LEWIS ACID MEDIATED *IN SITU* GENERATION OF MÜNCHNONES AIMED AT DIVERSITY ORIENTED SYNTHESIS OF NITROGEN CONTAINING DIHYDROHETEROCYCLES

By

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ABSTRACT

LEWIS ACID MEDIATED *IN SITU* GENERATION OF MÜNCHNONES AIMED AT DIVERSITY ORIENTED SYNTHESIS OF NITROGEN CONTAINING DIHYDROHETEROCYCLES

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This dissertation describes the development of Lewis acid mediated/catalyzed generation of mesionic 5-oxazolones (münchnones) from amino acid derived azlactones. Münchnones are highly reactive cyclic azomethine ylides, a class of 1, 3-dipoles used extensively for generation of five-membered nitrogen containing heterocycles. Our mild method allows for highly stereoselective cycloadditions with different dipolarophiles. Furthermore, it allows isolation of dihydroheterocyclic scaffolds without problems of decarboxylation, aromatization and isomerizations normally encountered in cycloadditions of traditionally used *N*-alkylated münchnones.

The generation of diverse small molecular scaffolds with potential biological activity is an ongoing theme in our group. Five-membered nitrogen containing rings are at the core of many natural products and prospective libraries of drug discovery programs. On account of the structural rigidity and the three dimensional disposition of functional groups, dihydroheterocyclic five-membered rings that we have accessed are perfectly suited for the aim of drug discovery. They have a different shape profile from aromatic heterocycles generally encountered in drug discovery programs and as such might interact with entirely new therapeutic targets. Chapter I lays a strong foundation for the need of such

molecules. Chapter II includes a survey of azlactones as a viable template for diversity oriented transformations. However, stereochemical diversity has not been efficiently achieved from azlactones. Stereochemical diversity is extremely important in screening for new ligands which can display functional groups for interactions with macromolecules that govern life as well as disease. Our proposed route to dihydroheterocycles from münchnones is discussed in the context of other stereoselective methods that employ lewis acids in 1, 3-dipolar cycloadditions of closely related nitrogen ylides.

Discovery of mild *in situ* method of generation of münchnones (cyclic azomethine ylides) from azlactones using Lewis acids and their use for stereoselective synthesis of nitrogen containing dihydroheterocycles; 2-imidazolines and Δ^1-pyrrolines are described in Chapter III and IV respectively. The scaffolds are obtained with high diastereoselectivity (stereochemical) and are amenable to diverse substitution (appendage diversity) and in many ways complement other methods towards these scaffolds. The dihydroheterocyclic scaffolds offer unexplored territory in terms of their structure (3-D disposition of functional groups) and their function (biological activity and catalysis). Chapter V describes selective and enhanced toxicity of the combination of imidazolines with chemotherapeutic drugs (camptothecin and cis-platin) in cancer cells. The mechanism and potential of this novel effect is being studied by other researchers in the group. The imidazoline scaffolds can catalyze a novel stereoselective reaction of ketenes with *N*-acylimines. We have also explored their use as analogs of amino alcohol ligands for diethyl zinc additions to electrophiles.

To

Vasudha

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KEY TO SYMBOLS AND ABBREVIATIONS

ADMET	Administration, distribution, metabolism, elimination, toxicity
ALLN	Acetyl-L-leucinyl-L-leucinyl-L-norleucinal
ATF	Activating transcription factor
CPT /CPT-11	Camptothecin
CDDP	*cis*- Diamminodichloro Platinum(II) (Cis-Platin)
CSA	camphor sulfonic acid
DBU	1, 5-Diazabicyclo[5.4.0]undec-5-ene
DCC	Dicyclohexylcarbodiimide
DMAP	4-(dimethylamino)pyridine
DCM	Dichloromethane
DNA	Deoxy ribo nucleic acid
DHFR	Dihydrofolate receptor
DOS	Diversity oriented synthesis
δ	chemical shift (parts per million)
ee	Enantiomeric excess
EDCI	Ethyl dimethylaminopropyl carbodiimide
eq.	Equivalent
FAP	bis-ferrocenyl amide phosphine
g	gram
HTS	High throughput screen
HRMS	High resolution mass spectrometry
h	hour
IR	Infra Red
I-κB	Inhibitor of κB
IKK	I-κB kinase
J	coupling constant
LAH	Lithium aluminium hydride
LDA	lithium diisopropylamide
M	Molar(concentration)
MHz	Mega Hertz
m/z	mass to charge ratio
MAPK	Mitogen-Activated Protein Kinase
MCR	Multi-component reaction
MCSL	Multiple core structure libraries
MEKK-1	MAPKinase Kinase
MS	Mass Spectrometry
MSA	methyl sulfonic acid
nM	nano molar
NBS	*N*-bromosuccinamide
NHC	N-Heterocyclic carbene
NMR	nuclear magnetic resonance
NF-κB	Nuclear factor-κB
PDTC	pyrrolinedithiocarbamate

PHOX	Phosphino-oxazolines
PHIM	Phosphino-imidazoline
PPTS	Pyridinium *p*-toluenesulphonic acid
Proteasome	multi-catalytic protease unit in cells
QUINAP	1-[2-(diphenylphosphino)-1-naphthalenyl]- Isoquinoline
RIF-1	Radiation induced fibrosarcoma
RNA	Ribonucleic acid
R	rectus(Cahn-Ingold-Prelog system)
S	sinister(Cahn-Ingold-Prelog system)
SMPPI	molecule inhibitors of protein-protein interactions
Tat/TAR	viral transactivation protein
TEA	Triethyl amine
TMSCl	Trimethylsilyl chloride
TNF-α	Tumor Necrosis Factor-α
TOS	Target oriented synthesis
μM	micro molar

CHAPTER I

SMALL HETEROCYCLIC SCAFFOLDS AND DRUG DISCOVERY.

A. Drug discovery process

One of the major goals in chemical and biological research is the identification of high affinity and specific ligands to receptors and enzymes. The identification of such ligands is a fundamental step in the development of molecular probes for the study of receptor and enzyme function, as well as for the eventual development of therapeutic agents or drugs.[1] Drug discovery is the process whereby compounds with activity against a specified target or function are identified, evaluated, and optimized for clinical applications.[2] The initial step in drug discovery (Figure I-1) involves the identification and validation of a target, generally a gene product, for which pharmacological modulation of target activity is predicted to produce a desired effect. Typical goals include enzyme inhibitors, receptor agonists or antagonists, and transporter inhibitors or activators. Target identification and validation may involve gene/protein expression profiling, phenotype analysis in cell culture and transgenic mouse models, and evaluation of humans with gene deletion/mutation. Follow-up preclinical evaluation includes analysis in animal models of compound efficacy and pharmacology (ADMET: administration, distribution, metabolism, elimination, toxicity) and studies of specificity and drug interactions. Initial drug discovery thus requires a robust assay of target activity and a collection of compounds for testing. "Hits" from initial screening are evaluated on the basis of many criteria, including but not limited to potency, specificity, toxicity, pharmacology, biopharmaceutical properties, and efficacy in

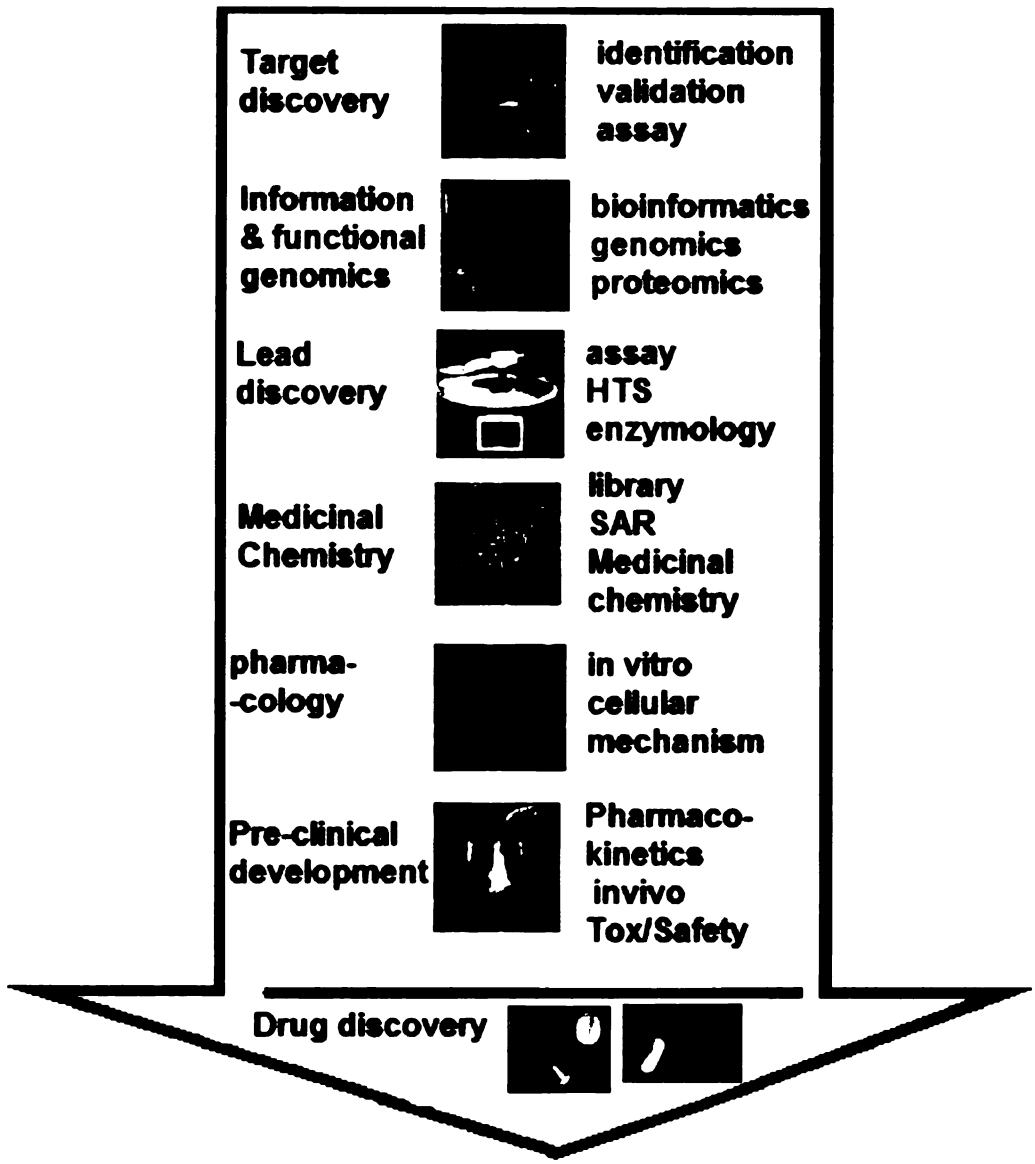


Figure I-1a. The drug discovery process. Adapted from www.signalpharm.com/ discovery_platforms.html.

animal models, to select lead compound(s) for optimization by synthetic chemistry and more extensive preclinical evaluation in animal models. These preclinical data form the basis to carry out clinical trials.[3]

B. A small molecule revolution

In a classical manner, lead compounds were derived from the extraction of natural products from plants, animals, insects, or microorganisms. Following positive

responses from several fractions, the next step is identification of the chemical entities responsible for the biological activity.

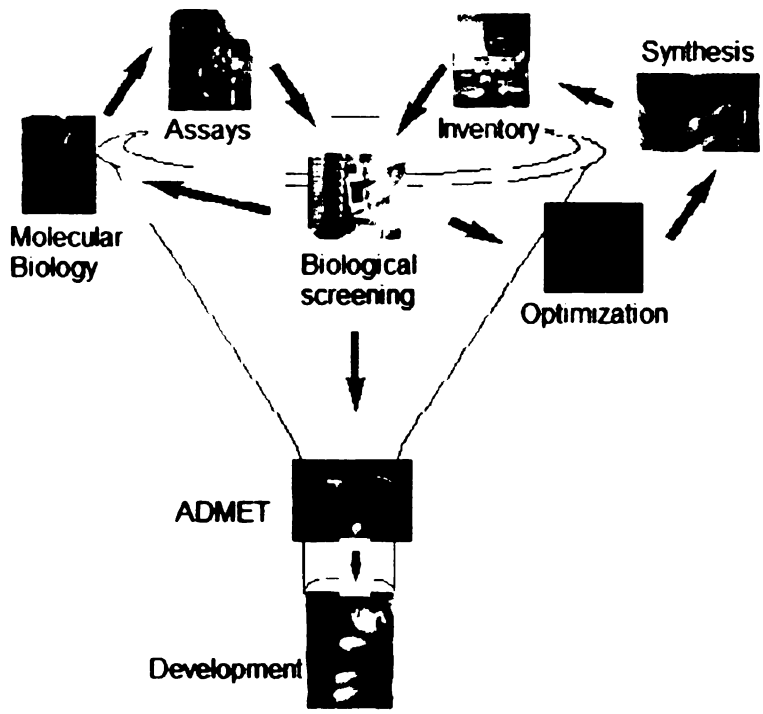


Figure I-1b. The drug discovery funnel. Adapted from www.akosgmbh.de / Drug_ discovery_process.html

Synthesis is then undertaken to obtain specific compound(s) in large quantities or to obtain simpler analogues that may exhibit similar biological response. These traditional approaches are time consuming and very expensive and the inability to identify multiple high-quality leads that are novel, tractable, and efficiently optimizable was a key bottleneck in the drug discovery environment.[4] Modern drug discovery has hence seen a paradigm shift to screening small molecule libraries for their ability to bind to a pre-selected protein target. Small molecules can exert powerful effects on the functions of macromolecules that comprise living systems. This remarkable ability makes them useful, both as research tools

for understanding life processes and as pharmacologic agents for promoting and restoring health. As compared to peptides and natural products, small-molecules posses numerous advantages in the drug discovery process such as easier synthesis, higher metabolic stability and bioavailability, easier access to analogues with increased potency, greater solubility and support for structure–activity relationship studies.[5]

C. Chemical genetics brings small molecules center stage

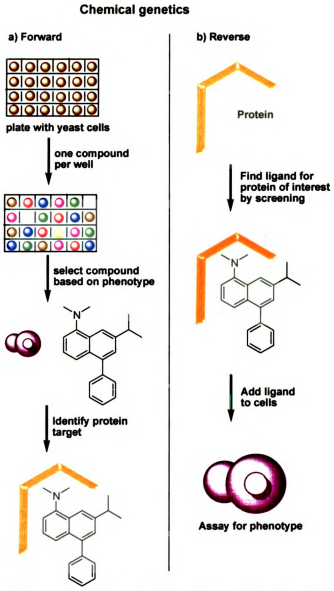


Figure I-2. Chemical Genetics. Adapted from Ref. 10.

Classic FORWARD-GENETICS is a powerful method for identifying genes that regulate biological processes in lower organisms. It is difficult, however, to use a genetic approach in mammals because of their slow rate of reproduction, large physical size, and large, diploid genome.[6] A second limitation of the genetic approach is that most mutations are not conditional — they cannot be turned on or off at will. Even when conditional mutations can be found (for example, temperature-sensitive mutations or mutant alleles under the control of an inducible promoter), expressing the mutant allele usually entails causing an environmental stress to the organism, such as a temperature shift, which itself can have marked consequences[7] and may confound the interpretation of results. This drawback prevents the functions of essential genes from being investigated because organisms with mutations in these genes are not viable. In addition, organisms that carry constitutive mutations may have time to compensate for their effects by up regulating related genes, which can obscure the initial effects of a mutation.

In a chemical-genetic approach, exogenous ligands (small molecules) are likewise used to alter the function of a single gene product within this complex cellular context. Chemical-genetic screens use a three-step procedure (Figure I-2) that entails: first, assembling a set of ligands (molecules capable of altering protein function) as mutation equivalents; second, doing a high-throughput screen for ligands that result in a phenotype or affect a biological process of interest (such as cell division, programmed cell death or embryonic pattern formation) and last, identifying protein targets of these active ligands. The advantages are as follows:

- The chemical-genetic approach is conditional and readily applicable to cells derived from complex organisms such as vertebrates. This is because a molecule can be added or removed at any time, enabling a kinetic analysis of the consequences of changes in protein function *in vivo*.
- This permits an analysis of the cellular or physiological events that occur immediately after altering the activity of a specific protein.
- In higher organisms, such as mice and humans, the approach can be used for 'genetic-like' screens in cells and tissues of these organisms, complementing genetic-screening methods.
- Not only protein-binding reagents, but other exogenous ligands such as RNA-binding antisense reagents and DNA-binding reagents [8, 9] can be similarly used.[10]
- Finding small molecules or mutations that affect a specific pathway and identifying the cellular target of the small molecule or the molecular sequence of the mutant gene can shed light on the pathway.[11]
- From the perspective of drug discovery, the "Chemical Genetics" approach offers the means for the simultaneous identification of proteins that can serve as targets for therapeutic intervention ("therapeutic target validation") and small molecules that can modulate the functions of these therapeutic targets ("chemical target validation"). The structures of the small-molecule modulators provide leads for the drug discovery process, where, for example, pharmacokinetic and pharmacodynamic properties can be optimized.

However the macromolecules that carry out the many functions required for life have enormous structural diversity, and this suggests that complementary levels of ***structural diversity*** will be needed in collections of candidate small molecules in order to find specific modulators for each of those functions. With the completion of the draft human genome sequence and genomics and proteomics research providing rapid information on the discovery of novel genes and proteins, there is a pressing need to study protein functions in a timely fashion. This has put small molecules on center stage and more efficient and systematic methods to identify specific molecular probes are in ever increasing demand. In particular, "natural product like" libraries are in great demand, complementing the available natural products that are utilized for modulating (i. e., activating or inactivating) protein function(s).[12] Synthetic organic chemists have used three different approaches to gain access to these compounds; target oriented synthesis, combinational chemistry (very often referred as 'combichem') and diversity oriented synthesis.

D. Target-oriented synthesis (TOS) (Trial and Error method)

The first approach uses target-oriented synthesis (TOS) and relies primarily on nature to discover small-molecules with useful, macromolecule-perturbing properties. Natural compounds can be identified in screens of extract mixtures, isolated, and then structurally characterized by using a variety of spectroscopic techniques (Figure I-3a). Once such a structure has been identified, it and related analogs can become a target for chemical synthesis. In universities, the targets are often natural products, whereas in pharmaceutical companies, the targets are

drugs or libraries of drug candidates. The aim of the synthesis effort in TOS is to access a precise region of **chemical space**, which is often defined by a complex natural product known to have a useful function (Figure I-3b). TOS as well as medicinal and combinatorial chemistries (for over 40 years ago) have been advanced by the development of a general planning strategy known as retro-synthetic analysis, in which a complex target is transformed into a sequence of progressively simpler structures by formally performing chemical reactions in the reverse-synthetic direction.

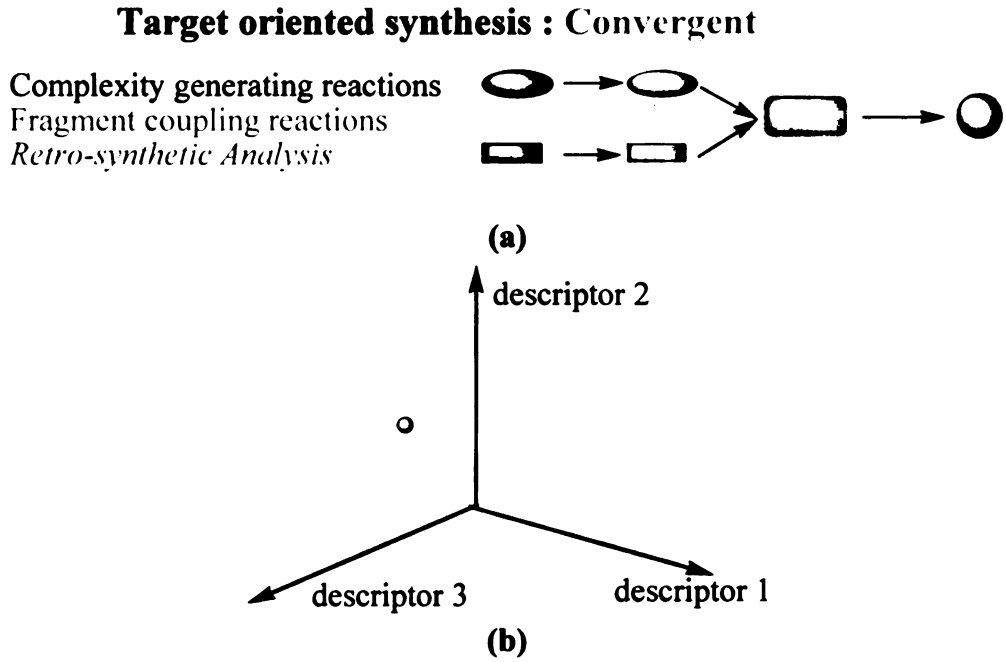


Figure I-3. (a) Target Oriented Synthesis (TOS); (b) Representation of a single target in chemical space. Adapted from Ref. 52

Prior to this, strategic solutions to the problems of synthesizing different target structures were developed on a case-by-case basis. Retro-synthetic concepts and thinking depend on the existence of a defined target structure. Synthesis pathways in TOS are linear and convergent, and they are planned in the reverse-synthetic direction by using retro-synthetic planning, which aims to move in the direction

of complex to simple. This problem-solving technique involves the recognition of key structural elements in reaction products, rather than reaction substrates, that code for synthetic transformations. Repetitive application of this process allows a synthetic chemist to start with a structurally complex target and find a structurally simple compound that can be used to start a synthesis. The basic subunit of retro-synthetic planning is 'to transform', that is, the theoretical transformation of a product into a substrate by formally performing a chemical reaction in the reverse-synthetic direction. To make use of a transform in retro-synthetic analysis one must first identify the corresponding "retron", that is, the enabling structural subunit ("keying element") that permits its application, in the chemical target. Structurally simplifying transforms are critical in TOS when devising a retro-synthesis for a complex target structure, and iterative application of these transforms can lead to a plan for an efficient synthesis. Reactions that join together two different building blocks, called fragment-coupling reactions, are of great importance. Reactions that generate structural complexity stereoselectively (e.g. oxy-Cope and Diels-Alder reactions) are also of considerable value and are used widely in target-oriented organic synthesis. TOS does not share the aim of accessing diversity.

E. Combinatorial chemistry (Trial and Selection method)

Peptide libraries constituted the first modular arrays of functionality to be explored in a prospecting fashion, with the vision that peptide leads could be transformed into more pharmacologically active molecules. *Solid phase peptide synthesis* was first introduced to overcome the technical challenge of performing

iterative couplings to yield long polypeptide chains. The nascent polypeptide chain is immobilized in this method, most commonly to spherical polystyrene beads, allowing coupling reagents to be added in high molar excess and by products (including the unused reagents) to be removed simply by washing the insoluble beads. This led to the generation of large combinatorial libraries of peptides[13] and oligonucleotides, [14] which were then screened against a receptor or enzyme to identify high-affinity ligands or potent inhibitors, respectively. These and the oligomeric systems that followed them, such as peptoids, [15] polycarbamates [16] and 'azatides' [17] were assembled readily, even robotically, on solid-phase and their input materials were available in great variety.[18] While these studies clearly demonstrated the power of library synthesis and screening strategies, peptides and oligonucleotides generally have poor oral activities and rapid *in vivo* clearing times, and therefore their utility as pharmacological probes or therapeutic agents was often limited.[19] Moreover, the formidable challenge of turning a flexible ligand with modest affinity into a potent lead has limited their relevance. Although solid phase peptide synthesis was only recently adapted to non-peptidic small molecules (<600-700 molecular weight), which have favorable pharmacokinetic properties, [20] simplification of the purification of synthetic intermediates on the solid phase method has led to an increase in synthetic productivity. Again taking a lead from solid phase peptide (and oligonucleotide) synthesis, [21] solid phase syntheses have been performed in parallel [15, 22] i. e., similar reactions are performed, but the structures of the building blocks in key fragment-coupling steps are varied. Solid phase, parallel synthesis is an example

of what is commonly referred to as ***combinatorial synthesis*** and is most commonly used by medicinal chemists in pharmaceutical companies and universities to synthesize a focused library of related compounds sharing structural features necessary for binding to a preselected protein target, allowing the general principles of retro-synthetic analysis to be applied readily. A second variation of solid phase synthesis, one that extends it beyond a mere purification technique, can provide a staggering increase in the ability of organic synthesis to produce collections of small molecules. This potential was realized originally in peptide synthesis with the invention of the split-and-pool (split-pool) strategy of synthesis.[23] The strategy has more recently also been used in organic synthesis, resulting in structurally complex and diverse libraries of synthetic small molecules.[24] In this method, a collection of beads is split into reaction vessels that subsequently each receive a unique set of reagents, for example, one of a collection of building blocks. Cycles of pooling, resplitting, and further chemistry then result in large collections of compounds that are spatially segregated on unique beads. **Split-pool synthesis** is referred to as the "one bead–one compound" approach, and it is analogous to genetic recombination. Encoding methods, which are analogous to the genetic code, have been developed that record the chemical history of the synthetic compounds, allowing the structures of compounds selected in screens to be inferred.[25]

Due to the extensive time period required for the identification of drug-like candidates, combinatorial chemistry is now firmly integrated in the drug discovery enterprise for both lead identification and lead optimization.[26] By

applying combinatorial chemistry, it is possible to obtain large sets of compounds over short periods of time, by applying parallel high-throughput synthesis. [1, 4, 27] The source of the starting or lead compounds can vary and may include a natural product, a known drug, or a rationally designed structure developed from a mechanistic hypothesis and/or a crystal structure of a macromolecule of interest (focused libraries) or simply exhibiting some intuitively appealing combination (prospecting libraries) of molecular weight, polarity, conformational constraint, novelty and so on.[18] Libraries of compounds that are deemed at the outset to be more 'drug-like' are more favored, comprising known pharmacological motifs. Library synthesis can be accomplished efficiently using solid-phase synthesis to append different sets of building blocks to a common molecular skeleton which facilitates binding to a preselected protein target.[22] Retro-synthetic planning is used in this context to devise pathways to the target structure that permit the addition of diverse sets of building blocks during the actual synthesis. If this common skeleton contains multiple reactive sites with potential for orthogonal functionalization, the powerful technique of split-pool synthesis [23, 28] can be used to access all possible combinations of building blocks (namely, the complete matrix) efficiently.

F. Number game (HTS) vs. quality of libraries

Since the human genome sequence has been solved, the pharmaceutical industry has more than 3500 potential drug targets while previously only about 400 targets were pursued.[29] The advent of genomic sciences, rapid DNA sequencing, combinatorial chemistry, cell-based assays, and automated high-throughput

screening (HTS) has led to a "new" concept of drug discovery (Figure I-4). In this new concept, the critical discourse between chemists and biologists and the quality of scientific reasoning are sometimes replaced by the magic of large numbers. Large numbers of hypothetical targets are incorporated into in vitro or cell-based assays and exposed to large numbers of compounds representing numerous variations on a few chemical themes or, more recently, fewer variations on a greater number of themes in high-throughput configurations.

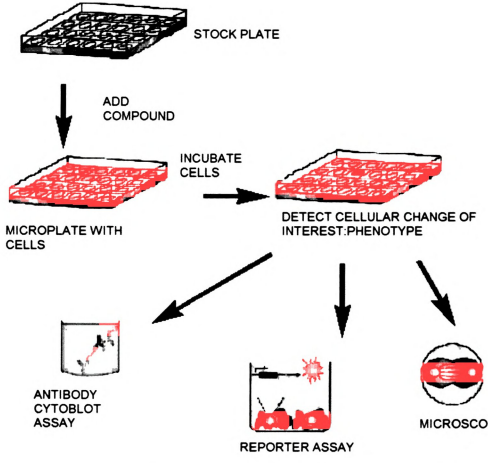


Figure I-4. High Throughput Screening (HTS).Adapted from Ref. 10

It was hoped that this experimental design would be suitable to identify many substances, which can modify the targets in question. Many such "hits"--

compounds that elicit a positive response in a particular assay--would then give rise to more leads, i.e., compounds that continue to show the initial positive response in more complex models (cells, animals) in a dose-dependent manner. Eventually, the number of compounds also would increase. Data points generated by large screening programs at a pharmaceutical company have amounted to roughly 200,000 at the beginning of the 1990s. Data points are screening results describing the effect of one compound at one concentration in a particular test. This Figure I- rose to 5 to 6 million at the middle of the decade and is presently approaching or even passing the 50-million mark.[33] The goal for such an endeavor, in part, was to obviate the need for a rational approach completely. A large enough library with the right HTS assay promised the ultimate brute-force method for obtaining bioactive compounds without biologists and organic chemists getting in the way.[30] However, the pharmaceutical industry is currently facing a major challenge (Figure I- 5a) As measured by the number of new compounds entering the market place, the top 50 companies of the pharmaceutical industry collectively have not improved their productivity during the 1990s.[31] Two-thirds of the prescription drugs approved by the US Food and Drug Administration (FDA) between 1989 and 2002 were modified versions of existing medicines or identical to drugs already on the market (Figure I- 5b). Over the last five years the number of 'new molecular entities' (NME) approved for use as drugs by the FDA has steadily decreased. In 2002, only 17 NME were approved, and of those only 7 were classified as being significant improvements over existing products.[29, 32, 33]

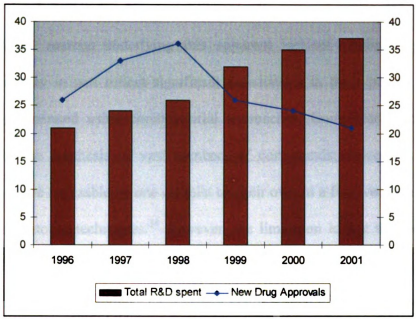


Figure I-5a. New drugs approved by FDA vs. R&D spending in billions. Adapted from **www.mindfully.org/GE/2004/Drug-Industry-Falls;** Peter Landers /Wall Street Journal 24 Feb 2004.

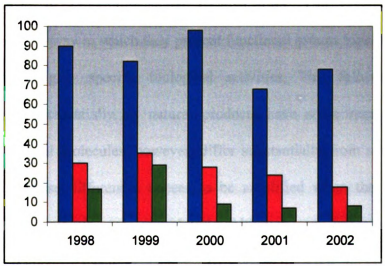


Figure I-5b. Number of US Food and Drug Administration (FDA) new drug approvals (NDA, blue), new molecular entities (NME, red) and NME with significant improvements over existing products (green), between the years 1998 and 2002. Adapted from Ref.29

G. Diversity deficit in combinatorial libraries vs. natural products

Although the reasons underlying this apparent lack of productivity remain unclear, it may in part reflect significant deficiencies in the types of chemical structures generated using combinatorial approaches. Combinatorial chemistry allows for the synthesis of vast numbers of compounds; indeed, millions of compounds are realizable by one chemist on their own in a few weeks using split-pool combinatorial techniques.[34] However, the limitation is that the compounds produced have limited structural diversity.

Traditionally, natural products have been a major source of new drugs, and many successful drugs were originally synthesized to mimic the action of molecules found in nature.[35] One of the unquestionable hallmarks of natural products is their exquisite level of three-dimensional sophistication. The diversity of ring skeletons, and the way in which they present functional groups topologically, and often provide highly specific biological activities. This follows from the proposition that essentially all natural products have some receptor binding capacity.[36] Natural molecules, however, differ substantially from synthetic ones (Figure I-6). These differences appear to be amplified when the products of combinatorial synthesis are considered. Although an important aim in combinatorial chemistry is to generate highly diverse libraries, the need for speed and automation introduces new structural idiosyncrasies into the method.

Since Lipinski first published his "rule of five",[37] describing statistically the optimal combination of properties of drug-like molecules, additional methods for identifying distinguishing features between drugs and other organic molecules

have been sought. Approaches have included the characterization of molecular frameworks and substituents, [38] the statistical analysis of different drug databases, [39] the application of artificial neural networks to differentiate drugs from reagents, [40] and the introduction of a drug-like index to rank compounds. [41] The differences between three different compound classes, natural products, molecules from combinatorial synthesis, and drug molecules, were investigated (Figure I-6). The major structural differences between natural and combinatorial compounds originate mainly from properties introduced to make combinatorial synthesis more efficient. These include the number of chiral centers, the prevalence of aromatic rings, the introduction of complex ring systems, and the degree of the saturation of the molecule as well as the number and ratios of different heteroatoms. Natural products generally have high binding affinities for specific receptor systems and their biological action is often highly selective. In view of these facts, it is interesting to consider that the search for the replacement of natural compounds with synthetic ones is usually based on exactly these kinds of 'unfavorable' modifications. Given the stereospecificity of most biological targets, it is likely that many non-stereospecific synthetic analogues, created, for example by the introduction of aromatic rings, represent suboptimal compromises, especially in terms of selectivity. This situation appears to be amplified in the case of combinatorially synthesized compounds. In addition, the greater flexibility of combinatorial products is likely to have detrimental entropic consequences for the binding of these compounds; it may also adversely affect their ability to induce conformational changes in the receptor required for biological function.

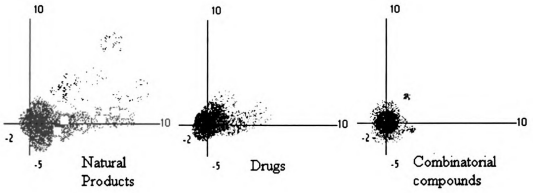


Figure I-6. Comparison of diversity: the plot of the first two principal components, obtained from a database containing a) a random selection of combinatorial compounds (n = 13 506), b) natural products (n = 3287), and c) drugs (n = 10 968). For clarity, the data points from the three databases are plotted separately but on the same axes. The Figure I-6 shows that combinatorial compounds cover a well-defined area in the diversity space given by these principal components. In contrast, natural products and drugs cover almost all of this space as well as a much larger additional volume. Drugs and natural products have approximately the same coverage of this space. Adapted from Ref. 43

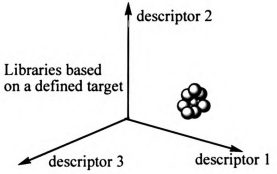


Figure I-7. The goal in medicinal and combinatorial chemistry is to synthesize a collection of analogues (blue spheres) of a target structure (**lead**) having known or predicted properties (red sphere). Adapted from Ref. 52

As well, the process of producing synthetic analogues radically alters the numbers and ratios of different atom types, such as nitrogen, oxygen, sulfur, and halogens. These distributions in turn have a direct impact on the patterns of donors and acceptors available to complement receptor surface properties.

We can view the production of unique bioactive libraries by plants and organisms as analogous and complementary to the combinatorial generation of synthetic libraries, each approach providing access to very different types of lead compounds.[11, 42] However, there is a significant difference between these processes. The generation of combinatorial libraries has been constrained primarily by the availability of reagents and suitable reactions. In contrast, the generation of natural product diversity has occurred not only within the constraints of available biosynthetic reactions and precursors but also in the context of biological utility. Most natural products have a function, and the synthetic routes generating these compounds have coevolved with the requirements of ligand functionality. This suggests that combinatorial synthesis must also evolve beyond synthetic feasibility to explicitly address the creation of compounds with proper biological function.[43]

H. Rescuing Combinational Chemistry (Combichem)

The question arises how to improve the diversity of synthetic and especially combinatorial compounds. Some features that are being focused on to rescue combinational chemistry are as follows:

- Chirality is an essential issue. As chiral separation is rather expensive, the number of chiral centers could be somewhat increased by using readily available chiral reagents more often in combinatorial syntheses.
- Attempting to change the ratios of different heteroatoms is another promising way of increasing diversity in combinatorial products. This will also impact donor/acceptor properties as well as lipophilicities and hence raise the diversity of designs.
- Drug-like filters, such as the Lipinski rules, are very helpful in removing likely problem molecules. However, overly strict adherence to it can have the adverse effect of restricting diversity and also reducing similarity to natural products.
- A large proportion of natural products is biologically active and has favorable ADMET properties, despite the fact that they often do not satisfy 'drug-like' criteria. It is likely that by mimicking certain distribution properties of natural compounds, a substantially more diverse set of combinatorial products might be made that could also have greater biological relevance. Analogously to different 'drug-like' filters, the concept of 'natural-product-like' filters can be introduced based on the statistical analysis of different properties described above.

Other methods that might help to bring some of the properties of combinatorial compounds closer to those of natural products, e.g.

- application of biocatalysis and biotransformations in the synthesis[44a] or using natural product templates in library design, [44b] have been suggested.

- Dixon and Villar[45] have shown that a protein can bind a set of structurally diverse molecules with very similar affinities in the nanomolar range, whereas a number of analogs closely related to one of the good binders display only weak affinities (>2.5 mM). The design and sampling of compound libraries should, therefore, be guided not only by structural descriptors, but also by descriptors of biological activity.

- In 'click chemistry' [46a] developed by Sharpless and co-workers, a biological receptor such as an enzyme is permitted to select the best fitting partial ligands (ligands that don't occupy the entire binding site) from a range of modules that are capable of reacting with one another. After the modules bind to the site their reactivity towards each other induces them to combine forming a compound that blocks and thus inhibits the entire catalytic site.

- Dynamic combinatorial chemistry (DCC) [46b] involves a target receptor which is exposed to a library of potential ligands. Each ligand is formed by reversible combinations of small building blocks in an equilibrium solution. Selective binding of one of the ligands to the target lowers the ligands concentration in solution, causing the equilibrium towards the formation of the ligand. Thus, the system enhances the amount of strong binding ligand and discriminates against poorly binding ones.

- The majority of drug targets cluster into densely populated target families. Numerous lead compounds from a multi-purpose 'privileged structure' libraries are generated, which can address a variety of targets in a single cluster irrespective of a therapeutic area.[46c] For e.g. a single library built around a 5,5-

trans- fused lactam as a core scaffold generated inhibitors for different serine proteases (a single family of proteases) involved in different diseases.[46c]

I. Chemical diversity and biological space

Combinatorial chemistry aims to access diversity to some degree, and usually involves synthesizing analogues of a given target structure i.e. to explore a dense region of ***chemical space*** in proximity to a precise or dense region (occupied by a lead) known to have useful properties (Figure I-8).[47a] Since the structural diversity of the products was only due to the building blocks and starting scaffold the resulting molecular framework is the same in every case.

If the protein binding sites for potential ligands are defined as a biological structure space, the task is to find compounds that are "complementary" to this structure space, that is, to correlate the biological structure space with a chemical structure space. The real question was neglected: how biologically relevant is the diversity created in chemistry? Even the most beautiful molecules synthesized using the most elegant methods are useless if they do not reach a biological target. Even experts fail to agree on how diversity should be defined (Figure I-9 & 10). We use the term "diversity" in the sense of structural variety on the basis of molecular scaffolds and substitution patterns. Despite the sequencing of the human genome, the biological structure space is largely unknown (Figure I-10). However, it is clear that it cannot be filled by using the substances that exist today. In theory, it is conceivable that the entire chemical structure space of all the possible drug molecules could be synthesized and hence filled. HTS would then automatically identify the suitable molecules. In practice, this approach is not

feasible: theoretical considerations have shown that the universe does not contain enough atoms to synthesize even one copy of every conceivable molecule.[47b] The number of 'drug-like' molecules possible has been estimated to be astronomic (10^{62} to 10^{200}).[48, 49]

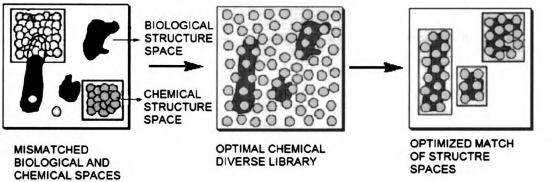


Figure I-8. Matching of biological & chemical structure spaces. Adapted from Ref. 47a.

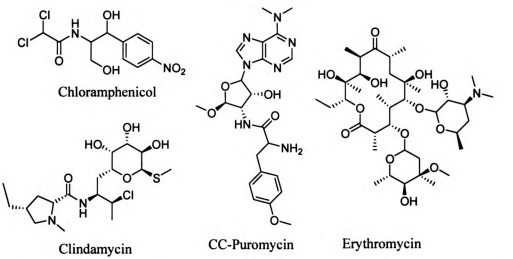


Figure I-9. Structural diversity is not identical to biological diversity. The four antibiotics chloramphenicol, clindamycin, erythromycin and puromycin are structurally very diverse. They are macrocyclic, heterocyclic or homocyclic. They bear different functional groups such as nitro, ester, keto, hydroxy, thioether, tertiary amine, or chloro. Nevertheless, their modes of action are the same. They all bind to the bacterial peptidyl transferase. They even have overlapping binding sites at the enzyme cavity Adapted from Ref. 47c.

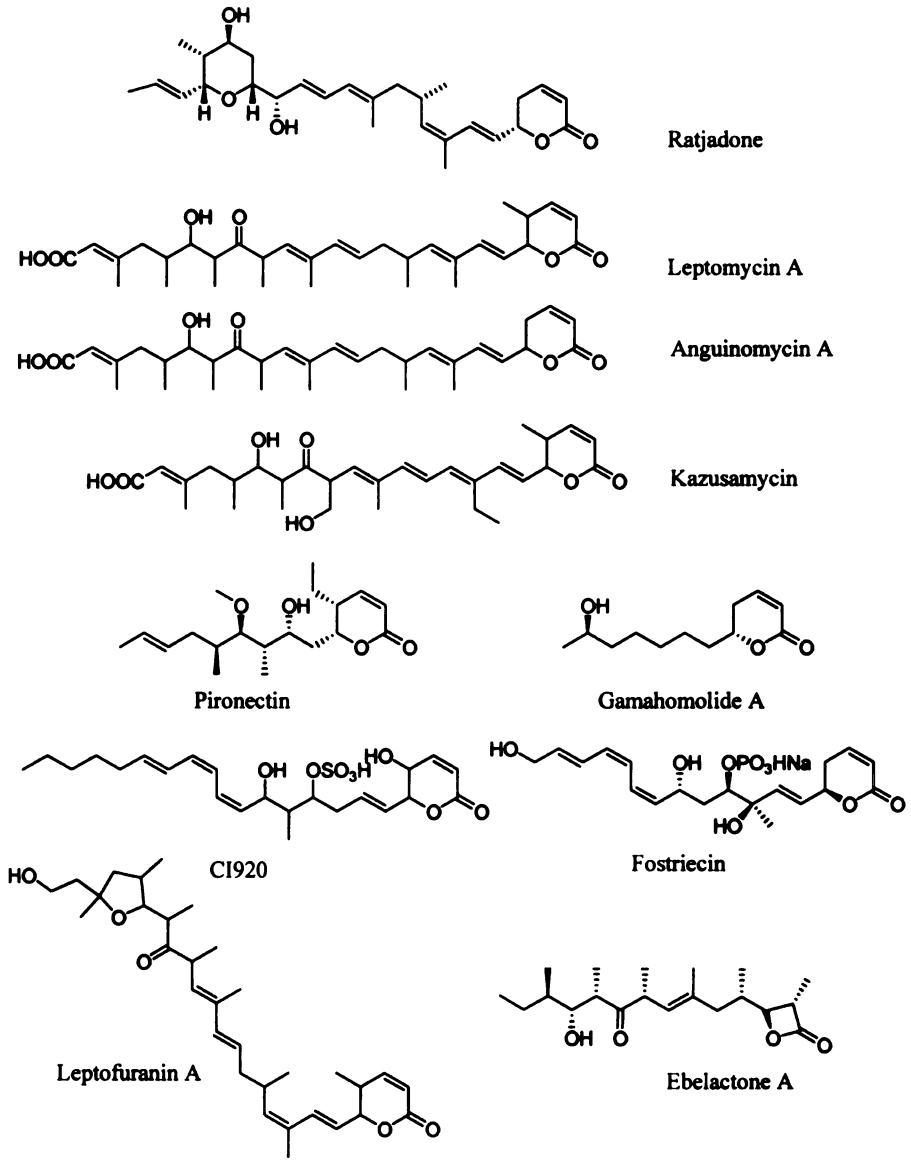


Figure I-10. Structural similarity is not identical with biological similarity and *vice versa*. A collection of similar natural products exerting a diversity of biological activities. Members of the highly bioactive family of pentenolide natural products and relatives. They contain a pentenolide head and a long (C_6–C_{28}), often branched unsaturated lipophilic tail with a spare ornamentation of hydroxy or keto functionalities: antifungal *Ratjadone*, the cytostatic *Leptomycin B* inhibitor of the nuclear export receptor CRM-1, *Anguinomycin A* cytotoxic against transformed cells, antibiotic *Kazusamycin*, immunosuppressant *Pironetin*, cytotoxic *Leptofuranin A* acting on retinoblastoma protein, antileukemic *CI 920*, antifungal *Gamahomolide A*, gap phase specific inhibitor of the mammalian cell

cycle *Leptolstatin* (formula not shown), tubulin inhibitor *Discodermolide* (formula not shown), and enzyme inhibitor *Ebelactone*.Adapted from Ref. 47c.

As a comparison there are approximately 10^{51} atoms on earth, so every 'drug-like' molecule (let alone ones not considered 'drug-like'); cannot be made and one must be selective. Fortunately, there is hope; there is more than one 'answer' to biological 'problems' (*e.g.* the HMG CoA reductase inhibitors: lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin...) so we don't need to make and screen everything. In fact, biological activity is not a rare chemical property; the reality is that all small molecules are active biologically in some way or another, even ethanol. In terms of lead generation it is quality (structural diversity) and, but not just, quantity (number of compounds) that counts.

J. Diversity Oriented Synthesis (DOS)

Diversity-oriented synthesis aims to pick up where traditional combinatorial chemistry left off.....Stu Borman, C&EN Washington.[46b]

Are the regions of chemistry space defined by natural products and known drugs, the best or most fertile regions for discovering small molecules that modulate macromolecular function in useful ways? DOS aims to answer this question. In contrast to target-oriented synthesis (TOS) and combinatorial chemistry, which aim to access precise or dense regions of chemistry space, diversity-oriented synthesis (DOS) populates chemical space broadly with small-molecules having diverse structures. The synthesis effort in DOS aims to create a broad distribution of compounds in chemistry space, including currently poorly populated (or even vacuous) space, and in the future, in space found empirically to correlate best with desired properties (Figure I-11).

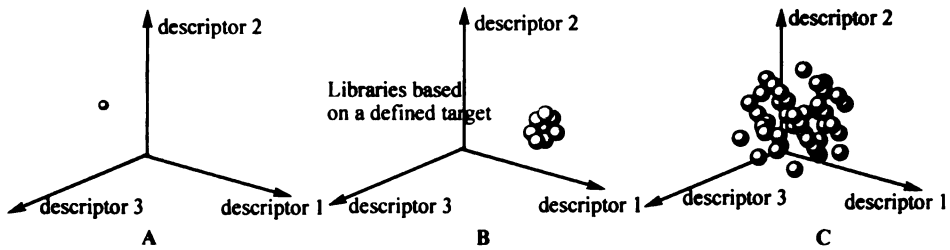


Figure I-11. Comparison of TOS (A), medicinal and combinatorial chemistry (B), and DOS (C). Each three-dimensional plot is meant to represent the chemical product or collection of products derived from a single synthesis pathway. Each axis plots a calculable or measurable property of a small molecule (for example, molecular weight, solubility). A) The aim in TOS is to synthesize a single target structure having known or predicted properties (red sphere). B) The goal in medicinal and combinatorial chemistry is to synthesize a collection of analogues (blue spheres) of a target structure having known or predicted properties (red sphere). C) The aim in DOS is to populate chemistry space broadly with complex and diverse structures having unknown properties (blue spheres) as a first step in the small molecule discovery process. In some ways, these three approaches to synthesizing small-molecules represent points along a continuum. Adapted from Ref. 52

The structures and functions of natural products suggest that structural complexity may be positively correlated with macromolecule-perturbing function and specificity of action. This correlation is particularly striking in small molecules known to disrupt protein–protein interactions. Hence, in contrast to the relatively flat molecular skeletons often used in medicinal and combinatorial chemistry that tend to project appendages outward along the perimeter of a circle, The goals of DOS include the development of pathways leading to the efficient (three- to five-step) synthesis of collections of small molecules having skeletal and stereochemical diversity with defined coordinates in chemical space. Ideally, these pathways also yield more globular or spherical molecular skeletons to which substituents can be potentially appended site- and stereo-selectively during a post-screening, optimization stage. The diverse skeletons and stereochemistry ensure

that the appendages can be positioned in multiple orientations about the surface of the molecules. Small molecules used in chemical genetic[50] screens can be synthesized with guidance from compounds known to have biological activity[51] or with the desire to distribute the products in chemical descriptor space. In the latter case, it may be advantageous to maximize the representation of different functional groups and conformations in a screen, since in most cases the nature of the small-molecule-target interaction can not be foreseen. [11, 52]

In DOS, where the structural complexity of the individual compounds and the structural diversity of the overall collection are maximized, synthesis pathways are branched and divergent, and they are planned in the forward-synthetic direction[52] by using forward-synthetic analysis. Forward-synthetic planning aims to move in the direction of simple and similar to complex and diverse. Forward-synthetic planning aimed at accessing these diversity elements relies on the use of diversity generating processes, which are defined as the transformation of a collection of relatively similar substrates into a collection of more diverse products. In an ideal DOS pathway all of the products of one diversity-generating process are substrates for another, thus making it possible to use split-pool synthesis to access combinatorially matrices of building blocks, stereochemical isomers, and even molecular skeletons. To maximize efficiency and to be compatible with one-bead/one-stock solution technology platforms, synthesis pathways in DOS should be no more than three to five steps (which leaves no room for protective-group manipulations). The products of one diversity-generating process should share some common inherent chemical reactivity. This

common reactivity serves as a keying element that makes the products collective substrates for a subsequent diversity-generating process. The goal of achieving diversity can be simplified by considering three distinct diversity elements: appendages, stereochemistry, and skeletons;

1) Appendage Diversity (Building Block)

The simplest diversity-generating process is the central feature of combinatorial chemistry and involves the use of coupling reactions to attach different appendages to a common molecular skeleton. In forward-synthetic analysis these are referred to as appending processes. If a molecular skeleton has multiple reactive sites with potential for orthogonal functionalization, then the technique of split-pool synthesis can be used to harness the power of combinatorics (a multiplicative increase in the number of products with an additive increase in the number of reaction conditions), and thereby generate all possible combinations of appendages (that is, the complete matrix) efficiently. The core of all the compounds in a library is same.

2) Stereochemical Diversity

Stereochemical diversity increases the number of relative orientations of potential macromolecule-interacting elements in small molecules. It can best be achieved by using stereospecific reactions that proceed with enantio- or diastereoselectivity. The collective transformation of chiral substrates into products having increased stereochemical diversity (namely, diastereoselective diversity-generating processes) requires powerful reagents that can override substrate bias and deliver diastereomeric products with very high selectivity.[53] It

is conceivable that these types of stereochemical diversity generating transformations could be carried out with spatially segregated, pooled substrates under common reaction conditions. Forward-synthetic planning that incorporates multiple stereochemical diversity-generating processes into a single pathway should also make it possible to generate stereochemical diversity in a combinatorial fashion, analogous to the ability of appending processes to generate building block diversity in a combinatorial manner.

3) Skeletal Diversity

Although efficient pathways leading to families of structurally complex small molecules are being reported with increasing frequency, [54] pathways leading to structurally diverse products, with many different skeletal arrays, are rare. The primary reason for this gap in our planning capabilities is that efficient and effective "branching" pathways remain elusive. Such pathways require the identification of a substrate or class of substrates that can be differentially manipulated, in single transformations, to afford products containing distinct skeletal arrays of connecting atoms.[55] There are, at present, two different strategies for planning DOS pathways that generate skeletal diversity.

i) Differentiation: The first strategy involves using different reagents to transform a common pluripotent substrate with the potential for diverse reactivity into a collection of products having distinct molecular skeletons (Figure I-12).

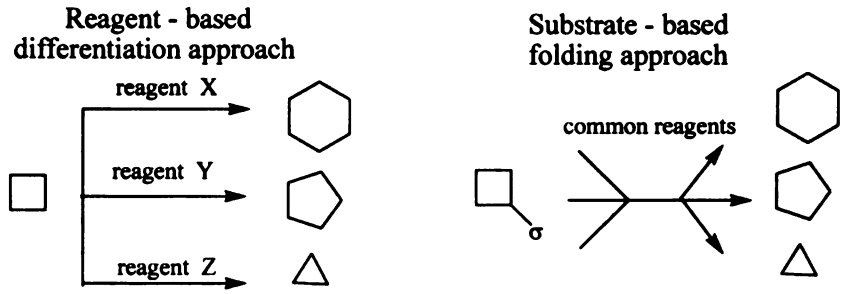


Figure I-12. General approaches for planning pathways to generate skeletal diversity. Adapted from Ref. 11.

To address the diversity of the core scaffold, some approaches involve the use of reaction-based templates[56] or reaction intermediates[57] that can be converted in subsequent steps into a highly diverse set of structures. This approach is analogous to the natural process of cell differentiation in which a pluripotent stem cell is transformed into different cell types on exposure to distinct differentiation factors. These reagent based skeletal diversity-generating transformations are, therefore, also referred to as differentiating processes. Nature has made extensive use of this diversification strategy, for example, enzyme-catalyzed construction of the various sesquiterpene carbon skeletons of secondary metabolites from one common precursor, farnesyl pyrophosphate (Figure I-13).[58]

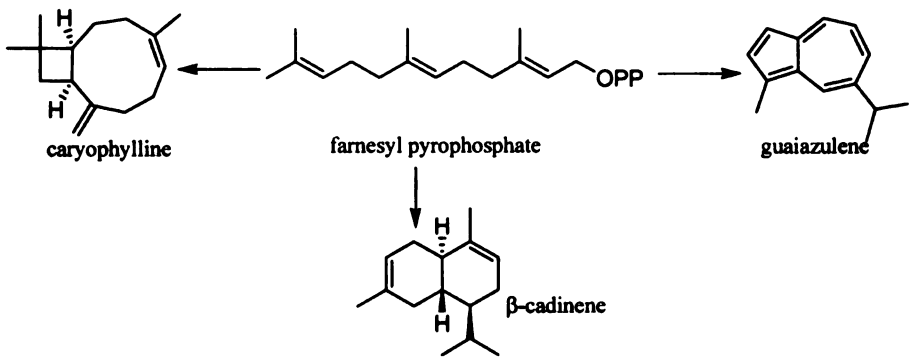


Figure I-13. Nature's Synthesis of Secondary Metabolites. Adapted from Ref. 58.

Several versatile molecules that were key intermediates used by traditional medicinal chemists, for example, Corey's lactone, the Wieland-Miescher ketone, and the Prelog-Djerassi lactone, could lead to a variety of apparently unrelated pharmacophoric frameworks. These starting materials are small molecules equipped with many reactive sites and functionalities, which can undergo both skeletal rearrangements and functional group interconversions. The use of such a polymorphic compound as the cornerstone of a library would be of great advantage since:

- Many known synthetic key intermediates lead to medicinally important or "privileged" scaffolds.
- They possess high potential for both structural and functional diversification.
- Their chemical transformations and modifications in solution are well-documented.
- The pharmacological activity of their descending structures is well-precedented.
- Finally, while the compounds generated so far are new and will be tested for biological activity, it is the unique reactivity profile of each scaffold and its potential to be differentially functionalized that is deemed to be the most useful feature of this approach.[58]

Varying the core scaffold as well as the substituents further increases the flexibility of small-molecule libraries (Figure I-14).

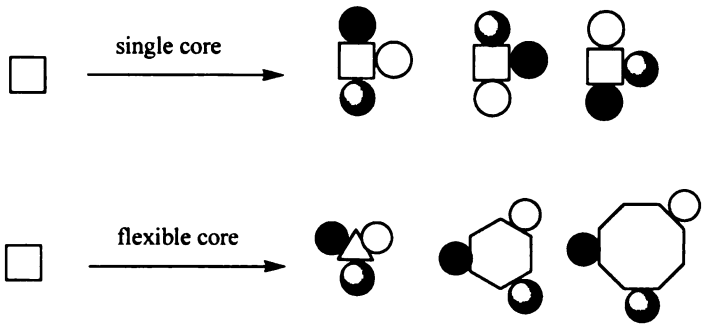
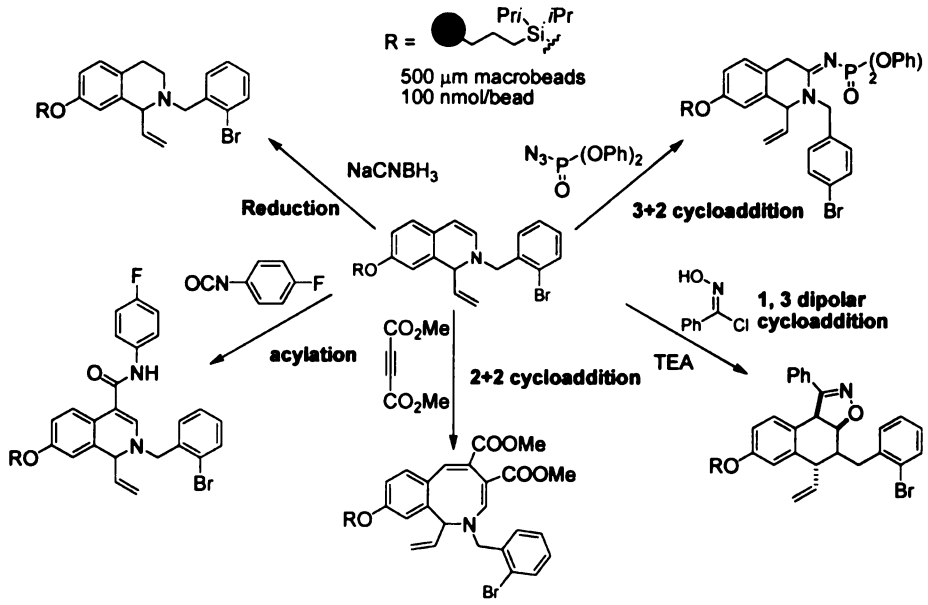


Figure I-14. Flexible core structure libraries vary functionalities as well as orientation of display. Adapted from Ref. 61.

Some prominent examples for reagent based differentiation approach from recent times are presented below.

1) Schreiber and co-workers report a three-step diversity-oriented synthetic pathway (Scheme I-1) based on reactive dihydroisoquinoline and dihydropyridine intermediates, which undergo a variety of transformations to generate skeletally diverse alkaloid-like compounds. The synthetic strategy presented herein enables the synthesis of skeletally diverse alkaloid-like compounds in only three steps. Key to the synthesis is the generation and isolation of reactive dihydropyridines and dihydroisoquinolines, which are useful substrates for a variety of skeleton-determining transformations.

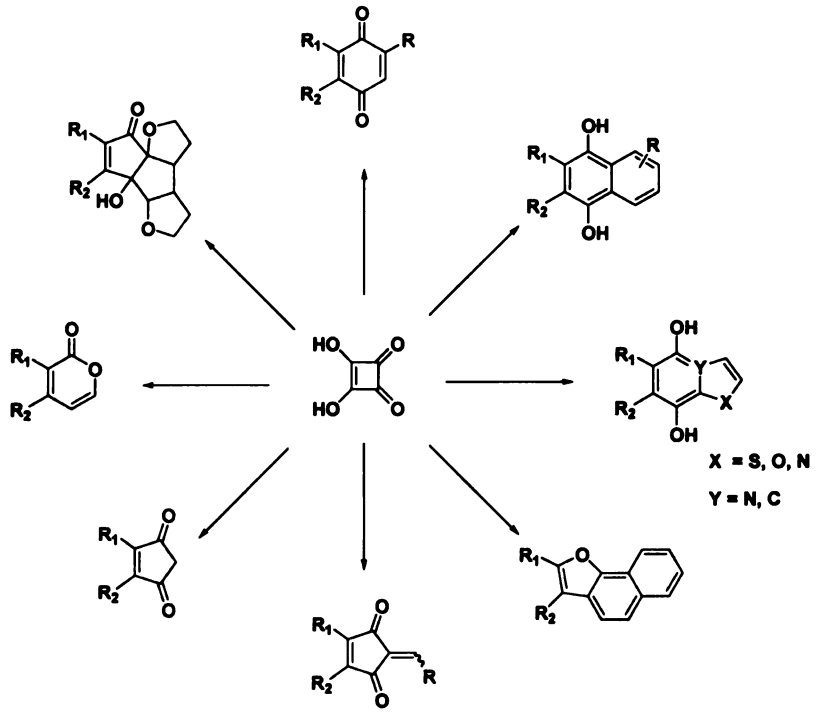


Scheme I-1. Skeletal diversity from isoquinoline intermediate on solid phase.

This synthetic sequence leads to twelve distinct skeletons, all of which contain a hydroxy group, which is important for the microarray technology used in protein-binding assays, [59] and all with high purity (80 % purity on average by LC-MS). The modularity of the synthetic pathway allows for the efficient incorporation of building blocks at a number of key sites on the skeletons. Efforts are currently underway to develop a library of alkaloid-like compounds through this synthetic pathway. [60]

2) Armstrong and co-workers have identified the squaric acid derived synthesis of fused aromatic and heteroaromatic cores (Scheme I-2) as a reaction platform to generate multiple core structure libraries (MCSLs). For example, quinones, phenols, naphthylfurans, [61a] pyrones, [61b] indoles, quinolizin- 4-ones, [61c] and multicyclic systems [61d, 61e] containing identical substituents can be generated from a common precursor. Transformations involving squaric acid derivatives can

provide libraries containing two variable sites prior to commitment to a final core structure. Subsequent manipulation of the differentiated hydroxyls or the use of substituted nucleophiles readily provides a library with up to six variable sites stereochemical aspects were neglected. An alkynyl allene has been converted to heterocycles possessing an α-alkylidene cyclopentenone, a 4-alkylidene cyclopentenone, or a cross-conjugated triene. Thus, a common intermediate has been converted to three structurally unique compounds by changing only the reaction conditions and, therefore, controlling various reaction pathways.[62]

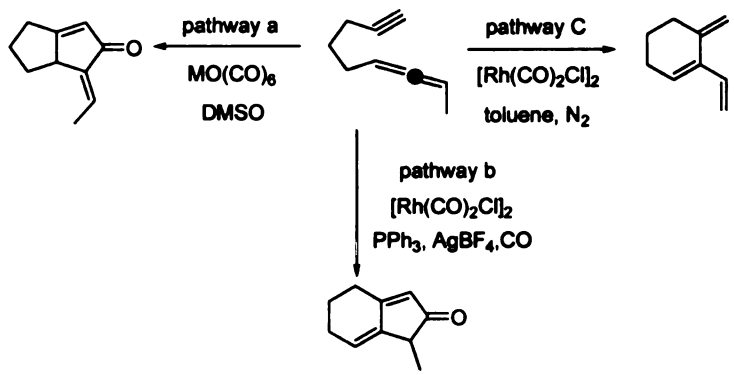


Scheme I-2. Squaric acid as a versatile precursor to various compound shapes.

Adapted from Ref. 61.

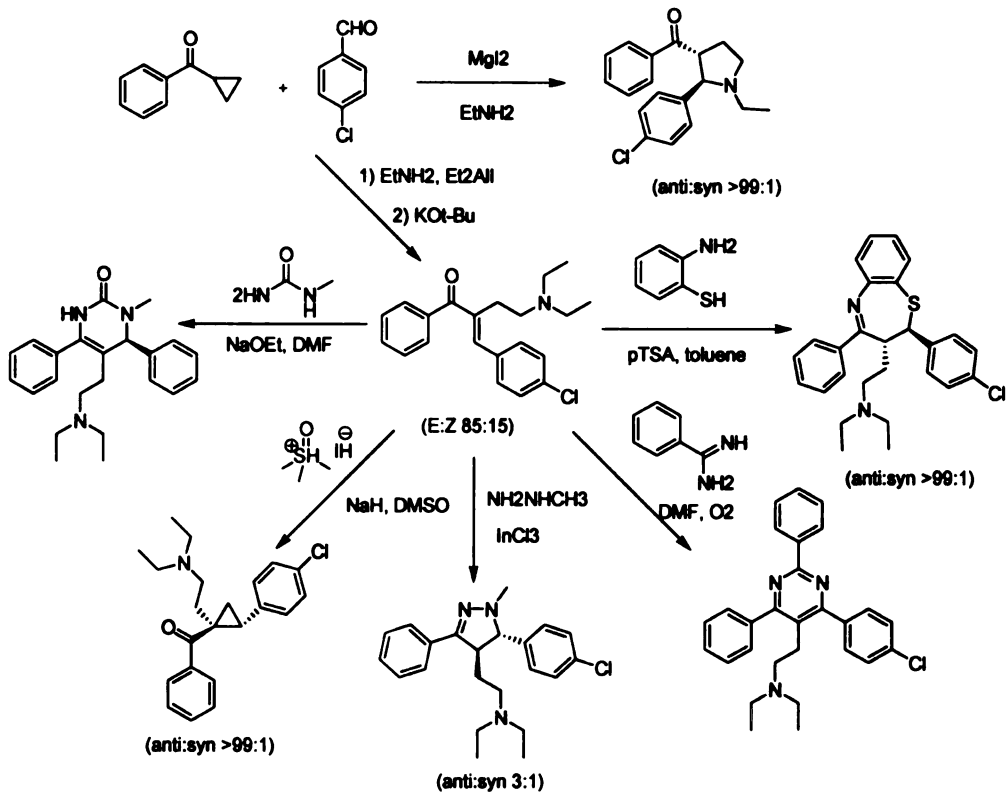
3) By taking advantage of competing reaction pathways available via transition metal-catalyzed carbocyclization processes, Brummond and co-workers[58] have shown the potential generality of converting a common intermediate to at least

three structurally unique and thus unknown hetereocycles (Scheme I-3). While the compounds generated thus far are new and will be tested for biological activity, it is the unique reactivity profile of each scaffold (α-alkylidene cyclopentenone, 4-alkylidene cyclopentenone, and cross-conjugated triene) and its potential to be differentially functionalized that are deemed to be the most useful feature of this approach.



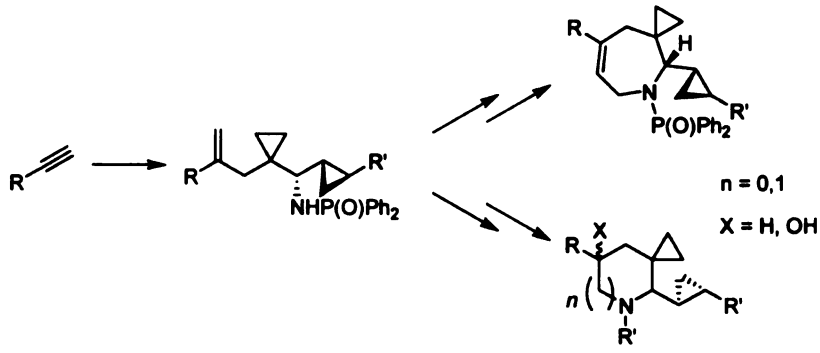
Scheme I-3. Allenes and Transition metals: A Diverging Approach to Heterocycles. Adapted from Ref. 62.

4) Olsson[63] reports a conceptually distinct methodology of combinatorial scaffolding built upon first generating the three necessary pharmacophore elements followed by constructing the central core unit as a fourth diversity point. This fourth diversity point is mainly the diverse spatial arrangement of the pharmacophore elements. A practical and efficient MgI_2 multi-component synthesis of α, β-enones incorporating three diversity elements was carried out using inexpensive starting materials. Branching into different cores (fourth diversity element) was achieved by stepwise cyclization (Scheme I-4).



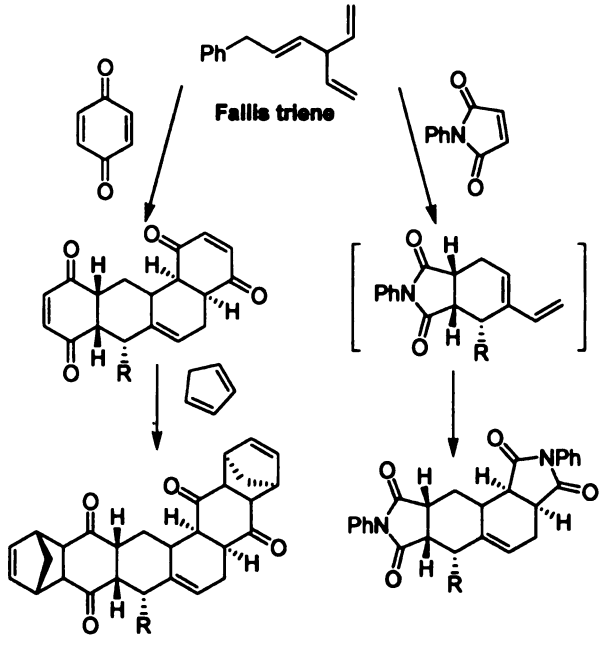
Scheme I-4. A combinatorial scaffold approach based upon a multicomponent reaction. Adapted from Ref. 63.

5) Wipf and co-workers[64] have extended the multicomponent condensation of alkenylzirconocenes with *N*-diphenylphosphinoyl imines and diiodomethane to the direct cyclopropanation-rearrangement of readily available alkynyl phosphinamides (Scheme I-5). The resulting *C*-[1-(2-arylallyl) cyclopropyl] alkylamines provided valuable starting points for the diversity-oriented synthesis of heterocycles. These novel building blocks were converted into heterocyclic 5-azaspiro[2.4]heptanes, 5-azaspiro-[2.5]octanes, and 5-azaspiro[2.6]nonanes by means of selective ring-closing metathesis, epoxide opening, or reductive amination. The resulting functionalized pyrrolidines, piperidines, and azepines are easily accessible in 2-3 steps in good overall yields and are of considerable relevance for chemistry-driven drug discovery.



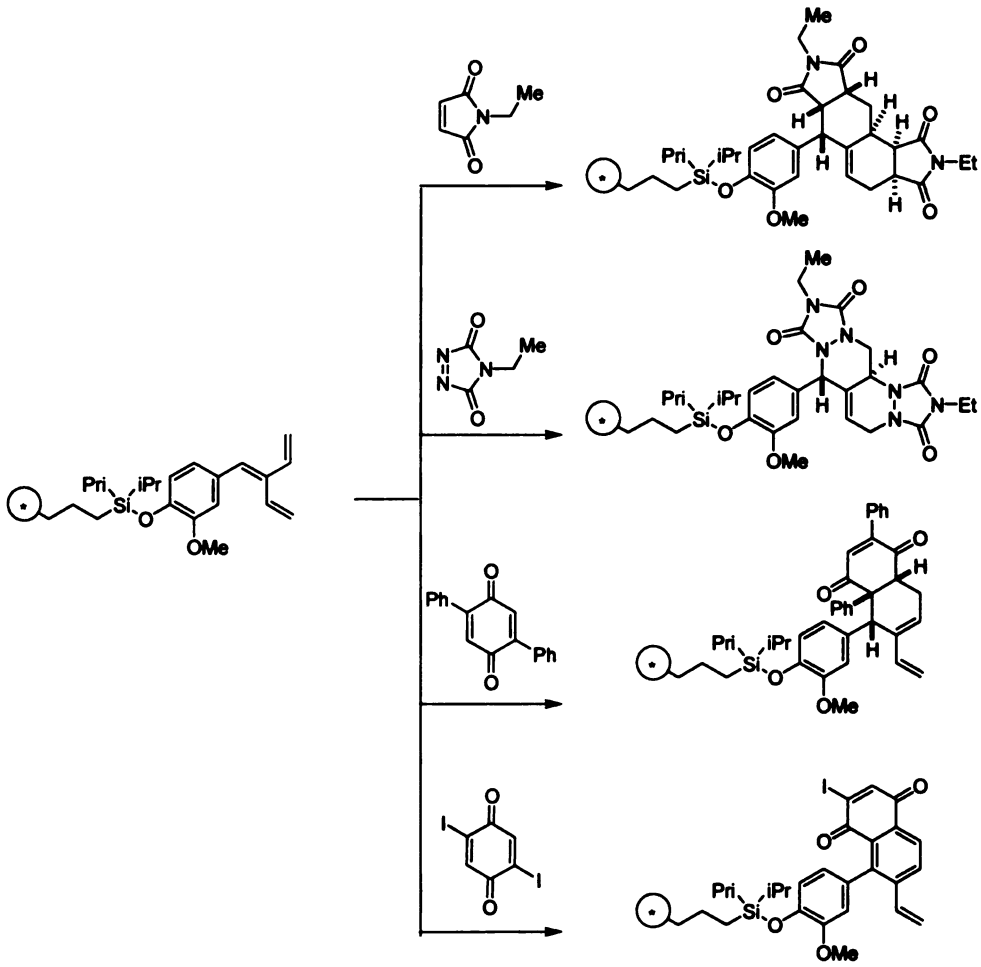
Scheme I-5. Diversity-Oriented Synthesis of Azaspirocycles.

6) Fallis and co-workers established that the organoindium reagent derived from 5-bromo-1, 3-pentadiene and indium metal reacts with excellent regioselectivity with a variety of aldehydes and ketones to afford the nonconjugated, (γ-pentadienylation) diene products in respectable yields (Scheme I-6). In addition, the trienes derived from dehydration of the condensation products afford rapid entry to complex multicyclic skeletons from tandem [4 + 2] cycloadditions.[65]



Scheme I-6. Cross-Conjugated Trienes for Diene-Transmissive Cycloadditions

Schreiber and co-workers[66] have reported a branching DOS pathway that builds on the report by Fallis and co-workers on the use of consecutive Diels-Alder reactions. The pathway yielded 29,400 discrete compounds comprising 10 distinct polycyclic skeletons. The six-step, stereoselective synthesis, which affords products having a central skeleton with between two and four rings and up to six stereocenters, was achieved using an inexpensive and accessible, "one bead-one stock solution" technology platform.



Scheme I-7. Skeletal diversity via a branched pathway. Adapted from Ref. 66.

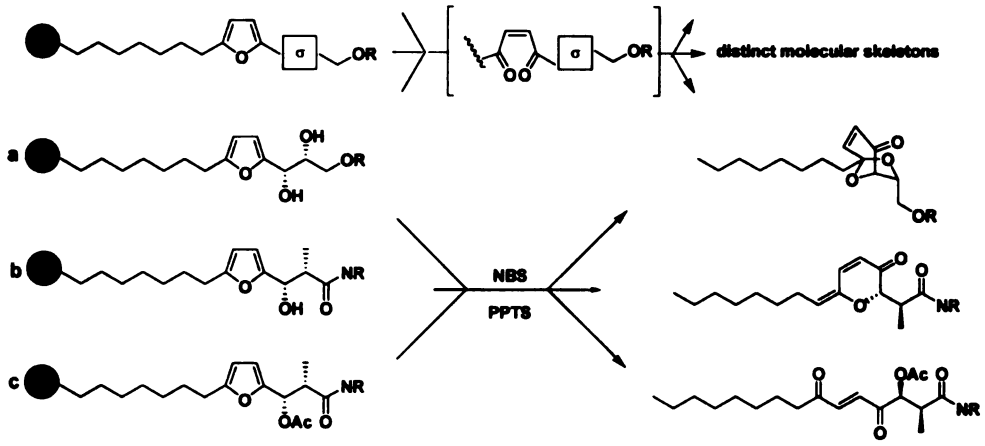
Schreiber has adapted the above triene synthesis and subsequent complexity-generating reactions to phenolic aldehyde-loaded macrobeads and discovered a set of dienophiles that react only once with the Fallis-type trienes. The latter observation provides a branch point to the pathway, where diene products are formed from a single Diels-Alder cycloaddition, and monoene products are formed from consecutive Diels-Alder reactions involving either the same or different dienophiles (Scheme I-7). An important feature of the branched pathway is that the diastereoselection observed in the original report has been extended to reaction sequences involving different dienophiles.

In contrast to appending processes, these differentiating processes have not (as of yet) been used to generate skeletal diversity combinatorially. Doing so will require the identification of differentiating processes having the products-equals-substrates relationship, that is, all of the skeletally distinct products of one differentiating process must share a common chemical reactivity that makes them all potential substrates for another differentiating process. This type of forward-synthetic planning is challenging, and will require nonmutually exclusive approaches to the two, potentially conflicting, goals of maximizing structural diversity and maintaining common reactivity.

ii) Folding: An alternative synthesis strategy circumvents this potential conflict. In this case, diverse skeletons of small molecules can be accessed combinatorially by transforming a collection of substrates having different appendages that pre-encode skeletal information (called σ elements) into a collection of products having distinct molecular skeletons using common reaction conditions (Figure I-

12).[67] This strategy is analogous to the natural process of protein folding,[68] in which different structural information pre-encoded in primary amino acid sequences is transformed into structurally diverse macromolecules using a common folding buffer. Thus, these substrate-based skeletal diversity-generating transformations are referred to as folding processes in forward-synthetic analysis. An advantage of this approach is that sets of σ elements can be identified that act in combination, that is, a matrix of σ elements can pre-encode all combinations of distinct skeletal outcomes. These folding processes can be planned by first identifying a relatively unreactive core structure that can be transformed into a more reactive intermediate upon treatment with mild reagents. Distinct skeletal outcomes can then be pre-encoded into a collection of substrates by attaching to this common core different appendages (σ elements) having complementary reactivity with the latent, reactive intermediate. Mild conditions can then be used to liberate the reactive intermediate and to realize the pre-encoded, complementary reactivity, thus resulting in the formation of different skeletons.

The aromatic furan ring, for example, is a relatively unreactive core structure that, upon treatment with a mild oxidant, can be transformed into a more reactive, electrophilic cis-enedione intermediate.[69] As shown in Scheme I-8, by appending three distinct two-carbon side chains containing two, one, or zero nucleophilic hydroxy groups to a common furan core, it was possible to transform three structurally similar substrates into three products having distinct molecular skeletons through a common set of oxidative and acidic reaction conditions (NBS and PPTS, respectively).



Scheme I-8. Skeletal diversity generating folding process. Adapted from Ref. 67.

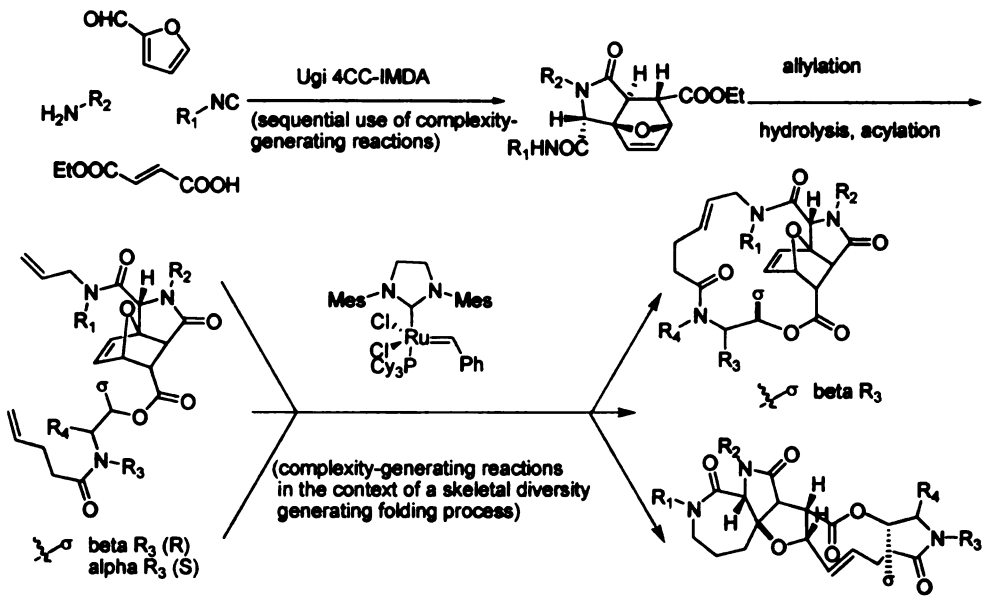
Furan derivative with a side chain containing two nucleophilic hydroxy groups, underwent NBS-mediated oxidative ring expansion and subsequent ketalization[70] to yield the [3.2.1]bicyclic ketal (**I-8a**). Alternatively, the Evans aldol product, with a single hydroxy group on its side chain, underwent oxidative ring expansion and acid-catalyzed dehydration to yield the alkylidene pyran-3-one (**I-8b**). Finally, treatment of furan derivative, with no nucleophilic hydroxy groups on its two-carbon side chain, under the same reaction conditions resulted in oxidative opening of the furan ring followed by olefin isomerization[71] to yield the trans-enedione (**I-8c**).

The use of this substrate-based approach to generate skeletal diversity combinatorially (namely, achieving a multiplicative increase in skeletons with an additive increase in appendages) requires at least two sets of σ elements that can be appended at different sites and function in combination to pre-encode a matrix of distinct skeletal outcomes. In contrast to the one-synthesis/one-skeleton

approach (which typically involves forming a single molecular skeleton early in a synthesis), a folding process can be used to generate new skeletons at the end of a synthesis pathway. This approach facilitates the generation of functionalized skeletons that might otherwise be difficult to access, such as those having building blocks coupled through carbon–carbon bonds at stereogenic quaternary carbon centers and/or potentially unstable structural elements. Additionally, σ elements can be attached to a common molecular skeleton by using appending processes (similar to the way building blocks are appended in the one-synthesis/one skeleton approach). The maintenance of structural similarity and, therefore, common reactivity until late in the synthesis pathway facilitates the realization of this approach using the split-pool technique.

4) Integrated Forward-Synthetic Analysis for Generating Both Complexity and Diversity (Simple and Similar to Complex and Diverse)

Achieving high levels of both complexity and diversity in the context of a single DOS pathway will require integrated forward-synthetic planning. One logical approach is to incorporate complexity generating reactions into stereochemical and skeletal diversity-generating processes.



Scheme I-9. Integrated skeletal complexity and diversity. Adapted from Ref. 72.

Recently, the potential of linking stereochemical control, to the challenging problem of skeletal diversity has been successfully demonstrated[72] by using σ element where stereochemistry of the σ-element and not its constitution controls the outcome of the pathway selected.

L. Small molecule heterocyclic scaffolds

Heterocyclic compounds are important structural motifs present both in natural and synthetic compounds. It is estimated that far more than half of the published chemical literature concerns heterocyclic structures. Small polyfunctionalized heterocyclic compounds play important roles in the drug discovery process [38a, 73] and in isolation and structural identification of biological macromolecules.[74] Substituted heterocyclic compounds generally offer a high degree of structural diversity and have had a substantial impact when used as therapeutic agents. Indeed, analysis of drugs in late development or on the market shows that 68% of

them are heterocycles.[30b] Therefore, the cost-effective creation of new and versatile heterocyclic core structures and the approach to them are vital for many innovative drug discovery programs. It is hence not surprising that research in the field of combinatorial synthesis of heterocycles has received special attention.[75]

One striking structural feature common to cyclic molecules and inherent to heterocycles, which continues to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in a defined three-dimensional representation, thereby allowing for far less degrees of conformational freedom than the corresponding conceivable acyclic structures. In addition, as a result of the presence of heteroatoms such as O, N, and S, heterocycles often exhibit altered absorption, distribution, metabolism, and excretion properties.[76] The design of rigid scaffolds which allow the incorporation of a variety of substituents is an attractive approach for the preparation of combinatorial libraries, especially rigid molecules that position amino acid functionality in 3-dimensional mimicry of peptide secondary structure, such as β-turns.[77] Small heterocycles, in particular, are used as rigid, highly functionalized molecular scaffolds and are biologically very interesting.[78] Although libraries of peptides and other linear oligoamides continue to play an important role in bioorganic and medicinal chemistry,[15, 79] more compact, conformationally constrained heterocyclic[78, 80] scaffolds hold greater appeal for lead discovery prospecting libraries[11, 18, 45] and represent a greater challenge for synthetic design.[81]

M. Conformational constraint/rigid scaffolds

Studies on conformationally constrained molecular structures indicated that rigidification of ligand molecules can potentially influence their biological activity either by modulating their potencies and selectivities for the target receptors. From the thermodynamic point of view, a conformationally constrained molecule with correct bioactive conformation should exhibit enhanced affinity as the reduction in flexibilities reduces loss of entropy upon binding normally occurring when a rotationally free compound becomes more restricted upon alignment with the binding site.[82a, 82b] In addition, such transformation is also a powerful tool to illustrate possible bioactive conformation of a flexible parent molecule. As a result of such transformations, it might improve their overall pharmacological properties such as the ability to cross blood-brain barrier. Structurally constrained versions of these molecules might produce interesting properties as they might display altered pharmacological and pharmacokinetic properties.[82c -85]

N. 1, 3-dipolar cycloadditions and conformationally constrained heterocycles

Compact structures which adopt specific conformations are often more valuable as leads than linear and very flexible molecules. The goals of DOS concur with above aim as it includes the development of pathways leading to the efficient (three- to five-step) synthesis of collections of small molecules having skeletal and stereochemical diversity with defined coordinates in chemical space. The development of solid-phase synthetic approaches to small molecules, particularly those which embrace polyfunctional heterocyclic targets is hence of great interest

in DOS.[86] Structural constraint can be introduced by cyclization more efficiently compared to sequential reactions, but reaction sequences are longer if rings are introduced one step at a time. Reactions that generate multiple linkages in one transformation are extraordinarily powerful in introducing complexity quickly. As a consequence, cycloaddition and cyclocondensation reactions, which generate more than one bond in a single step, are particularly attractive in diversity oriented synthetic design since a premium is placed on reducing the total number of transformations, to ensure adequate yield and purity. Cycloaddition and its intramolecular variants have hence become indispensable for the construction of mono- and polycyclic systems as a consequence of being able to deliver complex cyclic molecules with many positions where variation or substitution is possible from relatively simple and accessible precursors.

Inter- and intramolecular Diels-Alder reaction has been used by itself or in sequence with MCR's in atom economical approaches to conformationally constrained tricyclic nitrogen heterocycles.[87] Like the Diels-Alder reaction, 1, 3-dipolar cycloadditions are fundamental processes in organic chemistry for the synthesis of diverse heterocyclic compounds. The reaction of azomethine ylides with various dipolarophiles results in highly substituted five-membered nitrogen heterocycles. 1, 3 - dipolar cycloadditions are reactions of considerable interest in diversity oriented synthesis, since they can provide access to these polyfunctional molecules with overall good control of the relative configuration of several consecutive asymmetric centers under relatively simple and scalable experimental procedures. In addition to being versatile, it is also an atom economical process.

One of the most important classes of 1, 3-dipolar cycloadditions involves azomethine ylides. The recent explosion of interest in azomethine ylides is well justified when considering their synthetic utility in the construction of heterocycles and polycyclic systems. Not only does the wealth of ylide generation protocols permit application to a range of heterocyclic structures, but the advent of chiral control over reaction products and intramolecular protocols allows for azomethine ylide cycloadditions to be applied to challenging synthetic problems, particularly those developed by natural product synthesis. Generation of the ylide, usually *in situ*, followed by dipolarophile attack affords the heterocycle with operational simplicity. A noteworthy example is 1, 3-dipolar cycloaddition of azomethine ylides with electronic-deficient olefins which is of considerable interest in DOS because its stereospecificity enables stereochemical diversification of up to four tetrahedral centers on pyrrolidine rings. Achieving diastereoselectivity and enantioselectivity in this reaction is presently a field of intense scientific investigation. Although established methods for azomethine ylide generation have proven to be both general and efficient, new procedures are constantly being divulged. These new methods are not only for ylide generation, but are also for new chemical equivalents and by careful selection; the synthetic chemist has a wealth of technologies available at his disposal.

O. References

1. Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132 -143.

2. Verkman, A. S. *Am. J. Physiol. Cell Physiol.* **2004**, *286*, C465-C474.

3. Lipsky, M. S.; Sharp, L. K. *J. Am. Board Fam. Pract.* **2001**, *14*, 362-367.

4. Carr, R.; Hann, M. *Modern drug discovery* **2002**, *5* (4), 45-48.

5. Pagliaro, L.; Felding, J.; Audouze, K.; Neilson, S. J.; Terry, R. B.; Krog-Jensen, C.; Butcher, S. *Curr. Opin. Chem. Biol.* **2004**, *8*, 442-449.

6. Justice, M. J.; Noveroske, J. K.; Weber, J. S.; Zheng, B.; Bradley, A. *Hum. Mol. Genet.* **1999**, *8*, 1955-1963.

7. Schena, M.; Shalon, D.; Heller, R.; Chai, A.; Brown, P. O.; Davis, R. W. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 10614-10619.

8. Agrawal, S.; Zhao, Q. *Curr. Opin. Chem. Biol.* **1998**, *2*, 519-528.

9. Dervan, P. B.; Burli, R. W. *Curr. Opin. Chem. Biol.* **1999**, *3*, 688-693.

10. Stockwell, B. R. *Nature Reviews Genetics* **2000**, *1*, 116-125.

11. Schreiber, S. L. *Science*, **2000**, *287*, 1964-1969.

12. Ding, S.; Gray, N. S. Wu, Xu; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1594 -1596.

13. (a) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233-1251. (b) Pinilla, C.; Appel, J.; Blondelle, S.; Dooley, C.; Dorner, B.; Eichler, J.; Ostresh, J.; Houghten, R. A. *Biopolymers (Pept. Sci.)* **1995**, *37*, 221-240. (c) Pavia, M. R.; Sawyer, T. K.; Moos, W. H. *BioMed. Chem. Lett.* **1993**, *3*, 387-396. (d) Jung, G.; Becksickinger, A. G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 367-383. (e) Dower, W. J.; Fodor, S. P. A. *Annu. Rep. Med. Chem.* **1991**, *26*, 271-280.

14. (a) Gold, L.; Polisky, B.; Uhlenbeck, O.; Yarus, M. *Annu. Rev. Biochem.* **1995**, *64*, 763-797. (b) Ecker, D. J.; Vickers, T. A.; Hanecak, R.; Driver, V.; Anderson, K. *Nucleic Acids Res.* **1993**, *21*, 1853-1856. (c) Bock, L. C.; Griffin, L. C.; Latham, J. A.; Vermaas, E. H.; Toole, J. J. *Nature* **1992**, *355*, 564-566.

15. Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C. Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett , P. A. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 9367–9371.

16. Cho, C. Y.; Moran, E. J.; Cherry, S. R.; Stephans, J. C.; Fodor, S. P. A.; Adams, C. L.; Sundaram, A.; Jacobs, A. W.; Schultz, P. G. *Science* **1993**, *261*, 1303–1305.

17. Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539-2544.

18. Spaller, M. R.; Burger, M. T.; Fardis, M.; Bartlett, P. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 47-53.

19. Smith, A. B.; Hirschmann, R.; Pasternak, A.; Akaishi, R.; Guzman, M. C.; Jones, D. R.; Keenan, T. P.; Sprengeler, P. A.; Darke, P. L.; Emini, E. A.; Holloway, M. K.; Schleif, W. A. *J. Med. Chem.* **1994**, *37*, 215-218.

20. Kim, E. E.; Baker, C. T.; Dwyer, M. D.; Murcko, M. A.; Rao, B. G.; Tung, R. D.; Navia, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 1181-1182.

21. (a) Frank, R.; Heikens, W.; Heisterberg-Moutsis, G.; Blöcker, H. *Nucleic Acids Res.* **1983**, *11*, 4365-4377. (b) Geyson, H. M.; Meloen, R. H.; Barteling, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3998-4002. (c) Houghton, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131-5135.

22. (a) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997-10998. (b) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909-6913.

23. Furka, A.; Sebestyén, F.; Asgedom, M.; Dibó, G. *Int. J. Peptide Prot. Res.* **1991**, *37*, 487-493.

24. (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527-4554. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643-5678. (c) Dolle R. E.; Nelson, K. H. Jr., *J. Comb. Chem.* **1999**, *1*, 235-282. (d) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565-8566.

25. (a) Kerr, J. M.; Banville, S. C.; Zuckermann, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 2529-2531. (b) Nikolaiev, V.; Stierandova, A.; Krchnak, V.; Seligmann, B.; Lam K. S.; Salmon, S. E.; Lebl, M. *Peptide Res.* **1993**, *6*, 161-170. (c) Ohlmeyer, M. H. J.; Swanson, R. N.; Dillard, L. W.; Reader,

J. C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W. C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 10922-10926.

26. Arlens, E. J.; Beld, A. J.; Rodrigues, d. M. J. F.; Simonis, A. M. In The Receptors: A Comprehensive Treatise; O'Brien, R. D., Ed.; **1979**, *1*, 33-41.

27. Arya, P.; Chou, D. T. H.; Baek, M. -Y. *Angew. Chem. Int. Ed.* **2001**, *40* (2), 339-346.

28. (a) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84-86. (b) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W.M.; Knapp R. J. *Nature* **1991**, *354*, 82-84.

29. Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*(22), 3867 – 3870.

30. (a) Lesney, M. S. *Modern drug discovery* **2002**, *5*(2), 26–30. (b) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.*, **2002**, *124* (11), 2560 -2567.

31. (a) Drews, J.; Ryser, S. *Drug Inf. J.* **1996**, *30*, 97-108. (b) Drews, J. *Drug Discovery Today* **1998**, *3*, 491-494.

32. There are many reasons for this trend, for example, the drug discovery process has become much more expensive ($231 million in 1990 to $897 million in 2000; a 388% increase); and although investment in pharmaceutical research and development has also increased dramatically, it has not increased as much as drug discovery costs ($10 billion in 1990 to >$25 billion in 2000; a 250% increase). The Tufts Center for the Study of Drug Development, News Release: 13 May 2003: http://csdd.tufts.edu/NewsEvents/ $231 million in 1990 is equivalent to $318 million in year 2000 dollars.

33. Drews, J. *Science* **2000**, *287*, 1960-1964.

34. Terrett, N. K. *Combinatorial Chemistry*, Oxford University Press, **1998.**

35. Kingston, D. G. I. Natural Products as Pharmaceuticals and Sources for Lead Structures. In *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Academic Press: London, **1996.**

36. Verdine, G. L. *Nature*, **1996**, *384*, 11-13.

37. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Del. Rev.* **1997**, *23*, 3-25.

38. (a) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887-2993. (b) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1999**, *42*, 5095-5099.

39. (a) Oprea, T. I. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 251-264. (b) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C. Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett , P. A. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 9367–9371.

40. (a) Ajay; Walters, W. P.; Murcko, M. A. *J. Med. Chem.* **1998**, *41*, 3314-3324.(b) Sadowski, J.; Kubinyi, H. *J. Med. Chem.* **1998**, *41*, 3325-3329.(c) Frimurer, T. M.; Bywater, R.; Naerum, L.; Lauritsen, L. N.; Brunak, S. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1315-1324.

41. Xu, J.; Stevenson, J.; *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1177-1187.

42. Ortholand, J. – Y.; Ganesan, A. **2004**, *8*, 271-280.

43. Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.*, **2003**, *43* (1), 218 - 227.

44. (a) Zaks, A.; Dodds, D. R. *Drug Design Discovery* **1997**, *2*, 513-531. (b) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125-150.

45. Dixon, S. L.; Villar, H. O. *J. Chem. Inf. Comp. Sci.* **1998**, *38*, 1192-1203.

46. (a) Borman, S. *Chem. Eng. News* **2002**, *80*(6), 29-34. (b) Borman, S. *Chem. Eng. News* **2004**, *82*(40), 32-40. (c) Müller, G. *Drug Discovery Today*, **2003**, *8*(15), 681-691.

47. (a) Wess, G.; Urmann, M.; Sickenberger, B. *Angew. Chem. Int. Ed.* **2001**, *40*(18), 3341-3350. (b) Fenniri, H. *Curr. Med. Chem.* **1996**, *3*, 343-378. (c) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306-313.

48. Bohacek, R. S.; McMartin, C.; Guida, W. C. *Med. Res. Rev.*, **1996**, *16*, 3-50.

49. Owen, M. J. *Biotech Advantage* **2002**, *6*, 17. http://www.biotecplatform.gov.uk/newsletter/

50. Schreiber S. L. *Chem. Eng. News* **2003**, *81*, 51-61.

51. Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem.* **2002**, *114*, 3002-3015.

52. Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.

53. (a) Sharpless, K. B. *Chem. Scr.* **1985**, *25*, 71-75. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1-30. (c) Masamune, S. *Heterocycles* **1984**, *21*, 107-136. (d) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949-951 (e) Harrison, B. A.; Verdine, G. L. *Org. Lett.* **2001**, *3*, 2157-2159. (f) Gierasch, T. M.; Shi, Z.; Verdine, G. L. *Org. Lett.* **2003**, *5*, 621-624.

54. (a) Xu, R.; Greiveldinger, G.; Marenus, L. E.; Cooper, A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 4898-4899. (b) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648-10649. (c) Spring, D. R.; Krishnan, S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 5656-5657. (d) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709-712. (e) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740-6741.

55. Micalizio, G. C.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 152-154.

56. Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574-2583.

57. Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144-154.

58. Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6* (13), 2245 -2248.

59. (a) Hergenrother, P. J.; Depew, K. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 7849-7850; (b) Barnes-Seeman, D.; Park, S. B.; Koehler, A. N.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 2376-2379.

60. Taylor, S. J.; Taylor, A. M.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*(13), 1681-1685.

61. (a) Turnbull, P.; Heileman, M. J.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 2584-2585.(b) Xiang, Y.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1995**, *60*, 6460-6467. (c) Birchler, A. G.; Liu, F.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 7737-7745.(d) Paquette, L. A.; Doyon, J.; Kuo, L. H. *Tetrahedron Lett.* **1996**, *37*, 3299-3302. (e) Paquette, L. A.; Morwick, T. M.; Negri, J. T.; Rogers, R. D. *Tetrahedron* **1996**, *52*, 3075-3094.

62. Tempest, P. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1997,** *119,* 7607-7608.

63. Bertozzi, F.; Gundersen, B. V.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2003,** *5,* 1551-1554.

64. Wipf, P.; Stephenson, C. R. J.; Walczak, M. A. A. *Org. Lett.* **2004,** *6,* 3009-3012.

65. Woo, S.; Squires, N.; Fallis, A. G. *Org. Lett.* **1999,** *1*(4), 573 -576.

66. Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002,** *124,* 13402- 13404.

67. Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003,** *302,* 613-618.

68. Anfinsen, C. B. *Science* **1973,** *181,* 223-230.

69. (a) Clauson-Kaas, N.; Dietrich, P.; Nielson, J. T. *Acta Chem. Scand.* **1953,** *7,* 845-848. (b) Elming, N. *Advances Org. Chem. Methods results* **1960,** *2,* 67-115.

70. (a) Achmatowicz, O. Jr.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971,** *27,* 1973-1996. (b) Harris, J. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2000,** *41,* 183-187.

71. Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998,** *63* (21), 7505 -7515.

72. Sello, J. K.; Andreana, P. R.; Lee, D.; Schreiber, S. L. *Org. Lett.* **2003,** *5,* 4125-4127.

73. De Laet, A.; Hehenkamp, J. J. J.; Wife, R. L. *J. Heterocycl. Chem.* **2000,** *37,* 669-674.

74. (a) Hinterding, K.; Alons-Díaz, D.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1998,** *37,* 688-749. (b) Hung, D. T.; Jamison, T. F.; Schreiber, S. L. *Chem. Biol.* **1996,** *3,* 623-639.(c) Mitchison, T. J. *Chem. Biol.* **1994,** *1,* 3-6. (d) Schreiber, S. L. *Bioorg. Med. Chem.* **1998,** *6,* 1127-1152.

75. (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997,** *97,* 449-472. (b) Franzén, R. G. *J. Comb. Chem.* **2000,** *2,* 198-214. (c) Dolle, R, E. *J. Comb. Chem.* **2000,** *2,* 383-433.

76. Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2004,** 6 (1), 39-42.

77. (a) Souers, A. J.; Ellman, J. A. *Tetrahedron* **2001**, *57*, 7431-7448. (b) Wallace, O. B.; Whitehouse, D. L.; Dodd, D. S. *Combinatorial Synthesis of Peptidomimetics*; Abell, A., Ed.; JAI Press Inc.: Stamford CT, **1999**, *2*, 1-51. (c) *J. Comb. Chem.* **2003**, *5* (3), 278 -284.

78. Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195-214.

79. (a) Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H.; Moos, W. H. *J. Am. Chem. Soc.* **1992**, *114*, 10646-10647. (b) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568-6570.

80. (a)Andres, C. J.; Denhart, D. J.; Deshpande, M. S.; Gillman, K. W. *Comb. Chem. High Throughput Screening* **1999**, *2*, 191-210. (b) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477-517.

81. Oliver, S. F.; Abell, C. *Curr. Opin. Chem. Biol.* **1999**, *3*, 299-306.

82. (a) Hruby, V. J. *Life Sci.* **1982**, *31*, 189-199. (b) Avbelj, F.; Hadzi, D *Mol. Pharmacol.* **1985**, *27*, 466-470. (c) Kolhatkar, R. B.; Ghorai, S. K.; George, C.; Reith, M. E. A.; Dutta, A. K. *J. Med. Chem.* **2003**, *46*, 2205-2215.

83. Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789-12854.

84. (a) Wheal, H. V.; Thomson, A. M., Eds. *Excitatory Amino Acids and Synaptic Transmissions*; Academic Press: London, **1995**. (b) Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609-2645. (c) Ozawa, S.; Kamiya, H.; Tsuzuki, K. *Prog. Neurobiol.* **1998**, *54*, 581-618.

85. (a) Conti, P.; De Amici, M.; di Ventimiglia, S. J.; Stensbøl, T. B.; Madsen, U.; Bräuner-Osborne, H.; Russo, E.; De Sarro, G.; Bruno, G.; De Micheli, C. *J. Med. Chem.* **2003**, *46* (14), 3102 -3108.(b) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **1999**,*64*, 5764-5767. (c) Souers, A. J.; Rosenquist, A.; Jarvie, E. M.; Ladlow, M.; Feniuk, W.; Ellman, J. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*(24), 2731-2733.(d) Lewis, R. T.; Macleod, A. M.; Merchant, K. J.; Kelleher, F.; Sanderson, I.; Herbert, R. H.; Cascieri, M. A.; Sadowski, S.; Ball, R. G.; Hoogsteen, K. *J. Med. Chem.* **1995**, *38*, 923-933.

86. (a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385-1401. (b) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*,

8135-8173. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600. (d) Gong, Y. -D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63* (9), 3081 -3086.

87. Paulvannan, K. *J. Org. Chem.* **2004**, *69*, 1207-1214.

CHAPTER II

AZLACTONES TO NOVEL DIHYDROHETEROCYCLIC SCAFFOLDS.

Oxazolones represent an immensely versatile family of heterocyclic compound for future exploitation by synthetic chemists.....A. I. Myers[1]

A. Introduction

In our quest for small molecule heterocyclic scaffolds with novel biological activities, we focused on the azlactone template (5-oxazolone) on account of its versatility as a template for synthesis of other heterocycles. Oxazolones can exist in five isomeric forms all of which are known (Figure II-1)[2].

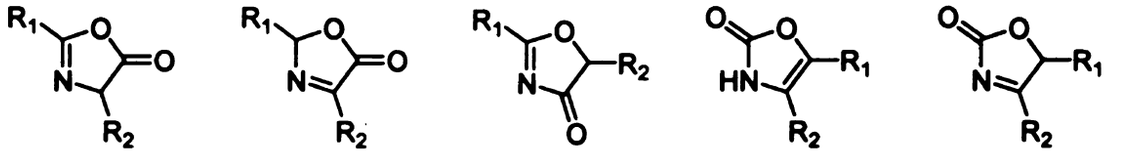


Figure II-1. Isomeric Oxazolones and structures.

Azlactones or 2-oxazolin-5-ones (5(4H)-oxazolone) are cyclic esters of N–acyl-α-amino acids. In 1883 Plöchl first discovered them by condensation of benzaldehyde and hippuric acid in acetic anhydride, but it was Erlenmeyer (1993) who rationalized the structure and christened them as "azlactones".[3] Because he failed to realize the ease of hydrolysis of saturated azlactones, it was in 1908-1910 that Mohr and co-workers were successful in preparing several of them by using acetic anhydride as dehydrating agent.[3] Azlactones gained prominence as the intermediates primarily responsible for racemization when *N*-acyl-α-amino acids

or *N*-protected peptides are coupled with nucleophiles (amino acids, amines, alcohols, etc.) using DCC or other reagents during peptide synthesis.[4] Since then the chemistry of azlactones has evinced great interest mainly as synthons for peptide synthesis and other heterocycles.[6]

Efficient multi-component reactions permit the incorporation of several elements of diversity in a single step and are ideal for application to the diversity-oriented synthesis of the libraries of complex molecules.[5] For our efforts, to generate natural product like libraries for chemical genetics, we decided to focus on azlactones as template/fluid core[7] for diversity oriented synthesis of other heterocycles. The following features of azlactones guided us in our choice;

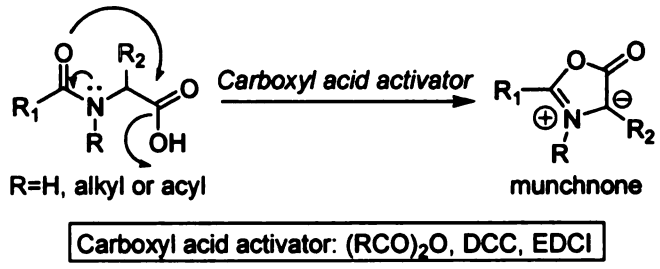


Figure II-2. Cyclodehydration of *N*-acyl-a-aminoacids to azlactones/münchnones.

1) Easily accessible starting materials.

As a source of input materials for the synthesis of azlactones, α-amino acids occupy a special position. They remain unmatched as a source of diverse starting materials: densely functionalized, commercially available in protected form, as pure enantiomers, as the natural as well as a myriad of "unnatural" derivatives.[8] A variety of *N*-acyl-α-amino acid can be obtained under Schotten-Baumann conditions or simple acylation of α-amino acid esters followed by mild basic

hydrolysis.[9] Traditionally the cyclodehydration of *N*-acyl-α-amino acid to azlactones has been carried out by refluxing in acetic anhydride.[10] This method suffers from side reactions, and it is hard to get rid of the acid impurity which is detrimental to sensitive azlactones. Milder versions involving trifluoroacetic anhydride (stoichiometric amounts) or mixed anhydrides have also been used routinely.[11] Although high yields are obtained by using DCC, removal of urea byproduct completely is not trivial.[12] Use of water soluble carbodimides like EDCI have gained popularity because of the high purity of final azlactones (which can be used without further purification for subsequent reactions) and also because they minimize racemization of optically pure products (Figure II-2).[12] Any discussion of azlactones is incomplete without the tautomeric mesionic 1,3-oxazolium-5-oxides (münchnones), formed during the preparation of azlactones with acetic anhydride or other acid anhydrides.[13, 14] Azlactones can also be trapped in mesionic form by *N*-alkylation.[15] A new palladium-catalyzed route to prepare münchnones directly from basic building blocks imine, carbon monoxide, and acid chloride has been developed recently providing an efficient way to add diverse substituents to this versatile template (Figure II-3).[16] Use of 1-isocyanocyclohexene as "universal isocyanide" enables postcondensation modification of Ugi four-component condensation products *via* münchnone that reacts with many external and internal nucleophiles to yield a variety of products.[17]

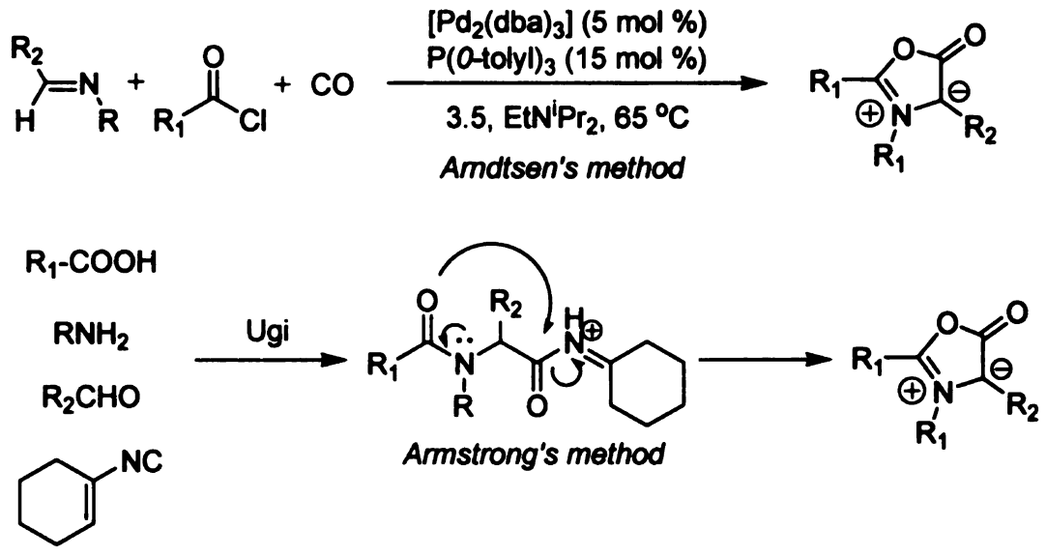


Figure II-3. Syntheses of münchnones from basic building blocks.

2) Pluripotency

Azlactones afford a host of diverse products with different reagents (Figure II-4) and the reaction may involve retention or collapse of the heterocycle itself. The azlactone is an activated internal ester (lactone) of the corresponding *N*-acyl-α-amino acid and as such can undergo nucleophilic attack by host of nucleophiles including alcohols, amines, carboxylates, etc.[2, 18] It also undergoes reactions of activated carbonyls like Friedel-Crafts arylation[19] and Wittig olefination.[20]

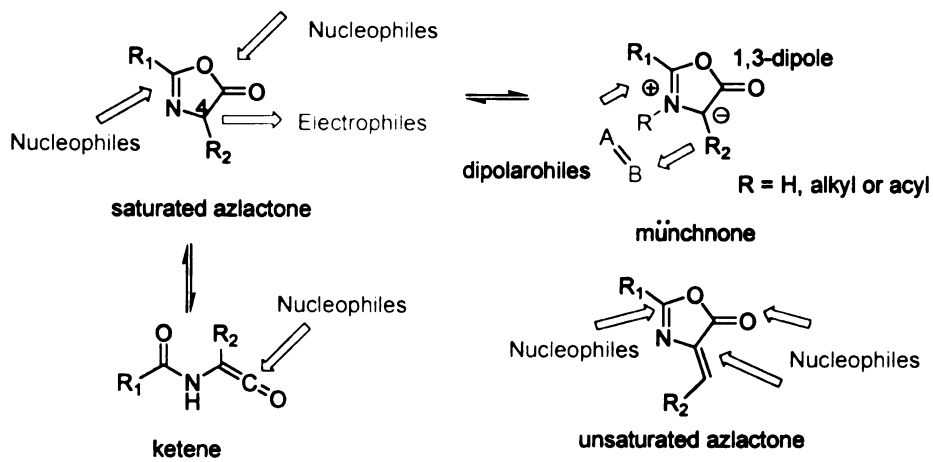


Figure II-4. Diverse reactive sites and intermediates accessible from azlactones.

Unsaturated azlactones (prepared by condensation with aldehydes or ketones) present a uniquely reactive exocyclic double bond for additional reactions with nucleophiles.[18] Monosubstituted azlactones at C_4 can react with a variety of electrophiles due to acidity of C_4-H bond. Alkylations, arylation, acylation, Claisen rearrangement, addition of azine *N*-oxides, addition of diazonium salts and Michael additions have been well documented.[18] Azadienes first undergo electrophilic addition at C_4 followed by a nucleophilc attack of nitrogen at C_2 of azlactones to afford 2-pyridones.[21] Münchnones and their α-amide substituted ketene tautomers, are an important family of substrates for the synthesis of biologically relevant molecules.[22] Münchnones are cyclic azomethine ylides and hence versatile 1,3-dipolar addition substrates and have proven key to the construction of a range of natural products and pharmacologically relevant heterocycles, including pyrroles,[22,23a,b] imidazoles,[23c,d] pyrrolines,[23e] and indole derivatives.[23f] Alternatively, the less stable ketene tautomer can serve as a precursor to α-amino acid and peptide derivatives, via reaction with alcohols or *N*-

terminated peptides,[24a] and their cycloaddition with imines provides access to peptide- based β-lactams.[24b,c]

3) Skeletal diversity through azlactones

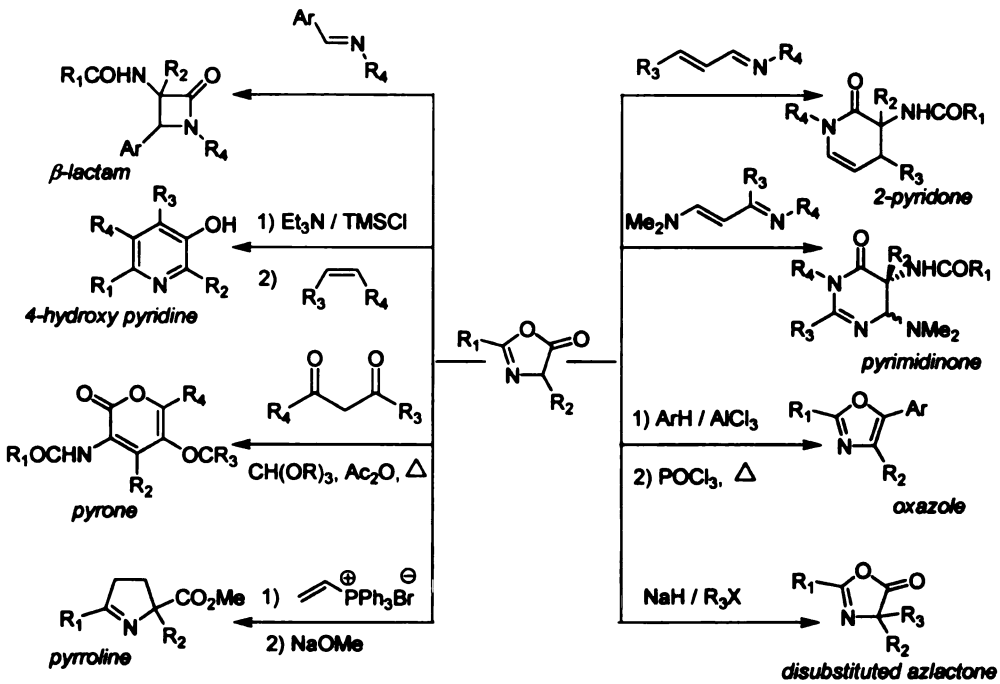


Figure II-5. Cyclocondensation reactions of azlactones to generate diverse heterocycles.

Azlactones are extremely versatile and reactive templates/intermediates and are well-suited for the synthesis of diverse heterocycles by both reagent/reaction condition based differentiating processes and substrate controlled folding (intramolecular) procedures.[25]

i. Differentiation/ Intermolecular reactions.

The azlactone template can be diversified into hetrocyclic skeletons[18] like oxazoles,[19] pyridines,[26,27] pyridones,[21] pyrimidinones,[28] pyrazolones,

imidazolones, isoxazolidinones, isoquinolines, tetrazoles, etc by short cyclocondensation sequences.[2,18]

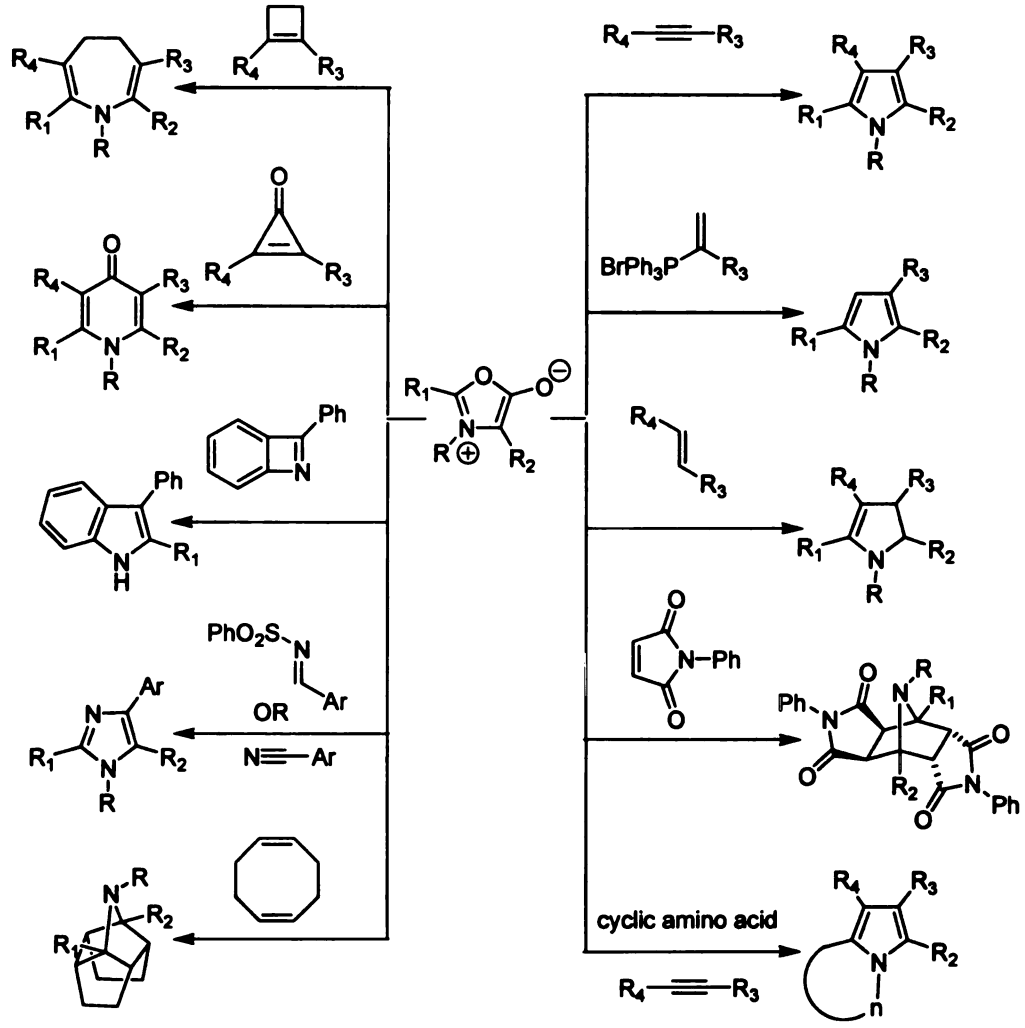


Figure II-6. Cycloadditions of münchnones to generate diverse heterocyclic skeletons.

Oxazoles, pyrananones, simple pyrrolines and quarternary amino acids can be accessed with diverse substituents and such diversity of substituents is hard to be rivaled by other methods (Figure II-5).[2,18] 1,3-Dipolar cycloaddition reactions of *N*-methylated mesoionic oxazolones or münchnone (Figure II-6), provides a general route for the syntheses of a host of heterocycles with diverse skeletons,

for example pyrroles, pyrrolines, azepines and imidazoles, etc.[14a, 23c, 36] By *N*-methylation, the azlactones are locked in the mesoionic form and are extremely reactive dipoles, which afford the heterocycles in very high yields. Strained rings like cyclopropenes and benazetes also participate in cycloadditions with münchnones to afford 4-pyridones and indoles respectively.[2] Gelmi and co-workers used vinyl phosphonium salts to overwhelm the effect of polarization of the vinyl group with the strong interaction of phosphonium group and carbonyl group.[29] Trisubstituted pyrrole can thus be accessed with high regiocontrol. Gribble and co-workers have shown münchnones can react in tandem fashion with cyclooctadiene to give caged compounds.[30] Tandem addition of maleimides to the mesionic Δ^1-pyrroline after decarboxylation occurs in exo fashion compared to the first endo addition resulting in complex tricyclic heterocycles.[13] Münchnones derived from cyclic amino acids like proline, can be used for efficient construction of pyrrolizidine and indolizidine skeletons, which form the core of several natural products and biologically active compounds.[31]

ii. Folding / Intramolecular reactions

The development of effective approaches to bridged heterocyclic ring systems is an important topic in organic synthesis. Because of the ease of constructing two rings simultaneously, intramolecular 1,3-dipolar cycloaddition strategies have emerged as an important tool for the synthesis of structurally complex fused heterocyclic ring systems.[32] Particularly, several bicyclic and polycyclic fused pyrrolidine ring systems are synthesized by the intramolecular cycloadditions of stabilized acyclic azomethine ylides with tethered dipolarophiles (σ elements).[25]

Combination of the intramolecular 1,3-dipolar cycloaddition with other reactions offers a number of interesting synthetic possibilities. In spite of copious literature dealing with bimolecular cycloaddition reactions of mesionic heterocycles, intramolecular examples have received only a minimum of attention.

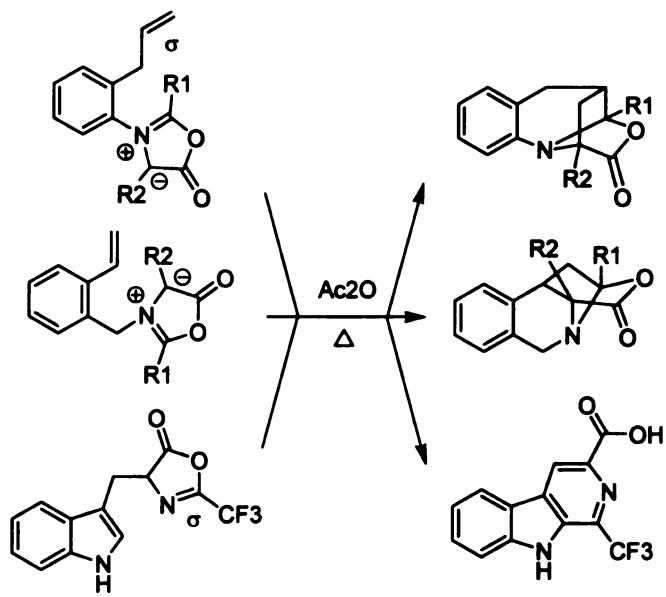


Figure II-7. Alkenes as intramolecular diversity elemnts (σ elements).

An attractive feature associated with the internal cycloaddition of mesionic compounds is the opportunity to control the stereochemistry of the products at several centers. In systems where the dipole and dipolarophile are linked by several atoms, the highly ordered transition state can also induce useful regiochemical control.[40] Padwa and co-workers utilized the intramolecular münchnone-alkene cycloadditions to craft a series of caged compounds with quinoline and isoquinoline cores (Figure II-7).[41] β-carbolines skeletons found frequently in alkaloids were generated by a Pictet-Spengler reaction of an intramolecular azlactone derived from tryptophan.[33] Alkynes tethered to *N*-acyl-

α-amino acids have been shown to undergo intramolecular cycloadditions when refluxed in acetic anhydride *via* the münchnones to afford benzopyrano[4,3-*b*] pyrrole and 1*H*-pyrrolo[1,2-*c*] thiazole derivatives.[14b] Martinelli and co-workers have developed a new approach to octahydroindoles *via* intramolecular cycloadditions of münchnones with tethered alkynes (Figure II-8).[34]

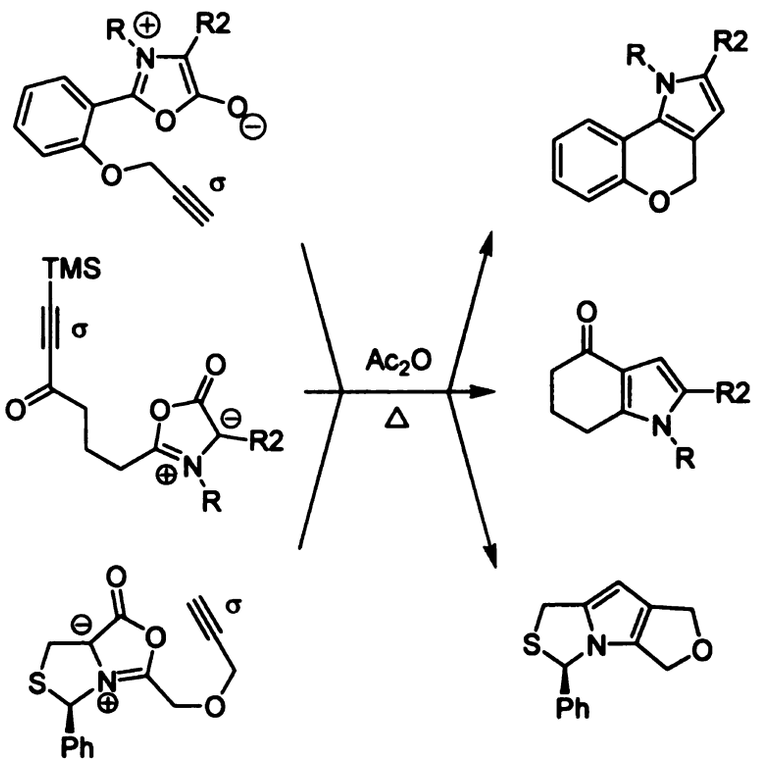


Figure II- 8. Alkynes as intramolecular diversity elemnts (σ elements).

The approach is simple, convergent, widely applicable and uses both natural and unnatural amino acids. It also provides quick entry to mitomycin skeleton and other medicinally important polycyclic heterocyclic compounds. The only limitation is the substituent on nitrogen needed for formation of münchnone intermediate.

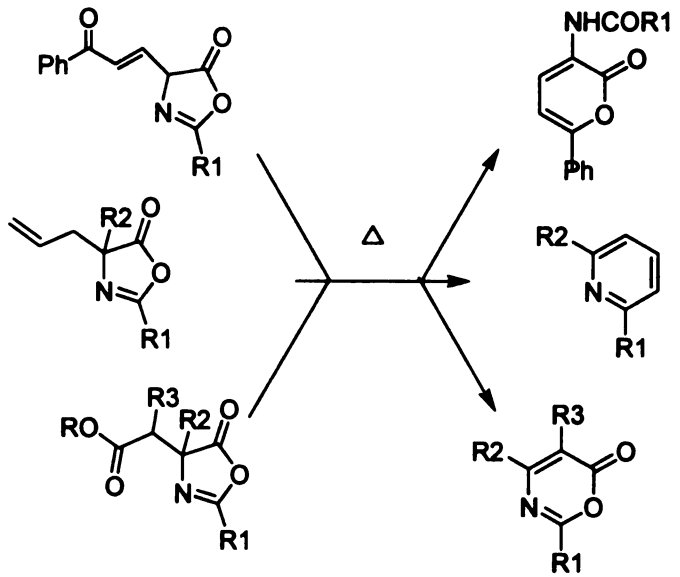


Figure II- 9. Alkenes as intramolecular diversity elements in condensations(σ elements).

Oxazinones, pyridines and pyrones are obtained after stepwise intramolecular cycloadditions (Figure II-9) depending on the σ element (reactive group that decides the skeleton of the product) on the C_4 carbon of the azlactones.[22a]

B. 1, 3-Dipolar cycloadditions and stereochemical diversity [25, 35]

Stereochemical diversity increases the number of relative orientations of potential macromolecule-interacting elements in small molecules. It can best be achieved by using stereospecific reactions that proceed with enantio- or diastereoselectivity. Since diversity-generating processes involve the transformation of a collection of substrates into a collection of products, it is critical that the processes used to generate new stereogenic centers are both selective and general. Many 1, 3-dipolar cycloadditions have the ability to generate rings (and functionality derived from the transformations of such rings)

containing several contiguous stereocenters in one synthetic operation. The configurations of these new stereocenters arise from the geometry of the dipole and dipolarophile as well as the topography (endo or exo) of the cycloaddition. Additional stereospecificity is possible when the reactive π faces of either of the cycloaddends are made diastereotopic by the use of chiral auxillaries or chiral complexes with external agents. Since the diastereoselectivity of 1,3-dipolar cycloaddition is under a powerful substrate control it is challenging to generate the opposite diastereomeric product. Double-diastereoselective reagents that can override the face selectivity of both coupling partners, for example, to achieve exo versus endo selectivity would be highly valuable and the discovery of these types of powerful reagents is critical to achieving stereochemical diversity in DOS. Forward-synthetic planning that incorporates multiple stereochemical diversity generating processes into a single pathway should also make it possible to generate stereochemical diversity in a combinatorial fashion, analogous to the ability of appending processes to generate building-block diversity in a combinatorial manner.

C. Lack of stereochemical diversity in münchnone cycloadditions

It has been well documented that instead of 1, 3-dipolar cycloaddition azlactones undergo a Staudinger-type reaction when heated with imines in toluene yielding β-lactams. The azlactone, which is in equilibrium with valence tautomeric ketene intermediate, undergoes a [2+2] cycloaddition reaction with the imine (Scheme II-3). It can be concluded that either mesoionic oxazolium oxide, which has the

nitrogen atom unsubstituted, is not in reasonable concentration and/or the imine nitrogen is not nucleophilic enough. Hence formation of ketene takes predominance, which reacts readily with the imines to afford the β-lactam.[6, 36, 37] In 1970, Huisgen had reported that a moderate equilibrium concentration of the mesoionic tautomer is essential for the 1, 3-dipolar cycloaddition leading to heterocycle formation (Figure II-10).[13] By *N*-alkylation or acylation, the azlactones are locked in the mesoionic form and are extremely reactive dipoles, which afford the pyrroles and other hetereocycles in very high yields.[15]

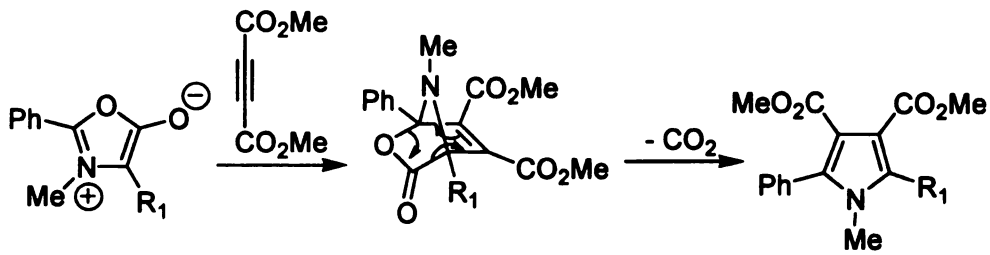


Figure II-10. Synthesis of pyrroles from münchnones.

The analogous reaction of a münchnone with a nitrile to provide an imidazole is not viable due to the low reactivity of nitriles. Imidazoles (Figure II-11) can be generated by treatment of the münchnones with tosylimines. Addition of the tosylimines results in an unstable bicyclic adduct that loses carbon dioxide and benzenesulphinic acid to gain aromaticity.[23c,d,e,38] The phenylsulphonyl residue as leaving group enhances the tendency to aromatize (Figure II-11). Münchnones with different substituents, at the 2 and 4-positions lead regioselectively to products in which a bond is always formed between the 2-carbon atom of the dipole and the imine nitrogen atom. This attack was explained on the basis of a dipole-dipole interaction between partially negative nitrogen of the imine and the

electrophilic C-2 atom of the münchnone. The yield reported for these reactions are low at least partly due to self-condensation of münchnones.[23d] The problem of self-condensation has been suppressed by using a solid-phase approach towards imidazoles. Bilodeau *et al*[23c] used a standard reductive amination protocol to hook an amino acid ester onto a aldehyde group on a commercially available resin. This path of attachment also served to alkylate the nitrogen atom of the azlactone that was made by subsequent cyclodehydration of the amino acid, which was condensed with tosylamines to afford the imidazoles in good yields and purities.

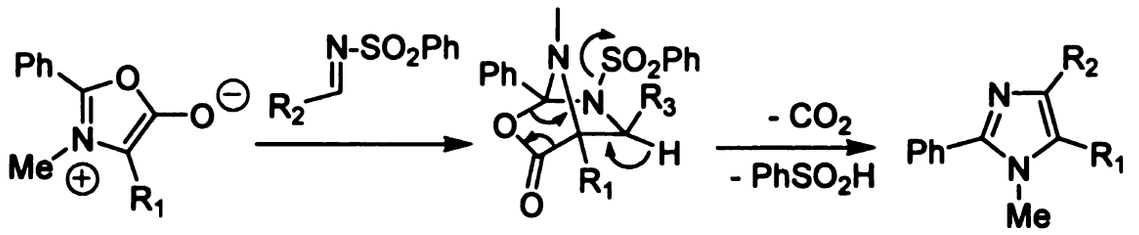


Figure II-11. Synthesis of imidazoles from münchnones.

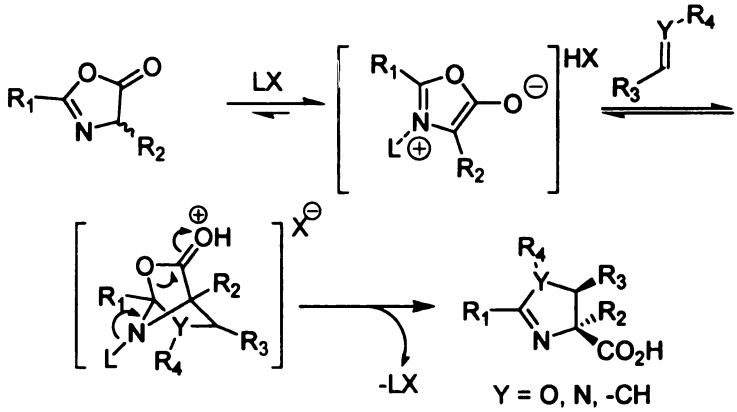
1, 3-dipolar cycloadditions of münchnones are simple thermal processes, unaided by external reagents. The products resulting from cycloadditions of münchnones with various dipolarophiles are aromatic and carry little or no stereochemical information. In intermolecular reactions, primary cycloadducts have generally not been isolated and identified because they readily eliminate carbon dioxide resulting in aromatization.[39] Double bond isomerization (in case of alkenes to Δ^2-pyrrolines) and multiple cycloadditions have been observed after decarboxylation, especially in case of addition of alkenes.[40] This results in loss of stereogenic centers from the cycloadditions in the final products. Although, the decarboxylation seems to be driven by the stability gained by aromatization, it is

not a concerted process and the harsh conditions often employed might play a major role. Maryanoff and co-workers have described one example of the isolation of a Δ^1-pyrroline-5-carboxylic acid from reaction of 1, 2-dicyanocyclobutene from the intermolecular cycloaddition of a münchnone.[41] A notable exception was reported by Padwa and co-workers who successfully isolated and characterized the primary adducts from intramolecular cycloadditions of münchnones to terminal alkenes.[42, 43] In the above reactions, expulsion of carbon dioxide is presumably impeded by the severe structural constraints in the intermediate polycycle. They were also able to show that the cycloadditions occurs with exo stereochemistry for the substituents on alkenes and concluded that it is reflective of the steric constraints imposed by a unimolecular transition state. The polycyclic heterocyclic compounds oxazoloquinolines and oxazoloisoquinoline products are potential precursors to amaryllidaceae alkaloids. Padwa and co-workers further diversified these heterocyclic systems by addition of organometallic reagents/reduction with LAH to tricyclic lactols. These lactols undergo ring opening to benzazepine scaffolds which are valuable peptidomimetics displaying diverse biological activities. [42, 43]

D. Potential of Lewis acid mediated generation of münchnones and synthesis of novel dihydroheterocyclic scaffolds.

We envisioned that coordination of a Lewis acid to nitrogen atom of the azlactone, would increase the equilibrium concentration of münchnone intermediate and accelerate the azomethine ylide cycloaddition reaction (Scheme II-1).[44] Moreover if milder protocols could be developed by Lewis acid

mediation, then it might be possible to isolate either the bicyclic cycloadduct or the dihydroheterocycles (Scheme II-1) without any decarboxylation or rearrangement.[45, 46] [3+2] cycloadditions in which heterodipolarophiles are employed to intercept reactive azomethine ylides represent a useful entry into functionalized, protected amino acids.[45,47] In case of münchnones, dihydroheterocycles isolated would be masked α,α-disubstituted (quarternary) amino acids. Interest in the synthesis of biologically active products containing quaternary carbon atoms has increased notably over the last decade.[48] The interesting properties of α- and β-amino acids with conformational rigidity, in particular , the α,β-disubstituted series have recently attracted the attention of numerous research groups since the incorporation of these products into peptides can drastically modify their properties.



Scheme II-1. Synthesis of dihydroheterocycles from münchnones.

During their efforts to utilize the 1, 3-dipolar cycloadditions in the diversity oriented synthesis of biomimetic probes, Austin and co-workers[49] discovered that the cycloadditions of vinyl ethers with isomünchnones proceeds with complete endo diastereoselectivity. Removal of chiral auxillary through an unusually facile

ester aminolysis resulted in efficient construction of bicyclic [2.2.1] scaffold (Figure II- 12). The hetero-bicyclic [2.2.1] scaffolds allows for the diversity both in terms of position and type of functionality incorporated and were used to interact with the HIV-1 Tat/TAR system. RNA-protein interactions constitute a rapidly growing area of research, especially because of their prevalent role in many cellular processes.

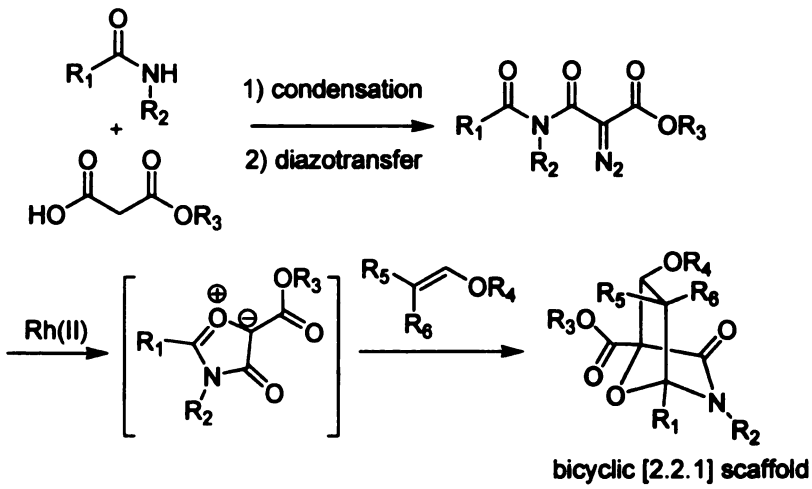


Figure II-12. Synthesis of bicyclic scaffolds from cycloaddition of isomunchnones.

Dihydro- and completely reduced five-membered heterocycles represent an important addition to the repertoire of small molecules that are being used to control complex biological processes. Mapp and co-workers[50] have described the design and synthesis of isoxazolidines, the very first examples of synthetic small molecule heterocycles that activate transcription at levels comparable to those of a natural activation domain. Transcriptional activators play an essential role in the regulatory network that controls gene-specific transcription (Figure II-13).[51]The misregulation of this complex event cascade is correlated with a growing number

of human diseases,[52] and thus interest in developing artificial transcriptional activators has intensified.[53] To identify a minimal functional unit for a small molecule-based activation domain, a series of isoxazolidines containing functional groups typically found in endogenous activation domains were designed (Figure II-13). The isoxazolidine scaffold was chosen due to the relative ease with which diverse functional groups could be incorporated in a stereocontrolled manner onto the conformationally constrained ring, [50, 54] thus displaying those groups in a three-dimensional array. Remarkably, one isoxazolidine (Figure II-13) was nearly as active as the positive control ATF14 (natural ligand) despite a considerable difference in size (MW 290 versus 1674). Similar to natural activation domains such as ATF14, a balance of hydrophobicity and polarity was found to be important for overall potency.[50, 55] Two factors were suggested to play a role in the isoxazolidine being nearly as active as ATF14 despite the size difference. As an organic molecule, the isoxazolidine ring is resistant to proteolytic degradation and thus probably has a longer lifetime. In addition, the isoxazolidine molecule likely populates conformations more closely related to the final bound state due to structural constraints imposed by the ring.

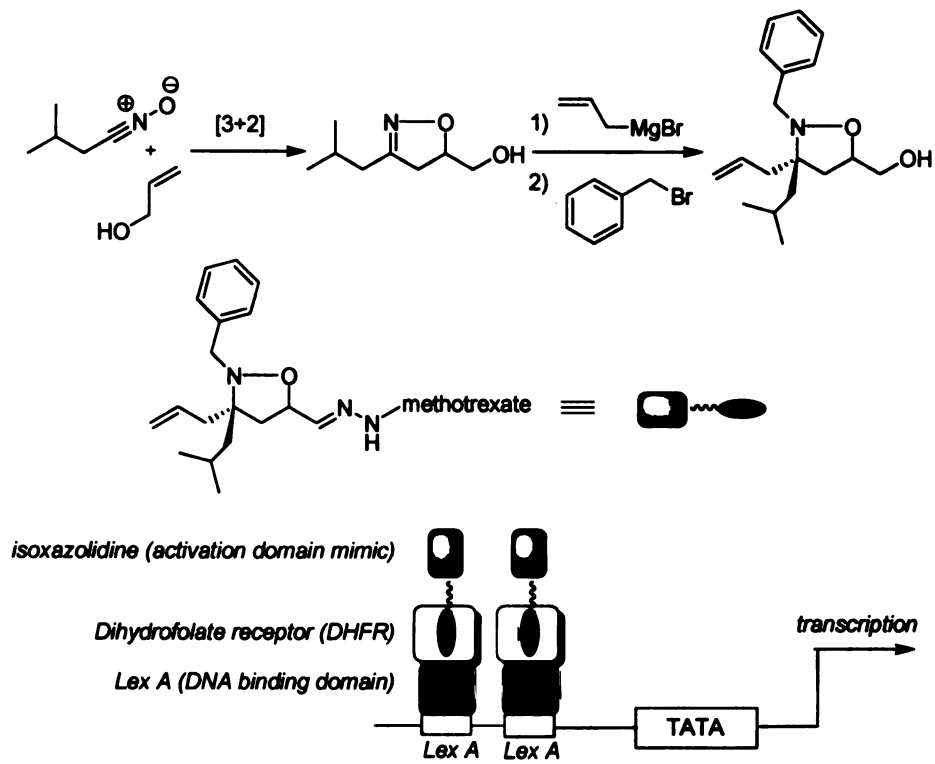


Figure II-13. Synthesis of isoxazolidines as mimic of transcription regulators.

E. Lewis acid mediated cycloadditions of nitrile ylides and azomethine ylides.[56]

Control of the stereo-, regio-, and enantioselectivity of 1, 3-dipolar cycloadditions with Lewis acids is a relatively new area and has been examined with only a limited number of dipoles. A common difficulty is the competition between the dipole and the dipolarophile for the external reagent when it is a Lewis acid. When one tries to activate electrophilic dipolarophiles with Lewis acids, binding to the 1, 3-dipole can predominate, resulting in a slower reaction. Such strong binding can also cause decreased reactivity of the 1, 3-dipole towards nucleophilic dipolarophiles. Strong binding of 1, 3-dipoles to a Lewis acid is often not avoidable because of the electronic structure of the 1, 3-dipoles and the typical

prescence of Lewis basic sites. Accordingly, Lewis acidic reagents may combine with the basic sites on certain 1, 3-dipoles, making relatively stable salt-like complexes. The co-ordinating power of external reagents must be carefully adjusted in order to be successful in attaining high rate enhancements. The nature of the ligands on the Lewis acid and the lability and exchangeability of these ligands are typical issues to be considered.

F. Nitrile ylides and Lewis acids

i. Syntheis of 2-oxazolines

Suga *et al* reported that 5-alkoxyoxazoles react with aldehydes giving 4,5-cis-2-oxazoline-4-carboxylates stereoselectively when activated with a stoichiometric amount of methylaluminium β-binapthoxide as the Lewis acid (Figure II-14).[57] This reaction has recently been extended to a catalytically enantioselective version using an enantiopure methylaluminium β-binapthoxide.[58] Although the actual reacting species were not assigned, 5-alkoxyoxazoles are known to behave as nitrile ylide 1, 3-dipole equivalents in Lewis acid catalyzed reactions with aldehydes. Ito *et al* developed new catalyzed asymmetric cycloadditions reactions of formal nitrile ylides. Thus, methyl α-isocyanoalkanoates were allowed to react with benzaldehyde or acetaldehyde in the prescence of 0.5-1 mol % of a chiral (aminoalkyl)ferrocenylphosphine-gold(I) complex to give optically active methyl 2-oxazoline-4-carboxylates with high enantoselectivity in quantitative yield.

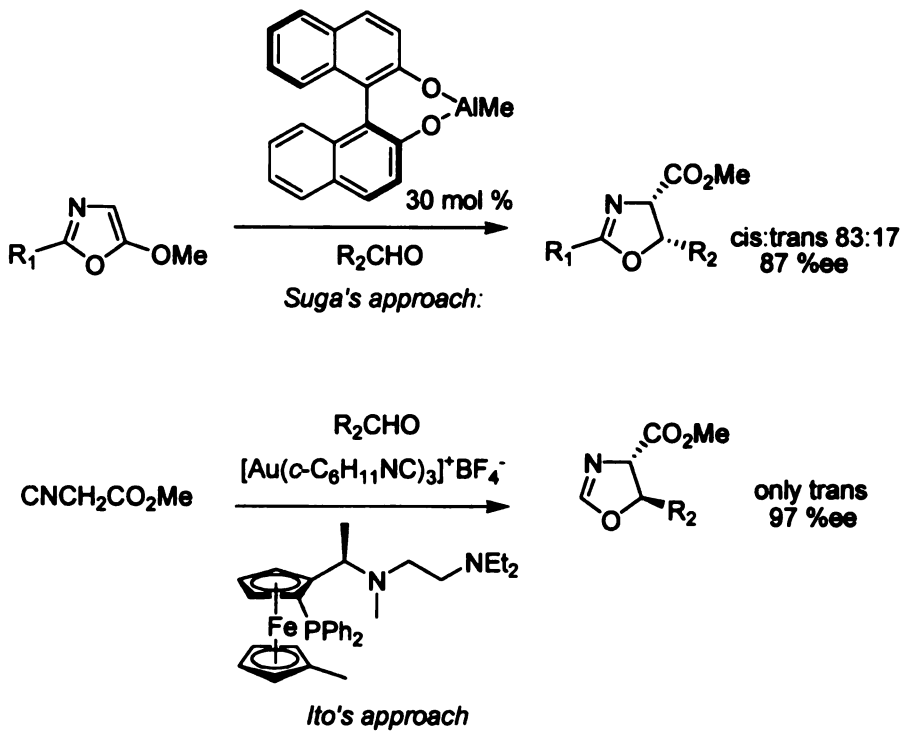


Figure II-14. Synthesis of oxazolines from oxazoles.

The oxazolines were converted into optically active β-hydroxy-α-amino acid methyl esters. The selective formation of cis-isomers of 2-oxazoline-4-carboxylates in suga's reactions is synthetically complimentry to Ito's method.[59]

ii. Synthesis of Δ^2-pyrrolines.

Grigg *et. al.* recently extended Ito's reaction to the Ag(I) catalyzed 1,3-dipolar cycloadditions of methyl isocyanate with α,β-unsaturated carbonyl compounds.[60] The rate of this reaction can be enhanced effectively with a catalytic amount of silver(I) acetate (1 mol%). Grigg *et al* proposed a reaction mechanism in which silver(I) acetate adds to the carbon atom of isocyano group to form an organometallic intermediate that is subsequently deprotonated to generate a nitrile

ylide 1, 3-dipole. After the cycloadditions, double-bond migration results from the imine-enamine tautomerism to afford Δ^2-pyrrolines (Figure II-15).[60]

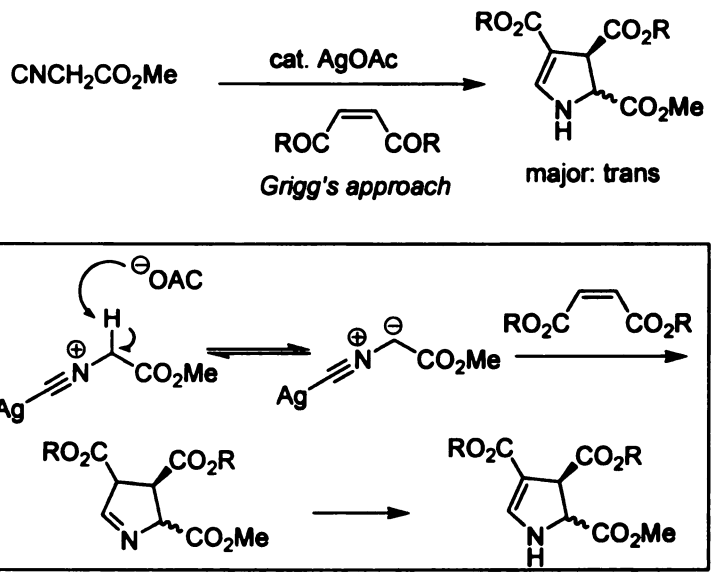


Figure II-15. Synthesis of Δ^2-pyrrolines from isocyanoacetates.

iii. Synthesis of 2-imidazolines.

Although mechanistically suggested to proceed through aldol reaction, 2-imidazolines (Figure II-16) have been synthesized from isocyanoacetate esters using Lewis acid catalysis. Hayashi and Ito *et al* reported a diastereoselective reaction of *N*-sulfonylimines with methyl isocyanoacetate catalyzed by Au (I) complexes, which provide efficient access to erythro 2, 3-diamino acids.[61]

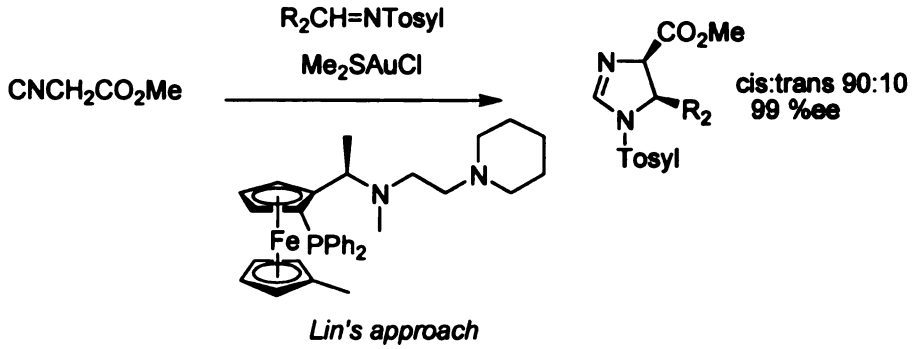


Figure II-16. Synthesis of 2-imidazolines from isocyanoacetates.

Lin *et al* have extended the reaction to enantioselective version using catalytic chiral ferrocenylphosphine Au(I) complex.[62]

G. Azomethine ylides and Lewis acids

i. Synthesis of 2-imidazolines.

Viso *et al* reported the very first examples of a highly diastereoselective 1,3-dipolar cycloadditions of azomethine ylides derived from α-iminoesters (Figure II-17) with chiral sulfinimines to produce *N*-sulfinyl imidazolidines and transformation into non-symmetrical vicinal diamines.[63] Dipole generation under standard conditions using LiBr, Et_3N, MeCN or AgOAc, DBU, toluene had failed. Use of LDA allowed for successful cycloadditions with a high degree of endo stereocontrol. Addition of $BF_3.OEt_2$ results in abrogation of cycloadditions pathway and the reaction proceeds with opposite diastereoselectivity via a step-wise mechanism.[64]

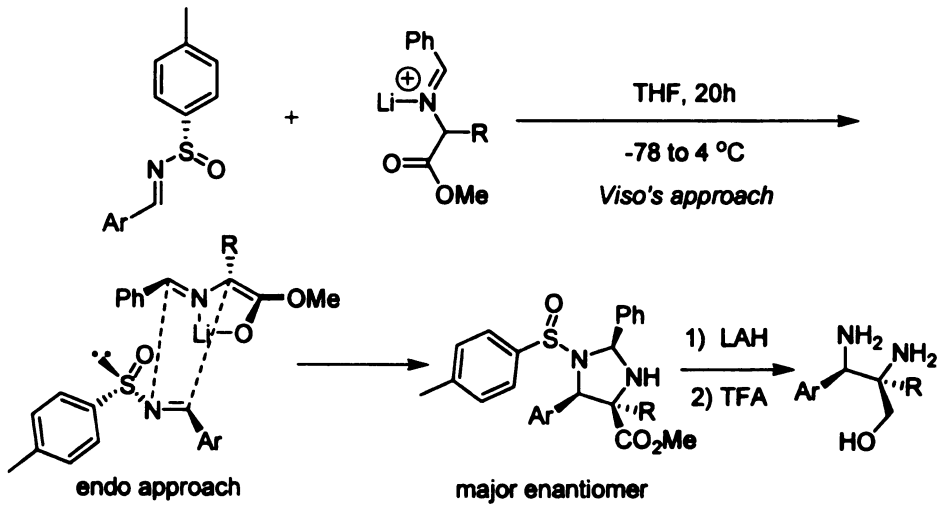


Figure II-17. Synthesis of 2-imidazolines from azomethine ylides.

ii. Synthesis of pyrrolidines: The reaction of azomethine ylide 1, 3-dipoles with olefinic dipolarophiles to form highly substituted pyrrolidines is a reaction of intense research interest.[65] It has been applied towards synthesis of substituted prolines, which can serve as catalysts and serve as important motifs in many biologically active molecules. Among the different versions of this reaction, the most practical approach has been the interaction between stabilized *N*-metalated azomethine ylides derived from α-imino glycinate esters and π-deficient alkenes (Figure II-18). The reaction proceeds under mild conditions and with a high degree of diastereocontrol. Silver (I) and Lithium (I) metal cations (usually stoichiometric amounts) are most commonly used along with an excess of tertiary amine base. Enantiocontrol has recently been extended to this reaction raising its stock for the generation of complex heterocyclic molecules. While Jorgensen *et al*[66] used chiral oxazoline complexes of Zn, Zhang and co-workers[65] employed Ag(I) complex with FAP ligands for above cycloadditions.

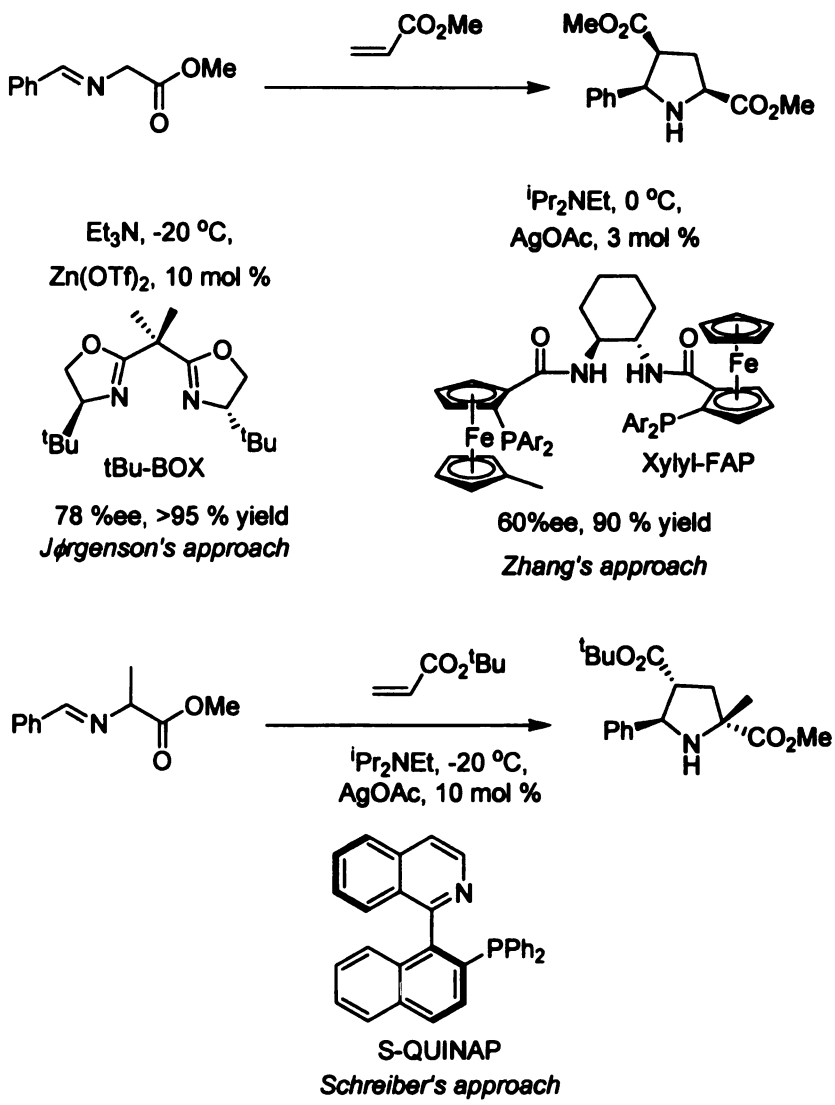


Figure II-18. Synthesis of pyrrolidines from α-iminoesters.

Schreiber and co-workers further improved on Zhang's protocol by expanding the substrate scope and increasing the enantioselectivities achieved by employing the QUINAP ligand.[67] An important highlight of this work is that they were able to generate quartenary stereogenic centers by employing substituted amino acids. Recently, the normal endo selectivity of the above cycloadditions has been

reversed by Komatsu *et al* by a opportune selection of bulky phosphine ligands in the cycloadditions of *N*-substituted maleimides and α-imino glycinate.[68] Reversing the diastereoselectivity which is under substrate control by using external reagents (Lewis acids) is highly desirable in a diversity oriented synthesis program.[25] Johnson and co-workers[45a] document reaction conditions that achieve the first productive cycloadditions of azomethine ylides obtained from Lewis acid catalyzed carbon-carbon bond cleavage of aziridines (Figure II-19).

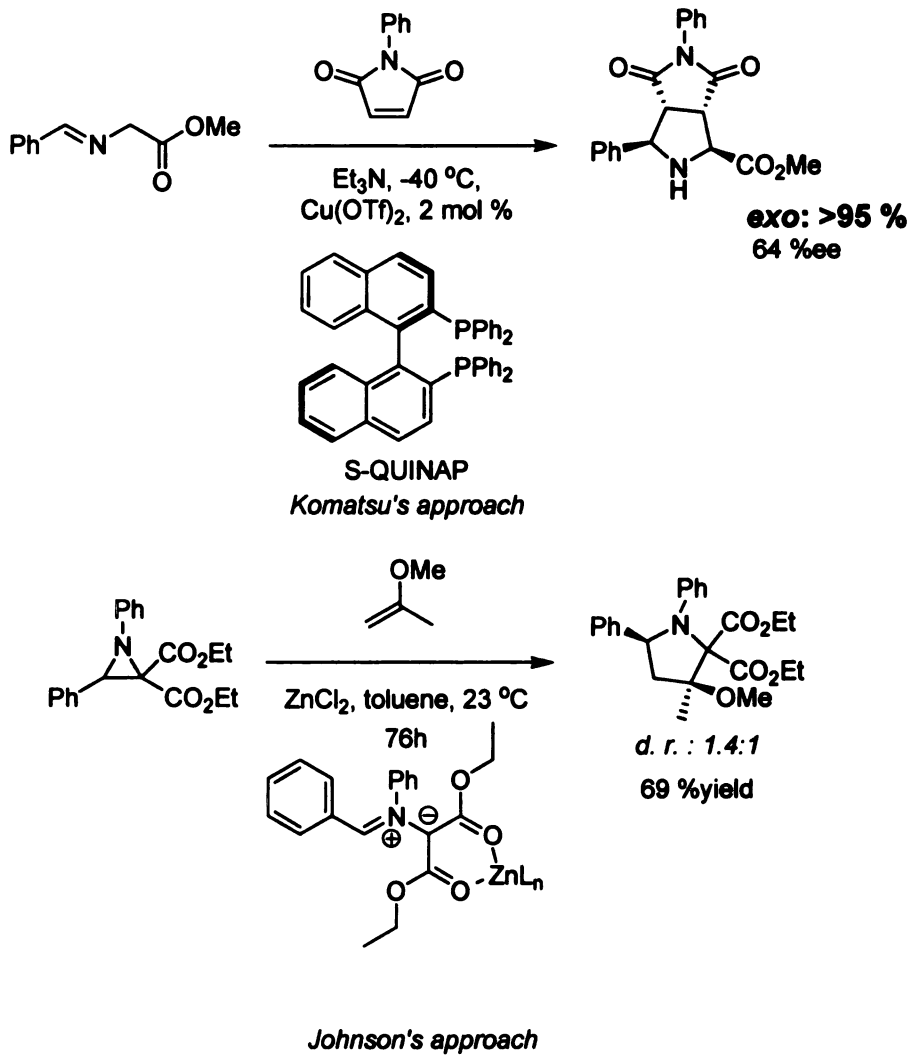
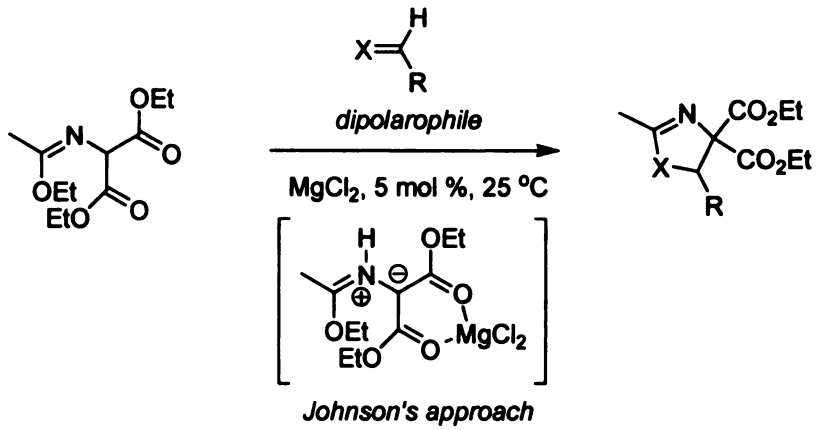


Figure II-19. Synthesis of pyrrolidines from aziridines and electron-rich alkenes.

The constitution of the cycloadduct (a [4+2] stepwise adduct or a [3+2] cycloadduct) obtained was further shown to be strongly dependent on the identity of the alkene trap employed. The activation barrier for electrocyclic carbon-carbon bond cleavage in a prototypical *N*-aryl-2,3-diester aziridine was measured by Huisgen to be ca. 29 kcal/mol, which translates to rather forcing conditions in thermal dipolar cycloadditions.[45a] Johnson *et al* hypothesized that the metal-coordinated ylide is extremely electron poor and thus belongs to type III in the Sustmann classification system of 1, 3-dipolar cycloadditions and that rate acceleration should be observed with electron rich dipolarophiles due to the correct HOMO/LUMO match. Accordingly, in presence of catalytic $ZnCl_2$ acyclic enol ethers intercept the metal-coordinated ylide via the [3+2] pathway to afford pyrrolidines in good yields and with modest diastereocontrol. It is important to note that we have been unable to effectively perform these cycloadditions in the absence of Lewis acid. These experiments indicate that Lewis acid promotion is essential and provide additional support for the type III classification of this family of cycloadditions.

iii. Synthesis of dihydroheterocycles.



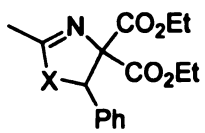
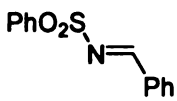
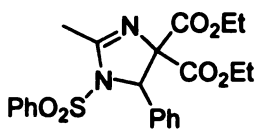
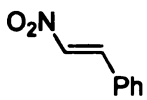
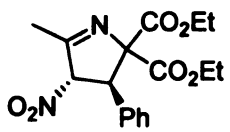
dipolarophile	product	% yield
PhCHO		89
		80
		64

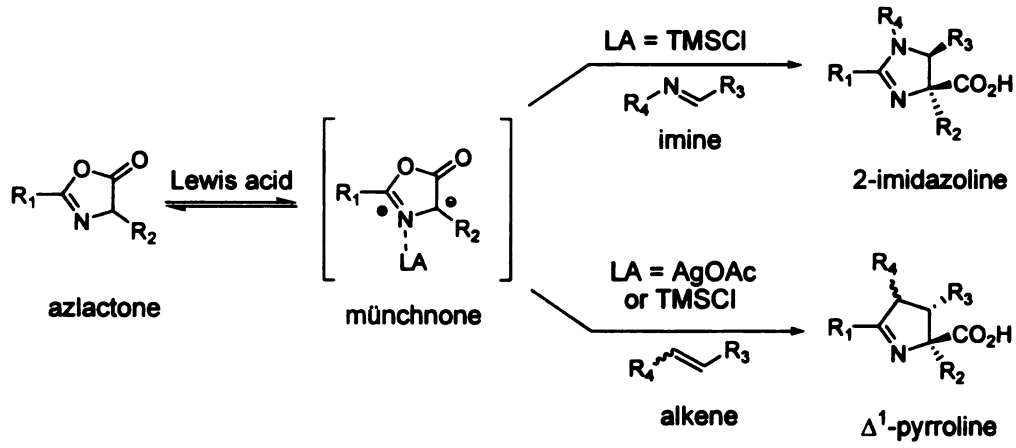
Figure II-20. Synthesis of dihydroheterocycles from soft enolization of imidates.

Johnson *et al* [45] have investigated *N*-metalated azomethine ylides formed via "soft enolization" of (imino)glycine esters as alternatives to ylides generated from the same compounds in the classic thermal [1, 2]-prototropy manifold which require a weak base working in concert with a metal salt.[45b] An evaluation of simple Lewis acids revealed that *N*-malonylimidates undergo catalyzed [3+2] cycloadditions reactions with aldehydes, imines, and activated olefins to form oxazolines, imidazolines, and pyrrolines, respectively (Figure II-20). The reactions proceed

optimally at ambient temperature with the addition of 5 mol % of $MgCl_2$ in CH_3CN. Based on experiments the authors suggest that the Mg Lewis acid promotes a 1, 2-prototropic shift to give a metal-coordinated azomethine ylide, rather than ionization and proton transfer to give a nitrile ylide. The use of a scalemic metal complex to catalyze the cycloadditions further opens up the possibility of enantioselective variants that are not possible thermolytically.

H. Current work

With the awareness that five-membered nitrogen containing skeletons make up the core of several natural products and prospective libraries, the generation of diverse small molecular scaffolds with potential biological activity is an ongoing theme in our group. Dihydroheterocyclic scaffolds on account of their structural rigidity and the three dimensional disposition of functional groups are perfectly suited for this aim. They have a different shape profile from aromatic heterocycles generally encountered in drug discovery programs and as such might access entirely new therapeutic target. There are very few reports in literature involving short and efficient syntheses of dihydroheterocycles, which would also result in appendage and stereochemical diversity. During my graduate work, I discovered a mild *in situ* method of generation of münchnones (cyclic azomethine ylides) from azlactones using Lewis acids.[44a] I have applied this condition for establishing new stereoselective methods to synthesize *N*-containing dihydroheterocycles; 2-imidazolines[44b] and Δ^1-pyrrolines.[44c] The scaffolds are obtained with high diastereoselectivity and are amenable to diverse substitution (Scheme II-2).

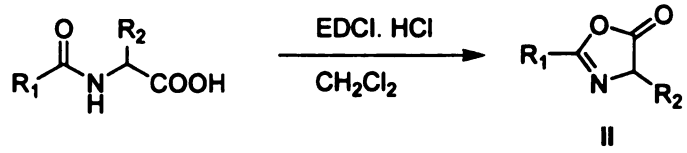


Scheme II-2. Lewis acid mediated *insitu* generation of münchnones from azlactones 1, 3 dipolar cycloaddition with dipolarophile.

These scaffolds offer unexplored territory in terms of their structure (3-D disposition of functional groups) and their function (biological activity and catalysis). In addition to the novel development of these molecules, we have been able to establish that the imidazoline scaffolds can catalyze a novel stereoselective reaction of ketenes with *N*-acylimines derived from glycine esters. This reaction is currently under investigation in the group. Most of my work has been published in peer reviewed reputed journals and in light of the potential therapeutic value of the compounds as inhibitors of activation of NF-κB and enhancers of chemotherapeutic potential of anti-cancer drugs; [69] we have been able to obtain patents for the above work.[70] The leads are being now carried through cellular and animal studies in active collaborations with other researchers and industry. In the future, enantiocontrol and application of the above mild method of generation of münchnones to other scaffolds, and natural products will be pursued.

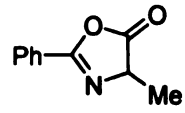
I. Experimental procedure

General procedure for synthesis of azlactones[12].



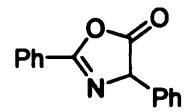
II

A solution of benzoyl amino acid (2 mmol) and EDCI.HCl (2 mmol) in dichloromethane (20 mL) was stirred at 0°C for 1h till the starting material disappeared. The reaction mixture was washed successively with cold (containing ice) water, aqueous $NaHCO_3$ (10 mL) and water (10mL). The solution was dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated to dryness *in vacuo* giving the oxazolones as solids or oils.



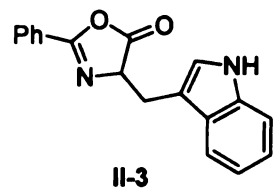
II-1

2-phenyl-4-methyl-4H-oxazolin-5-one II-1: Cyclodehydration of N-benzoyl-L-alanine (2 g, 10 mmol) with EDCI.HCl (1.92 g, 10 mmol.) gave 1.81g of **II-1** in 90 % yield. ^1H NMR (300 MHz) ($CDCl_3$): δ 1.6 (3H, d, J = 7.4 Hz), 4.46 (1H, q, J= 7.5 Hz), 7.47 (3H, m), 8.0 (2H, d); ^{13}C NMR (75 MHz) ($CDCl_3$): δ16.1, 60.3, 125.3, 127.2, 128.2, 132, 160.7, 178.2; IR (neat): 1828 cm^{-1}, 1653 cm^{-1}.



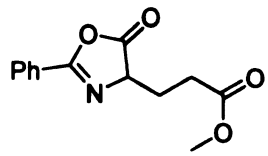
II-2

2, 4-diphenyl-4H-oxazolin-5-one II-2: Cyclodehydration of N-benzoyl-L-phenylglycine (2 g, 7.8 mmol) with EDCI.HCl (1.5 g, 7.8 mmol.) gave 1.3g of **II-2** in 70 % yield. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 5.5 (1H, s), 7.35-7.65 (8H, m), 8.05-8.15 (2H, m); ^{13}C NMR (75MHz) ($CDCl_3$): δ 176. 4, 162.8, 133.9, 133.2, 129.2, 129.18, 129.1, 129, 128.99, 128.96, 128.9, 128.7, 128.4, 127.1, 126.1, 68.4; IR (neat) 1825 cm^{-1}, 1655 cm^{-1}.



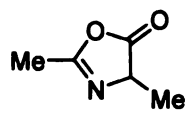
II-3

4-(1*H*-Indol-3-ylmethyl)-2-phenyl-4*H*-oxazol-5-one II-3: Cyclodehydration of N-benzoyl-L-tryptophan (2 g, 6.5 mmol) with EDCI.HCl (1.24 g, 6.5 mmol.) gave 1.5 g of **II-3** in 80 % yield. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 3.5 (2H, ddd, J_1 = 5 Hz, J_2 = 15 Hz, J = 50 Hz), 3.5 (2H, t, J = 5 Hz), 7.05-8.0 (9H, m), 8.18 (1H, b); ^{13}CNMR (75MHz) ($CDCl_3$): δ 178.1, 161.7, 135.9, 132.6, 128. 6, 127.8, 127.3, 125.8, 123, 122, 119.5, 119.1, 1 11. 1, 109.5, 66.6, 27.2; IR (neat) 3416.4 cm^{-1}, 1815 cm^{-1}, 1653 cm^{-1}.



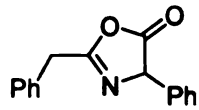
II-4

3-(5-Oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-propionic acid methyl ester II-4: Cyclodehydration of N-benzoyl-glutamic acid-5-metyl ester (4 g, 15 mmol) with EDCI.HCl (3.17g, 16.5 mmol.) gave 2.6g of **II-4** in 70 % yield. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 2.16 (1H, sextet, J = 6.6 Hz), 2.4 (1H, sextet, *J*= 6.5 Hz), 2.4 (3H, t, *J* = 9 Hz), 3.7 (3H, s), 4.54 (1H, t, *J* = 9 Hz), 7.4-7.6 (6H, m), 8.0 (2H, d, *J* = 9.9 Hz), 8.2 (2H, d, *J* = 9.9 Hz); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 177.8, 172.6, 162.2, 161.9, 134.5, 132.8, 130.4, 129.9, 129.8, 128.8, 128.7, 128.5, 128.2, 127. 8, 125.6, 51.7, 29.6, 26.6; IR (neat) cm^{-1}, 1828 cm^{-1}, 1651 cm^{-1}.



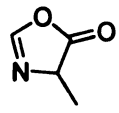
II-5

2, 4-dimethyl-4*H*-oxazolin-5-one II-5: Cyclodehydration of N-benzoyl-glutamic acid-5-metyl ester (4 g, 30 mmol) with EDCI.HCl (6.3g, 33 mmol.) gave 2.0g of **II-5** in 60 % yield. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.37 (3H, t, *J* = 8 Hz), 2.05 (3H, s), 4.0-4.16 (1H, m); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 179.2, 162.6, 60.4, 16.4, 15.1; IR (neat) cm^{-1}, 1826 cm^{-1}, 1686 cm^{-1}.



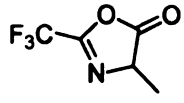
II-6

2-Benzyl-4-phenyl-4*H*-oxazol-5-one II-6: Cyclodehydration of N-phenacetylphenylglycine (2 g, 10 mmol) with EDCI.HCl (1.9g, 10 mmol.) gave 1.64g of **II-6** in 90 % yield. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 3.96 (2H, s), 5.35 (1H, s), 7.2-7.6 (10H, m); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 176.2,165.5,133.0, 132.7, 129.3, 128.9, 128.7, 128.5, 128.4, 128.3, 127.7, 127.4, 126.6, 125.42; IR (neat) cm^{-1}, 1829 cm^{-1}, 1674 cm^{-1}.



II-7

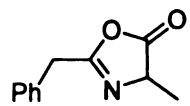
4-Methyl-4*H*-oxazol-5-one II-7: Cyclodehydration of N-formyl-alanine (2 g, 17 mmol) with EDCI.HCl (3.3g, 17 mmol.) gave 1.2g of **II-7** in 70 % yield. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.46 (3H, t, J = 7.5 Hz), 4.13 (1H, q, J= 7.5Hz), 7.52 (1H, s); ^{13}C NMR (75 MHz) ($CDCl_3$) 178.2, 152.8, 58.3, 16.2 ; IR (neat) cm^{-1}, 1817 cm^{-1}, 1676 cm^{-1}.



II-8

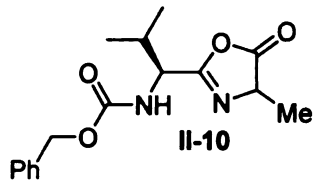
2-trifluoromethyl-4-Methyl-4*H*-oxazol-5-one II-8: Cyclodehydration of N-trifluoromethyl alanine (2 g, 10.8 mmol) with EDCI.HCl (2.06g, 10.8 mmol.)

gave **II-8** in 28 % yield. Partial data: IR (neat) cm^{-1}, 1840 cm^{-1}; Pseudooxazolone: IR (neat) cm^{-1} 1809 cm^{-1}.



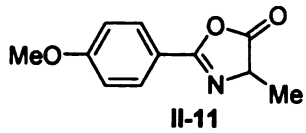
II-9

Partial data: 2-Benzyl-4-methyl-4H-oxazol-5-one II-9: Cyclodehydration of N-phenacetyl alanine (4 g, 19.3 mmol) with EDCI.HCl (3.71g, 19.3 mmol) gave 3.1g of **II-9** as viscous oil in 82 % yield. ^1H NMR (300 MHz) ($CDCl_3$): δ 1.47 (3H, d, J = 6.9 Hz), 4.35-4.5 (2H, m), 4.77 (1H, q, J = 7.5 Hz), 7.38 (2H, t, J = 7.2 Hz), 7.48 (1H, t, J = 7.2 Hz, 7.72 (2H, d, J = 7.8 Hz); IR (neat) cm^{-1}, 1824 cm^{-1}, 1676 cm^{-1}.



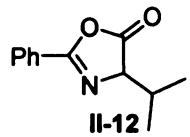
II-10

Partial data: Benzyl-(S)-1-(4,5-dihydro-4-methyl-5-oxooxazol-2-yl)-2-methyl propyl carbamate II-10: Cyclodehydration of N-benzoyl-L-Val-alanine (1 g, 3.25 mmol) with EDCI.HCl (0.63 g, 3.26 mmol.) gave 0.79 g of **II-10** as viscous oil in 84 % yield. ^1H NMR (300 MHz) ($CDCl_3$): δ 0.77 and 0.79(3H, 2d, J =4.5 Hz), 0.859 (3H, dd, J_1 = 2.1 Hz, J_2 = 6.6 Hz), 1.3 (3H, d, J = 7.5 Hz), 2.03 (1H, m), 4.065 (1H, q, J = 7.2 Hz), 4.4 (1H, q, J = 6 Hz), 4.97 (2H, m), 5.23 (1H, bs), 7.18 (5H, bs); IR (neat): 1828 cm^{-1}, 1722 cm^{-1}, 1672 cm^{-1}.



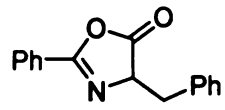
II-11

Partial data: 2-(4-methoxyphenyl)-4-methyl-4H-oxazolin-5-one II-11: Cyclodehydration of N-(4-methoxybenzoyl) alanine (3 g, 13 mmol) with EDCI.HCl (2.5 g, 13 mmol) gave 2g of **II-11** as a pale yellow oil in 75 % yield. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.547 (3H, d, J = 7.5 Hz), 3.85 (3H, s), 4.402 (1H, q, J= 7.8 Hz), 6.92-6.96 (2H, m), 7.88-7.91 (2H, m); IR (neat): 1824 cm^{-1}, 1653 cm^{-1}.



II-12

Partial data: 2-phenyl-4-isopropyl-4H-oxazolin-5-one II-12: Cyclodehydration of N-benzoyl-L-alanine (6 g, 27 mmol) with EDCI.HCl (5.2 g 27 mmol.) gave 4.93 g of **II-12** as a low melting solid in 90 % yield. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 1.055 (3H, d, J = 6.9 Hz), 1.12 (3H, d, J = 6.9 Hz), 2.3-2.41 (1H, m), 4.29 (1H, d, J= 4.5 Hz), 7.47 (3H, t, J = 7 Hz), 7.56 (3H, t, J = 7.2 Hz), 7.99 (2H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz) ($CDCl_3$): δ 17.18, 18.33, 70.13, 125.38, 127.61, 128.11, 128.47, 132.5, 161.7, 177.13; IR (neat): 1826 cm^{-1}, 1657 cm^{-1}.



II-13

2-phenyl-4-benzyl-4H-oxazolin-5-one II-13: Cyclodehydration of N-benzoyl-L-phenylalanine (2 g, 7.38 mmol) with EDCI.HCl (1.42 g, 10 mmol.) gave 1.77g of **II-1** as a white solid in 95 % yield. ^{1}H NMR (300 MHz) ($CDCl_3$): δ 3.17 (1H, dd, J_1 = 6.6 Hz, J_2 = 13.8 Hz), 3.35 (1H, dd, J_1 = 5.1 Hz, J_2 = 13.8 Hz), 4.67 (1H, dd, J_1 = 5.1 Hz, J_2 = 6.6 Hz), 7.17-7.25 (5H, m), 7.39-7.45 (2H, m), 7.5-7.55 (1H, m), 7.86-7.9 (2H, m); ^{13}C NMR (75 MHz) ($CDCl_3$): δ 37.3, 66.5, 125.7, 127.2, 127.8, 128.4, 128.7, 129.6, 132.7, 135.2, 161.7, 177.6; IR (neat): 1823 cm^{-1}, 1648 cm^{-1}.

I. References

1. Meyers, A. I., In Palmer, D. C., Ed., Oxazoles: Synthesis, Reactions and Spectroscopy, Vol. 60: Part B, *The Chemistry of Heterocyclic Compounds*; Jon Wiley and Sons, INC., New Jersey, **2002**, *foreword.*

2. Rao, Y. S.; Filler, R., In Turchi, I. J., Ed., Oxazoles: Synthesis, Reactions and Spectroscopy, Vol. 45, *The Chemistry of Heterocyclic Compounds*; Jon Wiley and Sons, INC., New York, **1986**, 363-691.

3. Carter, H. E. *Organic Reactions 3*, Jon Wiley and Sons, INC., New York, **1947**, 198-239.

4. Cornforth, J. W. In Clarke, H. T., Johnson, J., Robinson, R., Eds., *Chemistry of Penicillin*; Princeton University Press, Princeton, N. J., **1948**, 688-848.

5. (a) VonWangelin, A. J.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 4286 - 4294. (b) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306-313. (c) Dömling, A. and Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210. (d) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, D. S.; Keating T. A. *Acc. Chem. Res.* **1996**, *29*, 123-131. (e) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*(23), 4231-4233.

6. Mukerjee, A. K. *Heterocycles* **1987**, *26*, 1077-1097

7. Tempest, P. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7607-7608.

8. (a) Trump, R. P.; Bartlett, P. A. *J. Comb. Chem.* **2003**, *5*(3), 285-291. (b) Lewis, J. G.; Bartlett, P. A. *J. Comb. Chem.* **2003**, *5*(3), 278-284.

9. Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperleand, M.; Park, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 335-338.

10. Boyd, G. V., In Potts, K. T., Ed., *Comprehensive Heterocyclic Chemistry*, *6*, Pergamon Press, Oxford, UK, **1984**, 177-234.

11. (a) Bergman, J.; Lidgreen, G. *Tetrahedron Lett.* **1989**, *30*, 4597-4600; (b) Benoiton, N. L. *Int. J. Protein. Res.* **1991**, *38*, 285-286.

12. Chen, F. M. F.; Kuroda, K.; Benoiton, N. L. *Synthesis* **1970**, 230.

13. Gothardt, H.; Huisgen, R.; Bayer, H. O. *J. Am. Chem. Soc.* **1970**, *103*, 4340.

14. (a) Padwa, A., In Taylor, E. C.; Weissberger, A., Eds., 1, 3-Dipolar Cycloaddition Chemistry, *General Heterocyclic Chemistry Series*, Jon

Wiley and Sons, INC., New Jersey, **1984** .(b) Gribble, G. W., In Palmer, D. C., Ed., Oxazoles: Synthesis, Reactions and Spectroscopy, Volume 60 Part A, *The Chemistry of Heterocyclic Compounds*; Jon Wiley and Sons, INC., New Jersey, **2002**; 473-576.

15. Hershenson F. M.; Pavia, M. R. *Synthesis*, **1988**, 999-1001.

16. Dhawan, R.; Dghaym, R. D.; Arndtsen B. A. *J. Am. Chem. Soc.* **2003,** *125*, 1474-1475.

17. Keating, T. A. and Armstrong, R. W. *J. Am. Chem. Soc.* **1996,** *118,* 2574-2583.

18. Cativiela, C.; Diaz-de-Villegas, M. D., In Palmer, D. C., Ed., Oxazoles: Synthesis, Reactions and Spectroscopy, Volume 60: Part B, *The Chemistry of Heterocyclic Compounds*; Jon Wiley and Sons, INC., New Jersey, **2002**, 130-299.

19. (a) Balaban, A. T.; Bally, I.; Frangopol, P. T.; Bacescu, M.; Cioranescu, E.; Birladeanu, L. *Tetrahedron*, **1963**, *19*, 169.; (b) Frangopol, P. T.; Balaban, A. T.; Birladeanu, L. Cioranescu, E.; *Tetrahedron*, **1961**, *16*, 59.

20. Erba, E.; Gelmi, M. L.; Pocar, D. *Chem. Ber.* **1988**, *121*, 1519-1524.

21. Sain, B.; Baruah, J. N.; Sandhu, J. S. *J. Chem. Soc. Perkin Trans. 1.* **1985**, 773-777.

22. (a) Gingrich, H. L.; Baum, J. S. In *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, 1986; Vol. 45, p 731. (b) Potts, K. T. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, p 1.

23. (a) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574. (b) Santiago, B.; Dalton, C. R.; Huber, E. W.; Kane, J. M. *J. Org. Chem.* **1995**, *60*, 4947. (c) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800. (d) Consonni, R.; Dalla Croce, P.; Ferraccioli, R.; La Rosa, C. *J. Chem. Res., Synop.* **1991**, *7*, 188. (e) Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Chem. Ber.* **1970**, *103*, 2368. (f) Nayyar, N. K.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1997**, *62*, 982.

24. (a) Bayer, H. O.; Huisgen, R.; Knorr, R.; Schaefer, F. C. *Chem. Ber.* **1970**, *103*, 2581. (b) Funke, E.; Huisgen, R. *Chem. Ber.* **1971**, *104*, 3222. (c) Prajapati, D.; Mahajan, A. R.; Sandhu, J. S. *J. Chem. Soc. Perkin Trans. 1.* **1992**, 734.

25. Martin D. Burke and Stuart L. Schreiber *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58.

26. Takagaki, H.; Yasuda, N.; Asaoka, M.; Take, H. *Chem. Lett.* **1979**, 183.

27. Gotze, S.; Kubel, B.; Steglich, W. *Chem. Ber.* **1976**, *109*, 2331.

28. Konwar, D.; Prajapati, D.; Sandhu, J. S.; Kametani, T.; Honda, T. *Heterocycles* **1984**, *22*, 2483-2486.

29. Clerici, F.; Gelmi, M. L.; Trimarco, P. *Tetrahedron* **1998**, *54*, 5763-5774.

30. Gribble, G. W.; Sponholtz, W. R. III; Switzer, F. L.; D'Amato, F. J.; Byrn, M. P. *Chem. Commun.* **1997**, 993-994.

31. Anderson, W. K.; Mach, R. H. *J. Med. Chem.* **1987**, *30*, 2109-2115.

32. Pandey, G.; Sahoo, A. K.; Bagul, T. D.; *Org. Lett.*, **2000**, *2*(15), 2299 -2301.

33. Condie, G. C.; Bergman, J. *Eur. J. Org. Chem.* **2004**, 1286-1297.

34. Nayyar, N. K.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1997**, *62*, 982-991.

35. Padwa, A.; Pearson, W. H., In Padwa, A. Pearson, W. H., Eds., Synthetic Applications of 1, 3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products, Vol. 59: *The Chemistry of Heterocyclic Compounds*; Jon Wiley and Sons, INC., New Jersey, **2002**, *Preface.*

36. Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jimenez, J. L.; Light, M. E.; Lopez, I.; Palacios, J. C.; Silvero, G. *Chemistry* **2001**, *7*, 3033.

37. Prasad, K. K.; Petrzilka, T. *Helv. Chim. Acta* **1975**, *58*, 2504.

38. Croce, P. D.; Ferraccioli, R.; La Rosa, C. Tetrahedron **1999**, *55*, 201.

39. Padwa, A.; Pearson, W. Synthetic applications of dipolar cycloaddition chemistry towards heterocyclic and natural products; Wiley-VCH: Weinheim, **2002**.

40. (a) Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Chem. Ber.* **1970**, *103*, 2368-2387; (b) Gotthardt, H.; Huisgen, R.; Schaefer, F. C. *Tetrahedron Lett.* **1964**, *10*, 487-491; (c) Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Tetrahedron Lett.* **1964**, *9*, 481-485.

41. Maryanoff, C.; Karash, C. B.; Turchi, I. J. *J. Org. Chem.* **1989**, *54*, 3790-3792.

42. Padwa, A.; Gingrich, H. L.; Lim, R. *J. Org. Chem.* **1982**, *47*, 2447-2456.

43. Padwa, A.; Lim, R.; MacDonald, J. G. *J. Org. Chem.* **1985**, *50*, 3816-3823.

44. (a) Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, *4*(20), 3533-3535. (b) Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, *9*, 1433-1440. (c)Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2004**, *126*(40), 12776-12777.

45. (a) Pohlhaus, P. D.; Bowman, R. K.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*(8), 2294-2295. (b) Bowman, R. K.; Johnson, J. S. *J. Org. Chem.* **2004** ASAP Article.

46. (a) Grigg, R.; Kemp, J.; Sheldrick, G.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109-111. (b) Joucla, M.; Hamelin, J. *Tetrahedron Lett.* **1978**, 2885-2888.

47. (a) Pearson, W. H.; Stoy, P.; Mi, Y. *J. Org. Chem.* **2004**, *69*, 1919-1939. (b) Harwood, L. M.; Macro, J.; Watkin, D.; Williams, C. E.; Wong, L. F. *Tetrahedron: Asymmetry* **1992**, *3*, 1127-1130.

48. Denissova, I., Barriault, L. *Tetrahedron* **2003**,*59*(51), 10105-10146.

49. (a)McKenzie, K. M.; Austin, D. J.; Department of Chemistry, Yale University, New Haven, CT, USA.; Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, **2002**. (b) Savizky, R. M.; Savinov, S. N.; Nathan, D.; Crothers, D. M.; Austin, D. J.; Department of Chemistry, Yale University, New Haven, CT, USA.; Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, **2002**. (C) Savizky, R. M.; Savinov, S. N.; Nathan, D.; Crothers, D. M.; Austin, D. J.; Department of Chemistry, Yale University, New Haven, CT, USA.; Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, **2003**. (d) Savinov, S.N.; Austin, D. J. *Org. Lett.* **2002**, *4*(9), 1415-1418. (e) Savinov, S.N.; Austin, D. J. *Org. Lett.* **2002**, *4*(9), 1419-1422. (f) Savinov, S.N.; Austin, D. J. *Chem. Commun.* **1999**, 1813–1814.

50. Minter, A. R.; Brennan, B. B.; Mapp, A. K. *J. Am. Chem. Soc.* **2004**, *126*(34), 10504 -10505.

51. Ptashne, M.; Gann, A. *Genes & Signals*; Cold Spring Harbor Laboratory: New York, 2001.

52. (a) Darnell, J. E. *Nat. Rev. Cancer* **2002**, *2*, 740-749. (b) Duncan, S. A.; Navas, M. A.; Dufort, D.; Rossant, J.; Stoffel, M. *Science* **1998**, *281*, 692-695. (c) Pandolfi, P. P. *Oncogene* **2001**, *20*, 3116-3127.

53. (a) Ansari, A. Z.; Mapp, A. K. *Curr. Opin. Chem. Biol.* **2002**, *6*, 765-772. (b) Mapp, A. K. *Org. Biomol. Chem.* **2003**, *1*, 2217-2220. (c) Weatherman, R. V. *Org. Biomol. Chem.* **2003**, *1*, 3257-3260.

54. (a) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324-2339. (b) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082-2085. (c) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846-6847.

55. (a) Drysdale, C. M.; Duenas, E.; Jackson, B. M.; Reusser, U.; Braus, G. H.; Hinnebusch, A. G. *Mol. Cell. Biol.* **1995**, *15*, 1220-1233. (b) Regier, J. L.; Shen, F.; Triezenberg, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 883-887. (c) Lin, J. Y.; Chen, J. D.; Elenbaas, B.; Levine, A. J. *Genes Dev.* **1994**, *8*, 1235-1246. (d) Sullivan, S. M.; Horn, P. J.; Olson, V. A.; Koop, A. H.; Niu, W.; Ebright, R. H.; Triezenberg, S. J. *Nucleic Acids Res.* **1998**, *26*, 4487-4496.

56. Kanemasa, S., In Padwa, A. Pearson, W. H., Eds., Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products, Vol. 59: *The Chemistry of Heterocyclic Compounds*; Jon Wiley and Sons, INC., New Jersey, **2002**, 757-804.

57. (a) Suga, H.; Shi, X.; Ibata, T. *J. Org. Chem.* **1993**, *58*, 7397. (b) Suga, H.; Fujieda, H.; Hirotsu, Y.; Ibata, T. *J. Org. Chem.* **1994**, *59*, 3359.

58. (a) Suga, H.; Ikai, K.; Ibata, T. *Tetrahedron Lett.* **1998**, *39*, 869. (a) Suga, H.; Ikai, K.; Ibata, T. *J. Org. Chem.* **1999**, *64*, 7040.

59. (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215. (c) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 235. (d) Ito, Y.; Sawamura, M.; Shirakawa, K.; Hayashizaki, K.; Hayashi, T. *Tetrahedron Lett.* **1988**, *28*, 239. (d) Ito, Y.; Sawamura, M.; Shirakawa, K.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253.

60. Grigg, R.; Landsdell, M. I.; Thornton-Pett, M. *Tetrahedron* **1999**, *55*, 2025-2044.

61. Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*(28), 4969-4972.

62. Zhou, X-T.; Lin, Y-R.; Dai, L-X. *Tetrahedron Asymm.* **1999**, *10*, 855-862.

63. Viso, A.; Fernandez De La Pradilla, R.; Guerrero-Strachan, C.; Alonso, M.; Martinez Ripoll, M.; Andre, I. I. *J. Org. Chem.* **1997**, *62*, 2316-2317.

64. Viso, A.; Fernandez De La Pradilla, R.; Garcia, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martinez-Ripoll, M.; Fonseca, I.; Andre, I.; Rodriguez, A. *Chem. Eur. J.* **2003**, *9*, 2867-2876.

65. Longmire, J. M.; Wang, B.; Zhang X.; *J. Am. Chem. Soc.* **2002**, *124*, 13400-13401.

66. Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jφrgensen, K. A.; *Angew. Chem. Int. Ed.* **2002**, *41*(22), 4236-4238.

67. Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174-10175.

68. Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043-5046.

69. Sharma, V.; Lansdell, T. A.; Peddibhotla, S.; Tepe, J. J. *Chem. Biol.* **2004** (in print).

70. Tepe, Jetze J.; Peddibhotla, Satyamaheshwar. PCT Int. Appl, WO 2003101969.

CHAPTER III

SILICON MEDIATED DIASTEREOSELECTIVE MULTI-COMPONENT SYNTHESIS OF IMIDAZOLINES.

A. Biological Importance of 2-Imidazolines and Imidazoles

Derivatives of 2-imidazoline and 2-imidazole have attracted substantial interest due to their interesting biological activities.[1] Imidazolines are known to exhibit a wide range of pharmacological activities[2], including α-receptor stimulation; vasodepressor activity; α-adrenergic inhibition; and sympathomimetic, antihistaminic, histamine-like, and cholinomimetic activity. Imidazoline derivatives have also been found to exhibit anti-inflammatory[3], anti-nociceptive, immuno-modulating, antioxidant activities[4]. 4,5-Dihydro-1*H*-imidazoles (2-imidazolines) are useful intermediates for the synthesis of molecules with pharmacological activities such as anti-hypercholesterolemic, anti-diabetic, anti-hypertensive, or anti-cancer activity.[3, 5] Cyclic ureas and cyclic thioureas are reported to be potent inhibitors of human immunodeficiency virus (HIV) protease and HIV replication.[6] 2-imidazolines are also convenient building blocks for the synthesis of pharmaceutically relevant molecules such as azapenams, dioxocyclams, and diazapinones.[7] Also, suitably functionalized 2-imidazolines are easily converted to 2, 3-diamino acids, which are incorporated in a wide range of antibiotics and other biologically active compounds.[8] Streptolidine lactam[9] which incorporates a γ-hydroxy-α, β-diaminoacid moiety, is at the core of streptothricin antibiotics, which due to their high antibacterial activity have drawn a great deal of synthetic attention (Figure III-1). The structures of imidazolines and imidazoles

are analogous to those of oxazolines and oxazoles, or thiazolines, and thiazoles, respectively. The latter heterocycles are found in numerous macrolactams isolated from marine sources.[10] Imidazolines have been easily converted to imidazoles and incorporated into macrolactam analogues of bistratamide H without loss of stereochemical integrity.

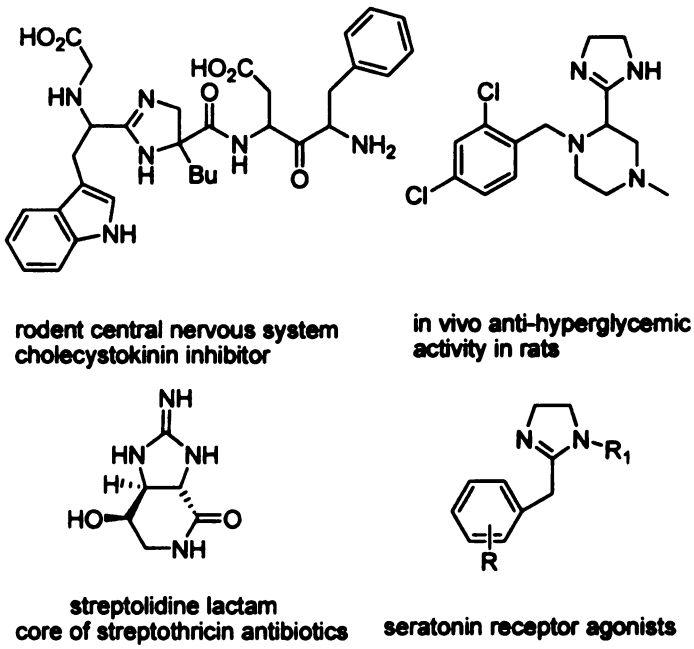


Figure III-1. Biological activity of molecules with 2-imidazoline nucleus.

Recent studies have also revealed that the imidazoline ring is a required pharmacophore for certain potent anti-hyperglycemic properties. Imidazoline derivatives, such as midaglizole, deriglidole, and efaroxan, have been identified as promising anti-hyperglycemic agents.[4] An imidazoline moiety has previously been incorporated into a known antihypertensive agent, clonidine.[11] During the past decade, the concept of imidazoline (I) receptors has been developed and gained consensus.[12] Findings from different laboratories have shown that they are widely distributed in different tissues and species and may participate in the

regulation of various physiological functions. Moreover, recent evidence suggests their involvement in diverse pathologies, and therefore a more definite knowledge of the structure and function of this receptor system could help in the search for therapeutic agents useful for treating efficaciously a variety of disorders such as hypertension, diabetes mellitus, gastric ulcer, endogenous depression, and stroke.[13] Imidazoline derivatives have been studied as α2-adrenoceptor or estrogen receptor modulators.[3b, 11, 14a] Imidazoline rings with appropriate substituents can serve as amino acid replacement in a peptide[15], making it less susceptible to proteolytic cleavage and hence improve the stability and therapeutic utility peptides.

In fact, the imidazoline scaffold like other rigid five-membered heterocycles can mimic functions of natural peptides and hence are of great therapeutic value.[16] Developing small-molecule inhibitors of non-enzyme protein-protein interactions has been a difficult task because binding pockets on protein surfaces involved are shallow and dynamic as compared to enzymes which have well defined and rigid binding pockets or active sites.[17] However, the crystal structure of MDM2 bound to a peptide from the transactivation domain of p53 has revealed that MDM2 possesses a relatively deep hydrophobic pocket that is filled primarily by three side chains from the helical region of the peptide.[18] The existence of such a well-defined pocket on the MDM2 molecule raised the expectation that compounds with low molecular weights could be found that would block the interaction of MDM2 with p53. One such class was a series of *cis*-imidazoline analogs named

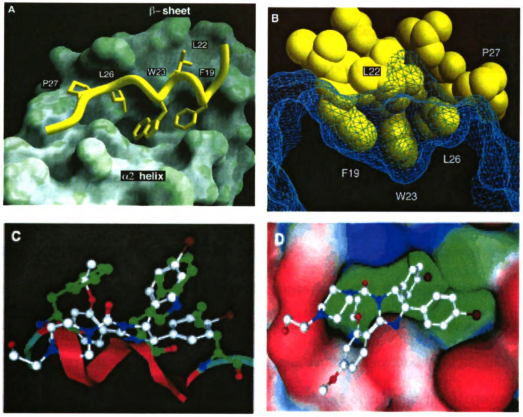


Figure III-2 (a&b): p53 bound to MDM2; key residues for binding **(c)** Overlay of p53 residues and nutlin **(d)** The bromo phenyl moiety of nutlin deep in the groove of MDM2 **(e)** Representative structure of a nutlin. Adapted from Ref. 18 and 19.

Nutlins (Figure III-2).[19] The imidazoline scaffold thus replaces the helical backbone of the p53 peptide and is able to direct, in a fairly rigid fashion, the projection of three groups into the pockets normally occupied by Phe[19], Trp[23], and Leu[26] of p53. By binding MDM2 in the p53-binding pocket the cis-imidazolines activate the p53 pathway in cancer cells, leading to cell cycle arrest, apoptosis, and growth inhibition of human tumor xenografts in nude mice. This example has served as a paradigm for the study and development of other small molecule inhibitors of protein-protein interactions (SMPPI's).[19]

B. Chemical significance of imidazolines

The most direct chemical utility of imidazolines has been their conversion to chiral diamines[20], which are widely preferred group of ligands for asymmetric synthesis. There is definitely a need for more synthetic methods, which can provide optically active imidazolines with greater choice of substituents. Hegedus *et al* have efficiently reacted optically active imidazolines photochemically with a chromium carbene complex to obtain azapenams[21] in good yield and high stereoselectivity. C_2 Symmetric imidazolines have been shown to induce excellent to modest acyclic diastereoselectivity to form quarternary benzylic centers[22], which to date remains a synthetic challenge. MacMillan *et al* have reported a very impressive use of imidazolidinones[23], as catalysts for highly enantioselective indole alkylations and Diels-Alder reactions. This represents an important example in the fast growing field of organocatalysis. Furthermore, chiral 2-imidazolines have attracted considerable interest as templates for asymmetric synthesis[24] and as chiral ligands for asymmetric catalysis[25, 26] and have found

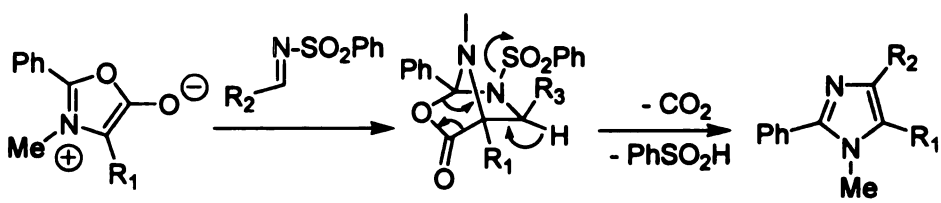
wide application as potent N-heterocyclic carbene ligands in organometallic catalysis.[27] N-Heterocyclic "carbene" ligands derived from imidazole were recently reported as alternatives for phosphines in organometallic catalysis. The authors claim that unlike the phosphines, the new imidazole ligands do not dissociate from the transition metals and hence provide sturdy catalysts.[27]

C. Lewis acid mediated synthesis of imidazolines

The synthesis of stereodefined imidazolines has been scarcely reported despite their usefulness. Methodologies are limited by the difficult availability of the precursors, and for this reason the variety of groups bonded at C-4 or C-5 of the ring is quite limited. Most of the imidazolines described are only 4-substituted[28] or 4, 5-disubstituted with the same group (generally phenyl).[29] Only a few examples of syntheses of 4, 5-disubstituted imidazolidines (containing a range of groups) have been reported.[20c, 28d, 30]

As part of our program to develop small molecular weight scaffolds containing a high degree of diversity, we focused on developing a stereoselective synthesis of substituted imidazolines. 1, 3-Dipolar cycloaddition reactions utilizing N-methylated mesoionic oxazolones (or münchnones) provide a general route for the syntheses of pyrroles and imidazoles.[31-33] A moderate equilibrium concentration of the mesoionic tautomer is essential for the 1, 3-dipolar cycloaddition leading to heterocycle formation.[34] By *N*-methylation, the azlactones are locked in the mesoionic form, which is extremely reactive with dipoles and affords the heterocycles in very high yields. Imidazoles can be generated by treatment of the münchnones with tosylimines. Addition of the tosylimines results in an unstable

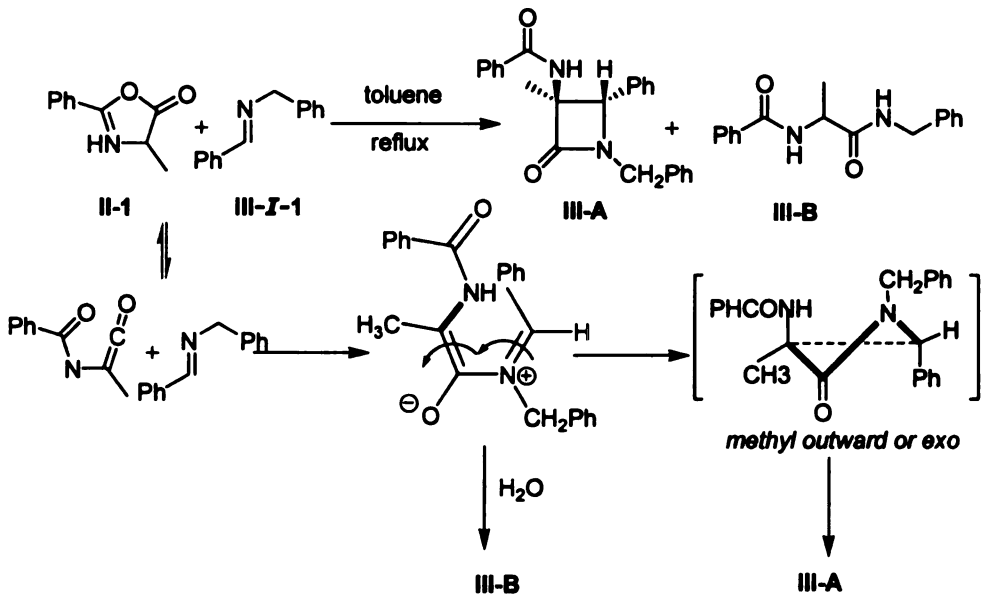
bicyclic adduct that loses carbon dioxide and benzenesulphinic acid to gain aromaticity.[32, 35] The phenylsulphonyl residue as leaving group enhances the tendency to aromatize (Scheme III-1). Münchnones with different substituents, at the 2 and 4-positions lead regioselectively to products in which a bond is always formed between the 2-carbon atom of the dipole and the imine nitrogen atom. This attack was explained on the basis of a dipole-dipole interaction between partially negative nitrogen of the imine and the electrophilic C-2 atom of the münchnone. The yield reported for these reactions are low at least partly due to self-condensation of münchnones.[32] The problem of self-condensation can be suppressed by using a solid-phase approach towards the preparation of imidazoles.[33] The münchnone generated on solid phase was condensed with tosylamines to afford the imidazoles in good yields and purities.



Scheme III-1. Addition of the tosylimines leads to loss of CO_2 and $PhSO_2H$ to gain aromaticity.

Surprisingly, the utilization of oxazolones (or azlactones) has not yet resulted in an efficient entry into a stereoselective highly diverse class of imidazoline scaffolds (Refer Chapter 2). It has been well documented that azlactones undergo a Staudinger-type reaction when heated with imines in toluene yielding β-lactams.[36-38] The azlactone, which is in equilibrium with valence tautomeric

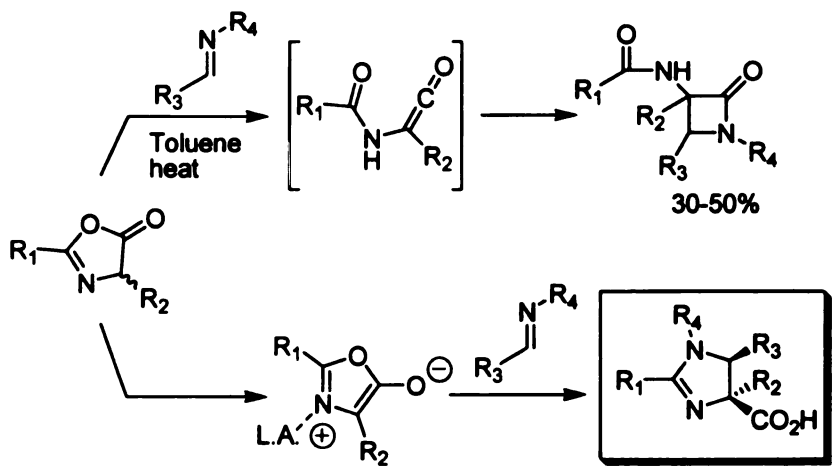
ketene intermediate, undergoes a [2+2] cycloaddition reaction with the imine (Scheme III-2). It can be concluded that either mesoionic oxazolium oxide, which has the nitrogen atom unsubstituted, is not in reasonable concentration and/or the imine nitrogen is not nucleophilic enough. Hence formation of ketene takes predominance, which reacts readily with the imines to afford the β-lactam.[36-38]



Scheme III-2. Staudinger reaction imines and ketenes generated from azlactones.

The 5-oxazolones (azlactones) in this study were prepared from different *N*-acyl α-aminoacids by EDCI-mediated dehydration to provide the pure oxazolones in high yields.[39] 4-methyl-2-phenyl-2-oxazolin-5-one (**II-1**) synthesized from N-benzoylalanine, when heated with N-benzilidene-benzyl amine in toluene under N_2 atmosphere to reflux, gave β-lactam **III-A** and the amide **III-B**.[40] The azlactone is in equilibrium with valence tautomeric ketene intermediate, which then undergoes a ketene-imine or the Staudinger[41] type reaction to form the β-lactam (**III-A**). The amide **III-B** is obtained by hydrolysis of the uncyclized

zwitterionic intermediate (Scheme III-2). Theoretical studies have predicted that torquo-electronic effects play a dominant role over steric effects in the cycloaddition of the zwitterionic intermediate to the β-lactam **III-1a**. [42] The imine preferably adopts the more stable (*E*) geometry because of the bulky aromatic substituents and the methyl group (positive inductive effect) on the ketene adopts an "outward" or *exo* position to the direction of attack by the imine. Electron withdrawing benzamido substituents adopts an *endo* or "outward" position in accordance with the predicted model for these cycloadditions. A conrotatory electrocyclic ring closure affords β-lactam with *cis* orientation for the methyl and phenyl groups in 30 % yield as reported before.[41]



Scheme III-3. Lewis acid mediated generation of münchnone and cycloaddition

We envisioned that a Lewis acid coordination to nitrogen of the azlactone would increase the equilibrium concentration of münchnone intermediate and mediate the azomethine ylide-imine cycloaddition reaction. The choice of the imine was important as unactivated or electron rich imines have rarely been used with münchnones before (tosylimines lead to enhanced aromatization). Only one

example where N-benzylidine-benzylamine (**III-*I*-1**) was used as the imine is by Arndtsen and co-workers.[43] They used Pd-catalysis to couple basic building blocks like an imine, acid chloride and carbon monoxide to generate N-alkylated münchnone *in situ.* Mild acidic conditions were suggested to accelerate the reaction to afford the products as N-alkylated imidazolium salts. The main shortcoming for this method is that only symmetrical imidazolines can be obtained as two equivalents of the imine are involved in the synthesis, one for generation of münchnone and other for cycloadditions. Also, only electron rich aromatic aldehydes can be used. Electron deficient imines and phosphine ligands, both stop the cycloadditions completely. One advantage was that the imidazolium salts were easily isolated from the reaction mixtures by precipitation from ethereal solutions.

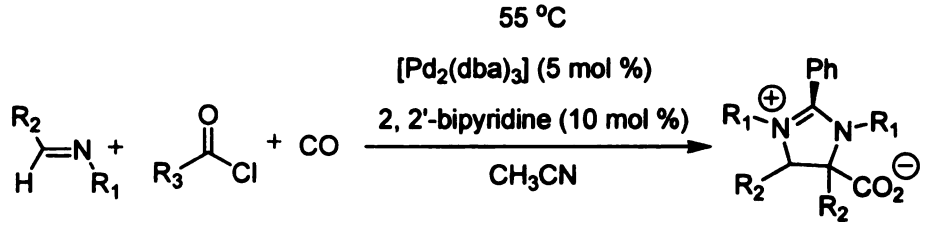


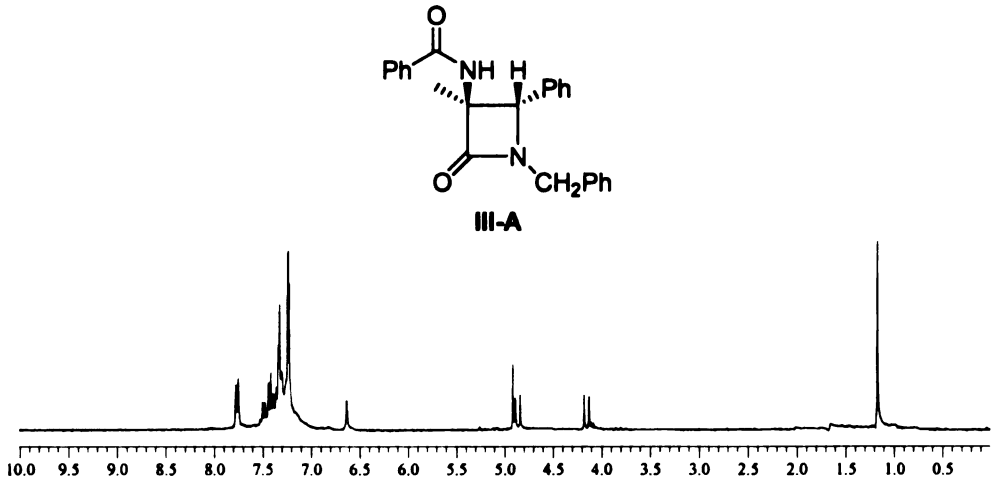
Figure III-3. Generation of imidazolium salt through Pd-catalysis.

D. Lewis acids for *in situ* generation of münchnones and cycloaddition

With one equivalent of $SnCl_4$, $TiCl_4$, $ZnCl_2$, silver triflate only degradation was observed in the reaction of 4-methyl-2-phenyl-2-oxazolin-5-one (**II-1**) and N-benzilidene-benzyl amine (**III-*I*-1**) in toluene. Harder lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ or protic acids such as camphor sulfonic acid (CSA) and methyl sulfonic acid (MSA) did not promote any product formation (Scheme III-4). Cu

and Al based lewis acids or lanthanides were not encouraging either. Only with TMSCl, on refluxing in toluene a white precipitate separated from the reaction mixture in 75 % yield, and was isolated and characterized as the imidazoline-4-carboxylic acid (**III-1-1**, Figure III-4).

β-lactam (in $CDCl_3$)



Imidazoline (in DMSO-d_6)

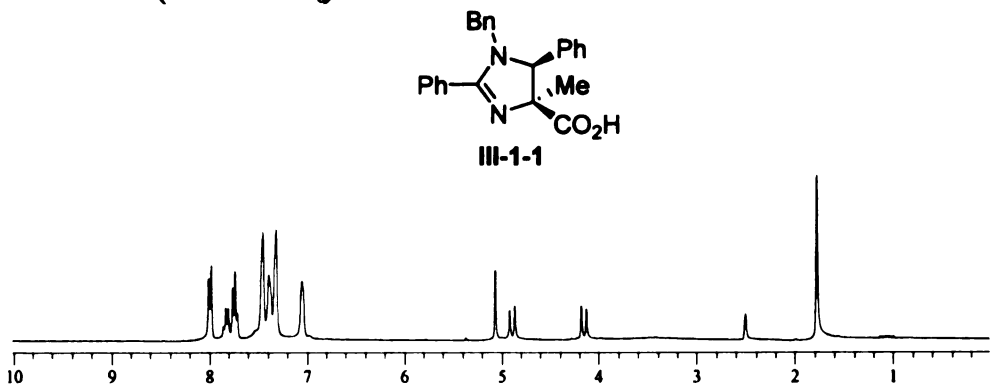
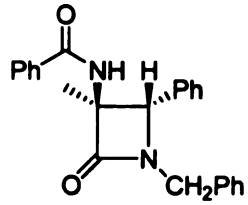
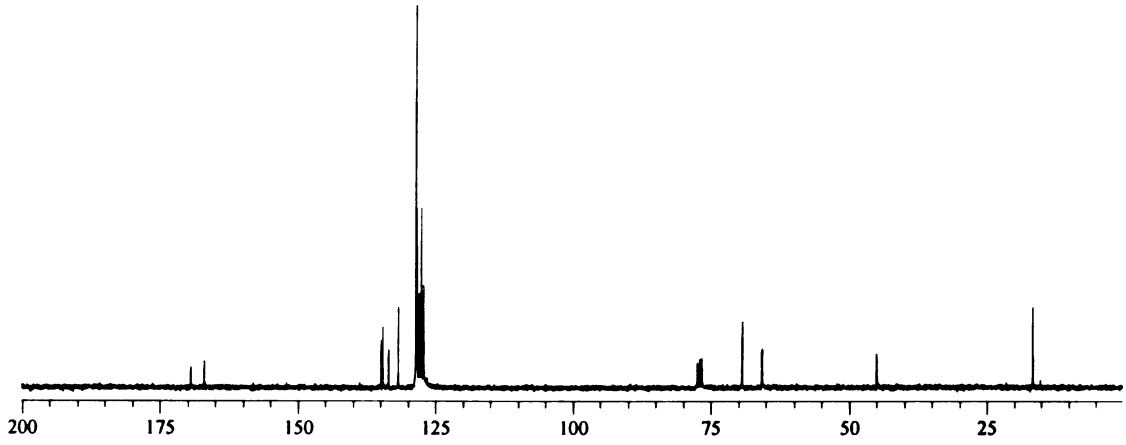


Figure III-4. (a) ^1H spectra for a representative β-lactam (**III-A**) and imidazoline (**III-1-1**).

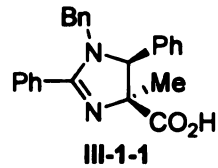
β-lactam: IR (cm^{-1}) 1751, 1654.



III-A



Imidazoline: IR (cm^{-1}) broad 3600-2500, 1734, 1610.



III-1-1

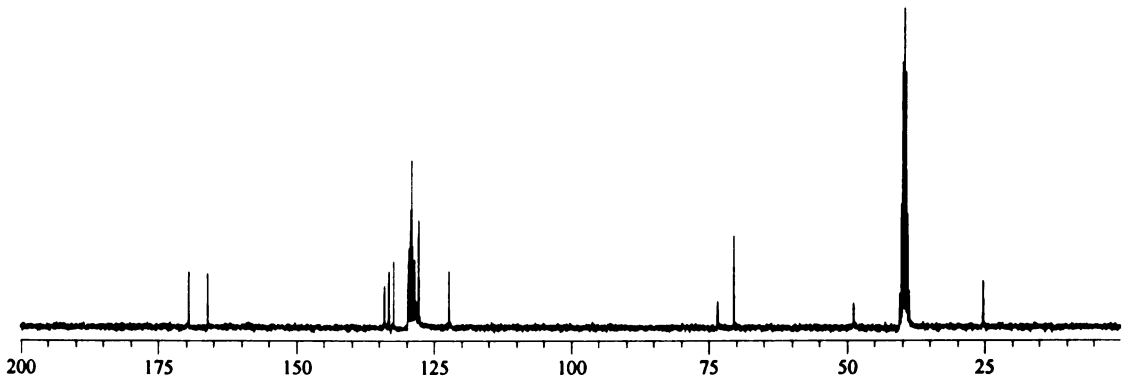


Figure III-4. (b) ^{13}C spectra for a representative β-lactam (**III-A; in $CDCl_3$**) and imidazoline (**III-1-1; in DMSO-*d_6***).

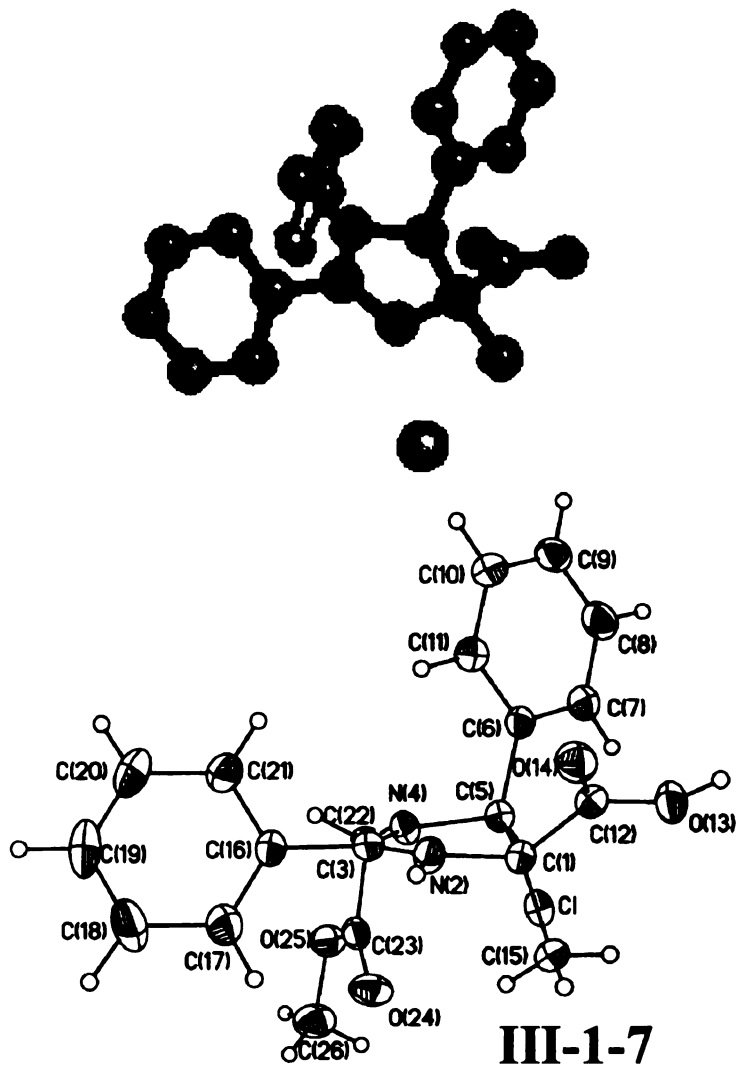
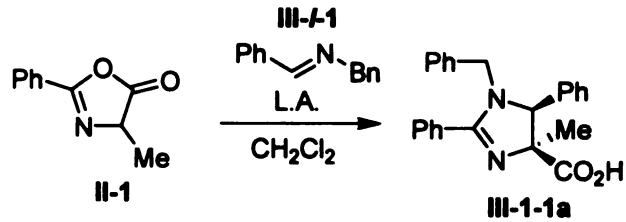


Figure III-4. (c)**Left:** X-ray crystal structure of **III-1-1**. **Right:** X-Ray crystal structure of **III-1-7**.

The relative stereochemistry has been established unambiguously by X-ray crystals structure of **III-1-1 and III-1-7** (Figure III-4).

The remaining filtrate is made up of 15-20 % of the β-lactam (Scheme III-2, **III-1a**). Subsequently, the same results were obtained in THF and dichloromethane as solvents. We were encouraged that TMSCl promotes the reaction of azlactones and imines to afford the imidazoline-4-carboxylate scaffold in very good yields as

a single diastereomer, with trans- relation between C_4 and C_5 substituents (Scheme III-4).



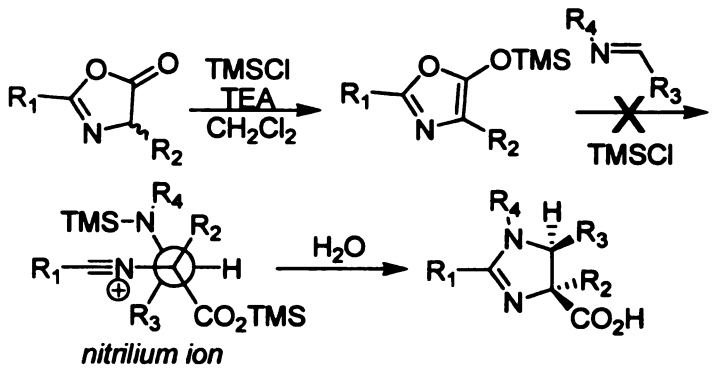
LA	% yield	LA	% yield
$TiCl_4$	0	TMSCl	70
SnCl4	0	1 eq. TMSCl / 1 eq. Et_3N	0
ZnCl2	0		
Et_2AlCl	0	2 eq. TMSCl / 1 eq. Et_3N	0
CuCl	0	TESCl	70
$B(OPh)_3$	0	Ph_3SiCl	45
AgOTf	0	CH_3COCl	55
YCl3	0	CSA	0
$Zr(O\text{-}iPr)_4$	0	TMSOTf	0

Scheme III-4. Lewis acid screen for the synthesis of imidazolines.

E. Possible mechanism for synthesis of imidazoline

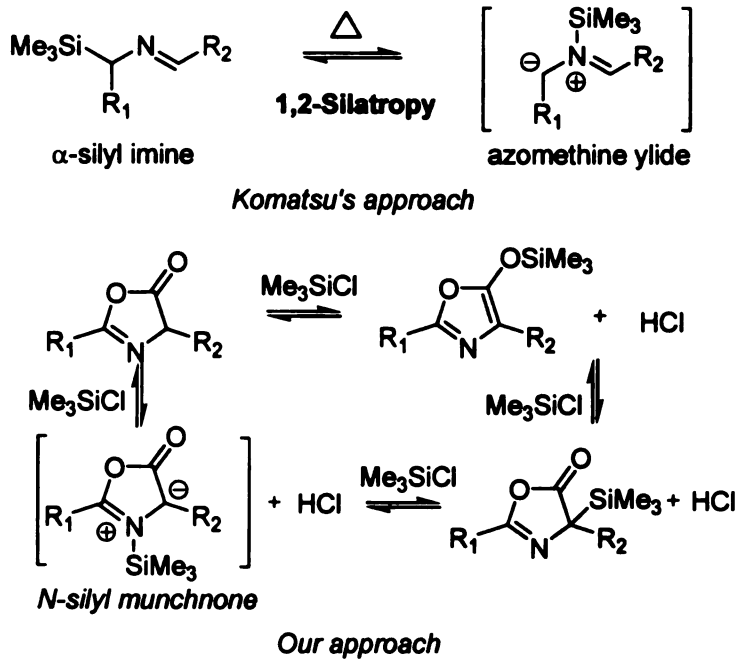
While the complete mechanistic details of this process are still under investigation, the reaction does not seem to proceed via a ring-opened nitrilium ion intermediate (Scheme III-5).[44, 45] A common method to trap nitrilium ions is by nucleophiles like water or methanol. After addition of TMSCl, the reaction mixture was refluxed with saturated sodium acetate solution. The azlactone was obtained intact and not even a trace of *O*-acetylimidate was observed. The possibility of a step-wise Michael-type addition (via the formation of the nitrilium

ion) and subsequent cycloaddition was investigated by first preparing the silyl enol ether[46] with TMSCl (1.0 equiv) and TEA (1.0 equiv) followed by the addition of the imine and an additional one equivalent of TMSCl.[47-50]



Scheme III-5. Nitrilium ion intermediate is not involved in the formation of Imidazolines

This resulted merely in isolation of starting materials. Excess of triethylamine also halted the reaction suggesting that acidic conditions were required. TMSOTf (likely *O*-silylation) also did not result in any product formation. This indicates the requirement of a nucleophilic counterion to establish possible equilibrium between *O*-silation and *N*-silation and a probable *C*-silation of the azlactone (Scheme III-6). The role of counterion in establishing such equilibrium has been reported by Wilde in his work with N-acyl münchnones.[51] The generation of azomethine ylides by "silatropy" has recently also been reported by Komatsu and co-workers.[52-54] The authors report the formation of an azomethine ylide after a 1, 2-silatropic shift of α-silylimines resulting in the formation of pyrrolidines as a mixture of stereoisomers.



Scheme III-6. Generation of azomethine ylides by silatropy

Johnson *et al* have investigated *N*-metalated azomethine ylides formed via "soft enolization" of (imino)glycine esters as alternatives to ylides generated from the same compounds in the classic thermal [1, 2]-prototropy manifold (Figure III-5), which require a weak base working in concert with a metal salt.[44] In light of these findings, we proposed that the reaction proceeds via a 1, 3-dipolar cycloaddition (Scheme III-7). While N-silyation results in reactive münchnone, acidic conditions, during the reaction activate the imine. This double activation should result in accelerated 1, 3-dipolar cycloadditions affording the bicyclic intermediate. NMR studies in $CDCl_3$ at elevated temperatures (not shown) indeed confirm the rapid consumption of azlactone in presence of the dipolarophile. The azlactone does not show any appreciable change in presence of TMSCl, if not heated with dipolarophile.

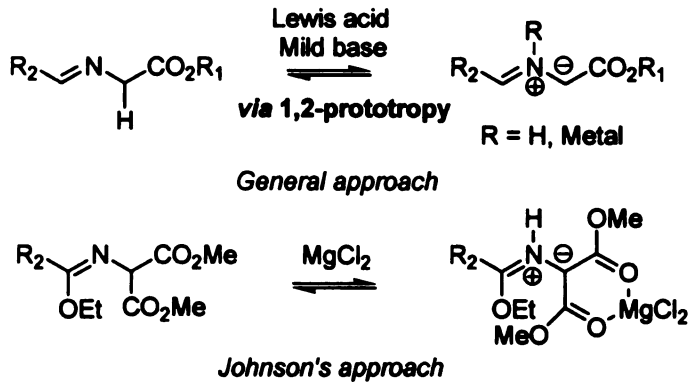
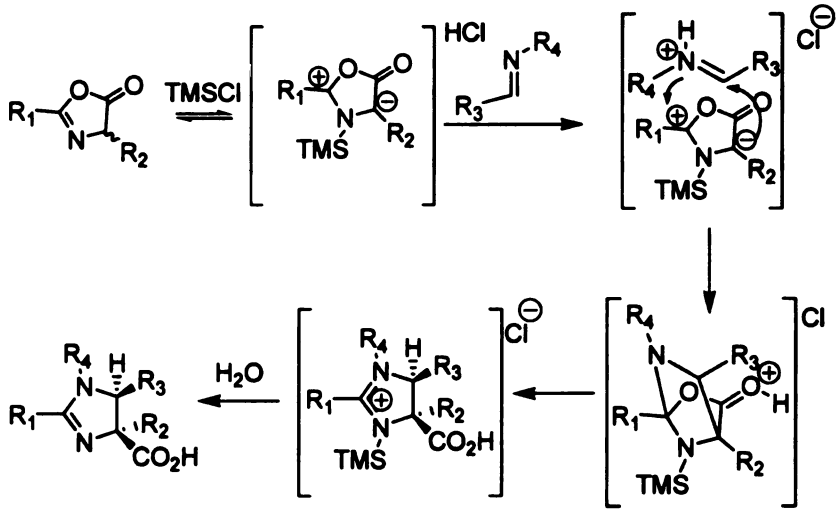


Figure III-5. Soft enolisation vs. 1, 2-Prototropy

Other silyl chlorides such as triphenyl silyl chloride and triethyl silyl chloride also provided the product as a single diastereomer, in notably longer reaction times and lower yields (Scheme III-4, 45% and 70%, respectively). Additional support of the proposed mechanism is shown in Scheme III-7. We found that one equivalent of acetyl chloride resulted in the formation of the imidazoline as well, albeit in somewhat lower yields (Scheme III- 4, 55%).[51]



Scheme III-7. Proposed mechanism for the formation of imidazolines via the 1, 3 dipolar cycloaddition

F. Diversity

The cycloaddition reactions proceeded well with a wide variety of imines at slightly elevated temperatures (dichloromethane, reflux) to provide the highly substituted imidazolines in very good yields. Only the *trans* diastereomers (with respect to R_2 and R_3) of the imidazolines were observed in almost all cases, as determined by NOE experiments and X-ray crystallography (Table III-1). A range of structurally diverse imidazolines were prepared and are listed in Table III-1 and -2. We have recently reported this highly diastereoselective multi-component one-pot synthesis of substituted imidazolines.[55, 56] These low molecular weight imidazoline scaffolds contain four point diversity applicable to alkyl, aryl, acyl, and heterocyclic substitution (Table III-1)

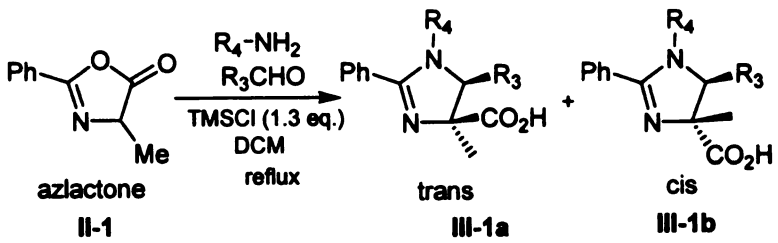
R_4 groups/amines: 4-methyl-2-phenylazlactone (**II-1**) derived from N-benzoyl alanine was reacted with a host of imines (**III-*I*-1** – **III-*I*-14**) to afford imidazolines in moderate to good yields. Benzyl, aryl and aminoacid ester derived imines of benzaldehyde could be used with good yields of imidazolines. Electron deficient 4-fluoroaniline as well as electron rich 4-methoxyaniline could be used successfully. However N-benzhydryl group is too sterically encumbered to afford any imidazoline (entry **III-1-6**, Table III-1).

R_3 group/aldehydes: Although aromatic aldehydes generally afforded cleaner reactions and higher yields, it is probably a reflection on the purity of imines derived from other aldehydes and not the cycloadditions. Benzaldehyde, p-anisaldehyde (4-methoxybenzaldehyde) derived imines reacted in very good yields. Electron deficient ethyl glyoxalate and 2-nitrobenzaldehyde can also be

used and afford good yields for imidazolines. Among the heterocyclic aldehydes, pyridine 4-carboxaldehyde was a good substrate, while with unprotected pyrrole-2-carboxaldehyde or indole-3-carboxaldehyde, imidazolines were not obtained at all. Aliphatic aldehydes could not be used because the imines suffered from possible enamine formation were not obtained in sufficient purity. We have also been able to extend the method to 5-unsbstituted imidazolines with the use of formaldehyde imines formed *in situ* by Lewis acid mediated cracking of triazines [data not shown].

R_2 group/amino acids: The diversity in R_2 substituents result from the use of various amino acids. Both natural and unnatural amino acids which are suitably protected can be utilized for the formation of azlactone component of this cycloadditions. Glycine could not be used because the corresponding 2-phenyl-5-oxazolone does not enolize under the current conditions. Simple α-alkyl amino acids; alanine, valine, isoleucine and phenylalanine can be used (Table III-2) and their corresponding 2-phenyl-4-alkyl-5-oxazolones result in excellent yield of imidazolines with N-benzyllidine-benzylamine (**III-*I*-1**). Phenylglycine (unnatural amino acid), tryptophan, and glutamate (acidic) have also been used with good results.

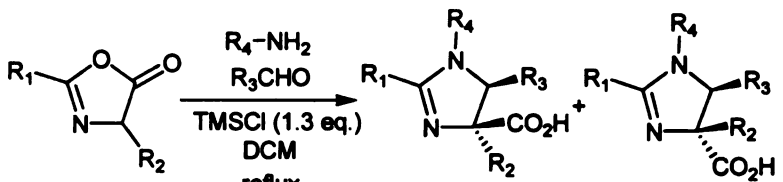
R_1 group/acyl halides: Phenyl and substituted phenyls, alkyl and benzyl groups could be introduced. Heterocyclic groups like 2-furyl and 2-pyridyl groups could not be used as the corresponding N-acyl-α-amino acids could not be cyclized to the azlactones.



Entry	R_3	R_4	% Yield a	Ratio a:b
III-1-1	Ph	Bn	75	>95:5
III-1-2	4-methoxyphenyl	Bn	78	>95:5
III-1-3	Ph	4-fluorophenyl	74	>95:5
III-1-4	4-pyridinyl	Bn	76	>95:5
III-1-5	$-CO_2Et$	4-fluorophenyl	72	>95:5
III-1-6	Ph	benzhydryl	0	—
III-1-7	Ph	$-CH_2CO_2Me$	70	>95:5
III-1-8	Ph	$-CH(CH_3)CO_2Me$	66	>95:5
III-1-9	Ph	$-CH_2CH_2CO_2Me$	51	>95:5
III-1-10	Ph	Bn	75	ethyl ester
III-1-11	4-pyridinyl	Bn	76	ethyl ester
III-1-12	Ph	Bn	79	alcohol
III-1-13	Ph	H	70	>95:5
III-1-14	Ph	4-methoxy phenyl	50	>95:5

Table III-1. Variation of R_3 and R_4 groups

Derivatives: The imidazolines can also be suitably derivatized into esters, alcohols or deprotected to afford N-unsubstituted imidazolines in excellent yields (entries **III-1-10, III-1-11, III-1-12, III-1-13,** Table III-1).



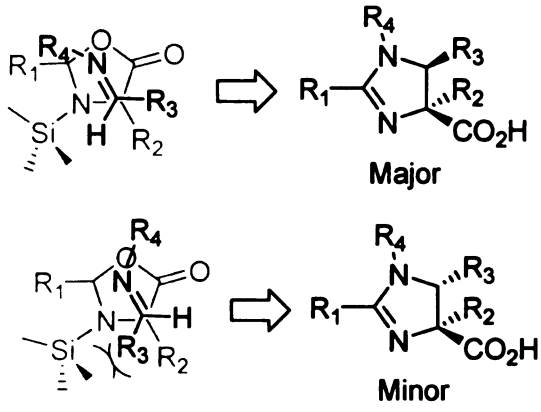
Entry	R_1	R_2	R_3	R_4	% Yield(II)	% Yield (IIIa)	Ratio (a:b)
III-1-1	Ph	Me	Ph	Bn	75	75	>95:5
III-2-1	Ph	Ph	Ph	Bn	70	65	>95:5
III-2-4	Ph	Ph	4-pyridinyl	Bn	75	55	>95:5
III-2-5	Ph	Ph	$-CO_2Et$	4-fluorophenyl	75	68	>95:5
III-3-1	Ph	indolyl-3-methyl	Ph	Bn	80	68	>95:5
III-4-1	Ph	$-CH_2CH_2CO_2Me$	Ph	Bn	69	60	>95:5
III-5-1	Me	Me	Ph	Bn	60	74	50:50
III-6-1	Bn	Ph	Ph	Bn	90	30	75:25
III-9-1	Bn	Me	Ph	Bn	76	15	67:33
III-11-1	4-methoxy phenyl	Me	Ph	Bn	75	62	>95:5
III-12-1	Ph	*iso*-Propyl	Ph	Bn	90	71	>95:5

Table III-2. Diversity of various groups on the imidazoline scaffold

G. Proposed origin of Diastereoselectivity

The diastereoselectivity appears to primarily arise from the steric interaction of the bulky silyl group of the azlactone and the R_3 moiety of the imine (Scheme III-8). This results in the imine approaching from *endo* type of orientation (with

respect to R_3) of the racemic azlactone resulting in the *trans*-isomer as the major/sole product. The electronic effects of the R_1 position also appear to play a significant role in the reactivity of the azlactone as well as the diastereoselectivity of the reaction.



Scheme III-8. Origin of diastereoselectivity

Reducing the resonance of the stabilized carbocation of the dipolarophile by changing R_1 from a phenyl to a methyl or benzyl group resulted in a significant decrease in diastereoselectivity (Table III-2). With R_1 was a benzyl group, there was significant erosion of diastereoselectivity. But it is clear that substituents R_2 still controls the outcome. Bulky phenyl as R_2 results in a 3:1 ratio in favor of the *trans*-imidazoline, while when R_2 is methyl, a 3:2 ratio of diastereomers was observed. The more reactive and unstable 2, 4-dimethylazlactone provided a 1:1 mixture of the *cis*- and *trans*-products. Complete switching of diastereoselectivity to the *cis*-imidazoline was seen when the positions of the methyl and phenyl groups were exchanged at C_2 and C_4 (data not shown). Figure III-6 shows the Chem 3D minimized structures of azlactones with Me and Ph groups at C_2 and C_4 positions. It is clear that the steric volume needed by a C_2 methyl results in

blocking the approach of *E*-imine required for the trans product. In comparison, the phenyl group can be rotated out of plane and hence is more directional and makes C_2 less hindered for approach of imine to result in *trans* (major) product.

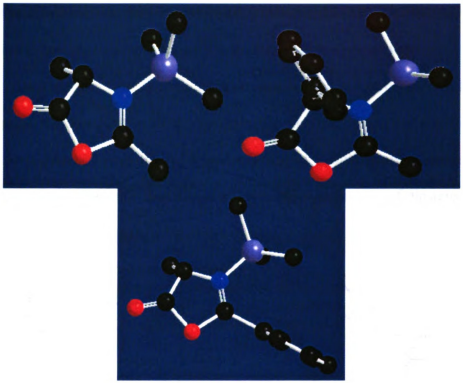


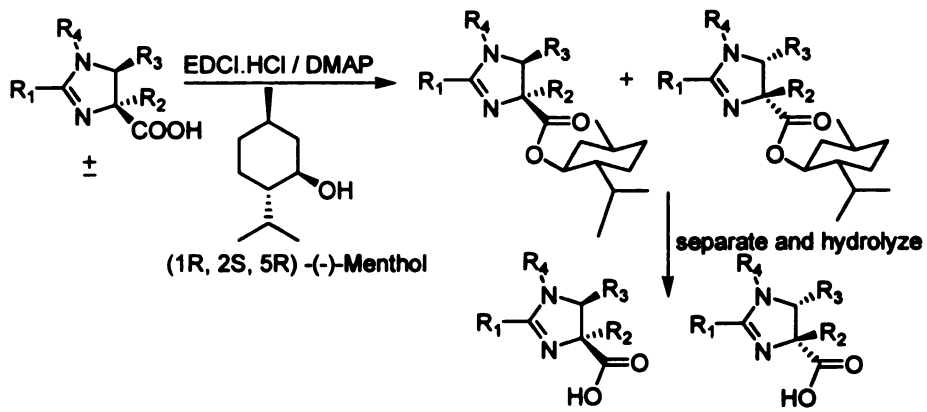
Figure III-6. Chem3D models for minimized structures of *TOP* (left) :2, 4 dimethylazlactone, *TOP*(right): 2-Methyl-4-phenyl azlactone, *BOTTOM*: 4-methyl 2-phenyl azlactone

H. Synthetic methods for chiral imidazolines

In contrast with more traditional lewis acids, the application of organosilicon compounds as lewis acids in selective organic synthesis has a relatively brief history.[57] Chiral silicon lewis acids are rarer to find in literature because of difficulty associated with their generation. Hence we decided to follow some conventional methods to get our hands on enantiomerically pure imidazolines.

1) Resolution of Enatiomers.

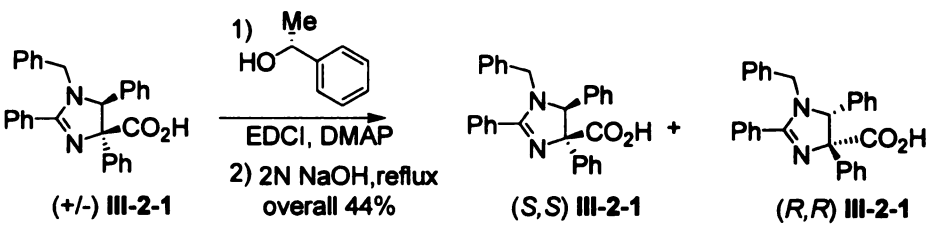
In view of the biological importance of imidazolines, it was important to evaluate bio-activity of the separate enantiomers (chapter V). In order to expedite this study the diastereomeric menthyl esters of imidazoline **III-1-1** were prepared (Scheme III-9) and separated by column chromatography. Although the R_f values for the diastereomers are very close, one of the diastereomers was separated clean in very small amount from the column and was subjected to hydrolysis with LiOH to explore the feasibility of this step (data not shown). The hydrolysis did not undergo as planned with the mild base and use of menthol was abandoned to screen for a chiral alcohol that would allow a better separation of diastereomers by column chromatography.



Scheme III-9. Resolution of racemic imidazolines using (-) Menthol

The use of (+) R and (-) S-1-phenylethanol resulted in better separation of diastereomers (chapter V) and racemic imidazoline (**III-2-1**) was resolved using (+) *R*-methyl benzyl alcohol. EDCI.HCl mediated esterification of the racemic imidazoline **III-2-1** and the auxilliary resulted in a mixture of diastereomers, which were separated using column chromatography. Hydrolysis of the diastereomers resulted only under reflux with 2N NaOH to give enantiopure

imidazolines **(-)III-2-1** and **(+)III-2-1**. Compound **(+)III-2-1** was successfully crystallized in $CHCl_3$/octane and the x-ray structure is shown in Figure III-7.[58] Even though we were able to successfully resolve the racemic imidazolines by converting to diastereomeric esters using chiral alcohols and subsequent hydrolysis, getting the cycloaddition would be more desirable because of the application for the imidazolines (refer chapter V).



Scheme III-10. Synthesis of racemic imidazoline **III-2-1**, (-) *S, S*- **III-2-1** and (+) *R, R*- **III-2-1**.

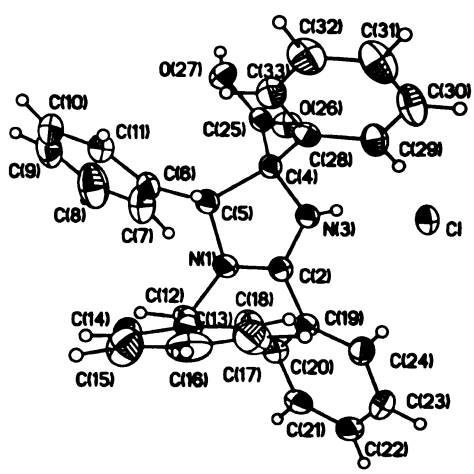
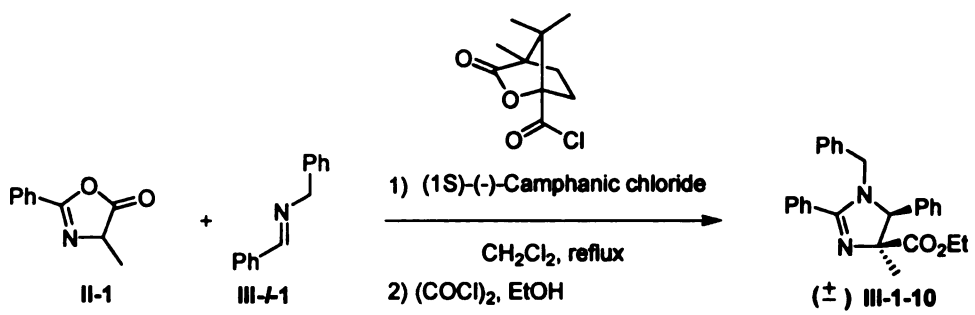


Figure III-7. X-Ray crystal structure of (+) (*R, R*) - **III-2-1**.

2) Use of Chiral auxillaries

i. Chiral acid chlorides

Acetyl chloride was observed to promote the reaction hence in order to explore the possibility of asymmetric induction by chiral acid chlorides, 4-methyl-2-phenyl-2-oxazolin-5-one (**II-1**), was heated with N-benzilidene-benzyl amine (**III-*l*-1**) in presence of one equivalent of S(-)-camphanic chloride in dichloromethane (Scheme III-11). The imidazoline-4-carboxylic acid product was converted to the ethyl ester and analyzed on a chiral HPLC column. No enantiomeric excess was observed (data not shown).

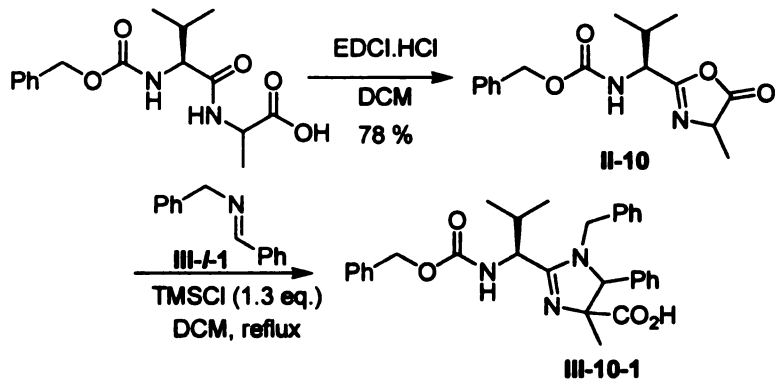


Scheme III-11. Asymmetric induction by chiral acid chloride

ii. Chiral amino acid derived R_1

We decided to use an amino acid as a chiral auxillary to influence enantiocontrol *via* the azlactone. Coupling of N-cbz-L-valine with L-alanine methyl ester and subsequent hydrolysis with 2N NaOH resulted in the dipeptide N-cbz-L-val-L-ala-CO_2H. The dipeptide acid was then cyclized with EDCI.HCl to obtain the corresponding azlactone (**II-10**), which was allowed to react with N-benzylidinebenzylamine in the usual conditions. One diastereomer has been isolated from the reaction mixture and characterized, demonstrating that this is a feasible method. Removal of the chiral auxillary is not possible easily. However,

the product is an imidazoline based amino acid and Kelly and co-workers have used similar strategy to develop enantiopure imidazoline-amino acids and incorporated them into biologically relevant macrolactams.[10]



Scheme III-12. Amino acid at R_1 position as a chiral template

iii. Chiral amines as auxillaries

Viso *et al* reported the very first examples of a highly diastereoselective 1,3-dipolar cycloadditions of azomethine ylides derived from α-iminoesters with chiral sulfinimines[59] to produce *N*-sulfinyl imidazolidines (Figure III-8) and transformation into non-symmetrical vicinal diamines.[49] Dipole generation under standard conditions using LiBr, Et_3N, MeCN or AgOAc, DBU, toluene had failed. Use of LDA allowed for successful cycloadditions with a high degree of *endo* stereocontrol.

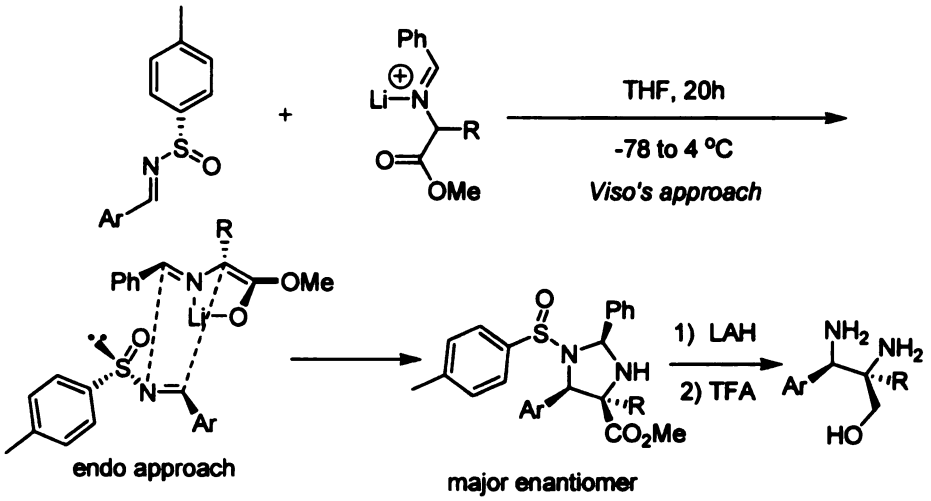
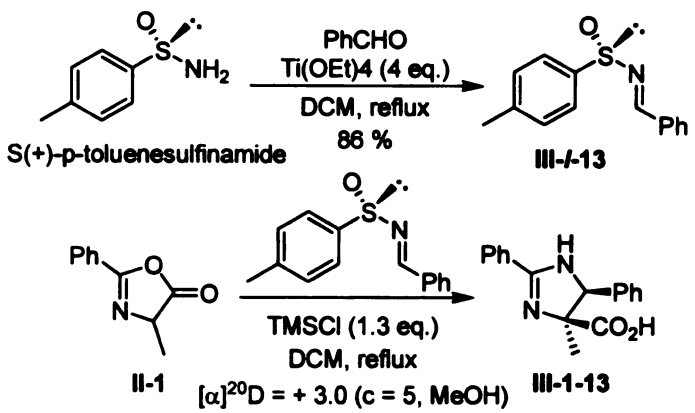


Figure III-8. Use of chiral sulphinimes in azomethine ylide cycloaddition

Addition of $BF_3.OEt_2$ results in abrogation of cycloadditions pathway and the reaction proceeds with opposite diastereoselectivity via a step-wise mechanism.[50] We realized that the above observations by Viso and co-workers would perfectly suit our purpose of generating additional reagent control on stereochemical diversity of the imidazoline scaffolds.

The chiral sulfinimines were readily prepared from commercially available chiral p-toluenesulfinamides using reported procedure.[49] Starting from S-(+)-p-toluene sulfonamide and benzaldehyde, the imine (**III-*I*-14**) was prepared and used for cycloaddition with 2-phenyl-4-methylazlactone (**II-1**). It was surprising, that the sulfinyl group was lost under the acidic reaction conditions and we isolated N-unsubstituted imidazoline (**III-1-13**) in 30 % yield after precipitation from DCM/ether (Scheme III-13). Since, it was not clear whether the chiral auxillary falls off during or after the cycloadditions, the optical rotation was measured and was not very promising.

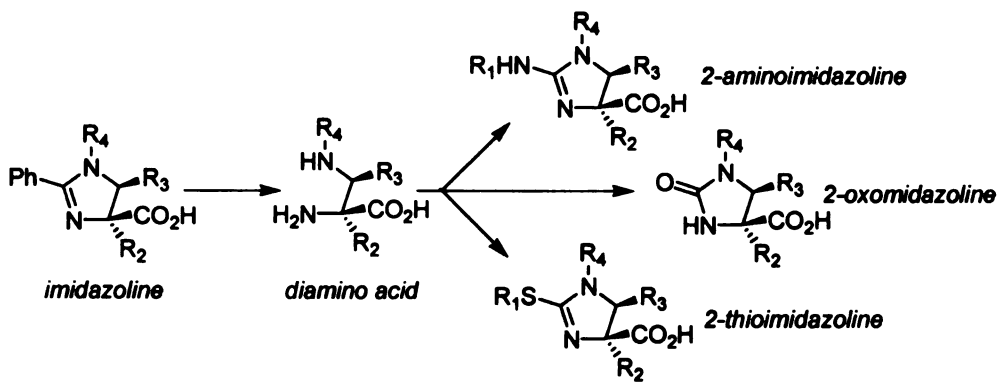


Scheme III-13. Use of chiral sulfinimine in münchnone cycloaddition.

1-Phenyl ethylamine was also tried as a chiral auxillary[61] but in accordance with the stereochemical model proposed above for these reactions, very poor conversions were seen. Moreover, azlactone (**II-1**) resulted in 3:2 mixture of diastereomers (data not shown) which were difficult to separate. The difficulty of separation combined with the difficulty in selective removal of the chiral 1-phenylethyl group in presence of other benzylic sites made us abandon this approach.

I. Synthesis of diamino acids and other scaffolds

The most direct chemical utility of imidazolines has been their conversion to chiral diamines,[20] which are widely preferred group of ligands for asymmetric synthesis. Efforts towards exploitation of the in-built diversity for synthesis of chiral diamines and introduction of heteroatom functional groups directly on the imidazoline ring to afford cyclic ureas (2-oxoimidazolines), 2-aminoimidazolines and 2-thioimidazolines have been planned as extension of the methodology we have developed for imidazolines (Scheme III-14). This "libraries from libraries" concept has been frequently in combinatorial chemistry and drug-design.[62]



Scheme III-14. Extension of methodology for other templates

Kohn and Jung[63] have developed a stereospecific route to vicinal diamines from imidazolines. Formamidine was obtained by catalytic hydrogenation of cynamide under acidic conditions with palladium on charcoal. Cyclization to imidazoline by NaOMe followed by mild alkaline hydrolysis with alcoholic aqueous NaOH afforded the diamines from starting alkenes in good yields (Figure III-9).

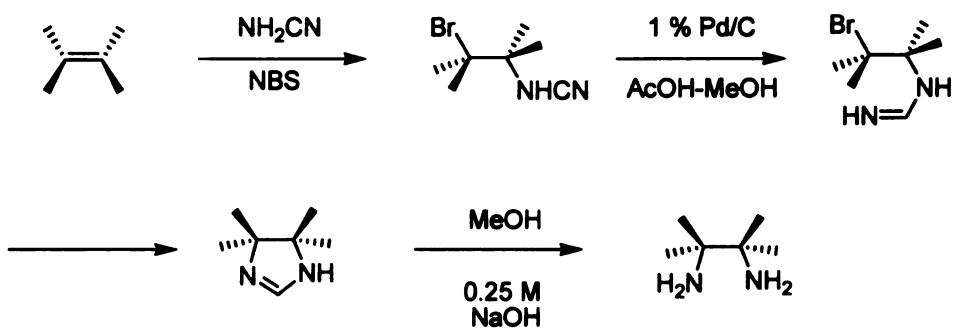


Figure III-9. Synthesis of vicinal diamine from imidazolines

1) 2-unsubstituted imidazolines.

N-formyl-alanine was cyclized to 4-methylazlactone (**II-7**) using EDCI.HCl and 2-unsubstituted imidazoline (**III-7-1**); (1:1 trans:cis, with respect to R_2:R_3) was

made from 4-methylazlactone and N-benzylidinebenzylamine(**III-*I*-1**) using the established cycloaddition conditions. Normal silica-gel chromatography was ineffective in separating the diastereomers. Even derivatization to ethyl esters did not yield good separation.

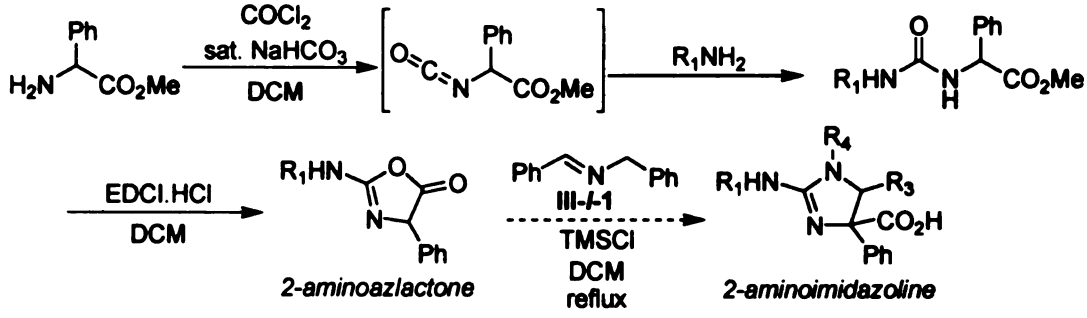
2) 2-trifluoromethylimidazolines.

Woodburn and Johnson[64] have reported that when trifluoroactonitrile is reacted with ethylene diamine, 2-trifluoromethylimidazoline is obtained. When they tried to isolate the hydrochloride salt of the imidazoline from a non-anhydrousrous ether solution, they isolated the diamine which shows the lability of the trifluoromethyl group to hydrolysis. With this precedent we set out to make 2-trifluoromethyl imidazolines using our route. N-trifluoroacetylalanine was made from alanine using reported procedure[65] in 90 % yield. Cyclodehydration of N-trifluoroacetylalanine using EDCI.HCl afforded the 2-trifluoromethyl-4-methyl-5-oxazolone (**II-8**). But the oxazolone is in equilibrium with the pseudooxazolone. The equlibrium is in favour of the pseudooxazolone.[66]

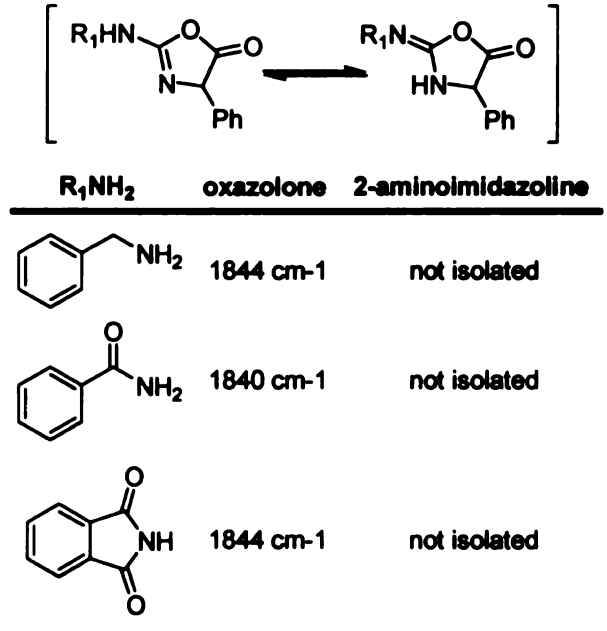
3) 2-amino-5-oxazolones.

At the onset, we tried to establish a common method to get to 2-amino-5-oxazolones with different substituents. The starting materials, the ureidoamino acids could be made by coupling an amine with isocyanate of an amino acid ester. Alanine methyl ester gave a volatile isocyanate, which was not practical to use. Hence the synthesis began with phenylglycine methyl ester, which when treated with phosgene[67] in a biphasic CH_2Cl_2/sat.$NaHCO_3$ (aq.) system yielded the pure isocyanate in almost quantitative yields. This isocyanate was then treated with

various amines and amides. The ureidoacids were then cyclodehydrated with EDCI.HCl to obtain the 2-aminoazlactones (Scheme III-15). The azlactones were condensed with imines in the presence of TMSCl under standard protocol and results are listed in Table III-1.



Scheme III-15. Synthesis of 2-aminoazlactones and 2-aminoimidazolines



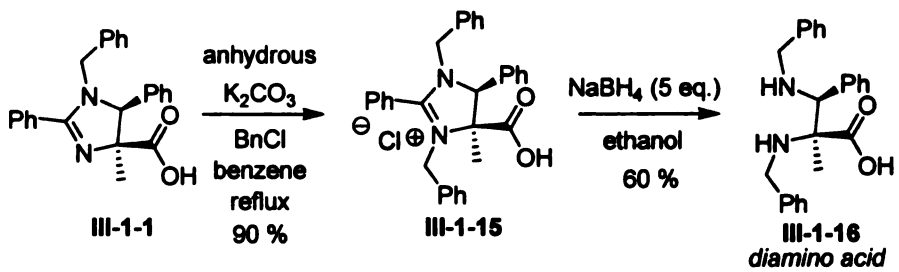
Scheme III-16. Tautomers of 2-aminoazlactones

The main problem encountered was isolation of these azlactones, because on concentration they led to multitude of products. Tautomerism with the iminooxazolidinones (Scheme III-16) can be expected to make the aminoazlactones highly unstable and moisture sensitive. It is possible that they

hydrolyse to the N-carboxy anhydrousrides and hence do not participate in cycloadditions.[68]

J. Ring opening of 2-phenyl imidazolines.

The imidazolines resisted direct reduction with sodium borohydride and with stronger hydride reducing agents like LAH, the 4-carboxylic acid group was reduced to the corresponding alcohol. Thus imidazoline **III-1-1** on reduction with LAH (0.3 eq) in THF resulted in 90 % yield of alcohol (**III-1-12**). This suggested that C_2 position in imidazolines is resonance stabilized and not sufficiently electrophilic. Zhou and co-workers have reported successful ring opening of simple 2-arylimidazolines to the corresponding diamimes.[69] They first alkylated the iminic nitrogen with methyl iodide to obtain *N*-methyl-2-arylimidazolium iodides, which then underwent a smooth reduction ring opening with sodium borohydride in ethanol to afford the diamines in high yields (Scheme III-17).



Scheme III-17. Reductive ring opening of imidazolines to diamino acids.

In order to have removable protecting group on the diamino acid product we chose benzylation over methylation. Imidazoline **III-1-1**, was refluxed with excess benzyl bromide in dry benzene, however no reaction ensued. After a couple of trials, we realized that addition of powdered anhydrous potassium carbonate leads to complete conversion, probably by quenching the acid produced

in the reaction. Due to purity issues with commercial benzyl bromide we switched to benzyl chloride. The N^1, N^3-dibenzylimidazolium chloride salt could be isolated by precipitation from DCM/hexanes mixture in almost 90 % yield. We had two options we could either hydrolyze or reduce the imidazolium salt. Hydrolysis with 2N NaOH resulted in ring opening, however the reaction was not very clean. Hence we opted for reduction of imidazolium salt with sodium borohydride in ethanol as reported. The diamino acid was isolated in good yield (60 %) by precipitation using DCM /ether.

K. Synthesis of Imidazoles from 2-imidazoline-4-carboxylic acids

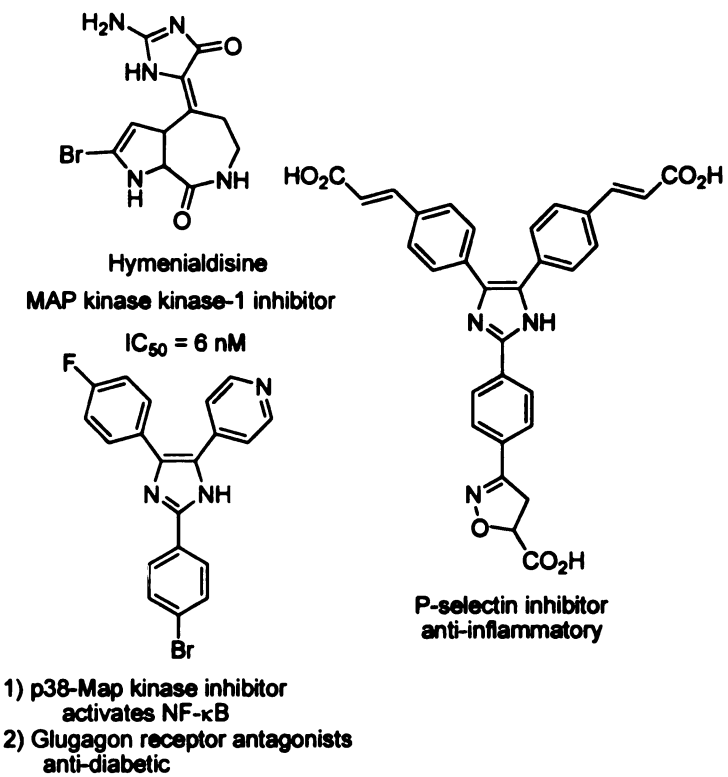
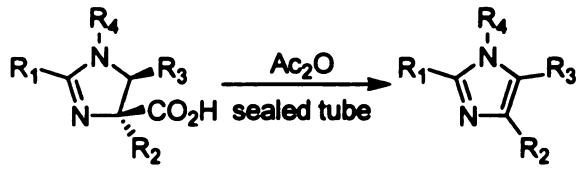


Figure III-10. Biological activity of molecules with imidazole nucleus.

The imidazole nucleus appears in a number of natural products, including the amino acid histidine and purines. Nitroimidazoles are well-known anti-bacterial and anticancer drugs. Recently triaryl imidazoles have been identified as p38 Mitogen-activated protein (MAP) kinase inhibitors. Chang *et al* [70] have been successful in optimizing this triaryl imidazole lead to a selective antagonist for human glucagons receptor, which should lead to improved drugs to control glucose levels in diabetics. Slee *et al*[71] have reported a novel-series of non-carbohydrate imidazole-based small molecule selectin inhibitors. They are the first class of non-carbohydrate selectin antagonists with potent anti-inflammatory activity. Hymenialdisine was recently[71] identified to be a nanomolar inhibitor of Mitogen-Activated Protein Kinase kinase-1 (MEK-1). Activated MEK-1 phosphorylates and activates MAP kinases which can translocate to the nucleus, and through the phosphorylation of a variety of substrates modulate cytoplasmic events such as cell-proliferation and differentiation (Figure III-10).



Entry	R_1	R_2	R_3	R_4	% yield
III-1-17	Ph	Me	Ph	Bn	23
III-1-18	Ph	Me	4-pyridinyl	Bn	22

Scheme III-18. Synthesis of imidazoles from imidazolines

In view of the biological importance of 2, 4, 5-trisubstituted imidazoles, we explored oxidative decarboxylation of 2-imidazoline-4-carboxylic acids. After a few trials heating the compound in neat acetic anhydride, afforded the 2, 4, 5-

trisubstituted imidazoles (Scheme III-18). These results are unoptimized and it is likely that instead of neat acetic anhydride, stoichiometric amounts and/or lower boiling solvents may result in higher yields. We and others have observed that refluxing imidazolines with excess MnO_2 results in higher yields and cleaner reaction.[10]

L. Experimental Procedure

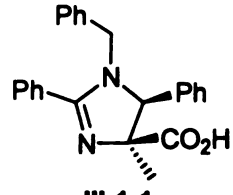
Reactions were carried out in oven-dried glassware under nitrogen atmosphere, unless otherwise noted. All commercial reagents were used without further purification. All solvents were reagent grade. THF was freshly distilled from sodium/benzophenone under nitrogen. Toluene, CH_2Cl_2, and TMSCl were freshly distilled from CaH2 under nitrogen. All reactions were magnetically stirred and monitored by TLC with Analtech 0.25 mm pre-coated silica gel plates. Column chromatography was carried out on silica gel 60 (230–400 mesh) supplied by EM Science. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were determined on a Mel-Temp (Laboratory devices) apparatus with a microscope attachment. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-300 spectrometer or a Varian VXR-500 spectrometer. Chemical shifts are reported relative to the residue peaks of the solvent CDCl3 (δ 7.24 for ^1H and δ77.0 for ^{13}C) and DMSO-*d*6 (δ 2.49 for ^1H and δ39.5 for ^{13}C). HRMS were obtained at the Mass Spectrometry Laboratory of the University of South Carolina, Department of Chemistry & Biochemistry with a Micromass VG-70S mass spectrometer. Gas chromatography/lowresolution mass

spectra were recorded on a Hewlet–Packard 5890 Series II gas chromatograph connected to a TRIO-1 EI mass spectrometer. All chemicals were obtained from Aldrich Chemical Co. and used as received.

General procedure for synthesis of imines (III-*I*-1 - III-*I*-14).

A solution of aldehyde(1mmol) in benzene/ toluene (20 mL) was refluxed with the amine (1 mmol) for 2h. The solvent was evaporated under vacuum to afford the imine in good yields. These imines were used as such without further purification.

Synthesis and Characterization of Imidazolines

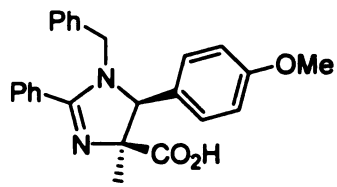


III-1-1

***dl*- (4*S*, 5*S*)-1-Benzyl-4-methyl 2,5-diphenyl-4,5-dihydro-1*H*-imidazole- 4-carboxylic Acid (III-1-1)**

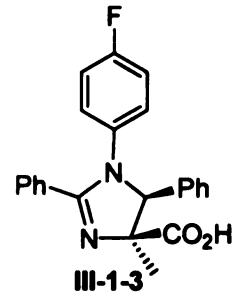
A solution of benzaldehyde (0.06 g, 0.57 mmol), benzylamine (0.061 g, 0.57 mmol) in anhydrous CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2h. 2-Phenyl-4-methyl-4*H*-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The solvent was evaporated under vacuum. The product was precipitated using CH_2Cl_2/hexanes (1:1); yield: 75% (0.155 g); white solid; ^{1}H NMR (300MHz) DMSO-d_6: δ 1.8 (3H, s), 4.05 (1H, d, J = 15Hz), 4.95 (1H, d, J = 14.8 Hz), 5.05 (1H, s), 7.05 (2H, s), 7.25-7.54 (8H, m), 7.74 (2H, t, J = 7.2Hz), 7.83 (1H, t, J = 6.9Hz), 8.0 (2H, d, J = 8.4Hz); ^{13}C NMR (75MHz)

DMSO-d_6: δ 25.2, 48.8, 70.4, 73.3, 122.3, 127.8, 128.3, 128.5, 128.9, 129.1, 129.3, 129.6, 129.7, 132.3, 133.2, 134, 166.1, 169.5; IR (neat): 3350 cm^{-1}, 1738cm^{-1}; M.P. 185–190 °C; HRMS (EI): *m/z* calcd. for $C_{24}H_{21}N_2O_2$ [M – H], 369.1603; found, 369.1610.



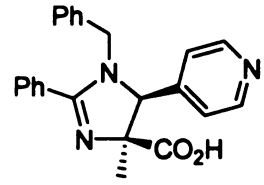
III-1-2

***dl*-(4S, 5S)-1-Benzyl-5-(4-methoxyphenyl)-4-methyl-2-phenyl- 4, 5-dihydro-1*H*-imidazole-4-carboxylic Acid (III-1-2)** A solution of *p*-anisaldehyde (0.077 g, 0.57 mmol), benzylamine (0.061 g, 0.57 mmol) in anhydrous CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4 methyl-4*H*-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2–hexanes (1:1); yield: 78% (0.180); ^{1}H NMR (300MHz) DMSO-d_6: δ 1.8 (3H, s), 3.8 (3H, s), 3.95 (1H, d, J = 15.3Hz), 4.5 (1H, s), 4.9 (1H, d, J = 15Hz), 6.83-6.92 (4H, m), 7.08-7.19 (3H, m), 7.3-7.4 (3H, dd, J_1 = 5.1Hz, J_2 = 1.8Hz), 7.54-7.62 (2H, t, J = 7.2Hz), 762-7.68 (1H, t, J = 7.2Hz), 7.9 (2H, d, J = 6.9 Hz); ^{13}C NMR (75MHz) DMSO-d_6: δ 25.3, 48.8, 55.6, 70.9, 74.1, 115.2, 122.2, 123, 125.5, 127.9, 128.4, 129.2, 129.3, 129.6, 129.9, 132.8, 134.2, 161.1, 166.3, 168.4; IR (neat): 3388 cm^{-1}, 1738 cm^{-1}; M.P. 205–208 °C; HRMS (EI): *m/z* calcd. for $C_{25}H_{23}N_2O_3$ [M – H], 399.1709; found, 399.1717.



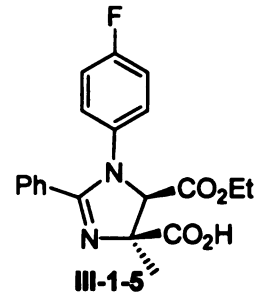
III-1-3

***dl*-(4*S*,5*S*)-1-(4-Fluorophenyl)-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4 carboxylic acid (III-1-3)** A solution of benzaldehyde (0.060 g, 0.57 mmol), 4-fluoroaniline (0.063 g, 0.57 mmol) in anhydrous CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2 h. 2 Phenyl-4-methyl-4*H*-oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2–hexanes (1:1) to give the titled compound; yield: 74% (0.160 g); white solid; ^{1}H NMR (300MHz) DMSO-d_6: δ 1.98 (3H, s), 5.98 (1H, s), 7.05-7.65 (14H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 25.2, 71.2, 77.9, 116.9, 117, 117.1, 117.3, 123, 125.1, 125.3, 129.3, 129.4, 129.6, 130.1, 130.3, 130.4, 130.5, 132.5, 133.3, 134.5, 160.4, 163.7, 165.3, 170.4; IR(neat): 3450 cm^{-1}, 1744 cm^{-1}; M.P. 230–232 °C. HRMS (EI): *m/z* calcd for $C_{23}H_{18}FN_2O_2$ [M – H], 373.1352; found, 373.1359.



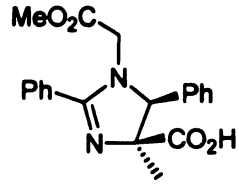
III-1-4

***dl*-(4*S*,5*S*)-1-Benzyl-4-methyl-2-phenyl-5-pyridin-4yl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid III-1-4** A solution of pyridin-4-carboxylaldehyde (0.061 g, 0.57 mmol), benzylamine (0.061 g, 0.57 mmol) in anhydrous CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2 h. 2-Phenyl-4-methyl-4*H* oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using EtOAc / MeOH (4:1); yield: 76% (0.161 g); off-white solid; ^{1}H NMR (300MHz) DMSO-d_6: δ 1.8 (3H, s), 4.24 (1H, d, J = 15.9Hz), 4.9 (1H, d, J = 14.8 Hz), 5.15 (1H, s), 7.0-7.15 (2H, m), 7.25-7.35 (3H, m), 7.4-7.5 (2H, m), 7.7-7.9 (3H, m), 7.95-8.05 (2H, m), 8.6-8.7 (2H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 25.1, 49.1, 70.6, 71.7, 122.1, 123, 127.9, 128.4, 128.8,129.2, 129.4, 132.8, 133.9, 141.4, 149.8, 166.5, 169.05; IR (neat): 3400 cm^{-1}, 1746 cm^{-1}; M.P. 185 190 °C. HRMS (EI): *m/z* calcd. for $C_{23}H_{20}N_3O_2$ [M – H], 370.1556; found, 370.1556.



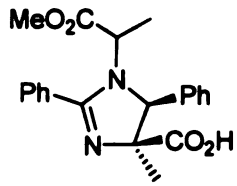
III-1-5

***dl*-(4*S*,5*S*)-1-(4-Fluorophenyl)-4-methyl-2-phenyl-4,5-dihydro- 1*H*-imidazole-4,5 dicarboxylic acid 5-ethyl Ester III-1-5** A solution of ethyl glyoxalate (0.058 g, 0.57 mmol) as a 50% solution in toluene (1.03 gmL^{-1}), 4-fluoroaniline (0.063 g, 0.57 mmol) in anhydrous CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2 h. 2- Phenyl-4-methyl-4*H* oxazolin-5-one (0.1 g, 0.57 mmol) and chlorotrimethylsilane (0.08 g, 0.74 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was purified by column chromatography on silica gel using EtOAc–MeOH (4:1); yield: 72% (0.152 g); white solid; ^{1}H NMR (300MHz) DMSO-d_6: δ 1.2 (3H, t, J = 7.2 Hz), 2.03 (3H, s), 4.9 (2H, dq, J_1 = 7.2 Hz, J_2 = 2.1 Hz), 5.48 (1H, s), 7.1-7.8 (9H, m); ^{13}C NMR (75MHz) DMSO-d_6: δ 12.8, 24.2, 62.9, 69.1, 75.1, 116.7, 116.9, 121.8, 129.3, 129.5, 129.6, 129.7, 131.5, 134.4, 162.1, 164.0, 166.2, 169.9; IR (neat): 3450 cm^{-1}, 1743 cm^{-1}; M.P. 190– 193 °C. HRMS (EI): *m/z* calcd for $C_{20}H_{18}FN_2O_4$ [M – H], 369.1251; found, 369.1255.



III-1-7

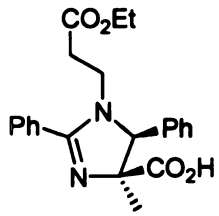
***dl*-(4*S*,5*S*)-1-Methoxycarbonylmethyl-4-methyl-2,5 diphenyl- 4,5-dihydro-1*H*-imidazole-4-carboxylic Acid III-1-7** To a well stirred solution of 2-phenyl-4-methyl-4*H*-oxazolin-5-one (0.5 g, 2.85 mmol) and TMSCl (0.37 g, 3.42 mmol) in anhydrous CH_2Cl_2 (50 mL) was added a solution of (benzylidene-amino)-acetic acid methyl ester (0.6 g, 3.42 mmol) in anhydrous CH_2Cl_2 (20 mL) and the mixture was refluxed under nitrogen for 10 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2– hexanes (1:1); yield: 70% (0.70 g); white solid; ^{1}H NMR (300 MHz) DMSO-d_6: δ 1.99 (3H, (1H, d, J = 18.3 Hz), 4.53 (1H, d, J = 18.3 Hz), 5.39 (1H, s), 7.47-7.50 (5H, m), 7.74-7.87 (5H, m); ^{13}C NMR (75MHz) DMSO-d_6: δ 24.23, 52.09, 70.83, 75.38, 121.84, 128.26, 128.69, 129.52, 129.75, 131.78, 134.02, 167.59, 168.62, 169.19c mp 215–217 °C (dec.) HRMS (EI): *m/z* calcd. for $C_{20}H_{21}N_2O_4$ [M + H] 352.1501, found, 353.1507.IR(neat): 3468 cm^{-1}, 1747 cm^{-1}.



III-1-8

***dl*-(4*S*,5*S*)-1-(1 Methoxycarbonyl-ethyl)-4-methyl-2,5-diphenyl- 4,5-dihydro-1*H*-imidazole-4 carboxylic Acid III-1-8:** To a well stirred solution of 2-phenyl-

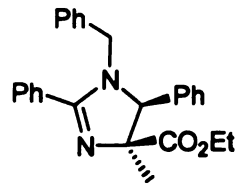
4-methyl-4*H*-oxazolin-5-one (0.25 g, 1.5 mmol) and TMSCl (0.23 ml, 1.8 mmol) in anhydrousrous CH_2Cl_2 (50 mL) added a solution of 2-(benzylidene-amino)-propionic acid methyl ester (0.34 g, 1.8 mmol) in anhydrous CH_2Cl_2 (20 mL) and the mixture was refluxed under nitrogen for 10 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2– hexanes (1:1); yield: 66% (0.340 g); white solid; ^1H NMR (300MHz) DMSO-d_6: δ 1.19 (d, J= 6.9, 3H), 2.06 (s, 3H), 3.38 (s, 3H), 4.89 (q, J = 6.9, 1H0, 5.44 (s, 1H), 7.43-7.46 (5H, m), 7.75-7.85 (5H, m). ^{13}C NMR (75MHz) DMSO-d_6: δ 14.9, 25.6, 52.7, 56.7, 71.9, 72.5, 122.2, 128.8, 128.9, 129.6, 130.0, 134.5, 135.8, 169.2, 169.4, mp 222–226 °C. HRMS (EI): *m/z* calcd for $C_{21}H_{23}N_2O_4$ [M + H], 367.1658; found, 367.1642. IR (neat): 3431cm^{-1}, 1740 cm^{-1}.



III-1-9

***dl*-(4*S*,5*S*)-1-(2-Ethoxycarbonyl-ethyl)-4-methyl-2,5-diphenyl- 4,5 dihydro-1*H*-imidazole-4-carboxylic Acid III-1-9:** To a well stirred solution of 2-phenyl-4 dimethyl-4*H*-oxazolin-5- one (1.0 g, 5.7 mmol) and TMSCl (1 mL, 6.8 mmol) in anhydrous CH_2Cl_2 (80 mL) added a solution of 3-(benzylidene-amino)-propionic acid ethyl ester (1.4 gm, 6.8 mmol) in anhydrous CH_2Cl_2 (60 mL) and the mixture was refluxed under nitrogen for 10 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was

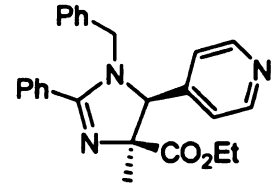
precipitated CH_2Cl_2–hexanes (1:1); yield: 51%; (1.08 g); ^1H NMR (300MHz) DMSO-d_6: δ 1.17 (t, J= 7.5, 3H), 1.9 (s, 3H), 2.47-2.52 (m, 1H), 2.52-2.71 (m, 1H), 3.34-3.39 (m, 1H), 3.40-4.09 (m, 3H), 5.42 (s, 1H), 7.46-7.49 (m, 5H), 7.72-7.87 (m, 5H). ^{13}C NMR (75MHz) DMSO-d_6: δ 13.3, 24.8, 30.6, 41.6, 61.0, 70.9, 73.5, 122.7, 128.9, 129.2, 129.8, 130.1, 132.7, 134.0, 167.3, 169.8, 170.9c mp 218–220 °C (dec.). HRMS (EI): *m/z* calcd for C22H25N2O4 [M + H], 381.1814; found, 381.1813. IR (neat): 3481 cm^{-1}, 1743 cm^{-1}



III-1-10

***dl*-(4*S*,5*S*)-1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro 1*H*-imidazole- 4-carboxylic Acid Ethyl Ester III-1-10:** To a well-stirred suspension of imidazoline-4-carboxylic acid **III-1-1** (0.1 g, 0.27 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0°C was added a solution of oxalyl chloride (0.14 g, 1.1 mmol) in anhydrous CH_2Cl_2 (5 mL). A solution of DMF (0.001 mL) in anhydrous CH_2Cl_2 (1 mL) was added to the reaction mixture and the mixture was stirred at 0 °C for another 2 h. The CH_2Cl_2 was evaporated under vacuum and the reaction mixture cooled to 0 °C after which absolute EtOH (20 mL) was added. The solution was allowed to stir for an additional 1 h. The solvent was evaporated under vacuum and the reaction mixture diluted with anhydrous CH_2Cl_2 (30 mL) and washed with sat. $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic layer was dried over Na2SO4 and was concentrated under vacuum to yield the crude product, which was further purified by silica-gel column chromatography (EtOAc); overall yield

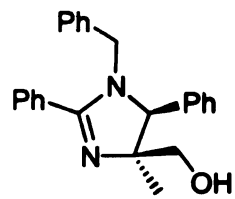
(2 steps from azlactone): 75% (0.095 g); colorless oil. ^{1}H NMR (300MHz) DMSO-d_6: δ 0.84 (3 H, t, J = 7.2 Hz), 1.57 (3 H, s), 3.60 (2 H, q, J = 7.2 Hz), 3.85 (1 H, d, J = 15.3 Hz), 4.32 (1 H, s), 4.74 (1 H, d, J = 15.3 Hz), 6.98 (2 H, dd, J_1 = 6.9 Hz, J_2 = 2.1 Hz), 7.27–7.35 (m, 8 H), 7.49–7.51 (2 H, m), 7.76–7.79 (2 H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 13.80, 27.13, 49.12, 60.06, 71.31, 127.98, 128.03, 128.12, 128.67, 129.02, 129.11, 130.96, 136.40, 136.80, 166.11, 171.78 ; HRMS (EI): *m/z* calcd for $C_{26}H_{27}N_2O_2$, 399.2073; found, 399.2072 ; IR(neat): 1730 cm^{-1}, 1595 cm^{-1}.



III-1-11

***dl*-(4*S*,5*S*)-1-Benzyl-4-methyl-2-phenyl-5-pyridin-4-yl-4,5 dihydro- 1*H*-imidazole-4-carboxylic Acid Ethyl Ester III-1-11:** To a well-stirred suspension of *dl*-(3*S*,4*S*)-1-benzyl-4-methyl-2- phenyl-5-pyridin-4yl-4,5-dihydro-1*H* imidazole-4-carboxylic acid (**III-1-4**) (0.1 g, 0.27 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0°C added a solution of oxalyl chloride (0.14 g, 1.1 mmol) in anhydrous CH_2Cl_2 (5 mL). A solution of DMF (0.001 mL) in anhydrous CH_2Cl_2 (1 mL) was added to the reaction mixture and was stirred at 0 °C for another 2 h. The CH_2Cl_2 was evaporated under vacuum and the reaction mixture cooled to 0 °C after which absolute EtOH (20 mL) was added. The solution was allowed to stir for an additional 1 h. The solvent was evaporated under vacuum and the reaction mixture diluted with CH_2Cl_2 (30 mL) and washed with sat.$NaHCO_3$ (10 mL) and H2O (10 mL). The organic layer was dried over $NaHSO_4$ and was

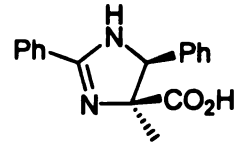
concentrated under vacuum to yield the crude product, which was further purified by silica-gel column chromatography (ethyl acetate); overall yield (from azlactone): 76% (0.97 g); pale yellow oil. ^{1}H NMR (300MHz) DMSO-d_6: δ 0.86 (3 H, t, J = 7.2 Hz), 1.57 (3 H, s), 3.64 (2 H, q, J = 7.2 Hz), 3.83 (1 H, d, J = 15.3 Hz), 4.27 (1 H, s), 4.77 (1 H, d, J = 15.3 Hz), 6.97 (2 H, dd, J_1 = 7.2 Hz, J_2 = 2.4 Hz), 7.22–7.54 (6 H, m), 7.31–7.54 (2H, m), 7.78–7.81 (2 H, m), 8.59–8.61 (2 H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 13.45, 27.13, 49.47, 60.83, 71.87, 77.94, 122.56, 127.79, 127.93, 128.55, 128.70, 130.21, 130.51, 135.82, 146.59, 149.75, 166.02, 171.37; HRMS (EI): *m/z* calcd for $C_{25}H_{27}N_3O_2$, 400.2025; found, 400.2038. IR (neat): 1734 cm^{-1}, 1597 cm^{-1}.



III-1-12

***dl*-(4S, 5S)-1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*imidazol- 4-yl) methanol III-1-12:** To a well stirred suspension of $LiAlH_4$ (0.12g, 0.3 mmol) in anhydrous THF (5 mL) was added a solution of 1-benzyl-4-methyll-2,5-diphenyl-4,5-ihydro-1*H* imidazole-4-carboxylic acid (0.1 gm, 0.27 mmol) in anhydrous THF (5 mL) dropwise at 0 °C, the mixture was stirred at the same temperature for 15 min quenched with ice cold sat. NH_4Cl solution (**caution**: NH_4Cl solution kept at 0 °C for about 30 min.; and should be added with extreme care; highly exothermic reaction and the reaction mixture should be at 0 °C) followed by 10% HCl (~10 mL). The reaction mixture was diluted with an excess of EtOAc (100 mL) washed with H_2O (20 mL) dried over anhydrous Na_2SO_4, filtered, and the

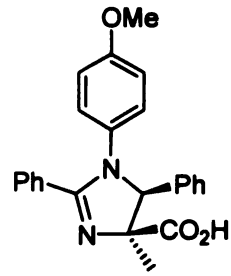
solvent evaporated under reduced pressure to yield the crude product which was purified by column chromatography (EtOAc); overall yield (2 steps): 79% (0.076 g); viscous oil. ^{1}H NMR (300MHz) DMSO-d_6: δ 1.25 (3 H, s), 3.48 (1 H, d, J = 12 Hz), 3.56 (1 H, d, J = 11.8 Hz), 3.75 (1 H, d, J =12.9 Hz), 3.87 (s, 1 H), 3.94 (1H, d, J = 12.9 Hz), 7.28–7.54 (m, 13 H), 7.77–7.79 (m, 2 H), 8.06 (1 H, br s) ^{13}C NMR (75MHz) DMSO-d_6: δ 17.25, 51.67, 61.54, 66.28, 66.93, 127.266, 127.68, 128.26, 128.56, 128.82, 129.06, 131.77, 135.48, 138.03, 139.90, 167.91; HRMS (FAB): *m/z* calcd for $C_{24}H_{25}N_2O$ [M + H], 357.1888; found, 357.1967. IR(neat): 3316 cm^{-1}.



III-1-13

***dl*-(4*S*,5*S*)-4-Methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole-4- carboxylic Acid III-1-13:** To a well-stirred suspension of imidazoline-4-carboxylic acid **III-1-1** (0.1 g, 0.27 mmol) and cyclohexene (0.1 mL, 1.25 mmol) in anhydrous THF (30 mL) was added 10% Pd/C (45 mg, 0.06 mmol). The suspension was refluxed for 36 h. The reaction mixture cooled to r.t. and EtOH (10 mL) was added. The mixture was filtered through celite, washed with EtOH, and the filtrate was evaporated under reduced pressure. The crude product was purified by column silicagel chromatography (EtOH); overall yield: 71% (0.070 g); white solid; ^{1}H NMR (300MHz) DMSO-d_6: δ 1.76 (s, 3 H), 5.34 (s, 1 H), 7.34–7.36 (br, 5 H), 7.69 (2 H, dd, J = 8.1, 7.2 Hz), 7.81 (1 H, dd, J_1 = 6.9 Hz, J_2 = 7.2 Hz), 8.15 (2 H, d, J = 8.4 Hz) ^{13}C NMR (75MHz) DMSO-d_6: δ 25.32, 55.66, 70.79, 72.57,

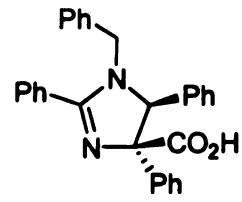
123.12, 128.24, 128.96, 129.42, 129.67, 130.12, 135.42, 136.24, 164.24, 170.77; mp 222–224 °C (dec.). HRMS (FAB): *m/z* calcd for $C_{17}H_{17}N_2O_2$ [M + H], 281.1212; found, 281.1289. IR(neat) : 3300 cm^{-1}, 1736 cm^{-1}



III-1-14

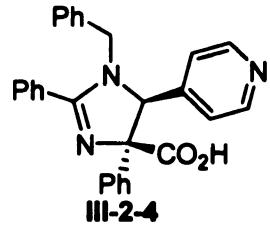
***dl*- (4*S*, 5*S*)-1-(4-methoxyphenyl)-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazole- 4-carboxylic Acid (III-1-14)**

A solution of benzaldehyde (1.42 g, 13.5 mmol), 4-methoxybenzylamine (1.4 g, 13.5 mmol) in anhydrous CH_2Cl_2 (50 mL) was refluxed under nitrogen for 2h. A mixture of 2-Phenyl-4-methyl-4*H*-oxazolin-5-one (2.2 g, 12.5 mmol) and chlorotrimethylsilane (2.03 g, 18.75 mmol) (premixed and stirred for 2h) in anhydrous CH_2Cl_2 (100 mL) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The solvent was evaporated under vacuum. The product was precipitated using CH_2Cl_2/hexanes (1:1); yield: 50 % (2.41 g); pale pink solid; ^{1}H NMR (300MHz) DMSO-d_6: δ 1.93 (3H, s), 3.59 (3H, s), 5.85 (1H, s), 6.74 (2H, d, J = 9 Hz), 7.15-7.6 (12H, m); ^{13}C NMR (75MHz) DMSO-d_6: δ 24.3, 55.1, 70.1, 77.2, 114.3, 122.3, 127.8, 128.3, 128.5, 128.7, 129.1, 129.5, 132.7, 133.5, 158.8, 164.3, 169.5; IR (neat): 3352 cm^{-1}, 1735cm^{-1}; LRMS (EI): *m/z* calcd. for $C_{24}H_{22}N_2O_3$ [M+], 386.163; found, 386.0.



III-2-1

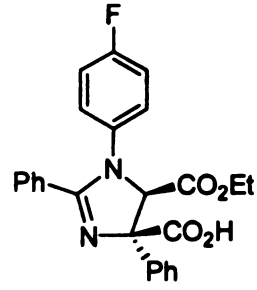
***dl*-(4*S*,5*S*)-1-Benzyl-2,4,5 triphenyl-4,5-dihydro-1*H*-imidazole- 4-carboxylic Acid III-2-1:** A solution of benzaldehyde (0.6 g, 5.7 mmol), benzylamine (0.61 g, 5.7 mmol) in anhydrous CH2Cl2 (120 mL) was refluxed under nitrogen for 2 h. 2,4-Diphenyl-4*H*-oxazolin-5-one (1.35 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The product was purified by silica-gel column chromatography (EtOH–EtOAc, 1:5); yield: 65% (2.1 g); off-white solid; ^{1}H NMR (300MHz) DMSO-d_6: δ 3.80 (1 H, d, J = 15.6 Hz), 4.62 (1 H, d, J = 15.6 Hz), 4.98 (1 H, s), 6.58 (2 H, d, J = 8.1 Hz), 7.05–7.65 (16 H, m), 7.90 (2 H, d, J = 7.2 Hz) ^{13}C NMR (75MHz) DMSO-d_6: δ 29.7, 48.3, 75.6, 79.1, 123.1, 125.7, 126.7, 127.3, 127.4, 127.9, 128.1, 128.2, 128.8, 128.9, 129, 129.3, 132.9, 133.8, 136, 143.1, 164.8, 168.1d mp 153– 155 °C. HRMS (EI): *m/z* calcd for $C_{28}H_{23}N_2$ [(M – H) – CO_2], 387.1526; found, 387.1539. IR(neat): 3400 cm^{-1}, 1738 cm^{-1}



III-2-4

***dl*-(4*S*,5*S*)- 1-Benzyl-2,4-diphenyl-5-pyridin-4-yl-4,5 dihydro- *1H*-imidazole-4-carboxylic Acid (2o)** A solution of pyridin-4 carboxylaldehyde (0.61 g, 0.57

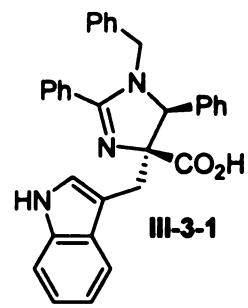
mmol), benzylamine (0.61 g, 5.7 mmol) in anhydrous CH_2Cl_2 (120 mL) was refluxed under nitrogen for 2 h. 2,4-Diphenyl-4*H*-oxazolin-5-one (1.35 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The product was precipitated using CH_2Cl_2–Et_2O; yield 55% (1.35 g); off-white solid. ^1H NMR (300MHz) DMSO-d_6: δ 4.00 (1 H, d, J = 15.6 Hz), 5.00 (1 H, d, J = 15.6 Hz), 5.38 (1 H, s), 7.1–7.65 (17 H, m), 8.5 (2 H, d, J = 7.2 Hz) ^{13}C NMR (75MHz) DMSO-d_6: δ 45.2, 66.3, 75.6, 123.7, 126.5, 126.9, 128.5, 128.6, 128.8, 129.2, 129.3, 131.9, 133.5, 134.4, 136.2, 143.4, 149.7, 166.6, 166.9; MS (EI): *m/z* calcd for C29H24FN3O2 [M +H], 434.34186; found, 434.1852. IR(neat): 3400 cm^{-1}, 1733 cm^{-1}.



III-2-5

***dl*-(4*S*,5*S*)-1-(4 Fluorophenyl)-2,4-diphenyl-4,5-dihydro-1*H*imidazole- 4,5-dicarboxylic Acid 5-Ethyl Ester III-2-5:** A solution of ethyl glyoxalate (0.85 g, 8.3 mmol) as 50% solution in toluene (1.03 g/mL), 4-fluoroaniline (0.93 g, 8.3 mmol) in anhydrous CH_2Cl_2 (250 mL) was refluxed under nitrogen for 2 h. 2,4-Diphenyl- 4*H*-oxazolin-5-one (2 g, 8.3 mmol) and chlorotrimethylsilane (1.16, 10.8 mmol) were added and the mixture was refluxed under nitrogen for 6 h and

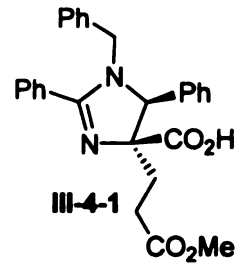
then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2–Et_2O; yield: 68% (2.4 g); white solid. ^{1}H NMR (300MHz) DMSO-d_6: δ 0.84 (3 H, t, J = 7.2 Hz), 3.89 (2 H, dq, J_1 = 7.2 Hz, J_2 = 3 Hz), 4.73 (1 H, s), 6.70–6.84 (2 H, m), 6.89 (2 H, t, J = 9 Hz), 7.34–7.5 (3 H, m), 7.55 (3 H, t, J = 7.5 Hz), 7.65 (2 H, t, J = 8.1Hz), 7.83 (2 H, dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz), 8.10–8.22 (2 H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 13.3, 61.1, 66.1, 76.3, 115.3, 115.6, 117.3, 117.4, 125, 126.1, 128.2, 128.6, 133, 134.6, 142, 142.1, 155.7, 162.1, 169, 176.8; HRMS (FAB): *m/z* calcd for $C_{25}H_{22}FN_2O_4$ [M + H], 433.1486; found: 433.1565. IR (neat): 3331 cm^{-1}, 1736 cm^{-1}.



III-3-1

***dl*-(4*S*,5*S*)-1-Benzyl-4-(1*H*-indol-3-ylmethyl)-2,5-diphenyl-4,5-dihydro-1*H* imidazole-4-carboxylic Acid III-3-1:** A solution of benzaldehyde (0.6 g, 5.7 mmol), benzylamine (0.61 g, 5.7 mmol) in anhydrous CH_2Cl_2 (120 mL) was refluxed under nitrogen for 2 h. 4-(1*H*-Indol-3-ylmethyl)-2-phenyl-4*H*-oxazol-5-one (1.65 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The product was purified by column chromatography on silica gel EtOH–EtOAc (1:5); yield: 68% (3.1 g); offwhite solid; ^{1}H NMR (300MHz) DMSO-d_6: δ 3.95 (1 H, d, J = 16.2 Hz), 4.6 (1 H, d, J = 16.2 Hz), 5.25 (1 H, s), 6.1 (2 H, d, J =

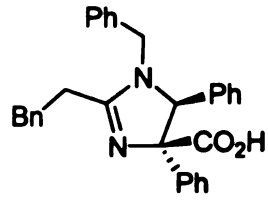
7.8 Hz), 6.90–7.30 (5 H, m), 7.30–8.00 (15 H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 32.3, 48.5, 70.4, 74.4, 105.8, 111, 119, 121.4, 122.7, 126.6, 126.7, 127.8, 127.9, 128.6, 128.7, 128.9, 129.4, 129.7, 132.3, 132.5, 133.7, 136.5, 166, 169.6; mp >250 °C (dec.). HRMS (EI): *m/z* calcd for $C_{32}H_{26}N_3O_2$ [M – H], 484.2025; found, 484.2011; IR (neat): 3420 cm^{-1}, 1741 cm^{-1}.



***dl*-(4*S*,5*S*)-1-Benzyl-4-(2-methoxycarbonyl-ethyl)-2,5-diphenyl- 4,5-dihydro-1*H*-imidazole-4-carboxylic Acid (2r)**

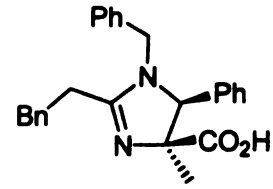
A solution of benzaldehyde (0.252 g, 2.4 mmol), benzylamine (0.258 g, 2.4 mmol) in anhydrous CH_2Cl_2 (100 mL) was refluxed under nitrogen for 2 h. 3-(5-Oxo-2-phenyl-4,5- dihydro-oxazol-4-yl)-propionic acid methyl ester **II-4** (0.5 g, 2 mmol) and chlorotrimethylsilane (0.282 g, 2.6 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product was precipitated using CH_2Cl_2/ hexanes (1:1); yield: 60% (0.54 g); white solid. ^{1}H NMR (300MHz) DMSO-d_6: δ 2.05–2.25 (2 H, m), 2.30–2.50 (2 H, m), 3.55 (3 H, s), 4.38 (2 H, ddd, J_1 = 4 Hz, J_2 = 9 Hz, J_3 = 25 Hz), 4.86 (1 H, q, J = 3.3), 7.10–7.60 (12 H, m), 7.70–7.90 (4 H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 27.6, 30.1, 43.3, 51.6, 52.7, 127.1, 127.2, 127.3, 128.2, 128.3, 131.5, 131.6, 133.3, 137.8, 167.5,

171.4, 173.6; HRMS (FAB): *m/z* calcd for $C_{27}H_{27}N_2O_4$ [M + H], 443.1893; found, 443.1971; IR(neat): 1734 cm^{-1}, 1653 cm^{-1}.



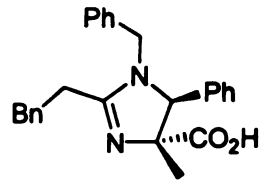
III-6-1

***dl*-(4*S*,5*S*)-1,2-dibenzyl-4,5 diphenyl-4,5-dihydro-1*H*-imidazole- 4-carboxylic Acid (2s)** A solution of benzaldehyde (0.6 g, 5.7 mmol), benzylamine (0.61 g, 5.7 mmol) in anhydrous CH_2Cl_2 (120 mL) was refluxed under nitrogen for 2 h. 2-Benzyl-4-phenyl-4*H*-oxazolin-5-one (1.43 g, 5.7 mmol) and chlorotrimethylsilane (0.8 g, 7.4 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The product was a mixture of diastereomers (3:1 ratio); yield: 60%. The above *trans*-diastereomer was obtained by repeated precipitation from MeOH–Et_2O. ^1H NMR (300MHz) DMSO-d_6: δ 3.47 (2 H, d, J = 15.6 Hz), 4.31 (2 H, d, J = 15.6 Hz), 5.80 (1 H, s), 6.40–7.40 (20 H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 30.7, 47.5, 72.1, 100.2, 126.2, 126.6, 126.8, 127.3, 127.7, 127.9, 128.0, 128.5, 128.6, 129.0, 131.4, 132.5, 133.4, 136.4, 164.4, 171.6a HRMS (FAB): *m/z* calcd for $C_{30}H_{27}N_2O_2$ [M + H] 447.2010; found, 447.2072; IR(neat): 3350 cm^{-1}, 1704 cm^{-1}.



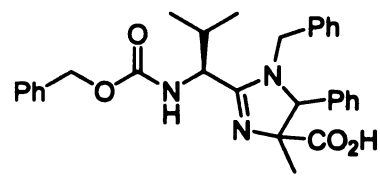
III-9-1a

***dl*-(4*S*,5*S*)-1,2-Dibenzyl-4-methyl 5-phenyl-4,5-dihydro-1*H*-imidazole- 4-carboxylic Acid III-9-1a and *dl*-(4*S*,5*R*)-1,2 Dibenzyl-4- methyl-5-phenyl-4,5-dihydro-1*H*-imidazole-4-carboxylic Acid II-9-1b:** A solution of benzaldehyde (1.13g, 10.58 mmol), benzylamine (1.13g, 10.58 mmol) in anhydrous CH_2Cl_2 (250 mL) was refluxed under nitrogen for 2 h. 2-Benzyl-4-methyl-4*H* oxazolin-5-one (2g, 10.58 mmol) and chlorotrimethylsilane (1.48 g, 10.58 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The reaction mixture was evaporated to dryness under vacuum. The product *cis* isomer **III-9-1b** was precipitated using CH_2Cl_2–Et_2O; yield: 30% (0.6 g); white solid. The *trans*-isomer **III-9-1a** was then precipitated out from the mother liquor. A small amount was then reprecipitated to remove traces of **III-9-1b**; yield: 17% (0.15g). **III-9-1a:** ^{1}H NMR (300MHz) DMSO-d_6: δ 1.74 (3 H, s), 3.67 (1 H, d, J = 15.3 Hz), 4.11 (1 H, d, J = 14.7 Hz), 4.38 (1 H, s), 4.46 (1 H, d, J = 14.7 Hz) 4.59 (1 H, d, J = 15.3 Hz), 6.77 (2 H, d, J = 7 Hz), 7.00–7.60 (13 H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 22.1, 32.4, 48.1, 70.6, 71.1, 127.6, 128.3, 128.6, 128.9, 129.1, 129.2, 129.7, 132.2, 132.8, 133.5, 164.8, 175.1; HRMS (FAB): *m/z* calcd for $C_{25}H_{25}N_2O_2$ [M + H], 385.1898; found, 385.1916; IR (neat): 3350 cm^{-1}, 1624 cm^{-1}.



III-9-1b

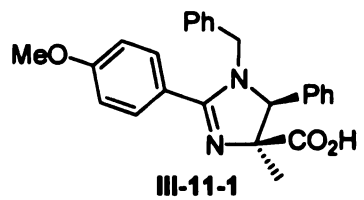
III-9-1b: ^{1}H NMR (300MHz) DMSO-d_6: δ 1.14 (3 H, s), 3.94 (1 H, d, J = 15.6 Hz), 4.24 (2 H, q, J = 8.7 Hz), 4.56 (1 H, d, J = 15 Hz), 5.74 (1 H, s), 6.65 (2 H, d, J = 7.5 Hz), 7.00–7.40 (13 H, m) ^{13}C NMR (75MHz) DMSO-d_6: δ 27.1, 38.7, 48.6, 71.5, 73.5, 127.9, 128.3, 128.5, 128.7, 128.9, 129, 129.3, 129.4, 129.5, 129.8, 120.9, 132.2, 133.5, 134.2, 165.6, 170.6 ; HRMS (FAB): *m/z* calcd for $C_{25}H_{25}N_2O_2$ [M + H], 385.1898; found, 385.1917; IR (neat): 3350 cm^{-1}, 1738 cm^{-1}.



III-10-1

Benzyl (S)-1-(1-Benzyl-4-methyl 2, 5-diphenyl-4,5-dihydro-*1H*-imidazolyl- 4-carboxylate)-2-methylpropyl carbamate (III-10-1): A solution of benzaldehyde (0.34 g, 3.3 mmol), benzylamine (0.35 g, 3.3 mmol) in anhydrous CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2h. 2-Phenyl-4-methyl-4*H*-oxazolin-5-one (1 g, 3.3 mmol) and chlorotrimethylsilane (0.53 g, 4.93 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The solvent was evaporated under vacuum. The product was precipitated using CH_2Cl_2/hexanes (1:1); yield: 25% (0.411 g); white foam; ^{1}H NMR (300MHz) DMSO-d_6: δ 0.4 (3H, d, J = 6.9 Hz), 0.54 (3H, d, J = 6.9 Hz),

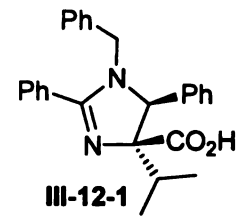
1.58 (3H, s), 1.8 (1H, s), 3.94 (1H, m), 3.64 (1H, d, 14.7 Hz), 4.25 (1H, s), 4.59 (1H, d, J =9 Hz), 4.76 (1H, d, J = 15.3 Hz), 4.916 (2H, s), 6.36 (1H, s), 6.96-7.22 (14H, m); ^{13}C NMR (75MHz) DMSO-d_6: δ 17.5, 17.9, 18.9, 30.6, 30.9, 43.2, 48.6, 60.5, 66.8, 127.2, 127.3, 127.5, 127.8, 128.0, 128.3, 128.4, 135.8, 137.7, 156.3, 171.1, 171.3, 171.6; HRMS (EI): *m/z* calcd. for $C_{30}H_{33}N_3O_4$ [M +H], 499.6007; found, 500.2.; IR (neat): 3302 cm^{-1}, 1759 cm^{-1}, 1672 cm^{-1}.



III-11-1

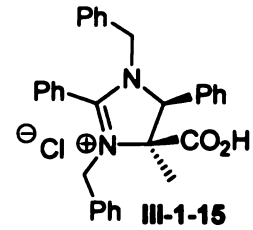
dl*- (4*S*, 5*S*)-1-Benzyl-4-methyl-2(4-methoxyphenyl), 5-diphenyl-4,5-dihydro-1*H*-imidazole- 4-carboxylic Acid (III-11-1):** A solution of benzaldehyde (1.026 g, 9.75 mmol), benzylamine (1.043 g, 9.75 mmol) in anhydrous CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2h. 2-(4-methoxyphenyl)-4-methyl-4*H*-oxazolin-5-one (2 g, 9.75 mmol) and chlorotrimethylsilane (1.58 g, 14.63 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The solvent was evaporated under vacuum. The product was precipitated using CH_2Cl_2/hexanes (1:1); yield: 62% (2.42 g); white solid (light sensitive in solution!***); ^{1}H NMR (300MHz) DMSO-d_6: δ 1.692 (3H, s), 3.851 (3H, s), 4.11 (1H, d, *J* = 15.9 Hz), 4.92 (2H, d, *J* = 15 Hz + s), 6.99-7.02 (2H, m), 7.22 (2H, d, J = 9 Hz), 7.27-7.29 (4H, m), 7.31-7.41 (4H, m), 7.9 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (75MHz) DMSO-d_6: δ 24.9, 48.6, 55.7, 69.7, 72.9, 113.5, 114.8, 127.4, 128.0, 128.2, 128.6, 128.8, 129.4, 131.3, 132.3, 133.1, 163.4, 165.4, 169.3;

LRMS (EI): *m/z* calcd. for $C_{25}H_{24}N_2O_3$ [M+], 400.4697; found, 400.6; IR (neat): 3350 cm^{-1}, 1738cm^{-1}.



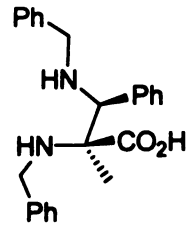
III-12-1

Partial data *dl*- (4*S*, 5*S*)-1-Benzyl-4-isopropyl 2, 5-diphenyl-4,5-dihydro-1*H*-imidazole- 4-carboxylic Acid (III-12-1): A solution of benzaldehyde (1.58 g, 15 mmol), benzylamine (1.605 g, 15 mmol) in anhydrous CH_2Cl_2 (15 mL) was refluxed under nitrogen for 2h. 2-Phenyl-4-methyl-4*H*-oxazolin-5-one (3 g, 15 mmol) and chlorotrimethylsilane (2.43 g, 22.5 mmol) were added and the mixture was refluxed under nitrogen for 6 h and then stirred overnight at r.t. The solvent was evaporated under vacuum. The product was precipitated using CH_2Cl_2/hexanes (1:1); yield: 71% (4.25 g); white solid; ^1H NMR (500MHz) DMSO-d_6: δ 0.8 (3H, d, J = 7 Hz), 0.93 (3H, d, 7 Hz), 2.35 (1H, q, J = 6.5 Hz), 3.97 (1H, d, J = 15 Hz), 4.78 (1H, d, J =15.5 Hz), 5.06 (1H, s), 6.88 (2H, d, J = 7 Hz), 7.265-7.527 (9H, m), 7.75 (1H, t, J =7.5 Hz), 7.847 (1H, t, J =7.5 Hz), 7.95 (2H, d, J = 7 Hz) ^{13}C NMR (125MHz) CD_3OD: δ 16.1, 18.1, 36.4, 42.8, 49.5, 70.5, 78.2, 122.5, 128.9, 129.1, 129.5, 129.54, 129.6, 129.7, 130, 130.2, 130.3, 132.9, 134, 134.6, 134.8, 166.5, 169.6; IR (neat): 3345 cm^{-1}, 1732cm^{-1}.

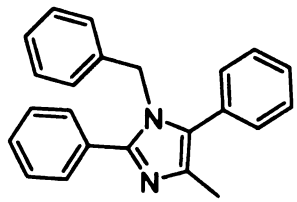


III-1-15

***dl*- (4*S*, 5*S*)-1,3-Dibenzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1*H*-imidazolinium- 4-carboxylic Acid. Chloride salt (III-1-15):** In a flame dried flask under nitrogen atmosphere, imidazoline **III-1-1** (0.9 g, 2.42 mmol) was suspended in 200 ml dry benzene. Solid anhydrous K_2CO_3 (4.5 g, 26 mmol) was weighed in followed by addition of benzyl chloride (0.367 g, 2.9 mmol) was added and the mixture was refluxed under nitrogen atmosphere overnight. After all the starting material was consumed, the solvent was removed under vaccum. The residue was dissolved in dichloromethane and the product imidazolium chloride was precipitated from dichloromethane/hexanes (1:1) mixture in 77 % yield (0.926 g) as white foam; ^{1}H NMR (300MHz) $CDCl_3$: δ 1.44 (3H, s), 3.658 (1H, d, J = 15.6), 4.17 (1H, s), 4.27 (1H, d, J = 12.3 Hz), 4.48 (1H, d, J = 12.3 Hz), 4.56 (1H, d, J = 15.6 Hz), 6.77-6.8 (2H, m), 6.91-6.93 (2H, m), 7.05-7.13 (10H, m) 7.32-7.34 (2H, m), 7.57-7.6 (2H, m); ^{13}C NMR (75MHz) $CDCl_3$: δ 26.5, 48.6, 66.0, 72.9, 77.6, 127.4, 127.4, 127.5, 127.7, 127.9, 128.1, 128.4, 129.9, 130.6, 135.3, 136.2, 136.5, 165.9, 171.5; LRMS (EI): *m/z* calcd. for $C_{31}H_{29}N_2O_2$ [M+], 461.2224; found, 461.2; IR (neat): 3350 cm^{-1}, 1736 cm^{-1}.

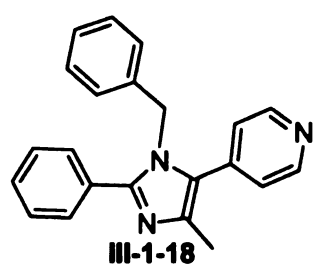


dl-(2S,3S)-2,3-bis(benzylamino)-2-methyl-3-phenylpropanoic acid III-1-16: In a round bottom flask equipped with a stirrer **III-1-15** (0.5g, 1 mmol) was suspended in 25 mL of MeOH. $NaBH_4$ (0.114 g, 3 mmol) was added in three portions and the mixture was stirred rapidly overnight. After all the starting material was consumed, MeOH was evaporated off. The residue was dissolved in ethyl acetate (50 mL) and extracted with saturated ammonium chloride solution. The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed under vaccum. The residue was dissolved in dichloromethane and the product diamino acid was precipitated from ether/dichoromethane mixture a solid foam in 65 % yield (0.24g); ^{1}H NMR (300MHz) ($CDCl_3$ + 2 drops D_2O): δ 1.19 (3H, s), 2.87 (1H, d, J = 12 Hz), 2.98 (1H, d, J = 12 Hz), 3.72 (1H, d, J = 15 Hz), 4.10 (1H, s), 4.57 (1H, d, J = 15 Hz), 6.71-7.6 (15H, m); ^{13}C NMR (75MHz) $CDCl_3$: δ 26.0, 48.8, 67.2, 71.6, 71.9, 127.7, 127.9, 128.0, 128.6, 128.6, 128.8, 130.3, 130.5, 135.9, 136.0, 165.3; LRMS (EI) *m/z* calcd. for $C_{24}H_{25}N_2O$ [M]+, 357.1; found, 357.3 ; HRMS (EI): *m/z* calcd. for $C_{24}H_{25}N_2O$ [M] +, 357.1966; found, 357.1967. IR (neat): 3182cm^{-1}, 3063 cm^{-1}, 2924 cm^{-1}, 2858.9 cm^{-1}, 1616 cm^{-1}, 1593.4 cm^{-1}, 1452 cm $^{-1}$.



III-1-17

1-Benzyl-4-methyl-2, 5-diphenyl-1*H*-imidazole III-1-17: A solution of **III-1-1** (0.5 g, 0.1.35 mmol) in acetic anhydride (15 mL) was heated to reflux for 6h. The acetic anhydride was evaporated to dryness *in vacuo*. The residue was chromatographed on silica-gel with 3:2 Diethyl ether / Hexanes to afford 0.1 g of **III-1-17** in 23 % yield. **Partial data:** ^{1}H NMR (300 MHz) ($CDCl_3$): δ 2.3 (3H, s), 5.18 (1H, s), 6.7 –6.8 (2H, m), 7.1 –7.65 (13H, m); ^{13}C NMR (75 MHz) ($CDCl_3$) δ; 13.0, 48.5, 125.9, 127.3, 127.9, 127.9, 128.4, 128.5, 128.7, 128.8, 129.7, 130.1, 130.2, 130.3, 130.6, 131.9, 135.4, 137.6, 147.4; MS(EI): calculated for $C_{23}H_{20}N_2$ (m/z) 324.4 and observed (m/z) 324.



III-1-18

4-(3-Benzyl-5-methyl-2-phenyl-3H-imidazol-4-yl)-pyridine III-1-18: A solution of **III-1-11** (0.1 g, 0.27 mmol) in acetic anhydride (15 mL) was heated to reflux for 6h. The acetic anhydride was evaporated to dryness *in vacuo*. The residue was chromatographed on silica-gel with ethyl acetate to afford 0.02 g of **III-1-18** in 22 % yield. **Partial data**: ^{1}H NMR (300 MHz) ($CDCl_3$): δ 2.3 (3H, s), 5.18 (1H, s), 6.7 –6.8 (2H, m), 7.1 –7.65 (12H, m); ^{13}C NMR (75 MHz) ($CDCl_3$):

δ13.5, 29.6, 50.1, 117.6, 126.5, 127.7, 128.4, 128.7, 128.9, 130.3, 137.1, 137.7, 147.4.

M. References

1. (a) Li, H. -Y.; Drummond, S.; DeLucca, I.; Boswell, G. A. *Tetrahedron* **1996**, *52*, 11153. (b) Ueno, M.; Imaizumi, K.; Sugita, T.; Takata, I.; Takeshita, M. *Int. J. Immunopharm.* **1995**, *17*, 597. (c) Rondu, F.; LeBihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, B.; Renard, P.; Guardiola-Lemaître, B.; Manéchez, D.; Pénicaud, L.; Ktorza, A.; Godfroid, J. -J. *J. Med. Chem.* **1997**, *40*, 3793-3803. (d) Bousquet, P.; Feldman, J. *Drugs* **1999**, *58*, 799.(e) Schann, S.; Bruban, V.; Pompermayer, K.; Feldman, J.; Pfeiffer, B.; Renard, P.; Scalbert, E.; Bousquet, P.; Ehrhardt, J. -D. *J. Med. Chem.* **2001**, *44*, 1588. (f) Gust, R.; Keilitz, R.; Schmidt, K.; von Rauch, M. *J. Med. Chem.* **2002**, *45*, 3356.

2. Acharya, A. N.; Ostresh, J. M; Houghten, R. A. *J. Comb. Chem.* **2001**, *3*, 612.

3. Concellón, J. M.; Riego, E.; Suárez, J. R.; García-Granda, S.; Rosario Díaz, M. *Org. Lett.* **2004**, *6*, 4499

4. Acharya, A. N.; Ostresh, J. M; Houghten, R. A. *J. Org. Chem.* **2001**, *66*, 8673.

5. Chern, J. -W.; Liaw, Y. -C.; Chen, C. -S.; Rong, J. -G.; Huang, C. -L.; Chan, C. -H.; Wang, A. H. -J. *Heterocycles* **1993**, *36*, 1091-1103.

6. De Lucca, G. V. *J. Org. Chem.* **1998**, *63*, 4755-4766.

7. (a) Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; de Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Lett.* **2003**, 5 (20), 3759 -3762. (b) Gentili, F.; Bousquet, P.; Brasili, L.; Dontenwill, M.; Feldman, J.; Ghelfi, F.; Gianella, M.; Piergentili, A.; Quaglia, W.; Pigini, M. *J. Med. Chem.* **2003**, *46*, 2169-2176.

8. (a) Dunn, P. J.; Haner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017-5025. (b) Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045-2048.

9. Fernandez-Megia, E.; Sardina, F. J. *Tetrahedron Lett.* **1997**, *38*(4), 673.

10. You, S.-L.; Kelly, J. W. *Org. Lett.* **2004**, *6*(10), 1681 -1683.

11. Munk, S. A.; Harcourt, D.; Ambrus, G.; Denys, L.; Gluchowski, C.; Burke, J. A.; Kharlamb, A. B.; Manplapaz, C. A.; Padillo, E. U.; Runde, E.; Williams, L.; Wheeler, L. A.; Garst, M. E. *J. Med. Chem.* **1996**, *39*, 3533.

12. Regunathan, S., Feinstein, D. L., Reis, D. J. *Ann. N. Y. Acad. Sci.* **1999** *881*, 410-419.

13. Dardonville, C.; Rozas, I. *Med. Res. Rev.* **2004**, *5*, 639-661.

14. (a) Schäfer, U.; Burgdorf, C.; Engelhardt, A.; Kurz, T.; Richardt, G. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 1163-1170. (b) Gust, R.; Keilitz, R.; Schmidt, K. *J. Med. Chem.* **2001**, *44*, 1963-1970.

15. (a) Gilbert, I. H.; Rees, D. C.; Crockett, A. K.; Jones, R. C. F. *Tetrahedron* **1995**, *51*, 6315. (b) Jones, R. C. F.; Dickson, J. *J. Peptide Sci.* **2000**, *6*, 621-624.

16. Minter, A. R.; Brennan, B. B.; Mapp, A. K. *J. Am. Chem. Soc.* **2004**, *126*(34), 10504 -10505.

17. Arkin, M. R.; Wells, J. A. *Nature Rev. Drug Discov.* **2004**, *3*(4), 301-317.

18. Kussie, P. H.; Gorina, S.; Marechal, V.; Elenbaas, B.; Moreau, J.; Levine, A. J.; Pavletich, N. P. *Science*, **1996**, *274*, 948-953.

19. Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu E. A. *Science*, **2004**, *303* , 844-848.

20. (a) Dai, L.; Lin, Y.; Hou, X.; Zhou, Y. *Pure. Appl. Chem.* **1999**, *71*(6), 1033. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580. (c) Zhou, X.; Lin, Y.; Dai, L.; Sun, J.; Xia, L.; Tang, M. *J. Org. Chem.* **1999**, *64*, 1331.

21. Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586.

22. (a) Dalko, P. I.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 8107 (b) Austin J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*(7), 1172.

23. (a) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707-1710. (b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1711-1714. (c) Dalko, P. I.; Langlois, Y. *Chem. Commun.* **1998**, 331-332.

24. Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713-4716.

25. Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290-1309.

26. Hermann, W. A.; Goossen, L. J.; Speigler, M. Organometallics. **1998**, *17*, 1172.

27. (a) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Obermann, U. *J. Organomet. Chem.* **1989**, *370*, 17-31. (b) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010-5017. (c) Jones, R. C. F.; Turner, I.; Howard, K. J. *Tetrahedron Lett.* **1993**, *34*, 6329-6332.(d) Boland, N. A.; Casey, M.; Hynes, S. J.; Matthews, J. W.; Smyth, M. P. *J. Org. Chem.* **2002**, *67*, 3919-3922.

28. (a) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Ku¨rzinger, A.; Obermann, U. *J. Organomet. Chem.* **1989**, *370*, 17-31. (b) Dauwe, C.; Buddrus, J. *Synthesis* **1995**, 171-172. (c) Dalko, P. I.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 8107-8117. (d) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Rusell, D. R. *J. Chem. Soc., Perkin Trans.* **2001**, 1500-1503. (e) Dupont, J.; Ebeling, G.; Delgado, M. R.; Consorti, C. S.; Burrow, R.; Farrar, D. H.; Lough, A. *J. Inorg. Chem. Commun.* **2001**, *4*, 471-474. (f) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 999-1002

29. (a) Legters, J.; Willems, J. G. H.; Thijs, L.; Zwanenburg, B. *Rec. Tra*V. *Chim. Pays-Bas* **1992**, *111*, 59-68.

30. Hershenson, F. M.; Pavia, M. R. *Synthesis* **1988**, 999-1001.

31. Consonni, R.; Croce, P. D.; Ferraccioli, R.; La Rosa, C. *J. Chem. Res., Synop.* **1991**, 188-189.

32. Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800-2801.

33. Gotthardt, H.; Huisgen, R.; Bayer, H. O. *J. Am. Chem. Soc.* **1970**, *92*, 4340.

34. Croce, P. D.; Ferraccioli, R.; La Rosa, C. *Tetrahedron* **1999**, *55*, 201.

35. Mukerjee, A. K. *Heterocycles* **1987**, *26*, 1077.

36. Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jimenez, J. L.; Light, M. E.; Lopez, I.; Palacios, J. C.; Silvero, G. *Chemistry* **2001**, *7*, 3033.

37. Prasad, K. K.; Petrzilka, T. *Helv. Chim. Acta* **1975**, *58*, 2504.

38. Chen, F. M. F.; Kuroda, K.; Benoiton, N. L. *Synthesis* **1979**, 230.

39. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, *309*, 3223.

40. Sain, B.; Sandhu, J. S. Heterocycles. **1985**, *23*, 1611.

41. Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995.

42. Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 3228.

43. Bowman, R. K.; Johnson, J. S. *J. Org. Chem.* **2004**, *69*(24), 8537-8540.

44. Roberts, R. M.; Higgins, T. D.; Noyes, P. R. *J. Am. Chem. Soc.* **1955**, *77*, 3801-3805.

45. Takagaki, H.; Yasuda, N.; Asaoka, M.; Take, H. *Chem. Lett.* **1979**, 183.

46. Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*(28), 4969-4972.

47. Zhou, X. -T.; Lin, Y. -R.; Dai, L. -X. *Tetrahedron Asymm.* **1999**, *10*, 855-862.

48. Viso, A.; Fernandez De La Pradilla, R.; Guerrero-Strachan, C.; Alonso, M.; Martinez-Ripoll, M.; Andre, I. I. *J. Org. Chem.* **1997**, *62*, 2316-2317.

49. Viso, A.; Fernandez De La Pradilla, R.; Garcia, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martinez-Ripoll, M.; Fonseca, I.; Andre, I.; Rodriguez, A. *Chem. Eur. J.* **2003**, *9*, 2867-2876.

50. Wilde, R. G. *Tetrahedron Lett.* **1988**, *29*(17), 2027-2030.

51. Okada, H.; Akaki, T.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *Tetrahedron* **2003**, *59*, 197.

52. Komatsu, M.; Okada, H.; Yokoi, S.; Minakata, S. *Tetrahedron Lett.* **2003**, *44*, 1603.

53. Komatsu, M.; Okada, H.; Akaki, T.; Oderaotoshi, Y.; Minakata, S. *Org. Lett.* **2002**, *4*, 3505.

54. Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, *4*, 3533-3535.

55. Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, *9*, 1433-1440.

56. Oishi, Masataka. Eds.: Yamamoto, Hisashi. Lewis Acids in Organic Synthesis (2000), 1 355-393. Publisher: Wiley-VCH Verlag GmbH, Weinheim, Germany.

57. Sharma, V.; Tepe, J. J. Enhancing efficacy of camptothecin using chiral imidazolines selectively in cancer cells. *J. Am. Chem. Soc.* **2004** (*in preparation*)

58. Zhou, P.; Chen B. -C.; Davis F. A. *Tetrahedron* **2004**, *60*, 8003–8030.

59. Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron Asymm.* **1999**, *10*, 2441–2495.

60. Nefzi, A.; Ostresh, J. M.; Yu, J.; Houghten R. A. *J. Org. Chem.* **2004**, *69*(11), 3603 -3609.

61. (a) Jung, S. -H.; Kohn, H. *J. Am. Chem. Soc.* **1985**, *107*, 2931. (b) Jung, S-H.; Kohn, H. *Tetrahedron Lett.* **1985**, *25*(4), 399.

62. Johnson, R. N.; Woodburn, H. M. *J. Org. Chem.* **1962**, *40*, 3958.

63. Chambers, J. J.; Kurrasch-Orbaugh, D. M.; Parker, M. A.; Nichols, D. E. *J. Med. Chem.* **2001**, *44*, 1010.

64. Johnson, M. A.; Sousa, L. R. *Synthesis.* **1978**, *43*, 317.

65. Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S. -L. *J. Org. Chem.* **1996**, *61*, 3929.

66. Perrin C. L.; Young. D. B. *J. Am. Chem. Soc.* **2001**, *123*(19), 4446-4450.

67. Xia, C.; Hao, J.; Tang, Y.; Ni, Y.; Zhou, P. *Syn. Commun.* **2002**, *32*(9), 1457-1464.

68. Chang, L. A.; Sidler, K. L.; Cascieri, M. A.; de Laszlo, S.; Koch, G.; Li, B.; MacCoss, M.; Mantlo, N.; O'keefe, A.; Pang, M.; Rolando, A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2549.

69. Slee, D. H.; Romano, S. J.; Yu, J.; Nguyen, T. U.; John, J. K.; Raheja, N. K.; Axe, F. U.; Jones, T. K.; Ripka, W. C. *J. Med. Chem.* **2001**, *44*, 2094.

70. Tasdemir, D.; Mallon, R.; Greenstein, M.; Feldberg, L. R.; Kim, S. C.; Collins, K.; Wojciechowicz, D.; Mangalindan, G. C.; Concepcion, G. P.; Harper, M. K.; Ireland, C. M. *J. Med. Chem.* **2002**, *45*, 529.

CHAPTER IV

SILVER ACETATE CATALYZED *EXO*-SELECTIVE SYNTHESIS OF Δ^1-PYRROLINES AND DERIVED PYRROLIDINES

A. Biological and chemical significance of Δ^1pyrrolines

Δ^1-pyrrolines can be found in nature as biosynthetic intermediates, and as a part of pheromones, and alkaloids, steroids, hemes and chlorophylls (Figure IV-1).[1, 2] Myosmine, amathaspiramide E, dysinosin A, broussonetine U1, solamalidine, veracintine and lanopylins are some recently isolated biologically active alkaloids which contain a pyrroline unit.[3] Moreover, these scaffolds have been shown to possess insecticidal, fungicidal, anti-viral, anti-tumor and immunoactivity. [3c, 4]

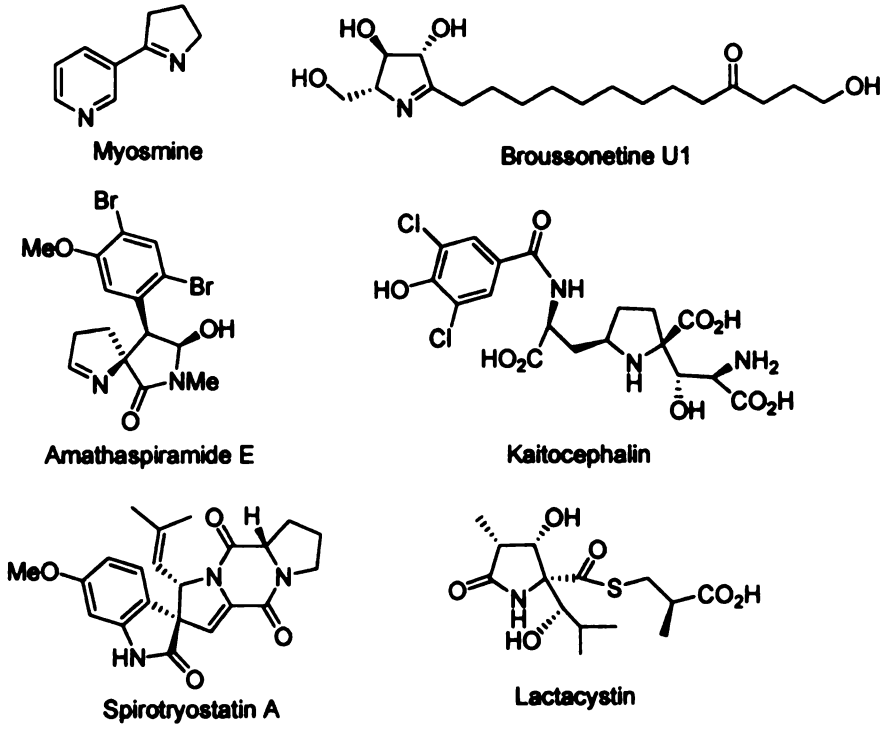


Figure IV-1. Biologically active pyrrolines and pyrrolidines

In addition to wide ranging biological activity, Δ^1-pyrrolines are important synthetic intermediates, as they have three contiguous stereocenters, and one

prochiral center as part of a cyclic imine, which is amenable to further synthetic manipulation such as addition of nucleophiles with stereocontrol.[1a, 5] Hence, they are of immense value for the synthesis of pyrrolidines and complex natural products containing highly functionalized five-membered N containing rings.[6, 7] Nitrones generated from Δ^1-pyrrolines have been employed in [3+2] cycloadditions to generate polycyclic heterocycles like pyrrolizidines, indolizidines and aza sugars.[8] Synthesis of α,α-disubstituted amino acids (especially prolines) and their analogs is a topic of intense synthetic interest because of their application in the field of peptidomimetics, catalysis and synthesis of natural products.[9] A stereoselective and efficient preparation of a general Δ^1-pyrroline template would provide rapid access to a range of biologically active natural products including the myosmines, amathaspiramides, lactacystin and kaitocephalin type alkaloids.[10]

B. Access to Δ^1-pyrrolines using münchnone-alkene cycloaddition

Although, there are some reports[11] for the synthesis of Δ^1-pyrrolines cycloaddition of münchnones to alkenes has not been fruitful as a synthetic method to access these compounds.[12,13] Extensive work by Huisgen and others has established 1,3-dipolar cycloaddition reactions of *N*-alkylated münchnones (Figure IV-2), as a general route for the syntheses of pyrroles, Δ^1-pyrrolines, azepines and imidazoles.[14] Synthesis of Δ^1-pyrrolines from intermolecular 1, 3- dipolar cycloaddition of münchnones to alkenes is fraught with following difficulties. [15] Under the conditions generally used (reflux in acetic anhydride) the reaction

cannot be controlled at the primary adduct stage as the decarboxylation of bicyclic intermediates is facile, leading to cyclic azomethine ylide/Δ^1-pyrroline.[16]

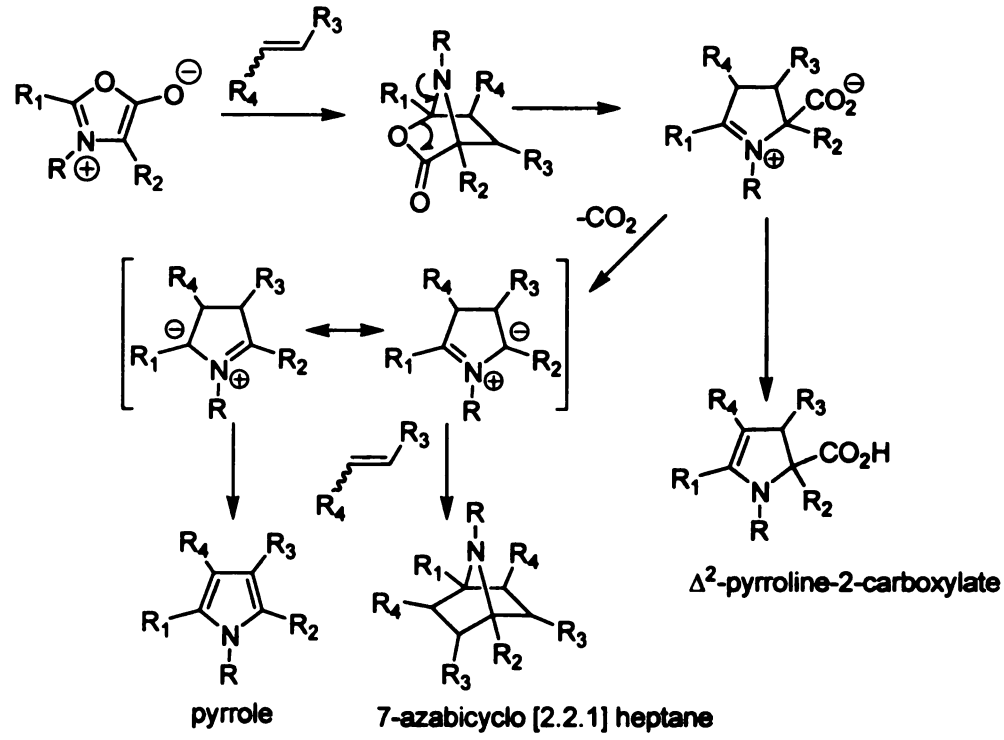


Figure IV-2. Dipolar cycloaddition reactions of *N*-alkylated münchnones

This cyclic azomethine ylide then undergoes the following transformations: [14]

1. Isomerization of double bond leads to formation of Δ^2-pyrrolines and partial loss of stereochemistry generated during cycloadditions.
2. The position of double bond in Δ^2-pyrrolines is determined by the C_3 and C_4 substituents and often results in mixture if unsymmetrically substituted. This results in complex inseparable mixtures.
3. Aromatization to pyrroles and complete loss of stereochemical information.
4. A second cycloaddition with excess alkene to afford 7-azabicyclo [2.2.1] heptane derivative.

5. α-olefins (monosubstituted alkenes) have been shown not to participate in the cycloaddition.
6. Even, if the decarboxylation is prevented when reactions are run at lower temperatures, isomerization to Δ^2-pyrrolines is inevitable.[17]

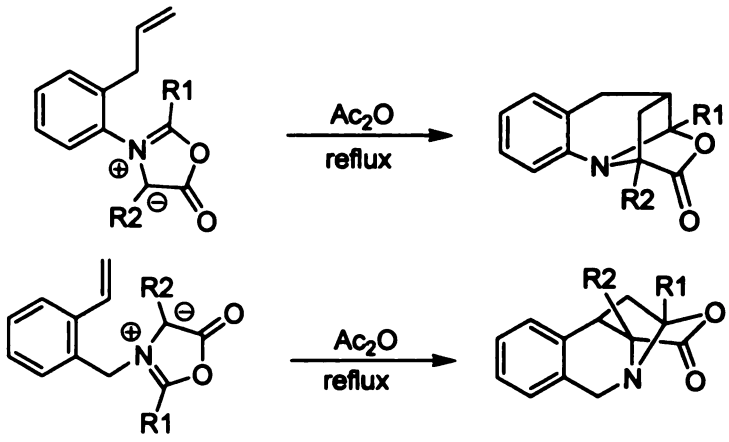


Figure IV-3. Primary cycloadducts isolated from intramolecular cycloadditions

However, Padwa and co-workers have been successful in isolating and characterizing primary adducts of intramolecular cycloadditions of münchnones to terminal alkenes (Figure IV-3).[18] Steric constraints (violation of Bredt's rule) on the transition state prevent the elimination of carbon dioxide from these cycloadducts and also result in the observed stereochemistry.

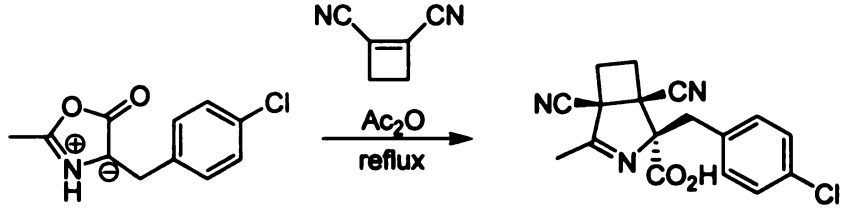
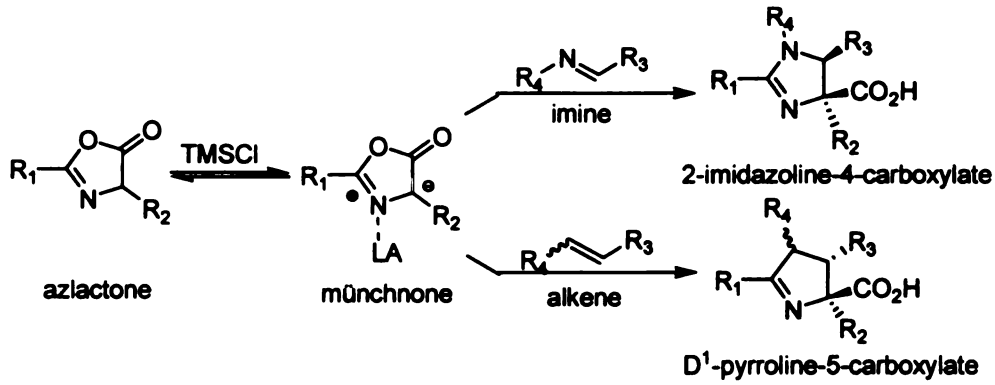


Figure IV-4. Primary cycloadducts isolated from intermolecular cycloadditions

Turchi and co-workers described the isolation of a Δ^1-pyrroline-5-carboxylic acid from the intermolecular cycloaddition of 1, 2-dicyanocyclobutene to a münchnone in refluxing acetic anhydride (Figure IV-4).[15] Decarboxylation and hydride migration are presumably prevented by structural constraints of the bicyclic product. The authors were able to decarboxylate the intermediate by thermolysis in refluxing decalin. Exclusive exo selectivity was observed in the primary cycloadduct.

C. TMSCl (Lewis acid) mediated mild protocol to Δ^1-pyrroline-5-carboxylates



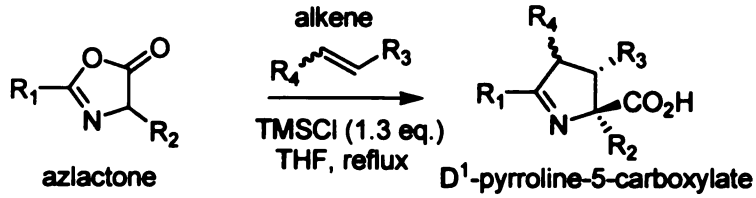
Scheme IV-1. Lewis acid mediated mild protocol to Δ^1-pyrroline-5-carboxylates

We had reported that coordination of a trimethylsilyl chloride to nitrogen atom of the azlactone, can increase the equilibrium concentration of münchnone intermediate and accelerate the cycloaddition reaction with imines (Scheme III-7).[19] Moreover, Lewis acid mediation leads to milder protocol (reflux in dichloromethane compared to acetic anhydride) and it was possible to isolate the 2-imidazoline-4-carboxylic acid without any decarboxylation to imidazole and in

excellent yields. [3+2] cycloadditions in which heterodipolarophiles are employed to intercept reactive azomethine ylides represent a useful entry into functionalized, protected amino acids.[20] In case of münchnones, dihydroheterocycles isolated are masked α, α-disubstituted (quarternary) amino acids. In case of münchnone-imine cycloadditions we obtained quarternary imidazoline-4-carboxylic acids. These scaffolds were formed with high diastereoselctivity. The scaffolds exhibit four-point diversity, are amenable to alkyl, aryl, acyl and heteroalkyl substitutions and display novel, interesting and important biological activity.[19, 21] Buoyed by our own results and the isolation of Δ^1-pyrroline-5-carboxylic acid by Maryanoff and co-workers, we decided to apply the mild TMSCl mediated condition for generation of münchnones to cycloadditions with alkenes.[15]

Azlactones were synthesized by cyclodehydration of N-acyl-α-amino acids with EDCI.HCl.[22] 2-Phenyl, 4-methyl azlactone (**II-1**) was refluxed in THF along with maleic anhydride in presence of 1.5 equivalents of TMSCl overnight. The residue after acid-base workup and extraction into ethyl acetate afforded crude product, which was shown to have pyrroline in substantial amount. We were gratified that the reaction did indeed occur, but unfortunately the product Δ^1-pyrroline could not be isolated pure (data not shown). Diethyl fumarate, after same extraction procedure resulted in a complex mixture of diastereomers of Δ^1-pyrroline-2-carboxylic acids and N-benzoylalanine (probably from unreacted azlactone). The mixture of acids was methylated with diazomethane. Column chromatography of the mixture resulted in 50 % combined yield of Δ^1-pyrrolines in a 2.5:1

diastereomeric ratio (Table IV-1, entry **IV-1-2**). Reaction of 2,4-dimethyl azlactone with t-butyl acrylate resulted in only 5 % isolated yield of diastereomer of Δ^1-pyrroline after methylation and column. Most of the N-benzoylalanine was recovered from unreacted azlactone (Table IV-1, entry **IV-1-3**). Methyl acrylate only resulted in 25 % yield of Δ^1-pyrroline-2-carboxylic acid, which was directly precipitated from the crude product using a mixture of ether and methanol. It is evident that the conversion of azlactone to product is not complete in THF for the reaction times and temperature, which were used. Moreover alpha olefins, which are reported not to react with münchnones, seem to be poor dipolarophiles. It also occurred to us that TMSCl might not be the ideal Lewis acid for this reaction.



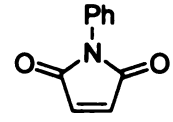
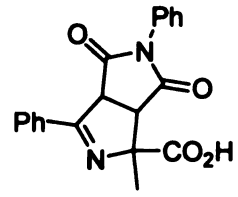
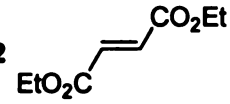
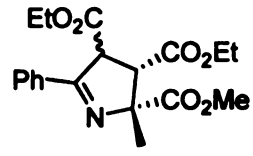
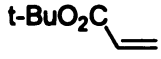
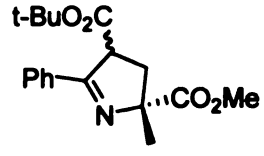
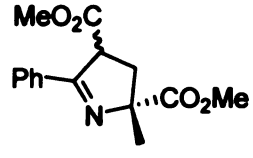
entry	alkene	% yield	product
IV-1-1		–	
IV-1-2		50 %	
IV-1-3		8 %	
IV-1-4		27%	

Table IV-1. TMSCl mediated synthesis of Δ^1-pyrroline.

Several manipulations of reaction conditions with respect to solvent, time of reaction and stoichiometry of alkene used were tried, without any success (data not shown). This led us to search for a different Lewis acid. Related to our work, Komatsu and co-workers had described *in situ* generation of *N*-silylated azomethine ylides carrying an alkoxy substituent by treatment of α-silylimidates with trifluorophenyl silane.[23] The resulting azomethine ylide is a nitrile ylide equivalent as it eliminates the alkoxy group after cycloaddition to alkenes, to afford Δ^1-pyrrolines in good yields (Figure IV-5). Although the configuration of

starting alkene (*cis-* or *trans-*) is retained in the cycloadditions, no diastereoselctivity was observed. This is presumably because of the interconversion of syn and anti forms of the dipole as is well known for acyclic systems.[7n]

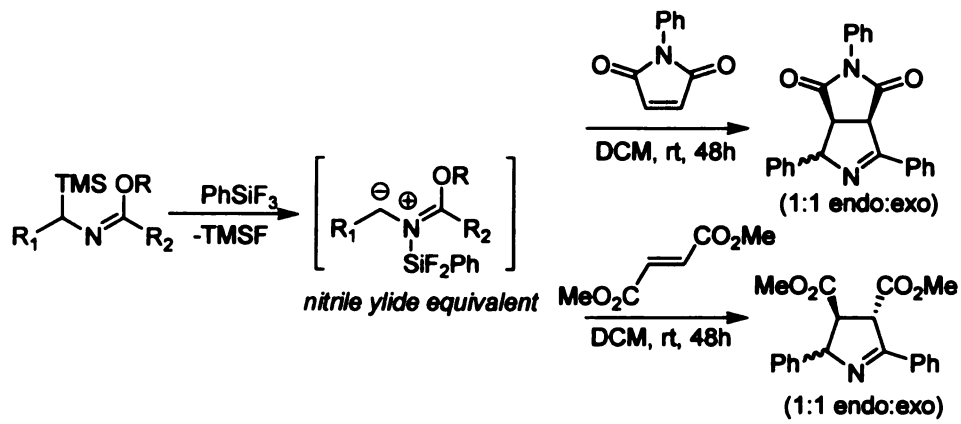
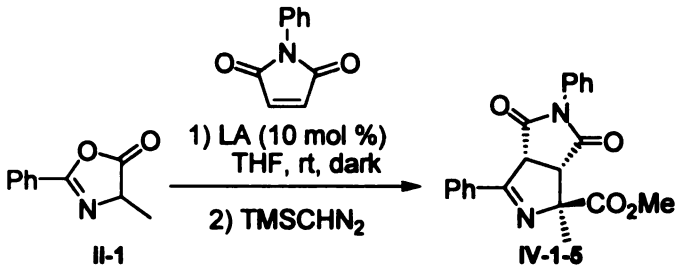


Figure IV-5. Azomethine generation by N-silylation.

D. Screening of additional Lewis acid for synthesis of Δ^1-pyrrolines

After screening a variety of Lewis acids we found that silver (I) acetate successfully catalyzed the cycloaddition reaction of 2-phenyl-4-methyl azlactone with N-phenyl maleimide generating the bicyclic Δ^1-pyrroline in excellent yield without isomerization to the Δ^2-pyrrolines or decarboxylation (Table IV-2).[8, 13] The Δ^1-pyrroline was isolated as methyl ester by *in situ* methylation with excess trimethylsilyl diazomethane. It was surprising to note that neither TMSCl nor TMSOAc resulted in any cycloadditions product. Both Cu (I) and Cu (II) both did catalyze the cycloadditions but Cu (I) definitely resulted in cleaner reaction and higher yields. The role of the counter anion seems to be important to favor equilibration to the *N*-metallated münchnone. Komatsu had concluded that the

exact number of fluorine ligands were important in their work with *N*-silylated azomethine ylides (Figure IV-5).[23]



entry	LA	% yield
1	$AgOAc^{\$}$	78
2	CuOAc	50
3	$Cu(OAc)_2$	30
4	$TMSCl^{*}$	0
5	$MgBr_2.Et_2O$	0
6	$Yb(OTf)_3^{\#}$	0
7	$ZnCl_2$	0
8	LiCl	0

$ No significant pyrrole fomation was detected;
*TMSCl was used in 1.3 eq.;
Yb(OTf)3 resulted in polymerization

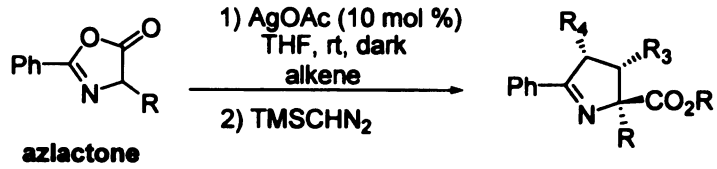
Table IV-2. Lewis acid screen for synthesis of Δ^1pyrrolines.

Grigg *et al* have recently reported[24] highly efficient synthesis of Δ^2pyrrolines from glycine derived isocyanate esters and alkenes using silver acetate as Lewis acid. The use of acetate has been suggested to arise from specific need to have a mild base like acetate ion to deprotonate α-position of the isocyanate ester to generate a highly reactive azomethine ylide for the 1, 3-dipolar cycloaddition. The products isolated, Δ^2-pyrrolines were obtained by *in situ* hydride migration of Δ^1-pyrrolines. Hydride migration was either blocked only by α-substitution of the isocyanoacetate or by constraining the β-position to the iminic N in the Δ^1-

pyrrolines. It is important to note that a mixture of diastereomers was seen, again highlighting the difficulty of achieving complete diastereocontrol because of equilibration between *syn* and *anti*-dipole geometry.[7n]

E. Diversity in AgOAc catalyzed synthesis of Δ^1-pyrroline-5-carboxylates

The cycloaddition reactions proceed well with electron deficient alkenes and 10 mol % silver acetate in THF at room temperature to provide the highly substituted Δ^1-pyrrolines, often in good yields. Only the *exo* adducts of the Δ^1-pyrrolines were observed with *cis*-olefins as determined by NOE experiments and X-ray crystallography (Figure IV-6 and Table IV-3).



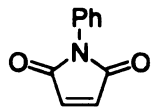
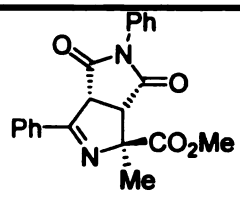
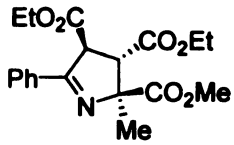
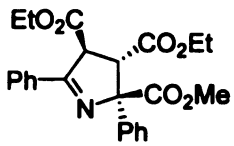
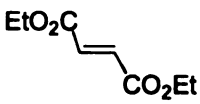
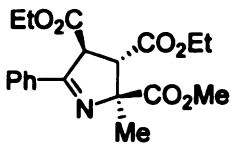
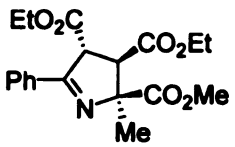
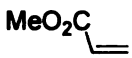
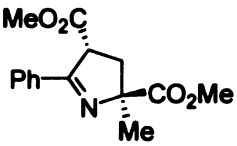
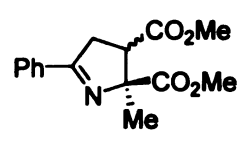
Entry	R	alkene	% yield (a:b)	Δ¹-pyrroline a	Δ¹-pyrroline b
1	Me		78	 IV-1-5	
2	Me		75	 IV-1-6	
3	Ph		15	 IV-2-6	
4	Me		75 (2:1)	 IV-1-7a	 IV-1-7b
5	Me		95 (1:1)	 IV-1-8a	 IV-1-8b

Table IV-3. Cycloaddition of various alkenes

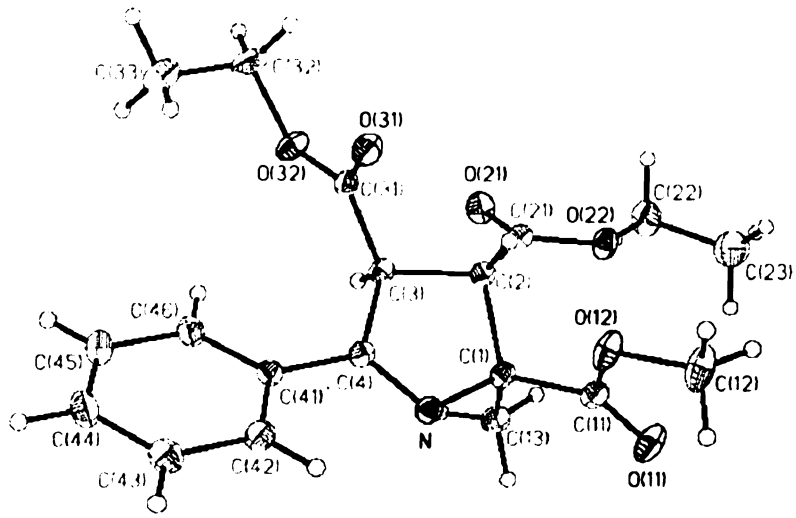
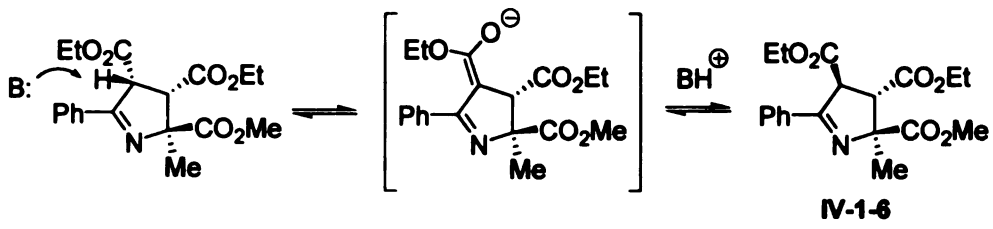


Figure IV- 6. X-ray crystal structure of **IV-1-6**.

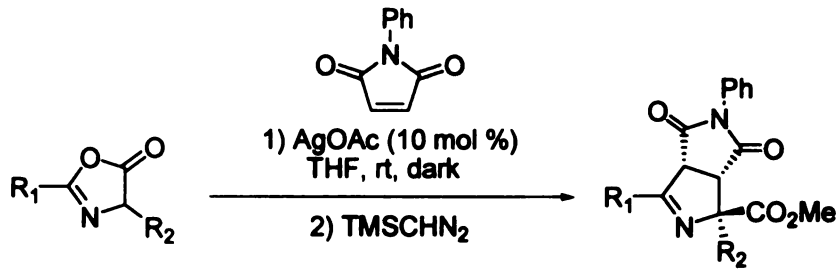
Alkenes (R_3 and R_4 substituents).

Electron deficient *cis*-alkenes (*N*-phenylmaleimide and diethyl maleate) as well as *trans* alkene (diethyl fumarate) resulted in very high yields for Δ^1-pyrrolines (entries **1, 2** and **4,** Table IV-3). However, *trans*-diethyl fumarate resulted in 2:1 ratio of *exo/endo*-diastereomers (entry **4**, Table IV-3). Diethylfumarate and diethylmaleate provided both a 3, 4-*trans* relationship of the ethoxycarbonyl groups. This is likely the result of the isomerization (Scheme IV-2) of the *cis*-substituted Δ^1-pyrroline to the thermodynamically more stable *trans*-product (entries **2** versus **4**, Table IV-3). This is in accordance with previous observation by other researchers.[14]



Scheme IV-2. Isomerization of *cis* Δ^1-pyrroline to *trans* Δ^1-pyrroline.

A main highlight is that, monosubstituted alkenes (methyl acryalate) which were previously not known to participate in intermolecular cycloadditions of münchnones also afforded very high yield for the Δ^1-pyrroline products.[18] The lack of regioselectivity is consistent with reported literature on intermolecular cycloadditions of münchnones with monosubstituted dipolarophiles.[26] Efforts to introduce alkyl or aryl substituents in 4-position with crotonic or cinnamic esters were not successful (entries **IV-2-5** and **IV-13-5**, Table IV-4). Electron rich alkenes such as vinyl trifluoroacetate (entry **IV-3-5**, Table IV-4) were also unreactive in the cycloaddition with münchnones in accordance with the Sustmann classification for these dipoles.[27]



entry	azlactone R_1	azlactone R_2	% yield
IV-2-5	Ph	Ph	0
IV-13-5	Ph	Bn	67
IV-3-5	Ph	3-indolylmethyl	70
IV-5-5	Me	Me	59
IV-9-5	Bn	Me	75

Table IV-4. Variation of substituents at C_2 and C_5 in Δ^1-pyrrolines.

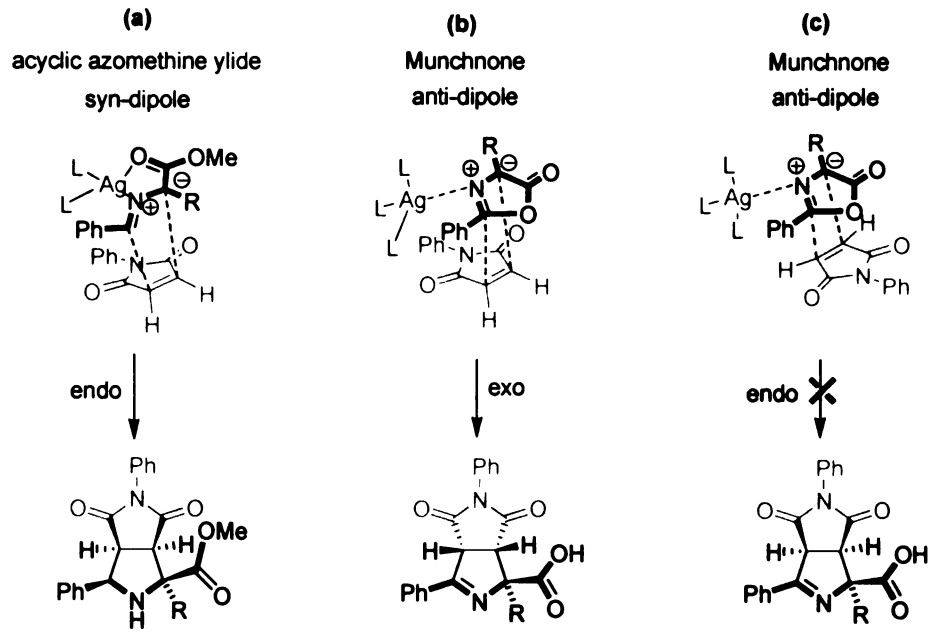
Amino Acids and acid chlorides (R_2 and R_1 substituents).

Very good yields were obtained with benzyl and indolylmethyl substituted azlactones (entries **IV-13-5** and **IV-3-5**, Table IV-4). The phenyl glycine derived azlactone reacted with diethyl maleate to afford the Δ^1-pyrroline in a modest 15% yield (entry **IV-2-5**, Table IV-4) and was unreactive towards maleimide. The 2-position on Δ^1-pyrroline scaffold is also amenable to different substituents including the 2-methyl and 2-benzyl (entries **IV-5-5**, and **IV-5-5**, Table IV-4).

F. Probable origin of diastereoselectivity

Only the *exo* adducts of the Δ^1-pyrrolines were observed as major products determined by NOE experiments and X-ray crystallography (Figure IV-6). The *exo*-preference is in contrast to the *endo*-preference observed in the synthesis of pyrrolidines from acyclic azomethine ylides.[28,29,30] A notable exception to this is the ligand induced *exo*-selectivity described by Komatsu.[31] The *exo*-selectivity

observed by Padwa was reported to reflect the influence of steric factors in a unimolecular transition state of an intramolecular cycloaddition.[32]



Scheme IV-3. (a) proposed *syn*-dipole orientation for acyclic azomethine ylides derived from imines of α-amino acid esters; **(b)** munchnöne (cyclic azomethine ylide) locked as an *anti*-dipole. Orientation of alkene is same and differing outcome from **(a)** and **(b)** could be a result of different dipole geometry.

Acyclic azomethine ylides derived from α-iminoesters have been proposed to adopt a preferred *syn* orientation in presence of Lewis acids due to chelation with the carboxyl oxygen.[28, 29, 30] With silver (I) Lewis acids the inter-conversion to the anti-orientation is minimum and hence the cycloadditions are highly *endo* selective.[7n] The münchnones are azomethine ylides locked in *anti*-orientation. This could be a possible basis for obtaining the opposite *exo* diastereoselectivity in the resulting product for the same orientation of alkene (Scheme IV-3).

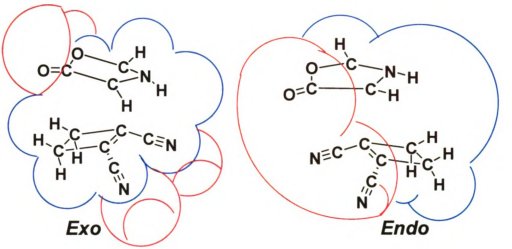


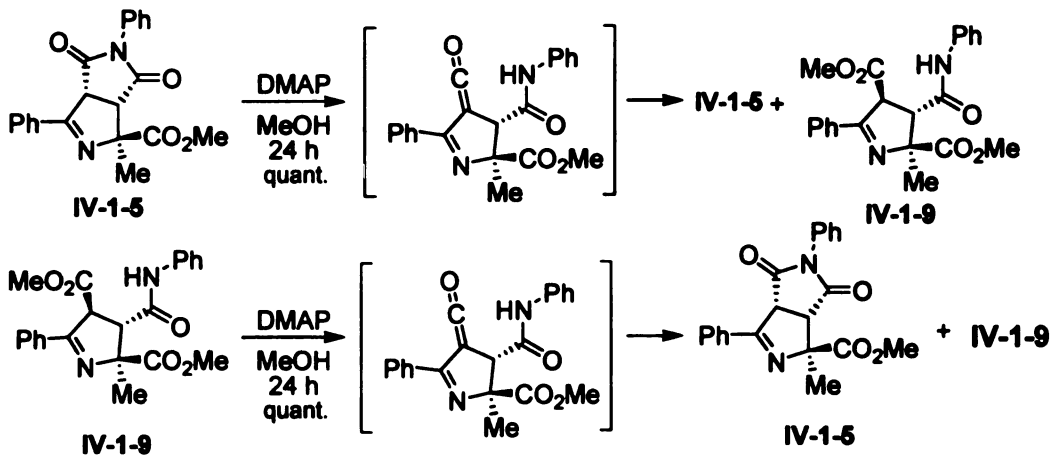
Figure IV-7. Calculated electrostatic isopotential surfaces for *exo*- and *endo*-approach of dicyanocyclobutene[33]

Turchi and co-workers have carried out extensive MO calculations to rationalize the stereochemical outcome.[33] AM1 calculations for additions of 1, 2-dicyanocyclobutene to münchnones indicated that the cycloaddition is a concerted but nonsynchronous process. Semi-empirical calculations (FMO) have not been successful in explaining regiochemical and stereochemical outcome of cycloadditions of münchnones. Electronic effects were suggested to play a dominant role in favouring the *exo*-product in intermolecular cycloaddition reaction.[33] Inspection of electrostatic isopotential surfaces revealed that the *exo* transition state shows attractive stabilizing interaction between the CH-NH-CH portion of dipole and the nitrile groups. In fact, it was found that the exo-adduct is also electrostatically favoured over the *endo*-adduct. This may provide a rationale for the formation of the *exo*-cycloadduct with this *in situ* generated münchnone-alkene cycloaddition reaction. *endo* transition state for reaction with munchnöne is proposed to be disfavoured due to repulsive destabilizing interactions between

O-C=O region of munchnöne and the carbonyls of *N*-phenyl maleimide (anti-orientation of carbonyl dipoles expected to be more stable).[25]

G. Expanding the diversity of Δ^1pyrroline templates[25]

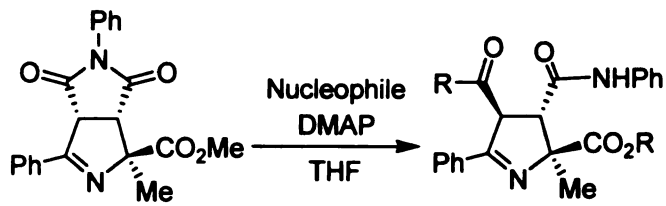
During isolation the bicyclic *cis* Δ^1-pyrroline-5-carboxylate by methylation using trimethyl diazomethane in protic solvents like methanol, we observed isomerization and equilibration to the thermodynamically more stable ring opened *trans* product. Of the various bases screened to convert **IV-1-5** to **IV-1-9**, DMAP resulted in clean conversion and afforded a 50:50 mixture of **IV-1-5** and **IV-1-9** in quantitative yields. Treatment of the isolated 3, 4-*trans* Δ^1- pyrroline methyl ester (**IV-1-9**) with DMAP in methanol reestablished the 1:1 ratio of **IV-1-5** and **IV-1-9**, indicating that the interconversion of **IV-1-5** and **IV-1-9** most likely proceeds via a common ring opened ketene intermediate (Scheme IV- 4).



Scheme IV-4. Ring opening and isomerization of cycloadducts.

We were successful in selectively trapping the ketene intermediate with benzylamine to afford the *trans* amide in good yield (entry **IV-1-10**, Scheme IV-

5). This selective ring-opening reaction provides an opportunity to expand on the stereochemical diversity of the scaffolds.



Entry	Nucleophile	R	% Yield
IV-1-9	MeOH	OMe	50 %
IV-1-10	NH_2Bn	NHBn	76 %

Scheme IV-5. Ring opening with different nucleophiles

Thus, we have developed a highly diastereoselective and efficient synthesis of Δ^1-pyrroline-5-carboxylic acid scaffolds via a Ag-(I) catalyzed generation of münchnones and subsequent [3+2] cycloaddition to alkenes. The *exo*-selectivity complements the endo-selective cycloaddition of related acyclic azomethine ylides very well. Diastereocontrol can be extended to the three stereocenters by appropriate choice of substrates and isolation conditions.

H. Synthesis of pyrrolidines and DOS

As a continuing theme of developing new diversity oriented synthetic methods for small molecule scaffolds with potential biological activity, we focused on developing stereoselective synthesis for novel Δ^1-pyrrolines and pyrrolidines derived from them. Stereochemical diversity is desirable as it increases the number of relative orientations of potential macromolecule-interacting elements in small molecules. It can best be achieved by using stereospecific reactions that proceed with enantio- or diastereoselectivity.

The dipolar cycloadditions of an azomethine ylide to an alkene is a very useful synthetic method for the synthesis of pyrrolidines. Two carbon-carbon bonds are formed in a single operation, usually with a a high degree of regioselectivity, while upto four new stereocenters are created, often in a highly stereoselective manner. Therefore, this method is of considerable interest in DOS because its stereospecificity enables stereochemical diversification of up to four tetrahedral centers on pyrrolidine rings.[30, 33] Achieving diastereoselectivity and enantionselectivity in this reaction has hence attracted intense scientific investigation.

I. Importance of diastereoselective diversity-generating pyrrolidine syntheses

Since diversity-generating processes[34] involve the transformation of a collection of substrates into a collection of products, it is critical that the processes used to generate new stereogenic centers be both selective and general. Greater stereochemical diversity requires powerful reagents that can override substrate bias and deliver diastereomeric products with very high selectivity. Double-diastereoselective reagents that can override the face selectivity of both coupling partners, for example, to achieve *exo* versus *endo* selectivity are highly desirable and the discovery of these types of powerful reagents is critical to achieving stereochemical diversity in DOS.[34]

Although established methods for azomethine ylide generation have proven to be both general and efficient, new procedures are constantly being divulged. These new methods are not only for ylide generation, but are also for new chemical

equivalents and by careful selection; the synthetic chemist has a wealth of technologies available at his disposal.

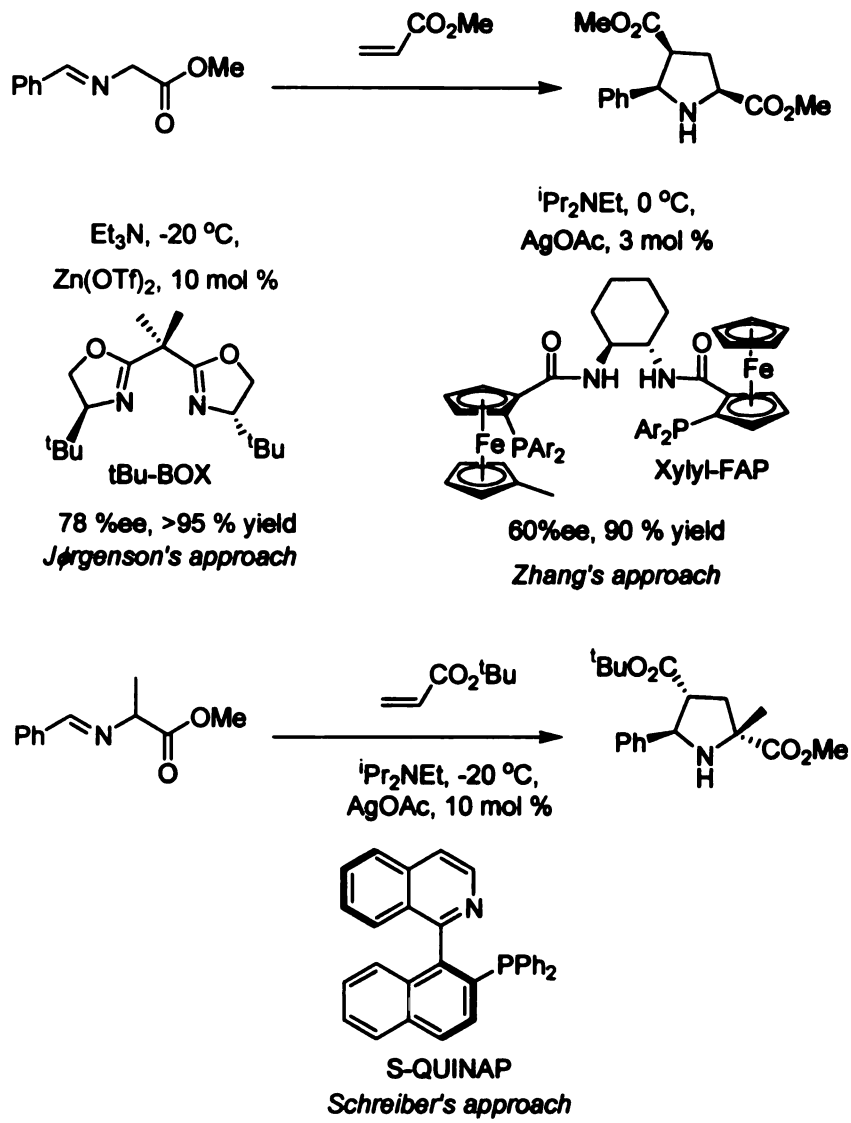


Figure IV- 8. Synthesis of pyrrolidines from α-iminoesters.

However, most 1, 3-dipolar cycloadditions of azomethine ylides catalyzed by chiral metal complexes have shown only *endo*-selectivity. Because it is important that any of the desired diastereomers of cycloadducts can be synthesized selectively, a study of methods of achieving *exo*-selectivity has attracted attention of researchers in recent times.[31]

Among the different versions of this reaction, the most practical approach has been the interaction between stabilized *N*-metalated azomethine ylides derived from α-imino glycinate esters and π-deficient alkenes (Figure IV- 8). The reaction proceeds under mild conditions and with a high degree of diastereocontrol. Silver (I) and lithium (I) metal cations (usually stoichiometric amounts) are most commonly used along with an excess of tertiary amine base. Enantiocontrol has recently been extended to this reaction raising its stock for the generation of complex heterocyclic molecules. While Jorgensen *et al*[29] used chiral oxazoline complexes of Zn, Zhang and co-workers[28] employed Ag (I) complex with FAP ligands for above cycloadditions. Schreiber and co-workers further improved on Zhang's protocol by expanding the substrate scope and increasing the enantioselectivities achieved by employing the QUINAP ligand.[30] An important highlight of their work is that they were able to generate quartenary stereogenic centers by employing substituted amino acids.

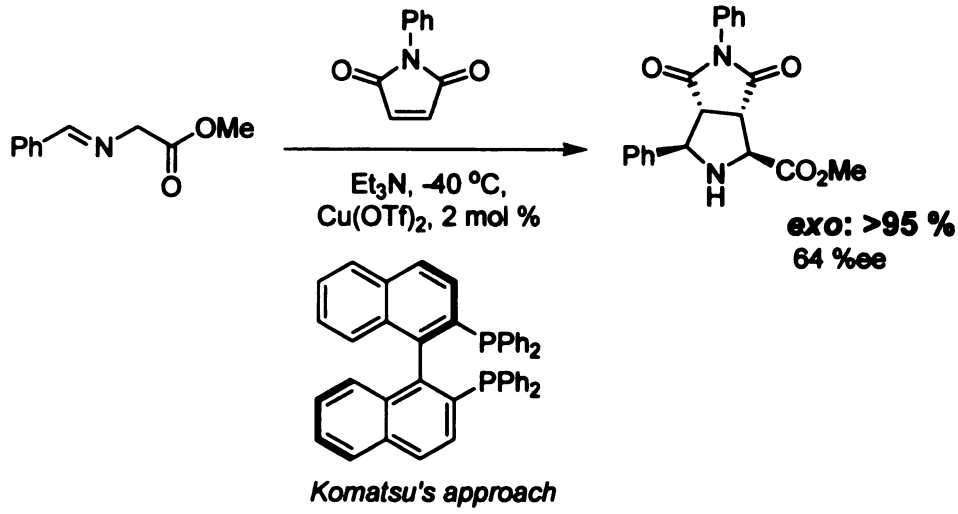


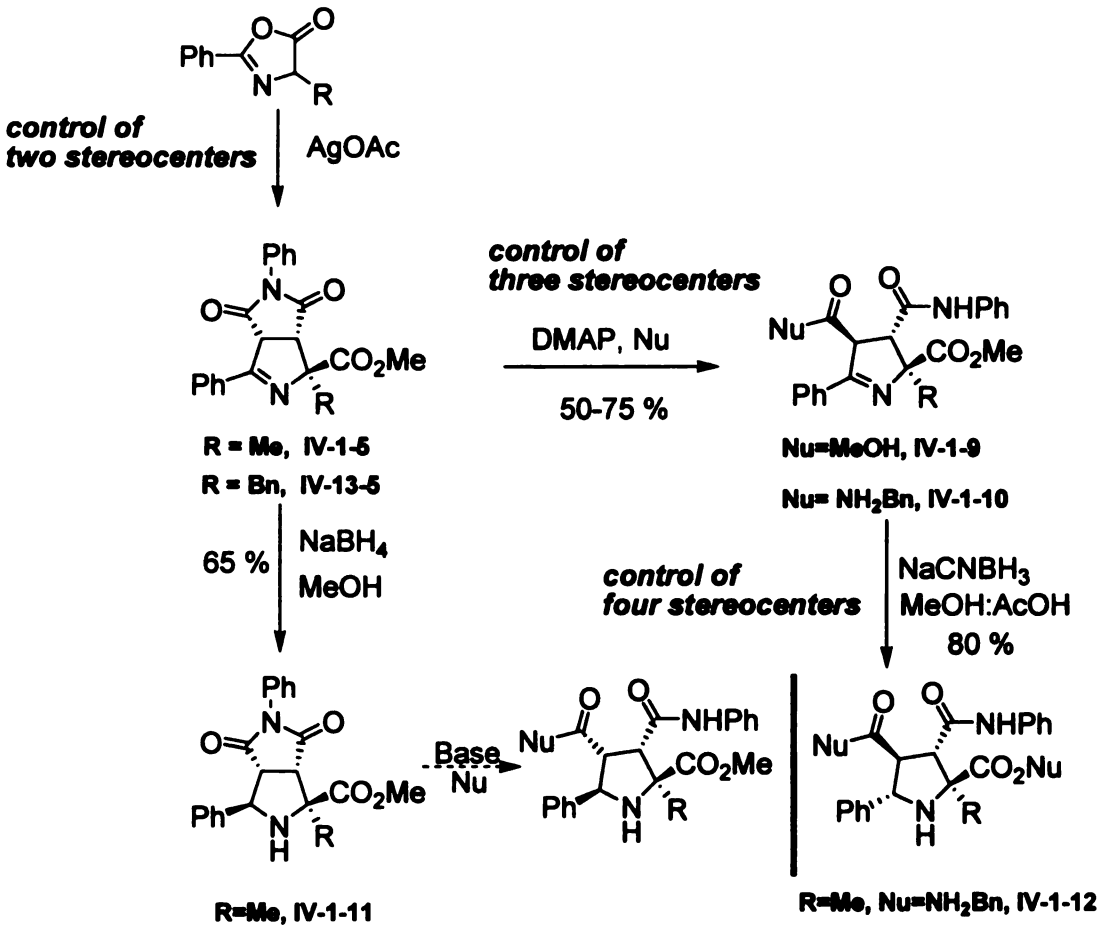
Figure IV-9. *Exo* selectivity tuned using bulky phosphine ligands

Recently, the normal *endo* selectivity of the above cycloadditions has been reversed by Komatsu *et al* by a opportune selection of bulky phosphine ligands in the cycloadditions of N-substituted maleimides and α-imino glycinate (Figure IV-9).[31] Reversing the diastereoselectivity which is under substrate control by using external reagents (Lewis acids) is highly desirable in a diversity oriented synthesis program.[34]

J. Extension of diastereocontrol and synthesis of *exo* pyrrolidines

Our ultimate aim to develop stereoselective methodology for Δ^1-pyrrolines was to diversify these templates to other heterocycles.[6, 7, 8, 9] Foremost among these aims, was reduction to pyrrolidines. α, α-disubstituted α-amino acids like lactacystin (proteosome inhibitor), kaitocephalin (Glutamate receptor antagonist), dysibetaine (glutamate agonist) have generated considerable interest due to their biological activities.[10]

Unusual regioselection and stereochemical outcome resulted in the reaction of these Δ^1-pyrroline scaffolds (having competing electrophilic centers) with various nucleophiles.[35] By a judicious choice of conditions we are able to extend diastereocontrol to all four centers of these scaffolds (Scheme IV-6).



Scheme IV-6. Extension of diastereocontrol to all four centers of Δ^1-pyrroline.

Thus, bicyclic Δ^1-pyrroline (*exo*, 3, 4-*cis*) on treatment with DMAP and nucleophiles (MeOH) resulted in ring opened Δ^1-pyrroline **IV-1-9** (*exo*, 3, 4-*trans*). Reduction of bicyclic Δ^1-pyrroline with $NaBH_4$ in MeOH resulted in bicyclic pyrrolidine **IV-1-11**(*exo*, 3, 4-*cis*, 2, 3-*trans*). Surprisingly, reduction of ring opened Δ^1-pyrroline with $NaBH_4$/ MeOH resulted in reduction of the 5-

carboxylic acid (appendage diversity; data not shown). After generation of iminium ion in 1:1 acetic acid/MeOH was facile with $NaCNBH_3$ and led to monocyclic pyrrolidine **IV-1-12** (*exo*, 2, 3, 4-all *trans*) diastereomer. Ring opening of bicyclic pyrrolidine was attempted under various conditions to obtain ring opened pyrrolidine (*exo*, 3, 4-*trans*, 2, 3-*cis*) without success. All the above structures have been corroborated with X-ray crystallographic data (Fig. IV-10).

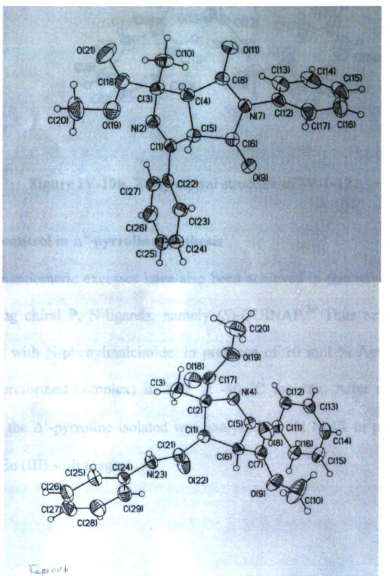


Figure IV-10a. X-ray crystal structure of *TOP*: **IV-1-5**, *BOTTOM*: **IV-1-9**

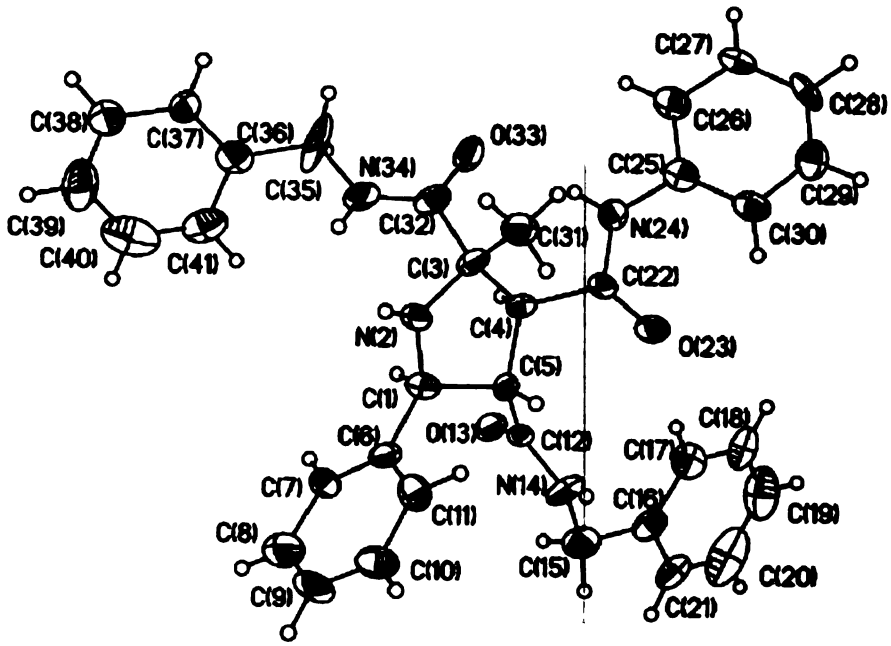
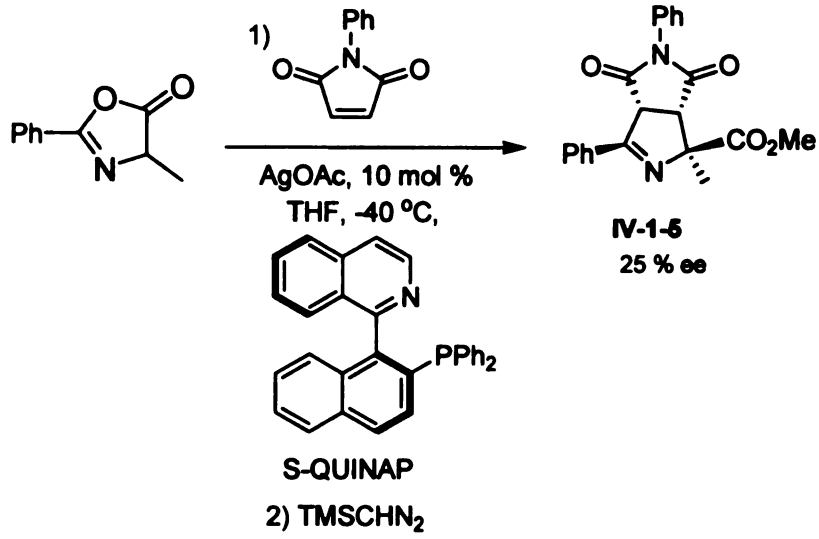


Figure IV-10b. X-ray crystal structure of **IV-1-12.**

K. Enantiocontrol in Δ^1-pyrroline synthesis

Moderate enantiomeric excesses have also been achieved in this silver catalyzed process using chiral P, N-ligands, namely (*S*)-QUINAP.[30] Thus azlactone **II-1** was reacted with N-phenylmaleimide, in presence of 10 mol % AgOAc and S-QUINAP (preformed complex) in THF at -40 °C for 48h. After methylation, purification the Δ^1-pyrroline isolated was analyzed by ^{1}H NMR in presence and absence of Eu (III) shift reagent.



Scheme IV-7. Asymmetric synthesis Δ^1-pyrroline

The enantiomeric excess estimated from the chemical shift was 25 %. Achieving practically useful enantioselectivity will be actively pursued in near future.

L. Experimental Section

Reactions were carried out in flame-dried glassware under nitrogen or argon atmosphere, unless otherwise noted. Commercial solvents and reagents were used as received. Anhydrous solvents were dispensed from a delivery system which passes the solvents through packed columns (tetrahydrofuran, methylene chloride: dry neutral alumina). All reactions were magnetically stirred and monitored by TLC with 0.25 μm pre-coated silica gel plates and column chromatography was carried out on Silica Gel 60 (230–400mesh) supplied by EM Science. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were determined on a Mel-Temp (Laboratory devices) apparatus with a microscope attachment. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-300 spectrometer, Varian VXR-500 spectrometer and Unity+-500

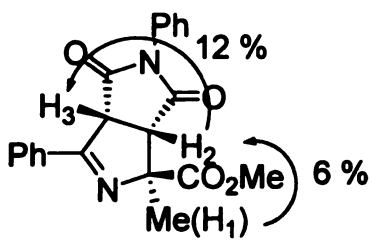
spectrometer. Chemical shifts are reported relative to the residue peaks of the solvent $CDCl_3$ (7.24 ppm for ^1H and 77.0 ppm for ^{13}C). HRMS were obtained at the Mass Spectrometry Facility of the Michigan State University with a JEOL JMS HX-110 mass spectrometer. Gas chromatography/ low resolution mass spectra were recorded on a Hewlet–Packard 5890 Series II gas chromatograph connected to a TRIO-1 EI mass spectrometer. Combustion analysis was carried out on Perkin Elmer Series II 2400 CHNS/O Analyzer.

General Procedure

1) Method A.

Synthesis of Δ^1-Pyrroline-2-carboxylic acid methyl ester: A solution of azlactone (1mmol), AgOAc (0.1 mmol) and alkene (2 to 3 mmol) in dry THF (50 mL) was stirred under argon in a flame-dried flask in dark for the requisite amount of time as monitored by TLC. Excess trimethylsilyl diazomethane was added and the mixture was stirred for 2 h. Completion of esterification was monitored by TLC (20 % MeOH / EtOAc). The solvent was removed under vacuum and residue was chromatographed on silica gel with an ether / hexanes mixture to isolate Δ^1-pyrroline-2-carboxylic acid methyl esters.

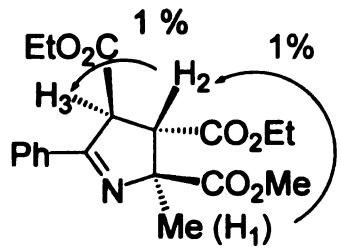
1,3a,4,5,6,6a-hexahydro-1-methyl-4,6-dioxo-3,5-diphenylpyrrolo[3,4-c]pyrrole-1-carboxylate methyl ester (IV-1-5):



According to general procedure using 4-methyl-2-phenyloxazol-5(4H)-one (0.4g, 2.28 mmol), AgOAc (0.038g, 0.228 mmol) and N-

phenylmaleimide (0.474g, 2.74 mmol) at room temperature for 48 h and methylation with excess trimethylsilyl diazomethane, 0.62 g of pyrroline **IV-1-5** was obtained (75 % yield) as a white solid after silica gel column chromatography (45 % ether / hexanes). ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.75 (s, 3H), 3.81 (s, 3H), 4.35 (d, J = 9 Hz, 1H), 4.91 (d, J = 9 Hz, 1H), 7.21-7.22 (m, 2H), 7.36-7.37 (m, 1H), 7.41-7.42 (m, 4H), 7.44-7.45 (m, 1H), 8.16-8.18 (m, 2H); NOESY1D: (H1 -> H2) 6 %, (H1 -> H3) 1 %, (H2 -> H3) 12 % , (H3 -> H2) 10 % (see X-ray data; crystallized from dichloromethane /octane); ^{13}C NMR + **DEPT** (125MHz) $CDCl_3$: 22.16 (-CH3), 50.30 (-CH), 53.62 (1–CO2CH3), 57.61 (-CH), 82.14 (quaternary C), 126.58, 128.65, 129.13, 129.42, 130.16, 132.17 (aromatic CH), 131.59, 131.66 (aromatic quaternary 1C), 167.08, 171.58, 172.90, 173.73; (IR (cm^{-1}): 3070, 1780.5, 1718, 1614; M. P. = 186-188 °C. HRMS (FAB): *m/z* calcd for $C_{21}H_{18}N_2O_4$ [M + H], 363.1345; found, 363.1348.; Anal Calcd. for C $_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.06; H, 4.98; N, 7.56.

3,4-diethyl 2-methyl 3,4-dihydro-2-methyl-5-phenyl-2H-pyrrole-2,3,4-tricarboxylate (IV-1-6): According to general procedure using 4-methyl-2-phenyloxazol-5(4H)-one (0.2g, 1.14 mmol), AgOAc (0.019g, 0.114 mmol) and diethyl maleate (0.37ml, 2.28 mmol) at room temperature for 48 h and methylation with excess trimethylsilyl diazomethane, 0.31 g of pyrroline **IV-1-6** was obtained (75 % yield) as a white solid after silica gel column chromatography (30 % ether / hexanes). ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.1 (t, J = 7 Hz, 3H), 1.27-1.29 (m, 3H), 1.48 (s, 3H),

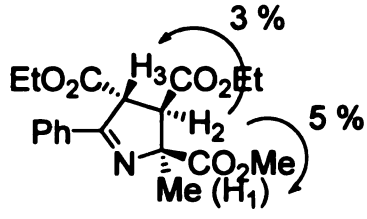


3.82 (d, J = 1 Hz, 3H), 4.04-4.12 (m, 2H), 4.16-4.26 (m, 3H), 4.73 (d, J = 6.5 Hz), 7.38 (t, J = 7 Hz, 2H), 7.43 (t, J = 6.5 Hz, 1H), 7.82 (d, J = 8Hz, 2H); NOESY1D: (H1 -> H2) 1 %; (H2 -> H3) 1 %;(H1 -> H3) 1 % (see X-ray crystallographic data; crystallized from ether); ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 13.73 (-CO2CH3) 14.06 (-CO2CH3) 20.61 (-CH3), 52.85 (–CO2CH3), 53.94 (-CH), 56.80 (-CH), 61.37 (-CH2), 61.56 (-CH2), 80.51 (quaternary 1C), 128.13, 128.27, 131.12 (aromatic CH), 132.51 (aromatic quaternary 1C), 169.13, 169.89, 170.39, 172.73 (IR (cm^{-1}): 2853, 1738.2, 1622.3; M. P. = 100-103 °C; HRMS (FAB): *m/z* calcd for $C_{19}H_{23}NO_6$ [M + H], 362.1604; found, 362.1602; Anal Calcd. For $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88. Found: C, 62.99; H, 6.37; N, 3.89.

3,4-Diethyl 2-methyl 3,4-dihydro-2,5-diphenyl-2H-pyrrole-2,3,4-tricarboxylate (IV-2-6) According to general procedure using 4-methyl-2-phenyloxazol-5(4H)-one (0.2g, 0.84 mmol), AgOAc (0.014g, 0.084 mmol) and diethyl maleate (0.273ml, 2.28 mmol) at room temperature for 60 h and methylation with excess trimethylsilyl diazomethane, 0.053 g of pyrroline **IV-2-6** was obtained (15 % yield) as a yellow oil after silica gel column chromatography (30 % ether / hexanes) which solidified in ether as a low melting pale yellow solid. ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.19-1.23 (m, 6H), 3.46 (d, J = 8.5 Hz, 1H), 4.1-4.16 (m, 2H), 4.2-4.3 (m, 5H), 3.53 (d, J = 8.5 Hz, 1H), 7.27-7.31 (m, 1H), 7.32-7.46 (m, 7H), 7.92 -7.8 (m, 2H); NOESY1D: (H1 -> H2) 2 %; ^{13}C NMR + **DEPT** (125MHz) $CDCl_3$: δ 13.83 (-CO2CH3), 14.05 (-CO2CH3), 61.33 (-CH2), 63.40

(-CH2), 65.90 (-COOCH3), 73.08 (-CH), 89.17 (quaternary 1C), 127.37, 127.67, 128.12, 128.47, 128.55, 131.05 (aromatic CH), 132.65, 141.88 (aromatic quaternary 1C), 168.85, 169.67, 171.99; (IR (cm^{-1}):2853, 1734.2, 1618.5; M. P. = 58-60 ° C; LRMS (EI): *m/z* calcd for $C_{24}H_{25}NO_6$ [M –CO2], 363.2; found, 363.3. Anal calcd. for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31. Found: C, 69.36; H, 6.17; N, 3.34;

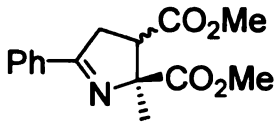
3,4-Diethyl-2-methyl-3,4-dihydro-2-methyl-5-phenyl-2H-pyrrole-2,3,4 tricarboxylate (IV-1-7b) According to general procedure using 4-methyl-2-phenyloxazol-5(4H)-one (0.2g, 1.14 mmol), AgOAc (0.019g, 0.114 mmol) and diethyl fumarate (0.37 mL, 2.28 mmol.) at room temperature for 48 h and methylation with excess trimethylsilyl diazomethane, 0.216 g (50 % yield) of **(IV-1-7a) / 2)** was obtained as a white solid after silica gel column chromatography (30 % ether / hexanes). 0.108 g of pyrroline **(IV-1-7b)** was obtained (25 % yield) colourless viscous liquid in later fractions. ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.13 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.86 (s, 3H), 3.52 (d, *J* = 9 Hz, 1H), 3.62 (s, 3H), 4.08-4.18 (m, 4H), 4.86 (d, *J* = 9 Hz, 1H), 7.34-7.43 (m, 3H), 7.79-7.82 (m, 2H); NOESY1D: (H2 -> H1) 5 %; (H2 -> H3) 3 %;(H3 -> H2) 2.5 %; ^{13}C NMR + **DEPT** (125MHz) $CDCl_3$: 14.11 (-CO2CH2CH3), 14.25 (-CO2CH2CH3), 25.42 (-CH3), 52.68 (-CO2CH3), 58.51 (-CO2CH2CH3), 58.74 (-CO2CH2CH3), 61.62 (-CH), 61.90 (-CH), 81.80 (-quaternary C), 128.03, 128.32, 131.17 (aromatic CH) 132.72



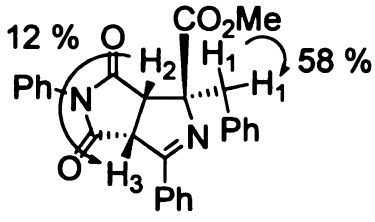
(aromatic quaternary **C**), 170.12, 170.8, 171.0, 171.5; HRMS (FAB): *m/z* calcd for $C_{19}H_{23}NO_6$ [M+H] = 361.1604 and found [M+H] = 361.1606.

Dimethyl 3,4-dihydro-2-methyl-5-phenyl-2H-pyrrole-2,4-dicarboxylate (IV-1-8a): According to general procedure using 4-methyl-2-phenyloxazol-5(4H)-one (0.2g, 1.14 mmol.), AgOAc (0.019g, 0.114 mmol.) and methyl acrylate (0.294 g, 3.42 mmol.) at room temperature for 60 h, 0.172 g of pyrroline **IV-1-8a** was obtained (55% yield) as a yellow viscous material after silica gel column chromatography (25 % ether / hexanes) ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.41 (s, 3H), 3.27 (dd, J_1 = 17 Hz, J_2 = 9.75 Hz, 1H), 3.53 (dd, J_1 = 17.5 Hz, J_2 = 8.25 Hz, 1H), 3.73 (s, 3H), 3.79 (s, 3H), 3.86 (dd, J_1 = 9.5 Hz, J_2 = 8.5 Hz, 1H), 7.38-7.41 (m, 2H), 7.43-7.46 (m, 1H), 7.82 -7.83 (m, 2H); NOESY1D: (H1 -> H2b) 2 % , (H2a -> H2b) 30 % , (H2a -> H3) 14 % (H3 -> H2a) 6 %; ^{13}C NMR + **DEPT** (125MHz) $CDCl_3$: 19.81 (-**C**H3), 38.19 (-**C**H2), 48.76 (-**C**H), 52.11 (–CO2**C**H3), 52.90 (-CO2CH3), 81.20 (quaternary 1**C**), 128.01, 128.49, 131.20 (aromatic **C**H), 133.32 (aromatic quaternary 1**C**), 172.31, 172.53, 173.63; (IR (cm^{-1}): 2953.4, 1738, 1612.7; HRMS (FAB): *m/z* calcd for $C_{15}H_{17}NO_4$ [M + H], 276.1236; found, 276.1235.

Dimethyl 3,4-dihydro-2-methyl-5-phenyl-2H-pyrrole-2,3-dicarboxylate (IV-1-8b): additional fractions afforded 0.142 g of product **IV-1-8b** (45 % yield) as a mixture of two stereoisomers. No further attempts to separate the two products were successful. ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.71 (s, 3H), 1.72 (s, 3H), 2.19 (d, J = 14 Hz, 1H), 2.44 (d, J = 14.5 Hz, 1H), 2.75 (d, J = 14 Hz, 1H), 3.12 (d, J = 14 Hz, 1H), 3.72 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.93 (s, 1H), 4.36 (s, 1H), 7.36 (t, J = Hz, 3H), 7.43 (t, J = Hz, 3H), 7.81-7.83 (m, 2H), 7.87-7.88 (m, 2H); ^{13}C NMR (125MHz) $CDCl_3$: δ 24.91, 27.20, 29.67, 48.68, 49.62, 52.60, 53.13, 53.42, 53.72, 86.48, 87.48, 128.03, 128.12, 128.5, 130.99, 131.05, 131.51, 169.0, 170.89, 173.55, 174.45, 174.6, 175.04.

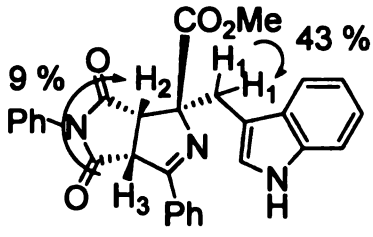


1-benzyl-1,3a,4,5,6,6a-hexahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-c]pyrrole-1-carboxylate methyl ester (IV-13-5): According to general procedure using 4-benzyl-2-phenyloxazol-5(4H)-one (0.2g, 0.8 mmol), AgOAc (0.013g, 0.08 mmol) and N-phenylmaleimide (0.165g, 0.956 mmol) at room temperature for 60 h, 0.24 g of pyrroline **IV-13-5** was obtained (68 % yield) as a off-white solid after silica gel column chromatography (55 % ether / hexanes). ^{1}H NMR (500 MHz), $CDCl_3$: δ 3.09 (d, J = 14 Hz, 1H), 3.73 (s, 3H), 3.97 (d, J = 15 Hz, 1H), 4.29 (d, J = 9 Hz, 1H), 4.88 (d, J = 8.5 Hz,



1H), 7.02 (d, J = 7 Hz, 2H), 7.21-7.22 (m, 3H), 7.32-7.34 (m, 2H), 7.36-7.41 (m, 4H), 7.49-7.55 (m, 4H), 8.24-8.25 (m, 2H); NOESY1D: (H1 -> H1) 58 %, (H2 -> H3) 12 % , (H3 -> H2) 16 % ; ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 41.4 (-PhCH2), 50.74 (-CH), 53.35 (1–CO2CH3), 56.87 (-CH), 85.51 (quaternary 1C), 126.64, 127.15, 127.2, 127.35, 128.35, 128.49, 128.71, 129.02, 129.15, 129.22, 129.42, 130.23, 131.21, 131.33, 132.22 (aromatic CH), 131.43, 131.68, 135.58 (aromatic quaternary 1C), 167.11, 171.08, 172.75, 173.19; (IR (cm^{-1}): 2980, 1780.5, 1718.8, 1614.6; M. P. = 165-168 °C. HRMS (FAB): *m/z* calcd for $C_{27}H_{22}N_2O_4$ [M + H], 439.1658; found, 439.1655. Anal calcd. for $C_{27}H_{22}N_2O_4$: C, 73.96; H, 5.06; N, 6.39. Found: C, 73.3; H, 5.14; N, 6.40.

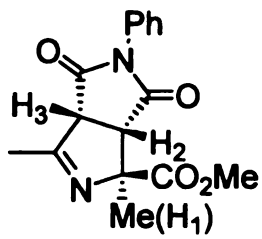
1-(1H-indol-3-yl)methyl)-1,3a,4,5,6,6a-hexahydro-4,6-dioxo-3,5 diphenylpyrrolo[3,4-c] pyrrole-1-carboxylate methyl ester (IV-3-5):



According to general procedure using 4-((1H-indol-3-yl)methyl)-2-phenyloxazol-5(4H)-one (0.2g, 0.69 mmol), AgOAc (0.012g, 0.069 mmol) and N-phenylmaleimide (0.143g, 0.826 mmol) at room temperature for 60h, 0.23 g of pyrroline **IV-3-5** was obtained (70 % yield) as a pale brown solid after silica gel column chromatography (80 % ether / hexanes) and precipitation from dichloromethane / ether mixture. ^{1}H NMR (500 MHz), $CDCl_3$ + DMSO-d_6: δ 3.55 (d, J = 15 Hz, 1H), 3.72 (s, 3H), 3.86 (d, J = 15 Hz, 1H), 4.23 (d, J = 9 Hz, 1H), 4.79 (d, J = 9.5 Hz, 1H), 6.29 (d, J = 8 Hz, 2H), 6.91 (m, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.0-7.02 (m, 3H), 7.07 (t, J = 7 Hz, 1H),

7.38 (t, J = 7 Hz, 2Hz), 7.43 (t, J = 7 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 8.17 (d, J = 8 Hz, 2H), 9.03 (broad s, 1H); NOESY1D: (H1 -> H1) 42.5 % , (H1 -> H2) 0.5 % , (H2 -> H3) 7.5 % , (H3 -> H2) 9 % ; ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$ + DMSO-d_6: 28.86 (-IndolylCH2), 48.86 (-CH), 52.74 (1–CO2CH3), 56.73 (-CH), 85.35 (quaternary 1C), 110. 66, 118.48, 119.03, 121.07, 123.97, 125.46, 125.55, 127.93, 128.02, 129.57, 131.3 (aromatic CH), 108.05, 130.67, 131.11, 135.27 (aromatic quaternary 1C), 167.08, 171.58, 172.9, 173.73; (IR (cm^{-1}): 3402, 1747.7, 1709.15, 1614.6; M. P. = 230-232 °C. HRMS (FAB): *m/z* calcd for $C_{29}H_{23}N_3O_4$ [M + H], 478.1767; found, 478.1768.; Anal Calcd. for $C_{29}H_{23}N_3O_4$: C, 72.94; H, 4.85; N, 8.8. Found: C, 71.4; H, 4.84; N, 8.44.

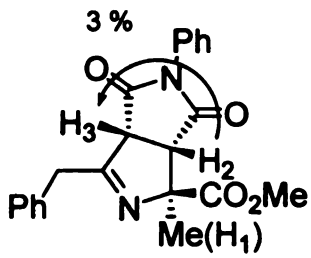
1,3a,4,5,6,6a-hexahydro-1,3-dimethyl-4,6-dioxo-5-phenylpyrrolo[3,4-c] pyrrole-1-carboxylate methyl ester (IV-5-5):



According to general procedure using 2,4-dimethyloxazol-5(4H)-one (0.2g, 1.77 mmol), AgOAc (0.029g, 0.177 mmol.) and N-phenylmaleimide (0.37g, 2.12 mmol) at room temperature for 48 h, 0.31 g of pyrroline **IV-5-5** was obtained (59 % yield) as a white solid after silica gel column chromatography (80 % ether / hexanes) and precipitation from dichloromethane / ether mixture. ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.65 (s, 3H), 2.3 (s, 3H), 3.8 (s, 3H), 4.17 (d, J = 8.5 Hz, 1H), 4.22 (d, J = 9 Hz, 1H), 7.21-7.23 (m, 2H), 7.4 (d, J = 6.5 Hz, 1H), 7.44-7.47 (m, 2H); NOESY1D: (H1 -> H2) 1 %, (H1 -> H3) 0.4 % (*H_2 and H_3 are coupled and have very close chemical shifts, hence no value for NOE could be obtained)*; ^{13}C

NMR + **DEPT** (125 MHz) $CDCl_3$: 18.56 (1-CH3), 21.96 (3-CH3), 49.47 (-CH), 53.34 (1–CO2CH3), 60.58 (-CH), 82.33 (quaternary 1C), 126.19, 126.3, 128.97, 129.28 (aromatic CH), 131.28 (aromatic quaternary C), 169.0, 171.57, 172.7, 173.61; (IR (cm^{-1}): 2955, 1780.5, 1716.8, 1653.2; M. P. = 156-158 °C. HRMS (FAB): *m/z* calcd for $C_{16}H_{16}N_2O_4$ [M + H], 301.1188; found, 301.1189.

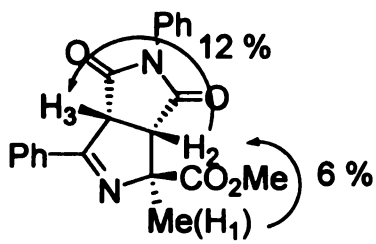
3-Benzyl-1,3a,4,5,6,6a-hexahydro-1-methyl-4,6-dioxo-5-phenylpyrrolo[3,4-c] pyrrole-1-carboxylate methyl ester (IV-9-5): According to general procedure using 2-benzyl-4-methyloxazol-5(4H)-one (0.2g, 1.057 mmol), AgOAc (0.018g, 0.106 mmol) and N-phenylmaleimide (0.22g, 1.26 mmol) at room temperature for 48 h, 0.31 g of pyrroline **IV-9-5** was obtained (75 % yield) as a hydroscopic white solid foam after silica gel column chromatography (65 % ether / hexanes). ^1H NMR (500 MHz), $CDCl_3$: δ 1.62 (s, 3H), 3.79 (s, 3H), 3.93-4.01 (m (d + q), 3H), 4.16 (d, J = 8.5 Hz, 1H), 7.18-7.2 (m, 2H), 7.27 (d, J = 7 Hz, 1H), 7.31-7.41 (m, 5H), 7.44-7.47 (m, 2H); NOESY1D: (H1 -> H2) 2 %, (H2 -> H3) 3 % ((*H_2 and H_3 are coupled and have very close chemical shifts, hence difficult to get a value for NOE)*); ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 21.77 (-CH3), 38.47 (PhCH2-), 49.37 (-CH), 53.27 (1–CO2CH3), 57.81 (-CH), 82.17 (quaternary C), 126.28, 127.29, 128.95, 128.99, 129.28, 129.51 (aromatic CH), 131.26, 134.76 (aromatic quaternary 1C), 170.8, 171.65, 172.51, 173.5; (IR (cm^{-1}): 2920, 1780.5, 1738,



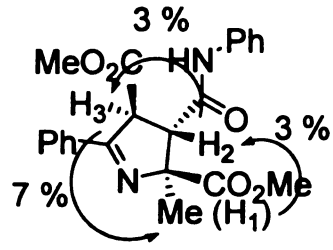
1722.6, 1643.5; M. P. = 46-48 °C. HRMS (FAB): *m/z* calcd for $C_{22}H_{20}N_2O_4$ [M + H], 377.1501; found, 377.1500.

2) Method B) Two step synthesis of Δ^1-Pyrroline-2-carboxylic methyl esters using silver acetate catalyst: A solution of azlactone (1.0 mmol), AgOAc (0.1 mmol.) and alkene (2 to 3 mmol) in dry THF (50mL) was stirred under argon in a flame-dried flask in dark for the requisite amount of time. The crude residue was dissolved in **9:1 benzene / methanol mixture (50 mL).** Assuming quantitative conversion from azlactone to the Δ^1-pyrroline-2-carboxylic acid, the equivalent amount of trimethylsilyl diazomethane was added and mixture stirred for 2 h and completion of methylation monitored by TLC. The solvent was removed under vacuum and residue was chromatographed on silica with ether / hexanes mixture to isolate Δ^1-pyrroline-2-carboxylic acid methyl esters.

1,3a,4,5,6,6a-hexahydro-1-methyl-4,6-dioxo-3,5-diphenylpyrrolo[3,4-c]pyrrole-1-carboxylate methyl ester (IV-1-5): Using 4-methyl-2-phenyloxazol-5(4H)-one (0.4g, 2.28 mmol), AgOAc (0.038g, 0.228 mmol) and N-phenylmaleimide (0.474g, 2.74 mmol) 0.2 g of pyrroline **IV-1-5** was obtained (50 % yield) as a white solid after silica gel column chromatography (45 % ether / hexanes) and precipitation from dichloromethane / ether mixture. Characterization was identical to method A.



Dimethyl 3-(phenylcarbamoyl)-3, 4-dihydro-2-methyl-5-phenyl-2H-pyrrole-2, 4-dicarboxylate (IV-1-9): After all **IV-1-5** was precipitated, the filtrate on evaporation afforded 0.15 g of pyrroline **IV-1-9** (35 % yield). ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.5 (s, 1H), 3.69 (s, 3H), 3.99 (s, 3H), 4.11 (d, *J* = 9.5 Hz, 1H), 5.09 (d, *J* = 9.5 Hz, 1H), 7.14 (t, *J* = 7 Hz, 1H), 7.36 (t, *J* = 8 Hz, 1H), 7.42 (t, *J* = 8 Hz, 2H), 7.48 (m, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8 Hz, 2H), 8.98 (s, 1H); NOESY1D: (H1 -> H2) 3 %, (H1 -> H3) 7 % (H2 -> H3) 3 % , (H3 -> H2) 3 % (see X-ray data; crystallized from dichloromethane /octane); ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 21.94 (1-**C**H3), 52.81 (4-CO2**C**H3), 53.67 (1–CO2**C**H3), 55.17 (-**C**H), 56.32 (-**C**H), 80.36 (quaternary 1**C**), 119.63, 124.39, 126.55, 127.82, 127.97, 128.54, 129.04, 131.34 (aromatic **C**H), 132.61, 137.78 (aromatic quaternary 1**C**), 166.26, 169.1, 171.42, 177.04; (IR (cm^{-1}): 3346, 2953, 1738 (broad), 1680.2, 1599.1; M. P. = 155-157 ° C; HRMS (FAB): *m/z* calcd for $C_{22}H_{22}N_2O_5$ [M + H], 395.1607; found, 395.1608; Anal Calcd. for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.1. Found: C, 67.16; H, 5.48; N, 7.13.

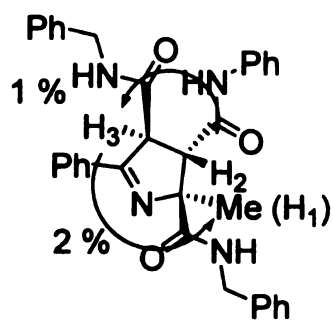


3) Synthesis of (IV-1-9) from (IV-1-5) in methanol using DMAP: Compound (**IV-1-5**) (0.02g, 0.055 mmol) was suspended in 20 ml of methanol in a glass vial

having a screw cap. DMAP (0.007g, 0.06 mmol) was added and reaction mixture stirred at room temperature. The reaction was monitored by TLC (**1**: R_f = 0.38 and 1b: R_f = 0.35, 50 % ether / hexanes) and aliquots were taken out and the solvent was evaporated and the residue dried under vaccum for ^{1}HNMR. After determination of ratio of 1:11 by 1H NMR, the residue was chromatographed as outlined above in procedure **2**.

4) **Synthesis of (IV-1-10) from (IV-1-5):** Compound **(IV-1-5)** (0.05g, 0.138 mmol) was suspended in 20 mL of benzylamine in a flame-dried flask under nitrogen and DMAP (0.016g, 0.14 mmol) was added and mixture stirred at room temperature for 36 hours. The mixture was dissolved in 50 mL dichloromethane and extracted with 10 % HCl solution (3x, 30 mL). The dichloromethane layer was dried over anhydrous sodium sulphate and evaporated under vacuum. The residue was chromatographed with 45 % ether / hexanes to afford the product as a white solid foam (0.057g, 76 % yield).

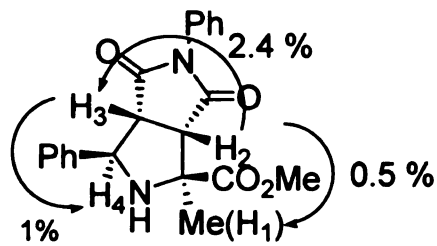
(2S, 3S, 4S)-*N*^{2},*N*^{4}-dibenzyl-3,4-dihydro-2-methyl-*N*^{3},5-diphenyl-*2H*-pyrrole-2,3,4-tricarboxamide (IV-1-10): ^{1}H NMR (500 MHz), $CDCl_3$: δ 1.62 (s, 1H),



3.84 (d, J = 10 Hz, 1H), 4.31 (dd, J1 = 4.5 Hz, J_2 = 14.5 Hz, 2H), 4.45 (dd, J1 = 4.5 Hz, J_2 = 14.5 Hz, 2H), 4.59 (dd, J1 = 6 Hz, J_2 = 15 Hz, 2H), 4.75 (dd, J1 = 6.5 Hz, J_2 = 14.5 Hz, 2H), 4.84 (d, J = 10 Hz, 1H), 6.98 (broad s, 1H), 7.15 (t, J = 7 Hz, 1H), 7.2-

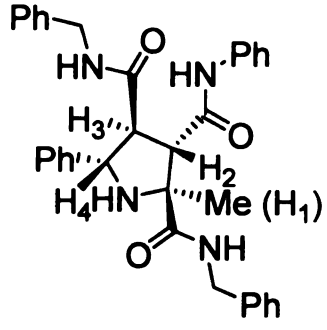
7.52 (m, 14H), 7.65 (d, J = 8 Hz, 2H), 7.75 (d, J = 6.5 Hz, 2H), 10.92 (s, 1H); NOESY1D: (H1 -> H2) 1 % , (H1 -> H3) 2 % (H2 -> H3) 1 % , (H3 -> H2) 1 %; ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 22.5 (1-**C**H3), 43.77 (-CONH**C**H2Ph), 43.9 (–CONH**C**H2Ph), 56.01 (-**C**H), 57.5 (-**C**H), 78.54 (quaternary 1**C**), 120.21, 124.55, 127.18, 127.76, 127.82, 127.93, 128.02, 128.2, 128.78, 128.87, 128.95, 129.07, 129.18, 129.24 (aromatic **C**H), 131.54, 133.13, 137.5, 138.27, 138.37 (aromatic quaternary 1**C**), 167.93, 170.21, 170.62, 176.75; (IR (cm^{-1}): 3325, 2925, 1676,1660,1649.3, 1599.2; M. P. = 80-83 ° C; HRMS (FAB): *m/z* calcd for $C_{34}H_{32}N_4O_3$ [M + H], 545.2552; found, 545.2554; Anal Calcd. for $C_{34}H_{32}N_4O_3$: C, 74.98; H, 5.92; N, 10.29. Found: C, 74.16; H, 5.88; N, 10.13.

4) **Synthesis of (IV-1-11) from (IV-1-5):** Compound (**IV-1-5**) (0.1g, 0.275 mmol) was suspended in 20 mL of MeOH in a flame-dried flask under nitrogen and $NaBH_4$ (0.020 g, 0.55 mmol) was added and mixture stirred at room temperature for 3 hours. After all the starting material had reacted, MeOH was evaporated off. The mixture was dissolved in 50 mL dichloromethane and extracted with 5 % HCl solution (3x, 30 mL). The dichloromethane layer was dried over anhydrous sodium sulphate and evaporated under vacuum. The residue was chromatographed with 80 % ether / hexanes to afford the product as white solid foam (0.076g, 76 % yield).



^{1}H NMR (500 MHz), $CDCl_3$: δ 1.71 (s, 3H), 3.72 (s, 3H), 3.97 (d, *J* = 15.5 Hz, 1H), 4.19 (d, *J* = 15.5 Hz, 1H), 5.52(d, *J* = 10 Hz, 1H), 7.18-7.48 (m, 8H), 7.94-7.97 (m, 2H); NOESY1D: (H1 -> H2) 0.5 %, (H2 -> H3) 2.4 %, (H3 -> H4) 1 % ; ^{13}C NMR + **DEPT** (125MHz) $CDCl_3$: 22.19 (-CH3), 50.95 (-CH), 53.25 (1–CO2CH3), 57.84 (-CH), 82.93 (quaternary C), 85.93(-CHPh), 124.49, 127.22, 128.94, 129.03, 129.16, 131.88 (aromatic CH), 131.96, 136.40 (aromatic quaternary 1C), 171.24, 171.78, 173.51; (IR (cm^{-1}): 3360, 2928.3, 1738.1, 1680.2; HRMS (FAB+): *m/z* calcd for $C_{21}H_{20}N_2O_4$ [M + H], 364.3945; found, 364.1413.

4) **Synthesis of (IV-1-12) from (IV-1-5):** Compound **(IV-1-5)** (0.05g, 0.091 mmol) was suspended in 20 mL of MeOH/AcOH (1:1) in a flame-dried flask under nitrogen and $NaBH_4$ (0.016g, 0.14 mmol) was added and mixture stirred at room temperature for 3 hours. After all the starting material had reacted, MeOH was evaporated off. The mixture was dissolved in 50 mL dichloromethane and extracted with saturated ammonium chloride (3x, 30 mL). The dichloromethane layer was dried over anhydrous sodium sulphate and evaporated under vacuum. The residue was chromatographed with 50 % Ether/hexanes to afford the product as white solid foam (0.032 g, 66 % yield).



^{1}H NMR (500 MHz), $CDCl_3$: δ 1.53 (s, 1H), 3.3.43 (t, J = 11 Hz, 1H), 3.74 (d, J = 12 Hz, 1H), 4.292-4.631 (complex multiplet , 5H), 6.6 (t, J = 6 Hz, 1H), 7.03 (t, J = 3.5 Hz, 2H), 7.12-7.39 (m, 15H), 7.62 (d, J = 8 Hz, 2H), 8.43 (t, J = 5.5 Hz, 1H), 10.334 (broad

singlet, 1H); NOESY1D: (H1 -> H3) 4 % , (H1 -> H2) 2 %, (H2 -> H3) 1 %, (H3 -> H2) 1 %, (H2 -> H4) 6 % , (H3 -> H4) 2 %; (see X-ray data; crystallized from dichloromethane /octane); ^{13}C NMR + **DEPT** (125 MHz) $CDCl_3$: 24.1 (1-**C**H3), 43.47 (-CONH**C**H2Ph), 43.73 (–CONH**C**H2Ph), 55.47 (-**C**H), 58.4 (-**C**H), 64.47 (-**C**HPh), 66.75 (quaternary 1**C**), 120.12, 124.41, 127.14, 127.35, 127.73, 127.94, 128.72, 129.14, 129.29 (aromatic **C**H), 137.83, 138. 36,138.38, 138.88 (aromatic quaternary 1**C**), 169.0, 170.66, 178.2.

M. References.

1. (a) Shvekhgeimer, M.-G. A. *Chemistry of Heterocyclic Compounds* **2003**, *39*(4), 405. (b) Miltyk, W.; Palka, J. A. *Comparative Biochemistry and Physiology Part A* **2000**, *125*, 265-271. (c) Bearne, S. L.; Hekmat, O.; MacDonnell, J. E. *Biochem. J.* **2001**, *356*, 223-232. (d) Bearne, S. L.; Wolfenden, R. W. *Biochemistry* **1995**, *34*, 11515-11520. (e) Stapon, A.; Li, R.; Townsend, C. A. *J. Am. Chem. Soc.* **2003**, *125*, 8486-8493.

2. (a)Leusch, H.; Hoffmann, D.; Hevel, J. M.; Becker, J. E.; Golakoti, T.; Moore, R. E. *J. Org. Chem.* **2002**, *68*, 83-91. (b) Stocking, E. M.; Martinez, R. A.; Silks, L. A.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 3391-3392. (c) Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L. *J. Org. Chem.* **1988**, *53*, 1298-1307. (d) Kuo, M. S.; Yurek, D. A.; Coats, J. H.; Chung, S. T.; Li, G. P. *J. Antibiot.* **1992**, *45*, 1773-1777.

3. (a) Kleinsasser, N. H.; Wallner, B. C.; Harreus, U. A. Zwickenpflug, W.; Richter, E. *Toxicology* **2003**, *192*, 171-177. (b) Ohkura, H.; Berbasov, D. O.; Soloshonok, V. A. *Tetrahedron Letters* **2003**, *44*, 2417-2420. (c) Morris, B. D.; Prinsep, M. R. *J.Natl. Prod.* **1999**, *62*, 688-693. (d) Hughes, C. C.; Trauner, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4556-4559.(e) Carroll, A. R.; Pierens, G. K.; Fechner, G.; de Almeida Leone, P.; Ngo, A.; Simpson, M.; Hyde, E.; Hooper, J. N. A.; Bostrom, S. L.; Musil, D.; Quinn, R. J. *J. Am. Chem. Soc.* **2002**, *124*, 13340-13341. (f) Tsukamoto, D.; Shibano, M.; Kusano, G. *Chem. Pharm. Bull.* **2001**, *49*, 1487-1491. (g) Usubillaga, A.; Zabel, V.; Watson, W. H. *Acta Crystallographica Section C-crytstal structure communications* **1982**, *B38*, 966-969. (h) Tomko, J.; Brazdova, V.; Voticky, Z. *Tetrahedron Lett.* **1971**, *32*, 3041-3043-3044. (i) Yuichi, S.; Masaki, S.; Atsuko, M.; Takahashi, Y.; Hiroshi, T.; Satoshi, O.; Yutaka, E. *J. Antibiot.* **2003**, *56*, 817-826.

4. (a) Moya, P.; Cantin, A.; Castillo, M.; Prino, J.; Miranda, M. A.; Primo-Yufera, E. *J. Org. Chem.* **1998**, *63*, 8530-8535.; (b) Birouk, M.; Harraga, S.; Panouse-Perrin, J.; Robert, J. F.; Damelincourt, M.; Theobald, F.; Mercier, R.; Pannouse, J. J. *European Journal of Medicinal Chemistry* **1991**, *26*, 91-99.; (c) Fuska, J.; Fuskova, A.; Vassova, A.; Voticky, Z. *Neoplasma* **1981**, *28*, 709-714.

5. (a) Dannhardt, G.; Keifer, W. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 183.; (b) Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Org. Lett.* **2003**, *5*(22), 4235.; (c) Lombardo, M.; Fabbroni, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264.; (d) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316.; (e) Clerici, F.; Gelmi, M. L.; Pocar, D.; Rondena, R. *Tetrahedron* **1995**, *51*(36), 9985.; (f)

Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett.* **2001**, *3*(9), 1367.

6. (a) Fehn, S.; Burger, K. *Tet. Asymm.* **1997**, *8*(12), 2001.; (b) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tet. Lett.* **1999**, *40*, 6941.; (c) Okue, M.; Kobayashi, H.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H.; Watanabe, H.; Kitahara, T. *Tet. Lett.* **2002**, *43*, 857.; (d) Watanabe, H.; Okue, M.; Kobayashi, H.;Kitahara, T. *Tet. Lett.* **2002**, *43*, 861.; (e) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507-3510.

7. (a) Tehrani, K. A.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 3099-3108.; (b) Peroche, S.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J. C. *Tetrahedron Lett.* **2001**, *42*, 4617-4619.; (b) Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2002**, *43*, 1597-1598.; (c) Pearson, W. H.; Stevens, E. P. *J. Org. Chem.* **1998**, *63*, 9812-9827.; (d) Graf v. Keyserlingk, N.; Martens, J. *Tetrahedron :Asymmetry* **2001**, *12*, 2213-2222.; (e) Yamago, S.; Miyazoe, H.; Nakayama, T.; Miyoshi, M.; Yoshida, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 117-120.; (f) Ohkura, H.; Berbasov, D. O.; Soloshonok, V. A. *Tetrahedron Letters* **2003**, *44*, 2417-2420.;(g) Yu, M.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8122-8123.; (h) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316-1318.; (i) Cordero, F. M.; Valenza, S.; Machetti, F.; Brandi, A. *Chem. Commun.* **2001**, 1590-1591.; (j) Shin-Ya, K.; Kim, J.-S.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 7079-7092.; (k) Watanabe, H.; Okue, M.; Kobayashi, H.; Kitahara, T. *Tetrahedron Lett.* **2002**, *43*, 861-864.; (l) Okue, M.; Kobayashi, H.; Shin-Ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2002**, *43*, 857-860.; (m) Plehiers, M.; Heilporn, S.; Ekelmans, D.; Leclercq, S.; Sangermano, M.; Braekman, J. C.; Daloze, D. *Can. J. Chem.* **2000**, *78*, 1030-1034. (n) Grigg, R.; Millington, E. L.; Thornton-Pett, M. *Tetrahedron Lett.* **2002**, *43*, 2605-2608.

8. (a) Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Org. Lett.* **2003**, *5*, 4235-4238. (b) Chapman, T. M.; Courtney, S.; Hay, P.; Davis, B. G. *Chem. Eur. J.* **2003**, *9*, 3397-3414. (c) Pisaneschi, F.; Monica, C. D.; Cordero, F. M.; Brandi, A. *Tetrahedron Letters* **2002**, *43*, 5711-5714. (d) Goti, A.; Cacciarini, M.; Cardona, F.; Cordero, F. M.; Brandi, A. *Org. Lett.* **2001**, *3*, 1367-1369. (e) Lombardo, M.; Fabbroni, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264-1268. (f) Black, D. S.; Edwards, G. L.; Evans, R. H.; Keller, P. A.; Laaman, S. M. *Tetrahedron* **2000**, *56*, 1889-1897.

9. (a) Belokon, Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; Maleev, V.; North, M.; Pertrosyan, A. Tetrahedron Lett. 2003, 44, 2045-2048. (b) Humphrey, J. M.; Chamberlin, A. R. Chem. Rev. 1997, 97, 2243-2266. (c) Dennisova, I.; Barriault, L. Tetrahedron 2003, 59, 10105-10146. (d)

Manthrope, J. M.; Gleason, J. L. Angew. Chem. Int. Ed. 2002, 41, 2338-2340. (e) Fenteany, G.; Standaert, R. F.; Soongyu Choi, W. S.; Corey, E. J.; Schreiber, S. L. Science 1995, 268, 726. (f) Corey, E. J.; Guzman-Perez, A. Angew. Chem. Int. Ed. 1998, 37, 388-401.

10. (a) Kleinsasser, N. H.; Wallner, B. C.; Harreus, U. A.; Zwickenpflug, W.; Richter, E. *Toxicology* 2003, *192*, 171-177; (b) Hughes, C. C.; Trauner, D. *Angew. Chem. Int. Ed.* 2002, *41*, 4556-4559; (c) Ma, D.; Yang, J. *J. Am. Chem. Soc.* 2001, *123*, 9706-9707.

11. (a) Kercher, T.; Livinghouse, T. *J. Org. Chem.* 1997, *62*, 805-812; (b) Campos, P. J.; Soldevilla, A.; Sampedro, D.; Rodriguez, M. A. *Org. Lett.* 2001, *3*, 4087-4089; (c) Pearson, W. H.; Stevens, E. P. *J. Org. Chem.* 1998, *63*, 9812-9827; (d) Harwood, L. M.; Vickers, R. J. *Chemistry of Heterocyclic Compounds* 2002, *59*, 169-252. (e) Uchiyama, K.; Yoshida, M.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1988**, 607-608.

12. (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, 1984; (b) Gribble, G. W. Mesoionic ring systems. *The Chemistry of Heterocyclic Compounds, Volume 60, Part A*; Jon Wiley and Sons, 2002; pp 681-753.

13. Padwa A.; Pearson, W. H., *Synthetic applications of dipolar cycloaddition chemistry towards heterocyclic and natural products*; Wiley-VCH: Weinheim, 2002.

14. (a) Huisgen, R.; Gotthardt, H. *Chem. Ber.* 1970, *103*, 2625-2632; (b) Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Chem. Ber.* 1970, *103*, 2368-2387; (c) Gotthardt, H.; Huisgen, R.; Schaefer, F. C. *Tetrahedron Lett.* 1964, *10*, 487-491; (d) Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Tetrahedron Lett.* 1964, *9*, 481-485; (e) Grigg, R.; Lansdell, M. I.; Thornton-Pett, M. *Tetrahedron* 1999, *55*, 2025-2044.

15. Maryanoff, C. A.; Karash, C. B.; Turchi, I. J. *J. Org. Chem.* **1989**, *54*, 3790-3792.

16. Gingrich, H. L.; Baum, J. S. In *Oxazoles*; Turchi, I. J., Ed.; Wiley: New York, **1986**; Vol. 45,731.

17. Friedrichsen, W.; Schöer, W.-D. *Tetrahedron Lett.* **1977**, 1603-1605.

18. Padwa, A.; Gingrich, H. L.; Lim, R. *J. Org. Chem.* 1982, *47*, 2447-2456.

19. (a) Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* 2002, *4*, 3533-3535; (b) Peddibhotla, S.; Tepe, J. J. *Synthesis* 2003, *9*, 1433-1440.

20. (a) Pearson, W. H.; Stoy, P.; Mi, Y. *J. Org. Chem.* **2004**, *69*, 1919-1939. (b) Harwood, L. M.; Macro, J.; Watkin, D.; Williams, C. E.; Wong, L. F. *Tetrahedron: Asymmetry* **1992**, *3*, 1127-1130.

21. Sharma, V.; Lansdell, T.; Peddibhotla, S.; Tepe, J. J. *Chem. Biol.* **2004**, *in print.*

22. Chen, F. M. F.; Kuroda, K.; Benoiton, N. L. *Synthesis* **1970**, 230.

23. Washizuka, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, *55*, 12969-12976.

24. Grigg, R.; Lansdell, M. I.; Thornton-Pett, M. *Tetrahedron* **1999**, *55*, 2025-2044.

25. Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2004**, *126*(40), 12776-12777.

26. Blazey, C. M.; Heathcock, C. H. *J. Org. Chem.* **2002**, *67*, 298-300.

27. Sustmann, R. *Pure Appl. Chem.* 1974, *40*, 569-593.

28. Longmire, J. M.; Wang, B.; Zhang X.; *J. Am. Chem. Soc.* **2002**, *124*, 13400-13401.

29. Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; J□rgensen, K. A.; *Angew. Chem. Int. Ed.* **2002**, *41*(22), 4236-4238.

30. Chen, C.; Li, X.; Schreiber, S. L.; *J. Am. Chem. Soc.* **2003**, *125*, 10174-10175.

31. Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043-5046.

32. Padwa, A.; Lim, R.; MacDonald, J. G. *J. Org. Chem.* **1985**, *50*, 3816-3823.

33. Galley, G.; Liebscher, J.; Patzel, M. *J. Org. Chem.* **1995**, *60*, 5005-5010.

34. Martin D. Burke and Stuart L. Schreiber *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58.

35. Gong, Y.-D.; Kim, S.-K.; Yoo, S.; Kurth, M. J. *Bull. Chim. Soc. Jpn.* **2002**, *75*, 2477-2480.

CHAPTER V

APPLICATIONS OF IMIDAZOLINE SCAFFOLDS IN THERAPY AND ORGANOCATALYSIS.

A. Sensitization of Tumor Cells towards Chemotherapy.

1) Enhancing the activity of Camptothecin by Novel Imidazolines

Apoptosis or programmed cell death is a cellular mechanism that maintains the cell number and eliminates damaged or mutated cells.[1, 2] Alterations in apoptotic pathways can disrupt the delicate balance between cell proliferation and cell death leading to a variety of diseases.[3, 4] In many cancers, apoptosis is abnormally down-regulated, either by the mutation of pro-apoptotic proteins or by the up-regulation of anti-apoptotic proteins.[5] Aberrant apoptosis provides an intrinsic survival advantage to cancer cells causing growth and expansion of the tumor, and resistance to pro-apoptotic signals including chemotherapeutic agents.[6, 7] Chemotherapeutic agents may also induce anti-apoptotic factors thereby adding to this intrinsic resistance to chemotherapy.[8] The combination of these anti-apoptotic mechanisms has resulted in an increased dose intensity of chemotherapeutics, often without the anticipated improved therapeutic results.[9] The search for new chemotherapeutic strategies has therefore shifted to small molecules that can selectively induce apoptosis in cancer cells or retard the cellular chemoresistance.[10] Strategies using combinations of inducers of apoptosis and/or inhibitors of anti-apoptotic factors and traditional chemotherapeutic drugs may provide an improved alternative to conventional chemotherapy.[10b, 11]

2) Chemotherapy and chemoresistance – camptothecin and cis-platin

The antitumor agent camptothecin (CPT) is an alkaloid isolated from the extracts of the fruit of *Camptotheca acuminata* and was identified as a topoisomerase I inhibitor.[12, 13] CPT-11 and several water soluble analogues including topotecan have successfully passed clinical trials in the United States.[14] Camptothecin exhibits its antitumor activity via the formation of a stable ternary topoisomerase I - DNA cleavable complex.[12, 15] Stabilization of this cleaved DNA complex initiates an apoptotic signaling pathway, ultimately resulting in cell death.[12, 16] Concomitant with the initiation of this apoptotic cell signal, these agents induce anti-apoptotic signaling pathways, which have compromised their efficacy in the clinic.[17, 27d] This cellular resistance has been attributed to the activation of anti-apoptotic signaling pathways mediated by several transcription factors, in particular the nuclear transcription factor, NF-κB.[8d, 18, 27f] cDNA microarrays using all annotated human genes have been used to establish the association between characteristic gene expression patterns in response to drug treatment by the topoisomerase poison camptothecin.[19] These studies in HeLa cells provided striking evidence that administration of camptothecin resulted in up-regulation in a large number of genes controlled by NF-κB.[19a] NF-κB mediated anti-apoptotic response induced by DNA damaging agents may also result from the NF-κB mediated initiation of cellular DNA repair mechanisms.[20] Topoisomerase inhibitors are in this context also considered DNA damaging agents, since they exert their apoptotic mode of action via the stabilization of a ternary DNA-drug-protein cleavable complex.[16] In addition to the induction of anti-apoptotic gene

transcription, the topoisomerase I inhibitor camptothecin was found to induce the NF-κB mediated activation of proto-oncogenes such as *c-Myc* and *cyclin D1* and indirect deregulation of the retinoblastoma tumor suppressor protein (Rb protein). [17a, 27d, 21-22] Cis-platin has also been shown to promote a biphasic activation of NF-κB in macrophages through a mechanism dependent on I-κB. [17d] It has also been shown to persistently activate N-terminal c- Jun Kinase which triggers induction of apoptosis. However, usage of a MEKK1 (common to NF-κB pathway Figure V- 1) also enables activation of NF-κB, leading to a cross talk between pro-apoptotic and anti-apoptotic signals. [17c] Thus, chemotherapeutic treatment by these agents often fails as a result of a NF-κB-mediated double stimulus, causing chemoresistance and favoring uncontrolled cell growth.

3) NF-κB, the master key to cell growth, differentiation and apoptosis

The mammalian nuclear transcription factor, NF-κB, is a multi-subunit complex involved in the regulation of gene transcription, including the regulation of apoptosis.[23, 24] Five distinct subunits of NF-κB are found in mammalian cells, which include, NF-κB1 (p105/p50), NF-κB2 (p100/p52), RelA (p65), RelB and c-Rel.[24] These subunits can compose a variety of homo-or heterodimers, which control the specificity and selectivity of specific DNA control elements.[25, 26] In most unstimulated mammalian cells, NF-κB exists mainly as a homodimer (p50/p50) or heterodimer (p50/p65) in the cytoplasm in the form of an inactive complex with the inhibitory protein I-κB (Figure V-1). Many cellular stimuli including: antineoplastic agents, [27] viruses (e.g. HIV), cytokines, phorbol esters and oxidative stress, result in the IKK mediated phosphorylation of I-κB on

serines 32 and 36, followed by ubiquitinylation and subsequent degradation by the 26 S proteosome.[23] Degradation of I-κB ensures the release of NF-κB.[28] Upon release, NF-κB translocates into the nucleus where the subunits bind with

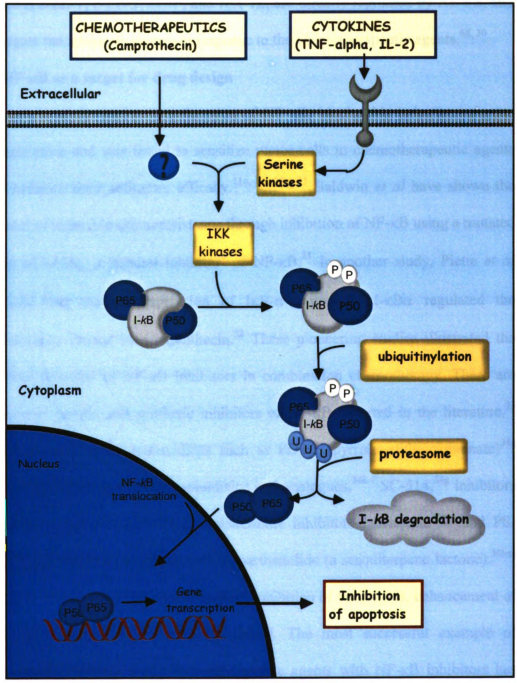


Figure V-1. General NF-κB activation pathway in eukaryotic cells.

specific DNA control elements and initiate gene transcription (Figure V- 1).

Prior to DNA binding, additional protein phosphorylation events are required for optimal and specific gene transcription.[29] Antiapoptotic genes such as, *TRAF1*, *TRAF2*, *c-IAP1*, *c-IAP2*, *IXAP*, and *IEX-1L*, are directly regulated by NF-κB, and abrogate the apoptotic signals in response to the chemotherapeutic agents.[8d, 30]

4) NF-κB as a target for drug design

Inhibition of the nuclear translocation of NF-κB, blocks this induction of gene transcription and was found to sensitize tumor cells to chemotherapeutic agents and enhance their antitumor efficacy.[11b, 21, 27g, 31] Baldwin *et al* have shown the control of inducible chemoresistance through inhibition of NF-κB using a mutated form of I-κBα, a 'natural inhibitor' of NF-κB.[21] In another study, Piette *et al* showed that the overexpression of IκB-α / mutated I-κBα regulated the cytotoxicity caused by camptothecin.[32] These pioneering studies illustrated the clinical potential of NF-κB inhibitors in combination chemotherapy. There are numerous natural and synthetic inhibitors of NF-κB reported in the literature,[33] which include many antioxidants such as PDTC (pyrrolinedithiocarbamate)[34a] kinase inhibitors such as hymenialdisine and analogues,[34b-f] SC-514,[34g] inhibitors of IκB degradation such as the proteosome inhibitors lactacystin[34h-j] and PS-341[34k] and the IKK inhibitors such as parthenolide (a sesquiterpene lactone).[34l-m] Even though many of these agents claim inhibition of the NF-κB, enhancement of chemotherapeutic effect has been limited. The most successful example of combination therapy using chemotherapeutic agents with NF-κB inhibitors has been illustrated by the proteasome inhibitor PS-341 (bortezomib), which is

currently in Phase II clinical trials in the US.[31b, 36] PS-341 inhibits the nuclear translocation of NF-κB *via* the inhibition of the 26 S proteasome-mediated degradation of IκB (Figure V-1). Since PS-341 exhibits significant cell cytotoxicity it may be used as a single agent or in combination regiments with classical anticancer agents providing a more than additive apoptotic response.[34k, 37]

5) Imidazoles, kinase inhibition and NF-κB

The imidazole nucleus appears in a number of natural products, including the amino acid histidine and purines. Nitroimidazoles are well-known anti-bacterial and anticancer drugs. Recently biaryl[38], triaryl[39a] and tetraaryl[39b] imidazoles have been identified as p38 mitogen-activated protein (MAP) kinase inhibitors. Chang *et al*[39] have been successful in optimizing this triaryl imidazole lead to a selective antagonist for human glucagons receptor, which should lead to improved drugs to control glucose levels in diabetics. Slee *et al* [40a] have reported a novel-series of non-carbohydrate imidazole-based small molecule selectin inhibitors. They are the first class of non-carbohydrate selectin antagonists with potent anti-inflammatory activity. Inhibition of NF-κB nuclear localization reduces human E-selectin expression and the systemic inflammatory response.[40b] Hymenialdisine was recently [41a] identified to be a nanomolar inhibitor of Mitogen-Activated Protein Kinase kinase-1 (MEKK-1).

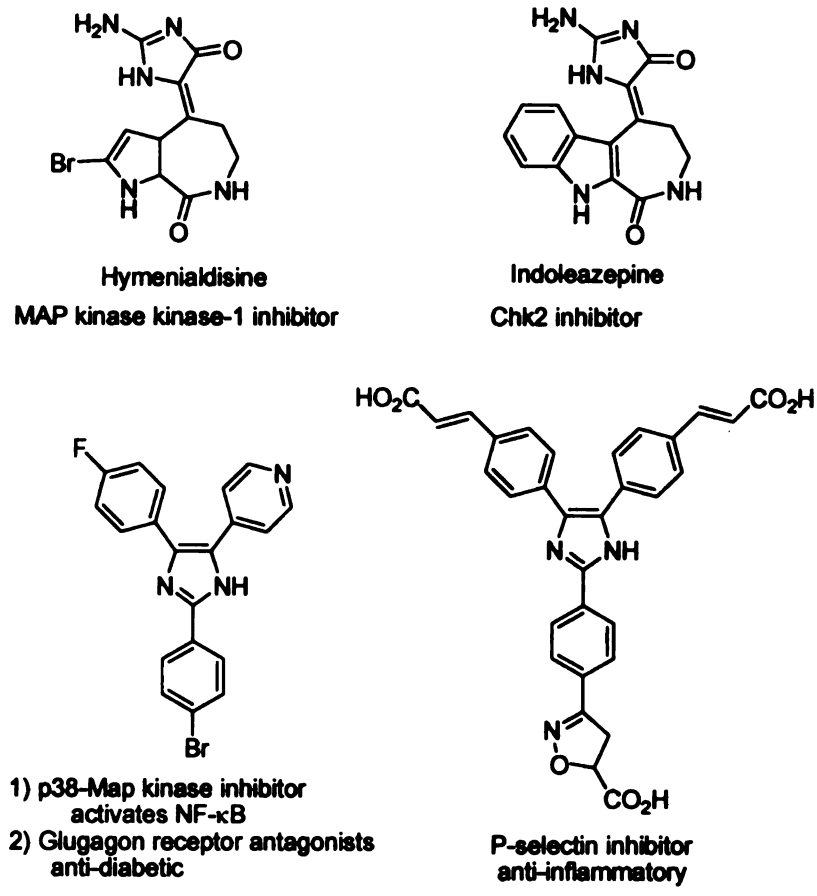


Figure V-2. Inhibition of NF-κB might play a key role in the pathways involved in inflammation, diabetes and cancer.

Activated MEK-1 phosphorylates and activates MAP kinases which can translocate to the nucleus, and through the phosphorylation of a variety of substrates modulate cytoplasmic events such as cell-proliferation and differentiation. Sharma *et al* showed the inhibition of cytokines such as TNF-α and IL-2 in Jurkat cells by hymenialdisine analogs, indoleazepines.[41b] They further showed selective inhibition of checkpoint kinases (involved in cell cycle) by these molecules as compared to the natural product itself. [41c]

6) From Imidazoles to Imidazolines

As a part of developing new small molecule scaffolds and then finding their biological activity, imidazolines were tested for prevention of nuclear translocation of NF-κB in Jurkat cells. The translocation of NF- κB across the nuclear membrane was inhibited, indicative of a potential mode of action upstream of nuclear translocation. As a primary screen, several of the imidazolines were screened for a possible enhancement of apoptotic response of camptothecin. Upon screening these compounds we found that they exhibited no apparent cytotoxicity, however further investigations revealed that the imidazolines enhanced the level of apoptosis induced by chemotherapeutics. Further, mechanistic studies were then performed on compound **1** (Figure V-3).

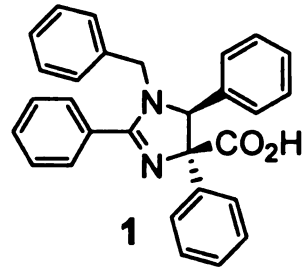


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Figure V-3. Imidazoline that showed maximum potentiation of apoptotic events

7) Sensitization of leukemia cells toward camptothecin

i. Imidazolines and Camptothecin.

The imidazolines were evaluated for their ability to enhance the activity of camptothecin (CPT) in cancer cells by evaluating the level of apoptosis induced by camptothecin in the presence and absence of compound **1**. Induction of apoptosis is the hallmark of most chemotherapeutic agents, including camptothecin.[12, 43] Investigation of the imidazolines as apoptotic modulators,

revealed that these agents drastically enhanced the level of apoptosis induced by camptothecin. The level of apoptotic cell death was measured using a caspase-based screen. Caspase activation plays a central role in the execution of apoptosis *via* the proteolytic cleavage of multiple protein substrates by caspase-3, -6 and -7.[44] The level of induction of apoptosis in cells was quantified using a commercially available Apo-ONE™ (Promega) assay, which takes advantage of caspase-3/7 activity. Treatment of the CEM leukemia T-cells with compound **1** did not induce significant amounts of apoptosis (tested up to 10 μM for 48 h by Apo-ONE™ and cell count, data not shown), indicating that **1** exhibits no significant cell cytotoxicity. The imidazoline **1** was subsequently screened for its ability to enhance apoptosis induced by the chemotherapeutics, camptothecin (CPT).[14]

Enhancement of CPT-induced apoptosis in CEM cells was first investigated at concentrations of ≤10 nM CPT, at which CPT has been reported to cause DNA aberrations but no significant levels of apoptosis in leukemia cells.[45] Figure V-4 illustrates the effect of the imidazoline on CEM cells when incubated with CPT over a 48 hour time period. Treatment of the cells with compound **1** had no effect on the level of apoptosis. Treatment of the cells with 10 nM CPT resulted in some cell death starting after 12 hours of drug treatment (Figure V- 2). Combination treatment of the non-cytotoxic imidazoline **1** (10 nM) with CPT (10 nM) resulted in enhancement in apoptotic cell death after 48 hours (Figure V-4).

Additional experiments were performed to quantify the enhancement of the apoptotic signal in leukemia cells. Having found a phenotype, the molecular

mechanism of the NF-κB signaling pathway was worked out. The imidazoline was found to block the nuclear translocation of NF-κB via the inhibition of I-κB degradation. [42]

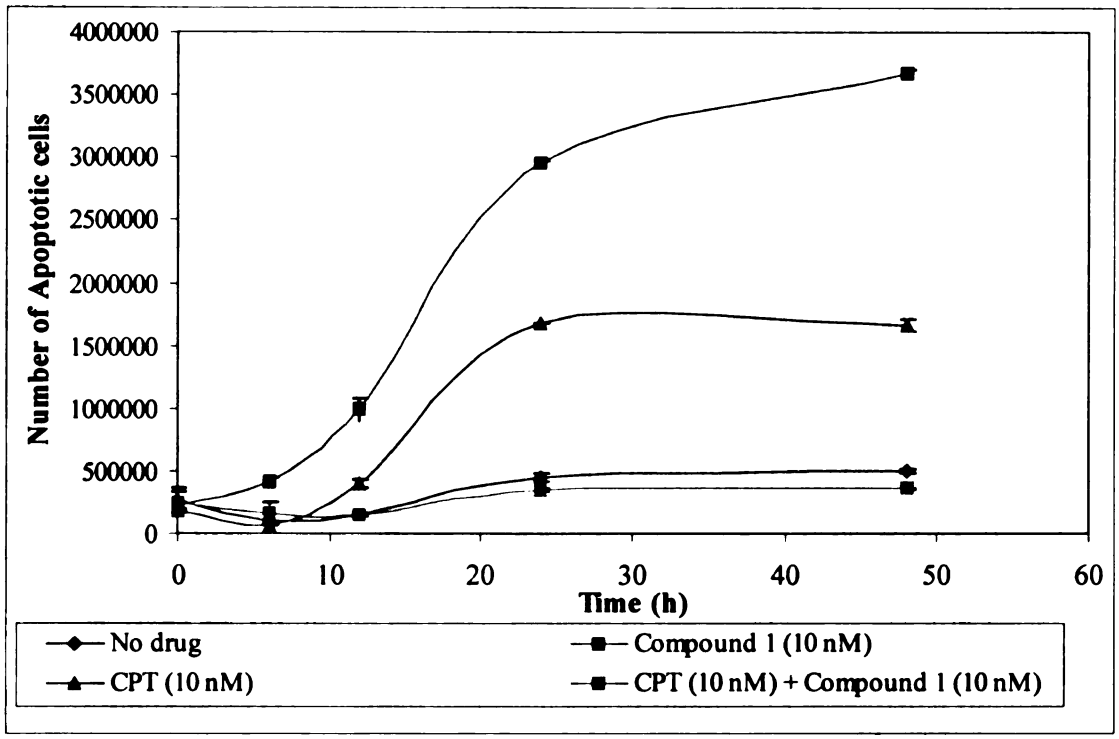


Figure V-4. Sensitization of CEM cells to camptothecin by imidazoline **1**, measured over 48 hours. Data reported as an average of two independent experiments (error margins are included) Figure V- 2 illustrates cell death through apoptosis as a function of time for cells alone (pink squares), imidazoline only (dark blue triangle), CPT (10 nM) (light blue triangle) and CPT (10 nM) in presence of imidazoline (10 nM) (red squares). [42]

ii. Inhibition of camptothecin induced NF-κB -DNA binding by imidazoline 1

Induction of NF-κB activation can proceed *via* a wide range of signaling pathways.[48] Thus, inhibition of NF-κB activation can proceed via the mediation of many different pathways. Modulators of these pathways may therefore act as general activation inhibitors, whereas others may inhibit specific induction pathways.[33] In order to investigate whether the imidazoline **1** inhibits the specific

of camptothecin induced NF-κB – DNA binding in the presence of the compound **1**. CEM cells were pre-treated with various concentrations of imidazoline **1**, followed by exposure to camptothecin (1 μM). Pyrrolidine dithiocarboxylic acid (PDTC), a non-selective NF-κB inhibitor was used as a positive control. The nuclei were isolated and treated with the labeled κB consensus sequence. As illustrated in Figure V- 5, the addition of imidazoline **1** inhibited camptothecin induced NF-κB nuclear binding in a dose dependent manner. Control lanes included: DNA only (lane 1), TNF-α activated NF-κB (lane 2), TNF-α activated NF-κB treated with a p65 antibody, which provided a supershift (lane 3) and the unactivated control (lane 4). Treatment of the cells with camptothecin resulted in the activation of NF-κB as indicated by the strong band of the NF-κB-DNA complex (lane 5). Inhibition of DNA binding in the presence of the non-selective NF-κB inhibitor PDTC resulted in a decrease of binding as anticipated (lane 6). A similar decrease of camptothecin induced DNA binding upon treatment of imidazoline **1** (concentrations ranging from 10 μM to 10 nM) is clearly illustrated in lanes 6-9. Comparison of lane 5 (activated by 1 μM CPT) with lane 7 (activated by 1 μM CPT + 1 μM compound **1**) indicates a significant decrease in NF-κB-DNA complex formation.

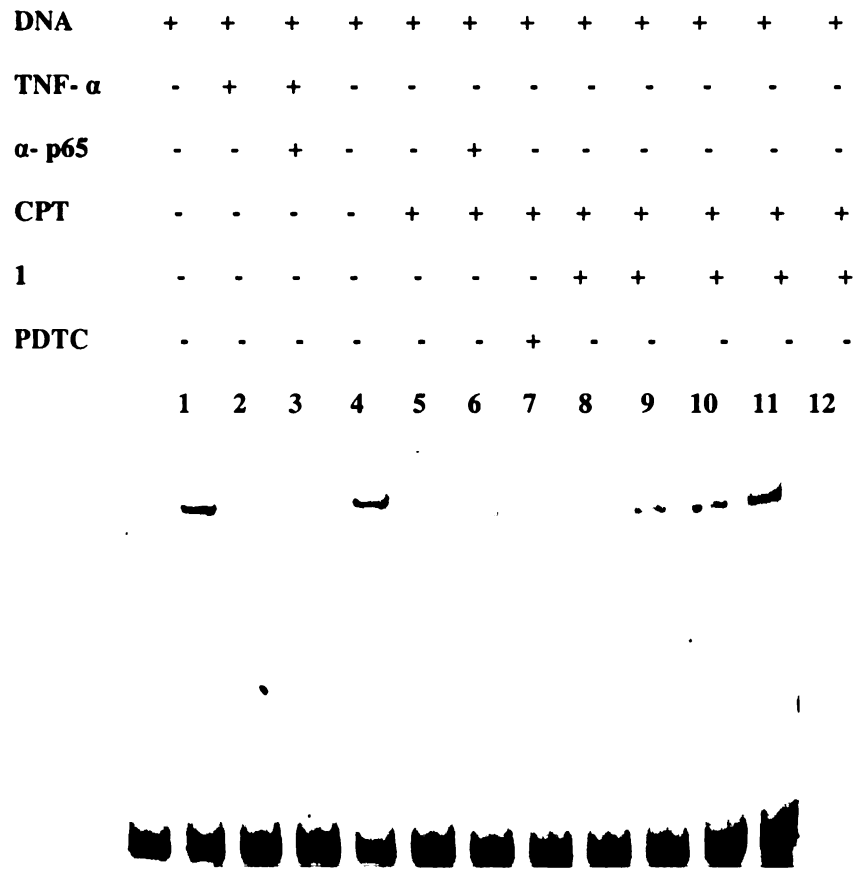


Figure V-5. Inhibition of CPT activated NF-κB binding by imidazoline **1** using EMSA. Lane1: κB consensus oligonucleotide; Lane2: NF-κB consensus oligo + nuclear extract (TNF-α); Lane3: NF-κB consensus oligo + nuclear extract (TNF-α)+ p65 antibody Lane4: NF-κB consensus oligo + nuclear extract(no activation); Lane 5: NF-κB consensus oligo + nuclear extract (1.0 μM CPT); Lane6: NF-κB consensus + nuclear extract (1.0 μM CPT)+ antibody p65; Lane 7: NF-κB consensus oligo + nuclear extract (1.0 μM CPT + 1 μM PDTC); Lane 8: NF-κB consensus oligo + nuclear extract (1.0 μM CPT + 1.0 μM imidazoline **1**); Lane 9: NF-κB consensus oligo + nuclear extract (1.0 μM CPT + 0.1 μM imidazoline **1**): Lane 10: NF-κB consensus oligo + nuclear extract (1.0 μM CPT + 0.01 μM imidazoline **1**); Lane 11: NF-κB consensus oligo + nuclear extract (1.0 μM CPT + 1.0 nM imidazoline **1**); Lane 12: NF-κB consensus oligo + nuclear extract (1.0 μM CPT + 0.1 nM imidazoline **1**).

Further, Sharma *et al* discovered that imidazoline **1** inhibits the translocation of NF-κB across the nuclear membrane in response to stimulation by camptothecin.[42]

iii. Effect of imidazoline 1 on I-κBα phosphorylation

As shown in Figure V- 1, the translocation of NF- κB requires the phosphorylation and subsequent degradation of its inhibitory protein I-κB by the 26 S proteosome resulting in the liberation of NF-κB.[47] Thus the effect of the imidazoline on I-κB phosphorylation and degradation was investigated using a pS32 ELISA on cytoplasmic extracts. Cytoplasmic extracts from CPT treated cells with or without a pre-treatment with imidazoline were analyzed for phosphorylation at ser-32 and 36. ALLN, a proteosome inhibitor[48] and parthenolide, an IKK inhibitor[34k-l] were used as controls to mark the two steps involved in I-κB degradation leading to NF-κB translocation and gene transcription. Parallel to the pS32 ELISA, the total I-κB levels in were measured to accurately determine the percent phosphorylation. As anticipated, the proteosome inhibitor, ALLN showed accumulation of phosphorylated I-κB, whereas the IKK kinase inhibitor indicated a decrease in phosphorylation. Pretreatment of the cells with imidazoline **1**, showed a profile similar to ALLN. Similar experiments were performed using TNF-α to activate the leukemia cells. Both TNF-α and camptothecin are known to activate NF-κB by I-κB degradation following phosphorylation at ser32 and ser36 in CEM cells though with varying kinetics.[42] These studies indicate that imidazoline **1** inhibits nuclear translocation of NF-κB via the inhibition of I-κB degradation (Figure V-6).

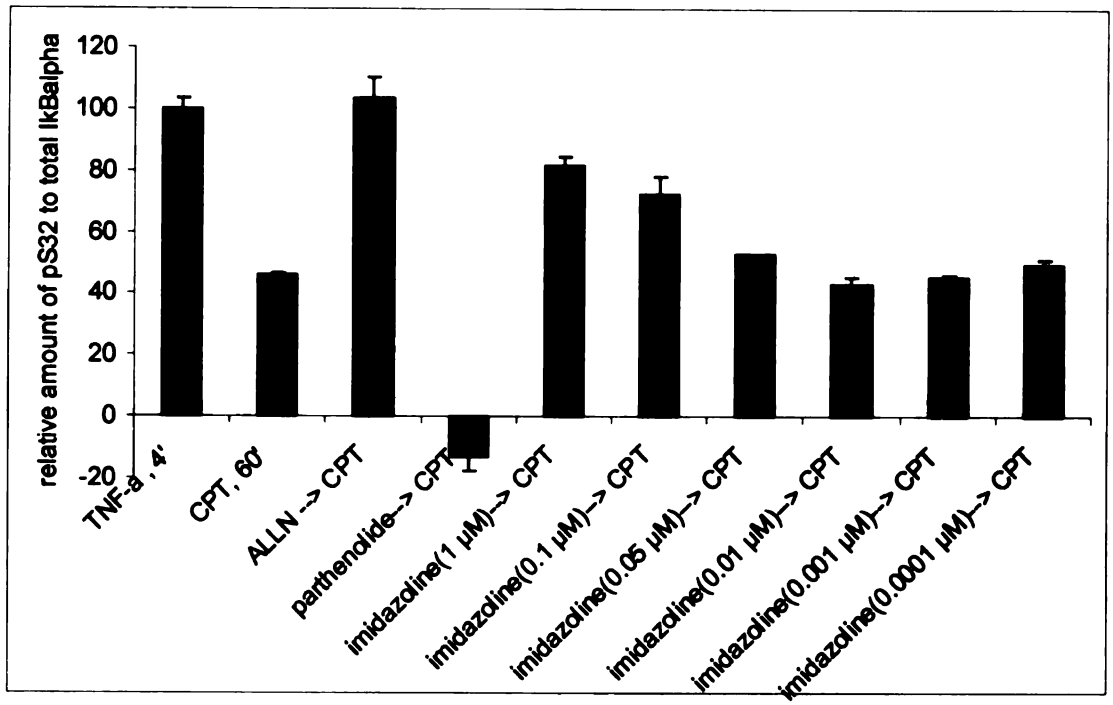


Figure V- 6. Relative amount of phosphorylated I-κB (at serine 32 and serine 36). All values were normalized to maximum accumulation seen in ALLN control. All experiments were run in duplicate and data reported as the average of the two independent experiments.

Further, luciferase based reporter assays were used to confirm the modulation of NF-κB pathway by imidazolines upstream of binding with DNA. 1 μM imidazoline inhibited NF-κB induced transcription by 52% and 35% for TNF-α and CPT mediated NF-κB activation signal respectively.[42]

In an active collaboration with Chemgenics Therapeutics Incorporation, Menlo Park, CA we studied the effect of these drugs in mouse models. RIF-1 tumor cells were injected sub-cutaneously and allowed to grow to approximately 100 mm^3. Administration of drugs was then started and the number of days that the tumor took to reach 'four times' its original size, were counted (Figure V- 7). Their observations were found to be in agreement with those done by us on CEM cells (Figure V-4).

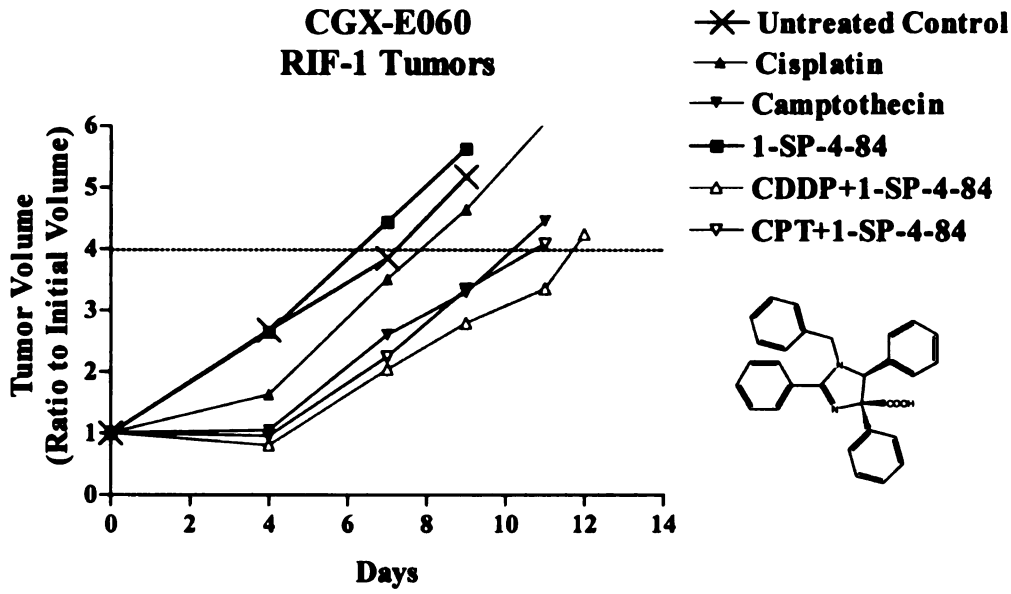


Figure V-7. Decrease in the tumor size in RIF-1 tumors. Tumor volume (y-axis) vs. Days (x-axis) to 'four times' volume. Chemotherapeutic drug: 8 mg/ 1kg; Imidazolines: 100 mg/ 1kg.[49]

8) Significance

Antitumor drugs exert their antitumor activity *via* the initiation of apoptotic signaling pathways ultimately resulting in cell death. Concomitant with the initiation of this apoptotic cell signal, many chemotherapeutic agents induce anti-apoptotic signaling pathways, which have compromised the efficacy of these antitumor agents in the clinic. Inhibition of this anti-apoptotic transcription factor retards this cellular resistance. The chemosensitizing agent **1** was found to sensitize leukemia cells at nanomolar concentrations to camptothecin and drastically enhance the level of camptothecin mediated apoptosis. Combination therapy of CEM cells with camptothecin and the imidazoline **1**, provided ~75 fold enhancement of efficacy after 48 hours. The ability of the imidazoline to enhance the apoptotic events initiated by camptothecin is postulated to be *via* the

inhibition of the NF-κB signaling pathway. These studies indicate that combination therapy of classical anticancer agents with small molecule NF-κB inhibitors has the potential to target this chemoresistance and provides a new strategy to treat chemoresistant tumors. Work towards a detailed molecular mechanism and the clinical potential of these agents is currently under investigation in our laboratory.

B. Catalytic Asymmetric Synthesis of 4, 5-dihydro-1, 3-oxazin-6-ones. Precursors to α, β-dialkyl-β-amino acids using Imidazoline-4-amides as Novel Organocatalysts

1) Introduction to β-amino acids.

During the last decade, stereoselective synthesis of β-amino acids has gained considerable attention due to their structural and important pharmacological properties.[50] They exhibit powerful anti-bacterial properties and are key constituents of naturally occurring peptides, terpenes, alkaloids, and macrolides, and as potential precursors for β-lactams.[51, 52] It is well known that the β-amino, α-hydroxyphenylpropionic acid side chain in taxol[53] and related terpenoids is crucial for their anti-cancer activity. Substituted aspartic acid derivatives are currently of interest medicinally for use as inhibitors of L-asparagine synthetase,[54] key constituents of several proteins involved in blood-clotting cascade[55] and for their ability to act as non-transportable glutamate transporter blockers.[56] Although less abundant than the α-amino acids, β-amino acids occur in nature in both free and bound form in peptides. They tend to be stronger bases and weaker acids compared to α-amino acids. β-amino acids are hence used as α-amino acid surrogates for the construction of peptides which, because of different skeletal pattern possess interesting folding patterns and conformational properties and hence enhanced activity and metabolic stability.[57]

The main approaches[58] available till date for the stereoselective synthesis of β-amino acids include Arndt-Eistert homologation of α-amino acids, enzymatic resolution, alkylation of enolates derived from perhydropyrimidin-4-ones and

aspartic acid derived oxazolidinones and butanolides, hydride reduction of chiral aziridine carboxylate esters and subsequent oxidation of product alcohols[59], addition of enolates or their equivalents to imines, Curtius rearrangement, Michael addition of nitrogen nucleophiles to α,β-unsaturated esters or imides with or without trapping of intermediate enolates with electrophiles at the α-position, hydrogenation, amino hydroxylation and β-lactam synthesis. Although a plethora of synthetic methods use chiral auxillaries or substrate control for achieving stereoselectivity, catalytic asymmetric synthesis of β-amino acids is just coming of age. Jacobsen[60]and Miller[61, 62] have exploited the sequential azidation/ reduction of α, β-unsaturated carbonyl compounds to this end. A different approach recently reported by Boger utilizes the Sharpless asymmetric amino hydroxylation of cinnamate esters.[63]

2) Nucleophilic catalysts and stereocontrol in reaction of ketenes and imines

Chemists have long used ketenes as useful intermediates in the synthesis of organic molecules. Since Staudinger's original discovery, numerous research groups have made advances both in the generation and reactions of ketenes. Catalytic stereoselective transformations of ketenes *via* [2+2] and [4+2] cycloadditions are at the forefront of research in present times.[64]

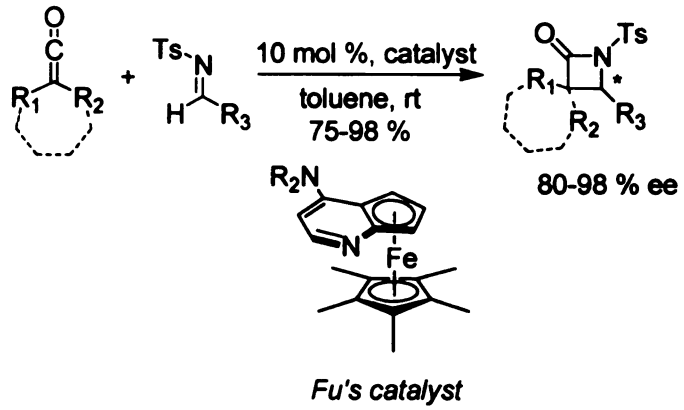


Figure V-8. Planar chiral heterocycles for enantioselective additions to ketenes

Fu and co-workers have used the planar-chiral heterocycles (Figure V-8) as catalysts for the enantioselective addition of alcohols to ketenes and anhydrides.[65] They have also extended the utility of these catalysts in the enantioselective synthesis of β-lactam derivatives.[66] The reaction is mechanically distinct /inverse from the usual [2+2] cycloaddition or the Staudinger reaction between ketenes and imines. General mechanism for a nucleophilic catalyst mediated stereocontrol in β-lactam synthesis is shown in Figure V-9. Addition of a tertiary amine to a ketene presumably generates ammonium enolate A. This enolate can react with an electrophilic imine generating zwitterionic intermediate B. Cyclization of the intermediate B generates the β-lactam and regenerates the catalyst. Asymmetric induction is imparted at the intermediate A, where the catalyst blocks one π-face of the ammonium enolate, thereby setting the α-stereogenic center. The catalyst further controls the orientation of the approaching electrophile (imine) through non-bonding interactions, thereby setting the β-stereogenic center.

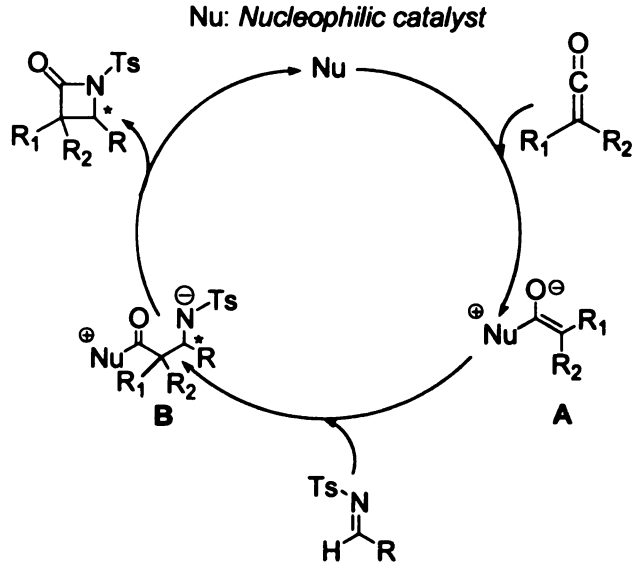


Figure V-9. Mechanism for stereocontrol by a nucleophilic catalyst

Lectka[67] and co-workers have reported a remarkable catalytic system consisting (Figure V-10) of a chiral organic base and a Lewis acid. They have used 10 mol % benzoylquinine (Cinchona alkaloid) as chiral nucleophile or organocatalyst. Addition of 10 mol % In (III) triflate resulted in dramatic enhancement of reaction rates and chemical yields. In fact, the same catalyst performs additional roles of generating the imine *in situ* and also ring-opening by alcohols amines and amino acids to provide β-amino acid derivatives.

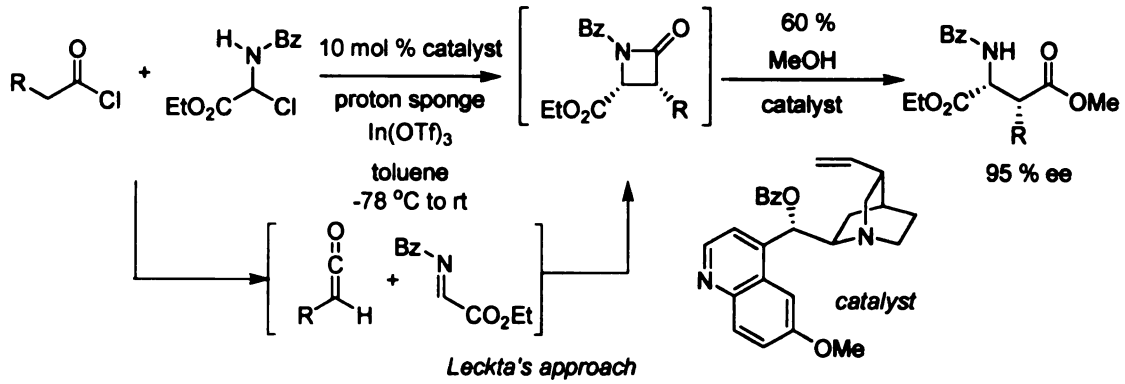
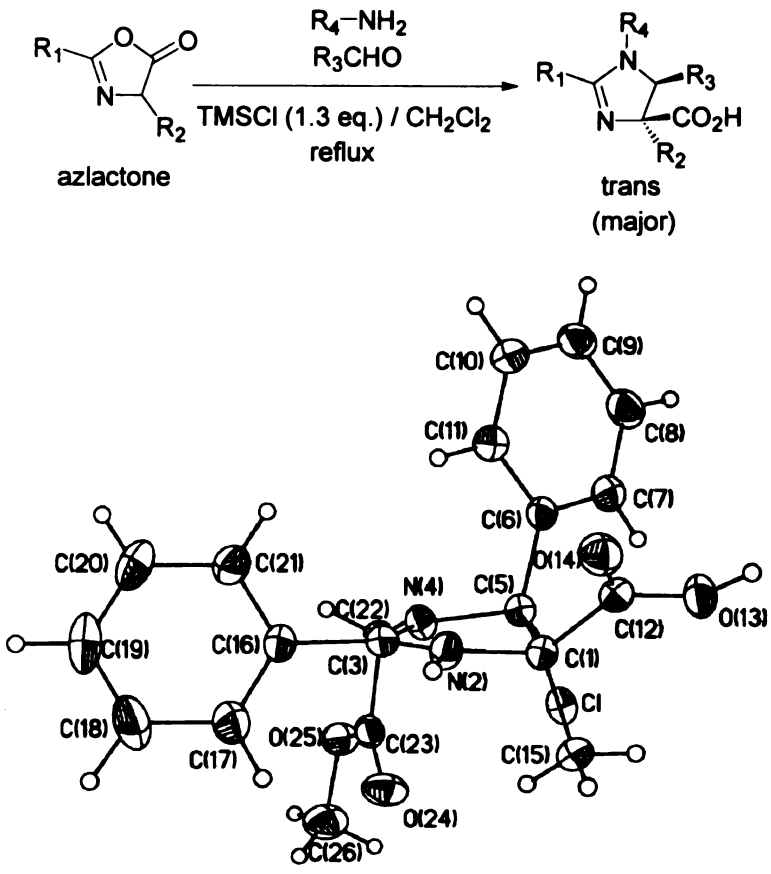


Figure V-10. Use of Cinchona alkaloid derivative as a multifunctional nucleophilic catalyst

3) Imidazolines as nucleophilic catalysts

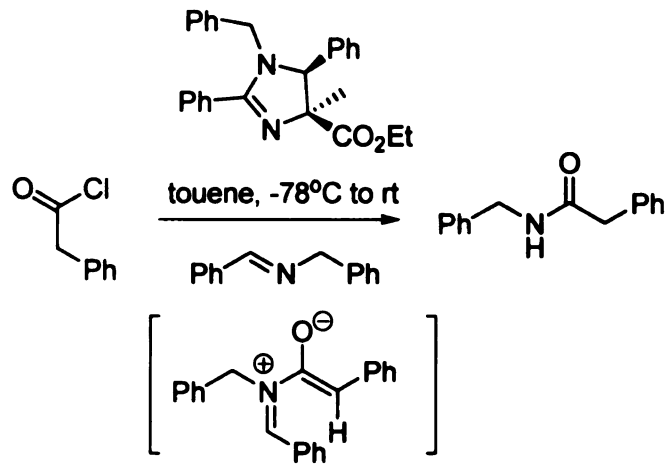
We recently[68, 69] reported a diastereoselective multi-component synthesis of highly functionalized imidazolines (Scheme V-1). A silicon mediated 1, 3 dipolar cycloaddition of the *in situ* generated münchnone with an imine resulted in the formation of highly substituted imidazolines. The imidazolines contain four-point diversity and two stereocenters and the cycloaddition reaction is applicable to aryl, alkyl, acyl and heterocyclic substitutions. The most widely used organocatalysts have a five membered heterocyclic moiety, proline, Kagans's prolinol, MacMillian's imidazolidinone catalyst.[70] We realized that above imidazolines, on account of unique arrangement of groups around a rigid five-membered ring had a accessible face comprising of the iminic nitrogen and carboxyl group and a hindered face. Hence they seem to have a pocket or catalytic core with requisite groups and could possibly be used as organocatalysts. Thus, the present studies focused on the synthesis of enantiopure imidazoline derivatives and their use as chiral organic bases / catalysts for the reaction of ketenes with imines.



Scheme V-1. *TOP*: Multi-component synthesis of imidazolines.
BOTTOM: X-ray structure of **III-7-1**.

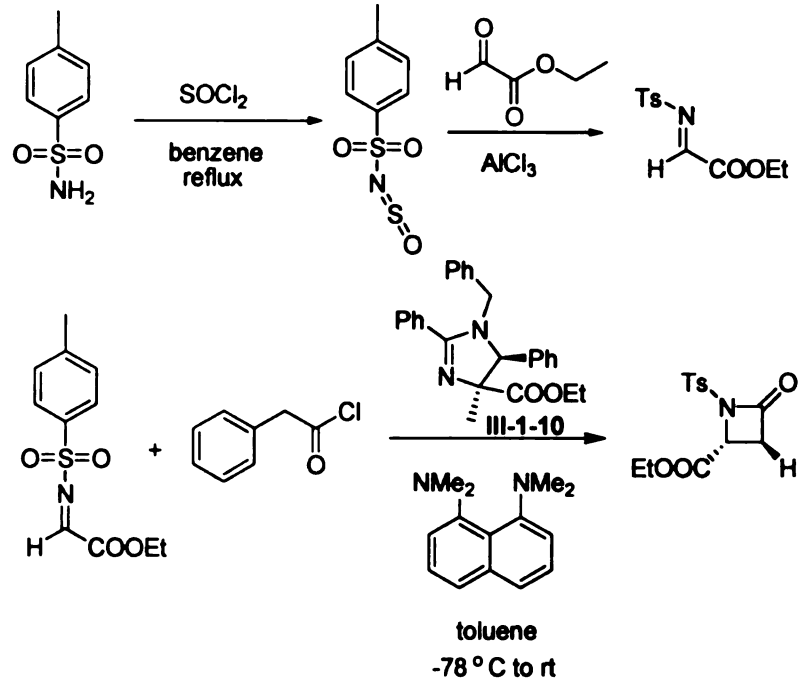
In order to achieve imidazoline catalyzed enantioselective β-lactam synthesis few reactions were attempted. They have resulted in the formation of the amide probably formed from the intermediate acyliminium ion (Scheme V-2). It has been found in the literature that only *N*-tosyl iminoesters[71] (electron deficient) have been used in the asymmetric synthesis using nucleophilic catalysts. But there is no report concerning the use of nucleophilic imines in the catalytic synthesis of β-lactam. Initial attempts to achieve the β-lactam synthesis using *N*-benzylidene-benzylamine (**III-*I*-1**) in presence of racemic imidazoline-4-carboxylic acid and

esters were not successful and resulted in the formation of the corresponding amide (Scheme V-2).



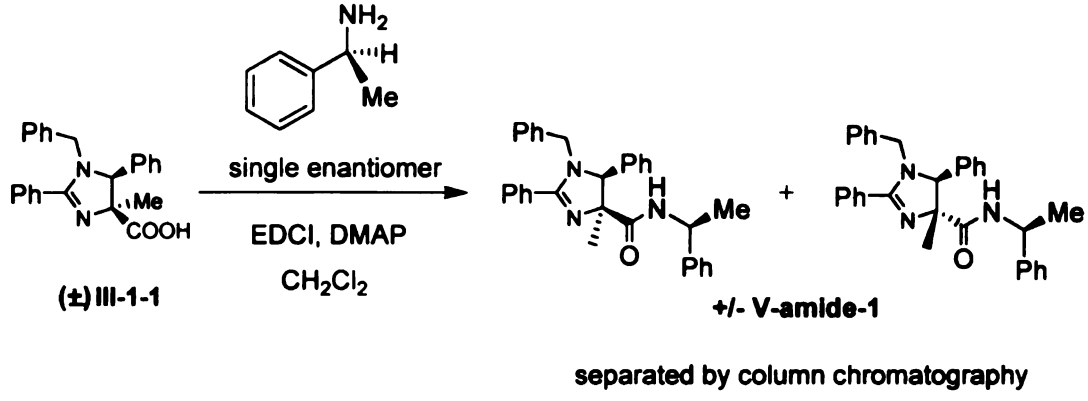
Scheme V-2. Failed attempt to β-lactams using racemic imidazoline-4-carboxylates.

N-tosyl imine of ethyl glyoxylate resulted in the formation of *trans*-β-lactam in moderate yield, using non nucleophilic base (proton sponge) and racemic ethyl imidazoline-4-carboxylate. Whereas the synthesis of β-lactam using only DMAP and TEA resulted in the formation of mixture of *cis* and *trans* (1:4) β-lactam in good yields (Scheme V-3).[72]



Scheme V-3. β-lactams from *N*-tosyl-α-iminoester using racemic imidazoline catalyst

4) Preparation of chiral imidazoline-4-amides catalysts



Scheme V-4. Synthesis of chiral imidazoline-4-amide catalysts

Resolution of 1-benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid with *R*-(+)-1-phenyl-ethylamine using EDCI and DMAP in DCM resulted in the diastereomeric mixture which was separated by column chromatography, providing enantiopure amides (Scheme V-4). Similarly *S*-(-)-1-phenyl-ethylamine also resulted in the formation of diastereomers separable by

column chromatography.[72] We decided to use imidazoline 4-amide as catalysts for following reasons;

i) they could be obtained in enantiomerically pure form.

ii) the amide side chain may form a hydrogen bond with the enolate (zwitterionic species formed with ketene) and thus stabilize the enolate.

iii) it may enhance the steric block on a π-face of the enolate and achieve high amount of stereocontrol. The absolute configurations are unknown for the amides because in the x-ray structure the α-methyl group was missing in the amide side chain and hence had to be discarded.

5) Three component synthesis of 4, 5-dihydro-1, 3-oxazin-6-ones

(Toluene-4-sulfonylimino)-acetic acid ethyl ester (1 mmol) and phenyl ketene generated in presence of proton sponge (1 mmol) and the catalyst **(+)-V-amide-1** (30 mol %) were allowed to react at -78°C for 12 h and two products, which could not be separated by column chromatography were obtained (Entry **V-1**, Table V-1). The reaction was carried out over a longer time (-78°C, 36h) (Entry **V-4**, Table V-1) and the 4, 5-dihydro, 1, 3-oxazin-6-one was formed in moderate yields after some optimization (by crude spectra) and was purified by column chromatography. The mass spectra of the product indicated the addition of two molecules of ketene to (toluene-4-sulfonylimino)-acetic acid ethyl ester. The ^{1}H NMR spectra and ^{13}C NMR spectra also supported the addition of two molecules of ketene to (toluene-4-sulfonylimino)-acetic acid ethyl ester. The structure of the product 2-benzylidene-6-oxo-5-phenyl-3-(toluene-4-sulfonyl)-[1, 3] oxazinane-4-

carboxylic acid ethyl ester **V-6a** was unequivocally established by X-ray crystallographic data (Figure V-11).

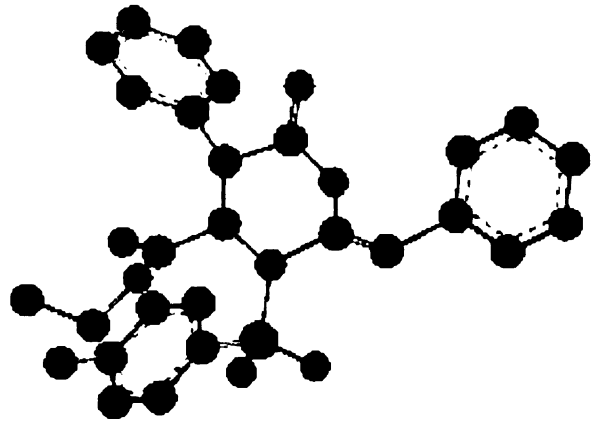
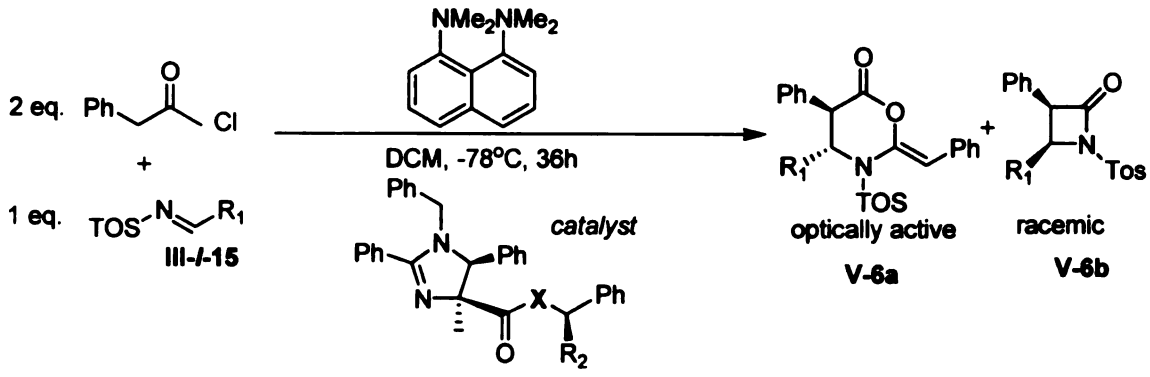


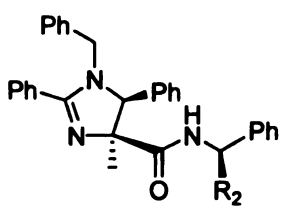
Figure V-11. X-ray structure showing *trans* geometry of dihydrooxazinone.

The reaction was repeated using 7 equivalents of ketene (Entry **V-7**, Table V-1) and 60 mol % of catalyst (Entry **V-6**, Table V-1) but no significant increase in the yield was achieved. Use of stoichiometric catalyst led to complex reaction mixture.[72]

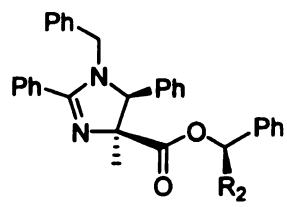


Entry	R_1	R_2	X	Catalyst	Acid chloride & Proton sponge	% yield(a)	% yield(b)
V-1	$-CO_2Et$	Me	N	(+)-V-amide-1, 0.3 eq.	1 eq.	products not separable[d]	
V-2	$-CO_2Et$	Me	N	(+)-V-amide-1, 0.3 eq.	1 eq.	products not separable[e]	
V-3	$-CO_2Et$	Me	N	(+)-V-amide-1, 0.3 eq.	1 eq.	poor yields	
V-4	$-CO_2Et$	Me	N	(+)-V-amide-1, 0.3 eq.	2.5 eq.	30 %	-
V-5	$-CO_2Et$	Me	N	(-)-V-amide-1 0.3 eq.	2.5 eq.	30 %	-
V-6	$-CO_2Et$	Me	N	(+)-V-amide-1 0.6 eq.	2.5 eq.	37%	10 %
V-7	$-CO_2Et$	Me	N	(+)-V-amide-1 0.6 eq.	7 eq.	37%	10 %
V-8	$-CO_2Et$	Me	N	(+)-V-amide-1, 1 eq.	2.5 eq.	messy reaction	
V-9	-Ph	Me	N	(+)-V-amide-1, 0.3 eq.	2.5 eq.	20%	10%
V-10	-Ph	Me	N	(+)-V-amide-1, 0.6 eq.	2.5 eq.	35%	10%
V-11	-Ph	Me	O	(-)V-ester-2, 0.6 eq.	2.5 eq.	0%	50%
V-12	-Ph	H	N	(+/-)V-amide-2, 0.6 eq.	2.5 eq.	0%	0%

d. toluene, -78 °C, 12h; e. DCM, -78°C, 12h



+/- V-amide-1

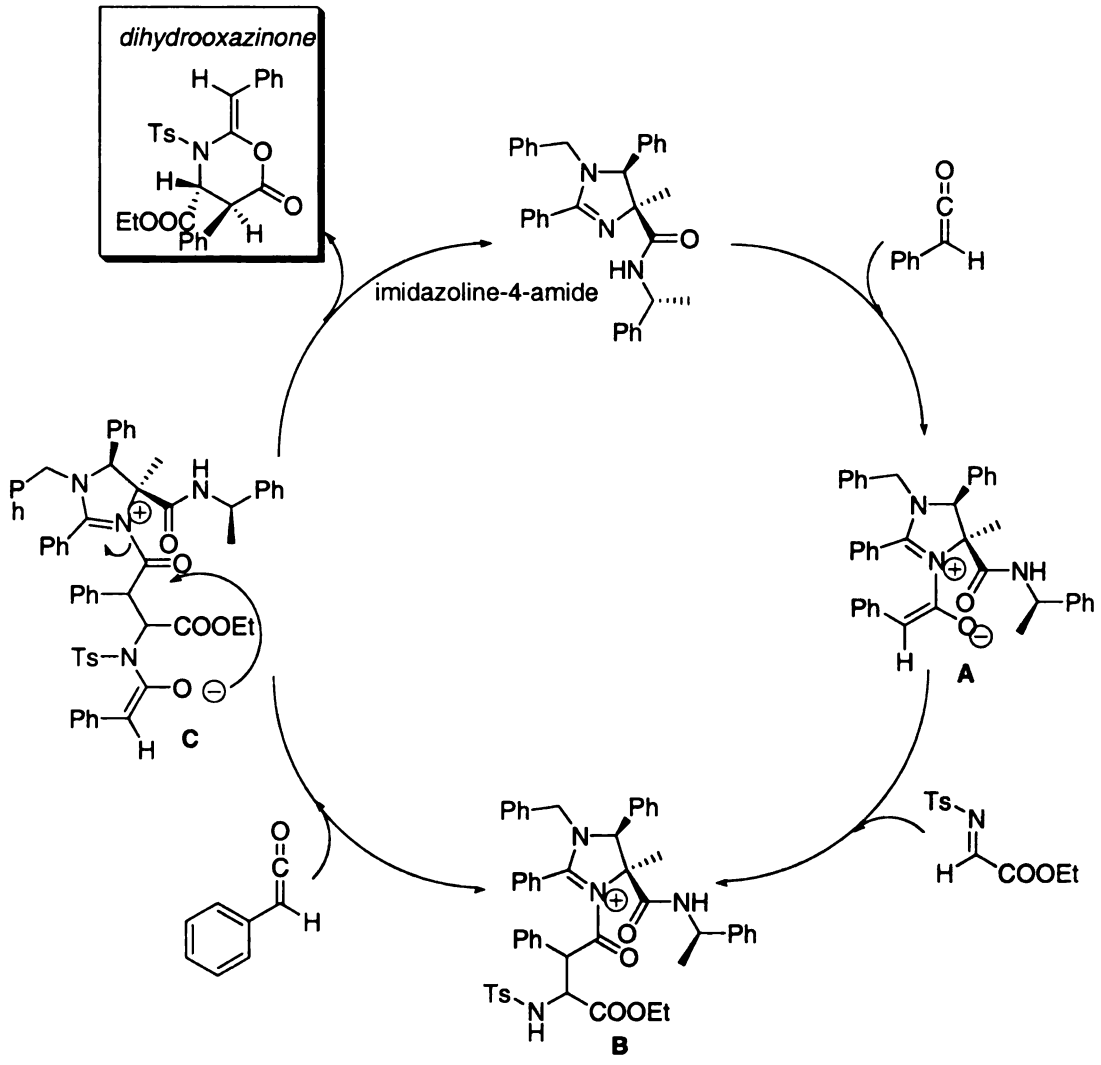


+/- V-ester-2

Table V-1. Synthesis of dihydrooxazinones using imidazoline based catalysts

Several reports in the 1970's indicated the formation of the racemic form of the above dihydrooxazinone.[73-77] One report from Furukawa *et al*[78] described the asymmetric synthesis of β-amino-α, α-dimethyl-β-phenylpropionic acid via the asymmetric synthesis of the dihydrooxazinones by using a chiral imine auxillary. To our knowledge, this is the first example of a catalytically induced asymmetric multi-component synthesis of dihydrooxazinones. These dihydrooxazinones can simply be hydrolyzed to the chiral α,β-substituted,β-amino acids.[78]

The proposed mechanism for the formation of the dihydrooxazinones is depicted in the following Scheme V-5.[72] Acid chloride or ketene can react with imidazolines-amide leading to the formation of intermediate A (see also Figure V-2). It is possible intermediate **A**, the ammonium enolate is stabilized because of the hydrogen bond with the amide -NH. Intermediate **A** on reaction with imine leads to another intermediate **B** (only one π-face of enolate blocked by catalyst). Intermediate **B** collapses to form β-lactam in cases where other catalysts are used. In our case steric block (possibly the α-methyl of amide side chain) prevents C-N bond rotation and cyclization. Intermediate B hence reacts with another molecule of ketene and leads to the formation of intermediate C which on intramolecular ring closure and elimination of catalyst affords the 2-alkylidene-4, 5-dihydro-1,3-oxazin-6-one (Scheme V-6). The above proposed mechanism seems very likely as, the dihydrooxazinone was obtained as a single diastereomer and in 70 % enantiomeric excess.



Scheme V-5. Proposed mechanism for catalytic synthesis of dihydrooxazinones

6) Problems so far[72]

1. Importance of the 4-amide side chain, need to be ascertained clearly.

2. The preparation of (toluene-4-sulfonylimino)-acetic acid ethyl ester is not trivial and the imine has to be used immediately because it decomposes very fast.

3. The highest yield obtained is 30 % and this results in very difficult separation problems. The product has to be subjected to column chromatography at least three times to get analytically pure material.

4. The absolute stereochemistry of catalyst imidazoline-4-amides is not known as the x-ray structure misses the α-methyl group from the 1-phenylethyl side chain. This observation could not be rationalized by simple reasoning.

5. The enantiomeric excess need to be determined with more confidence. The racemic dihydrooxazinone is needed for this purpose. To this end, resolution by aminolytic ring opening with optically active amino acid has been attempted but without any success.

7) Modifications to methodology

1. (Toluene-4-sulfonylimino)-acetic acid ethyl ester is highly unstable and the preparation is neither trivial nor reliable in terms of yields or purity. Hence, we decided to try aromatic aldimines, which are more stable and hence allow several manipulations of the reaction condition and optimization of product yields and enantiomeric excess. Under identical conditions as used before, catalyst **(+)-V-amide-1** (30 mol %) resulted in 20 % yield with N-benzylidinetosylamine (**III-*I*-15**) (Entry **V-9**, Table V-1). Doubling the amount of catalyst increased the yields to 35 %, indicating that aryl aldimines are less reactive than α-iminoesters. However, they are a lot easier to prepare and are stable molecules which have long shelf life. Even the multi-component reaction is much cleaner than with the tosylimino ester.

2. Replacing the 4-amide side chain with the ester, catalyst V-ester-1 (60 mol %) afforded the β-lactam in 50 % yield. No dihydrooxazinone was observed (Entry **V-11**, Table V-1).

3. Racemic benzylamide **V-amide-2** did not result in a productive reaction (Entry **V-12**, Table V-1).

8) Three component to a two-component synthesis of dihydrooxazinones

Continuing with our pursuit for a more reactive imine than *N*-benzylidine tosylamine (**III-*I*-15**) and more stable than the tosyliminoesters, made us focus on the improved procedure by Lectka and co-workers[79] for synthesis of β-amino esters with Cinchona alkaloid derivatives. They generated *N*-acylimines by *in situ* dehydrohalogenation of *N*-acyl-α-chloroaminoesters. The imines were reactive but again unstable; hence preparation of imines *in situ* was preferred. Kobayashi[80] have reported an asymmetric Mannich reaction using *N*-acylimines generated by using polymer bound bases. We decided to pursue the use of Kobayashi's method for the generation of N-acylimines from *N*-acyl-α-chlorogylcinate ethyl ester using polystyrene bound piperidine as the base of choice (Scheme V-6).[80]

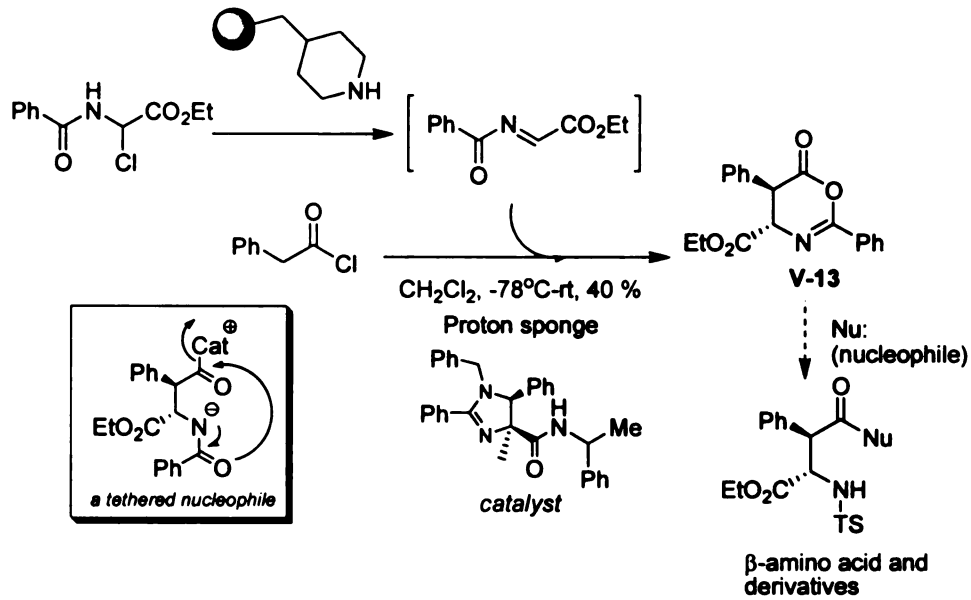
We realized an inherent advantage in using the N-acylimines, not only because they are they reactive but they present an internal nucleophile after enolization.

i. In essence, we would have achieved tethering of the second equivalent of ketene involved in the three component synthesis of dihydrooxazinones.

ii. The internal nucleophile (enolic –OH) would probably lead to higher rates of dihydrooxazinone synthesis vs. the background non-catalyzed β-lactam synthesis.

iii. More diversity can be introduced, because of replacement of second equivalent of ketene with the acyl group from the imine.

iv. The product can be expected to be more reactive than the 2-exo-substituted dihydrooxazinones that were obtained before.



Scheme V-6. Synthesis of 2-aryl dihydrooxazinones from N-acylimines

N-benzoylimino ethyl glycinate was made by dehydrohalogenation of N-benzoyl-α-chloro ethylglycinate in a separate vessel using polystyrene bound piperidine. The imine was then transferred to a separate reaction vessel and reacted with phenylacetyl chloride using **(+) V-amide-1** and proton sponge, using the same conditions as before (Scheme V-6). After acid-base workup and a short silica-gel column, the product was precipitated using DCM/ether/hexanes mixture. Although, both proton NMR and EIMS indicated the proposed dihydrooxazinone, the material could not be obtained analytically pure. Dihydrooxazinones like **V-13**, six membered analogues of azlactones have been reported as intermediates during Arndt-Eistert reaction of peptides.[81] They are extremely short-lived and prone to polymerization.[82]

Though disappointing, the chemistry is possible and with appropriate substitution it should be possible to isolate pure 2-aryldihdyrooxazinones. It would be interesting to see their use as templates for synthesis of heterocycles in comparison to azlactones.

C. Chiral 4-hydroxymethyl imidazolines as ligands for diethylzinc addition.

1) Introduction

The synthesis of organic compounds is ultimately dependent on the formation of carbon-carbon bonds. It is, therefore, clear that the most expeditious route to chiral compounds is one in which a carbon-carbon bond and a stereocenter are formed in a single step with high enantioselectivity.[83] The use of catalytic quantities of metal complexes containing chiral ligands has proven to be a particularly fruitful approach to asymmetric catalysis.[84] Generally, the emphasis in designing ligands has been on maximizing the difference in steric effects between the alternative pathways in the enantio discriminating step. However, in recent times the important role of electronic effects in influencing enantioselectivity is being recognized and exploited, and some examples of strong electronic effects have been reported, mostly involving phosphorus ligands. [85]

2) Imidazolines as N-heterocyclic carbene ligands

2-Imidazolines have found wide application as potent N-heterocyclic carbene ligands in organometallic catalysis.[86] N-Heterocyclic carbenes (NHCs) are being used increasingly in organometallic chemistry as neutral two-electron-donor ligands, commonly replacing phosphines in that role. Some attractive features[87] of NHCs are:

i. The strong σ-donating capability and low level of π-acidity of these ligands provide their metal complexes with electronic properties that are often quite different from those with phosphines or other traditional neutral ligands.[88] This change can sometimes enhance the reactivity of metal-based catalysts that feature

NHCs. Examples of this improved reactivity include ruthenium-based olefin metathesis catalysts[89] and palladium-based catalysts for C-C and C-N coupling reactions.[90]

ii. The possible diversity in the substituents on the nitrogen atoms, which allows for a wide range of steric, [91] asymmetric, [92, 93] and electronic features.

iii. It is possible to functionalize these nitrogen substituents in such a way as to make ligands capable of chelation.[94, 95] Such variability has led to the synthesis of NHC analogues of many traditional ligands.

iv) In contrast, to the corresponding phosphine complexes, ligand dissociation has never been observed so that these catalysts normally do not depend on an excess of ligand.[86] These properties make them suitable for chiral modifications.

3) Imidazolines as nitrogen ligands

Nitrogen ligands are widely used in asymmetric catalysis and, while relatively few examples of electronic tuning have been reported pronounced effects have been noted.[84] Oxazolines and amines are the most widely used chiral nitrogen ligands, but unfortunately there is no straightforward approach to electronic tuning of either of these types of donor. Although ligands carrying an imidazoline unit are structurally very similar to oxazoline ligands, they have not received much attention.[94] 4-Substituted 2-imidazolines are potentially useful as catalysts and ligands, especially since they have the same shape as oxazolines and should therefore give comparable enantioselectivity. Phosphino-oxazolines **2** (PHOX ligands) are versatile chiral ligands that have found a wide range of applications in asymmetric catalysis.[95] Cationic iridium complexes derived from these ligands

have proven to be highly effective catalysts for the enantioselective hydrogenation of imines and olefins, including unfunctionalized alkenes.[96] Crystal structures of PHIM (Phosphino-imidazoline) complex and the corresponding PHOX complex, bearing the same substituents at the phosphorus atom (*o*-Tol) and the stereogenic center (*t*Bu), closely resemble each other (Figure V-12). However, the torsion angles (τ) between the central phenyl ring and the five-membered heterocycle differ by 20 ° (C-C-C-O angle = -11 ° vs C-C-C-N angle = -31 °). The Ir-P distances (2.3009(12) in **1i** vs 2.3055(17) Å in **Ir-2**) and the Ir-N distances (2.080(5) vs. 2.106 (3) Å) are almost identical, indicating that the electron densities on the coordinating nitrogen atoms are similar.[94]

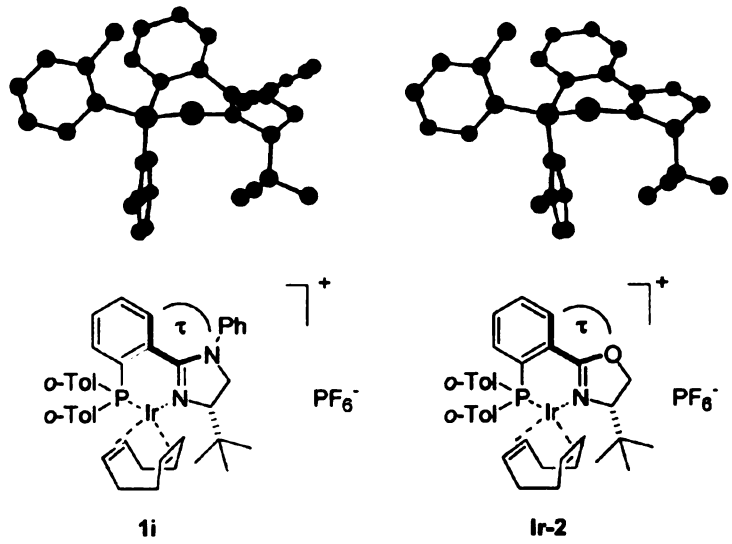


Figure V-12. PHIM and PHOX ligands in solid state. Anions and COD's not shown.

However there are some important differences between the two ring systems: [84, 94]

i. Imidazolines are much stronger bases than oxazolines. As a result they are stronger donors, which may be an advantage in some reactions.

ii. The additional nitrogen atom provides a handle for tuning the electronic and conformational properties of the ligand by proper choice of the R_3 group.

iii. R_3 group could also serve as a linker for attaching the ligand to a solid support.

iv. Importantly, changes in R_3 substituents do not significantly affect the chiral environment created by the group at the 4-position, i.e. the electronic and steric properties can be varied independently of each other.

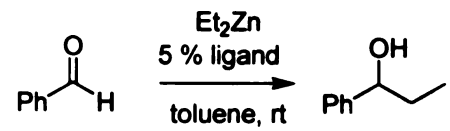
Despite this potential, there are few reports of their use as chiral ligands. Brunner made a brief reference to their use in Rh-catalyzed hydrosilation reactions[97] and Morimoto showed that imidazolines bearing an additional sulfur donor gave excellent enantioselectivity in Pd-catalyzed allylations.[98] Recently, Davies used ruthenium complexes of pyridyl imidazolines as Lewis acids.[99] Dupont used biiimidazolones in Pd-catalyzed hydroarylations.[100] Claver reported that pyridyl imidazolines are useful ligands for Pd-catalyzed alkene/CO copolymerizations and noted some electronic effects.[101] Brusacca found that the nature of the 1-substituent of 2-(phosphinoaryl)imidazoline ligands had a substantial effect on the yield and enantioselectivity of an intramolecular Heck reaction.[102]

i. 2-hydroxymethylimidazolines ligands for diethylzinc additions to aldehydes

Substantial effort has been put forth to develop methods to promote the asymmetric addition of alkyl groups to aldehydes and ketones since 50 years.[83] For many years, these investigations were largely unsuccessful due to the highly reactive nature of the organomagnesium and organolithium reagents employed. The breakthrough did not come until 1984, when Oguni[103] discovered that organozinc reagents added enantioselectively to aldehydes in the presence of chiral amino alcohols.[104, 105] Extensive mechanistic studies, primarily from the Noyori group with DAIB (Figure V-12),[106-110] have greatly contributed to the present understanding of the mechanism of reaction. The design of catalysts for the asymmetric addition of organozinc reagents to aldehydes to give chiral secondary alcohols has become the focus of intensive research in present times.[104, 105, 108] A large number of catalysts for this reaction have been developed that rely on either Lewis basic or Lewis acidic for catalyzing the reaction.[111] The addition of diethylzinc to aldehydes has been studied exhaustively and amino alcohol catalysts are available that give excellent enantioselectivity for a wide range of aldehydes. While there is no pressing need to develop new catalysts, the surprising and dramatic electronic effects described above with imidazoline are deserving of further study in their own right.

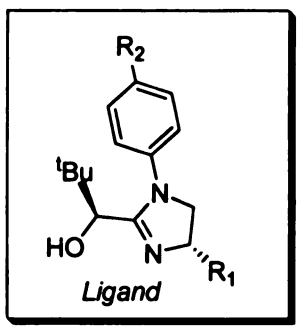
Casey *et al* prepared a series of chiral 2-(hydroxyalkyl)imidazolines from enantiopure amino alcohols.[84,112] These imidazolines were expected to be similar to β-aminoalcohols in electronic properties, and were used as catalysts for the

addition of diethylzinc to aldehydes (Figure V-13). The study was designed mainly to observe the effect of ligand electronics on enantioselctivity as this aspect has rarely been studied so far.[84]

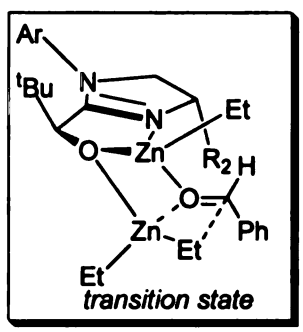


aldehyde

R_1	R_2	% ee, configuration
Bn	CF_3	15%, *R*
^{i}Pr	CF_3	62%, *S*
^{i}Pr	Me	21%, *R*
^{i}Pr	OMe	87%, *S*
^{t}Bu	OMe	26%, *S*



Ligand



transition state

Figure V-13. 2-hydroxymethylimidazoline ligands for diethyl zinc addition.

The following trends were observed by Casey *et al*[84]

i. Diastereomer with C_4 substituent on opposite face of carbinol group as shown in Figure V-13, was the only active isomer. This indicated that the stereochemistry at both centers and especially at carbinol center was important.

ii. The predominant formation of (*S*)-alcohols from (*S*)-carbinol ligands was consistent with the observed trend for amino alcohol catalysts.

iii. Isopropyl substituent at C_4, gave the best result, but further increase in size to t-butyl was detrimental.

iv. The predominant formation of (*S*)-alcohol has been explained based on accepted models as shown in Figure V-13.

v. Most striking feature of the para substituents on 1-aryl group ($\mathbf{R_2}$), are that groups with stronger inductive effects gave higher % ee's.

vi. The electron donating 4-methoxy substituent results in *R*-alcohol like the electron withdrawing 4-trifluoromethyl group. This was suggested to be because of co-ordination of diethyl zinc, which makes 4-methoxy sucbstituent to be electron withdrawing.

The results reported above emphasize the importance of the concept of ligand designs that readily permit 'orthogonal' tuning of steric and electronic effects, and illustrate the potential of imidazolines in asymmetric catalysis, especially as electronically tunable alternatives to oxazolines.

ii. Our 4-hydroxymethylimidazolines as ligands for diethylzinc additions

To gain quick access to a diversity of ligands, a modular system comprised of simple components is essential. Utilizing amino acids from the chiral pool allows for the easy incorporation of chirality into the ligands and opens the way for a number of straightforward chemical modifications. Amino acids have been used as the basis for a variety of catalyst systems, and ligands that are based on proline, valine, tyrosine, tryptophan, serine, and leucine have been reported.[111] We have recently reported highly diastereoselective multicomponent one-pot synthesis of substituted imidazolines from amino acid based azlactones.[113, 114] These low

molecular weight imidazoline scaffolds contain four point diversity applicable to alkyl, aryl, acyl, and heterocyclic substitution. In light of the exciting work by Casey *et al* and the use of modular ligands based on amino acids for diethyl zinc additions to aldehydes, we decided to explore our chiral 4-hydroxymethyl imidazolines as ligands.

For this purpose racemic imidazoline-4-carboxylic acids derived from the cycloadditions were converted to diastereomeric esters using *R* (+)-1-phenylethanol. The diastereomeric esters were separated by column chromatography. Reduction with LAH, afforded the chiral 4-hydroxymethylimidazolines in excellent yields (Scheme V-7). The absolute configuration was determined for one pair of enantiomeric 4-hydroxymethyl imidazolines (Figure V-14).

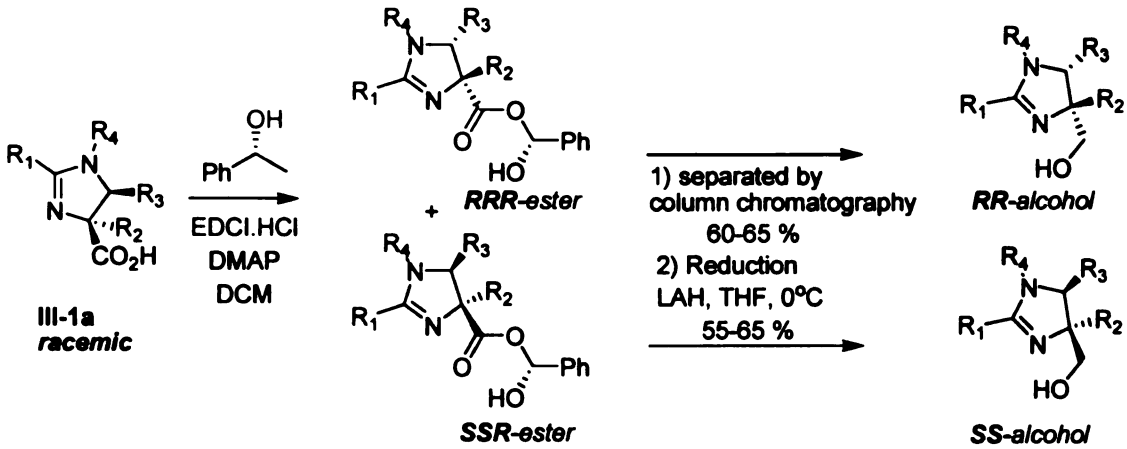
The 4-hydroxymethyl imidazolines tested proved to be moderately good ligands for addition of diethyl zinc to benzaldehyde. The following trend could be seen from the limited number of experiments performed (Table V-2).

i. The *S, S*-carbinol imidazolines resulted in S-configuration 1-phenylpropanol.

ii. The 1-(4-methoxyphenyl) substituted ligand showed reverse preference for configuration of 1-phenylpropanol as was seen by Casey and co-workers.

iii. Use of stoichiometric quantity of additive Lewis acid, Titanium isopropoxide following the method of Walsh and co-workers (Method B,

Table V-2) also resulted in opposite configuration of 1-phenylpropanol. There was no improvement in observed ee values.



Ester	R_1	R_2	R_3	R_4	alcohol
V-1-14	Ph	Me	Ph	Bn	V-1-17
V-1-15	Ph	Me	Ph	4-methoxy phenyl	V-1-18
V-11-16	4-methoxy phenyl	Me	Ph	Bn	V-11-19

Scheme V-7. Synthesis of chiral 4-hydroxymethyl imidazolines from racemic imidazoline-4-carboxylic acid (**III-1a**)

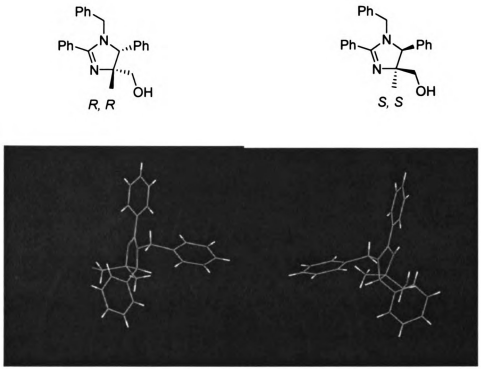
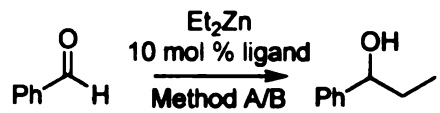
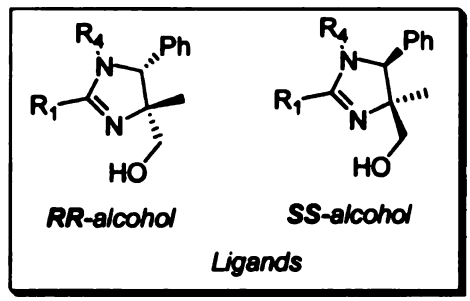


Figure V- 14. X-ray structures of chiral 4-hydroxymethylimidazolines (***R, R***) **-V-1-17** and (***S, S***) **-V-1-17** as ViewerLite 3D models.

iv. Use of chiral amides (of R-1-phenylethylamine), as Seto and co-workers have successfully employed, did not work in this case.

v. 4-isopropyl ligands could not be obtained as the corresponding esters could not be separated by column chromatography.





R_1	R_4	catalyst configuration	Method	% yield	% ee, configuration
Ph	Bn	*SS*	A	60	29%, *S*
Ph	Bn	*SS*	B	80	0%
Ph	Bn	*RR*	A	89	27%, *R*
Ph	Bn	*RR*	B	95	35%, *S**
Ph	4-methoxy phenyl	*SS*	A	50	30%, *R*
4-methoxy phenyl	Bn	*RR*	A	65	32%, *R*

Method A: toluene, rt

Method B: $Ti(O^iPr)_4$ (1.2 eq.), toluene, rt

* only 15 mol %$Ti(O^iPr)_4$

Table V- 2. Chiral 4-hydroxymethy imidazoline ligands in diethyl zinc additions.

Although, additional experiments are needed to establish synthetic utility of the quarternary 4-methyl-4-hydroxymethylimidazolines as ligands for diethyl zinc additions their performance is not all too disappointing in comparison to the 2-hydroxymethylimidazolines.[84]

D. Experimental Section

General: Melting points were determined by open capillary method using Electrothermal Melting Point apparatus (Melt-Temp) and are uncorrected. IR spectra were recorded on a Nicolet spectrophotometer. ^{1}H NMR spectra were recorded with Varian [(Inova or Gemini) 300MHz] spectrometers. Chemical shift values are expressed as δ-(ppm) and J values are in Hz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, q: quartet and br: broad peak. ^{13}C-NMR spectra were also recorded on Varian [(Inova or Gemini) 75.MHz] spectrometers. The symbols q, t, d and s indicate the number of protons (3, 2, 1, and 0 respectively) attached to each carbon atom, as determined by the ^{13}C DEPT technique. Mass spectra were recorded on Perkin Elmer mass spectrometer. Column chromatography was performed on a silica gel (60-120) mesh. THF/diethyl ether were dried over sodiumbenzopenone ketyl and distilled under nitrogen. Dichloro methane dried over calcium hydride distilled under nitrogen. All manipulations were conducted over a nitrogen atmosphere by use of standard Schlenck techniques.

Synthesis of 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (1-phenyl-ethyl)-amide V-amide-1 from 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid: To a well-stirred suspension of 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid **III-1-1**(1.0g, 0.27 mmol) in dry methylene chloride (25mL), (R)-

(+)-1-Phenyl-ethylamine (0.36g, 29mmol) was added EDCI.HCl (0.57g, 29mmol), after five minutes added a solution of DMAP (.35 gm, 29 mmol) in methylene chloride (10mL) and stirred for 5-6 hrs. The reaction mixtures was washed with water (2× 10 mL), saturated sodium bicarbonate (20 mL), water (20mL), 2N HCl (20 mL) and then with water (30mL). The organic layer dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by column silica-gel chromatography using ethyl acetate hexane mixture (1:1).

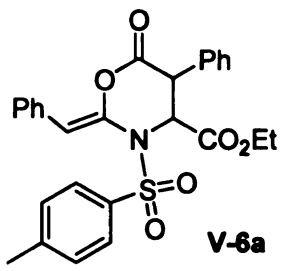
(+)-V-amide-1: Yield: (0.26 g, 66.6%). {$[\alpha]_D$= +41.5°)} ^{1}H NMR (300MHz) : δ 1.02 (d, *J* = 6.9, 3H), 1.56 (s, 3H), 3.85 (d, *J* = 15.6, 1H), 4.40 (s, 1H), 4.66(d, *J* =15.6 ,1H), 4.72 (t, *J*= 6.9, 1H), 7.07-7.09 (m, 2 H), 7.17-7.55(m, 16 H), 7.69-7.73 (m, 2H).; ^{13}C NMR (75MHz): 21.39, 27.56, 48.09, 48.73, 72.66, 126.52, 127.24, 127.71, 127.99, 128.42, 128.57, 128.67, 128.95, 129.01, 129.14, 130.75, 130.82, 137.38, 137.60, 143.29, 165.44, 171.61. IR (neat) 1874 cm-, 1498 cm-; m/z= 473(M+)

(-)-V-amide-1: (0.24 g, 61%). {$[\alpha]_D$= -37.7°)} ^{1}H NMR (300 MHz) : δ 1.40 (d, *J* = 7.2, 3H), 1.61 (s, 3H), 3.77 (d, *J* = 15.6, 1H), 4.37 (s, 1H), 4.60(d, *J* =15.6 ,1H), 4.75 (t, *J*= 7.5, 1H), 6.922-7.090 (m, 2H), 7.11-7.22 (m, 13H), 7.507-7.529 (m,3H), 7.651-7.682(m, 2H).: ^{13}C NMR (75MHz): 21.58, 28.08, 47.97, 48.59, 72.62, 126.66, 126.99, 127.200, 127.69, 127.96, 128.21, 128.51, 128.58, 128.64, 129.13, 129.122, 130.70, 130.83, 137.184, 137.22, 143.28, 165.35, 171.62. IR (neat) 1872 cm-, 1498 cm-; m/z=325 (M+-CO-NH-CH(CH3)Ph).

Synthesis of 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid benzylamide from 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid V-12: To a well-stirred suspension of 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (0.5g, 1.34 mmol) in dry methylene chloride (150 mL) at 0 °C, was added EDCI.HCL (0.31g, 1.608 mmol), after five minutes DMAP (0.2 g, 1.6 mmol) and stirred for 20 minutes. Benzyl amine (0.17 g, 1.6 mmol) was then added dropwise. The reaction mixture was then stirred overnight at room temperature. The reaction mixtures was washed 2N HCl (2 x 50 mL), saturated sodium bicarbonate (2 x 50 mL),, and then with brine (50mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford the amide product as a white foam **V-12:** Yield: (0.5 g, 66.6%). ^{1}H NMR (300MHz), $CDCl_3$: δ 1.53 (s, 3H), 3.77 (d, J = 15.3, 1H), 3.91 (dd, J_1 = 14.7 Hz, J_2 = 5.1 Hz, 1H), 4.21 (dd, J_1 = 15 Hz, J_2 = 6 Hz, 1H), 4.35 (s, 1H), 4.60 (d, J =15.6 ,1H), 6.81-7.64 (m, 20 H).; ^{13}C NMR (75MHz), $CDCl_3$: 27.71, 42.77, 48.45, 72.18, 76.57, 126.89, 127.46, 127.7, 127.79, 128.03, 128.26, 128.37, 128.4, 128.73, 128.81, 130.39, 130.46, 136.99, 137.17, 138.28, 165.02, 172.26.; EIMS: m/z= 459.3 (M+)

Synthesis of 2-Benzylidene-6-oxo-5-phenyl-3-(toluene-4-sulfonyl)-[1,3]oxazinane-4-carboxylic acid ethyl ester from (Toluene-4-sulfonylimino)-acetic acid ethyl ester V-6 using 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (1-phenyl-ethyl)-amide (+)-V-amide-1

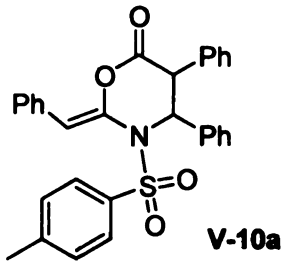
To a well stirred solution of phenylacetyl chloride (0.3 mL, 2.1 mmol) in dry DCM (4 mL) at -78°C added proton sponge (0.4 gm, 2.1 mmol), after 5-10 min the color of the solution changes to pale yellow then added a solution of 1-benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (1-phenyl-ethyl)-amide (**V-amide-1**) (0.28 gm, 0.6 mmol or 0.14 gm, 0.3 mmol) in 3 mL of dry DCM. The reaction allowed to stir for 5-10 min on which the color changes to deep yellow then added a solution of (toluene-4-sulfonylimino)-acetic acid ethyl ester (0.25 gm, 1 mmol) in dry DCM (3mL). The reaction mixture allowed to stir for 36 hrs at –78 °C and then allowed to come to room temperature. The reaction mixture was passed through a silica gel bed to remove unreacted acid chloride and washed with ethyl acetate (20 mL). The solution was subjected to column chrotography using 1:3 ethyl acetate: hexanes to isolate pure 2-benzylidene-6-oxo-5-phenyl-3-(toluene-4-sulfonyl)-[1, 3]oxazinane-4-carboxylic acid ethyl ester (**V-6a**). Further elution with same solvent give mixture of 2-benzylidene-6-oxo-5-phenyl-3-(toluene-4-sulfonyl)-[1,3]oxazinane-4-carboxylic acid ethyl ester and β-lactam **V-6b**, and further pure β-lactam.



V-6a

2-Benzylidene-6-oxo-5-phenyl-3-(toluene-4-sulfonyl)-[1,3]oxazinane-4-carboxylic acid ethyl ester V-6a: Yield: 0.17 gm, 34.7%, ^{1}H NMR (300MHz) : δ 0.98 (t, *J* = 7.5, 3H), 2.49 (s, 3H), 4.05 (q, *J*=7.5, 2H), 4.16 (d, *J*= 11.4, 1H),

4.50 (d, J =11.4, 2H), 6.45 (s, 1H), 7.10-7.13 (m, 2H), 7.27-7.41 (m, 8H), 7.60 (dd, J= 0.6 and 7.5, 2H), 7.80 (d, J= 8.4, 2H); ^{13}C NMR (300MHz) : δ 13.65, 21.74, 49.72, 61.05, 62.15, 115.34, 127.77, 128.56, 128.67, 128.92, 129.02, 129.34, 129.55, 129.86, 130.27, 130.53, 131.75, 134.12, 136.71, 145.50, 165.66, 168.26. IR (neat); 1794, 1749, 1670, 1369; MS; m/z=491.2



V-10a

Synthesis of 2-Benzylidene-4, 5-diphenyl-3(toluene-4-sulfonyl)-[1, 3]oxazinan-6-one V-10a.

To a well stirred solution of phenylacetyl chloride (0.3 mL, 2.1 mmol) in dry DCM (4 mL) at -78°C added proton sponge (0.4 gm, 2.1 mmol), after 5-10 min the color of the solution changes to pale yellow then added a solution of 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (1-phenyl-ethyl)-amide (0.28 gm, 0.6 mmol or 0.14 gm, 0.3 mmol) in 3 mL of dry DCM. The reaction allowed to stir for 5-10 min on which the color changes to deep yellow then added a solution of N-benzylidine-(Toluene-4-sulfonyl)amine (0.25 gm, 1 mmol) in dry DCM (3mL). The reaction mixture allowed to stir for 36 hrs at -78 °C and then allowed to come to room temperature. The reaction mixture was passed through a silica gel bed to remove unreacted acid chloride and washed with ethyl acetate (20 mL). The solution was subjected to column chromatography using 1:4 ether : hexanes to isolate pure 2-Benzylidene-4,5-

diphenyl-3(toluene-4-sulfonyl)-[1,3]oxazinan-6-one **V-10a**. Further elution with same solvent give mixture of 2-Benzylidene-4, 5-diphenyl-3(toluene-4-sulfonyl)-[1, 3]oxazinan-6-one and β-lactam dl-(3R, 4R)-Diphenyl-1-(toluene-4-sulfonyl)-azetidin-2-one **V-10b**, and further pure β-lactam.

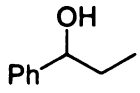
(3R, 4S)-2-Benzylidene-4,5-diphenyl-3(toluene-4-sulfonyl)-[1,3]oxazinan-6-one V-10a. Yield: 0.17 g, 35 %, ^{1}H NMR (500MHz) : δ 2.47 (s, 3H), 3.95 (d, J= 11.5 Hz, 1H), 5.05 (d, J =11.0 Hz, 1H), 6.41 (s, 1H), 6.849-6.867 (dd, 2H, J_1 = 7 Hz, J_2 = 1.5 Hz, 2H), 7.09-7.1 (dd, 2H, J_1 = 7 Hz, J_2 = 1.5 Hz, 2H), 7.2-7.24 (m, 6H), 7.32-7.36 (t, 2H, J = 8.5 Hz, 3H), 7.38-7.41 (t, 2H, J = 8.5 Hz, 3H), 7.63-7.64 (d, J =7.5 Hz, 2H), 7.72-7.73 (d, J =7.5 Hz, 2H); ^{13}C NMR (125 MHz) : δ 21.84, 29.86, 55.3, 64.36, 115.46, 126.77, 128.07, 128.53, 128.71, 128.71, 128.82, 128.9, 129.72, 129.79, 130.23, 132.26, 132.29, 135.46, 138.53, 139. 63, 145.19, 166.06; IR (neat); 1738, 1666; EIMS; m/z=495.2.

dl-(3R, 4R)-Diphenyl-1-(toluene-4-sulfonyl)-azetidin-2-one [V-10b]. Yield 0.037 g, 10 %, ^{1}H NMR (300MHz) : δ 2.43 (s, 3H), 4.25 (t, J= 3.3 Hz, 1H), 4.96 (d, J =3 Hz, 1H), 7.03-7.3 (m, 15H), 7.67-7.7 (m, 2H); ^{13}C NMR (75 MHz) : δ 21.68, 64.17, 65.78, 126.5, 127.23, 127.55, 128.07, 128.36, 128.6, 128.93, 129.05, 129.13, 129.66, 129.83, 132.79, 135.66, 135.93, 145.29, 165.37; IR (neat); 1795,; MS; m/z=377.9.

General procedure for diethyl zinc reduction:

Method A: According to general procedure by Soai *et al*, a 1M solution of diethyl zinc in hexane (2.2 mL, 2.2 mmol) was added to a solution of the chiral ligand (10 mol %) and the aldehydes (1mmol) in toluene (5 mL). The mixture was stirred under alkylation was complete under argon atmosphere in a sealed flask. The reaction mixture was diluted with dichloromethane (50 mL) and extracted with 10 % HCl solution. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to obtain an oily residue. The residue was chromatographed with 20 % ether/hexanes to obtain the 1-phenyl propanol. The enantiomeric excess was found by comparison to literature values. [Soai, K.; Yokayama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264.]

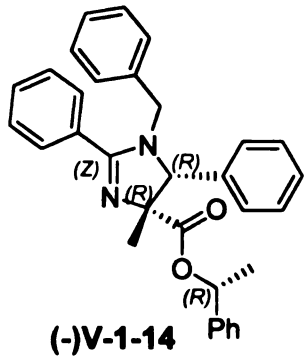
Method B: Stoichiometric or catalytic Ti-isopropoxide was added was added to a solution of the chiral ligand (10 mol %) in toluene (5 mL) and stirred for 20 minutes followed by 1M solution of diethyl zinc in hexane (2.2 mL, 2.2 mmol) the aldehydes (1mmol). The mixture was stirred under alkylation was complete under argon atmosphere in a sealed flask. The reaction mixture was diluted with dichloromethane (50 mL) and extracted with 10 % HCl solution. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to obtain an oily residue. The residue was chromatographed with 20 % ether/hexanes to obtain the 1-phenyl propanol. The enantiomeric excess was found by comparison to literature values [Walsh P. J. *Acc. Chem. Res.*, **36** (10), 739 -749, 2003.]



^{1}H NMR (300MHz), $CDCl_3$: δ 0.89 (t, J = 7.5 Hz, 3H), 1.67-1.85 (m, 2H), 1.97 (broad singlet, 1H), 4.561 (t, J = 6.6 Hz, 1H), 7.23-7.35 (m, 5H); ^{13}C NMR (75MHz), $CDCl_3$: δ 10.07, 31.75, 75.87, 125.92, 127.35, 128. 28, 144.53.

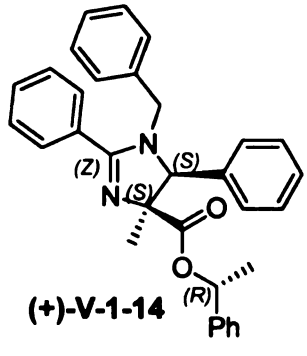
Synthesis of 1-Benzyl-4-methyl-2, 5-diphenyl-4, 5-dihydro-1H-imidazole-4-carboxylic acid 1-phenyl-ethyl ester V-1-14.

A well-stirred suspension of 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid **III-1-1** (1.0g, 2.7 mmol) in dry methylene chloride (150mL) was made in a flame dried flask under nitrogen atmosphere and cooled in an ice-bath to 0 °C. To this mixture was added EDCI.HCl (0.57g, 2.9mmol), followed by DMAP (0.35 gm, 2.9 mmol) and stirred for 20 minutes. (R)-(+)-1-phenyl-ethanol (0.72g, 2 eq., 5.8 mmol) was added and mixture stirred overnight at room temperature. The reaction mixtures was washed, 2N HCl (2 x 50 mL), saturated sodium bicarbonate (2 x 50 mL), and then with brine (50mL). The organic layer dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by column silica-gel chromatography using 70 % ether / hexane mixture.



(-)V-1-14

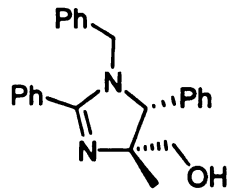
(-)- (RRR) V-1-14. Yield: (0.34 g, 61 %). $[\alpha]_D$= -118 °, c = 1.2, $CHCl_3$; ^1H NMR (500MHz), $CDCl_3$: δ 1.236 (d, *J* = 6.5, 3H), 1.62 (s, 3H), 3.83 (d, *J* = 15.5 Hz, 1H), 4.34 (s, 1H), 4.70 (d, *J* =15.5 Hz,1H), 5.32 (q, *J*= 6.5, 1H), 6.94-7.16 (m, 4 H), 7.17-7.28 (m, 11H), 7.48-7.49 (t, *J* = 3.5 Hz, 3H) 7.76-7.77 (m, 2H).; ^{13}C NMR (125MHz) $CDCl_3$: 21.8, 26.95, 48.88, 72.81, 73.27, 77.61, 125.87, 127.2, 127.57, 127.7, 127.77, 128.0, 128.27, 128.55, 128.64, 130.08, 131.12, 136.59, 136.64, 141.35, 165.92, 171.08.; EIMS: m/z = 474.1(M+).



(+)-V-1-14

(+)- (SSR) V-1-14: (0.38 g, 66 %). $[\alpha]_D$= +113 °, c = 1.2, $CHCl_3$; ^1H NMR (500MHz), $CDCl_3$: δ: 0.957 (d, *J* = 6.5, 3H), 1.61 (s, 3H), 3.77 (d, *J* = 15.5 Hz, 1H), 4.33 (s, 1H), 4.66 (d, *J* =15.5 Hz,1H), 5.33 (q, *J*= 6.5, 1H), 6.92-6.94 (m, 2 H), 7.17-7.29 (m, 13H), 7.47-7.48 (m, 3H) 7.73-7.75 (m, 2H).; ^{13}C NMR (125MHz), $CDCl_3$: 21.44, 26.85, 48.83, 72.74, 73.57, 77.58, 126.0, 127.45,

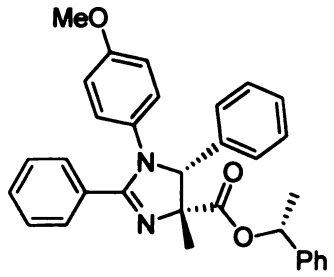
127.54, 127.79, 127.9, 128.0, 128.14, 128.37, 128.51, 128.53, 128.62, 130.03, 131.15, 136.52, 137.06, 141.77, 165.94, 170.86.; EIMS: m/z = 474.2 (M+).



(-)V-1-17

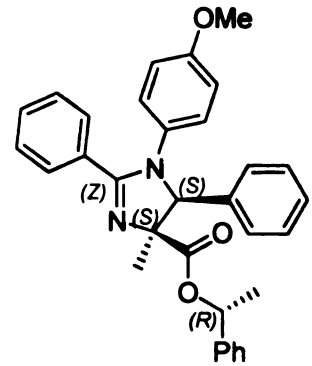
[(-)(4R, 5R)-1-benzyl-4,5-dihydro-4-methyl-2,5-diphenyl-1H-imidazol-4-yl] methanol V-1-17: Lithium aluminum hydride (0.04 g, 1.06 mmol) was suspended in 100 mL of dry THF in a flame dried flask under nitrogen atmosphere. The suspension was cooled to 0 °C in an ice-bath. (-)-RRR ester **V-1-14** (0.34 g, 0.71 mmol) solution in dry THF (10 mL) was added dropwise. The mixture was stirred at 0 °C and monitored with TLC for complete disappearance of the ester spot. The reaction mixture was diluted with ethyl acetate (100 mL) and organic layer was extracted with 5 % HCl solution (3x, 100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under vacuum. The residue was chromatographed with 20 % MeOH/ethyl acetate to afford the (-) RR alcohol **V-1-17** as colourless oil (0.2 g, 79 % yield) which solidified on standing under high vacuum.

$[\alpha]_D$= -98 °, c = 1.0, $CHCl_3$; ^1H NMR (500MHz), $CDCl_3$: δ: 1.35 (s, 3H), 3.08 (d, J = 11.7 Hz, 1H), 3.17(d, J = 11.7 Hz, 1H), 3.58 (broad singlet, 1H), 3.89 (d, J = 15.6 Hz, 1H), 4.28 (s, 1H), 4.72 (d, J = 15.3 Hz, 1H), 6.83-6.86 (m, 2H), 7.2-7.72 (m, 13H).

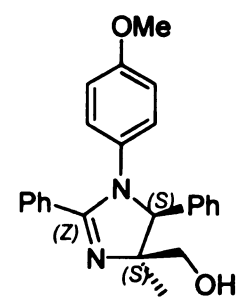


V-1-15

4, 5-dihydro-1-(4-methoxyphenyl)-4-methyl-2, 5-diphenyl-1H imidazole-4-carboxylic acid 1-phenylethyl ester V-1-15. A well-stirred suspension of 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid **III-1-1** (1.0g, 2.6 mmol) in dry methylene chloride (150mL) was made in a flame dried flask under nitrogen atmosphere and cooled in an ice-bath to 0 °C. To this mixture was added EDCI.HCl (0.6g, 3.1 mmol), followed by DMAP (0.38 gm, 3.1 mmol) and stirred for 20 minutes. (*R*)- (+)-1-phenyl-ethanol (0.72g, 2 eq., 58 mmol) was added and mixture stirred overnight at room temperature. The reaction mixtures was washed, 2N HCl (2 x 50 mL), saturated sodium bicarbonate (2 x 50 mL), and then with brine (50mL). The organic layer dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by column silica-gel chromatography using 50 % ether / hexane mixture.



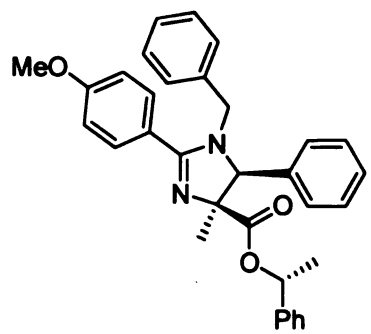
(+)-V-1-15 (SSR): (0.2 g, 31%). $[\alpha]_D$= +138 °, c = 1.0, $CHCl_3$; ^1H NMR (300MHz), $CDCl_3$: δ: 1.2 (d, J = 6.3, 3H), 1.785 (s, 3H), 3.63 (s, 3H), 4.73 (s, 1H), 5.28 (q, J= 6.3, 1H), 6.56 (d, J = 9Hz, 1H), 6.58-6.66 (m, 2H), 7.02-7.35 (m, 13H), 7.62 (d, J = 9 Hz, 2H); ^{13}C NMR (125MHz), $CDCl_3$: 21.44, 26.85, 56.83, 72.74, 73.57, 77.58, 126.0, 127.45, 127.54, 127.79, 127.9, 128.0, 128.14, 128.37, 128.51, 128.53, 128.62, 130.03, 131.15, 136.52, 137.06, 141.77, 165.94, 170.86.



[(+)(4S,5S)-4,5-dihydro-1-(4-methoxyphenyl)-4-methyl-2,5-diphenyl-1H-imidazol-4-yl]methanol V-1-18: Lithium aluminum hydride (0.03 g, 0.78 mmol) was suspended in 100 mL of dry THF in a flame dried flask under nitrogen atmosphere. The suspension was cooled to 0 °C in an ice-bath. (+)-SSR ester **V-1-15** (0.2 g, 0.52 mmol) solution in dry THF (10 mL) was added dropwise. The mixture was stirred at 0 °C and monitored with TLC for complete disappearance

of the ester spot. The reaction mixture was diluted with ethyl acetate (100 mL) and organic layer was extracted with 5 % HCl solution (3x, 100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under vacuum. The residue was chromatographed with 10 % MeOH/ethyl acetate to afford the (+)-SS alcohol **V-1-18** as colourless oil (0.130 g, 65 % yield).

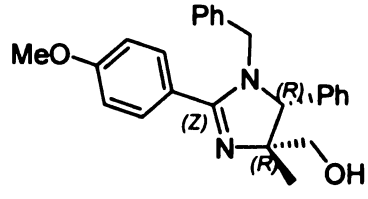
(+)-SS alcohol V-1-18 $[\alpha]_D$= +100 °, c = 1.0, $CHCl_3$; ^1H NMR (500MHz), $CDCl_3$: δ: 1.51 (s, 3H), 2.97 (broad s, 1H), 3.14 (d, J = 11.1 Hz, 1H), 3.21(d, J = 11.7 Hz, 1H), 3.63 (s, 3H), 4.61 (s, 1H), 6.554 (d, J = 9 Hz, 1H), 6.65 (d, J = 9 Hz, 1H), 7.21-7.35 (m, 8H), 7.52 (d, J = 7.2 Hz, 2H), ^{13}C NMR (125MHz), $CDCl_3$: δ 21.7, 64.19, 65.74, 65.8, 77.42, 126.52, 127.08, 127.25, 127.57, 127.75, 128.09, 128.21, 128.37, 128.62, 128.87, 128.95, 129.07, 129.15, 129.53, 129.68, 129.85, 130.48, 130.67, 132.81, 135.67, 135.95, 145.31, 165.39.



1-benzyl-4,5-dihydro-4-methyl-2, 5-diphenyl-1H-imidazole-4-carboxylic acid 1-phenylethyl ester V-11-16: A well-stirred suspension of 1-Benzyl-4-methyl-2,5-diphenyl-4,5-dihydro-1H-imidazole-4-carboxylic acid (1.0g, 2.5 mmol) in dry methylene chloride (150mL) was made in a flame dried flask under nitrogen atmosphere and cooled in an ice-bath to 0 °C. To this mixture was added EDCI.HCL (0.57g, 3.0 mmol), followed by DMAP (0.36 gm, 3.0 mmol) and

stirred for 20 minutes. (R)-(+)-1-Phenyl-ethanol (0.67g, 2 eq., 5.5 mmol) was added and mixture stirred overnight at room temperature. The reaction mixtures was washed, 2N HCl (2 x 50 mL), saturated sodium bicarbonate (2 x 50 mL), and then with brine (50mL). The organic layer dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by column silica-gel chromatography using 60 % ether / hexane mixture.

(+)- (SSR) V-11-16: (0.27 g, 46%). $[\alpha]_D$= +130°, c = 1.2, $CHCl_3$; ^1H NMR (300MHz), $CDCl_3$: δ: 1.17 (d, J = 6.3, 3H), 1.55 (s, 3H), 3.78 (d, J = 15.9 Hz, 1H), 3.83 (s, 3H), 4.27 (s, 1H), 4.72 (d, J =15.3 Hz, 1H), 5.23 (q, J= 6.6, 1H), 6.91-6.98 (m, 6H), 7.15-7.28 (m, 12H), 7.68 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125MHz), $CDCl_3$ 21.6, 26.74, 48.63, 55.02, 72.46, 72.74, 77.27, 113.66, 122.9, 125.59, 126.94, 127.3, 127.37, 127. 46, 127.7, 127.74, 128.0, 128.3, 129.88, 136.41, 136.46, 141.0, 160.74, 165.46, 171.0.



[(-)(4R,5R)-1-benzyl-4,5-dihydro-2-(4-methoxyphenyl)-4-methyl-5-phenyl-1H-imidazol-4-yl]methanol V-11-19: Lithium aluminum hydride (0.03 g, 0.78 mmol) was suspended in 100 mL of dry THF in a flame dried flask under nitrogen

atmosphere. The suspension was cooled to 0 °C in an ice-bath. (-)-RRRester **V-11-16** (0.28 g, 0.55 mmol) solution in dry THF (10 mL) was added dropwise. The mixture was stirred at 0 °C and monitored with TLC for complete disappearance of the ester spot. The reaction mixture was diluted with ethyl acetate (100 mL) and organic layer was extracted with 5 % HCl solution (3x, 100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under vacuum. The residue was chromatographed with 10 % MeOH/ethyl acetate to afford the (-)-RR alcohol **V-11-19** as colourless oil (0.144 g, 68% yield).

$[\alpha]_D$= +114 °, c = 1.0, $CHCl_3$; ^1H NMR (300MHz), $CDCl_3$: δ: 1.317 (s, 3H), 2.98 (d, J = 12.0 Hz, 1H), 3.11(d, J = 11.4 Hz, 1H), 3.42 (broad s, 1H), 3.86 (s, 3H), 3.87 (d, J = 15.0 Hz, 1H), 4.23 (s, 1H), 4.78 (d, J = 15.6 Hz, 1H), 6.83-6.86 (m, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.22-7.65 (m, 9H), 7.67 (d, J = 9 Hz); ^{13}C NMR (75MHz), $CDCl_3$: δ 25.7, 48.57, 66.84, 71.4, 71.7, 127.37, 127.58, 127.65, 128.18, 128.26, 128.4, 128.46, 130.08, 135.65, 135.76, 164.79.

E. References

1. Green, D. R. *Cell* **1998**, *94*, 695-698.

2. Hengartner, M. O. *Nature* **2000**, *407*, 770-776.

3. Fesik, S. W. *Cell* **2000**, *103*, 273-282.

4. Thompson, C. B. *Science* **1995**, *267*, 1456-1462.

5. Hanahan, D.; Weinberg, R. A. *Cell* **2000**, *100*, 57-70.

6. Johnstone, R. W.; Ruefli, A. A.; Lowe, S. W. *Cell* **2002**, *108*, 153-164.

7. Lowe, S. W.; Lin, A. W. *Carcinogenesis* **2000**, *21*, 485-495.

8. (a) Pommier, Y.; Sordet, O.; Antony, S.; Hayward, R. L.; Kohn, K. W. *Oncogene* **2004**, *23*, 2934-2949. (b) Mayo, M. W.; Baldwin, A. S. *Biochim. Biophys. Acta* **2000**, *1470*, M55-62. (c) Wang, C. Y.; Mayo, M. W.; Korneluk, R. G.; Goeddel, D. V.; Baldwin, A. S., Jr. *Science* **1998**, *281*, 1680-1683. (d) Wang, C. Y.; Mayo, M. W.; Baldwin, A. S., Jr. *Science* **1996**, *274*, 784-787.

9. Makin, G.; Hickman, J. A. *Cell Tissue Res.* **2000**, *301*, 143-152.

10. (a)Nesterenko, V.; Putt, K. S.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 14672-14673.(b) Nicholson, D.W. *Nature* **2000**, *407*, 810-816.(c) Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita, K. -I.; Seto, H. *J. Am. Chem. Soc.* **1998**, *120*, 3524-3525.

11. (a)Mitsiades, N.; Mitsiades, C. S.; Richardson, P. G.; Poulaki, V.; Tai, Y. T.; Chauhan, D.; Fanourakis, G.; Gu, X.; Bailey, C.; Joseph, M.; Libermann, T. A.; Schlossman, R.; Munshi, N. C.; Hideshima, T.; Anderson, K. C. *Blood* **2003** *101*, 2377-2380. (b) Weaver Kyle, D.; Yeyeodu, S.; James, C., Jr.; Baldwin, A. S., Jr.; Ewend, M. G. *Journal of Neuro-Oncology* **2003**, *61*, 187-196. (c) Chen, L.; Agrawal, S.; Zhou, W.; Zhang, R.; Chen, J. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 195-200.

12. Pommier, Y.; Pourquier, P.; Fan, Y.; Strumberg, D. *Biochim. Biophys. Acta* **1998**, *1400*, 83-105.

13. Wall, M. E.; Wani, M. C. Camptothecin and Analogues. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; (Washington: ACS) **1995**, 293-310.

14. Wall, M. E. *Med. Res. Rev.* **1998**, *18*, 299-314.

15. Macdonald, T. L.; Labroli, M. A.; Tepe, J. J. DNA topoisomerase II inhibitors. In *Comprehensive natural products chemistry*; Vol. 7, Kool, E. T., Ed.; Amsterdam: Elsevier-North Holland, **1999**, 593-614.

16. Pourquier, P.; Pommier, Y. *Adv Cancer Res* **2001**, *80*, 189-216.

17. (a) Huang, T. T.; Wuerzberger-Davis, S. M.; Seufzer, B. J.; Shumway, S. D.; Kurama, T.; Boothman, D. A.; Miyamoto, S. *J. Biol. Chem.* **2000**, *275*, 9501-9509. (b) Piret, B.; Piette, J. *Nucleic Acids Res.* **1996**, *24*, 4242-4248. (c) Xu, Y.; Villalona-Calero, M. A. *Annals of Oncology* **2002**, *13*, 1841-1851. (d) Sodhi, A.; Singh, R. A. K. *Immunology Letters* **1998**, *63*, 9-17. (e) Sánchez-Pérez, I.; Benitah, S. A.; Martínez- Gomariz, M.; Lacal, J. C.; Perona, R. *Mol. Biol. Cell* **2002**, *13*, 2933-2945.

18. Cusack, J. C., Jr.; Liu, R.; Baldwin, A. S. *Drug Resist.* **1999** Update *2*, 271-273.

19. (a) Carson, J. P.; Zhang, N., Frampton, G. M.; Gerry, N. P.; Lenburg, M. E.; Christman, M. F. *Cancer Res.* **2004**, *64*, 2096-2104. (b) Zhou, Y.; Gwadry, F. G.; Reinhold, W. C.; Miller, L. D.; Smith, L. H.; Scherf, U.; Liu, E. T.; Kohn, K. W.; Pommier, Y.; Weinstein, J. N. *Cancer Res.* **2002**, *62*, 1688-1695.

20. Boland, M. P. *Biochem. Soc. Trans.* **2001**, *29*, 674-678.

21. Cusack, J. C., Jr.; Liu, R.; Baldwin, A. S., Jr. *Cancer Res.* **2000**, *60*, 2323-2330.

22. Guttridge, D. C.; Albanese, C.; Reuther, J. Y.; Pestell, R. G.; Baldwin, A. S., Jr. *Mol. Cell Biol.* **1999**, *19*, 5785-5799.

23. Baeuerle, P. A.; Henkel, T. *Annu. Rev. Immunol.* **2000**, *12*, 141-179.

24. Baldwin, A. S., Jr. *Annu. Rev. Immunol.* **1996**, *14*, 649-683.

25. Perkins, N. D. *Int. J. Biochem. Cell Biol.* **1997**, *29*, 1433-1448.

26. Webster, G. A.; Perkins, N. D. *Mol. Cell Biol.* **1999**, *19*, 3485-3495.

27. (a) Das, K. C.; White, C. W. *J. Biol. Chem.* **1997**, *272*, 14914-14920.(b) Baldwin, A. S. *J. Clin. Invest.* **2001**, *107*, 241-246. (c) Hideshima, T.; Chauhan, D.; Richardson, P.; Mitsiades, C.; Mitsiades, N.; Hayashi, T.; Munshi, N.; Dang, L.; Castro, A.; Palombella, V.; Adams, J.; Anderson, K. C. *J. Biol. Chem.* **2002**, *277*, 16639-16647.(d) Bottero, V.; Busuttil, V.; Loubat, A.; Magne, N.; Fischel, J. L.; Milano, G.; Peyron, J. F. *Cancer*

Res. **2001**, *61*, 7785-7791. (e)Um, J. H.; Kang, C. D.; Lee, B. G.; Kim, D. W.; Chung, B. S.; Kim, S. H. *Oncogene* **2001**, *20*, 6048-6056. (f) Weldon, C. B.; Burow, M. E.; Rolfe, K. W.; Clayton, J. L.; Jaffe, B. M.; Beckman, B. S. *Surgery* **2001**, *130*, 143-150. (g) Arlt, A.; Vorndamm, J.; Breitenbroich, M.; Folsch, U. R.; Kalthoff, H.; Schmidt, W. E.; Schafer, H. *Oncogene* **2001**, *20*, 859-868. (h) Liu, S.; Yu, Y.; Zhang, M.; Wang, W.; Cao, X. *J. Immunol.* **2001**, *166*, 5407-5415. (i) Kim, J. Y.; Lee, S.; Hwangbo, B.; Lee, C. T.; Kim, Y. W.; Han, S. K.; Shim, Y. S.; Yoo, C. G. *Biochem. Biophys. Res. Commun.* **2000**, *273*, 140-146.

28. Lin, Y. C.; Brown, K.; Siebenlist, U. *Proc. Natl. Acad. Sci. U S A* **1995**, *92*, 552-556.

29. (a) Karin, M.; Lin, A. *Nat. Immunol.* **2002**, *3*, 221-227. (b)Zhong, H.; SuYang, H.; Erdjument-Bromage, H.; Tempst, P.; Ghosh, S. *Cell* **1997**, *89*, 413-424. (c) Sizemore, N.; Leung, S.; Stark, G. R. *Mol. Cell Biol.* **1999**, *19*, 4798-4805. (d) Madrid, L. V.; Wang, C. Y.; Guttridge, D. C.; Schottelius, A. J.; Baldwin, A. S., Jr.; Mayo, M. W. *Mol. Cell Biol.* **2000**, *20*, 1626-1638.

30. Wu, M. X.; Ao, Z.; Prasad, K. V.; Wu, R.; Schlossman, S. F. *Science* **1988**, *281*, 998-1001.

31. (a) Jones, D. R.; Broad, R. M.; Madrid, L. V.; Baldwin, A. S., Jr.; Mayo, M. W. *Ann. Thorac Surg.* **2000**, *70*, 930-936; discussion 936-937. (b) Cusack, J. C., Jr.; Liu, R.; Houston, M.; Abendroth, K.; Elliott, P. J.; Adams, J.; Baldwin, A. S., Jr. *Cancer Res.* **2001**, *61*, 3535-3540.

32. Habraken, Y.; Piret, B.; Piette, J. *Biochemical Pharmacol.* **2001**, *62*, 603-616.

33. Epinat, J. C. ; Gilmore, T. D. *Oncogene* **1999**, *18*, 6896-6909.

34. (a) Cuzzocrea, S., Chatterjee, P. K.; Mazzon, E.; Dugo, L.; Serraino, I.; Britti, D.; Mazzullo, G.; Caputi, A. P.; Thiemermann, C. *Br. J. Pharmacol* , **2002**, *135*, 496-510. (b) Roshak, A.; Jackson, J. R.; Chabot-Fletcher, M.;Marshall, L. A. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 955-961. (c) Breton, J. J.; Chabot-Fletcher, M. C. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 459-466. (d) Sharma, V.; Tepe, J. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4319-4321. (e) Meijer, L.; Thunnissen, A. M.; White, A. W.; Garnier, M.; Nikolic, M.; Tsai, L. H.; Walter, J.; Cleverley, K. E.; Salinas, P. C.; Wu, Y. Z.; Biernat, J.; Mandelkow, E. M.; Kim, S. H.; Pettit, G. R. *Chem. Biol.* **2000**, *7*, 51-63. (f) Wan, Y.; Hur, W.; Cho, C. Y.; Liu, Y.; Adrian, F. J.; Lozach, O.; Bach, S.; Mayer, T.; Fabbro, D.; Meijer, L.; Gray, N. S. *Chem. Biol.* **2004**, *11*, 247-259. (g) Kishore, N.; Sommers, C.; Mathialagan, S.; Guzova, J.; Yao, M.; Hauser, S.; Huynh, K.; Bonar, S.;

Mielke, C.; Albee, L.; Weier, R.; Graneto, M.; Hanau, C.; Perry, T.; Tripp, C. S. *J. Biol. Chem.* **2003**, *278*, 32861-32871. (h) Grisham, M. B., Palombella, V. J.; Elliott, P. J.; Conner, E. M.; Brand, S.; Wong, H. L.; Pien, C.; Mazzola, L. M.; Destree, A.; Parent, L.; Adams, J. *Methods Enzymol.* **1999**, *300*, 345-363. (i) Nemeth, Z. H.; Wong, H. R.; Odoms, K.; Deitch, E. A.; Szabo, C.; Vizi, E. S.; Hasko, G. *Mol. Pharmacol.* **2004**, *65*, 342-349. (j) Fenteany, G.; Standaert, R. F.; Soongyu Choi, W. S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726. (k) Teicher, B. A.; Ara, G.; Herbst, R.; Palombella, V. J.; Adams, J. *Clin. Cancer Res.* **1999**, *5*, 2638-2645. (l) Kwok, B. H.; Koh, B.; Ndubuisi, M. I.; Elofsson, M.; Crews, C. M. *Chem. Biol.* **2001**, *8*, 759-766.

35. Hehner, S. P.; Hofmann, T. G.; Droge, W.; Schmitz, M. L. *J. Immunol.* **1999**, *163*, 5617-5623.

36. Shah, S. A.; Potter, M. W.; McDade, T. P.; Ricciardi, R.; Perugini, R. A.; Elliott, P. J.; Adams, J.; Callery, M. P. *J. Cell. Biochem.* **2001**, *82*, 110-122.

37. Ma, M. H.; Yang, H. H.; Parker, K.; Manyak, S.; Friedman, J. M.; Altamirano, C.; Wu, Z. Q.; Borad, M. J.; Frantzen, M.; Roussos, E.; Neeser, J.; Mikail, A.; Adams, J.; Sjak-Shie, N.; Vescio, R. A.; Berenson, J. R. *Clin. Cancer Res.* **2003**, *9*, 1136-1144.

38. (a) Laufer, S. A.; Striegel, H. - G.; Wagner, G. K. *J. Med. Chem.* **2002** *45*(21), 4695-4705. (b) Mc Kenna, J. M.; Halley, F.; Souness, J. E.; McLay, I. M.; Pickett, S. D.; Collis, A. J.; Page, K. M.; Ahmed, I. **2002**, *45*, 2173-2184. (c) Collis, A. J.; Foster, M. L.; Halley, F.; Maslen, C.; McLay, I. M.; Page, K. M.; Redford, E. J.; Souness, J. E.; Wilsher, N. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 693-696.

39. (a) Chang, L. A.; Sidler, K. L.; Cascieri, M. A.; de Laszlo, S.; Koch, G.; Li, B.; MacCoss, M.; Mantlo, N.; O'keefe, A.; Pang, M.; Rolando, A.; Hagmann, W. K.; *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2549. (b) Liverton, N. J.; Butcher, J. W.; Claiborne, C. F.; Claremon, D. A.; Libby, B. E.; Nguyen, K. T.; Pitzenberger, S. M.; Selnick, H. G.; Smith, G. R.; Tebben, A.; Vacca, J. P.; Varga, S. L.; Agarwal, L.; Dancheck, K.; Forsyth, A. J.; Fletcher, D. S.; Frantz, B.; Hanlon, W. A.; Harper, C. F.; Hofsess, S. J.; Kostura, M.; Lin, J.; Luell, S.; O'Neill, E. A.; Orevillo, C. J.; Pang, M.; Parsons, J.; Rolando, A.; Sahly, Y.; Visco, D. M.; O'Keefe, S. J. *J. Med. Chem.* **1999**, *42*(12), 2180-2190.

40. (a) Slee, D. H.; Romano, S. J.; Yu, J.; Nguyen, T. U.; John, J. K.; Raheja, N. K.; Axe, F. U.; Jones, T. K.; Ripka, W. C. *J. Med. Chem.* **2001**, *44*, 2094. (b) Boyle, E. M., Jr.; Kovacich, J. C.; Canty, T. G., Jr.; Morgan, E.

N.; Chi, E.; Verrier, E. D.; Pohlman, T. H. *Circulation*, **1998**, *98*, II282-II288.

41. (a) Tasdemir, D.; Mallon, R.; Greenstein, M.; Feldberg, L. R.; Kim, S. C.; Collins, K.; Wojciechowicz, D.; Mangalindan, G. C.; Concepcion, G. P.; Harper, M. K.; Ireland, C. M. *J Med Chem* **2002**, *45*, 529-532. (b) Sharma, V.; Lansdell. T.; Jin, G. Y.; Tepe, J. J. *J Med Chem* **2004**, *47*(14), 3700-3703. (c) Sharma, V.; Tepe, J. J. *Bioorg. Med. Chem. Lett.* **2004**, *14* (16), 4319-4321.

42. Sharma, V.; Lansdell, T.; Peddibhotla, S.; Tepe, J. J. *Chem. Biol.* **2004** (in print)

43. Lansiaux, A.; Facompre, M.; Wattez, N.; Hildebrand, M. P.; Bal, C.; Demarquay, D.; Lavergne, O.; Bigg, D. C.; Bailly, C. *Mol. Pharmacol.* **2001**, *60*, 450-461.

44. (a) Nicholson, D. W.; Thornberry, N. A. *Science* **2003**, *299*, 214-215. (b) Nicholson, D. W.; Thornberry, N. A. *Trends Biochem. Sci.* **1997**, *22*, 299-306. (c) Thornberry, N. A. *Chem. Biol.* **1998**, *5*, R97-103.

45. Johnson, N.; Ng, T. T. C.; Parkin, J. M. *Leukemia Research* **1997**, *21*, 961-972.

46. (a) Delhase, M.; Hayakawa, M.; Chen, Y.; Karin, M. *Science* **1999**, *284*, 309-313. (b) Karin, M. *Oncogene* **1999**, *18*, 6867-6874.

47. Thanos, D.; Maniatis, T. *Cell* **1995**, *80*, 529-532.

48. (a)Tozawa, K.;Okamoto, T.; Hayashi, Y.; Sasaki, S.; Kawai, N.; Kohri, K. *Urological Res.* **2002**, *30*, 53-58. (b) Schow, S. R.; Joly, A. *Cell Immunol.* **1997**, *175*, 199-202.

49. Tepe, J. J.; Sharma, V.; Lansdell, T.; Peddibhotla, S.; Michaels, S.; Brown, D. M. **2003**, Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003.

50. Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, 7991-8035.

51. (a) Sivakumar, A. V.; Babu, G. S.; Bhat, S. V. *Tetrahedron: Asymmetry* **2001**, 1095-1099. (b) Waisvisz, J.M.; van der Hoeven, M.G.;te Nijenhuis, B. *J. Am. Chem. Soc.* **1957**, 4524-4527. (c) Helms, G. L.; Moore, R. E.; Niemezura, W. P.; Patterson, G. M. L.; Tomer, K.B.; Gross, M.L.; *J. Org. Chem.* **1988**, 1298-1307. (d) Hechi, S.M. *Acc. Chem. Res.* **1986**, 383-391.

52. (a) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F.A. *J. Am. Chem. Soc.* **1980**, 6161-6163. (b) Okano, K.; Izawa, T.; Ohno, M. *Tetrhedron Lett.* **1983**, 217. (c) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **984**, 1465. (d) Kim, S.;Chang, S. B.; Lee, P. H. *Tetrahedron Lett.* **1987**, 2735. (e) Kim, S.; Lee, P. H.; Lee, T. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1242. (f) Kunieda, T.; Nagamatsu, T; Higuchi, T.; Hirobe, M. *Tetrahedron Lett.* **1988**, 2203. (g) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, 613.

53. (a) J.D. Winker *Tetrahedron* **48** (1992), p. 6953-6969. (b) Nicolaou, K.C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15-17.

54. (a) Mokotoff, M.; Bagaglio, J. F.; Parikh, B. S. *J. Med. Chem.* **1975**, *18*, 354-358. (b) Hansson, T. G.; Kihlberg, J. O. *J. Org. Chem.* **1986**, *51*, 4490-4492.(c) Wagner, R.; Tilley, J. W. *J. Org. Chem.* **1990**, *55*, 6289-6291. (d) Wagner, R.; Tilley, J. W.; Lovey, K. *Synthesis* **1990**, 785-786.

55. Shimamoto, K.; Shigeri, Y.; Yasuda-Kamatani, Y.; Lebrun, B.; Yumoto, N.; Nakajima, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2407-2410.

56. (a) von Riniker, B.; Schwyzer, R. *Helv. Chim. Acta* **1964**, *47*, 2357. (b) Ondetti, M.; Engel, S. L. *J. Med. Chem.* **1975**, *18*, 761. (c) Stachowiak, K.; Khosla, M. C.; Plucinska, K.; Khairallah, P. A.; Bumpus, F. M. *J. Med. Chem.* **1979**, *22*, 1128 (d) Hintermann, T.; Seebach, D. *Chimia* **1997**, *50*, 244.

57. Sibi, M. P.; Liu, M. *Tetrahedron* **2002**, *58*, 7991-8035.

58. (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (b) Rzasa, R. M.; Shea, H. A.; Romo, D. *J. Am. Chem. Soc.* **1998**, *120*, 591-592. (c) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517-9582 (d) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049-10053 (e) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548-4549 (f) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615-6616. (g) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991-8035.

59. Davis, F. A.; Reddy, G. V.; Liang, C. H. *Tetrahedron Lett.* **1997**, *38*, 5139-5142.

60. Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959-8960.

61. Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635-3638.

62 Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134-2136.

63. Boger, D. L.; Lee, R. J.; Bounaud, P.-Y.; Meier, P. *J. Org. Chem.* **2000**, *65*, 6770-6772.

64. Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, 3545-3565.

65. Fu, G.C. Acc. Chem. Res. 2000, 33, 412 and references there in.

66. Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578-1579.

67. (a) Taggi, A.E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D; Lectka, T. *J. Am. Chem. Soc.* **2002**, 124, 6626-6635.(b) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, 4, 627-629. (c) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387-390. (d) Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 10853-10859. (e) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831-7832 and references therein.

68. Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, *4*, 3533-3535.

69. Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, *9*, 1433-1440.

70. Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, 4108-4109.

71. Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058 – 5064.

72. Jayakumar, S.; Peddibhotla, S.; Tepe, J. J. *unpublished results.*

73. Satsumabayashi, S. *J. Org. Chem.* **1976**, *41*, 156-157.

74. Martin, J. C.; Brannock, K. C.; Burpitt, R. D.; Gott, P. G.; Hoyle, Jr. V. A. *J. Org. Chem.* **1971**, *36*, 2211-2215.

75. Davis, B. A.; Masanobu, M.; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 826-827.

76. Martin, J. C.; Hoyle, Jr. V. A.; Brannock, K. C.; Kent, C. *Tet. Lett.* **1965**, *40*, 3589-3594.

77. Schaumann, E.; Mrotzek, H. *Chem. Ber.* **1978**, *111*, 661-672.

78. Furukawa, M.; Okawara, T.; Noguchi, H.; Terawaki, Y. *Heterocycles* **1977**, *6*, 1323-1328.

79. Hafez, A. M.; Dudding, T.; Wagerle, T. R.; Shah, M. H.; Taggi, A. E.; Lectka, T. *J. Org. Chem.* **2003**, 5819-5825.

80. Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, 143-145.

81. Podlech, J.; Seebach, D.; *Angew. Chem. Int. Ed. Engl.* **1995**, 471-472.

82. Kobayashi, S.; Tsukamoto, Y.; Saegusa, T. *Macromolecules* **1990**, 2609-2612.

83. Walsh P. J. *Acc. Chem. Res.*, **36** (10), 739 -749, 2003.

84. Casey, M.; Smyth, M. P. *Synlett.* **2003**, 102.

85. (a) Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett.* **1992**, 169. (b) Mashima, K.; Kusano, K. H.; Sato, N.; Matsumara, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064. (c) Clyne, D. S.; Mermet-Bouvier, Y. C.; Nomura, N.; Rajan Babu, T. V. *J. Org. Chem.* **1999**, *64*, 7601. (d) Gambs, C.; Consiglio, G.; Togni, A. *Helv. Chim. Acta* **2001**, *84*, 3105.

86. Hermann, W. A.; Goossen, L. J.; Speigler, M. *Organometallics* **1998**, *17*, 1172.

87. Waltman, A. W.; Grubbs, R. H. *Organometallics* **2004**, *23*(13), 3105 - 3107.

88. (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956. (b) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153-3155.

89. (a) Viciu, M. H.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 2229-2231. (b) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053-4056. (c) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290-1309. (d) McGuinness, D. S.; Cavell, K. J. *Organometallics* **1999**, *18*, 1596-1605. (e) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741-748.

90. Ma, Y.; Song, C.; Jiang, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 3317-3319.

91. Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225-3228.

92. Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954-4955.

93. (a) Younkin, T. R.; Connor, E. F.; Henderson, J. I.; Friedrich, S. K.; Grubbs, R. H.; Bansleben, D. A. *Science* **2000**, *287*, 460-462. (b) Connor, E. F.; Younkin, T. R.; Henderson, J. I.; Waltman, A. W.; Grubbs, R. H. *Chem. Commun.* **2003**, 2272-22. (c) Matsui, S.; Mitani, M.; Saito, J.; Tohi, Y.; Makio, H.; Matsukawa, N.; Takagi, Y.; Kazutaka, T.; Nitabaru, M.; Nakano, T.; Tankaka, H.; Kashiwa, N.; Fujita, T. *J. Am. Chem. Soc.* **2001**, *123*, 6847-6856 (d) Tian, J.; Hustad, P. D.; Coates, G. W. *J. Am. Chem. Soc.* **2001**, *123*, 5134-5135.(e) Gibson, V. C.; Mastroianni, S.; Newton, C.; Redshaw, C.; Solan, G. A.; White, A. J. P.; Williams, D. J. *Dalton* **2000**, 1969-1971.

94. Menges, F.; Neuburger,M.; Pfaltz, A. *Org. Lett.*, **2002**, *4* (26), 4713 -4716.

95. Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336-345.

96. (a) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887-892. (b) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, 37, 2897-2899. (c)Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000**, *12*, 442-449.

97. Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A. Oberman, U.; *J. Organomet. Chem.* **1989**, *370*, 17.

98. Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783.

99. Davenport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R.; *J. Chem. Soc., Perkin Trans. 1* **2001**, 1500.

100. Dupont, J.; Ebeling, G.; Delgado, M. R.; Consorti, C. S.; Burrow, R.; Farrar, D. H.; Lough, A. J. *Inorg. Chem. Commun.* **2001**, *4*, 471.

101. Bastero, A.; Ruiz, A.; Claver, C.; Castillon, S. *Eur. J. Inorg. Chem.* **2001**, 3009.

102. Bussaca, C. A. US Patent 6316620, **2001**.

103. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823-2824.

104. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833-856.

105. Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757-824.

106. Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800-9809.

107. Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028-4036.

108. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49-69.

109. Chen, Y. K.; Costa, A. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 5378-5379.

110. Buono, F.; Walsh, P. J.; Blackmond, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 13652-13653.

111. Richmond, M. L.; Seto, C. T. *J. Org. Chem.* **2003**; *68*(19); 7505-7508.

112. Boland, N. A.; Casey, M.; Hynes, S. J.; Matthews, J. W.; Smyth, M. P. *J. Org. Chem.* **2002**; *67*(11); 3919-3922.

113. Peddibhotla, S.; Jayakumar, S.; Tepe, J. J. *Org. Lett.* **2002**, *4*, 3533-3535.

114. Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, *9*, 1433-1440.

APPENDIX

EFFICIENT TWO-STEP SYNTHESIS OF METHYLPHYTYLBENZO QUINONES: PRECURSOR INTERMEDIATES IN THE BIOSYNTHESIS OF VITAMIN E

A. Introduction to Tocopherols.

Tocopherols are a class of lipid-soluble antioxidants synthesized in higher plants and other oxygenic photosynthetic organisms such as cyanobacteria.[1] The four tocopherols synthesized (α, β, δ, and γ-tocopherol) differ only in the number and position of methyl groups on the chroman head group. Tocopherols are important in limiting lipid peroxidation in a variety of organisms and are an essential component of mammalian diets as vitamin E (2*R*,4′*R*,8′*R*-[α]-tocopherol).[2, 3] The production of tocopherols for animal nutrition and various industrial purposes has sparked renewed interest in the synthesis and enzymology of the tocopherol biosynthetic enzymes.[2, 4-6] Although the tocopherol pathway has been studied for many years,[7] it is only recently that pathway enzymes have been cloned, providing new opportunities to study the substrate specificity and kinetics of the reactions. [5, 6, 8, 9]

B. Biosynthesis of α-tocopherol.

The pathway leading to the synthesis of α-tocopherol is shown in Figure VI-1. The committed intermediate in the tocopherol biosynthetic pathway is 2-methyl-6-phytyl-1,4-benzoquinone (MPBQ), the product of the condensation of the aromatic compound homogentisate (HGA) and the 20-carbon isoprenoid derived compound, phytyl pyrophosphate.[9, 10] MPBQ methyltransferase catalyzes the first

methylation reaction in tocopherol synthesis and the methylation of the same ring position of a related compound in plastoquinone synthesis. [11, 12]

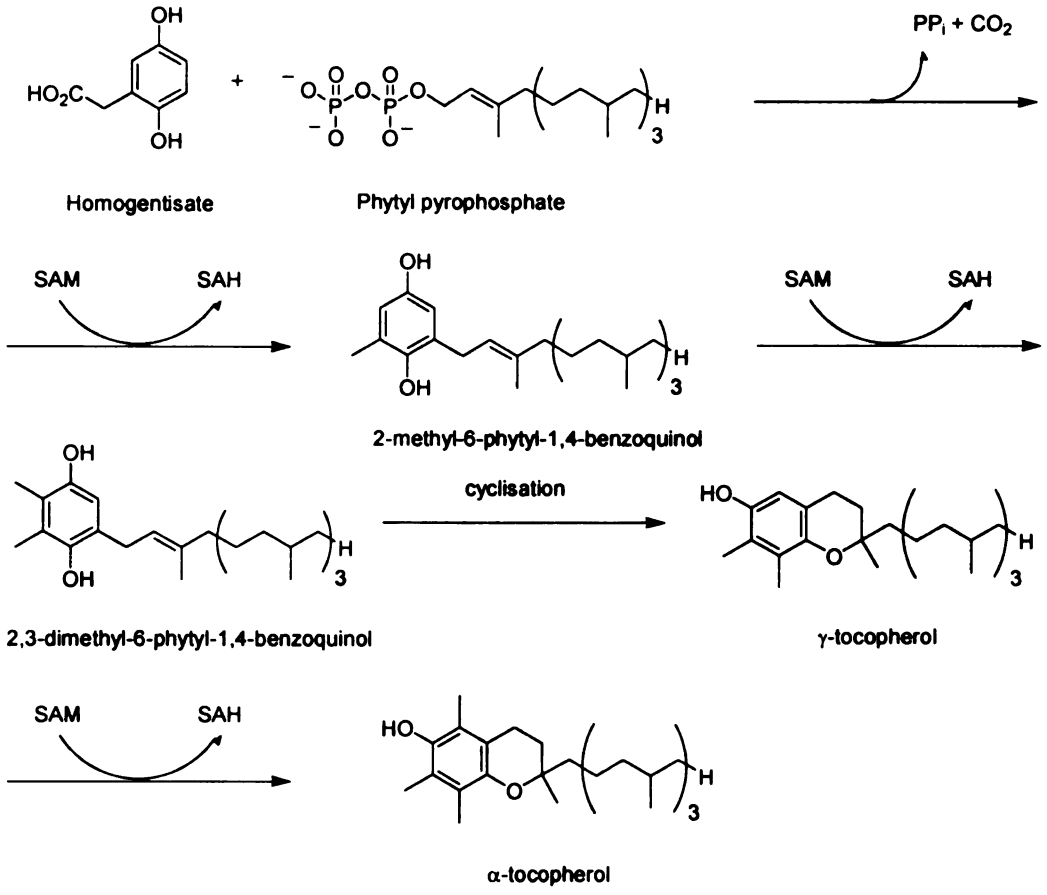


Figure VI-1. Biosynthesis of α-tocopherol.

Access to a variety of methylated phytylbenzoquinone precursors and intermediates is required in order to elucidate the regulation and the activity of MPBQ/MSBQ methyltransferase. [11] Previously reported methods provide some of these substrates in relatively low yields and as multiple isomers. [12-14] The development of a short and efficient synthetic method applicable to generating a wide range of these substrates has therefore become an integral part of elucidation of the biosynthetic pathway. We developed an efficient two-step synthesis of

methylphytylbenzoquinones (MPBQs) to study the kinetics and substrate specificity of MPBQ methyltransferase.

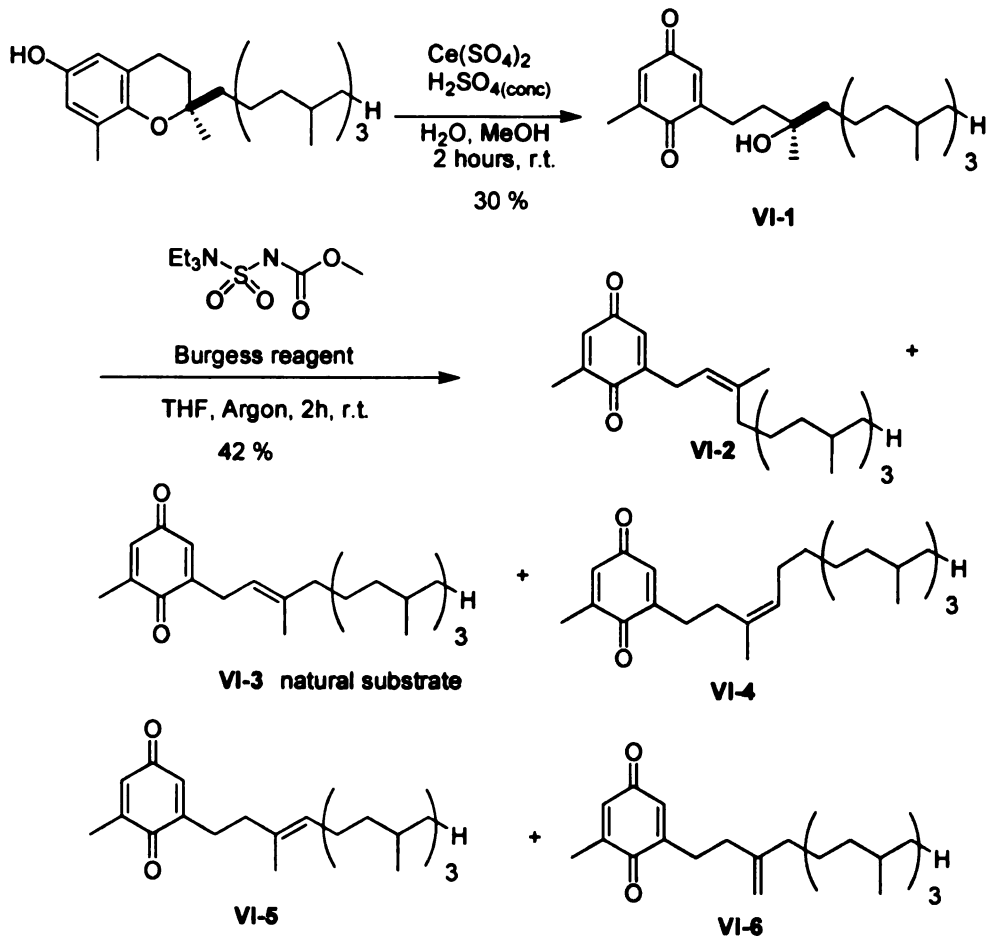
The earlier reported chemical synthesis of MPBQ involved oxidation of commercially available methylated phenols to methyl quinones followed by coupling of the phytyl side chain in the presence of $BF_3 \cdot OEt_2$ resulting in a mixture of positional isomers. [10] Oxidation of the resulting quinols with Ag_2O provided a mixture of isomers, which were separated by repeated thin-layer chromatography.

Unfortunately, due to the limited availability of the required isophytol side chain, the generation of wide mixtures of isomers, and corresponding low yielding reactions, this procedure was quite limited as a routine method for the large scale preparation of the many different tocopherol precursors. We discovered an alternative preparation of MPBQ derivatives from the naturally available tocopherols to provide more efficient access to these biosynthetic precursors.

C. Synthesis of required methylphytlbenzoquinone.

Oxidative cleavage of a chroman ring with cerium sulfate affords the quinone alcohol. [15] The well established $FeCl_3$ oxidation as described by Cohen has also successfully been used in the conversion of α-tocopherol to α-tocopheroquinones.[16] Cerium sulfate oxidation of δ-tocopherol resulted in a mixture of products from which the quinone alcohol **VI-1** was readily isolated in 30% yield at multigram scale. The quinone alcohol **VI-1** was subjected to

dehydration with Burgess reagent under argon atmosphere to afford a mixture of methylphytylquinones **VI-2** – **VI-6** (Scheme VI-1)[17,18]



Scheme VI-1. Synthesis of methylphytylbenzoquinone.

The positional and geometric isomers **VI-2** – **VI-6** were isolated by flash chromatography, followed by two rounds of HPLC purification using a silica column with hexane/isopropyl ether (992:8) as the eluant. Compounds **VI-2** – **VI-6** were isolated in a relative ratio of 1:2:1.1:1.5:2.2. The positional and geometric isomers from the dehydration will be further used as competitive inhibitors for

evaluating the reaction mechanism and kinetic parameters of the MPBQ methyltransferase.[11]

D. Experimental Section

Synthesis of VI-2 – VI-6: The quinone alcohol **VI-1** (0.4 g, 9 mmol) was weighed into a flame dried flask under argon atmosphere and dry THF (50 mL) was added. To this solution was added Burgess reagent (0.4 g, 1.8 mmol) and the mixture stirred at room temperature overnight. The reaction mixture was then diluted with ether (200 mL) and extracted twice with water and the organic layer was dried over anhydrous sodium sulfate and the ether layer was evaporated to obtain a yellow residue. The residue was flash chromatographed on silica-gel (5% ether:hexane) to obtain the methylphytylbenzoquinone as a mixture of five isomers (0.16 g, 42%) They were further separated by HPLC. **Spectral data: VI-3** ^{1}H NMR (500 MHz, acetone-d_6) δ 6.6 (1H, td, J_1=1.5 Hz, J_2=4.5 Hz), 6.46 (1H, td, J_1=1.5 Hz, J_2=3.5 Hz), 5.22 (1H, qt, J_1=1.5 Hz, J_2=7.5 Hz), 3.14 (2H, d, J=7.5 Hz), 2.06–2.07 (3H, m), 2.02 (2H, d, J=1.5 Hz), 1.66 (3H, s), 1.0–1.6 (18H, m), 0.85–0.9 (12H, m); ^{13}C NMR (125 MHz, acetone-d_6) δ187.61, 148.56, 146.07, 139.55, 133.01, 132.04, 118.87, 39.85, 39.41, 37.43, 37.42, 37.31, 36.56, 32.81, 32.66, 28.82, 28.67, 27.99, 27.48, 25.25, 24.8, 24.43, 22.29, 22.2, 19.4, 15.36, 15.15; IR (neat): 1670 cm^{-1}, 1600 cm^{-1}. MS (EI): calculated for $C_{27}H_{44}O_2$ $[M]^+$ 400.64, found $[M]^+$ 400.33.

Purification of MPBQ and its isomers: The mixture of isomeric methylphytylbenzoquinones was injected on a ReliaSil Silica, 5 μm, 250×4.6 mm

normal phase column (Column Engineering, Ontario, CA) with a guard column containing the same matrix. Chromatography was performed at 30°C with a mobile phase of 992:8 (v/v) hexane:isopropyl ether flowing at 1.0 mL/min. For large-scale purification, a preparative column of the same matrix (Column Engineering, Ontario, CA) was used. The collected fractions were dried down under vacuum before a small portion was injected onto the analytical column to monitor the purity. The natural substrate **VI-3** was eluted as the second HPLC peak.

Enzyme Assay: Assays of MPBQ methyltransferase activity were carried out in a 100 μL reaction containing 10 μL of solubilized *E. coli* extract (50 and 75 μg protein) expressing the MPBQ methyltransferase of Synechocystis PCC6803, [11] 50 mM Tris pH 8.0, 10 mM DTT, 80 μM [^{14}C-methyl]*S*-adenosylmethionine (56 mCi/mmol), 40 μM unlabeled *S*-adenosylmethioine, and 100 μM each of the individual MPBQ compounds **VI-2** – **VI-6**. After incubation at 30°C for 2 h, the reactions were stopped by the addition of 200 μL of 0.9% (w:v) NaCl, extracted with 450 μL of 2:1 (v:v) methanol:chloroform, centrifuged, and the organic phase collected and dried under a stream of nitrogen gas. The resulting residue was resuspended in hexane and fractionated on 250 μ60A KF6 silica gel TLC plates (Whatman, Clifton, NJ, USA) developed with 3:7 (v:v) diethylether:petroleum ether. The TLC plates were exposed on a Molecular Dynamics low energy phosphor screen (Amersham) to determine the incorporation of ^{14}C into the products.

Interestingly, MPBQ methyltransferase was found to utilize all five MPBQ isomers **VI-2 – VI-6** however the activity with the genuine substrate **VI-3** (Figure VI-2) results in specific activity that is 10–100 times higher than those of its isomers. The method described in this report has also been successfully applied to large-scale preparation of phytylquinone precursors of α-tocopherol (data not shown) and is applicable to a wide range of methylphytylbenzoquinone precursors.

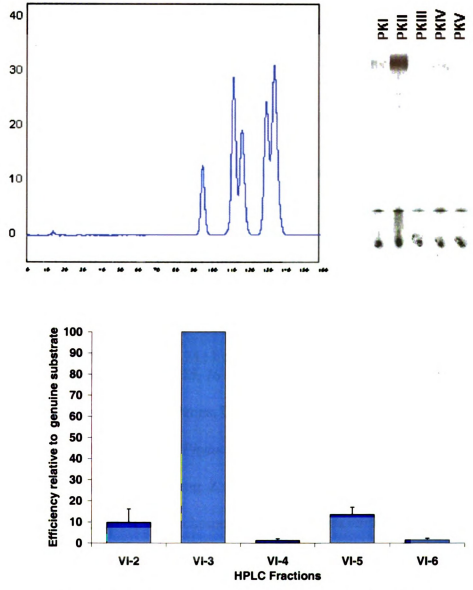


Figure VI-2. *TOP (left)*: HPLC trace of **VI-2** – **VI-6**.*TOP(right)*: Efficacy of isomers **VI-2** – **VI-6** compared to natural MPBQ as substrates monitored on TLC using ^{14}C-adenosyl methionine. *BOTTOM*: Efficacy of isomers **VI-2** – **VI-6** compared to natural MPBQ as substrates for methyltransferase activity. The percent efficacy of the isomers was based on the average of three independent assays.

E. References

1. Kamal-Eldin, A.; Appelqvist, L. A. *Lipids* **1996**, *31*, 671–701.

2. Fryer, M. J. *Plant Cell Environ.* **1992**, *15*, 381–392.

3. Topinka, J.; Binkova, B.; Sram, R. J.; Erin. A. N. *Mutat. Res.* **1989**, *225*, 131–136.

4. Weber, P.; Bendich, A.; Machlin, L. J. *Nutrition* **1997**, *13*, 450–460.

5. Grusak, M. A.; DellaPenna,D.*Annu. Rev. Physiol. Plant Mol. Biol.* **1999**, *50*, 133–161.

6. DellaPenna, D. *Science* **1999**, *285*, 375–379.

7. Trelfall, D. R.; Whistance, G. R. *Aspects of Terpenoid Chemistry and Biochemistry*, Academic Press, London **1971.**

8. Garcia, I.; Rodgers, M.; Lenne, C.; Rolland, A.; Sailland A.; Matringe, M. *Biochem. J.* **1997**, *325*, 761–769.

9. Shintani, D.; DellaPenna, D. *Science* **1998**, *282*, 2098–2100.

10. Soll, J.; Schultz, G. *Phytochemistry* **1980**, *19*, 215–218.

11. Shintani, D. K.; Cheng, Z.; DellaPenna, D. *FEBS Lett.* **2002**, 511,1–5.

12. Chenevert, R.; Courchesne, G. *Tetrahedron Lett.* **2002**, *43*,7971–7973.

13. Soll, J. *Methods Enzymol.* **1987**, *248*, 383–387.

14. Henry, A.; Powls, R.; Pennock, J. F. *Biochem. J.* **1987**, *242*, 367–373.

15. Cohen, N.; Lopresti R. J.; Saucy, G. *J. Am. Chem. Soc.* **1979**, *101*, 6710–6716.

16. Cohen, N.; Lopresti, R. J.; Neukom, C. *J. Org. Chem.* **1981**, *46*, 2445–2450.

17. Burgess, E.M.; Penton, H. R. J. ; Taylor, E. A. *J. Org. Chem.* **1973**, 38, 26–31.

18. Peddibhotla, S.; Cheng, Z.; Dellapena, D.; Tepe, J. J. *Tetrahedron Lett.* **2003**, *47*, 237-239.