 6% yield.¹³³ The first application of monopyrroles towards the synthesis of porphyrins (1978) allowed the use of the simple building blocks and construction of porphyrins in one step.¹³⁴ Use of condensation reaction, despite a low yield of the product, opened a relatively simple approach to a variety of porphyrin structures. Other approaches use small building blocks, for instance, aminopyrroles,¹³⁵ for stepwise construction of porphyrin core. Modifications of the porphyrin synthesis in pursue of an improved yield and ease of purification of the product remains an ongoing

research. The field was greatly enriched by work of Lindsey and coworkers focusing of synthesis of dipyrromethanes and porphyrin bearing different substituents (Figure I-31).¹³⁶⁻¹⁴⁸

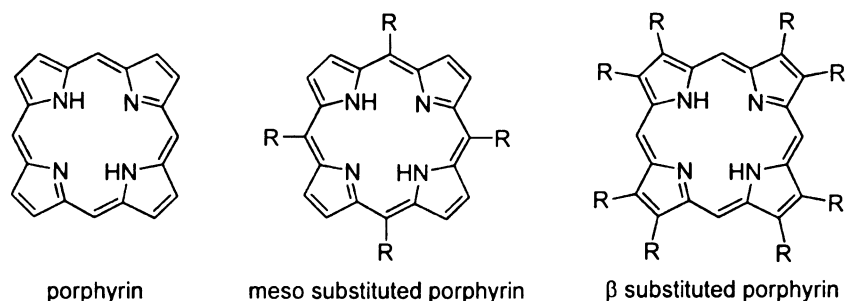


Figure I-31: Structures of porphyrins.

Since the ECCD method is based on interaction of the electric dipole transition moments, identification of direction of the dipole is crucial. With non-symmetric porphyrins the dipole can be clearly defined. Figure I-32 presents a non-symmetric 5-(4-methylcarboxyphenyl)-10,15,20-triphenyl porphyrin (type A_3B ; A_3 refers to three identical substituents at the porphyrin) that is routinely used in exciton CD studies. The UV-spectrum of a free base porphyrin generates multiple absorption bands of different intensity. There are four Q-bands in the visible region between 500 and 700 nm that are responsible for the purple color of the porphyrins and the main B-band at 418 nm, also called Soret band. All bands, B and Q, are ascribed to in-plane π - π^* transitions, which can be rationalized by the four-orbital model, i.e., the spectra are related to the properties of the two highest occupied and two lowest unoccupied π orbitals.¹⁴⁹⁻¹⁵¹ Because of the higher intensity of the Soret bands as compared to Q-bands the former is usually used in CD studies.

The Soret band consists of two perpendicularly polarized transitions B_x and B_y (Figure I-31) with the electric dipole transition moment B_x oriented in the NH-NH direction and B_y in direction of N-N. Since the free base porphyrin has a lower D_{2h} symmetry, the transitions B_x and B_y are not completely degenerate. However, there is no sizable splitting or intensity difference observed experimentally in the appearance of the Soret band. The near degeneracy and approximate equivalence of B_x and B_y transitions allows the use of a linear combination such as B_x' and B_y' to represent the two transition moments of the porphyrins. Thus the direction of the effective electric dipole transition moment in non-symmetrical porphyrin A_3B is oriented in C_{15} - C_5 direction.

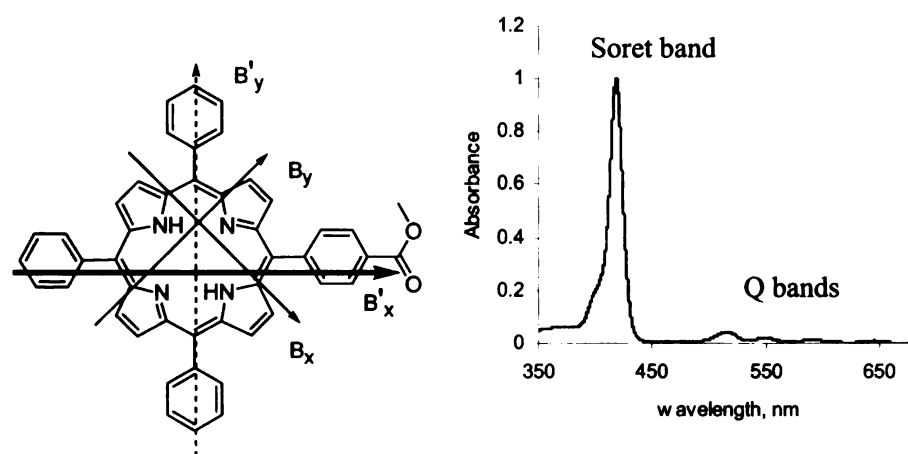


Figure I-32: Electric dipole transition moment of 5-(4-methylcarboxy-phenyl)-10,15,20-triphenyl porphyrin gives rise to the Soret band and the Q-bands.

The advantage of the porphyrin as the chromophore for ECCD studies is summarized on the Figure I-33, depicting the stereochemical determination of (*R*, *S*) steroidal diol. The CD analysis of the substrate performed with 3,6-bismethylaminobenzoate as a chromophore results in a positive ECCD with amplitude of +86, while the amplitude of the corresponding porphyrin derivative is enhanced nearly 8

fold (+680) due to the high extinction coefficient of the porphyrins.¹²⁰ The sign of the spectrum can be easily correlated to the relative orientation of the chromophores and, hence, the absolute stereochemistry of the two hydroxyl groups can be deduced.

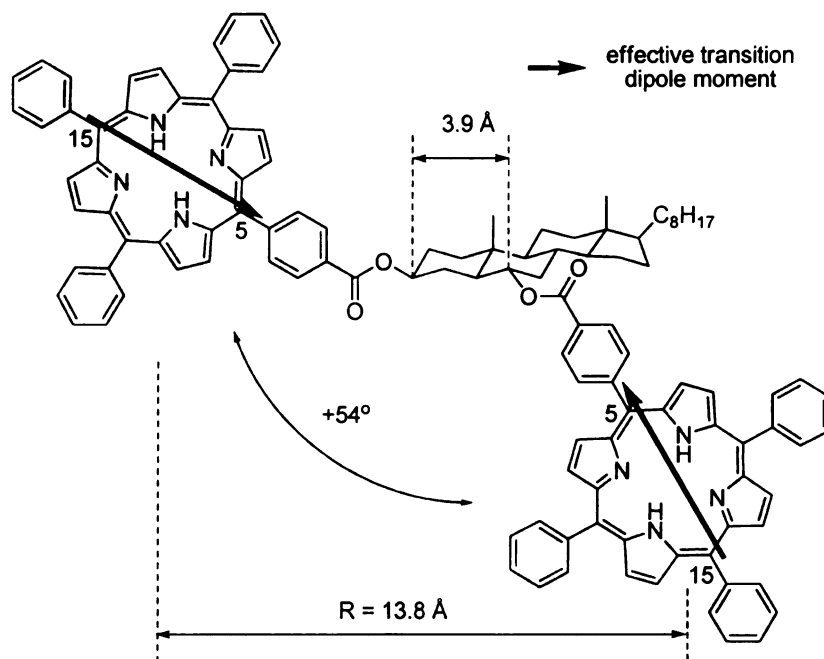


Figure I-33: Application of porphyrins as chromophores for determination of absolute stereochemistry of steroidal diols.

I.9. Porphyrin tweezer – bis-chromophoric host for stereochemical determination

The ability of porphyrins to incorporate metal atoms into their core led to the development of a new porphyrin system employing non-covalent coordination as opposed to the covalent introduction of chromophores. Figure I-34 depicts a bis-triphenylporphyrin system¹⁵² (from here on referred to as porphyrin tweezer) used as a chromophoric host for stereochemical determination. Zinc metal incorporated into the porphyrin core allows for complexation of the porphyrin with a suitable functional group.

Since the ECCD signal originates between two chromophores with fixed orientation, one can envision that utilization of a bis-porphyrin host requires the presence of a substrate bearing two coordinating groups. For instance, binding of a diamine with a porphyrin tweezer leads to formation of a complex, where each porphyrin is bound to the amino group of the guest substrate. The alkyl linker (in this case 1,5-pentanediol is used to connect the porphyrins) plays a dual role: it facilitates coordination of bis-porphyrin to guest substrate and defines the orientation of electric dipole transition moment in the system. The former statement is related to the fact that if coordination of one functional group of a guest to the porphyrin occurs in an intermolecular fashion, the second coordination and, hence, formation of a complete complex (1:1) occurs intramolecularly. Thus, formation of 1:1 bis-porphyrin – diamine complex is favored over the complexation of the second amino group with a porphyrin of a different molecule. The relative orientation of dipole transition moments stabilized through linking of two porphyrins is crucial for interpretation of the observed CD signal and its correlation with the chirality of the complexed guest.

A classic example is the use of porphyrin tweezer for the stereochemical determination of chiral diamines based on ECCD. The two zinc atoms in the porphyrins represent a suitable coordination site for two amino groups of the chiral guest. Complexation of diamine to tweezer leads to formation of a 1:1 complex,¹⁵² where two porphyrins experience non-equivalent steric environment. The porphyrin coordinated to the terminal amino group is put into a symmetric environment, while the other porphyrin, bound to the amino group at the asymmetric center, faces the unequal steric interaction caused by two different substituents at the chiral carbon (Figure I-35).

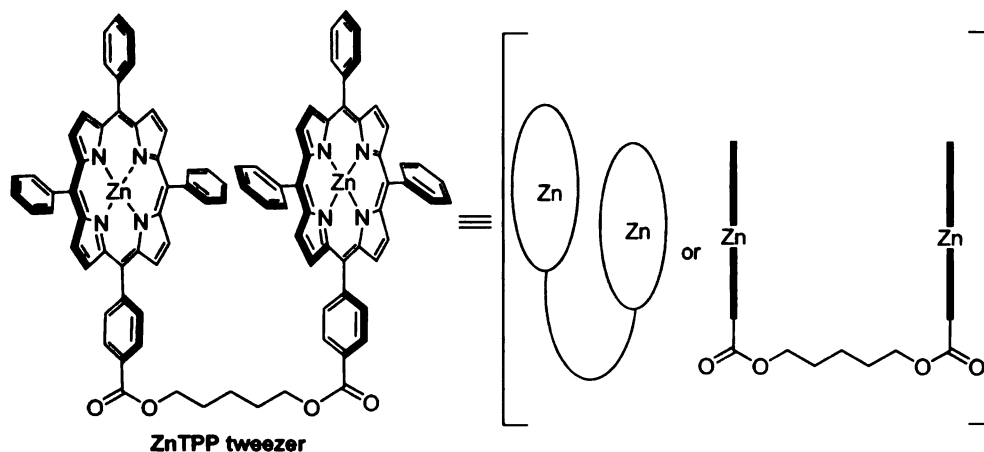


Figure I-34: Zinc bis-triphenylporphyrin tweezer (ZnTPP-tz) I, structure and schematic representation.

It is believed that since the two substituents at the chiral center are of different size, the porphyrin differentiates between the larger and smaller substituent and moves toward the latter in order to alleviate the steric strain in the complex. It is noteworthy, that, the large (L) and medium (M) substituents can be distinguished on the basis of conformational energy differences for the cyclohexane model, or so-called *A*-values (kcal/mol) defined by Winstein and Holness,^{153, 154} and later described by Eliel⁵ and Bushweller,¹⁵⁵ and more recently by Lightner.¹⁵⁶ This movement induces a twist between the tweezer chromophores (i.e. between electric dipole transition moments of chromophores) that is detected by the CD spectrometer as a bisignate ECCD curve. Depending on the absolute stereochemistry of the bound diamine the twist can be clockwise or counterclockwise and lead to positive or negative ECCD, respectively.

Figure I-35 depicts the stereochemical determination of (*S*)-Lysine methyl ester with ZnTPP tweezer. Upon complexation of the porphyrin tweezer with (*S*)-diamine the

porphyrin closest to the stereocenter differentiates between the ester CO₂Me group and hydrogen and slides towards the smaller group (hydrogen) to reduce the steric strain (the sizes of substituents are defined based on conformational energy values, A-value, kcal/mol.⁵ The counterclockwise twist formed between two chromophores is detected as a negative ECCD curve. The clockwise orientation of porphyrins in this particular case is disfavored due to a higher steric interaction with the CO₂Me group.

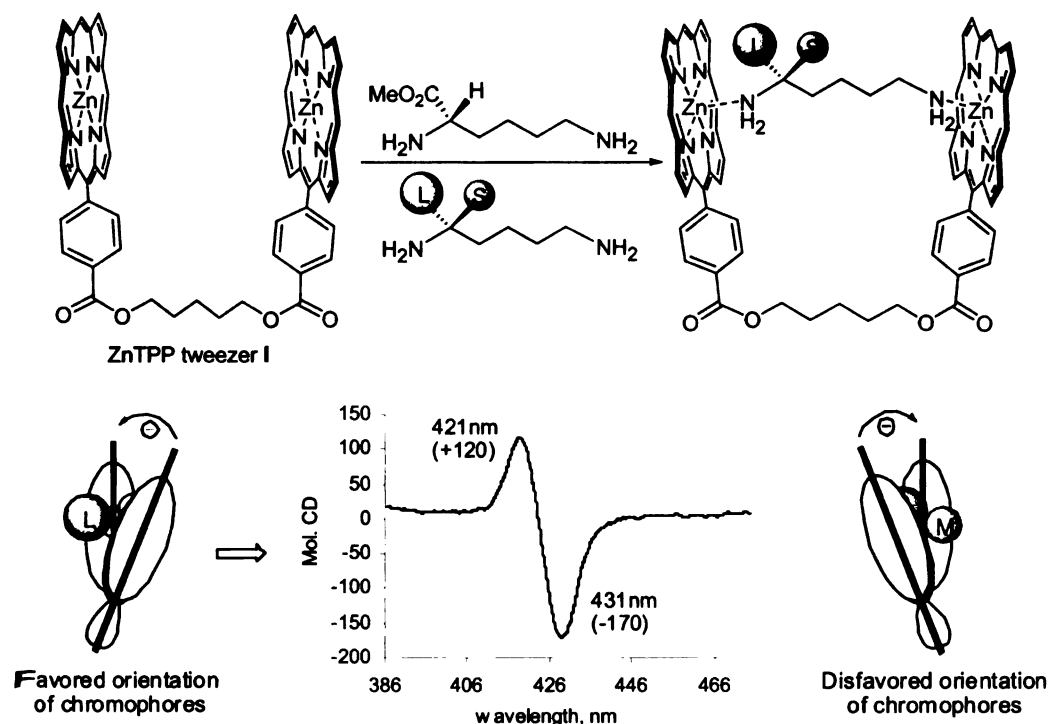
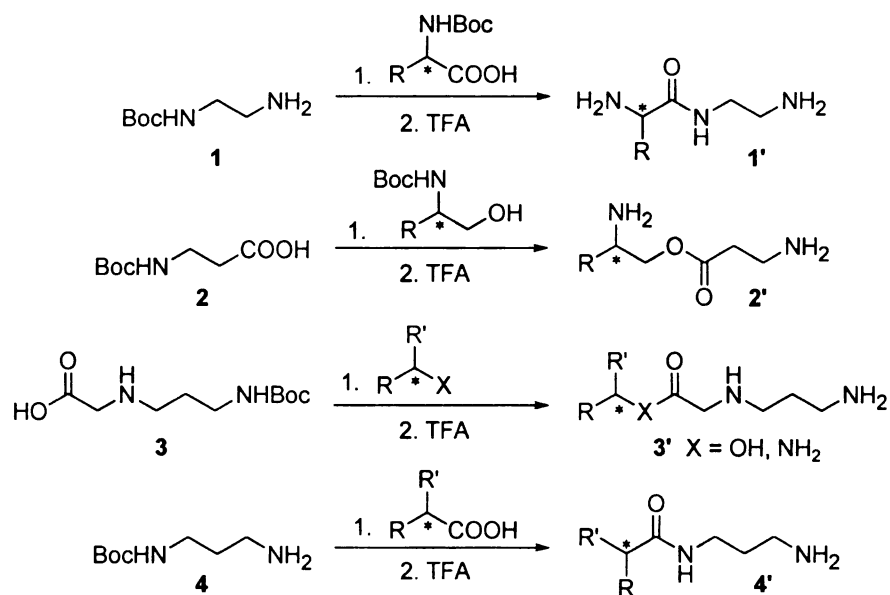


Figure I-35: Stereochemical determination of (*S*)-Lysine methyl ester in hexane at 0 °C with zinc bis-porphyrin tweezer I.

The series of diamines tested with tweezer I followed a consistent trend and resulted in the CD bisignates expected from the stereodifferentiation described above, thus proposing the bis-porphyrin method as a reliable and easily analyzable non-empirical approach to stereochemical determination. After the first successful

application, the method was utilized to stereochemical determination of amino acids and amino alcohols,¹⁵⁷ and later to α -chiral carboxylic acids, primary alcohols and amines, and secondary and tertiary amines.¹⁵⁸⁻¹⁶⁰



Scheme I-1: Derivatization of amino acids, amino alcohols, primary alcohols and amines and α -chiral carboxylic acids with carrier molecules for complexation to zinc porphyrin tweezer **I**

Even though amino acids and amino alcohols possess two potentially coordinating functionalities (NH₂ and COOH or OH) they cannot be used with porphyrin tweezer directly due to the weak binding affinity between the zinc metal and oxygen atoms. Stereochemical determination of α -chiral carboxylic acids represents another challenging task, since the latter do not provide any binding sites appropriate for coordination to zinc porphyrin (the COOH group does not support coordination with zinc metal). In order to overcome such limitation, the molecules were derivatized with compounds that would provide the necessary binding sites, i.e. additional amino groups or other coordinating functionalities. These compounds are referred to as “carrier” molecules. In addition to

providing binding sites, for the ease of the ECCD analysis the “carrier” should also satisfy the following requirements: it has to be achiral (since an additional chirality might affect the quality and sign of CD bisignate) and rigid enough to avoid multiple conformations that can also affect the CD signal.

Each of the cases mentioned above required introduction of a specific carrier molecule. Scheme I-1 presents the carriers (**1-4**) that were used for introduction of the coordinating sites and the final structures (**1'-4'**) that have been used for stereochemical determination with ZnTPP (**I**). Carriers **1** and **2**, used for amino acids and amino alcohols, after introduction into a molecule provide a second free amino group necessary for complexation with porphyrin tweezer. It is noteworthy that the carbonyl oxygen of an ester in **2'** is found to be not nucleophilic enough for coordination to zinc metal.

Similarly, stereochemical determination of primary amines and alcohols derivatized with carrier **3** occurs after complexation of the two amines (primary NH_2 and secondary NH) to the porphyrin tweezer. Carrier **4** used with α -chiral carboxylic acids induces a different mode of binding. While the first coordination of **4'** occurs through the free NH_2 , the second porphyrin is bound through the carbonyl oxygen of the amide functionality. The later $\text{C=O} \rightarrow \text{Zn}$ binding to the ZnTPP-tz was identified by IR for the case of carrier **4** derivatized (S)-2-phenylpropionic acids (complex formed in CH_2Cl_2). Based on previous reports it was expected that after complexation of the amide to the Zn in the porphyrin, the C=O stretching frequency (amine I band) would decrease.^{161, 162} The amide I band of the free conjugate **4'** occurs at 1666 cm^{-1} while the ester carbonyl C=O stretch of the tweezer is observed at 1714 cm^{-1} . Subtraction of the free tweezer IR from that of the complex showed that the amide I band has shifted to $1658\text{-}1661\text{ cm}^{-1}$.

The approximately 8 cm^{-1} shift to lower frequencies upon complexation suggests that a Zn ligation occurs through the carbonyl oxygen of the amide group (Figure I-36).

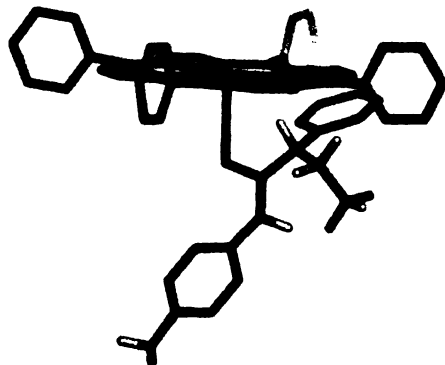


Figure I-36: Complexation of carrier derivatized carboxylic acids with zinc porphyrin occurs through the carbonyl oxygen of the amide group and the zinc atom of the porphyrin.

All chiral substrates after derivatization with carriers produce 1:1 complexes with porphyrin with the stereocenter placed close to one of the porphyrins (Figure I-37). The asymmetry of the chiral substrate results in steric interaction between the chromophore and the substituents at the chiral center and is alleviated through the twist of the porphyrin toward the smaller substituent facing the plane of the chromophore.

While the analysis of the observed ECCD spectrum with **1'** and **2'** follows the same rationale as given for chiral diamines (Figure I-37),¹⁵⁷ correlation of the sign of the CD bisignate induced by **3'** and **4'** with the absolute chirality of the asymmetric carbon is complicated by conformational flexibility of the chiral entity. Thus, both α -chiral carboxylic acids and primary alcohols or amines experience free rotation along the $\text{C}_{\text{C=O}}\text{-C}_{\alpha}$ and X-C_{α} bond respectively leading to several potentially ECCD active rotamers.^{158,}

¹⁵⁹ Therefore, the success of stereochemical determination of substrates like **3'** and **4'**

relies on the presence and subsequent identification of one major ECCD active conformation.

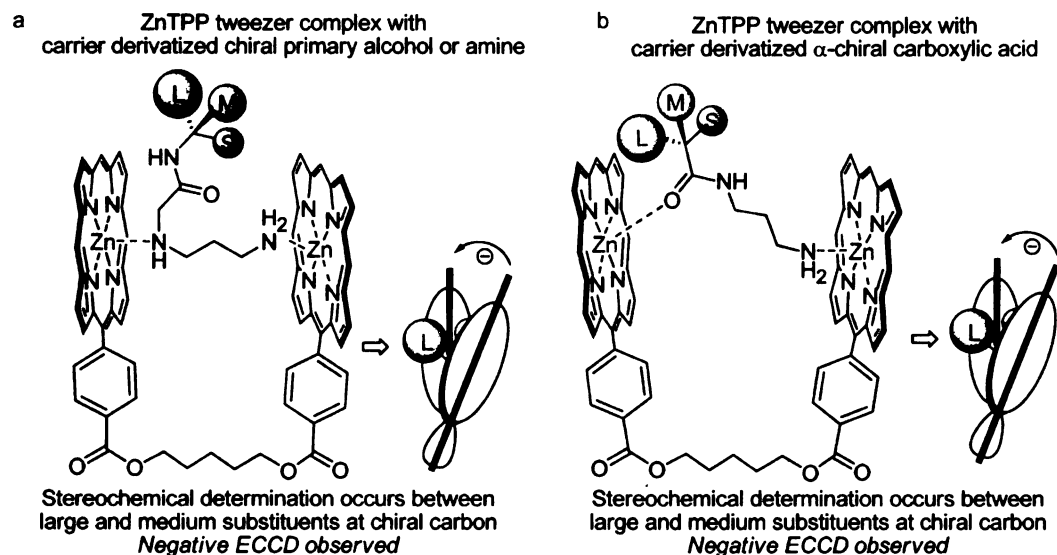
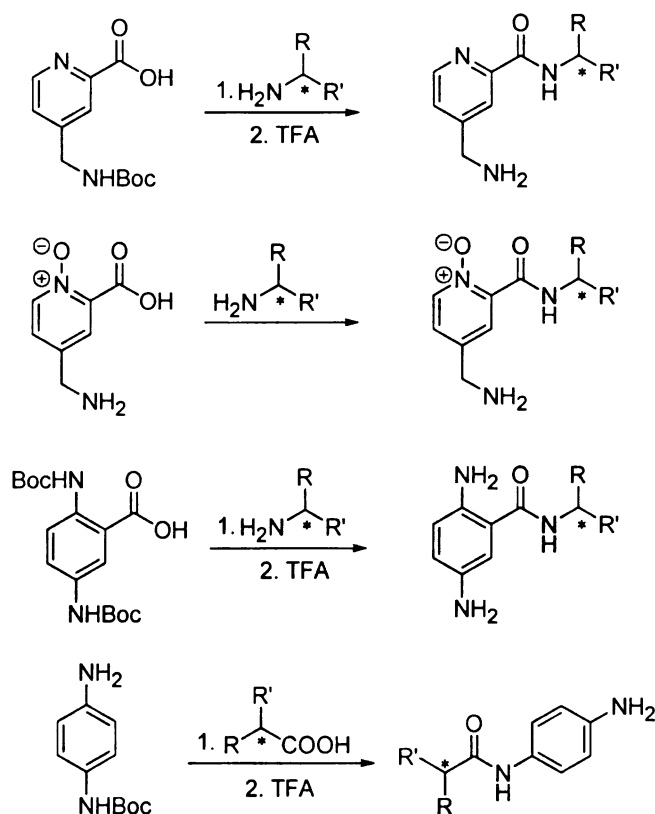


Figure I-37: Stereochemical determination of primary alcohols (amines) (a) and α -chiral carboxylic acids (b) with ZnTPP porphyrin tweezer I (phenyl rings on the porphyrins are omitted for clarity of picture).

In an analogous manner, the stereochemical determination of primary amines and alcohols requires derivatization with carrier 3 and complexation with zinc porphyrin tweezer. The CD data obtained showed a consistent trend that after detailed conformational analysis led to the establishment of the major ECCD active conformation of the stereocenter leading to the observed CD bisignates. Thus, based on modeling and $^1\text{H-NMR}$ studies was found that upon complexation the chiral carbon places the large and medium group closer to the porphyrin and orients the small group inside of the complex. Since each of the groups on the stereocenter is of different size, the steric environment between the porphyrin and the two groups facing it is different. Thus, in order to release steric strain built by the asymmetry of the chiral carbon, porphyrin, presumably slides

away from the larger substituent and towards the smaller one. In this manner, the steric differentiation between the two groups facing the porphyrin induces a chiral twist between the chromophores of the porphyrin tweezer. Based on this analysis a general mnemonic for the stereochemical determination of primary alcohols and amines derivatized with carrier **3** depicted on Figure I-36a was proposed.



Scheme I-37: Rigid carriers for stereochemical determination of primary amines and α -chiral carboxylic acids.

Stereochemical determination of carrier derivatized α -chiral carboxylic acids also led to identification of a major conformation contributing to the observed CD bisignate, which revealed to be similar to **3'** orientation of the substituents on the chiral carbon, where large and medium group are oriented toward the porphyrin and stereochemical

determination occurs in favor of the medium substituent (Figure I-37b). Ultimately, the conformational stability of the substrate in complex with the porphyrin tweezer and the identification of the major conformation depend on the type of carrier. The latter is important since the conformation of the carrier could affect the arrangement of the substituents on the asymmetric carbon and consequently could influence the spatial orientation of chromophores and sign of the ECCD spectrum. To increase the rigidity of the system new carriers **5-7** and **8** depicted on Scheme I-2 were designed for the stereochemical determination of primary amines (alcohols) and α -chiral carboxylic acids respectively.^{158, 163, 164}

Carrier **5** proved to be a functional and reliable derivatizing agent with chiral amines.¹⁵⁸ The chiral amine conjugates of **5** gave ECCD spectra of large amplitude with the sign of bisignates easily correlated with the absolute configurations of amides **5'**. Molecular modeling of the conjugate **5'** suggested that the molecule is rigid and has a predictable energetically favored conformation, which is depicted on Figure I-38. In this conformation the rotation around the single bonds: C_{C=O}-C_{pyr}, C_{C=O}-NH is restricted by electrostatic repulsion and is preferred by ~30 kJ/mol. Rigidity of C_{chiral}-NH bond is ensured by pseudo A_{1,3}-interaction, that places the small group *syn* to the carbonyl oxygen. Yet, some of the substrates gave ECCD signs of which did not correlate with the known absolute stereochemistry of the tested amines. The result was contributed to the free rotation possible around single bonds of the carrier **5** (Figure I-38).¹⁶⁵

In order to further restrict the conformation of chiral carrier conjugates the pyridine oxide conjugates **6'** were formed.¹⁶⁶ The electrostatic interaction induced between the negatively charged pyridine oxide and the carbonyl carbon reduces the

conformational flexibility of the amine conjugates **6'**. Similarly, in the case of carrier **7** the intramolecular hydrogen bond between the amino group and the carbonyl oxygen also makes its conformation less flexible. The complexes of **6'** and **7'** with ZnTPP tweezer indeed gave exciton-coupled CD spectra in non-polar solvents but their signal could not be correlated unambiguously with the known absolute configuration of the chiral amine.¹⁶⁶

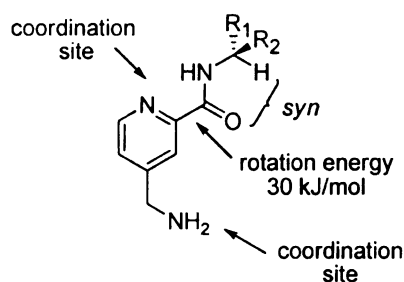


Figure I-38: Primary amine derivatized with carrier **5** for the absolute stereochemical determination.

While the above discussion focused on conformational stability of carrier conjugates **5'**-**7'**, it is worth noting that the sign of ECCD could change if the binding mode of the porphyrin with the chiral conjugate is altered. The conjugates **5'** bear three potential coordinating groups, terminal amino group, the sp^2 nitrogen of pyridine ring and the carbonyl oxygen of the amide group. In the model depicted in Figure I-38a, complexation of the conjugate **5'** proceeds through the terminal amino group and the sp^2 nitrogen of pyridine ring. On the other hand it is important to consider that complexation of the carbonyl oxygen of an amide with a zinc porphyrin has been described in literature and was successfully utilized in stereochemical determination of α -chiral carboxylic acids employing carrier **3** (Figure I-39b). Thus, it becomes apparent that complexation of

porphyrin tweezer to amine conjugate **5'** could occur through the carbonyl oxygen of an amide group and primary amine of the carrier (Figure I-39b). Such change in binding mode could also result in unexpected ECCD sign for secondary amines derivatized with carrier **5**. It is also noteworthy that coordination of the carbonyl oxygen with porphyrin could be preferred over the coordination with sp^2 nitrogen of pyridine ring due to a better accessibility of the former.

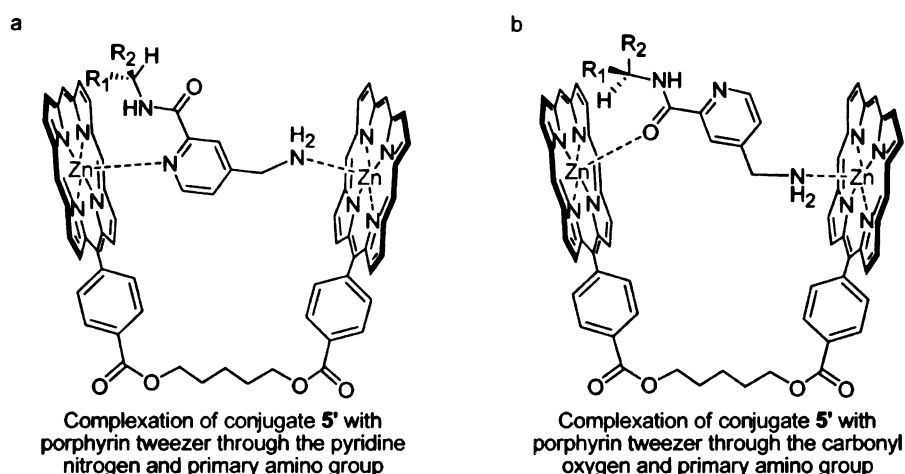


Figure I-39: Two possible coordination mode of carrier conjugate **5'** with porphyrin tweezer (phenyl rings on the porphyrins are omitted for clarity of picture).

The influence of rigidity of the carrier onto the ECCD results was also studied on α -chiral carboxylic acids with 1,4-phenylenediamine **8** (Figure I-40a). Complexation of conjugates **8'** with ZnTPP tweezer gave rise to ECCD signal that followed a consistent trend, although different from the one obtained with carrier **3** (Figure I-40b). In particular, the derivative of (*S*)-2-methylbutyric acid with carrier **3** induced a positive ECCD signal, i.e. porphyrins orient clockwise, while conjugate of carrier **8** gave a negative CD bisignate. The change in sign was found to be due to the change of the

major ECCD contributing conformation in the porphyrin complex with **8'**. While for conjugates **3'** steric differentiation occurred between the large and the medium groups at the chiral center, carrier conjugates **5'** upon complexation orient the large and medium groups toward the porphyrin coordinated to the carbonyl. Steric differentiation from the porphyrin of these two groups results in helical twist of chromophores that is observed experimentally. It is noteworthy that ECCD method uses the A-values as a measure of a size of a substituent. Use of A-values proved to be reliable for correlation of the major ECCD active conformation with the ECCD sign observed for the substrate within a porphyrin tweezer.

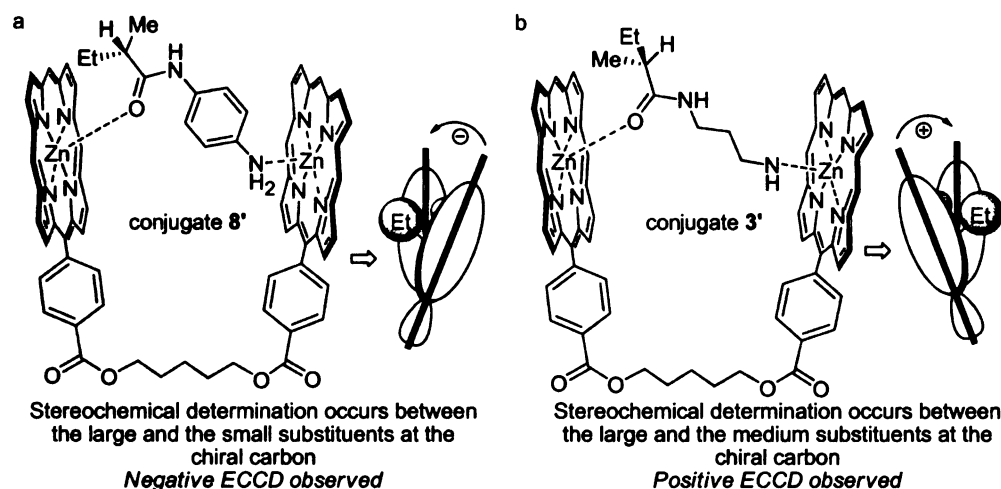


Figure I-40: Stereochemical determination of α -chiral carboxylic acids derivatized with carriers **8** and **3** (phenyl rings on the porphyrins are omitted for clarity of picture).

Unusual behavior of carrier **8** conjugates was noticed when an aromatic group was present at the chiral center. While the ECCD sign observed for carrier **3** derivatives of chiral α -alkyl, alkoxy or aryl conjugates could be explained by one common mode of steric differentiation depicted in Figure I-40b, presence of an aromatic group at the chiral

center of conjugates **8'** switched the ECCD sign. For instance, based on the mode of steric differentiation deduced for chiral α -alkyl and alkoxy amides, the expected ECCD sign for carrier **8** conjugate of (*S*)-2-phenylpropionic acids is negative. Nevertheless, positive ECCD was observed upon complexation with ZnTPP tweezer (**I**). The observed discrepancy can be rationalized through π - π stacking taking place between the phenyl ring at the chiral center and the aromatic core of the porphyrin. The detailed analysis of the observed result will be discussed further in Chapter III.

The present research focuses on detailed studies of the porphyrin tweezer-chiral substrate complexes. This has lead us to the identification of the major ECCD contributing conformation of 1,4-phenylenediamine derivatized chiral α -halocarboxylic acids and α -chiral alkyl, aryl, alkoxy and halo butyrolactams; studies of the effect of steric interaction on to the conformation of the guest in the complex and amplitude of the observed ECCD spectrum; use of steric interaction for application of porphyrin tweezer method toward substrates bearing distal chirality and identification of a role of the linker in the process of stereodifferentiation. The thesis also describes the porphyrin tweezer mimics developed with consideration of properties of porphyrins to form stable aggregates. The achiral porphyrin aggregates were constructed and helicity was induced though introduction of a chiral entity.

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Chapter II

Stereochemical Determination of α -Chiral Amides and Lactams

II.1. An unusual ECCD active conformation of α -halo carboxylic acids

Since the first application of Exciton Coupled Circular Dichroism (ECCD) as a non-empirical method for absolute stereochemical determinations of chiral organic molecules.^{1, 2} The method has been successfully used for assignment of a wide variety of compounds including polyols and carbohydrates,³⁻⁵ monoamines and monoalcohols,^{6, 7} diamines and amino acids,^{8, 9} amino alcohols,¹⁰ and hydroxyacids.¹¹ Briefly, ECCD is observed between two or more independently conjugated chromophoric systems that interact through space in a chiral fashion. The absolute orientation of the two chromophores results in a predicted sign of the couplet; i.e., a clockwise orientation of two interacting chromophores yields a positive couplet and vice versa.^{12, 13} Thus, the sign of an ECCD spectrum can be directly related to the orientation of the interacting chromophores, which in turn can lead to the assignment of helicity and subsequently the absolute stereochemistry of the system, which leads to the non-empirical nature of the method. The chromophores used for stereochemical determination either preexist in the system or are introduced through chemical derivatization^{3, 14-18} or non-covalent binding. The latter mode of binding has been explored by the use of bis-porphyrin “tweezer” systems as a chromophoric host.^{8, 19-21} Incorporation of a metal in the porphyrin core enables binding of the two porphyrins (the host) with a chiral substrate (the guest) that possesses two suitable sites of attachment and allows for the formation of a porphyrin tweezer – chiral substrate complex (Figure II-1). For instance, incorporation of a Zn(II)

atom into the porphyrin core allows for binding of substrates containing amino groups,^{7, 8} while exchange of Zn for Mg enables the direct binding of hydroxyl group containing substrates.¹⁹ The stereochemistry of the chiral substrate is induced within the porphyrin-tweezer complex based on the steric interactions between the porphyrin rings and the substituents at the chiral center. It is believed that the porphyrin ring closest to the chiral center differentiates between the two substituents at the chiral center that point towards it, thus sliding away from the large group and towards the smaller group in order to alleviate steric clash. This movement leads to a “chiral twist” of the porphyrins relative to each other, detected as an exciton CD couplet, the sign of which directly reflects the absolute orientation of the two chromophores.

The porphyrin tweezer method, however, is not directly applicable to chiral compounds with only one site of attachment since the two porphyrin groups cannot be oriented relative to each other. To solve this problem, Nakanishi and coworkers derivatized chiral substrates with small, achiral molecules (carriers) that contain within them the two necessary sites of attachment. In this manner, the derivatized carrier accomplishes the binding of the chiral guest with the porphyrin tweezer, and if chosen well, should present the chiral center towards the porphyrin for steric differentiation. Utilizing this method, the stereochemistry of derivatized chiral monoamines, monoalcohols and α -chiral carboxylic acids has been determined in a non-empirical fashion according to the sign of the obtained ECCD spectra.^{6, 7, 20, 21} Recently, improving binding affinity of Zn-porphyrin tweezer toward the oxygenated functional groups achieved by introducing the electron withdrawing substituent onto the porphyrin core extended the application of porphyrin tweezer toward the vicinal diamines and more importantly, diols and amino alcohols.²²

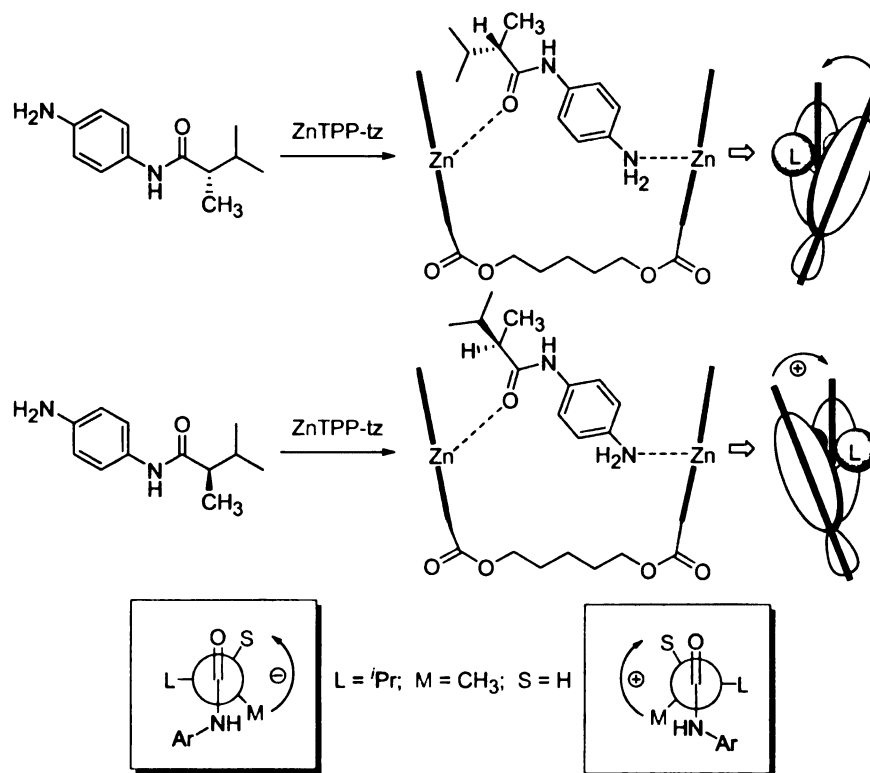


Figure II-1: Stereochemical determination of α -chiral carboxylic acids derivatized with 1,4-phenylenediamine with ZnTPP-tz as the chromophoric host.

For complexation with porphyrin tweezer, chiral carboxylic acids were derivatized with 1,4-phenylenediamine as a carrier molecule. The formed amide bears two coordinating groups – primary amino group and oxygen of the amide group – that ensure complexation of the chiral amide to a metal containing chromophoric host. Thus, addition of a derivatized carboxylic acid to the host zinc bis-triphenylporphyrin tweezer system (two zinc-5-(4-carboxyphenyl)-10,15,20-triphenyl porphyrins connected through a 1,5-pentanediol linker, ZnTPP-tz) yields a tweezer-substrate complex shown in Figure II-1.^{20, 23} Complete description of the stereochemical studies of a series of carboxylic acids is thoroughly described in a thesis work by Qifei Yang.²³

The formation of this chiral complex results in a bisignate ECCD spectrum the sign of which directly reflects the relative orientation of the two porphyrin rings. In this system, the induced helicity within the porphyrin tweezer is believed to be governed exclusively by the major conformation around the C_{carbonyl}-C_{chiral} bond that places the medium (M) group pseudo-*syn* with the amide bond and the large (L) group perpendicular to the plane of the carbonyl. Steric differentiation between the small (S) and L groups leads to the induced chirality of the porphyrin tweezer, and as such directly depends on the absolute stereochemistry of the chiral acid (the relative size of the chiral center substituents is determined according to their reported A-values²⁴).

A series of ECCD data obtained for various derivatized chiral carboxylic acids yielded a proposition of a mnemonic that predicts the expected ECCD sign for a given chiral acid based on the A-values of the substituents on the chiral center (it should be noted that Nakanishi and coworkers utilize a different carrier, and thus have arrived at a different mnemonic for derivatized carboxylic acids²¹). Considering an orientation such that the group characterized by a larger A-values (here and further in the text referred to as the large group) is almost perpendicular to the carbonyl with the small group (the group characterized by a the smallest A-value with respect to the other two substituents at the chiral center) pointed toward the porphyrin plane and the medium group staggered with respect to the amide proton (Figure II-1, dashed box), the expected ECCD sign can be determined by taking into account the rotation from the large, through the medium and towards the small group. A clockwise orientation would translate into a positive ECCD bisignate signal, and *vice versa*. This mnemonic was proven reliable for chiral carboxylic acids with a variety of alkyl, alkoxy and aryl groups on the alpha carbon. In all cases, the observed ECCD sign was in agreement with the expected sign as derived from the

mnemonic, considering the size of the substituents on the chiral center based on A-values.²⁴

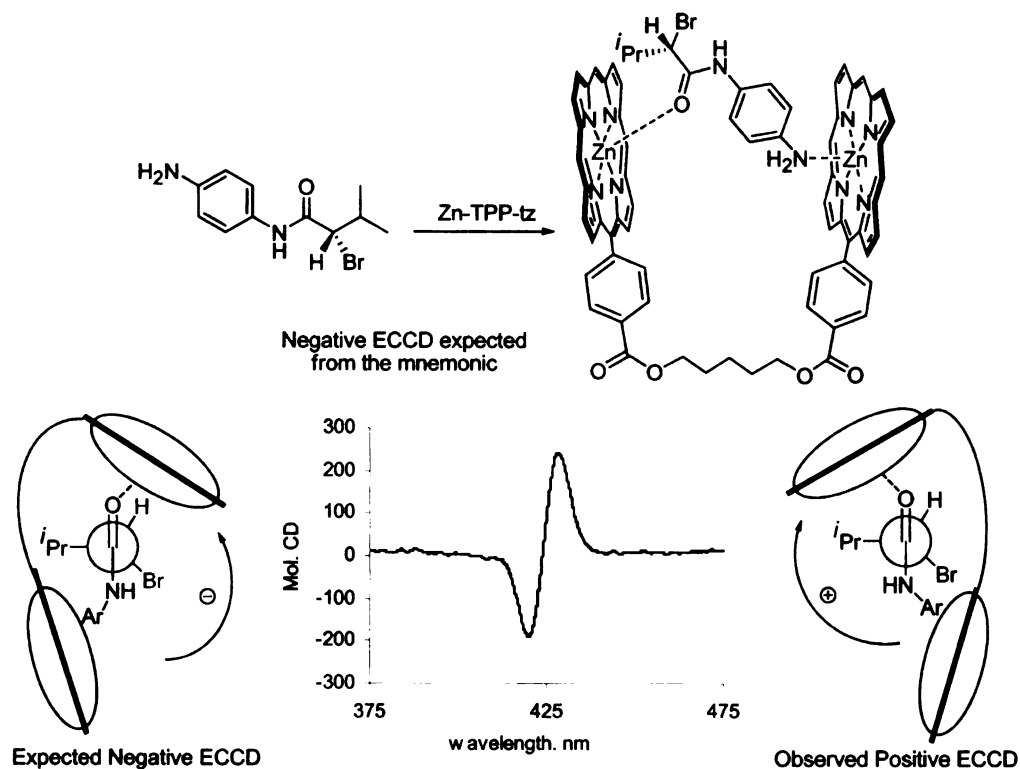


Figure II-2: Unexpected positive ECCD observed with (S)-2-bromo-3-methylbutyric acid carrier conjugate (spectra in methylcyclohexane at 20 equiv of chiral guest).

However, in the course of further studies we have observed that carboxylic acids bearing a halide at the asymmetric center do not follow the rules determined previously. As shown in Figure II-2, the predicted ECCD sign, according to the established mnemonic, for the amide derivative of (S)-2-bromo-3-methyl butyric acid complexed with the porphyrin tweezer I would be negative, i.e., considering that the *i*-Pr group behaves as the large group and the Br as the medium size group on the chiral center, as their corresponding A values indicate (2.2 for *i*-Pr and 0.58 for Br) the stereochemical

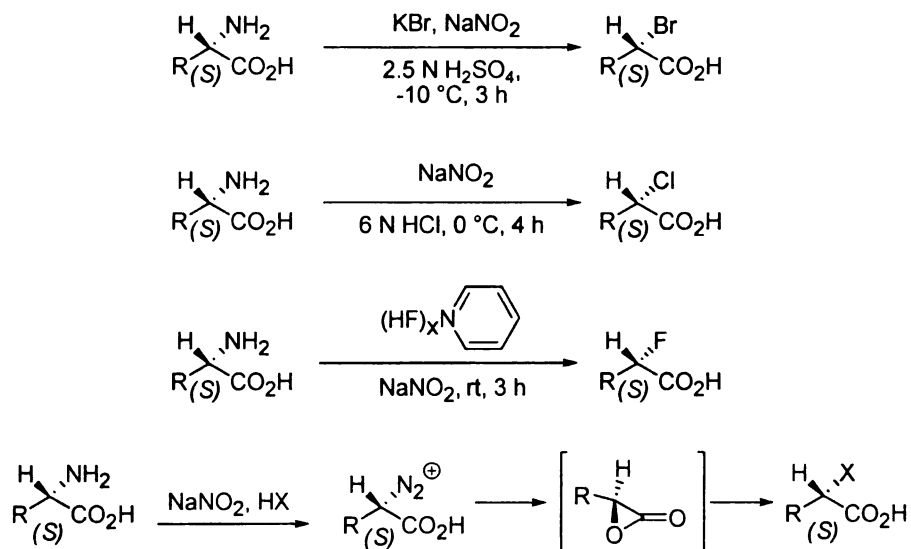
determination in the porphyrin tweezer complex must occur between a large *i*-Pr group and a small hydrogen in favor of the latter and induce a counterclockwise orientation of chromophores yielding a negative CD bisignate. Nonetheless, the experimentally obtained ECCD revealed a positive couplet with a large amplitude (+194), suggestive of the presence of a dominant clockwise orientation that leads to the strong ECCD spectrum.

It is noteworthy, that similar deviation from the mnemonic has been previously observed in the stereochemical determination of the α -chiral halogen containing carboxylic acids derivatized with 1,3-diaminopropane.²⁵

II.1-1: Synthesis and ECCD studies of α -halocarboxylic acids

For thorough studies of the influence of a halide onto the sign of the ECCD spectrum the series of chiral α -bromo, chloro, and fluorocarboxylic acids were synthesized according to previously reported procedures, starting from the corresponding optically pure amino acids (Scheme II-1).²⁵

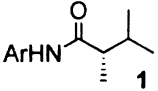
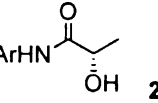
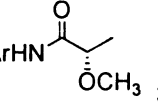
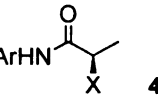
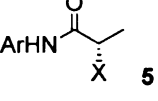
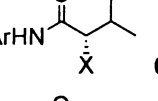
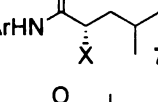
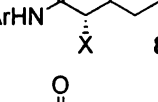
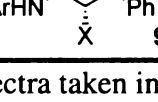
Scheme II-1: Synthesis of α -chiral halocarboxylic acids



Bromination of the (*S*)-amino acid with potassium bromide and sodium nitrite in 2.5 M sulfuric acid afforded α -chiral bromocarboxylic acid. The chiral chloro and fluorocarboxylic acids were synthesized in a similar manner. Namely, α -chloro carboxylic acids were produced by adding sodium nitrite to a solution of (*S*)-amino acid in 2.5 N HCl, and α -fluorocarboxylic acids were obtained by reaction of (*S*)-amino acid with sodium nitrite in hydrogen fluoride-pyridine as the reaction solvent. These reactions occur through double inversion of the asymmetric center and result in the starting (in this particular case (*S*)) stereochemistry.²⁵

The reaction was completed within 4 hours and the formed halo carboxylic acids were easily extracted with dichloromethane from the acidified aqueous solution. Derivatization of the obtained carboxylic acids with 1,4-phenylenediamine as a carrier molecule yielded the substrates ready for ECCD analysis with ZnTPP tweezer I. A stock solution of the zinc porphyrin tweezer in dichloromethane ($c = 1$ mM) was diluted with methylcyclohexane to a final concentration of 1 μ M, and the appropriate derivatized carboxylic acid was added as a 1 mM solution in dichloromethane. Spectra were obtained at tweezer:substrate ratios from 1:1 to 1:40 equiv and the data collected at 1:20 is reported in Table II-1. As can be seen, the discrepancy from the previously proposed mnemonic was consistent for all α -chiral halocarboxylic acid derivatives submitted for ECCD analysis (Br, Cl, and F) with enantiomeric amides resulting in opposite ECCD signs (that is 2-bromopropionic acid with (*R*) configuration produced negative ECCD spectra and *vice versa*). For comparison several carrier derivatized α -alkyl and α -alkoxycarboxylic acids are also included in the Table. As previously reported 1,4-phenylenediamine derivatives of α -alkyl carboxylic acids produce an ECCD couplet consistent with the previously established mnemonic.

Table II-1: ECCD data for 1,4-phenylenediamine derivatized α -halocarboxylic acids with ZnTPP-tz I.

	Substrate	λ , nm, ($\Delta\epsilon$)	A	$\theta\theta$, %	λ , nm, ($\Delta\epsilon$)	A	$\theta\theta$, %	λ , nm, ($\Delta\epsilon$)	A	$\theta\theta$, %
1	 1	428 (-43) 418 (+41)	- 84	98	-	-	-	-	-	-
2	 2	430 (-58) 419 (+65)	-123	99	-	-	-	-	-	-
3	 3	430 (-67) 418 (+72)	-139	99	-	-	-	-	-	-
X =		Br		Cl		F				
4	 4	430 (-236) 421 (+136)	-372	99	-	-	-	-	-	-
5	 5	429 (+116) 421 (-130)	+296	90	429 (+25) 42 (-38)	+63	99	428 (+34) 419 (-31)	+65	50
6	 6	429 (+103) 421 (-91)	+194	90	428 (+132) 421 (-82)	+214	90	428 (+114) 420 (-30)	+207	64
7	 7	429 (+107) 421 (-75)	+182	90	429 (+24) 421 (-30)	+54	90	428 (+31) 420 (-30)	+61	80
8	 8	429 (+94) 421 (-81)	+175	80	429 (+108) 421 (-124)	+232	80	429 (+96) 420 (-66)	+162	80
9	 9	429 (+47) 421 (-43)	+90	90	429 (+22) 421 (-19)	+41	75	428 (+28) 419 (-22)	+50	56

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest

For example, in the case of the amide of *S*-2,3-dimethylbutyric acid, where the *iso*-propyl group is considered as the large group and the methyl group as the medium group, the expected ECCD sign is negative according to the binding mode described in Figure II-1. Indeed, a negative ECCD sign is observed, verifying that in the presence of alkyl substituents on the chiral center, the steric factor is what defines the helicity of the

porphyrin tweezer (Table II-1, entry 1). In particular, upon binding, the porphyrin closer to the chiral center slides away from the larger groups and prefers to cover the small group (H) resulting in a counterclockwise disposition of the two porphyrin rings that translates into a negative ECCD couplet.²⁰

Following the same rationale, one would expect that a similar binding mode should also be assumed for 1,4-diphenylenediamine (carrier) derivatized (*S*)-2-bromo-3-methylbutyric acid. The two chiral molecules are very similar, with the halogen having replaced a methyl group, maintaining groups with the same relative sizes on the chiral center (*iso*-propyl remains the largest group (A-value = 2.2), followed by the bromine (A-value = 0.58)). If the stereodifferentiation were to follow the previously described mnemonic, the porphyrin would have to slide away from the large group and toward the hydrogen atom on the α -carbon resulting in a negative ECCD. However, derivatized (*S*)-2-bromo-3-methylbutyric acid yields a positive ECCD spectrum upon binding to the porphyrin tweezer (Table II-1, entry 4).

A similar trend was observed for carrier derivatized α -halocarboxylic acids **4-9** summarized in Table II-1. In all cases the halogen is considered as the medium size group according to the reported A-values (F = 0.30, Cl = 0.59, Br = 0.62). Nevertheless, all chiral α -haloamides tested result in ECCD spectra of opposite sign from the one expected according to the mnemonic derived previously for alkylamides. Thus, it appears that the presence of a halide at the α -carbon induces a conformational change of the chiral substrate in the Zn-porphyrin tweezer complex, resulting in a chiral twist between the two porphyrins that is opposite from that observed for the alkyl substituted chiral amides.

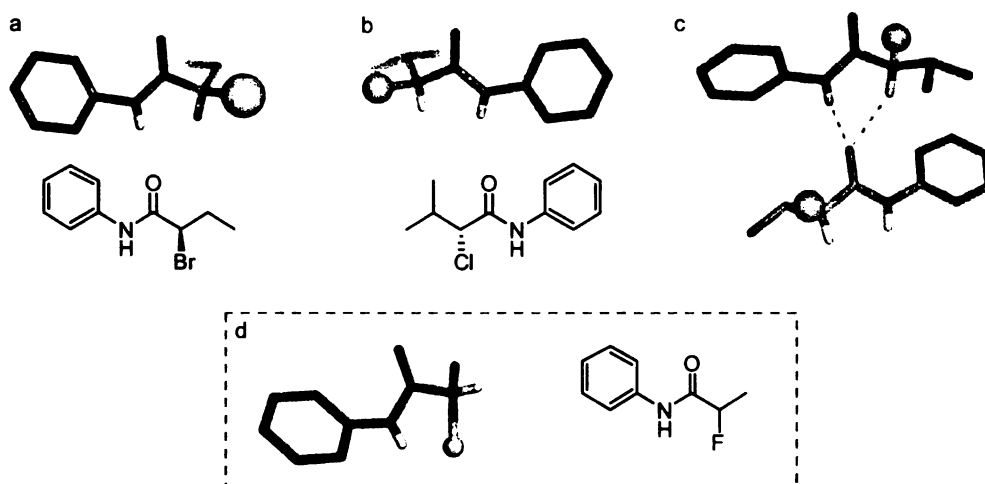


Figure II-3: Crystal structures of a) N-phenyl (*R*)-2-bromobutanamide, b) N-phenyl (*S*)-2-chloro-3-methylbutanamide, c) crystal packing of N-phenyl (*S*)-2-chloro-3-methylbutanamide d) N-phenyl 2-fluorobutanamide.

Interestingly, this discrepancy does not appear to depend on the kind of the halogen present. Namely, consistent results were obtained for all Br, Cl and F substituted α -halogenated amides. The fact that the steric differentiation occurs regardless of the different nature of the halides (F vs. Cl and Br) becomes even more interesting after comparing the conformations of free halogenated amides. For instance, the crystal structures of N-phenyl (*S*)-2-chloro-3-methylbutanamide and N-phenyl (*R*)-2-bromobutanamide revealed that both substrates exist in a similar conformations (Figure II-3a and b). Namely, the large alkyl group and the halide are bisecting the carbonyl with the $C=O-C_{\alpha}-Cl$ dihedral angle of -67.3° and $C=O-C_{\alpha}-Br$ dihedral angle of 73.6° . The crystal packing shows a prominent double H-bonding between the $C=O$ and α -hydrogen and NH, presumably contributing to the stabilization of the observed conformation (Figure II-3c). The conformation of α -fluorinated amides was found to be stabilized by gauche effect²⁶ between the C-F bond and N-H bond orienting the fluoride *anti* to the

carbonyl.²⁷ Hence, the free haloamides exist in different conformations and if not for the stabilization of one common conformation upon complexation with ZnTPP tweezer, the (*S*)-2-fluoroamides and (*S*)-bromo (chloro) amides would be expected to yield the ECCD spectra of opposite sign. Namely, (*S*)-chloro and bromoamides are expected to give a positive ECCD, while (*S*)-fluoroamides – negative bisignate (steric differentiation would occur between the alkyl group and hydrogen). Nevertheless, as is summarized in Table II-1, all (*S*)-haloamides yield positive ECCD. The fact that all haloamides induce the same helicity directly suggests that α -halides play a more active part in equilibration of a major ECCD active conformation.

II.1-2: Conformational analysis of α -halocarboxylic acids derivatized with 1,4-phenylenediamine

Figure II-4 depicts conformational analysis of carrier derivatized chiral α -carboxylic acid (in this case (*S*)-2-chloropropionic acid) complexed with ZnTPP (the second porphyrin ring of the porphyrin tweezer that should be coordinated to the aniline nitrogen of the carrier is not shown for clarity). Taking into consideration the conformational flexibility of the $C_{C=O}-C_{\alpha}$ bond, there are four major ECCD contributing conformations. Conformation **A** follows the previously established mnemonic placing the large group (Me) perpendicular to the carbonyl, the small group (H) pseudo-*syn* and the medium group (Cl) *anti*-periplanar to the carbonyl. In this rotomer, stereodifferentiation takes place between a small and a large group resulting in a predicted negative ECCD spectrum. Since the observed ECCD sign for carrier derivative

of (*S*)-2-chloropropionic acid is positive, conformation A, favored for alkyl chiral α -alkoxycarboxylic acids, can be excluded from consideration.

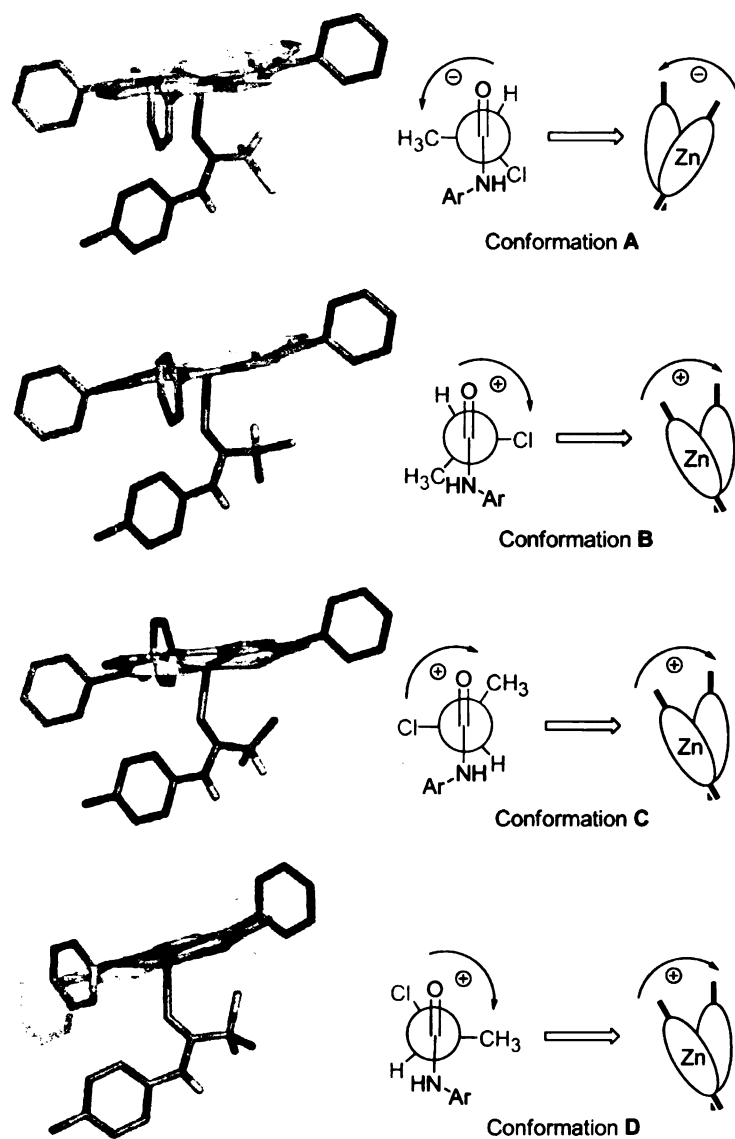


Figure II-4: Possible ECCD active conformations of carrier derivatized (*S*)-2-chloropropionic acid (5-Cl) when bound to the zinc porphyrin.

Conformations **B** and **C** derived from predicted geometries for electronegative substitutions of a carbonyl systems as described by polar Felkin-Ahn considerations (halogen occupies a position perpendicular to the carbonyl due to σ^* - π interaction).^{28, 29} Both conformations **B** and **C** lead to the observed positive ECCD sign. Conformation **B** maintains the small group (H) *syn* to the carbonyl, placing the medium group (Cl, A-value = 0.59) perpendicular, and the large group (Me, A-value = 1.74) *anti*-periplanar. With such a disposition, stereodifferentiation would take place between the small hydrogen and the medium halogen group, resulting in an expected positive ECCD couplet. Conformation **C** could experience stereodifferentiation between a medium halide and a large methyl group and also result in clockwise orientation of the chromophores (positive ECCD) with a porphyrin sliding toward the halide and away from the large methyl substituent. Although the expected ECCD sign for this conformation is in agreement with that observed experimentally, rotamer **B** is not expected to be favored due to a significant $A_{1,3}$ strain between the large Me group and the amide N-Ar group. Rotamer **C**, placing the large methyl group *syn* and the small hydrogen *anti* to the carbonyl, is characterized by reduced $A_{1,3}$ interaction and is expected to be energetically more favorable as compared to conformation **B**, and thus is considered as a plausible contributor to the observed ECCD.

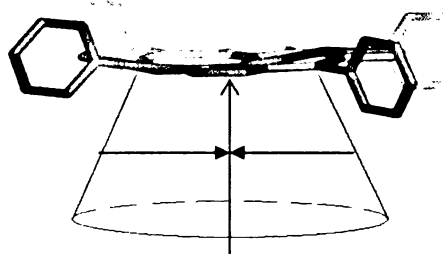
It is worth noting that upon complexation to the porphyrin tweezer the alkyl group in this conformation may experience steric interaction with the chromophore, which can cause additional rotation along the $C_{C=O}-C_{\alpha}$ bond and rise of the conformation **D**, also yielding the observed positive ECCD bisignate. Since increase of the size of the alkyl substituent in this conformation may induce $A_{1,3}$ strain, we expect conformation **D** to be mobile and vary the dihedral angle between carbonyl and an alkyl substituent just enough

to alleviate the strain. This adjustment, consequently, varies the position of a halide from pseudo-*syn* to *syn*, not affecting the sign of ECCD. Such mobility of the conformation **D** may also explain a significant change in amplitude observed with increase of the steric bulk at the β -position. As it can be seen from the Table II-1 replacement of a methyl group of **2-Cl** and **2-F** (entry 5, methyl A-values = 1.74) with either an *iso*-propyl (entry 6, A-values = 2.2) or a *sec*-butyl (entry 6, A-values = 2.4) group results in greater than 3-fold increase in the ECCD amplitude. On the contrary, altering the substitution of the γ position does not appear to significantly affect the amplitude of the ECCD spectrum, as evident from entries 5 and 7 in Table II.1-1. Thus, one can envision that increased substitution on the β -carbon would increase the $A_{1,3}$ strain, further destabilizing conformation **B** and stabilizing conformation **D** (Figure II-3). The presence of the benzyl group (entry 7, A-value = 1.76) also indicates that the ECCD active conformation is not affected by aromatic substitution.

While conformations **C** and **D** explain the observed ECCD sign, the driving force causing the observed change of the mode of stereochemical determination is unknown. Since the observed phenomenon occurs only in halogenated substrates (no conformational change is observed with substrates containing hydroxyl or alkoxy group at the chiral center) it is plausible to assume that there is an additional interaction between halogen atom and porphyrin that facilitates and stabilizes appearance of a new ECCD active conformation. In order to gain insight into the observed phenomenon several $^1\text{H-NMR}$ experiments were designed and performed.

II.1-3: ^1H -NMR and UV based identification of halogen effect onto the porphyrin-substrate binding

As widely discussed in the literature, the aromatic core of a porphyrin generates a large shielding cone. Thus, when the substrate binds to the metal incorporated into the porphyrin core, the strong diamagnetic anisotropy of the porphyrin ring induces an upfield shift of the protons (shielding). The magnitude of this effect depends on the position of the substrate relative to the plane of the porphyrin and the central axis of the shielding cone. Thus, protons located closer to the porphyrin plane and closer to the center of the shielding cone produced by the chromophore experience larger upfield shifts (Figure II-5). Consequently, the shifts of the protons of the chiral substrate coordinated to the porphyrin, as detected by ^1H -NMR, can help to map the disposition of the substituents relative to the porphyrin plane within the shielding cone and reveal the orientation of the substituents relative to the carbonyl group.



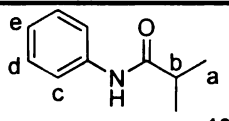
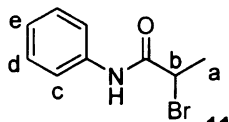
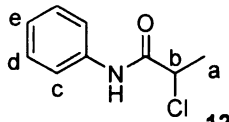
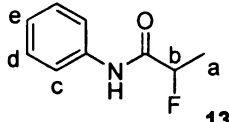
(shielding enhances with the direction of arrows)

Figure II-5: Shielding cone of the porphyrin causes an upfield shift of protons upon coordination to the substrate.

To simplify the NMR studies, zinc tetraphenylporphyrin (ZnTPP) was used as a mimic of the zinc porphyrin tweezer, and was complexed with aniline-derivatized carboxylic acids (instead of 1,4-phenylenediamine used for complexation with the

porphyrin tweezer). Application of a single chromophore also requires confirmation of the binding mode, i.e., that complexation of a single porphyrin to the substrates strictly corresponds to the coordination formed by bis-porphyrin. Previous reports have verified that the binding mode achieved with the model ZnTPP corresponds to the complexation of tweezer to a chiral amide and occurs through an amide carbonyl.⁶⁻⁹ Therefore, we can be reasonably assured that our model studies - the binding of the chiral amide to the mono-chromophoric system (ZnTPP) - is representative of the actual binding mode within the tweezer system.

Table II-2. Change in chemical shifts of halo amides upon addition of ZnTPP

Substrate	$\Delta\delta = \delta_{\text{complex}} - \delta_{\text{free}}$				
	H _a	H _b	H _c	H _d	H _e
 10	-0.019	-0.084	-0.068	0	0
 11	-0.093	-0.177	-0.104	-0.036	-0.024
 12	-0.086	-0.162	-0.095	-0.022	-0.017
 13	-0.092	-0.156	-0.104	-0.021	-0.016

Spectra taken in CDCl₃ at 1.2:1 porphyrin/substrate ratio

Based on the changes in the chemical shift between a free and a bound form of a chiral amide, we expect to gather conformational information regarding the effect of an α -halogen on the overall binding, as well as establish the relative position of the substituents on the chiral center with respect to the plane of porphyrin ring, when the

amide is complexed with the Zn-porphyrin. Table II-2 lists the changes in chemical shift ($\Delta\delta$) for a series of α -halocarboxylic acids derivatized with aniline, upon coordination to ZnTPP. The data was obtained after complexation of ZnTPP with a chiral substrate at 1.2:1 ratio in CDCl_3 (the concentration of porphyrin in ^1H -NMR tube was retained constant $c = 0.018\text{ M}$, the amount of the chiral guest was adjusted). More negative $\Delta\delta$ value indicates that the corresponding proton falls deeper inside the porphyrin shielding cone and *vice versa*.

For example, the methyl protons of derivatized α -bromopropionic acid (Table II-2, entry 2) resonate at 1.955 ppm. Upon addition of ZnTPP, the methyl protons shift upfield to 1.862 ppm ($\Delta\delta = -0.093$) indicating that they lie within the porphyrin's shielding cone. It is important to note the difference in the shift of the alpha protons versus the methyl protons. Both sets of protons are more shielded when the molecule is complexed to the ZnTPP, as expected. However, the larger shift of the alpha proton upon complexation is due to the inherent difference in distance from the porphyrin center (alpha protons will always be closer to the central axis of the shielding cone), and not due to the conformation adopted upon complexation. Particularly noticeable is the change in the chemical shift of the aryl protons. Although rather far away from the coordination site, in the presence of a α -halogen the aromatic protons appear to experience enhanced shielding, indicating that they might be placed closer to the porphyrin ring due to tighter or better binding.

The observations described above are consistent for derivatized halocarboxylic acids bearing either a Br, Cl or F atoms (Entries 2-4, Table II-2). However, in the absence of an α -halogen (derivatized α -methylpropionic acid, entry 1, Table II-2) the corresponding $\Delta\delta$ values observed for each proton are significantly lower, possibly

indicating that the distance of the amide from the porphyrin plane is greater than what is observed when an alpha halogen is present. These results directly suggest that the presence of the α -halogen possibly promotes a tighter binding between the derivatized acid and the zincated porphyrin, thus supporting the proposal for a carbonyl, halogen cooperative binding.

On the other hand one has to consider that since the presented above analysis is performed on the complex of two molecules, the observed result must also depend on the quantity of the complexed species formed in the solution, i.e. binding affinity. Since the NMR spectrum represents an average signal, the observed difference in shielding between non-halogenated and halogenated substrates might also be attributed to the enhanced binding affinity of the later due to additional interaction between the porphyrin and the halide. Thus, to validate this supposition the binding constants of ZnTPP tweezer with carrier conjugate of alkylcarboxylic acid (1) and halocarboxylic acid (6-Cl) were calculated based on the procedure described below.³⁰

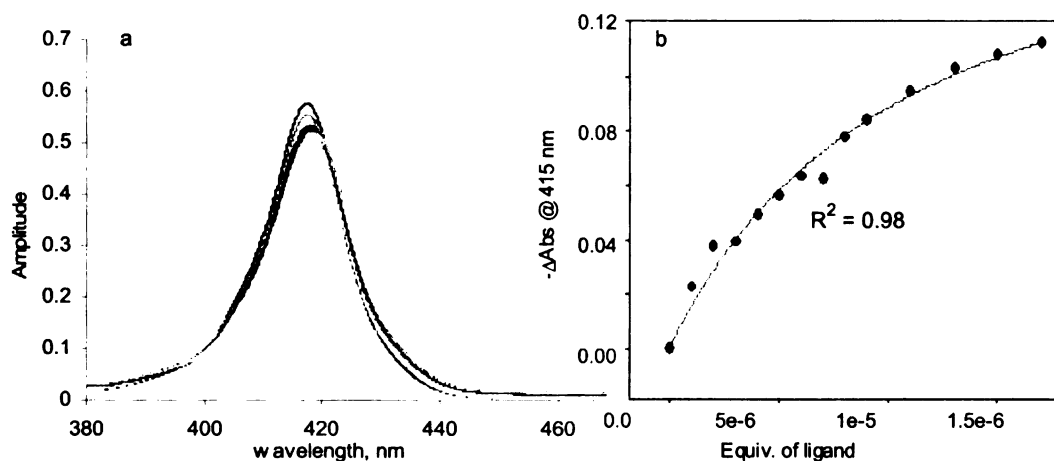


Figure II-6: Determination of binding constants for α -haloamide: a) titration of ZnTPP-tz with substrate 6-Cl; b) non-linear least square fits of the change in absorption vs. equiv of ligand leads to the calculation of binding constant and fitting curve.

Solution of ZnTPP tweezer (1 μ M in methycyclohexane) was titrated with chiral substrates **1** and **6-Cl** (10 mM solution in dichloromethane) at 10 equiv increments and the UV-vis spectra were recorded up to 200 equiv of ligand. Upon formation of the chiral complex the Soret band of the porphyrin tweezer red shifts through a clean isosbestic point which is indicative of the formation of a new complexed species.

For construction of a titration curve, the decay of the free porphyrin tweezer in the solution was monitored and the change in the amplitude between the UV curves after addition of every equivalent of the chiral substrates was collected at one specific wavelength. The change of absorption at 415 nm as a function of the added ligand concentration yields an exponential saturation curve (Figure II-6). The binding constant can be derived, as previously reported by Shoji et al.,³¹ by fitting the latter data through the following non-linear least square equation:

$$f = L \frac{(1 + kx + ka) - \sqrt{L^2(kx + ka + 1)^2 - 4axk^2L^2}}{2ka}$$

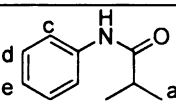
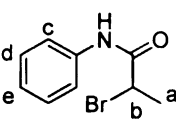
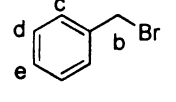
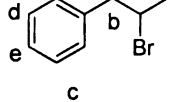
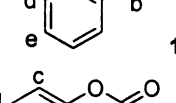
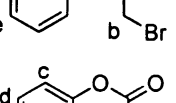
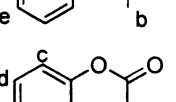
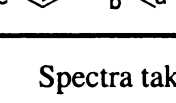
where: $L = \Delta\text{abs}$ at the point of saturation; x = chiral substrate equivalents;

k = calculated K_a ; a = concentration of porphyrin tweezer.

The method afforded the following association constants: $K_a = 4.37 \times 10^4 \text{ M}^{-1}$ with substrate **1** and $K_a = 1.01 \times 10^5 \text{ M}^{-1}$ with substrate **6-Cl**, with $R^2 = 0.98$. Based on the latter binding affinities it is clear that the presence of a halide on the asymmetric center enhances the complexation process, and the observed shielding of the halogenated substrates might be attributed to the larger amount of the complexed species present in the solution of ZnTPP and α -halogenated amides.

To further probe the effect of α -halogens on the substrate binding to the porphyrin, $\Delta\delta$ values were calculated for a series of additional compounds bearing possible coordinating functional groups of different types on α -carbon. The results, as summarized in Table II.1-3, reveal that porphyrin binding evidently decreases when either the halogen or the amide moiety is removed from the molecule.

Table II-3: Chemical shift changes for various molecules with ZnTPP

Entry	Substrate	$\Delta\delta = \delta_{\text{complex}} - \delta_{\text{free}}$				
		H _a	H _b	H _c	H _d	H _e
1		-0.019	-0.084	-0.068	n.d.	n.d.
2		-0.093	-0.177	-0.104	-0.036	-0.024
3		----	-0.023	n.d.	n.d.	n.d.
4		0	-0.004	-0.008	n.d.	n.d.
5		----	-0.003	-0.005	n.d.	n.d.
6		----	-0.014	-0.017	-0.013	-0.010
7		----	-0.029	-0.028	-0.015	-0.013
8		-0.005	-0.011	-0.017	-0.012	-0.008

Spectra taken in CDCl₃ at 1.2:1 porphyrin/substrate ratio.

Removal of the α -halogen results in significantly decreased $\Delta\delta$ values for all the amide protons (Table II-3, entries 1 and 2), supporting the suggestion that the α -halogen

assists in the porphyrin binding. Similar results were observed when the amide functionality is removed, while a halide is maintained in the molecule (entries 1 versus 3 and 4). The calculated $\Delta\delta$ values for entries 3 and 4 are much lower indicating that the sole presence of a halide in the molecule cannot account for the tight binding observed for α -haloamides. The effect of π - π interactions between the porphyrin and the phenyl ring of the carrier molecule is also insignificant (Table II-3, entry 5). Thus, interestingly, it appears that α -haloamides constitute a special case, since the same mode of binding is not observed for either esters or α -haloesters (Table II-3, entries 6-8). These additional ^1H -NMR results further support the suggestion that there is a possible cooperative binding between the amide carbonyl and the α -halogen to the porphyrin.

II.1-4: Identification of conformers C/D as the major ECCD contributing rotomers in porphyrin/ α -halogenated amide complex

The later ^1H -NMR and UV experiments focus on identification of additional stabilization of the complex due to the presence of a halide at the asymmetric center, and in conjunction with ^1H -NMR data support preference of conformers **C** and/or **D** as major ECCD contributing rotomers. Thus, at this point a reevaluation of postulated conformers depicted in Figure 4 is in order. As discussed before, conformations **C** and **D** (or any transition rotamer between the two) positioning the halide (medium group according to A-values) pseudo-*syn* or perpendicular to the amide carbonyl both are able to involve cooperative interaction with porphyrin. Conformation **B** leading to the observed ECCD sign does not invoke cooperative binding of the halogen and could be omitted from

consideration. Further support for the illegibility of conformation **B** is obtained from the following $^1\text{H-NMR}$ experiment.

It is worth noting that unambiguous identification of conformer **C, D** vs. **B** would be possible if a direct correlation of the shielding of an alkyl group (R) with either X (halide) or H (hydrogen) could be performed. Nevertheless, as it was mentioned earlier, $^1\text{H-NMR}$ studies reported in Tables 2-3 do not allow direct correlation between the shielding of the large group and α -hydrogen. The reasoning is in the intrinsically larger shift of α -hydrogen caused by the closer proximity to the center of the shielding cone of the porphyrin, as compare to shift of β -hydrogens of the large substituent. Thus, introducing a methyl substituent at the chiral center of amide **22** (Figure II-7) allows direct comparison of β -hydrogens of the large (ethyl) and the medium (methyl) groups (bromine atom here pays the role of the small substituent). A relative shielding of these two sets of β -hydrogens experienced from ZnTPP will allow us to identify the position of each group (the large ethyl group and the medium methyl substituent) relative to the carbonyl and, consequently, help to distinguish between conformations. The results can be further related to the conformation favored for substrates **4-9**.

Figure II-7 depicts the results obtained upon complexation of **21** and **22** with ZnTPP. In the case of 2-bromo-2-methylbutyric acid **21**, the bromine is considered as the small group (according to reported A-values) and, based on size discrimination one would expect that addition of ZnTPP would stabilize conformation placing the large group (ethyl) perpendicular and the medium group (methyl) away from the carbonyl. Thus, the expected conformation for substrate **21** is **A**, which corresponds to the major rotomer **A** derived for absolute stereochemical determination of α -alkyl(alkoxy)carboxylic acids derivatized with 1,4-phenylenediamine (Figure II-7a). In

this conformation, the large group (C_2H_5 , A-value of 1.79) is placed perpendicular to the carbonyl and, therefore, closer to the coordinated porphyrin than the medium group (CH_3 , A-value of 1.74), positioned pseudo-eclipsed to the NHAr group. This conformation is further verified by the observed $\Delta\delta$ values of proton groups *a* and *b*. Since the $\Delta\delta$ for the methylene protons of the large group (-0.049 ppm) is greater than that of the medium methyl group (-0.031 ppm) we can say that the large group is positioned further inside the porphyrin shielding cone. Another possible conformation of substrate **21** - conformation **C** - although satisfies larger shielding of ethyl substituent, would be less stable due to a dual $\text{A}_{1,3}$ strain within the molecule and additional steric interaction between the porphyrin and the ethyl group. Conformation **B** of the carrier derivatized 2-bromo-2-methylbutyric acid, in turn does not satisfy the ^1H -NMR result, since it places the medium group closer to the porphyrin plane which should induce larger shielding of methyl group over the ethyl. Thus, based on ^1H -NMR results conformation **B** of **21** can be ruled out from consideration.

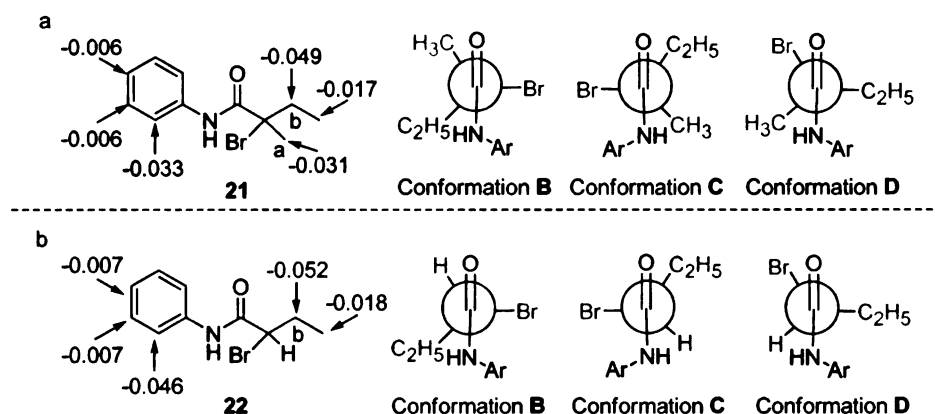


Figure II-7: Chemical shift changes and corresponding conformations of its Newman projection as bound to ZnTPP of: a) *N*-phenyl-2-bromo-2-methylbutanamide (**21**) and b) *N*-phenyl-2-bromobutanamide (**22**).

It is important to note that the $\Delta\delta$ value calculated for the corresponding methylene group of 2-bromo-butyrac acid **22** is very similar (-0.052 ppm) to shift detected for the corresponding methylene of **21** (Figure II-7b). Similarity in the shielding suggests that the two ethyl groups in both **21** and **22** are placed equally in the shielding cone of the porphyrin. Hence, for substrate **22** the large group (C_2H_5) remains perpendicular to the carbonyl, while it is the medium group (Br) and not the small group (H) that is *syn* to the carbonyl, once more supporting the cooperative binding suggestion. It is important to note that in both cases the $\Delta\delta$ s experienced by the aromatic groups are very similar suggesting that the overall binding remains the same. Consequently, the similarity of shielding experienced by the ethyl group in both **21** and **22** supports stabilization of **C** and/or **D** conformers, while rotamer **B** can be excluded from consideration.

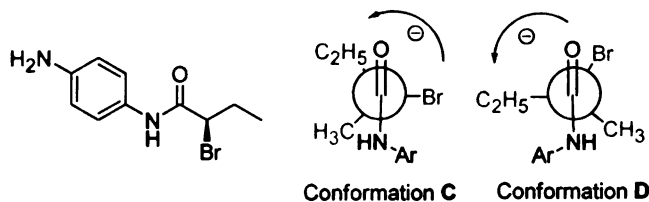


Figure II-8: Two possible conformation of (*R*)-2-bromobutanoic acid carrier conjugate yielding a negative ECCD spectrum.

The similarity in $\Delta\delta$ of ethyl and methyl groups of **21** and **22** could also indirectly help to identify conformation **D** as a major ECCD contributing rotamer. In particular, conformer **C** of derivatized 2-bromo-2-methylbutanamide (**21**) can be considered disfavored as compared to **D** due to the $A_{1,3}$ strain within the molecule and additional steric interaction of the large group with the bound porphyrin. Hence, the major conformation expected for **21** is rotamer **D**. Since the observed similarity in $\Delta\delta$ indicates

spatial distribution of groups in **21** and **22** is close to identical, we can assume that substrate **21** also exists predominantly in conformation **D** over **C**.

As a final test for these studies, enantiomerically pure (*R*)-2-bromobutanoic acid (**26**) was synthesized according to Scheme and coupled with the 1,4-phenylenediamine (carrier) to give carrier conjugate **27** for ECCD determination.^{32, 33} Upon complexation of (*R*)-2-bromobutanoic acid carrier conjugate with the porphyrin tweezer a negative ECCD spectrum ($A = -134$, first couplet at 429 (-84), second couplet at 420 (+50)) was observed. The observed ECCD sign is in agreement with conformation **C/D** that places the medium halide *pseudo syn* to the carbonyl, i.e., employing the halogen- π interaction (Figure II-8). Namely, steric differentiation taking place between the medium bromine and the large ethyl substituent results in counterclockwise orientation of porphyrins and gives rise to a negative ECCD spectrum. Similar conformation applied to the (*S*)- α -halogenated amides presented in Table II.1-1 leads to a positive ECCD.

II.1-5: Halogen- π interaction as a driving force for the conformational stability of α -halogenated amides in ZnTPP tweezer complexes



Figure II-9: Two views of the molecular structure of (*N*-phenyl-*N*-nitrosohydroxylamino)(*meso*-tetra-4-methoxyphenylporphyrinato)iron (III): a) along the porphyrin plane; b) perpendicular to the porphyrin plane (the anisole groups on the porphyrin are omitted).³⁴ Hydrogen atoms are omitted for clarity.

The experimental data obtained so far (both ECCD and ^1H -NMR data) indicate that the presence of a halide on the chiral center of the carrier derivatized carboxylic acid enhances its binding to the metallated porphyrin tweezer, suggesting a direct interaction between the halide and the porphyrin system. However, the exact nature of this interaction is still under investigation with two possible binding modes being directly suggested by the data: either a bidentate-type coordination of the α -haloamides (both the carbonyl oxygen and the halide atom) to the zinc in the porphyrin core or a direct interaction between the halide and the aromatic system of the porphyrin (halogen- π interaction).

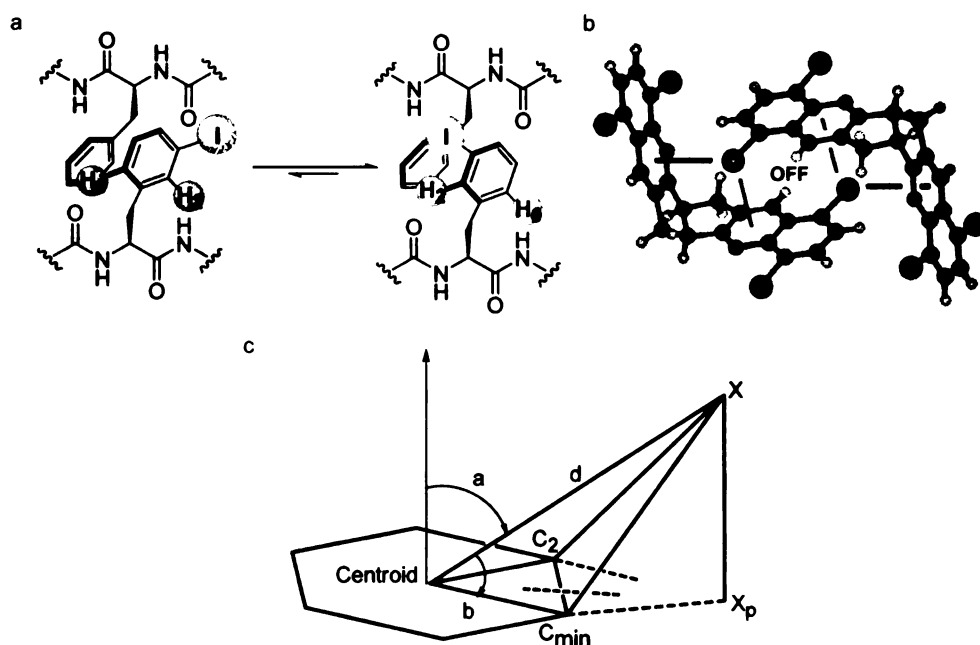


Figure II-10: Halogen- π interaction in a) β -hairpin peptide; b) hexabromodiquinoline host and c) halogen- π stabilizing van der Waals interaction.

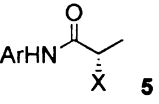
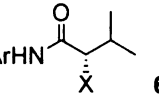
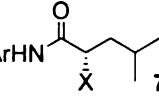
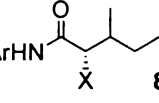
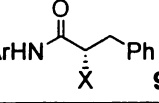
The former (bidentate coordination) has been observed previously in the crystal structures of iron porphyrins and has been attributed to the ability of iron to “fall out” of

the porphyrin ring (Figure II-10).^{34, 35} However, unlike iron porphyrins, zincated porphyrins are not known to undergo similar bidentate coordinations. Nevertheless, there are a large number of reports that address the nature, magnitude and practical application of halogen- π ($C-X\cdots\pi$) interaction (Figure II-10 a,b). This kind of interaction is rather common in a variety of supramolecular structures, both host-guest systems and two-dimensional networks.³⁶ It is also very important in biological systems, since halogenation is a common method for improving binding of pharmaceutical leads while also providing additional stabilization in peptides.^{37, 38 and ref. within} Recent computational reports have shown that when suitably positioned, a halogen experiences van der Waals interaction with a π -system, the latter dominates over the electrostatic repulsion between the partial negative charges at the halogen and π -cloud (Figure II-10c).³⁹ Thus, based on ECCD and 1H -NMR results, we propose that the major ECCD active conformation must reflect a $C-X\cdots\pi$ interaction contributing to the binding of the α -halo amides to the ZnTPP-tz.

Accounting for the different nature of the halides, it is worth noting that the strength of halogen- π interactions may not be similar for all complexes. Since the intensity of the CD bisignate spectrum depends on the population of one ECCD active conformation in the solution, one would expect to correlate the amplitude of the spectrum with conformational stability of substrate in the complex with tweezer. Hence, estimation of a relative strength of halogen- π interaction could be obtained from comparison of the ECCD amplitudes obtained for different haloamides after correction for enantiomeric excess (%ee). Regretably, such analysis does not reveal a reliable trend that could relate the strength of the secondary interaction with the nature of the halide.

Namely, the magnitude of the observed ECCD spectra varies regardless the type halide. For instance, while for the set of substrate **5-X** (X = F, Cl, Br) the highest ECCD amplitude is observed for (*S*)-2-bromopropanamide (**5-Br**) (A = +328, normalized for %ee), the **6-X** series give the highest ECCD magnitude for (*S*)-2-fluoro-3-methylbutanamide (**6-F**) (amplitude A = +323 normalized for %ee).

Table II-4: ECCD data for 1,4-phenylenediamine derivatized α -halocarboxylic acids with ZnTPP-tz **I**.

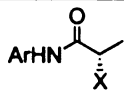
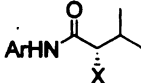
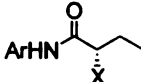
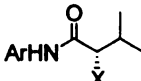
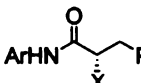
	Substrate	λ , nm, ($\Delta\epsilon$)	A A(norm)	λ , nm, ($\Delta\epsilon$)	A A(norm)	λ , nm, ($\Delta\epsilon$)	A A(norm)
	X =	Br		Cl		F	
5		429 (+116) 421 (-130)	+296 (+328)	429 (+25) 42 (-38)	+63 (+64)	428 (+34) 419 (-31)	+65 (+130)
6		429 (+103) 421 (-91)	+194 (+215)	428 (+132) 421 (-82)	+214 (+238)	428 (+114) 420 (-30)	+207 (+323)
7		429 (+107) 421 (-75)	+182 (+202)	429 (+24) 421 (-30)	+54 (+60)	428 (+31) 420 (-30)	+61 (+77)
8		429 (+94) 421 (-81)	+175 (+218)	429 (+108) 421 (-124)	+232 (+290)	429 (+96) 420 (-66)	+162 (+202)
9		429 (+47) 421 (-43)	+90 (+100)	429 (+22) 421 (-19)	+41 (+55)	428 (+28) 419 (-22)	+50 (+89)

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest

Important information, however, can be obtained from the results observed during the studies of the halogenated amides with the Lewis acidic ZnTPFP tweezer.³⁰ Complexation of haloamides **4-X** through **9-X** (X= Br, Cl, F) with this tweezers yields negative ECCD (as opposed to the positive bisignates observed with ZnTPP-tz) (Table 12). The observed result can be used to reveal the nature of halogen- π interaction taking place in the complex with ZnTPP-tz. Namely, the interaction might be similar to the one

observed between the halides (mostly I, Br and Cl) with heteroatoms,⁴⁰⁻⁴⁵ in which all halides behave as electron acceptors (however, it is possible that interaction of highly electronegative fluoride with porphyrin might differ from that of Cl and Br). Considering that halogen- π interaction is based on the ability of the porphyrin to serve as an electron donor (the halide is an electron acceptor), then incorporation of an electron withdrawing substituent onto the porphyrin core would affect the ability of the porphyrin to stabilize the donor-acceptor interaction with the porphyrin. As a result, the observed disruption of cooperative binding would be expected.

Table II-5: ECCD data obtained for halogenated amides with ZnTPFP tweezer

Entry	Substrate	λ , nm, ($\Delta\epsilon$)	A	λ , nm, ($\Delta\epsilon$)	A	λ , nm, ($\Delta\epsilon$)	A
	X =	Br		Cl		F	
1	 5	424 (-37) 417 (+144)	-181	425 (+64) 417 (-75)	+139	423 (-18) 413 (+31)	-49
2	 6	423 (-387) 417 (+288)	-675	426 (-32) 417 (+57)	-89	427 (+4) 418 (-5)	+9
3	 7	425 (+29) 416 (-15)	+44	424 (+458) 418 (-263)	+720	427 (-23) 418 (+35)	-58
4	 8	426 (-137) 418 (+65)	-202	425 (-61) 415 (+4)	-65	428 (-138) 420 (+104)	-423
5	 9	423 (-26) 417 (+19)	-45	424 (-101) 416 (+83)	-184	424 (-118) 417 (+77)	-195

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of ligand.

The secondary interaction operating within the complexes of haloamides with ZnTPP is indirectly supported after comparison of the crystal structures of aniline derivatized (*S*)-2-chloro-3-methylbutanoic acid and its complexes with ZnTPP and

ZnTPFP. The free *N*-phenyl (*S*)-2-chloro-3-methylbutanamide exists in conformation with the halide and the alkyl group bisecting the carbonyl (see Section II.1-1 for details). The conformation is stabilized by an apparent hydrogen bond taking place between the carbonyl oxygen of the amide and the hydrogen of the amide nitrogen (NH) and the α -hydrogen (see Figure II-3c and Appendix II). The complexed to the porphyrin *N*-phenyl (*S*)-2-chloro-3-methylbutanamide, however, exists in a different conformation. In both ZnTPP and ZnTPFP complexes the chlorine atom of the amide is oriented away from the carbonyl (dihedral angle = 161°) (Figure II-11).

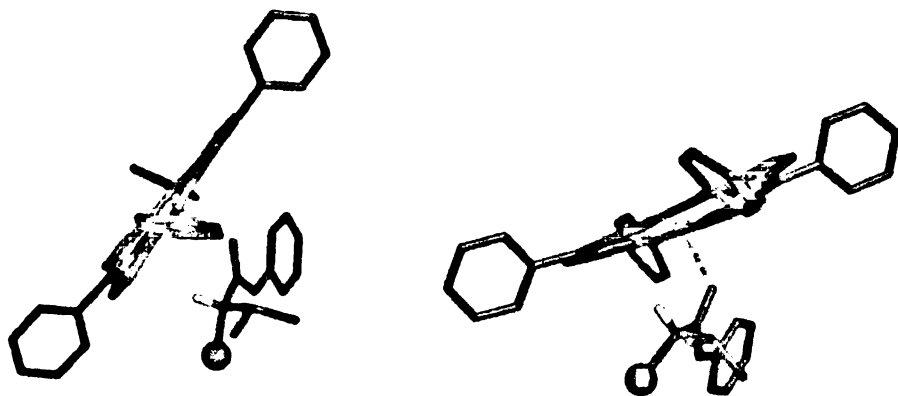


Figure II-11: *N*-phenyl (*S*)-2-chloro-3-methylbutanamide in the complex with ZnTPP. (crystal structure, crystallized from dichloromethane/benzene/hexane 1:2:2)

Based on the crystal structures, *N*-phenyl (*S*)-2-chloro-3-methylbutanamide exists in the same conformation when complexed with either ZnTPP or ZnTPFP (halogen oriented *anti* to the carbonyl). If the substrate is complexed with both ZnTPP-tz and ZnTPFP-tz in the same form, they both are expected to produce analogous ECCD and NMR results. Nevertheless, the complexation of the carrier derivative of (*S*)-2-Cl-3-methylbutanoic acid with these two tweezers yields ECCD spectra of an opposite sign (positive for ZnTPP-tz and negative for ZnTPFP-tz), implying that in the solution the two

complexes stabilize two different rotomers. While the conformer stabilized within ZnTPFP-tz is a general rotamer found prevalent in the complexes with α -alkoxyamides, the conformation of the amide within ZnTPP tweezer is changed due to the favored halogen- π interaction with the ZnTPP porphyrin.

In summary, the results discussed above indicate that due to the electron deficiency the halogen- π interaction with ZnTPFP-tz is disrupted, allowing the stabilization of the other conformation yielding a change of the ECCD sign. It is plausible to propose that the conformation stabilized within ZnTPFP-tz is similar to the one determined for alkylamides and alkoxyamides.

II.2. Rigid α -halolactams as the model for testing halogen- π interaction

Although the $^1\text{H-NMR}$ results support the premise for a halogen effect with regards to binding of α -halo substituted amides with zincated porphyrins, the free rotation along the $\text{C}_{\text{C=O}}\text{-C}_{\text{chiral}}$ bond can lead to multiple coexisting conformations. Any or a combination of each population can result in a host-guest complex that can be CD active. In order to remove from play the possibility of having multiple conformations (as a result of different rotameric conformations), α -chiral lactams were pursued such that the $\text{C}_{\text{C=O}}\text{-C}_{\text{chiral}}$ bond could not rotate and would instead adopt a defined geometry with a rigid conformation (Figure II-12).

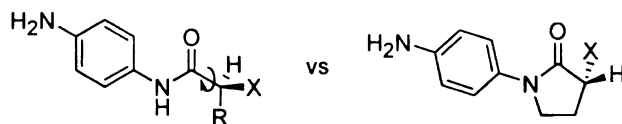


Figure II-12: Restricted conformational flexibility of butyrolactams.

In α -chiral lactams the position of both the α -halogen and the α -H relative to the amide carbonyl is locked, i.e. both the halide and the H are forced to always be gauche to the carbonyl. As shown in Figure II-12, with the latter constraints in place the bound porphyrin will have to choose between the hydrogen (small group) and the halide (large group). If the stereodifferentiation solely depends on sterics, the porphyrin should prefer to slide toward the small hydrogen group resulting, in the case of the depicted derivatized (*R*)- α -chloro lactam, a negative ECCD (Figure 13a).

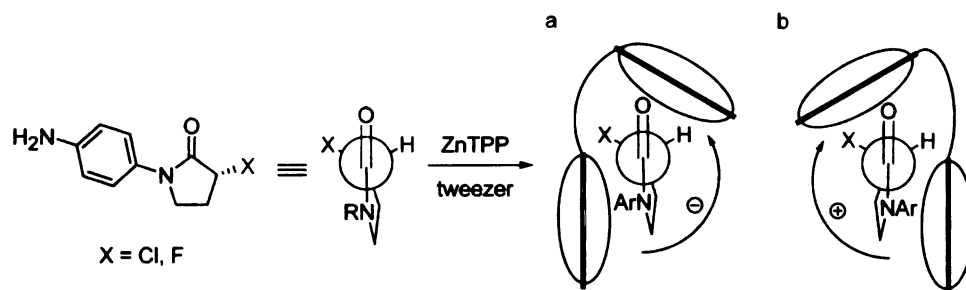


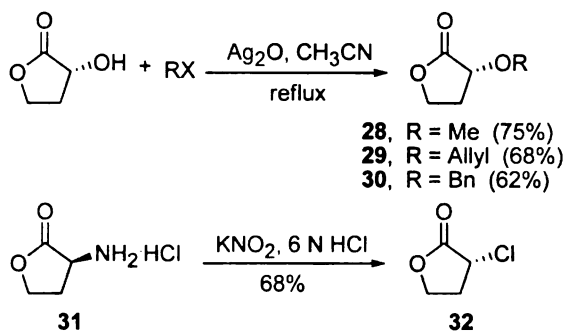
Figure II-13: ECCD sign expected for α -chloro- γ -butyrolactam upon complexation with ZnTPP-tz: a) in absence and b) in presence of the halogen- π interaction.

On the other hand, if there is a cooperative binding between the halide and the carbonyl a positive ECCD spectrum should be observed (Figure II-13b). However, prior to using halo-lactams for verifying our halogen- π interaction hypothesis, it is important to ensure that stereodetermination of lactams occurs through a similar mode as what was observed with acyclic amides. For these purposes several α -alkoxy butyrolactams were synthesized, complexed with ZnTPP-tz and studied spectroscopically. As it was discussed above, chiral α -alkoxy amides closely mimic halogenated substrates due to the similarity in a relative distribution of sizes of the substituents at the asymmetric center: alkyl group – large, alkoxy or halo – medium and hydrogen – small. However, while the

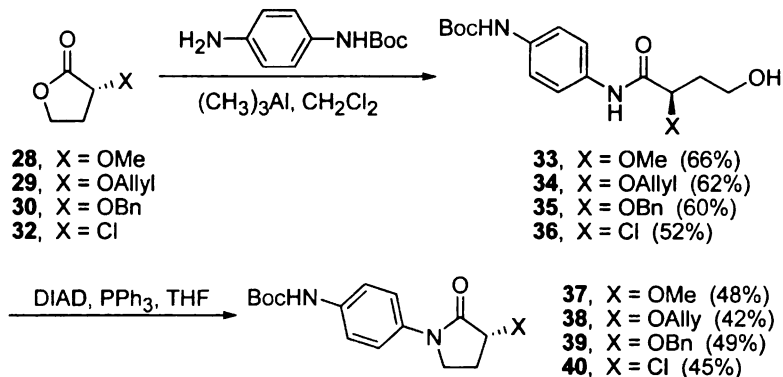
presence of a halide at the chiral center induces a switch of the ECCD sign, alkoxy substrates are differentiated strictly based on the sizes of the substituents.

Thus, chiral α -halo- and α -alkoxy- γ -butyrolactams were synthesized using previously reported procedures from chiral homoserine and chiral α -hydroxy- γ -butyrolactone respectively (Scheme II-2).^{25, 46, 47} Enantiomerically pure (*R*)- α -hydroxy- γ -butyrolactone was submitted to silver catalyzed alkylation⁴⁸ to produce (*R*)- α -alkoxy- γ -butyrolactones (**28-30**). (*R*)- α -chloro- γ -butyrolactone (**32**) was accessed through conversion of the amino group of (*S*)- α -amino- γ -butyrolactone **31** derived from chiral homoserine⁴⁹ and proceeds with inversion of stereochemistry at the chiral center.²⁵

Scheme II-2: Synthesis of chiral α -halo and alkoxy- γ -butyrolactones



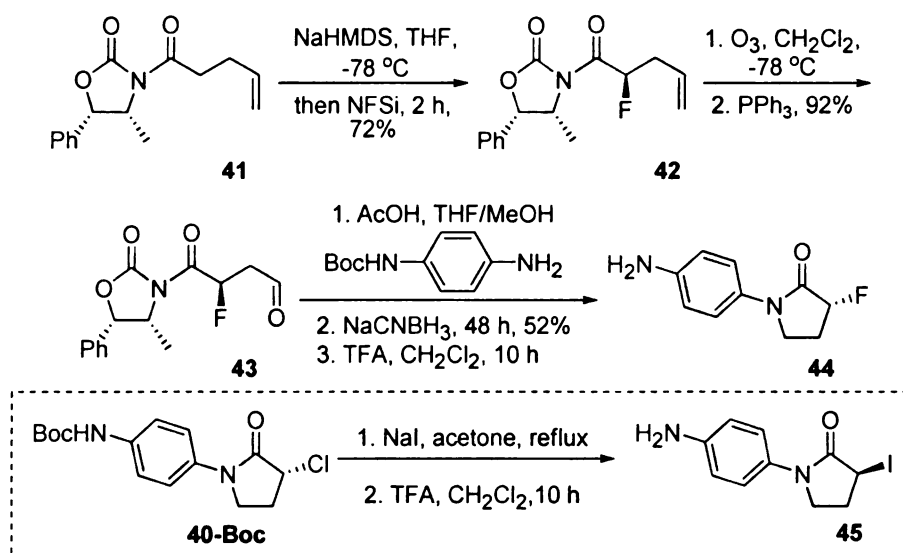
Scheme II-3: Synthesis of chiral α -halo and α -alkoxy- γ -butyrolactams



Lewis acid mediated opening of chloro and alkoxy lactones with mono-N-Boc-1,4-phenylenediamine (carrier) gave 2-alkoxy-4-hydroxybutanamides **33-36**, which were subjected to Mitsunobu cyclization to give the N-Boc protected butyrolactams **37-40** (Scheme II-3).

The (*R*)- α -fluoro- γ -butyrolactam **44** was accessed through Evans auxiliary controlled asymmetric fluorination of compound **41** (Scheme II-4),⁵⁰ followed by oxidative ozonolysis,⁵¹ and one pot reductive amination and cyclization.⁵² The (*R*)- α -iodo- γ -butyrolactam **45** was synthesized from **40-Boc** by S_N2 displacement of chlorine with NaI in acetone in quantitative yield. The ECCD studies of the synthesized γ -butyrolactams were carried out in methylcyclohexane at 1 μ M concentration of the ZnTPP-tz and are summarized in Table II-6.

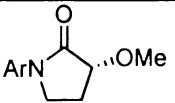
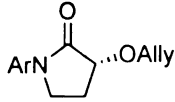
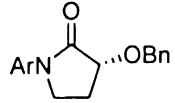
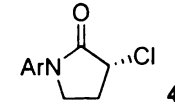
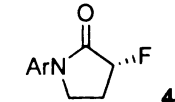
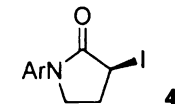
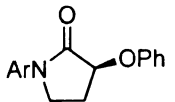
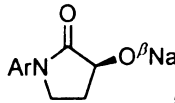
Scheme II-4: Synthesis of chiral α -fluoro and α -iodo- γ -butyrolactams



As a result, it can be seen that (*R*)- α -alkoxy- γ -butyrolactams **37-39** induce a negative helicity into the porphyrin tweezer. The observed results can be rationalized after viewing a porphyrin tweezer – lactam interaction. It is accepted that the formation

of the tweezer - lactam complex is a stepwise process. The first porphyrin of the tweezer binds to the amino group of the carrier due to the accessibility and high affinity of the zinc metal towards nitrogen. The coordination of a second porphyrin has to proceed with consideration of the position of the lone pair of the carbonyl oxygen which is oriented in the plane of the C_{C=O}-C_α bond.

Table II-6: ECCD results of α -alkoxy and α -halo- γ -butyrolactams with ZnTPP-tz

Entry	Substrate	ECCD sign predicted	ZnTPP-tz	
			λ_{max} , ($\Delta\epsilon$)	A
1	 37	neg	429 (-57) 421 (+53)	-110
2	 38	neg	429 (-34) 420 (+19)	-53
3	 39	neg	429 (-45) 421 (+55)	-100
4	 40	pos	427 (+25) 419 (-36)	+61
5	 44	pos	429 (+27) 418 (-21)	+48
4	 45	neg	429 (-14) 420 (+9)	-23
5	 50	neg*	429 (-20) 418 (+25)	-45
6	 51	neg*	430 (-18) 418 (+34)	-52

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest

* - ECCD sign governed by π - π interaction between -OAr group and porphyrin.

Thus, the favored coordination mode will place the porphyrin facing the alkoxy group and the hydrogen at the asymmetric center (Figure II-12a). Size based

differentiation between these two groups, must proceed in favor of small hydrogen which will lead to a counterclockwise orientation of the chromophores and give rise to a negative bisignate, that was indeed observed with lactams **37-39**. The set of α -aryloxylactams **50** and **51** (entries 5 and 6, Table II-6), also induce a negative ECCD, which is expected with consideration of π - π interaction between the aryl group of the chiral center and porphyrin (the same trend is observed upon complexation of α -arylamides).

When an alkoxy group on the chiral center of the lactam is replaced by a halide the relative distribution of the substituents based on their A-values remains the same (alkoxide A-values = 0.5-0.8, halogen A-value = 0.3-0.6). Nevertheless, the resulting halolactam after complexation with ZnTPP tweezer induces the ECCD sign opposite to that of alkoxy lactam. Based on the size differentiation used above for α -alkoxy- γ -butyrolactams the expected ECCD sign for the (*R*)- α -halo- γ -butyrolactams **40** and **44** is negative. Similarly, (*S*)-halo- γ -butyrolactam **45** should induce positive helicity of porphyrin tweezer. Yet positive bisignates were observed with both (*R*)- α -chloro and (*R*)- α -fluoro substrates, and negative ECCD with (*S*)- α -iodo- γ -butyrolactam, indicating the presence of a different mode of stereodifferentiation induced by a halide atom at the chiral center (Table II-6, entries 4-6).

As it is depicted on Figure II-14b and c, while alkoxylactams are determined on the basis of size differentiation, the detected clockwise orientation of porphyrins in the complexes with (*S*)- α -chloro and (*S*)- α -fluoro- γ -butyrolactams might be induced if the chromophore covers the halide as oppose to the small hydrogen.⁵³ Similarly, a negative ECCD of (*R*)- α -iodo- γ -butyrolactam would be expected if porphyrin covers the iodine atom as opposed to the smaller hydrogen. The mode of binding appears the same

regardless of the nature of the halide present, i.e., chloro, fluoro and iodo substituted substrates behave in a similar way. This trend can be attributed to the presence of a secondary interaction between halogen and the aromatic porphyrin.

Thus far all ECCD experiments carried out in order to identify the mode of stereodifferentiation taking place in α -halogenated substrates are supportive of a secondary coordination, in particular C-X $\cdots\pi$ interaction, stabilizing a new conformation of the porphyrin tweezer complexes with acyclic α -halo amides and resulting in inversion of the ECCD sign.

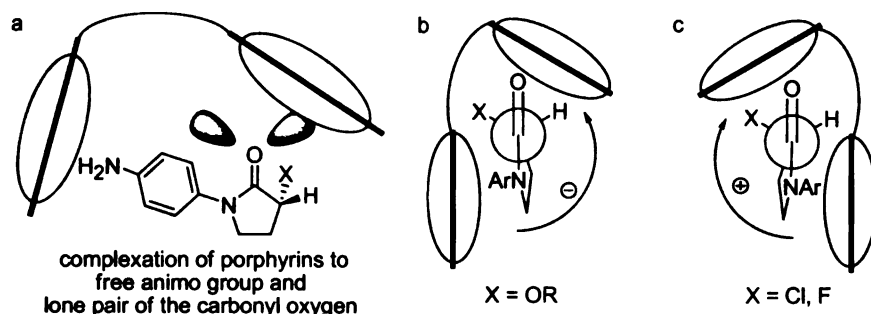


Figure II-14: a) Mode of binding of porphyrin tweezer to butyrolactams, b) counterclockwise orientation of chromophores in (*R*)- α -alkoxy- γ -butyrolactams, c) clockwise orientation of chromophores in (*R*)- α -halo- γ -butyrolactams.

Further information about the stereodifferentiation taking place in α -alkoxy- and α -halo- γ -butyrolactams can be gathered from the following ^1H -NMR experiment. As it has been discussed above, the effect of the porphyrin onto the shielding of the protons can be easily monitored by ^1H -NMR (see part II.1). It has been established that deshielding and shielding experienced by the protons of the chiral guest complexed to the porphyrin can be correlated to the spatial orientation of the substituents relative to the porphyrin plane. Thus, a similar analysis carried out with butyrolactams might reveal the position of the porphyrin relative to an alkoxy group or a halide. Since neither the

oxygen atom nor the halide atom can be monitored in the ^1H -NMR experiment, we focus on the shielding/deshielding of β -methylene hydrogens upon complexation of the carbonyl to the porphyrin. The ^1H -NMR of halolactams and alkoxy lactams shows two distinct sets of diastereotopic protons for the β and γ -methylene.

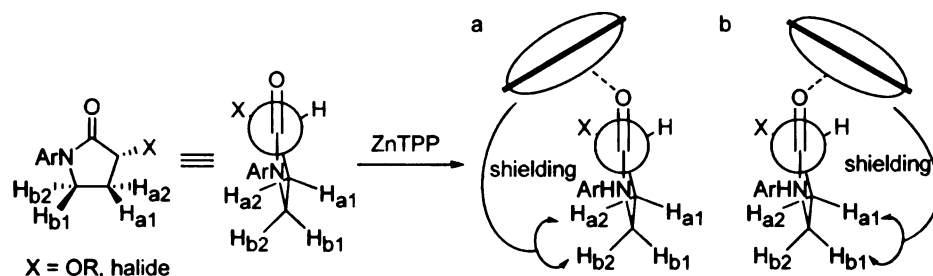


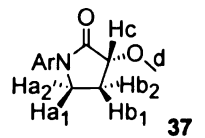
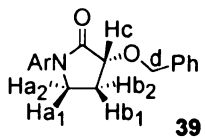
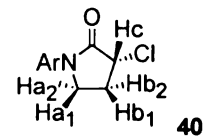
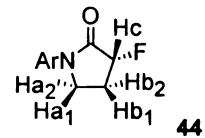
Figure II-15: Analysis of shielding of diastereomeric protons of α -alkoxy and α -halo- γ -butyrolactams by ZnTPP for identification of halogen- π interaction: a) shielding of protons H_{a2} and H_{b2} due to halogen- π interaction; b) shielding of H_{a1} and H_{b1} due to the size differentiation.

The appearance of ECCD signifies a twist of the porphyrin coordinated to the carbonyl oxygen either towards the α -hydrogen or away from it. This twist should create a nonequivalent shielding environment for the diastereotopic protons of β - and γ -methylenes (Figure II-15). Hence, monitoring the relative shift of β - and γ -hydrogens might help to identify the exact position of the porphyrin relative to the substituents at the asymmetric center. For this purpose a detailed NOESY-1D analysis of substrates **33**, **35**, **40** and **41** was performed and the protons of the lactam ring were assigned as follows: H_{a1} and H_{b1} are hydrogen atoms of γ - and β -methylene, respectively, that are *cis* to the α -hydrogen (H_{c}), while H_{a2} and H_{b2} are hydrogen atoms of γ - and β -methylene, respectively, and *trans* to the α -hydrogen (H_{c}). Hence, the substrates **37**, **37**, **40** and **44** were complexed with 2.2 equiv of ZnTPP (to ensure the complexation of both coordinating sites) in chloroform- D and ^1H -NMR spectra were collected. The relative

shielding of the protons induced by porphyrin ($\Delta\delta$) was obtained by subtraction of δ of the free lactam from δ of the complex and are summarized in Table II-7.

As it can be deduced from the relative shifts of the methylene protons H_a and H_b , complexation of zinc porphyrin to alkoxy lactams **37** and **39** induced a two times larger shift of H_{a1} and H_{b1} (*cis* to the H_c) as compare to H_{a2} and H_{b2} . This result can be explained by suggesting that the porphyrin slides towards the α -hydrogen which would result in counterclockwise orientation of the two tweezer chromophores and induce the observed negative ECCD. α -Halolactams **40** and **44**, on the contrary, experience larger shielding of H_{a2} and H_{b2} (*trans* to the H_c) as compared to H_{a1} and H_{b1} , which might come from the position of the porphyrin closer to a halide and away from the α -hydrogen (H_c).

Table II-7: ^1H -NMR shift observed upon complexation of butyrolactams with ZnTPP

H	$\Delta\delta = \delta_{\text{complex}} - \delta_{\text{free}}, \text{ ppm}$			
				
a ₁	-0.130	-0.102	-0.038	-0.061
a ₂	-0.081	-0.076	-0.046	-0.071
b ₁	-0.110	-0.091	-0.034	-0.045
b ₂	-0.074	-0.054	-0.048	-0.056
c	-0.220	-0.252	-0.141	-0.108
d	-0.123	-0.183	----	----

Spectra obtained in CDCl_3 at 1.2:1 porphyrin/substrate ratio.

Thus, we conclude that the series of ECCD and ^1H -NMR experiments described above unambiguously support the presence of a cooperative binding between the carbonyl group of chiral amides and the halogen atom on the α -carbon with the ZnTPP

tweezer. Additional C-X $\cdots\pi$ interaction of the chiral substrate with the porphyrin plane results in a conformation that does not agree with what was previously observed for 1,4-phenylenediamine derivatives of chiral α -alkyl and α -alkoxycarboxylic acids, preventing the use of the established mnemonic for determining the absolute stereochemistry.

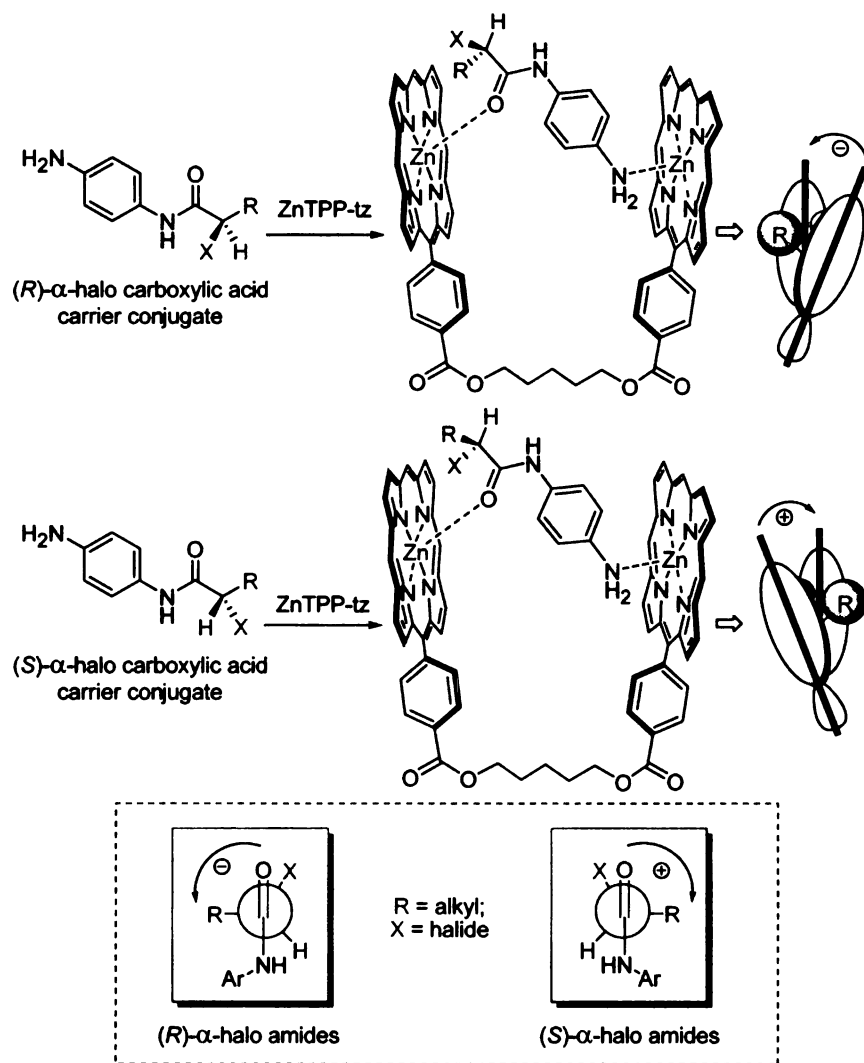


Figure II-16: Mnemonic (dashed box) derived for stereochemical determination of chiral α -halocarboxylic acids derivatized with 1,4-phenylenediamine with ZnTPP-tz as a chromophoric host (phenyl rings on the porphyrin are omitted for clarity).

Based on the newly established ECCD active conformation, a new mnemonic is deduced for determining the absolute stereochemistry of α -halocarboxylic acids derivatized with 1,4-phenylenediamine. As shown in Figure II-16, due to the cooperative binding the halide is placed pseudo-*syn* to the amide carbonyl while the large group (L) is perpendicular and the small group (S) staggered. The expected ECCD sign can be determined by taking into account the orientation of the rotation from the large group, through the small group and towards the halide. A clockwise orientation would translate into a positive ECCD bisignate signal, and *vice versa*.

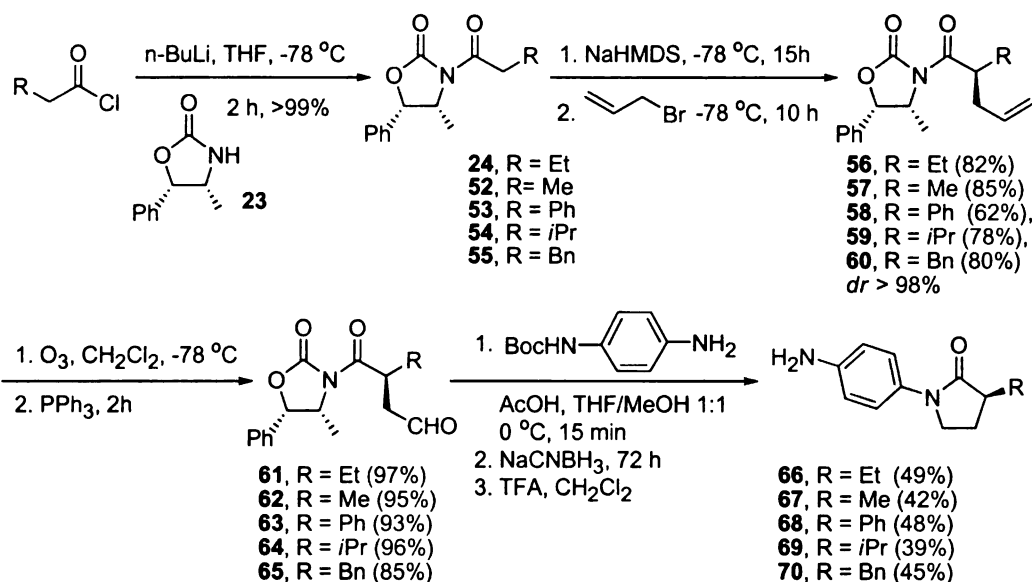
II.3. Stereochemical determination of α -alkyl- γ -butyrolactams

For completion of the stereochemical studies of α -chiral butyrolactams a series of α -alkyl- γ -butyrolactams were synthesized following the transformations presented on Scheme II-5. Asymmetry of α -carbon was accessed employing Evans auxiliary conjugates **24**, **52-55**, bearing different alkyl substituents, which were assembled through base promoted acylation of chiral oxazolidine **23** and obtained in nearly quantitative yield.⁵⁴ The following stereoselective allylation established the chirality of the α -carbon and afforded substrates **56-60** in high yield and diastereoselectivity.⁵⁵ Obtained allyl-derivatives were subjected to reductive ozonolysis that yielded aldehydes **61-65**.⁵⁰ The lactam core was assembled through one pot reductive amination/cyclization of the aldehydes with mono-N-Boc-1,4-phenylenediamine (carrier) and produced Boc-protected butyrolactams **66-70** in moderate yield (39-49%).⁵² The synthesized lactams were deprotected with TFA (20% solution in dichloromethane), neutralized with Na₂CO₃ and

diluted to 1 mM concentration with dichloromethane. The ECCD data obtained for chiral alkyl lactams and μM ZnTPP-tz is summarized in Table II-8.

Considering that the binding of an α -alkyl- γ -butyrolactam with bis-porphyrin tweezer is similar with the previously discussed alkoxy and halo lactams, i.e., occurs through the primary amine of the carrier and the carbonyl oxygen, the stereodifferentiation in the complex should occur between an alkyl substituent and the hydrogen oriented toward the porphyrin bound to the carbonyl. Steric interactions with an alkyl group should cause the porphyrin to twist towards the hydrogen and induce a clockwise orientation of the tweezer chromophores. Hence, the expected sign of ECCD for alkyl lactams with ZnTPP tweezer is positive (Figure II-17a).

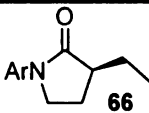
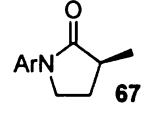
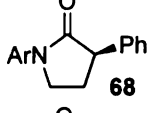
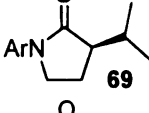
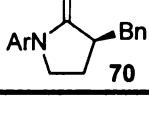
Scheme II-5: Stereoselective synthesis of chiral α -alkyl- γ -butyrolactams



Yet, as it can be seen from the table above, chiral α -alkyl- γ -butyrolactams **66-70** induce a negative helicity into the bis-porphyrin host. The possible differentiation resulting in the observed ECCD spectrum and occurring with conservation of binding

mode would imply the twist of the porphyrin toward the large alkyl group, as it is depicted on Figure II-17b, which would be sterically disfavored. Hence, since the locked structure of the lactam ring restricts the conformational flexibility of $C_{C=O}-C_{\alpha}$ bond, appearance of an unexpected negative ECCD can be counted as indication of an alternative mode of binding or the mode of steric differentiation that has not been considered yet.

Table II-8: ECCD data obtained for chiral α -alkyl- γ -butyrolactams with ZnTPP-tz

Entry	Substrate	ZnTPP-tz		Predicted ECCD sign
		λ , nm ($\Delta\epsilon$)	A	
1	 66	428 (-18) 420 (+36)	-54	pos
2	 67	427 (-10) 419 (+13)	-23	pos
3	 68	429 (-108) 421 (+93)	-211	pos
4	 69	429 (-266) 421 (+262)	-528	pos
5	 70	428 (-23) 420 (+27)	-50	Pos

Spectra taken in methylcyclohexane at 0 °C and reported at 10 equiv of chiral guest.

The possible rationale for the negative ECCD detected with alkyl lactams becomes apparent when one considers that despite the locked conformation of the lactam ring, the stereocenter remains as a sp^3 hybridized carbon, bearing four different substituents. While the rigidity of the five member ring forbids the change of conformation of the stereocenter relative the carbonyl, the approach of the porphyrin to the lone pair of the amide carbonyl must still occur with consideration of the steric environment build by

three substituents at the chiral center (i.e., the alkyl group, the hydrogen and the methylene of the ring; the carbonyl group being the coordination site is omitted from consideration).

After looking closely into the steric differentiation of α -alkoxy- γ -butyrolactams **37-39** it becomes apparent that coordination of the tweezer to the carbonyl oxygen occurs in a way that places the large group (methylene of the ring) away from the porphyrin. The steric differentiation between the small hydrogen and the medium alkyl substituent facing the porphyrin results in the twist of the chromophore towards the hydrogen as a small group. Similar complexation mode takes place in α -halo- γ -butyrolactams, where the differentiation between the two groups facing the porphyrin is in favor of the medium halide (as opposed to the small hydrogen) due to the secondary halide- π interaction. After analyzing the relative sizes of the substituents at the chiral centers in alkoxy and alkylactams, it becomes apparent that, unlike alkoxy and halolactams, where β -methylene was assigned as the large group, the alkylactams present an alkyl group as the large substituent. Consequently, it is plausible to assume that stereodifferentiation in the tweezer-alkylactam complex proceeds differently. In case of the alkoxyactams binding of the lactam to the porphyrin tweezer occurs in a way that places methylene (the large group) away from the porphyrin and leads to stereodifferentiation between small and medium group at the chiral center. If applied to alkylactams, (see Figure II-16b) such geometry of the porphyrin-substrate coordination exposes the large group (alkyl substituent at the chiral center) to the direct steric interaction with porphyrin. Thus, an alternative approach of the porphyrin to the chiral center is from the side that is opposite to the alkyl substituent.

It is plausible to assume that coordination of the alkylactam to the ZnTPP may occur in a way that places the large alkyl substituent at the chiral center away from the porphyrin. In such a case, after coordination the porphyrin faces the methylene (medium group) and the hydrogen (small group). Size based steric differentiation in favor of the smaller group (hydrogen) induces a counterclockwise orientation of chromophores and results in the unexpected negative ECCD for alkyl lactams **66-70**. Figure II-17a depicts a proposed binding mode for (*S*)- α -methyl- γ -butyrolactam resulting in the observed negative ECCD: the large alkyl substituent here is oriented away from the chromophore, thus reducing the steric encumbrance within the complex.

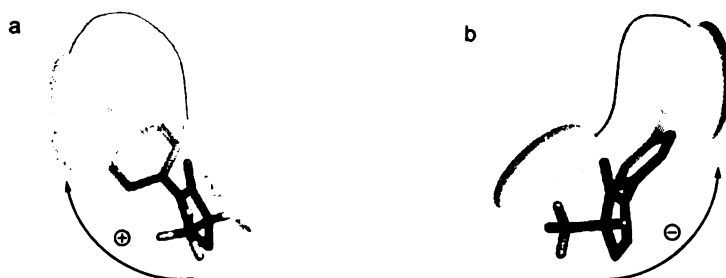


Figure II-17: (*S*)- α -Methyl- γ -butyrolactam complex with porphyrin tweezer I: a) an expected steric differentiation inducing a positive helicity into the porphyrin tweezer; b) possible interaction leading to the observed negative ECCD.

In summary, the two systems – alkyl and alkoxy lactams – represent the case where the position of the substituents with respect to the carbonyl is changed. Namely, while in alkoxy lactams the carbonyl is bisecting the medium (alkoxy) and small (hydrogen) groups, in alkyl lactams the carbonyl is positioned between the large and small substituents. Hence, it is expected that the change in the distribution of the substituents relative to the carbonyl will change a sign of the ECCD spectrum (as is observed from the experiment). On the other hand, one would expect that alkyl lactams having an alkyl group as the medium substituent should lead to the mode of steric differentiation similar

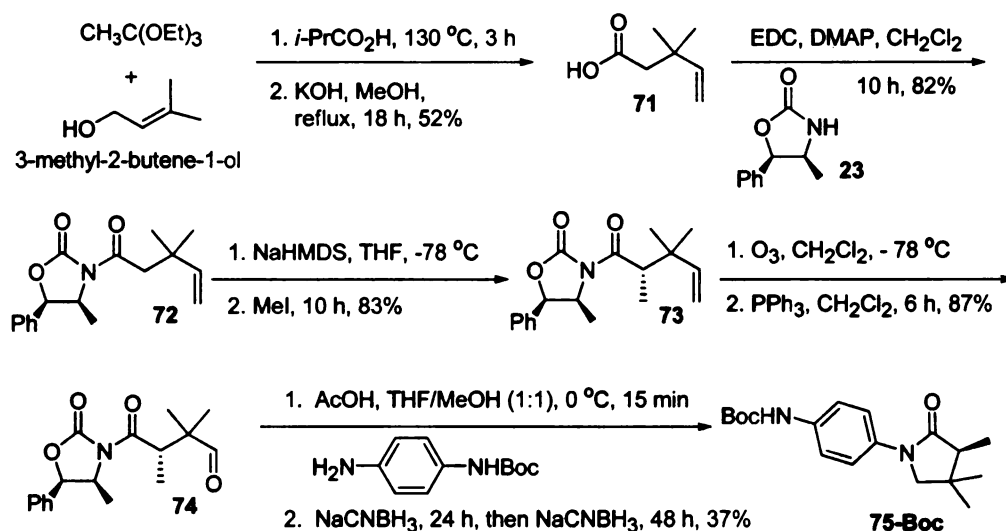
to that of alkoxylactams. Namely, the coordination of the porphyrin should take place between the small hydrogen and the medium alkyl substituent at the chiral center and yield the corresponding ECCD sign.

In order to test the validity of this supposition we introduce additional substitution at the β -carbon of the alkyl lactam and synthesize (*S*)-2,3,3-trimethyl- γ -butyrolactam. Here, an additional substitution at β -position of the lactam ring will change the size based distribution of substituents relative to the carbonyl. In particular, while the methylene of the ring in lactams **66-70**, based on A-values, was referred to as a medium group, introduction of gem-dimethyl substitution increases the size of the methylene. Thus, based on A-values size distribution of the substituents in lactam **75** relative the carbonyl is as follows: hydrogen (the small group) and methyl at the chiral center (the medium group) are bisecting the carbonyl and the large group - substituted methylene – is oriented away from it. Subsequently, if the stereochemical determination of lactam **75** with ZnTPP-tz follows the mode that was derived from the analysis of the alkyl and alkoxylactams (i.e. porphyrin differentiates between the small and medium substituents), the ECCD sign for (*S*)-**75** is positive. Namely, porphyrin coordinated to the carbonyl between the methyl substituent (here the medium group) and the small hydrogen and away from the substituted methylene (here the large group). A twist of the porphyrin towards the small hydrogen will induce clockwise helicity of the tweezer, yielding positive ECCD.

The bulky lactam **75** with dimethyl substitution at β -position was synthesized according to the Scheme II-6. The starting carboxylic acids **71** bearing gem-dimethyl group at the β -carbon was accessed through Claisen condensation of 3-methyl-2-buten-1-ol and triethylorthoacetate, yielding the corresponding ethyl ester, which was

hydrolyzed *in situ* to afford 3,3-dimethylpent-4-enoic acid in 52% yield.⁵⁶ Consequently, EDC/DMAP catalyzed coupling of the carboxylic acid **71** with chiral auxiliary (4*S*, 5*R*)-4-methyl-5-phenyloxazolidin-2-one (**23**) yields the auxiliary conjugate **72** in 82% yield. Stereoselective methylation of **72** affords the methyl derivative **73** in high yield and diastereoselectivity (only one diastereomer detected was by ¹H-NMR). Reductive ozonolysis of the double bond furnishes the aldehyde **74**, which was submitted to one-pot reductive amination-cyclization to construct the lactam **75-Boc** in moderate (37%) yield. The formed **75-Boc** was deprotected in standard conditions to afford lactam **75**.

Scheme II-6: Synthesis of bulky (*S*)-2,3,3-trimethylbutyrolactam **75-Boc**



Complexation of the bulky lactam **75** with ZnTPP tweezer, as it was expected, gave rise to a positive ECCD of significantly high amplitude (*A* = +346). The observed sign is expected if the stereochemical determination takes place between the alkyl group at the asymmetric center and the hydrogen, yielding clockwise orientation of the chromophores in the tweezer. The observed result supports the proposed model of steric

differentiation operating in cyclic structures, i.e. binding of the porphyrin to the carbonyl occurs from the site opposite to the large group (Figure II-18).

Additional support for the proposed model is presented by ^1H -NMR analysis of alkylactam-ZnTPP complexes in Table II-9. Similarly to the previous analysis performed with alkoxy and halolactams, complexation of the alkylactams to the porphyrin and comparison of the relative shielding of hydrogens by the porphyrin allows to identify the approximate position of the porphyrin relative the carbonyl.

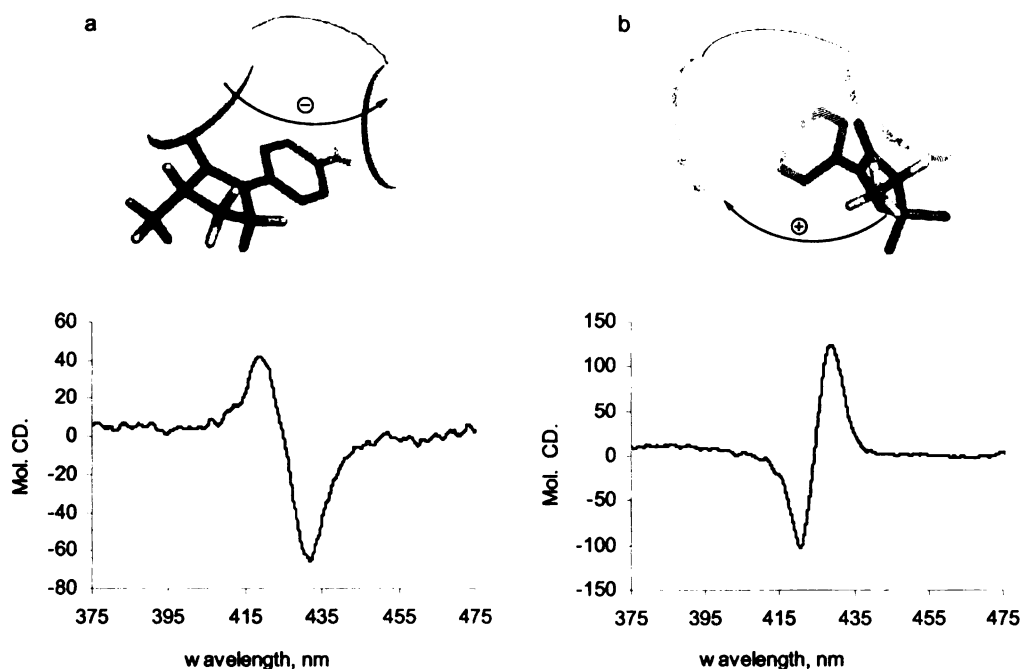
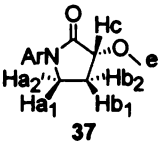
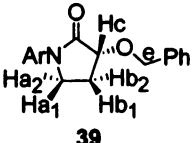
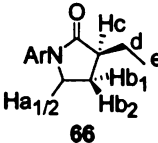
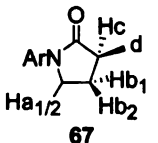
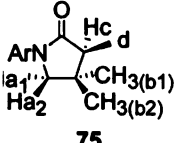


Figure II-18: Binding of the porphyrin to alkylactam occurs opposite to the large group inducing: a) negative ECCD with substrates **66-70** and b) positive ECCD with **75**.

As can be seen from the relative shifts of the substrates in Table II-9, proton H_c at the chiral center of lactams **66** and **67**, similar to alkoxy lactams, is affected to a greater extent by the shielding cone of the porphyrin than the other protons. Nevertheless, unlike α -alkoxy- γ -butyrolactams, where protons H_c experience significant shielding by

the porphyrin, the same protons in lactam **66** are less shielded, presumably due to the farther positioning from the porphyrin. Prominent shift of protons H_{b1} indicates closer position of the porphyrin, as compare to the H_{b2}. Thus, in summary, it appear that complexation of the porphyrin to the lactams **66** and **67** occurs from the side of H_{b1} and, hence away from the alkyl group at the asymmetric center. Such coordination exposes the methylene of the ring and α -hydrogen towards the porphyrin to dictate steric differentiation, resulting in the observed negative ECCD. Similar analysis of ¹H-NMR data obtained for substrate **75** shows a larger shielding of α -methyl substituent (CH₃) as compare β -methyl groups. Additionally, it appears that CH₃₍₁₎ – *syn* to H_c – and proton H_{a1} experience larger shielding as compared to CH₃₍₂₎ and H_{a2}, which indicates that the porphyrin is positioned between H_c and H_d and is twisted twist towards the small H_c. Such binding is in agreement with the proposed above and leads to the observed positive ECCD spectrum.

Table II-9: ¹H-NMR shift observed upon complexation of butyrolactams with ZnTPP

$\Delta\delta = \delta_{\text{complex}} - \delta_{\text{free}}, \text{ ppm}$					
					
a ₁	-0.130	-0.102	-0.076	-0.060	-0.137
a ₂	-0.081	-0.076			-0.103
b ₁	-0.110	-0.091	-0.123	-0.118	-0.064
b ₂	-0.074	-0.054	-0.079	-0.060	-0.035
c	-0.220	-0.252	-0.235	-0.163	-0.204
d	---	---	-0.063	-0.066	-0.119
e	-0.123	-0.183	-0.071	-0.041	---

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

Thus, based on the cumulative analysis of ECCD and ^1H -NMR shielding we propose a general mnemonic for stereochemical determination of α -alkyl (aryl), α -alkoxy and α -halo- γ -butyrolactams. In this model binding of the porphyrin to the carbonyl carbon occurs from the site opposite to the large group at the chiral center, i.e., between the small and the medium substituents. Consequent steric differentiation occurs between the medium and the small group induces a twist of the porphyrin towards the latter (Figure II-19) and results in the ECCD bisignate reflecting the absolute stereochemistry of the asymmetric center of alkyl and alkoxy lactams. Steric differentiation of α -halo- γ -butyrolactams follows the same model with consideration of halogen- π interaction taking place between the halide at the asymmetric center and the porphyrin.

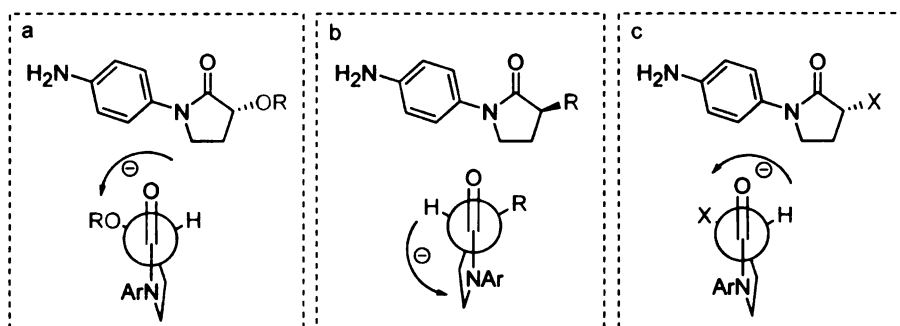


Figure II-19: General mode of steric differentiation for α -alkyl (aryl), α -alkoxy and α -halo- γ -butyrolactams with ZnTPP tweezer.

II.4. Experimental procedures.

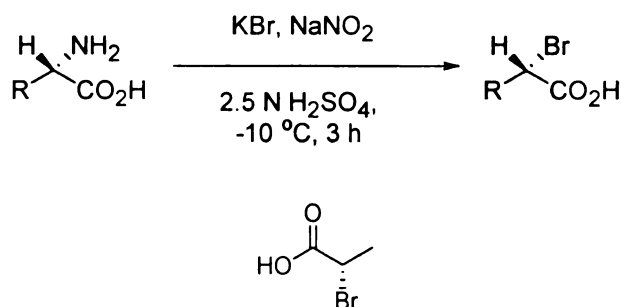
Anhydrous CH_2Cl_2 was dried over CaH_2 and distilled. The solvents used for CD measurements were purchased from Aldrich and were spectra grade. All reactions were performed in dried glassware under nitrogen. Column chromatography was performed using SiliCycle silica gel (230-400 mesh). ^1H -NMR spectra were obtained on Varian Inova 300 MHz or 500 MHz instrument and are reported in parts per million (ppm) relative to the solvent resonances (δ), with coupling constants (J) in Hertz (Hz). IR studies were performed on a Galaxy series FTIR 3000 instrument (Matteson). UV/Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer, and are reported as λ_{max} [nm]. CD spectra were recorded on a JASCO J-810 spectropolarimeter, equipped with a temperature controller (Neslab 111) for low temperature studies, and is reported as λ [nm] ($\Delta\epsilon_{\text{max}}$ [$\text{mol}^{-1} \text{ dm}^3 \text{ cm}^{-1}$]). Optical rotation was measured on Perkin Elmer Polarimeter 341 (micro aperture, 1 mL cell) at 20 °C.

General procedure for CD measurement:

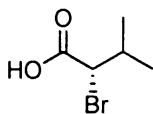
ZnTPP tweezer (1 μL of a 1 mM solution in anhydrous CH_2Cl_2) was added to methylcyclohexane (1 mL) in a 1.0 cm cell to obtain a 1 μM tweezer solution. The background spectrum was taken from 550 nm to 350 nm with a scan rate 100 nm/min at 0 °C. Prepared solution of porphyrin tweezer **1** was titrated with 1 mM solution of the carrier/chiral acid conjugate from ratio 1:1 to 1:30. The ECCD data obtained with 10 or 20 equivalents of chiral substrate is reported. The CD spectra were measured immediately (minimum of 4 accumulations). The resultant spectra is recorded in

millidegrees and normalized based on the tweezer concentration and is referred to as $\Delta\epsilon/\lambda$ [nm] units.

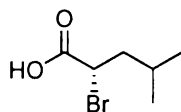
Synthesis of chiral α -bromocarboxylic acids:⁵⁷



(S)-2-Bromopropionic acid:⁵⁸ Sodium nitrite (1.16 g, 16.8 mmol) and potassium bromide (2 g, 16.8 mmol) were added to a solution of alanine (0.5 g, 5.6 mmol) in 2.5 N sulfuric acid (9 mL) at -10 °C. The reaction mixture was stirred for 3 h and then extracted with CH_2Cl_2 (3 $\times$ 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude carboxylic acid was obtained as a yellow oil in 66% (0.57 g) yield and was coupled with mono-N-Boc-1,4-phenylenediamine (carrier) without further purification. HRMS (Q-TOF MS (ES-)): calc'd for $\text{C}_3\text{H}_4\text{BrO}_2$ $[\text{M}-\text{H}]^-$ 150.9395, obs'd 150.9348. ^1H -NMR (CDCl_3 , 300 MHz): δ 1.90 (d, 3H, J = 7.1), 4.38 (q, 1H, J = 7.1), 11.08 (s, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 21.2, 39.3, 176.0.

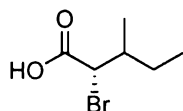


(S)-2-Bromo-3-methylbutyric acid:⁵⁹ Sodium nitrite (0.88 g, 12.8 mmol) and potassium bromide (1.5 g, 12.8 mmol) were added to a solution of valine (0.5 g, 4.3 mmol) in 2.5 N sulfuric acid (9 mL) at -10 °C. The reaction mixture was stirred for 3 h and then extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude carboxylic acid was obtained as a yellow oil in 59% (0.46 g) yield and was coupled with the carrier without further purification. HRMS (Q-TOF MS (ES-)): calc'd for C₅H₈BrO₂ [M-H]⁻ *m/z* = 178.9708, obs'd 179.9055; ¹H-NMR (CDCl₃, 300 MHz): δ 1.01 (d, 3H, *J* = 6.6), 1.07 (d, 3H, *J* = 6.6), 2.14-2.24 (m, 1H), 4.03 (d, 1H, *J* = 7.8), 8.20 (s, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 19.6, 20.0, 32.0, 54.1, 174.9.

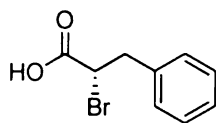


(S)-2-Bromo-4-methylpentanoic acid:⁶⁰ Sodium nitrite (0.78 g, 11.4 mmol) and potassium bromide (1.36 g, 11.4 mmol) were added to a solution of leucine (0.5 g, 3.8 mmol) in 2.5 N sulfuric acid (9 mL) at -10 °C. The reaction mixture was stirred for 3 h and then extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude carboxylic acid was obtained as a yellow oil in 53% (0.4 g) yield and was coupled with the carrier without further purification. HRMS (Q-TOF MS (ES-)): calc'd for C₆H₁₀BrO₂ [M-H]⁻ *m/z* = 192.9864, obs'd 192.9816; ¹H-NMR (CDCl₃, 300 MHz): δ 0.97 (d, 3H, *J* = 6.6), 1.02 (d, 3H, *J* =

6.6), 1.91 (m, 3H), 4.37 (m, 1H), 8.9 (br, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 21.3, 21.5, 24.1, 42.7, 48.2, 176.8.



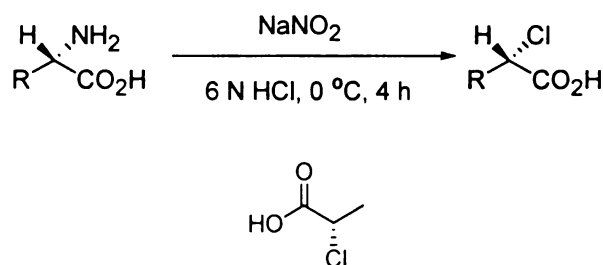
(S)-2-Bromo-3-methylpentanoic acid:⁶¹ Sodium nitrite (0.78 g, 11.4 mmol) was added to a solution of *iso*-leucine (0.5 g, 3.8 mmol) and potassium bromide (1.36 g, 11.4 mmol) in 2.5 N sulfuric acid (9 mL) at $-10\text{ }^\circ\text{C}$. The reaction mixture was stirred for 3 h and then extracted with CH_2Cl_2 ($3 \times 25\text{ mL}$). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude carboxylic acid was obtained as a yellow oil in 45% (0.34 g) yield and was coupled with the carrier without further purification. HRMS (Q-TOF MS (ES $^-$)): calc'd for $\text{C}_6\text{H}_{10}\text{BrO}_2$ $[\text{M}-\text{H}]^-$ m/z = 192.9864, obs'd 193.0013; ^1H -NMR (CDCl_3 , 300 MHz): δ 0.88 (t, 3H, J = 7.5), 1.02 (d, 3H, J = 6.6), 1.27 (m, 1H), 1.68 (m, 1H), 1.96 (m, 1H), 4.27 (d, 1H, J = 4.9), 9.13 (s, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 10.55, 16.17, 26.14, 38.04, 52.50, 175.24.



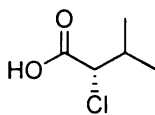
(S)-2-Bromo-3-phenylpropionic acid:⁶² Sodium nitrite (0.62 g, 9.0 mmol) was added to a solution of phenylalanine (0.5 g, 3.062 mmol) and potassium bromide (1.1 g, 9.0 mmol) in 2.5 N sulfuric acid (9 mL) at $-10\text{ }^\circ\text{C}$. The reaction mixture was stirred for 3 h and then extracted with CH_2Cl_2 ($3 \times 25\text{ mL}$). The combined organic layers were dried over anhydrous sodium sulfate and evaporated. The crude carboxylic acid was obtained as a yellow oil in 66% (0.46 g) yield and was coupled with the carrier without further

purification. HRMS (Q-TOF MS (ES-)): calc'd for $C_9H_8BrO_2$ m/z = 226.9708, obs'd 226.9715; 1H -NMR ($CDCl_3$, 300 MHz): δ 3.24-3.36 (m, 1H), 3.43-3.51 (m, 1H), 4.34 (t, 1H, J = 7.2), 7.22-7.40 (m, 5H), 8.8 (s, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 40.7, 44.9, 128.5, 129.1, 130.3, 136.3, 174.8.

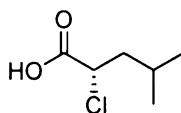
Synthesis of chiral α -chlorocarboxylic acids:



(S)-2-Chloropropionic acid:^{58, 63} To a vigorously stirred solution of alanine (0.5 g, 5.6 mmol) in 6 N HCl (6 mL) at 0 °C was added sodium nitrite (1.16 g, 16.8 mmol) in small portions. This mixture was stirred for 4 h at 0 °C and then extracted with CH_2Cl_2 (3×25 mL). The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as a colorless oil in 52% yield (0.32 g) and coupled with the carrier without further purification. HRMS (Q-TOF MS (ES-)): calc'd for $C_3H_4ClO_2$ $[M-H]^-$ m/z = 106.9900, obs'd 106.9991; 1H -NMR ($CDCl_3$, 300 MHz): δ 1.65 (d, 3H, J = 7.1), 4.40 (q, 1H, J = 7.1), 9.82 (s, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 21.4, 52.3, 175.2.

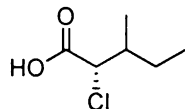


(S)-2-Chloro-3-methylbutyric acid:⁶⁴ To a vigorously stirred solution of valine (0.5 g, 4.3 mmol) in 6 N HCl (6 mL) at 0 °C was added sodium nitrite (0.88 g, 12.9 mmol) in small portions. This mixture was stirred for 4 h at 0 °C and then extracted with CH₂Cl₂ (3 × 25 mL). The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as a yellow oil in 58% (0.34 g) yield and coupled with the carrier without further purification. HRMS (Q-TOF MS (ES⁻)): calc'd for C₅H₈ClO₂ [M-H]⁻ *m/z* = 135.0213, obs'd 135.0191; ¹H-NMR (CDCl₃, 300 MHz): δ 1.01 (d, 3H, *J* = 6.6), 1.08 (d, 3H, *J* = 6.6), 2.36 (m, 1H), 4.18 (d, 1H, *J* = 3.3), 10.95 (s, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 17.8, 19.6, 64.0, 174.6.

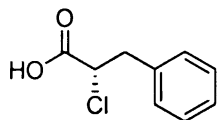


(S)-2-Chloro-4-methylpentanoic acid:⁵⁸ To a vigorously stirred solution of leucine (0.5 g, 3.8 mmol) in 6 N HCl (6 mL) at 0 °C was added sodium nitrite (0.79 g, 10.6 mmol) in small portions. This mixture was stirred for 4 h at 0 °C and then extracted with CH₂Cl₂ (3 × 25 mL). The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as a colorless oil in 54% (0.31 g) yield and coupled with the carrier without further purification. HRMS (Q-TOF MS (ES⁻)): calc'd for C₆H₁₀ClO₂ [M-H]⁻ *m/z* = 149.0369, obs'd 149.0361; ¹H-NMR (CDCl₃, 300 MHz): δ 0.95 (d, 3H, *J* = 6.6), 0.98 (d, 3H, *J* =

6.6), 1.84 (m, 3H), 4.31 (t, 1H, $J = 6.6$), 8.64 (s, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 21.2, 22.5, 25.1, 43.3, 55.6, 175.8.



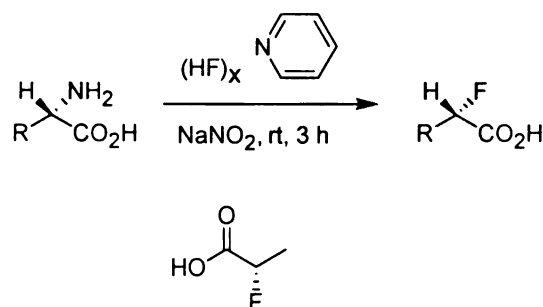
(S)-2-Chloro-3-methylpentanoic acid:⁶⁵ To a vigorously stirred solution of *iso*-leucine (0.5 g, 3.8 mmol) in 6 N HCl (6 mL) at 0 °C was added sodium nitrite (0.79 g, 10.6 mmol) in small portions. This mixture was stirred for 4 h at 0 °C and then extracted with CH_2Cl_2 (3 $\times$ 25 mL). The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as a colorless oil in 55% (0.32 g) yield and coupled with the carrier without further purification. HRMS (Q-TOF MS (ES⁻)): calc'd for $\text{C}_6\text{H}_{10}\text{ClO}_2$ $[\text{M}-\text{H}]^-$ m/z = 149.0369, obs'd 149.0422; ^1H -NMR (CDCl_3 , 300 MHz): δ 0.93 (d, 3H, $J = 7.5$), 1.03 (d, 3H, $J = 7.2$), 1.25-1.37 (m, 1H), 1.58-1.69 (m, 1H), 2.05-2.11 (m, 1H), 4.21 (d, 1H, $J = 6.3$), 9.98 (s, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 10.9, 15.9, 24.8, 38.8, 61.8, 175.1.



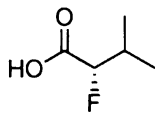
(S)-2-Chloro-3-phenylpropionic acid:⁶⁶ To a vigorously stirred solution of phenylalanine (0.5 g, 3.0 mmol) in 6 N HCl (6 mL) at 0 °C was added sodium nitrite (0.79 g, 10.6 mmol) in small portions. This mixture was stirred for 4 h at 0 °C and then extracted with CH_2Cl_2 (3 $\times$ 25 mL). The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as a yellow oil in 68% (0.38 g) yield and coupled with the

carrier without further purification. HRMS (Q-TOF MS (ES-)): calc'd for C₉H₈ClO₂ [M-H]⁻ *m/z* = 183.0213, obs'd 183.0220; ¹H-NMR (CDCl₃, 300 MHz): δ 3.21 (m, 1H), 3.39 (m, 1H), 4.44 (m, 1H), 7.32 (m, 5H), 10.96 (s, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 40.6, 43.8, 127.4, 128.5, 129.1, 138.2, 175.2.

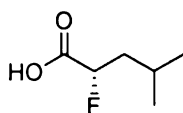
Synthesis of 2-fluoro carboxylic acids:⁶⁷



(S)-2-Fluoropropionic acid:²⁷ Sodium nitrite (1.16 g, 16.8 mmol) was added to a solution of alanine (0.5 g, 5.6 mmol) in hydrogen fluoride-pyridine (5 mL) at -10 °C, and the reaction mixture was stirred for 3 h at room temperature, at which time the reaction was quenched with water (10 mL). The resulting solution was adjusted to pH 4.0 with solid sodium bicarbonate. The mixture was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as yellow oil in 62% yield (0.32 g) and was coupled with the carrier without further purification. HRMS (Q-TOF MS (ES-)): calc'd for C₃H₄FO₂ [M-H]⁻ *m/z* = 91.0195, obs'd 91.0203; ¹H-NMR (CDCl₃, 300 MHz): δ 1.59-1.67 (dd, 3H, *J*₁ = 6.9, *J*₂ = 24.0), 4.95-5.19 (dq, 1H, *J*₁ = 42.6, *J*₂ = 6.9); ¹³C NMR (CDCl₃, 75 MHz): δ 18.4, 18.6, 88.7, 89.7, 165.6, 166.0.

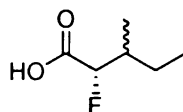


(S)-2-Fluoro-3-methylbutyric acid:^{68, 69} Sodium nitrite (0.9 g, 12.8 mmol) was added to a solution of valine (0.5 g, 4.3 mmol) in hydrogen fluoride-pyridine (5 mL) at $-10\text{ }^{\circ}\text{C}$, and the reaction mixture was stirred for 3 h at room temperature, at which time the reaction was quenched with water (10 mL). The resulting solution was adjusted to pH 4.0 with solid sodium bicarbonate. The mixture was extracted with CH_2Cl_2 ($3 \times 25\text{ mL}$). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as a yellowish oil in 56% yield (0.29 g) and was coupled with the carrier without further purification. HRMS (Q-TOF (ES-)): calc'd for $\text{C}_5\text{H}_8\text{FO}_2$ $[\text{M}-\text{H}]^-$ $m/z = 119.1142$, obs'd 119.1151; ^1H -NMR (CDCl_3 , 300 MHz): δ 0.97 (d, 3H, $J = 6.9$), 1.06 (d, 3H, $J = 6.9$), 2.17-2.27 (m, 1H), 4.75 (dd, 1H, $J_1 = 42.8$, $J_2 = 3.6$), 10.59 (s, br, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 15.8, 15.9, 18.2, 30.1, 32.2, 91.4, 93.8, 175.3, 175.6.

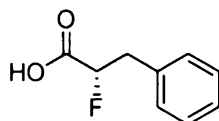


(S)-2-Fluoro-4-methylpentanoic acid:⁶⁸ Sodium nitrite (0.8 g, 11.6 mmol) was added to a solution of leucine (0.5 g, 3.8 mmol) in hydrogen fluoride-pyridine (5 mL) at $-10\text{ }^{\circ}\text{C}$, and the reaction mixture was stirred for 3 h at room temperature, at which time the reaction was quenched with water (10 mL). The resulting solution was adjusted to pH 4.0 with solid sodium bicarbonate. The mixture was extracted with CH_2Cl_2 ($3 \times 25\text{ mL}$). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as a

yellow oil in 54% yield (0.28 g) and was coupled with the carrier without further purification. HRMS (Q-TOF (ES-)): calc'd for C₆H₁₀FO₂ [M-H]⁻ m/z = 133.0665, obs'd 133.1412; ¹H-NMR (CDCl₃, 300 MHz): δ 0.91 (d, 6H, J = 9), 1.60-1.95 (m, 3H), 4.87-5.08 (dd, 1H, J_1 = 9.0, J_2 = 49.5), 9.43 (s, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 21.4, 22.9, 24.4, 40.7, 40.9, 86.1, 88.5, 175.8, 176.1.



(S)-2-Fluoro-4-methylpentanoic acid:^{68, 70} Sodium nitrite (0.9 g, 12.8 mmol) was added to a solution of *iso*-leucine (0.5 g, 4.3 mmol) in hydrogen fluoride-pyridine (5 mL) at -10 °C, and the reaction mixture was stirred for 3 h at room temperature, at which time the reaction was quenched with water (10 mL). The resulting solution was adjusted to pH 4.0 with solid sodium bicarbonate. The mixture was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as a yellow oil in 56% yield (0.29 g) as a 1:1 mixture of diastereomers and was coupled with the carrier without further separation or purification. HRMS (Q-TOF (ES-)): calc'd for C₅H₈FO₂ [M-H]⁻ m/z = 119.1142, obs'd 119.1197; ¹H-NMR (CDCl₃, 300 MHz): δ 0.9-1.1 (m, 4.5 H (CH₃-CH₂ and 1.5 CH₃-CH), 1.09 (d, 1.5H, CH₃-CH, J = 7.2), 1.50 (s, 9H), 2.00-2.23 (complex multiplet, 1H), 4.85 (dd, 0.5H, J_1 = 3.3, J_2 = 48.9), 4.94 (dd, 0.5H, J_1 = 2.4, J_2 = 49.8), 9.22 (s, br, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 11.8, 11.9, 13.0, 15.4, 23.1, 26.0, 28.7, 37.6, 37.8, 93.6, 95.1, 95.2, 96.7, 174.4, 174.6, 174.9, 175.2.



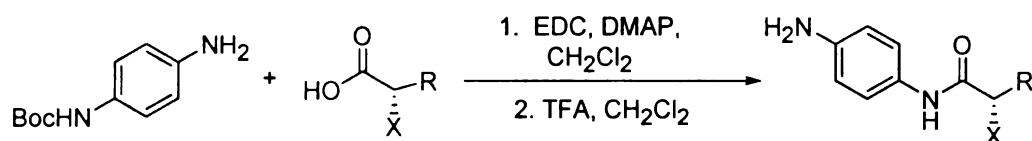
(S)-2-Fluoro-3-phenylpropionic acid:⁷¹ Sodium nitrite (0.79 g, 9.0 mmol) was added to a solution of amino acid (0.5 g, 3.0 mmol) in hydrogen fluoride-pyridine (5 mL) at -10°C , and the reaction mixture was stirred for 3 h at room temperature, at which time the reaction was quenched with water (10 mL). The resulting solution was adjusted to pH 4.0 with solid sodium bicarbonate. The mixture was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude carboxylic acid was obtained as a yellow oil in 54% yield (0.28 g) and was coupled with the carrier without further purification. HRMS (Q-TOF (ES⁻)): calc'd for $\text{C}_9\text{H}_8\text{FO}_2$ $[\text{M}-\text{H}]^-$ $m/z = 167.0508$, obs'd 167.0514; ^1H -NMR (CDCl_3 , 300 MHz): δ 3.07-3.35 (m, 2H), 5.02-5.22 (ddd, 1H (CHF), $J_1 = 9.0$, $J_2 = 48.9$), 7.26-7.34 (m, 5H), 10.44 (s, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 67.7, 87.5, 90.0, 127.2, 128.5, 129.3, 134.9, 173.8, 174.1.

Chiral acids	X = Br	X = Cl	X = F
	90%	99%	50%
	90%	90%	64%
	90%	90%	80%
	80%	80%	80%
	90%	75%	56%

For determination of the enantiomeric ratio each of the chiral α -halocarboxylic acids were derivatized with aniline by EDC/DMAP coupling reaction and analyzed by GC (Chiralcel OD, 5% *i*PrOH/hexanes, $\lambda = 254$ nm, flow rate = 0.8). The enantiomeric ratio of the α -chiral halocarboxylic acids is listed in table above.

General procedure for preparation of carrier/halocarboxylic acid conjugates:

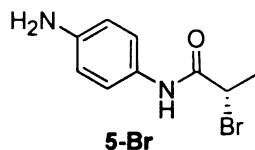
Scheme 7: Derivatization of chiral acids with carrier



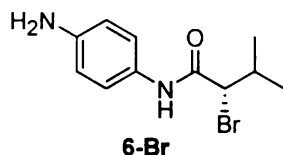
To a solution of the α -halocarboxylic acid (0.2 g) in CH₂Cl₂ (10 mL) were added carrier (mono-N-Boc-1,4-phenylenediamine) (2 equiv), EDC (1.2 equiv) and DMAP (1.2 equiv). The mixture was stirred at room temperature overnight. After removal of most of the solvent under reduced pressure the mixture was transferred onto a short path silica gel column and the product was eluted with 20% solution of EtOAc in hexane.

The Boc-group was then cleaved with 20% solution of TFA in CH₂Cl₂ (10 mL) (stirred for 2 h). Solvent and the majority of TFA were removed under reduced pressure. The product was then dissolved in CH₂Cl₂ and the remaining acid was neutralized with anhydrous Na₂CO₃.

1 mM stock solution of carboxylic acid/carrier conjugates was directly used for ECCD studies with porphyrin tweezer.

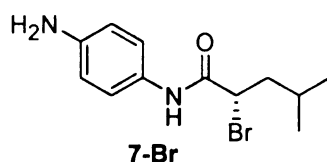


Carrier/bromocarboxylic acid conjugate 5-Br: (*S*)-2-Bromopropionic acid (0.2 g, 1.3 mmol), mono-Boc-1,4-phenylenediamine (0.54 g, 2.6 mmol), EDC (0.25 g, 1.6 mmol) and DMAP (0.16 g, 1.6 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **5-Br** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and isolated in 82% (0.21 g) yield. HRMS (Q-TOF MS (ES⁺)): calc'd for C₉H₁₂BrN₂O [M+H]⁺ m/z = 243.0133, obs'd 243.0072; [α]_D²⁰ = -32 (*c*, 0.23 in CH₂Cl₂); IR (KBr): 3472, 3072, 2936, 2860, 1693, 1466, 1198, 848, 603; ¹H-NMR (CDCl₃, 300 MHz): δ 1.98 (d, 3H, *J* = 7.1), 3.63 (br, 2H), 4.56 (q, 1H, *J* = 7.1), 6.67 (d, 2H, *J* = 8.8), 7.30 (d, 2H, *J* = 8.8), 7.91 (br, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 22.8, 45.1, 122.2, 122.4, 128.8, 143.3, 165.8.

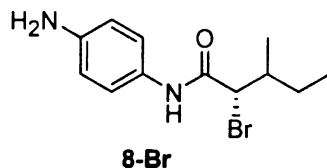


Carrier/bromocarboxylic acid conjugate 6-Br: (*S*)-2-Bromo-3-methylbutanoic acid (0.2 g, 1.1 mmol), mono-Boc-1,4-phenylenediamine (0.45 g, 2.2 mmol), EDC (0.2 g, 1.3 mmol) and DMAP (0.11 g, 1.3 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **6-Br** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 85% (0.24 g) yield. HRMS (Q-TOF MS (ES⁺)): calc'd for

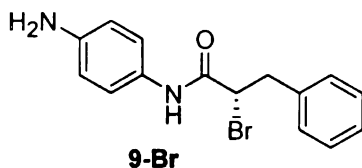
$C_{11}H_{16}BrN_2O$ $[M+H]^+$ $m/z = 271.0446$, obs'd 271.0406; $[\alpha]_D^{20} = -52$ (c, 0.27 in CH_2Cl_2); IR (KBr): 3410, 3271, 3067, 2963, 2924, 2868, 1653, 1611, 1543, 1516, 1464, 1431, 1317, 1275, 1246, 1167, 993, 933, 833, 742, 700, 642, 515; 1H -NMR ($CDCl_3$, 300 MHz): δ 1.05 (d, 3H, $J = 6.6$), 1.12 (d, 3H, $J = 6.6$), 2.48 (m, 1H), 4.43 (d, 1H, $J = 4.4$), 6.68 (d, 2H, $J = 8.8$), 7.30 (d, 2H, $J = 8.8$), 8.12 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 18.3, 21.1, 32.6, 56.1, 115.2, 122.2, 128.9, 143.9, 165.9.



Carrier/bromocarboxylic acid conjugate 7-Br: (S)-2-Bromo-4-methylbutanoic acid (0.2 g, 1.0 mmol), mono-Boc-1,4-phenylenediamine (0.41 g, 2.2 mmol), EDC (0.2 g, 1.3 mmol) and DMAP (0.11 g, 1.3 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **7-Br** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 79% (0.23 g) yield. HRMS (Q-TOF MS (ES+)) calc'd for $C_{12}H_{17}BrN_2O$ $[M+H]^+$ $m/z = 285.0524$, obs'd 285.0531; $[\alpha]_D^{20} = -39.2$ (c, 0.25 in CH_2Cl_2); IR (KBr): 3004, 3284, 2960, 2924, 2854, 1684, 1576, 1456, 1251, 1169, 1010, 827, 671; 1H -NMR (300 MHz, $CDCl_3$): δ 0.95 (d, 3H, $J = 6.6$), 1.00 (d, 3H, $J = 6.6$), 1.98 (m, 3H), 4.44 (m, 1H), 6.68 (d, 2H, $J = 8.8$), 7.30 (d, 2H, $J = 8.8$), 8.02 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 165.9, 143.9, 128.8, 128.3, 122.2, 115.3, 62.2, 32.6, 21.1, 18.3.

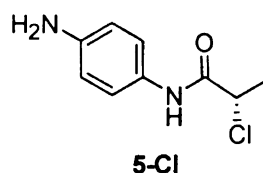


Carrier/bromocarboxylic acid conjugate 8-Br: (*S*)-2-Bromo-3-methylbutanoic acid (0.2 g, 1.0 mmol), mono-Boc-1,4-phenylenediamine (0.41 g, 2.2 mmol), EDC (0.2 g, 1.3 mmol) and DMAP (0.11 g, 1.3 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **8-Br** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 62% (0.14 g) yield. HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₂H₁₇BrN₂O [M+H]⁺ *m/z* = 285.0524, obs'd 285.0537; [α]_D²⁰ = -45 (c, 0.14 in CH₂Cl₂); IR (KBr): 3276, 2967, 2934, 2856, 1658, 1542, 1520; ¹H-NMR (300 MHz, CDCl₃): δ 0.96 (t, 3H, *J* = 7.5), 1.09 (d, 3H, *J* = 6.6), 1.35 (m, 1H), 1.61 (m, 1H), 2.25 (m, 1H), 4.43 (d, 1H, *J* = 4.9), 6.60 (d, *J* = 8.8, 2H), 7.30 (d, 2H, *J* = 8.8), 8.04 (br, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 11.3, 17.3, 25.7, 39.1, 60.9, 115.3, 122.1, 128.0, 143.7, 165.0.

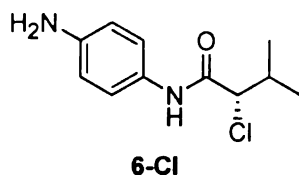


Carrier/bromocarboxylic acid conjugate 9-Br: (*S*)-2-Bromo-3-phenylpropionic acid (0.2 g, 0.8 mmol), mono-Boc-1,4-phenylenediamine (0.34 g, 1.6 mmol), EDC (0.16 g, 1.0 mmol) and DMAP (0.11 g, 1.1 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **9-Br** was purified by column chromatography (Silica gel, 20% EtOAc in

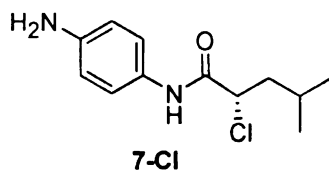
hexane) and obtained in 78% (0.21 g) yield. HRMS (Q-TOF MS (ES+)): calc'd for $C_{15}H_{15}BrN_2O$ $[M+H]^+$ $m/z = 319.0466$, obs'd 319.0468; $[\alpha]_D^{20} = -47$ (c, 0.17 in CH_2Cl_2); IR (KBr): 3284, 3231, 2924, 2834, 1678, 1617, 1516, 1257, 1169, 827, 692; 1H -NMR (300 MHz, $CDCl_3$): δ 3.35 (m, 1H), 3.62 (m, 1H), 4.60 (t, 1H, $J = 7.2$), 6.65 (d, $J = 8.8$, 2H), 7.21 (d, $J = 8.8$, 2H), 7.30 (m, 5H), 7.76 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 42.2, 62.5, 116.1, 123.0, 127.8, 129.2, 128.8, 130.5, 136.9, 144.8, 167.3.



Carrier/chlorocarboxylic acid conjugate 5-Cl: (S)-2-Chloropropionic acid (0.2 g, 1.8 mmol), mono-Boc-1,4-phenylenediamine (0.74 g, 3.6 mmol), EDC (0.35 g, 2.2 mmol) and DMAP (0.24 g, 2.2 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **5-Cl** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 75% (0.27 g) yield. HRMS (Q-TOF MS (ES+)): calc'd for $C_9H_{11}ClN_2O$ $[M+H]^+$ $m/z = 199.0638$, obs'd 199.0631; $[\alpha]_D^{20} = -11$ (c, 0.3 in CH_2Cl_2); 1H -NMR ($CDCl_3$, 300 MHz): δ 1.95 (d, 3H, $J = 7.1$), 3.64 (br, 2H), 4.60 (q, 1H, $J = 7.1$), 6.67 (d, 2H, $J = 8.8$), 7.31 (d, 2H, $J = 8.8$), 7.89 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 22.8, 56.3, 115.4, 122.1, 128.2, 143.9, 165.6.

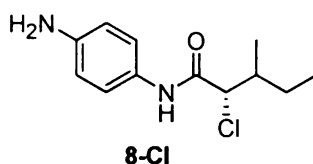


Carrier/chlorocarboxylic acid conjugate 6-Cl: (*S*)-2-Chloro-3-methylbutanoic acid (0.2 g, 1.4 mmol), mono-Boc-1,4-phenylenediamine (0.60 g, 3.2 mmol), with EDC (0.28 g, 1.6 mmol) and DMAP (0.20 g, 1.6 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **6-Cl** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 60% (0.20 g) yield. HRMS (Q-TOF MS (ES+)) $C_{11}H_{25}ClN_2O$ $[M+H]^+$ m/z = calc'd 227.0951, obs'd 227.0949; $[\alpha]_D^{20}$ = -67.7 (*c*, 4.8 in CH_2Cl_2); IR (KBr): 3420, 3284, 2966, 2925, 2878, 2848, 1657, 1611, 1546, 1517, 1464, 1428, 1269, 1240, 1169, 986, 833, 680; 1H -NMR ($CDCl_3$, 300 MHz): δ 1.01 (d, 3H, J = 6.6), 1.12 (d, 3H, J = 6.6), 2.66 (m, 1H), 4.42 (d, 1H, J = 3.3), 6.67 (d, 2H, J = 8.8), 7.31 (d, 2H, J = 8.8), 8.20 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 16.5, 20.2, 32.5, 69.0, 115.3, 122.2, 128.9, 143.9, 166.3.

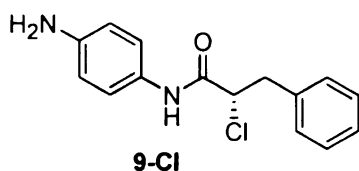


Carrier/chlorocarboxylic acid conjugate 7-Cl: (*S*)-2-Chloro-4-methylpentanoic acid (0.2 g, 1.3 mmol), mono-Boc-1,4-phenylenediamine (0.54 g, 2.6 mmol), EDC (0.25 g, 1.6 mmol) and DMAP (0.17 g, 1.6 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **7-Cl** was purified by column chromatography (Silica gel, 20% EtOAc in

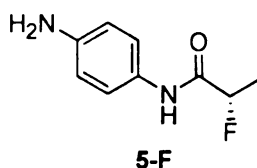
hexane) and obtained in 72% (0.23 g) yield. HRMS (Q-TOF MS (ES+)): calc'd for $C_{12}H_{17}ClN_2O$ $[M+H]^+$ m/z = 241.1108, obs'd 241.1086; $[\alpha]_D^{20}$ = -43.2 (*c*, 1.63 in CH_2Cl_2); 1H -NMR ($CDCl_3$, 300 MHz): δ 1.00 (m, 6H), 1.98 (m, 3H), 4.46 (m, 1H), 6.68 (d, 2H, J = 8.8), 7.32 (d, 2H, J = 8.8), 8.12 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 167.1, 165.5, 143.8, 128.3, 122.0, 115.4, 60.2, 44.4, 25.3, 22.9, 20.8.



Carrier/chlorocarboxylic acid conjugate 8-Cl: (*S*)-2-Chloro-3-methylpentanoic acid (0.2 g, 1.3 mmol), mono-Boc-1,4-phenylenediamine (0.54 g, 2.6 mmol), EDC (0.25 g, 1.6 mmol) and DMAP (0.17 g, 1.6 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **7-Cl** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 75% (0.24 g) yield. HRMS (Q-TOF MS (ES+)): calc'd for $C_{12}H_{17}ClN_2O$ $[M+H]^+$ m/z = 241.1108, obs'd 241.1094; $[\alpha]_D^{20}$ = -47 (*c*, 0.48 in CH_2Cl_2); IR (KBr): 3414, 3283, 3069, 2964, 2926, 2856, 1657, 1616, 1543, 1516, 1460, 1431, 1375, 1273, 1244, 1174, 983, 920, 831, 740, 677, 516; 1H -NMR ($CDCl_3$, 300 MHz): δ 0.95 (t, 3H, J = 6.7), 1.11 (d, 3H, J = 7.1), 1.35 (m, 1H), 1.53 (m, 1H), 2.39 (m, 1H), 4.45 (d, 1H, J = 3.7), 6.68 (d, 2H, J = 8.8), 7.30 (d, 2H, J = 8.8), 8.20 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 11.8, 16.9, 24.4, 39.4, 68.3, 115.7, 122.3, 128.2, 143.9, 165.3.

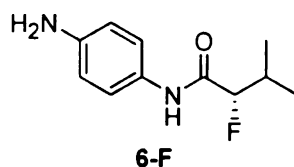


Carrier/chlorocarboxylic acid conjugates 9-Cl: (*S*)-2-Chloro-3-phenylpropionic acid (0.2 g, 1.1 mmol), mono-Boc-1,4-phenylenediamine (0.45 g, 2.2 mmol), EDC (0.20 g, 1.3 mmol) and DMAP (0.13 g, 1.3 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **9-Cl** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 71% (0.21 g) yield. HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₅H₁₅ClN₂O [M+H]⁺ m/z = 275.0951, obs'd 275.0959; [α]_D²⁰ = -29 (*c*, 0.66 in CH₂Cl₂); ir (KBr): 3366, 3284, 2960, 2926, 2855, 1662, 1611, 1518, 1428, 1251, 1175, 829, 744, 698, 516; ¹H-NMR (CDCl₃, 300 MHz): δ 3.31 (m, 1H), 3.54 (m, 1H), 4.68 (m, 1H), 6.67 (d, 2H, *J* = 8.8), 7.23 (d, 2H, *J* = 8.8), 7.98 (br, 1H), 7.32 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 41.4, 61.9, 115.3, 122.3, 127.2, 128.4, 128.0, 129.7, 136.0, 144.0, 166.32.

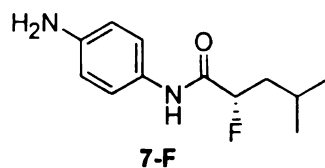


Carrier/fluorocarboxylic acid conjugates 5-F: (*S*)-2-Fluoropropionic acid (0.2 g, 2.2 mmol), mono-Boc-1,4-phenylenediamine (0.92 g, 4.4 mmol), EDC (0.40 g, 2.6 mmol) and DMAP (0.31 g, 2.6 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **5-F** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 79% (0.21 g) yield. HRMS (Q-TOF MS (ES⁺)): calc'd for C₉H₁₁FN₂O

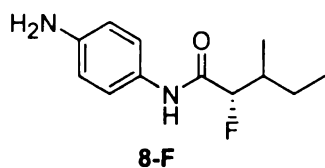
$[M+H]^+ m/z = 183.0934$, obs'd 183.0926; $[\alpha]_D^{20} = -21$ (c, 0.3 in CH_2Cl_2); IR (KBr): 3478, 3314, 3066, 2978, 2925, 1676, 1617, 1517, 1452, 1310, 1228, 1086, 851, 609; 1H -NMR ($CDCl_3$, 300 MHz): δ 1.71 (m, 3H), 3.66 (br, 2H), 5.19-5.03 (dd, 1H, $J_1 = 3.0$, $J_2 = 49$), 6.69 (d, 2H, $J = 8.8$), 7.34 (d, 2H, $J = 8.8$), 7.84 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 18.6, 18.7, 54.6, 54.7, 115.4, 121.9, 128.0, 143.8, 165.6, 165.7.



Carrier/fluorocarboxylic acid conjugates 6-F: (*S*)-2-Fluoro-3-methylbutanoic acid (0.2 g, 1.6 mmol), mono-Boc-1,4-phenylenediamine (0.66 g, 3.2 mmol), EDC (0.31 g, 2.0 mmol) and DMAP (0.27 g, 2.0 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **6-F** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 68% (0.23 g) yield. HRMS (Q-TOF MS (ES⁺)): calc'd for $C_{11}H_{15}FN_2O$ $[M+H]^+ m/z = 211.1168$, obs'd 211.1171; $[\alpha]_D^{20} = -29$ (c, 0.14 in CH_2Cl_2); 1H -NMR ($CDCl_3$, 300 MHz): δ 1.01 (d, 3H, $J = 7.1$), 1.15 (d, 3H, $J = 7.1$), 2.35-2.41 (m, 1H), 4.86 (dd, 1H, $J_1 = 3.0$, $J_2 = 49$), 6.69 (d, 2H, $J = 8.8$), 7.35 (d, 2H, $J = 8.8$), 7.81 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 15.8, 15.9, 18.2, 18.3, 30.1, 32.1, 90.4, 91.9, 120.8, 132.0, 135.3, 152.7, 168.3, 168.4.

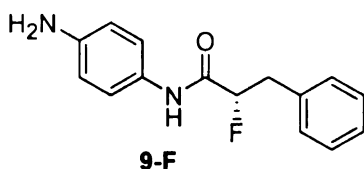


Carrier/fluorocarboxylic acid conjugates 7-F: (*S*)-2-Fluoro-4-methylpentanoic acid (0.2 g, 1.5 mmol), mono-Boc-1,4-phenylenediamine (0.62 g, 3.0 mmol), EDC (0.28 g, 1.8 mmol) and DMAP (0.22 g, 1.8 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **7-F** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 73% (0.24 g) yield. HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₂H₁₈FN₂O [M+H]⁺ *m/z* = 225.1403, obs'd 225.1447; [α]_D²⁰ = -35 (c, 0.13 in CH₂Cl₂); ¹H-NMR (CDCl₃, 300 MHz): δ 1.02 (d, 6H, *J* = 6), 1.14 (m, 2H), 2.21 (m, 2H), 4.94-5.06 (dd, 1H, *J*₁ = 5.7, *J*₂ = 41), 6.68 (d, 2H, *J* = 8.8), 7.35 (d, 2H, *J* = 8.8), 7.85 (br, 1H (NH)); ¹³C-NMR (CDCl₃, 75 MHz): δ 21.6, 23.1, 24.7, 24.8, 41.1, 41.3, 80.6, 90.5, 91.9, 119.1, 120.8, 132.0, 135.3, 152.7, 168.2, 168.4.

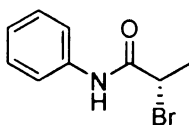


Carrier/fluorocarboxylic acid conjugates 8-F: (*S*)-2-Fluoro-3-methylpentanoic acid (0.2 g, 1.5 mmol), mono-Boc-1,4-phenylenediamine (0.62 g, 3.0 mmol), EDC (0.28 g, 1.8 mmol) and DMAP (0.22 g, 1.8 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **8-F** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 82% (0.27 g) yield. HRMS (Q-TOF MS (ES⁺)): calc'd for

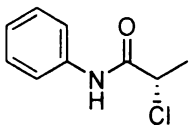
$C_{12}H_{18}FN_2O$ $[M+H]^+$ $m/z = 225.1403$, obs'd 225.1356; $[\alpha]_D^{20} = -40$ (c, 0.2 in CH_2Cl_2); IR (KBr): 3425, 3290, 2972, 2930, 2866, 1660, 1599, 1539, 1434, 1281, 1181, 1134, 1039, 833; 1H -NMR ($CDCl_3$, 300 MHz): δ 0.8-1.00 (m, 4.5 H ($\underline{CH_3}$ - CH_2 and 1.5 $\underline{CH_3}$ -CH), 1.07 (d, 1.5H, $\underline{CH_3}$ -CH, $J = 7.2$), 1.50 (s, 9H), 2.00-2.21 (complex multiplet, 1H), 4.85 (dd, 0.5H, $J_1 = 3.4$, $J_2 = 48.9$), 4.94 (dd, 0.5H, $J_1 = 2.4$, $J_2 = 49.8$), 6.53 (s, br, 1H (NH_2)), 7.31 (d, 2H, $J = 8.8$), 7.46 (d, 2H, $J = 8.8$), 7.92 (br, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 11.6, 11.7, 12.7, 12.8, 15.1, 15.2, 23.0, 25.8, 28.3, 37.1, 37.3, 37.4, 37.5, 80.6, 93.7, 95.0, 95.1, 96.6, 119.1, 120.8, 120.8, 131.9, 135.3, 152.7, 167.3, 167.5, 167.8, 167.9.



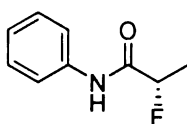
Carrier/fluorocarboxylic acid conjugates 9-F: (*S*)-2-Fluoro-3-phenylpropionic acid (0.2 g, 1.2 mmol), mono-Boc-1,4-phenylenediamine (0.50 g, 2.4 mmol), carrier (EDC (0.22 g, 1.4 mmol) and DMAP (0.18 g, 1.4 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting carrier conjugate **5-F** was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 81% (0.24 g) yield. HRMS (Q-TOF MS (ES+)): calc'd for $C_{15}H_{16}FN_2O$ $[M+H]^+$ $m/z = 259.1247$, obs'd 259.1295; $[\alpha]_D^{20} = -96$ (c, 0.27 in CH_2Cl_2); 1H -NMR ($CDCl_3/CD_3OD$, 300 MHz): δ 1.39 (s, 9H), 3.00-3.46 (m, 2H), 4.98-5.18 (dd, 1H, $J_1 = 3.6$, $J_2 = 49.2$), 7.26-7.13 (m, 9H); ^{13}C -NMR ($CDCl_3/CD_3OD$, 75 MHz): δ 28.4, 102.4, 121.8, 125.9, 127.7, 128.6, 133.6, 134.1, 152.5, 172.7.



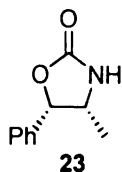
(S)-N-Phenyl-2-bromopropionamide:⁷² (S)-2-Bromopropionic acid (0.2 g, 1.3 mmol), aniline (0.36 g, 5.2 mmol), EDC (0.24 g, 1.6 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting amide was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 90% (0.34 g) yield. ¹H-NMR (CDCl₃, 300 MHz): δ 1.94 (d, 3H, J = 7.2), 4.53 (q, 1H, J = 7.2), 7.13 (t, 1H, J = 7.5), 7.33 (t, 2H, J = 8.1), 7.51 (d, 2H, J = 8.1), 8.07 (s, br, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 22.9, 45.2, 120.0, 125.0, 129.0, 137.1, 167.3.



(S)-N-Phenyl-2-chloropropionamide:^{73, 74} (S)-2-Chloropropionic acid (0.2 g, 1.8 mmol), aniline (0.51 g, 7.4 mmol), EDC (0.34 g, 2.2 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting amide was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 79% (0.26 g) yield. ¹H-NMR (CDCl₃, 300 MHz): δ 1.81 (d, 3H, J = 7.2), 4.52 (q, 1H, J = 7.2), 7.13 (t, 1H, J = 7.5), 7.33 (t, 2H, J = 8.1), 7.51 (d, 2H, J = 8.1), 8.24 (s, br, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 22.7, 56.21, 119.9, 125.0, 129.2, 136.9, 167.4.



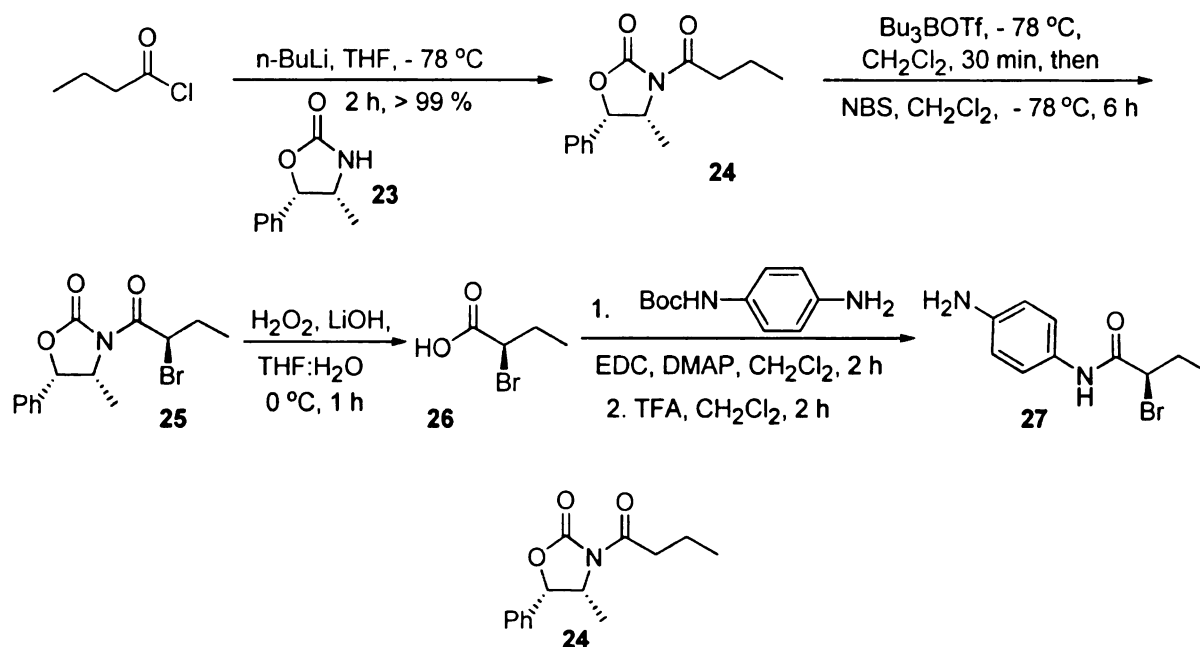
(S)-N-Phenyl-2-fluoropropionamide:⁷⁵ (S)-2-Fluoropropionic acid (0.2 g, 2.1 mmol), aniline (0.6 g, 8.7 mmol), EDC (0.4 g, 2.5 mmol) were dissolved in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature for 10 h. The resulting amide was purified by column chromatography (Silica gel, 20% EtOAc in hexane) and obtained in 78% (0.28 g) yield. ¹H-NMR (CDCl₃, 300 MHz): δ 1.94 (d, 3H, J = 7.2), 4.53 (q, 1H, J = 7.2), 7.13 (t, 1H, J = 7.5), 7.33 (t, 2H, J = 8.1), 7.51 (d, 2H, J = 8.1), 8.07 (s, br, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 22.9, 45.2, 119.9, 124.9, 129.0, 137.1, 167.3.



Synthesis of oxazolidone (23):⁵⁴ Norephedrin (25 g, 165 mmol) and diphenyl carbonate (39 g, 182 mmol) were placed in to a round bottom flask and heated neat to 110 °C for 6 hours. The reaction was cooled to room temperature and MeOH (100 mL) was added followed by dilution with dichloromethane (500 mL). Reaction mixture next was washed three times with 2 N NaOH (500 mL), 10 % HCl (500 mL) and brine (500 mL). The organic layer was dried with anhydrous sodium sulfate, filtered and reduced to a crude solid, which was mixed with dichloromethane and precipitated with hexanes to provide long white crystalline product **23** in 86% yield. ¹H-NMR (CDCl₃, 300 MHz): δ 0.77 (d, 3H, J = 6.6), 4.17 (p, 1H, J = 6.6), 5.67 (d, 1H, J = 7.8), 6.40 (s, 1H (NH)), 7.23-7.38 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 17.4, 52.3, 80.9, 125.8, 128.3, 128.4, 134.8, 159.7;

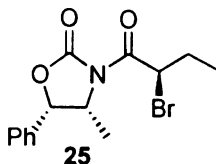
$[\alpha]_D^{20} = +167$ (c 2.2 in DCM) [literature value: $[\alpha]_D^{20} = +168$ (c 2.2 in DCM)], $ee = 99.4\%$.

Scheme II-8: Synthesis of chiral 2-bromobutaneamide / carrier conjugate (27):



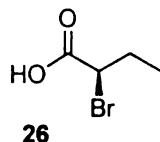
Coupling of chiral auxiliary with acid-halide (24):⁵⁴ The oxazolidone (**23**) (4 g, 22 mmol) was dissolved in dry THF (0.5 M) and cooled to $-78\text{ }^{\circ}\text{C}$. $n\text{-BuLi}$ (1.6 M in hexanes, 1.01 equiv) was added slowly until a noticeable yellow color (of the dianion) persisted. Acid chloride (1.5 equiv) was added immediately in one portion and solution was removed from ice bath, slowly warmed to room temperature (over 1 h period) and stirred for 2 h at room temperature. Reaction was quenched with 1 M K_2CO_3 (100 mL) and stirred for another 30 min and extracted with Et_2O the aqueous layer ($3 \times 100\text{ mL}$). The combined layers were dried with sodium sulfate, filtered and concentrated to the crude oil, which was chromatographed (Silica gel, 10 % EtOAc in hexane) to provide pure products **24** as a single diastereomer in $> 99\%$ yield. m. p. = $54\text{--}55\text{ }^{\circ}\text{C}$ (white

crystalline); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 0.87 (d, 3H, $J = 6.6$), 0.97 (t, 3H, $J = 7.2$), 1.2-1.75 (m, 2H), 2.80-3.01 (m, 2H), 4.70-4.78 (p, 1H, $J = 6.6$), 5.64 (d, 1H, $J = 7.2$), 7.27-7.43 (m, 5H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 13.6, 14.6, 17.7, 37.4, 54.7, 78.9, 125.6, 128.7, 128.7, 133.3, 156.1, 173.0.

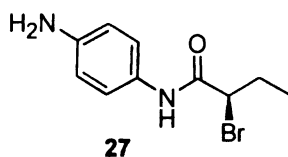


Bromination of 24:⁷⁶ To a solution of (**25**) (2d, 8 mmol) in dry dichloromethane (50 mL) at $-78\text{ }^\circ\text{C}$ was dropwise added di-*n*-butylboron triflate (9.7 mL, 9.7 mmol, 1.2 equiv, 1 M dichloromethane solution) under N_2 atmosphere. Mixture was stirred at $-78\text{ }^\circ\text{C}$ for 15 min, then for 1 h at $0\text{ }^\circ\text{C}$ and was cooled back to $-78\text{ }^\circ\text{C}$. In a separate flask dichloromethane (10 mL) was added to NBS (1.7 g 9.7 mmol, 1.2 equiv), and mixture cooled to $-78\text{ }^\circ\text{C}$. Boron enolate was then transferred fast in to the NBS flask via cannula and reaction mixture was stirred for 6 h. Reaction was then quenched with 0.5 M solution of NaHCO_3 in brine and allowed to warm to room temperature. Layers were separated, aqueous layer was extracted with dichloromethane (2 x 10 mL) and combined organic layers were washed with 0.5 M solution of $\text{Na}_2\text{S}_2\text{O}_3$ in brine, then with water, dried over anhydrous Na_2SO_4 and concentrated. Mixture was purified by column chromatography (Silica gel, 10% EtOAc in hexane) and brominated product (**25**) was separated in 72% yield as a single diastereomer (dr ~ 96%). HRMS (Q-TOF MS (ES⁺)): calc'd for $\text{C}_{14}\text{H}_{16}\text{BrNO}_3$ $[\text{M}+\text{H}]^+$ $m/z = 326.0392$, obs'd 326.0413; $[\alpha]_{\text{D}}^{20} = +16.5$ (c, 1.4 in DCM); IR (KBr): 2990, 2963, 2883, 1778, 1709, 1499, 1458, 13975, 1348, 1275, 1234, 1201, 1147, 1068, 1039, 1001, 910, 790, 765, 731, 698, 542; m. p. = $80\text{--}81\text{ }^\circ\text{C}$

(yellow crystalline); ^1H -NMR (CDCl_3 , 300 MHz): δ 0.89 (d, 3H, $J = 6.6$), 1.05 (t, 3H, $J = 6.9$), 2.03-2.18 (m, 2H), 4.81 (p, 1H, $J = 6.6$), 5.50-5.54 (dd, 1H, $J_1 = 6.3$, $J_2 = 7.2$), 5.68 (d, 1H, $J = 7.5$), 7.27-7.43 (m, 5H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 11.9; 13.5, 27.2, 46.0, 54.8, 79.0, 125.6, 128.7, 128.9, 133.0, 152.0, 168.8.



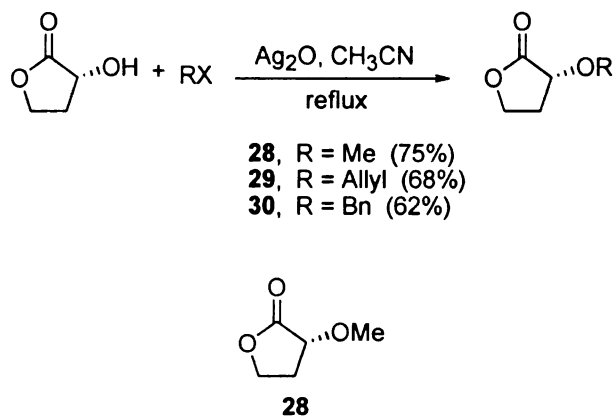
(*R*)-2-Bromobutanoic acid (26):⁵⁵ A 30% aqueous solution of hydrogen peroxide (3.4 ml, 29 mmol) and an aqueous solution of LiOH (0.35 g, 14 mmol) were added to a solution of 0.2 g (0.61 mmol) of imide **25** in THF/ H_2O (20 mL, 3:1) at 0 °C. After 1 h reaction was quenched with 1.5 M aqueous NH_4Cl and THF was removed under reduced pressure. The residue (pH = 13) was extracted with dichloromethane (3 x 10 mL). Remaining aqueous solution was acidified with 1M HCl to pH ~1 and extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give unpurified carboxylic acid as clear, colorless oil in 96% yield. ^1H -NMR spectrum showed absence of the auxiliary (~99% purity). HRMS (Q-TOF MS (ES-)): calc'd for $\text{C}_4\text{H}_7\text{BrO}_2$ $[\text{M}-\text{H}]^-$ $m/z = 164.9551$, obs'd 164.9557; $[\alpha]_{\text{D}}^{20} = +32.2$ (c, 2.5 in MeOH), [literature value $[\alpha]_{\text{D}}^{20} = +36.6$ (c, 2.74 in MeOH), literature value for the (*S*)-enantiomer $[\alpha]_{\text{D}}^{20} = +32.9$ (c, 2.50 in MeOH)⁷⁷]; IR (film): 3308, 2976, 1734, 1458, 1422, 1234, 1163, 1022, 957, 789; ^1H -NMR (CDCl_3 , 300 MHz): δ 1.03 (t, 3H, $J = 7.2$), 1.94-2.15 (complex multiplet, 2H), 4.15-4.19 (m, 1H), 11.16 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 11.7, 28.1, 47.1, 175.5.



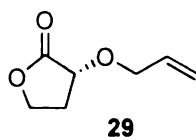
(R)-2-Bromobutanoic acid / carrier conjugate (27): Obtained carboxylic acid **26** was then coupled to the mono-N-Boc-1,4-phenylenediamine according to the general procedure described above. The mixture was purified by column chromatography (Silica gel, 10% EtOAc in hexane) to yield pure Boc-protected carrier conjugate **27** in 68% yield.

Deprotection of the amino group with 20% TFA in dichloromethane for 2 h, followed by removal of the solvent resulted in compound **27** used for ECCD studies. HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₀H₁₄BrN₂O [M+H]⁺ *m/z* = 257.0290, obs'd 257.0228; ¹H-NMR (CDCl₃, 300 MHz): δ 1.06 (t, 3H, *J* = 7.2), 2.07-2.21 (m, 2H), 4.35-4.39 (dd, 1H, *J*₁ = 5.8, *J*₂ = 7.6), 6.45 (s, 1H (NH)), 7.30 (d, 2H, *J* = 9.0), 7.41 (d, 2H, *J* = 9.0), 8.02 (s, 1H (NH)); ¹³C-NMR (CDCl₃, 75 MHz): δ 18.3, 32.4, 55.1, 115.1, 122.2, 128.9, 143.9, 166.0.

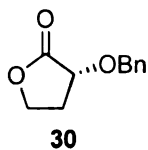
Scheme II-9: Synthesis of (R)-α-alkoxy-γ-butyrolactones



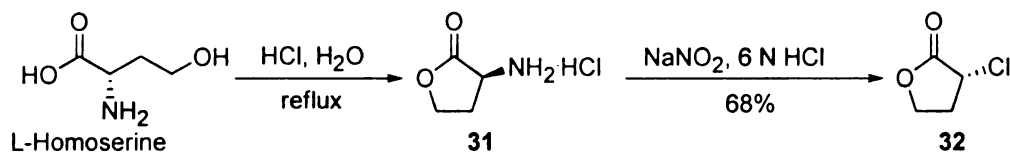
(*R*)- α -Methoxy- γ -butyrolactone (28):⁷⁸ (*R*)- α -Hydroxy- γ -butyrolactone (100 mg, 1.0 mmol), methyl iodide (0.56 g, 4 mmol) and silver oxide (0.56 g, 4 mmol) was refluxed in acetonitrile (10 mL) overnight. The precipitate was filtered away, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with 5% EtOAc in hexane) to yield compound **28** in 75% (0.12 g) yield. HRMS (Q-TOF MS (ES+)): calc'd for C₅H₉O₃ [M+H]⁺ *m/z* = 117.0552, obs'd 117.0722; [α]_D²⁰ = +43.2 (*c*, 1.04 in CH₂Cl₂); ¹H-NMR (CDCl₃, 300 MHz): δ 4.39 (m, 1H), 4.28 (m, 1H), 4.07 (m, 1H), 3.58 (s, 3H), 2.49 (m, 1H), 2.11 (m, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 172.4, 77.7, 57.3, 43.7, 25.1.



(*R*)- α -Allyloxy- γ -butyrolactone (29): (racemic compound⁷⁹) (*R*)- α -Hydroxy- γ -butyrolactone (100 mg, 1.0 mmol), allyl bromide (0.48 g, 4 mmol) and silver oxide (0.56 g, 4 mmol) was refluxed in acetonitrile (10 mL) overnight. The precipitate was filtered away, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with 5% EtOAc in hexane) to yield compound **29** in 68% (0.10 g) yield. HRMS (Q-TOF MS (ES+)): calc'd for C₇H₁₁O₃ [M+H]⁺ *m/z* = 143.0708, obs'd 143.0723; ¹H-NMR (CDCl₃, 300 MHz): δ 2.12 (m, 1H), 2.39 (m, 1H), 4.38-4.06 (m, 5H), 5.15 (m, 2H), 5.79 (m, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 29.3, 65.0, 70.8, 72.3, 117.7, 133.3, 174.7.



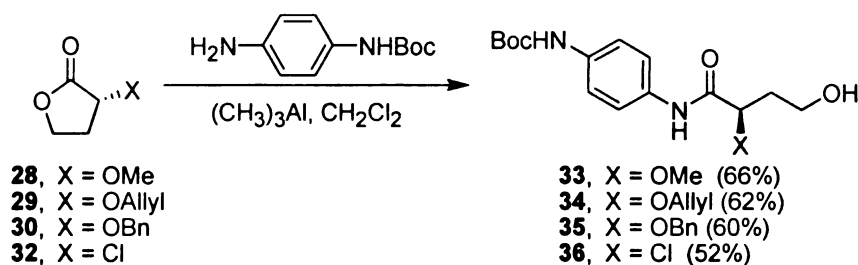
(R)-α-Benzoyloxy-γ-butyrolactone (30):⁸⁰ (R)-α-Hydroxy-γ-butyrolactone (100 mg, 1.0 mmol), benzyl bromide (0.68 g, 4 mmol) and silver oxide (0.56 g, 4 mmol) were refluxed in acetonitrile (10 mL) overnight. The precipitate was filtered away, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (Silica gel, eluted with 5% EtOAc in hexane), to yield compound **30** in 62% (0.11 g). HRMS Q- (TOF MS (ES⁺)): calc'd for C₁₁H₁₃O₃ [M+H]⁺ *m/z* = 193.0865, obs'd 193.0882; [α]_D²⁰ = +72 (c, 12.2 in CH₂Cl₂) [literature value for the enantiomer [α]_D²⁰ = -100.3 (c, 1.19 in CHCl₃)⁸⁰]; IR (KBr): 3065, 3032, 2924, 2858, 1782, 1606, 1496, 1454, 1337, 1344, 1221, 1176, 1138, 1020, 949, 746, 689, 516; ¹H-NMR (CDCl₃, 300 MHz): δ 2.23 (m, 1H), 2.41 (m, 1H), 4.16 (m, 2H), 4.36 (m, 1H), 4.70 (d, 1H, *J* = 11.5), 4.90 (d, 1H, *J* = 11.5), 7.34 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ 29.5, 65.1, 71.8, 72.7, 127.7, 128.2, 133.6, 174.7.



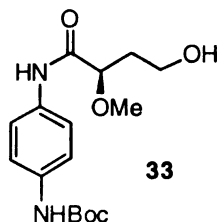
Synthesis of α-chloro-γ-butyrolactone (32):^{81, 82} To a vigorously stirred solution of homoserine (137 mg, 1 mmol) in 6 N HCl (3 mL) at 0 °C was added sodium nitrite in small portions. This mixture was stirred for 4 h at 0 °C and then extracted with CH₂Cl₂ (3 × 25 mL). The combined extracts were dried over anhydrous Na₂SO₄ and solvent was removed under reduced pressure. The residue was purified by column chromatography

(Silica gel, 5% EtOAc in hexane) and provided the pure title compound **32** in 68% yield.

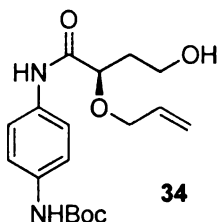
HRMS (Q-TOF MS (ES+)): calc'd for $C_4H_6ClO_2$ $[M+H]^+$ m/z = 121.0056, obs'd 121.0036; $[\alpha]_D^{20}$ = -8.2 (c, 1.5 in CH_2Cl_2); IR (KBr): 2981, 2924, 1782, 1376, 1215, 1167, 1020, 931, 890, 696, 607; 1H -NMR ($CDCl_3$, 300 MHz): δ 2.46 (m, 1H), 2.75 (m, 1H), 4.38 (m, 2H), 4.51 (m, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 33.0, 50.12, 66.4, 172.6.



General procedure for the synthesis of amides:⁴⁸ To a solution of mono-Boc-protected carrier (1.5 equiv) in anhydrous dichloromethane at room temperature was added trimethyl aluminum (2.0 N in hexane, 1.6 equiv) dropwise, under nitrogen. The resulting mixture was stirred for 15 min, then the α -chiral butyrolactone (1 equiv) in dry THF was added slowly and the mixture was refluxed for 3 h. The reaction was then cooled to room temperature and quenched with aqueous citric acid (2 N, 2 mL), glycerin (5 drops) and saturated aqueous potassium sodium tartrate (10 mL). The mixture was stirred for another 6 h. The reaction mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extract were dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to yield the pure amides **33-36**.

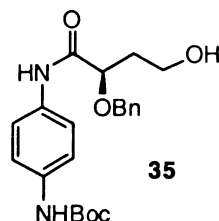


(R)-tert-Butyl 4-(4-hydroxy-2-methoxybutanamido)phenylcarbamate (33): Yield: 66%; HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₆H₂₅N₂O₅ [M+H]⁺ *m/z* = 325.1763, obs'd 325.1770; [α]_D²⁰ = +55 (*c*, 0.69 in CH₂Cl₂); IR (KBr): 3438, 3362, 3292, 2997, 2936, 2876, 1695, 1658, 1606, 1525, 1406, 1313, 1244, 1161, 1118, 1057, 941, 904, 829, 767, 646, 518; m. p. = 160-161 °C; ¹H-NMR (CDCl₃, 300 MHz): δ 1.49 (s, 9H), 2.04 (m, 2H), 3.28 (s, 1H (OH)), 3.48 (s, 3H), 3.77 (m, 2H), 3.88 (dd, 1H, *J*₁ = 6.6, *J*₂ = 1.2), 6.62 (br, 1H), 7.31 (d, 2H, *J* = 8.2), 7.46 (d, 2H, *J* = 8.2), 8.33 (br, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 28.3, 29.7, 34.9, 58.7, 59.7, 80.6, 81.3, 119.1, 120.5, 120.6, 132.2, 135.1, 152.7, 170.3.

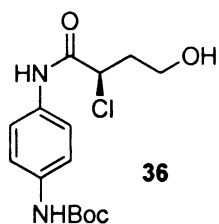


(R)-tert-Butyl 4-(2-(allyloxy)-4-hydroxybutanamido)phenylcarbamate (34): Yield: 62%; HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₈H₂₇N₂O₅ [M+H]⁺ *m/z* = 351.1920, obs'd 351.1851; [α]_D²⁰ = +59 (*c*, 2.3 in CH₂Cl₂); IR (KBr): 3362, 3308, 3090, 2984, 2930, 2878, 1697, 1664, 1611, 1525, 1048, 1310, 1244, 1163, 1057, 927, 831, 768, 645; m. p. = 124-125 °C; ¹H-NMR (CDCl₃, 300 MHz): δ 1.49 (s, 9H), 2.01-2.08 (q, 2H, *J* = 5.7), 2.25 (br, 1H (OH)), 3.76-3.40 (m, 2H), 4.07 (t, 1H, *J* = 6.3), 4.13 (d, 2H, *J* = 5.2), 5.24-5.37 (dd, 2H, *J*₁ = 15.9, *J*₂ = 8.7), 5.87-6.00 (m, 1H), 6.53 (br, 1H (NH)), 7.27 (d, 2H, *J* = 8.8),

7.40 (d, 2H, $J = 8.8$), 8.35 (br, 1H (NH)); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 28.0, 35.2, 58.7, 71.6, 77.8, 80.0, 118.2, 118.9, 120.4, 131.8, 133.1, 134.9, 152.6, 170.7.

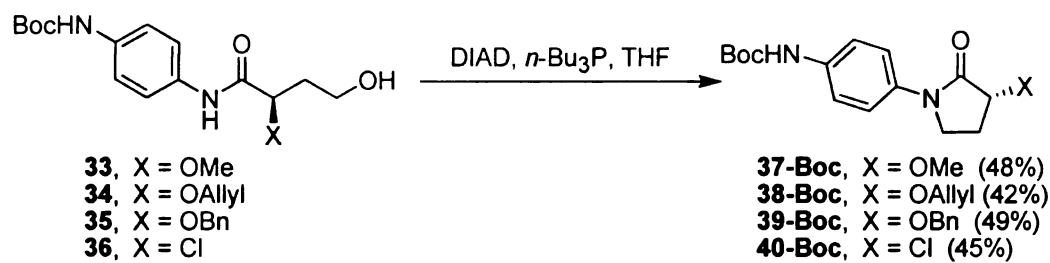


(*R*)-tert-Butyl 4-(2-(benzyloxy)-4-hydroxybutanamido)phenylcarbamate (35): Yield: 60%; HRMS (Q-TOF MS (ES+)) $[\text{M}+\text{H}]^+$: calc'd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ $m/z = 401.2076$, obs'd 401.2278; $[\alpha]_{\text{D}}^{20} = +48.3$ (c, 0.56 in CH_2Cl_2); IR (KBr): 3358, 3302, 2926, 2855, 1697, 1664, 1611, 1527, 1406, 1309, 1246, 1163, 1055, 829, 698; m. p. = 131-132 °C; ^1H -NMR (CDCl_3 , 300 MHz): δ 1.49 (s, 9H), 2.05 (m, 2H), 2.62 (br, 1H), 3.76 (t, 2H, $J = 6.4$), 4.13 (t, 1H, $J = 6.0$), 4.62 (s, 2H), 6.62 (br, 1H), 7.34 (m, 9H), 8.37 (br, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 28.0, 35.3, 59.1, 73.1, 78.5, 80.3, 118.7, 120.4, 127.8, 128.2, 128.5, 131.9, 134.7, 136.1, 152.5, 170.5.

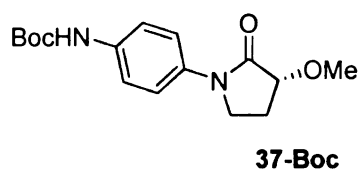


(*R*)-tert-Butyl 4-(2-chloro-4-hydroxybutanamido)phenylcarbamate (36): Yield: 52%; HRMS (Q-TOF MS (ES+)): calc'd for $\text{C}_{15}\text{H}_{22}\text{ClN}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ $m/z = 329.1268$, obs'd 329.1255; $[\alpha]_{\text{D}}^{20} = +14$ (c, 0.9 in CH_2Cl_2); IR (KBr): 3343, 3314, 2978, 2930, 1698, 1644, 1611, 1532, 1517, 1405, 1387, 1251, 1163, 1063, 827, 762, 639; $m_p = 182$ -184 °C (yellow flakes); ^1H -NMR (CDCl_3 , 300 MHz): δ 1.51 (s, 9H), 2.09-2.20 (m, 1H), 2.29-

2.40 (m, 1H), 3.06 (s, 1H (OH)), 3.80 (t, 2H, $J = 5.1$), 4.60-4.65 (dd, 1H, $J_1 = 8.7$, $J_2 = 3.3$), 7.24 (br, 1H (NH)), 7.33 (d, 2H, $J = 8.8$), 7.48 (d, 2H, $J = 8.8$), 9.06 (br, 1H (NH)); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 28.0, 37.4, 48.6, 56.7, 57.9, 118.9, 120.8, 132.0, 135.2, 153.0, 167.5.

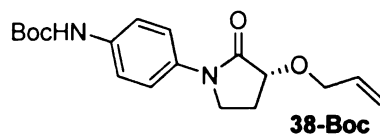


Synthesis of chiral butyrolactams: Tri-*n*-butylphosphine (1.1 equiv) was added to a solution of DIAD (1.1 equiv) in dry THF at room temperature. The resulting mixture was stirred for 5 min and added dropwise to a solution of chiral amide (1 equiv) in THF at 0 °C under nitrogen. The reaction mixture was allowed to warm slowly to room temperature and was stirred overnight. The reaction was quenched with saturated NaHCO_3 (5 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic extract were dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to yield the Boc-protected lactams **37-40**.

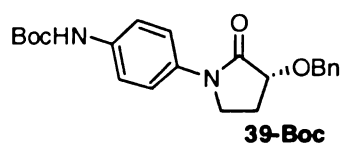


N-Boc-(R)- 2-OMe-butyrolactam/carrier conjugate (37-Boc): Yield: 48%; HRMS (Q-TOF MS (ES+)): calc'd for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ $m/z = 307.1658$, obs'd 307.1588; $[\alpha]_{\text{D}}^{20} = +36$ (c, 0.13 in CH_2Cl_2); IR (KBr): 2934, 2856, 1691, 1619, 1518, 1307, 1228, 833;

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.49 (s, 9H), 2.04 (m, 1H), 2.45 (m, 1H), 3.57 (s, 3H), 3.71 (m, 2H), 4.05 (t, 1H, $J = 7.7$), 6.57 (br, 1H), 7.33 (d, 2H, $J = 8.8$), 7.52 (d, 2H, $J = 8.8$); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 25.9, 28.3, 45.0, 71.4, 78.8, 80.5, 118.8, 120.6, 134.3, 135.3, 152.7, 158.0.

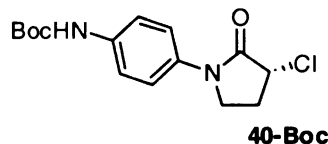


N-Boc-(*R*)-2-Oallyl-butylolactam/carrier conjugate (38-Boc): Yield: 42%; HRMS (Q-TOF MS (ES⁺)): calc'd for $\text{C}_{18}\text{H}_{24}\text{NaN}_2\text{O}_4$ [$\text{M}+\text{Na}$]⁺ $m/z = 355.1634$, obs'd 355.1588; $[\alpha]_{\text{D}}^{20} = +7.2$ (c, 1.0 in CH_2Cl_2); IR (KBr): 3308, 3255, 2922, 2849, 1701, 1616, 1516, 1456, 1402, 1313, 1265, 1228, 1130, 1068, 1028, 929, 835, 736, 702, 524; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 2.06 (m, 1H), 2.44 (m, 1H), 3.87-3.60 (m, 2H), 4.20 (m, 2H), 4.43 (m, 1H), 5.26 (m, 2H), 5.96 (m, 1H), 6.66 (d, 2H, $J = 8.8$), 7.35 (d, 2H, $J = 8.8$); $^{13}\text{C-NMR}$ (CDCl_3 , 75MHz): δ ;



N-Boc-(*R*)-2-OBn-butylolactam/carrier conjugate (39-Boc): Yield: 49%; HRMS (Q-TOF MS (ES⁺)): calc'd for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}$]⁺ $m/z = 383.1971$, obs'd 383.1910; $[\alpha]_{\text{D}}^{20} = +30.1$ (c, 1.4 in CH_2Cl_2); IR (KBr): 3484, 3449, 2936, 2860, 1699, 1462, 1210, 1140, 851, 599; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.47 (s, 9H), 2.12 (m, 1H), 2.35 (m, 1H), 3.62-3.87 (m, 2H), 4.20 (t, 1H, $J = 7.7$), 4.79 (d, 1H, $J = 12.1$), 4.99 (d, 1H, $J = 12.1$), 6.65 (d,

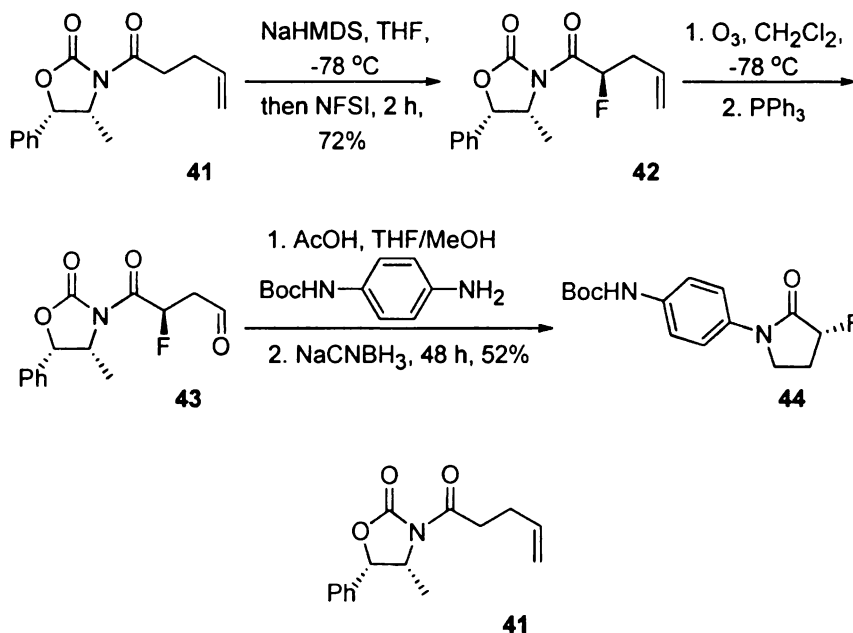
2H, $J = 8.8$), 7.36 (m, 7H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 26.4, 28.3, 45.1, 72.1, 76.4, 80.6, 118.8, 120.5, 127.8, 128.1, 128.4, 128.5, 134.3, 135.2, 137.7, 152.7, 171.7.



N-Boc-(*R*)-2-chloro-butyrolactam/carrier conjugate (40-Boc): Yield: 45%; HRMS (Q-TOF MS (ES⁺)): calc'd for $\text{C}_{15}\text{H}_{19}\text{ClN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ $m/z = 311.1162$, obs'd 311.1133; $[\alpha]_{\text{D}}^{20} = -20.1$ (c , 1.37 in CH_2Cl_2); m.p. = 182-184 °C; IR (KBr): 3468, 3234, 2964, 2930, 1693, 1452, 1190, 1022, 906, 866, 856, 601; ^1H -NMR (CDCl_3 , 300 MHz): δ 1.49 (s, 9H), 2.30-2.37 (m, 1H), 2.64-2.71 (m, 1H), 3.74-3.82 (m, 1H), 3.91-3.99 (m, 1H), 4.51 (dd, 1H, $J_1 = 2.7$, $J_2 = 7.8$), 6.57 (br, 1H), 7.35 (d, 2H, $J = 8.8$), 7.51 (d, 2H, $J = 8.8$); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 28.3, 29.5, 46.2, 56.1, 80.4, 118.9, 120.8, 133.8, 135.7, 152.7, 168.8.

The Boc-group was removed by a lactam stirring overnight in TFA/ CH_2Cl_2 (1:4) at room temperature. The solvent was then removed by purging nitrogen. The residue was dissolved in CH_2Cl_2 , and anhydrous Na_2CO_3 (20 mg) was added. This solution was stirred at room temperature for an hour, and the Na_2CO_3 was filtered off. The solvent was evaporated under reduced pressure to provide deprotected lactams that were used directly for the ECCD studies.

Synthesis of (*R*)-2-fluoro- γ -butyrolactam:



Coupling of chiral auxiliary with acid-halide (41**):**⁵⁴ The oxazolidone (**23**) (4 g, 22 mmol) was dissolved in dry THF (0.5 M) and cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 1.01 equiv) was added slowly until a noticeable yellow color (of the dianion) persisted. Acid chloride (1.5 equiv) was added immediately in one portion and solution was removed from ice bath, slowly warmed to room temperature (over 1 h period) and stirred for 2 h at room temperature. Reaction was quenched with 1 M K₂CO₃ (100 mL) and stirred for another 30 min and extracted with Et₂O the aqueous layer (3 × 100 mL). The combined layers were dried with anhydrous sodium sulfate, filtered and concentrated to the crude oil, which was purified by column chromatography (Silica gel, 10% EtOAc in hexane) to provide the products **41** in > 99% yield. HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₅H₁₈NO₃ [M+H]⁺ *m/z* = 260.1287, obs'd 260.1312; m. p. = 65-66 °C (white crystals); ¹H-NMR (CDCl₃, 300 MHz): δ 0.87 (d, 3H, *J* = 6.6), 0.97 (t, 3H, *J* = 7.2), 1.2-1.75 (m, 2H), 2.80-3.01 (m, 2H), 4.70-4.78 (p, 1H, *J* = 6.6), 5.64 (d, 1H, *J* = 7.2), 7.27-

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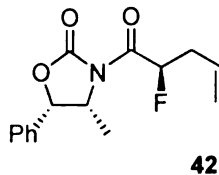
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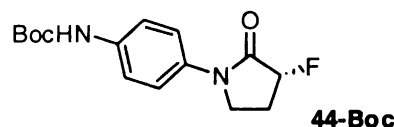
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7.43 (m, 5H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 13.6, 14.6, 17.7, 37.4, 54.7, 78.9, 125.6, 128.7, 128.7, 133.3, 156.1, 173.0.



(4*R*, 5*S*)-3-((*R*)-2-Fluoropent-4-en-1-yl)-4-methyl-5-phenyloxazolidin-2-one (42):⁸³ To a solution of **41** (1.5 g, 5.75 mmol) in dry THF (50 mL) at $-78\text{ }^{\circ}\text{C}$ was dropwise added NaHMDS (6.4 mL, 6.4 mmol, 1.1 equiv, 1 M solution in THF) under N_2 atmosphere. After 45 min enolate was transferred into $-78\text{ }^{\circ}\text{C}$ solution of NFSi in THF (10 mL) via cannula and reaction stirred for 2 h at $-78\text{ }^{\circ}\text{C}$. Reaction was then quenched with saturated solution of NH_4Cl and allowed to warm to room temperature. Mixture was extracted with EtOAc (3 x 50 mL), extracts were combined, dried over anhydrous Na_2SO_4 and concentrated. Purification with column chromatography (5% EtOAc in hexane) afforded fluorinated compound **42** as a single diastereomer (de > 98%) in 72% yield. HRMS (Q-TOF MS (ES $^{+}$)): calc'd for $\text{C}_{15}\text{H}_{17}\text{FNO}_3$ $[\text{M}+\text{H}]^{+}$ m/z = 278.1114, obs'd 278.1231; ^1H -NMR (CDCl_3 , 300 MHz): δ 0.99 (d, 3H, J = 4.5), 2.63-2.81 (m, 2H), 4.80 (p, J = 6.6), 5.29-5.22 (m, 2H, $\text{CH}=\underline{\text{CH}_2}$), 5.76 (d, 1H, J = 7.2), 5.87-6.01 (m, 1.5H ($\text{CH}\underline{\text{F}}$ and $\text{CH}=\text{CH}_2$)), 6.12-6.16 (dd, 0.5 H ($\text{CH}\underline{\text{F}}$, J_1 = 4.2, J_2 = 7.2), 7.29-7.49 (m, 5H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.3, 36.6, 36.9, 55.1, 80.0, 87.1, 89.6, 115.6, 119.3, 127.7, 128.7, 129.6, 131.1, 131.1, 132.6, 134.3, 152.5, 168.8, 169.1.

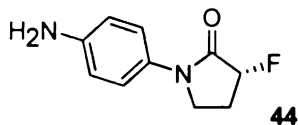
Ozonization procedure:⁸⁴ Ozonolysis of **42** (2 g, 7.2 mmol) was carried out in round bottom flask at -78 °C (dry ice/acetone) in dry CH₂Cl₂ (60 mL). Ozone was generated by a laboratory ozonator using commercial-grade oxygen as a source. [Voltage setting (90 V), pressure (5.5-6 lb./in.²) and flow rates (0.3 ft.³/min)]. The completion of reaction was detected by the appearance of intense blue color in the reaction solution. The reaction mixture was flushed with nitrogen for 10-15 min at -78 °C and solution of PPh₃ (1.1 equiv) in CH₂Cl₂ (10 mL) was added. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was concentrated and diluted with CH₂Cl₂ (5 mL). The solution was triturated with hexane and phosphine oxide was precipitated and filtered off. The filtrate was concentrated under reduced pressure and the obtained aldehyde was submitted to the cyclization without further purification.



Reductive amination / cyclization⁵² - **(R)-2-Fluoro butyrolactam (44-Boc)**: Obtained from the ozonolysis aldehyde **43** (0.3 g, 0.107 mmol) was added in to round-bottomed flask and dissolved in the THF/MeOH (1:1) mixture and cooled to 0 °C under N₂ atmosphere. To this solution mono-Boc-protected 1,4-phenylenediamine (0.67 g, 3.22 mmol) followed by acetic acid (0.2 g, 3.22 mmol) were added and the reaction mixture was stirred at 0 °C for 10 min. NaCNBH₃ (0.27 g, 4.3 mmol) was added to the reaction mixture, which was allowed to warm to and stir at room temperature during 24 h period. Another portion of NaCNBH₃ (0.47 g, 4.3 mmol) was then added and the reaction mixture was stirred for 48 h. The reaction was then quenched with H₂O and extracted

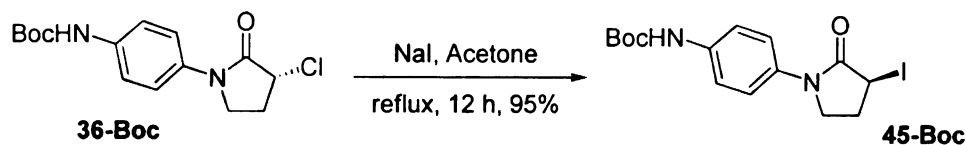
with EtOAc (3 x 50 mL). The combined layers were washed with aqueous NaHCO₃ (2 x 100 mL) and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was dissolved in dichloromethane and extracted ones with 10% HCl (5-7 mL) (purified from unreacted amine), washed with water and brine, dried with anhydrous Na₂SO₄ and concentrated to the crude oil which then crystallized. ¹H-NMR of this fraction showed presence of the lactam, cleaved chiral auxiliary and non-cyclized secondary amine. No carrier was detected. Resulted mixture was purified by column chromatography (Silica, 20% EtOAc in hexane) to afford lactam **44-Boc** in 52% yield. HRMS (Q-TOF MS (ES+)): calc'd for C₁₅H₂₀FN₂O₃ [M+H]⁺ *m/z* = 295.1458, obs'd 295.1451; ¹H-NMR (CDCl₃, 300 MHz): δ 1.49 (s, 9H), 2.28-2.41 (m, 1H), 2.56-2.59 (m, 1H), 3.71-3.80 (m, 1H), 3.84-3.92 (m, 1H), 5.07-5.12 (dd, 0.5H (HC-F), *J*₁ = 7.8, *J*₂ = 1.2), 5.24-5.29 (dd, 0.5H (HC-F), *J*₁ = 7.8, *J*₂ = 0.6), 6.47 (s, 1H (NH)), 7.36 (d, 2H, *J* = 5.4), 7.56 (d, 2H, *J* = 5.4); ¹³C-NMR (CDCl₃, 75 MHz): δ 25.9, 26.1, 28.3, 44.6, 80.1, 88.5, 90.0, 118.9, 119.7, 120.7, 133.7, 135.9, 157.8, 167.4, 167.5.

Deprotection of the primary amine with TFA in dichloromethane afforded lactam **44**.



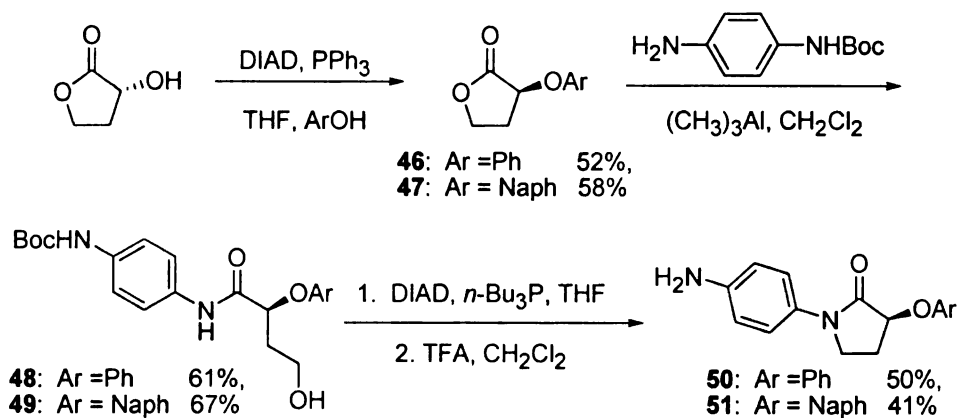
¹H-NMR (CDCl₃, 300 MHz): δ 2.26-2.36 (m, 1H), 2.56-2.60 (m, 1H), 3.71-3.80 (m, 1H), 3.65 (s, 2H (NH₂)), 3.69-3.75 (m, 1H), 3.82-3.86 (m, 1H), 5.17 (t, 0.5H (HC-F), *J* = 6.0), 5.22 (t, 0.5H (HC-F), *J* = 6.0), 6.67 (d, 2H, *J* = 9.0), 7.37 (d, 2H, *J* = 9.0); ¹³C-NMR (CDCl₃, 75 MHz): δ 28.3, 44.6, 88.5, 90.0, 116.9, 120.3, 121.1, 134.6, 172.2, 172.3.

Synthesis of (S)-2-iodo- γ -butyrolactam:

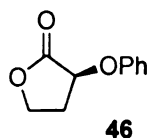


To a solution of **36-Boc** (0.05 g, 0.16 mmol) in acetone (5 mL) was added NaI (0.072 g, 0.48 mmol) and mixture was stirred at reflux for 12 h. Solvent was then removed and crude mixture was dissolved in dichloromethane. The organic solution was washed with water, dried over anhydrous sodium sulfate and concentrated to give the title lactam **45-Boc** in 95% (0.062 g) yield. HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₅H₂₀IN₂O₃ [M+H]⁺ *m/z* = 403.0519; obs'd 403.0529; [α]_D²⁰ = +14.3 (c, 0.36 in CH₂Cl₂); ¹H-NMR (CDCl₃, 300 MHz): δ 1.47 (s, 9H), 2.12 (m, 1H), 2.35 (m, 1H), 3.64-3.71 (m, 1H), 3.82-3.90 (m, 1H), 4.68-4.71 (dd, 1H, *J*₁ = 1.8, *J*₂ = 6.9), 6.56 (s, br, 1H (NH)), 7.33-7.36 (d, 2H, *J* = 8.8), 7.50-7.53 (d, 2H, *J* = 8.8); ¹³C-NMR (CDCl₃, 75 MHz): δ 20.8, 20.9, 28.3, 31.4, 47.5, 47.6, 80.7, 119.0, 120.7, 120.9, 134.3, 135.6, 152.7, 171.2.

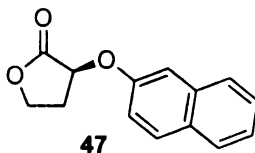
Scheme II-9: Synthesis of (S)- α -aryloxybutyrolactams



General procedure for the synthesis of (*S*)- α -aryloxy- γ -butyrolactones: Aromatic alcohol (1 equiv), (*R*)- α -hydroxy- γ -butyrolactone (1 equiv) and PPh₃ (2 equiv) were dissolved in dry THF. To this solution at 0 °C was added DIAD (2 equiv) dropwise via syringe and mixture was allowed to warm to room temperature and stirred for 6 h. The reaction was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂ (2 x 50 mL). Combined extracts were dried over anhydrous Na₂SO₄ and filtered. Solvent was removed under reduced pressure and the concentrate was purified by column chromatography (Silica gel, 10% EtOAc in hexane).



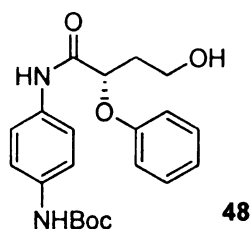
(*S*)- α -Phenoxy- γ -butyrolactone (46): (synthesis of racemic substrate available⁸⁵) Yield: 52%; MS (DCI): calc'd for C₁₀H₁₀O₃ m/z = 178.06, obs'd 178.2; IR (KBr): 3142, 2924, 1788, 1597, 1495, 1385, 1354, 1242, 1172, 1099, 1020, 991, 949, 895, 754, 692, 587; ¹H-NMR (CDCl₃, 300 MHz): δ 2.35-2.42 (m, 1H), 2.63-2.70 (m, 1H), 4.26-4.32 (dq, 1H, J_1 = 1.5, J_2 = 7.0), 4.43-4.47 (dq, 1H, J_1 = 3.5, J_2 = 8.0), 4.92 (t, 1H, J = 7.5), 7.02-7.05 (m, 3H), 7.26-7.30 (m, 2H); ¹³C-NMR (CDCl₃, 75 MHz): δ 29.6, 65.2, 72.3, 115.8, 122.2, 129.5, 157.2, 173.5.



(*S*)- α -[2-Naphthyloxy]- γ -butyrolactone (47): (synthesis of racemic substrate available⁸⁶) Yield: 58%; MS (DCI): calc'd for C₁₄H₁₂O₃ m/z = 228.07, obs'd 228.2; IR (KBr): 2989,

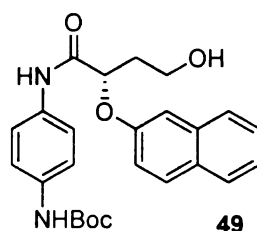
2942, 2878, 1717, 1522, 1387, 1246, 1104; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 2.38-2.49 (m, 1H), 2.72-2.77 (m, 1H), 4.31-4.36 (m, 1H), 4.47-4.51 (m, 1H), 5.04-5.07 (t, 1H, $J = 8.0$), 4.90 (d, 1H, $J = 19.1$), 7.18 (d, 1H $J = 8.5$), 7.28 (s, 1H), 7.32 (t, 1H, $J = 7.0$), 7.68-7.73 (m, 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 29.6; 65.3, 69.9, 72.3, 124.3, 126.3, 126.9, 127.6, 129.5, 129.7, 173.4.

General procedure for the synthesis of amides: To a solution of mono-Boc-1,4-phenylenediamine (carrier) (1.5 equiv) in anhydrous CH_2Cl_2 (5 mL) at room temperature was added trimethylaluminum (2 N in hexane, 1.6 equiv) dropwise under nitrogen. The resulting mixture was stirred for 15 min, then the chiral α -aryloxybutyrolactone (1 equiv) in CH_2Cl_2 (2 mL) was added slowly and stirring was continued at room temperature overnight. The reaction was quenched with aqueous citric acid (2 N, 2 mL), glycerin (5 drops) and saturated aqueous potassium sodium tartrate (10 mL), and kept stirring for another 6 h. The reaction mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extract were dried over anhydrous Na_2SO_4 , and concentrated. The residue was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to yield the pure amides **48** and **49**.



(S)- α -Phenoxy- γ -butaneamide (48): Yield: 61%; MS (DCI): calc'd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5$ m/z = 386.18, obs'd 387.4 $[\text{M}+\text{H}]^+$; $[\alpha]_{\text{D}}^{20} = -24.6$ (c, 0.5 in CH_2Cl_2); IR (KBr): 3366, 3306,

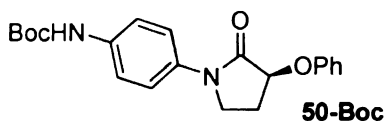
2980, 2928, 2885, 1697, 1653, 1597, 1523, 1315, 1230, 1167, 1070, 1041, 831, 758, 646, 515; m. p. = 176-178 °C (white flakes); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.49 (s, 9H), 2.14-2.20 (q, 2H, J = 6.0), 2.32 (br, 1H), 3.75-3.81 (q, 2H, J = 6.0), 4.85 (t, 1H, J = 6.6), 6.47 (br, 1H), 6.93-7.00 (m, 3H), 7.23-7.29 (m, 4H), 7.39 (d, 2H, J = 8.8), 8.31 (br, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 28.3, 35.8, 49.2, 58.4, 115.6, 119.0, 119.0, 121.0, 122.5, 129.9, 157.0, 170.4.



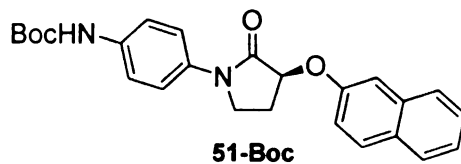
(S)- α -[2-Naphthyloxy]-butaneamide (49): Yield: 67%; MS (DCI): m/z 436; $[\alpha]_{\text{D}}^{20}$ = -28 (c , 0.19 in CH_2Cl_2); IR (KBr): 3366, 3302, 2984, 2954, 2936, 2833, 1695, 1658, 1599, 1523, 1493, 1316, 1230, 1165, 1975, 1039, 833, 758, 698, 515; m. p. = 175 °C (white flakes); $^1\text{H-NMR}$ ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 300 MHz): δ 1.49 (s, 9H), 2.23-2.30 (q, 2H, J = 6.3), 2.72 (br, 1H), 3.83-3.88 (q, 2H, J = 5.1), 4.98 (t, 1H, J = 6.0), 6.60 (br, 1H), 7.22-7.30 (m, 4H), 7.73-7.46 (m, 4H), 7.71 (d, 1H, J = 7.5), 7.78 (t, 2H, J = 6.3), 8.53 (br, 1H); $^{13}\text{C-NMR}$ ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 75 MHz): δ 28.3, 35.9, 58.2, 80.2, 109.0, 118.3, 118.8, 118.9, 119.1, 121.1, 124.5, 126.7, 127.1, 127.6, 129.6, 130.0, 131.7, 133.2, 135.1, 154.9, 170.4.

General procedure for the synthesis of chiral butyrolactams: Tri-*n*-butylphosphine (1.1 equiv) was added to a solution of DIAD (1.1 equiv) in dry THF (2 mL) at room temperature. The resulting mixture was stirred for 5 min and added dropwise to a solution of chiral amide (1 equiv) in THF (1 mL) at 0 °C under nitrogen. The reaction

mixture was allowed to warm slowly to room temperature and stirred overnight. The reaction was quenched with saturated NaHCO₃ (5 mL) and extracted with CH₂Cl₂ (2 × 10 mL). The combined organic extract were dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 10% EtOAc in hexane) to yield the Boc-protected lactam as a white solid.



N-Boc-(S)-α-Phenoxy-γ-butyrolactam (50-Boc): Yield: 50%; HRMS (Q-TOF MS (ES⁺)): calc'd for C₂₁H₂₄IN₂NaO₄ [M+Na]⁺ 391.1634, obs'd 391.1627; [α]_D²⁰ = -55.4 (c, 0.7 in CH₂Cl₂); ¹H-NMR (CDCl₃, 500 MHz): δ 1.49 (s, 9H), 2.22-2.30 (m, 1H), 2.60-2.67 (m, 1H), 3.77-3.82 (m, 1H), 3.85-3.88 (m, 1H), 4.99 (t, 1H, *J* = 7.5), 6.50 (br, 1H), 6.79 (t, 1H, *J* = 7.0), 7.05 (d, 2H, *J* = 9.0), 7.27 (t, 1H, *J* = 8.0), 7.36 (d, 1H, *J* = 8.5), 7.58 (d, 2H, *J* = 9.0); ¹³C-NMR (CDCl₃, 125 MHz): δ 26.3, 28.3, 29.7, 45.0, 76.2, 80.6, 116.0, 118.9, 120.6, 121.8, 129.5, 134.2, 135.5, 152.7, 157.9, 169.9.



N-Boc-(S)-α-[2-Naphthyloxy]-γ-butyrolactam (51-Boc): Yield: 41%; HRMS (Q-TOF MS (ES⁺)): calc'd for C₂₅H₂₇IN₂O₄ [M+H]⁺ 419.1971, obs'd 419.1955. ¹H-NMR (CDCl₃, 500 MHz): δ 1.49 (s, 3H), 2.23 (m, 1H), 2.71-2.78 (m, 1H), 3.83-3.88 (m, 1H), 3.90-3.95 (dt, 1H, *J*₁ = 4.0, *J*₂ = 10.0), 5.15 (t, 1H, *J* = 7.0), 6.42 (s, br, 1H (NH)), 7.26 (d, 1H, *J* = 8.0), 7.31-7.43 (complex multiplet, 4H), 7.62 (d, 1H, *J* = 7.0), 7.71-7.76

(20)

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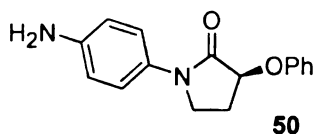
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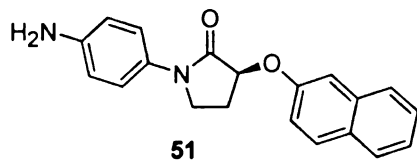
fo

(complex multiplet, 3H); ^{13}C NMR: δ 14.1, 28.4, 45.0, 80.1, 92.6, 105.9, 118.7, 121.7, 124.1, 126.7, 126.9, 129.3, 129.5, 129.6, 131.6, 133.6, 135.2, 157.3, 152.7, 168.9.

The Boc-group was removed by stirring the lactams overnight in TFA/ CH_2Cl_2 (1:4) at room temperature. The solvent was then removed by purging nitrogen. The residue was dissolved in anhydrous CH_2Cl_2 , and anhydrous Na_2CO_3 (20 mg) was added. This solution was stirred at room temperature for an hour, and the Na_2CO_3 was filtered. The solvent was evaporated under reduced pressure to the deprotected lactams **50** and **51** for ECCD studies.



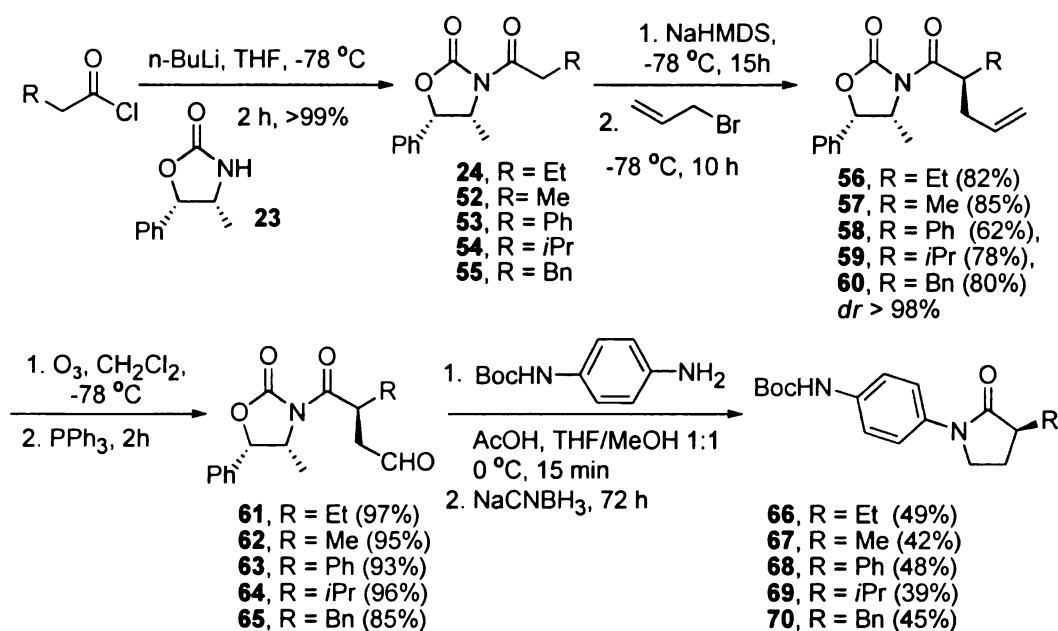
(S)- α -Phenoxy- γ -butyrolactam (50): IR (KBr): 3466, 2922, 2843, 1780, 1659, 1460, 1236, 848; ^1H -NMR (CDCl_3 , 300 MHz): δ 2.22-2.29 (m, 1H), 2.60-2.66 (m, 1H), 3.63 (s, 2H, NH_2), 3.75-3.80 (m, 1H), 3.82-3.86 (m, 2H), 6.66 (t, 2H, $J = 7.5$), 6.87 (d, 2H, $J = 7.0$), 6.97 (t, 1H, $J = 7.5$), 7.27 (t, 1H, $J = 7.0$), 7.41 (d, 1H, $J = 7.5$); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 26.3, 45.0, 76.2, 118.0, 118.9, 120.6, 121.8, 129.5, 134.2, 135.5, 144.7, 171.8.



(S)- α -[2-Napthyloxy]- γ -butyrolactam (51): IR (KBr): 3455, 3361, 2960, 2930, 2860, 1678, 1629, 1599, 1512, 1464, 1416, 1281, 1257, 1216, 1175, 1116, 839, 875, 739, 615; ^1H -NMR (CDCl_3 , 500 MHz): δ 2.20 (m, 1H), 2.70-2.76 (m, 1H), 3.80-3.86 (m, 1H),

3.88-3.94 (dt, 1H, $J_1 = 4.2$, $J_2 = 10.6$), 5.04 (t, 1H, $J = 7.2$), 6.68 (s, br, 2H (NH₂)), 7.26 (d, 1H, $J = 7.6$), 7.32-7.44 (complex multiplet, 4H), 7.62 (d, 1H, $J = 7.6$), 7.71-7.76 (complex multiplet, 3H); ¹³C NMR: δ 28.4, 45.0, 92.6, 106.0, 117.7, 121.7, 124.1, 126.7, 126.9, 129.3, 129.5, 129.6, 131.6, 133.7, 134.6, 137.2, 188.2, 171.1.

Scheme Synthesis of chiral α -alkyl butyrolactams:

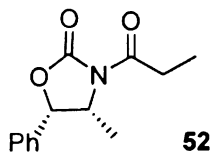


General procedure for auxiliary coupling with acid-halides:^{54, 55, 57, 87} The

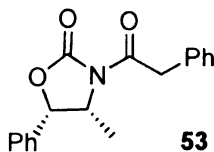
oxazolidone **23** (4 g, 22 mmol) was dissolved in dry THF (0.5 M) and cooled to -78 °C. *n*-BuLi (1.6 M in hexanes, 1.01 equiv) was added slowly until a noticeable yellow color (of the dianion) persisted. Acid chloride (1.5 equiv) was added immediately in one portion and solution was removed from ice bath, slowly warmed to room temperature (over 1 h period) and stirred for 2 h at room temperature. Reaction was quenched with 1 M K₂CO₃ (100 mL) and stirred for another 30 min.

The two layers were separated and the aqueous layer was extracted with Et₂O (3 × 100 mL). The combined layers were dried with anhydrous Na₂SO₄, filtered and

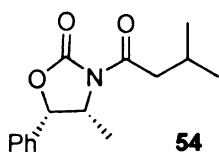
concentrated to the crude oil, which was purified by flash chromatography (Silica gel, 10% EtOAc in hexane) to provide pure product **23** in > 99% yield.



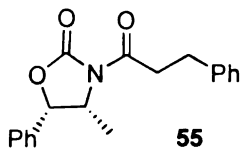
(4R, 5S)-4-Methyl-5-phenyl-3-propionyloxazolidin-2-one (52)⁸⁷ was obtained according to general procedure above (Scheme 3) in 98% yield. HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₃H₁₆NO₃ [M+H]⁺ 243.1130, obs'd 243.1133; ¹H-NMR (CDCl₃, 300 MHz): δ 0.92 (d, 3H, *J* = 6.6), 1.20, (t, 3H, *J* = 7.2), 2.89-3.1 (m, 2H), 4.79 (p, 1H, *J* = 6.6), 5.69 (d, 2H, *J* = 7.2), 7.29-7.47 (m, 5H). ¹³C-NMR (CDCl₃, 75 MHz): δ 13.3, 14.2, 17.4, 37.1, 54.4, 78.6, 125.3, 128.4, 133.0, 152.7, 172.7.



(4R, 5S)-4-Methyl-5-phenyl-3-(2-phenylacetyl)oxazolidin-2-one (53)⁸⁸ was obtained to general procedure above (Scheme 3) in 99% yield. HRMS (EI⁺): calc'd for C₁₈H₁₈NO₃ [M+H]⁺ 296.1287, obs'd 296.1290; ¹H-NMR (CDCl₃, 300 MHz): δ 0.87 (d, 3H, *J* = 6.6), 4.49 (d, 2H, *J* = 1.5), 4.73 (p, 1H, *J* = 6.6), 5.62 (d, 1H, *J* = 7.2), 7.40-7.23 (m, 10H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.4, 41.6, 54.9, 78.9, 125.6, 127.1, 128.5, 128.6, 128.7, 129.6, 133.2, 133.6, 170.9.



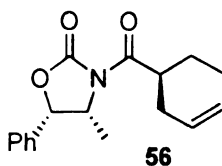
(4*R*, 5*S*)-4-Methyl-3-(3-methylbutanoyl)-5-phenyloxazolidin-2-one (54)⁸⁹ was obtained according to general procedure above (Scheme 3) in 99% yield. HRMS (Q-TOF MS (ES+)): calc'd for C₁₅H₁₉NO₃ [M+H]⁺ 262.1443, obs'd 262.1448; m. p. = 58-60 °C (white crystals); ¹H-NMR (CDCl₃, 300 MHz): δ 0.83 (d, 3H, *J* = 6.6); 0.93 (d, 3H, *J* = 6.6), 2.19 (m, 1H), 2.89-2.65 (m, 2H), 4.72 (p, 1H, *J* = 6.6), 5.60 (d, 1H, *J* = 7.2), 7.37-7.24 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.4, 22.3, 22.4, 24.9, 43.9, 54.6, 78.7, 125.6, 128.6, 133.3, 152.9, 172.3.



(4*R*, 5*S*)-4-Methyl-5-phenyl-3-(3-phenylpropanoyl)oxazolidin-2-one (55)⁸⁷ was obtained according to general procedure above (Scheme 3) in 98% yield. MS (DCI): *m/z* 309; m. p. = 93-94 °C (white crystals); ¹H-NMR (CDCl₃, 75 MHz): δ 0.86 (d, 3H, *J* = 6.6), 2.99 (m, 2H), 3.23-3.30 (m, 2H), 4.72 (p, 1H, *J* = 6.9), 5.61 (d, 1H, *J* = 7.2), 7.18-7.40 (m, 10 H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.5, 30.3, 37.2, 54.8, 79.0, 125.6, 126.3, 128.4, 128.5, 128.7, 128.8, 133.3, 140.4, 153.0, 172.2.

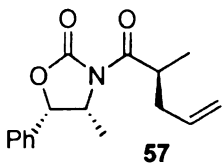
General procedure for α-allylation:⁵⁵ NaHMDS (1.1 equiv, 1 M in THF) was placed in the round bottom flask and cooled to -78 °C. Oxazolidone conjugate (10 mmol) was dissolved in a separate flask in dry THF (100 mL), cooled to -78 °C and added via

cannula to the base over 40 min. The solution was stirred at -78 °C for 1 h and allylbromide (1.5 equiv) was added drop wise over 1 h. Reaction mixture was stirred at -78 °C for 10 h, quenched with 10% HCl and further diluted with diethyl ether. The organic layer was separated, dried with anhydrous Na₂SO₄, concentrated to crude oil which was then submitted to the column chromatography purification (Silica gel, 5% EtOAc in hexane).



(4R, 5S)-3-((S)-2-Ethylpent-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (56):^{90, 91}

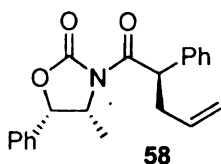
Yield: 82%; MS (DCI): *m/z* 287; [α]_D²⁰ = +43 (c, 3.2 in DCM) [literature value [α]_D²⁰ = +26.1 (c, 1.4 in CHCl₃)⁹⁰]; dr > 98%; IR (KBr): 3072, 2970, 2934, 2878, 782, 1699, 1641, 1496, 1458, 1388, 1342, 1234, 1196, 1120, 1068, 1030, 993, 920, 808, 767, 700, 636; ¹H-NMR (CDCl₃, 300 MHz): δ 0.6 (d, 3H, *J* = 6.6), 0.88 (t, 3H, *J* = 7.5), 1.44-1.58 (m, 2H), 1.62-1.78 (m, 1H), 2.23-2.29 (m, 2H), 2.28-2.4 (m, 1H), 4.90-5.03 (dd, 2H, *J*₁ = 15, *J*₂ = 18.6), 5.65 (d, 2H, *J* = 6.6), 5.77-5.86 (m, 1H), 7.21 (d, 2H, *J* = 8.7), 7.35 (d, 2H, *J* = 8.7); ¹³C-NMR (CDCl₃, 75 MHz): δ 13.6, 14.6, 17.7, 37.4, 54.7, 78.9, 116.8, 125.3, 125.6, 128.4, 128.6, 128.7, 133.3, 156.1, 173.0.



(4R, 5S)-4-Methyl-3-((S)-2-methylpent-4-enoyl)-5-phenyloxazolidin-2-one (57):^{92, 93}

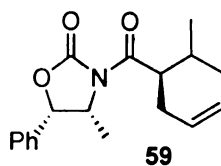
Yield: 85%; HRMS (Q-TOF MS (ES+)): calc'd for C₁₆H₂₀NO₃ [M+H]⁺ 274.1443, obs'd

274.1441; $[\alpha]_D^{20} = +40.3$ (c, 2.5 in DCM); [literature value $[\alpha]_D^{22} = +47.0$ (c, 2.36 in DCM)⁹³], dr > 99%; IR (KBr): 3063, 2986, 2934, 2878, 1774, 1701, 1639, 1498, 1458, 1346, 1298, 1278, 1196, 1066, 1020, 958, 916, 812, 769, 734, 696; ¹H-NMR (CDCl₃, 300 MHz): δ 0.87 (d, 3H, $J = 6.6$), 1.16 (d, 3H, $J = 6.9$), 2.14-2.23 (m, 1H), 2.41-2.51 (m, 1H), 3.84 (q, 1H, $J = 6.6$), 4.74 (p, 1H, $J = 7.2$), 4.96-5.06 (dd, 2H, $J_1 = 9.0$, $J_2 = 12.0$), 5.62 (d, H, $J = 6.9$), 5.67-5.86 (m, 1H), 7.26-7.42 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.3, 17.2, 36.8, 37.6, 54.5, 78.4, 116.8, 125.3, 128.5, 128.4, 133.0, 134.9, 152.4, 175.9.



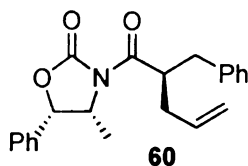
(4R, 5S)-4-Methyl-5-phenyl-3-((R)-2-phenylpent-4-enoyl)oxazolidin-2-one (58):

Yield: 62%; HRMS (Q-TOF MS (ES⁺)): calc'd for C₂₁H₂₂NO₃ [M+H]⁺ 336.1600, obs'd 336.1603; $[\alpha]_D^{20} = +12.2$ (c, 1.8 in DCM); dr > 99%; IR (KBr): 3067, 3030, 2984, 2924, 2856, 1780, 1699, 1604, 1496, 1456, 1385, 1342, 1305, 1248, 1196, 1143, 1122, 1066, 1030, 987, 945, 918, 899, 767, 700, 632; ¹H-NMR (300 MHz, CDCl₃): δ 0.89 (d, 3H, $J = 6.6$), 2.45-2.54 (m, 1H, $J = 7.2$), 2.85-2.94 (m, 1H, $J = 7.2$), 4.68 (p, 1H, $J = 6.6$), 4.96 (d, 1H, $J = 12.0$), 5.04 (d, 1H, $J = 17.4$), 5.16-5.21 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 8.7$), 5.46 (d, 1H, $J = 7.6$), 5.66-5.79 (m, 1H), 7.41-7.21 (m, 10H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.5, 48.3, 38.2, 55.3, 78.5, 116.3, 125.6, 127.4, 128.6, 128.7, 133.2, 135.2, 138.4, 152.6, 173.3.



(4R, 5S)-3-((R)-2-Isopropylpent-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (59):⁹⁴

Yield: 78%; HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₈H₂₄NO₃ [M+H]⁺ 302.1756, obs'd 302.1761; [α]_D²⁰ = +11.4 (c, 2.1 in DCM); dr > 99%; IR (KBr): 3074, 2966, 2878, 1782, 1697, 1641, 1456, 1342, 1307, 1234, 1198, 1155, 1118, 1068, 1033, 997, 918, 887, 767, 698, 638; ¹H-NMR (CDCl₃, 300 MHz): δ 0.80 (d, 3H, *J* = 6.6), 0.94 (d, 6H, *J* = 6.9), 1.89-2.01 (m, 1H), 2.30-2.44 (m, 2H), 3.78-3.86 (m, 1H), 4.75 (p, 1H, *J* = 6.6), 4.89-5.02 (dd, 2H, *J*₁ = 10.9, *J*₂ = 17.1), 5.58 (d, 1H, *J* = 7.2), 5.67-5.81 (m, 1H), 7.22-7.39 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.4, 19.2, 20.8, 30.2, 33.8, 48.3, 54.9, 78.5, 116.7, 125.6, 128.6, 133.3, 135.4, 152.8, 175.5.

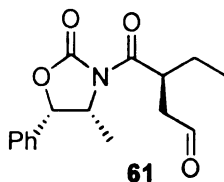


(4R, 5S)-3-((R)-2-Benzylpent-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (60):⁹⁵

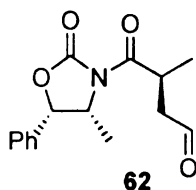
Yield: 80%; HRMS (Q-TOF MS (ES⁺)): calc'd for C₂₂H₂₄NO₃ [M+H]⁺ 350.1756, obs'd 349.1699; [α]_D²⁰ = -38.4 (c, 0.9 in DCM); dr > 98%; IR (KBr): 3072, 3033, 2984, 2934, 1780, 1697, 1636, 1597, 1495, 1456, 1344, 1249, 1194, 1145, 1118, 1066, 1033, 991, 918, 814, 763, 698; ¹H-NMR (CDCl₃, 300 MHz): δ 0.78 (d, 3H, *J* = 6.6), 2.28-2.37 (m, 1H), 2.47-2.57 (m, 1H), 2.81-2.97 (dq, 2H, *J*₁ = 13.2, *J*₂ = 9.0), 4.28-4.38 (m, 1H), 4.48-4.57 (p, 1H, *J* = 6.6), 5.00-5.09 (dd, 2H, *J*₁ = 10.2, *J*₂ = 17.1), 5.17 (d, 1H, *J* = 7.2), 5.75-5.88 (m, 1H), 7.16-7.39 (m, 10 H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.4, 31.8, 36.3, 38.3,

44.0, 54.8, 78.6, 117.2, 125.5, 126.4, 128.3, 128.6, 129.1, 133.2, 134.9, 139.0, 152.5, 175.0.

Ozonization procedure:⁸⁴ Ozonolysis was carried out in round bottom flask at -78 °C in dry CH₂Cl₂. Ozone was generated by a laboratory ozonator using commercial-grade oxygen as a source. [Voltage setting (90 V), pressure (5.5-6 lb./in.²) and flow rates (0.3 ft.³/min)]. The completion of reaction was detected by the appearance of intense blue color in the reaction solution. The reaction mixture was flushed with nitrogen for 10-15 min at -78 °C and solution of PPh₃ (1.1 equiv) in CH₂Cl₂ was added. Mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was concentrated and submitted to the column chromatography (Silica gel, 10% EtOAc in hexane).

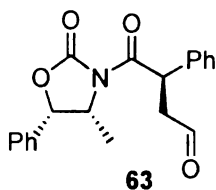


(S)-3-((4R, 5S)-4-Methyl-2-oxo-5-phenyloxazolidine-3-carbonyl)pentanal (61): Yield 98%; HRMS (Q-TOF MS (ES⁺)): calc'd for C₁₆H₂₀NO₄ [M+H]⁺ 290.1392, obs'd 290.1432; [α]_D²⁰ = +17.6 (c, 0.6 in DCM); m.p. = 74-75 °C (white crystals); ¹H-NMR (CDCl₃, 300 MHz): δ 0.86 (d, 3H, J = 6.6), 0.94 (t, 3H, J = 7.5), 1.45-1.60 (m, 1H), 1.60-1.78 (m, 1H), 2.58-2.66 (dd, 1H, J₁ = 3.9, J₂ = 12.9), 2.94-3.03 (dd, 1H, J₁ = 9.4, J₂ = 18.3), 4.01-4.19 (m, 1H), 4.73 (p, 1H, J = 7.1), 5.63 (d, 1H, J = 7.5), 7.27-7.40 (M, 5H), 9.71 (s, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 10.9, 13.7, 24.7, 38.1, 45.0, 54.7, 78.5, 125.3, 128.3, 128.4, 132.9, 152.4, 174.8, 199.8.



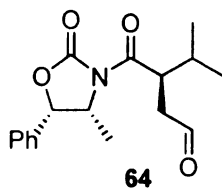
(S)-3-Methyl-4-((4R, 5S)-4-methyl-2-oxo-5-phenyloxazolidin-3-yl)-4-oxobutanal (62):

Yield: 96% (colorless oil); MS (DCI): calc'd for C₁₅H₁₇NO₄ m/z = 275.1, obs'd M⁺ = 375.4; IR (KBr): 2944, 2939, 2873, 2762, 1763, 1713, 1702, 1453, 1348, 1196, 1120, 1035, 964, 773; ¹H-NMR (CDCl₃, 300 MHz): δ 0.87 (d, 3H, J = 6.6), 1.22 (d, 3H, J = 6.9), 2.51-2.58 (dd, 1H, J_1 = 4.1, J_2 = 13.5), 2.99-3.09 (dd, 1H, J_1 = 9.1, J_2 = 18.4), 4.16-4.23 (m, 1H), 4.72 (p, 1H, J = 6.9), 5.65 (d, 1H, J = 7.2), 7.27-7.41 (m, 5H), 9.70 (s, 1H); ¹³C-NMR (CDCl₃): δ 14.3, 16.2, 36.8, 37.6, 54.5, 78.4, 116.8, 125.3, 128.3, 128.4, 133.0, 134.9, 152.4, 175.9, 198.9.



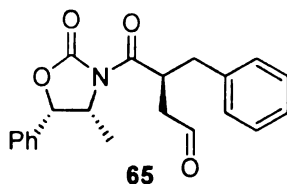
(R)-4-((4R, 5S)-4-Methyl-2-oxo-5-phenyloxazolidin-3-yl)-4-oxo-3-phenylbutanal

(63): Yield: 93%; MS (DCI): calc'd for C₂₀H₁₉NO₄ m/z = 337.1, obs'd M⁺ = 337.4; $[\alpha]_D^{20}$ = -71.1 (*c*, 0.6 in DCM); m.p. = 146-147 °C (white crystals); IR (KBr): 3044, 2994, 2934, 2834, 2735, 1780, 1720, 1693, 1603, 1495, 1456, 1376, 1346, 1257, 1196, 1147, 1122, 1089, 1066, 983, 958, 810, 763, 700; ¹H-NMR (CDCl₃, 300 MHz): δ 0.93 (d, 3H, J = 6.6), 2.79-2.86 (dd, 1H, J_1 = 4.2, J_2 = 18.9), 3.46-3.56 (dd, 1H, J_1 = 10.5, J_2 = 19.5), 4.49-4.56 (m, 1H), 4.66 (p, 1H, J = 6.9), 5.47-5.52 (m, 2H), 7.25-7.41 (m, 10H), 9.74 (s, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 13.9, 42.8, 48.7, 55.2, 78.6, 125.6, 127.7, 128.4, 128.6, 128.7, 128.8, 133.2, 137.0, 152.3, 172.6, 199.4.



(R)-4-Methyl-3-((4R, 5S)-4-methyl-2-oxo-5-phenyloxazolidine-3-carbonyl) pentanal

(64): Yield 96 % (colorless oil); MS (DCI): calc'd for $C_{17}H_{21}NO_4$ m/z = 303.1, obs'd M^+ = 303.3; $[\alpha]_D^{20}$ = + 6.0 (c, 0.86 in DCM); IR (KBr): 3070, 2964, 2934, 2745, 1768, 1720, 1697, 1496, 1456, 1394, 1350, 1242, 1197, 1153, 1118, 1087, 1066, 1028, 985, 954, 769, 704; 1H -NMR ($CDCl_3$, 300 MHz): δ 0.88 (d, 3H, J = 6.6), 0.91 (d, 3H, J = 6.6), 1.0 (d, 3H, J = 6.6), 1.94-2.09 (m, 1H, J = 6.9), 2.61-2.68 (dd, 1H, J_1 = 3.6, J_2 = 18.6), 2.97-3.07 (dd, 1H, J_1 = 11.7, J_2 = 18.6), 4.13-4.19 (m, 1H), 4.73 (p, 1H, J = 6.6), 5.63 (d, 1H, J = 7.2), 7.28-7.40 (m, 5H), 9.73 (s, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 14.0, 38.2, 42.8, 44.8, 48.8, 55.3, 78.6, 125.6, 125.7, 127.8, 127.9, 128.4, 128.4, 128.5, 128.7, 128.8, 128.9, 133.1, 133.2, 136.7, 137.0, 152.3, 172.7, 199.5.



(S)-3-Benzyl-4-((4R, 5S)-4-methyl-2-oxo-5-phenyloxazolidin-3-yl)-4-oxobutanal (65):

Yield 92 % (yellow oil); MS (DCI): calc'd for $C_{21}H_{21}NO_4$ m/z = 351.1, obs'd M^+ = 351.4; $[\alpha]_D^{20}$ = -23.4 (c, 0.3 in DCM); IR (KBr): 4072, 3033, 2928, 2856, 2729, 1780, 1699, 1653, 1604, 1496, 1456, 1388, 1367, 1344, 1250, 1196, 1145, 1122, 1089, 1068, 1030, 1001, 949, 812, 767, 736, 700, 632; 1H -NMR ($CDCl_3$, 300 MHz): δ 0.86 (d, 3H, J = 6.6), 2.53-2.68 (m, 2H), 2.97-3.07 (m, 2H), 4.60 (p, 1H, J = 6.6), 5.36 (d, 1H, J = 7.5),

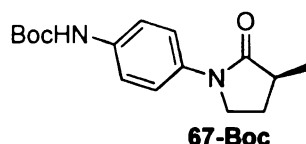
7.19-7.41 (m, 10H), 9.64 (s, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.0, 38.2, 39.2, 45.4, 55.0, 78.2, 125.6, 126.9, 128.5, 128.6, 128.7, 129.2, 133.2, 137.8, 152.6, 174.6, 199.7.

Reductive amination / cyclization (lactams **66-70**):⁹⁵ Obtained from the ozonolysis aldehyde (3.05 mmol) was added in to round-bottomed flask, dissolved in THF/MeOH (1:1, 60 mL) mixture and cooled to 0 °C under N_2 atmosphere. Mono-Boc-1,4-phenylenediamine (3.78 g, 18.8 mmol) followed by acetic acid (2.1 g, 36 mmol) was added to reaction mixture which was stirred at 0 °C for 10 min. NaCNBH_3 (0.57 g, 9.08 mmol) was added to the reaction mixture, which was allowed to warm and to stir at room temperature during 24 h period. NaCNBH_3 (0.25 g, 4.5 mmol) was added and the reaction mixture was stirred for another 48 h. The reaction mixture was then quenched with H_2O and extracted with EtOAc (3 x 100 mL). The combined layers were washed with aqueous NaHCO_3 (2 x 100 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography (Silica gel, 20% EtOAc in hexane). The product came out with the admixture of carrier. The solution of this mixture was acidified with 10% HCl (pH ~ 1) and extracted with water. Two layers were then separated and organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford pure alkyl butyrolactams.

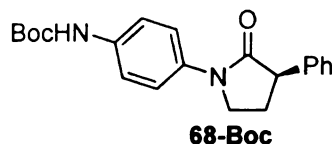


N-Boc-(S)-1-(4-Aminophenyl)-3-ethylpyrrolidin-2-one (66-Boc): Yield 35%; MS (DCI): calc'd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_3$ m/z = 304.1, obs'd M^+ = 304.2; $[\alpha]_{\text{D}}^{20}$ = -51 (c, 2.8 in

DCM); IR (KBr): 3321, 2963, 2932, 2874, 1722, 1684, 1593, 1531, 1456, 1398, 1365, 1327, 1292, 1236, 1163, 1053, 1018, 893, 846, 773, 723, 665, 584; m. p. = 183 °C (yellow powder); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.26 (d, 3H, $J = 7.2$), 1.49 (s, 9H), 1.66-1.80 (m, 2H), 2.28-2.34 (m, 1H), 2.57-2.67 (m, 1H), 3.67-3.79 (m, 2H), 6.50 (s, 1H (NH)), 7.31 (d, 2H, $J = 9.0$), 7.52 (d, 2H, $J = 9.0$); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 16.2, 26.9, 38.1, 46.7, 48.0, 120.4, 134.7, 134.8, 150.1, 177.0.

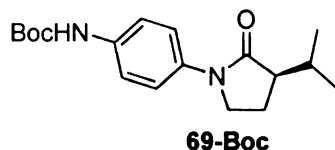


N-Boc-(S)-1-(4-Aminophenyl)-3-methylpyrrolidin-2-one (67-Boc): Yield 28%; MS (DCI): calc'd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3$ $m/z = 290.3$, obs'd $\text{M}^+ = 290.1$; $[\alpha]_{\text{D}}^{20} = -13.9$ (c, 1.3 in DCM); IR (KBr): 3325, 3290, 2978, 2930, 2895, 1717, 1672, 1599, 1531, 1411, 1363, 1305, 1236, 1167, 1047, 1010, 825, 721, 662, 515; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 0.98 (d, 3H, $J = 7.2$), 1.48 (s, 9H), 1.66-1.78 (m, 1H), 2.28-2.38 (m, 1H), 2.57-2.69 (m, 1H), 3.67-3.76 (m, 2H), 6.51 (s, 1H (NH)), 7.32 (d, 2H, $J = 9.0$), 7.52 (d, 2H, $J = 9.0$); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 16.2, 27.0, 28.3, 38.1, 46.7, 48.0, 79.1, 120.4, 128.5, 134.5, 149.3, 176.4.

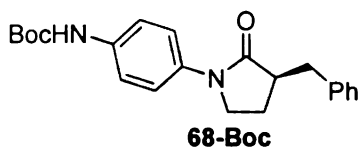


N-Boc-(R)-1-(4-Aminophenyl)-3-phenylpyrrolidin-2-one (68-Boc): Yield 32%; MS (DCI): calc'd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3$ $m/z = 352.4$, obs'd $\text{M}^+ = 352.2$; $[\alpha]_{\text{D}}^{20} = +30$ (c, 0.7 in DCM); IR: 3360, 2936, 2878, 1692, 1657, 1549, 1516, 1459, 1402, 1226, 829, 968; $^1\text{H-NMR}$

NMR (CDCl₃, 500 MHz): δ 1.49 (s, 9H), 2.23-2.28 (m, 1H), 2.57-2.63 (m, 1H), 3.82-3.89 (m, 3H), 6.46 (s, 1H (NH)), 7.23-7.35 (m, 7H), 7.59 (d, 2H, J = 6.6); ¹³C-NMR (CDCl₃, 125 MHz): δ 27.6, 28.3, 46.8, 49.5, 80.5, 120.5, 125.9, 127.1, 127.9, 128.5, 128.7, 134.8, 139.2, 152.7, 173.8.



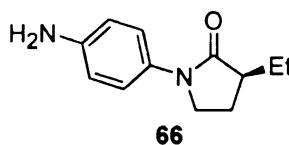
N-Boc-(R)-1-(4-Aminophenyl)-3-isopropylpyrrolidin-2-one (69-Boc): Yield 39%; MS (DCI): calc'd for C₁₈H₂₆N₂O₃ m/z = 318.4, obs'd M⁺ = 318.2; [α]_D²⁰ = +25.6 (c, 0.63 in DCM); IR (KBr): 3294, 3190, 2957, 2930, 2872, 1716, 1664, 1599, 1529, 1423, 1365, 1298, 1238, 1165, 1053, 835, 713, 528; m. p. = 200 °C (white powder); ¹H-NMR (CDCl₃, 500 MHz): δ 0.87 (d, 3H, J = 7.0), 1.00 (d, 3H, J = 7.0), 1.48 (s, 9H), 1.83-1.90 (m, 1H), 2.04-2.10 (m, 1H), 2.22-2.28 (m, 1H), 2.51-2.60 (m, 1H), 3.63-3.72 (m, 2H), 6.81 (s, 1H (NH)), 7.29 (d, 2H, J = 8.6), 7.59 (d, 2H, J = 8.6); ¹³C-NMR (CDCl₃, 125 MHz): δ 17.5, 19.3, 20.5, 28.2, 47.1, 48.9, 80.3, 118.9, 120.7, 134.5, 134.9, 135.0, 152.9, 175.5.



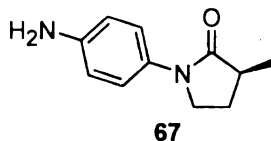
N-Boc-(S)-4-(3-benzyl-2-oxopyrrolidin-1-yl)phenylcarbamate (68-Boc): Yield 45%; MS (DCI): calc'd for C₁₈H₂₆N₂O₃ m/z = 366.1, obs'd M⁺ = 366.2; [α]_D²⁰ = (c, in DCM); IR (KBr): 3262, 2989, 2930, 1697, 1533, 1496, 1406, 1367, 1313, 1242, 1159, 1059, 831, 640; m. p. = 220 °C (yellow powder); ¹H-NMR (CDCl₃, 500 MHz): δ 1.40 (s, 9H), 1.72-

1.78 (m, 1H), 2.03-2.09 (m, 1H), 2.66-2.70 (dd, $J_1 = 14$, $J_2 = 5$, 1H), 2.78-2.83 (m, 1H), 3.12-3.15 (dd, $J_1 = 9$, $J_2 = 13.5$, 1H), 3.53-3.60 (m, 2H), 6.92 (s, 1H (NH)), 7.11-7.26 (m, 7H), 7.33 (d, 2H, $J = 8.5$); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 23.5, 28.1, 36.8, 44.8, 47.1, 48.5, 80.1, 109.7, 118.9, 119.2, 121.0, 126.3, 128.3, 128.8, 138.8, 152.4, 175.4.

The obtained amides were submitted to the Boc-deprotection with 20% TFA in CH_2Cl_2 for 2 h. The solvent was then removed under reduced pressure and the remaining oil was dissolved in dichloromethane and neutralized with NaCO_3 , filtered and concentrated to afford the deprotected lactams **66-70** that were used for ECCD studies.

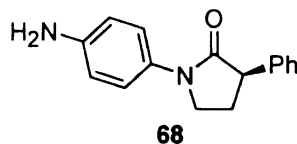


(S)-1-(4-Aminophenyl)-3-ethylpyrrolidin-2-one (66): IR (KBr): 3319, 3296, 2963, 2930, 2872, 1722, 1664, 1593, 1529, 1458, 1402, 1365, 1327, 1292, 1236, 1163, 1051, 1022, 1018, 891, 846, 833, 773, 723, 661, 582, 524; ^1H -NMR (CDCl_3 , 500 MHz): δ 1.26 (d, 3H, $J = 7.6$), 1.66-1.80 (m, 2H), 2.28-2.34 (m, 1H), 2.57-2.67 (m, 1H), 3.58 (s, 2H, NH_2), 3.69-3.82 (m, 2H), 7.31 (d, 2H, $J = 9.0$), 7.52 (d, 2H, $J = 9.0$); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 16.2, 26.9, 38.1, 46.7, 48.0, 120.4, 134.7, 134.8, 150.1, 177.0.

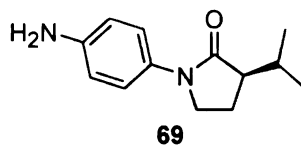


(S)-1-(4-Aminophenyl)-3-methylpyrrolidin-2-one (67): IR (KBr): 3467, 3366, 3066, 2978, 1684, 1517, 1456, 1399, 1310, 1234, 1175, 1069, 1016, 863, 845, 596; ^1H -NMR (CDCl_3 , 500 MHz): δ 1.28 (d, 3H, $J = 7.2$), 1.71-1.78 (m, 1H), 2.32-2.37 (m, 1H), 2.37-

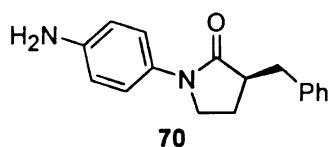
2.57 (m, 1H), 3.58 (s, 2H (NH₂)), 3.67-3.75 (m, 2H), 6.68 (d, 2H, *J* = 8.5), 7.35 (d, 2H, *J* = 8.5); ¹³C-NMR (CDCl₃, 75 MHz): δ 20.2, 37.7, 46.4, 47.6, 120.0, 123.6, 133.1, 142.5, 175.5.



(R)-1-(4-Aminophenyl)-3-phenylpyrrolidin-2-one (68): IR (KBr): 3357, 2926, 2862, 1680, 1630, 1518, 1459, 1402, 1286, 1227, 829, 698; ¹H-NMR (CDCl₃, 300 MHz): δ 2.22-2.29 (m, 1H), 2.60-2.66 (m, 1H), 3.63 (s, 2H, NH₂), 3.75-3.80 (m, 1H), 3.82-3.86 (m, 2H), 6.66 (t, 2H, *J* = 7.5), 6.87 (d, 2H, *J* = 7.0), 6.97 (t, 1H, *J* = 7.5), 7.27 (t, 1H, *J* = 7.0), 7.41 (d, 1H, *J* = 7.5); ¹³C-NMR (CDCl₃, 75 MHz): δ 37.7, 46.4, 50.1, 115.2, 120.0, 121.9, 123.6, 131.2, 133.2, 142.5, 143.4, 175.5.

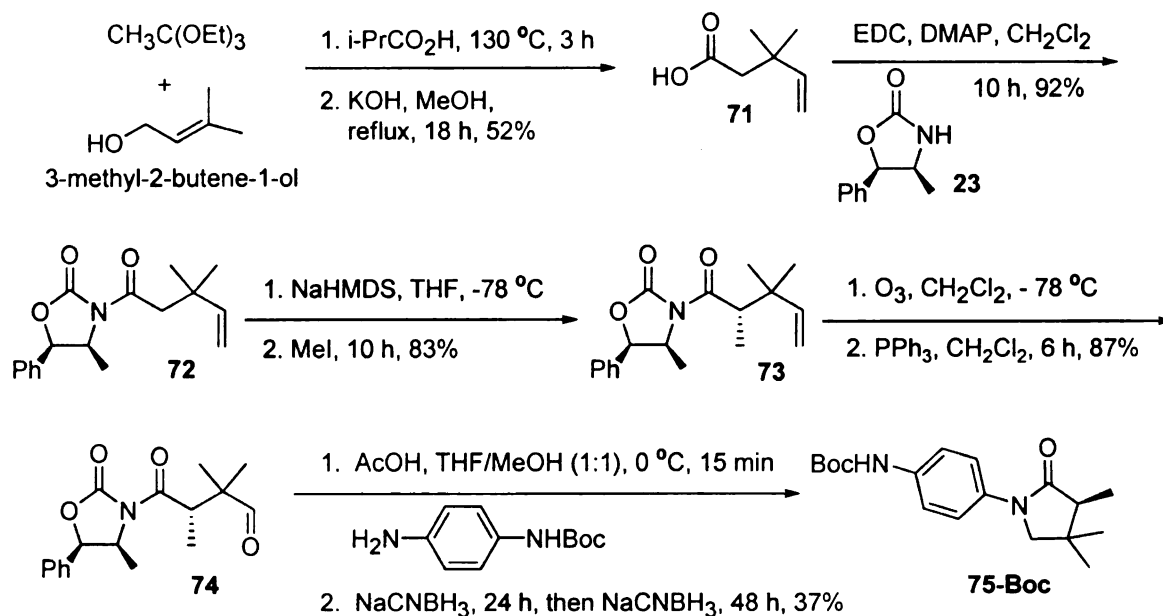


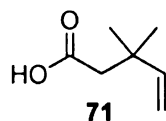
(R)-1-(4-Aminophenyl)-3-isopropylpyrrolidin-2-one (69): ¹H-NMR (CDCl₃, 500 MHz): δ 0.89 (d, 3H, *J* = 7.0), 1.00 (s, 3H, *J* = 7.0), 1.84-1.92 (m, 1H), 2.05-2.14 (m, 1H), 2.25-2.31 (m, 1H), 2.52-2.56 (m, 1H), 3.58 (s, 1H (NH₂)), 3.63-3.74 (m, 2H), 6.65 (d, 2H, *J* = 8.5), 7.34 (d, 2H, *J* = 9.0); ¹³C-NMR (CDCl₃, 125 MHz): δ 17.6, 19.5, 20.5, 47.4, 48.8, 115.2, 121.9, 131.2, 143.4, 175.0.



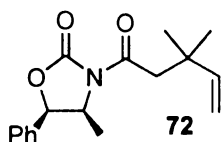
(S)-1-(4-Aminophenyl)-3-benzylpyrrolidin-2-one (70): IR (KBr): 3348, 3237, 3044, 2957, 2872, 1676, 1657, 1516, 1466, 1402, 1367, 1302, 1230, 1105, 987, 893, 827, 704, 611, 520; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 1.70-1.76 (m, 1H), 2.00-2.06 (m, 1H), 2.62-2.69 (dd, $J_1 = 12$, $J_2 = 5.5$, 1H), 2.76-2.81 (m, 1H), 3.12-3.15 (dd, $J_1 = 9.5$, $J_2 = 14$, 1H), 3.26 (s, 2H (NH_2)), 3.50-3.58 (m, 2H), 6.58 (d, 2H, $J = 8.5$), (7.11-7.26 (m, 7H); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 23.6, 36.9, 44.8, 47.1, 48.5, 109.7, 118.9, 119.2, 121.9, 126.5, 128.2, 138.9, 143.2, 175.1.

Scheme II-10: Synthesis of (R)-1-(4-aminophenyl)-3,4,4-trimethylpyrrolidin-2-one (75)



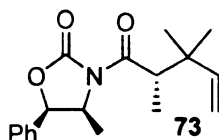


Ethyl 3,3-dimethyl-4-pentenoic acid (71):⁹⁶ A 100 mL single-neck round-bottom flask equipped with reflux condenser was charged with 3-methyl-butene-1-ol (2.0 g, 23.2 mmol), triethylorthoacetate (15 g, 92.8 mmol), and propionic acid (0.17 g, 2.3 mmol). Boiling chips were added, and then the mixture was heated to reflux for 3 h. A Dean-Stark trap was then attached and the mixture heated until no more ethanol could be removed. After 4.5 h, the reaction was cooled to room temperature and potassium hydroxide (3.11 g, 55.4 mmol) and methanol (30 mL) were added and the solution was refluxed for 18 h. The reaction was cooled to room temperature and concentrated under reduced pressure. The resulting residue was taken up in diethyl ether and extracted with a saturated solution of sodium bicarbonate three times. The aqueous extracts were combined, acidified with 6 N HCl and extracted with dichloromethane (5 x 30 mL). The organic extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **71** as yellowish oil in 52% yield. ¹H-NMR (CDCl₃, 300 MHz): δ 1.13 (s, 3H), 2.03 (s, 2H), 4.91-4.99 (dd, 2H, $J_1 = 10.8$, $J_2 = 12.0$), 5.83-5.92 (dd, 1H, $J_1 = 16.0$, $J_2 = 14.7$); ¹³C-NMR (CDCl₃, 75 MHz): δ 26.8, 35.9, 46.6, 111.1, 146.4, 178.5.



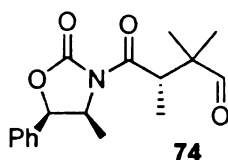
(4*R*, 5*S*)-3-(3,3-Dimethylpent-4-enoyl)-4-methyl-5-phenyloxazolidin-2-one (72): In to the round-bottom flask containing dry dichloromethane (50 mL) were added ethyl 3,3-

dimethyl-4-pentenic acid (2 g, 16 mmol), (4*S*, 5*R*)-4-methyl-5-phenyloxazolidin-2-one (**23**) (3.3 g, 18.7 mmol), 4-dimethylaminopyridine (2.2 g, 18.7 mmol) and DCC (2.9 g, 18.7 mmol). The reaction mixture was stirred for 12 h, solvent was removed and mixture was separated by column chromatography (10% EtOAc in hexane) to afford the coupled product **72** as a white crystalline solid in 82% yield. MS (DCI): calc'd for C₁₇H₂₁NO₃ m/z = 287.3, obs'd M^+ = 287.1; $[\alpha]_D^{20}$ = -24 (*c*, 2.85 in CH₂Cl₂); ¹H-NMR (CDCl₃, 300 MHz): δ 0.84 (d, 3H, J = 6.6), 1.16 (s, 3H), 1.23 (s 3H), 1.291-3.11 (AB quartet, 2H, J_1 = 31.5, J_2 = 60.6), 4.75 (p, 1H, J = 6.9), 4.92-4.98 (m, 2H), 5.58 (d, 1H, J = 7.2), 5.92-6.02 (dd, 2H, J_1 = 10.0, J_2 = 17.0), 7.26-7.41 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.5, 26.9, 27.0, 36.9, 45.4, 54.8, 78.6, 111.0, 125.6, 128.6, 128.7, 133.3, 146.5, 153.0, 170.9.



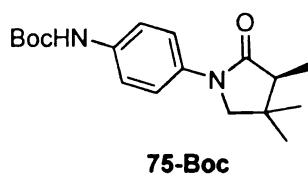
(*S*)-2,3,3-Trimethyl-pentenoyl amide (73): NaHMDS (10 mL, 10 mmol) was added in to a dry round bottom flask, cooled to -78 °C and flashed with nitrogen for 5-10 min. Auxiliary conjugate **72** (2 g, 7 mmol) was dissolved in THF (60 mL) in separate flask, cooled to -78 °C and added dropwise via cannula to the base. Mixture was stirred at -78 °C for 1 h and iodomethane (3 g, 21 mmol) was added via syringe over 30 min. After addition mixture was stirred at -78 °C for another 10 h and quenched with 10% HCl. Neutralized solution was further diluted with ether and warmed to room temperature. Organic layer was separated, washed with brine, dried with anhydrous sodium sulfate and solvent was removed under reduced pressure to afford crude yellowish oil. Column

chromatography (Silica gel, 10% EtOAc in hexane) afforded 81% (2.1 g) of the compound. MS (DCI): calc'd for $C_{18}H_{23}NO_3$ m/z = 301.3, obs'd M^+ = 301.7; $[\alpha]_D^{20}$ = +17.6 (c, 1.5 in CH_2Cl_2); 1H -NMR ($CDCl_3$, 300 MHz): δ 0.84 (d, 3H, J = 6.3), 1.07 (s, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 4.94 (q, 1H, J = 7.2), 4.69 (p, 1H, J = 6.6), 4.93-4.99 (m, 2H), 5.95 (d, 1H, J = 7.2), 5.88-5.97 (dd, 1H, J_1 = 10.0, J_2 = 17.0), 7.25-7.40 (m, 5H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 12.7, 14.3, 23.5, 24.6, 39.5, 44.3, 55.1, 78.6, 111.9, 125.6, 128.6, 133.2, 146.0, 153.0, 175.6.



(S)-2,2,3-Tirimethyl-4-(((4S,5R)-4-methyl-2-oxo-5-phenyloxazolidin-3-yl)-4-

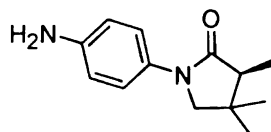
oxobutanal (74) was obtained from ozonolysis according to the presedure described above in 87% yield. MS (DCI): calc'd for $C_{17}H_{21}NO_4$ m/z = 303.1, obs'd M^+ = 303.4; $[\alpha]_D^{20}$ = (c, in CH_2Cl_2); IR (KBr): 3061, 2976, 2878, 2729, 1780, 1718, 1695, 1496, 1456, 1437, 1387, 1363, 1342, 1246, 1197, 1120, 1089, 1068, 1028m 958, 767, 746, 723, 696; 1H -NMR ($CDCl_3$, 300 MHz): δ 0.84 (d, 3H, J = 6.6), 1.14 (s, 3H), 1.21 (s, 3H), (1.27 d, 3H, J = 7.2), 3.98 (q, 1H, J = 7.5), 4.74 (p, 1H, J = 6.6), 5.68 (d, 1H, J = 7.2), 7.26-7.40 (m, 5H), 9.66 (s, 1H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 12.7, 14.7, 19.5, 21.3, 43.2, 47.9, 54.9, 78.9, 125.6, 128.4, 131.9, 133.8, 153.6, 175.5, 206.7.



N-Boc-(S)-4-(3,4,4-trimethyl-2-oxopyrrolidin-1-yl)phenylcarbamate (75-Boc):

Obtained from the ozonolysis aldehyde **74** (0.13 g, 0.42 mmol) was added in to round-bottomed flask and dissolved in the THF/MeOH mixture (1:1, 30 mL) and cooled to 0 °C under N₂ atmosphere. Mono-Boc-1,4-phenylenediamine (0.45 g, 2.14 mmol) followed by acetic acid (0.12 g, 2.14 mmol) was added to reaction mixture which was stirred at 0 °C for 10 min. NaCNBH₃ (0.067 g, 1.07 mmol) was added to the reaction mixture, which was allowed to warm to and stir at room temperature during 24 h period. Another portion of NaCNBH₃ (0.067 g, 1.07 mmol) was added and the reaction mixture was stirred for another 48 h. The reaction mixture was then quenched with H₂O and extracted with EtOAc (3 x 100 mL). The combined layers were washed with aqueous NaHCO₃ (2 x 100 mL) and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was dissolved in dichloromethane and extracted ones with 10% HCl (5-7 mL) (purified from unreacted amine), washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated to the crude oil which then crystallized. ¹H-NMR of this fraction showed presence of the lactam and cleaved chiral auxiliary. No carrier was detected. Resulted mixture was purified by chromatography (Silica gel, 10% EtOAc in hexane) to afford lactam **75-Boc** in 36 % yield. MS (DCI): calc'd for C₁₈H₂₆N₂O₃ *m/z* = 318.1, obs'd M⁺ = 318.2; [α]_D²⁰ = +5.5 (*c*, 2.5 in CH₂Cl₂); IR (KBr): 3300, 2974, 2876, 1718, 1674, 1597, 1523, 1483, 1456, 1423, 1408, 1365, 1313, 1282,

1236, 1161, 1048, 1024, 900, 835, 771, 711, 582, 522, 462; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 0.97 (s, 3H), 1.08 (d, 3H, $J = 7.5$), 1.16 (s, 3H), 1.46 (s, 9H), 2.32 (q, 1H, $J = 7.2$), 3.34-3.50 (dd, 2H, $J_1 = 9.3$, $J_2 = 38.4$), 6.70 (s, 1H), 7.31 (d, 2H, $J = 8.7$), 7.47 (d, 2H, $J = 9.0$); $^{13}\text{C-NMR}$ (CDCl_3 , 300 MHz): δ 9.2, 21.9, 26.0, 28.2, 36.1, 48.8, 60.3, 80.3, 114.8, 120.8, 134.7, 144.1, 175.7.



75

(*S*)-1-(4-Aminophenyl)-3,4,4-trimethylpyrrolidin-2-one (75): $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 0.12 (s, 3H), 1.08 (d, 3H, $J = 7.5$), 1.18 (s, 3H), 2.36 (q, 1H, $J = 7.0$), 3.36-3.54 (dd, 2H, $J_1 = 9.2$, $J_2 = 38.2$), 3.82 (s, 2H (NH_2)), 6.77 (d, 2H, $J = 8.6$), 7.52 (d, 2H, $J = 8.6$); $^{13}\text{C-NMR}$ (CDCl_3 , 300 MHz): δ 9.4, 22.0, 26.4, 36.7, 50.1, 60.5, 118.8, 120.2, 134.7, 134.9, 152.8, 175.3.

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Chapter III

Influence of Steric Interaction on the Amplitude and Sign of the ECCD Spectrum

III.1. Design and studies of bulky tweezers

III.1-1: Background

The previous chapter covers the stereochemical determination of various α -chiral cyclic and acyclic acids derivatized with 1,4-phenylenediamine (carrier) using a host zinc bis-triphenylporphyrin tweezer system (ZnTPP-tz I). As it was discussed, formation of the tweezer-chiral substrate complex gives rise to a bisignate CD spectrum, reflecting the relative orientation of the chromophores, induced by the absolute stereochemistry of the asymmetric center. A series of ECCD data obtained for various cyclic and acyclic α -chiral amides allowed us to propose mnemonics that predict the expected ECCD sign for a given amide and lactams based on: a) size differentiation of the substituents (note that “size” refers to the relative A-values) on the chiral center in α -alkyl and α -alkoxy substrates (Figure III-1a, b); b) the possible aromatic interaction between π -system of the aryl substituent at the asymmetric center and the porphyrin core in α -aryl and α -aryloxyamides and lactams (Figure III-1c); c) halogen- π interaction taking place between a halide and a porphyrin in α -haloamides and lactams (Figure III-1d).

In the course of these studies it was found that the chiral substrates bearing substituents of relatively similar size gave ECCD spectra of low amplitude.^{1, 2} For instance while (*S*)-2,3-dimethylbutanamide **1** yields negative ECCD of relatively high

amplitude (-84), carrier (1,4-phenylenediamine) derivative of (*S*)-2-methylbutyric acid gives ECCD spectrum of significantly lower magnitude (Table III-1). This result was attributed to the higher conformational flexibility of the substrate **79** in the porphyrin tweezer complex as compared to the amide **1** resulting in the different magnitude of steric interaction within these two complexes. Namely, stabilization of ECCD active conformation in ZnTPP-tz complex with **79** proceeds through steric interaction with the two alkyl groups, that are characterized by significantly different A-values: *i*-Pr = 2.21 and CH₃ = 1.74.

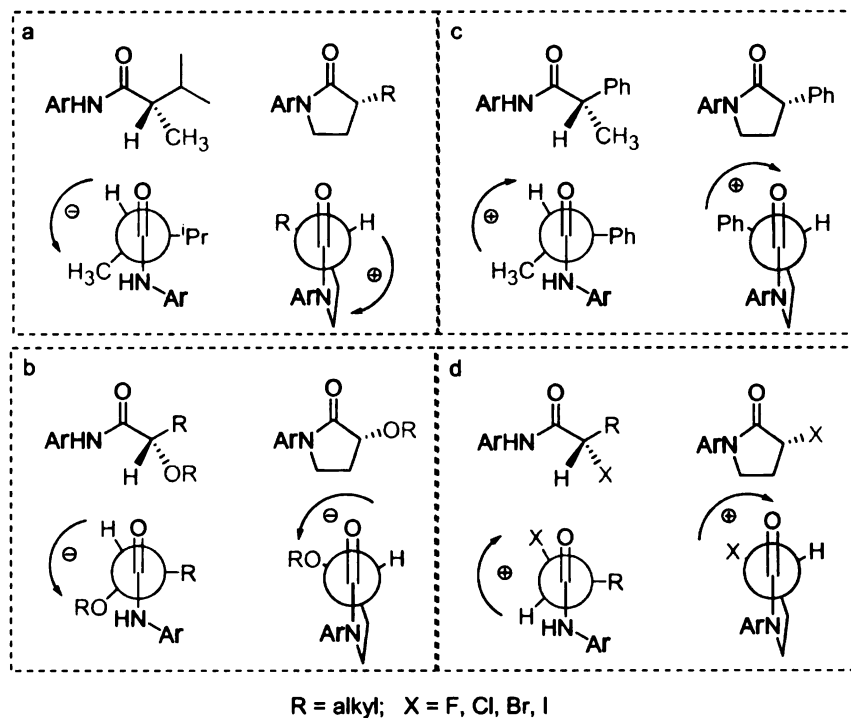
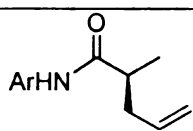
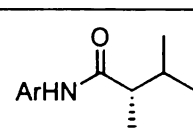
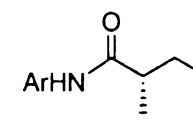
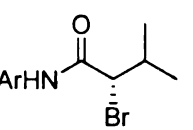
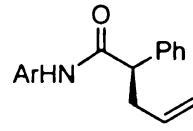
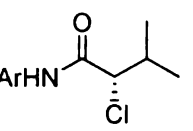
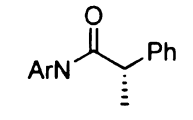
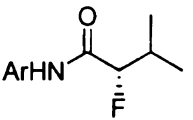


Figure III-1: Mnemonics derived for stereochemical determination of a) chiral α -alkylcarboxylic acids and lactams; b) α -alkoxycarboxylic acids and lactams; c) α -arylcaboxylic acids and lactams; d) α -halocarboxylic acids and lactams derivatized with 1,4-phenylenediamine.

As a result, large difference in the relative A-values of the substituents allows better stabilization of one ECCD active conformer versus the others, and for the ZnTPP-tweezer complex with amide **1** gives the ECCD spectrum of relatively high amplitude.

Table III-1: ECCD data for 1,4-phenylenediamine derivatized α -alkyl, α -halo and α -arylamides with ZnTPP-tz.

Substrate	λ , nm, ($\Delta\epsilon$)	A	Substrate	λ , nm, ($\Delta\epsilon$)	A
 86	428 (-23) 421 (+18)	-41	 1	428 (-43) 418 (+41)	-84
 90	429 (-11) 420 (+12)	-23	 6-Br	429 (+103) 421 (-91)	+194
 89	428 (-75) 421 (+60)	-135	 6-Cl	428 (+132) 421 (-82)	+214
 95	426 (+127) 416 (-46)	+173	 6-F	428 (+114) 420 (-30)	+207

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral substrate.

Same process in the tweezer complex with the amide of (*S*)-2-methylbutyric acid (**90**) proceeds through steric interaction with ethyl and methyl groups that have similar A-values: $\text{CH}_3\text{CH}_2 = 1.79$ and $\text{CH}_3 = 1.74$. This complex, due to the similarities in the relative sizes (A-values) of the two alkyl substituents, can stabilize different conformations with significantly smaller preference of one over the other. Thus, the presence different rotamers (possibly contributing to the opposite helicity of the porphyrins within the tweezer-**90** complex) yields the resulting spectrum of a significantly lower magnitude. Similar process takes place within a tweezer complex with amide **86**. The two alkyl substituents have relatively similar A-values

($\text{CH}_2=\text{CH}_2\text{CH}_2 = 1.76$ and $\text{CH}_3 = 1.74$) affecting the stabilization of the ECCD contributing rotomers and resulting in the spectrum of low amplitude. The influence of the difference between the A-values of the substituents on the ECCD amplitude underlines the fact that process of stereochemical determination with ZnTPP-tz is based on steric differentiation of a major ECCD active rotamer.

Influence of the conformational stability on the amplitude of the ECCD spectrum can be clearly observed in stereochemical determination of 1,4-phenylenediamine derivatives of α -aryl and α -halocarboxylic acids. Several examples (substrates **89**, **95**, **6-X** ($\text{X} = \text{F}, \text{Cl}, \text{Br}$)) summarized in Table III-1 display this phenomenon. Significant improvement in amplitude of the spectrum is believed to be due to enriched population of one rotomer, stabilized by the secondary interaction – aromatic π -stacking (for **89** and **95**) or halogen- π interaction (**6-X**, $\text{X} = \text{F}, \text{Cl}, \text{Br}$). As a result, presence of a halide at the asymmetric center causes 2-3 fold increase of the magnitude of ECCD signal. Similar effect is observed with aromatic substrates. Namely, 3-4 fold increase in amplitude is observed after with substrates **89** and **95** as compared to the alkyl analog **86**.

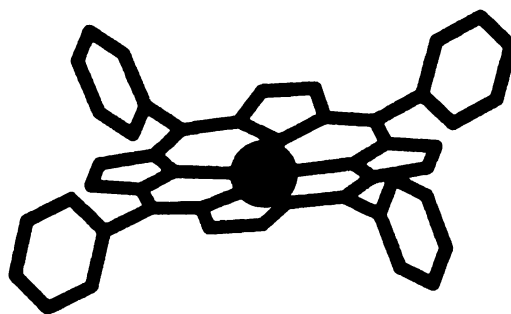


Figure III-2: Crystal structure of zinc tetraphenyl porphyrin (ZnTPP) obtained upon crystallization from dichloromethane/benzene solution.

Apart from the conformational stability of the chiral substrate complexed with porphyrin tweezer, the amplitude of the ECCD spectrum derives from a combination of factors such as the interchromophoric distances and the dihedral angle of the interacting electric transition dipole moments (see Chapter I.8).³ The latter observations raise the possibility that additional steric interactions between the substituents of the chiral center and the porphyrin ring in close contact with the chiral center may influence these parameters and improve the amplitudes of the ECCD spectra.

Based on previously published results by Nakanishi, Berova and coworkers, increase in the size of the porphyrin surface (tetrabenzoporphyrin was used as the porphyrin monomer to build the tweezer) is not sufficient for the amplification of the ECCD amplitude.⁴ Since the crystal structure of zinc tetraphenyl porphyrin reveals a perpendicular arrangement of the aromatic rings with respect to the porphyrin plane (Figure III-2),⁵ it is plausible to assume that one of the factors leading to the steric differentiation taking place within the porphyrin tweezer complex with chiral substrates is the interaction between the phenyl ring on the *meso* position of the porphyrin ring and the substituents at the asymmetric center (Figure III-3). Hence, additional steric interaction, introduced by placing substituents on the phenyl ring, could lead to greater steric differentiation, and thus enhancement of the ECCD amplitudes. Furthermore, additional steric interaction with the asymmetric center can increase the dihedral angle between the chromophores of the tweezer, which can also contribute to increased ECCD amplitude.

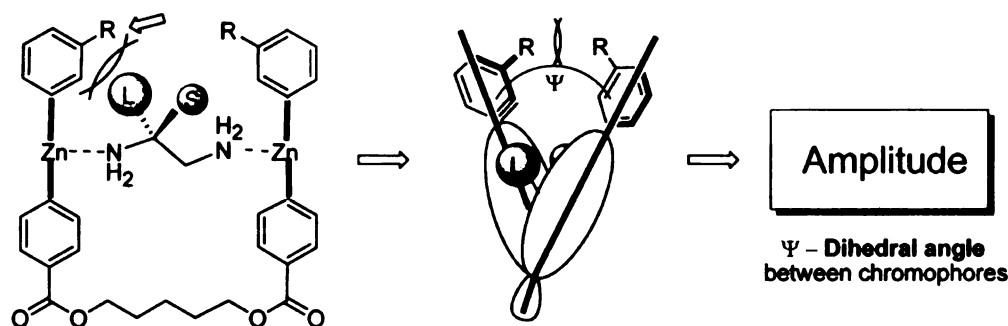


Figure III-3: Additional steric interaction as a means for improving ECCD amplitudes.

It is also possible that increased steric interaction will affect the conformational flexibility and promote equilibration of the chiral guest in one CD active conformer. A higher population of the major ECCD contributing rotamer might directly influence the ECCD amplitude. Based on the latter suppositions, we began to investigate the effect of varying the aryl groups at the *meso*-position of the porphyrin rings. For this purposes we have synthesized porphyrin tweezers **II-V** bearing different substituents at *ortho* and *meta*-positions on the *meso*-phenyl rings (see part III.5 for synthetic details).

III.1-2. Studies of modified zinc bis-5-(4-carboxyphenyl)-10,15,20-trimesitylporphyrin tweezer **II** (ZnTMsP-tz).

The first tweezer designed for these studies carried a 2,4,6-trimethyl substitution on the *meso* phenyl groups and yielded zinc bis-5-(4-carboxyphenyl)-10,15,20-trimesitylporphyrin tweezer **II** (ZnTMsP-tz, Figure III-4b). The distances between the *ortho* substitution of the phenyl ring and the bound guest, as measured when the tweezers **II** and **I** are complexed with 1,2-diaminoethane, allows to compare the steric environment build into the new porphyrin. As depicted in Figure III-4 introduction of the *ortho* methyl substitution decreases the distance to the prochiral carbon to 3.0 Å, as compared to 3.7 Å

measured with similar complex of tweezer **I**. Another significant interaction introduced into the complex is detected between two methyl substituents of the opposite porphyrins that are 2.98 Å apart. Thus, based on these models, it is possible to expect that each of these interactions (or combination of both) might influence the parameters (dihedral angle or interchromophoric distance) that could improve the amplitude of the ECCD bisignate.

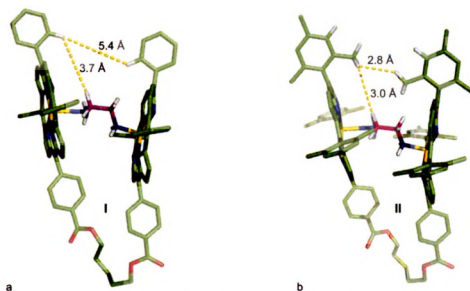


Figure III-4: a) Zn-TPP tweezer **I** and b) Zn-TMsP tweezer **V** complexes with 1,2-diaminoethane (molecular mechanics, Force Field MMFF94, Spartan v.5.1.3).

Since the symmetry of the methyl substitutions on the phenyl rings in ZnTMsP-tz **II** ensures that one set of methyl groups on each phenyl ring would always point into the cavity of the tweezer upon complexation with the chiral guest, this could obviously hinder the approach of the guest molecule to the metallo-porphyrin, and therefore, affect formation of the porphyrin tweezer-substrate complex. Qualitative examination of the effect of the newly introduced bulk onto the complexation process can be obtained from

UV-vis monitored portion wise addition of 1,n-diamines of different length to a solution of porphyrin tweezer.

It is well known that coordination of an amine group with the metalloporphyrin induces a red shift of the Soret band.⁶ Moreover, it has been established that complexation of ZnTPP-tz with diamines of different length results in the formation of a 1:1 complex at equimolar ratio of diamine to porphyrin tweezer. The Soret band of the new species red shifts to values that depend on the separation of the two interacting porphyrin planes, namely, closer interacting porphyrin rings red shift to a lesser degree as opposed to porphyrin rings that are well separated.⁶ This phenomenon is explained as a result of two counteracting effects: binding of the amine to the metalloporphyrin that leads to ~12 nm red shift and blue shift of the absorption as a result of bringing the two porphyrin planes close to each other.

Similar studies with the new porphyrin tweezer **II** after comparison with the known data obtained with ZnTPP-tz **I** should provide qualitative information with regards to their binding characteristics. For example, the amount of diamine necessary to fully complex the porphyrin tweezers will provide a measure for steric encumbrances due to the newly introduced aryl groups. Analysis of the extent of red shifting⁷ could yield qualitative information with regards to the separation of the two porphyrin planes complexed with the diamine as a result of substitution on the phenyl rings.

Table III-2 presents a comparative UV-vis study of porphyrin tweezer-diamine complexes for ZnTPP-tz **I** and ZnTMsP-tz **II**. A set of 1,n-diamines of different length was used for the titration experiments. As can be seen from entry 1, binding of 1,2-ethanediamine with ZnTMsP-tz results in a significantly smaller red shift as compared to

the shift obtained with ZnTPP-tz. This result is unexpected, since the complexation of both porphyrins occurs with the same substrate and, consequently, the separation of the porphyrins in both complexes is expected to be the same. In order to clarify the observed difference in red shift it is necessary to note that along with the distance between porphyrins the red shift of the complex is also affected by the geometry of porphyrin-porphyrin interaction. Namely, whether porphyrins are set face-to-face or are off-set.⁸⁻¹⁰ The former orientation is known to blue shift the porphyrin absorption, while the later induces a red shift of the Soret band. Thus, we can propose that two porphyrins in the complex of ZnTPP-tz (**I**) have relatively larger off-set orientation as compared to the porphyrins in ZnTMsP-tz (**II**) complex, which will lead to the larger red shift of ZnTPP-tz complex. Additionally, unlike tweezer **I**, which required an equimolar ratio of diamine, full complexation of tweezer **II** was detected after 30 equivalents of 1,2-ethanediamine.

Table III-2: Red-shift of tweezers upon titration with diamines

Entry	NH ₂ CH ₂ (CH ₂) _n NH ₂	Tweezers, $\Delta\lambda$ nm ($\Delta\lambda = \lambda_{\text{complex}} - \lambda_{\text{tweezer}}$)	
		I	II
1	n=1	3.0	1.5*
2	n=2	3.9	4.3
3	n=3	4.3	5.0
4	n=4	6.7	6.2
5	n=5	6.9	6.3
6	n=6	7.2	7.6
7	n=7	8.2	7.9
8	n=8	8.6	8.1

Data obtained in dichloromethane at 1:1.2 host-guest ratio;

* - shift obtained at 30 equivalents of diamine.

On the other hand, binding of ZnTMsP-tz with 1,3-diaminopropane required only 1 equivalent of substrate for complete complexation, also leading to a similar red shift as that observed for ZnTPP-tz (Table III-2, entry 2, 4.3 nm shift for **II**, 3.9 nm shift for **I**).

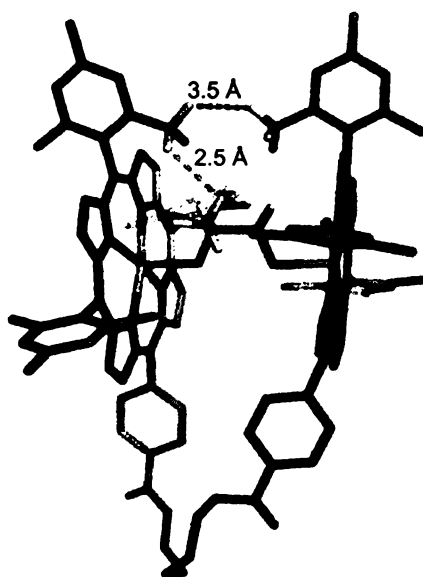


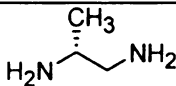
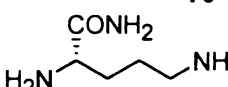
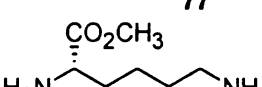
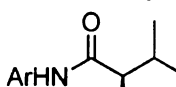
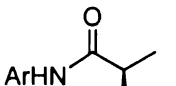
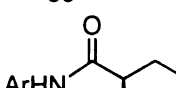
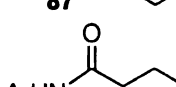
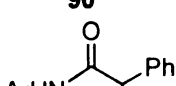
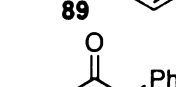
Figure III-5: ZnTMsP-tz **II** complexes with (*S*)-1,2-diaminopropane (molecular mechanics, Force Field MMFF94, Spartan v.5.1.3).

Complexation of all diamines of larger size with tweezer **II** (entries 3-8) also yielded similar red shifting as compared with ZnTPP-tz, suggesting similar binding behavior with the two tweezers. A general understanding of the observed results can be gained from the molecular modeling of the porphyrin tweezer-diamine complex. Figure III-4 depicts the models of ZnTMsP and ZnTPP tweezers complexed with 1,2-ethanediamine. Binding of the small diamine with ZnTMsP-tz is hindered by the steric interaction between the two methyl groups, which can explain the need for 30 equivalents of the diamine for full complexation. The interaction between the two methyl groups on opposing porphyrin rings is diminished with the lengthening of the substrate, thus leading

to the similar red shift behavior observed for both ZnTMsP-tz and ZnTPP-tz with diamines that are well separated.

Having shown that the binding of ZnTMsP-tz **II** with various diamines mimics closely what has been observed with ZnTPP-tz **I**, we next investigated the effect of the added steric bulk on the amplitude of the ECCD spectra upon complexation with a number of different chiral guests. As can be seen from Table III-3 (entries 1-3), both ZnTPP and ZnTMsP tweezers gave ECCD signals that exhibit the same helicity with diamines **76-78**.⁷ This implies that complexation proceeds through the same mode of binding and results in analogous conformations for both chromophoric systems. Interestingly, the ECCD amplitude of (*R*)-1,2-diaminopropane (**76**) complexed with ZnTMsP-tz was enhanced 3 fold. The source of this improvement can be rationalized by examination of the model depicted on Figure III-5. The distance between the *ortho*-hydrogen of the phenyl group on ZnTPP-tz **I** and the methyl substituent of the asymmetric carbon is estimated to be at 3.2 Å. Placement of the methyl group at the *ortho*-position shortens the distance to 2.5 Å, hence increasing the steric differentiation as a result of larger interaction between the two groups. Considering that the interchromophoric distance in both tweezer complexes is similar (based on the results obtained above, see Table III-3), relaxation of the complex might occur through increase of the dihedral angle between the chromophores, which contributes to the increase in the amplitude of the ECCD signal. It is also possible that the co-facially complexed porphyrins adopt a more twisted arrangement to avoid steric interaction. This would also increase the chiral twist formed within the complex, and thus contribute to the observed enhancement of the ECCD amplitude.

Table III-3: Stereochemical determination of diamines and carrier derivatized α -chiral carboxylic acids

Entry	Substrate	Tweezer			
		I		II	
		λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
1	 76	426 (-82) 416 (+58)	-160	432 (-310) 418 (+262)	-572
2	 77	428 (-20) 418 (+16)	-36	432 (-30) 419 (+43)	-73
3	 78	429 (-260) 419 (+132)	-392	431 (-60) 416 (+52)	-112
4	 81	425 (+31) 418 (-20)	+51	431 (+18) 414 (-9)	+27
5	 86	429 (-11) 420 (+12)	-23	-----	n/o
6	 87	429 (+15) 420 (-9)	+24	-----	n/o
7	 90	428 (-23) 421 (+18)	-41	-----	n/o
8	 89	428 (-75) 421 (+60)	-135	431 (-51) 414 (+44)	-95
9	 91	429 (-16) 420 (+21)	-37	432 (-8) 414 (+11)	-19

Spectra obtained in hexane and methylcyclohexane for amines and amides respectively at 0 °C and reported at 20 equiv of chiral guest.

Although an increase in amplitude is also observed for (*S*)-ornithine methyl amide **77**, a decrease in amplitude is registered for (*S*)-lysine methyl ester **78**. Significant drop in amplitude was also observed upon complexation of ZnTMsP-tz **II** with the carrier derivatized α -chiral carboxylic acids (Table III-3, entries 4-9). The most dramatic effect

of the steric hindrance induced by the ortho methyl groups of the TMsP porphyrin was observed with the amides of (*S*)-2-methyl-4-pentenoic acid (**86**), (*S*)-2-ethyl-4-pentenoic acid (**87**) and (*S*)-methylbutyric acid (**90**), which represent the set of substrates that initially induce a small helical preference when complexed with tweezer due to the similarity in the size of substituents at the chiral center (A-values: ¹¹ CH₃ = 1.74, C₂H₅ = 1.79, CH₂=CHCH₂ = 1.76). Complexed with tweezer **II**, compounds **86**, **87** and **90** did not lead to CD active bands. The other carrier-derivatized substrates **81**, **89** and **91** upon complexation with tweezer **II** led to observable ECCD spectra of significantly lower amplitude as compared to the ones observed with ZnTPP tweezer **I**. It is noteworthy, that despite the induced steric interaction the ECCD sign observed for substrate **89** remains negative, which implies presence of intact aromatic interaction between the phenyl group of the chiral substrate and the porphyrin ring. Parallel UV-vis titration of the tweezers with carrier-derivatized carboxylic acids **86-90** revealed a significantly lower binding affinity with ZnTMsP-tz **II** ($1.85 \times 10^3 \text{ M}^{-1}$ measured for **89** in methylcyclohexane) as compared to ZnTPP-tz **I** ($2.94 \times 10^4 \text{ M}^{-1}$ measured for **89** in methylcyclohexane). Therefore, it appears that functionalization of the porphyrins at *ortho*-position of the phenyl rings hinders the binding of chiral substrates to the tweezer and is not a globally applicable solution for improvement of ECCD amplitudes.

III.1-3. Studies of modified bis-porphyrin tweezers bearing *meta*-substitution on the phenyl groups: tweezers III, IV and V.

Modeling studies with tweezer complexes containing *meta* substitution of the phenyl groups suggested the possibility of increased interaction between the phenyl

groups of the tweezer and the substituents on the complexed chiral center, without the undesired weakening of binding affinity due to increased interchromophoric steric interactions. Consequently, the following three porphyrins were synthesized: zinc bis-5-(4-carboxyphenyl)-10,15,20-tri-1-naphthyl porphyrin (**II**, ZnTNP-tz, $\lambda_{\text{max}} = 421 \text{ nm}$, $\epsilon = 623,800 \text{ M}^{-1} \text{ cm}^{-1}$), bis-5-(4-carboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenyl porphyrin (**III**, ZnTMP-tz, $\lambda_{\text{max}} = 419 \text{ nm}$, $\epsilon = 1,150,000 \text{ M}^{-1} \text{ cm}^{-1}$), and bis-5-(4-carboxyphenyl)-10,15,20-tri-3,5-di-*t*-butylphenyl porphyrin (**V**, ZnTBP-tz, $\lambda_{\text{max}} = 419 \text{ nm}$, $\epsilon = 630,880 \text{ M}^{-1} \text{ cm}^{-1}$) (Figure III-6). The binding study (UV-vis) of the three new tweezers **III-V**, performed with a set of 1,*n*-diamines, is summarized in Table III-4. It is noteworthy that all new tweezers resulted in complete complexation after addition of 1 equivalent of the diamines, including 1,2-diaminoethane with the bulky ZnTBP-tz **V**, suggesting similar binding as compared to ZnTPP-tz **I**. The red shift induced upon complexation of tweezers **III-V** with diamines of various lengths closely follows the trend observed with ZnTPP-tz **I**, suggesting that the interchromophoric distance is not altered greatly.

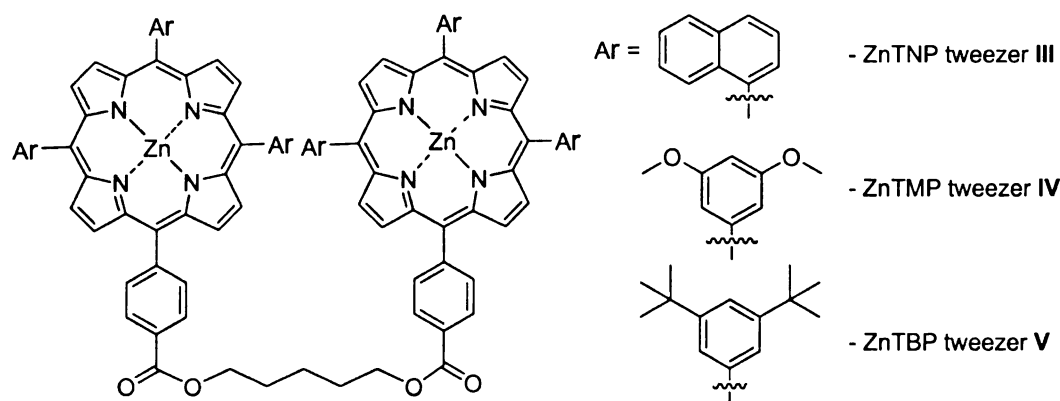


Figure III-6: Alternative tweezers **III-V**

The utility of porphyrin tweezers **III-V** was evaluated with chiral diamines **76-78** and carrier derivatized chiral carboxylic acids **81, 86-91** (Table III-5). ZnTNP-tz **III** yielded variable results, producing the opposite ECCD than what was anticipated with amides **81, 85** and **86**. Although the ECCD amplitude was enhanced for all amides the change in the steric differentiation within a complex is unexpected and not desired. In retrospect, the observed switch of helicity is surprising, since the naphthyl groups of ZnTNP-tz **III** can rotate away from the interior of the complexed tweezer/chiral substrate system, and thus not participate in steric differentiation. Tweezers **IV** and **V** are symmetrically substituted on both *meta* positions, and thus either rotamer of the *meso*-phenyl group would place the aryl substituent within the interior of the complexed system.

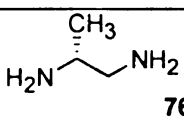
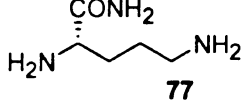
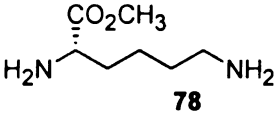
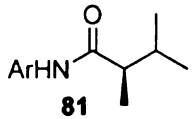
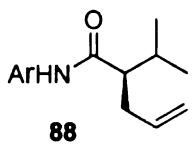
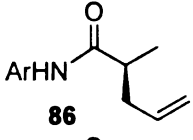
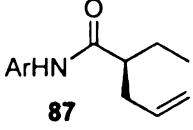
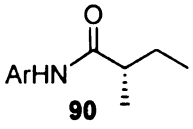
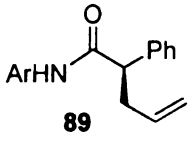
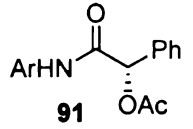
Table III-4: Red-shift of tweezers upon titration with diamines

Entry	NH ₂ CH ₂ (CH ₂) _n NH ₂	Tweezers			
		$\Delta\lambda$ nm ($\Delta\lambda = \lambda_{\text{complex}} - \lambda_{\text{tweezer}}$)			
		I	III	IV	V
1	n=1	3.0	3.5	2.1	3.5
2	n=2	3.9	3.7	4.5	4.3
3	n=3	4.3	5.7	5.9	5.7
4	n=4	6.7	6.7	6.5	6.5
5	n=5	6.9	6.9	6.9	6.7
6	n=6	7.2	7.2	7.3	7.2
7	n=7	8.2	8.2	8.1	8.0
8	n=8	8.6	8.6	8.1	8.4

Data obtained in dichloromethane at 1:1.2 host-guest ratio.

As listed in Table III-5, binding of ZnTMP-tz **IV** with diamines **76-78**, and carrier-derivatized chiral carboxylic acids **81, 86-91**, supports the latter supposition. For a number of cases a significant increase in the ECCD amplitude is observed. Most

Table III-5: Stereochemical determination of chiral diamines and carrier derivatized carboxylic acids with modified tweezers **III-V**

Substrate	Tweezers						
	I	III		IV		V	
	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
 76	-160	434 (-28) 419 (+32)	-60	432 (-117) 425 (+94)	-211	433 (-150) 418 (+140)	-290
 77	-36	434 (-18) 419 (+17)	-35	433 (-16) 417 (+6)	-22	433 (-85) 414 (+77)	-162
 78	-392	433 (-157) 423 (+141)	-198	430 (-39) 421 (+59)	-98	430 (-194) 422 (+178)	-372
 81	+98	432 (-40) 424 (+43)	-83	431 (+171) 422 (-137)	+308	430 (+268) 422 (-158)	+426
 88	+51	431 (-980) 422 (+820)	-1800	430 (+890) 422 (-732)	+1622	430 (+453) 422 (-338)	+891
 86	-23	430 (+27) 420 (-10)	+28	430 (-15) 420 (+18)	-33	430 (-20) 422 (+28)	-46
 87	+24	432 (+20) 424 (-10)	+30	430 (+20) 422 (-14)	+35	430 (+38) 422 (-23)	+61
 90	-41	431 (-10) 420 (+18)	-28	432 (-10) 421 (+12)	-24	430 (-47) 422 (+49)	-96
 89	-135	432 (-192) 424 (+141)	-333	432 (-504) 422 (+594)	-1098	430 (-1204) 422 (+1163)	-2367
 91	-37	430 (-94) 420 (+73)	-167	428 (-111) 418 (113)	-224	430 (-30) 418 (+43)	-73

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

striking is the effect of the *meta*-substituted methoxy groups in the steric differentiation of substituents, of the carrier-derivatized chiral carboxylic acids **81**, **86** and **89**, for which up to a nine fold increase in the amplitude is observed. Nevertheless, for the most

challenging substrates compounds **86**, **87** and **90**, where the steric difference between the substituents on the chiral center is small, ZnTMP-tz did not show any improvement of amplitude. It is noteworthy, that unlike ZnTNP-tz (**III**) tweezer **V** did not show any deviation from the mode of steric differentiation observed with ZnTPP-tz.

Favorable changes observed in the ECCD amplitude with *meta* substitution of the *meso* phenyl groups as demonstrated by ZnTMP-tz validated the idea of gaining better steric differentiation by substituting the *meso* position. Thus, to further enhance the steric differentiation of the substituents on the chiral center of the bound guest molecules, the *meta* substitutions were enlarged by utilizing *t*-butyl groups. Table III-5 lists the ECCD data generated upon complexation of diamines **76-78** and carrier derivatized chiral carboxylic acids **81**, **86-91** with ZnTBP-tz **V**. Gratifyingly, tweezer **V** bound to all of the chiral substrates and led to strong ECCD spectra. In all cases the anticipated sign of the bisignate curve is attained, including aromatic interaction with the substrate **91**, and for all cases the ECCD amplitudes were enhanced to a great degree. The challenging substrates **86**, **87** and **90** exhibited a two-fold increase in amplitude, signifying a better discrimination of the substituents by the sterically demanding *t*-butyl groups. The largest change was observed upon complexation of compound **88** and **89** with ZnTBP-tz, which led to >17 fold enhancement of the ECCD amplitude as compared to ZnTPP-tz **I**.

Figure III-7 illustrates an energy minimized molecular model of ZnTBP-tz complexed with diamine **76** and substrate **89**. Although speculative in nature, we believe these models along with the data in Table III-5 suggest a rationale for the increased amplitudes observed with ZnTBP-tz (**V**). Our working hypothesis is that increased bulk at the *meta* position leads to greater steric differentiation of substituents on the chiral

center, which consequently affects the amplitude of the ECCD spectrum through increase of the dihedral angle between the tweezer chromophores.

This reasoning is plausible for the tweezer complexes with derivatized chiral carboxylic acids, where, as it can be seen from the model (Figure III-7), the substituents at the chiral center experience dual interaction with the porphyrin tweezer: one with the *ortho* hydrogen and a new interaction with bulky *t*-butyl group that might positively contribute to chiral twist of chromophores. Calculation of the binding constant of **89** with ZnTBP-tz revealed similar binding properties for tweezers **V** and **I** ($1.27 \times 10^4 \text{ M}^{-1}$ and $2.94 \times 10^4 \text{ M}^{-1}$ in methylcyclohexane, respectively). Hence, considering that both tweezers bind the substrate with similar affinity, the increase in the amplitude cannot be contributed to the concentration of the complex in the solution and must arise from the change in the steric environment of the porphyrin tweezer. Thus, as a result one can summarize as discussed above, the *ortho* methyl-substituted ZnTMsP-tz **II** had >10 fold lower binding constant, leading to weak ECCD signals, *meta* substitution with the larger *t*-butyl group in tweezer **V** does not unfavorably affect the binding constant, but does lead to a great enhancement of the amplitude due to steric interaction with the substituents at the chiral center.

Steric interaction between the chiral center and the *t*-butyl group can also contribute to the enhancement of the observed amplitude with diamines. Although as it appears from the model of the complex (Figure III-7) binding of diamines to tweezer **V** can lead to additional interaction between the two bulky *t*-butyl groups, inducing a larger interchromophoric twist and, thus, enhancing the amplitude. Supporting data for this can be surmised from comparing the changes in amplitude observed for diamines **76** and **77**,

where the close proximity of the two porphyrin rings can lead to a more twisted conformation in order to avoid steric clash with the *meta*-substituted *t*-butyl groups. On the other hand, complexation of diamine **78** does not lead to an enhancement of the amplitude, although when compared with diamine **77**, the size of the substituents on the chiral center in both cases is similar. What is different is the separation of the two complexed porphyrins; diamine **78** is longer than diamine **77**, thus the complexed porphyrins are held further apart when complexed with diamine **78**, and consequently the *t*-butyl groups are not as effective in dictating a larger interchromophoric twist. This results in similar amplitude for both ZnTBP-tz (**V**) and ZnTPP-tz **I** when bound to diamine **78**. As such, it seems likely that the *meta*-substituents of the porphyrin tweezers do not directly interact with the bound chiral diamine, but lead to a greater interchromophoric twist as a consequence of the porphyrin-porphyrin interaction.

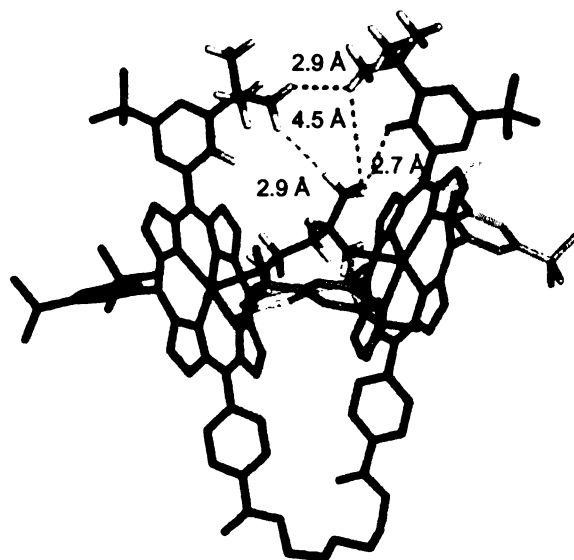


Figure III-7: ZnTBP tweezer **V** complex with (*R*)-1,2-diaminopropane (molecular mechanics, Force Field MMFF94, Spartan v.5.1.3).

In summary, the ECCD data suggest that *ortho* substituents placed onto the phenyl rings are not well tolerated, however, *meta* substituents do lead to enhanced ECCD amplitudes. In particular, ZnTBP tweezer, with *t*-butyl groups on the *meta*-positions is an effective tweezer with enhanced ECCD amplitudes for most systems tested. It is believed that the enhancement in the ECCD amplitude is the result of an increased interchromophoric twist induced by the steric clash of *t*-butyl groups on opposing porphyrin rings as they are brought close to each other via complexation with a chiral guest molecule.¹² It is noteworthy, that enhancement of the amplitude is observed despite the increased interchromophoric distance caused by the bulk of the porphyrins. Thus, while the distance between centers of the two porphyrins (Zn-Zn) in ZnTPP-tz complex with 1,2-diaminopropane is 6.9 Å, addition of steric bulk onto the porphyrin tweezer **V** increases the distance between the two chromophores to 7.5 Å, which could decrease the amplitude since the latter is inversely proportional to the square of the interchromophoric distance R .

As it was discussed above, the ability for the bulky porphyrin tweezer to affect the amplitude of CD bisignates obtained with derivatized α -chiral carboxylic acids arises from an increase of the dihedral angle between the two chromophores due to a larger steric interaction experienced by the porphyrin and the substituents at the stereocenter. Another outcome of the induced steric interaction can be the increased population of the major ECCD active conformation. Since the resultant ECCD spectrum is a summation of all signals generated by the complex, improved conformational stability of the substrate would also positively contribute to the amplitude of the bisignate. While the influence of induced sterics onto a dihedral angle can be identified through modeling studies of the

complexes (as it was discussed above), the conformational population cannot be easily quantified. The only way to quantitatively test the change in ratio of the major conformation in the complexes of two different porphyrins is to compare their ^1H -NMR spectra, in particular correlate the relative shielding induced by the porphyrins in each complex.

Table III-6: Relative shifts of ZnTPP and ZnTBP complexes with alkyl amides **92-94**

Substrate	$\Delta\delta = \delta_{\text{complex}} - \delta_{\text{free}}$							
	ZnTPP	ZnTBP	ZnTPP	ZnTBP	ZnTPP	ZnTBP	ZnTPP	ZnTBP
	(H _a)	(H _a)	(H _b)	(H _b)	(H _c)	(H _c)	(H _d)	(H _d)
 92	-0.112	-0.065	-0.108	-0.064	-0.061	-0.033	-0.042	-0.027
 93	-0.110	-0.063	-0.097	-0.060	-0.059	-0.020	-0.041	-0.016
 94	-0.124	-0.064	-0.102	-0.070	----	----	-0.102	-0.051

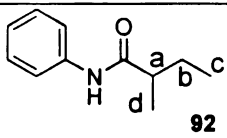
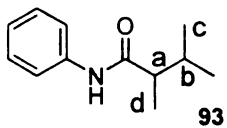
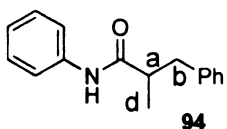
$\Delta\delta$ obtained in CDCl_3 at 1.2:1 porphyrin/amide ratio (12 mg (0.017 mmol) of Zn-TPP porphyrin and 20 mg (0.017 mmol) of Zn-TBP porphyrin were complexed with 0.014 mmol of substrate).

Since the NMR signal is an averaged result of all possible rotamers that exist in the solution, one could expect that change in the ratios of the conformers present in the complex, when averaged in a NMR spectrum, can affect the overall shift (shielding or deshielding) of peaks. In particular, if one of the complexes contains higher population of a specific rotamer, larger shielding effect might be expected. In order to check the possibility to apply this analysis to a qualitative analysis of conformational preference of the substrate, complexes of ZnTPP and ZnTBP with aniline derivatized carboxylic acids

92-94 were prepared in CDCl_3 (tetra-substituted porphyrins were used for simplicity of the experiment). The obtained data is summarized in Table III-6 as $\Delta\delta$ obtained by subtraction of δ (ppm) of the free compound from δ (ppm) of the substrate complex with porphyrin.

Comparing the shifts of protons in complexes of the two porphyrins reveals that ZnTPP caused significantly larger shielding of substrates **92-94** as compared to the corresponding complexes of ZnTBP. The larger upfield shift experienced by the substrates can be attributed to a better stabilization of one rotamer around the $\text{C}_{\text{C=O}}\text{-C}_{\alpha}$ bond in complex with ZnTPP. On the other hand, higher conformational stability of the substrate in the complex with porphyrin or porphyrin tweezer must also be reflected by the amplitude of ECCD spectrum. Controversially, the ECCD amplitudes of ZnTPP-tz complexes are significantly lower with all chiral amides presented in Table III-4. Hence, the stabilization of might not be the factor affecting the shielding of the substrates **92-94** in ZnTPP complexes.

Table III-7: Relative shifts of ZnTPP and ZnTBP complexes with amides **92-94**.

Substrate	$\Delta\delta_{\text{ZnTPP}} = \Delta\delta / 2.31$							
	ZnTPP	ZnTBP	ZnTPP	ZnTBP	ZnTPP	ZnTBP	ZnTPP	ZnTBP
	(H _a)	(H _a)	(H _b)	(H _b)	(H _c)	(H _c)	(H _d)	(H _d)
 92	-0.048	-0.065	-0.046	-0.064	-0.026	-0.033	-0.018	-0.027
 93	-0.047	-0.063	-0.041	-0.060	0.025	-0.020	-0.017	-0.016
 94	-0.05	-0.067	-0.044	-0.102	----	----	-0.044	-0.062

$\Delta\delta$ of ZnTPP is normalized for difference in binding constants

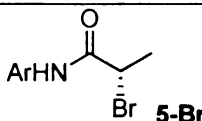
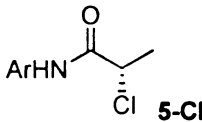
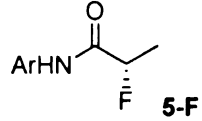
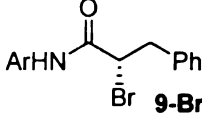
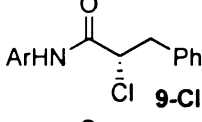
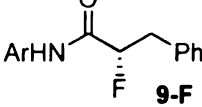
Another factor that has to be considered for interpretation of the observed result is binding of affinity of ZnTPP and ZnTBP with chiral amide. Since the system represents the non-covalent complex of porphyrin with substrate (complexation occurs through coordination of zinc in the porphyrin with carbonyl oxygen) relative binding affinities of two porphyrins can affect the shielding value. As it was established above, ZnTBP-tz is characterized by weaker binding constant (~ 2.31 times) as compared to ZnTPP-tz ($1.27 \times 10^4 \text{ M}^{-1}$ and $2.94 \times 10^4 \text{ M}^{-1}$ in methylcyclohexane, respectively for V and I). Thus, if normalized for binding difference, the overall shielding produced by ZnTBP porphyrin appears to be more significant for all protons as compared to ZnTPP porphyrin (Table III-7) and, hence might imply improved conformational stability of the chiral substrate in Zn-TBP tweezer (V) complexes. It is important to note that although successful in this particular case, a general applicability of this method for quantitative analysis of conformational preference in porphyrin/substrate complexes is yet to be tested on other porphyrin systems.

III.2. Halogen- π and π - π interaction in sterically encumbered porphyrin tweezers II-V

While identification of a major conformation of a substrate in the tweezer complex is essential for interpretation of the ECCD spectrum, understanding of the factors that influence conformational stability of the substrate in the complex might be beneficial for predicting the ECCD results. The latter might be especially interesting for the cases where the complexation of a chiral substrate with porphyrin tweezer results in a major rotamer that is stabilized not by steric encumbrance but through secondary

interactions, for instance through halogen- π interaction identified with chiral α -halo carboxylic acid derivatives.

Table III-8: ECCD results for carrier derivatized chiral α -halocarboxylic acids with tweezers I, III-V

Substrate	Tweezer						
	I	III		IV		V	
	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
 5-Br	+372	431 (+53) 423 (-60)	+113	432 (+78) 424 (-85)	+163	432 (+237) 423 (-215)	+452
 5-Cl	+75	431 (+203) 423 (-139)	+342	434 (+45) 424 (-56)	+105	432 (+57) 423 (-61)	+118
 5-F	+168	431 (+155) 423 (-108)	+263	430 (-72) 422 (93)	-165	431 (-162) 422 (+127)	-289
 9-Br	+90	431 (+201) 423 (-142)	+343	433 (+83) 424 (-81)	+164	432 (+115) 423 (-108)	+223
 9-Cl	+41	431 (+205) 423 (-151)	+356	431 (+104) 422 (-83)	+187	431 (+149) 422 (-104)	+253
 9-F	+40	431 (+59) 424 (-44)	+103	444 (-54) 422 (65)	-199	431 (-41) 420 (+38)	-79

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

The fact that additional steric interaction induced by *t*-butyl groups into the porphyrin tweezer complexes with α -chiral carboxylic acid derivatives does not affect the sign of the bisignates implies a high stability of the identified ECCD active conformation. Thus, the same tool, i.e. induced steric interaction, can be used for testing the presence and the stability of a secondary halogen- π interaction in porphyrin tweezer complexes with derivatized chiral α -halo carboxylic acids. For this purpose, 1,4-phenylenediamine

derivatized α -halogenated acids were complexed with tweezers **III-V** in methylcyclohexane and the ECCD spectra were measured. The results are summarized in Table III-8 and compared with ZnTPP-tz **I**.

Table III-8 presents the ECCD results for α -halogenated amides bearing non-branched alkyl substituents (methyl, benzyl) with bulky tweezers **III-V**. As it was expected ZnTNP-tz **III** produced results that were similar to ZnTPP-tz **I**, i.e., induced positive ECCD with (*S*)- α -haloamides **5-X** and **9-X** ($X = \text{Br}, \text{Cl}, \text{F}$). Interestingly, all ECCD spectra of complexes with tweezer **III** were of significantly higher amplitude, supposedly due to the improved steric interaction with the naphthyl groups.

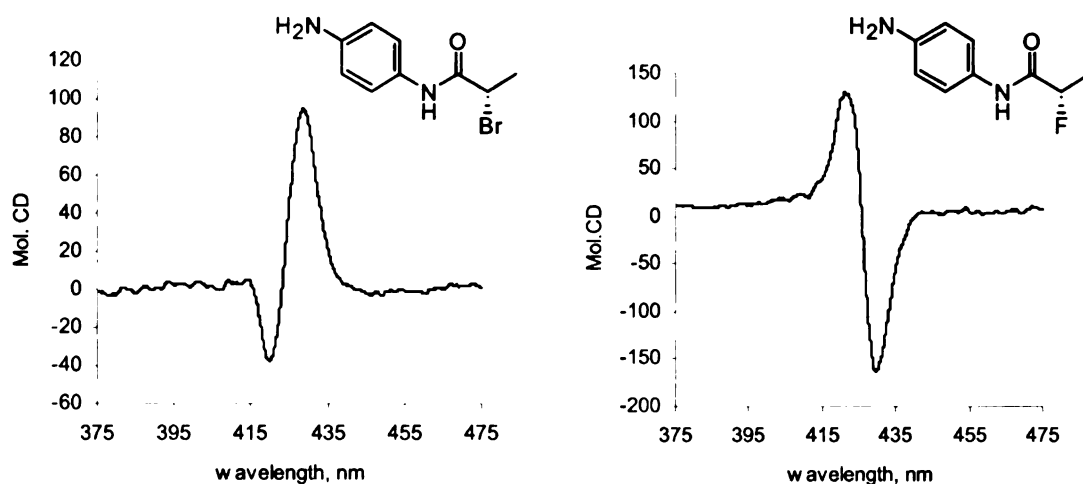
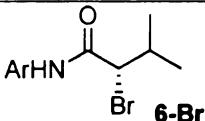
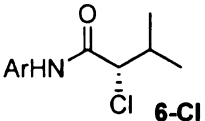
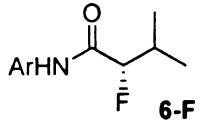
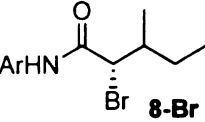
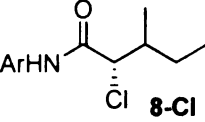
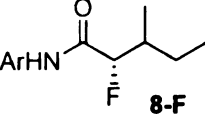


Figure III-8: ECCD spectra of carrier derivatized (*S*)-2-bromopropionic acid **5-Br** and (*S*)-2-fluoropropionic acids **5-F** with ZnTBP tweezer **V**. Spectra taken in methylcyclohexane and reported at 20 equiv of chiral guest

Unexpected switch of sign of ECCD was observed upon complexation of (*S*)-fluoroamides **5-F** and **9-F** with ZnTMP-tz and ZnTBP-tz. Here, while (*S*)- α -chloro and α -bromoamides induced positive helicity, (*S*)-fluoroamides resulted in appearance of a negative CD bisignate (Figure III-8). It is noteworthy, that the amplitudes of all spectra

are either in the range comparable with tweezer **I**, or for the majority of the substrates, significantly enhanced. Interestingly, despite the conformational change observed with derivatized (*S*)-2-fluoropropionic acids when complexed with tweezers **IV** and **V**, ZnTBP-tz gave significantly larger amplitude as compared to the presumed halogen- π interaction in complex with ZnTPP-tz. (*S*)-2-Fluoro-3-phenylpropionic acids **9-F** also switched the sign of ECCD with tweezers **IV** and **V**, but induced larger amplitude when complexed with ZnTMP-tz.

Table III-9: ECCD results for carrier derivatized chiral α -halocarboxylic acids bearing branched alkyl groups with tweezer **I**, **III-V**

Substrate	Tweezer			
	I	III	IV	V
	λ , nm ($\Delta\epsilon$)	λ , nm ($\Delta\epsilon$)	λ , nm ($\Delta\epsilon$)	λ , nm ($\Delta\epsilon$)
 6-Br	429 (+103) 421 (-91)	431 (163) 423 (-107)	430 (-227) 521 (188)	430 (-140) 421 (150)
 6-Cl	428 (+132) 421 (-82)	431 (290) 423 (-310)	430 (-190) 421 (155)	430 (-150) 420 (150)
 6-F	428 (+114) 420 (-30)	431 (222) 423 (-172)	430 (-21) 422 (23)	430 (-72) 420 (82)
 8-Br	429 (+94) 421 (-81)	431 (298) 423 (-207)	429 (-93) 420 (82)	431 (-78) 421 (69)
 8-Cl	429 (+108) 421 (-124)	431 (424) 423 (-320)	430 (-89) 421 (75)	431 (-92) 422 (90)
 8-F	429 (+96) 420 (-66)	431 (221) 423 (-193)	430 (-54) 420 (+51)	431 (-74) 422 (68)

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

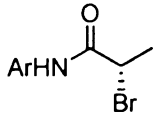
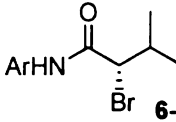
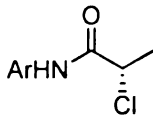
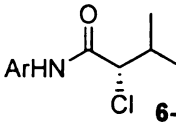
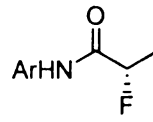
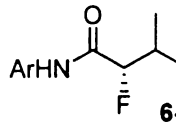
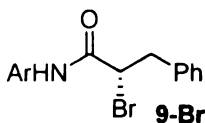
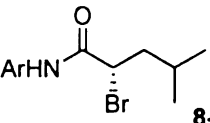
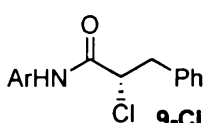
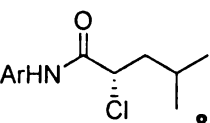
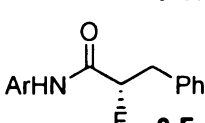
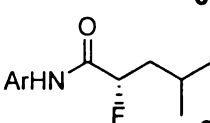
Complexation of (*S*)- α -halogenated amides bearing branched alkyl groups gives even more dramatic changes (Table III-9). While the substrates **6-X** and **8-X** (X = Br, Cl, F) induced the predicted positive chirality into ZnTPP-tz **I** and ZnTNP-tz **III**, the chromophores of tweezers **IV** and **V** adopted a counterclockwise orientation giving rise to a negative bisignate. Thus, it appears that steric encumbrance build by interaction between bulky porphyrins **IV** and **V** and isopropyl or isobutyl group at the chiral center of halo amides **6-X** and **8-X** (X = Br, Cl, F) destabilizes the major ECCD active conformation present in complexes of tweezers **I** and **III**. If summarized, the data in Tables III-8 and III-9 suggests the dependence of the stability of halogen- π interaction on the steric environment in the complex.

Taking into consideration that the sign of the CD bisignate is a direct consequence of the major ECCD active conformation of the chiral substrate in the complex, we assume that ZnTMP and ZnTBP tweezers result in a strong steric interaction with the chiral center affecting the secondary interaction of the halide with the porphyrin plane, which could lead to stabilization of a different ECCD active conformation, as seen previously with ZnTPP-tz **I**. Looking more closely at the data for substrates **5-X/7-X** and **6-X/8-X** (X = Br, Cl, F) it becomes apparent that compounds with smaller carbon substituents (Table III-8; A values: CH₃ = 1.74, CH₂Ph = 1.76) switch sign only in case of fluorine substitution, while substrates with branched β -position (Table III-9; A-values: $i\text{-Pr} \sim \text{sec-Bu} = 2.21$) switch the ECCD sign regardless of the type of halide present.

Similar studies of (*S*)- α -haloamides with ZnTMsP-tz **V** reveal a random change of the major ECCD active conformation. As it is summarized in Table III-10, most of the complexes resulted in unstable ECCD signal which changed or disappeared upon

addition of another equivalent of guest. Thus, substrates **6-Cl** and **7-Cl** after addition of 10 equivalents yielded a negative helicity into the porphyrin complex. Substrates **9-Br** and **9-Cl** being of the same helicity yet give rise to an opposite positive ECCD (10 equiv of chiral ligand). Increase of the concentration of chiral guest **9-Br** and **9-Cl** to 15 equiv resulted in a change of ECCD spectrum to negative, which disappeared upon addition of 20 equiv of the ligand. Other substrates induced either a complex CD signal (overlap of several ECCD bisignates), or were ECCD silent.

Table III-10: ECCD results for carrier derivatized chiral α -halo carboxylic acids with ZnTMsP tweezer

Substrate	Tweezer II		Substrate	Tweezer II	
	λ , nm ($\Delta\epsilon$)	A		λ , nm ($\Delta\epsilon$)	A
 5-Br	424 (-16) 413 (+18)	-34*	 6-Br	0	---
 5-Cl	0	---	 6-Cl	423 (-29) 412 (+15)	-44*
 5-F	0	---	 6-F	0	---
 9-Br	420 (+21) 415 (-25) 423 (-58) 413 (+54)	+46* -102**	 8-Br	0	---
 9-Cl	421 (+49) 415 (-38) 423 (-58) 413 (+54)	+87* -102**	 8-Cl	423 (-19) 412 (+10)	-29**
 9-F	0	---	 8-F	0	---

Spectra taken in methylcyclohexane at 0 °C: * - 10 equiv of substrate;
** - 15 equiv of substrate.

The conformational stability of a chiral substrate in porphyrin tweezer complex in most of the cases depends on affinity (binding constant) of the chiral guest with the metal (in this particular case, zinc) incorporated within the porphyrin core. It has been observed that weak binders induce multiple conformations resulting in unpredictable CD bisignates, overlapping signals or even absence of chiral induction.^{13, 14} Hence, the conformational change observed with (*S*)- α -haloamides with porphyrin tweezer **II** might be the result of 10 fold lower binding affinity as compared to ZnTPP-tz **I**. Nevertheless, as it was discussed above, complexation of α -chiral alkyl and alkoxy amides, results in CD bisignates of lower amplitude, yet induces the same helicity as observed with ZnTPP-tz throughout the range of substrate ratio tested (from 1 to 20 equiv). Thus, despite the lower binding constants, the conformational change observed with halogenated substrates can be the result of steric interaction between the *ortho*-methyl groups of the *meso*-phenyl rings and the stereocenter, leading to the destabilization of the putative halogen- π interaction.

In earlier studies of 1,4-phenylene (carrier) derivatized α -halocarboxylic acids (Chapter II) the major conformation of the substrate in the complex with ZnTPP-tz **I** was identified through comparison of the relative shielding experienced by α -alkyl and α -halogenated amides upon binding to the ZnTPP. As a result it was found that as a consequence of the halogen- π interaction taking place in ZnTPP complexes with carrier derivatized α -halocarboxylic acids, a larger shielding of substituents at the chiral center is observed as compared to the corresponding complexes of alkyl or alkoxy carboxylic acids, presumably due to an increased rate of complexation, stabilized by the secondary interaction. Thus, it is plausible to assume that similar analysis of α -haloamide

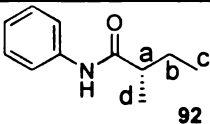
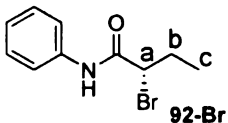
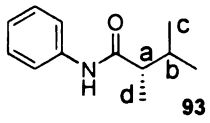
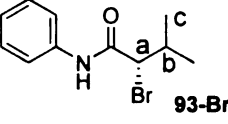
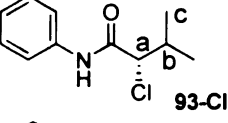
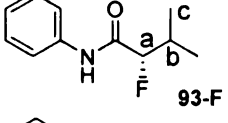
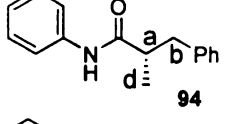
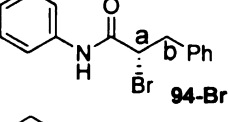
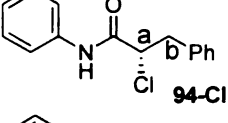
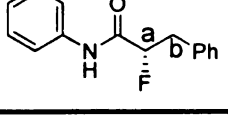
complexes with ZnTBP might also lead to identification of a major conformation. Here, one would expect that a change in conformation caused by disruption of halogen- π interaction would diminish the shielding of the bound halogenated substrate. Hence, substrates yielding positive ECCD with ZnTBP-tz should experience a larger shielding due to a favored secondary interaction with porphyrin, while the ones yielding a negative ECCD should be less shielded. Thus, for this purpose, several N-phenyl- α -haloamide complexes with ZnTBP were prepared and the resultant $\Delta\delta = \delta_{\text{complex}} - \delta_{\text{free}}$ from ^1H -NMR spectra were obtained and compared. For accuracy, the concentration of the porphyrin in the NMR tube was kept constant. In particular ZnTBP (20 mg, 0.017 mmol) was complexed with the substrate (0.014 mmol) in 0.2 mL of CDCl_3 to give 1.2:1 porphyrin/amide ratio. The resultant data is presented in Table III-11.

As it can be seen from entries 1 and 2, complexation of ZnTBP with N-phenyl-2-bromobutanamide **92-Br** induces significantly larger upfield shift of protons H_a , H_b and H_c , as compared to its alkyl analog **92**. This result is consistent with the trend observed upon complexation of halogenated amides with ZnTPP (Chapter II, Table II-2) suggesting the presence of halogen- π interaction. The carrier derivatized analog of **92-Br** – substrate (*S*)-**27** (see Chapter II for synthetic details) – gave positive ECCD ($A = +297$, first couplet at 430 (+154), second couplet at 422 (-143)), which arises from the conformation stabilized by halogen- π interaction.

Entries 3-6 in Table III-11 reveal an opposite result, namely, all N-phenyl-2-halo-3-methylbutanamides **93-X** ($X = \text{Br}, \text{Cl}, \text{F}$) and their methyl analog **93** experience similar $\Delta\sigma$ disregarding the presence of a halide at the asymmetric center. The upfield shift

observed is within a range that is usually detected upon complexation of carbonyl to the zinc porphyrin.

Table III-11: NMR analysis of α -chiral alkyl and halo amides in ZnTBP-tz complex

Entry	Substrate	ZnTBP porphyrin $\Delta\sigma = \sigma_{\text{complex}} - \sigma_{\text{free}}$				Tweezer V ECCD sign with carrier derivatives
		$\Delta\sigma$ (H _a)	$\Delta\sigma$ (H _b)	$\Delta\sigma$ (H _c)	$\Delta\sigma$ (H _d)	
1	 92	-0.065	-0.064	-0.033	-0.027	neg
2	 92-Br	-0.201	-0.090	-0.038	----	pos
3	 93	-0.063	-0.060	-0.020	-0.016	neg
4	 93-Br	-0.037	-0.019	-0.006	----	neg
5	 93-Cl	-0.053	-0.039	-0.009	----	neg
6	 93-F	-0.027	-0.016	-0.005	----	neg
7	 94	-0.064	-0.060	----	-0.051	neg
8	 94-Br	-0.187	-0.109	----	----	pos
9	 94-Cl	-0.200	-0.114	----	----	pos
10	 94-F	-0.044	-0.032	----	----	neg

Spectra obtained in CDCl₃ at 1.2:1 porphyrin/substrate ratio.

Thus, it can be concluded that halogenated substrates **93-Br**, **92-Cl** and **93-F** do not experience any additional halogen- π interaction with ZnTBP and the result can be attributed to the bulk of the alkyl substituent at the asymmetric center. The NMR data is supported by the ECCD experiment, where complexation of substrates **6-Br**, **6-Cl** and **6-F** with ZnTBP-tz leads to negative bisignate (rising from the conformation orienting the halide away from the porphyrin). If summarized, the data in Table III-11 indicates that presence bulky alkyl group at the chiral center in α -halogenated amides induces stabilization of a conformation which, based on previous studies, corresponds to the one assigned in the general mnemonic for α -alkyl and α -alkoxycarboxylic acids presented on Figure III-9.

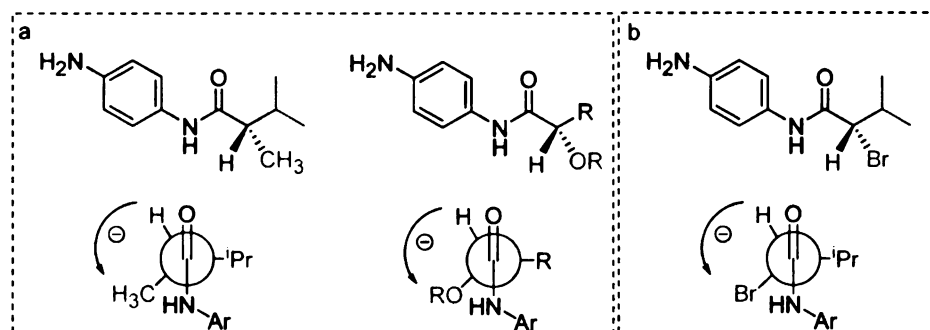


Figure III-9: a) Mnemonics derived for stereochemical determination of 1,4-phenylenediamine derivatized chiral α -alkyl and α -alkoxycarboxylic acids with porphyrin tweezers **I**, **III-V**; b) conformation derived for α -halogenated amides bearing a branched alkyl group at the asymmetric center.

Unlike amides in entries 3-6 (Table III-10), substrates **94**, **94-Br**, **94-Cl** and **94-F** (entries 7-10) experience a different shielding by the porphyrin. While the alkyl analog **94** exhibits $\Delta\sigma$ within a range common for alkylamides, N-phenyl-2-bromo and N-phenyl-2-chloropropanamides show significant upfield shift due to the present halogen- π interaction (note that the carried analogs of these two amides give rise to a positive

ECCD). The fluorinated analog **94-F**, on the contrary, induces a negative ECCD with ZnTBP tweezer, and similarly with alkyl substituted amide **94** and exhibit significantly lower shielding as a result of binding with ZnTBP, which suggests stabilization of a new conformation that does not involve interaction between halide and porphyrin.

Thus, the data obtained in these studies support the observation that increase of the bulk on the porphyrin affects the conformational stability of the substrates in the complex and causes disruption of halogen- π interaction, leading to a conformational change and consequently switch of the sign of the ECCD spectrum. The degree of such influence depends on the steric environment that is composed by both the interacting porphyrin and the substituent at the chiral center.

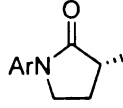
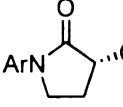
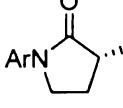
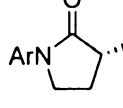
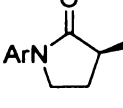
III.3. Influence of sterically encumbered porphyrin tweezers on the stereochemical determination of α -chiral butyrolactams

III.3-1: Chiral α -halo and α -aryloxy butyrolactams with bulky tweezers III-V

It is noteworthy that destabilization of halogen- π interaction is also prominent when cyclic amides are used. Thus, as it can be seen in Table III-12, while stereochemical determination of chiral α -alkoxy butyrolactams **37** and **38** with tweezer ZnTPP-tz (**I**) and bulky tweezers **III-V** occurs through the similar mode of stereodifferentiation (i.e. same porphyrin adopts the same helicity that correlated with the relative distribution of substituents at the chiral center), complexation of bulky tweezers **III-V** with halogenated lactams **40**, **44** and **45** leads to inversion of ECCD sign. In particular, while complexation of tweezer **I** with (*R*)-chloro butyrolactam (**40**) and (*R*)-

fluoro butyrolactam (**44**) induces a positive CD bisignate, tweezers **III-V** adopt a negative helicity. The (*S*)-iodo butyrolactam **41** also induces a counterclockwise orientation of porphyrins (negative ECCD) with tweezer **I** which switches to clockwise (positive) orientation when sterically demanding porphyrin tweezers are used.

Table III-12: Stereochemical determination of α -chiral alkoxy and halo butyrolactams with bulky tweezers **III-V**

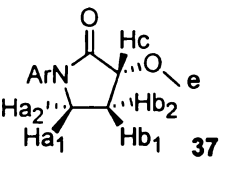
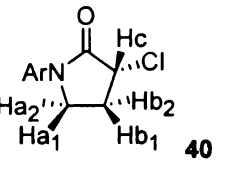
Substrate	Tweezers						
	I	III		IV		V	
	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
 37	-110	432 (-212) 423 (+163)	-375	433 (-54) 423 (+52)	-106	430 (-410) 422 (+333)	-743
 38	-55	432 (-127) 422 (+77)	-204	432 (-51) 423 (+49)	-100	430 (-340) 421 (+239)	-579
 40	+61	433 (-73) 423 (+46)	-119	433 (-17) 422 (+29)	-46	431 (-49) 421 (+44)	-93
 44	+48	431 (-17) 420 (+13)	-30	429 (-27) 418 (+21)	-48	430 (-25) 421 (+31)	-56
 45	-27	433 (+15) 425 (-8)	+23	433 (+24) 422 (-18)	+42	431 (+32) 421 (-29)	+61

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

Since the cyclic structure of the chiral lactams ensures their conformational stability in the complex with the porphyrin tweezer, the switch of ECCD sign must be caused either by a change in binding mode of the bulky tweezers with the butyrolactams or occur due to an inverted relative orientation of the two porphyrins caused by disruption of the halogen- π interaction resulting in the porphyrin covering the small hydrogen rather than the halide. The former can be overruled by the similarity observed in stereodetermination of alkoxy butyrolactams with all four porphyrin tweezers applied.

Thus, all alkoxy lactams complexed with tweezers **I** and **III-V** resulted in a negative ECCD. The later, can be verified by comparative NMR analysis of complexes formed with bulky porphyrins, for instance ZnTBP, with α -alkoxy butyrolactam **37** and α -halo butyrolactam **40**.

Table III-13: Shielding of the protons observed upon complexation of substrates **37** and **40** with Zn-TBP

H	$\Delta\sigma = \sigma_{\text{complex}} - \sigma_{\text{free}}$	
	 37	 40
a ₁	-0.029	-0.009
a ₂	-0.017	-0.001
b ₁	-0.046	-0.015
b ₂	-0.020	-0.001
c	-0.121	-0.052
d	-0.053	-----

Spectra obtained in CDCl₃ at 1.2:1 porphyrin/substrate ratio.

The NOESY-1D experiments discussed earlier in Chapter II were used for assignment of the diastereotopic protons of lactams **37** and **40**. NMR samples were prepared in 1 mL of CDCl₃ from N-Boc protected precursors of **37** (3 mg, 10 mmol) and **40** (3 mg, 10 mmol) complexed with zinc tetraarylporphyrin ZnTBP (2.2 equiv of porphyrin used to ensure excess of the porphyrin per each coordinating site of the chiral lactam) and the relative shift of each proton induced by shielding of the porphyrin is summarized in Table III-13. As a result of this analysis it becomes apparent that despite the different intensity of shielding experienced by the two substrates the position of the porphyrin relative the methoxy group and the chlorine atom of the two lactams is similar.

ZnTBP in both complexes coordinates to the carbonyl and produces larger shielding of protons H_{a1} and H_{b1} (located in the same plane with H_c) as compared to H_{a2} and H_{b2} (located in the same plane with OCH_3 or Cl), which can be a direct consequence of the porphyrin sliding away from the methoxy group or chlorine atom and residing closer to the hydrogen (H_c) on the asymmetric center.

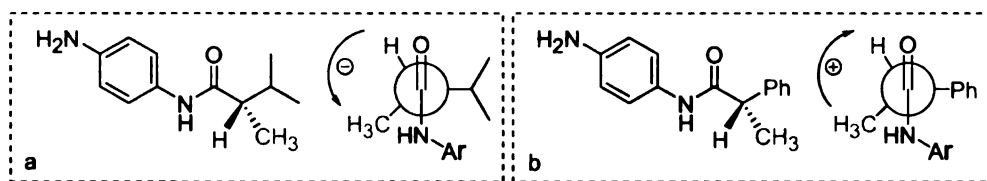


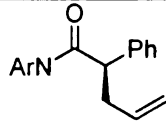
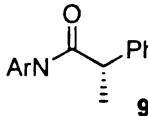
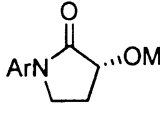
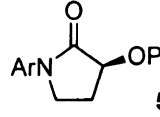
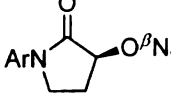
Figure III-10: Stereochemical determination of 1,4-phenylenediamine derivatized: a) chiral α -alkyl carboxylic acids and b) α -aryl carboxylic acids with porphyrin tweezers **I**, **III-V**

Another type of secondary interaction has been observed in ZnTPP tweezer **I** complexes with acyclic amides bearing aromatic substitution at the chiral center and α -aryloxy lactams. Stereochemical determination of 1,4-phenylenediamine derivatives of chiral α -aryl carboxylic acids with ZnTPP-tz resulted in ECCD spectra that were of opposite sign to the one expected from the mnemonic proposed for chiral α -alkyl and α -alkoxy amides (Figure III-10). For instance, while stereochemical determination of carrier derivative of (*S*)-2,3-dimethylbutyric acid results in negative ECCD (porphyrin differentiated between the small hydrogen and large *iso*-propyl, the medium methyl substituent is oriented away from the porphyrin), change of *iso*-propyl group to phenyl ring gives rise to positive CD bisignate (note that the size of the substituents is based on their relative A-values).

Similarly, as is presented in the Table III-14, the expected sign for carrier derivatized (*S*)-2-phenylpropionic acids **91** with ZnTPP-tz **I** is negative, since the

expected stereodifferentiation between the small hydrogen and the large phenyl ring leads to a counterclockwise orientation of the chromophores. Nevertheless, the observed positive ECCD signal signifies a clockwise orientation of chromophores in the complex. Similarly, substrate **88** induced a negative helicity within the ZnTPP tweezer **I** complex as opposed to the expected positive ECCD.

Table III-14: Influence of steric encumbrance on π - π interaction.

Substrate	Tweezers						
	I	III		IV		V	
	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
 88	-135	432 (-192) 424 (+141)	-333	432 (-504) 422 (+594)	-1098	430 (-1204) 422 (+1163)	-2367
 91	+173	430 (+219) 420 (-126)	+345	428 (+459) 419 (-276)	+735	428 (+545) 420 (-402)	+947
 37	-110	432 (-212) 423 (+163)	-375	433 (-54) 423 (+52)	-106	430 (-409) 422 (+322)	-731
 50	-45	430 (+52) 422 (-61)	+113	431 (+102) 422 (-95)	+197	430 (+402) 422 (-336)	+738
 51	-52	432 (+87) 424 (-90)	+177	432 (+198) 423 (-191)	+389	431 (+211) 424 (-243)	+454

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

When aromatic substrates were complexed with tweezers **III-V**, no change in stereodifferentiation was detected. On the contrary, all substrates induced ECCD of significantly larger magnitude. Thus, ZnTMP tweezer **IV** and ZnTBP tweezer **V** yielded a 10 fold enhancement of amplitude. Analogous effect of aromatic interaction on the sign of ECCD spectrum is observed for ZnTPP-tz **I** complexes of α -aryloxy- γ -butyrolactams. Namely, while (*R*)-2-OMe-butyrolactam **37** induces a negative helicity

with the porphyrin tweezer complex, the expected sign of CD bisignate for (*S*)-2-OPh-butyrolactam (**50**) and (*S*)-2-ONaph-butyrolactam (**51**) is positive (Table III-14) (the stereodifferentiation is expected to take place between the medium aryloxy group and small hydrogen in favor of the latter). Nevertheless, both complexes resulted in counterclockwise orientation of chromophore giving rise to negative ECCD when complexed with ZnTPP-tz **I**. Considering the rigidity of the cyclic structure of lactams and that the relative sizes of alkoxy and aryloxy groups are characterized by a similar A-value (0.5-0.75) that fall into the category of a “medium group”, the difference in ECCD observed between substrates **37** and **50** (**51**) can be explained by π - π interaction between the aromatic porphyrin ring and phenyl (naphthyl) group. Effective π - π stacking between the phenyl ring of the chiral substrate and the porphyrin can be clearly seen on the molecular model of ZnTPP tweezer complex with (*S*)-2-OPh-butyrolactam (Figure III-11).

It is important to note that while acyclic α -arylamides exhibit aromatic interaction in all porphyrin tweezer complexes, addition of aryloxylactams to bulky tweezers **III-V** results in switch of ECCD sign. Thus, both lactams **50** and **51** induce positive helicity within the porphyrin tweezer complex as opposed to the negative ECCD detected with ZnTPP-tz **I**. Nevertheless, despite the disruption of aromatic interaction, the bulk of the porphyrin positively affects ECCD amplitudes, i.e., 8-15 fold enhancement of amplitude was observed with increase of bulk from tweezer **III** to **V**.

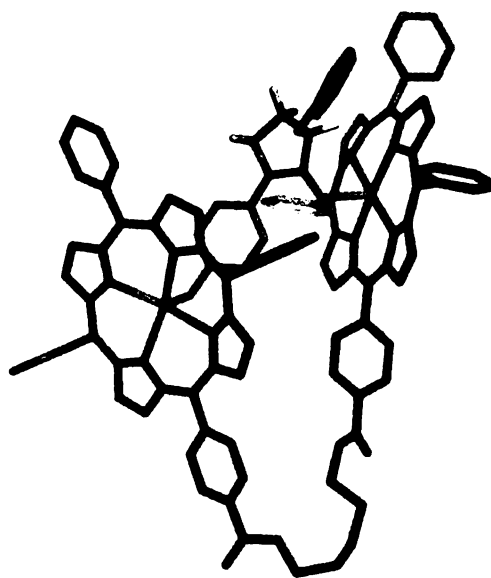


Figure III-11: ZnTPP tweezer complex with (*S*)-2-OPh-butyrolactam (molecular mechanics, Force Field MMFF94, Spartan v.5.1.3)

III.3-2: Chiral α -alkyl butyrolactams with bulky tweezers III-V

α -Alkyl butyrolactams present one more class of compounds that exhibit an unusual behavior in stereochemical determination with ZnTPP tweezer I. Considering that the binding of an α -alkyl lactam with bis-porphyrin tweezer is similar with the previously discussed alkoxy and halo lactams, i.e., occurs through the primary amine of the carrier and the carbonyl oxygen, the stereodifferentiation in the complex should occur between an alkyl substituent and the hydrogen oriented toward the porphyrin bound to the carbonyl. Steric interactions with an alkyl group should cause the porphyrin to twist towards the hydrogen and induce a clockwise orientation of the tweezer chromophores. Hence, the expected sign of ECCD for alkyl lactams with ZnTPP tweezer is positive (Figure III-12a).

However, as can be seen from the Table III-15, chiral α -alkyl lactams **66-70** induce a negative helicity into the ZnTPP-tz **I**. After comparison (see section II.3, chapter II) of the relative distribution of the substituents at the chiral centers in alkoxy and alkyl lactams, it becomes apparent that unlike alkoxy and halo lactams, where the β -methylene was assigned as the large group, the alkyl lactams present the alkyl group as the large substituent. Hence, it was proposed that coordination of the alkyl lactam to the ZnTPP occurs in a way that places the large alkyl substituent at the chiral center away from the porphyrin. In such a case, upon coordination, the porphyrin faces the methylene (medium group) and the hydrogen (small group). Size based steric differentiation in favor of the smaller group induces a counterclockwise orientation of chromophores and results in the unexpected negative ECCD for alkyl lactams **66-70**.

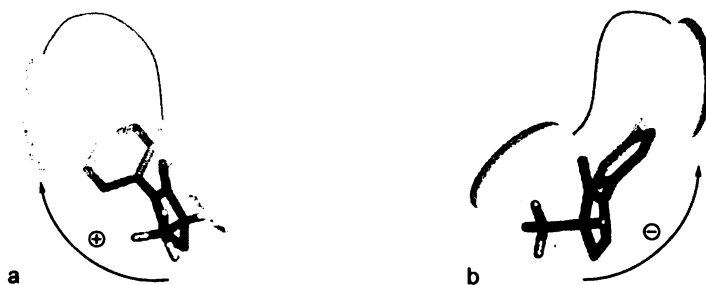


Figure III-12: (*S*)-2-Methylbutyrolactam with porphyrin tweezer **I**: a) an expected steric differentiation inducing a positive helicity into the porphyrin tweezer; b) possible interaction leading to the observed negative ECCD.

Subsequently, the working hypothesis on the porphyrin-lactam interaction is that the complexation of the tweezer **I** to α -alkoxy (aryloxy), α -halo and α -alkyl butyrolactams occurs between the medium (alkoxy (aryloxy), halo and methylene group respectively) and small hydrogen, and away from the large group of the asymmetric

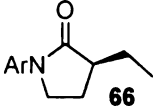
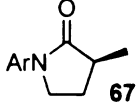
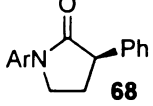
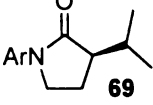
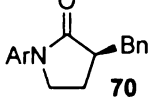
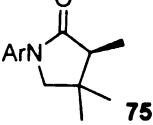
center, i.e., the methylene of the cycle in alkoxy or halobutyrolactams and an alkyl substituent in alkylactams.

This hypothesis was supported by the ECCD and NMR results obtained with (*S*)-2,3,3-trimethylbutyrolactam (**75**). Substrate **75** has an additional substitution at β -position of the lactam ring. Presence of *gem*-dimethyl group on the methylene changes the size based distribution of substituents relative to the carbonyl. In particular, unlike the alkyl lactams **66-70**, the α -methyl here plays the role of the medium group. Consequently, based on the proposed mode of stereodetermination, the stereodifferentiation is expected to take place between the α -methyl (the medium group) and the small hydrogen and give rise to positive ECCD. Indeed, complexation of **75** with ZnTPP-tz **I** resulted in a positive CD bisignate of high amplitude ($A = +346$). Thus, the observed result supports the proposed model of steric differentiation operating in cyclic structures, i.e. binding of the porphyrin to the carbonyl occurs from the site opposite to the large group.

Unlike ZnTPP tweezer **I** complexation of alkyl butyrolactams **66-70** with tweezers **III-V** leads to a clockwise orientation of porphyrins and gives rise to a positive ECCD. Considering the conformational stability of butyrolactams, the observed outcome could originate from the change in binding mode between the porphyrin tweezer and an α -alkyl butyrolactam. The most unexpected is the result obtained with ZnTNP-tz **III**. Despite its close resemblance with tweezers **I**, and the fact that during all previous studies tweezer **III** has strictly mimicked the behavior of ZnTPP-tz, complexation of alkyl lactams **66-70** induces a change of the ECCD sign. This might be an important indication of the specificity of the interactions taking place in tweezer **I** complexes with alkyl

lactams, which are altered even by an insignificant change in the structure of a bis-chromophore.

Table III-15: ECCD sign of α -chiral alkyl butyrolactams switches with increase of the bulk of the porphyrin tweezer

Substrate	Tweezers						
	I	III		IV		V	
	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
 66	-54	433 (+101) 424 (-68)	+169	431 (+51) 422 (-50)	+101	432 (+42) 422 (-26)	+68
 67	-23	432 (+118) 423 (-84)	+302	431 (+95) 422 (-79)	+174	431 (+70) 421 (-40)	+110
 68	-211	433 (+136) 424 (-79)	+215	432 (+105) 422 (-56)	+161	431 (+140) 421 (-87)	+207
 69	-528	433 (1865) 422 (-1034)	+2899	431 (+564) 421 (-479)	+1033	431 (+210) 421 (-292)	+602
 70	-50	433 (+214) 424 (-121)	+335	431 (+74) 422 (-64)	+138	431 (+104) 421 (-66)	+170
 75	+346	432 (-676) 423 (+434)	-1110	430 (-832) 422 (+653)	-1485	431 (-429) 422 (+327)	-756

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

In order to gain an insight into the binding mode taking place in complexes of tweezers **III-V**, let us focus on substrate **75**. As it can be seen from the ECCD results presented in the table, the sign of (*S*)-2,3,3-trimethylbutyrolactam carrier conjugate remains the same with all tweezers applied and, hence, indicates similarity in complexation and stereodifferentiation. The proposed mode of stereodifferentiation in this structure involves complexation of the porphyrin and the carbonyl oxygen with the methyl group and the hydrogen bisecting the carbonyl (Figure III-13), which is similar to

the coordination proposed for the alkoxy butyrolactams **37-39** and halo butyrolactams **40**, **44** and **45**. One can envision a similar type of binding taking place between substrate **75** and bulky tweezers and giving rise to a positive ECCD bisignate.

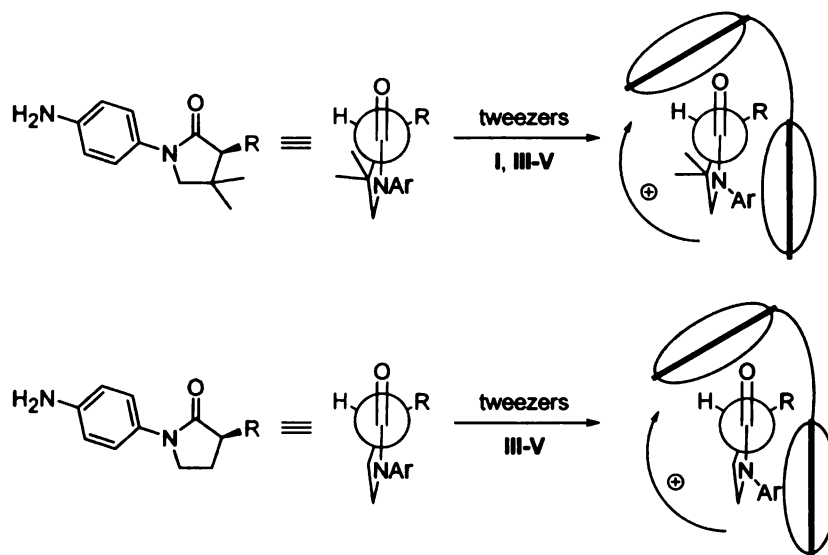


Figure III-13: Complexation of (*S*)-2,3,3-trimethylbutyrolactam carrier conjugate with tweezers **I**, **III-V** results in negative ECCD spectra. Bulky tweezers **III-V** adopt positive helicity with lactams **66-70**.

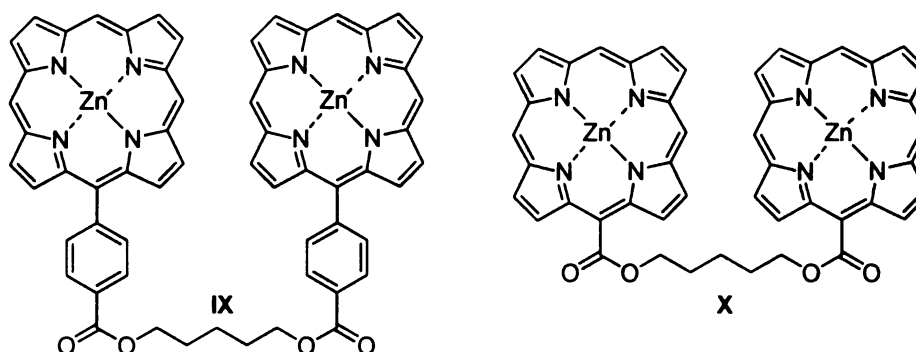
Analogous mode of binding, if applied to substrates **66-70** explains the clockwise orientation of the porphyrins in tweezers **III-V**, resulting in positive ECCD. Thus, we can conclude that complexation of all chiral α -alkyl lactams, with tweezers **III-V** occurs through a binding mode similar to the one proposed for α -alkoxy and α -halogenated lactams, and the stereodifferentiation between the two substituents at the asymmetric center occurs in favor of the smaller group. Nevertheless, despite the identified geometry of porphyrin-lactam interaction in bulky tweezers, no additional insight into unusual mode of complexation of ZnTPP-tz with alkyl lactams could be gained.

III.4. Investigation of the role of the phenyl rings in stereodifferentiation.

***Meso*-monosubstituted porphyrin tweezers **VI** and **VII**.**

The results discussed up to this point in Chapter II and III, while focusing on establishment of working mnemonics for several types of chiral substrates and improvement of ECCD amplitude, served also a greater cause - understanding of possible interactions in tweezer-chiral substrate complex that induce formation of chiral twist between chromophores. Thorough investigation of these interactions is necessary for the improvement of the porphyrin tweezer technique and development of more effective universal chromophoric host. The studies presented above concluded that increase of steric interaction between the porphyrin tweezer and the complexed chiral substrate positively contribute to the amplitude of ECCD spectrum and in some cases helped to destabilize the secondary interaction within the complex (halogen- π) or stabilize one common mode of binding within one class of substrates (butyrolactams). From the data presented above it is plausible to assume that the stereochemical determination taking place in the complex is a direct consequence of the interaction of the orthogonal phenyl ring (or any substituent on the latter) with the asymmetric center. If being proved, the role of the porphyrin core can be then diminished to the role of a provider of primary coordination and exciton interaction (although the size of the porphyrin might play crucial role in the binding mode of the tweezer to the substrate). A possible proof for such an assumption would be the disappearance of the ECCD signal with deletion of meso-substituents providing the steric interaction of interest. Thus, in order to check the validity of the proposed hypothesis, the syntheses of “non-substituted” porphyrin **VI** and **VII** (Scheme III-1) were pursued.

Scheme III-1: *Meso*-monosubstituted porphyrin tweezers **VI** and **VII** for identification of the role of the substitution at the porphyrin in the process of stereodifferentiation.

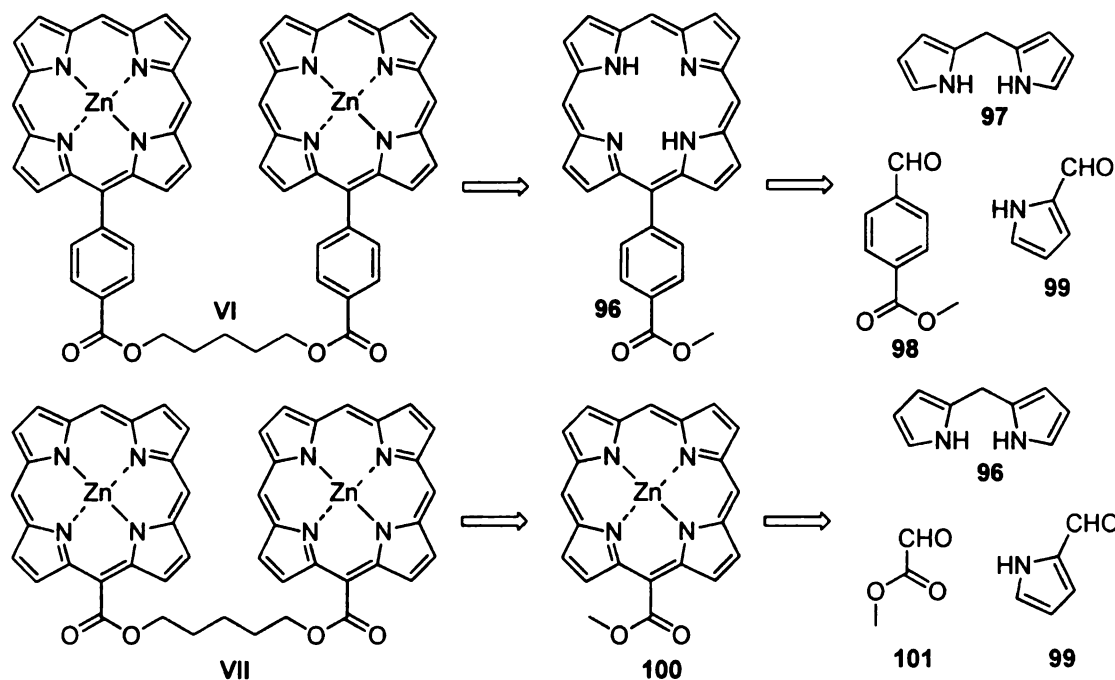


Structure **VI** represents the system that could potentially reveal the role of three *meso* phenyl groups in the process of stereodifferentiation. Deletion of the fourth phenyl ring in structure **VII** might also help to establish a role of this fragment during the complexation process, for the stabilization of the ECCD major conformation.

In retrospect, the porphyrin tweezer **VI** and **VII** can be obtained from the *meso*-monosubstituted porphyrins **96** and **100** respectively (Scheme III-2), through a sequence of reactions previously used for synthesis of porphyrin tweezers **I-V**. Construction of porphyrins **96** and **100** can be achieved through the previously reported condensation of commercially available 2-pyrrolicarboxaldehyde (**99**) and 4-methylcarboxybenzaldehyde (**98**) or synthesized aldehyde **100** with dipyrromethane (**97**), which can be accessed through acid catalyzed condensation of paraformaldehyde and pyrrole.^{15, 16} Assembly of porphyrin from (**97**), (**98**) and (**99**) results in formation of a mixture of two products 5-[4-carboxyphenyl]porphyrin (**96**) and *meso*-disubstituted 5,15-di[4-methylcarboxyphenyl] porphyrin in 9 % and 18 % yield respectively, the desired product being a minor product of the reaction. Construction of porphyrin tweezers requires linkage of two porphyrins through pentanediol via coupling of alcohol with the porphyrin

acid. Hence, a hydrolysis of porphyrin (**96**) was performed. Unfortunately, the formed porphyrin acid, unlike the porphyrin acids used for synthesis of tweezers **I-V**, is highly hydrophilic and cannot be extracted from the aqueous medium.

Scheme III-2: Retrosynthetic analysis of porphyrin tweezers VI and VII

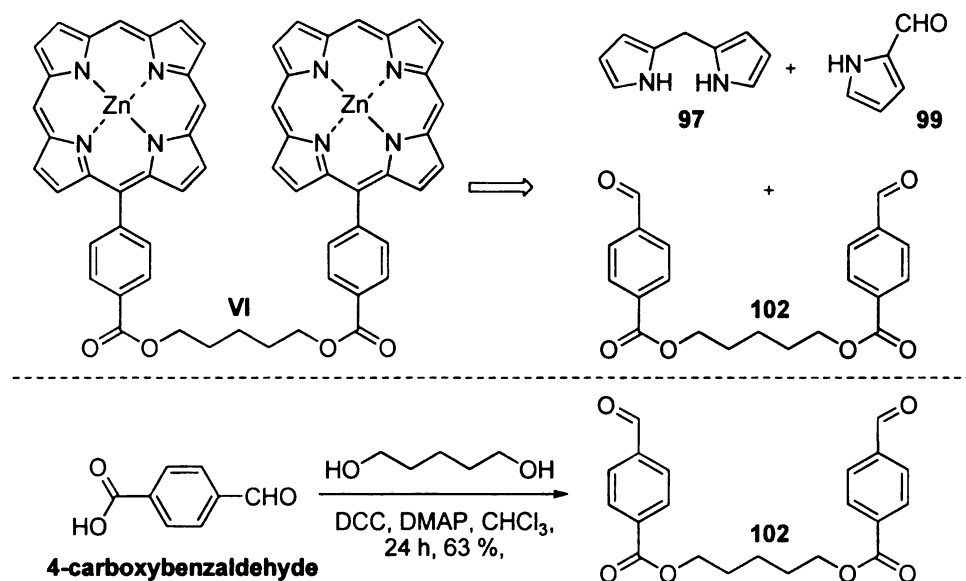


To overcome the solubility issue and construct the tweezer without hydrolysis of the porphyrin ester transesterification methods were used. Both bromoacetate-Zinc mediated and granular iodine catalyzed transesterification methods,^{17, 18} developed for construction of benzoate esters failed, presumably due to the low reactivity of the porphyrin ester.

Alternative route for synthesis of the porphyrin tweezer is presented on Scheme (III-3) and is based on simultaneous construction of the two porphyrins onto the dialdehyde (**102**), which can be obtained in decent yield from DCC/DMAP catalyzed coupling of commercially available 4-carboxybenzaldehyde and pentanediol. The

following condensation of **97**, **99** and **102** in dichloromethane gave, unfortunately, only a trace of mono-assembled porphyrin. No desired bis-porphyrin was detected.

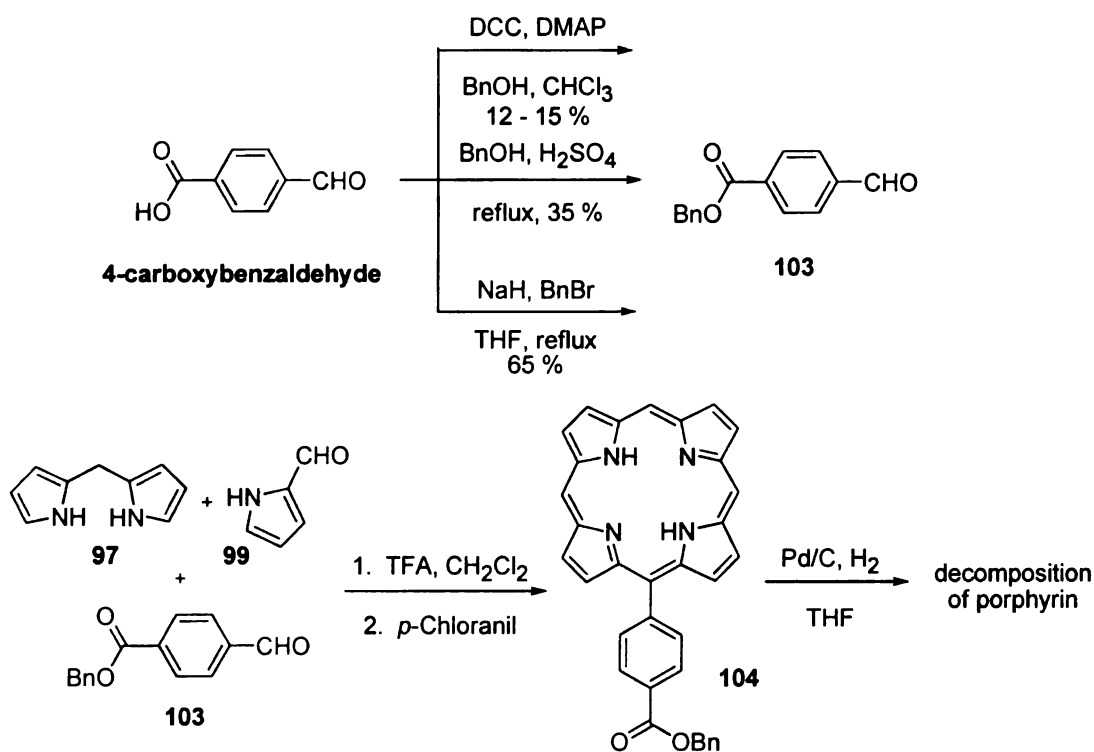
Scheme III-3: An alternative route to porphyrin tweezer **VI**



The non-hydrolytic formation of porphyrin acid might be envisioned through hydrogenation of the porphyrin benzyl ester. Thus, the synthesis of 5-[4-benzylcarboxyphenyl] porphyrin **104** was undertaken. The necessary for the condensation reaction 4-benzylcarboxybenzaldehyde was synthesized in several ways to optimize the yield of the reaction (Scheme III-4). DCC/DMAP coupling carried out in different solvents (dichloromethane, chloroform and DMF) and classical esterification catalyses with mineral acid resulted in a low yield (10-15 %) of the product (starting material recovered). Base (K_2CO_3) catalyzed benzylation of the carboxylic acid also yielded a small amount of the product. A satisfactory yield (65 %) was obtained after application of NaH as a base and reflux of the reaction mixture in THF overnight. The obtained substrate **103** was further used in condensation with dipyrromethane (**97**) and pyrrole-2-

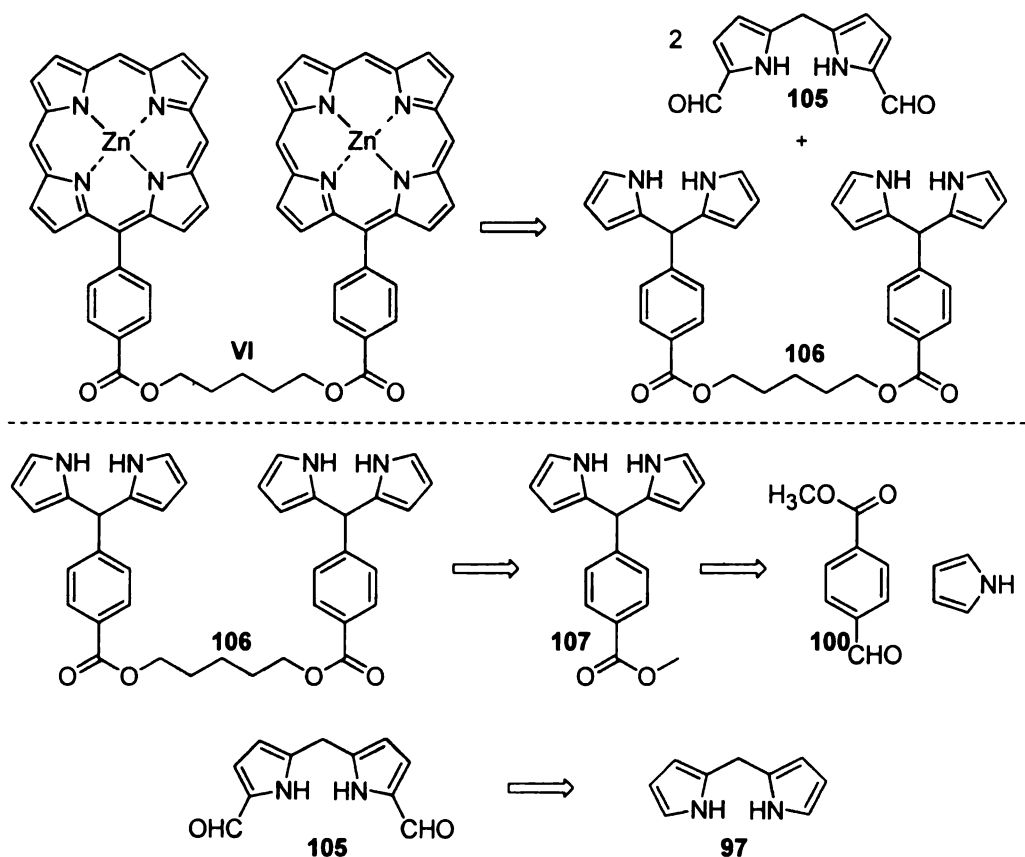
carboxaldehyde (**97**) for construction of porphyrin **103**. The condensation in dichloromethane catalyzed by TFA, followed by oxidation with *p*-Chloranil resulted in formation of desired *meso*-monosubstituted product in 15 % yield. The disubstituted porphyrin was obtained in 12 % yield. Hydrogenolysis of the porphyrin **104** with Pd/C as a catalyst has to be carried in THF due to a poor solubility of the porphyrin in more commonly used solvents (EtOAc and MeOH or their combination).

Scheme III-4: Synthesis of tweezer **VI** through 5-[4-benzylcarboxyphenyl] porphyrin



Unfortunately, after 4 h of reaction complete decomposition of porphyrin was observed. To improve the stability of porphyrin **104**, it was metallated with Zn(OAc)₂ and then submitted to hydrogenolysis conditions, which again yielded the decomposition of the porphyrin.

Scheme III-5: Synthesis of **VI** through a [2 + 2] type of condensation



Another approach to the porphyrin tweezer **IX** that can be pursued in future work, would be an assembly of porphyrin onto the preformed linker in [2+2] type of reaction (Scheme III-5), i.e. condensation of dipyrromethane **105** (2 pyrrole units) and dipyrromethane dialdehyde **106** (2 pyrrole units).¹⁹ **106** can be synthesized from **107** through sequence of DCC/DMAP couplings. Dipyrromethane **107** can be obtained quantitative yield from hydrolysis of its methyl ester, methyl 4-(di(1H-pyrrol-2-yl)methyl)benzoate, which is easily synthesized through condensation of 4-methylcarboxybenzaldehyde (**98**) with pyrrole. Compound **105** can be accessed by formylation of dipyrromethane **97**.

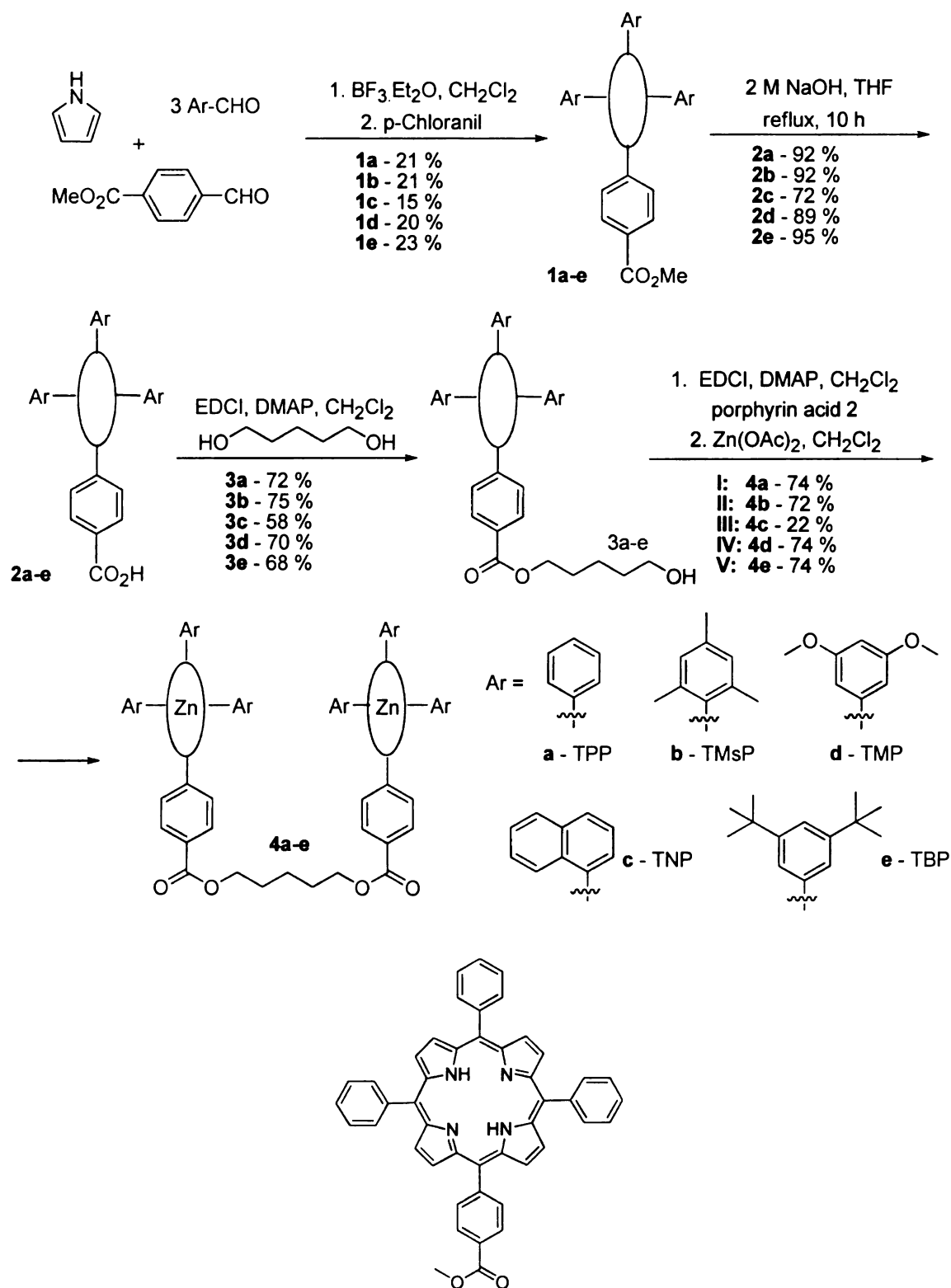
III.5. Experimental procedures.

Anhydrous CH_2Cl_2 was dried over CaH_2 and distilled. The solvents used for CD measurements were purchased from Aldrich and were spectra grade. All reactions were performed in dried glassware under nitrogen. Column chromatography was performed using SiliCycle silica gel (230-400 mesh). ^1H -NMR spectra were obtained on Varian Inova 300 MHz or 500 MHz instrument and are reported in parts per million (ppm) relative to the solvent resonances (δ), with coupling constants (J) in Hertz (Hz). IR studies were performed on a Galaxy series FTIR 3000 instrument (Matteson). UV/Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer and are reported as λ_{max} [nm]. CD spectra were recorded on a JASCO J-810 spectropolarimeter, equipped with a temperature controller (Neslab 111) for low temperature studies, and is reported as λ [nm] ($\Delta\epsilon_{\text{max}}$ [$\text{l mol}^{-1} \text{cm}^{-1}$]).

General procedure for synthesis of 5-(4-methylcarboxyphenyl)-10,15,20-triarylporphyrins:

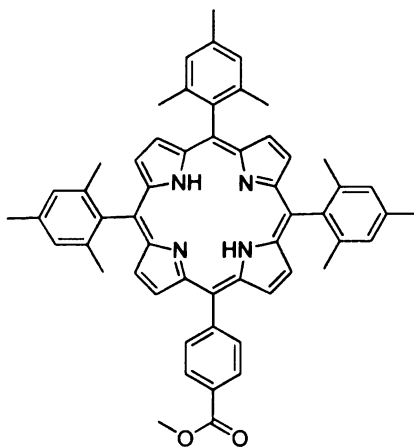
Pyrrole (4 equiv), arylaldehyde (3 equiv) and 4-methylcarboxybenzaldehyde (1 equiv) were dissolved in dichloromethane (chloroform was used for porphyrin **1b**) (0.01M solution) and stirred under the nitrogen for 30 min. $\text{BF}_3 \cdot \text{OEt}_2$ (0.3 equiv) was then added and reaction mixture stirred for 4 h. *p*-Chloranil (2 equiv) was added to the reaction mixture in one portion and reaction was stirred for additional 1-2 h. After completion of oxidation (monitored by TLC) solvent was removed under reduced pressure and the crude mixture of porphyrins was submitted to column chromatography and triarylporphyrin monomethyl ester was separated.

Scheme III-6: Synthesis of porphyrin tweezers I-V



5-(4-Methylcarboxyphenyl)-10,15,20-triphenylporphyrin (TPP-methyl ester, 1a):

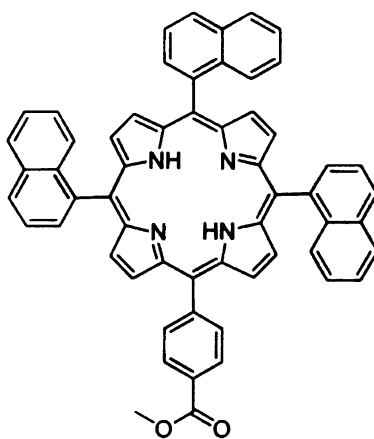
Benzaldehyde (2 g, 18 mmol), pyrrole (1.6 g, 24 mmol) and 4-methylcarboxybenzaldehyde (0.99 g, 6 mmol) were dissolved in CH₂Cl₂ (1.8 L). The solution was flushed with N₂ for 30 min, then BF₃·OEt₂ (0.26 mL) was added and the reaction mixture was stirred for 4 h. Then *p*-chloranil (3 g, 12.5 mmol) was added and reaction mixture stirred for another 2 h. Solvent was removed under reduced pressure and the crude solid was submitted to column chromatography (Silica, 50% CH₂Cl₂/hexane) to elute the title compound as a purple solid in 21% (0.88 g) yield. ¹H NMR (CDCl₃, 500 MHz): δ -2.18 (s, 2H (NH)), 4.09 (s, 3H), 7.71-7.77 (m, 9H), 8.19-8.22 (m, 4H), 8.30 (d, 6H, *J* = 8.1), 8.43 (d, 2H, *J* = 8.1), 8.78 (d, 2H, *J* = 4.5), 8.95 (m, 6H). MS (DCI): calc'd for C₄₆H₃₂N₄O₂ *m/z* = 672.2; obs'd M⁺ = 673.8 [M+H]⁺, M⁺² = 336.3.



5-(4-Methylcarboxyphenyl)-10,15,20-tri-mesitylporphyrin (TMsP-methyl ester, 1b):

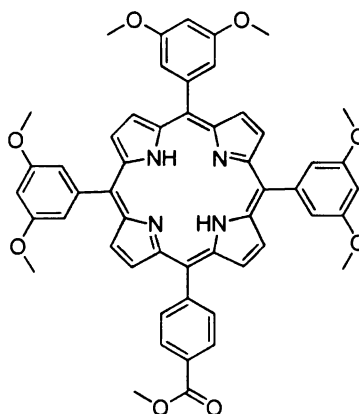
Mesitaldehyde (1 g, 7 mmol), pyrrole (0.7 g, 9.4 mmol) and 4-methylcarboxybenzaldehyde (0.42 g, 2.5 mmol) were dissolved in chloroform (1 L). The solution was flushed with N₂ for 30 min, then BF₃·OEt₂ (1.2 mL) was added and the

reaction mixture stirred for 1 h. Then *p*-Chloranil (1.7 g, 7 mmol) was added and the reaction mixture was stirred for another 1 h. Solvent was removed under reduced pressure and the crude solid was submitted to column chromatography (Silica, 20% CH₂Cl₂/hexane) to elute the title compound as a purple solid (0.29 g) in ~21% yield. ¹H-NMR (CDCl₃, 500 MHz): δ -2.5 (s, 2H (NH)), 1.86 (s, 18H), 2.63 (s, 9H), 4.11 (s, 3H), 7.28 (s, 6H), 8.30 (d, 2H, *J* = 7.5), 8.43 (d, 2H, *J* = 8.1), 8.65 (s, 6H), 8.72 (s, 2H). MS (DCI): calc'd for C₅₅H₅₀N₄O₂ *m/z* = 798.4, obs'd M⁺ = 798.8, M⁺² = 399.2.

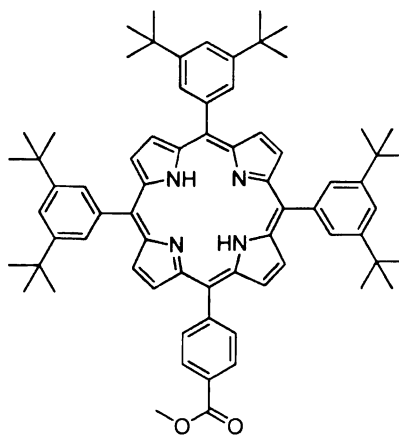


5-(4-Methylcarboxyphenyl)-10,15,20-tri-1-naphthylporphyrin (TNP-methyl ester, 1c): 1-naphthaldehyde (2 g, 12.8 mmol), pyrrole (1.16 g, 17.2 mmol) and 4-methylcarboxybenzaldehyde (0.7 g, 4.3 mmol) were dissolved in CH₂Cl₂ (1.28 L). The solution was flushed with N₂ for 30 min, then BF₃·OEt₂ (0.18 mL) was added and the reaction mixture was stirred for 16 h. *p*-Chloranil (2 g, 8.5 mmol) was then added and the reaction mixture was stirred for another 2 h. Solvent was removed under reduced pressure and the crude solid was submitted to column chromatography (Silica, 50% CH₂Cl₂/hexane) to elute the title compound as a purple solid (0.82 g) in 23% yield. ¹H-NMR (CDCl₃, 500 MHz): δ -2.8 (s, 2H (NH)), 4.05 (s, 3H), 7.05-7.24 (m, 6H), 7.43-7.47

(m, 4H), 7.76-7.85 (m, 4H), 8.06-8.11 (m, 3H), 8.20-8.28 (m, 6H), 8.37 (d, 2H, $J = 8.7$), 8.42-8.47 (m, 4H), 8.56 (t, 2H, $J = 4.8$), 8.66 (d, 2H, $J = 4.8$). MS (DCI): calc'd for $C_{58}H_{38}N_4O_2$ $m/z = 822.1$, obs'd $M^+ [M + H] = 823.1$, $M^{+2} = 411.3$



(4-Methylcarboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenylporphyrin (TMP-methyl ester, 1d): 3,5-dimethoxybenzaldehyde (2 g, 12 mmol), pyrrole (1.07 g, 16 mmol) and 4-methylcarboxybenzaldehyde (0.65 g, 4 mmol) were dissolved in CH_2Cl_2 (1.6 L). The solution was flushed with N_2 for 30 min, then $BF_3 \cdot OEt_2$ (0.17 mL) was added and the reaction mixture was stirred for 10 h. *p*-Chloranil (2 g, 8.5 mmol) was then added and the reaction mixture was stirred for another 2 h. Solvent was removed under reduced pressure and the crude solid was submitted to column chromatography (Silica, 10% EtOAc/ CH_2Cl_2) to elute the title compound as a purple solid (0.54 g) in 15% yield. 1H -NMR ($CDCl_3$, 500 MHz): δ -2.6 (s, 2H (NH)), 3.95 (s, 18H), 4.01 (s, 3H), 6.88 (m, 3H), 7.39 (m, 6H), 8.29 (d, 2H, $J = 8.4$), 8.43 (d, 2H, $J = 8.4$), 8.77 (d, 2H, $J = 4.5$), 8.95 (m, 6H). MS (DCI): calc'd for $C_{52}H_{44}N_4O_8$ $m/z = 852.3$, obs'd $M^+ = 853.3$ $[M+H]^+$, $M^{+2} = 428.8$.

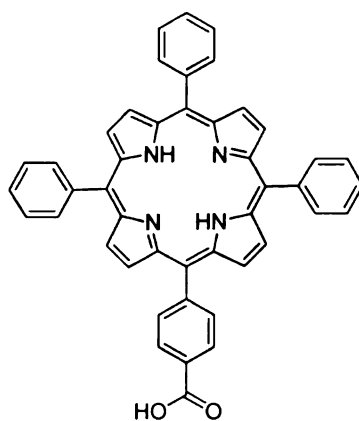


5-(4-Methylcarboxyphenyl)-10,15,20-tri-3,5-di-*t*-butylphenylporphyrin (TBP-methyl ester, **1e):** 3,5-di-*t*-butylbenzaldehyde (2 g, 9.1 mmol), pyrrole (0.82 g, 12 mmol) and 4-methylcarboxybenzaldehyde (0.5 g, 3 mmol) were dissolved in CH₂Cl₂ (1.2 L). The solution was flushed with N₂ for 30 min, then BF₃•OEt₂ (0.13 mL) was added and the reaction mixture was stirred for 10 h. *p*-Chloranil (2 g, 8.5 mmol) was then added and the reaction mixture was stirred for another 18 h. Solvent was removed under reduced pressure and the crude solid was submitted to column chromatography (Silica, 30% CH₂Cl₂/hexane) to elute the title compound as a purple solid (0.62 g) in 20% yield. ¹H-NMR (CDCl₃, 500 MHz): δ -2.7 (s, 2H (NH)), 1.72 (s, 54H), 4.09 (s, 3H), 7.71-7.77 (m, 4H), 8.19-8.22 (m, 7H), 8.33 (d, 2H, *J* = 7.8), 8.43 (d, 2H, *J* = 7.8), 8.78 (d, 2H, *J* = 4.5), 8.54-8.57 (m, 7H). MS (DCI): calc'd for C₇₀H₈₀N₄O₂ *m/z* = 797.8, obs'd M⁺ = 798.8 [M+H]⁺, M⁺² = 399.2.

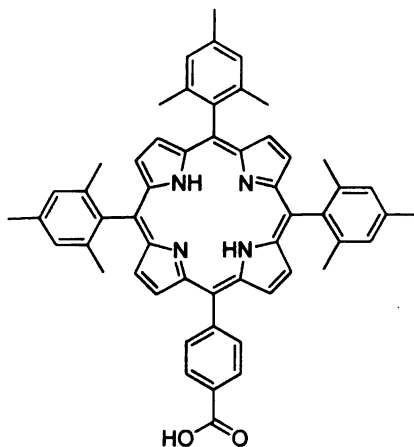
General procedure for hydrolysis of 5-(4-methylcarboxyphenyl)-10,15,20-triarylporphyrins:

Obtained from condensation porphyrin ester (0.3 - 0.5 mmol) was dissolved in THF (30 mL) and 2M NaOH (20 mL) was added. The mixture was refluxed for 16 h

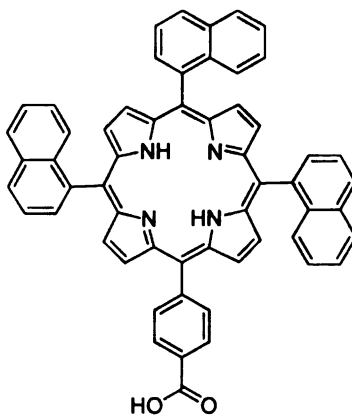
under N₂ atmosphere and cooled to the room temperature, acidified with 10% HCl (color changed from purple to green) and the THF was removed under reduced pressure. The remained aqueous phase was extracted with dichloromethane (6 x 100 mL). The extracts were combined, washed with water (3 x 100 mL, color changed back to purple) and dried with anhydrous Na₂SO₄. The solvent was removed and the resulting purple solid was precipitated with hexane from dichloromethane solution to afford pure 5-(4-carboxyphenyl)-10,15,20-triarylporphyrin. Residue was filtered out and crystals were washed ones with hexane and dried.



5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin (TPP-acid, 2a): TPP-methyl ester (**1a**) was hydrolyzed according to the general procedure described above to afford TPP-acid in 92% yield as pure purple solid. ¹H-NMR (CDCl₃, 500 MHz): δ -2.2 (s, 2H (NH)), 7.73-7.78 (m, 10H), 8.19-8.23 (m, 4H), 8.31 (d, 4H, J = 8.1), 8.45 (d, 2H, J = 8.1), 8.8 (d, 2H, J = 4.5), 8.95 (m, 6H); MS (DCI): calc'd for C₄₅H₃₀N₄O₂ m/z = 658.7, obs'd M^+ = 658.9.

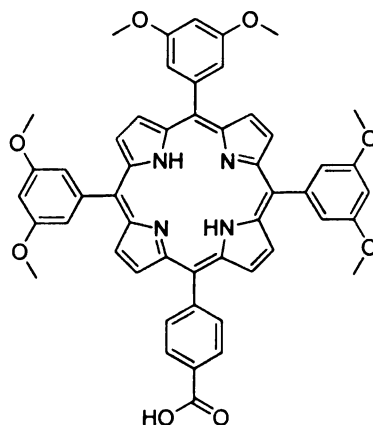


5-(4-Carboxyphenyl)-10,15,20-tri-mesitylporphyrin (TMsP-acid, 2b): TMsP-methyl ester (**1b**) was hydrolyzed according to the general procedure described above to afford TMsP-acid in 92% yield as pure purple solid. $^1\text{H-NMR}$: δ -2.8 (s, 2H (NH)), 1.82 (s, 18H), 2.58 (s, 9H), 7.22-7.24 (m, 6H), 8.32 (d, 2H, $J = 8.1$), 8.52 (d, 2H, $J = 8.1$), 8.60 (s, 4H), 8.68 (d, 2H, $J = 4.5$), 8.71 (d, 2H, $J = 4.5$). MS (DCI): calc'd for $\text{C}_{54}\text{H}_{48}\text{N}_4\text{O}_2$ m/z = 784.9, obs'd $\text{M}^+ = 785.0$, $\text{M}^{+2} = 391.9$.



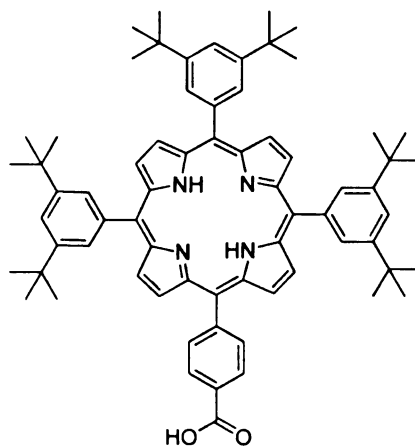
5-(4-Carboxyphenyl)-10,15,20-tri-1-naphthylporphyrin (TNP-acid, 2c): TNP-methyl ester (**1c**) was hydrolyzed according to the general procedure described above to afford TNP-acid in 95% yield as pure purple solid. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ -2.4 (s, 2H (NH)), 7.05-7.15 (m, 6H), 7.43-7.48 (m, 3H), 7.77-7.85 (m, 3H), 8.06-8.12 (m, 3H),

8.20-8.28 (m, 5H), 8.37 (d, 2H, $J = 8.7$), 8.42-8.47 (m, 2H), 8.59 (t, 2H, $J = 4.8$), 8.69 (d, 2H, $J = 4.8$). MS (DCI): calc'd for $C_{56}H_{36}N_4O_2$ $m/z = 808.9$, obs'd $M^+ = 808.3$, $M^{+2} = 404.2$.



5-(4-Carboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenylporphyrin (TMP-acid, 2d):

TMP-methyl ester (**1d**) was hydrolyzed according to the general procedure described above to afford TMP-acid in 72% yield as pure purple solid. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ -2.2 (s, 2H (NH)), 3.95 (s, 18H), 6.88 (m, 3H), 7.39 (m, 6H), 8.29 (d, 2H, $J = 8.4$), 8.43 (d, 2H, $J = 8.4$), 8.77 (d, 2H, $J = 4.5$), 8.95 (m, 6H); MS (DCI): calc'd for $C_{51}H_{42}N_4O_8$ $m/z = 838.9$, obs'd $M^+ = 838.8$, $M^{+2} = 419.3$.

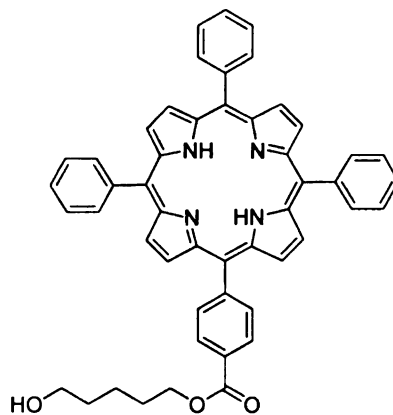


5-(4-Carboxyphenyl)-10,15,20-tri-3,5-di-*t*-butylphenylporphyrin (TBP-acid, 2e):

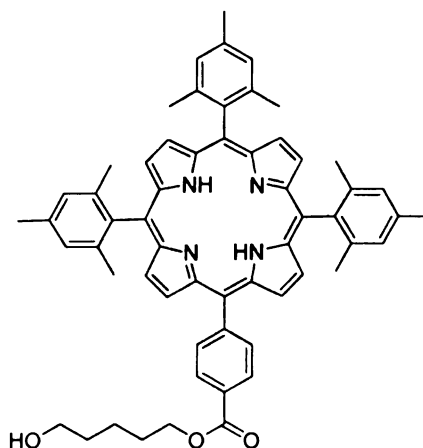
TBP-methyl ester (**1e**) was hydrolyzed according to the general procedure described above to afford TBP-acid in 89% yield as pure purple solid. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ -2.7 (s, 2H (NH)), 1.72 (s, 54H), 7.71-7.77 (m, 8H), 8.19-8.22 (m, 6H), 8.33 (d, 2H, $J = 8.0$), 8.43 (d, 2H, $J = 8.0$), 8.54-8.57 (m, 4H); MS (DCI): calc'd for $\text{C}_{69}\text{H}_{78}\text{N}_4\text{O}_2$ $m/z = 995.4$, obs'd $\text{M}^+ = 996.3$, $\text{M}^{+2} = 479.0$.

General conditions for coupling of 5-(4-carboxyphenyl)-10,15,20-triarylporphyrin with 1,5-pentanediol:

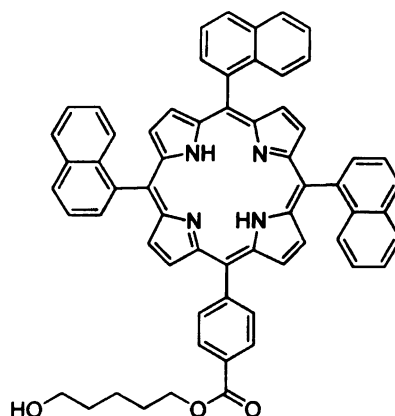
Porphyrin acid **2a-e** (1 equiv), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 1.4 equiv), 4-dimethylaminopyridine (DMAP, 1.4 equiv) and 1,5-pentanediol (3 equiv) were added in a round bottom flask and dissolved in dry dichloromethane (50 mL per 0.2 mmol of acid). The mixture was allowed to stir for 12-14 h at room temperature under nitrogen atmosphere and then was directly submitted to column chromatography, eluted with 10% EtOAc/ CH_2Cl_2 to afford the following compounds:



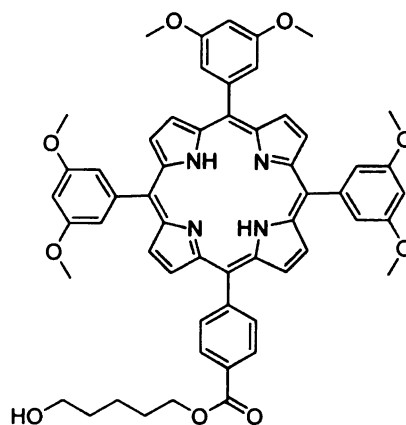
5-[4-(5-Hydroxypentyl)-carboxyphenyl]-10,15,20-tri-phenyl porphyrin (TPP-OH, 3a): TPP-acid (**2a**) was coupled with 1,5-pentanediol according to the general conditions described above to afford the title compound in 72% yield. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ -2.8 (2H (N)), 1.82-1.86 (m, 2H), 1.90-1.95 (m, 4H), 3.73 (t, 2H, $J = 4.6$), 4.52 (t, 2H, $J = 4.5$), 7.72-7.78 (m, 9H), 8.16-8.20 (m, 4H), 8.31 (d, 6H, $J = 8.6$), 8.43 (d, 2H, $J = 8.6$), 8.78 (d, 2H, $J = 4.2$), 8.82-8.87 (m, 6H); MS (DCI): calc'd for $\text{C}_{50}\text{H}_{40}\text{N}_4\text{O}_3$ $m/z = 744.3$, obs'd $[\text{M}+\text{H}]^+ = 745.5$.



5-[4-(5-Hydroxypentyl)-carboxyphenyl]-10,15,20-tri-mesitylporphyrin (TMsP-OH, 3b): TMsP-acid (**2b**) was coupled with 1,5-pentanediol according to the general conditions described above to afford the title compound in 75% yield. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ -2.4 (s, 2H (NH)), 1.70-1.76 (m, 2H), 1.88-2.0 (m, 4H), 1.87 (s, 18H), 2.63 (s, 9H), 3.72 (t, 2H, $J = 3.3$), 4.54 (t, 2H, $J = 3.6$), 7.30 (s, 6H), 8.31 (d, 2H, $J = 7.8$), 8.44 (d, 2H, $J = 7.8$), 8.66 (s, 6H), 8.71 (d, 2H, $J = 4.5$), 8.74 (d, 2H, $J = 4.5$); MS (DCI): calc'd for $\text{C}_{59}\text{H}_{58}\text{N}_4\text{O}_3$ $m/z = 871.1$, obs'd $\text{M}^+ = 1081.5$ $[\text{M}+\text{H}]$, $\text{M}^{+2} = 539.9$.

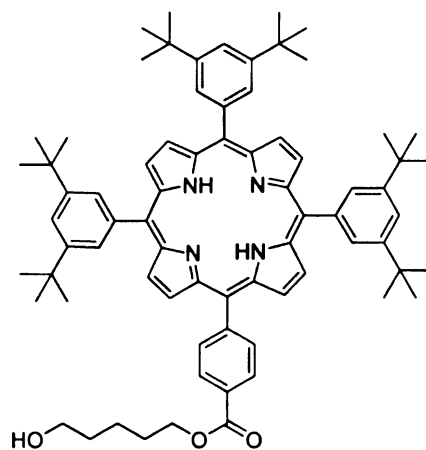


5-[4-(5-Hydroxypentyl)-carboxyphenyl]-10,15,20-tri-1-naphthyl porphyrin (TNP-OH, 3c): TNP-acid (**2c**) was coupled with 1,5-pentanediol according to the general conditions described above to afford the title compound in 68% yield. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 1.58-1.78 (m, 4H), 1.79-1.83 (m, 2H), 3.75 (t, 2H, $J = 6.6$), 4.31 (t, 2H, $J = 6.6$), 7.03-7.21 (m, 6H), 7.28-7.36 (m, 3H), 7.68-7.73 (m, 3H), 8.19-8.41 (m, 3H), 8.21-8.36 (m, 8H), 8.37-8.39 (d, 2H, $J = 4.8$), 8.55-8.57 (m, 4H), 8.62-8.65 (m, 2H), 8.76 (d, 2H, $J = 4.8$). MS (DCI): calc'd for $\text{C}_{62}\text{H}_{46}\text{N}_4\text{O}_3$ $m/z = 895.0$, obs'd $\text{M}^+ = 895.9$, $\text{M}^{+2} = 404.2$.



5-[4-(5-Hydroxypentyl)-carboxyphenyl]-10,15,20-tri-3,5-dimethoxyphenylporphyrin (TMP-OH, 3d): TMP-acid (**2d**) was coupled with 1,5-pentanediol according to the general conditions described above to afford the title compound in 58% yield. $^1\text{H-NMR}$

(CDCl₃, 500 MHz): δ -2.8 (s, 2H (NH)), 1.29 (m, 2H), 1.70 (m, 2H), 1.94 (m, 2H), 3.76 (t, 2H, J = 6.8), 3.94 (s, 18H), 4.50 (t, 2H, J = 6.8), 6.85-6.89 (m, 6H), 7.36-7.38 (m, 10H), 8.30 (d, 4H, J = 7.4), 8.86 (d, 4H, J = 7.2), 8.77(d, 4H, J = 5.1), 8.92-8.94 (m, 10H). MS (DCI): calc'd for C₅₆H₅₂N₄O₉ m/z = 924.3, obs'd M^+ = 925.8 [M + H]⁺.



5-[4-(5-Hydroxypentyl)-carboxyphenyl]-10,15,20-tri-3,5-di-*t*-butyl phenyl porphyrin

(TBP-OH, 3e): TBP-acid (**2e**) was coupled with 1,5-pentanediol according to the general conditions described above to afford a title compound in 70% yield. ¹H-NMR (CDCl₃, 500 MHz): δ -2.6 (2H (N)), 1.52 (s, 54 H), 1.86-1.88 (m, 2H), 1.92-1.98 (m, 4H), 3.74 (t, 2H, J = 4.6), 4.53 (t, 2H, J = 4.5), 7.78-7.82 (m, 4H), 8.06-8.09 (m, 8H), 8.33 (d, 2H, J = 8.4), 8.43 (d, 2H, J = 8.4), 8.80 (d, 2H, J = 4.6), 8.88-8.93 (m, 8H); MS (DCI): calc'd for C₇₄H₈₈N₄O₃ m/z = 1080.7, obs'd M^+ = 1081.9.

Compounds **3a-e** were submitted to a second round of coupling to complete the synthesis of porphyrin tweezers **I-V**. For the coupling porphyrins **3a-e** (1.5 equiv), EDCI (1.2 equiv) and DMAP (1.2 equiv) and corresponding porphyrin acids **2a-e** (1 equiv) were dissolved in dry dichloromethane and stirred at room temperature for 14 h. The

crude mixture was purified by column chromatography (Silica, CH₂Cl₂) to afford the following symmetrical porphyrin tweezers:

Bis-5-(4-carboxyphenyl)-10,15,20-tri-phenyl porphyrin tweezer (TPP-tz) in 74% yield. ¹H-NMR (CDCl₃, 500 MHz): δ -2.6 (s, 4H (NH)) 1.88-1.92 (m, 4H), 2.02-2.16 (m, 4H), 4.61 (t, 4H, J = 6.6), 7.67-7.75 (m, 18H), 8.14 (d, 6H, J = 7.8), 8.19 (d, 6H, J = 7.6), 8.32 (d, 4H, J = 8.4), 8.47 (d, 4H, J = 8.4), 8.79-8.82 (m, 16H).

Bis-5-(4-carboxyphenyl)-10,15,20-tri-mesityl porphyrin tweezer (TMSP-tz) in 72% yield. ¹H-NMR (CDCl₃, 500 MHz): δ -2.5 (s, 4H (NH)), 1.84 (s, 18H), 1.86 (s, 18H), 2.05-2.18 (m, 4H), 2.61 (s, 18H), 4.62 (t, 4H, J = 6.2), 7.26 (s, 12H), 8.31 (d, 4H, J = 7.8), 8.46 (d, 4H, J = 7.8), 8.64 (s, 8H), 8.71 (d, 4H, J = 4.5), 8.74 (d, 4H, J = 4.5).

Bis-5-(4-carboxyphenyl)-10,15,20-tri-1-naphthyl porphyrin tweezer (TNP-tz) in 50% yield. ¹H-NMR (CDCl₃, 500 MHz): δ -2.4 (s, 4H (NH)), 1.59-1.71 (m, 2H), 1.82-1.91 (m, 4H), 4.20 (t, 4H, J = 6.6), 7.06-7.23 (m, 12H), 7.23-7.41 (m, 6H), 7.71-7.78 (m, 6H), 8.00-8.05 (m, 6H), 8.14-8.25 (m, 20H), 8.55-8.57 (m, 8H), 8.62-8.65 (m, 4H), 8.76 (d, 4H, J = 4.8).

Bis-5-(4-carboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenylporphyrin tweezer (TMP-tz) in 22% yield. ¹H-NMR (CDCl₃, 500 MHz): δ -2.8 (s, 4H, (NH)), 1.89 (m, 2H), 2.1 (m, 4H), 3.92 (s, 6H), 3.94 (s, 12H), 4.60 (t, 4H, J = 6.3), 6.85-6.89 (m, 6H), 7.36-7.38 (m, 10H), 8.30 (d, 4H, J = 7.8), 8.86 (d, 4H, J = 8.6), 8.77 (d, 4H, J = 5.1), 8.92-8.94 (m, 10H).

Bis-5-(4-carboxyphenyl)-10,15,20-tri-3,5-di-*t*-butyl phenyl porphyrin tweezer (TBP-tz) in 74% yield. ¹H-NMR (CDCl₃, 500 MHz): δ -2.7 (s, 4H (NH)), 1.49 (s, 108H), 1.82-

1.85 (m, 2H), 2.05-2.11 (m, 4H), 4.58 (t, 4H), 7.53-7.77 (m, 6H), 8.04-8.06 (m, 12H), 8.32 (d, 4H, $J = 6.9$), 8.41 (d, 4H, $J = 6.9$), 8.87-8.98 (m, 16H).

Porphyrin tweezers synthesized above were stirred with 4 equiv of $\text{Zn}(\text{OAc})_2$ in dry dichloromethane overnight. The metallated compounds were purified by column chromatography (Silica, CH_2Cl_2) to afford pure Zn-porphyrin tweezers.

Bis-Zn-5-(4-carboxyphenyl)-10,15,20-tri-phenyl porphyrin tweezer I (ZnTPP-tz, 4a): $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 1.88-1.92 (m, 4H), 2.02-2.16 (m, 4H), 4.61 (t, 4H, $J = 6.6$), 7.67-7.75 (m, 18H), 8.14 (d, 6H, $J = 7.8$), 8.19 (d, 6H, $J = 7.6$), 8.32 (d, 4H, $J = 8.4$), 8.47 (d, 4H, $J = 8.4$), 8.79-8.82 (m, 16H); MS (FAB+): calc'd for $\text{C}_{95}\text{H}_{64}\text{N}_8\text{O}_4\text{Zn}_2$ $m/z = 1511.3$, obs'd $\text{M}^+ = 1512.2$.

Bis-Zn-5-(4-carboxyphenyl)-10,15,20-tri-mesityl porphyrin tweezer II (ZnTMsP-tz, 4b): $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ -2.5 (s, 4H (NH)), 1.84 (s, 18H), 1.86 (s, 18H), 2.05-2.18 (m, 4H), 2.61 (s, 18H), 4.62 (t, 4H, $J = 6.2$), 7.26 (s, 12H), 8.31 (d, 4H, $J = 7.8$), 8.46 (d, 4H, $J = 7.8$), 8.64 (s, 8H), 8.71 (d, 4H, $J = 4.5$), 8.74 (d, 4H, $J = 4.5$); MS (FAB+): calc'd for $\text{C}_{113}\text{H}_{100}\text{N}_8\text{O}_4\text{Zn}_2$ $m/z = 1766.5$, obs'd $\text{M}^+ = 1760.5$.

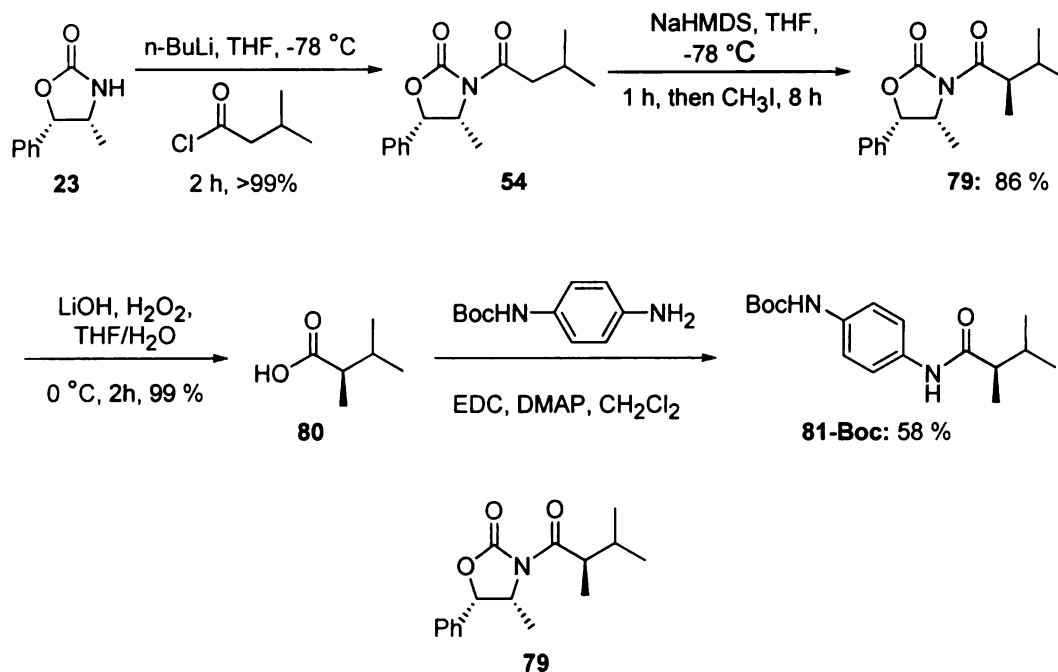
Bis-Zn-5-(4-carboxyphenyl)-10,15,20-tri-1-naphthyl porphyrin tweezer III (ZnTNP-tz, 4c): $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 1.59-1.71 (m, 2H), 1.82-1.91 (m, 4H), 4.20 (t, 4H, $J = 6.6$), 7.06-7.23 (m, 12H), 7.23-7.41 (m, 6H), 7.71-7.78 (m, 6H), 8.00-8.05 (m, 6H), 8.14-8.25 (m, 20H), 8.55-8.57 (m, 8H), 8.62-8.65 (m, 4H), 8.76 (d, 4H, $J = 4.8$); MS (FAB+): calc'd for $\text{C}_{119}\text{H}_{76}\text{N}_8\text{O}_4\text{Zn}_2$ $m/z = 1812$, obs'd $\text{M}^+ = 1806.2$.

Bis-Zn-5-(4-carboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenylporphyrin tweezer IV (ZnTMP-tz, 4d): $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 1.89 (m, 2H), 2.1 (m, 4H), 3.92 (s, 6H), 3.94 (s, 12H), 4.60 (t, 4H, $J = 6.3$), 6.85-6.89 (m, 6H), 7.36-7.38 (m, 10H), 8.30 (d,

4H, $J = 7.8$), 8.86 (d, 4H, $J = 8.6$), 8.77(d, 4H, $J = 5.1$), 8.92-8.94 (m, 10H); MS (FAB+): calc'd for $C_{107}H_{88}N_8O_{16}Zn_2$ $m/z = 1872$, obs'd $M^+ = 1868.2$.

Bis-Zn-5-(4-carboxyphenyl)-10,15,20-tri-3,5-di-*t*-butyl phenyl porphyrin tweezer V (ZnTBP-tz, 4e): 1H -NMR ($CDCl_3$, 500 MHz): δ 1.49 (s, 108H), 1.82-1.85 (m, 2H), 2.05-2.11 (m, 4H), 4.58 (t, 4H), 7.53-7.77 (m, 6H), 8.04-8.06 (m, 12H), 8.32-8.43 (dd, 8H, $J=6.9$, 34), 8.87-8.98 (m, 16H); MS (FAB+): calc'd for $C_{143}H_{164}N_8O_4Zn_2$ $m/z = 2184.1$, obs'd $M^+ = 2182.6$.

Scheme III-7: Synthesis of (*R*)-N-(4-aminophenyl)-2,3-dimethylbutanamide **81**



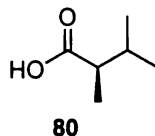
(4*R*, 5*S*)-3-((*R*)-2,3-Dimethylbutanoyl)-4-methyl-5-phenyloxazolidin-2-one (**79**):²⁰

NaHMDS (1.1 equiv, 1 M in THF) was placed in a round bottom flask and cooled to $-78\text{ }^{\circ}\text{C}$. 10 mmol of auxiliary conjugate **54** was dissolved in separate flask in dry THF (100 mL), cooled to $-78\text{ }^{\circ}\text{C}$ and added via cannula to the base over 40 min. The solution was

stirred for 1 h at $-78\text{ }^{\circ}\text{C}$ and iodomethane (1.5 equiv) was added dropwise over 1 h. Reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 8 h, quenched with 10% HCl and further diluted with diethyl ether. The organic layer was separated, dried with anhydrous sodium sulfate, concentrated to a crude oil, which was then submitted to the column purification (Silica, 5% EtOAc/hexane, $R_f = 0.25$) to provide **76** as the viscous oil in 86% yield. HRMS (EI+): calc'd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$ $[\text{M}+\text{H}]^+ m/z = 276.1600$, obs'd $\text{M}^+ = 276.1621$; $[\alpha]_{\text{D}}^{20} = 7.2$ (c, 0.88 in CH_2Cl_2); IR (film): 2964, 2876, 1782, 1699, 1456, 1367, 1342, 1305, 1196, 1161, 1145, 1118, 1089, 1068, 1030, 987, 954, 767, 700; ^1H NMR (CDCl_3 , 300 MHz): δ 0.86 (d, 3H, $J = 6.6$), 0.91 (d, 3H, $J = 6.6$), 0.94 (d, 3H, $J = 6.6$), 1.11 (d, 3H, $J = 6.9$), 1.91-2.08 (m, 1H), 3.57 (p, 1H, $J = 6.9$), 4.73 (p, 1H, $J = 6.6$), 5.62 (d, 1H, $J = 7.2$), 7.26-7.42 (m, 5H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 13.6, 14.2, 18.5, 21.1, 30.6, 43.6, 54.9, 78.6, 86.1, 125.5, 128.6, 133.3, 138.9, 152.7, 176.7.

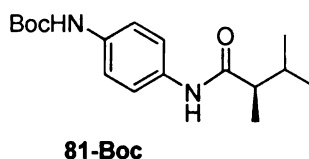
General procedure for auxiliary cleavage²⁰

Auxiliary conjugate **79** (10 mmol) was dissolved in THF/ H_2O 5:1 (20 mL) mixture and cooled in an ice bath. To the cold solution was added LiOH monohydrate (20 mmol) followed by 50 mmol of 30 % H_2O_2 solution. The mixture was allowed to stir at room temperature for 2 h and the THF was removed under reduced pressure. The aqueous phase was washed with dichloromethane (3 x 20 mL) to remove free chiral auxiliary and then acidified with 10% HCl to pH $\sim$ 1. The acidic solution was extracted with dichloromethane (2 x 25 mL), organic extracts were combined, dried over Na_2SO_4 and concentrated to give the desired chiral carboxylic acid **80**.



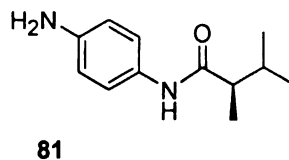
(*R*)-2,3-Dimethylbutanoic acid (80):²¹ HRMS (Q-TOF (EI-)): calc'd for C₆H₁₂NO₂ [M-H]⁻ m/z = 115.0759, obs'd 115.0801; [α]_D²⁰ = -9.2 (c, 2.81 in CH₂Cl₂); IR (film): 3248(broad), 2970, 2873, 1707, 1453, 1420, 1232, 951, 742; ¹H-NMR (300 MHz, CDCl₃): δ 0.81 (d, 3H, J = 6.9), 0.83 (d, 3H, J = 6.9), 1.42-1.48 (m, 1H), 1.51 (s, br, 1H (OH)), 1.59-1.72 (m, 1H), 3.38-3.44 (dd, 1H, J_1 = 7.2, J_2 = 11.4), 3.53-3.58 (dd, 1H, J_1 = 8.7, J_2 = 10.5); ¹³C-NMR (CDCl₃, 75 MHz): δ 13.3, 18.9, 20.6, 25.5, 30.7, 45.9, 182.4.

Carboxylic acid **80** (0.25 mmol) was dissolved in dry dichloromethane (10 mL). To this solution was added mono-Boc-1,4-phenylenediamine (0.5 mmol), DMAP (0.25 mmol) and EDC (0.30 mmol). Mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. Purification by column chromatography (Silica gel, 20% EtOAc in Hexane) gave the target amide **81**.



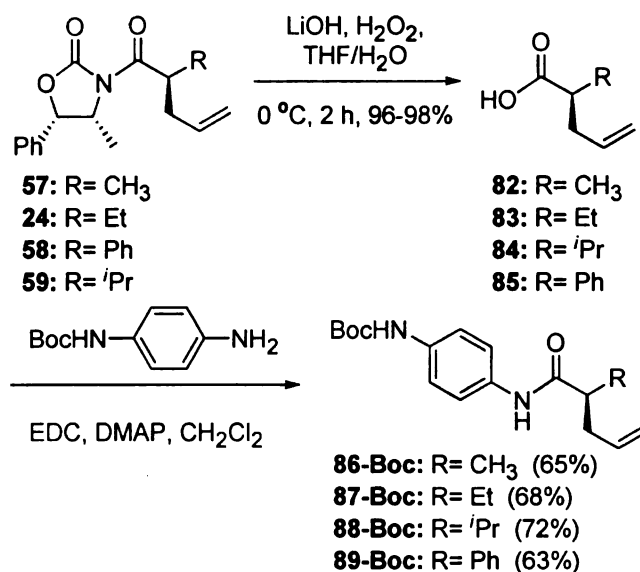
(*R*)-N-(4-aminophenyl)-2,3-dimethylbutanamide (81-Boc): HRMS (Q-TOF (EI+)): calc'd for C₁₇H₂₆N₂O₃ [M+H]⁺ m/z = 307.2022, obs'd 306.1952; IR (KBr): 3325, 3260, 2966, 2930, 2872, 1658, 1534, 1516, 1251; ¹H-NMR (CDCl₃, 500 MHz): δ 0.86 (d, 3H, J = 7.0), 0.98 (d, 3H, J = 7.0), 1.02 (d, 3H, J = 7.2), 1.54 (s, 9H), 1.92-1.96 (m, 1H), 1.99-2.06 (m, 1H), 6.44 (s, 1H (NH)), 7.08 (s, 1H (NH)), 7.31 (d, 2H, J = 8.0), 7.45 (d, 2H, J =

9.0); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 14.9, 19.5, 21.08, 28.3, 31.6, 49.5, 80.5, 126.9, 128.7, 133.2, 134.6, 152.7, 174.3.



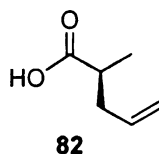
(*R*)-N-(4-aminophenyl)-2,3-dimethylbutanamide (81): ^1H -NMR (CDCl_3 , 500 MHz): δ 0.88 (d, 3H, $J = 7.0$), 0.99 (d, 3H, $J = 7.0$), 1.04 (d, 3H, $J = 7.2$), 1.92-1.98 (m, 1H), 1.99-2.07 (m, 1H), 3.68 (s, 2H (NH_2)), 6.44 (s, 1H (NH)), 6.86 (d, 2H, $J = 8.0$), 7.28 (d, 2H, $J = 9.0$); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 14.9, 19.5, 21.08, 31.6, 49.5, 80.5, 126.9, 128.7, 133.2, 143.4, 175.2.

Scheme III-8: Synthesis of α -chiral amides **86-89**

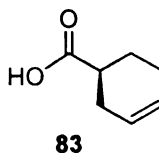


General procedure for auxiliary cleavage:²²

Auxiliary conjugate (10 mmol) was dissolved in THF/H₂O (5:1, 20 mL) mixture and cooled on ice bath. To the cold solution was added LiOH monohydrate (20 mmol) followed by 50 mmol of 30% H₂O₂ solution. The mixture was allowed to stir at room temperature for 2 h and the THF was removed under reduced pressure. Aqueous phase was washed with dichloromethane (3 x 20 mL) to remove free chiral auxiliary and then acidified with 10% HCl to pH ~ 1. The acidic solution was extracted with dichloromethane (2 x 25 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated to give the chiral carboxylic acids **82-85**.

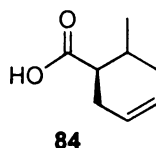


(S)-2-Methylpent-4-enoic acid (82):²³ HRMS (Q-TOF (EI-)): calc'd for C₆H₉O₂ [M-H]⁻ m/z = 113.0603, obs'd 113.1067; $[\alpha]_D^{20}$ = 45.7 (*c*, in 2.2 CH₂Cl₂) [literature value $[\alpha]_D^{22}$ = +46.2 (*c*, 2.26 in CH₂Cl₂)²³]; IR (KBr): 3325-2883 (broad, OH), 3080, 2980, 2939, 2883, 1709, 1643, 1558, 1541, 1464, 1419, 1286, 1244, 1213, 995, 918, 715, 650; ¹H-NMR (300 MHz, CDCl₃): δ 1.14 (d, 3H, *J* = 4.5), 2.11-2.20 (m, 1H), 2.35-2.43 (m, 1H), 2.45-2.56 (m, 1H), 4.99-5.07 (m, 2H), 6.75-5.79 (m, 1H), 11.85 (s, br, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 15.9, 37.1, 38.8, 116.7, 134.7, 182.4

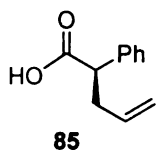


(S)-2-Ethylpent-4-enoic acid (83):²⁴ HRMS (Q-TOF (EI-)): calc'd for C₇H₁₁O₂ [M-H]⁻ m/z = 127.0759, obs'd 127.0991; $[\alpha]_D^{20}$ = -2.4 (*c*, in 3.0 CHCl₃) [literature value $[\alpha]_D^{24}$ =

-2.5 (c, 2.0 in CHCl₃)²⁴]; ¹H-NMR (300 MHz, CDCl₃): δ 1.14 (d, 3H, *J* = 4.5), 2.11-2.20 (m, 1H), 2.35-2.43 (m, 1H), 2.45-2.56 (m, 1H), 4.99-5.07 (m, 2H), 6.75-5.79 (m, 1H), 11.85 (s, br, 1H); ¹³C-NMR (CDCl₃, 75 MHz): δ 15.9, 37.1, 38.8, 116.7, 134.7, 182.4



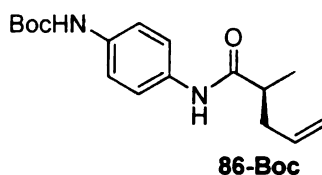
(*R*)-2-Isopropylpent-4-enoic acid (84):²⁵ HRMS (Q-TOF (EI-)): calc'd for C₈H₁₃O₂ [M-H]⁻ *m/z* = 141.0916, obs'd 141.0224; IR (film): 3294, 3078, 2964, 2932, 2876, 1734, 1070, 1643, 1368, 1238, 1118, 1022, 700; ¹H-NMR (300 MHz, CDCl₃): δ 1.14 (d, 6H, *J* = 4.5), 1.80-1.94 (m, 1H), 2.16-2.33 (m, 3H), 4.96-5.07 (dd, 2H, *J*₁ = 9.9, *J*₂ = 18.3), 5.58-5.81 (m, 1H), 11.15 (s, br, 1H (OH)); ¹³C-NMR (CDCl₃, 75 MHz): δ 20.0, 20.1, 30.0, 33.5, 52.2, 181.4.



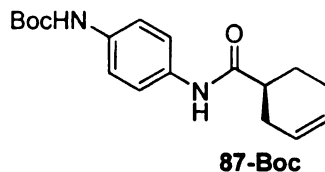
(*R*)-2-Phenylpent-4-enoic acid (83):²⁶ HRMS (Q-TOF (EI-)): calc'd for [M-H]⁻ C₁₁H₁₁O₂ *m/z* = 175.0759, obs'd 113.0922; ¹H-NMR (CDCl₃, 300 MHz): δ 2.52-2.63 (m, 1H), 2.97-3.03 (m, 1H), 3.59 (t, 1H, *J* = 7.5), 4.96-5.02 (dd, 2H, *J*₁ = 9.0, *J*₂ = 10.6), 5.67-5.82 (m, 1H), 7.25-7.39 (m, 5H), 10.2 (s, br, 1H (OH)); ¹³C-NMR (CDCl₃, 75 MHz): δ 35.5, 51.4, 116.4, 127.5, 129.1, 129.7, 134.1, 137.5, 173.2.

All obtained carboxylic acids were derivatized with carrier through EDC/DMAP coupling according to the following procedure: Carboxylic acid (0.25 mmol) was

dissolved in dry dichloromethane (10 mL). To this solution was added mono-Boc-1,4-phenylenediamine (carrier) (0.5 mmol), DMAP (0.25 mmol) and EDC (0.30 mmol). The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. Purification by column chromatography (Silica gel, 20% EtOAc/hexane) gave the target amide:

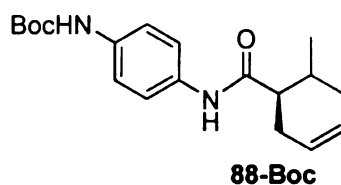


N-Boc-(S)-(4-Aminophenyl)-2-methylpent-4-enamide (86-Boc): HRMS (Q-TOF (EI+)): calc'd for $C_{17}H_{25}N_2O_3$ $[M+H]^+$ m/z = 305.1865, obs'd 305.1862; $[\alpha]_D^{20}$ = +20.6 (c, 1.1 in CH_2Cl_2); IR (KBr): 3355, 3325, 3143, 2984, 2936, 2913, 1699, 1658, 1599, 1540, 1458, 1405, 1299, 1234, 1157, 1110, 1051, 916, 827, 774, 651, 515; m. p. = 165 °C (yellow powder); 1H -NMR ($CDCl_3$, 300 MHz): δ 1.14 (d, 3H, J = 6.6), 1.47 (s, 9H), 2.09-2.18 (m, 1H), 2.32-2.42 (m, 1H), 2.45-2.54 (m, 1H), 4.96-5.07 (dd, 2H, J_1 = 6.9, J_2 = 10.0), 5.71-5.82 (m, 1H), 7.29 (d, 2H, J = 6.0), 7.40 (d, 2H, J = 6.0); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 17.8, 28.7, 39.5, 42.4, 80.2, 117.0, 120.1, 122.0, 134.7, 136.8, 137.0, 155.3, 177.1.

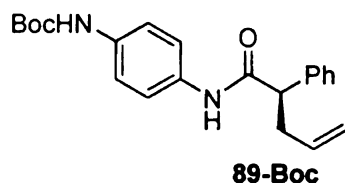


N-Boc-(S)-(4-Aminophenyl)-2-methylpent-4-enamide (87-Boc): HRMS (Q-TOF (EI+)): calc'd for $C_{17}H_{25}N_2O_3$ $[M+H]^+$ m/z = 305.1865, obs'd 305.1862; $[\alpha]_D^{20}$ = +20.6

(c, 1.1 in CH₂Cl₂); IR (KBr): 3352, 3325, 2964, 2932, 2874, 1695, 1653, 1604, 1523, 1453, 1400, 1392, 1367, 1309, 1242, 1165, 1115, 1072, 1059, 1022, 991, 914, 833, 773, 694, 644, 516; m. p. = 191 °C (white crystals); ¹H-NMR (CDCl₃, 300 MHz): δ 0.86 (t, 3H, *J* = 6.6), 1.42 (s, 9H), 1.45-1.69 complex multiplet, 2H), 2.09-2.20 (m, 2H), 2.30-2.38 (m, 1H), 2.45-2.54 (m, 1H), 4.90-5.03 (dd, 2H, *J*₁ = 12.3, *J*₂ = 18.6), 5.602-5.78 (m, 1H), 7.20 (d, 2H, *J* = 8.7), 7.40 (d, 2H, *J* = 8.7); ¹³C-NMR (CDCl₃, 75 MHz): δ 11.8, 26.2, 28.7, 39.5, 49.7, 79.5, 115.7, 120.1, 122.0, 134.7, 135.7, 137.0, 155.9, 176.9.



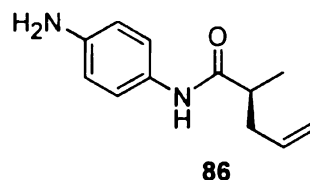
(*R*)-tert-Butyl 4-(2-isopropylpent-4-enamido)phenylcarbamate (88-Boc): HRMS (Q-TOF (EI+)): calc'd for [M+H]⁺ C₁₉H₂₉N₂O₃ *m/z* = 333.2178, obs'd 333.2112; [*α*]_D²⁰ = +6.3 (c, 0.5 in CH₂Cl₂); IR (KBr): 33540, 3319, 2960, 2924, 2860, 169, 1658, 1610, 1540, 1522, 1408, 1311, 1244, 1165, 1059; 910, 831, 644, 518; m. p. = 172 °C (yellow powder); ¹H-NMR (CDCl₃, 300 MHz): δ 0.97 (d, 3H, *J* = 5.7), 0.99 (d, 3H, *J* = 5.7), 1.49 (s, 9H), 1.56-1.68 (m, 1H), 1.87-1.97 (m, 1H), 2.29-2.45 (m, 2H), 4.97-5.11 (dd, 2H, *J*₁ = 10.2, *J*₂ = 17.1), 5.71-5.83 (m, 1H), 6.44 (s, 1H (NH)), 7.05 (s, 1H (NH)), 7.27 (d, 2H, *J* = 8.7), 7.40 (d, 2H, *J* = 8.7); ¹³C-NMR (CDCl₃, 75 MHz): δ 20.3, 20.8, 28.3, 30.7, 34.5, 55.9, 79.9, 116.9, 119.2, 120.5, 128.8, 133.0, 136.0, 152.9, 172.9.



N-Boc-(*R*)-(4-Aminophenyl)-2-phenylpent-4-enamide (89-Boc): HRMS (Q-TOF (EI+)): calc'd for $C_{22}H_{27}N_2O_3$ $[M+H]^+$ m/z = 367.2022, obs'd 367.2054; $[\alpha]_D^{20}$ = -51 (*c*, 0.1 in CH_2Cl_2); IR (KBr): 3361, 3331, 3078, 2989, 2942, 1701, 1658, 1605, 1546, 1520, 1408, 1310, 1234, 1155, 1059, 910, 837, 748, 645, 518, 497; m. p. = 182 °C (white powder); 1H -NMR ($CDCl_3$, 300 MHz): δ 1.47 (s, 9H), 2.50-2.60 (m, 1H), 2.92-3.01 (m, 1H), 3.51 (t, 1H, J = 7.5), 4.94-5.08 (dd, 2H, J_1 = 9.1, J_2 = 10.8), 5.65-5.79 (m, 1H), 6.37 (s, 1H (NH)), 6.98 (s, 1H (NH)), 7.22-7.37 (m, 9H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 28.1, 37.3, 53.2, 116.6, 120.6, 127.2, 127.8, 128.6, 134.6, 135.5, 139.2, 159.8, 171.5.

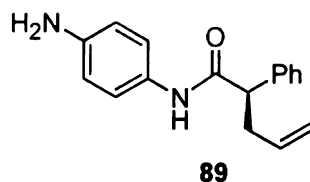
(*R*)-2-Methylbutanoic acid and (*S*)-OAc-mandelic acid were purchased from Aldrich and used for construction of carrier conjugates **88** and **89**, respectively.

For Boc-deprotection synthesized amides were dissolved in 20% TFA solution in dichloromethane and stirred at room temperature for 2 h. Solvent was then removed under reduced pressure. The residue was re-dissolved in dichloromethane and the remaining acid was neutralized with Na_2CO_3 . Solution was then filtered and concentrated to give the free amides ready for ECCD analysis.



(*S*)-N-(4-Aminophenyl)-2-methylpent-4-enamide (86): IR (KBr): 3467, 3308, 2987, 2928, 2860, 1699, 1660, 1545, 1456, 1466, 1304, 1236, 1165, 1063, 916, 846, 603; 1H -

NMR (CDCl₃, 300 MHz): δ 1.14 (d, 3H, J = 6.8), 2.10-2.20 (m, 1H), 2.30-2.38 (m, 1H), 2.45-2.54 (m, 1H), 4.96-5.07 (dd, 2H, J_1 = 6.8, J_2 = 10.0), 5.72-5.80 (m, 1H), 6.64 (d, 2H, J = 6.9), 7.28 (d, 2H, J = 6.9); ¹³C-NMR (CDCl₃, 75 MHz): δ 17.6, 39.2, 42.0, 116.1, 121.3, 123.0, 134.5, 136.8, 137.0, 172.1.



(R)-N-(4-Aminophenyl)-2-phenylpent-4-enamide (89): IR (KBr): 3449, 3296, 3066, 2984, 2913, 2866, 1658, 1599, 1518, 1422, 1251, 1169, 986, 827, 739, 692, 515; ¹H-NMR (CDCl₃, 500 MHz): δ 2.52-2.58 (m, 1H), 2.92-2.99 (m, 1H), 3.51 (t, 1H, J = 7.5), 3.53 (s, 2H (NH₂)), 4.95-4.97 (dd, 1H, J_1 = 2.0, J_2 = 7.0), 5.03-5.07 (dd, 1H, J_1 = 2.0, J_2 = 7.0), 5.67-5.77 (m, 1H), 6.56 (d, 2H, J = 9.0), 7.02 (s, 1H (NH)), 7.15 (d, 2H, J = 9.0), 7.25-7.33 (m, 5H); ¹³C-NMR (CDCl₃, 125 MHz): δ 37.5, 53.9, 115.3, 116.8, 121.9, 127.5, 128.1, 128.9, 129.1, 135.8, 139.3, 143.3, 170.7.

Determination of extinction coefficient for tweezers II, III, IV and V (4a-4e).

Determination of extinction coefficient (ϵ) is important for establishment of the exact concentration of the chromophore in the solution as well as for complete characterization of spectroscopic properties of the chromophore.

Determination of ϵ was carried out by using Lambert-Beer's law:

$$A = \epsilon cl \quad \text{(III-1)}$$

where A is the absorption observed by UV-vis, ϵ is the extinction coefficient, c is the concentration of the compound, and l is the length of the UV cell used for measurements (1 cm).

According to the equation, the extinction coefficient ϵ of a compound can be determined if the concentration of the solution is known: $\epsilon = A/cl$.

1 mM stock solution of zinc porphyrin tweezers were prepared with 5 mg of chromophoric host in dry dichloromethane and A (UV-vis) of each tweezer was measured in methylcyclohexane. The measurements were repeated three times and (ϵ) was calculated according to equation above as follows: zinc bis-5-(4-carboxyphenyl)-10,15,20-tri-1-naphthyl porphyrin (**III** (**4c**), Zn-TNP-tz, $\lambda_{\text{max}} = 421$ nm, $\epsilon = 623,800 \text{ M}^{-1}\text{cm}^{-1}$), bis-5-(4-carboxyphenyl)-10,15,20-tri-3,5-dimethoxyphenyl porphyrin (**IV** (**4d**), Zn-TMP-tz, $\lambda_{\text{max}} = 419$ nm, $\epsilon = 1,150,000 \text{ M}^{-1}\text{cm}^{-1}$), and bis-5-(4-carboxyphenyl)-10,15,20-tri-3,5-di-*t*butylphenyl porphyrin (**V** (**4e**), Zn-TBP-tz, $\lambda_{\text{max}} = 419$ nm, $\epsilon = 630,880 \text{ M}^{-1}\text{cm}^{-1}$).

Determination of binding constant for tweezers I, II and V

Solutions of Zn-porphyrin tweezers **4a**, **4b** and **4e** (1 mM in methylcyclohexane) were titrated with chiral substrate **89** (10 mM solution in dichloromethane) at 10 equiv increments and the UV-vis spectra were recorded. The addition of the chiral substrate

$$f = L \frac{(1 + kx + ka) - \sqrt{L^2(kx + ka + 1)^2 - 4axk^2L^2}}{2ka}$$

continued until no visible change in the spectra was observed. Upon formation of the chiral complex the Soret band of the porphyrin tweezers red shifts through an isosbestic point. Figure III-14a depicts the binding of Zn-TBP-tz **4e** with chiral substrate **89**. The change of absorption at 414 nm as a function of the added ligand concentration yields an exponential saturation curve (Figure III-14b). The binding constant can be derived, as previously reported by Shoji et al.,²⁷ by fitting the latter data through the following non-linear least square equation:

where: L - Δabs at the point of saturation; x - chiral substrate equivalents; k - calculated K_a ; a - concentration of porphyrin tweezer.

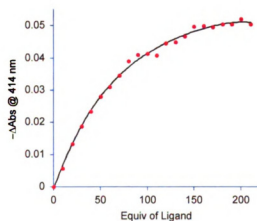
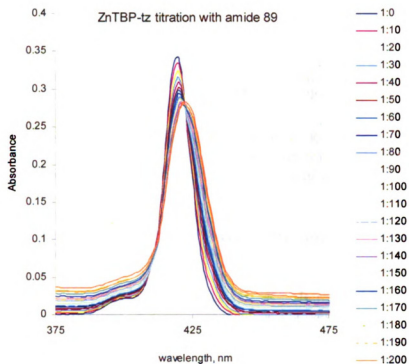


Figure III.-14: a) Titration of ZnTBP tweezer **V** with substrate **89**; b) Non-linear least square fits of the change in absorption vs. equiv of ligand leads to the calculation of binding constant and fitting curve.

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**PORPHYRIN TWEEZERS FOR THE ABSOLUTE STEREOCHEMICAL
DETERMINATION OF SMALL MOLECULES THROUGH ECCD**

Volume II

By

Marina Tanasova

A DISSERTATION

**Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of**

DOCTOR OF PHILOSOPHY

Chemistry

2009

Chapter IV

Designing the “Universal” Porphyrin Tweezer

IV.1. Background

As evident from the literature published in the field of stereochemical determination using Exciton Coupled Circular Dichroism (ECCD)^{1, 2} has been successfully applied towards the absolute stereochemical determination of a wide variety of chiral compounds. Since the application of the method requires the presence of chromophores, they can be introduced into the system either through chemical derivatization, or non-covalent binding^{3, 4} such as utilizing a bis-porphyrin tweezer.⁵ First application of a ZnTPP tweezer as bis-chromophoric host was for stereochemical determination of chiral diamines. The two amino group of chiral diamine are able to complex with zinc atom incorporated into the porphyrin core and, hence, form equimolar bis-coordinated complex with chromophoric host (Figure IV-1a).⁶

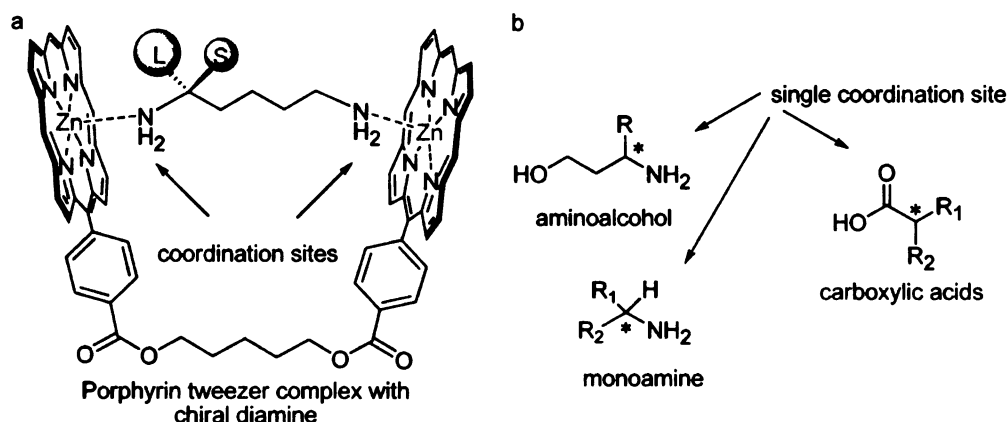
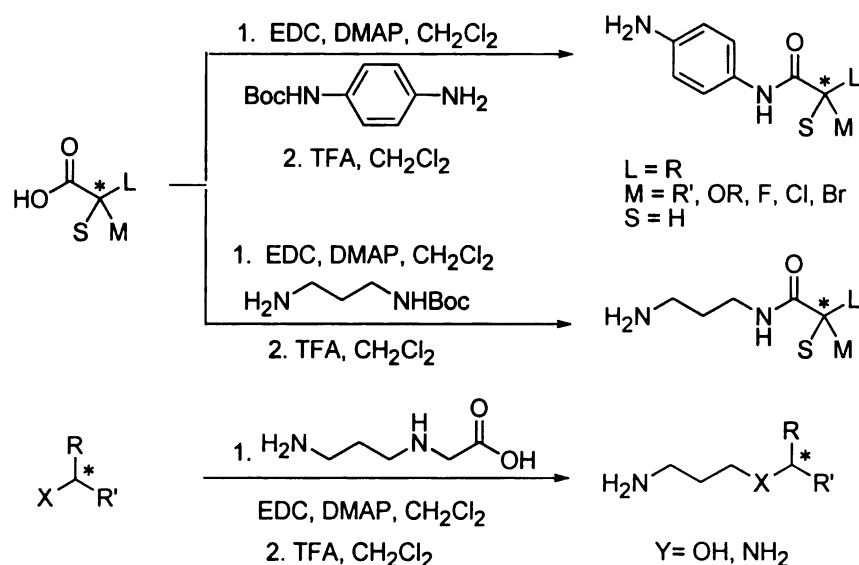


Figure IV-1: Complexation of chiral substrate with porphyrin tweezer requires two coordination sites: a) two amino groups of diamine used for complexation; b) substrates unable to form the complex due to the lack of the coordinating functional group (phenyl rings on the porphyrins are omitted for clarity of picture).

Scheme IV-1: Introduction of the carrier molecules for application of ECCD for the stereochemical determination of mono-amines and carboxylic acids



While diamines are able to coordinate to the ZnTPP tweezer directly, monoamines^{7, 8} or carboxylic acids⁹⁻¹¹ are not able to form the equimolar bis-coordinated complex with bis-porphyrin since they lack the coordination site(s). On the other hand amino alcohols having two functional groups yet provides a single coordination to tweezer (the amino group coordinated to the porphyrin), since the coordination of hydroxyl to zinc atom is significantly weaker as compared to $\text{N} \rightarrow \text{Zn}$ coordination.¹² The solution to this problem was to introduce an achiral molecule that could provide one or two (if necessary) functional group for complexation with the porphyrin tweezer. Hence, the “carrier” molecules of different type were used for derivatization of chiral substrates and the resulting carrier conjugates were complexed directly with the porphyrins of the host. Scheme IV-1 presents the carriers applied to provide the lacking coordination site for the chiral monoamines,^{7, 8} aminoalcohols¹² and

carboxylic acids^{9, 10} for their absolute stereochemical determination with porphyrin tweezer.

The complexes of the porphyrin tweezer with a carrier derivatized chiral substrates exhibit strong exciton coupling originating from a helical twist between the two chromophores, induced by the steric interactions of the porphyrins with the substituents at the chiral center. In particular, when a chiral molecule coordinates to the two porphyrins of the tweezer, one of the porphyrins is placed close to the asymmetric center. Thus, for tweezer complex with a chiral diamine (Figure IV-1) one porphyrin is facing the two substituents of the chiral center.

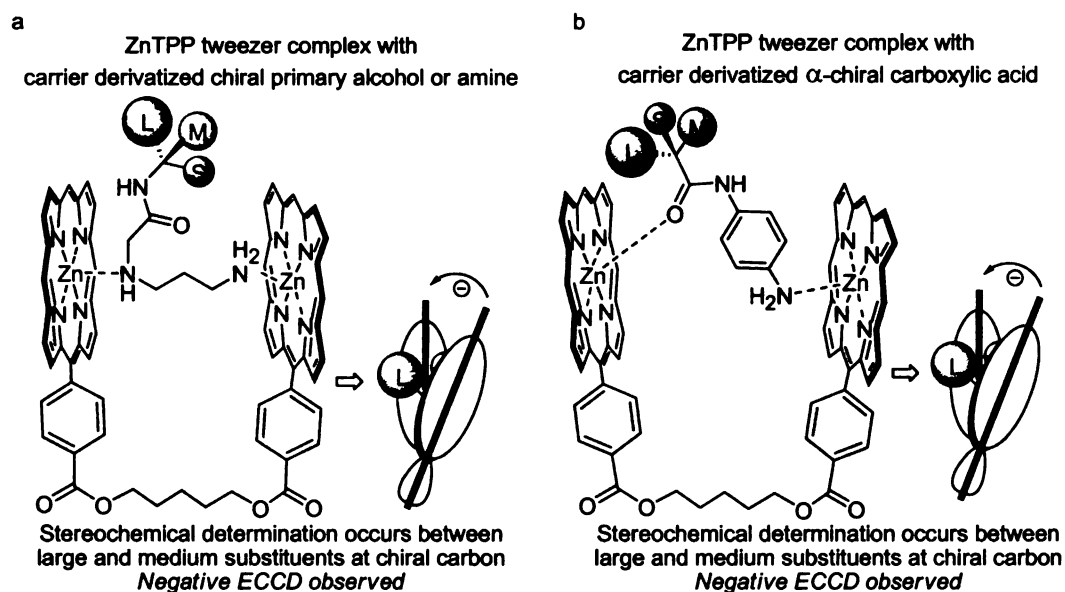


Figure IV-2: Stereochemical determination of carrier derivatized chiral primary alcohols and amines (a) and α -chiral carboxylic acids (b) with ZnTPP-tz I. Helicity on the chromophoric host is defined by the asymmetry of the complexed chiral guest (phenyl rings on the porphyrins are omitted for clarity of picture).

Since the substituents at the chiral carbon differ in size (the relative sizes are defined from corresponding A-values¹³) the porphyrin experiences different steric

interaction with the two substituents. It is believed that in order to equilibrate the steric environment in the complex, the porphyrin coordinated closer to the asymmetric carbon slides away from the larger substituent towards the smaller one. This movement twists the chromophore with respect to the second porphyrin, resulting in helical arrangement of the chromophores in the complex. A “chiral twist” of the porphyrins relative to each other is detected as an exciton CD couplet (ECCD spectrum).

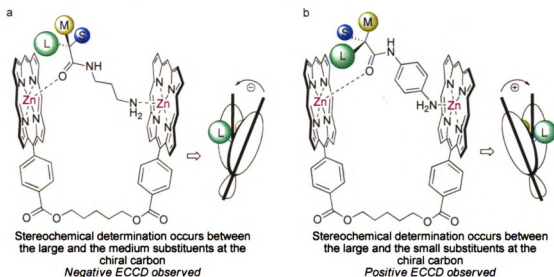


Figure IV-3: Stereochemical determination of α -chiral carboxylic acids derivatized with different carrier proceeds through stabilization of the different ECCD active conformations: a) 1,3-diaminopropene derivative and b) 1,4-phenylenediamine derivative complexed with porphyrin tweezer (phenyl rings on the porphyrins are omitted for clarity of picture).

The sign of the bisignate curve (either positive or negative) can be directly correlated to the relative orientation of chromophores and further to the absolute stereochemistry of coordinated chiral guest. For instance, the steric differentiation between the large and the small substituents at the chiral carbon of diamine depicted in Figure IV-1 occurs in favor of the smaller group and, the resulting clockwise orientation of chromophores is observed as positive ECCD. Stereochemical determination of the

chiral monoamines and α -chiral carboxylic acids presented in Figure IV-2 is more complicated due to the rotation around $C_{NH}-C_{chiral}$ (a) or $C_{C=O}-C_{chiral}$ (b). For these substrates correlation of the ECCD sign with absolute stereochemistry of chiral guest is possible after identification of the major ECCD contributing rotamer.

It is noteworthy, that the use of the porphyrin tweezer method for the absolute stereochemical determination of α -chiral carboxylic acids led to the application of two different types of carriers: flexible 1,3-diaminopropane¹⁰ and rigid 1,4-phenylenediamine.⁹ Each carrier results in the steric differentiation proceeding through different ECCD active conformations. Namely, 1,3-diaminopropane derivatives tend to stabilize the conformation where the small group (hydrogen) is oriented *anti* to the carbonyl and the steric differentiation occurs between the large (based on A-values¹³) and the medium substituents on the asymmetric carbon. Derivatives of 1,4-phenylenediamine orient the medium group *anti* to the carbonyl and the steric differentiation takes place between the large and the small groups. Thus, the two derivatives of the same carboxylic acids stabilize different conformation within ZnTPP tweezer and yield the ECCD spectra of opposite sign (Figure IV-3).

Stabilization of different ECCD active conformations was also detected between different types of α -chiral carboxylic acids derivatized with the same carrier. For instance, steric differentiation of 1,4-phenylenediamine derivatives of α -alkyl (alkoxy) and α -halogenated carboxylic acids proceeds through different rotamers (see Chapter II for details). In particular, it was derived that stereochemical determination of α -alkyl (alkoxy) carboxylic acids derivatized with 1,4-phenylenediamine occurs in a conformation that orients large and small groups towards the porphyrin, with the medium

group oriented away from the porphyrin (Figure IV-4a). As a result of steric differentiation, the porphyrin coordinated to the carbonyl prefers to slide away from the large group and covers the small group. This results in a negative ECCD for all (*S*)- and a positive ECCD sign for (*R*)-alkyl (alkoxy) amides.⁹

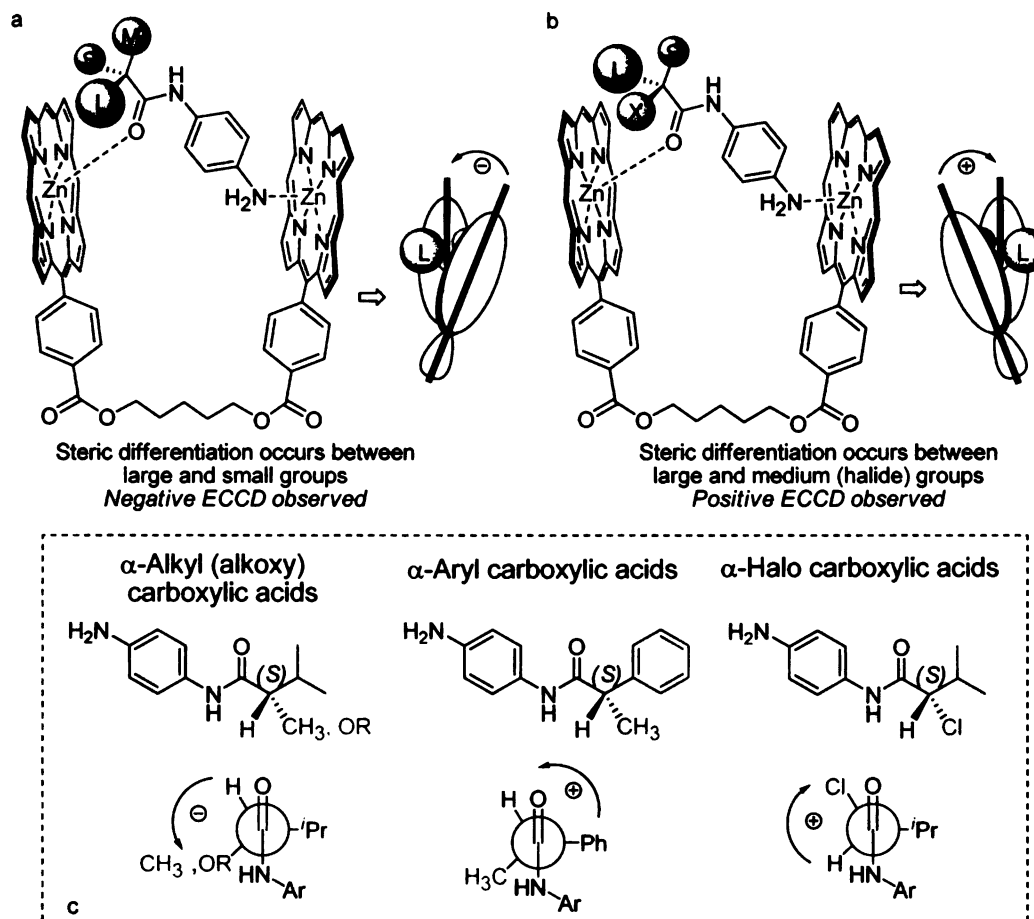


Figure IV-4: Stereochemical determination of 1,4-phenylenediamine derivatized chiral a) α -alkyl(alkoxy) and b) α -halocarboxylic acids with ZnTPP-tz; Working mnemonic for the stereochemical determination of chiral a) α -alkyl(alkoxy), b) α -aryl and c) α -halocarboxylic acids.

Introduction of an aromatic moiety at α -position changes the mode of steric differentiation. In particular, a sign of ECCD spectrum obtained with 1,4-

phenylenediamine derivatized α -arylcarboxylic acid is induced by the conformation derived for alkyl substrates, although, presumably, originates due to the π - π interaction between the chromophore and the aryl substituent leading to the porphyrin covering the large aromatic substituent instead of sliding away from it (Figure 4b).⁹ (It is worth noting that the change is observed only with substrates bearing the aromatic moiety directly at the asymmetric carbon.)

The presence of a halogen atom on the chiral center changes the orientation of the substituents relative to the carbonyl, which leads to inversion of the ECCD sign (Figure IV-4c). Namely, the major ECCD active conformation of 1,4-phenylenediamine derivatized α -halocarboxylic acids places a small group *anti* to the carbonyl, hence supporting steric differentiation between the halide (medium) and the alkyl (large) group (Figure IV-4c). As was discussed in Chapter II, this result is believed to be due to the secondary interaction between the halogen atom and an aromatic the system of the porphyrin. The possibility of halogen- π interaction was supported by complementary NMR and UV studies of the α -haloamide-ZnTPP complexes.

It is also noteworthy, that although tuning of the porphyrin surface by introduction of bulky substituents at its periphery induces a significant improvement in sensitivity of the tweezer (up to 10 fold increase of amplitude was observed), the steric differentiation of alkyl (alkoxy) and haloamides proceeds through different rotamers (see Chapter III for details)) leading to a switch of ECCD sign. An exception was found when α -haloamides were complexed to ZnTBP tweezer (V). Depending on the type of a halide and the size of the alkyl substituent at the chiral center tweezer V stabilized the conformation previously observed with α -alkyl (alkoxy) amides.

Thus, we can conclude that while the porphyrin tweezer method presents a convenient, reliable and, by all means, important tool for stereochemical determination of organic molecules, its main drawback is that all studies performed with 1,4-phenylenediamine derivatized α -chiral carboxylic acids discussed in previous chapters required introduction of different working mnemonic. Hence, stabilization of a single ECCD active conformation within carrier α -chiral amides remains an open task.

In order to address the issue of stabilizing a single ECCD active conformation for all types of α -chiral amides designing a universal porphyrin tweezer is necessary. Considering the fact that the porphyrin tweezers **I-V** discussed in Chapters I-III are assembled through a long and flexible pentane linker we can assume that stabilization of secondary interactions - π - π and C-X-- π - is a direct consequence of the flexibility of the porphyrin tweezer. Thus, in order to gain an insight into the role of the tweezer linker in the process of stereochemical determination of α -chiral carboxylic acids we focused on studying the effect of the length and rigidity of the linker onto the conformational stability of substrates in the complex and the mode of steric differentiation.

IV.2. ZnTPP-acetylene porphyrin tweezer VIII

IV.2-1: Design, synthesis and spectroscopic studies

In order to study the influence of flexibility of the pentane linker onto the conformational stability of the carrier derivatized α -alkyl, alkoxy, aryl and halocarboxylic acids we refer to the previously synthesized in our laboratory zinc bis-acetylene porphyrin tweezer **VIII** (ZnTPP-Ac-tz) (Figure IV-5).¹⁴

The bis-acetylene linker was designed to take advantage of the rigidity provided by the acetylene triple bond. At the same time, the possible rotation around the bis-acetylene single bonds of the linker allows for the formation of the chiral twist between the porphyrins. Position of the linker (*meta* position on the phenyl ring relative to the porphyrin) was chosen with consideration of the size of the binding cavity necessary for incorporation of chiral guests. Linking of the porphyrins through the *ortho*-position, would align the porphyrins face-to-face, yet could create a binding pocket of limited capacity. However, if the acetylenes are connected through the *meta* positions of the phenyl substituents on the porphyrins, the chromophores will have a fixed angle of approximately 120° relative to the acetylene (Figure IV-5) which is sufficient for exciton interaction and also provides a large enough pocket for incorporation of chiral substrates.

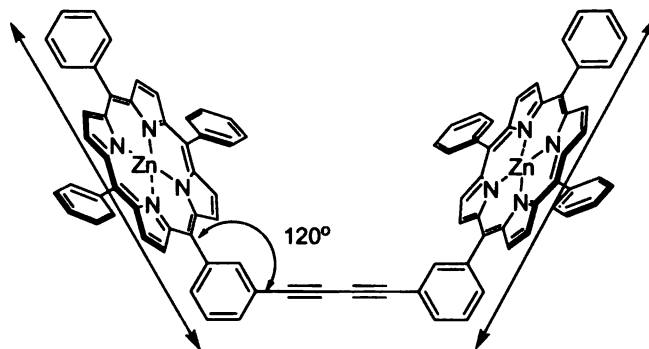
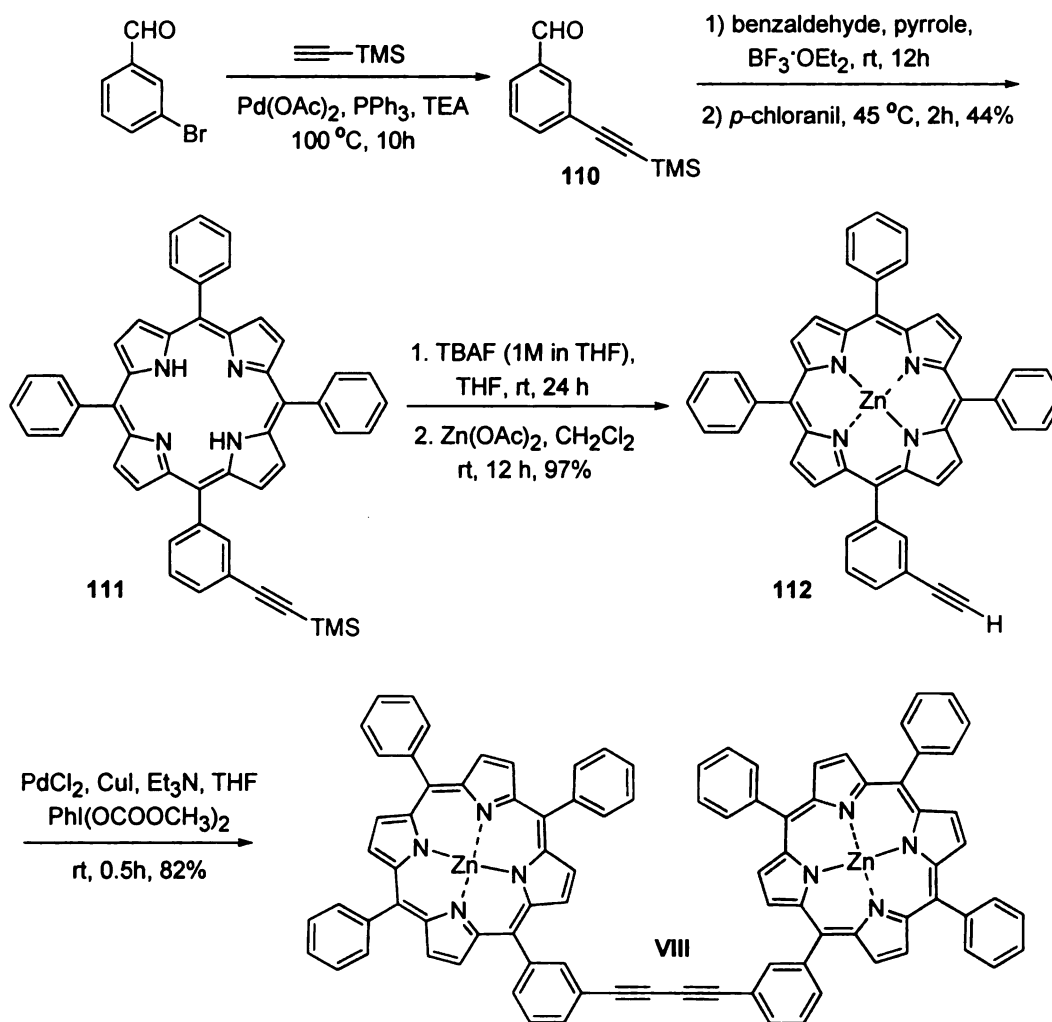


Figure IV-5: ZnTPP-acetylene tweezers VIII

Similar to the ZnTPP tweezer I (Chapter II), the porphyrins of the bis-acetylene tweezer are not oriented face-to-face. Random orientation of chromophores is restricted by the guest molecule that, upon binding will bring the porphyrins face-to-face due to the formation of 1:1 tweezer/substrate complex, which can further adopt a helical twist induced by the chirality of the bound guest and result in the observed ECCD bisignate.

Nevertheless, the angular alignment of chromophores in tweezer **VIII** might also contribute to the lower amplitude of the ECCD signal.

Scheme IV-2: Synthesis of zinc bis-acetylene porphyrin tweezer **VIII**



The synthesis of the porphyrin tweezer **VIII** (Scheme IV-2) starts with palladium catalyzed coupling between 3-bromobenzaldehyde and (trimethylsilyl)ethyne to produce 3-[(trimethylsilyl)ethynyl]benzaldehyde **108**.¹⁵ The resulting aldehyde was used for the construction of 5,10,15-triphenyl-20-(3-trimethylsilylphenylethynyl)porphyrin **109** in $\text{BF}_3\cdot\text{Et}_2\text{O}$ catalyzed condensation with pyrrole and benzaldehyde.¹⁶ Cleavage of the

TMS group followed by metallation of the porphyrin results in compound **110**. It is noteworthy, that zincation of the porphyrin at this stage is necessary for the application of the standard Glaser-Hay procedure. Metal free porphyrin submitted to the coupling undergoes copper insertion, hence, preventing the coupling reaction to occur. The zincated porphyrin was submitted to Pd catalyzed alkyne-alkyne coupling in THF that resulted in porphyrin tweezer **VIII** in 82% yield.¹⁷

To explore the binding ability of the new ZnTPP-Ac tweezer, it was titrated with benzylamine and a set of diamines of different lengths. Titration with benzylamine was used as a standard for identification of a 1:2 tweezer/amine complex presented on Figure IV-6. Addition of benzylamine to tweezer **VIII** induces gradual formation of a 1:2 complex, where each porphyrin is coordinated with separate molecule of benzylamine (Figure VI-7).

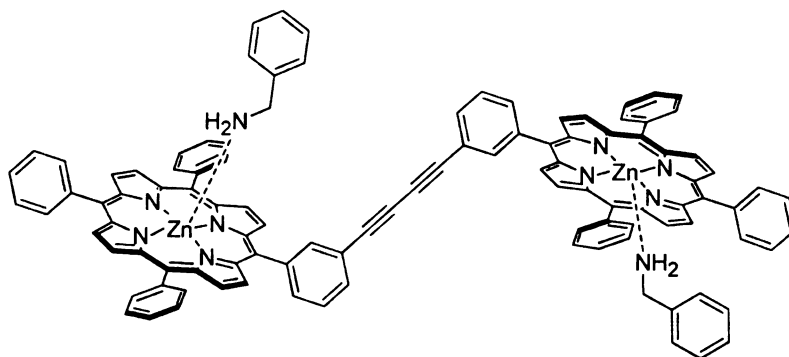


Figure IV-6: Complexation of ZnTPP-Ac tweezer with benzylamine (1:2 complex).

Complexation becomes prominent after addition of 10 equivalents of amine and is fully completed after addition of 400 equiv of benzylamine. Overall, binding of a monoamine induces a 10 nm bathochromic shift of the Soret band (from $\lambda_{\text{max}} = 419.3$ nm to 429.0 nm).

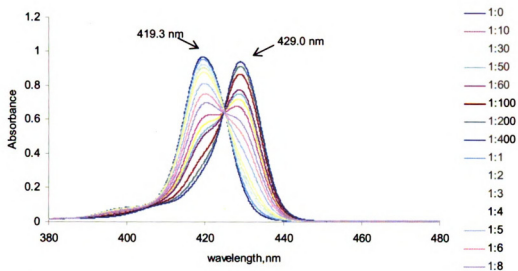


Figure IV-7: Titration of ZnTPP-Ac tweezer (VIII) with benzylamine results in formation of a 1:2 tweezer/benzylamine complex (in dichloromethane).

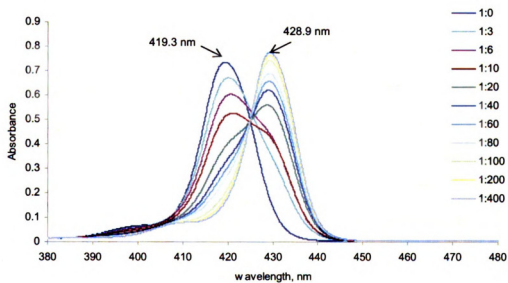


Figure IV-8: Titration of ZnTPP-Ac tweezer (VIII) with 1,2-ethanediamine results in formation of the 1:2 tweezer/diamine complex (in dichloromethane).

In order to avoid dilution of the sample, titration experiments were performed using three sets of dichloromethane solutions of diamines: 1mM solution for addition of 1-10 equiv

of amine, 10 mM solution for concentration from 10 to 100 equiv, and 100 mM for concentrations of diamine within a range of 100-1000 equivalents.

Analogous titrations carried out with diamines of different sizes gave the following results. It was detected that addition of 1,2-ethanediamine to tweezer **VIII** does not induce the formation of a 1:1 complex, as it was observed with flexible tweezers (**I-V**). On contrary, the titration pattern and close to 10 nm red shift of the Soret band resemble the pattern observed during addition of mono-amine and implies formation of 1:2 complex (Figure IV-8). Similar shift of the Soret band is observed upon addition of 1,3-propanediamine. These results are expected since the rigidity of the bis-acetylene linker restricts a change of the interchromophoric distance. After viewing the molecular models of these complexes it appears that the structure of the tweezer is too rigid to permit binding of 1,2- or 1,3-diamines and coordination would cause a large degree of strain in the linkage between the porphyrins.

Complexation of longer diamines is different. For instance, addition of 1,4-diaminobutane induces two transitions. Addition of 1 equiv of 1,4-diaminobutane induces a new transition at 424 nm (5 nm shift) with a small shoulder peak present, corresponding to the free tweezer. Complete complexation is observed at 2.5 equiv of diamine.

The red shift induced by complexation (5 nm) is similar to the one detected with flexible tweezers **I-V** and is indicative of the formation of 1:1 porphyrin/diamine complex. Increase of diamine concentration led to a saturation of the complex with a second molecule of diamine and appearance of an 1:2 tweezer/diamine complex with

absorption maximum at 428.6 nm (9.3 nm shift) and was completed after addition of 400 equiv of 1,4-diaminobutane (Figure IV-9).

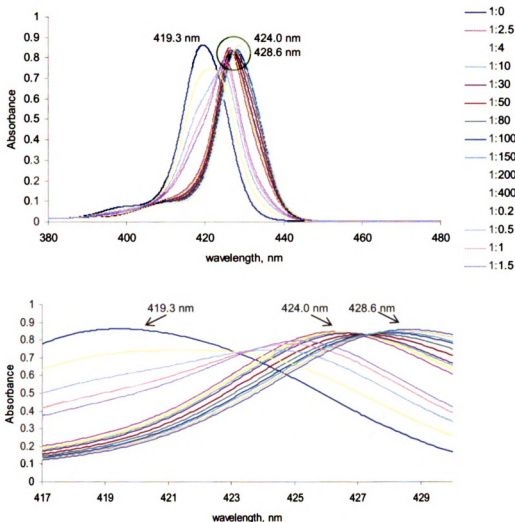


Figure IV-9: Titration of ZnTPP-Ac tweezer (**VIII**) with 1,4-ethanediamine results in the formation of the 1:1 tweezer/diamine complex (424 nm) and gradual transition into the open 1:2 complex (428.6 nm) (in dichloromethane).

Intramolecular complexation improves with increasing length of the diamine introduced into the porphyrin binding pocket. Thus, addition of 1,6-diaminohexane results in complete formation of the complex with absorption at 425 nm when 1 equiv of

diamine is added (6 nm red shift for this substrate is also consistent with the shift observed with flexible tweezers). The complex appears to be stable even with 100 equiv of diamine added. Slow transition of the 1:1 species into the 1:2 complex is observed after addition of great excess of diamine (1000 equiv) (Figure IV-10). From the binding studies of ZnTPP-Ac tweezer we can conclude that formation of the 1:1 tweezer/substrate complex is strictly dependent on the size of the substrate.

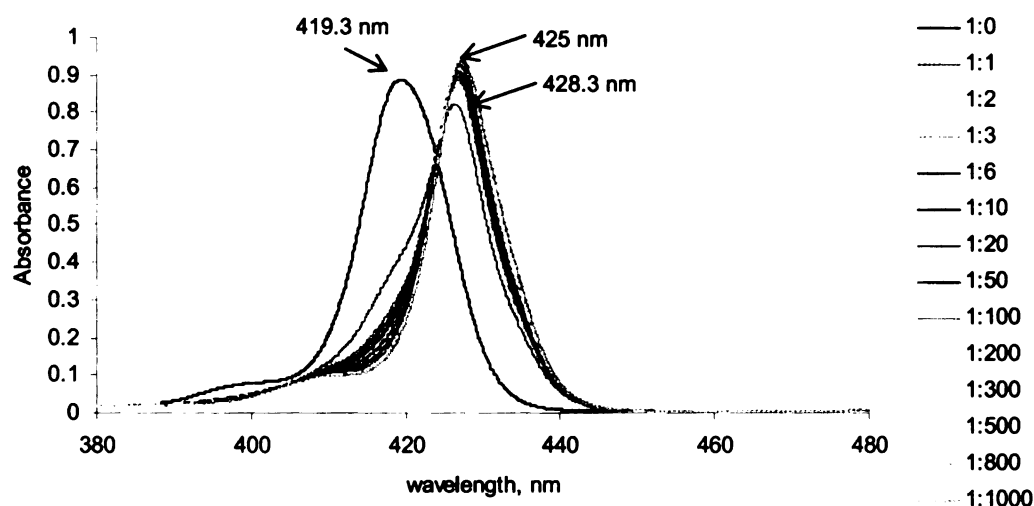


Figure IV-10: Titration of ZnTPP-Ac tweezer (**VIII**) with 1,6-ethanediamine results in the formation of the 1:1 tweezer/diamine complex (in dichloromethane).

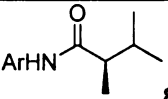
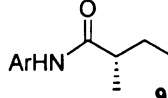
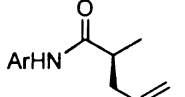
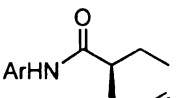
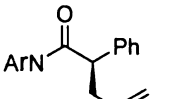
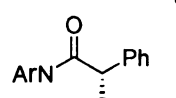
IV.2-2. Bis-Acetylene porphyrin tweezer in stereochemical determination of 1,4-phenylenediamine derivatized α -alkyl and aryl carboxylic acids

After identification of binding ability of tweezer **VIII** with diamines, the ECCD of chiral diamines bound to **VIII** in hexanes was measured. (*S*)-Ornithine methyamide (1,4-diamine) and (*S*)-Lysine methyl ester (1,5-diamine), yielded observable ECCD

spectra. As expected the small (*R*)-1,2-diaminopropane was ECCD silent due to its inability to form a 1:1 complex with the rigid tweezer.

In order to examine the general behavior of the new ZnTPP-Ac tweezer upon binding of carrier derivatized carboxylic acids, several previously synthesized and reported alkyl and aryl substituted substrates were tested. ECCD experiments were conducted in methylcyclohexane at 0 °C with 1 μ M solution of the tweezer **VIII**. The data obtained is reported in Table IV-1 at 10 equivalents of chiral substrate.

Table IV-1: α -Chiral carboxylic acid with ZnTPP and ZnTPP-Ac tweezers.

Entry	Substrate	Tweezers			
		I		VIII	
		λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
1	 81	428 (+40) 420 (-48)	+98	427 (+22) 420 (-25)	+45
2	 90	429 (-23) 421 (+18)	-41	428 (-10) 418 (+6)	-16*
3	 86	431 (+10) 422 (-9)	+19	-----	-----
4	 87	429 (+41) 420 (-40)	+80	429 (+12) 418 (-14)	+26*
5	 89	430 (-75) 418 (+60)	-135	430 (+40) 425 (-25)	+65
6	 95	426 (+127) 416 (-48)	+175	430 (-47) 423 (+35)	-82

Spectra taken in methylcyclohexane at 0 °C and reported at 10 equiv of chiral guest

* - spectra reported at 4 equivalents of substrate.

As expected from the low mobility of the linker, complexation of derivatized carboxylic acids with bis-acetylene tweezer (Table IV-1) shows ECCD of significantly lower amplitude. Nonetheless, it is important to note that all alkyl substrates bound to **VIII** (entries 1-4) give the chiral induction with the same sign as detected with ZnTPP tweezer. This result indicates that despite the major difference in flexibility of the bis-chromophores, both tweezers **I** and **VIII** exhibit a similar mode of binding with carrier derivatized α -chiral alkyl carboxylic acids. Additionally, this implies that complexation of the ZnTPP-Ac tweezer with 1,4-phenylenediamine derivatized α -chiral carboxylic acids involves the stabilization of the same ECCD active conformation as was reported for the tweezers **I-V**, orienting the large and small groups towards the carbonyl coordinated the porphyrin. Nevertheless, it appears that low sensitivity of the tweezer **VIII** might be an important drawback for its application as a tool for stereochemical determination of derivatized carboxyl compounds and in particular, its use for substrates bearing substituents of a relatively similar size at the asymmetric center.

For instance, 1,4-phenylenediamine (carrier) derivative of (*S*)-2-methylbutyric acid (Table IV-1, entry 2) shows a complicated ECCD pattern. While addition of the first four equivalents of the substrate induces the expected negative helicity into the complex (Figure IV-11a), increase of the concentration of the carrier conjugate to 8 equivalents results in the appearance of a mixed ECCD - the result of two overlapping signals – that persists during further addition of substrate (Figure IV-11b). The positive couplet at higher wavelength indicates the presence of a new ECCD active conformation of the substrate in the complex. The negative couplet at lower wavelength corresponds to the major conformation observed at low equivalents of substrate.

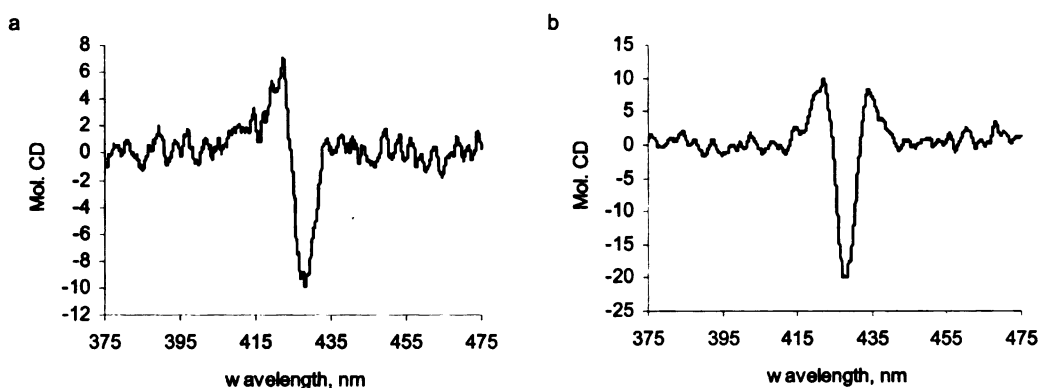


Figure V-11: (*S*)-2-Methylbutyric acid carrier conjugate with ZnTPP-Ac-tz (**VIII**): a) ECCD at 4 equiv of chiral substrate, b) ECCD at 8 equiv of chiral substrate (spectra in methylcyclohexane).

Decrease in ECCD amplitude is also observed with substrates that give an intense and prominent chiral induction with ZnTPP-tz. For instance, screening of tweezer **VIII** with amides of (*S*)-2-ethyl-4-pentenoic acid, (*R*)-2,3-dimethylbutanoic acid (entry 4) or α -aromatic acids (entries 5 and 6) also results in spectra of lower amplitude. Combining these observations and considering that rigidity of the bis-acetylene tweezer implies a fixed interchromophoric distance, it is plausible to propose that decrease in amplitude must be contributed by diminished dihedral angle that might be the consequence of a lower mobility of the porphyrins due to the bis-acetylene linker.

Low flexibility of the new bis-acetylene tweezer might be beneficial for disruption of the aromatic interactions observed with chiral α -aryl substrates. In particular, while the flexibility of the ZnTPP-tz allows the secondary π -interaction in the tweezer-substrate complex (see Chapters III for details), ZnTPP-Ac-tz might not be able to accommodate the suitable geometry for porphyrin-aryl group interaction, which would result in switch in the sign of bisignate spectrum (Figure IV-12).

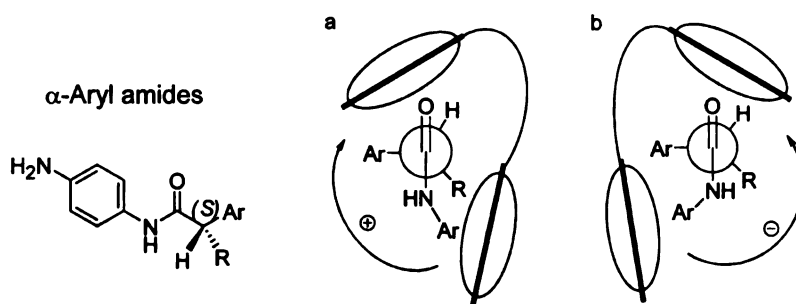


Figure IV-12: Major ECD active conformation of α -arylamides of 1,4-phenylenediamine leading to: a) positive ECD due to the aromatic interaction between the aryl group at the chiral center and the carbonyl coordinated porphyrin and b) negative ECD in the absence of secondary interaction.

Indeed, screening of the tweezer with aromatic substrates gave inversion of the ECD sign (Table V-1, entry 5, 6). In particular, (*S*)-2-phenylpropionic acid carrier conjugate **95** yielding a positive bisignate with ZnTPP tweezer resulted in a negative spectrum with tweezer **VIII** (Figure IV-13). Similarly, carrier derivative of (*R*)-2-phenylpent-4-enoic acid (amide **89**) resulted in a positive ECD couplet, opposite to the negative ECD detected with ZnTPP and other modified tweezers discussed in Chapter III.

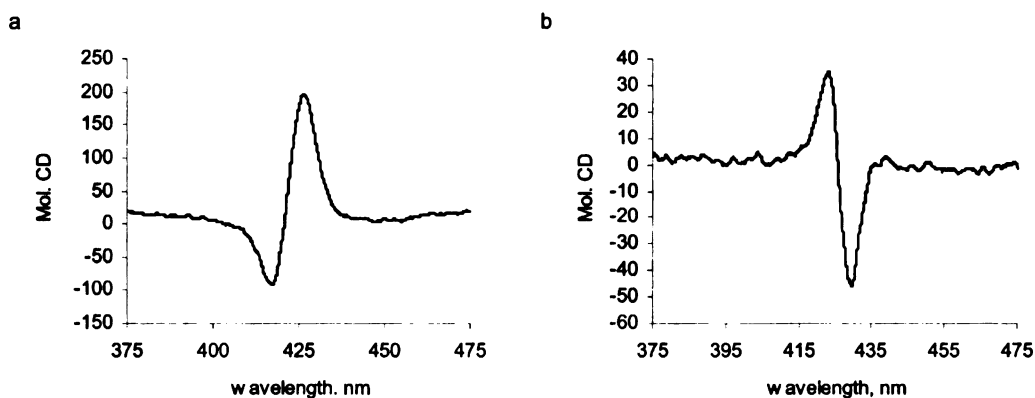
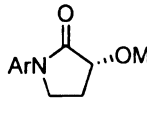
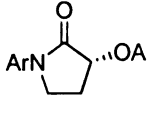
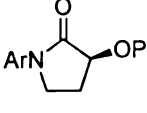
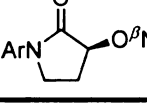


Figure IV-13: (*S*)-2-Phenylpropionic acid carrier conjugate **89** resulting in a) positive ECD with ZnTPP-tz (**I**) and b) negative ECD ZnTPP-Ac-tz (**VIII**). Spectra are taken in methycyclohexane and reported at 1:10 tweezer to substrate ratio.

The observed switch of the sign originates from the same major conformation postulated in the complex (the large and the small groups oriented towards the porphyrin), but with porphyrin covering the small hydrogen instead of the phenyl ring (no aromatic interaction present), hence yielding the sign predicted based on the mnemonic proposed for the alkyl and alkoxy substituted carboxylic acids (Figure IV-12).

Table IV-2: ECCD data of α -alkoxy (aryloxy) butyrolactams obtained with ZnTPP-tz (I) and ZnTPP-Ac-tz (VIII)

Entry	Substrate	Tweezers			
		I		VIII	
		λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
1	 37	429 (-57) 421 (+53)	-110	432 (-242) 424 (+188)	-430
2	 38	433 (-30) 420 (+25)	-55	432 (-45) 422 (+28)	-73
3	 50	429 (-20) 418 (+25)	-45	430 (+12) 421 (-18)	+30
4	 51	430 (-18) 418 (+34)	-52	432 (+28) 422 (-36)	+64

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

Aromatic interactions have also been observed in cyclic structures. Table IV-2 presents a number of α -aryloxy- γ -butyrolactams where aromatic interaction inverts the expected ECCD sign. Thus, while stereodifferentiation of (*R*)- α -alkoxy and (*S*)-aryloxy- γ -butyrolactams by tweezers I-V occurs through the similar mode – porphyrin discriminates between the medium alkoxy or aryloxy group and the small hydrogen oriented towards the carbonyl, both types of lactams yield ECCD of the same sign (entries 1, 2 and 3, 4). Such outcome is explained by an aromatic interaction taking place

between the aryloxy substituent at the chiral center and the stereodifferentiating porphyrin (Figure VI-14). π - π interaction directs the porphyrin coordinated to the carbonyl towards the larger aryloxy group, as opposed to the small hydrogen, yielding a negative ECCD as opposed to the expected positive bisignate. Unlike tweezers I-V, bis-acetylene tweezer VIII upon complexation with (*S*)-2-aryloxy- γ -butyrolactams **50** and **51** adopts clockwise orientation of the porphyrins and results in the expected positive ECCD. The observed positive ECCD implies due to the rigidity of the bis-acetylene linker, ZnTPP-Ac tweezer does not support π - π interaction in the complex.

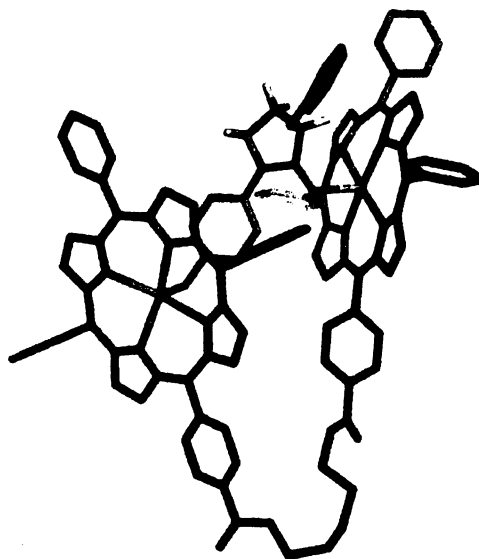


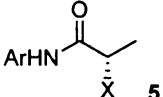
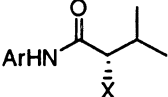
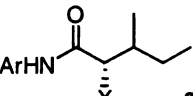
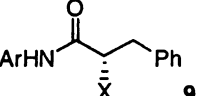
Figure IV-14: ZnTPP tweezer complex with (*S*)-2-OPh-butylolactam.

Application of the ZnTPP-Ac tweezer (VIII) reveals that although the rigidity of this chromophoric host induces a significant decrease of amplitude when used with acyclic carboxylic acid derivatives, it is quite efficient for identification of a secondary interaction, and for obtaining an ECCD sign based solely on size differentiation.

IV.2-3: ZnTPP-Ac tweezer in study of C-X--- π interaction with α -halo amides and α -halo lactams

Another type of secondary interaction detected in tweezer-substrate complex is the halogen- π interaction discussed in Chapter II. Based on the results obtained with different halogenated substrates and different tweezers one could conclude that the C-X-- π interaction is sensitive towards the sterics and electronics of the porphyrin system. Yet, none of the tweezers tested has equally disrupted C-X- π complexation in all substrates. The following paragraph presents the studies of halogenated carboxylic acids with rigid tweezer **VIII**.

Table IV-3: ECCD of α -halo carboxylic acid carrier conjugates with ZnTPP-Ac tweezer

Entry	Substrate, X =	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
		Br		Cl		F	
1	 5	432 (+35) 422 (-26)	+61	428 (+35) 423 (-30)	+65	433 (-16) 427 (+50) 422 (-28)	mix
2	 6	429 (+31) 421 (-20)	+51	429 (+15) 422 (-22)	+37	428 (-23) 420 (+19)	-42
3	 8	430 (+25) 422 (-22)	+47	429 (+35) 422 (-30)	+65	427 (-50) 420 (+28)	-78
4	 9	429 (+42) 421 (-30)	+72	430 (+27) 422 (-29)	+56	432 (-10) 427 (+30) 422 (-7)	mix

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

As it is summarized in Table IV-3, tweezer **VIII**, similar to other modified tweezers, induces a switch in the conformation of the bound halogenated guest, which can be observed as the change in the sign of the ECCD spectrum. In particular, while

ZnTPP-tz gave positive ECCD for the complexes of (*S*)- α -haloamides (regardless the type of halide atom or size of the alkyl substituent present at the chiral center), ZnTPP-Ac-tz switched the helicity of the complexes for fluorinated amides **5F-9F**. Thus, (*S*)-2-bromopropionamide and (*S*)-2-chloropropionamide (Table IV-3, Entries 1 and 2) induce a positive helicity into the ZnTPP-Ac tweezer (it is noteworthy that the observed sign is governed by C-X $\cdots\pi$ interaction), and the fluorinated **5-F** analog gives a mixture of two overlapping ECCD signals. The first negative couplet implies a new conformation of the halogenated chiral guest, where the halide is oriented away from the porphyrin, while the second, positive bisignate is a result another conformation stabilized within a complex (Figure IV-15) (possibly the rotamer observed with tweezers I-V for alkyl and alkoxyamides).

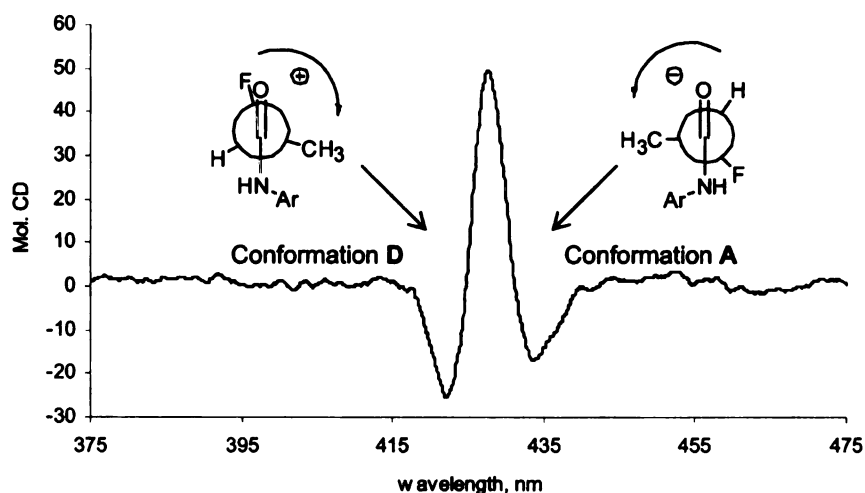


Figure V-15: Complex spectrum of (*S*)-2-fluoropropionic acid carrier conjugate with ZnTPP-Ac tweezer: negative bisignate induced by a new conformation A of the substrate, while the following positive couplet is contributed by conformation D stabilized through CF- π interaction.

Same trend is detected with substrate **6** (Table 3, entry 2), although the fluorinated analog results in a stable negative ECCD induced by the conformation **A**, where stereodifferentiation occurs between the small hydrogen and the large alkyl group (Figure IV-16). Analogous results were observed with all the other sets of halogenated carboxylic acids presented in the table. It appears that the rigidity of the tweezer **VIII** does not affect the bromine or chlorine interaction with aromatic system, while interaction of the fluorine with the porphyrin is dependent on the steric environment around the chiral center, i.e. branching of β -position destabilizes C-F $\cdots\pi$ interaction.

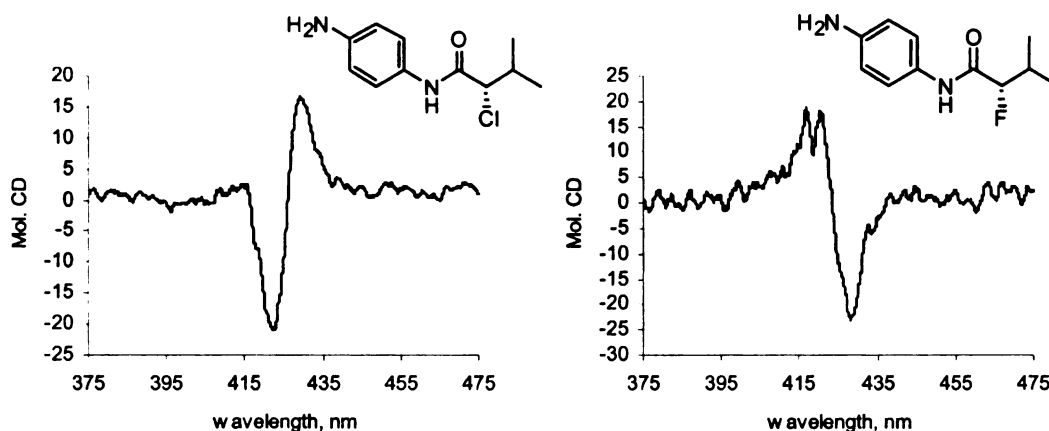
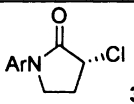
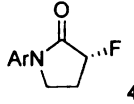
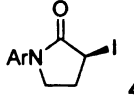


Figure IV-16: Inversion of the ECCD sign with the change of the halide: positive ECCD of derivatized (*S*)- α -chloro-3-methylbutyric acid versus negative ECCD of (*S*)- α -fluoro-3-methylbutyric acid carrier conjugate

After analysis of the results obtained with chiral α -halo carboxylic acid carrier conjugates it appears that fluorine interaction with the porphyrin is the weakest of all, since any changes made with the porphyrin tweezer (steric hindrance on the porphyrin core or flexibility of the tweezer) largely destabilize the fluorine-porphyrin interaction. Br and Cl interactions tend to be more stable, and are affected only by combination of sterics of the porphyrin and a bulk of α -alkyl substituent (Chapter III). Thus, one can

conclude that despite the rigidity of the linker the ZnTPP-Ac tweezer is not effective for disruption of halogen- π interaction in acyclic halo-carboxylic acids.

Table IV-4: ECCD of α -halo- γ -butyrolactams with ZnTPP-Ac tweezer

Entry	Substrate	λ , nm ($\Delta\epsilon$)	A
5	 36	432 (-102) 424 (+65)	-167
6	 40	431 (-94) 422 (+108)	-202
7	 41	431 (+66) 422 (-83)	+149

Spectra were measured in methylcyclohexane (1 μ M of tweezer) at 0 °C and reported at 20 equiv of chiral guest

Unlike acyclic haloamides, halogenated lactams upon complexation with ZnTPP-Ac tweezer do not exhibit any secondary interaction with the porphyrin, and induce ECCD signal expected on the basis of size differentiation (porphyrin differentiates between medium halide and small hydrogen and slides toward the latter) (Table IV-4). Thus, both (*R*)-chloro and (*R*)-fluoro- γ -butyrolactams switched the ECCD sign from positive (observed with ZnTPP) to negative (Figure IV-17).

Along with switching the ECCD sign, halolactams produced spectra of significantly enhanced amplitude. (*S*)-Iodobutyrolactam also induced an enhanced helicity in the ZnTPP-Ac tweezer and gave positive ECCD, opposite from the negative ECCD observed with ZnTPP tweezer (I). All the results indicate an absence of a halogen- π interaction, and imply stereodifferentiation based on the sizes of the substituents at the asymmetric center.

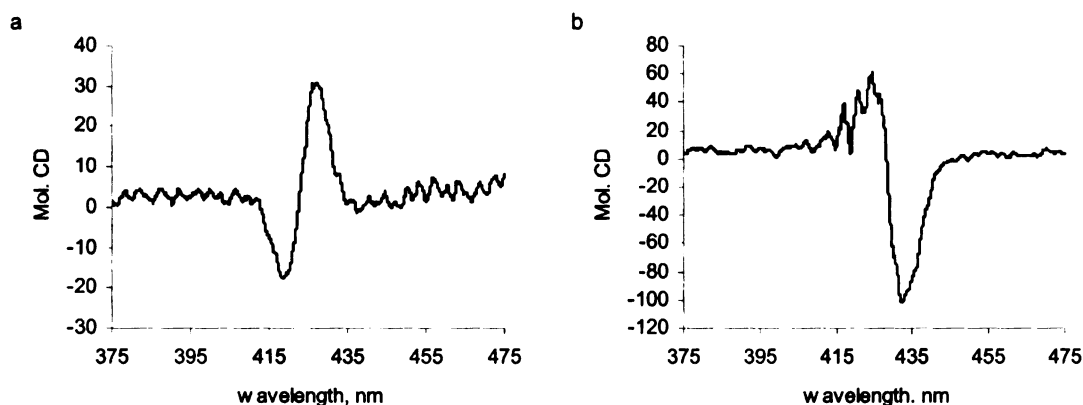
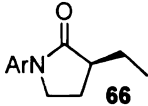
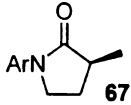
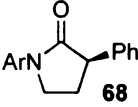
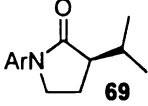
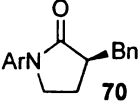
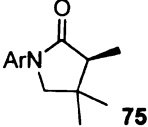


Figure IV-17: Inversion of the ECCD sign of (*R*)-2-chlorobutyrolactam from a) positive (with ZnTPP tweezer **I**) to b) negative (with ZnTPP-Ac tweezer). Spectra taken in methycyclohexane and reported at 10 equiv of chiral guest.

The switch of the ECCD sign accompanied with significant improvement of amplitude was observed upon screening of alkyl butyrolactams **54-60** with bis-acetylene tweezer **VIII** (Table IV-5). Here, instead of a negative ECCD observed with tweezer **I** α -substituted butyrolactams induced positive helicity into the ZnTPP-Ac tweezer complex. Since the rigidity of the lactam structure restricts conformational flexibility of the chiral guest, the observed change in chiral induction can originate from the new binding mode favored for tweezer **VIII**. As it was discussed in Chapter II steric differentiation of the α -alkyllactams constitutes a special case where binding of the porphyrin tweezer is altered with respect to the complexation observed with α -alkoxy and α -halolactams. Thus, while coordination of the porphyrin to the carbonyl oxygen of α -alkoxy and α -halolactams occurs between the two substituents at the chiral center, binding to α -alkyllactam occurs between the small group at the chiral center and the methylene of the five member ring. Such binding in all lactams places the large group away from the porphyrin, thus alleviating the steric strain in the complex.

Considering the fact that the rigidity of the bis-acetylene linker restricts the geometry of the tweezer-substrate interaction, the observed switch in chiral induction can be rationalized by binding of the tweezer to the carbonyl between the alkyl substituent and the hydrogen at the asymmetric center. Steric discrimination of the substituents in such complex will occur in favor of the small hydrogen, inducing a clockwise orientation of chromophores and result in the observed positive bisignate (Figure IV-18).

Table IV-5: ECCD data for α -alkyl- γ -butyrolactams with ZnTPP-Ac-tz (**VIII**)

Entry	Substrate	Tweezers			
		I		VIII	
		λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
1	 66	428 (-18) 420 (+36)	-54	432 (+117) 423 (-89)	+206
2	 67	427 (-10) 419 (+13)	-23	432 (+27) 423 (-28)	+55
3	 68	429 (-108) 421 (+93)	-211	432 (+52) 424 (-27)	+79
4	 69	429 (-266) 421 (+262)	-528	432 (+254) 424 (-220)	+474
5	 70	428 (-23) 420 (+27)	-50	432 (+29) 423 (-38)	+67
6	 75	427 (+187) 419 (-159)	+346	433 (+65) 423 (-41)	+106

Spectra were measured in methylcyclohexane (1 μ M of tweezer) at 0 °C and reported at 20 equiv of chiral guest.

It is noteworthy that complexation of **VIII** to β -dimethyl substituted lactam **71** results in the same sign observed with ZnTPP-tz. Here, both tweezers **I** and **VIII** exhibit similar binding mode and differentiation between the medium (for this particular

substrate) methyl group and the small hydrogen atom at the stereocenter resulting in the positive ECCD sign.

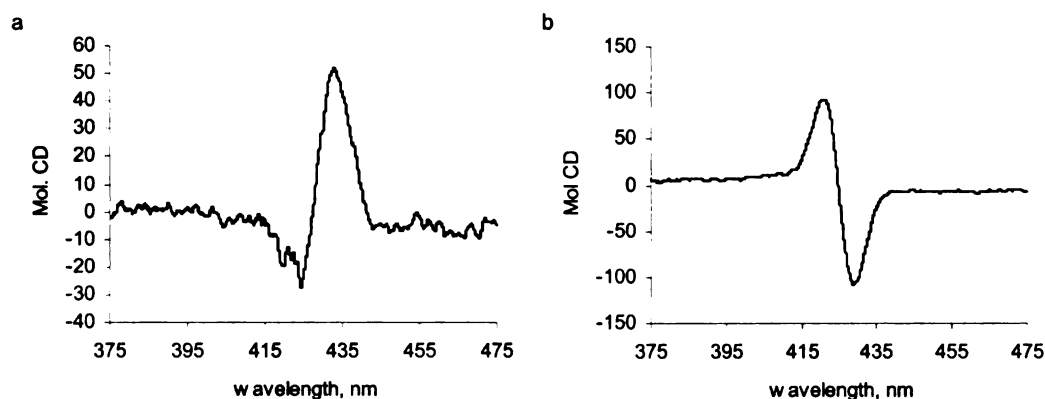


Figure IV-18: (*R*)-2-Phenylbutyrolactam carrier conjugate resulting in a) positive ECCD with tweezer **VIII** and b) negative ECCD with tweezer **I**.

Thus, from the studies presented above it can be concluded that tweezer **VIII** might be considered a useful tool for stereochemical determination of chiral lactams, since the steric differentiation of alkoxy, halo and alkyl lactams occurs in a similar way. Namely, porphyrin coordinates to the carbonyl oxygen between the two groups at the chiral center and slides towards the smaller substituent (no secondary interaction is operating in the complex). Another advantage of the rigid linker is prominent destabilization of π - π interaction in acyclic amides. Nonetheless, low amplitudes observed with acyclic amides and random destabilization of halogen- π interaction with α -halocarboxylic acids diminishes the applicability of the ZnTPP-Ac-tz.

IV.3. Bulky ZnTBP-acetylene tweezer

As was discussed in Chapter III, it appears that destabilization of C-X-- π interaction requires cumulative influence of sterics of the substrate and the porphyrin. Consequently, we have synthesized the bis-acetylene porphyrin **IX** bearing bulky *t*-butyl substituents at the meta-position of the phenyl rings (Figure IV-19).

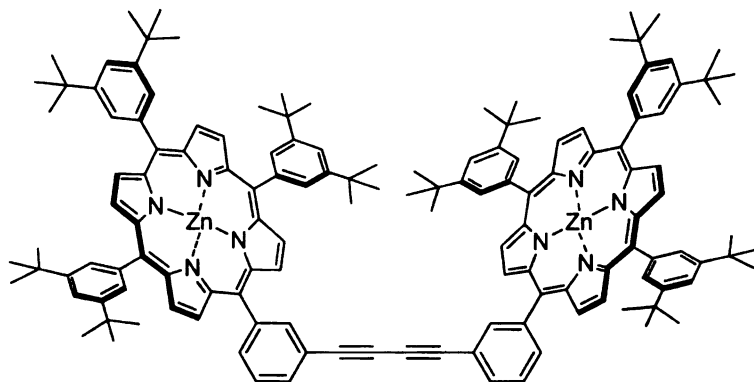
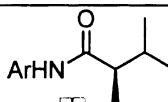
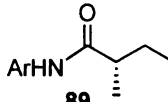
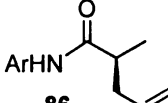
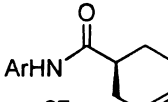
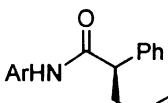
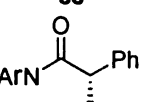


Figure IV-19: Zinc TBP-acetylene tweezer **IX** (ZnTBP-Ac-tz)

The synthesis of this tweezer follows the procedure used for assembling tweezer **VIII**. Alkyne-alkyne coupling carried out at room temperature over 0.5 h results in formation of the porphyrin tweezer in 85% yield. Obtained in this manner, ZnTBP-Ac-tz (**IX**) was then complexed with the substrates used in pervious studies and ECCD measurements were carried out in methylcyclohexane at 1 μ M. The data obtained upon complexation of alkyl and aryl carboxylic acids is summarized in Table IV-6.

Despite the introduction of bulky *t*-butyl groups no improvement in stereodifferentiation of substrates **86-89** was observed. On the contrary, while tweezer **VIII** gave a detectable ECCD, tweezer **IX** complexes with these substrates were ECCD silent.

Table IV-6: ECCD data for α -alkyl and α -arylamides with ZnTBP-Ac tweezer (**IX**)

Entry	Substrate	Tweezers			
		VI		IX	
		λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
1		427 (+22) 420 (-25)	+45	433 (+32) 424 (-34)	+66
2	 89	428 (-10) 418 (+6)	-16*	-----	n.d.
3	 86	-----	-----	-----	n.d.
4	 87	429 (+12) 418 (-14)	+26*	-----	n.d.
5	 88	430 (-47) 423 (+35)	-82	439 (+33) 533 (-40)	+73
6	 91	430 (+40) 425 (-25)	+65	443 (-25) 434 (+55) 424 (-33)	mix

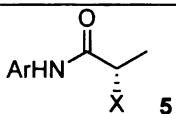
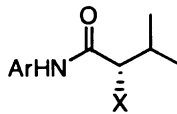
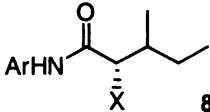
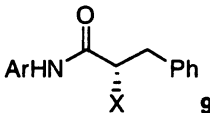
Spectra taken in methylcyclohexane (1 μ M porphyrin tweezer) at 0 °C and reported at 10 equiv of chiral guest. * - ECCD spectra detected at 4 equiv of chiral guest.

An interesting trend was observed upon complexation of aromatic substrates **88** and **91**. Unlike tweezer **VIII**, complexation of bulky analog **IX** with α -aryl amides result in inversion of the ECCD sign or complicated ECED pattern. Thus, substrate **88** gives prominent positive ECCD. Substrate **91** induced a mixed ECCD – an overlap of a negative and positive bisignates implying presence of two different conformations.

Binding of the bulky tweezer **IX** with halogenated amides gave ECCD results analogous to the ones detected with the ZnTPP-Ac-tz (Table IV-7). Namely, halogen- π interaction remains prominent upon complexation of chlorine and bromine atom bearing substrates, and switches for the fluorinated substrates regardless of the size of the alkyl

substituent at the chiral center. Hence, it can be concluded that despite the combination of rigidity of the tweezer and additional steric interaction introduced by the bulky *t*-butyl groups the rigid bis-acetylene tweezers failed to differentiate α -chiral alkyl (alkoxy) and α -halocarboxylic acids based on a single mnemonic.

Table IV-7: ECCD data for α -halocarboxylic acid with ZnTBP-Ac tweezer (**IX**)

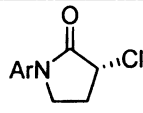
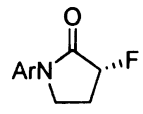
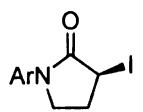
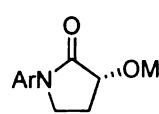
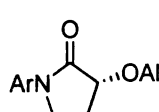
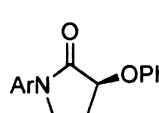
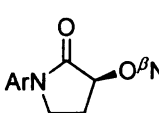
Entry	Substrate, X =	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
		Br		Cl		F	
1	 5	437 (+42) 428 (-56)	+98	434 (+35) 427 (-59)	+94	435 (+29) 426 (-28)	+57
2	 6	437 (+19) 428 (-46)	+65	435 (+47) 427 (-54)	+101	436 (-32) 426 (+28)	-60
3	 8	436 (+42) 426 (-32)	+74	435 (+65) 427 (-77)	+142	436 (-40) 427 (+37)	-77
4	 9	435 (+38) 425 (-35)	+72	437 (+32) 429 (-21)	+53	435 (+25) 426 (-15)	+40

Spectra taken in methylcyclohexane (1 μ M porphyrin tweezer) at 0 °C and reported at 20 equiv of chiral guest.

It is noteworthy that despite unsuccessful application of the tweezers **VIII** and **IX** for steric differentiation of acyclic substrates (i.e., no stabilization of one common confirmation was achieved) complexation of the tweezer **IX** with cyclic lactams gave satisfactory results both in terms of ECCD sign and the magnitude of the chiral induction. Thus, as summarized in Table IV-8, both ZnTPP-Ac and ZnTBP-Ac tweezers tend to perform steric differentiation of α -alkoxy, α -aryloxy and α -halo- γ -butyrolactams based on a similar mode, where complexation of the porphyrin to the carbonyl oxygen occurs

between the medium and the small group and steric interaction is alleviated by the twist of the porphyrin towards the latter group. Similar to **VIII**, tweezer **IX** does not support any secondary interaction with a cyclic substrate.

Table IV-8: ECCD data for α -alkoxy and α -halo- γ -butyrolactams with **IX**

Entry	Substrate	Tweezers			
		VI		IX	
		λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
1	 40	432 (-102) 424 (+65)	-167	433 (+40) 425 (-12)	+52
2	 44	431 (-94) 422 (+108)	-202	435 (-12) 427 (+10)	-22
3	 45	431 (+66) 422 (-83)	+149	435 (+22) 426 (-18)	+40
4	 37	432 (-242) 424 (+188)	-430	434 (-60) 426 (+45)	-105
5	 38	432 (-45) 422 (+28)	-73	435 (-82) 426 (+61)	-143
6	 50	430 (+12) 421 (-18)	+30	435 (+18) 427 (-16)	+34
7	 51	432 (+28) 422 (-36)	+64	434 (+33) 425 (-29)	+62

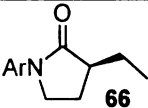
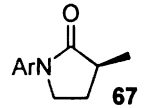
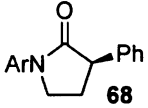
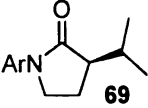
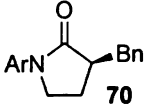
Spectra taken in methylcyclohexane (1 μ M porphyrin tweezer) at 0 °C and reported at 20 equiv of chiral guest

Analogous trend for both ZnTPP-Ac-tz and ZnTBP-Ac-tz is observed upon complexation with alkylactams (Table IV-9). Here, similar to the substrates in Table IV-8, complexation of the porphyrin to the carbonyl leads to the steric differentiation

between the alkyl substituent and the small hydrogen, and, despite the enhanced bulk of the tweezer, results in spectra of comparable amplitudes.

The results presented above allow us to conclude that the rigid tweezers, unlike the tweezers **I-V** have only limited applicability, and cannot be used as a general tool for stereochemical determination. Nevertheless, ZnTPP-Ac tweezer **VIII** might be successfully used in complement with tweezer **I** for identification of the secondary interactions in porphyrin tweezer-chiral substrate complexes.

Table IV-9: ECCD data for α -alkyl butyrolactams with ZnTBP-Ac tweezer **IX**

Entry	Substrate	Tweezers			
		VIII		IX	
		λ , nm ($\Delta\epsilon$)	A	A	λ , nm ($\Delta\epsilon$)
1	 66	432 (+117) 423 (-89)	+206	432 (+146) 422 (-152)	+298
2	 67	432 (+27) 423 (-28)	+55	432 (+92) 424 (-58)	+150
3	 68	432 (+52) 424 (-27)	+79	435 (+60) 528 (-30)	+90
4	 69	432 (+254) 424 (-220)	+474	433 (+300) 425 (-270)	+570
5	 70	433 (+65) 423 (-41)	+106	432 (+242) 423 (-145)	+387

Spectra taken in methylcyclohexane (1 μ M porphyrin tweezer) at 0 °C and reported at 20 equiv of chiral guest

IV.4. ZnTPP-propane tweezer X

IV.4-1. Use of ZnTPP-propane tweezer for the absolute stereochemical determination of α -chiral alkyl and aryl amides of 1,4-phenylenediamine

The studies presented in the sections above focus on the rigid ZnTPP tweezers. Despite some improvements observed in stereo determination of cyclic systems (chiral lactams) the bis-acetylene tweezers failed in the absolute stereochemical determination of acyclic amides. Hence, the stabilization of one common conformation of all acyclic amides remains an open challenge.

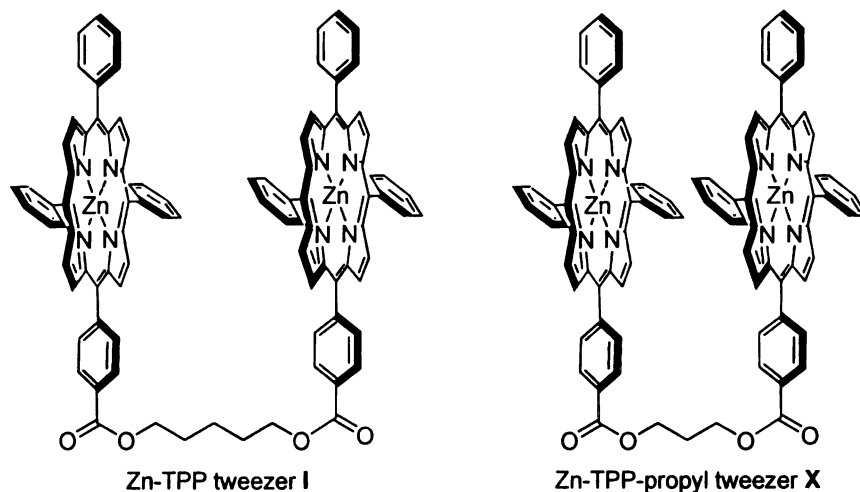


Figure IV-20: ZnTPP-tz I and the alternative tweezer X linked through 1,3-propanediol.

An alternative approach to test the influence of the linker onto the conformational preference of a chiral substrate in the complex with porphyrin tweezer complex is to vary the length of an alkyl chain connecting the two porphyrins of the tweezer. Considering the fact that the five carbon linker provides a tweezer with enough flexibility to perform steric differentiation of substrates of different size, stabilize various secondary interactions (π - π or C-H-- π and C-X-- π) and, support different modes of complexation

(α -alkyl vs. α -alkoxy- γ -butyrolactams), the shortening of the linker could provide useful information. In particular, the piece of information we are interested in would be whether the length of the linker affects the conformational preference of the substrate-tweezer complex. Subsequently, we shortened the length of the linker connecting the two chromophores of the tweezer to three carbons employing 1,3-propanediol and, the ZnTPP-propane tweezer (**X**) (Figure IV-20) was assembled through the sequence of transformations¹¹ discussed previously in Chapter III.

Table IV-10: Red-shift of tweezers upon titration with diamines

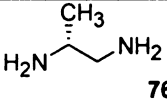
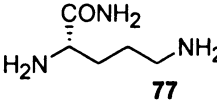
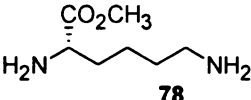
Entry	$\text{NH}_2\text{CH}_2(\text{CH}_2)_n\text{NH}_2$	Tweezer, $\Delta\lambda$ nm ($\Delta\lambda = \lambda_{\text{complex}} - \lambda_{\text{tweezer}}$)	
		I	X
1	n=1	3.0	3.2
2	n=2	3.9	3.8
3	n=3	6.0	6.1
4	n=4	6.7	6.5
5	n=5	6.9	6.8
6	n=6	7.2	7.1
7	n=7	8.2	8.3
8	n=8	8.6	8.5

Data obtained in dichloromethane at 1:1.2 host-guest ratio.

The UV-vis absorption of ZnTPP-propane-tz has a $\lambda_{\text{max}} = 419$ nm in dichloromethane and $\lambda_{\text{max}} = 416$ nm in hexane or methylcyclohexane. The extinction coefficient $\epsilon \sim 646,000 \text{ M}^{-1} \text{ cm}^{-1}$ which is comparable to $\lambda_{\text{max}} = 419$ nm and $\epsilon = 650,000 \text{ M}^{-1} \text{ cm}^{-1}$ of ZnTPP-tz **I**. The UV titration of tweezer **X** with diamines of different length, presented In Table IV-10, did not show any deviations from the analogous data with tweezer **I**, which is indicative of similar binding affinities for both tweezers.

The application of ZnTPP-propane-tz (**X**) as the chromophoric host for the absolute stereochemical determination starts with its complexation with (*R*)-1,2-diaminopropane (**76**), (*S*)-ornithine methyl amide (**77**) and (*S*)-lysine methyl ester (**78**). The complexes were formed in hexane and measured at 0 °C at 1 μ M concentration of porphyrin tweezer. The complexes with chiral diamines induced the helicity that was expected from size-based steric differentiation and gave results consistent with those obtained for ZnTPP-tz (**I**) (Table IV-11). Thus, short tweezer **X** gave negative ECCD for (*R*)-1,2-diaminopropane, (*S*)-ornithine methyl amide and (*S*)-lysine methyl ester. Based on this result we can conclude that ZnTPP-propane-tz follows the general size-based steric differentiation. Namely, porphyrin coordinated to the secondary amino group slides away from the large group at the chiral center and covers the small hydrogen, thus forming a counterclockwise twist with respect to the second porphyrin.

Table IV-11: ECCD data for chiral diamines with tweezers **I** and **X**

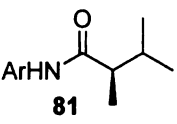
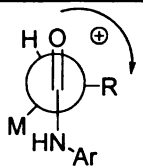
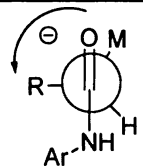
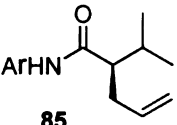
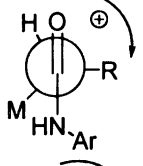
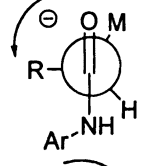
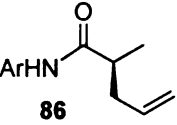
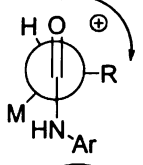
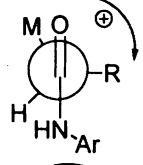
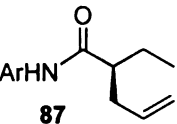
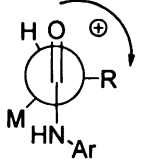
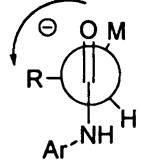
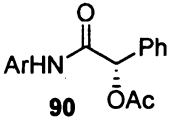
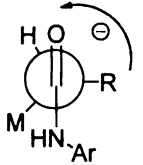
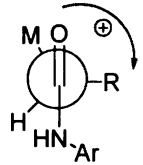
Entry	Substrate	Tweezer			
		I		X	
		λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
1	 76	426 (-82) 416 (+58)	-160	429 (-110) 420 (+165)	-275
2	 77	428 (-20) 418 (+16)	-36	430 (-82) 421 (+74)	-156
3	 78	429 (-260) 419 (+132)	-392	429 (-198) 421 (+202)	-400

Spectra taken in hexane (1 μ M porphyrin tweezer) at 0 °C and reported at 20 equiv of chiral guest.

Further, tweezer **X** was complexed with different chiral α -alkyl, alkoxy and aryl amides of 1,4-phenylenediamine in methylcyclohexane at 0 °C and ECCD spectra were

collected. Table IV-12 summarizes the comparative studies of alkyl, aryl and alkoxy carboxylic acids with tweezers **I** and **X**. Interestingly, all complexes of tweezer **X** with chiral amides gave ECCD spectra of opposite sign from that of ZnTPP-tz. In particular, while steric differentiation of alkyl amides in entries 1-4 with ZnTPP tweezer is accompanied with rise of positive ECCD, change of the size of the linker from five carbons to three results in the change of stereodifferentiation yielding a negative CD bisignates.

Table IV-12: ECCD data for α -alkyl amides with ZnTPP-tz (**I**) and ZnTPP-propane-tz (**X**)

Substrate	tweezer I		Conformation A	tweezer X		Conformation C
	λ , nm ($\Delta\epsilon$)	A		λ , nm ($\Delta\epsilon$)	A	
 81	425 (+31) 418 (-20)	+51		429 (-48) 422 (+44)	-92	
 85	428 (+45) 420 (-42)	+87		428 (-98) 421 (+77)	-175	
 86	429 (-11) 420 (+12)	-23		429 (+41) 422 (-49)	+90	
 87	429 (+29) 420 (-25)	+54		428 (-74) 421 (+75)	-149	
 90	429 (-16) 420 (+21)	-37		429 (+68) 420 (-59)	+127	

Spectra taken in methylcyclohexane (1 μ M porphyrin tweezer) at 0 °C and reported at 20 equiv of chiral guest

Since the stereochemical determination taking place in the tweezer-substrate complex is a process involving several non-covalent interactions and depends on the geometry of complexation, geometry of amide (*cis* or *trans*) and a conformational preference of the substrate in the complex, at this point it is hard to conclude an exact factors contributing to the observed switch of ECCD sign with tweezer **X** vs. tweezer **I**. However, if the modes of binding of the tweezers **X** and **I** with chiral amides are similar, and the geometry of amide in these two complexes does not change, i.e. the *cis* amide is populated, then the factor inducing the observed change of ECCD sign could be a stabilization of a different rotamer around the C_{C=O}-C_{chiral} bond. Below we will be considering an influence of different rotamers onto the ECCD sign.

Figure IV-21 depicts the conformational analysis of α -chiral amide **81**. From the three major ECCD active rotamers depicted in Figure IV-21 conformation **A** corresponds to the one observed in complexes of chiral α -alkyl and α -alkoxyamides with ZnTPP-tz. In this conformation steric differentiation occurs between the large and the small group oriented towards the porphyrin coordinated to the carbonyl oxygen and results in clockwise twist of chromophores and, subsequently, a positive ECCD. The other two rotamers, **B** and **C**, following the same rationale, both induce counterclockwise orientation of chromophores of the tweezer and give rise to a negative ECCD. Rotamer **B** orients the medium methyl substituent and the small hydrogen towards the porphyrin coordinated to the carbonyl oxygen. Twist of the porphyrin towards the hydrogen will lead to a counterclockwise helicity of the complex, giving rise to a negative CD bisignate. However, it is expected that positioning of the large substituent *anti* to the carbonyl will lead to a significant A_{1,3}-strain in the substrate and could disfavor conformation **B**.

Rotamer **C** (Figure IV-21) orienting the small hydrogen away from the carbonyl could be considered energetically more favored and preferred over rotamer **B**. Here, the stereo differentiating porphyrin faces the medium methyl group and the large isopropyl substituent and slides towards the smaller substituent (here the methyl group). The resulting counterclockwise twist between porphyrins leads to a negative ECCD spectrum.

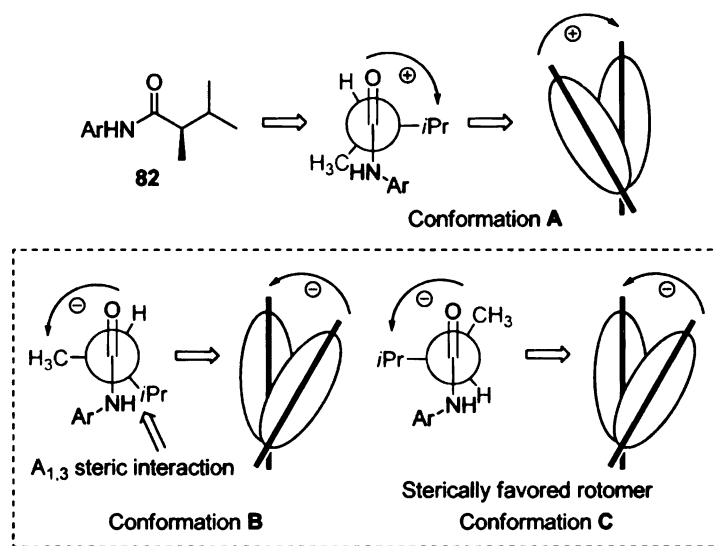


Figure IV-21: ECCD active rotamers A-C of amide **81**: conformer **A** induces positive ECCD, conformations **B** and **C** – negative ECCD with porphyrin tweezer.

This rationale is also valid when applied to the analysis of the ECCD sign observed with substrates **85-87**. Similarly to amide **81**, negative CD bisignate could originate from conformation **C**, where steric differentiation takes place between the large group and the medium group. Hence, the major rotamer contributing to the sign of the bisignate curve in the complexes of ZnTPP-propane-tz (**X**) with α -chiral alkyl amides is different from that of ZnTPP-tz, where the porphyrin coordinated to the carbonyl oxygen faces the large and the small group and slides towards the latter. Substrate **91** (Table 13) with ZnTPP-propane-tz induces a positive ECCD, which is opposite from the one

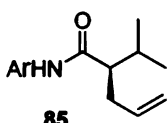
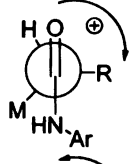
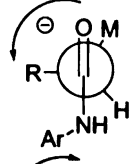
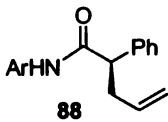
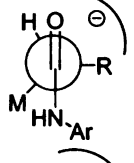
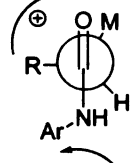
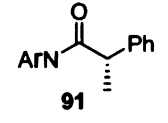
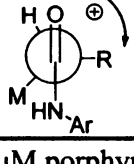
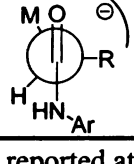
detected for tweezer **I**, and could also originate from rotamer **C** positioning the large phenyl and the medium acetate close to the porphyrin coordinated to the carbonyl oxygen.

From the results discussed above it is plausible to propose a model for stereochemical determination of 1,4-phenylenediamine derivatized chiral α -alkyl and α -alkoxy carboxylic acids with ZnTPP-propane tweezer as follows. Upon complexation with α -chiral alkyl and alkoxy amides tweezer **X** stabilizes a conformation that is different from the one identified in the similar complexes of ZnTPP-tz (**I**). Namely, as opposed to the orientation of the medium group *anti* to the carbonyl in the complexes of tweezer **I**, tweezer **X** places the small group *anti* to the carbonyl and the two other substituents (the medium and the large groups) at the chiral center are oriented towards the porphyrin coordinated to the carbonyl oxygen. However, for the final proposition of the working model for the tweezer **X** complexes verification of the binding mode in the complex is necessary.

A switch of the helicity between the tweezers **I** and **X** is also observed upon their complexation with α -aryl amides. Before going into the analysis of these results, it is worth noting that steric differentiation of the aryl amides with ZnTPP tweezer proceeds with consideration of the secondary interaction taking place between the aromatic substituent at the asymmetric carbon and the porphyrin ring. Thus, while tweezer **I** with both alkyl and aryl amides stabilizes a common ECCD active conformation, the steric differentiation of the latter proceeds in favor of the large aromatic substituent as opposed to the small hydrogen due to the secondary π -interaction. As a result the α -aryl amide **88** upon complexation with ZnTPP-tz produces a positive bisignate curve as opposed to the

expected negative ECCD. Subsequently, amide **91** complexed with ZnTPP-tz gives rise to a negative ECCD (Table IV-13, substrates **88** and **91**).

Table IV-13: ECCD data for α -aryl amides with ZnTPP-tz (**I**) and ZnTPP-propane-tz (**X**)

Substrate	I		Conformation A	X		Conformation C
	λ , nm ($\Delta\epsilon$)	A		λ , nm ($\Delta\epsilon$)	A	
 85	428 (+45) 420 (-42)	+87		428 (-74) 421 (+75)	-149	
 88	428 (-75) 421 (+60)	-135		427 (+98) 421 (-108)	+216	
 91	428 (+66) 420 (-36)	+102		428 (-103) 421 (+119)	-366	

Spectra taken in methylcyclohexane (1 μ M porphyrin tweezer) at 0 °C and reported at 20 equiv of chiral guest

Unlike ZnTPP-tz, short tweezer **X** upon complexation with the aromatic amide **88** adopts a positive helicity. Similarly, switch in helical arrangement between the porphyrins occurs upon coordination of the substrate **91** with ZnTPP-propane-tz, and a negative ECCD is observed. A possible explanation for the observed change in ECCD sign could be a stabilization of a different ECCD conformation that does not account for aromatic interaction. Figure IV-22 depicts the conformational analysis for amide **95**. From the three ECCD active conformers, rotamer **A** is the major conformer detected for chiral amides in complexes of tweezer **I** (the small and the large group oriented towards the carbonyl). If the stereochemical determination in this conformation occurs solely on the basis of steric discrimination, then the expected sign of CD bisignate is negative.

Such mode of differentiation would explain the experimentally observed negative ECCD with tweezer **X**. The other two rotamers **B** and **C** based on size differentiation yield a positive ECCD (Figure IV-22c) while a negative ECCD is observed and, hence may not contribute to the observed helicity of the bis-chromophore.

However, if binding of the two tweezers **X** and **I** with chiral α -arylamides is similar, then it would be expected for conformation **A** to exhibit an aromatic interaction with the porphyrin of tweezer **X**. In such a case rotamer **A** will yield a positive helicity (Figure 22b), as opposed to the observed negative ECCD. An analogous π -interaction is expected for rotamer **C**, placing the large and medium groups bisecting the carbonyl. In this case, an aromatic interaction between the phenyl group and the porphyrin would lead to the observed negative ECCD for amide **91** (Figure IV-22d). Similar rotamer (conformation **C**) of amide **88** could be responsible for positive ECCD detected with ZnTPP-propane tweezer (**X**) (Table IV-13, entry 3).

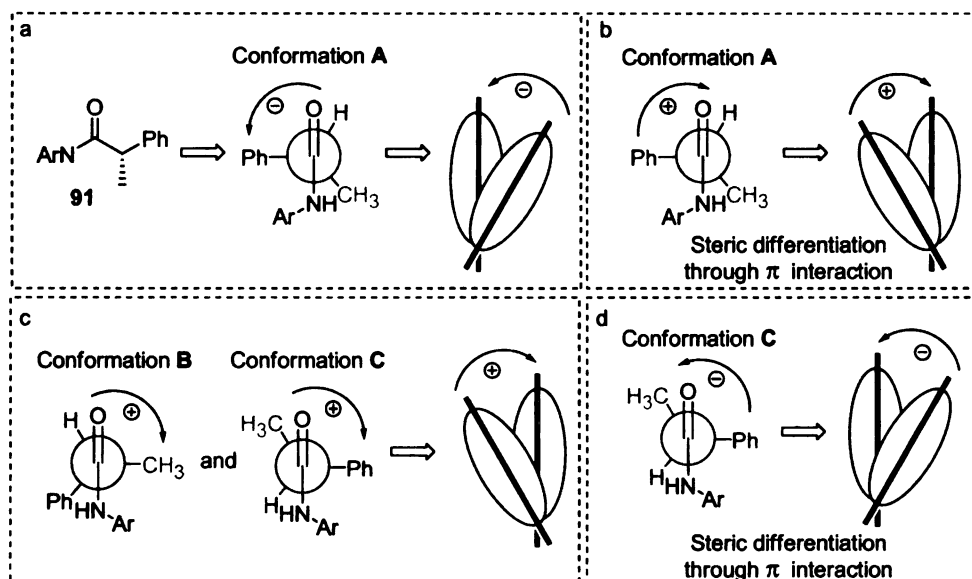


Figure IV-22: Conformational analysis of aryl amide **95** in the complex with tweezer **X**.

Thus, considering the possible similarity in binding modes of tweezers **X** and **I**, it is plausible to assume that the stereochemical determination of α -arylamides occurs with consideration of rotamer **C** exhibiting π - π interaction with the porphyrin.

Additional supports for the secondary aromatic interaction present in the ZnTPP-propane-tz complex with α -arylamides can be obtained after comparing the amplitudes of the ECCD spectra observed with aromatic amides **88** and **91** (Table IV-13) and the α -alkylamide **85**.

It is known that the amplitude of an ECCD spectrum is the sum of signals produced by all ECCD active complexes in solution.¹⁸ Since the tweezer-chiral amide complexes can support different rotamers of the chiral ligand, the amplitude of the ECCD spectrum is influenced by the population of each ECCD active complex. The presence of different rotamers inducing an opposite helicity of the tweezer complexes can lead to cancelation of the signals resulting in the decrease of magnitude of the ECCD spectrum. Stabilization of one conformer over the others must positively contribute to the amplitude of the ECCD spectrum. Subsequently, for complexes that exhibit an additional stabilization of one rotamers over others through π - π or halogen- π interaction a significant enhancement of ECCD amplitude is expected. Indeed, during our previous studies of aryl amides with ZnTPP-tz, complexes of the porphyrin tweezer **I** with carrier derivatized arylcarboxylic acids gave ECCD spectra of significantly higher magnitude. Table IV-13 summarizes the ECCD amplitudes for aromatic amides **90** and **95** with ZnTPP-tz, which are significantly increased as compared to the α -alkylamides presented in Table IV-12.

Prominent enhancement of the ECCD amplitude is also observed for aryl substrates **88** and **91** with tweezer **X**, which in similar manner can be contributed to the secondary interaction between the aromatic substituent at the chiral carbon and the porphyrin coordinated to the carbonyl oxygen. In such cases the highly populated conformation of the carrier derivatized α -arylcarboxylic acids within the ZnTPP-propane tweezer complex must satisfy the orientation of the aromatic group towards the carbonyl.

Thus, we can conclude that, despite the shortness of the propane linker, tweezer **X** is flexible enough to support the secondary interactions in the complex. Moreover, the steric differentiation of α -alkyl, α -alkoxy and α -aryl-amides occur through a similar conformation orienting the medium and the large group towards the carbonyl (Figure IV-23).

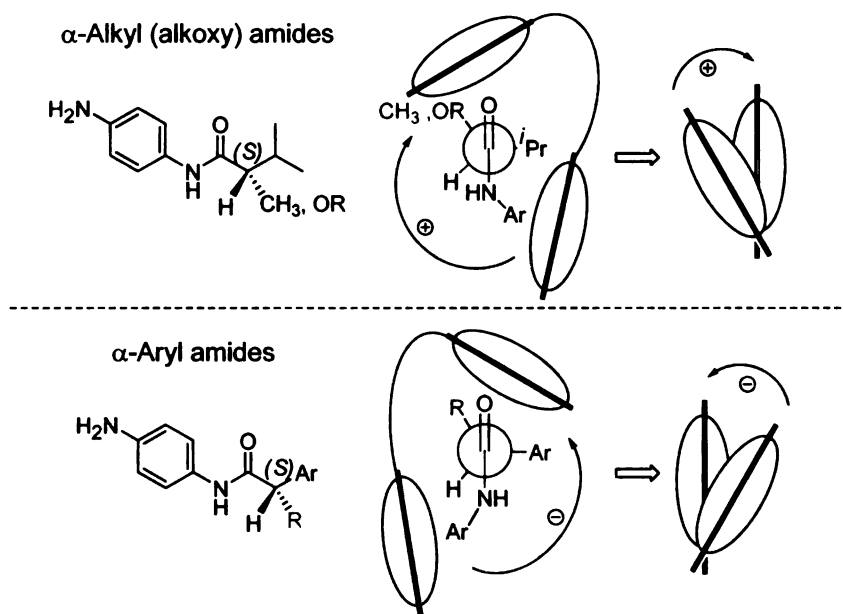


Figure IV-23: Stereochemical determination of carrier derivatized α -chiralalkyl (alkoxy) and α -arylcarboxylic acids proceeds through the conformation orienting the large and the medium group towards the carbonyl.

IV.4-2. ZnTPP-propane tweezer for stereochemical determination of α -haloamides.

The absolute stereochemical determination of α -chiralalkyl and α -arylamides with ZnTPP-propane tweezer (X), along with improved sensitivity of the stereodifferentiation resulting in significantly enhanced amplitudes of ECCD spectra, gave another important piece of information. That is, the conformation of the chiral alkyl and arylamides of 1,4-phenylenediamine stabilized in the complex with tweezer X is similar to the rotamer that was observed in the complexes of ZnTPP-tz (I) with 1,4-phenylenediamine derivatized chiral α -halocarboxylic acids.

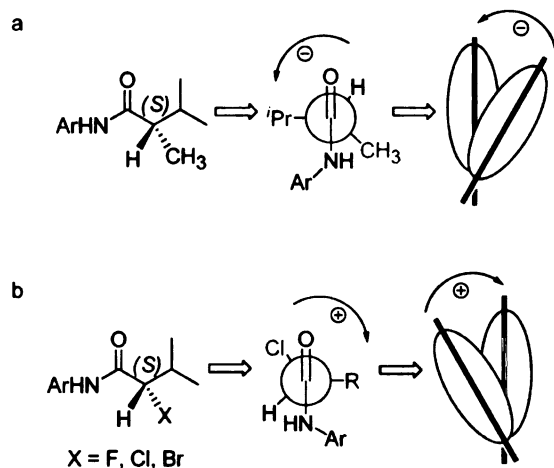


Figure IV-24: Stereochemical determination of 1,4-phenylenediamine derivatized chiral (a) α -alkyl (alkoxy) and (b) α -halocarboxylic acids with ZnTPP tweezer (I) proceeds through different conformations.

Briefly, during our studies of 1,4-phenylenediamine derivatized chiral α -halocarboxylic acids (see Chapter II for details) it was observed that the complexes of these substrates with tweezer I tend to stabilize a conformation that differs from the major rotamer identified for carrier derivatized α -alkyl, α -aryl or α -alkoxycarboxylic acids. In particular, as is depicted in Figure IV-24, while α -alkyl(alkoxy)amides after

binding to the porphyrin tweezer **I** adopt a conformation orienting the large and the small group towards the carbonyl (Figure IV-24a), the orientation of substituents in α -halogenated amides changes. Namely, the steric differentiation occurs between the large and the medium (halide atom) group (the new conformation was confirmed after UV-vis and $^1\text{H-NMR}$ studies) (Figure IV-24b). The “unusual” conformation of α -haloamides in the complexes with ZnTPP-tz was contributed to the halogen- π interaction. It was also found that the observed conformation is stable regardless of the type of halide or the size of the alkyl group at the asymmetric carbon.

An interesting observation arises from the comparison of the ECCD active conformations of the complexes of ZnTPP-tz and ZnTPP-propane-tz. As it was discussed in the section above, change of an ECCD sign for the complexes of α -aryl and α -arylamides with tweezers **I** and **X** could be a result of the stabilization of different rotamers. In particular, the observed sign of CD bisignates obtained for α -alkyl and α -arylamides with ZnTPP-tz could be explained by the conformation presented in Figure IV-24a, where the large and the small group oriented towards the carbonyl. Tweezer **X**, supposedly, stabilizes the conformation placing the large and the medium groups facing the porphyrin coordinated to the carbonyl oxygen (Figure IV-25a). The new conformation of α -alkyl(alkoxy) and α -arylamides observed with ZnTPP-propane tweezer is similar to that of α -haloamides with ZnTPP-tz (Figure IV-25b).

The ECCD data obtained for the various (*S*)-haloamides with tweezer **X** is summarized in Table IV-14. All amides give positive helicity regardless the type of the halide or the size of the alkyl group at the asymmetric center. It is noteworthy, (*S*)-haloamide complexes with ZnTPP-tz also result in positive ECCD. Hence, it is plausible

to propose that stereochemical determination of chiral α -halocarboxylic acids with both tweezers proceeds through the same ECCD active conformation **C** (Figure VI-26), placing the large alkyl group and the medium halide towards the porphyrin coordinated to the carbonyl on the amide. The other rotamer, possibly contributing to the observed positive ECCD, conformation **B**, places the large group *syn* to the amide NH and inducing $A_{1,3}$ strain may not be considered as the major conformer.

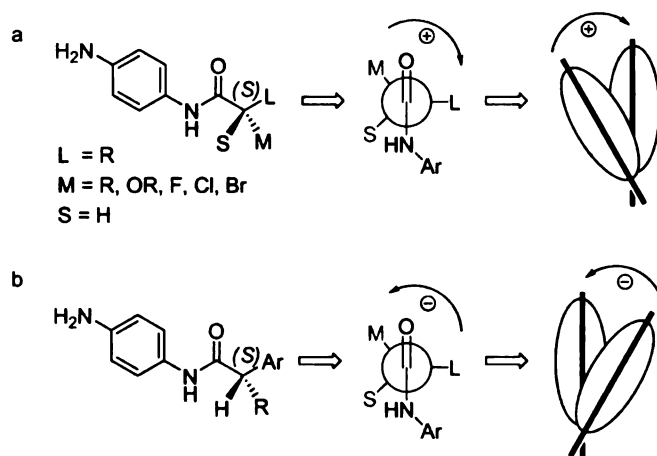
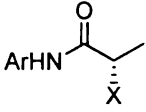
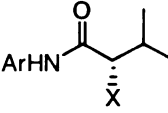
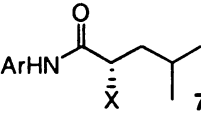
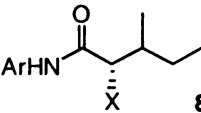
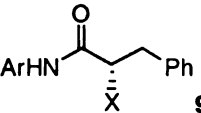


Figure IV-25: Stereochemical determination of 1,4-phenylenediamine derivatized α -chiral carboxylic acids with ZnTPP-propane tweezer (**X**) occurs through stabilization of a single ECCD active conformation regardless the type of substituents at the asymmetric center.

It is noteworthy, that similar to the complexes of ZnTPP-tz, the ECCD spectra of α -haloamides with tweezer **X** are significantly higher in amplitude, as compared to the ones detected for α -alkylamides. The enhanced ECCD signal can be a direct consequence of the improved stabilization of the ECCD active rotamer, here due to the halogen interacting with the aromatic porphyrin.

Table IV-14: ECCD data for 1,4-phenylenediamine derivatized α -halocarboxylic acids with ZnTPP-propane tweezer (**X**)

Entry	Substrate	λ , nm, ($\Delta\epsilon$)	A	λ , nm, ($\Delta\epsilon$)	A	λ , nm, ($\Delta\epsilon$)	A
	X =	Br		Cl		F	
1	 5	428 (+168) 421 (-120)	+288	428 (+112) 421 (-98)	+210	428 (+42) 419 (-38)	+80
2	 6	428 (+322) 421 (-264)	+586	428 (+185) 421 (-164)	+349	428 (+150) 420 (-140)	+290
3	 7	429 (+146) 421 (-140)	+186	428 (+100) 421 (-90)	+190	428 (+82) 420 (-82)	+165
4	 8	428 (+176) 421 (-207)	+383	428 (+154) 421 (-159)	+313	429 (+122) 421 (-100)	+222
5	 9	429 (+52) 421 (-53)	+105	429 (+71) 421 (-54)	+125	428 (+43) 419 (-39)	+82

Spectra obtained in methylcyclohexane and reported at 10 equiv of ligand.

The most significant result that was observed after the studies of the 1,4-phenylenediamine derivatized chiral α -alkyl (alkoxy), α -aryl and α -halocarboxylic acids is that absolute stereochemical determination of all tested amides occurred through stabilization of one common ECCD active conformation (Figures IV-25 and IV-26). Namely, α -alkyl (alkoxy), α -aryl and α -haloamides upon complexation with short ZnTPP-propane-tz (**X**) orient the large and the medium groups at the chiral carbon towards the porphyrin coordinated to the carbonyl carbon. The small group is oriented *anti* to the carbonyl. In such conformation steric differentiation takes place between the two larger substituents. In the complexes with the α -alkyl (alkoxy) and α -haloamides steric differentiation occurs in favor of the medium substituent, while α -arylamides invert

the steric differentiation due to the π -aryl interaction between the aromatic substituent and the stereodifferentiating porphyrin.

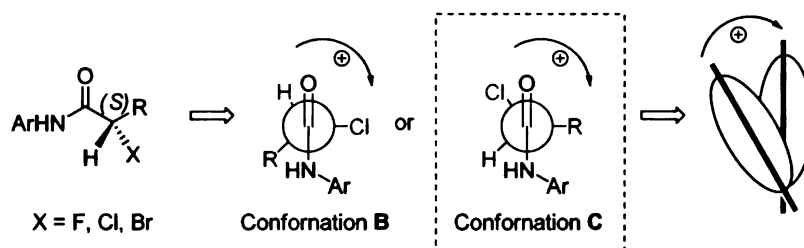


Figure IV-26: Conformations **B** and **C** contributing to the ECCD sign observed in stereochemical determination of (*S*)- α -haloamides of 1,4-phenylenediamine.

IV.4.3. ZnTPP-propane tweezer for the absolute stereochemical determination of α -chiral butyrolactams

α -Chiral γ -butyrolactams of 1,4-phenylenediamine represent another set of compounds that gave unexpected switch of ECCD sign with ZnTPP tweezer (**I**) upon exchanging the type of substituents at the chiral center. While the alkoxy and halo lactams followed the same mode of steric differentiation and gave the expected ECCD sign, the alkyl lactams resulted in bisignates with helicity opposite that anticipated. Briefly, the α -chiral butyrolactams were used in our previous studies as a mimic of acyclic amides with the fixed disposition of the substituents at the chiral center relative to the carbonyl. The necessity for introduction of a cyclic system was brought by the change in conformational preference observed for 1,4-phenylenediamine derivatized α -alkoxy and α -haloamides. Namely, while upon complexation with α -alkoxyamides ZnTPP-tz stabilizes the conformation placing the medium alkoxy group *anti* to the

carbonyl, the major conformation of α -haloamides bound to the tweezer **I** orients the medium group (halogen atom) *syn* or *pseudo-syn* to the carbonyl. As was discussed above, such conformational preference of α -haloamides arises from the secondary interaction taking place between the halide at the asymmetric carbon and the porphyrin coordinated to the carbonyl oxygen (Figure IV-27).

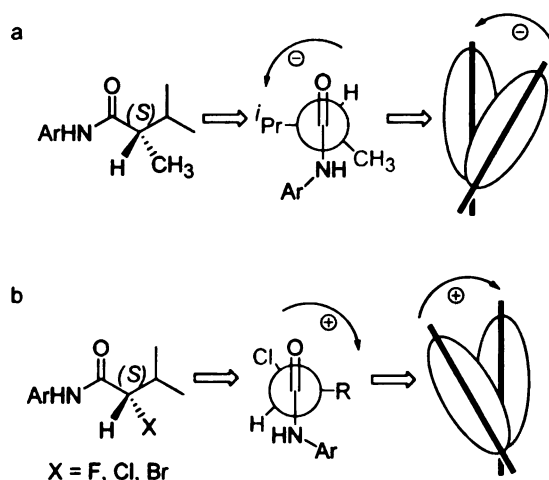
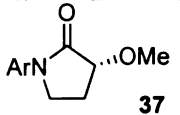
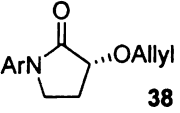
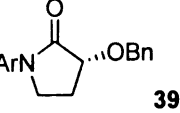
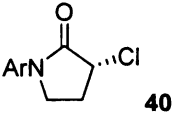
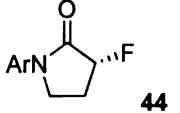
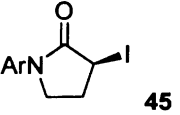
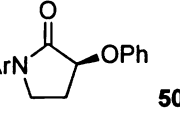
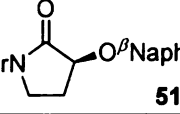


Figure IV-27: Stereochemical determination of 1,4-phenylenediamine derivatized chiral α -halocarboxylic acids with ZnTPP-tz proceeds through the conformation accommodating a secondary interaction with the porphyrin.

Although the putative C-X $\cdots$ π interaction was supported by ^1H -NMR and UV-vis experiments, the free rotation along the C $\equiv$ O-C_{chiral} bond could lead to multiple conformations in the tweezer complex. Thus, rigidifying the carbon skeleton of the amide through cyclization would lock the position of an alkoxy group or a halide relative to the carbonyl and the hydrogen relative to the carbonyl and, hence, eliminate the free rotation from consideration. The expected outcome of this experiment would be a direct correlation of the observed ECCD sign with the position of the medium group at the chiral center. Namely, if stereodifferentiation depends on sterics, the porphyrin should

slide away from the medium group (here alkoxy or halide substituents) and towards the small hydrogen.

Table IV-14: ECCD results of α -alkoxy and α -halo- γ -butyrolactams with ZnTPP-tz (**I**)

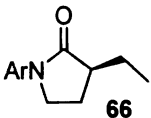
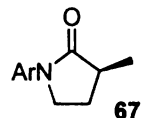
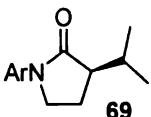
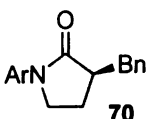
Entry	Substrate	I	
		λ_{max} , ($\Delta\epsilon$)	A
1	 37	429 (-57) 421 (+53)	-110
2	 38	429 (-34) 420 (+19)	-53
3	 39	429 (-45) 421 (+55)	-100
4	 40	427 (+25) 419 (-36)	+61
5	 44	429 (+27) 418 (-21)	+48
6	 45	429 (-14) 420 (+9)	-23
7	 50	429 (-20) 418 (+25)	-45
8	 51	430 (-18) 418 (+34)	-52

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

In the case of the halogen- π interaction, the porphyrin will cover the medium halogen as opposed to the small hydrogen. After complexation of chiral butyrolactams with ZnTPP-tz it was found that the stereochemical determination of both α -alkoxy and α -halo- γ -butyrolactams proceeds through a similar conformation, i.e., porphyrin

differentiates between the small and the medium groups (Table IV-15, see Chapter II for details). However, the halolactams, although being of the same helicity with alkoxy lactams, produced ECCD spectra of opposite sign. This result presented in Table IV-15 (entries 4-6) clearly indicated the presence of an additional halogen-porphyrin interaction in the complexes of α -halo lactams with ZnTPP-tz.

Table IV-16: ECCD data obtained for chiral α -alkyl- γ -butyrolactams with ZnTPP-tz

Entry	Substrate	ZnTPP-tz		Predicted ECCD sign
		λ , nm ($\Delta\epsilon$)	A	
1	 66	428 (-18) 420 (+36)	-54	<i>pos</i>
2	 67	427 (-10) 419 (+13)	-23	<i>pos</i>
3	 69	429 (-266) 421 (+262)	-528	<i>pos</i>
4	 70	428 (-23) 420 (+27)	-50	<i>pos</i>

Spectra taken in methylcyclohexane at 0 °C and reported at 10 equiv of chiral guest.

Another important observation arises after comparing the ECCD data collected for alkoxy- γ -butyrolactams **37-39** and aryloxy- γ -butyrolactams **50, 51** (Table IV-15, entries 7 and 8). Namely, despite being of opposite stereochemistry (note that the rank of substituents at the chiral center based on Kahn-Ingold-Prelog rule is equivalent), the (*R*)- α -alkoxy and (*S*)- α -aryloxy- γ -butyrolactams induced the same helical twist for porphyrin tweezer **I**. The result can also be explained by the secondary interaction operating between the aromatic substituent at the chiral center and the stereodifferentiating

porphyrin. Thus, presence of a secondary C-X-- π and π - π interactions in halo and aryloxylactams, respectively, required application of a new mnemonic.

The α -alkyl- γ -butyrolactams also followed a different mode of steric differentiation with ZnTPP-tz (I). Thus, while the expected helicity of the tweezer complex with substrates **66-70** summarized in Table IV-16 is positive (porphyrin slides away from the large alkyl group at the chiral carbon and covers the small hydrogen), negative ECCD spectrum was observed.

After analyzing the relative sizes of the substituents at the chiral centers in alkoxy and alkylactams, it became apparent that, unlike alkoxy and halolactams, where β -methylene was assigned as the large group, the alkyl lactams present an alkyl group as the large substituent. Consequently, it is plausible to assume that stereodifferentiation in the tweezer-alkylactam complex proceeds differently. In the case of the alkoxy lactams, binding to the porphyrin tweezer occurs in a way that places the methylene (the large group) away from the porphyrin and leads to stereodifferentiation between the small and the medium group at the chiral center. If applied to alkylactams such porphyrin-substrate coordination exposes the large group (alkyl substituent at the chiral center) towards the porphyrin, thus inducing a large steric interaction within the complex. The alternative approach of the porphyrin must occur from the site opposite of the alkyl substituent and between the small and the medium substituents. This mode of binding, operating in cyclic α -alkylamides, was supported by ECCD and ^1H -NMR analysis. The same type of binding was found applicable with complexes of porphyrin tweezer with α -alkoxy and α -halo- γ -butyrolactams, i.e. porphyrin binds closer to the medium and the

small groups at the asymmetric carbon and away from the methylene (the large group) of the five member ring (Figure IV-28).

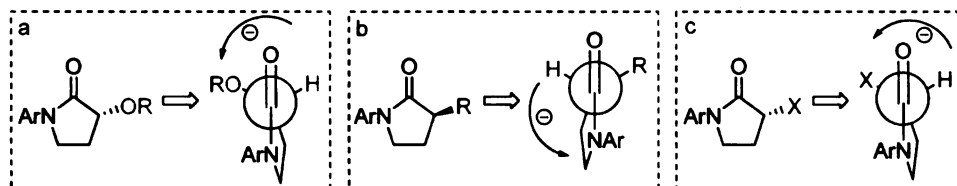


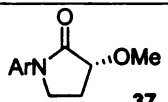
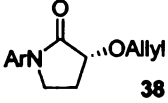
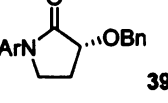
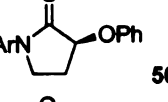
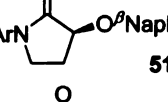
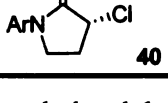
Figure IV-28: General mode of steric differentiation for a) α -alkoxy, b) α -alkyl and c) α -halo- γ -butyrolactams with ZnTPP tweezer

Thus, despite the rigidity of the lactam core, ZnTPP-tz is able to choose between binding modes and prefer the one, favored based on the overall steric interaction in the complex. Again, the absolute stereochemical determination of the new class of compounds - α -chiral lactams - with ZnTPP-tz required introduction of a new mnemonic.

After successful stabilization of one common conformation for 1,4-phenylenediamine derivatized α -alkyl (alkoxy), α -aryl and α -halocarboxylic acids with short ZnTPP-propyl tweezer (**X**), complexation of tweezer **X** with cyclic amides was performed. The resulting data for α -alkoxy and α -aryloxylactams is summarized in Table IV-17.

As can be seen from the data summarized in Table 17 (entries 1-5) unlike tweezer **I**, the porphyrins of tweezer **X** adopt an opposite helicity with the change of the absolute stereochemistry of α -alkoxy/aryloxy lactams. Thus, positive ECCD is observed for complexes of **X** with (*R*)- α -alkoxy- γ -butyrolactams (opposite from the ECCD sign observed with ZnTPP-tz) and negative for (*S*)- α -aryloxy- γ -butyrolactams. The halogenated lactam **40**, however, induces a helicity similar to that of tweezer **I** (Table 17, entry 6).

Table IV-17: ECCD data obtained for chiral α -alkoxy, α -chloro and α -aryloxy- γ -butyrolactams with ZnTPP-tz (**I**) and ZnTPP-propane-tz (**X**)

Entry	Substrate	I		X	
		λ , nm, ($\Delta\epsilon$)	A	λ , nm, ($\Delta\epsilon$)	A
1	 37	429 (-57) 421 (+53)	-110	429 (+120) 421 (-87)	+207
2	 38	429 (-34) 420 (+19)	-53	428 (+79) 421 (-81)	+160
3	 39	429 (-45) 421 (+55)	-100	429 (+132) 422 (-112)	+244
4	 50	429 (-20) 418 (+25)	-45	428 (-87) 421 (+60)	-147
5	 51	430 (-18) 418 (+34)	-52	429 (-105) 422 (+90)	-195
6	 40	427 (+25) 419 (-36)	+61	428 (+80) 421 (-97)	+177

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest

If combined, the data in Table 17 shows that while tweezer **I** changes the direction of the helical twist in the complexes of alkoxy and halolactams of the same absolute stereochemistry (i.e., negative with (*R*)-**36-39** and positive with (*R*)-**40**), short ZnTPP-propane-tz gives positive ECCD with all α -chiral (*R*)-butyrolactams regardless of the heteroatom present at the chiral center. Moreover, the change of the absolute stereochemistry, as it is presented with aryloxy substrates **50** and **51**, results in the change of the ECCD sign. Thus, it appears that the complexes of α -alkoxy, α -aryloxy and α -halo- γ -butyrolactams with ZnTPP-propane-tz lack any secondary interaction, previously observed with tweezer **I** and the stereodifferentiation in the complexes operates through a novel mode. It also appears that similar to chiral acyclic amides, stereodifferentiation of

cyclic compounds with ZnTPP-propane-tz also proceeds through one common conformation. The conformational analysis of the tweezer-alkoxy lactam complex reveals a single possible mode of stereodifferentiation that would result in the observed positive ECCD detected with (*R*)-alkoxy- γ -butyrolactams **37-39**. Namely, the porphyrin of the tweezer is differentiating between the methylene group and the small hydrogen, orienting the medium group away from the porphyrin (Figure IV-29a). The other two modes – porphyrin placed between the large and the medium group (Figure IV-29b) or the medium and the small group (Figure IV-29c) – yield negative ECCD. Analogous differentiation taking place in the complex of **X** with (*R*)-chloro- γ -butyrolactam (**40**) leads to the observed positive ECCD.

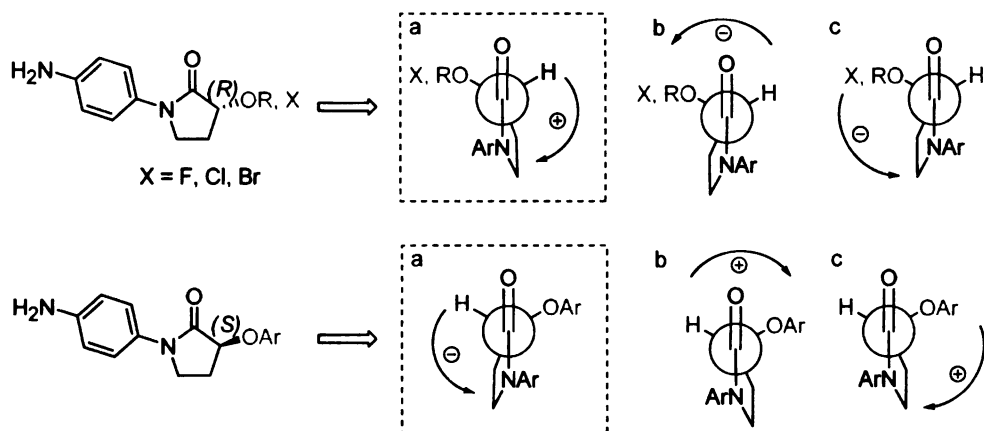
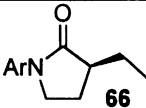
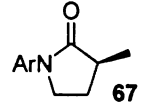
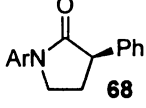
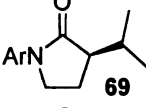
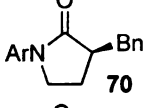
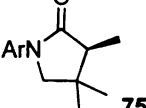


Figure IV-29: Mode of steric differentiation taking place in the complexes of tweezer **X** with (*R*)- α -alkoxy, (*R*)- α -halo and (*S*)- α -aryloxy- γ -butyrolactams. Steric differentiation between the large and the small group leads to the observed ECCD sign.

Similarly, a negative ECCD is expected for the complexes of (*S*)-aryloxy- γ -butyrolactams **50** and **51** with tweezer **X** due to the steric differentiation that occurs between the small hydrogen and the methylene group of the five member ring (Figure IV-29a). The porphyrin slides towards the smaller group and induces a counterclockwise

twist between the porphyrins of the tweezers. The other two possible modes of stereodifferentiation depicted in Figure IV-29 (b and c) result in clockwise twist between the porphyrins and, subsequent positive ECCD spectrum. It is important to note, that the position of the medium substituent (OAr or halide) away from the stereodifferentiating porphyrin explains the absence of any secondary interaction in these complexes.

Table IV-18: ECCD data obtained with α -alkoxy and α -alkyllactams with ZnTPP-tz (I) and ZnTPP-propane-tz (X)

Entry	Substrate	I		X	
		λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
1	 66	428 (-18) 420 (+36)	-54	429 (-96) 422 (+116)	-212
2	 67	427 (-10) 419 (+13)	-23	428 (-56) 421 (+64)	-120
3	 68	429 (-108) 421 (+93)	-211	428 (-351) 421 (+384)	-635
4	 69	429 (-266) 421 (+262)	-528	428 (-400) 421 (+366)	-766
5	 70	428 (-23) 420 (+27)	-50	428 (-233) 421 (+302)	-535
6	 75	427 (+187) 419 (-159)	+346	427 (-88) 420 (+61)	-149

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest

Analogous conformation can explain the negative ECCD sign observed with α -alkyl- γ -butyrolactams **66-70** summarized in Table IV-18 (entries 1-6). In particular, similar to the ZnTPP-tz, the porphyrins of tweezer X adopt a counterclockwise helicity, resulting in a negative CD bisignate. Based on the conformational analysis of alkyllactams performed for the complexes with ZnTPP-tz the observed sign could be

generated if the steric differentiation occurred between the small hydrogen and the methylene group of the ring (medium substituent at the asymmetric center). On the other hand, while this conformation was plausible for ZnTPP complexes and satisfies ECCD results observed with alkoxy and halolactams, there is an alternative mode of steric differentiation yielding the observed negative ECCD. The mode of steric differentiation depicted in Figure IV-30b represents the case when steric differentiation occurs between the medium methylene group of the ring and the large alkyl substituent at the chiral center. In order to alleviate the steric interaction with the large alkyl substituent the porphyrin slides towards the methylene group, hence inducing a negative helical twist relative to the second porphyrin coordinated to the primary nitrogen of the carrier. Nevertheless, based on the NMR studies carried out on the complexes of alkyl lactams with tetraphenyl zinc porphyrin (ZnTPP), it is more likely to accept this mode of binding as a major pathway of steric differentiation operating in the complexes of alkylactams with both ZnTPP-tz and ZnTPP-propane-tz.

It is also important to note that tweezer **I** and tweezer **X** adopt opposite helicity when complexed with alkylactam **75** (Table IV-18, entry 6). As was discussed earlier, the ECCD sign observed for lactams **66-70** with tweezer **I** is due to the stereodifferentiation taking place between the small hydrogen and the medium methylene of the ring (the large alkyl substituent is oriented away from the porphyrin). Unlike the structures **66-70**, the size distribution of the substituents relative the carbonyl in lactam **75** is changed. Thus, while the alkyl substituent at the chiral center in cyclic amides **66-70** plays the role of the large group, here the place of the large substituent is taken by the gem-dimethyl substituted methylene. Subsequently, the steric differentiation occurs

between the small hydrogen and the methyl substituent (medium group) at the asymmetric carbon giving rise to the observed positive ECCD. A negative ECCD observed with the short ZnTPP-propane tweezer corresponds to the one expected if the steric differentiation occurred between the hydrogen and the methylene of the ring.

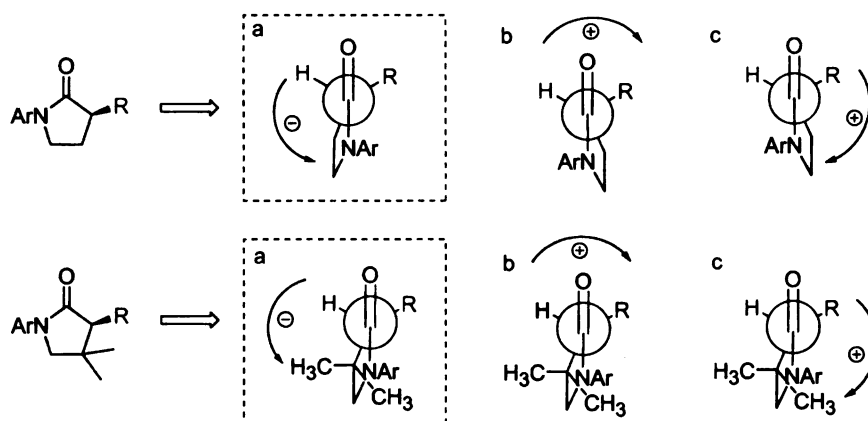


Figure IV-30: Steric differentiation of α -chiral alkyl lactams with porphyrin tweezer.

From this, we can conclude that the absolute stereochemical determination of α -chiral cyclic amides with short ZnTPP-propane tweezer (**X**) proceeds through the binding of the stereodifferentiating porphyrin between the small hydrogen and the methylene of the ring. Twist of the porphyrin towards the smaller substituent induces a helical orientation of the chromophores of the tweezer yielding the observed ECCD spectra. It is noteworthy, that the complexes of tweezer **X** and α -chiral- γ -butyrolactams do not support any secondary C-X $\cdots\pi$ or π - π interaction, previously observed with ZnTPP-tz.

V.4. Conclusion

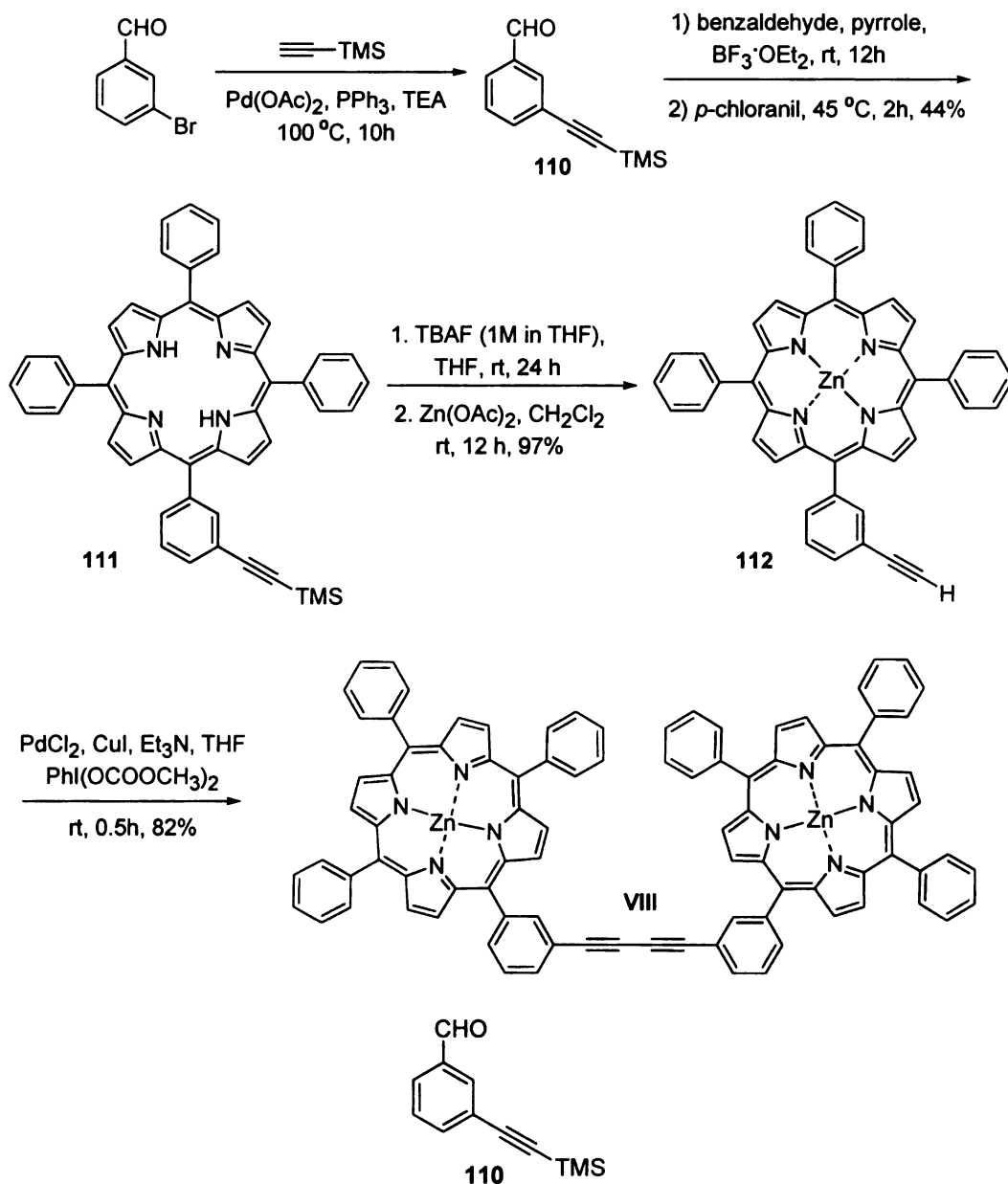
The results presented in this chapter underline the role of the linker in the process of stereodifferentiation taking place in the tweezer-substrate complexes. In particular, an enhanced rigidity of the bis-chromophore accessed through introduction of bi-acetylene linker (tweezer **VIII**) affects the sensitivity of the system resulting in the drop of amplitude of the ECCD signal. The attempt to improve steric differentiation by introducing the bulky *t*-butyl substituent at the *meta*-position of the phenyl rings of the porphyrin (tweezer **IX**) did not give the expected result. On the contrary, even more dramatic decrease of the CD amplitude was observed. The result can be contributed to the complementary effect of the rigidity of the bis-acetylene linker and the crowding of the binding pocket of the tweezer by the bulky *t*-butyl substituents. Nevertheless, both tweezers **VIII** and **IX** upon binding to 1,4-phenylenediamine derivatized α -chiral carboxylic acids tend to stabilize one conformation around the asymmetric carbon. The conformation observed corresponds to the one derived for the complexes of α -chiral amides with ZnTPP-tweezer (**I**) with conservation of the halogen- π interaction.

Shortening of the linker from five to three carbons yields porphyrin tweezer **X**, which is able to stabilize one common conformation and one common mode of steric differentiation within 1,4-phenylenediamine derivatized α -chiral carboxylic acids. Namely, while steric differentiation of chiral α -alkyl and α -haloamides with tweezers **I-IX** proceeds through different conformations due to the secondary interaction between the halide atom and the porphyrin, tweezer **X** stabilizes one common rotamer for all α -chiral amides regardless the type of the substituent at the chiral center. This allows stereochemical determination of all α -chiral carboxylic acids through a single mnemonic

where the substrate adopts the conformation orienting the large and the medium groups towards the porphyrin coordinated to the carbonyl oxygen. Steric differentiation in favor of a smaller group (with exception of α -arylamides) yields the ECCD spectrum that is observed experimentally. Another significant improvement achieved with ZnTPP-propane-tz is enhanced magnitude of the CD bisignates. In average 2-5 fold increase of the ECCD amplitude was observed with acyclic and cyclic amides.

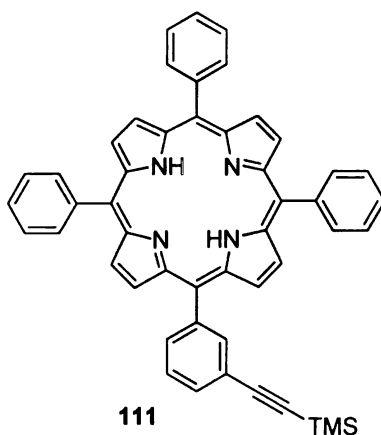
V.4. Experimental procedures.

Scheme IV-2: Synthesis of zinc bis-acetylene porphyrin tweezer **VIII**



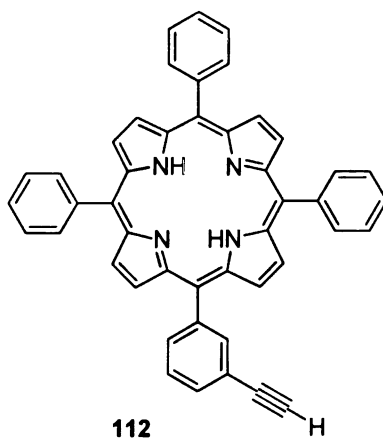
3-(Trimethylsilyl)ethynylbenzaldehyde (110):¹⁵ Trimethylsilylacetylene (3.8 g, 0.0387 mol, 1.8 equiv), 3-bromobenzaldehyde (4 g, 0.0216 mol, 1 equiv), $\text{Pd}(\text{OAc})_2$ (56 mg, 0.25 mmol, 0.01 equiv), triphenylphosphine (112 mg, 0.43 mmol, 0.02 equiv), and

dry deaerated triethylamine (21 mL) were combined in a round bottom flask and brought to quick reflux under argon by placing the flask in an oil bath preheated to 100 °C. The solution was refluxed for 10 h and cooled to room temperature. The reaction mixture was filtered and the filtrate was extracted with saturated NaHCO₃ (2 x 15 mL) and CH₂Cl₂ (2 x 20 mL). The organic layers were combined and the solvent was removed under reduced pressure to give the crude aldehyde as brown oil. The oil was purified by column chromatography (Silica gel, 5% EtOAc in hexanes) to give the title 3-(1-trimethylsilylethynyl)benzaldehyde in 77% yield (3.342 g). ¹H-NMR (CDCl₃, 300MHz): δ 0.07 (s, 9H), 7.72 (d, 1H, *J* = 7.4), 7.81 (d, 1H, *J* = 7.4), 7.97 (dd, 1H, *J*₁ = 1.6, *J*₂ = 1.2), 9.87 (s, 1H); ¹³C-NMR (CDCl₃, 75MHz): δ 3.4, 98.9, 103.2, 124.4, 128.6, 128.9, 133.2, 136.3, 136.8, 191.6; MS (DCI): C₁₂H₁₄OSi *m/z* = 202.2.



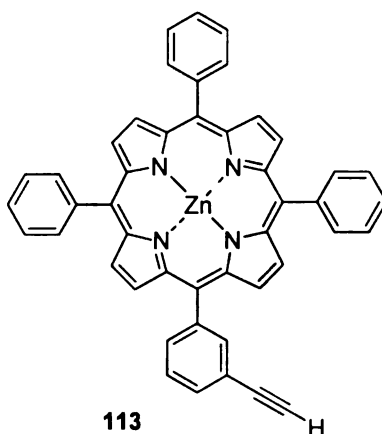
5-(3-Trimethylsilylphenyl)-10,15,20-triphenylporphyrin (111): 3-(Trimethylsilylphenyl)benzaldehyde (**110**) (200 mg, 1 mmol, 1 equiv), pyrrole (260 mg, 4 mmol, 4 equiv), and benzaldehyde (318 mg, 3 mmol, 3 equiv) were combined in a flask with CH₂Cl₂ (150 mL) and the solution purged with N₂ for 15 minutes. BF₃•OEt₂

(50 μ L, 0.4 mmol, 0.1 equiv) was added, the reaction vessel was shielded from light, and the reaction mixture was stirred at room temperature overnight. *p*-Chloranil (980 mg, 4 mmol, 4 equiv) was then added in one portion and the flask was placed in a preheated oil bath at 45 $^{\circ}$ C. The solution was refluxed for 2 h, then cooled to room temperature and the solvent volume was reduced under reduced pressure. The reaction mixture was submitted to flash chromatography (Silica gel, 20% CH_2Cl_2 in hexane) that afforded the mixture of porphyrins. The second round of purification by column chromatography (Silica gel, hexane) gave 5-(3-trimethylsilanylethynylphenyl)-10,15,20-triphenylporphyrin in 36.5% yield (256 mg). ^1H -NMR (300 MHz, CDCl_3): δ -2.7 (s, 2H), 0.92 (s, 9H), 7.8 (m, 9H), 7.9 (dd, 2H, $J_1 = 1.8$, $J_2 = 1.0$), 8.2 (m, 7H), 8.4 (s, 1H), 8.9 (m, 8H); MS (DCI): $\text{C}_{49}\text{H}_{38}\text{N}_4\text{Si}$ $m/z = 710.7$.



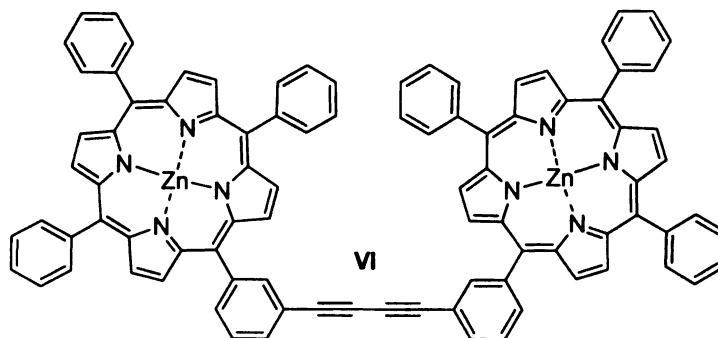
5-(3-Ethynylphenyl)-10,15,20-triphenylporphyrin (112): To a solution of 5-(3-trimethylsilanylethynylphenyl)-10,15,20-triphenylporphyrin (**111**) (88.5 mg, 0.1355 mmol, 1 equiv) in dry THF (5 mL) was added tetrabutylammonium fluoride (1M solution in THF, 0.4 mL, 0.4 mmol, 3 equiv) and the mixture was stirred at room temperature for 24 h. The reaction mixture was then partitioned between water (10 mL) and CH_2Cl_2 (20

mL), the organic layer was separated, dried with anhydrous Na_2SO_4 , and the solvent was removed under reduced pressure to yield crude 5-(3-ethynylphenyl)-10,15,20-triphenylporphyrin. Column chromatography (Silica gel, 10% CH_2Cl_2 in hexane) afforded the title porphyrin **112** in 98% yield (77 mg). ^1H -NMR (300 MHz, CDCl_3): δ - 2.8 (s, 2H), 3.2 (s, 1H), 7.8 (m, 9H), 7.9 (dd, 2H, $J_1 = 1.8$, $J_2 = 1.0$), 8.2 (m, 7H), 8.4 (s, 1H), 8.9 (m, 8H); MS (DCI): calc'd for $\text{C}_{46}\text{H}_{30}\text{N}_4$ $m/z = 638.5$; obs'd $\text{M}^+ = 639.4$ $[\text{M}+\text{H}]^+$, $\text{M}^{+2} = 319.2$.

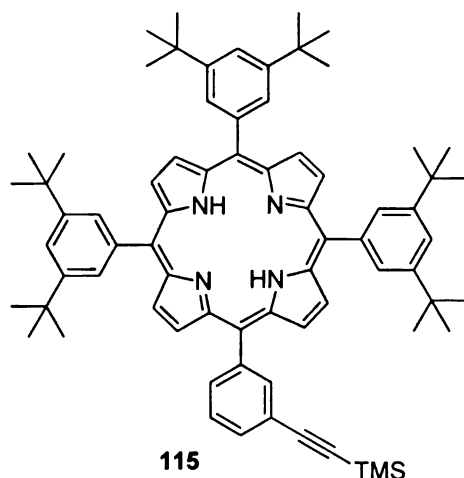


5-(3-Ethynylphenyl)-10,15,20-triphenylzincporphyrin (113): 5-(3-Ethynylphenyl)-10,15,20-triphenylporphyrin (**112**) (18 mg, 0.0282 mmol, 1 equiv) and $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (93 mg, 0.423 mmol, 15 equiv) were combined in CH_2Cl_2 and stirred at room temperature overnight. The color of the solution changed from dark purple to reddish purple during the course of the reaction. The reaction mixture was purified by column chromatography (Silica gel, CH_2Cl_2) and the purple band was collected. The solvent was removed under reduced pressure to yield 5-(3-ethynylphenyl)-10,15,20-triphenylzincporphyrin as a purple solid in 76.8% yield (16.6 mg). ^1H -NMR (300 MHz, CDCl_3): δ 3.2 (s, 1H), 7.8 (m, 9H), 7.9 (dd, 2H, $J_1 = 1.6$, $J_2 = 1.2$), 8.2 (m, 7H), 8.4 (s,

1H), 8.9 (m, 8H); MS (DCI): calc'd for $C_{46}H_{28}N_4Zn$ m/z = 700.1; obs'd M^+ = 701.8
 $[M+H]^+$, M^{+2} = 350.0.



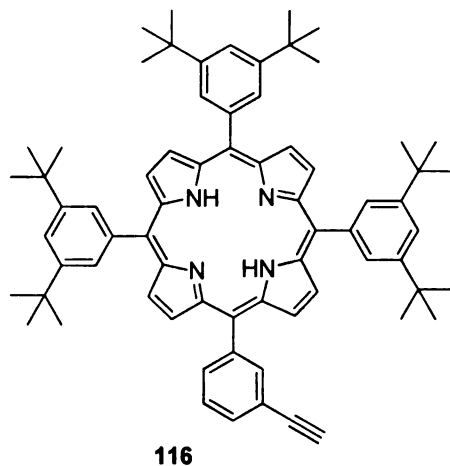
Bis[5-(3-Ethynylphenyl)-10,15,20-triphenylzincporphyrin] (VIII):^{16, 17} 5-(3-Ethynylphenyl)-10,15,20-triphenylzincporphyrin (**113**) (90 mg, 0.1397 mmol, 1 equiv) was combined with $Cu(OAc)_2 \cdot H_2O$ (235 mg, 1.174 mmol, 8.4 equiv) and pyridine (12 mL). The solution was stirred at 40 °C under oxygen atmosphere for 24 h and the color of the reaction mixture changed from purple to blue-green over the course of the reaction. The reaction mixture was then cooled to room temperature and extracted with H_2O (10 mL) and $NaHCO_3$ (20 mL) until the aqueous layer was clear. The organic layer was dried with anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a crude purple-blue film, which was purified by flash chromatography (Silica gel, hexane) to yield the bis-5-(3-ethynylphenyl)-10,15,20-triphenylzincporphyrin (**VIII**) in 82% yield (79 mg). 1H -NMR (300 MHz, $CDCl_3$): δ 7.7 (m, 12H), 7.95 (d, 4H), 8.2 (m, 7H), 8.4 (s, 2H), 8.9 (m, 8H); MS (FAB+): calc'd for $C_{92}H_{54}N_8Zn_2$ m/z = 1402.28; obs'd $[M+Na]^+$ 1424.2.



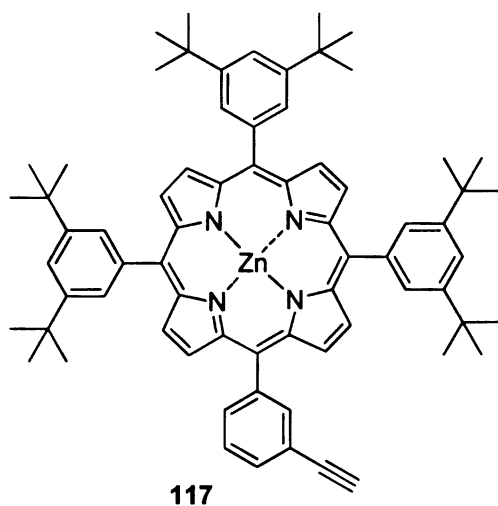
5-(3-Trimethylsilanylethynylphenyl)-10,15,20-tri-3,5-di-*t*-butylphenylporphyrin

(115): 3-(Trimethylsilanylethynyl)benzaldehyde (**110**) (200.2 mg, 1 mmol, 1 equiv), pyrrole (260 mg, 4 mmol, 4 equiv), and 3,5-di-*t*-butylbenzaldehyde (654 mg, 3 mmol, 3 equiv) were combined in a flask with CH₂Cl₂ (150 mL) and the solution was purged with N₂ for 15 minutes. BF₃•OEt₂ (50 μL, 0.4 mmol, 0.1 equiv) was added, the reaction vessel was shielded from light, and was stirred at room temperature overnight. *p*-Chloranil (980 mg, 4 mmol, 4 equiv) was then added in one portion and the flask was placed in a preheated oil bath at 45 °C. The solution was refluxed for 2 h, then cooled to room temperature and the solvent volume was reduced under vacuum. The reaction mixture was subjected to flash chromatography (Silica gel, 20% CH₂Cl₂ in hexane) that afforded the title porphyrin with mixed tetra-porphyrin. The mixture was further separated by column chromatography (Silica gel, hexane) to give the title 5-(3-trimethylsilanylethynylphenyl)-10,15,20-tri-3,5-di-*t*-butylphenylporphyrin in 14% yield (23 mg). ¹H-NMR (300 MHz, CDCl₃): δ -2.6 (s, 2H), 0.92 (s, 9H), 1.49 (s, 18H), 1.68 (s, 36H), 7.35-7.43 (m, 4H), 7.59 (s, 2H), 7.86 (t, 2H, *J* = 7.8), 7.94 (m, 4H), 8.09 (d, 2H, *J* =

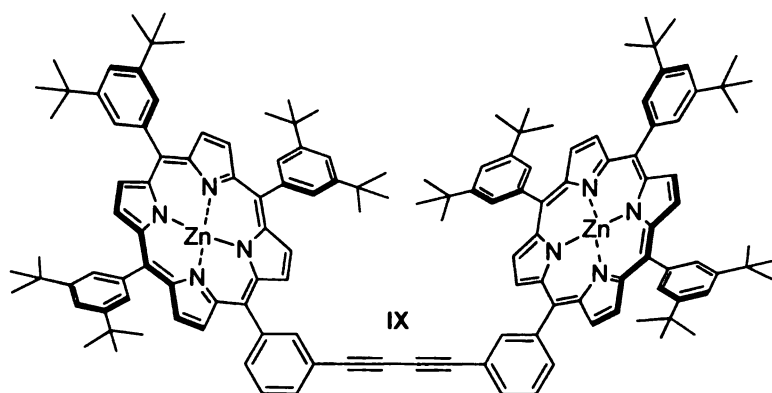
7.8), 8.21-8.26 (m, 8H), 8.38 (d, 2H, $J = 7.8$), 8.57 (s, 2H), 9.06 (m, 4H), 9.14 (s, 2H), 9.17 (s, 6H); MS (FAB+): calc'd for $C_{73}H_{86}N_4Si$ $m/z = 1046.6$, obs'd 1040.9.



5-(3-Ethynylphenyl)-10,15,20-tri-3,5-di-*t*-butylphenylporphyrin (116): To the solution of porphyrin **115** (80 mg, 0.076 mmol, 1 equiv) in dry THF (5 mL) was added tetrabutylammonium fluoride (1M solution in THF, 0.2 mL, 0.2 mmol) and the mixture was stirred at room temperature for 24 h. The reaction mixture was then partitioned between water (10 mL) and CH_2Cl_2 (20 mL), the organic layer dried with anhydrous Na_2SO_4 , and the solvent removed under vacuum to give the title 5-(3-ethynylphenyl)-10,15,20-triphenylporphyrin in 95% yield (70 mg). 1H -NMR (300 MHz, $CDCl_3$): δ -2.7 (s, 2H), 1.48 (s, 18H), 1.68 (36 H), 7.35-7.43 (m, 1H), 7.59 (s, 1H), 7.86 (t, 1H, $J = 7.8$), 7.94 (m, 1H), 8.21-8.26 (m, 8H), 8.57 (s, 2H), 9.14 (s, 2H), 9.17 (s, 8H); MS (FAB+): calc'd for $C_{70}H_{78}N_4$ $m/z = 974.6$, obs'd 974.8.



5-(3-Ethynylphenyl)-10,15,20-triphenylzincporphyrin (117): Porphyrin **116** (30 mg, 0.028 mmol, 1 equiv) and $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (93 mg, 0.423 mmol, 15 equiv) were combined in CH_2Cl_2 (10 mL) and stirred at room temperature overnight. The color of the solution changed from dark purple to reddish purple during the course of the reaction. The reaction mixture was purified with column chromatography (Silica gel, CH_2Cl_2) and the purple band was collected. The solvent was removed under reduced pressure and 5-(3-ethynylphenyl)-10,15,20-triphenylzincporphyrin was obtained in 99% yield (32 mg) as a purple solid. ^1H -NMR (300 MHz, CDCl_3): δ 1.48 (s, 18H), 1.68 (36 H), 7.35-7.43 (m, 1H), 7.59 (s, 1H), 7.86 (t, 1H, $J = 7.8$), 7.94 (m, 1H), 8.21-8.26 (m, 8H), 8.57 (s, 2H), 9.14 (s, 2H), 9.17 (s, 8H); MS (FAB+): calc'd for $\text{C}_{70}\text{H}_{76}\text{N}_4\text{Zn}$ $m/z = 1036.5$, obs'd 1032.0.



Bis[5-(3-ethynylphenyl)-10,15,20-tri-3,5-tri-*t*-butylphenylzincporphyrin] (IX):

Porphyrin **117** (30 mg, 0.028 mmol, 1 equiv) was combined with Cu(OAc)₂•H₂O (40 mg, 0.224 mmol, 8.4 equiv) and pyridine (6 mL). The solution was stirred at 40 °C under oxygen atmosphere for 24 h and the color of the reaction mixture changed from purple to blue-green. The reaction mixture was then cooled to room temperature and extracted with H₂O (25 mL) and NaHCO₃ (2 x 15 mL) until the aqueous layer was clear. The organic layer was dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a crude purple-blue film, which was purified by flash chromatography (Silica gel, hexane) to yield the bis-5-(3-ethynylphenyl)-10,15,20-triphenylzincporphyrin **IX** in 70% yield (42 mg). ¹H-NMR (300 MHz, CDCl₃): δ -2.7 (s, 2H), 1.48 (s, 36H), 1.68 (72 H), 7.35-7.43 (m, 4H), 7.59 (s, 2H), 7.86 (t, 2H, *J* = 7.8), 7.94 (m, 4H), 8.09 (d, 2H, *J* = 7.8), 8.21-8.26 (m, 8H), 8.38 (d, 2H, *J* = 7.8), 8.57 (s, 2H), 9.06 (m, 4H), 9.14 (s, 2H), 9.17 (s, 6H). MS (FAB⁺): calc'd for C₁₄₀H₁₅₀N₈Zn₂ *m/z* = 2074.0, obs'd 2076.4.

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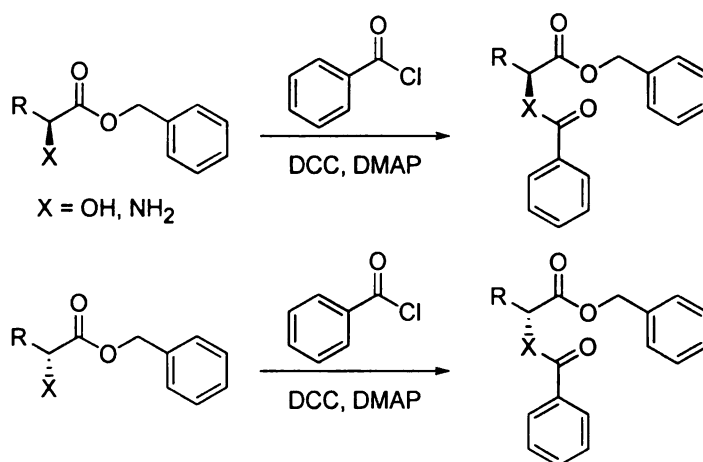
Chapter V

Absolute Stereochemical Determination of β and γ -Chiral Amides

V.1. ECCD in determination of absolute stereochemistry of a distal chirality

Determination of the absolute stereochemistry of chiral molecules bearing a single or multiple stereocenters has been an active area of research for several decades. Among the different methods developed, the Exciton Coupled Circular Dichroism (ECCD)¹ is considered to be a powerful non-empirical technique that can be applied for establishing the absolute chirality of a wide variety of substrates.²⁻¹² The basis of the stereochemical assignment used for different types of molecules depends on whether they contain chromophores or not. The molecules that have two chromophores for exciton coupling are used for ECCD measurements directly. In the case that the molecule lacks the chromophores they can be introduced through derivatization of the functional groups (either OH or NH) as is depicted on Scheme V-1.

Scheme V-1: Chemical derivatization of benzylic esters of α -amino or α -hydroxy carboxylic acids allows for the application of ECCD method for absolute stereochemical determination.



For instance, stereochemical determination of α -amino or α -hydroxy carboxylic presented in Scheme V-1 requires two chromophore for exciton coupling. Derivatization of the substrates with benzyl group introduces one chromophore. The second aromatic group is built in through acylation of the hetero group (OH or NH). The exciton coupling of the introduced chromophores gives rise to a CD bisignate reflecting the absolute stereochemistry of the asymmetric center. The sign of an observed ECCD signal originates from the relative orientation of the two chromophores present in the conformer of highest population.^{3, 5, 7, 13-15}

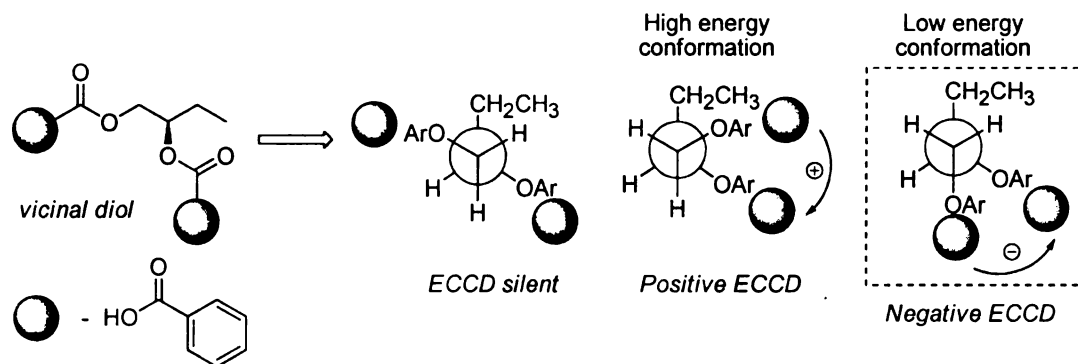


Figure V-1: Stereochemical determination of 1,2-diols by dibenzoate method.

Chemical derivatization and subsequent ECCD analysis was successfully applied to the absolute stereochemical determination of diols and amino alcohols. Figure V-1 depicts conformational analysis of (*R*)-1,2-diol resulting in a negative CD bisignate. Three gauche conformations are the low energy conformations expected for the substrate. The first conformation places the two chromophores to antiperiplanar each other, hence diminishing the ECCD signal. The second conformation would induce a clockwise orientation of chromophores, although being of higher energy is less populated. The highly populated lower energy conformation orients the chromophores counterclockwise

and, hence, gives rise to the negative ECCD spectrum. Thus, establishment of the major ECCD active conformation is the key for the interpretation of the spectrum.

Non-covalently introduced chromophoric hosts¹⁶ reflects the chirality of the coordinated substrates due to steric interaction with substituents at the asymmetric center. The latter method has been explored for a wide variety of chiral amines, alcohols and carboxylic acids,^{6, 8, 9, 12, 17} and was successfully used for substrates with vicinal substitution (*erythro* and *threo* diamines, amino alcohols and diols).¹⁸ However, the method is limited to chiral substrates with the chiral center either directly attached or on the α -carbon relative to the site of attachment of the chromophore. Stereochemical determination of distal stereo centers (β , γ , δ , etc. stereocenters) is an open and challenging area of research.

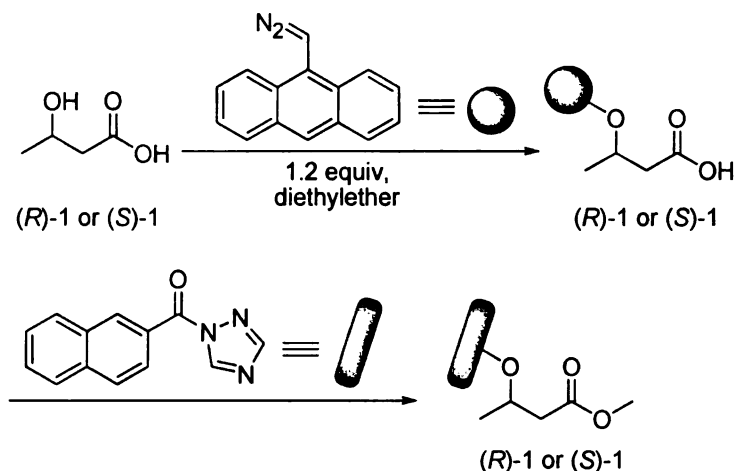


Figure V-2: Stereochemical determination of chiral β -hydroxy carboxylic acids¹⁹ using ECCD requires a derivatization of substrate with chromophores.

There are only few reports addressing the application of the ECCD method to the stereochemical determination of β -chiral substrates. To our knowledge, exciton coupling was used for the stereochemical assignment of β -chiral carboxylic acids that carry either

an aromatic moiety²⁰ or a hydroxyl/amino functionality at the β -carbon, which is used for introduction of a chromophore through O- or N- acylation (Figure V-2).^{19, 21} In both cases the β -position has been used as a chromophoric site. It is important to note that chromophores cannot be introduced in the structures that lack the sites of derivatization, thus limiting the application of the dibenzoate method. Moreover, no reports about the absolute stereochemical determination of γ -chiral carboxylic acids can be found in literature, clearly due to the high conformational flexibility of the substrates.

This chapter describes a general non-empirical method for the stereochemical determination of β - and γ -chiral carboxylic acids using ECCD with the recently developed zinc bis-[5,10,15-(tri-3,5-di-*t*-butylphenyl)] porphyrin tweezer (ZnTBP-tz, V).

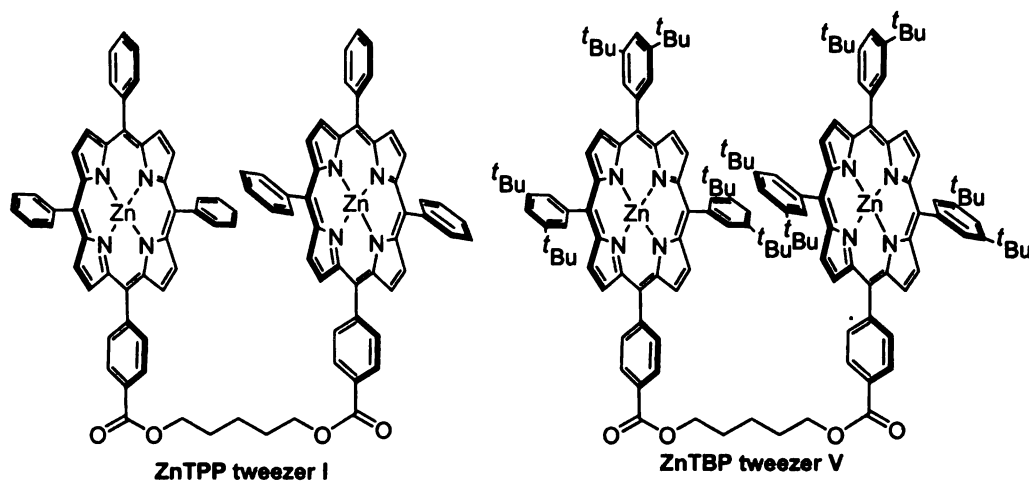


Figure V-3: Zinc bis-[5,10,15-(triphenyl)]porphyrin tweezer (ZnTPP-tz, I) and zinc bis-[5,10,15-(tri-3,5-di-*t*-butylphenyl)] porphyrin tweezer (ZnTBP-tz, V).

Although the widely used zinc bis-[5,10,15-triphenyl]porphyrin tweezer **I** represents a powerful tool for the stereochemical determination of a variety of compounds,^{6, 8, 9, 12, 17} its application to the stereochemical assignment of remote (β and

γ) stereocenters was unsuccessful (Table V-1). None of the substrates complexed with tweezer **I** induced detectable ECCD spectrum. This result can be explained by insufficient interaction between the porphyrin and the stereocenter. Indeed, the complex of ZnTPP-tz with 1,4-phenylenediamine (carrier) derivatized β -chiral carboxylic acids depicted in Figure V-4 shows a lack of steric hindrance between the porphyrin and the distal chiral center.

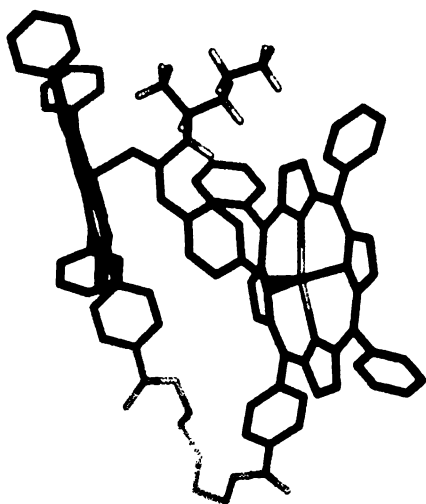
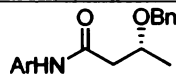
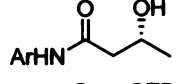
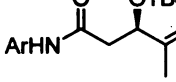
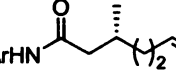
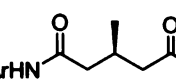


Figure V-4: ZnTPP tweezer (**I**) complex with 1,4-phenylenediamine derivatized (*R*)-3-methylbutyric acid (Molecular mechanics, Force Field MMFF94).

Table V-1: ECCD data for 1,4-phenylenediamine derivatized β -chiral carboxylic acids with ZnTPP tweezer (**I**)

Substrate	ZnTPP-tz
	λ , nm ($\Delta\epsilon$)
 118	0
 119	0
 120	0
 121	0
 122	0

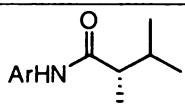
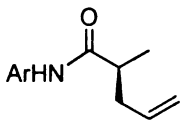
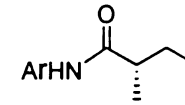
Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral substrate.

In the course of our studies in the field of stereochemical determination of α -chiral carboxylic acids with ZnTPP tweezer we have observed that chiral substrates bearing substituents of a relatively similar size result in ECCD spectra of low amplitude.^{8,}

¹² For instance while (*S*)-2,3-dimethylbutane amide **1** yields negative ECCD with high

amplitude (-84), carrier derivatives of (*S*)-2-methylbutyric acid (**83**) and give the ECCD spectra of a significantly lower magnitude (Table V-2, entry 1). Relatively low ECCD amplitude was also detected for the carrier derivatized (*S*)-2-methyl-4-pentenoic acid (**89**) (Table V-2, entry 2). After analysis of the sizes of the substituents at the chiral center becomes apparent that while the methyl and the *iso*-propyl groups at the chiral carbon of the substrate **1** are significantly different in size (A-value 1.76 and 2.2 respectively), the substituents in chiral amides **83** and **89** are characterized by a relatively similar A-value ($\text{CH}_3 = 1.74$, $\text{CH}_3\text{CH}_2 = 1.79$, allyl = 1.76).²²

Table V-2: ECCD data for 1,4-phenylenediamine derivatized α -alkyl carboxylic acids with ZnTPP-tz

Entry	Substrate	λ , nm, ($\Delta\epsilon$)	A
1	 1	428 (-43) 418 (+41)	- 84
2	 86	429 (+21) 420 (-21)	+42
3	 89	428 (-23) 421 (+18)	-41

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral substrate.

The drop in amplitude observed with amides **86** and **89** can be explained by high conformational flexibility of the substrate in the porphyrin tweezer complex. Similar steric interactions between the porphyrin and both substituents at the asymmetric center yield a small preference of one ECCD active population over the other and, therefore, results in low amplitude for the spectrum. Subsequently, relatively high difference between the sizes of the substituents at the chiral carbon leads to the prominent

improvement in the amplitude of the CD bisignate suggesting a better stabilization of one ECCD active conformation over the others.

Investigating this theory, and in pursuit of larger steric interaction with the asymmetric center, we modified the ZnTPP-tz by introducing a bulky substituent at the phenyl ring. Several substitutions were introduced onto the meso-position of the porphyrin core: mesityl, 2-naphthalene, 3,5-dimethoxyphenyl and 3,5-di-*t*-butylphenyl.

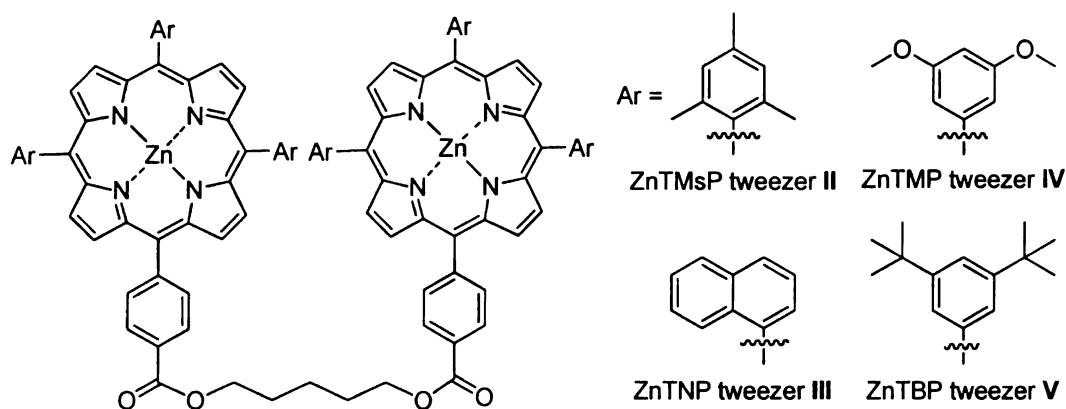
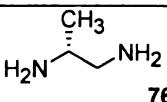
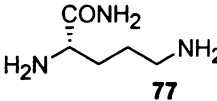
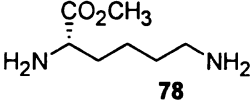
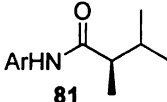
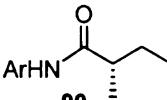
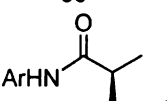
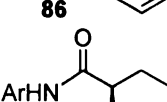
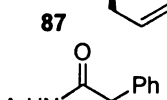
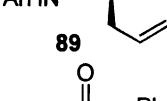


Figure V-5: Alternative tweezers **II-V**

After thorough spectroscopical studies of new tweezers **II-V** was established that binding of bulky tweezers to diamines and chiral amides of 1,4-phenylenediamine is similar to that of ZnTPP-tz (**I**) (see Chapter III for details). Upon complexation of various α -chiral alkyl, alkoxy, aryl and haloamides of 1,4-phenylenediamine with tweezers **II-V** enhancement of ECCD amplitude was observed with increase of the steric interaction between porphyrin host and a chiral guest. For instance, the complexes of chiral amides with bulky ZnTBP-tz **V** gave up to 10 fold enhancement of ECCD amplitude. Table V-2 summarized the ECCD data obtained with tweezers **I** and **V**. As can be seen from the amplitude values, ZnTBP-tz improves the magnitude of the ECCD

signal for all substrates presented in the Table. More importantly, the amplitudes of the substrates **86** and **89** that bear at the chiral center substituents of a similar size (entries 5 and 6) are also enhanced. Along with the increase of the amplitude, the consistence in steric discrimination between tweezers **I** and **V** for chiral α -alkyl, alkoxy and aryl amides was observed. The results indicate that steric differentiation of the chiral amide with both

Table V-3: ECCD data of chiral diamines and α -chiral amides with ZnTPP-tz (**I**) and ZnTBP-tz (**V**)

Entry	Substrate	I		V	
		λ , nm ($\Delta\epsilon$)	A	λ , nm ($\Delta\epsilon$)	A
1	 76	426 (-82) 416 (+58)	-160	433 (-150) 418 (+140)	-290
2	 77	428 (-20) 418 (+16)	-36	433 (-85) 414 (+77)	-162
3	 78	429 (-260) 419 (+132)	-392	430 (-194) 422 (+178)	-372
4	 81	425 (+31) 418 (-20)	+98	430 (+268) 422 (-158)	+426
5	 90	428 (-23) 421 (+18)	-41	430 (-47) 422 (+49)	-96
6	 86	429 (+11) 420 (-12)	+23	430 (-20) 422 (+28)	-46
7	 87	429 (+14) 420 (-10)	+24	428 (-64) 422 (+65)	-129
8	 89	428 (-75) 421 (+60)	-135	430 (-1204) 422 (+1163)	-2367
9	 91	429 (-16) 420 (+21)	-37	430 (-30) 418 (+43)	-73

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

tweezers proceeds in a similar ECCD contributing rotamer orienting the small and the large group towards the carbonyl, and the medium group *anti* to the carbonyl.

Enhancement in magnitude of ECCD signal with ZnTBP-tz (V) can be attributed to an improved steric interaction between the asymmetric center and the bulky substituent at the phenyl rings of the porphyrin tweezer. Comparing the complexes of ZnTPP-tz and ZnTBP-tz (Figure V-6a and b), it becomes apparent that the main advantage of the ZnTBP tweezer is in a broader coverage of the binding cavity of the porphyrin tweezer provided by the large *t*-butyl substituents. Prominent steric interaction can also be detected in the complex of ZnTBP-tz with 1,4-phenylenediamine (carrier) derivatized β -chiral carboxylic acids. Therefore the ZnTBP-tz would make an ideal candidate for sensing remote chirality upon binding of β - or γ -chiral substituents.

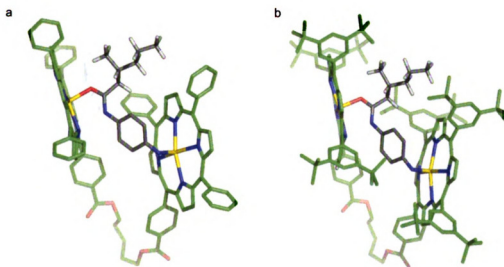


Figure V-6: a) ZnTPP tweezer I and b) ZnTBP tweezer V complex with 1,4-phenylenediamine (carrier) derivatized (*R*)-3-methylbutyric acid (Molecular mechanics, Force Field MMFF94).

V.2. Absolute stereochemical determination of β -alkyl and alkoxy carboxylic acids derivatized with 1,4-phenylenediamine

Our initial focus was to apply the ECCD method for determining the absolute stereochemistry of β -chiral carboxylic acids. The first complexation of modified commercially available (*R*)-3-benzyloxybutyric acid (**1**) (derivatized with 1,4-phenylenediamine to provide the second site of attachment¹²) with ZnTBP-tz **V** induced strong negative helicity in the complex detected as a negative ECCD spectrum (Figure V-7, Table V-4, entry 1).

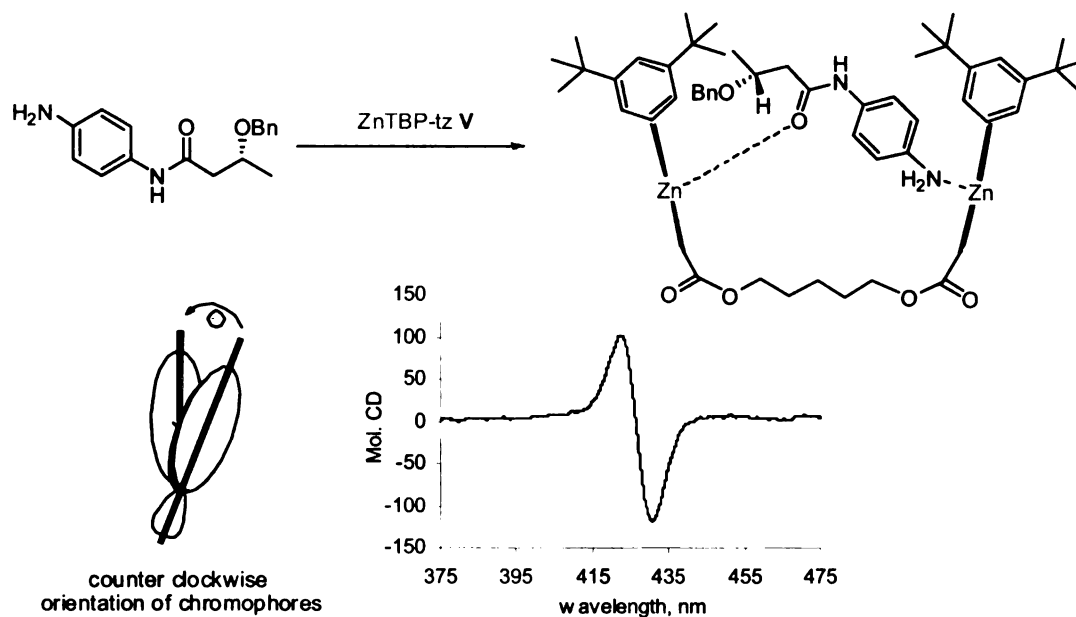


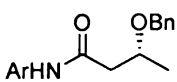
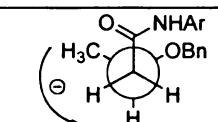
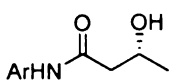
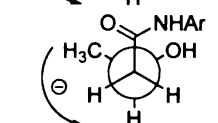
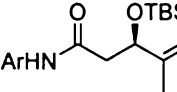
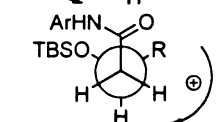
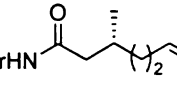
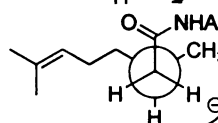
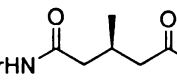
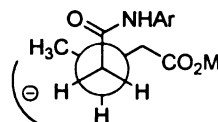
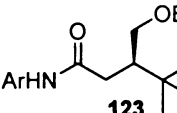
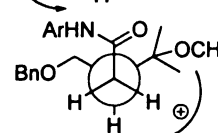
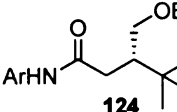
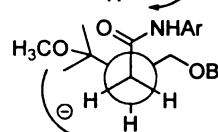
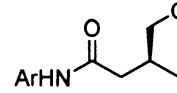
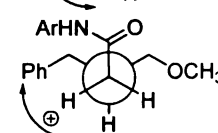
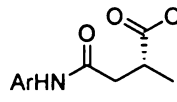
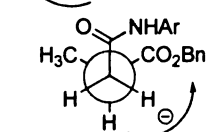
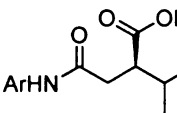
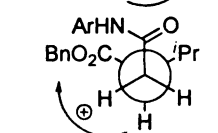
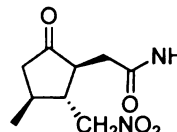
Figure V-7: Stereochemical determination of carrier derivatized (*R*)-3-benzyloxybutanoic acids with ZnTBP-tz **V**. Spectrum obtained in methylcyclohexane and reported at 20 equiv of chiral guest.

It is noteworthy that attempts to detect chirality with ZnTPP-tz and ZnTPFP-tz (this tweezer was specifically developed in order to improve the binding of oxygenated functional groups due to increased electron deficiency of the zinc atom)¹⁸ were

unsuccessful. After successful application of tweezer **V** with substrate **1**, a series of chiral β -carboxylic acids bearing alkyl, alkoxy and aryl substituents on the asymmetric center were synthesized and derivatized with 1,4-phenylenediamine (carrier). All of the chiral substrates tested resulted in chiral induction of the complex and the subsequent ECCD, which follows consistent and predictable trend that can be rationalized by the relative A-values²² of the substituents at the chiral center. For instance, substrate **1** carries three groups at the asymmetric center that can be identified by relative A-values as small – hydrogen, medium – benzyloxy group (A-value of 0.65) and large – methyl group (A-value of 1.74). Similar relative size distribution is present in substrate **3**, i.e., small – hydrogen, medium – OTBS group and large – alkyl group. Taking into account only the relative sizes and not the nature of the substituents, these two substrates can be viewed as the *pseudo*-enantiomeric, giving ECCD signals of an opposite sign, negative for substrate **118**, and positive for substrate **120** (Table V-4, entries 1 and 3). Similar analogy can be drawn between substrates **126** and **127**, where benzyl carboxylate is the group of medium size (A-value of 1.2-1.3) and alkyl group is the large substituent. These two *pseudo*-enantiomeric structures also resulted in opposite ECCD signals.

Substrates **121** and **122** although of opposite chirality, (*S*) and (*R*) respectively, based on the relative sizes of their substituents are expected to behave similarly. Namely, while the substituents at the asymmetric center of structure **121** can be assigned as follows: hydrogen – small group, alkyl – large group and methyl - medium group, the substrate **122** presents a methyl substituent as a large group. Hence, these two structures result in ECCD spectra of the same sign. The enantiomeric structures **124** and **125** induce, as expected, opposite helicity of the ZnTBP tweezer complex.

Table V-4: ECCD data obtained with 1,4-phenylenediamine derivatized β -chiral carboxylic acids with ZnTBP tweezer (V)

Entry	Substrate	Zn-TBP tweezer		Conformation
		λ , nm ($\Delta\epsilon$)	A	
1	 118	430 (-118) 422 (+102)	- 220	
2	 119	431 (-36) 422 (+39)	-75	
3	 120	432 (+27) 423 (-21)	+48	
4	 121	431 (-104) 422 (+80)	-184	
5	 122	430 (-26) 423 (+28)	-54	
6	 123	431 (+33) 421 (-42)	+75	
7	 124	431 (-40) 421 (+21)	-61	
8	 125	430 (-32) 421 (+44)	- 76	
9	 126	431 (-120) 421 (+115)	-235	
10	 127	432 (+163) 421 (-133)	+296	
11	 128	435 (-14) 422 (+12)	-28	see Figure V-9

Spectra taken in methylcyclohexane and reported at 20 equiv of chiral guest

Utilization of the method as a non-empirical approach for determination of β -chirality requires identification of the major ECCD active conformation favored for β -chiral carboxylic acids upon binding to ZnTBP tweezer and subsequent formulation of a working mnemonic. Similar to the 1,4-phenylenediamine derivatives of α -chiral carboxylic acids studied earlier, an induced helicity of the porphyrin tweezer complex must come from the major conformer of the chiral guest. Since the coordination of the ligand to the porphyrin is still through the carbonyl oxygen, we have to consider the position of the substituents at the asymmetric center with regards to the C=O bond. Thus, all possible ECCD active rotamers of C_{α} - C_{β} with respect to the carbonyl bond must be analyzed.

Figure V-8 depicts a conformational analysis of substrates **118** and **120**. As can be seen, there are three major ECCD active conformations. Conformation **A** mimics the conformation identified for α -alkoxy carboxylic acids²³ and places the small hydrogen and large alkyl towards the coordinated carbonyl. Size differentiation taking place in this conformation is expected to result in a positive ECCD for structure **118** and negative bisignate with substrate **120**, which does not correspond to the experimentally observed data. Both other rotamers - **B** and **C** - can contribute to the observed negative ECCD for ligand **118** and positive bisignate for substrate **120**.

The sign of CD bisignates observed with substrates **121-127** presented in Table V-4 can also be explained through conformations **B** and **C**. Thus, the stereodifferentiation proceeds either in **B** between a large and medium alkyl groups in substrates **121-125** or large alkyl group and medium carbonyl substituent in ligands **126** and **127** in favor of the last one, or in **C**, orienting the large group away from the

porphyrin bound to the carbonyl. Rotamer **B** can be considered more favored energetically as compared to rotamer **C**, since it decreases the steric interaction between the large group and the second porphyrin (coordinated to the free amino group of the carrier).

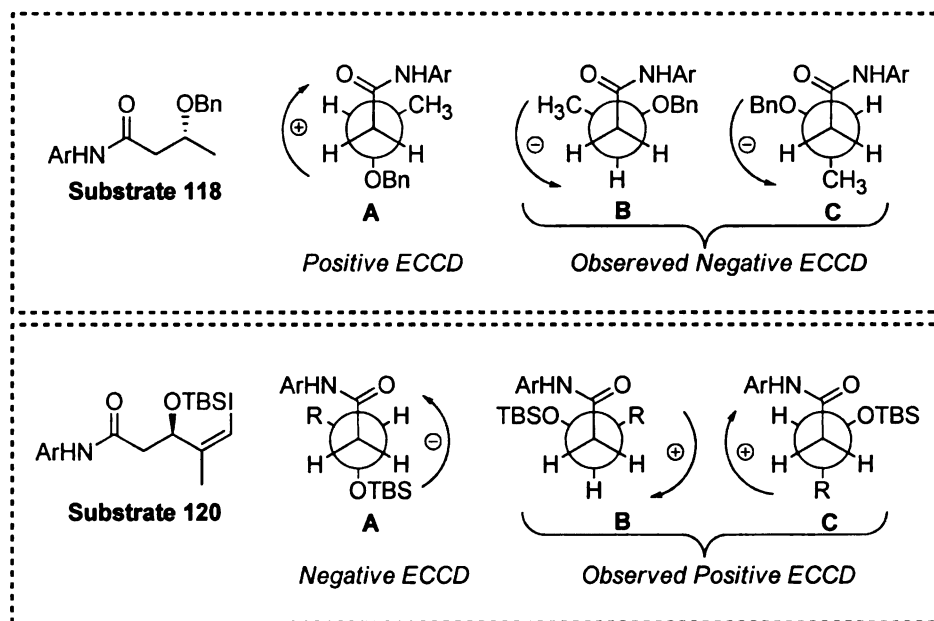


Figure V-8: ECCD contributing rotamers of derivatized β -chiral carboxylic acids **118** and **120**: Substrate **118**: rotamer **A** leads to positive ECCD, conformations **B** and **C** result in observed negative bisignate. Substrate **120**: conformations **B** and **C** result in observed positive ECCD.

Entry 11 in Table V-4 depicts the ECCD obtained with cyclic ketone **128** where the sign of the bisignate is the result of stereodifferentiation between the medium carbonyl and the large tertiary methyne of the five-member ring. As is depicted in Figure V-9, complexation of ZnTBP-tz with amide **128** yields the complex, where the porphyrin coordinated to the carbonyl oxygen of the amide group faces the keto-group and the β -methylene of the cycle. Steric differentiation between these two in favor of the smaller ketone results in the counterclockwise twist between the chromophores of the porphyrin

tweezer, giving rise to the observed negative ECCD. The mode of steric differentiation in this complex also follows the mode proposed in conformation B.

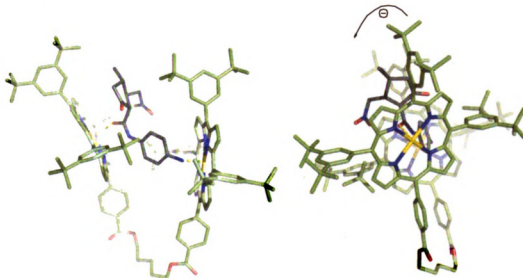
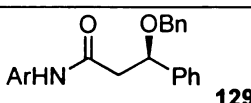
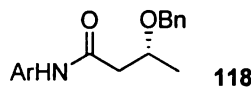
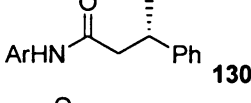
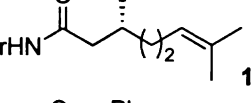
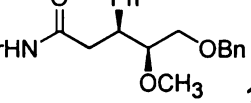
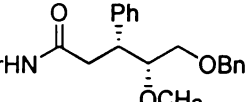
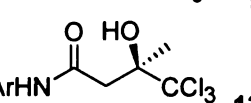


Figure V-9: Stereochemical determination of cyclic amide **128** with ZnTBP-tz.

Further, we investigated the stereochemical determination of β -chiral carboxylic acids bearing either aromatic groups or halides at the asymmetric center. It is essential to point out that during our previous work in stereochemical determination of α -chiral carboxylic acids both sets of compounds have shown to experience a secondary interaction with the porphyrin tweezer, resulting in the opposite sign of ECCD.^{8, 12} These interactions include aromatic π - π stacking between aryl substituents at the chiral center¹² and the porphyrin or halogen- π interactions of halides present at the asymmetric center with the porphyrin resulting in bisignates of opposite sign from the one predicted by the mnemonic derived for alkyl and alkoxy carboxylic acids (Chapter 2, Figure II-1). Table V-5 summarized the ECCD data obtained with several β -aryl carboxylic acids **12-15** and with halogenated amide **16**.

Table V-5: ECCD data for chiral β -aryl and halo carboxylic acids with ZnTBP-tz (**V**)

Entry	Substrate	V	
		λ , nm ($\Delta\epsilon$)	A
1	 129	435 (-44) 425 (+40)	-88*
2	 118	430 (-96) 421 (+84)	- 220
3	 130	430 (+240) 421 (-130)	+370*
4	 121	431 (-104) 422 (+80)	-184
5	 131	435 (+58) 424 (-53)	+111*
6	 132	436 (-58) 426 (+65)	-123*
7	 133	430 (+26) 421 (-20)	+46*

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest

* - ECCD sign due to a secondary interaction

As is evident from the entries 1, 3, 5 and 6, the ligands of opposite chirality induce opposite helicity onto the porphyrin tweezer complex. However, the absolute sense of chiral induction seems to differ from what was observed with alkyl and alkoxy amides. For instance, if the carrier derivatized (*R*)-3-OBn-butanoic acid **118** gives a negative ECCD spectrum the expected result for the carrier conjugate of (*S*)-3-OBn-3-phenylpropionic acid would be a positive CD bisignate (note that a relative size distribution in both substrates is similar, i.e., methyl and phenyl are the large substituents and OBn-medium size groups). Nevertheless, a negative Cotton effect is observed (Table V-5, Entry 1). Similarly, despite the identical size distribution of substituent in substrates

121 and **130** the latter gives rise to positive ECCD as opposed to the expected negative bisignate. Such a trend may be indicative of previously detected aromatic interactions (or C-H--- π interaction) between the porphyrin and the aryl substituent at the asymmetric center.¹² It is noteworthy that secondary aromatic interaction within bulky ZnTBP tweezer is preceded during our studies of chiral α -aryl amides (Chapter III), i.e., the stereochemical determination of aryl amides with both tweezers **I** and **V** occurs through the same ECCD active conformation with consideration of aromatic interaction.

An interesting observation comes from comparison of the substrates **125** (Table V-4, entry 8) and **130** (Table V-5, entry 3). Amide **125** while having the phenyl substituent as a part of the structure yet does not show any secondary interaction with the porphyrin coordinated to the carbonyl. However, substrate **130** inverts the sign of ECCD presumably due to the π -interaction with the stereodifferentiating chromophore. Thus, it appears that the position of the aromatic group is crucial and the secondary interaction affects the sign of ECCD spectrum only if the interacting group is placed directly at the stereocenter.

The analysis of ECCD contributing conformers of substrate **129** (Table V-5, entry 1) reveals two rotamers that are able to induce an observed helicity (Figure V-10). Namely, conformation **A**, placing a phenyl group and hydrogen toward the porphyrin coordinated to the carbonyl, will result in negative ECCD if the stereodifferentiation occurs in favor of the small hydrogen, i.e., porphyrin is sliding away from the large phenyl ring and toward the small hydrogen will produce a counterclockwise orientation of the two porphyrins. Another possibility for the negative ECCD is stabilization of conformation **B** where the stereodifferentiation takes place between the large phenyl and

the medium OBn groups. Here, aromatic interaction between the phenyl ring and the porphyrin can push the latter to slide toward the large group and induce the observed negative bisignate. Similarly, the ECCD sign obtained for halogenated amide **133** can be explained through conformations **A** and **B***, where **B*** involves a secondary interaction between a chlorine atom and the porphyrin.

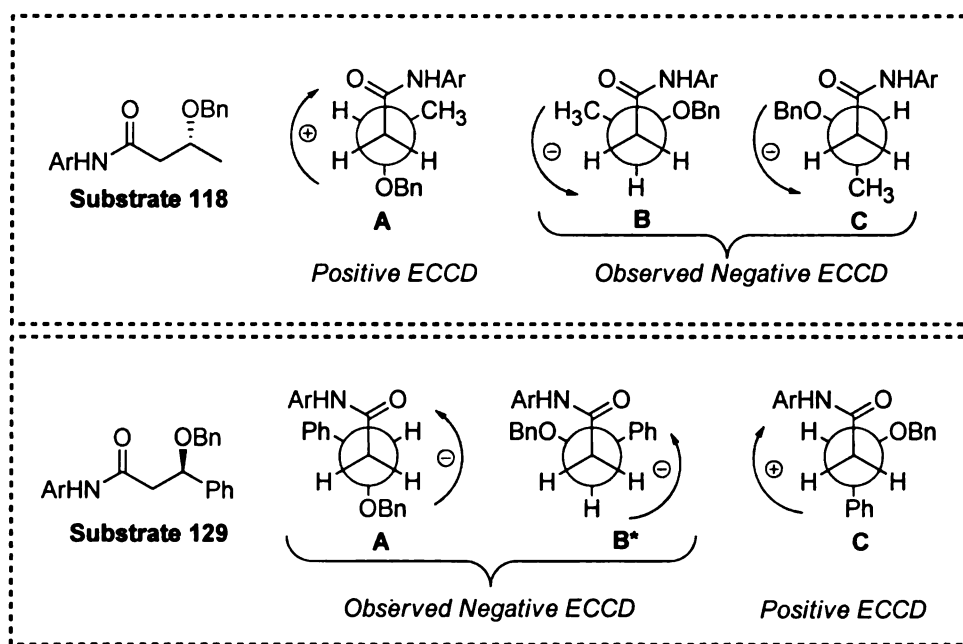


Figure V-10: Conformational analysis of substrates **118** and **129**). Conformation **B*** induces a negative ECCD due to the aromatic interaction between the phenyl ring and the porphyrin.

More detailed identification of the major conformation present in these complexes can be possible through NMR studies. Similar to α -chiral amides, the NMR analysis of the complexes of β -chiral amides with ZnTBP could provide the necessary information about the position of the substituents within the shielding cone produced by the porphyrin. Namely, protons located closer to the porphyrin plane and closer to the center of the shielding cone produced by the chromophore would experience larger upfield shift (Figure V-11). Consequently, the shift of the protons of the chiral substrate coordinated

to the porphyrin, as detected by ^1H -NMR, can help to map the disposition of the substituents relative to the porphyrin plane within the shielding cone and reveal the orientation of the substituents relative to the carbonyl group.

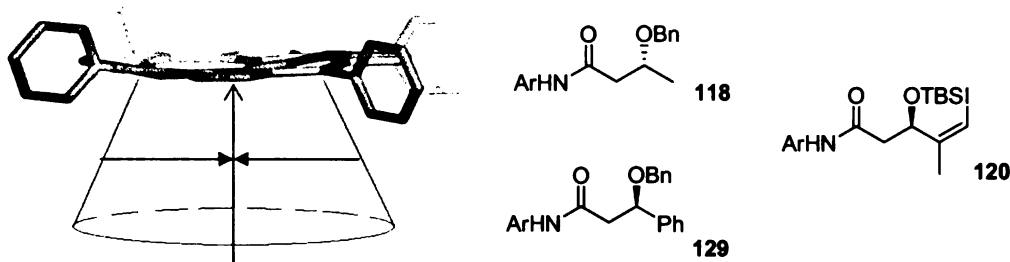


Figure V-11: Shielding cone produced by the porphyrin (shielding enhances with the direction of arrows).

Thus, similar to the studies of halogenated substrates in Chapter II, the complexes of ZnTBP with substrate **118**, **120** and **129** (Figure 9) were preformed and NMR spectra of free ligand and porphyrin complex were analyzed ($\Delta\delta = \delta_{\text{complex}} - \delta_{\text{free}}$). Unfortunately, while complexation to ZnTPP yields an upfield shift of the NMR spectra of α -chiral amides (the anisotropic effect of the aromatic ring onto the bound substrate), the complexes of β -chiral amides did not provide any significant shielding of the chiral center. The result can be expected since the position of the stereocenter is moved farther from the center of the porphyrin, where the largest anisotropic effect is expected. Hence, the obtained $\Delta\delta$ change is not significant enough to draw any conclusions.

The computational conformational search performed for ZnTBP tweezer complex with carrier conjugate of (*R*)-3-OBn-butyric acid (**118**) gave conformation **B**, projecting the medium and the small groups toward the porphyrin coordinated to the carbonyl, as the lower energy conformation (Figure V-12).

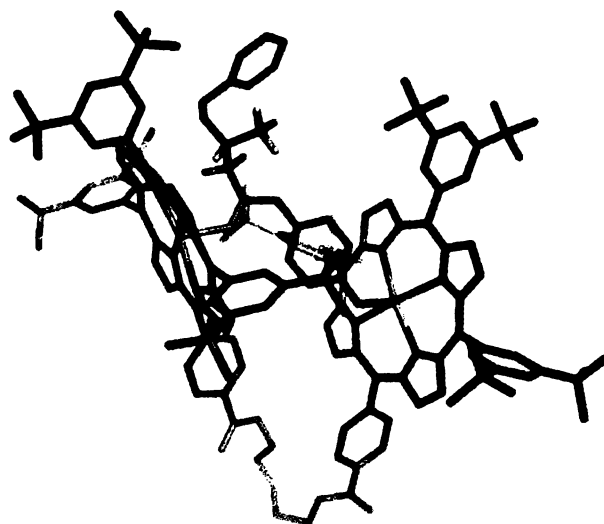


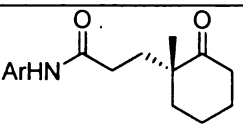
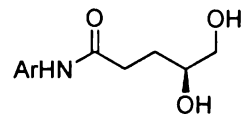
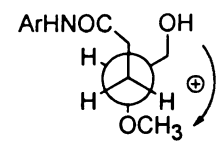
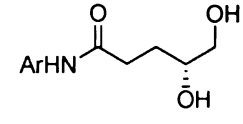
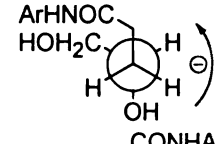
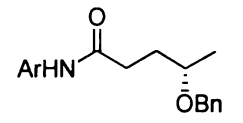
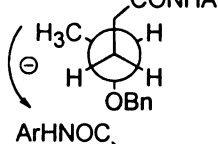
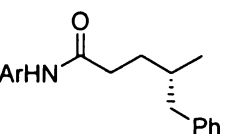
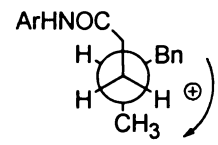
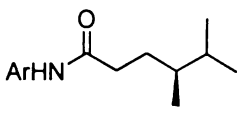
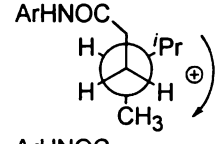
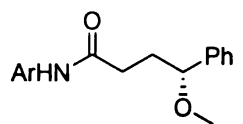
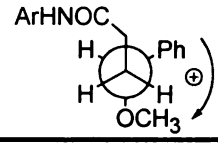
Figure V-12: Favored ECCD active conformation of β -chiral carrier derivatized carboxylic acid **118** in porphyrin tweezer **V** (Conformational search, Monte Carlo).

V.3. ECCD in determination of absolute stereochemistry of γ -alkyl and alkoxy carboxylic acids derivatized with 1,4-phenylenediamine

Identification of γ -chirality constitutes another challenging part of the project. Luckily despite the remote position of the chiral center from the carbonyl – the main coordination site of the ligand to the porphyrin – we were able to detect exciton coupling between two porphyrins in ZnTBP tweezer **VIII**. It is significant that the method is applicable for differentiation of tri- and tetra-substituted chiral centers of cyclic and acyclic structures.

Table V-6 summarizes ECCD data observed with synthesized γ -carboxylic acids derivatized with 1,4-phenylenediamine as a carrier. The quaternary substrate **134** induces a prominent negative helicity of the porphyrin tweezer. As expected the enantiomeric substrates **135** and **136** induce CD bisignates of opposite sign. The analogous amides

Table V-6: ECCD data for γ -chiral carboxylic acids derivatized with 1,4-phenylenediamine with ZnTBP-tz

Entry	Substrate	λ , nm ($\Delta\epsilon$)	A	Conformation
1	 134	430 (-17) 425 (10)	-27	
2	 135	430 (61) 422 (+45)	+106	
3	 136	430 (-58) 422 (40)	-98	
4	 137	430 (-130) 423 (+120)	-250	
5	 138	431 (+95) 423 (-75)	+170	
6	 139	430 (+105) 423 (-87)	+192	
7	 140	435 (+25) 422 (-27)	+52*	

Spectra taken in methylcyclohexane at 0 °C and reported at 20 equiv of chiral guest.

136 and **137** (note that a relative size distribution of substituents at the chiral center is similar) both give rise to a negative ECCD. The similarity in stereodifferentiation suggests that both substrates bind similarly to the porphyrin tweezer **V** and stabilize similar ECCD active conformation. It is noteworthy, that the presence of the free hydroxyl does not influence the sign of the chiral induction. The substrate **138** and **139** both give rise to a positive ECCD, which can also be explained by the relative A-values of the substituents. Namely, the steric differentiation of amide **138** occurs between the

benzyl group and hydrogen, with the medium methyl substituent being oriented away from the carbonyl (A-values: methyl = 1.74, benzyl = 1.76). Similarly, amide **139** adopts the conformation placing the medium methyl group *anti* to the carbonyl. Steric differentiation between the large *iso*-propyl and hydrogen yields positive ECCD.

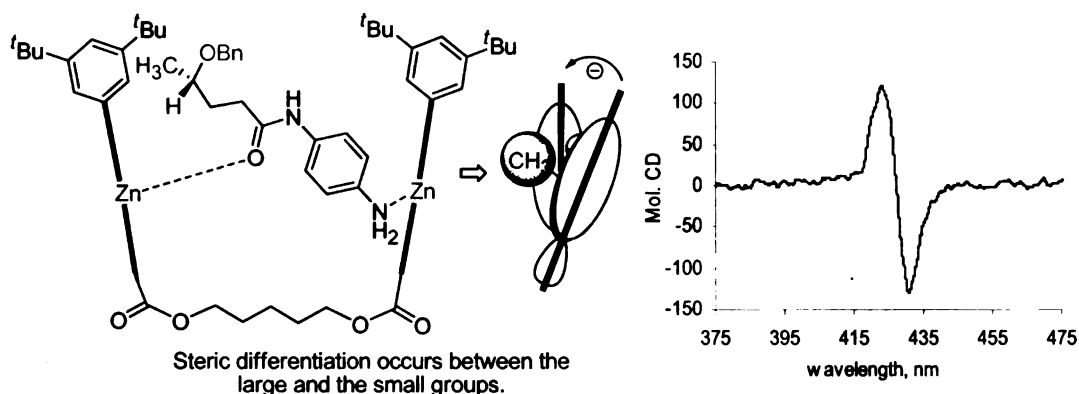


Figure V-13: Stereochemical determination of 1,4-phenylenediamine derivatized (*R*)-4-benzyloxypentanoic acid (**137**) with ZnTBP-tz V.

Looking closely into the complex of γ -chiral amide with porphyrin tweezer we can propose that the observed ECCD sign generates from the conformation orienting the large and the small groups towards the porphyrin coordinated to the carbonyl. As it is depicted in Figure V-13 the helicity of the tweezer complex with (*R*)-2-benzyloxybutane amide (**137**) is governed by the conformation orienting the large methyl and the small hydrogen substituents at the chiral carbon. Steric differentiation in favor of the small group leads to counterclockwise orientation of chromophores of the host tweezer resulting in negative ECCD. Thus, it is expected that enantiomeric amide or the substrates with opposite distribution of the substituents (based on A-values) will result in positive CD bisignates. Indeed, as can be seen from the Table V-3, substrates **135** and **130** induce positive helicity of porphyrin tweezer.

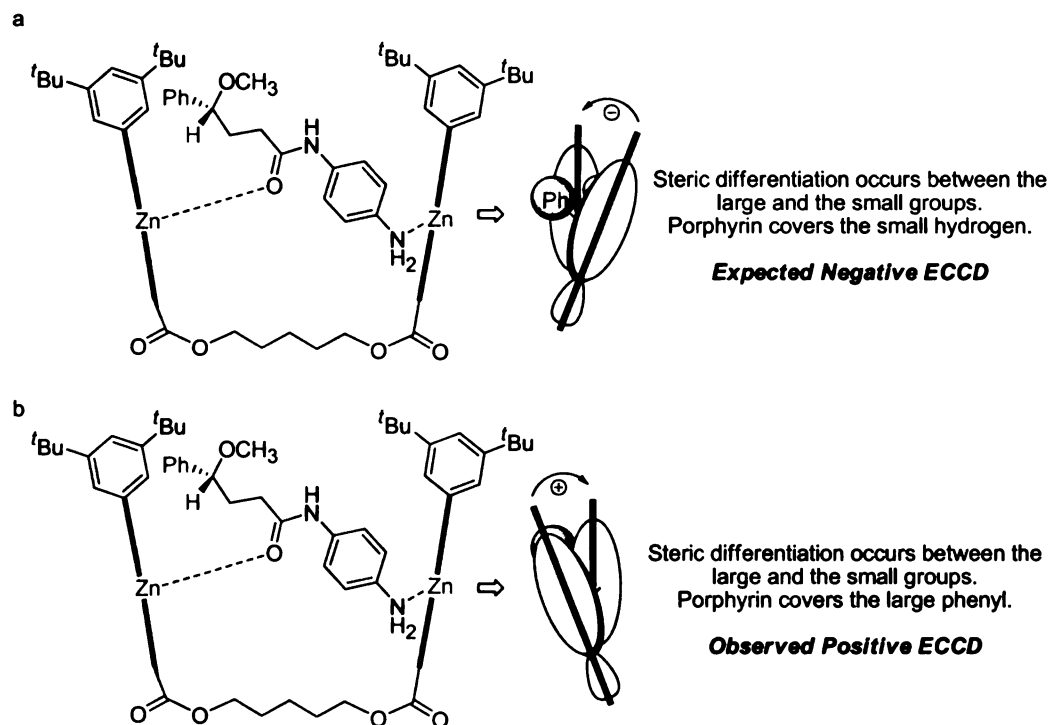


Figure V-14: Stereochemical determination of 1,4-phenylenediamine derivatives of γ -aryl carboxylic acids proceeds with consideration of aromatic interaction taking place between the large phenyl substituent at the asymmetric center and the porphyrin.

Substrate **140** (entry 7) bearing an aromatic substitution at the asymmetric carbon induces a positive helicity of the porphyrin tweezer complex. The relative distribution of the substituents at the chiral center of **140** is similar to **137**, i.e. phenyl is the large group, methoxy – the medium and hydrogen – the small substituent. Thus, the relative spatial distribution of both **140** and **137** is the same and the expected ECCD sign, based on the common conformation observed for substrates was **136** and **137** is negative (Figure V-14a). Yet, the ECCD sign observed for **140** is opposite of that of **137** (Table V-3, entries 4 and 7).

Previous studies of α - and β -chiral systems with ZnTBP-tz (**V**) revealed that substrates bearing an aromatic substituents at the asymmetric center induce helicity of the

porphyrin tweezer opposite from that detected for alkyl and alkoxy amides. The effect was assigned to the secondary interaction between the aromatic substituent and the porphyrin coordinated to the carbonyl. It is plausible to assume that the same type interaction occurs in the complexes of ZnTBP-tz with carrier derivatized chiral γ -aryl carboxylic acids. Thus, positive ECCD obtained for the aromatic substrate **140** can be contributed to the conformer experiencing a secondary aromatic interaction with chromophoric host. This interaction causes the porphyrin to cover the large aromatic substituent instead of the small hydrogen leading to clockwise orientation of chromophores resulting in positive ECCD (Figure V-14b).

It worth noting that similar to the cases observed with α - and β -aryl amides, secondary interaction is limited to the position of the aromatic group. Thus, while substrate γ -aryl amides **140** (Table V-3, entry 7) gives positive ECCD presumably due to the aromatic interaction taking place within the complex, the tweezer complex with amide **138** carrying the phenyl ring at δ -position does not exhibit any secondary interaction and the stereochemical determination occurs through the mode proposed for γ -alkyl (alkoxy) amides.

V.4. Conclusion

In conclusion, based on the results provided in this chapter, we have successfully applied the porphyrin tweezer methodology for absolute stereochemical determination the β - and γ -chiral carboxylic acids. The results became possible after successful modification of the porphyrin tweezer by introducing a bulky *t*-butyl group onto the *meso*-phenyl rings, which generated a chromophoric system sensitive for detection of

distal chirality. Testing of the series of substrates revealed a consistent trend of ECCD signal, originating from stabilization of a single ECCD active conformation within a type of amides tested. Thus, β -chiral carboxylic acids presumably stabilize a conformation where steric differentiation from the porphyrin coordinated to the carbonyl oxygen occurs between the large and the medium substituent. The small group is oriented *anti* to the carbonyl. γ -Carboxylic acids stabilize the conformation that orients the medium group away from the carbonyl and places the large and the small substituents towards the differentiating porphyrin (Figure V-15).

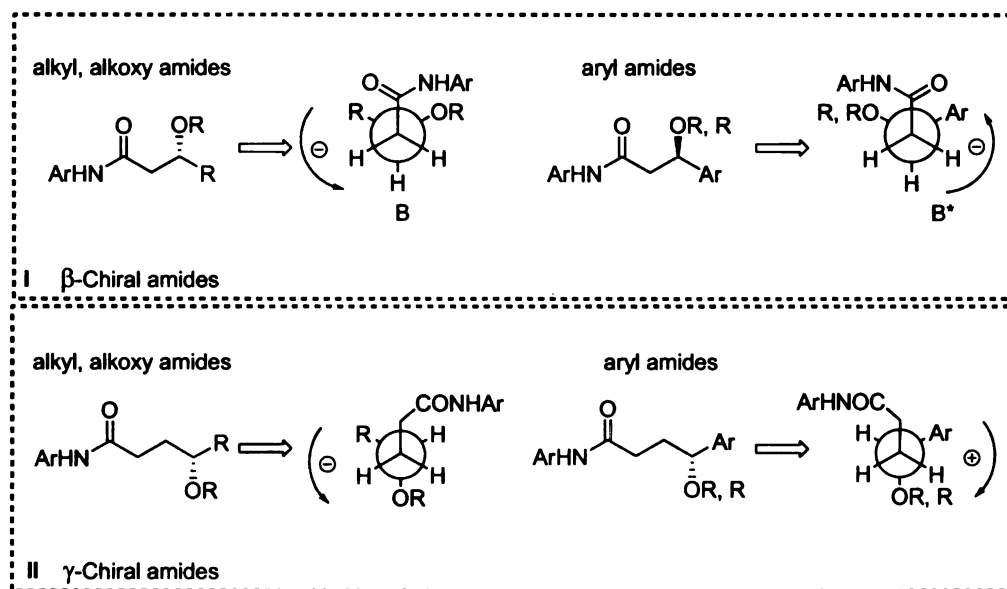


Figure V-15: General mnemonic for absolute stereochemical determination of 1,4-phenylenediamine derivatized β - (Box I) and γ -chiral carboxylic acids (Box II) with ZnTBP-tz (V). It is important to note that despite the distance of the chiral center from the carbonyl, secondary interactions that were earlier identified for chiral α -aryl carboxylic acids with ZnTBP-tz continue to operate within β - and γ -chiral substrates. As a result,

presence of the aryl substituent at the chiral center yields the ECCD spectrum, the sign of which is opposite to that of the alkyl analog. Namely, while the steric differentiation of both alkyl and aryl substrates occurs in the same conformation, aromatic interaction between the porphyrin and the aryl group at the asymmetric carbon twists the chromophore towards the large aryl ring as opposed to the small substituent, thus inverting the sign of ECCD.

The possible modification of the methodology that could provide significant information is synthesis and ECCD studies of β - and γ -chiral substrates with the C_3 -linker analog of ZnTPP tweezer. As it was discussed in the Chapter IV, unlike ZnTPP-tz, its C_3 analog – ZnTPP-propane tweezer (**X**) – was found to be more sensitive chromophoric host. Despite the similarity in the bulk of the porphyrin (both tweezers have phenyl rings as substituents at *meso*-position) a 2-5 fold increase in amplitude of ECCD spectra was observed with tweezer **X**. Along with that, unlike ZnTPP-tz, tweezer **X** produced stereodifferentiation of 1,4-phenylenediamine derivatized α -chiral carboxylic acids through the one conformation, similar for all amides regardless the type of substituents at the chiral center (note that ZnTPP-tz changes the mode of stereodifferentiation between α -alkyl and α -halo amides). Based on the advantageous characteristic of short tweezer **X** with respect to the tweezer **I** we can expect it to be applicable to sensing the β - and γ -chirality directly.

Another aspect worth noting would be enhancement of the steric interaction in ZnTPP-propane-tz (**X**) by introducing the bulky *t*-butyl group onto the phenyl rings and construction of a new ZnTBP-propane tweezer (**XI**) (Figure V-16). Enhanced steric interaction improving the sensitivity of the chromophoric host could contribute to the

stabilization of one common ECCD active conformation for carrier derivatized β - and γ -chiral carboxylic acids. The high sensitivity of the tweezers **X** and **XI** might be also beneficial for determination of absolute stereochemistry of δ -chiral carboxylic acids.

Figure V-16: ZnTBP-tz **V** and ZnTBP-propyl-tz (**XI**) – the bulky analog with shorter propane linker.

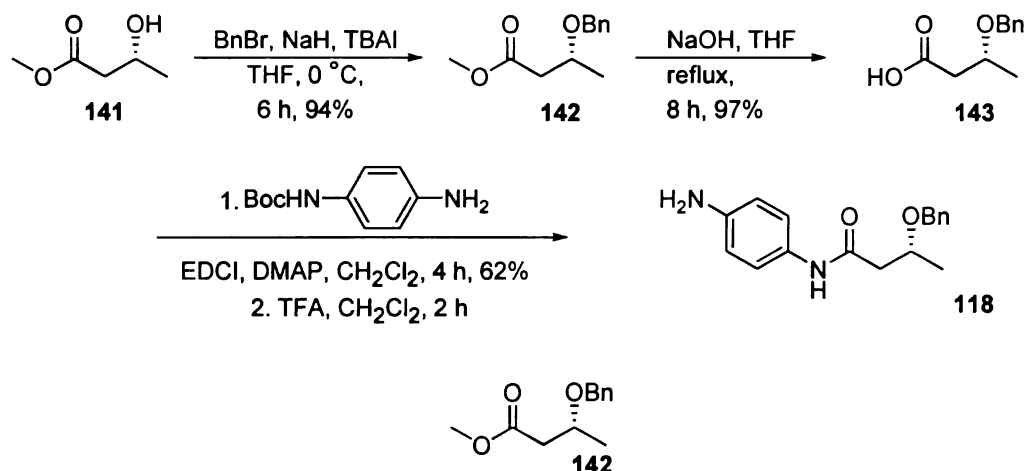
V.5. Experimental procedures.

Anhydrous CH_2Cl_2 was dried over CaH_2 and distilled. The solvents used for CD measurements were purchased from Aldrich and were spectra grade. All reactions were performed in oven or flame dried glassware under nitrogen. Solvents used for synthesis of substrate were dried as follows: THF dried over sodium, dichloromethane dried over CaH . Column chromatography was performed using SiliCycle silica gel (230-400 mesh). ^1H -NMR spectra were obtained on Varian Inova 300 MHz or 500 MHz instrument and are reported in parts per million (ppm) relative to the solvent resonances (δ), with coupling constants (J) in Hertz (Hz). IR studies were performed on a Galaxy series FTIR 3000 instrument (Matteson). CD spectra were recorded on a JASCO J-810 spectropolarimeter, equipped with a temperature controller (Neslab 111) for low temperature studies, and is reported as λ [nm] ($\Delta\epsilon_{\text{max}}$ [$\text{mol}^{-1} \text{cm}^{-1}$]). ZnTBP tweezer V was synthesized as previously described (Chapter III).²³

General procedure for CD measurement:

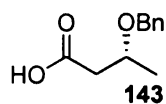
All N-Boc protected substrates were de-protected with 20% TFA in dichloromethane (10 mg in 10 mL) over 2 h at room temperature, concentrated on rotary evaporator, dissolved in dichloromethane and neutralized by Na_2CO_3 . Prepared 1 mM solutions were used for ECCD studies. All the CD spectra were taken with 1 μM solution of porphyrin tweezer in methylcyclohexane (1 mL) with 20 equiv of the carrier/chiral acid conjugate. The CD spectra were measured in millidegrees and normalized to $\Delta\epsilon/\lambda$ [nm] units.

Scheme V-2: Synthesis of N-4-animophenyl-(*R*)-3-benzyloxybutaneamide (**118**)



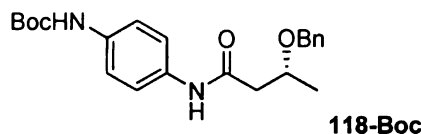
Methyl-(*R*)-3-benzyloxybutanoate (142):²⁴ Into a 100 mL flame dried one necked flask equipped with magnetic stir bar and cooled on ice bath were added dry THF (50 mL) and NaH (110 mg, 4.4 mmol (NaH was previously washed with pentane and dried over nitrogen)), followed by tetrabutylammonium iodide (154 mg, 0.37 mmol) and benzyl bromide (0.66 g, 4.1 mmol). To this mixture a solution of methyl-(*R*)-3-hydroxybutanoate (500 mg, 3.7 mmol) in THF (5 mL) was added in portions. After addition was complete the cooling bath was removed and the mixture was stirred at room temperature overnight (8 h). The reaction was then cooled to $0\text{ }^{\circ}\text{C}$ and quenched with water (10 mL). The mixture was stirred for 5 min and dichloromethane (50 mL) was added. Layers were separated with separatory funnel and the aqueous phase was extracted with dichloromethane (20 mL). Organic extracts were combined, washed with brine (50 mL) and water (50 mL), and dried over anhydrous Na_2SO_4 . The product was concentrated under reduced pressure on a rotary evaporator ($25\text{ }^{\circ}\text{C}$, 200 mmHg). The crude product was purified by column chromatography (Silica gel, 2% EtOAc in hexane, $R_f = 0.32$) to give the compound **142** in 94% (0.79 g) yield. $[\alpha]_{\text{D}}^{20} = -23.4$ (c , 2.06 in

DCM); MS (DCI): calc'd for C₁₂H₁₆O₃ m/z = 208.1, obs'd M⁺ = 208.2; IR (KBr): 3065, 3032, 2858, 1747, 1603, 1496, 1454, 1392, 1365, 1265, 1095, 1070, 1028, 947, 910, 738, 690, 605, 484; ¹H-NMR (CDCl₃, 300 MHz): δ 1.24 (d, 3H, J = 6.0), 2.38-2.67 (d of AB quartets 2H, J₁ = 7.2, J₂ = 66.9, J₃ = 82.2), 3.65 (s, 3H), 3.63-4.04 (m, 1H), 4.46-4.57 (AB quartet, 2H, J = 11.7), 7.22-7.35 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 19.7, 41.7, 51.4, 70.7, 71.7, 127.4, 127.5, 128.2, 138.4, 171.7.



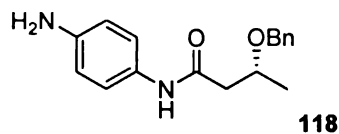
(R)-3-Benzyloxybutanoic acid (143):²⁴ Methyl ester **142** (500 mg, 2.25 mmol) was placed into a one-necked flask equipped with magnetic stir bar and dissolved in THF and aqueous NaOH (2 M) (30 mL of 1:1 mixture by volume). The mixture was heated at reflux in a heating mantle for 8 h and cooled to room temperature. THF was then removed on a rotary evaporator (25 °C, 100 mmHg) and the remaining aqueous phase was extracted once with diethyl ether (10 mL). The aqueous phase was then acidified with 1 N aqueous HCl solution to pH~1 and extracted with dichloromethane (3 x 10 mL). Organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated on rotary evaporator at 25 °C and 200 mmHg. The crude carboxylic acid was obtained in 97% yield (0.42 g) as a colorless liquid. [α]_D²⁰ = -28.5 (c, 3.22 in DCM); MS (DCI): calc'd for C₁₁H₁₄O₃ m/z = 194.0, obs'd M⁺ = 194.4; IR (KBr): 3449-2889 (broad, COOH), 3034, 2978, 2936, 2889, 1713, 1540, 1496, 1456, 1383, 1304, 1192, 1136, 1084, 1028, 941, 740, 698, 611, 461; ¹H-NMR (CDCl₃, 500 MHz): δ 1.31 (d, 3H, J = 7.5), 2.51-2.74 (d of AB quartets, 2H, J₁ = 5.5, J₂ = 15.5, J₃ = 98.5, J₄ = 7.5), 4.01-4.08 (m,

1H), 4.54-4.67 (AB quartet, 2H, $J_1 = 11.5$, $J_2 = 35.0$), 7.28-7.40 (m, 5H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 19.6, 41.6, 70.7, 71.5, 127.5, 127.6, 128.2, 138.1, 177.4;

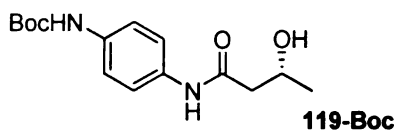


(*R*)-tert-Butyl 4-(3-(benzyloxy)butanamido)phenylcarbamate (118-Boc): (*R*)-3-benzyloxybutanoic acid (**143**) (50 mg, 0.26 mmol) was dissolved in dry dichloromethane (10 mL). To this solution was added mono-Boc protected 1,4-phenylenediamine (100 mg, 0.5 mmol), DMAP (30 mg, 0.26 mmol) and EDCI (55 mg, 0.31 mmol). The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. Purification by column chromatography (Silica gel, 20% EtOAc in hexane) gave the target amide (**118-Boc**) in 62% yield (61 mg) as yellowish solid. HRMS (EI⁺): calc'd for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 385.2127, obs'd 385.2152; IR (KBr): 3268, 2929, 2878, 1697, 1649, 1580, 1530, 1420, 1263, 855, 733, 700, 519; ^1H -NMR (CDCl_3 , 300 MHz): δ 1.18 (d, 3H, $J = 6.2$), 1.48 (s, 9H), 2.23-2.26 (m, 1H), 2.47-2.50 (m, 1H), 3.82-3.86 (m, 1H), 4.63-2.73 (AB quartet, 2H, $J = 11.6$), 7.18 (s, br, 1H (NH)), 7.28 (d, 2H, $J = 6.0$), 7.45-7.52 (m, 7H), 7.62 (s, br, 1H (NH)); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 19.4, 28.9, 44.6, 71.0, 73.0, 80.32, 120.3, 128.0, 128.1, 128.3, 128.5, 133.8, 134.3, 137.7, 152.8, 169.1.

Amide **118-Boc** (10 mg, 0.026mmol) of was then dissolved in 20% TFA/ CH_2Cl_2 solution (10 mL) and stirred at room temperature for 2 h. To this solution was then added anhydrous NaHCO_3 (1g), mixture stirred for 2 min and filtered. Solvent was removed to give the deprotected amine (**118**) as brownish viscous oil.



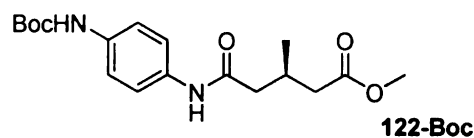
(R)-N-(4-Aminophenyl)-3-(benzyloxy)butanamide (118): IR (KBr): 3331, 3060, 2924, 2860, 1651, 1581, 1518, 1428, 1263, 833, 733, 700, 509; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.19 (d, 3H, $J = 6.6$), 2.25-2.27 (m, 1H), 2.49-2.53 (m, 1H), 3.81-3.86 (m, 1H), 2.73-4.63 (AB quartet, 2H, $J = 11.0$), 6.76 (s, br, 2H (NH)), 6.87 (d, 2H, $J = 6.6$), 7.26-7.46 (m, 7H), 7.62 (s, br, 1H (NH)); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 29.0, 44.8, 71.3, 73.5, 120.5, 128.0, 128.1, 128.3, 128.5, 133.9, 134.2, 138.5, 170.1.



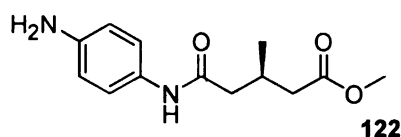
(R)-tert-Butyl 4-(3-hydroxybutanamido)phenylcarbamate (119-Boc): The amide **118-Boc** (10 mg, 0.026mmol) and Pd/C (10 mg) were placed into a round bottom flask and dry dichloromethane (10 mL) was added. The reaction mixture was stirred at room temperature under H_2 atmosphere for 4 h and filtered through a pad of Celite. The filtrate was concentrated to yield pure **119-Boc**. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.14 (d, 3H, $J = 6.3$), 1.40 (s, 9H), 2.32-2.34 (m, 2H), 4.09-4.15 (m, 1H), 7.17 (s, 1H (NH)), 7.21 (d, 2H, $J = 7.2$), 7.32 (d, 2H, $J = 9$); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 22.1, 28.4, 45.7, 64.8, 79.5, 121.6, 121.8, 133.6, 134.1, 152.6, 172.9; HRMS (EI+) $[\text{M}+\text{Na}]^+$: calc'd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{NaO}_4$ 317.1477, obs'd 317.1367.

Substrates **121**, **122** and **128** were synthesized from commercially available enantiomerically pure carboxylic acid through EDCI (1.2 equiv) /DMAP (1 equiv)

coupling with 3 equivalents of carrier in dichloromethane at room temperature for 4 h, and purified by column chromatography with 20% EtOAc/hexane solution.

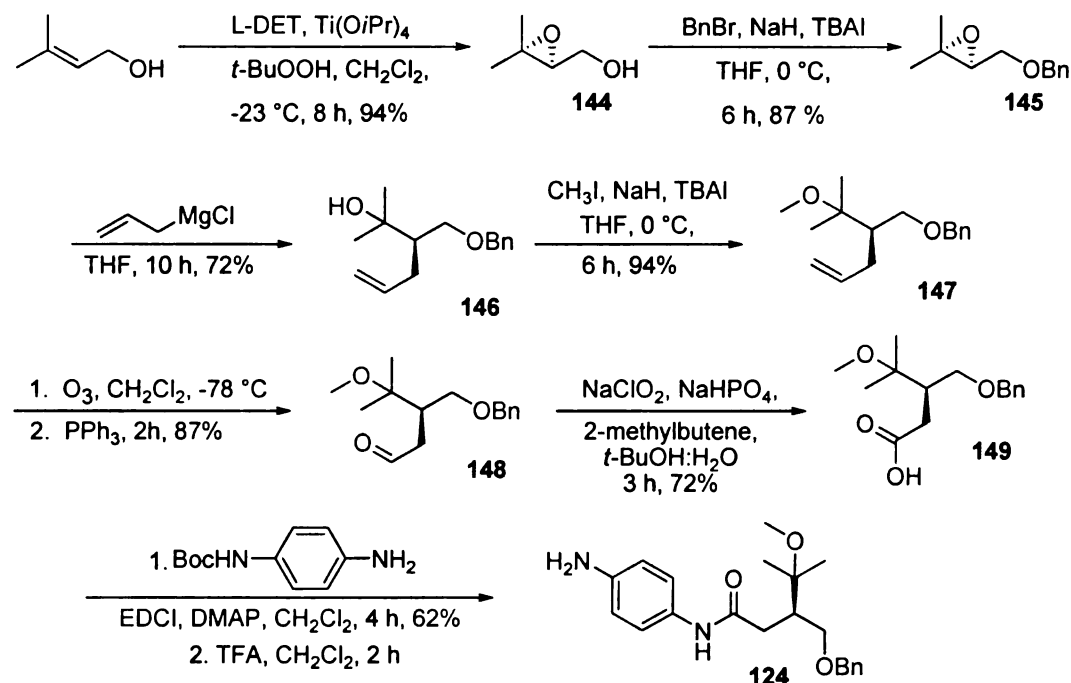


4-(4-*tert*-Butoxycarbonylamino-phenylcarbamoyl)-3-methyl-butyrac acid methyl ester (122-Boc): isolated in 73% yield, HRMS (EI⁺): calc'd for C₁₈H₂₆N₂NaO₅ [M+Na]⁺ 373.1739, obs'd 373.1759; IR (KBr): 3312 (OH), 2972, 2926, 2854, 1726, 1699, 1653, 1611, 1516, 1456, 1406, 1167, 833, 742, 698, 516; ¹H-NMR (CDCl₃, 300 MHz): δ 1.06 (d, 3H, *J* = 6.3), 1.48 (s, 9H), 2.21-2.51 (m, 5H), 3.67 (s, 3H), 6.42 (s, 1H (NH)), 7.25 (d, 2H, *J* = 6.0), 7.42 (d, 2H, *J* = 6.0), 7.54 (s, 1H (NH)); ¹³C-NMR (CDCl₃, 75 MHz): δ 19.4, 28.0, 28.4, 40.0, 43.2, 51.9, 79.5, 121.8, 133.6, 134.1, 137.1, 152.5, 173.0, 173.1.

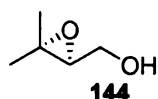


(*R*)-Methyl 5-(4-aminophenylamino)-3-methyl-5-oxopentanoate (122): ¹H-NMR (CDCl₃, 300 MHz): δ 1.06 (d, 3H, *J* = 6.6), 2.25-2.55 (m, 5H), 3.69 (s, 3H), 6.79 (s, 1H (NH)), 6.88 (d, 2H, *J* = 6.8), 7.42 (d, 2H, *J* = 6.8), 7.62 (s, 1H (NH)); ¹³C-NMR (CDCl₃, 75 MHz): δ 19.4, 28.0, 40.3, 43.7, 52.3, 79.5, 116.5, 122.2, 128.6, 144.1, 172.0, 173.1.

Scheme V-3: Synthesis of carrier conjugate **124**

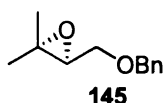


The enantiomeric to **124** compound **123** was synthesized following the Scheme 3 with use of ethyl D-(-)-tartrate forming the enantiomeric to (S)-**144** (R)-2,2-dimethyloxiranylmethanol.



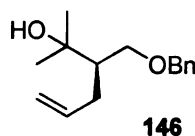
(S)-3,3-Dimethyloxiranylmethanol (**144**):²⁵ Molecular sieves (4 Å, 6 g) were placed into a one-necked 500 mL round bottom flask and heated on heating mantel at 300 °C under reduced pressure for 10 h. The flask was then cooled under nitrogen atmosphere and dry dichloromethane (200 mL) was added, stirred for 5 min and cooled to -23 °C. To the cold solution was added L-(+)-diisopropyl tartrate (3.2 mL, 12.1 mmol) followed by Ti(O^{*i*}Pr)₄ (3.4 mL, 11.8 mmol). The catalyst was allowed to age for 30 min and *t*-BuOOH (24 mL of 6 M solution in toluene) was then added via syringe and the mixture

was allowed to stir for another 30 min. 3-Methyl-2-butene-1-ol (6 ml, 59 mmol) was dissolved in dry dichloromethane (20 mL) and slowly added to the main solution over 1 h. The reaction mixture was stirred at $-23\text{ }^{\circ}\text{C}$ for 7 h, warmed to $-12\text{ }^{\circ}\text{C}$ and quenched with NaOH in brine (40 mL of 40% solution: 16 g NaOH, 40 mL H_2O and 2 g NaCl). The cooling bath was removed and after 20 min MgSO_4 was added and stirring was continued for 10 min. The reaction mixture was allowed to warm to room temperature and filtered through a pad of Celite. The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to give the epoxyalcohol **144** in 94% yield (5 g). $[\alpha]_{\text{D}}^{20} = -17.6$ (c, 2.0 in CHCl_3) [Published value $[\alpha]_{\text{D}}^{20} = -18$ (c, 2.0 in CHCl_3)]²⁵; MS (DCI): calc'd for $\text{C}_5\text{H}_{10}\text{O}_2$ m/z 102.0, obs'd 102.2; ^1H -NMR (CDCl_3 , 300 MHz): δ 1.31 (s, 3H), 1.34 (s, 3H), 2.97 (dd, 1H, $J_1 = 4.2$, $J_2 = 6.4$), 3.68–3.59 (m, 1H), 3.83–3.75 (m, 1H), 3.93 (br, s, 1H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 63.8, 60.9, 58.5, 24.4, 18.4.



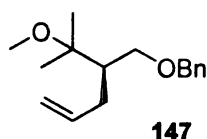
(S)-3-Benzyloxymethyl-2,2-dimethyl-oxirane (145): (racemic substrate available²⁶) Dry THF (100 mL) was added into a 250 mL flame dried one necked flask equipped with magnetic stir bar and cooled on ice bath. NaH (0.11 g, 4.4 mmol, NaH was previously washed with pentane and dried over nitrogen), followed by tetrabutylammonium iodide (0.15 mg, 0.37 mmol) and BnBr (0.66 g, 4.1 mmol) were added in to the flask and stirred for 10 min. To this a solution of epoxyalcohol **144** (0.71 g, 3.7 mmol) in THF (5 mL) was added in portions. After addition was complete the cooling bath was removed and

the mixture was stirred at room temperature overnight (8 h). The reaction was then cooled to 0 °C and quenched with water (10 mL). The mixture was stirred for 5 min and dissolved with dichloromethane (50 mL). The layers were separated with separatory funnel and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, washed with brine (50 mL) and water (50 mL), and dried over anhydrous Na₂SO₄. Mixture was concentrated under reduced pressure on a rotary evaporator (35 °C, 100 mmHg). The crude product was purified by column chromatography (Silica gel, 2% EtOAc in hexane, R_f = 0.32) to give pure **145** in 87% (0.73 g) yield. $[\alpha]_D^{20} = +2.4$ (c, 1.5 in CHCl₃); ¹H-NMR (CDCl₃, 300 MHz): δ 1.30 (s, 3H), 1.37 (s, 3H), 3.04 (t, 1H, *J* = 5.4), 3.57–3.73 (m, 2H), 4.54–4.69 (AB q, 2H, *J*₁ = 12.0, *J*₂ = 32.7), 7.29–7.40 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 18.8, 24.6, 62.0, 68.9, 73.2, 127.7, 127.7, 128.4; HRMS (EI+) [M+H]⁺: calc'd for C₁₂H₁₇O₂ 193.1229, obs'd 193.1246.



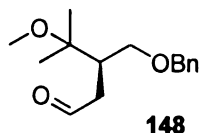
(R)-3-Benzyloxymethyl-2-methyl-hex-5-en-2-ol (146): Epoxide **145** (3 g, 15.6 mmol) was placed into a one-neck round bottom flask (flame dried and cooled under nitrogen) dissolved in dry dichloromethane (100 mL) and cooled with ice bath. To the cold solution was added 2 M solution of allylmagnesium chloride (12 mL, 23.4 mmol) dropwise under nitrogen atmosphere. After addition was completed the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 10 h (overnight). The reaction flask was then cooled on ice bath and quenched with aqueous

saturated solution of NH_4Cl (100 mL). After 10 min of stirring organic layer was separated with separatory funnel and aqueous phase was extracted with EtOAc (25 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. Column chromatography with 5% EtOAc ($R_f = 0.25$) in hexane afforded alcohol **146** in 72% yield (2.6 g). $[\alpha]_D^{20} = -2.9$ (c , 1.78 in CHCl_3); HRMS (EI+): calc'd for $\text{C}_{15}\text{H}_{22}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 257.1517, obs'd 273.1552; IR (KBr): 3433 (OH), 2976, 2930, 2883, 1643, 1456, 1379, 1277, 1113, 1075, 1022, 914, 742, 702; ^1H -NMR (CDCl_3 , 300 MHz): δ 1.62 (s, 3H), 1.23 (s, 3H), 1.66-1.75 (m, 1H), 1.93-2.04 (m, 1H), 2.25-2.32 (m, 1H), 3.52-3.70 (m, 2H), 4.42-4.63 (AB q, 2H, $J_1 = 6.0$, $J_2 = 18.0$), 4.96-5.03 (m, 2H), 5.68-5.81 (m, 1H), 7.23-7.34 (m, 5H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 26.0, 29.0, 31.9, 47.4, 70.6, 72.8, 73.4, 116.6, 127.7, 128.3, 128.4, 137.4.



(R)-[2-(1-Methoxy-1-methylethyl)-pent-4-enyloxymethyl]-benzene (147): Alcohol **146** (2 g, 8.5 mmol) was placed into a 100 mL round bottom flask (flame dried and cooled under nitrogen atmosphere), dissolved in dry THF (60 mL) and cooled on ice bath. To this solution NaH (0.3 g, 12.2 mmol) was added (NaH was previously washed with pentane and dried over nitrogen), followed by iodomethane (2.4 g, 12.7 mmol). After addition was complete the cooling bath was removed and the mixture was stirred at room temperature overnight (8 h). The reaction was then cooled to 0 °C and quenched with water (10 mL). The reaction mixture was stirred for another 5 min and dichloromethane (50 mL) was added. The layers were separated with separatory funnel and aqueous phase

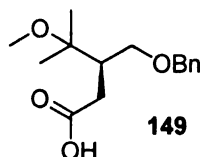
was extracted with dichloromethane (3 x 20 mL). The organic extracts were combined, washed with brine (50 mL) and water (50 mL), and dried over anhydrous Na₂SO₄. The mixture was concentrated under reduced pressure on a rotary evaporator (35 °C, 100 mmHg). The crude product was purified by column chromatography (Silica gel, 2% EtOAc in hexane, R_f = 0.32) to give the title compound **147** in 94% yield (0.79 g). [α]_D²⁰ = +8.6 (c, 1.17 in CHCl₃); HRMS (EI⁺): calc'd for C₁₆H₂₄NaO₂ [M+Na]⁺ 271.1674, obs'd 271.1698; ¹H-NMR (CDCl₃, 300 MHz): δ 1.20 (s, 3H), 1.23 (s, 3H), 1.88-2.09 (m, 1H), 2.11-2.17 (m, 1H), 2.19-2.42 (m, 1H), 3.22 (s, 3H), 3.48-3.62 (d of AB quartet, 2H, $J_1 = 5.1$, $J_2 = 9.9$, $J_3 = 14.7$), 4.50 (s, 2H), 5.00-5.10 (dd, 2H, $J_1 = 11.4$, $J_2 = 17.4$), 5.85-5.99 (m, 1H), 7.29-7.37 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 23.0, 23.3, 31.9, 46.0, 48.6, 69.8, 73.0, 76.5, 115.3, 127.3, 127.4, 128.2, 138.4, 138.7.



(R)-3-Benzyloxymethyl-4-methoxy-4-methyl-pentanal (148): Ozone was generated by a laboratory ozonator using commercial-grade oxygen as a source [Voltage setting (90 V), pressure (5.5-6 lb./in.²) and flow rates (0.3 ft.³/min)].

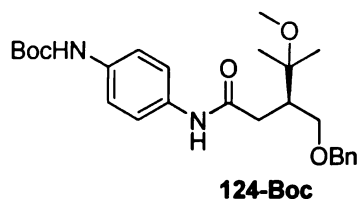
Olefin **147** (2 g, 0.8 mmol) was placed into a 100 mL one-neck round bottom flask and dissolved in dry CH₂Cl₂ (50 mL). The solution was cooled to -78 °C on dry ice-acetone bath and ozone was purged through the solution via glass pipette until the appearance of intense blue color in the reaction solution. The ozone source was then removed and the reaction mixture was flushed with nitrogen until clear colorless solution was observed. To the obtained ozonide at -78 °C was added solution of PPh₃ (2.3 g, 8.8

mmol) in dry CH₂Cl₂ (10 mL) and the mixture was allowed to warm and stirred for 2 h at room temperature. The reaction mixture was concentrated and submitted to the column chromatography (Silica gel, 10% EtOAc in hexanes) to provide the title aldehyde **147** in 94% yield (1.9 g). $[\alpha]_D^{20} = +5.7$ (*c*, 1.0 in CHCl₃); HRMS (EI+): calc'd for C₁₅H₂₂NaO₃ [M+Na]⁺ 273.1467, obs'd 273.1454; IR (KBr): 3037, 2980, 2936, 2878, 2707, 1707, 1605, 1493, 1458, 1369, 1277, 1145, 1072, 1022, 939, 740, 698; ¹H-NMR (CDCl₃, 300 MHz): δ 1.06 (s, 3H), 1.14 (s, 3H), 2.40-2.57 (m, 3H), 3.31 (t, 1H, *J* = 9.0), 3.59-3.63 (m, 1H), 4.44 (s, 2H), 7.24-7.34 (m, 5H), 9.68 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 21.8, 23.2, 42.9, 43.0, 48.5, 70.5, 73.1, 75.3, 127.4, 127.5, 128.3, 138.0, 202.2.



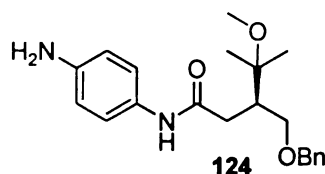
(R)-3-Benzyloxymethyl-4-methoxy-4-methyl-pentanoic acid (149): Aldehyde **148** (0.5 g, 2 mmol) was dissolved in 4:1 mixture of *t*-BuOH in water (3 mL). To this solution 2-methylbutene (0.2 mL) and NaH₂PO₄ (0.48 g, 4 mmol) was added and the mixture cooled on ice bath. NaClO₂ (0.37 g, 4 mmol) was dissolved in 4:1 mixture of *t*-BuOH in water (2 mL) and added to the reaction mixture dropwise. The cooling bath was then removed and the solution was allowed to stir at room temperature for 2 h. The mixture was then extracted with dichloromethane (2 x 20 mL). The aqueous phase was separated, acidified with 10% HCl to pH~1 and extracted with dichloromethane (2 x 20 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give the title carboxylic acid **149** as colorless oil in 72% yield. MS (DCI): *m/z* calc'd for C₁₅H₂₂O₄ *m/z* = 266.1, obs'd 266.2; IR (KBr): 3391 (broad, OH), 3072,

2978, 2830, 1720, 1634, 1599, 1456, 1388, 1277, 1116, 1070, 918, 739, 711; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.08 (s, 3H), 1.15 (s, 3H), 2.25-2.28 (m, 2H), 2.44-2.58 (m, 1H), 3.30 (s, 3H), 3.47-3.52 (m, 2H), 4.46 (s, 2H), 7.24-7.34 (m, 5H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 21.8, 23.2, 29.5, 43.9, 49.0, 68.9, 73.3, 80.1, 127.4, 127.6, 127.8, 137.5, 178.7.



(R)-[4-(3-Benzyloxymethyl-4-methoxy-4-methyl-pentanoylamino)-phenyl]-carbamic acid tert-butyl ester (124-Boc): The carboxylic acid **148** (50 mg, 0.19 mmol) was dissolved in dry dichloromethane (10 mL). To this solution was added mono-Boc protected 1,4-phenylenediamine (62 mg, 0.3 mmol), DMAP (23 mg, 0.19 mmol) and EDCI (44 mg, 0.22 mmol). The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. Purification by column chromatography (Silica gel, 20% EtOAc in hexane) gave the target amide **124-Boc** in 62% yield (60 mg). MS (DCI): calc'd for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_5$ m/z = 456.2, obs'd 456.2; IR (KBr): 3308, 2984, 2936, 2842, 1699, 1670, 1611, 1558, 1522, 1405, 1369, 1316, 1234, 1157, 1051, 833, 733, 704, 521; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.15 (s, 3H), 1.17 (s, 3H), 1.48 (s, 9H), 2.40 (m, 2H), 2.54 (m, 1H), 3.17 (s, 3H), 3.50 (m, 1H), 3.71 (m, 1H), 4.49 (s, 2H), 6.44 (s, 1H (NH)), 7.13-7.30 (m, 9H), 8.07 (s, 1H, (NH)); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 22.9, 23.0, 37.3, 44.0, 48.9, 71.3, 73.6, 75.9, 80.3, 118.9, 119.9, 127.9, 128.0, 128.5, 133.83, 134.0, 137.8, 152.8, 171.4;

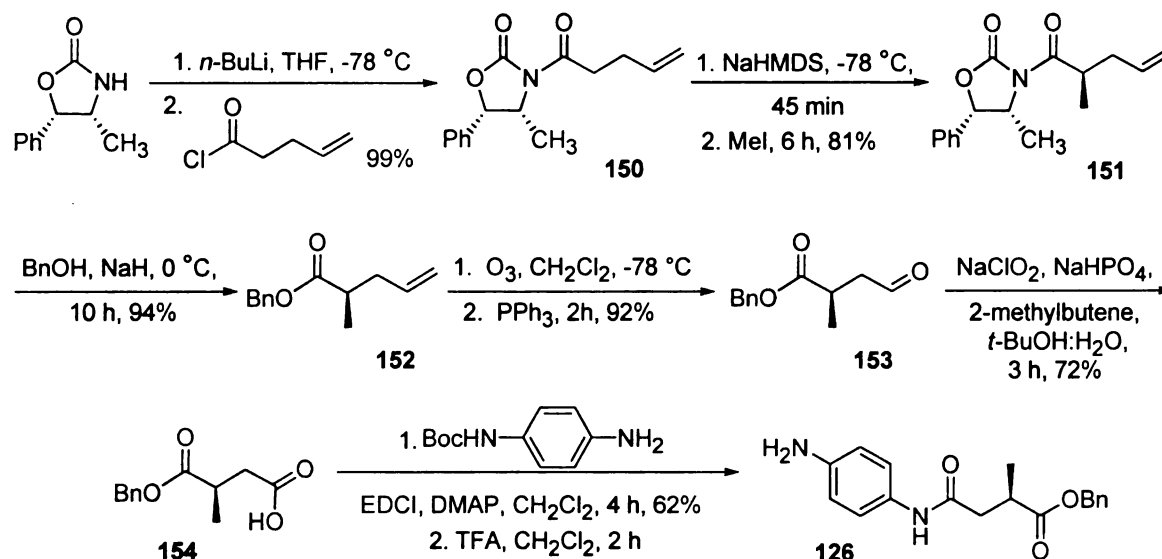
Amide **124-Boc** (10 mg, 0.026mmol) of was then dissolved in 20% TFA/CH₂Cl₂ solution (10 mL) and stirred at room temperature for 2 h. To the reaction mixture was added anhydrous NaHCO₃ (1g) and the solution stirred for 2 min, and filtered. The solvent was removed under reduced pressure to give the deprotected amine **124** as brownish viscous oil.

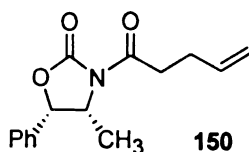


(R)-N-(4-Aminophenyl)-3-(benzyloxymethyl)-4-methoxy-4-methylpentanamide

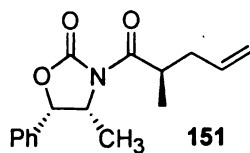
(124): ¹H-NMR (CDCl₃, 300 MHz): δ 1.17 (s, 3H), 1.20 (s, 3H), 2.44 (m, 2H), 2.52 (m, 1H), 3.21 (s, 3H), 3.51 (m, 1H), 3.71 (m, 1H), 4.49 (s, 2H), 6.76 (s, 2H (NH)), 7.13-7.30 (m, 9H), 8.16 (s, 1H, (NH)); ¹³C-NMR (CDCl₃, 75 MHz): δ 25.5, 27.5, 29.2, 44.8, 49.9, 69.3, 80.0, 116.5, 122.7, 127.4, 128.5, 128.0, 128.5, 133.83, 144.0, 171.4.

Scheme V-4: Synthesis of carrier conjugate **126**



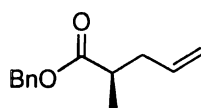


(4R, 5S)-4-Methyl-3-pent-4-enoyl-5-phenyl-oxazolidin-2-one (150):²⁷ The oxazolidine (4 g, 22 mmol) was dissolved in dry THF (0.5 M) and cooled to $-78\text{ }^{\circ}\text{C}$. *n*-BuLi (10 mL, 2.5 M in hexane, 22.5 mmol) was added slowly until a noticeable yellow color (of the dianion) persisted. 4-Pentenoyl chloride (2.9 g, 24 mmol) was added immediately in one portion and the solution was removed from ice bath, slowly warmed to room temperature (over 1 h period) and stirred for 2 h at room temperature. The reaction was quenched with 1 M K_2CO_3 (100 mL) and stirred for another 30 min. The two layers were separated and the aqueous phase was extracted with Et_2O ($3 \times 100\text{ mL}$). The organic extracts were layers were combined, dried with over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to the crude oil, which was purified by column chromatography (Silica gel, 5% EtOAc in hexanes) to provide pure products **150** in 99% yield (5.8 g). ^1H -NMR (CDCl_3 , 300 MHz): δ 0.87 (d, 3H, $J = 6.6$), 2.35-2.46 (m, 2H), 2.93-3.14 (m, 2H), 4.74 (p, 1H, $J = 6.9$), 4.97-5.11 (dd, 2H, $J_1 = 10.2$, $J_2 = 18.9$), 5.64 (d, 1H, $J = 7.2$), 5.78-5.89 (m, 1H), 7.26-7.42 (m, 5H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.5, 28.2, 34.9, 54.7, 78.0, 115.7, 125.6, 128.7, 133.3, 136.6, 153.0, 172.3, 186.6; MS (DCI): m/z 259.2.



(2R, 4R, 5S)-4-Methyl-3-(2-methyl-pent-4-enoyl)-5-phenyl-oxazolidin-2-one (151):²⁷ NaHMDS (21 mL, 21 mmol, 1 M in THF) was placed in a round bottom flask and cooled to $-78\text{ }^{\circ}\text{C}$. The auxiliary conjugate **150** (5 g, 19.3 mmol) was dissolved in a separate

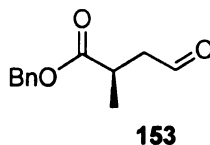
flask in THF (100 mL), cooled to -78 °C and added via cannula to the base over 40 min. The solution was stirred for 1 h at -78 °C and then iodomethane (2.8 g, 23 mmol) was added dropwise over 1 h. The reaction mixture was stirred at -78 °C for 10 h, quenched with 10% HCl and further diluted with diethyl ether (100 mL). The organic layer was separated, dried over anhydrous Na₂SO₄, concentrated to a crude oil, which was then submitted to the column purification (Silica, 5% EtOAc in hexane, R_f = 0.25) to provide pure products **151** in 81% yield (4.37 g). $[\alpha]_D^{20} = -45.3$ (c, 2.5 in DCM), [literature value for the enantiomer $[\alpha]_D^{20} = +47$ (2.8 in DCM)²⁸]; IR (KBr): 3084, 2982, 2936, 2883, 1782, 1701, 1640, 1499, 1458, 1344, 1246, 1196, 1120, 1028, 962, 918, 765, 698, 633, 503; ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (d, 3H, *J* = 6.6), 1.16 (d, 3H, *J* = 6.9), 2.14 - 2.23 (m, 1H), 2.41 - 2.251 (m, 1H), 3.68-3.72 (m, 1H), 4.61 - 4.8 (m, 1H), 4.79 - 5.06 (dd, 2H, *J*₁ = 9.0, *J*₂ = 12.0), 5.63 (d, 2H, *J* = 6.6), 5.07-5.86 (m, 1H), 7.26-7.42 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.3, 1.2, 36.8, 37.6, 54.5, 78.4, 116.8, 125.3, 128.5, 128.4, 133.0, 134.9, 152.4, 175.9; MS (DCI): *m/z* 273.2.



152

Benzyl (*R*)-2-methyl-4-pentenoate (152):²⁹ To the solution of benzyl alcohol (0.73 g, 6.7 mmol) in dry THF (100 mL) was added NaH (0.18 g, 7.5 mmol, washed with pentane). The mixture was stirred at room temperature for 30 min and cooled on an ice bath. The solution of **151** in dry THF (15 mL) was then added dropwise and the mixture was stirred at room temperature for 5 h. After cooling of the solution on ice bath, the reaction was quenched with water and diluted with EtOAc. The organic phase was

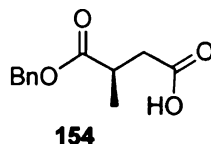
separated, washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The reaction mixture was purified by column chromatography (Silica gel, 2% EtOAc in hexane, $R_f = 0.23$) and the title product was separated in 94% yield (1.3 g) as colorless liquid. $[\alpha]_D^{20} = -2.4$ (c, 2.1 in CHCl_3); [literature value for the enantiomer $[\alpha]_D^{20} = -2.5$ (c, 4.3 in CHCl_3)]²⁹; HRMS (EI+) $[\text{M}+\text{H}]^+$: calc'd for 205.1229, obs'd 205.1227; IR (KBr): 2980, 2939, 1736, 1645, 1498, 1456, 1383, 1352, 1176, 995, 918, 750, 698; ^1H NMR (CDCl_3 , 300 MHz): δ 1.17 (d, 3H, $J = 2.4$), 2.17-2.24 (m, 1H), 2.39-2.48 (m, 1H), 2.54-2.61 (m, 1H), 4.98-5.07 (m, 2H), 5.11 (s, 2H), 5.66-5.78 (m, 1H), 7.30-7.36 (m, 5H); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 16.4, 22.6, 37.7, 39.2, 66.0, 76.5, 103.9, 116.9, 128.0, 128.1, 128.4, 135.3, 136.1, 175.8.



Benzyl (*R*)-2-methyl-4-oxo-butanoate (153):³⁰ Ozone was generated by a laboratory ozonator using commercial-grade oxygen as a source [Voltage setting (90 V), pressure (5.5-6 lb./in.²) and flow rates (0.3 ft.³/min)].

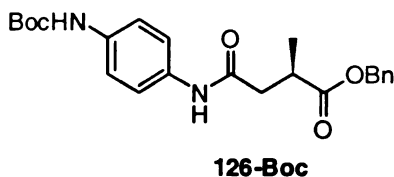
Olefin **152** (2 g, 9.7 mmol) was placed in a 100 mL one-neck round bottom flask and dissolved in dry CH_2Cl_2 (50 mL). The solution was cooled to $-78\text{ }^\circ\text{C}$ on dry ice-acetone bath and ozone was purged through the solution via glass pipette until the appearance of intense blue color in the reaction solution. The reaction mixture was flushed with nitrogen for 10-15 min at $-78\text{ }^\circ\text{C}$ and a dichloromethane solution of PPh_3 (2.62 g, 10.6 mmol in 10 mL of DCM) was added and the mixture was allowed to warm and stirred for 2 h at room temperature. The reaction mixture was concentrated and

submitted to the column chromatography (Silica gel, 10% EtOAc in hexane) to provide the compound **153** in 92% yield. $[\alpha]_D^{20} = +0.62$ (c, 1.0, CHCl₃), [literature value for the enantiomer $[\alpha]_D^{20} = +0.7$ (c, 1.0, CHCl₃), 95% ee]³⁰; HRMS (EI): calc'd for C₁₂H₁₄O₃Na $[M+Na]^+$ 229.0841, obs'd 229.0845; ¹H-NMR (CDCl₃, 300 MHz): δ 9.83 (t, $J = 1.5$, 1H), 8.02 (d, $J = 7.0$, 2H), 7.57 (d, $J = 7.4$, 1H), 7.45 (t, $J = 8.0$, 2H), 4.29 (q, $J = 5.4$, 1H), 4.17 (q, $J = 6.7$, 1H), 2.65–2.61 (m, 2H), 2.43–2.41 (m, 1H), 1.11 (d, 3H, $J = 6.8$); ¹³C NMR (CDCl₃, 125 MHz) δ 17.1, 28.0, 47.9, 68.8, 128.4, 129.6, 130.0, 133.1, 166.4, 201.2.



Benzyl (*R*)-2-methyl-succinoate (154):³¹ Aldehyde **153** (0.5 g, 2.8 mmol) was dissolved in mixture of *t*-BuOH in water (3 mL of 4:1 mixture v/v). To this solution 2-methylbutene (0.2 mL) and NaH₂PO₄ (0.67 g, 5.6 mmol) was added and the mixture was cooled on an ice bath. NaClO₂ (0.50 g, 5.6 mmol) was dissolved in *t*-BuOH in water (2 mL of 4:1 mixture v/v) and added to the reaction mixture dropwise. Cooling bath was then removed and the solution was allowed to stir at room temperature for 2 h. The mixture was then extracted with dichloromethane. The aqueous phase was separated, acidified with 10% HCl to pH~1 and extracted with dichloromethane (2 x 20 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give the title carboxylic acid in 72% yield. IR (KBr): 3331-2883 (broad, OH), 2980, 2948, 2883, 1735, 1711, 1505, 1458, 1405, 1281, 1222, 1170, 1045, 969, 945, 914, 750, 698, 592; ¹H-NMR (CDCl₃, 500 MHz): δ 1.25 (d, 3H, $J = 6.6$), 2.43-

2.48 (dd, 1H, $J_1 = 6.0$, $J_2 = 11.0$), 2.77-2.82 (dd, 1H, $J_1 = 12.0$, $J_2 = 15.0$), 2.92-2.96 (m, 1H), 5.12 (2H), 7.2-7.35 (m, 5H); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 16.9, 35.6, 37.2, 66.6, 138.0, 128.2, 128.5, 135.8, 174.9, 177.5; HRMS (EI-): calc'd for $\text{C}_{12}\text{H}_{13}\text{O}_3\text{Na}$ $[\text{M}-\text{H}]^-$ 221.0814, obs'd 221.0782.

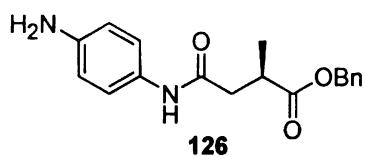


(R)-N-(4-*tert*-Butoxycarbonylamino-phenyl)-2-methyl-succinamic acid benzyl ester

(126-Boc): The amide **126-Boc** was obtained by ECD/DMAP coupling described above.

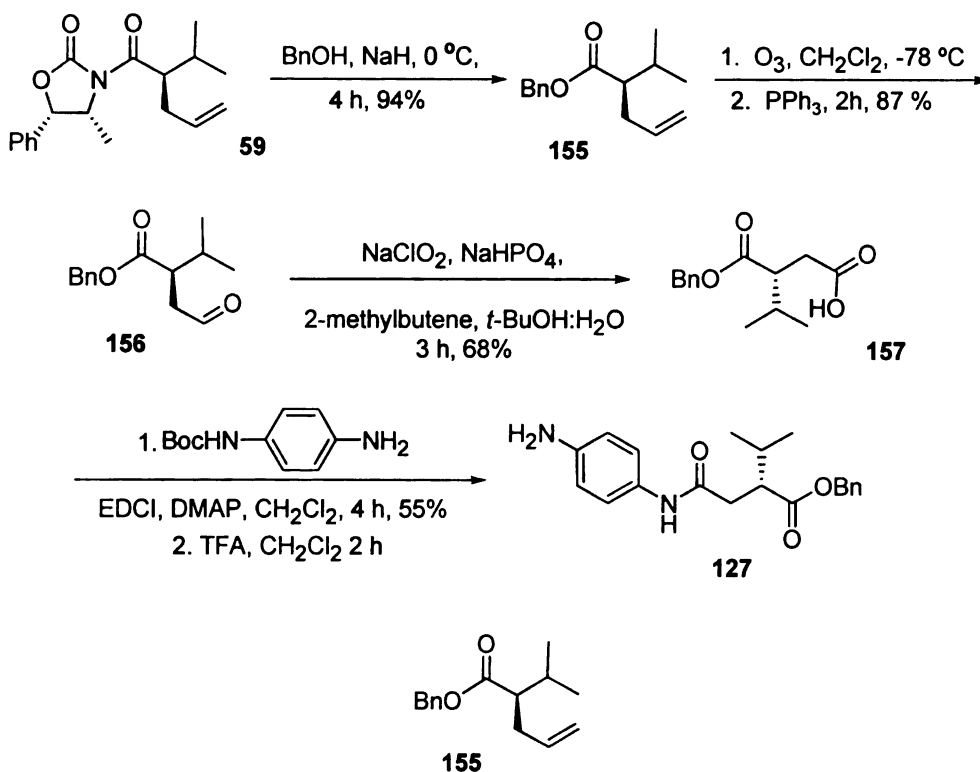
The crude product was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to give the title amide in 62% yield. HRMS (EI+): calc'd for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 413.2076, obs'd 413.2068; IR (KBr): 3343, 2984, 2930, 2848, 1723, 1693, 1664, 1605, 1546, 1517, 1399, 1363, 1305, 1234, 1157, 1051, 833, 692, 509; ^1H -NMR (CDCl_3 , 500 MHz): δ 1.20 (d, 3H, $J = 6.6$), 1.48 (s, 9H), 2.38-2.41 (dd, 1H, $J_1 = 6.0$, $J_2 = 11.0$), 2.74-2.79 (dd, 1H, $J_1 = 12.0$, $J_2 = 15.0$), 2.81-2.87 (m, 1H), 5.08 (2H), 7.21-7.35 (m, 7H), 7.42 (d, 2H, $J = 6.0$), 7.54 (s, 1H (NH)); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 17.2, 28.4, 36.2, 41.9, 66.7, 79.5, 121.8, 121.9, 127.1, 127.6, 128.9, 133.6, 134.1, 136.1, 152.0, 170.7, 173.0.

Amide **126-Boc** (10 mg) of was then dissolved in 20% TFA/ CH_2Cl_2 solution (10 mL) and stirred at room temperature for 2 h. To the reaction mixture was added anhydrous NaHCO_3 (1g) and the solution stirred for 2 min, and filtered. The solvent was removed under reduced pressure to give the deprotected amine **126** as yellow viscous oil.



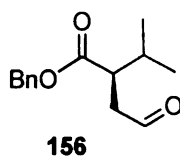
(R)-Benzyl 4-(4-aminophenylamino)-2-methyl-4-oxobutanoate (126): $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 1.22 (d, 3H, $J = 6.6$), 2.41-2.45 (dd, 1H, $J_1 = 6.2$, $J_2 = 11.4$), 2.72-2.78 (dd, 1H, $J_1 = 12.0$, $J_2 = 15.0$), 2.85-2.90 (m, 1H), 5.10 (s, 2H), 6.68 (s, 2H (NH)), 7.24-7.39 (m, 7H), 7.44 (d, 2H, $J = 6.8$), 7.66 (s, 1H (NH)); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 17.1, 36.5, 50.1, 66.7, 116.5, 122.4, 127.1, 127.8, 128.5, 129.0, 136.1, 144.0, 171.0, 173.2.

Scheme V-5: Synthesis of carrier conjugate 127



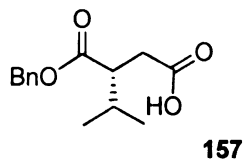
(R)-Benzyl 2-isopropylpent-4-enoate (155):³² To the solution of benzyl alcohol (1.1 g, 9.2 mmol) in dry THF (100 mL) was added NaH (0.24 g, 10 mmol, washed with

pentane). The mixture was stirred at room temperature for 30 min and cooled on an ice bath. The solution of **155** (2.5 g, 8 mmol) in dry THF (20 mL) was then added dropwise and the mixture was stirred at room temperature for 5 h. After cooling of the solution on ice bath, the reaction was quenched with water and diluted with EtOAc. The organic phase was separated, washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The reaction mixture was purified by column chromatography (Silica gel, 2% EtOAc in hexane, R_f = 0.25) in and the title product was separated in 94% yield (1.9 g) as colorless liquid. $[\alpha]_D^{20} = -8.6$ (c, 2.1 in DCM); IR (KBr): 3037, 2966, 2883, 1736, 1646, 1499, 1458, 1387, 1263, 1170, 1134, 1122, 983, 916, 750, 698; ¹H-NMR (CDCl₃, 300 MHz): δ 0.90 (d, 3H, *J* = 6.6), 0.93 (d, 3H, *J* = 6.6), 1.87 (m, 1H, *J* = 6.6), 2.24-2.38 (m, 3H), 4.94-5.10 (d, 2H, *J*₁ = 17.2, *J*₂ = 20.7), 5.01-5.79 (m, 1H), 7.28-7.35 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 20.1, 20.3, 30.2, 33.9, 52.4, 65.8, 116.4, 128.0, 128.2, 128.4, 135.8, 136.1, 174.7; MS (DCI): calc'd for C₁₅H₂₀O₂ *m/z* 232.1, obs'd 232.2.

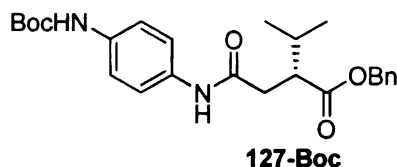


(R)-benzyl 2-isopropyl-4-oxobutanoate (156): Ozonolysis was carried out according to the procedure described above. The aldehyde **156** was obtained in 87% yield. MS (DCI): calc'd for C₁₄H₁₈O₃ *m/z* 234.1, obs'd 234.2; IR (KBr): 3031, 2972, 2883, 2754, 1735, 1717, 1505, 1458, 1387, 1264, 1222, 1169, 988, 951, 733, 698; ¹H-NMR (CDCl₃, 500 MHz): δ 1.08 (d, 3H, *J* = 6.9), 1.54 (d, 3H, *J* = 6.6), 2.36-2.58 (complex multiplet, 2H),

2.63-2.68 (m, 2H), 4.43-4.47 (m, 2H), 7.25-7.33 (m, 5H), 9.68 (s, 1H); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 22.4, 23.2, 33.3, 43.1, 70.4, 127.3, 127.4, 128.3, 138.8, 179.1, 202.4.

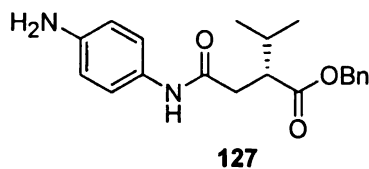


(R)-3-(Benzyloxycarbonyl)-4-methylpentanoic acid (157): Aldehyde **156** (1 g, 4.2 mmol) was dissolved in mixture of *t*-BuOH in water (5 mL of 4:1 mixture v/v). To this solution 2-methylbutene (0.2 mL) and NaH_2PO_4 (1 g, 8.4 mmol) was added and the mixture was cooled on an ice bath. NaClO_2 (0.75 g, 5.6 mmol) was dissolved in *t*-BuOH in water (5 mL of 4:1 mixture v/v) and added to the reaction mixture dropwise. Cooling bath was then removed and the solution was allowed to stir at room temperature for 2 h. The mixture was then extracted with dichloromethane. The aqueous phase was separated, acidified with 10% HCl to pH~1 and extracted with dichloromethane (2 x 30 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to give the title carboxylic acid in 68% yield (0.72 g). $[\alpha]_{\text{D}}^{20} = -8.0$ (c, 0.78 in DCM); IR (KBr): 3355-2878 (broad, OH), 3066, 2966, 2878, 1734, 1705, 1587, 1496, 1440, 1387, 1263, 1163, 1122, 992, 745, 721, 696, 542; ^1H -NMR (CDCl_3 , 500 MHz): δ 0.89 (d, 3H, $J = 7.0$), 0.91 (d, 3H, $J = 7.0$), 2.00-2.03 (m, 1H), 2.42-2.48 (m, 1H), 2.75-2.82 (m, 2H), 5.12 (AB q, 2H, $J_1 = 12.0$, $J_2 = 3.5$), 7.28-7.34 (m, 5H), 8.68 (s, br, 1H); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 19.4, 20.0, 30.0, 32.7, 47.2, 66.3, 128.1, 128.4, 132.1, 135.9, 174.1, 177.7; MS (DCI): calc'd for $\text{C}_{14}\text{H}_{18}\text{O}_4$ m/z 250.1, obs'd 250.3.



(R)-Benzyl 4-(4-(*tert*-butoxycarbonylamino)phenylamino)-2-isopropyl-4-oxobutanoate (127-Boc): The amide **127-Boc** was obtained by ECD/DMAP coupling described above. The crude product was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to give the title amide in 55% yield. IR (KBr): 3361, 2966, 2925, 2860, 1699, 1952, 1629, 1517, 1393, 1257, 1198, 1163, 1104, 1016, 804, 668, 515; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 1.23-1.26 (m, 6H), 1.48 (s, 9H), 2.39-2.43 (dd, 1H, $J_1 = 5.0$, $J_2 = 15.0$), 2.68-27.3 (dd, 1H, $J_1 = 7.8$, $J_2 = 15.0$), 3.09 (m; 1H, $J = 6.0$), 5.12 (AB q, 2H, $J = 12.5$), 6.45 (s, 1H, (NH)), 6.61 (d, 2H, $J = 9.0$), 7.23-7.35 (m, 7H), 7.46 (s, 1H (NH)); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 17.3, 28.4, 29.7, 36.4, 40.6, 66.6, 115.7, 119.1, 120.7, 127.0, 128.0, 128.2, 128.5, 133.1, 134.6, 135.8, 152.8, 169.0, 175.8; MS (DCI): m/z 440.3.

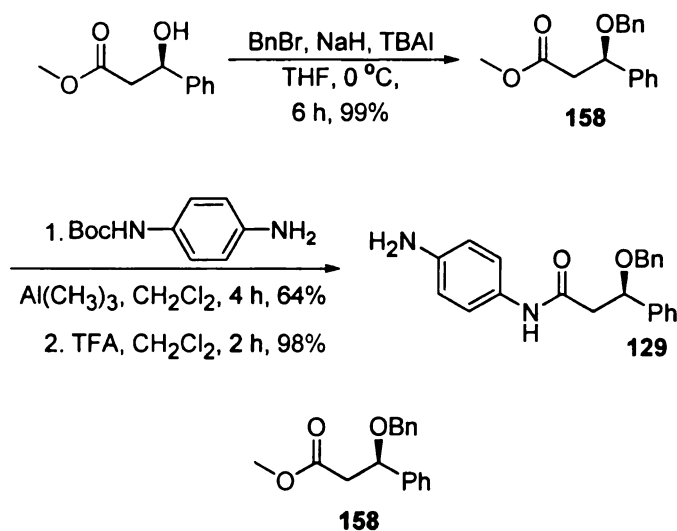
Amide **127-Boc** (5 mg) of was then dissolved in 20% TFA/ CH_2Cl_2 solution (10 mL) and stirred at room temperature for 2 h. To the reaction mixture was added anhydrous NaHCO_3 (1 g) and the solution stirred for 2 min, and filtered. The solvent was removed under reduced pressure to give the deprotected amine **124** as brownish viscous oil.



(R)-Benzyl 4-(4-aminophenylamino)-2-isopropyl-4-oxobutanoate (127): $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 1.25-1.29 (m, 6H), 2.44-2.49 (dd, 1H, $J_1 = 5.2$, $J_2 = 15.2$), 2.70-

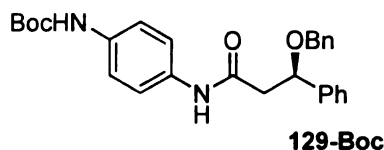
27.5 (dd, 1H, $J_1 = 7.6$, $J_2 = 15.0$), 3.09 (m, 1H, $J = 6.0$), 3.65 (s, 2H (NH₂), 5.20 (AB q, 2H, $J = 12.0$), 6.68 (d, 2H, $J = 8.6$), 7.23-7.35 (m, 7H), 7.55 (s, 1H (NH)); ¹³C-NMR (CDCl₃, 125 MHz): δ 16.9, 29.0, 35.5, 40.2, 66.5, 112.6, 120.1, 120.8, 127.2, 128.6, 128.6, 128.5, 133.7, 134.6, 144.8, 169.2, 175.2.

Scheme V-6: Synthesis of carrier conjugate 129



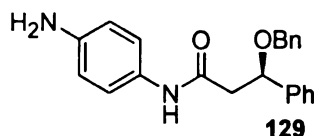
Methyl-(R)-3-benzyloxy-3-phenylpropanoate (158):²⁴ Dry THF (50 mL) was added into a 100 mL flame dried one necked flask equipped with a magnetic stir bar, cooled on an ice bath and NaH (110 mg, 4.4 mmol) [NaH was previously washed with pentane and dried under nitrogen], followed by tetrabutylammonium iodide (154 mg, 0.37 mmol) and BnBr (0.66 g, 4.1 mmol). To this a solution of methyl-(R)-3-hydroxybutanoate (660 mg, 3.7 mmol) in THF (5 mL) was added in portions. After addition was complete the cooling bath was removed and the mixture was stirred at room temperature overnight (8 h). The reaction was then cooled to 0 °C and quenched with water (10 mL). The mixture was stirred for 5 min and dichloromethane (50 mL) was added. The layers were

separated with separatory funnel and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The organic extracts were combined, washed with brine (50 mL) and water (50 mL), and dried over anhydrous Na₂SO₄. The mixture was concentrated under reduced pressure on a rotary evaporator (25 °C, 200 mmHg). The crude product was purified by column chromatography (Silica gel, 2% EtOAc in hexane, R_f = 0.3) to give pure **158** in 99% (0.98 g) yield. MS (DCI): *m/z* 270.2; IR (KBr): 2972, 2883, 1729, 1517, 1405, 1316, 1228, 833; ¹H-NMR (CDCl₃, 500 MHz): δ 2.59-2.63 (dd, 1H, *J*₁ = 5.0, *J*₂ = 15.0), 2.85-2.90 (dd, 1H, *J*₁ = 6.0, *J*₂ = 15.5), 3.65 (s, 3H), 4.28-4.30 (d, 1H, *J* = 11.5), 4.43-4.45 (d, 1H, *J* = 11.5), 4.83-4.85 (dd, 1H, *J*₁ = 5.0, *J*₂ = 9.0), 7.25-7.28-7.39 (m, 5 H); ¹³C-NMR (CDCl₃, 125 MHz): δ 43.4, 51.6, 70.7, 77.8, 127.6, 127.8, 128.1, 128.4, 128.6, 130.1, 138.0, 140.6, 171.3.



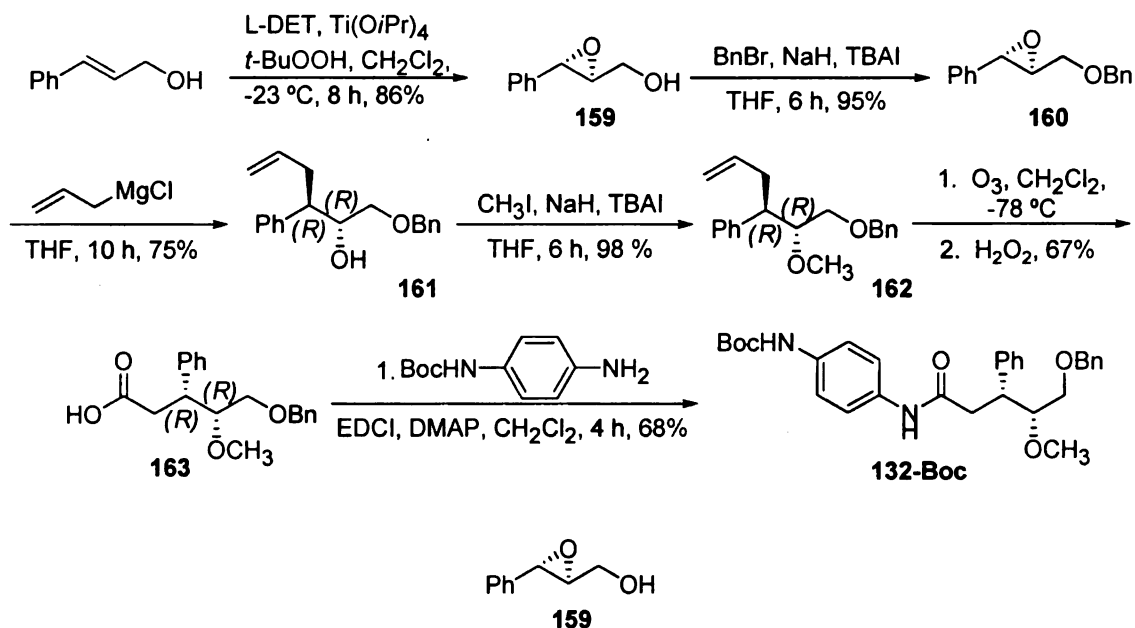
(*R*)-N-(4-Aminophenyl)-3-(benzyloxy)-3-phenylpropanamide (129-Boc): Mono-Boc protected 1,4-phenylenediamine (100 mg, 0.5 mmol) was dissolved in dry dichloromethane (15 mL) and trimethylaluminum solution (0.3 mL, 2M in THF) was added and mixture stirred at room temperature for 20 min. To this solution a dichloromethane solution of methyl-(*R*)-3-benzyloxy-3-phenylpropanoate **158** (115 mg, 0.26 mmol) was added. The mixture was stirred at room temperature overnight and quenched with water (5 mL) and glycerol (1 mL). After 4 h of stirring the organic layer was separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). Combined organic extracts were concentrated under reduced pressure. Purification by

column chromatography (Silica gel, 20% EtOAc in hexane) gave the target amide **129-Boc** in 64% (115 mg) yield. MS (DCI): calc'd for $C_{29}H_{30}N_2O_4$ m/z = 446.2, obs'd $[M+H]^+$ 447.4; IR (KBr): 1730, 1676, 1657, 1612, 1519, 1405, 1220; 1H -NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 9H), 2.56-2.59 (dd, 1H, J_1 = 6.0, J_2 = 14.0), 2.82-2.84 ((dd, 1H, J_1 = 6.0, J_2 = 16.0), 4.31-4.31 (d, 1H, J = 11.5), 4.42-4.44 (d, 1H, J = 10.5), 4.80-4.82 (m, 1H), 7.25-7.37 (m, 9 H); 7.44 (s, 1H (NH)); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 28.4, 46.0, 71.2, 80.1, 84.0, 120.9, 121.8, 127.4, 127.6, 127.8, 127.9, 128.1, 128.6, 128.8, 133.1, 133.5, 134.1, 134.6, 135.8, 142.2, 147.0, 152.6, 169.8.



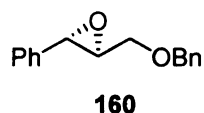
Amide **129-Boc** (10 mg, 0.026mmol) of was then dissolved in a 20% TFA/ CH_2Cl_2 solution (10 mL) and stirred at room temperature for 2 h. To this solution was added anhydrous $NaHCO_3$ and the reaction mixture stirred for 2 min and filtered. Solvent was removed under reduced pressure to give the deprotected amine **129** as brownish viscous oil. 1H -NMR ($CDCl_3$, 300 MHz): δ 2.53-2.57 (dd, 1H, J_1 = 6.2, J_2 = 14.4), 2.85-2.89 ((dd, 1H, J_1 = 6.6, J_2 = 16.0), 3.63 (s, 2H (NH_2)), 4.35 (d, 1H, J = 11.0), 4.43 (d, 1H, J = 10.6), 4.76-4.80 (m, 1H), 6.68 (d, 2H, J = 8.67), 7.25-7.44 (m, 7 H); ^{13}C -NMR ($CDCl_3$, 75 MHz): δ 46.2, 71.6, 84.5, 127.8, 128.2, 128.9, 129.1, 129.6, 130.5, 131.1, 133.8, 134.4, 134.7, 135.3, 135.9, 144.6, 147.8, 172.8.

Scheme V-7: Synthesis of carrier conjugate 132



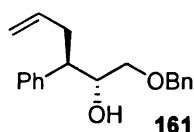
(2R, 3S)-(3-Phenyl-oxiranyl)-methanol (159):^{33, 34} Molecular sieves (4 Å, 6 g) were placed into a one-necked 500 mL round bottom flask and heated on heating mantle at 300 °C under reduced pressure for 10 h. The flask was then cooled under nitrogen atmosphere and dry dichloromethane (200 mL) was added, stirred for 5 min and cooled to $-23\text{ }^\circ\text{C}$. To the cold solution was added L-(+)-diisopropyl tartrate (1.5 mL, 5.6 mmol) followed by $\text{Ti}(\text{O}^i\text{Pr})_4$ (1.5 mL, 5.2 mmol). The catalyst was allowed to age for 30 min and 3.3 M $t\text{-BuOOH}$ solution in toluene (42 mL) was then added via syringe and the mixture was allowed to stir for another 30 min. Cinnamyl alcohol (3.9 g, 29.1 mmol) was dissolved in dry dichloromethane (20 mL) and slowly added to the main solution over 1 h. The reaction mixture was stirred at $-23\text{ }^\circ\text{C}$ for 8 h, warmed to $-12\text{ }^\circ\text{C}$ and quenched with 40% solution of NaOH in brine (40 mL, 16 g NaOH, 40 mL H_2O and 2 g NaCl). The cooling bath was removed and after 20 min MgSO_4 was added and stirring was continued for 10 min. The reaction mixture was allowed to warm to room temperature

and filtered through a pad of celite. The filtrate was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to yield the epoxyalcohol **159** in 86% yield (3.7 g). $[\alpha]_D^{20} = -48$ (c, 1.0 in CHCl₃) [literature value, $[\alpha]_D^{20} = -49$ (c, 0.01 in CH₂Cl₂)]³⁴; m.p. = 40-43 °C (white soft crystals); ¹H-NMR (CDCl₃, 300 MHz): δ 2.17 (dd, 1H, $J_1 = 5.0$, $J_2 = 6.0$), 3.26-3.28 (m, 1H), 3.79-3.88 (ddd, 1H, $J_1 = 4.0$, $J_2 = 8.0$, $J_3 = 12.0$), 3.97 (d, 1H, $J = 2.1$), 4.05-4.12 (ddd, $J_1 = 2.1$, $J_2 = 5.0$, $J_3 = 13.0$), 7.26-7.42 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 55.6, 61.2, 62.5, 125.6, 128.2, 128.3, 136.6; MS (DCI): m/z 150.1.



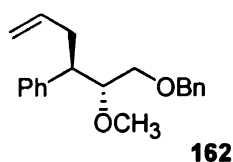
((2S, 3S)-3-Phenyloxiran-2-yl)methanol (161):³⁵ To dry THF (100 mL) in a 250 mL flame dried one necked flask equipped with magnetic stir bar and cooled on ice bath was added NaH (0.48 g, 20 mmol, prior to use, NaH was washed with pentane and dried over nitrogen)), followed by tetrabutylammonium iodide (0.5 g, 1.33 mmol) and BnBr (2.4 g, 14 mmol). To this a solution of epoxyalcohol **150** (2 g, 13.3 mmol) in THF (10 mL) was added dropwise. After addition was completed, the cooling bath was removed and the mixture was stirred at room for 6 h. The reaction was then cooled to 0 °C and quenched with water (10 mL). The mixture was stirred for 5 min and dichloromethane (50 mL) was added. The layers were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The organic extracts were combined, washed with brine (50 mL) and water (50 mL), and dried over anhydrous Na₂SO₄. The mixture was concentrated under reduced pressure on a rotary evaporator (25 °C, 200 mmHg). The

crude product was purified by column chromatography (Silica Gel, 2% EtOAc in hexane, $R_f = 0.35$) to give pure **160** in 95% yield (3 g). $[\alpha]_D^{20} = -38.1$ (c, 1.84, CHCl_3) [literature value $[\alpha]_D^{20} = -38.9$ (c, 0.82 in CHCl_3)]³⁶; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 3.24-3.27 (m, 1H), 3.61-3.66 (dd, 1H, $J_1 = 5.1$, $J_2 = 11.4$), 3.80-3.89 (ddd, 1H, $J_1 = 2.1$, $J_2 = 3.3$, $J_3 = 13.8$), 4.64 (d, 2H, $J = 2.7$), 7.26-7.38 (m, 10 H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 55.8, 61.1, 69.8, 73.3, 125.6, 127.7, 127.8, 128.1, 128.3, 128.4, 136.8, 137.8; HRMS (EI+): calc'd for $\text{C}_{16}\text{H}_{16}\text{NaO}_2$ ($\text{M}+\text{Na}$)⁺ 263.1048; obs'd 263.1048.



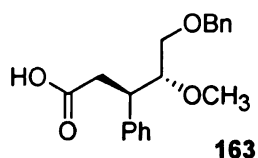
(2R, 3R)-1-(Benzyloxy)-3-phenylhex-5-en-2-ol (161):³⁶ Epoxide **160** (3 g, 15.6 mmol) was placed in a one-neck round bottom flask (flame dried and cooled under nitrogen), dissolved in dry dichloromethane (100 mL) and cooled on an ice bath. To the cold solution was added 2 M solution of allylmagnesium chloride (12 mL, 23.4 mmol) dropwise under nitrogen atmosphere. After the addition was completed, the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 10 h. The reaction flask was then cooled on ice bath and quenched with aqueous saturated solution of NH_4Cl (100 mL). After 10 min of stirring the organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 25 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by column chromatography (Silica gel, 5% EtOAc in hexane) and afforded the alcohol **161** in 72% yield (2.6 g). $[\alpha]_D^{20} = -6.9$ (c, 0.92 in CH_2Cl_2), IR (KBr): 3321, 3067, 3032, 2930, 1643, 1603, 1496, 1454, 1275, 1111, 1022,

914, 756, 704; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 2.19 (s, 1H (OH)), 2.50-2.56 (m, 1H), 2.60-2.66 (m, 1H), 2.87-2.91 (m, 1H), 3.30-3.32 (dd, 1H, $J_1 = 9.5$, $J_2 = 9.3$), 3.49-3.51 (dd, 1H, $J_1 = 4.0$, $J_2 = 5.5$), 4.09-4.12 (m, 1H), 4.52 (s, 2H), 4.97-5.07 (m, 2H), 5.66-5.75 (m, 1H), 7.26-7.40 (m, 10 H); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 36.3, 48.0, 72.2, 72.8, 73.3, 116.3, 126.6, 127.7, 128.2, 128.3, 128.4, 128.9, 136.5, 137.9, 140.5; HRMS (FAB): calc'd for $\text{C}_{19}\text{H}_{23}\text{O}_2$ ($\text{M}+\text{H}^+$) 283.1698, obs'd 283.1690.



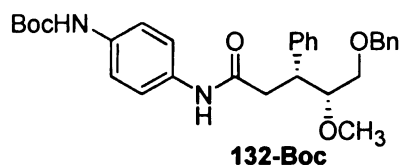
((2R, 3R)-1-(Benzyloxy)-2-methoxyhex-5-en-3-yl)benzene (162): Alcohol **161** (2 g, 8.5 mmol) was placed in a round bottom flask (100 mL, flame dried and cooled under nitrogen atmosphere), dissolved in dry THF (60 mL) and cooled on an ice bath. To this solution NaH (0.3 g, 12.2 mmol, NaH was washed with pentane and dried over nitrogen) was added, followed by iodomethane (2.4 g, 12.7 mmol). After the addition was completed, the cooling bath was removed and the mixture was stirred at room for 6 h. The reaction was then cooled to 0 °C and quenched with water (10 mL). The mixture was stirred for 5 min and dissolved with dichloromethane (50 mL). The layers were separated with separatory funnel and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The organic extracts were combined, washed with brine (50 mL) and water (50 mL), dried over anhydrous Na_2SO_4 , and the solvent was removed under reduced pressure on a rotary evaporator (25 °C, 200 mmHg). The crude product was purified by column chromatography (Silica gel, 2% EtOAc in hexane, $R_f = 0.32$) to give the olefin **162** in 98% yield (2.05 g). $[\alpha]_D^{20} = -5.0$ (c, 1.23 in CH_2Cl_2), $^1\text{H-NMR}$

(CDCl₃, 500 MHz): δ 2.52-2.58 (m, 1H), 2.61-2.67 (m, 1H), 2.98-3.02 (m, 1H), 3.33-3.36 (m, 1H), 3.44-3.47 (m, 1H), 3.48 (s, 3H), 3.62-3.66 (q, 1H, $J = 4.5$), 4.49 (s, 2H), 4.5-76 (d, 1H, $J = 10.5$), 5.07 (d, 1H, $J = 17$), 5.70-5.78 (m, 1H), 7.22-7.40 (m, 10 H); ¹³C-NMR (CDCl₃, 125 MHz): δ 36.4, 47.4, 59.1, 70.8, 73.3, 82.1, 116.1, 126.3, 127.5, 126.6, 127.9, 128.2, 129.2, 136.9, 138.2, 141.0; MS (DCI): m/z 296.3.



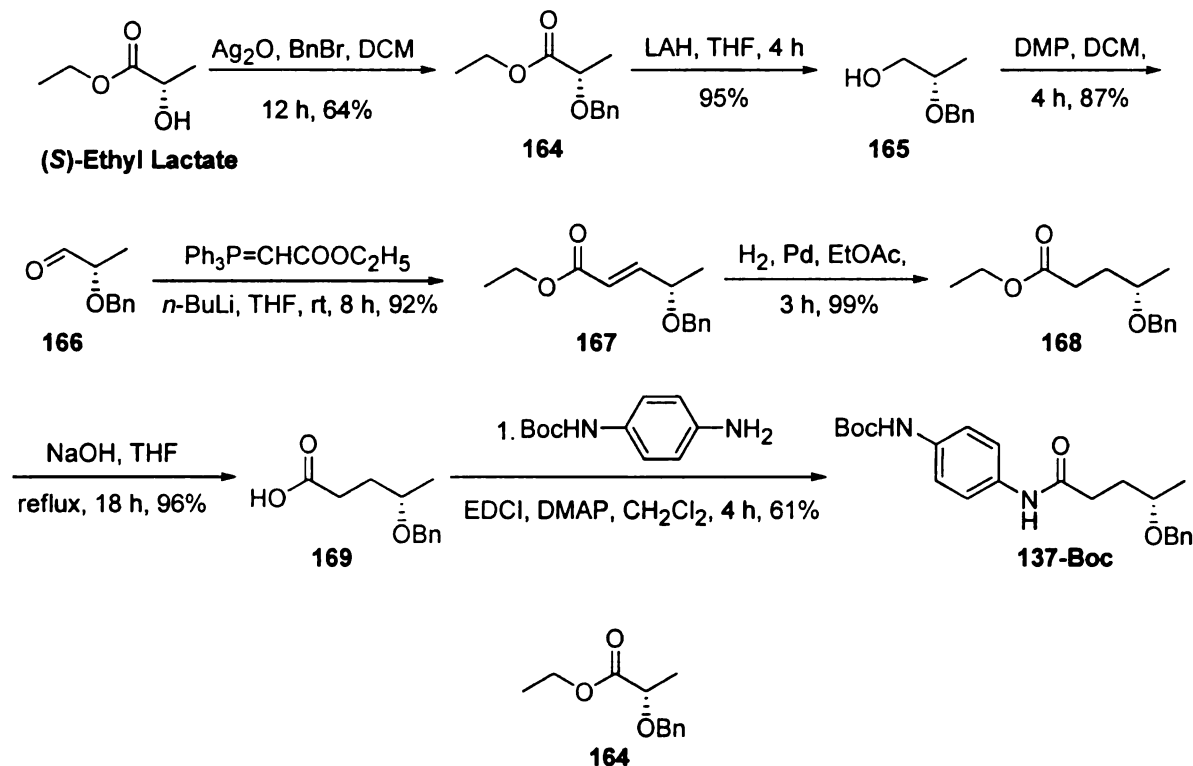
(3R, 4R)-5-(Benzyloxy)-4-methoxy-3-phenylpentanoic acid (163): Olefin **162** (1.5 g, 0.5 mmol) was placed in a 100 mL one-neck round bottom flask and dissolved in dry CH₂Cl₂ (50 mL). The solution was cooled to -78 °C on dry ice-acetone bath and ozone was purged through the solution via glass pipette until the appearance of intense blue color in the reaction solution. The ozone source was then removed and the reaction mixture was flushed with nitrogen until clear colorless solution was observed. To the obtained ozonide at -78 °C was added 50% solution of H₂O₂ (5 mL) and mixture was allowed to warm and stirred for 2 h at room temperature. The reaction mixture was concentrated and submitted to the column chromatography (Silica gel, 10% EtOAc in hexanes) to provide the carboxylic acid **163** in 67% yield. $[\alpha]_D^{20} = +2.2$ (c , 0.98 in CH₂Cl₂), IR (KBr): 3431-2836 (broad, OH), 1709, 1603, 1496, 1454, 1275, 1109, 1028, 1022, 740, 700; ¹H-NMR (CDCl₃, 300 MHz): δ 2.79-3.01 (d of AB quartet, 2H, $J_1 = 6$, $J_2 = 34.8$, $J_3 = 65.4$), 3.30-3.46 (d of AB quartet, 2H, $J_1 = 5.4$, $J_2 = 15$, $J_3 = 47.4$), 3.5 (s, 3H), 3.65-3.69 (q, 1H, $J = 5.4$), 4.48 (s, 2H), 7.26-7.40 (m, 10H); ¹³C-NMR (CDCl₃, 75

MHz): δ 36.2, 43.1, 59.1, 70.3, 73.2, 81.9, 126.6, 127.5, 127.7, 128.1, 128.5, 129.5, 137.9, 139.5, 177.3; MS (DCI): m/z 314.2.

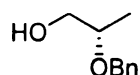


tert-Butyl 4-((3R,4R)-5-(benzyloxy)-4-methoxy-3-phenylpentanamido)phenylcarbamate (132-Boc): Carboxylic acid **163** (50 mg, 0.19 mmol) was dissolved in dry dichloromethane (10 mL) and followed by DMAP (23 mg, 0.19 mmol) and EDCI (44 mg, 0.22 mmol). The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. Purification by column chromatography (Silica gel, 20% EtOAc in hexane) gave the target amide **132-Boc** in 68% yield (55 mg) $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.15 (s, 3H), 1.17 (s, 3H), 1.48 (s, 9H), 2.40 (m, 2H), 2.54 (m, 1H), 3.17 (s, 3H), 3.50 (m, 1H), 3.71 (m, 1H), 4.49 (s, 2H), 6.44 (s, 1H (NH)), 7.13-7.30 (m, 9H), 8.07 (s, 1H, (NH)); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 22.9, 23.0, 37.3, 44.0, 48.9, 71.3, 73.6, 80.3, 118.9, 119.9, 127.9, 127.9, 128.5, 133.8, 134.0, 137.8, 138.5 152.8, 171.4; MS (DCI): m/z 504.4.

Scheme V-8: Synthesis of carrier conjugate 137

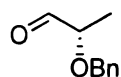


(S)-Methyl 2-(benzyloxy)propanoate (164):³⁷ To a solution of (S)-ethyl lactate (5 g, 42 mmol) in dry dichloromethane (150 mL) was added benzylbromide (7.9 g, 45 mmol) and silver oxide (10 g, 43 mmol). The reaction mixture was stirred at room temperature for 24 h and filtered through a pad of Celite. The filtrate was concentrated and the obtained crude oil was purified by column chromatography (Silica gel, 2% EtOAc in hexane) to afford compound **164** in 64% yield (5.6 g). $[\alpha]_{\text{D}}^{20} = -72.7$ (*c*, 6.6 in CHCl_3) [literature value $[\alpha]_{\text{D}}^{20} = -74.5$ (*c*, 2.92 in CHCl_3), *ee* = 99%]³⁷; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.32 (t, 3H, *J* = 7.6), 1.44 (d, 3H, *J* = 6.9), 4.05 (q, 1H, *J* = 7), 4.22 (q, 2H, *J* = 7), 4.57 (AB quartet, 2H, *J*₁ = 11.7, *J*₂ = 49.2), 7.25-7.33 (m, 5H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 14.2, 19.5, 60.6, 72.2, 74.0, 127.8, 128.0, 128.5, 136.7, 170.9; MS (DCI): *m/z* 208.1.



165

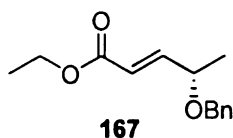
(S)-2-(Benzyloxy)propan-1-ol (165):³⁸ Ester **164** (2.5 g, 12 mmol) was dissolved in dry THF (100 mL) and cooled on an ice bath. To this solution LiAlH₄ (0.5 g, 13 mmol) was added portionwise and the reaction mixture was stirred at room temperature for 4 h. Cooled on an ice bath the reaction mixture was then quenched slowly with water (30 mL), diluted with EtOAc (50 mL) and stirred for another 30 min. The layers were separated, the aqueous layer extracted with EtOAc (2 x 20 mL) and the combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification of the crude product with column chromatography (Silica gel, 10% EtOAc in hexane) afforded alcohol **165** as colorless oil in 95% yield (1.9 g). $[\alpha]_D^{20} = +42.8$ (c, 5 in CH₂Cl₂) [literature value $[\alpha]_D^{20} = +45.9$ (c, 6 in CHCl₃)]³⁸; IR (KBr): 3414, 3031, 2972, 2930, 2872, 1493, 1458, 1369, 1204, 1092, 1057, 986, 904, 739, 692; ¹H-NMR (CDCl₃, 300 MHz): δ 1.5 (d, 3H, $J = 6$), 2.07 (s, br, 1H (OH)), 3.44-3.60 (m, 2H), 3.62-3.68 (m, 1H), 4.44-4.64 (AB q, $J_1 = 11.7$, $J_2 = 49.2$), 7.25-7.33 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 15.1, 66.3, 70.7, 75.5, 127.5, 127.7, 128.4, 138.4; MS (DCI): m/z 166.2.



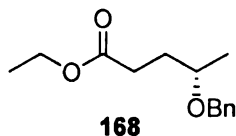
166

(S)-2-(Benzyloxy)propanal (166):³⁹ To a solution of alcohol **165** (3 g, 18 mmol) in dry dichloromethane (200 mL) was added DMP (10 g, 23 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Column chromatography (Silica gel, 10% EtOAc in hexane) afforded the title aldehyde as colorless oil in 87%

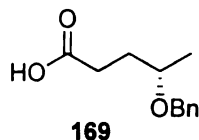
yield. $[\alpha]_D^{20} = -64.7$ (c, 2 in CHCl_3) [literature value³⁹ $[\alpha]_D^{20} = -66$ (c, 6 in CHCl_3)]; IR (KBr): 3422, 3065, 3032, 2976, 2934, 2876, 2789, 1724, 1496, 1454, 1375, 1344, 1207, 1093, 910, 806, 738, 696, 611; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.34 (d, 3H, $J = 7$), 3.90 (qd, 1H, $J_1 = 7$, $J_2 = 1.7$), 4.60 (d, 1H, $J = 11.7$), 4.66 (d, 1H, $J = 11.7$), 7.25-7.33 (m, 5H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 15.3, 71.9, 79.4, 127.9, 128.0, 137.2, 203.4; MS (DCI) m/z : 164.1.



(*S,E*)-Ethyl 4-(benzyloxy)pent-2-enoate (167): A solution of aldehyde **166** (2 g, 13 mmol) and ylide (4.7 g, 13.1 mmol) were dissolved in dry dichloromethane (150 mL) and stirred at room temperature for 8 h. The solvent was removed under reduced pressure and the remaining mixture was purified by column chromatography (Silica gel, 10% EtOAc in hexane) to afford ester **167** as a mixture of isomers (*E/Z* ratio 9:1) as colorless oil in 92% yield (2.6 g). $[\alpha]_D^{20} = +20.3$ (c, 5.1 in CH_2Cl_2); MS (DCI) m/z : $[\text{M}+\text{H}]^+$ 235.1; IR (KBr): 2982, 2936, 2878, 1720; 1657, 1496, 1456, 1369, 1271, 1184, 1097, 1032, 983, 866, 740, 698; $^1\text{H-NMR}$ (major isomer) (CDCl_3 , 300 MHz): δ 1.29 (t, 3H, $J = 7.0$), 1.31 (d, 3H, $J = 6.6$), 4.08-4.12 (m, 1H), 4.38 (q, 2H, $J = 7.2$), 4.41 (d, 1H, $J = 12.0$), 5.46 (d, 1H, $J = 12.0$), 5.98-6.03 (dd, 1H, $J_1 = 1.5$, $J_2 = 15.9$), 6.84-6.91 (dd, 1H, $J_1 = 6.0$, $J_2 = 15.9$), 7.23-7.36 (m, 5H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 14.2, 20.6, 60.5, 70.7, 73.8, 121.3, 126.9, 127.6, 128.4, 138.1, 149.2, 166.3.

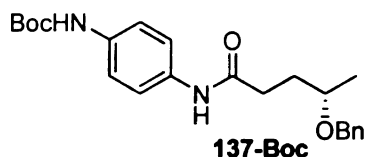


(S)-Ethyl 4-(benzyloxy)pentanoate (168): To a solution of unsaturated ester **167** (1 g, 4.2 mmol) in ethyl acetate was added Pd/C (10 mg). The reaction mixture was stirred under hydrogen atmosphere for 3 h and was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give the title product **168** as colorless oil in quantitative yield (no benzyl cleavage was detected). $[\alpha]_D^{20} = +21.3$ (*c*, 6.26 in CHCl₃); IR (KBr): 3031, 2978, 2942, 2878, 1736, 1493, 1452, 1369, 1269, 1182, 1098, 749, 700; ¹H-NMR (CDCl₃, 300 MHz): δ 1.25 (d, 3H, *J* = 6.0), 1.27 (t, 3H, *J* = 7.0), 1.89 (q, 2H, *J* = 7.2), 2.43-2.46 (dt, 2H, *J*₁ = 3.0, *J*₂ = 7.5), 3.60 (m, 1H, *J* = 6), 4.10-4.17 (q, 2H, *J* = 6.9), 4.47 (d, 1H, *J* = 11.7), 4.62 (d, 1H, *J* = 11.7), 7.29-7.40 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.1, 19.3, 30.3, 31.6, 60.1, 70.3, 73.7, 127.4, 127.6, 128.2, 138.7, 173.6; MS (DCI): calc'd for C₁₄H₂₀O₃ *m/z* 236.1, obs'd [M+H]⁺ 237.3.



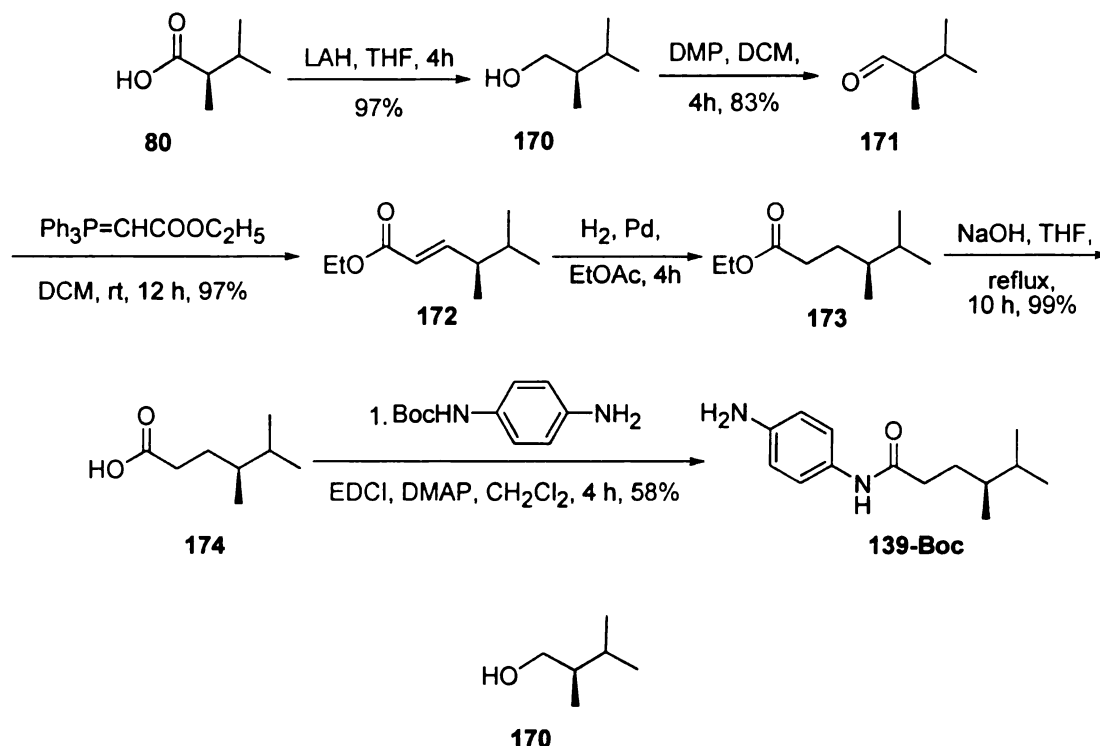
(S)-4-(Benzyloxy)pentanoic acid (169): Ester **168** (0.3 g, 1.27 mmol) was dissolved in THF (5 mL) and 2 M NaOH (3 mL) and refluxed overnight. THF was then removed under reduced pressure and the remaining solution was acidified with 10% HCl and extracted with DCM (3 x 10 mL). The extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude carboxylic acid **169** as colorless oil in 96% yield. $[\alpha]_D^{20} = +7.8$ (*c*, 0.26 in CHCl₃); IR (KBr): 3296-2878 (broad, OH), 3067, 3034, 2974, 2878, 1714, 1603, 1558, 1498, 1454, 1383, 1273, 1176,

1109, 1070, 945, 910, 790, 740, 713, 696, 603, 461; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.22 (d, 3H, $J = 6.0$), 1.84 (q, 2H, $J = 7.5$), 2.47 (dt, 2H, $J_1 = 2.1$, $J_2 = 7.5$), 3.60 (m, 1H, $J = 6.0$), 4.41-4.68 (AB q, 2H, $J_1 = 11.4$, $J_2 = 46.8$), 7.28-7.39 (m, 5H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 19.4, 30.2, 31.3, 70.4, 73.6, 127.5, 127.7, 128.3, 138.5, 179.7; MS (DCI): m/z 208.2.



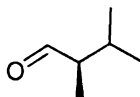
(S)-tert-Butyl 4-(4-(benzyloxy)pentanamido)phenylcarbamate (137-Boc): The amide **137-Boc** was obtained by ECD/DMAP coupling described above. The crude product was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to give the title amide in 61% yield. IR (KBr): 3346, 3031, 2974, 2936, 2878, 1697, 1652, 1605, 1543, 1522, 1406, 1311, 1244, 1163, 1057, 906, 833, 734, 696, 515, 459; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.18 (d, 3H, $J = 6.6$), 1.81 (q, 2H, $J = 7.2$), 2.20 (m, 2H), 3.45 (m, 1H), 4.44 (d, 1H, $J = 11.0$), 4.66 (d, 1H, $J = 11.5$), 6.51 (s, 1H (NH)), 7.28-7.39 (m, 9H), 8.31 (s, 1H (NH)); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 19.4, 28.3, 30.2, 31.3, 71.0, 72.7, 80.4, 112.0, 120.4, 127.9, 128.0, 128.6, 133.4, 134.4, 137.7, 152.8, 169.1; MS (DCI): m/z 398.8.

Scheme V-9: Synthesis of carrier conjugate 139



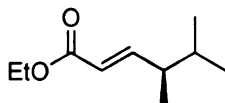
(R)-2,3-Dimethylbutan-1-ol (170):⁴⁰ To a cold solution of carboxylic acid **80** (3 g, 25 mmol) in dry THF (100 mL) was added LiAlH_4 (2.1 g, 55 mmol) portionwise and the reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The reaction mixture was cooled to 0 °C, slowly quenched with water (10 mL) and diluted with EtOAc (40 mL). The organic layer was separated and the remaining aqueous phase was extracted with EtOAc (2 x 20 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude alcohol **170** was isolated in 97% yield and was used without purification. $[\alpha]_{\text{D}}^{20} = +3.6$ (c, 0.96 in DCM) [literature value of the enantiomer $[\alpha]_{\text{D}}^{25} = -2.9$ (c, 60.5 in CHCl_3)]⁴¹; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 0.81 (d, 3H, $J = 6.9$), 0.83 (d, 3H, $J = 6.9$), 0.88 (d, 3H, $J = 6.9$), 1.42-1.48 (m, 1H), 1.51 (s, br, 1H (OH)), 1.59-1.72 (m, 1H), 3.38-3.44 (dd, 1H, $J_1 = 7.2$,

$J_2 = 11.4$), 3.53-3.58 (dd, 1H, $J_1 = 8.7$, $J_2 = 10.5$); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): 12.5, 18.0, 20.6, 28.8, 41.4, 66.6; MS (DCI): m/z 102.2.



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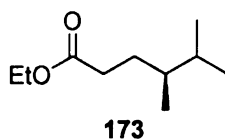
(R)-2,3-Dimethylbutanal (171):^{40, 42} To a solution of alcohol **170** (2 g, 18 mmol) in dry dichloromethane (150 mL) was added DMP (9.4 g, 21 mmol) and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Column chromatography (Silica gel, 10% EtOAc in hexane) afforded the title aldehyde in 83% yield (1.6 g). MS (DCI): m/z 126.1; $[\alpha]_{\text{D}}^{20} = +60.6$ (c, 0.96 in DCM) [literature value for enantiomer $[\alpha]_{\text{D}}^{25} = -65.6$ (c, 5.6 in CHCl_3)]⁴¹; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 0.94 (d, 3H, $J = 6.9$), 1.02 (d, 3H, $J = 6.9$), 1.06 (d, 3H, $J = 6.9$), 2.05-2.17 (m, 1H), 2.98-2.25 (m, 1H), 9.69 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 18.5, 20.4, 28.2, 52.2, 205.6.



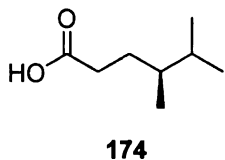
172

(R, E)-Methyl 4,5-dimethylhex-2-enoate (172):⁴³ A solution of aldehyde **171** (2 g, 20 mmol) and Wittig reagent (7.2 g, 13.1 mmol) were dissolved in dry dichloromethane (150 mL) and stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the remaining mixture was purified by column chromatography (Silica gel, 10% EtOAc in hexane) to afford ester **172** as a mixture of isomers (E/Z ratio 9:1) in 97% yield (1.35 g). IR (KBr): 2972, 2882, 1720, 1701, 1653, 1468, 1371, 1311, 1286, 1184, 1095, 1037, 987, 868, 769, 727; $^1\text{H-NMR}$ (major isomer) (CDCl_3 , 300 MHz): δ 0.81 (d,

3H, $J = 4.5$), 0.83 (d, 3H, $J = 6.9$), 0.89 (d, 3H, $J = 6.6$), 1.23 (t, 3H, $J = 6.0$), 1.53-1.63 (m, 1H), 2.00-2.11 (m, 1H), 4.12 (q, 2H, $J = 6.9$), 5.68-5.74 (dd, 1H, $J_1 = 1.2$, $J_2 = 18.6$), 6.84 (dd, 1H, $J_1 = 8.1$, $J_2 = 11.0$); ^{13}C -NMR (CDCl_3 , 75 MHz): 14.2, 16.1, 19.6, 22.3, 32.3, 42.7, 60.0, 120.3, 153.3, 166.7; MS (DCI): m/z 170.2.

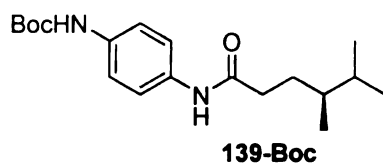


(S)-Methyl 4,5-dimethylhexanoate (173): To a solution of unsaturated ester **172** (1 g, 5.8 mmol) in ethyl acetate was added Pd/C (12 mg). The reaction mixture was stirred under hydrogen atmosphere for 4 h and was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give the title product **176** in quantitative yield (no benzyl cleavage was detected). $[\alpha]_{\text{D}}^{20} = -21.6$ (c, 4.53 in DCM); IR (KBr): 2964, 2878, 1740, 1653, 1466, 1375, 1261, 1182, 1116, 1039, 943, 862, 792, 704; ^1H -NMR (CDCl_3 , 300 MHz): δ 0.82 (d, 3H, $J = 4.5$), 0.84 (d, 3H, $J = 4.5$), 0.88 (d, 3H, $J = 6.9$), 1.26 (t, 3H, $J = 7.2$), 1.21-2.04 (m, 4H), 2.19-2.59 (m, 2H), 4.11 (q, 2H, $J = 6.9$); ^{13}C -NMR (CDCl_3 , 75 MHz): δ 14.9, 17.9, 20.0, 29.1, 31.7, 32.5, 38.3, 60.1, 174.1 MS (DCI): m/z $[\text{M}+\text{H}]^+$ 173.2.



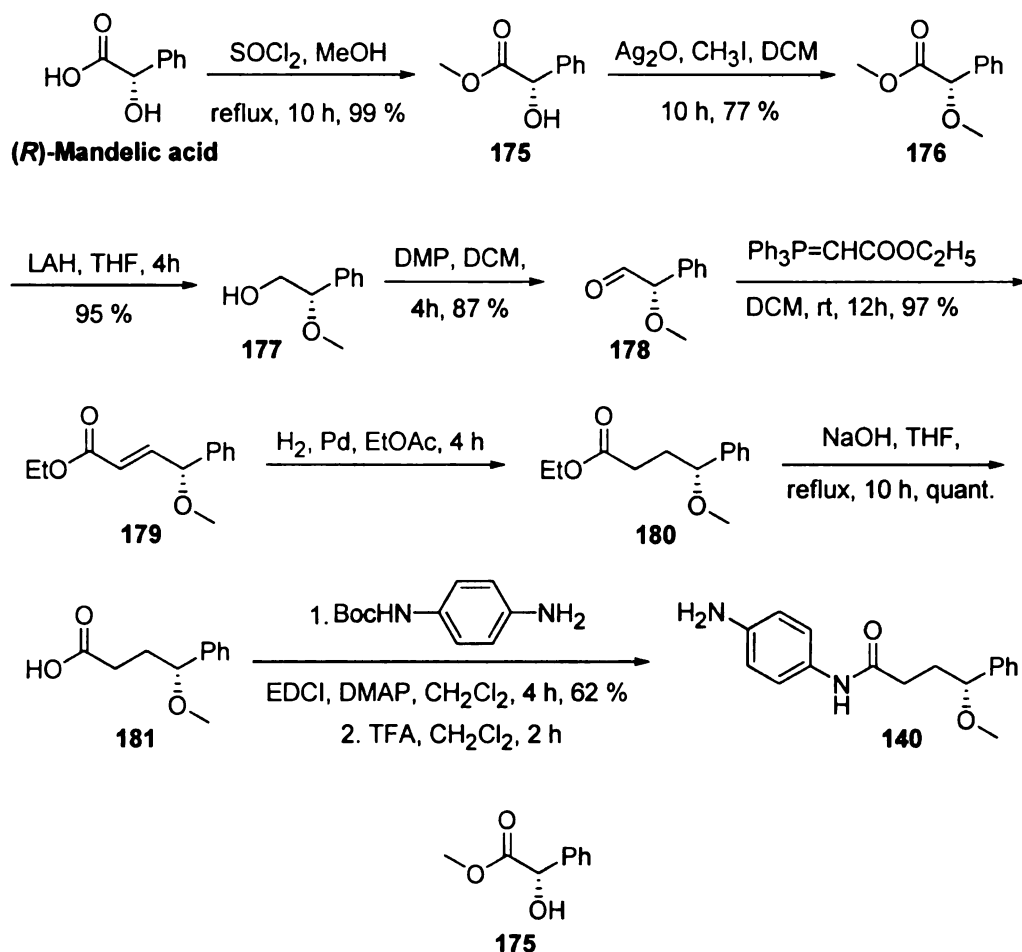
(S)-4,5-Dimethylhexanoic acid (174): Ester **173** (0.7 g, 4.1 mmol) was dissolved in THF (10 mL) and 4 M NaOH (3 mL) and refluxed overnight. THF was then removed under reduced pressure and the remaining solution was acidified with 10% HCl and extracted

with DCM (3 x 10 mL). The extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude carboxylic acid **174** in 99% yield (0.58 g). $[\alpha]_D^{20} = -11.8$ (c, 2.81 in DCM); IR (KBr): 3278-2860 (broad, OH), 2963, 2878, 1711, 1464, 1417, 1388, 1369, 1278, 1221, 1116, 1030, 945, 742, 699; ¹H-NMR (CDCl₃, 500 MHz): δ 0.89 (d, 3H, $J = 6.9$), 0.84 (d, 3H, $J = 6.9$), 0.85 (d, 3H, $J = 6.9$), 1.15-1.45 (m, 2H), 1.49-1.74 (m, 2H), 2.21-2.42 (m, 2H), 10.56 (s, br, 1H); ¹³C-NMR (CDCl₃, 125 MHz): 15.0, 17.9, 20.0, 22.4, 28.9, 31.8, 38.1, 180.9; MS (DCI): m/z [M+H]⁺ 144.1.



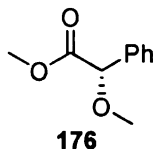
(S)-tert-Butyl 4-(4,5-dimethylhexanamido)phenylcarbamate (139-Boc): The amide **139-Boc** was obtained by ECD/DMAP coupling described above. The crude product was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to give the title amide in 58% yield. $[\alpha]_D^{20} = -7.2$ (c, 0.78 in DCM); IR (BKr): 3337, 2964, 2878, 1965, 1658, 1605, 1516, 1446, 1390, 1316, 1305, 1251, 1167, 1070, 837, 768, 515; m. p. = 203-204 °C (white crystals); ¹H-NMR (CD₃OD, 300 MHz): δ 0.83 (d, 3H, $J = 6.9$), 0.88 (d, 3H, $J = 6.9$), 0.89 (d, 3H, $J = 6.6$), 1.30-1.39 (m, 1H), 1.41-1.51 (m, 1H), 1.49 (s, 9H), 1.54-1.67 (m, 1H), 1.70-1.81 (m, 1H), 2.21-2.42 (m, 2H), 7.31 (d, 2H, $J = 8.6$), 7.42 (d, 2H, $J = 8.6$); ¹³C-NMR (CD₃OD, 75 MHz): 16.3, 19.2, 21.4, 29.7, 32.1, 33.9, 36.9, 40.3, 81.5, 120.9, 122.6, 135.5, 137.4, 156.1, 175.4; MS (DCI): m/z [M+H]⁺ 335.2.

Scheme V-10: Synthesis of carrier conjugate 140

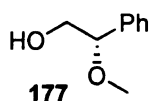


(S)-Methyl 2-hydroxy-2-phenylacetate (175):⁴⁴ Mandelic acid (3g, 19.7 mmol) was dissolved in methanol (50 mL) and cooled on ice bath. To this solution thionyl chloride (4.65 g, 40 mmol) was added dropwise and the reaction mixture was refluxed overnight (10 h). The reaction mixture was cooled on an ice bath and quenched with aqueous NaHCO₃. Methanol was removed on rotary evaporator and the remaining oil was dissolved with dichloromethane. The organic phase was separated, washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Methyl mandelate (**175**) was obtained in 99% as white crystalline solid. $[\alpha]_{\text{D}}^{20} = -145$ (c, 3.1 in DCM); m.p. = 48-49 °C; ¹H-NMR (CDCl₃, 500 MHz): δ 3.70 (s, 3H), 3.79 (s, br, 1H

(OH)), 5.16 (s, 1H), 7.30-7.41 (m, 5H); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 52.7, 72.8, 126.5, 128.3, 128.4, 138.2, 173.9; MS (DCI): m/z 166.2.

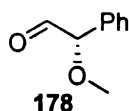


(S)-Methyl 2-methoxy-2-phenylacetate (176):^{45, 46} To a solution of **175** (3g, 18 mmol) in dry dichloromethane (50 mL) was added iodomethane (3.6 g, 21.6 mmol) and silver oxide (5 g, 21.6 mmol). The reaction mixture was stirred at room temperature for 10 h and filtered through a pad of Celite. The filtrate was concentrated and the obtained crude oil was purified by column chromatography (Silica gel, 2% EtOAc in hexane) to afford compound **175** in 77% yield (2.5 g). ^1H -NMR (CDCl_3 , 500 MHz): δ 3.37 (s, 3H), 3.69 (s, 3H), 4.74 (s, 1H), 7.31-7.42 (m, 5H); ^{13}C -NMR (CDCl_3 , 125 MHz): δ 57.2, 127.5, 129.3, 129.4, 139.2, 198.9; MS (DCI): m/z 150.1.

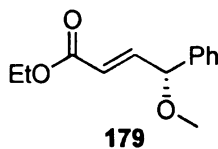


(S)-2-Methoxy-2-phenylethanol (177): To the ice cold solution of **176** (2g, 11 mmol) in dry THF (60 mL) was added LiAlH_4 (0.5 g, 13.3 mmol) portionwise and reaction mixture was stirred at room temperature for 4 h. The mixture was then cooled back to 0 °C and was slowly quenched with cold water. After 30 min Na_2SO_4 (10 g) was added and mixture was stirred for additional 30 min. The solution was then filtered through a pad of Celite, the filter cake was washed with dichloromethane (2 x 25 mL) and the filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (Silica gel, 10% EtOAc in hexane) afforded alcohol **177** as colorless oil

in 95% yield (1.6g). $[\alpha]_D^{20} = +113.2$ (c, 3.57 in DCM); IR (KBr): 3443, 3066, 2937, 2883, 2830, 1499, 1456, 1269, 1113, 1064, 1028, 896, 740, 702; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 2.54 (s, 1H (OH)), 3.28 (s, 3H), 3.57-3.68 (m, 2H), 4.27-4.30 (dd, 1H, $J_1 = 4.0$, $J_2 = 8.0$), 7.27-7.36 (m, 5H); $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 56.8, 67.3, 84.6, 126.8, 128.1, 128.5, 138.3; MS (DCI): m/z 152.1.

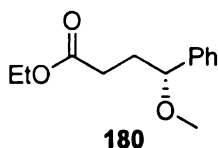


(S)-2-Methoxy-2-phenylacetaldehyde (178):⁴⁷ To a solution of alcohol **177** (2 g, 13 mmol) in dry dichloromethane (150 mL) was added DMP (8.0 g, 21 mmol) and the mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. Column chromatography (Silica gel, 10% EtOAc in hexane) afforded the title aldehyde in 87% yield (1.6 g). MS (DCI): calc'd for $\text{C}_9\text{H}_{10}\text{O}_2$ m/z = 126.1, obs'd 121.1; $[\alpha]_D^{20} = +58.6$ (c, 1.5 in DCM) [literature value for enantiomer $[\alpha]_D^{25} = -66$ (c, 1.0 in CHCl_3)]⁴⁷; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 2.79-3.19 (m, 2H), 3.38 (s, 3H), 3.79-3.98 (m, 1H), 7.26-7.38 (m, 1H), 9.65 (s, 1H); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz): δ 18.5, 20.4, 28.2, 52.2, 205.6.



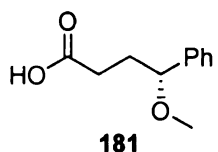
(R, E)-Methyl 4-methoxy-4-phenylbut-2-enoate (179):^{47, 48} (racemic substrate available)⁴⁹ Solution of aldehyde **181** (0.5 g, 3.3 mmol) in dry dichloromethane (50 mL) and ylide (1 g, 3.6 mmol) was stirred at room temperature for 12 h, concentrated and directly transferred into the Silica gel column. The resulting ester was eluted with 2%

EtOAc in hexane in 97% (0.66 g) yield. MS (DCI) calc'd for C₁₃H₁₆O₃ m/z = 220.1, obs'd [M+H]⁺ 221.3; ¹H-NMR (CDCl₃, 500 MHz): δ 1.25 (t, 3H, J = 7.2), 3.31 (s, 3H), 4.16 (q, 2H, J = 7.2), 4.74-4.77 (dd, 1H, J_1 = 2.5, J_2 = 6.5), 6.02-6.08 (dd, 1H, J_1 = 1.2, J_2 = 15.9), 6.90-6.97 (dd, 1H, J_1 = 5.4, J_2 = 15.6), 7.26-7.41 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.1, 20.1, 42.0, 60.3, 120.2, 127.0, 127.6, 128.9, 143.6, 152.9, 167.0.



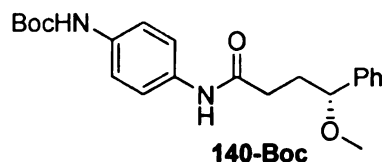
(R)-Methyl 4-methoxy-4-phenylbutanoate (180): (racemic substrate available)⁵⁰

Unsaturated ester **179** (0.6 g, 2.9 mmol) was dissolved in ethyl acetate and Pd/C was added (12 mg). The reaction mixture was stirred under hydrogen atmosphere for 4 h and filtered through Celite. The filtrate was concentrated to afford ester **183** in quantitative yield. MS (DCI): calc'd for C₁₃H₁₈O₃ m/z = 222.1, obs'd [M+H]⁺ 223.2; [α]_D²⁰ = +48.6 (c, 3.40 in DCM); IR (KBr): 2984, 2936, 2824, 1736, 1657, 1558, 1456, 1375, 1186, 1107, 1030, 906, 761, 702, 565; ¹H-NMR (CDCl₃, 500 MHz): δ 1.25 (t, 3H, J = 7.2), 1.95-2.02 (m, 1H), 2.04-2.12 (m, 1H), 2.38 (t, 2H, J = 7.6), 3.22 (s, 3H), 4.11 (q, 2H, J = 7.0), 4.16 (dd, 1H, J_1 = 5.5, J_2 = 2.5), 7.26-7.38 (m, 5H); ¹³C-NMR (CDCl₃, 75 MHz): δ 14.8, 30.6, 33.1, 56.7, 60.2, 82.8, 126.6, 127.6, 128.3, 141.5, 173.4;



(R)-4-Methoxy-4-phenylbutanoic acid (181): Ester **180** (0.8 g, 3.6 mmol) was dissolved in THF (10 mL) and 4 M NaOH (3 mL) and refluxed overnight (10 h). THF was then

removed under reduced pressure and the remaining solution was acidified with 10% HCl and extracted with DCM (3 x 10 mL). The extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude carboxylic acid **184** in quantitative yield (0.7 g). MS (DCI): calc'd for C₁₁H₁₄O₃ *m/z* = 194.1, obs'd 194.3; [α]_D²⁰ = +58.0 (*c*, 0.67 in DCM); IR (KBr): 3349-2824 (broad, OH), 3031, 2936, 2824, 1709, 1493, 1452, 1288, 1105, 908, 760, 574; ¹H-NMR (CDCl₃, 500 MHz): δ 1.97-2.17 (m, 2H), 2.47-2.52 (m, 2H), 3.26 (s, 3H), 4.20-4.25 (dd, 1H, *J*₁ = 5.1, *J*₂ = 7.1), 7.29-7.43 (m, 5H), 11.26 (s, br, 1H (OH)); ¹³C-NMR (CDCl₃, 125 MHz): δ 30.4, 32.8, 56.7, 84.2, 126.5, 127.8, 128.4, 141.3, 179.6.



(*R*)-tert-Butyl 4-(4-methoxy-4-phenylbutanamido)phenylcarbamate (140-Boc): The amide **140-Boc** was obtained by ECD/DMAP coupling described above. The crude product was purified by column chromatography (Silica gel, 20% EtOAc in hexane) to give the title amide in 62% yield. MS (DCI): *m/z* [M+H]⁺ 385.2; [α]_D²⁰ = +34.0 (*c*, 0.23 in DCM); m.p. = 153-155 °C (yellowish powder); IR (KBr): 3361, 2976, 2930, 2830, 1701, 1664, 1610, 1534, 1522, 1454, 1406, 1367, 1309, 1232, 1163, 1105, 1057, 906, 833, 769, 700, 549, 518; ¹H-NMR (CDCl₃, 500 MHz): δ 1.48 (s, 9H), 2.08 (q, 2H, *J* = 7.5), 2.41 (q, 2H, *J* = 6.6), 3.22 (s, 3H), 4.22 (t, 1H, *J* = 6.3), 6.44 (s, br, 1H (NH)), 7.26-7.36 (m, 7H), 7.40 (d, 2H, *J* = 9), 7.55 (s, br, 1H (NH)); ¹³C-NMR (CDCl₃, 125 MHz): δ 28.3, 33.5, 34.0, 56.7, 80.5, 83.1, 119.2, 120.5, 126.6, 127.8, 128.5, 133.4, 134.5, 141.4, 152.8, 170.8.

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Chapter VI

Induction of Chirality into Porphyrin Aggregates

VI.1. Introduction

As the “Central Science”, chemistry certainly touches on many disciplines, but its impact is particularly significant as a bridge between the biological and material sciences. Chemical principles explain how biomolecules self-assemble to form functional nanostructures, while providing the tools to synthesize analogous structures in non-biological environments. The last couple of decades have seen an explosion of interest in the special properties that may be imparted to molecular assemblies. This interest is fueled by the concept of molecular engineering, or the purposeful design of structures that are supermolecular in scale and in which molecular units are arranged in specific spatial (and possibly temporal) arrangements to realize a coordinated functional goal. An early example of this is the *Langmuir-Blodgett film*, consisting of layers of amphiphilic molecules assembled on a solid surface. These nanostructures mimic some of the properties of cell membranes, while also having a number of important applications in material science.¹⁻⁴

Another example of chemistry’s role in linking biology with material science is the increasing use of DNA as a template or a scaffold in the controlled assembly of nanostructures.⁵ The DNA itself can exhibit motor-like properties through coupling conformational changes to addition of external stimuli.^{3,4} Alternatively, metals can be deposited onto a pre-formed DNA structure to produce conducting nanowires.⁶⁻⁸ The ability to assemble both linear and branched DNA nanostructures with precise and

predictable dimensions has generated considerable interest for their use in molecular electronics.

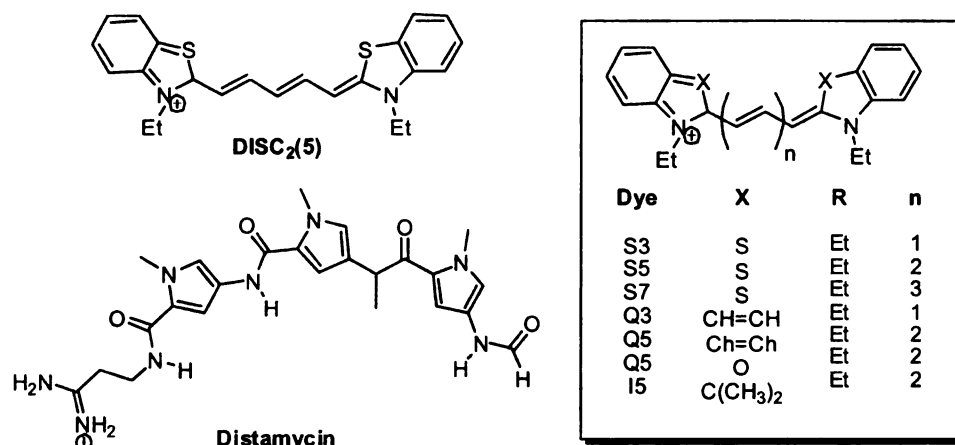


Figure VI-1: Structures of unmodified cyanine dyes and distamycin.

A vast area in this field is occupied by application of the self-assembled cyanine dyes and porphyrins. The cyanine dyes were first reported more than 150 years ago.⁹ They are characterized by two heterocyclic components connected by a polymethine bridge having an odd number of carbons (Figure VI-1). Variation of the heterocycle and bridge length causes changes in absorption and emission maxima that span the visible and near-IR regions of the spectrum. Cyanine dyes exhibit high extinction coefficients ($\epsilon_{\text{max}} > 10^4 \text{ M}^{-1}\text{cm}^{-1}$) and moderate fluorescence quantum yields, leading to wide applications as photosensitizers, stains and fluorescent probes.¹⁰

Given the fact that cyanine dyes are both hydrophobic and cationic, they have been found to aggregate on anionic templates. For instance, interactions of cyanine dye with polyanionic DNA duplex have been extensively studied and a variety of non-covalent binding modes have been identified.¹¹ Intercalation of the cyanine dyes between adjacent

base pairs of DNA leads to large enhancement in fluorescence quantum yield, that puts these dyes among the most widely used stains for detecting DNA in solutions and gels.¹²

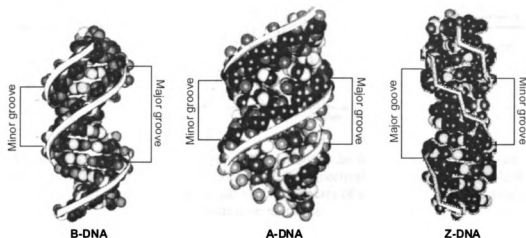


Figure VI-2: Three types of DNA. Z-DNA is one of the many possible double helical structures of DNA. It is a left-handed double helical structure in which the double helix winds to the left in a zig-zag pattern (instead of to the right, like the more common B-DNA form). Z-DNA is thought to be one of the three biologically active double helical structures along with A- and B-DNA.

Porphyrins have extensively used as sensors of handedness of DNA.^{13, 14} For instance, interaction of water soluble *trans*-bis-(N-methylpyridinium-4-yl)diphenylporphyrin ($t\text{-H}_2\text{P}_{\text{agg}}$) with B-DNA, induces a CD signal of an unusual shape and size observed in the Soret band region. Interaction of the porphyrin with DNA occurs through three different binding modes: intercalation, that is used for sequence identification and leads to negative CD; outside groove binding (positive CD), and outside stacking (bisignate CD), both reflecting the helicity of DNA. The latter method requires application of pentacoordinated metalloporphyrins, which are unable to intercalate into the DNA sequence due to the steric hindrance created by axially coordinated water molecules. Such property of the metalloporphyrins has led to their application as chiroptical probes for Z-DNA, where intercalation is known to facilitate the Z-to-B transition (Figure VI-2).

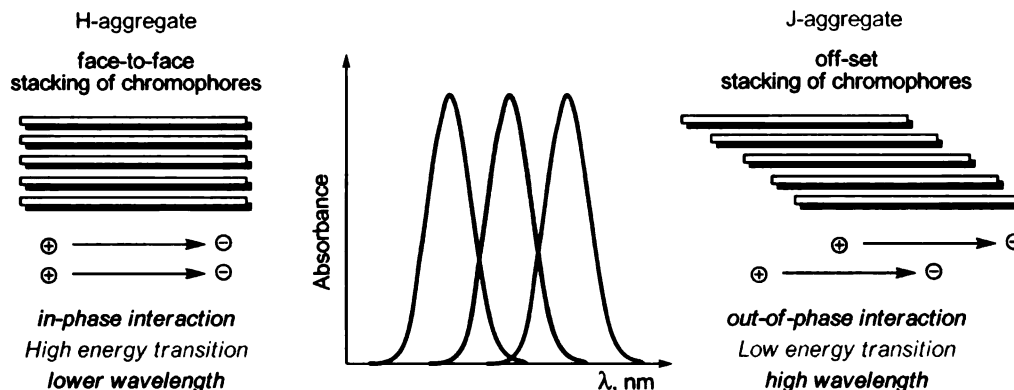


Figure VI-3: Aggregation of chromophores leads to the formation of H- and J-type assemblies. The characteristic blue and red shift, respectively, of the Soret band (black curve) of the chromophore is governed by the geometry of interaction of electric dipole transition moments.

Along with that, the Soret band in the visible region and ease of self-assembly due to facile π - π interactions allow for the formation of different types of dimeric and multi-molecular assemblies.^{15, 16} A study of the crystal structure of the zinc tetraphenyl porphyrin suggested that interaction between phenyl-phenyl and phenyl pyrrole are effective for molecular packing.¹⁷ Early papers describe that π -stacking induced aggregation results in formation of a mixture of H- (first introduced by Kasha and Hochstrasser)^{18, 19} and J-assemblies (so called in honor of their discoverer, E. E. Jelley),^{20, 21} which is detected as appearance of the split Soret band, where face-to-face H-stacking leads to a blue-shifted part of the absorption peak and J-assembly is identified by a red-shifted absorption (Figure VI-3). J-aggregates are formed with porphyrins arranged in one dimension. The transition moments of these assemblies are parallel to the line connecting their centers and the angle between the molecular centers is zero (ideal case).^{22, 23} J-aggregation of monomers results in the formation of an intense narrow absorption band that is red shifted relative to the absorption spectrum of the monomer. The origin of this

band is explained by the formation of an excitonic state through the electronic coupling of tightly packed molecules. H-assemblies are again one-dimensional arrangement of monomers, but the transition moments of monomers are perpendicular (ideal case) to the line of centers.²² In contrast to side-to-side arrangement of molecules in J-assembly, the arrangement in H-aggregates is face-to-face, and the dipolar coupling between monomers results in blue shift of the absorption band.

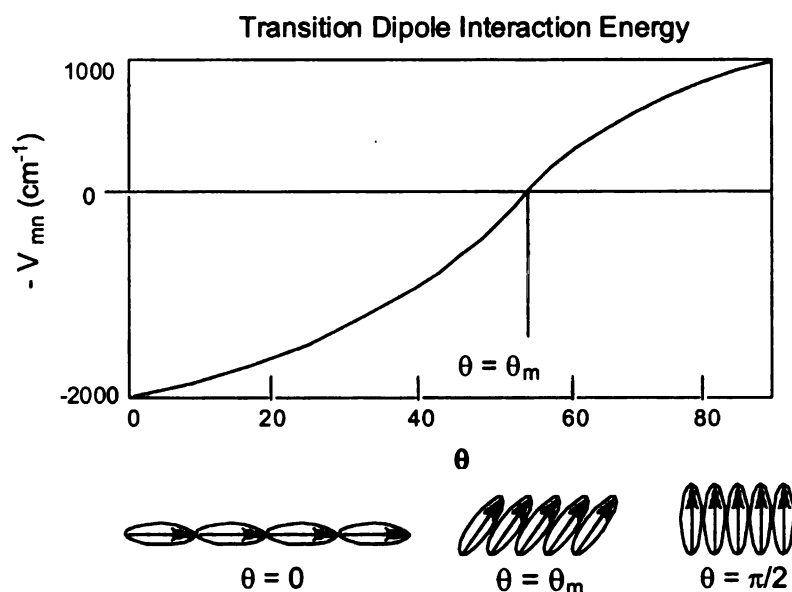


Figure VI-4: Interaction energy as a function of the orientation dipoles in aggregate structures.²²

Figure VI-4 depicts the energy of interaction between molecules in aggregate. θ is the angle made by the projection of the transition dipole onto the plane and the line between centers of the species in the aggregate. The calculation is implemented for a nominal interaction of 1000 cm^{-1} . The interaction energies show that J-aggregate absorption is red-shifted and H-aggregate absorption is blue-shifted from the isotropic orientation distribution ($\theta = \theta_m$), and these observations form the basis of the operational definition for the two types of aggregates.

Potential application of porphyrin aggregates with controlled geometry as robust devices for photochemical energy conversion,²⁴⁻²⁶ generation of optoelectronic devices for telecommunication,²⁷ optical switching, and information storage and transfer²⁸⁻³¹ ensures development of the field and gives a fruitful ground for detailed investigation of the aggregation process. However, the porphyrin assemblies reported to date are limited to water-soluble porphyrins and a specific picket-fence porphyrin,^{23, 32-36} which can be forced to aggregate by controlling the pH, temperature and ionic strength. The porphyrins that are used for the formation of superstructures possess cationic or anionic substitution at the periphery of the porphyrin ring (mainly at *meso* position) (Figure VI-5). Electrostatic interaction between such porphyrins allows for formation of aggregates with controlled relative alignment of the chromophores.³⁷ Aggregation of anionic porphyrins in aqueous media is achieved by changing the pH of the solution. After protonation of the inner nitrogen atoms (pKa~4.8) the positive charges on the macrocycle core interact with the negative charges of the peripheral groups leading to the formation of J- or H-aggregates.³⁸ While formation of aggregates in aqueous media has been widely investigated, only few address the formation of aggregate in non-aqueous media,^{15, 36, 39, 40} and even less approach the formation of chiral superstructures. Induction of chirality into the aggregates of porphyrin and cyanine dyes has become an active area of research due to their potential application as sensors for chiral recognition and possible utilization in forming artificial light-harvesting proteins or the mimics of bacteria light harvesting antennas and the chlorosome.^{15, 26}

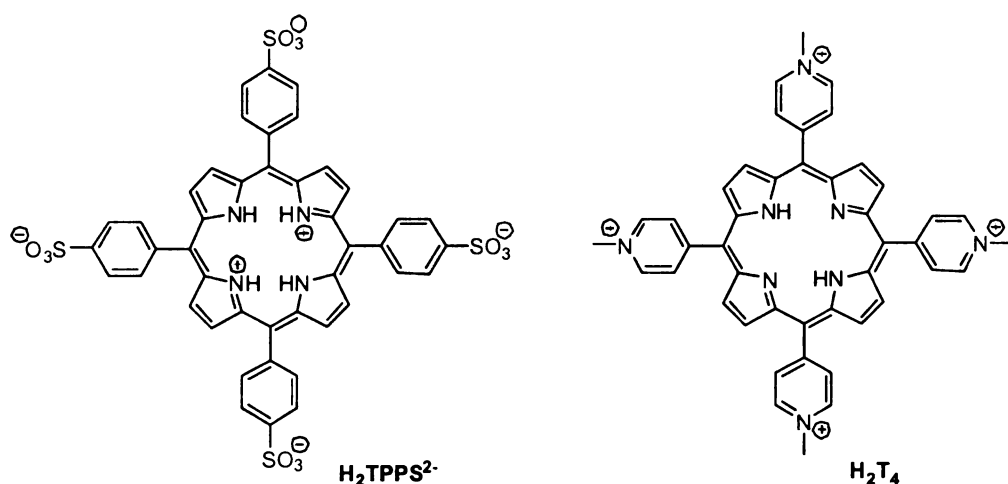


Figure VI-5: Aggregation of anionic tetrakis(4-sulfonatophenyl) porphyrin (H_2TPPS^{2-}) and cationic meso-tetrakis(N-methylpyridyl-4) porphyrin (H_2T_4) in aqueous media allow formation of homogeneous or heterogeneous J- and H-aggregates.

Although generating chiral aggregates with predictable helicity has not been thoroughly studied, there are several examples of inducing helicity into the porphyrin aggregates upon addition of small chiral molecules to biopolymers or achiral porphyrin aggregates. For instance, Purello and coworkers form chiral assemblies in water through the arrangement of achiral oppositely-charged porphyrins in the presence of L- and D-aromatic amino acids.⁴¹ Periasami and coworkers have achieved chiral induction by growing the porphyrin architectures on chiral template. Yashima and coworkers approach chiral superstructures by immobilization of negatively charged porphyrins on the surface of cationic template and further induction of chirality with asymmetric aromatic guests.⁴² Paolese and coworkers were able to achieve control in the molecular organization of the porphyrins along with chiral induction by aggregation of amphiphilic chiral cationic porphyrin derivatives with their anionic chiral analog.⁴³

VI.2. Design, synthesis and aggregation of ZnTPP-tail porphyrin

Construction of porphyrin aggregates in non-aqueous media excludes the use of charged species due to their poor solubility in organic solvents and, hence, suggests application of neutral porphyrins. Compared to cationic or anionic porphyrins that form aggregates at μM concentrations, spectroscopic studies of neutral porphyrin systems reveal presence of only monomeric non-aggregated porphyrin species. Thus, absence of the charged functional groups disables intermolecular interaction of porphyrins at low concentrations and prevents formation of aggregates. The alternative approach to achieve aggregation of the species is to increase their concentration in the solution. If applied to porphyrins, this approach can facilitate aromatic interaction favored by decreased intermolecular distance between the porphyrin molecules and consequently formation of porphyrin aggregates. Lack of the charged components may also affect the geometry of the porphyrin interaction. Particularly, if electrostatic interaction between cationic and anionic porphyrins leads to the formation of aggregates with specific geometry (mostly J-aggregates), spontaneous self-assembly triggered by π -stacking lacks the element of control and results in formation of a mixture of both H- and J-aggregates. Hence, the challenge of construction of neutral porphyrin aggregates in non-aqueous media is to control the geometry of the formed assembly. Due to the presence of coordination sites (zinc metal in a porphyrin) one can envision that both species could be transformed into a single superstructure, either H- or J-type, through coordination of a guest molecule. The previous chapters discuss formation of face-to-face porphyrin complexes upon coordination of porphyrin tweezers with diamines or other guests that possess two coordination sites. A similar approach, if applied to the preformed aggregate, might result

in the formation of complexed aggregates of a specific geometry. Moreover, it is plausible to propose that complexation of the porphyrin aggregate with a chiral guest would control the geometry of the assembly.

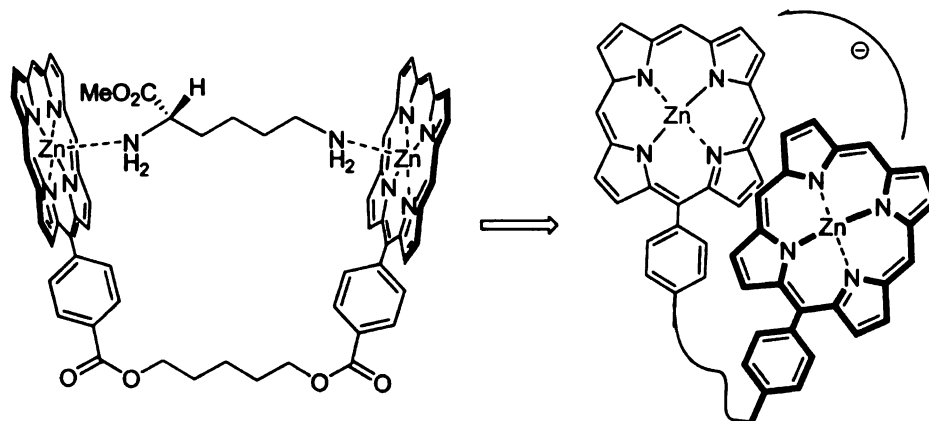


Figure VI-6: Binding of diamine to the porphyrin tweezer yields a complex of fixed helical arrangement.

As was discussed in previous chapters, coordination of diamines to bis-porphyrin systems induces an asymmetric environment in the complex resulting in a helical arrangement of chromophores. For instance complexation of porphyrin tweezer L-lysine methyl ester induces a counterclockwise orientation of porphyrins in the tweezer leading to the negative ECCD spectrum (Figure VI-6). We envision that a similar approach can be taken for formation of chiral aggregates in non-aqueous media. The asymmetry of the bound guest can affect the handedness of the formed assembly and generate an optically active aggregate, the helicity of which can be identified through Exciton Coupled Circular Dichroism (ECCD).⁴⁴ Detection of an exciton coupling brings up the issue that must be considered during the construction of aggregates; that is, the relative orientation of the electric dipole transition moment of porphyrins in the assembly. It is known that the appearance of ECCD signal and correlation of its sign with the helicity of the bis- or

multi-chromophoric system is based on the relative orientation of the electric dipole transition moments (edtm) of porphyrins,⁴⁵ and thus depends on the existence of a such transition. A defined orientation of the electric dipole transition moment in porphyrin can be achieved by breaking the symmetry of the porphyrin through introduction of an electron withdrawing carboxylate group onto the *meso*-position of the porphyrin (Figure VI-6b, edtm oscillates in C₁₅-C₅ direction). The large electric dipole transition moment in this porphyrin is oriented approximately collinearly with the long axis of the porphyrin ester and almost parallel to the direction of the C-O ester bond.

Another aspect requiring consideration is that unlike porphyrin dimers (porphyrin tweezer complexes) porphyrin aggregates consist of the number of porphyrin molecules and, therefore, are able to incorporate more than one molecule of chiral ligand. In such a case each of the complexes formed within the aggregate can give rise to a CD bisignate and the overall spectrum observed can be viewed as a summation of the signals of all chiral complexes.⁴⁶

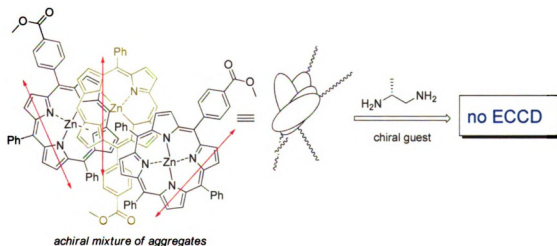


Figure VI-7: Random orientation of edtm of the chromophores could lead to cancellation of the ECCD signal.

Since the ECCD sign of the bis- or multi-chromophoric system depends on the relative orientation of the electric dipole transition moments, the stabilization of the latter within the monomer might not be sufficient for the complex aggregate assembly. As depicted in Figure IV-7, lack of stabilizing interactions between the ester groups may cause a random directionality of the chromophore's edtms within the aggregate, and hence lead to complicated or cancellation of the ECCD signal.

Our approach to controlling the relative orientation of the transition moments of porphyrins within the aggregate is based on introducing an oxygenated tail (positioned at one of the *meso*-positions of the porphyrin ring) such that intermolecular hydrophilic interaction would orient the porphyrins in the same direction (Figure VI-8).

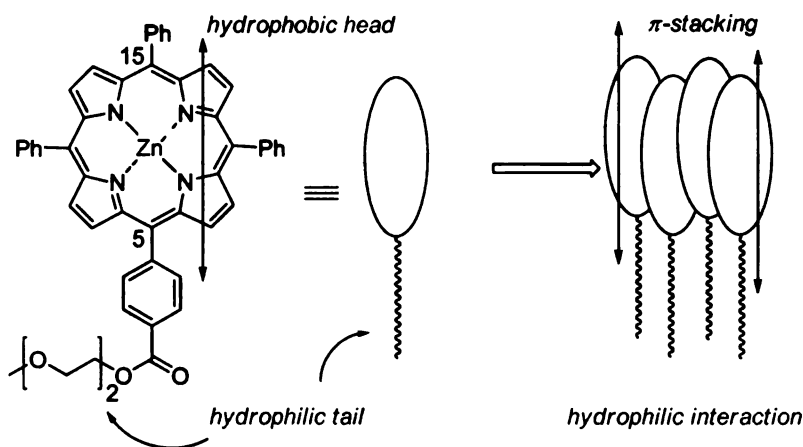


Figure VI-8: Controlled by hydrophobic/hydrophilic interactions aggregation of porphyrins leads to fixed relative orientation of the transition moment in the assembly and makes possible detection of chirality by ECCD and identification of the relative orientations of the porphyrins in the assembly.

Consequently, while spontaneous aggregation of hydrophobic porphyrins triggers the formation of the mixture of H- and J-type assemblies, hydrophilic interaction between the oxygenated tails should orient the porphyrins in the assembly. Incorporation of a chiral guest in this assembly could potentially control the helicity of the aggregate, i.e.,

upon binding to the chiral guest a single chiral assembly could be formed. The chirality of the chiral additive can yield the induction of either positive or negative helicity into the aggregate rising from the steric interaction of the porphyrins with the asymmetric chiral center (Figure VI-9). A controlled orientation of the transition moments will also be helpful for interpretation of the sign observed upon chiral induction. The correlation of the helicity of the aggregates with the asymmetry of a chiral guest represents another aspect of interest. Direct correlation may be useful for induction of the asymmetry of choice.

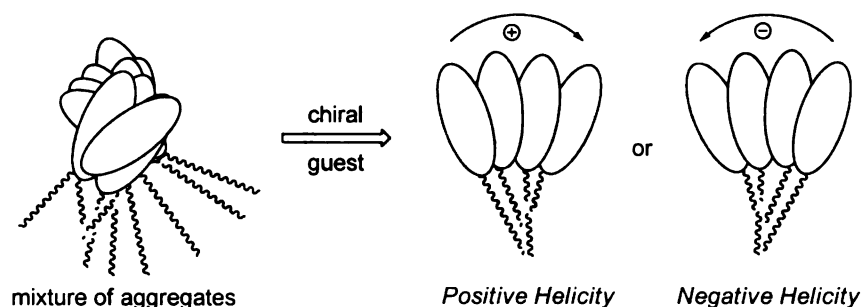
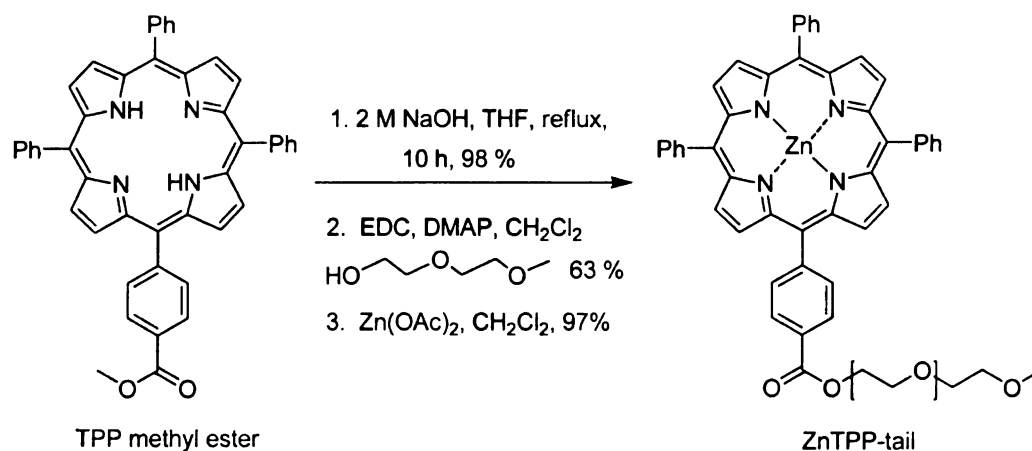


Figure VI-9: Triggered by π -stacking, aggregation of porphyrins results in formation of a mixture of H- and J-assemblies, which upon complexation with a chiral guest form a single helical aggregate.

For the purpose discussed above we introduce diethyleneglycol monomethyl ether as a tail onto the ZnTPP porphyrins (Scheme VI-1). The synthesis of the tail-porphyrin starts with the previously reported TFA catalyzed condensation of pyrrole, benzaldehyde and 4-methylcarboxy benzaldehyde (4:3:1 ratio respectively) in dichloromethane, followed by oxidation with *p*-chloranil.⁴⁷ Isolated from the formed mixture of porphyrins 5-(4-methylcarboxy)-10,15,20-triphenyl porphyrin (TPP-ester) is dissolved in THF and hydrolyzed with aqueous solution of 2 M NaOH to yield porphyrin acid (TPP-acid), which is further derivatized with di-ethyleneglycol monomethyl ether via EDCI/DMAP

coupling. Metallation of the porphyrin with $\text{Zn}(\text{OAc})_2$ in dichloromethane for 10 h gives ZnTPP-tail (Scheme VI-1).

Scheme VI-1: Synthesis of ZnTPP-tail porphyrin (XI)



Since the aggregation of porphyrins in organic media has not been thoroughly studied, we performed a detailed UV-vis monitored investigation of ZnTPP-tail assembly in hexane, methylcyclohexane and dichloromethane at room temperature and 0 °C. For aggregate assembly 1 mM stock solution of the tail-porphyrin **XI** in dichloromethane is used. In order to minimize the error in concentration 10 mM stock solution of ZnTPP-tail porphyrin is prepared from 20 mg of the porphyrin dissolved in 12 mL of dichloromethane. A second 1:10 dilution with dichloromethane affords the 1 mM solution of porphyrin used for aggregation studies.

For detection of the aggregation process 1 mM porphyrin solution is added in 1 μL portion into 1 mm UV cell containing a solvent of choice (0.2 mL). After addition of the first portion ($C = 5 \times 10^{-6} \text{ M}$) the λ_{max} of the Soret band of the monomeric porphyrin is measured as follows: dichloromethane: $\lambda_{\text{max}} = 419 \text{ nm}$; methylcyclohexane: $\lambda_{\text{max}} = 416 \text{ nm}$; hexane: $\lambda_{\text{max}} = 415 \text{ nm}$. The addition of the porphyrin is continued until

aggregation is observed as broadening of the Soret band (Figure VI-10, yellow curve). It is worth noting that while hexane and methylcyclohexane lead to aggregation at 40 μM concentration, no porphyrin assembly was detected even at 0.1 mM concentration of the porphyrin in dichloromethane, which can be explained by the high solubility of the porphyrin in CH_2Cl_2 . Further increase of porphyrin concentration in hexane and methylcyclohexane induced a split of the broaden band into two peaks: bathochromic and hypsochromic. Shifting of the peaks continued upon addition of porphyrin solution into the UV cell and at 50 μM concentration resulted in a separation of 10 nm between the two bands (blue shifted in hexane: $\lambda_{\text{max}} = 411 \text{ nm}$; methylcyclohexane: $\lambda_{\text{max}} = 412 \text{ nm}$) nm and red shifted (hexane: $\lambda_{\text{max}} = 419 \text{ nm}$; methylcyclohexane: $\lambda_{\text{max}} = 421 \text{ nm}$).

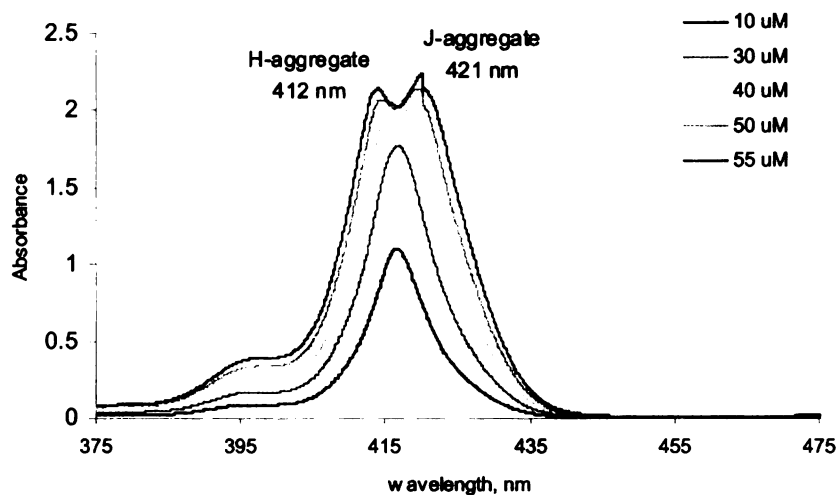


Figure VI-10: Aggregation of Zn-TPP-tail porphyrin in hexane starts at $3 \times 10^{-5} \text{ M}$ concentration (broadening of the Soret band). Further increase of porphyrin concentration (40 μM and higher) results in a split of the Soret band.

According to literature precedents a split in the Soret band can be attributed to the aggregation of the porphyrins into a mixture of two geometrically different assemblies: H-aggregate (face to face - “sandwich” type) and J-aggregate (edge-to-edge - “cascade”

type)). The H-aggregate appears at a shorter wavelength and the band of the J-assembly at a longer wavelength, as compared to the Soret band of the corresponding porphyrin monomer.^{48, 49} Along with the split of the Soret band, we observe that aggregation results in noticeable quenching of the extinction of the aromatic system (Figure IV-10). Screening of the solutions with the formed aggregates after 1 h does not give any significant changes in the appearance of the UV spectrum indicating a high stability of the porphyrin assembly. Cooling of the aggregate solutions to 0 °C led to gradual decrease in the absorption value due to precipitation of the porphyrin aggregate from the solution.

VI.3. Induction of chirality into porphyrin aggregates

When a chiral diamine is added to preformed aggregates of porphyrin **XII**, the formation of the complex can be clearly monitored by UV-vis. For this choice of solvent is crucial, i.e., while both non-polar solvents (hexane and methylcyclohexane) promote the aggregation process, monitoring of chiral induction is possible only in methylcyclohexane, due to precipitation of the complexed aggregate from hexane solution. Namely, when aggregates preformed in hexane are complexed with (*S*)-1,2-diaminopropane addition of the first two equivalents of diamine causes transformation of both aggregates into one assembly with transition at 420 nm (Figure VI-11). Further addition of diamine leads to a drop in the absorbance of the spectrum due to the appearance of a fluffy green precipitate in the UV cell. It is noteworthy, that the UV curve of the remaining solution has a main absorption at 415 nm corresponding to the porphyrin monomer, while the 420 nm peak induced by complexed aggregate is significantly decreased (Figure VI-11, red curve). Saturation of the solution with diamine yields the complete complexation of the remaining

porphyrins in the assembly with the main absorption at 420 nm (Figure VI-11, light blue and blue curves).

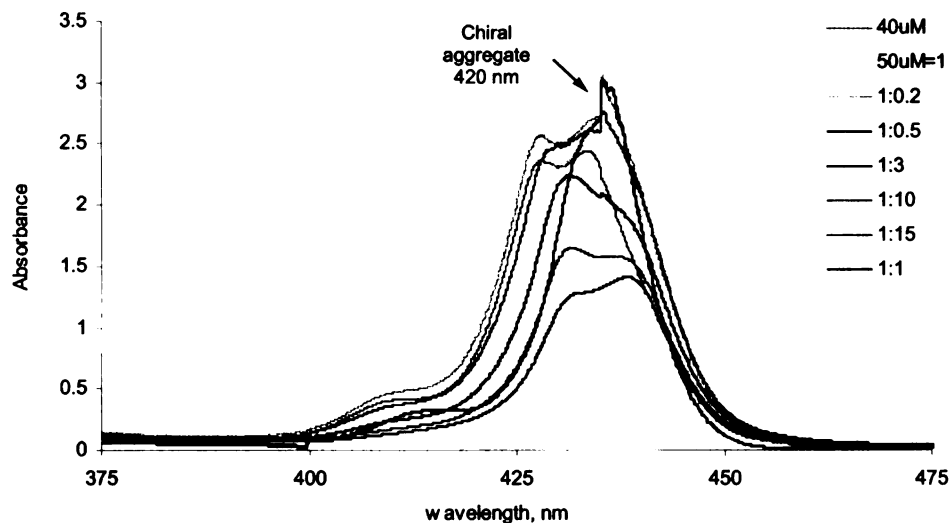


Figure VI-11: UV-vis titration of porphyrin aggregate with (*S*)-1,2-diaminopropane. Addition of 1 equiv of diamine to Zn-TPP-tail aggregate (50 μ M, yellow curve) in hexane gives formation of red shifted complex with absorption at 420 nm (green curve): red curve – 3 equiv of diamine; navy blue curve – 10 equiv; blue curve – 15 equiv of diamine.

It is noteworthy that when the isolated precipitate is dissolved in a mixture of hexane and dichloromethane (10:1), the UV absorption at 420 nm corresponding to the complexed aggregate is restored. Additionally, the ^1H -NMR spectrum of the formed precipitate showed the presence of the diamine. Thus, although the formation of sediment opens the possibility to isolate the aggregates from the solution for studying their structure, use of hexane for chiral induction is not possible. The same experiment performed in methylcyclohexane proceeds without precipitation and gives the porphyrin aggregate complexed with (*S*)-1,3-diaminopropane with absorption at 422 nm.

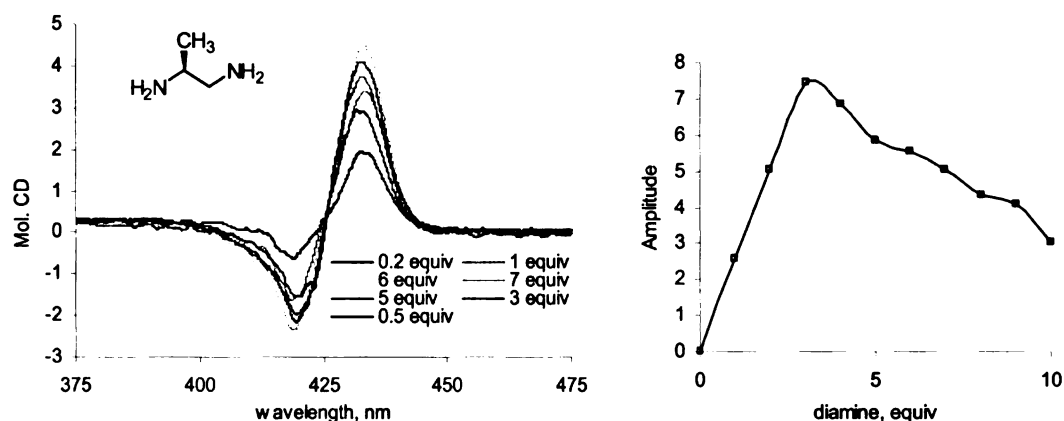


Figure VI-12: Induction of helicity into the porphyrin aggregate (50 μ M) with (*S*)-2-diaminopropane yields a positive ECCD. The maximal amplitude obtained with 3 equiv of chiral diamine. Spectra normalized to the concentration of porphyrin.

Further UV-vis and ECCD studies were performed with 50 μ M ZnTPP-tail solution in methylcyclohexane. For chiral induction three chiral diamines of different length were used: (*S*)-1,2-diaminopropane, (*S*)-ornithine methyl amide (1,4-diamine) and (*S*)-lysine methyl ester (1,5-diamine). Upon addition of (*S*)-1,2-diaminopropane to achiral porphyrin aggregates chiral induction is observed at porphyrin/substrate ratio 1:0.2 as a positive ECCD curve (Figure VI-12). Increase of diamine concentration in the solution leads to the gradual enhancement of ECCD amplitude that leveled off after addition of more than 5 equiv of diamine. Further addition of diamine (7 equiv and higher) leads to a drop on the amplitude of the spectrum and complete disappearance of the ECCD signal presumably due to the saturation of the binding sites of the porphyrins and disruption of the porphyrin assembly. The UV-vis spectra of the aggregate-(*S*)-1,2-diaminopropane complexes show a red shift of both H- and J-bands (414 nm and 420 nm respectively) to a single transition at 423 nm, which could indicate the formation of a new assembly (see Figure VI-13).

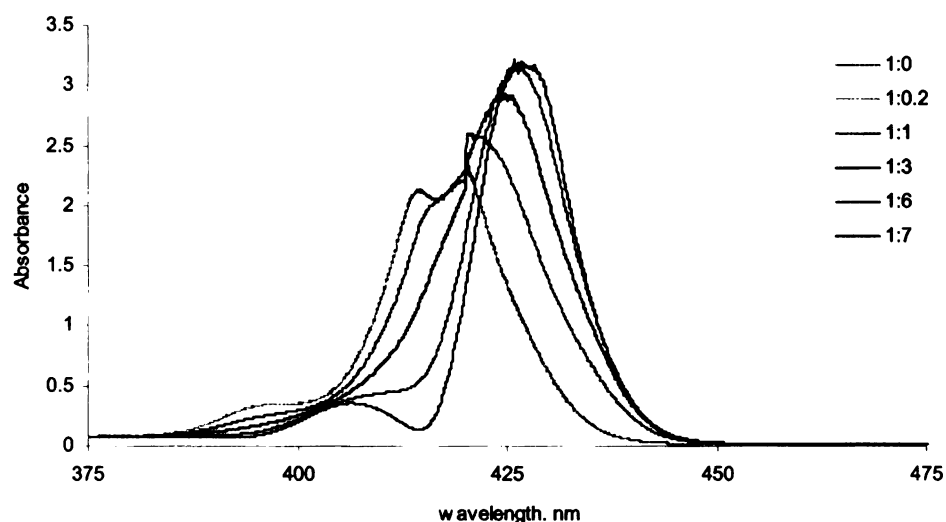


Figure VI-13: Addition of (*S*)-1,2-diaminopropane to the porphyrin aggregate yields the formation of a single assembly (UV-vis spectra).

The other two chiral diamines, L-ornithine methyl amide and L-lysine methyl ester induce a negative helicity of the porphyrin aggregate (Figure 14). It is noteworthy, that both L-ornithine methyl amide and L-lysine methyl ester cause a similar transformation of the J- and H-species into a single assembly absorbing at 423 nm. L-Lysine methyl ester gave ECCD spectrum of much higher amplitude as compared to the (*S*)-1,2-diaminopropane and L-ornithine methyl amide. Enhanced amplitude observed for L-Lysine methyl ester is consistent with the result obtained with ZnTPP-tz.⁵⁰

The sign of the observed CD couplets also corresponds to that previously reported for these substrate with bis-porphyrin tweezer.⁵¹ Such consistency suggests that the complexation in both systems - porphyrin tweezer and porphyrin aggregate - occurs through an identical binding mode and similar ECCD active conformation of the substrate in the formed complex. In every case the helicity of the chiral assembly can be rationalized on the basis of steric interaction taking place between the porphyrin and the

two substituents at the asymmetric center of the chiral substrate.⁵¹ Alleviating the steric strain in the complex with (*S*)-1,2-diaminopropane leads to a clockwise relative orientation of the porphyrins, and results in positive ECCD signal. Similarly, the negative ECCD observed with L-ornithine methyl amide and L-lysine methyl ester arises from the counterclockwise orientation of the porphyrins induced by steric interaction between the porphyrin and the carbonyl group.⁵⁰

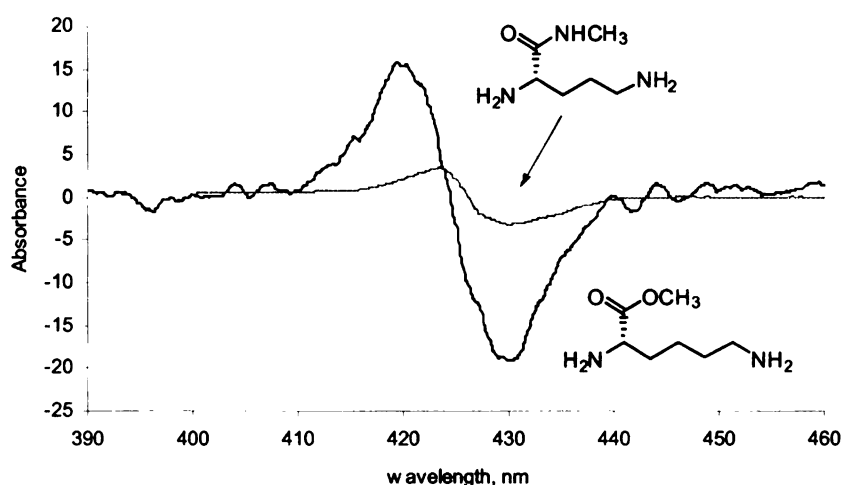


Figure VI-14: ECCD of ZnTPP-tail with: Magenta - L-Ornithine methyl amide ($\Delta\epsilon = -9$); Blue - L-Lysine methyl ester ($\Delta\epsilon = -47$) at aggregate/substrate ratio 1:0.1. Spectra normalized to the concentration of porphyrin.

VI.4. Geometry of porphyrin-porphyrin interaction

The geometry of the formed aggregate could potentially be established through analysis of the precipitate formed upon addition of chiral diamine. Unfortunately, the isolated solid aggregate is non-crystalline, hence impossible to analyze through crystallography. Parallel experiments to grow a crystal of porphyrin **XI** complex were

unsuccessful most probably due to the flexibility of the oligomeric tail. Moreover, complexation of the amine with porphyrins is also problematic. All attempts to crystallize ZnTPP with mono- or diamine yielded free porphyrin crystals.

Nevertheless, we can use the information provided by a bathochromic or a hypsochromic shift of the Soret band caused by aggregation of the porphyrins for identification of the type of species formed upon chiral induction. It is well known that coordination of an amine group with the metalloporphyrin induces a red shift of the Soret band.⁵¹ Moreover, it has been established that complexation of bis-porphyrin tweezer with diamines of different length results in the formation of a 1:1 complex at equimolar ratio of diamine to porphyrin tweezer. The Soret band of the new species red shifts to values that depend on the separation of the two interacting porphyrins, namely, closer interacting porphyrin rings red shift to a lesser degree as opposed to porphyrin rings that are well separated.⁵¹ For instance, complexation of zinc tetraphenyl porphyrin (ZnTPP) to a monoamine results in 12 nm bathochromic shift of λ_{max} , indicating formation of 1:1 porphyrin-amine complex. Binding of bis-porphyrin with 1,9-diamine results in up to 9 nm red shift of the main absorption (Table VI-1). Shortening of the diamine to two carbons results in 3 nm red shift of the Soret band. This phenomenon is explained as a result of two counteracting effects: binding of the amine to the metalloporphyrin and blue shift of the absorption as a result of bringing the two porphyrin planes close to each other.

Similar to the change in the absorption maxima of the monomeric complexes, we can expect the absorption of the aggregate to shift upon binding to the chiral guest. Moreover, it is expected that both H- and J- transitions can be affected equally by the complexation if the geometry of the assembly is not altered by binding. Namely, if

coordination of bis-porphyrin to 1,3-diamine causes 4 nm to red shift of the Soret band, it is plausible to expect the absorption maxima of both H- and J- transitions red shift for 4 nm. Since the length of the bound substrate could influence an interchromophoric distance between the two porphyrins in the aggregate the relative red shift could change with the length of the diamine incorporated into the aggregate. On the other hand, the complexation of the diamine to the porphyrin aggregate can change the geometry of the porphyrin assembly. Thus, it could be possible to identify the geometry of the formed species by monitoring the shift of the absorption maxima.

Table VI-1: Red-shift of tweezers upon titration with diamines
 $(\Delta\lambda = \lambda_{\text{complex}} - \lambda_{\text{porphyrin}})$

Entry	$\text{NH}_2\text{CH}_2(\text{CH}_2)_n\text{NH}_2$	ZnTPP-tz
1	n=1	3.0
2	n=2	3.9
3	n=3	4.3
4	n=4	6.7
5	n=5	6.9
6	n=6	7.2
7	n=7	8.2
8	n=8	8.6

Data obtained in dichloromethane at 1:1.2 host-guest ratio

The other approach might be to analyze the change in the absorption of monomeric complexes upon aggregation. Namely, the absorption of the porphyrin-amine complex should be altered if porphyrin aggregates are formed. Formation of aggregate can either contribute positively to a shift of the Soret band of the complex if it is J-type, or negatively, i.e. induce blue shift of the Soret band of the aggregate upon H-aggregation. As it is depicted in Figure VI-15, addition of L-lysine methyl ester to the monomeric

ZnTPP-tail (5 μM , no aggregate present) leads to formation of new complexed species that absorb at 427 nm, i.e., total 12 nm shift from the Soret band of the free porphyrin.

The shift corresponds to the formation of a 1:1 porphyrin-amine complex.

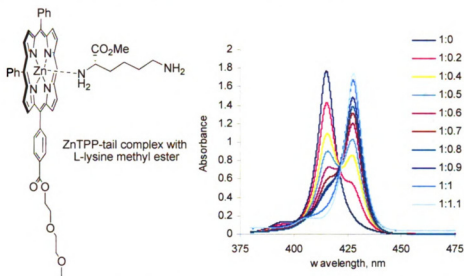


Figure VI-15: Complexation of porphyrin-tail monomer with L-lysine-methyl ester results in a 12 nm red shift upon formation of 1:1 complex.

Complexation of ZnTPP-tail aggregate (Figure VI-16, teal curve) with 0.1 equivalent of L-lysine methyl ester in methylcyclohexane gives rise to a single new transition at 421 nm and disappearance of the blue shifted absorption of the H-aggregate at 412 nm (Figure VI-16, black curve). The overall 9 nm shift of the H-transition is in agreement with formation of monomeric porphyrin-diamine 2:1 complex reported earlier for the bis-porphyrin systems. If compared to the Soret band of the fully complexed monomeric porphyrin (427 nm), the aggregate-diamine complex absorbing at 421 nm is 6 nm blue shifted with respect to the non-aggregates species.

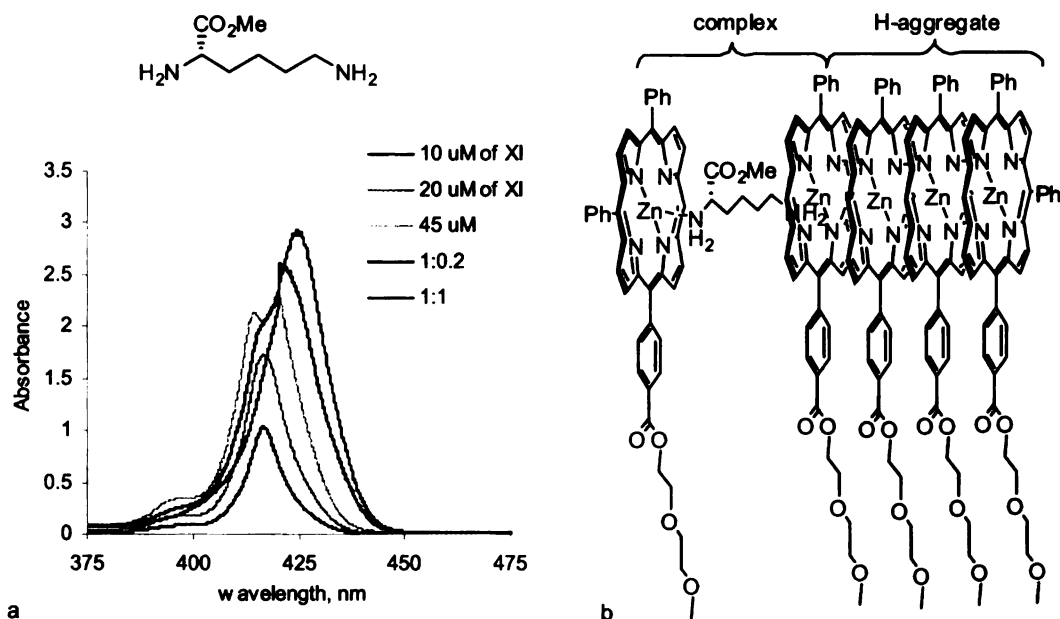


Figure VI-16: Complexation of the ZnTPP-tail aggregates (H- and J-) with L-lysine methyl ester in methylcyclohexane results in the equilibration of a single UV-vis transition
a) Teal – porphyrin aggregate, Black – aggregate with 0.2 equiv of diamine (421 nm); Blue – aggregate with 1 equiv of diamine (423 nm); b) Pictorial representation of the H-aggregate-diamine complex formed in the solution.

It is also noteworthy that the complexed aggregates do not show any indication of the J-assembly formed in the solution. Since the complexation of the aggregate with L-lysine methyl ester causes a 9 nm red shift, it is expected for the complexed J-aggregate to induce a new transition, further red shifted as compared to the complexed H-aggregate. Since the absorption maxima for the J-aggregate in this experiment is at 419 nm, the new J-complexed species are expected to have a Soret band at 428 nm (starting 419 nm plus 9 nm of the red shift contributed by binding to the diamine). Nevertheless, no such absorption is detected. Moreover, presence of a single band refers to equilibration of both H- and J-aggregates in one chiral superstructure that is blue shifted with respect to the monomeric complex. Subsequently, since the blue shift in porphyrin aggregates

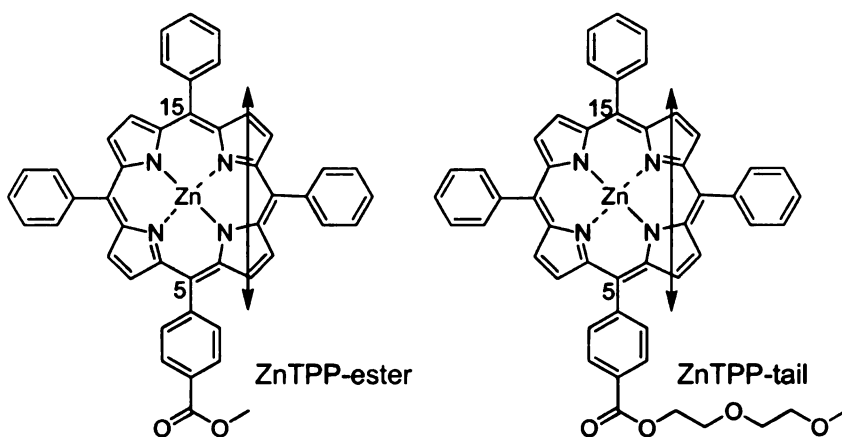
accompanies formation of H-species we can identify the geometry of the formed chiral aggregate as face-to-face (Figure VI-16b).

Further we took out to investigate whether the observed chiral induction requires the presence of an aggregate. In other words, since the monomeric porphyrins are able to form a complex with the chiral diamine, is it possible that the chiral induction observed on the aggregate is the result of complexation of the remaining monomeric species with a chiral guest? For this purpose, we perform CD monitored titration of the ZnTPP-tail porphyrin solutions at concentration where no aggregation is detected (concentrations used: 3×10^{-5} mM, 1×10^{-5} mM and 5×10^{-6} mM). Interestingly, none of the three solutions tested produced ECCD signal after binding to the previously used chiral diamines (binding was verified by UV-vis) hence, strongly suggesting that chiral induction is taking place in the aggregate and not due to complexation of the remaining ZnTPP monomers. The absence of chiral induction with monomeric species could be due to lack of stabilization of the relative orientation of the chromophore's transition moments upon complexation with a chiral ligand.

VI.5. The role of the hydrophilic interaction in chiral induction

In order to get an insight into the role of the hydrophilic tail as a control element we use 5-[4-methylcarboxyphenyl]-10,15,20-triphenylporphyrin (ZnTPP methyl ester) as a truncated version of the tail porphyrin. Similar to the tail porphyrin the carboxylate moiety of ZnTPP-ester provides a defined direction of the transition moment in C_5-C_{15} direction.

Scheme VI-2: ZnTPP-methyl ester as a truncated structure of ZnTPP-tail.



Consequently, we may expect both porphyrins to have relatively similar aggregation properties. Indeed, aggregates of ZnTPP-ester is detected in both hexane and methylcyclohexane as broadening of the Soret band, although a slightly elevated concentration (60 μ M) of the porphyrin was used (Figure VI-17b). UV-vis monitored titration of ZnTPP-ester aggregate with L-lysine methyl ester in methylcyclohexane shows formation of a single complex with an absorption at 421 nm (Figure VI-17b), which is similar to that of the ZnTPP-tail aggregate – diamine complex (Figure VI-17a). The characteristic red shift corresponds to the formation of H-type complexes with both ZnTPP-ester and ZnTPP-tail porphyrins.

Nevertheless, while tail-porphyrin aggregates give detectable chiral induction, the diamine complexes of both monomeric and aggregated species of ZnTPP methyl ester are ECCD silent. Namely, neither (*S*)-1,2-diaminopropane, L-ornithine methyl amide or L-lysine methyl ester gave any detectable helicity of the aggregate. The result can be attributed to the improper alignment of porphyrins in the aggregate. While the carboxylate moiety breaks the symmetry of the porphyrin, the interaction between the ester groups in the aggregate is not sufficient enough for controlling the alignment of the transition

moments in the porphyrin assembly. Although the binding of the aggregate to a chiral guest yields a new complexed species, most probably the random orientation of transition moments in the complexed aggregate interferes with generation of detectable ECCD signal.

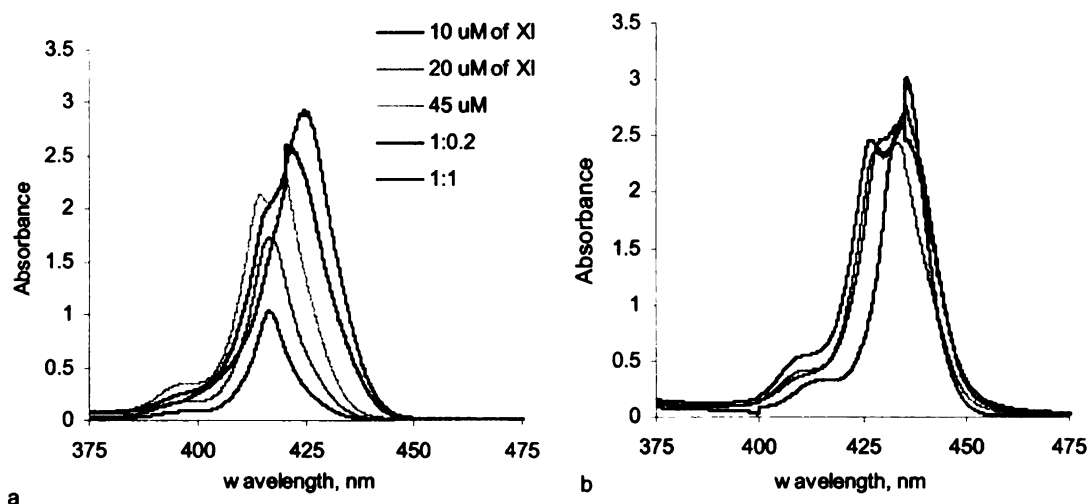
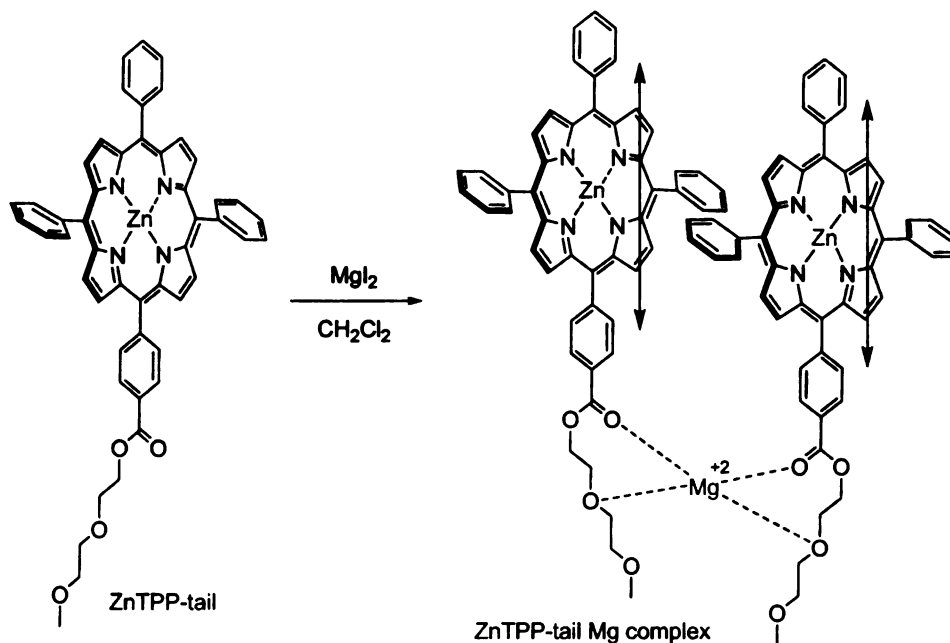


Figure VI-17: UV-vis spectra of the a) ZnTPP-tail aggregate (50 μM) and b) ZnTPP-ester (60 μM) complexed with L-lysine methyl ester (1:0.2) in methylcyclohexane.

Another experiment that could underline the contribution of the oxygenated tail in stabilization of the relative orientation of porphyrins in the assembly is to compare an aggregate with a bimolecular mimic of tail-porphyrin having a similar relative orientation of the chromophores. As it was discussed before one of the functions of the hydrocarbon linker in the porphyrin tweezer is to stabilize the relative orientation of the electric dipole transition moments of the chromophores in the porphyrin-substrate complex. Analogous stabilization of the edtm orientation in the aggregate is achieved, presumably, by hydrophilic interactions of the oxygenated tail. Hence, the stabilization of the transition moments in non-aggregates solutions could also result in detectable chirality.

Scheme VI-3: Complexation of oxygenated tails with Mg metal leads to formation of bis-porphyrin complex and ensures parallel alignment of transition moments of two chromophores.



The presence of an oxygen atom in the tail of the ZnTPP-tail porphyrin allows for the use of metal coordination for setting the relative orientation of the tails in the complex. As is depicted on Scheme VI-3, addition of Mg^{+2} to the non-aggregated solution of the ZnTPP-tail could lead to coordination of oxygenated tails of two zincated chromophores and secure parallel orientation of transition moments.

The ZnTPP-tail- Mg^{+2} complex was formed by addition of an equimolar amount of MgCl_2 to a solution of ZnTPP-tail in dichloromethane. After 4 h the reaction mixture was filtered through celite and concentrated under reduced pressure.

The ECCD studies of the two non-aggregated systems: ZnTPP-tail and ZnTPP-tail- Mg^{+2} gave the following results. While the complexation of monomeric (concentrations below the aggregation point, 1-30 μM) ZnTPP-tail with chiral diamines did not show chiral induction, addition of diamines to the non-aggregated ZnTPP-tail-

Mg⁺² results in prominent ECCD signal. Thus, when 5 μ M solution of ZnTPP-tail-Mg⁺² represents the system equivalent to the 5 μ M solution of **XI** where no aggregates can be detected with UV-vis. However, when complexed with (*R*)-1,2-diaminopropane ZnTPP-tail-Mg⁺² yields a negative ECCD bisignate (the enantiomeric (*S*)-1,2-diaminopropane gives positive ECCD with ZnTPP-tail aggregate) at 1 equivalent of diamine (Figure VI-18). Unlike the porphyrin aggregate, for the dimeric complex increase of diamine concentration to 20 equiv enhanced the amplitude of the spectrum indicating an increase of the bound species in the solution.

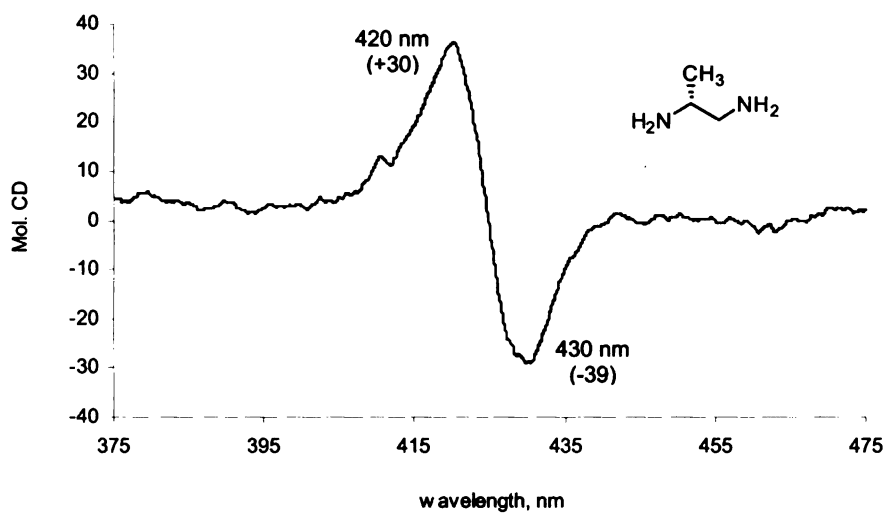


Figure VI-18: ECCD spectrum observed for (*S*)-1,2-diaminopropane with ZnTPP-tail-Mg complex in hexane at 0 °C at 1:20 porphyrin-diamine ratio (spectrum is normalized to the concentration of bis-porphyrin).

It is noteworthy that although the complexation of a ZnTPP-tail-Mg⁺² with L-ornithine methyl amide or L-lysine methyl ester was accompanied by red shift of Soret band, they did not yield ECCD active complexes. One has to consider that unlike the porphyrin tweezer or porphyrin aggregate, the two porphyrins in ZnTPP-tail-Mg⁺² are held in the complex through metal coordination. Subsequently, the complex can be sensitive

towards the size of the ligand incorporated into the binding pocket, since the length of the diamine directly affects interchromophoric distance between the porphyrins. For instance binding of a long diamine to the complex can pull porphyrins away and disrupt the magnesium-oxygen coordination. The loss of Mg^{+2} coordination in $\text{ZnTPP-tail-Mg}^{+2}$ could yield the formation of unorganized monomeric porphyrins and result in randomized orientation of the electric dipole transition moments. The effect of such process would be a disappearance of the ECCD signal.

It is also worth noting that complexation of the formed aggregates of ZnTPP-tail chiral substrates bearing a carbonyl or a hydroxyl as the coordination sites to the porphyrin was unsuccessful. Namely, addition of chiral amides, diols and amino alcohols did not show any complexation present in the solution and, subsequently, no ECCD could be detected. The result can be explained by the significantly lower binding affinity of these types of substrates with Zn porphyrin.

VI.7. An alternative porphyrin for construction of chiral aggregates

The aggregation of porphyrins into the assemblies that could be potentially used for chiral induction was found to depend on the steric bulk of the porphyrin. For instance introduction of the mesityl group on to the *meso*-position of the porphyrin ring gives the ZnTMsP-tail (Figure VI-19) that shows significantly decreased ability to aggregate. The aggregates with ZnTMsP-tail were detected only at mM concentration of porphyrin (compared with 45 μM of ZnTPP-tail) in methylcyclohexane (Figure VI-19). This outcome is expected since the bulk of the methyl group oriented inside of the porphyrin

plane interferes with the π - π interaction between the porphyrins that is necessary for the formation of the aggregates.

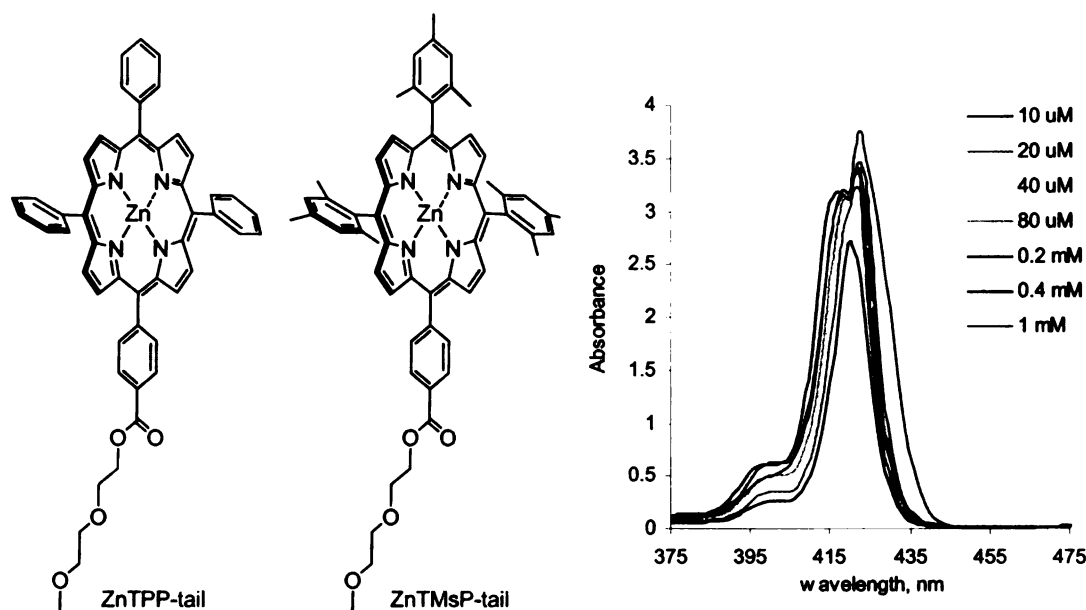


Figure VI-19: Influence of the bulk of the porphyrin on the aggregation. Aggregation of the ZnTMsP-tail in methylcyclohexane achieved at mM concentration.

When (*R*)-1,2-diaminopropane or L-lysine methyl ester were added to the aggregated solutions no ECCD was detected. At the same time, the UV-vis spectrum of the assembly titrated with (*R*)-1,2-diaminopropane shows the red shift of the absorption maxima of the aggregate from 422 nm to 424 nm. Since the complexation of the porphyrins in the aggregate is not affected by the bulk of the porphyrin, the absence of ECCD with ZnTMsP-tail aggregate might be a result of an improper orientation of the porphyrin within an aggregate.

Another modification to the porphyrin was the introduction of the pentafluorinated phenyl groups onto the *meso*-positions of the porphyrin ring. Highly fluorinated substitution at the *meso*-position of the porphyrin ring improve a Lewis acidity of the zinc

atom incorporated in the core and enables binding of zinc porphyrin with oxygen containing functional groups.⁵² Hence, it is expected that the aggregates of ZnTPFP-tail (Figure VI-20a) could accept the ligands bearing carbonyl or hydroxyl groups as the coordination sites. However, despite the similarity in the steric encumbrance between ZnTPP and ZnTPFP, the aggregate with the fluorinated analog was detected at significantly higher concentrations (80 μM) as compared to that of ZnTPP-tail (Figure VI-20b).

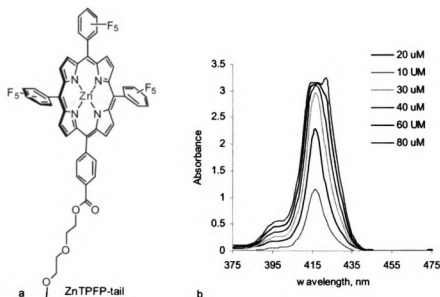


Figure VI-20: Aggregation of the Lewis acidic ZnTPFP-tail in methylcyclohexane.

Complexation of chiral diamines to the aggregate of ZnTPFP-tail did not induce any detectable helicity. However, similar to the other aggregates the Soret band red shifted upon complexation with diamine. Nevertheless, it was unexpected to observe that unlike ZnTPP-tail aggregates, where addition of the ligand shifts both H- and J-assembly to a single superstructure yielding the UV curve with one absorption maximum (Figure IV-21a), the UV curve of ZnTPFP-tail red shifts but retains its shape (Figure VI-21b). These result

suggests that unlike the aggregates of porphyrin XI, geometry of the ZnTPFP-tail aggregate is not affected by complexation with ligand.

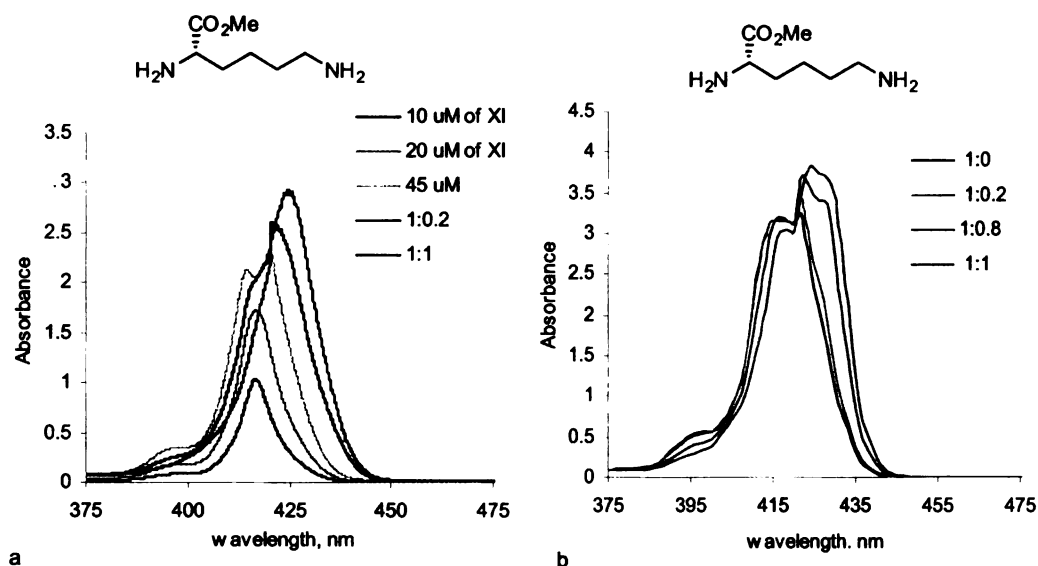


Figure VI-21: Complexation of (a) ZnTPFP-tail and (b) ZnTPFP-tail aggregates with (*R*)-1,2-diaminopropane yields assemblies of a different geometry.

Since the UV-vis spectrum confirms the coordination of the ligand with the assembly of ZnTPFP-tail, the retention of the shape of the UV-vis curve upon complexation and an absence of chiral induction within this aggregate could be a result of aggregate inability to form 2:1 porphyrin-diamine complex necessary for chiral induction. Subsequently, it is plausible to assume that aggregation of ZnTPFP-yield the geometrical assemblies that differ from the classical mixture of H- and J aggregates. Considering the nucleophilic nature of the fluorine and enhanced Lewis acidity of the zinc atom in the pentafluorinated porphyrin it is possible to envision the formation of the assembly depicted in Figure VI-22, where the superstructure is constructed through the coordination of fluorine with the zinc atom in the porphyrin core.

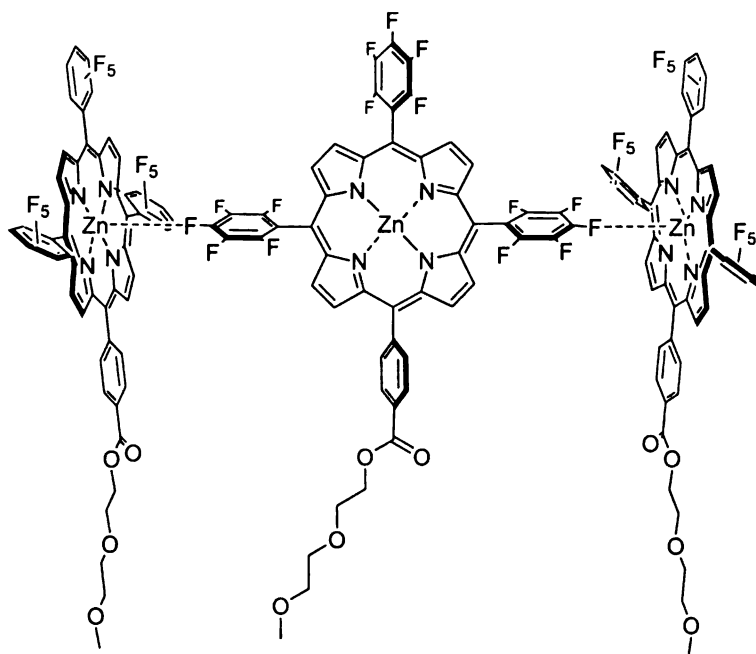


Figure VI-22: Possible superstructure formed upon aggregation of ZnTPFP-tail.

This assembly, if formed could potentially complex with the diamine without disruption of the geometry of aggregate. Upon addition of diamine only mono-coordinated species are expected to form due to the geometry of the aggregate. While the complexation of the assembly with the ligand can be observed as the red shift in UV-vis spectrum of the superstructure, no ECD signal is expected to be generated due to the absence of the bis-chromophoric complex formed in the solution.

Thus, despite the similarity of the steric encumbrance of ZnTPP and ZnTPFP use of the latter for assembly of chiral superstructures was not successful and the ZnTPP-tail is the most promising porphyrin structure applicable towards the construction of chiral aggregates.

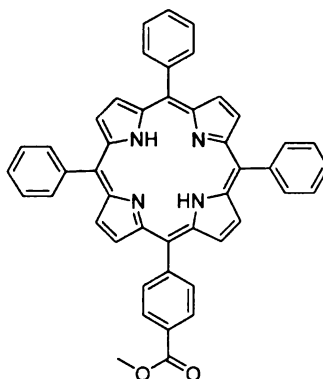
VI.8. Experimental procedures.

Anhydrous CH_2Cl_2 was dried over CaH_2 and distilled. The solvents used for CD measurements were purchased from Aldrich and were spectra grade. All reactions were performed in dried glassware under nitrogen. Column chromatography was performed using SiliCycle silica gel (230-400 mesh). ^1H -NMR spectra were obtained on Varian Inova 300 MHz or 500 MHz instrument and are reported in parts per million (ppm) relative to the solvent resonances (δ), with coupling constants (J) in Hertz (Hz). IR studies were performed on a Galaxy series FTIR 3000 instrument (Matteson). UV/Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer and are reported as λ_{max} [nm]. CD spectra were recorded on a JASCO J-810 spectropolarimeter, equipped with a temperature controller (Neslab 111) for low temperature studies, and is reported as λ [nm] ($\Delta\epsilon_{\text{max}}$ [$\text{l mol}^{-1} \text{cm}^{-1}$]).

General procedure for synthesis of 5-(4-methylcarboxyphenyl)-10,15,20-triarylporphyrins:

Pyrrole (4 equiv), arylaldehyde (3 equiv) and 4-methylcarboxybenzaldehyde (1 equiv) were dissolved in dichloromethane (chloroform was used for porphyrin **1b**) (0.01M solution) and stirred under the nitrogen for 30 min. $\text{BF}_3 \cdot \text{OEt}_2$ (0.3 equiv) was then added and reaction mixture stirred for 4 h. *p*-Chloranil (2 equiv) was added to the reaction mixture in one portion and reaction was stirred for additional 1-2 h. After completion of oxidation (monitored by TLC) solvent was removed under reduced pressure and the crude

mixture of porphyrins was submitted to column chromatography and triarylporphyrin monomethyl ester was separated.

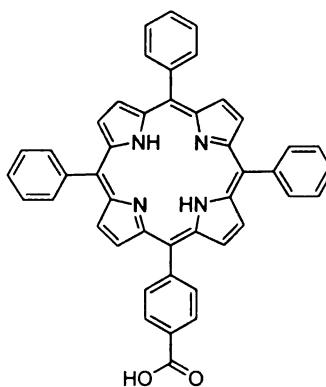


5-(4-Methylcarboxyphenyl)-10,15,20-triphenylporphyrin (TPP-methyl ester):

Benzaldehyde (2 g, 18 mmol), pyrrole (1.6 g, 24 mmol) and 4-methylcarboxybenzaldehyde (0.99 g, 6 mmol) were dissolved in CH_2Cl_2 (1.8 L). The solution was flushed with N_2 for 30 min, then $\text{BF}_3 \cdot \text{OEt}_2$ (0.26 mL) was added and the reaction mixture was stirred for 4 h. Then *p*-chloranil (3 g, 12.5 mmol) was added and reaction mixture stirred for another 2 h. Solvent was removed under reduced pressure and the crude solid was submitted to column chromatography (Silica, 50% CH_2Cl_2 /hexane) to elute the title compound as a purple solid in 21% (0.88 g) yield. ^1H NMR (CDCl_3 , 500 MHz): δ -2.18 (s, 2H (NH)), 4.09 (s, 3H), 7.71-7.77 (m, 9H), 8.19-8.22 (m, 4H), 8.30 (d, 6H, $J = 8.1$), 8.43 (d, 2H, $J = 8.1$), 8.78 (d, 2H, $J = 4.5$), 8.95 (m, 6H). MS (DCI): calc'd for $\text{C}_{46}\text{H}_{32}\text{N}_4\text{O}_2$ $m/z = 672.2$; obs'd $M^+ = 673.8$ $[\text{M}+\text{H}]^+$, $M^{+2} = 336.3$.

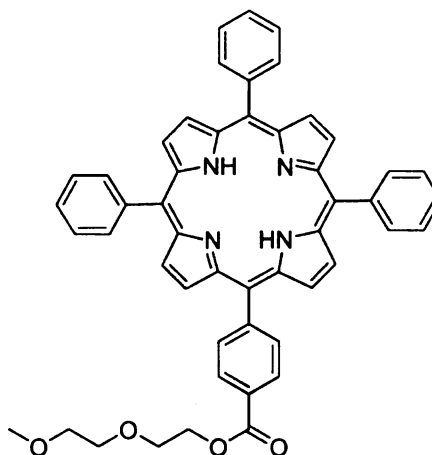
General procedure for hydrolysis of 5-(4-methylcarboxyphenyl)-10,15,20-triarylporphyrins:

Obtained from condensation porphyrin ester (0.3 - 0.5 mmol) was dissolved in THF (30 mL) and 2M NaOH (20 mL) was added. The mixture was refluxed for 16 h under N₂ atmosphere and cooled to the room temperature, acidified with 10% HCl (color changed from purple to green) and the THF was removed under reduced pressure. The remained aqueous phase was extracted with dichloromethane (6 x 100 mL). The extracts were combined, washed with water (3 x 100 mL, color changed back to purple) and dried with anhydrous Na₂SO₄. The solvent was removed and the resulting purple solid was precipitated with hexane from dichloromethane solution to afford pure 5-(4-carboxyphenyl)-10,15,20-triarylporphyrin. Residue was filtered out and crystals were washed ones with hexane and dried.



5-(4-Carboxyphenyl)-10,15,20-triphenylporphyrin (TPP-acid): TPP-methyl ester was hydrolyzed according to the general procedure described above to afford TPP-acid in 92% yield as pure purple solid. ¹H-NMR (CDCl₃, 500 MHz): δ -2.2 (s, 2H (NH)), 7.73-7.78

(m, 10H), 8.19-8.23 (m, 4H), 8.31 (d, 4H, $J = 8.1$), 8.45 (d, 2H, $J = 8.1$), 8.8 (d, 2H, $J = 4.5$), 8.95 (m, 6H); MS (DCI): calc'd for $C_{45}H_{30}N_4O_2$ $m/z = 658.7$, obs'd $M^+ = 658.9$.



5-[4-(DEGMME)-carboxyphenyl]-10,15,20-tri-phenyl porphyrin (TPP-tail):

Porphyrin acid (1 equiv), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 1.4 equiv), 4-dimethylaminopyridine (DMAP, 1.4 equiv) and DEGMME (3 equiv) were added in a round bottom flask and dissolved in dry dichloromethane (50 mL per 0.2 mmol of acid). The mixture was allowed to stir for 12-14 h at room temperature under nitrogen atmosphere and then was directly submitted to column chromatography, eluted with 10% EtOAc/ CH_2Cl_2 to afford the porphyrin tail in 75% yield. 1H -NMR ($CDCl_3$, 500 MHz): δ -2.6 (2H (N)), 3.38 (s, 3H), 3.57-3.60 (m, 2H), 3.73-3.76 (m, 2H), 3.93-3.96 (m, 2H), 4.61-4.64 (m, 2H), 7.82 (m, 10H), 8.34-8.36 (m, 8H), 8.48 (d, 2H, $J = 8.6$), 8.58 (d, 2H, $J = 8.6$), 8.97-9.02 (m, 7H); MS (DCI): calc'd for $C_{50}H_{40}N_4O_4$ $m/z = 760.8$, obs'd $[M+H]^+ = 760.1$.



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