This is to certify that the
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Symmetry as a Guiding Tool in the Development of Strategies
for the Synthesis of Calix[4]arenes and Related Macrocycles

presented by

Vijayagopal Gopalsamuthiram

has been accepted towards fulfillment
of the requirements for the

Ph.D. degree in Chemistry

Major Professor's Signature

8/4/05

Date

SYMMETRY AS A GUIDING TOOL FOR DEVELOPMENT OF STRATEGIES IN THE SYNTHESIS OF CALIX[4]ARENES AND RELATED MACROCYCLES

By

Vijayagopal Gopalsamuthiram

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

2005

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ABSTRACT

SYMMETRY AS A GUIDING TOOL IN THE DEVELOPMENT OF STRATEGIES FOR SYNTHESIS OF CALIXARENES AND RELATED MACROCYCLES

By

Vijaygopal Gopalsamuthiram

Symmetry commonly associated with beauty is a distinct feature present in many objects natural or artificial. Sometimes the symmetry embedded in molecular structures is either obvious or subtler nevertheless it affects the molecular properties to a significant extent. The synthetic strategies explored in this thesis rely principally on targeting certain symmetry elements present in the three dimensional structure of calix[4]arenes.

A new convergent "*Triple Annulation*" approach has been realized in this regard for the preparation of several calixarenes and other related macrocycles. The studies described herein are exploratory so as to examine the scope of this strategy and fall into three broad categories.

Calix[4]arenes with ABAB and ABAC substitution pattern exhibiting C_2 and C_S symmetry were synthesized directly via the reaction of bis-carbene complexes and diynes. This method is unique compared to existing methods for calix[4]arene formation in that it involves the formation of two of the four benzene rings of the calixarene and the macrocyclic ring of the calixarene in the same step. The

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syntheses of calix[4]arenes with specific substitution patterns in the inner and outer rims was also accomplished by this strategy and the conformations of these macrocycles was examined in detail.

One of the most important attractive features of the "*Triple Annulation*" approach is that the two adjacent arene rings of the calix skeleton are non-identical and this unique feature has been exploited in developing an efficient synthesis of chiral methylene substituted calix[4]arenes with either C_2 or C_1 symmetry. These calix[4]arenes were an unknown class of supramolecules prior to this study and hold significant potential for development as chiral building blocks for variety of applications. Moreover, the syntheses of several regio and stereoisomers of methylene functionalized calix[4]arenes has also been demonstrated during the course of this work.

Homocalix[4]arenes have been less examined due to the lack of conformational rigidity in these macrocycles and the limited methods for their preparation. The macrocyclization of bis-carbene complex and diyne allows for the construction of larger macrocycles as illustrated in the synthesis of a bis-homocalix[4]arene.

My grandp

Dedicated to the loving memory of

My grandparents Mr.G.K.Venkatraman, Mrs.Lakshmi Venkatraman

and Mr.A.Tirumalachari

I would dee

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Finally, I w

Raman, my brother

for their never-ending

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I would also like to thank my second reader Professor Maleczka who has been of immense help in tackling problems related to my research and also my other committee members Professor Smith and Professor Tepe.

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Finally, I would like to thank my parents Dr.K.V.Raman, Mrs.Usha Raman, my brother Arvind and my grand mother Mrs.Komalam Tirumalachari for their never-ending love and support throughout the past five years. I would

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also like to extend my gratitude to Miss. Lavenya for her constant support and appreciation over the last few months.

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DMF

$AlCl_3$

BINOL

NMR

ESI MS

LDA

$CDCl_3$

THF

HPLC

$Cr(CO)_6$

NOE

DMSO

CS_2

$C_2D_2Cl_4$

CCl4

EXSY

MM94

HMPA

TBS

TBSOTf

LIST OF ABBREVIATIONS

DMF	N,N-Dimethyl formamide
$AlCl_3$	Aluminum trichloride
BINOL	1,1'-Bi-2-naphthol
NMR	Nuclear magnetic resonance
ESI/MS	Electrospray ionization mass spectrometry
LDA	Lithium diisopropylamide
$CDCl_3$	Chloroform-*d*
THF	Tetrahydrofuran
HPLC	High pressure liquid chromatography
$Cr(CO)_6$	Chromium hexacarbonyl
NOE	Nuclear overhauser effect
DMSO	Dimethyl sulfoxide
CS_2	Carbon disulfide
$C_2D_2Cl_4$	Tetrachloroethane-d_2
CCl4	Carbon tetrachloride
EXSY	Chemical exchange spectroscopy
MM94	Molecular mechanics 94 calculations
HMPA	Hexamethyl phosphoramide
TBS	*tert*-butyl dimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate

D_2O

TLC

HMQC

S-PHOS

D_2O	Deuterated water
TLC	Thin layer chromatography
HMQC	Heteronuclear multiple quantum coherence
S-PHOS	Buchwald's biaryl phosphine ligand **324**

1.1 Historical

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Figure 1.1

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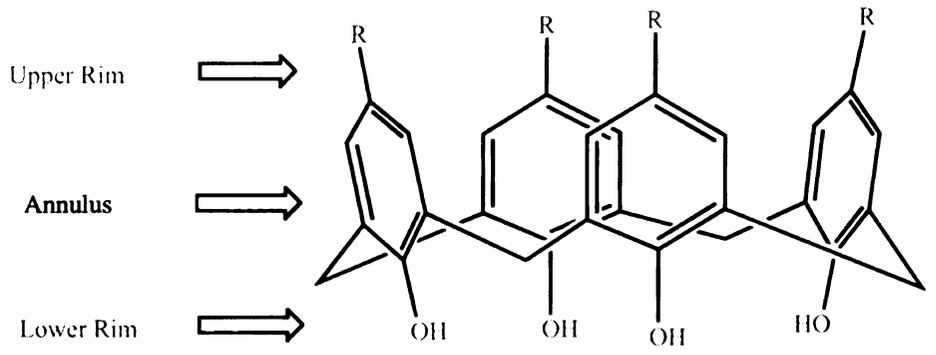
CHAPTER ONE

INTRODUCTION TO CALIXARENES

1.1 Historical perspective of calix[4]arene synthesis

Many of the discoveries in science are often made by accident rather by an ingenious (or) thought provoking ideas. Such a discovery was made in 1940's when Zinke found that the base induced reaction of *p*-alkyl phenols with formaldehyde provided cyclic oligomers as the predominant products.[1] The exact structural identification of the original Zinke mixture as well as a practical synthesis was not made available till the 1970s when Gutsche and coworkers reinterpreted his results and subsequently developed methods for selectively accessing three of the major cyclic oligomers that comprised the Zinke mixture in reproducible yields.[2] These were found to be cyclic tetramer (Calix[4]arene), hexamer (Calix[6]arene) and octamer (Calix[8]arene). The classical definition of the term calix[4]arene refers to macrocycles wherein four of the non-planar aromatic rings are linked by methylene bridges in the meta position so as to provide a cup or bowl-like structure, more commonly referred to as the cone conformation. A calix[4]arene is often characterized by an "Upper and Lower rim" as well as an "annulus". (Figure 1.1)

Figure 1.1 Calix[4]arene in a cone conformation



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After three decades since the pioneering work done by Gutsche, there have been remarkable advances made not only with respect to development of new methods for calixarene synthesis but also in their applications, which display a broad spectrum ranging from metal-ion complexation, inclusion of organic molecules pertinent as drug delivery systems, ligands in coordination chemistry and catalysis, synthetic receptors (enzyme mimics) and even as stationary phases in chromatography.[3] The following chapter will briefly address the different synthetic routes that have been instrumental for the preparation of calixarenes designed for such specific applications.

1.1.1 Base catalyzed phenol formaldehyde condensation process

The base induced synthesis is still regarded as the method of choice for a single step synthesis of the cyclic oligomers. These processes have now been widely classified as the "Modified Zinke-Cornforth Procedure" which affords *p-tert*-butyl calix[4]arene, "Modified Petrolite Procedure" which yields *p-tert*-butyl calix[6]arene and " Standard Petrolite Procedure" which yields *p-tert*-butyl calix[8]arene.[4] The following discussion will enumerate the reaction variables, which have been successfully implemented in gaining access to each of the calixarenes.

Modified Zinke-Cornforth Procedure: A mixture containing *p-tert*-butyl phenol, 37 % formaldehyde solution, and sodium hydroxide corresponding to 0.045 equivalents with respect to the phenol is heated for 2 h at 110-120°C to produce a resinous mass called the "precursor". The precursor is then heated in diphenyl ether for 2 h, the reaction mixture is cooled and treated with ethyl acetate upon which a copious precipitate is removed by filtration. Re-crystallization from toluene produces *p-tert*-butyl calix[4]arene [R = *t*-Bu Fig1.1] in 49 % yield as glistening white crystals.

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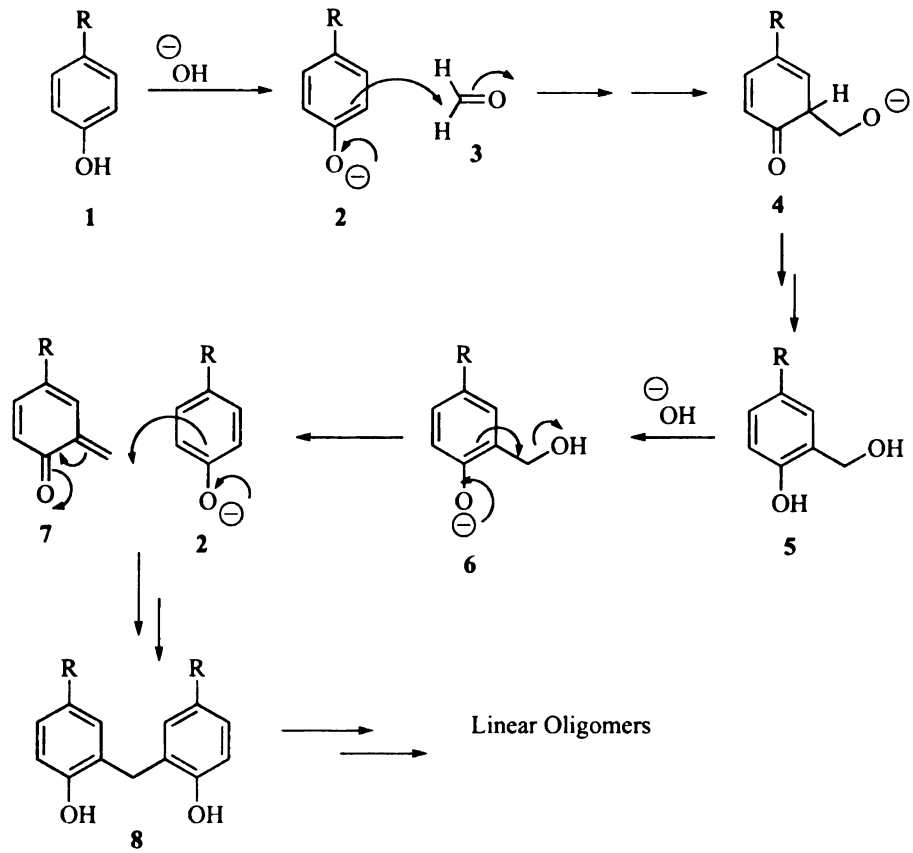
Modified Petrolite Procedure: A mixture containing *p-tert*-butyl phenol, 37 % formaldehyde solution, and potassium hydroxide corresponding to 0.35 equivalents with respect to the phenol is heated for 2 h to produce the precursor. The precursor is then heated in xylene for 2 h, the reaction mixture is then cooled and treated as before to afford *p-tert*-butyl calix[6]arene as the exclusive product. Crystallization from chloroform / acetone provides the hexamer as white powder in 85 % yield.

Standard Petrolite Procedure: Slurry prepared from *p-tert*-butyl phenol, formaldehyde and sodium hydroxide corresponding to 0.03 equivalents with respect to the phenol in xylene is stirred and refluxed for 4 h. The cooled solution is filtered and the copious precipitate is crystallized from chloroform to afford *p-tert*-butyl calix[8]arene as glistening crystals in 65 % yield.

The mechanism by which calixarenes are formed from the reaction of phenol and formaldehyde has been a matter unresolved for decades.[5] The initial sequence of reactions that are believed to occur involves hydroxymethylation to form an *o*-hydroxymethyl phenol **5** followed by an arylation via an *o*-quinone methide **7** as depicted in Scheme 1.1 to form **8**. Further sequence of reactions result in linear oligomer formation. Dehydration to form dibenzyl ethers is also conceivable under the reaction conditions. Thus, calixarenes probably arise from a mixture of diphenyl methane type and dibenzyl ether intermediates in various degrees of oligomerization as was shown by HPLC studies wherein at least three dozen non-cyclic components were present.

Scheme 1.1 Possible pathway for oligomerization under basic conditions



Gutsche and coworkers have addressed the issue of how either of these putative intermediates could be transformed to the cyclic oligomers.[5] They propose that a hemicalix[8]arene is initially formed by dimerization induced by intermolecular hydrogen bonding in a linear tetramer. The resultant hemicalix[8]arene undergoes an extrusion of water and formaldehyde to yield calix[8]arene as the major product which transforms to calix[4]arene by fragmentation / recombination pathway to a pair of cyclic tetramers. The exact mechanism for calix[6]arene formation is not well understood but believed to arise due to a template effect. Overall, cyclic octamer is postulated to be the product of *kinetic control*, hexamer the product of *template control* and tetramer the product of *thermodynamic control.*

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The careful control of reaction conditions in the synthesis of *p*-tert-butyl calixarene has however failed to provide useful calixarene syntheses from other *p*-alkyl phenols. The only other successful example is in the case of *p*-cresol wherein only the hexamer can be obtained in 74 % yield.[6] Electronically deactivated phenols do not afford any of the cyclic oligomers. *p*-Benzyl[7], *p*-ethyl[8], *p*-isopropyl[9] and *p*-isopropenyl phenols[10] afford difficult to separate mixtures of cyclic hexamers, heptamers and octamers in poor yields. *p*-phenyl phenol is an important substrate for synthesis of calixarenes with deepened hydrophobic cavities,[11] but the reaction again is not selective affording mixture of all the above in very low yields. The major disadvantage with the single step synthesis is that only symmetrical calixarenes are accessible by this methodology.

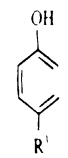
1.1.2 Non convergent stepwise strategy

Multistep syntheses of calix[4]arenes are often long and the yields are modest but the method has the advantage of introducing different groups into *p*-positions allowing the preparation of several unsymmetrical calixarenes. *o*-bromination of phenol **1** followed by hydroxymethylation affords the *o*-hydroxymethyl phenol **10**, which upon deprotonation affords the phenoxide species **11**. Loss of a hydroxide ion from **11** results in the formation of *o*-quinone methide **12**, which undergoes Michael addition from a different phenol **13** to afford the dimer **14**. A second Michael addition on the *o*-quinone methide obtained from phenol **15** that has a different *p*-substituent affords the trimer **16**, which upon dehalogenation by hydrogenation affords the linear trimer **17.** As the last step in the sequence, the condensation reaction of this trimer **17** with another 2,6-bis-

hydroxymethyl s

another water mo

Scheme 1.



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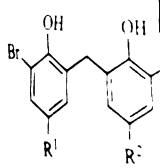

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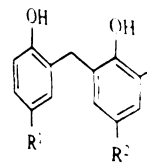

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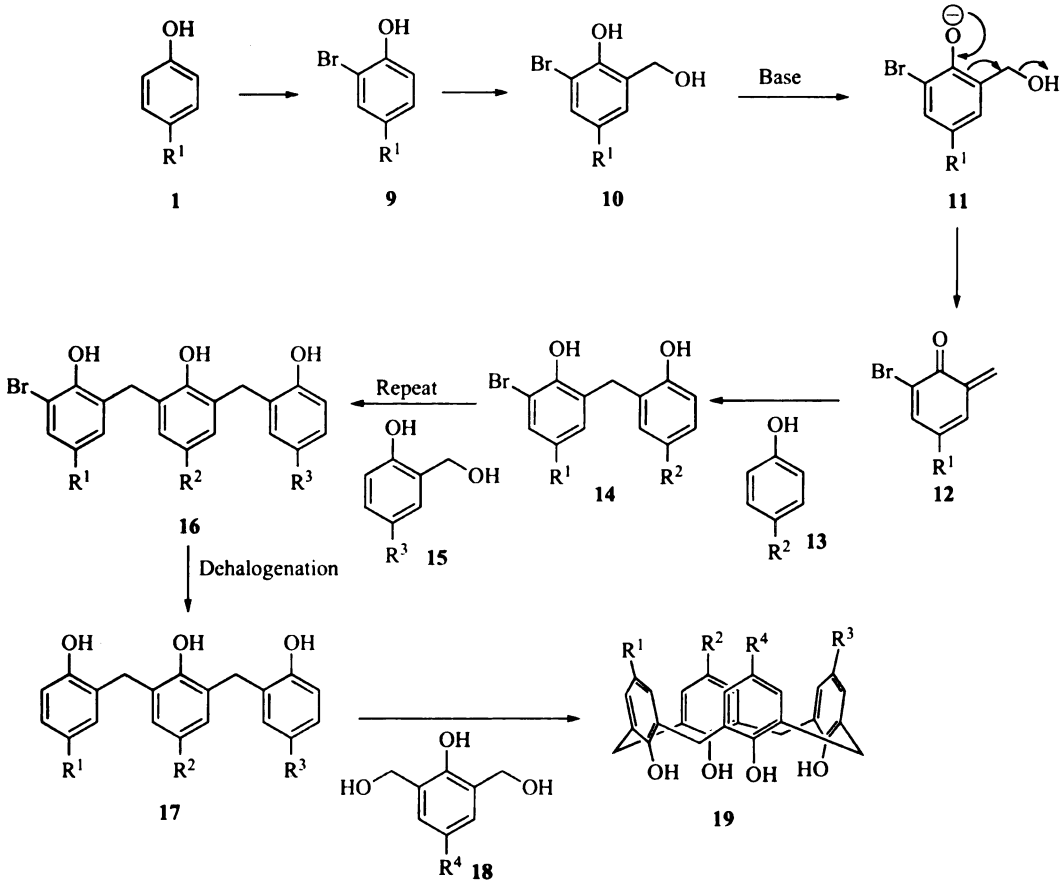
An examp

calix[4,5,6]arenes

incorporated linea

hydroxymethyl substituted phenol **18** affords the linear tetramer, which upon loss of another water molecule results in formation of calix[4]arene **19** (Scheme 1.2).[12]

Scheme 1.2 Stepwise calixarene synthesis



19a] R^1= *t*-Bu, $R^2 = R^3 = R^4$ = Me, 52 %

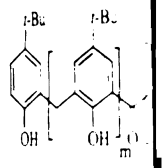
19b]$R^1 = R^3$ = *t*-Bu, $R^2 = R^4$ = Me, 53 %

19c]$R^1 = R^2$ = t-Bu, $R^3 = R^4$ = Me, 62 %

19d]$R^1 = R^2 = R^3 = R^4$ = t-Bu, 84 %

An example of this strategy was reported in the synthesis of carbonyl containing calix[4,5,6]arenes **21** in modest yields by the acid catalyzed cyclization of the carbonyl incorporated linear oligomers **20** (Scheme 1.3).[13]

Scheme 1.3 Oxo meth



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1.1.3.1 [3+1] Frag

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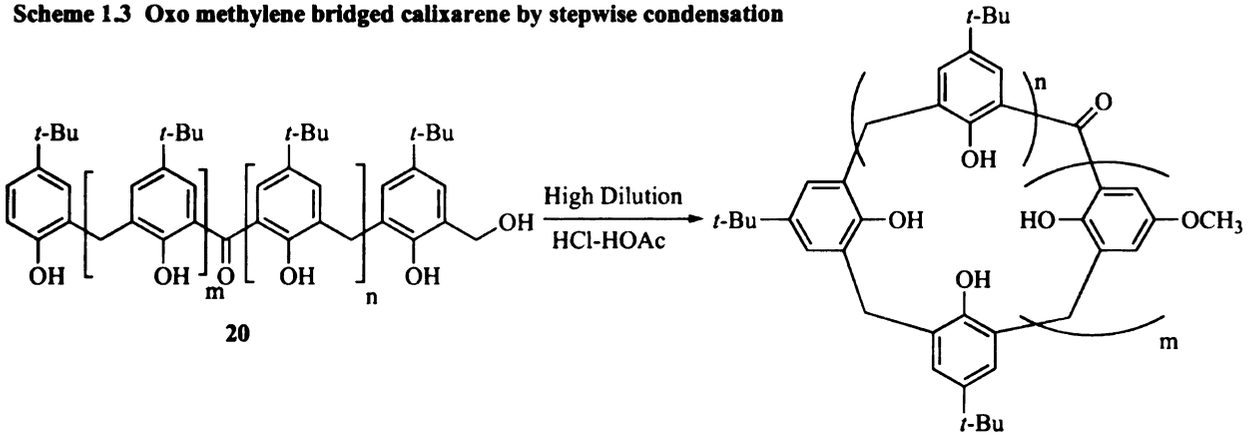
tetramer[15] and Me

Scheme 1.3 Oxo methylene bridged calixarene by stepwise condensation



m = n = 1, **21a** 40 %
m = 1, n = 2, **21b** 37 %
m = 2, n = 2, **21c** 61 %

1.1.3 Convergent syntheses (Fragment condensation)

The non-convergent strategy suffers from the tedious and often cumbersome preparation of the linear oligomers and also from the need to carry out the cyclization event under high dilution conditions. Hence, it has been abandoned largely in favor of the convergent processes for which the term "fragment condensation" has been frequently used.[14] Fragment condensation offers the same advantage of incorporating different substituents on aromatic rings resulting in synthesis of asymmetrically substituted calixarenes. There are four different strategies and, depending upon the fragments used to form the macrocycle, they are conveniently labeled as [3+1], [2+2], [2+1+1], [1+1+1+1] fragment condensations. All of them require the presence of a stoichiometric amount of Lewis acid, which acts as a template for the formation of the macrocycle.

1.1.3.1 [3+1] Fragment coupling

Two successful approaches are known in the literature wherein Method A: The condensation of the linear trimer with a bis-(halomethyl)-phenol affords the cyclic tetramer[15] and Method B: The condensation of bromomethyl containing linear trimers

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(Scheme 1.4). Th

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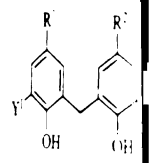
Scheme 1.4 [3+1]



22

Method A Y = H, Y

Method B Y = CH2Br

The reaction yield

as phenyl, benzoyl

1.1.3.2 [2+2] Frag

The [2+2]

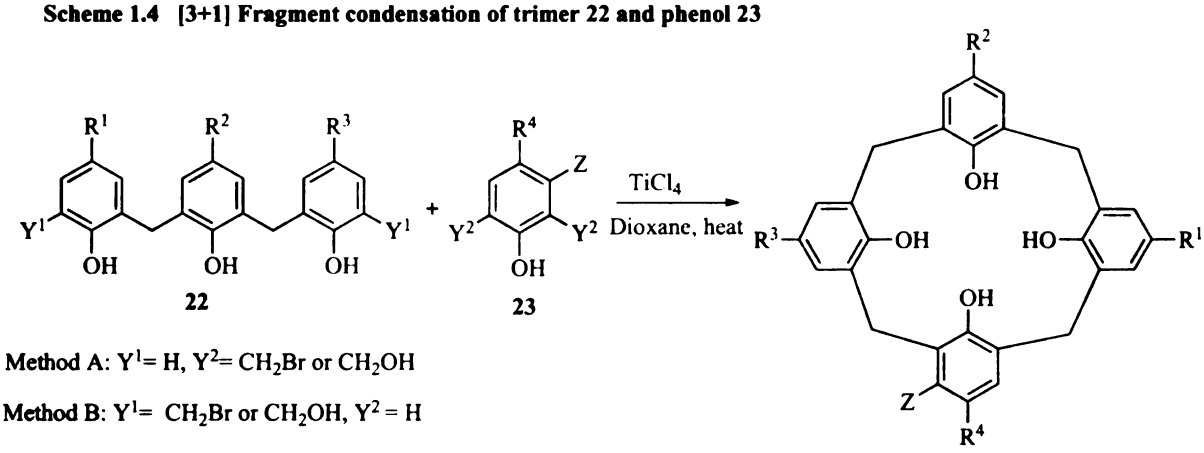
bis-(bromomethyl)

in which again the

1.5).[16]

with a phenol affords the same product in modest yields. Both these processes are carried out under the influence of titanium tetrachloride as the lewis acid in hot or refluxing dioxane for extended period of time and the yields of the products never exceed 40 % (Scheme 1.4). The [3+1] Fragment condensation strategy is extremely useful for the synthesis of calix[4]arenes with either C_2, C_s or C_1 symmetry.

Scheme 1.4 [3+1] Fragment condensation of trimer 22 and phenol 23



Method A: Y^1= H, Y^2= CH_2Br or CH_2OH

Method B: Y^1= CH_2Br or CH_2OH, Y^2 = H

24 Z = H

25 Z = Me

The reaction yields are insensitive to varying substitution patterns at the *p*-positions such as phenyl, benzoyl, chloro, propionate and nitro groups.

1.1.3.2 [2+2] Fragment coupling

The [2+2] Fragment condensation is similar to the previous strategy except that a bis-(bromomethyl) or bis-(hydroxymethyl) dimer **27** with phenolic dimer **26** to form **24** in which again the same *p*-substituents as mentioned above can be introduced (Scheme 1.5).[16]

Scheme 1.5

Self-condensation

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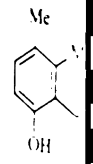
Scheme 1.6



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The [2+1+1

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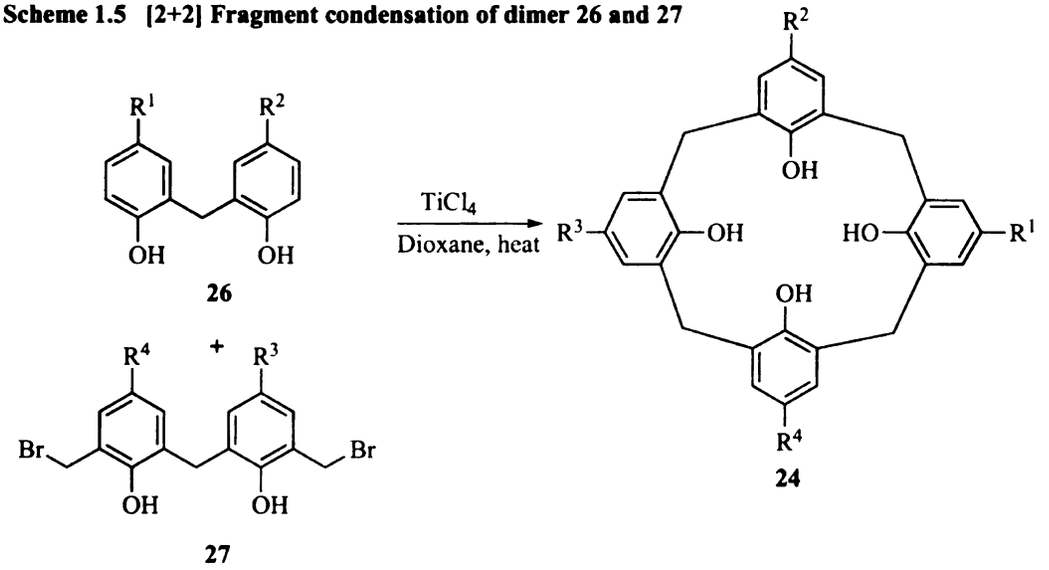
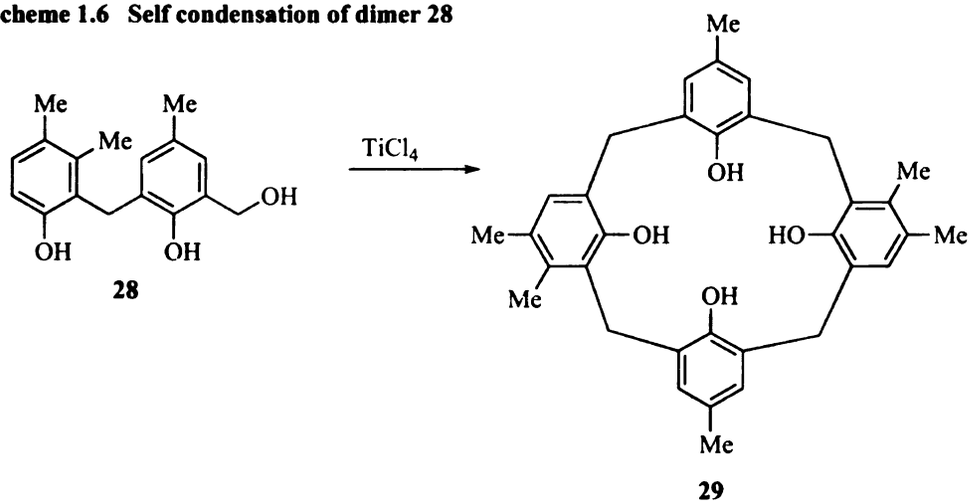
(bromomethyl) aren

Scheme 1.5 [2+2] Fragment condensation of dimer 26 and 27



Self-condensation of dimer **28**, which possesses a single hydroxymethyl group, has also been used to prepare C_2 symmetric calixarenes such as **29** (Scheme 1.6).[17]

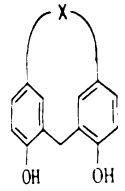
Scheme 1.6 Self condensation of dimer 28



1.1.3.3 [2+1+1] Fragment coupling

The [2+1+1] approach has been used predominantly in the synthesis of bridged calixarene **32** from the reaction of bis(*p*-hydroxyphenyl)alkanes **30** with bis-(bromomethyl) arene **31** (Scheme 1.7).[18]

Scheme 1.7 [2+1+1] Fr



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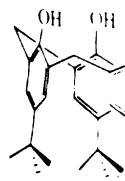
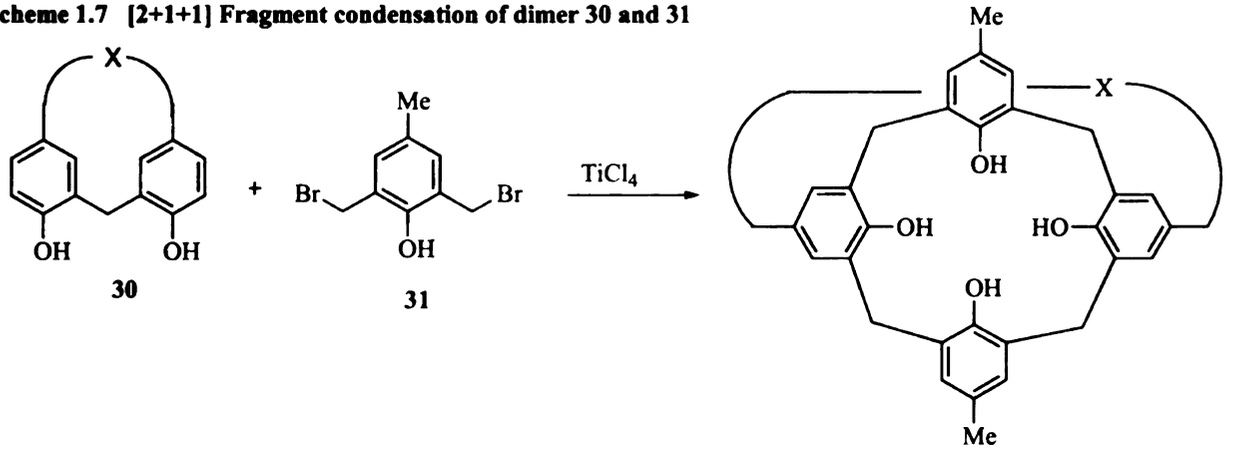
Scheme 1.8



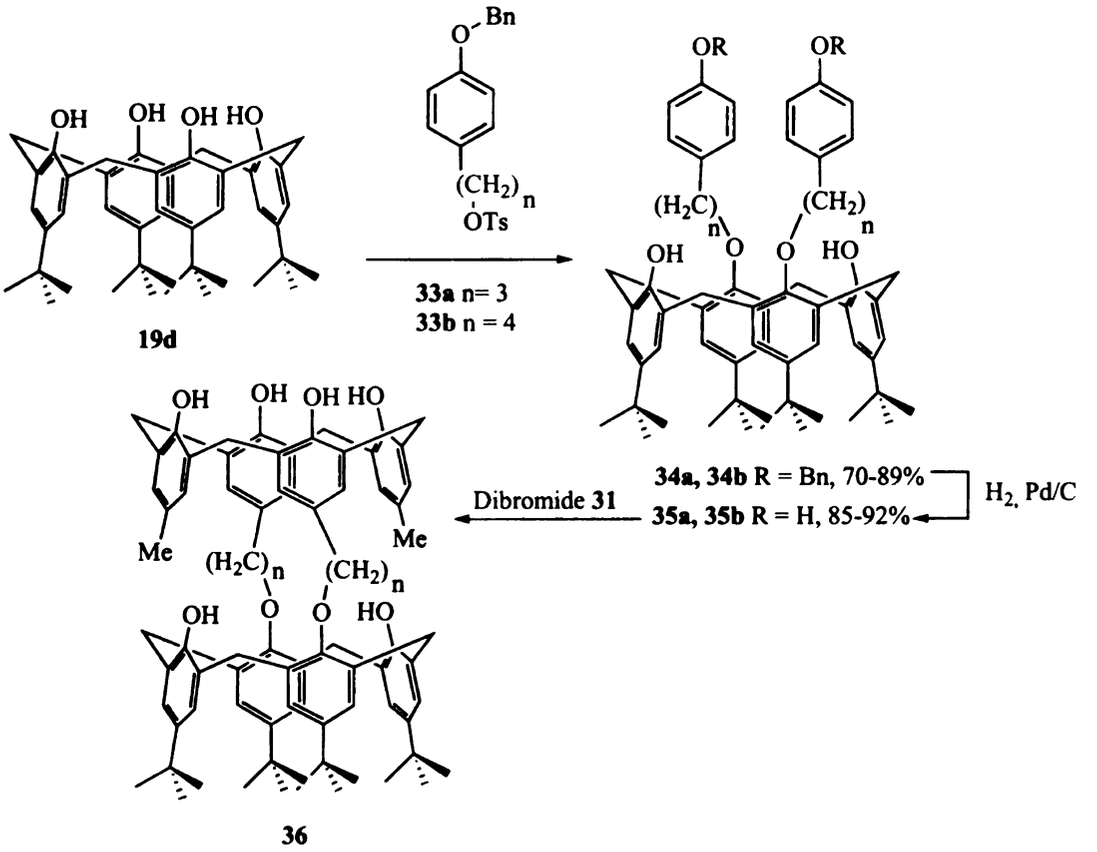
19d

Scheme 1.7 [2+1+1] Fragment condensation of dimer 30 and 31



The yields for the calixarenes typically range from 2-20% and they were found to be dependent upon the nature of the tether length and the *p*-substituent although a direct correlation doesn't seem to exist. Another unique example was reported in the synthesis of "head to tail" linked double calixarene **36** in 4-5% yield from the reaction of diphenols **35** tethered via the lower rim of a calix[4]arene with **31** (Scheme 1.8).[19]

Scheme 1.8 "Head to Tail" linked double calixarene 36



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An interesting ap

calix[4]arene 41

Scheme 1.10 [2x1+2x

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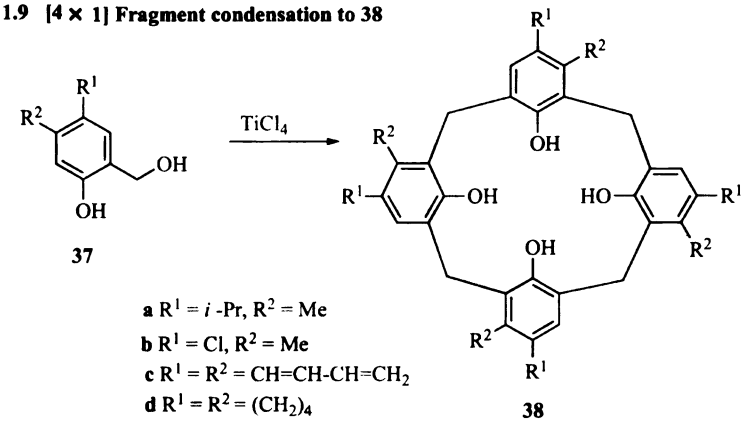
1.1.3.4 [1+1+1+1]Fragment coupling

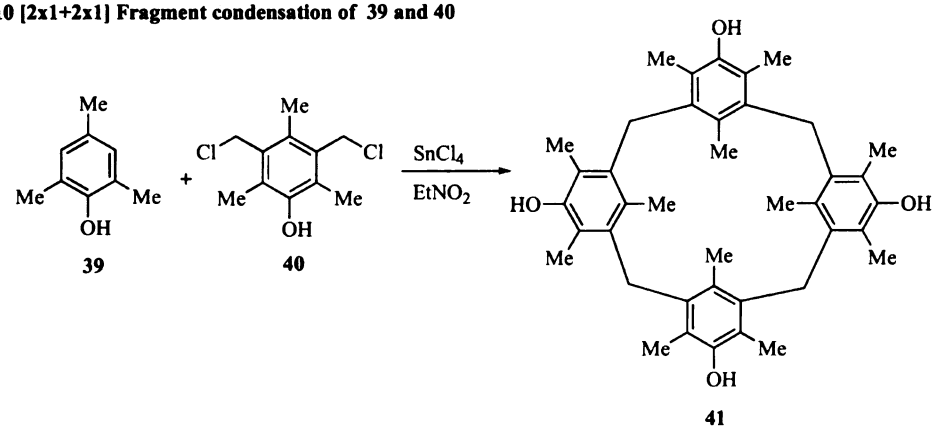
A [1+1+1+1] or (4×1) fragment condensation is analogous to the single step formation of calix[4]arenes from phenols except that the methylene unit is already present in the starting phenol. The starting materials are conveniently prepared by hydroxymethylation of the phenols with formaldehyde and base or by reduction of carboxylic acids. The reaction of *o*-(hydroxymethyl) phenol **37** produces calix[4]arenes **38** in typically 18-30 % yields (Scheme 1.9).[17]

Scheme 1.9 [4 × 1] Fragment condensation to 38



An interesting application of this strategy was reported recently in the preparation of calix[4]arene **41** with four *exo*-hydroxyl groups in 66 % yield (Scheme 1.10).[20]

Scheme 1.10 [2x1+2x1] Fragment condensation of 39 and 40



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1.2 Physical p

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Figure 1.

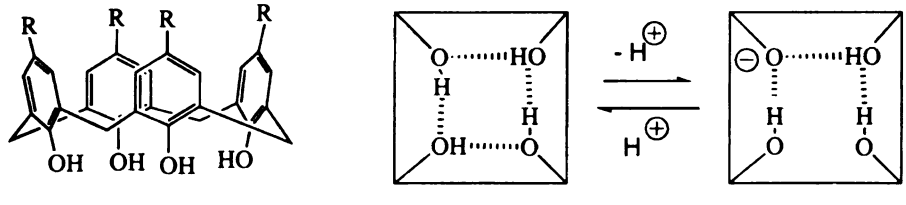
The above transformation is rather unique in that the *ortho* position of the phenolic group in **39** is blocked and hence cyclization occurs from the *meta* position to give the cyclization product **41**.

1.2 Physical properties of calixarenes

1.2.1 Acidity constants and Hydrogen bonding

The phenolic hydroxy groups in calixarenes are known to form strong intramolecular hydrogen bonds and hence its acid dissociation properties are affected. Owing to the low solubility of proto-typical calixarenes such as **19d** in water, water-soluble derivative **42** was prepared. The dissociation of the first proton of **42** (pK_{a1} = 3.26) was found to occur at unusually low pH values representing a shift by 8 pK_a units relative to phenol. Subsequent dissociation of the protons occurs at normal or higher pH regions than phenol (Pk_{a2} = 11.8, Pk_{a3} = 12.8 and Pk_{a4} = 14).[21] The undissociated calixarenes contain a circular hydrogen-belt composed of four intramolecular hydrogen bonds. The net result of this stabilization may suppress the dissociation of the first proton, however, the mono-dissociated species comprised of one oxide anion and three hydrogen-bonds is more stabilized by stronger intramolecular hydrogen bonding. Hence, the pK_{a1} drops down to 3.3 (Figure 1.2).

Figure 1.2 Hydrogen bonding in calixarene monoanion from 42



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1.2.2 Melting p

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1.2.3 Spectral p

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1.3 Conforma

IR (typically around 3150 cm^{-1}) and ^1H NMR spectroscopy (δ = 9-10 for OH) have been observed for calixarenes which indicate strong hydrogen bonding as has X-ray crystallography by examination of O···O internuclear distances.

1.2.2 Melting points and Solubility

Almost all of the calixarenes having free –OH groups are characterized by very high melting points typically around 350°C. It is also well known that the substituent at the *p*-position can significantly influence the melting point temperature. Derivatization of the calixarenes usually results in slightly lower melting points.

Another important feature of these macrocycles is their insolubility in water, aqueous base and low solubility in organic solvents. Furthermore, *p*-substituents that lower the melting point of the calixarene offer enhanced solubility in organic solvents. Water-soluble carboxyl and sulfonate containing calixarenes have been prepared which offer interesting properties.[22]

1.2.3 Spectral properties

A rather distinct feature in the infrared spectra of calixarenes is the unusually low frequency of the stretching vibrations of the OH groups, which are in the range of ~3150 cm^{-1}. This low frequency has been attributed to the strong intramolecular hydrogen bonding that exists in these macrocycles. In the ^{1}HNMR spectra of calixarene **19d** (Scheme 1.2), the OH, ArH and *tert*-butyl resonances appear as singlets and the methylene resonance appears as a pair of doublets indicating that the minimum energy conformation contains equivalent methylene groups carrying non-equivalent hydrogens.[23]

1.3 Conformational behaviour of calix[4]arenes

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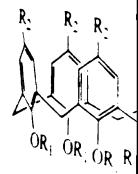
Figure 1.3 Schema



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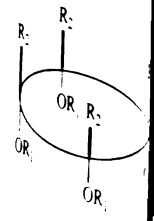
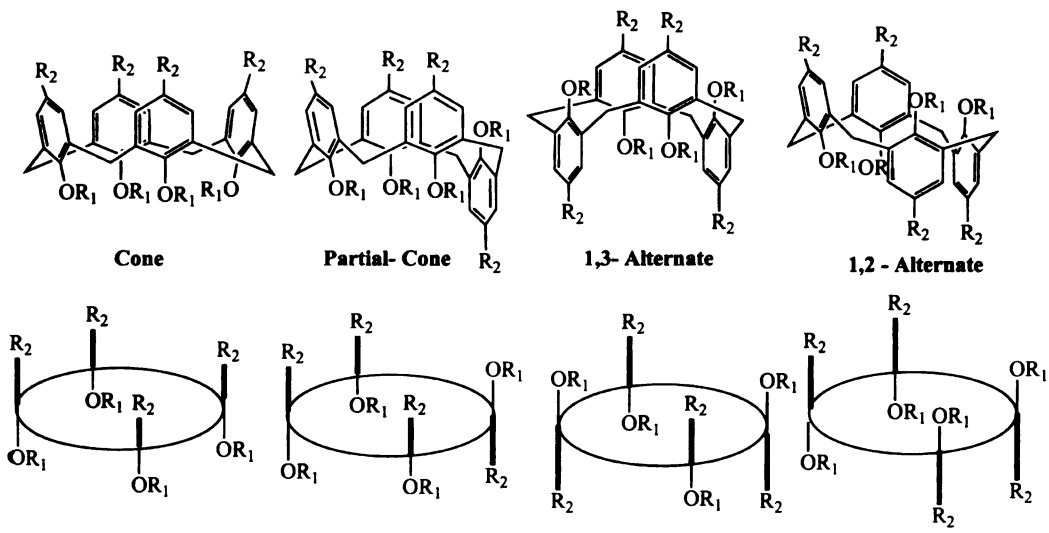


One of the most challenging facets of calixarene chemistry concerns their conformations in solution, which subsequently impact the utilization of these building blocks for the construction of supramolecular systems and artificial receptors. As it was mentioned earlier, the name calixarene arises due to the fact that the conformation adopted by the macrocycle is "bowl-like" or a cone conformation. However, this is a simplistic picture of a calixarene conformation as there are at-least four different conformers possible for a calix[4]arene. There have been quite a number of review articles written or published concerning this field over the past two decades.[24] It was originally realized by Cornforth that these conformers are stereoisomers, which can inter-convert by the rotation of the aryl groups with respect to the annulus.[25] The one with all aryl groups *syn* to one another is referred to as the "Cone" conformer, one with three aryl groups *syn* and one *anti* as "Partial-Cone", one with adjacent pairs of aryl groups *syn* and *anti* as "1,2-alternate" and one with non-adjacent pairs of aryl groups *syn* and adjacent ones *anti* as "1,3-alternate". The different schematic representations for all these conformers are depicted below in Figure 1.3.

Figure 1.3 Schematic representation of all four possible conformers



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All of these representations are mere idealized structures and symmetry descriptors are often assigned to each of these conformers [Cone conformer C_{4v}, partial cone (paco) C_s, 1,3-alternate C_{2h} and 1,2-alternate D_{2d} symmetry]. The actual structures of each of these conformers in solution may be slightly different as a result of torsional changes in alignment of the aryl groups. The cone conformer for example may tend to adopt a "pinched" or "flattened-cone" conformation in which case two of the aryl rings are splayed outward and the other two aryl groups are almost parallel to each other.[26] Molecular models and theoretical calculations have aided the assignment of stereochemistry and evaluate inter as well as intramolecular interactions. Information gained from these modeling studies as well as crystallographic results and the development of advanced two-dimensional spectroscopic techniques has provided ample information about their structures.

One of the main problems associated with structure determination of calixarenes by single crystal X-ray diffraction aside from the fact that the crystals may not of good quality is the fact that many parameters need to be determined and refined as they are fairly large molecules. The net result is that hydrogen atoms are located with difficulty and many structures have been reported over the years with calculated positions of hydrogen atoms. Disorder problems frequently arise due to inclusion of solvent molecules inside the cavity. An advantage of structure elucidation in the solid state has often been that the macrocycle is relatively rigid and hence accurate representation of the molecular conformation is obtained. *p*-tert-Butyl calix[4]arene obtained in the solid state as 1:1 complex with toluene was the first to be studied by diffraction studies for which cone conformation was ascribed with a four-fold symmetry axis.[27]

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In general, it has been found that calixarenes with free hydroxy groups are stabilized by intra-molecular hydrogen bonding which consequently imparts thermodynamic stability to the cone conformer. The tetramethoxy derivative of **19d** (Scheme 1.2) adopts a partial cone conformation in solid-state whereas the 1,2-dimethyl ether as well as 1,3-dimethyl and trimethyl ethers adopt cone conformations.[28] The "Mendoza rule" has been frequently applied to structure determination in calix[4]arenes and it has been found that for adjacent aryl rings that are *syn* to each other in the macrocylic array the ^{13}C chemical shifts of the corresponding bridging methylene carbons for a set of known calix[4]arenes range from 30.2 to 32.7 ppm for cone and 36.7 to 38.2 ppm for 1,3-alternate.[29] The observed chemical shift differences were then rationalized by examining the X-ray data of some calixarenes in cone and 1,3-alternate conformations, which displayed for the methylene carbons a shorter $C(sp^2)$-$C(sp^3)$-$C(sp^2)$ bond angle and an increased van der Waals energy in the former compared to the latter. Partial-cone and 1,2-alternate had two methylene resonances at 31 and 37 ppm respectively due to the presence of two syn and anti orientations of the arenes in the macrocycle.

Ring inversion is another phenomenon, which increases the complexity of the problem in structural assignment. Calixarenes with free hydroxy groups are conformationally mobile as indicated by the variable temperature ^1H NMR spectra. At room temperature, a pair of doublets is observed for the bridging methylene hydrogens, which are conveniently labeled as equatorial and axial hydrogens as their positions in a cyclic array resemble those set of hydrogens in cyclohexane derivatives. At high

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1.4 Functional

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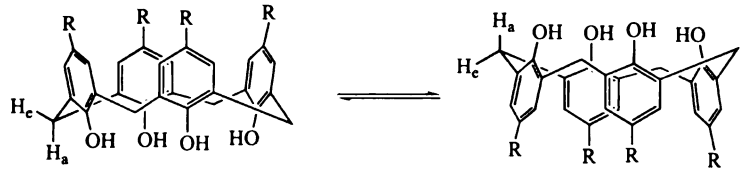
temperatures, these pair of doublets coalesces to a singlet at high temperatures reminiscent again of similar pattern observed in cyclohexane (Scheme 1.11).[23]

Scheme 1.11 Ring inversion in calix[4]arene



The conformational ring-flip is dependent upon the nature of the *p*-substituents in the calix to a lesser extent than the solvent. Polar solvents such as pyridine-d_5 are known to decrease the barrier for ring inversion ($\Delta G^{\neq}$ = 57.3 kJ mol^{-1} at coalescence temperature T_c = 15°C) compared to chloroform-*d* ($\Delta G^{\neq}$ = 63-67 kJ mol^{-1}). Gutsche has studied the mechanism for conformational inversion in detail and two distinct scenarios are possible.[23] The 1,3-alternate conformer formed by rotation of two opposite aryl rings by concomitant disruption of hydrogen bonding has been believed to be an intermediate which can either revert to the original cone or inverted cone conformer. Alternatively, aryl groups can swing through the annulus in se quence via an activated complex that resembles a skewed 1,2-alternate conformer thereby maintaining hydrogen bonding throughout the process with minimal distortion of bond angles.

Nuclear Overhauser Effect has been useful for structure elucidation by identifying through space interactions between hydrogens on aryl rings and methylene bridges whereas chemical exchange spectroscopy (EXSY) has been used to analyze inter-conversion processes between conformers.

1.4 Functional group modification of calixarenes

The commercial availability of *p-tert*-butyl calixarene **19d** (Scheme 1.2) enables the development of strategies towards further functional group manipulations. Such

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transformations can be done at three different locations on a calix[4]arene namely the upper and lower rims of the macrocycle as well as on the methylene bridges. Functionalization at the upper and lower rims will only be addressed in this section while a separate section (Section 1.5) will be entirely devoted to functionalization of the methylene bridges.

1.4.1 Functionalization at the lower rim (Transformations involving –OH group)

Complete alkylation or acylation of **19d** (Scheme 1.2) can be performed under a wide variety of reaction conditions to give tetraalkyl ethers and ester derivatives normally as a mixture of all possible conformers if larger substituents are introduced at the lower rim.[30] Control of stereochemistry can be achieved by proper choice of base and solvent. For example, alkylation of **19d** using sodium hydride in dimethyl formamide and THF as the solvents invariably yields the cone conformer **43**.[21,24c,31] No other mono, di or trialkylated products was observed in this reaction. Cesium carbonate in acetonitrile affords 1,3-alt conformer **45** whereas partial cone **44** is exclusively obtained using potassium *tert*-butoxide in benzene (Scheme 1.12).[24c,32] 1,2-Alternate conformer **46** was obtained in four steps from **19d** in 56 % yield.[30] Again, no other side products resulting from incomplete alkylation at the intermediate stage was observed under these conditions. The mechanistic picture for selective formation of either of these conformers under different reaction conditions has not been described. Several methods have been developed for selective functionalization of calixarenes at the lower rim. The premise behind chemo-selective functional group manipulations relies on the difference in acidities of the phenolic hydroxy groups in the calix[4]arene (Section 1.2.1). Often, the use of a slight excess of a weak base such as cesium fluoride in DMF and an excess of

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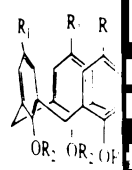
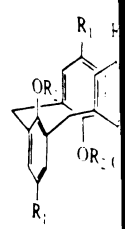
Scheme 1.12 Syn



R_2 = *n*-Pr, R_1

Cone **43** 34 %



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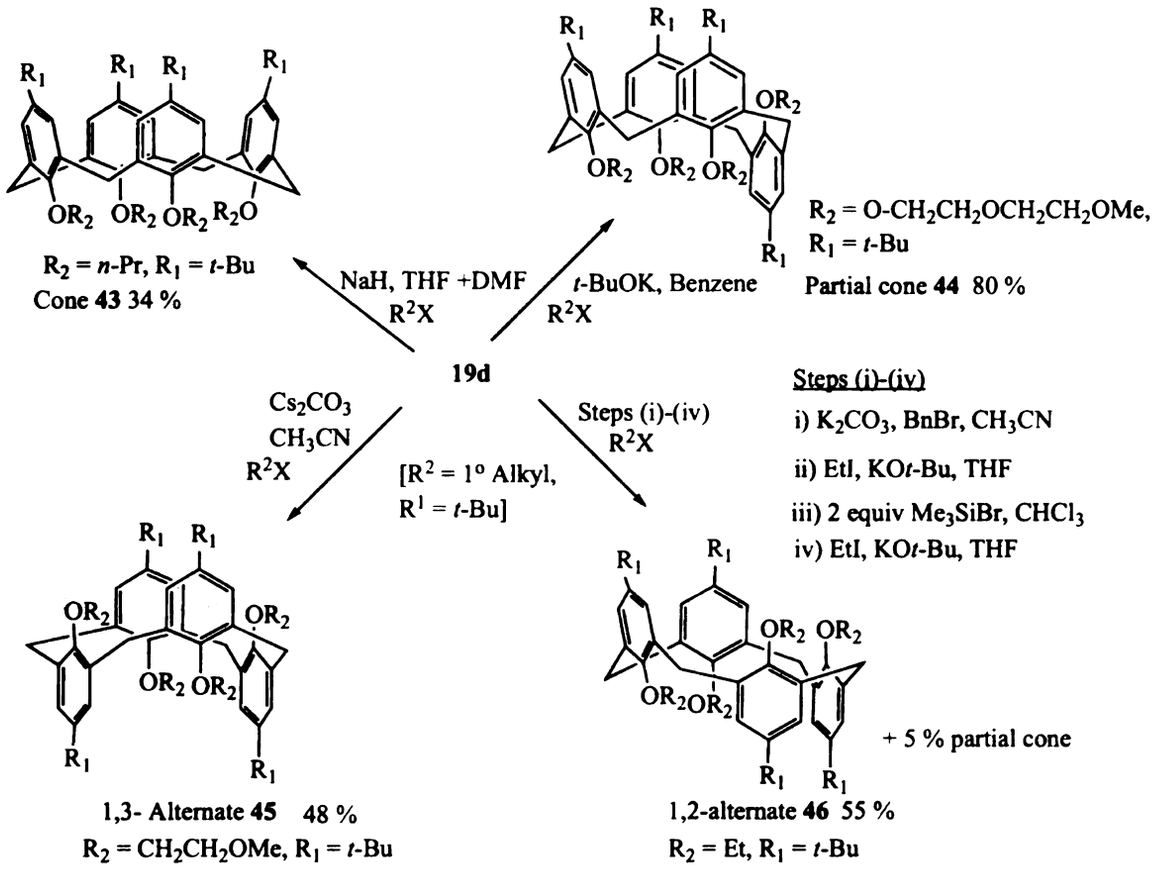
alkylating agent results in selective formation of monoalkoxy calixarene **47**.[33] Distal 1,3-dialkoxy calixarenes **48** can be obtained chemoselectively by the use of potassium carbonate in acetone or acetonitrile[34] whereas adjacent 1,2-dialkoxy calixarenes **49** by using sodium hydride in DMF as the solvent and 2.2 equivalents of the alkylating agent.[35] Alkylation using barium hydroxide / barium oxide in DMF affords the trialkoxy calixarenes **50**. (Scheme 1.13).[36]

Scheme 1.12 Synthesis of specific conformers of calix[4]arene tetraethers



The rationale behind the exclusive formation of (1,3) distal isomer with potassium carbonate was explained by an initial formation of monoanionic species **a**, which is stabilized by three intramolecular hydrogen bonds. Subsequent alkylation yields the monoalkyl ethers **47**, which upon further deprotonation afford another monoanionic species **b**. This species is stabilized by two intramolecular hydrogen bonds to the

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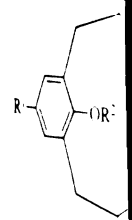
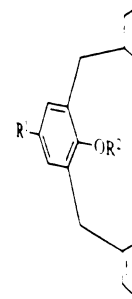
Scheme 1.13 Selectiv



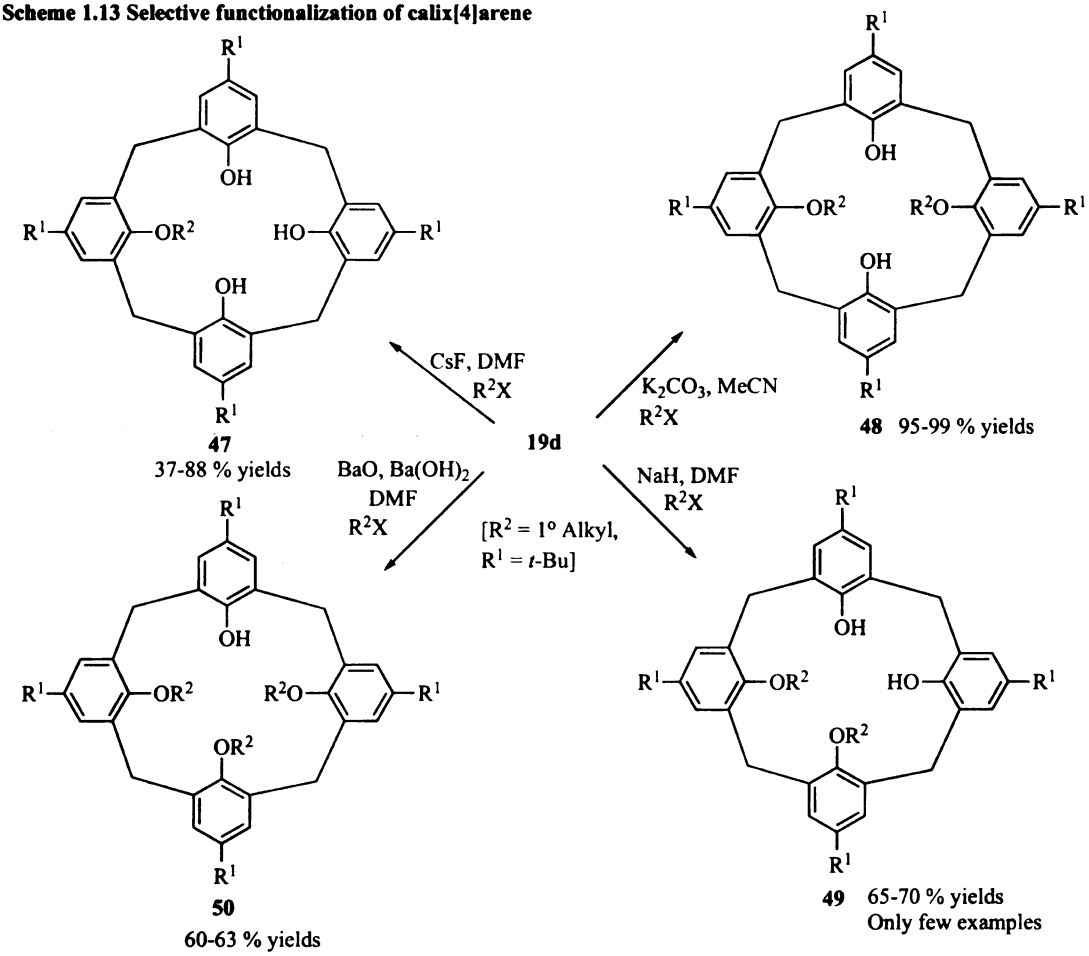


Excellent

C_1 and C_2 symm

neighbouring phenols. Alkylation of the monoanion **b** leads to the (1,3) distal disubstituted calix[4]arene **48**. The formation of the (1,2) proximal isomer was invoked to occur only under the influence of a strong base that leads to the formation of dianion **c** than dianionic species **d** due to the presence of two intramolecular hydrogen bonds in the former and one in the latter (Figure 1.4).[37] While the selective formation of alkyl ethers has been extensively studied, ester formation can be accomplished with a similar degree of control by proper choice of reaction variables.

Scheme 1.13 Selective functionalization of calix[4]arene



Excellent stereoselectivity can be achieved in the preparation of calixarenes with C_s and C_2 symmetry by acylation of distal 1,3-dialkoxy calix[4]arenes **48** with acetyl

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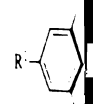
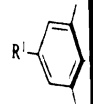
1.14).[38]

Figure 1.





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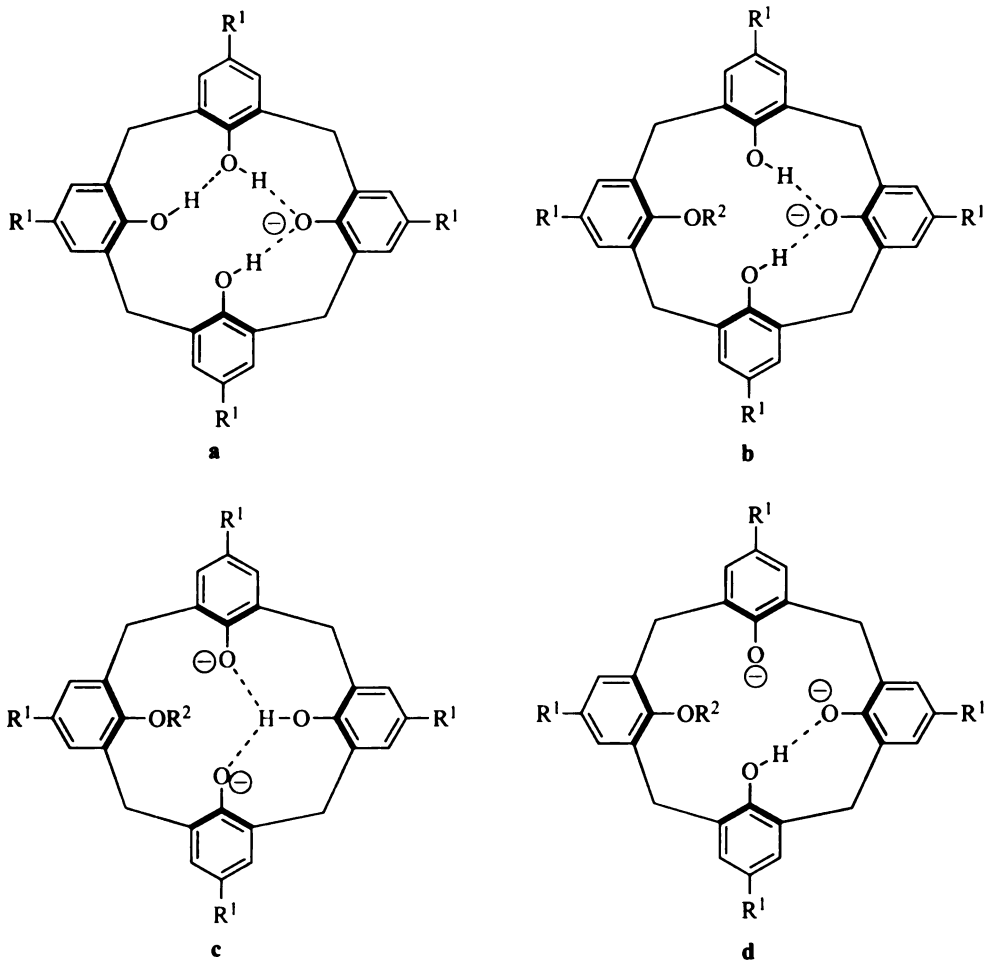
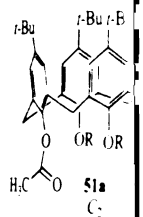
chloride in ethyl ether. The use of sodium hydride as a base yields the cone conformer **51a** while thallium ethoxide gives the partial cone isomer **51b** in high yields (Scheme 1.14).[38]

Figure 1.4 Calixarene mono and dianions



Although the precise origin of the stereoselectivity is not completely understood, metal-ion template effect is believed to be operative wherein the smaller sodium cation favors the formation of the cone conformer due to its tighter chelating ability to the oxygen substituents at the lower rim compared to the larger thallium cation which gives partial cone by rotation of one phenol unit.

Scheme 1.14 Stereo



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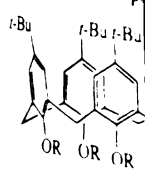

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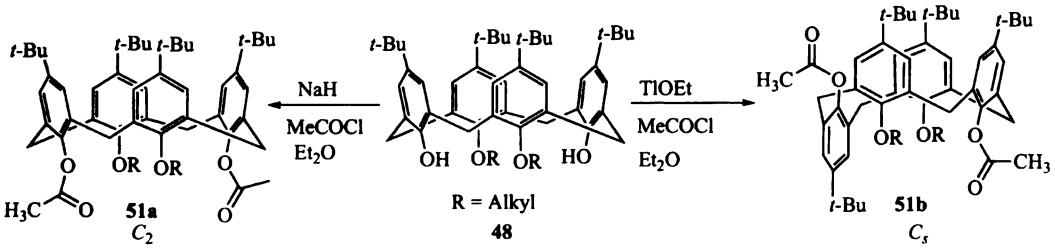
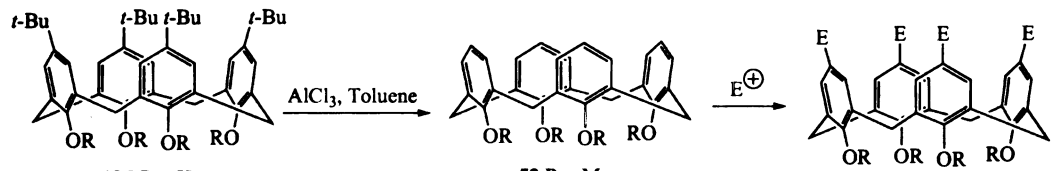
Scheme 1.14 Stereochemical control in formation of calixarenes with C_2 and C_s symmetry



1.4.2 Functionalization at the upper rim

The replacement of the *t*-butyl groups with other substituents on calixarene **19d** and the tetramethyl ether **52** has been done by Friedel-Crafts dealkylation using $AlCl_3$ as a catalyst in toluene, which acts as the solvent and acceptor for the *tert*-butyl cation. This is followed by electrophilic aromatic substitutions at the free *p*-positions.[39] This process allows for the introduction of a variety of substituents into the *p*-position such as nitro, sulfonate, halogens (Br or I), formyl, acetyl etc (Scheme 1.15).

Scheme 1.15 Electrophilic aromatic substitutions on 53 and 54



E = Br, SO_3H, NO_2, COR_2, CH_2NR_2, Allyl, CHO, I etc.

These functionalized calixarenes are amenable towards further chemical transformations at the lower rim. In addition, it has been demonstrated that selective functional group introduction at the *p*-position could be accomplished by transferring the selectivity that is normally obtained in the alkylation or esterification of –OH groups based on the difference in reactivity of phenols and phenol ethers or esters leading to the preparation of C_2 symmetric calixarenes (Scheme 1.16). Chemoselective distal diallylation of **54** to **57** followed by Claisen rearrangement affords *p*-allyl calix[4]arene

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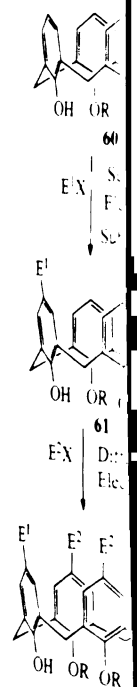

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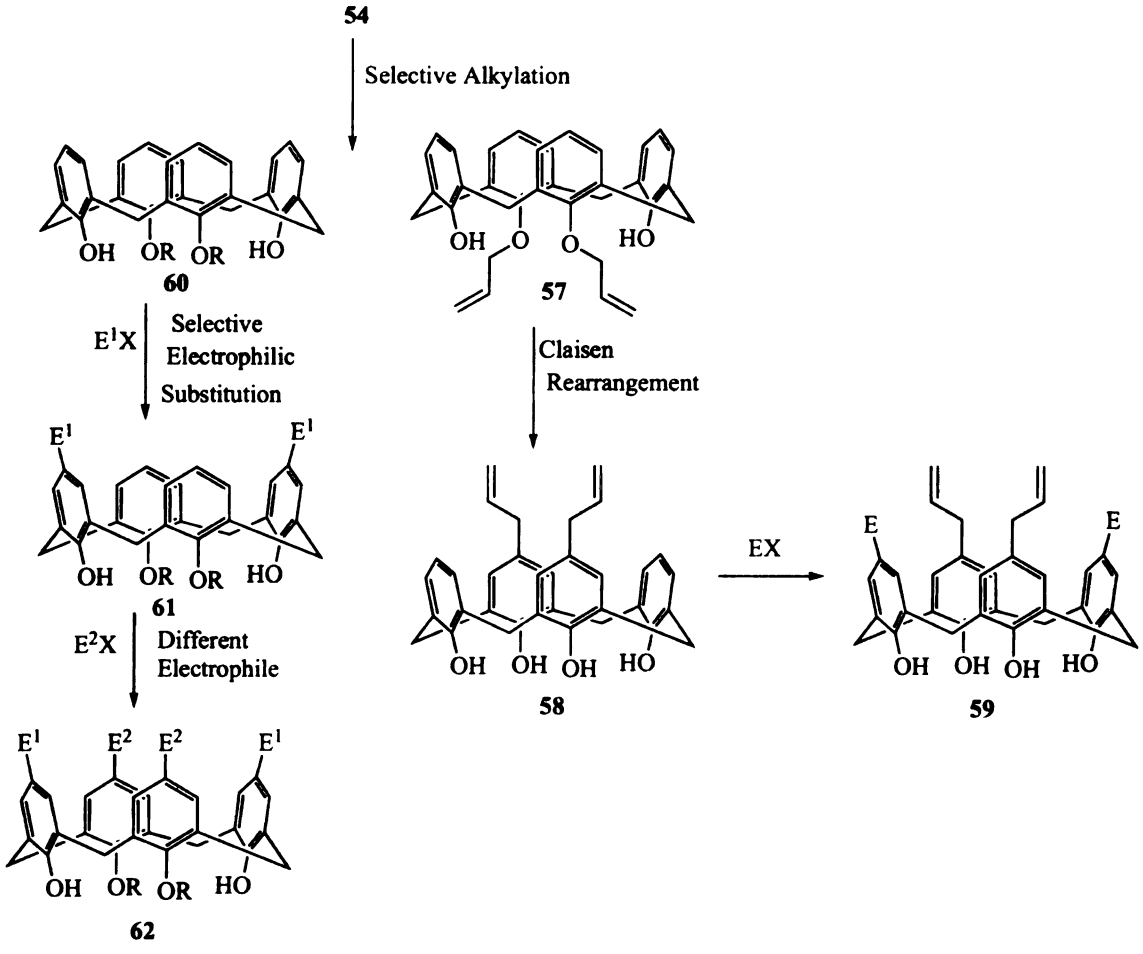
58 which upon further electrophilic aromatic substitution resulted in formation of **59**.[40] Sequential electrophilic aromatic substitutions on **60** have been used as a versatile route towards formation of calixarene **62**.

Scheme 1.16 Selective functional group transformations of calixarenes



1.5 Chiral calixarenes

Chiral calixarenes have been of recent interest due to their applications as potential drug candidates (vancomycin mimics), molecular receptors for recognition of specific cell lines (glycocalixarenes, peptido-calixarenes etc.) and non-enzymatic reagents for chiral recognition of racemic carboxylic acids. Two approaches have been successful in the preparation of such calixarenes a] molecular asymmetry is a consequence of the presence of aryl rings having different substitution patterns and b] functionalization at the

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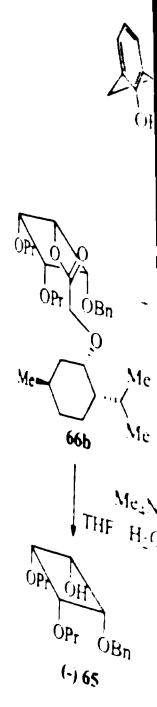


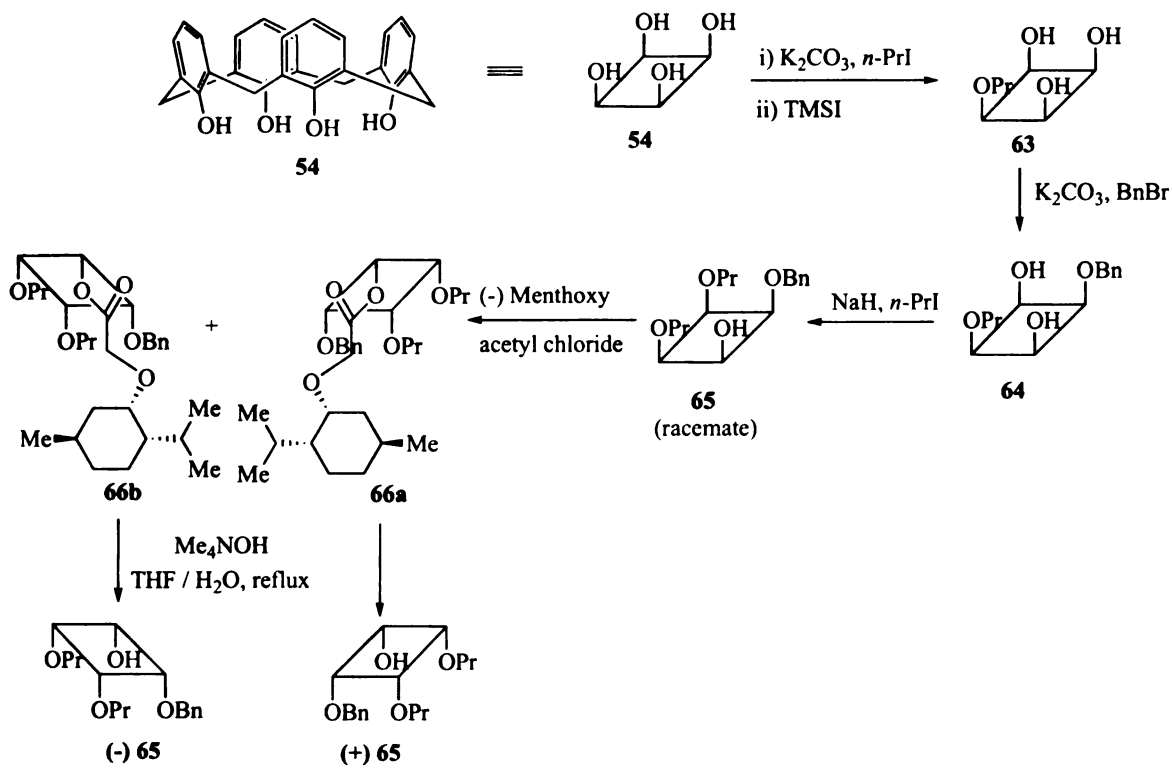
lower rim with a chiral reagent. The following section briefly elaborates on these strategies taking into consideration the advantages and disadvantages of each methods.

1.5.1 Traditional methods for induction of chirality

1.5.1.1 Molecular asymmetry

The incorporation of different substituents on at-least three of the aryl moities in a cone conformation or two different aryl groups with one of aryl groups *anti* to the other three aromatic rings (i.e., partial cone) renders molecular asymmetry to the calixarene. The substituents which are introduced on the lower rim must be larger than an ethyl group in order to slow the ring-inversion process that would result in racemization of a calix[4]arene with molecular asymmetry. However, the larger substituent could also lead to formation of other conformers than the cone. The resulting chiral calixarene **65** could be resolved into a pair of diastereomers **66a** and **66b** by derivatization with a chiral reagent.

Scheme 1.17 Chiral calixarene with molecular asymmetry



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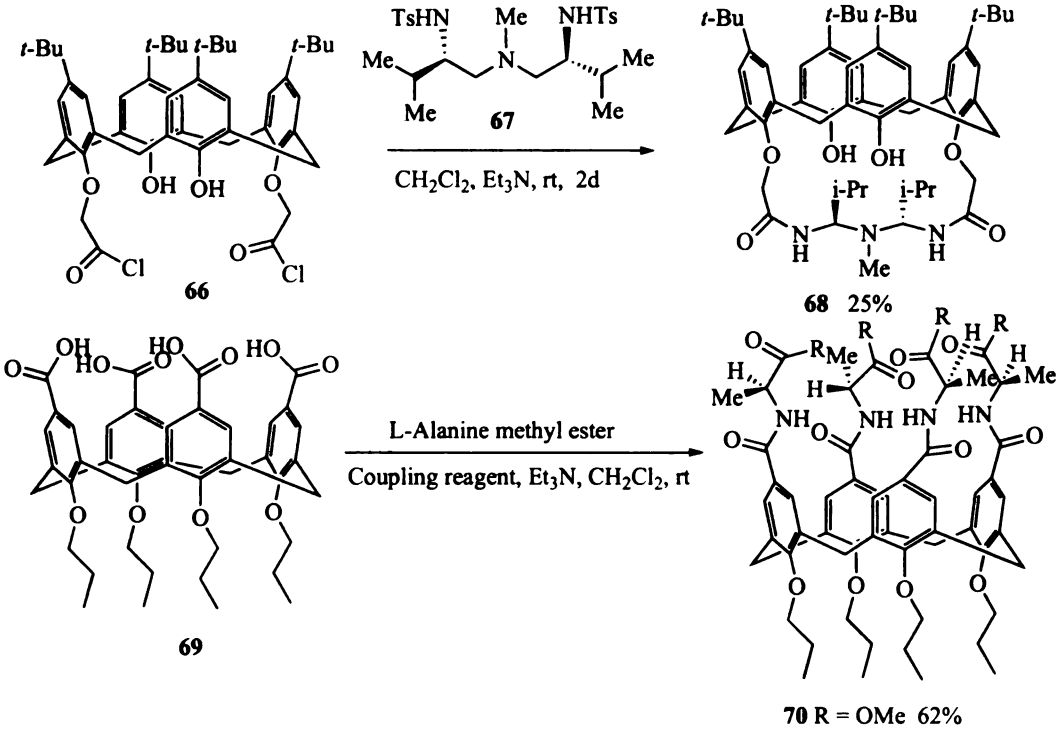
Hydrolysis of either diastereomer so formed with aqueous tetramethyl ammonium hydroxide results in formation of enantiomers of **65** in excellent optical purity (Scheme 1.17).[41]Another example that has been reported recently is in the preparation of calixcrown which was resolved by using BINOL as the chiral derivatizing agent.[42] The diastereomers formed could be separated by preparative thin layer chromatography and hydrolysis results in the formation of either antipode of the chiral crown. The presence of the crown motif imparts rigidity to the macrocycle and thus ring inversion leading to racemization is not observed.

1.5.1.2 Introduction of chiral functionalities on the lower and upper rim

There are several known methods for the incorporation of chiral functionalities on the lower rim, which involve several steps from calix[4]arene as the starting material. For example, L-valine was used as the starting material in the synthesis of calixazacrown **68**. The chiral diamine **67** was prepared from L-valine by conventional methods and reaction with the calixarene diacid chloride **66** resulted in the formation of calixazacrown **68** in 25% yield (Scheme 1.18). [43]

In contrast, the reaction of calix[4]arene tetra-acid **69** with the methyl ester of alanine under standard peptide coupling conditions resulted in the formation of upper rim modified peptido-calixarene **70** in good yield.[44] The calixazacrown **68** was used in molecular recognition of specific enantiomer of racemic carboxylic acids, whereas the peptidocalixarene **70** was designed in an effort to synthesize hybrid molecular receptors which exhibited anti-microbial activity against Gram-positive bacteria.

Scheme 1.18 Chiral calixarene 68 by lower and 70 by upper rim functionalization



1.5.2 Applications of chiral calix[4]arenes

The facile preparation of chiral calixarenes by reaction of suitable stoichiometric chiral reagents with reactive functionalities either on the lower or upper rim in recent years has provided the necessary tools for developing a variety of applications. There are numerous reports on the utility of chiral calix[4]arenes in molecular recognition where the basic recognition element is non-covalent interactions between polar substituents on the calixarene and the chiral reagent. For example, calixarene **71** bearing chiral amino alcohol groups tethered at the lower rim preferentially interacted with the (*S*)-enantiomer of racemic mono carboxylic acids **73, 74** and with (L)-isomer of dicarboxylic acid **75**.[45] The extent of the chiral recognition event was monitored by the difference in chemical shifts of the methine protons of the carboxylic acids and the selectivity for one enantiomer over the other was ascertained by determination of the association constants.

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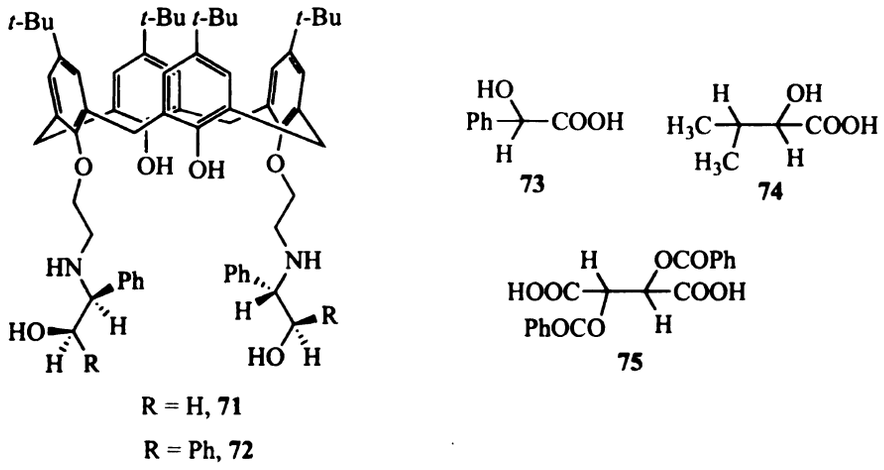
The phenyl-substituted analogue **72** displayed remarkable recognition ability for (*S*)-**74** due to an additional CH_3-π interaction. Mono carboxylic acids formed 2:1 complexes with the chiral calixarene whereas dicarboxylic acids resulted in 1:1 complexes (Figure 1.5). For racemic **73**, **74** and **75**, the selectivity of binding of the hosts **71** or **72** for the carboxylic acids (*S*)-**73**, (*S*)-**74** and (L)-**75** was calculated to be 96 %.

Figure 1.5 Chiral calixarenes for molecular recognition



Recently, the macrobicyclic calixarene **76** has been reported to have a biological profile similar to that of Vancomycin, which is an important glycopeptide antibiotic for resistance to infection by gram-positive bacteria.[46] The basic nitrogen group in **76** is protonated at physiological pH and NMR as well as ESI/MS studies indicated the formation of a 1:1 complex with N-acetyl-D-alanyl-alanine **77**. Furthermore, a binding model **78** was proposed where electrostatic, hydrogen-bonding and CH-π interactions could all be involved (Figure 1.6). Glycocalixarenes bearing multiple sugar residues have also been synthesized and they show remarkable binding affinities with carbohydrate binding proteins such as lectin.[47]

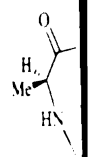


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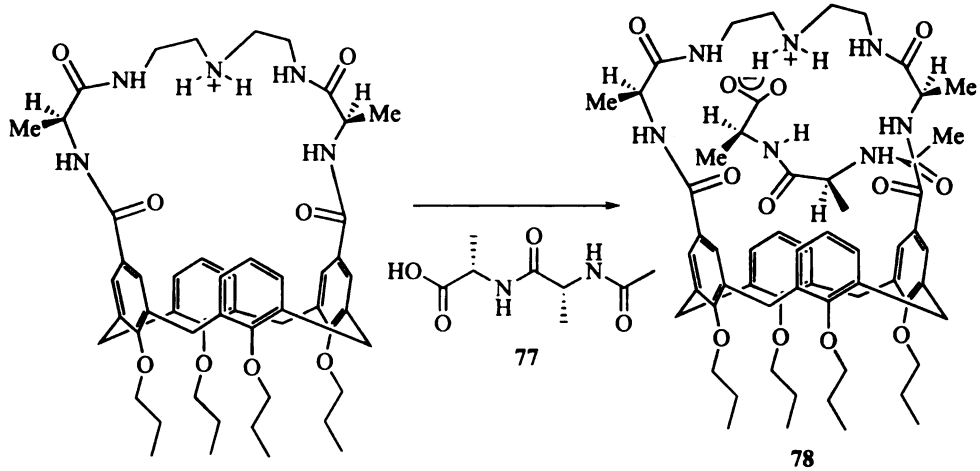
Figure.1.6 1:1 Complex between N-Acetyl D-Alanyl Alanine and 76



76 77 78

1.6 Methylene functionalized calix[4]arenes

There have been very few reports in the literature on the functionalization of the methylene bridges in a calix[4]arene. The difficulty in accessing this class of compounds has often been attributed to the complex mixture of stereoisomers that occur upon inclusion of substituents at the methylene bridges.[48] Chiral calixarenes result from introduction of a substituent at a methylene position of either C_2 symmetric or C_4 symmetric calix[4]arene but so far no examples of optically active calixarenes of this type have been reported.

1.6.1 Stereoisomerism in methylene functionalized calixarenes

In order to present a simplified picture of the stereoisomers that result upon substitution at the methylene bridges, only cone conformers of the starting material will be considered in the following discussion.

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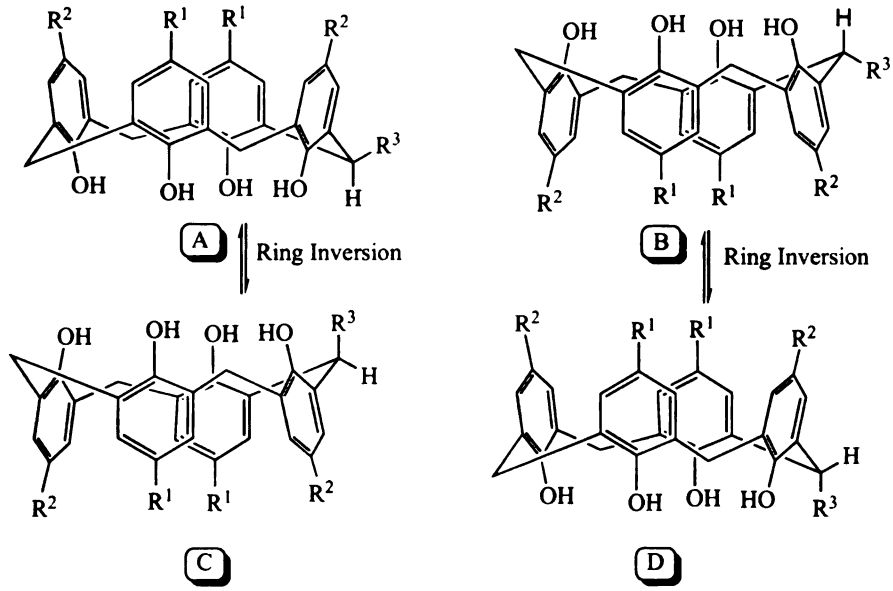
Derivatization of the methylene bridge by monosubstitution results in the formation of two diastereomers. These diastereomers differ by introduction of the new functionality at either the axial or equatorial positions of the calixarene (Figure 1.7).

Figure 1.7 Stereoisomers formed upon monosubstitution



The stereoisomerism that results upon substitution at one methylene bridge by a methyl, ethyl, isopropyl or *tert*-butyl group (R^3 = Me, Et or *t*-Bu) has been studied in detail and it was found that the bulkier the alkyl group, the greater is the preference for the equatorial position as in isomer **A**.[49] The interconversion barrier between the axial isomer **C** and equatorial isomer **A** was estimated by theoretical calculations to be increasing from methyl to isopropyl ($\Delta G^{\pm}$ = 15-17.2 kcal/mol) but then decreases for *tert*-butyl group. The decrease for the *tert*-butyl group was attributed to a low inversion barrier due to steric destabilization of the axial isomer **C**.

Monoaryl methylene substituted calixarenes (R^3 = Ar) were also studied by NMR spectroscopy and they exist as 1:1 mixtures of axial and equatorial isomers. This result is in stark contrast to phenyl substitution at cyclohexane derivatives wherein an equatorial

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phenyl group is 2.8 kcal/ mol more stable than axial phenyl group. Moreover, it would be concievable that enantiomers **B** and **D** for each of these diastereomers if $R^2 \neq R^1$ would exist but no studies have been reported concerning either the existence or isolation of these specific stereoisomers.

1.6.1.2 Disubstitution at methylene bridges

Proximal (1,2) and distal (1,3) disubstituted calixarenes are obtained by the introduction of a second substituent at the methylene bridges. Each of these two compounds is known to have two distinct stereoisomeric forms labeled as the *cis* and *trans* isomers depending upon the position of introduction of the second substituent relative to the first one. Furthermore, the *1,3-cis* and *1,3*-trans isomers **E** and **G** are known to undergo ring inversion by rotation of the aryl rings through the annulus to their diastereomers **F** and **H** (Figure 1.8).[50] Finally, there are two enantiomers for each of those possible diastereomers (not shown). Extensive theoretical investigations have been carried out on the relative stability of the 1,3- cis isomers and the two alkyl groups at the methylene bridges ($R^3 = R^4$ = alkyl) are known to increase the energy barrier for ring inversion from the equatorial to axial forms. Aryl substituents ($R^3 = R^4$ = Ar) do not affect the inversion process at all and an equal mixture of *cis* and *trans* isomers are often found in solution at room temperature. Interconversion between *cis* and *trans* isomers for alkyl and aryl substituted calixarenes was not observed but was found to occur for heteroatoms introduced on the bridges (e.g. thiomethoxy, anilino) wherein the *cis* isomer was found to be the most thermodynamically stable. The interconversion process occurs via the cleavage of the Ar-CH-R^4 bond.[50] The analogy between the cyclohexane chair conformation and the calixarene cone conformation still exists for the *trans* isomer G.

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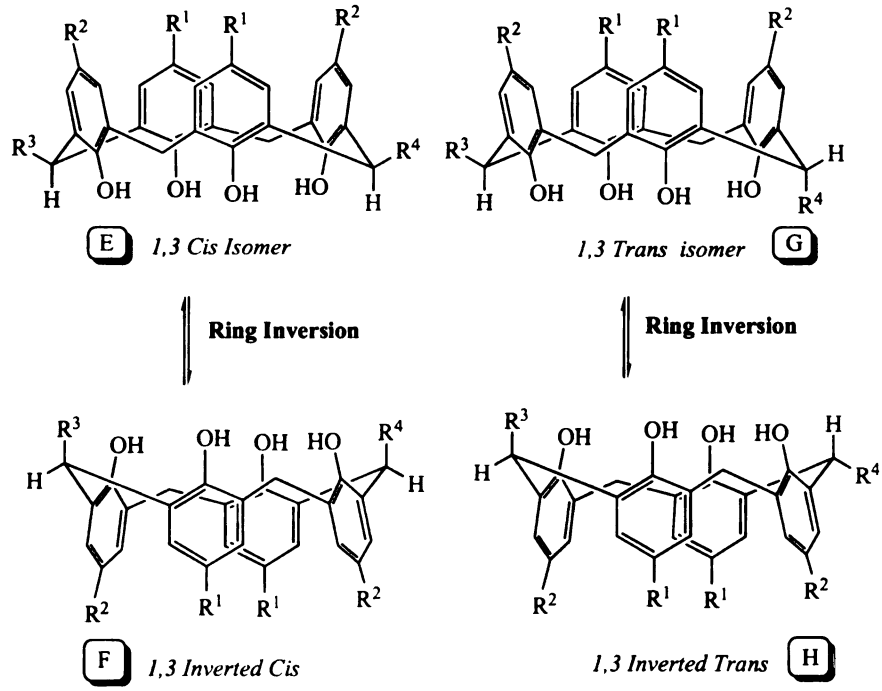
Figure 1.8 Stereoisomerism in 1,3 or distal disubstituted calixarene



One of the substituents in the cone conformer is forced to adopt an axial position in G or H. Hence, 1,2-alternate conformer has been observed as the only conformer for *trans* distal-substituted calixarenes with bulky groups (eg., $R^3 = R^4 =$ *t*-Bu). Mixtures of cone and 1,2-alternate conformers was observed for groups of smaller size as both the substituents occupy equatorial position in 1,2-altermate conformation compared to an axial equatorial orientation in the former.[48] This is very similar to cyclohexanes wherein a bulky axial substituent destabilizes the chair form of cyclohexane and a twist form is thereby rendered the most preferred conformation.

The proximal (1,2) disubstituted calix[4]arene also exhibits *cis* / *trans* isomerism. There are four diastereomers, each of which has an enantiomer resulting in a total of eight stereoisomers (If $R^2 \neq R^1$) (Figure 1.9). Computational studies on proximally functionalized calixarenes with regard to measurement of inversion barriers however do not exist.

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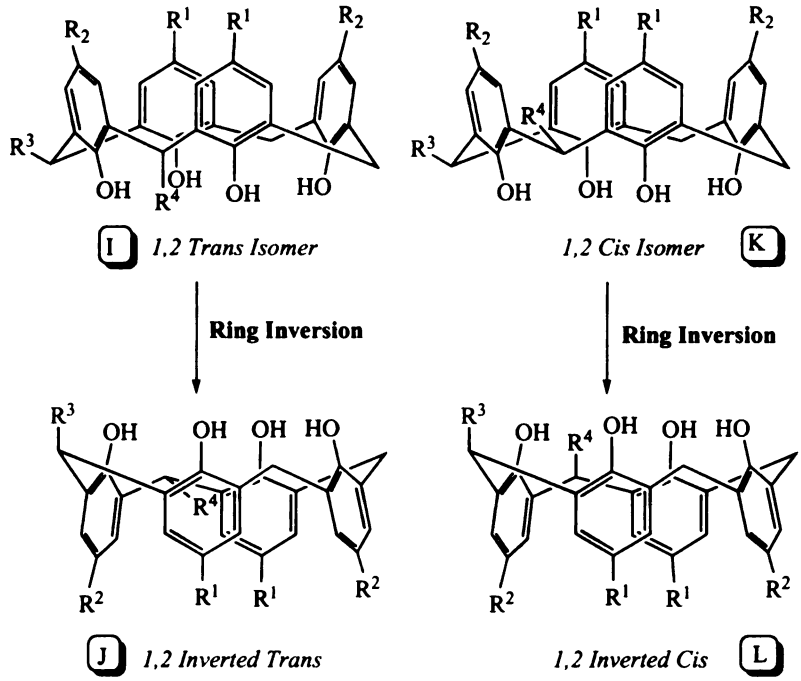
Figure 1.9 Stereoisomerism in 1,2 or proximal disubstituted calixarene



1.6.1.3 Tri and tetrasubstitution at methylene bridges

No examples of trisubstituted calixarenes resulting from substitution at three different methylene bridges are currently known in the literature. Conformational analyses of the corresponding tetrafunctionalized calixarenes have not been reported yet as there are only a few methods for their preparation (See Following section). The syntheses of this family of methylene substituted calixarenes will be the subject of discussion in the forthcoming sections.

1.6.2 Synthesis of monomethylene substituted calixarenes

There have been a few successful methods for the preparation of calixarenes monosubstituted at the bridges. They include fragment condensation of linear dimers and lithiation / carboxylation of tetramethoxy-*p*-tert-butyl calixarene.

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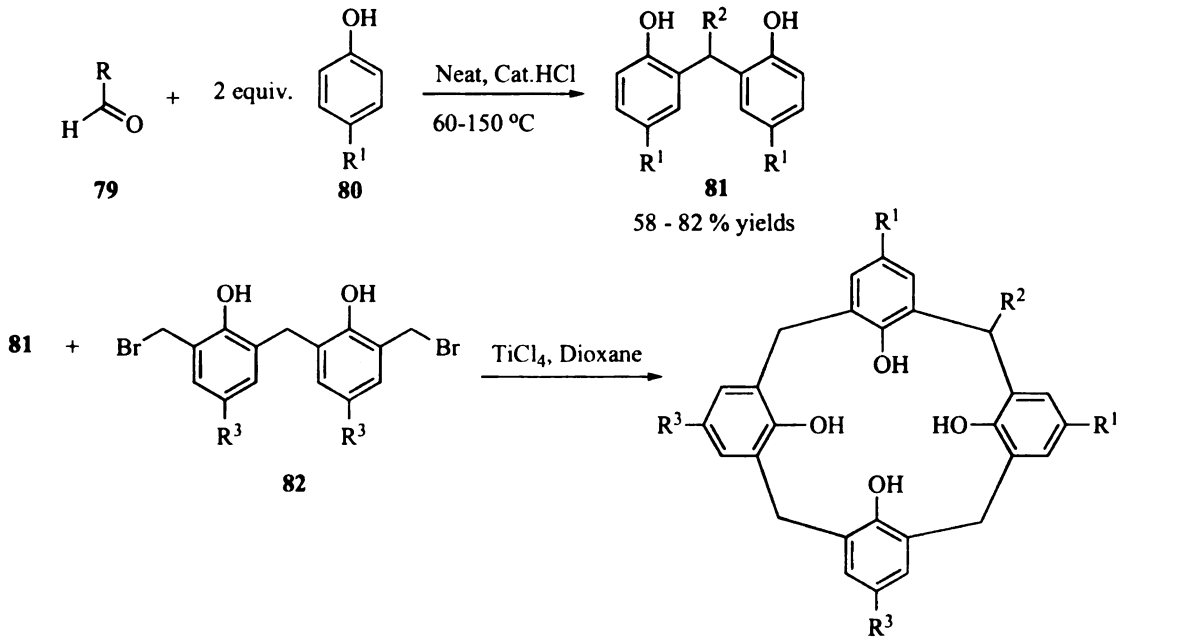
The alkanediyl phenols **81** were obtained by the condensation of the appropriate aldehyde **79** with an excess of the corresponding phenol **80** in 58-80 % yields. [2+2] fragment condensation of an alkanediyl phenol **81** and the bis-bromomethylated dimer **82** under reaction conditions similar to that mentioned earlier in Sec 1.1.3.2 for preparation of **24** (Scheme 1.5) resulted in the formation of calixarene **83** that is monosubstituted at a methylene bridge.[49] Alkyl and aryl substituted calixarenes are conveniently prepared in this manner in 12-36 % yields (Scheme 1.19).

Scheme 1.19 [2+2] Fragment condensation to monomethylene substituted calix[4]arenes



83 R^1 = Me, R^2 = Me, Et, *i*-Pr, *t*-Bu, *p*-Nit

R^3 = Me or *t*-Bu

12-36 % yields

1.6.2.2 Lithiation / alkylation of calix[4]arene

In this method, tetramethoxy-*p*-tert-butyl calix[4]arene **52** is metalated at the methylene bridge with *n*-butyl lithium to give lithio derivative **84** and subsequent treatment with an electrophile gives **85** which can be demethylated to afford the equatorially disposed monosubstituted derivative **86** (Scheme 1.20).[51]

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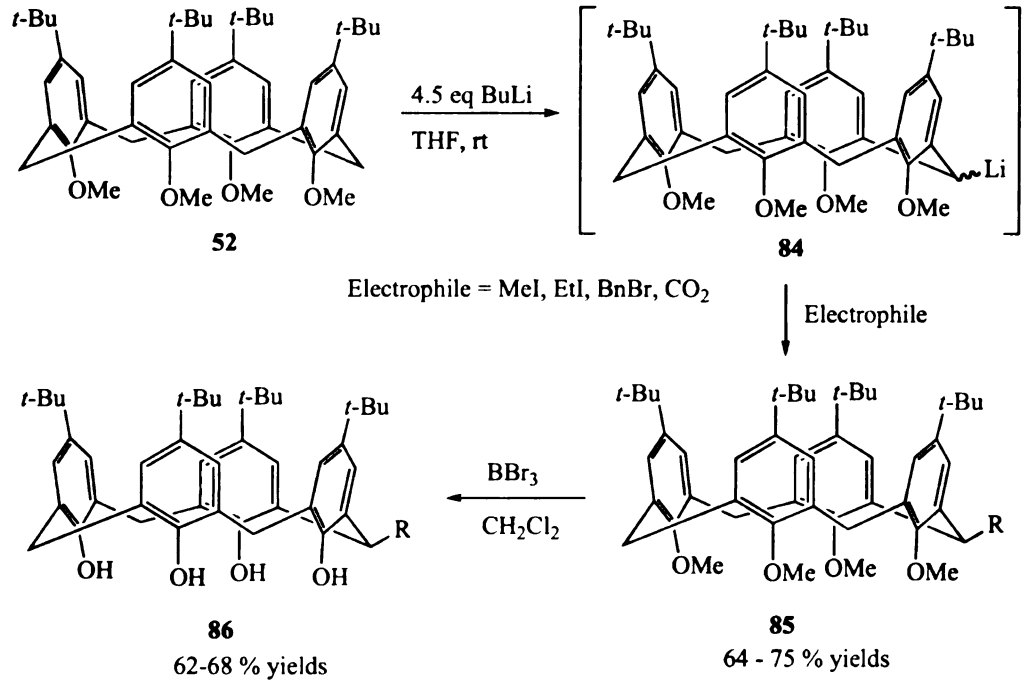
Scheme 1.20 Lithiation / trapping with electrophile to monofunctionalized calixarene 86



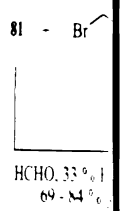
1.6.3 Synthesis of methylene disubstituted calixarenes

The synthesis of calixarenes substituted at two different methylene bridges has been widely studied in the past few years. A number of available methods exist that include [2+2] fragment condensation, Ortho-Fries rearrangement of carbamate derivatives and nucleophilic addition to spirodienones.

1.6.3.1 [2+2] Fragment condensation

The fragment condensation strategy of an alkanediyl phenol **81** and methylene substituted bis-bromomethyl arene **87** has been successfully applied in the stereoselective synthesis of *cis* 1,3-dialkylsubstituted calixarenes **88** in 19-28 % yields and 1,3-diaryl disubstituted calixarenes **89** as mixture of *cis* and *trans* isomers in ratios varying from 1:1 to 2:1 and in 15-21 % yields (Scheme 1.21).[49]

Scheme 1.21



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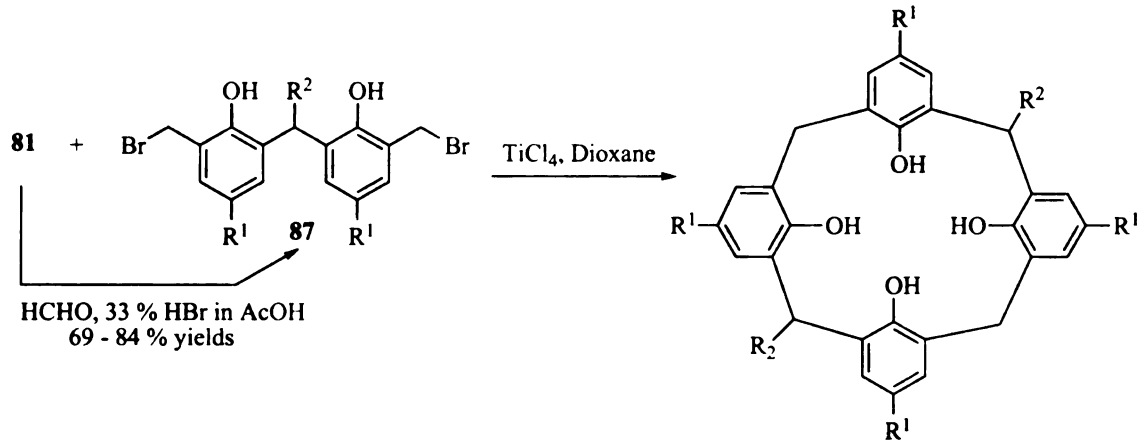
Scheme 1.21 [2+2] Fragment condensation to methylene disubstituted calix[4]arenes



88 R^1 = Me or *t*-Bu
R^2 = Me, Et, *i*-Pr, *t*-Bu

89 R^1 = Me or *t*-Bu
R^2 = *p*-Tol, *p*-Nit

1.6.3.2 Ortho-Fries rearrangement of calixarene carbamates

The homologous anionic Ortho-Fries rearrangement was recently developed as an expedient methodology to both proximal (1,2) and distal (1,3) methylene functionalized calixarenes.[52] Careful control over the reaction conditions was needed to be exercised in order to provide for the selective formation of either the proximally or the distally substituted products (Figure 1.10 & Table 1.1). The reaction is carried out by deprotonation at the bridge usually with a large excess of LDA as the base, followed by stirring the reaction mixture for varied reaction times and temperatures with the result that good control over stereo and regioselectivity could be attained in product formation. Furthermore, the conformation of the starting calixarene often played a crucial role in determining the product distribution with the cone conformer **90** predominantly yielding the diaxial proximally functionalized product **93** upon Fries rearrangement. A mixture of axial-equatorial and equatorial-equatorial proximally substituted products **94, 95** along with mono-rearranged product **97** resulted from partial cone **91** whereas proximal, distal

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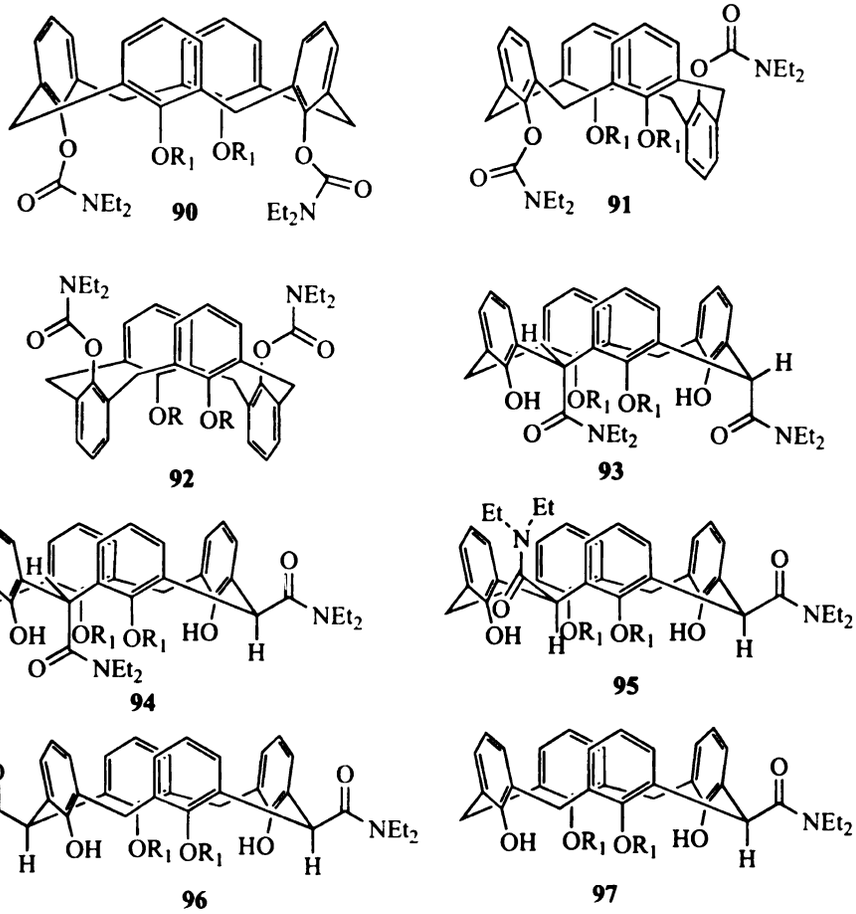
diequatorial products **95, 96** and mono equatorial substituted product **97** from 1,3-alternate carbamate derivatives **92** as starting materials.

Figure 1.10 List of calixarene carbamates and amides



$$\textbf{90, 91, 92} \xrightarrow[\text{ii) } NH_4Cl]{\text{i) LDA, THF}} \textbf{93, 94, 95, 96, 97}$$

Table 1.1 Results of migration studies on carbamates

Entry	SM (mM)	RC[a]	93	94	95	96	97
1	**90**	A	63-80	-	-	-	-
2	**91**	B	.	42	21	-	23
3	**92**	A	-	-	16-17	64-65	11-18

[a] Reaction Conditions:

A] Add SM in THF to a solution of 12 equiv of LDA in THF at 0°C and warm to room temperature for 4h before quenching with NH_4Cl (aq)

B] same as Method A except reaction temperature is -24°C for 6h followed by warming to room temperature and stirring overnight

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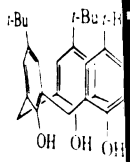
Scheme 1.22 Oxida



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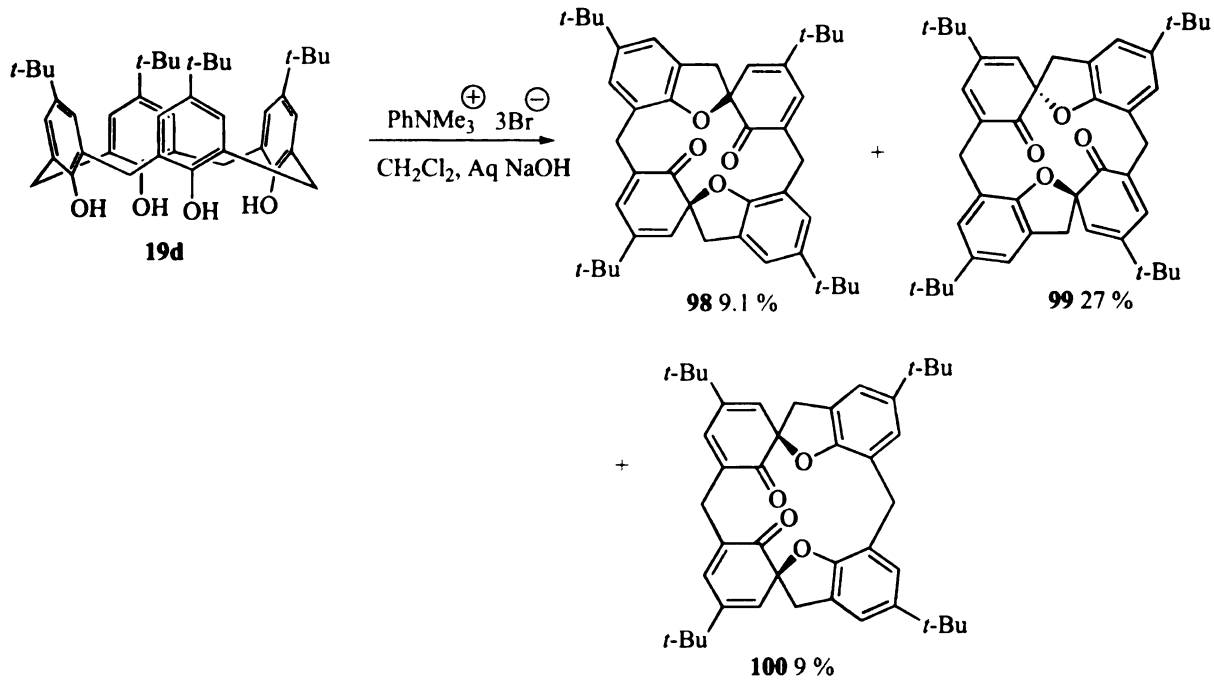
The precise mechanism for the stereo and regioselectivity obtained was not described.

1.6.3.3 Spirodienone method of functionalization

The oxidation of *p-tert*-butyl calix[4]arene **19d** with phenyl trimethyl ammonium tribromide under biphasic conditions resulted in the formation of three isomeric calixspirodienone derivatives **98**, **99** and **100** (Scheme 1.22).[53]

Scheme 1.22 Oxidationof 19d to spirodienones 98, 99 and 100



Bromination of spirodienone **99** gave **101**, which upon thermolysis afforded **102** in good yields. Bis-Michael addition to **102** followed by reduction with lithium aluminum hydride afforded the respective distal methylene functionalized calixarenes **104** as *trans* isomers exclusively (Scheme 1.23). The bis-thiomethyl ether and bis-anilino derivative underwent isomerization from *trans* to the more thermodynamically stable *cis* isomer.

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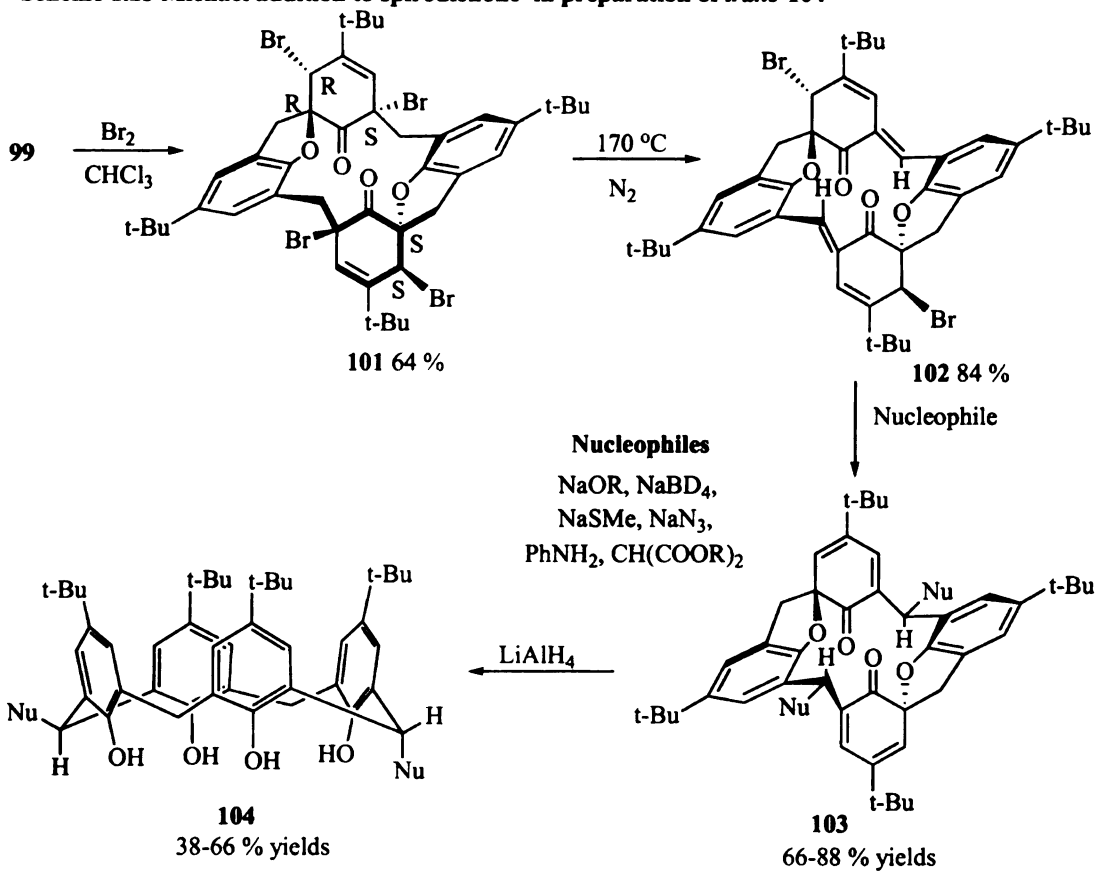
Scheme 1.23 Michael addition to spirodienone in preparation of *trans*-104



1.6.4 Synthesis of tetrasubstituted derivatives

In contrast to the available methods for the preparation of either *cis* or *trans* 1,3-disubstituted calixarenes, there are very few reports on the tetrasubstituted analogs. The two methods that are known so far include the over oxidation of the methylene bridges of **19d** to tetraketone calixarenes followed by reduction to tetraols **105** in four steps.[54] The second method involves the direct bromination of the bridges in the tetramethyl ether **52** (Scheme 1.7) to give the tetrabromoderivative **106** as mixture of cone and partial cone conformers (Scheme 1.24).[55] Molecular mechanics and semi-empirical calculations were used as tools to predict the stereochemistry at the bridges wherein it was found that the equatorial disposition of bromine substituents is more favored.

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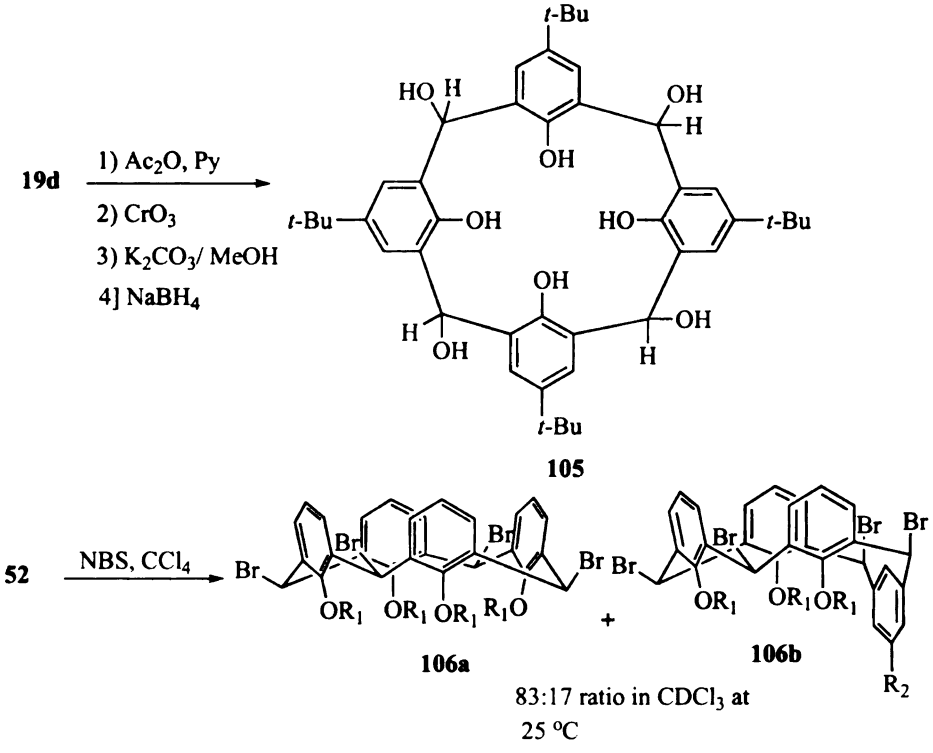
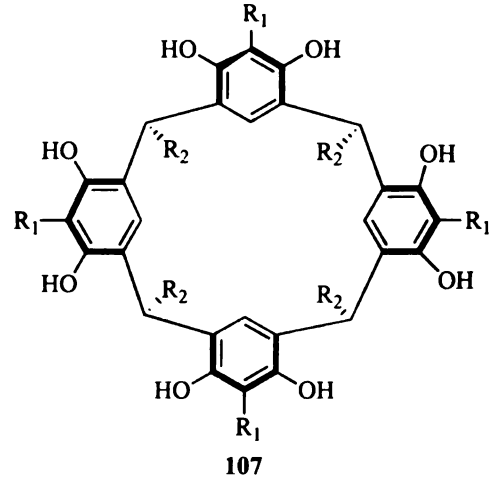
Scheme 1.24 Tetrafunctionalization of calixarenes 19d and 52



1.6.5 Stereoisomerism in resorcinarenes

Resorcinarenes **107** (Figure 1.11) are analogous to calixarenes in that they are often prepared by the acid catalyzed condensation of a phenol (resorcinol) and an aldehyde.[56]

Figure 1.11 Resorcinarene with all *cis* methylene substitutents



The non-planarity of the arene rings in the resorcarene framework also accounts for its existence in several stereoisomeric forms. The stereochemistry is often defined as a

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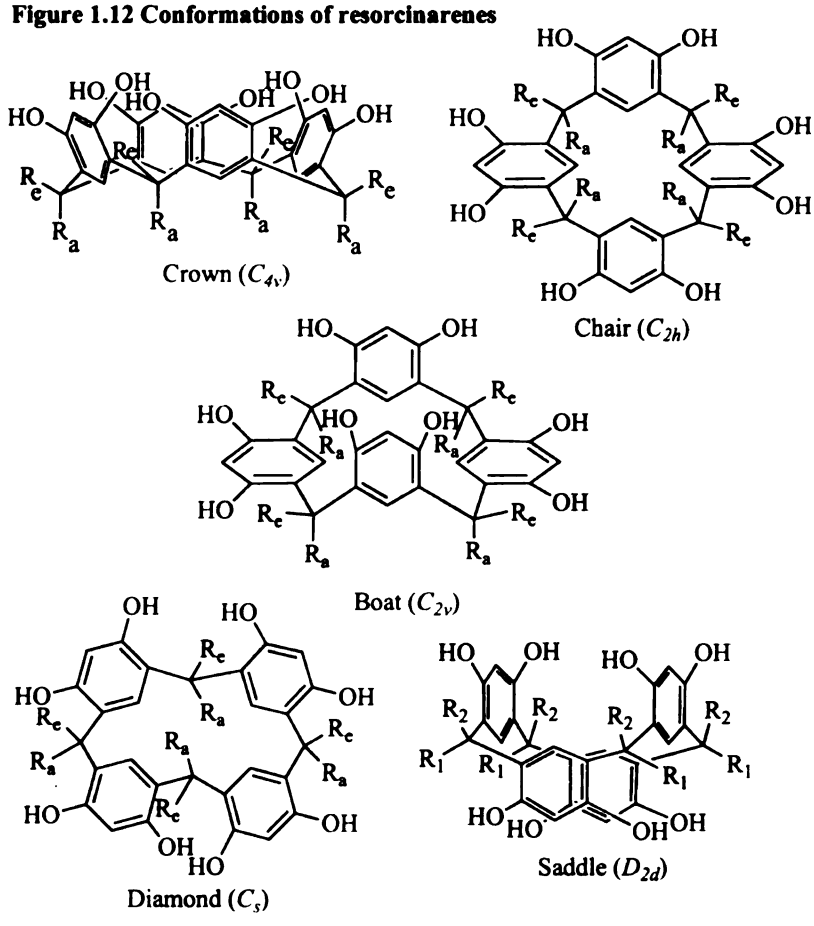
combination of three stereochemical elements, which include a] conformation of the macrocycle b] the relative configuration of substituents at the methylene bridges and c] the absolute configuration of the substituents at the bridges with respect to whether they are in equatorial or axial positions. A vast number of possible stereoisomers would be expected to result from a combination of these stereochemical elements.

1.6.5.1 Conformation of the macrocycle

The conformation of the macrocyclic ring can exist in five different symmetrical arrangements whch are referred to as the crown (C_{4v}), boat (C_{2v}), chair (C_{2h}), diamond (C_s) and saddle (D_{2d}) conformations respectively (Figure 1.12).

Figure 1.12 Conformations of resorcinarenes



The crown form in resorcinarene is similar to the cone conformer of a calix[4]arene whereas the saddle form resembles 1,3-alternate conformer of the calixarene. The ratio

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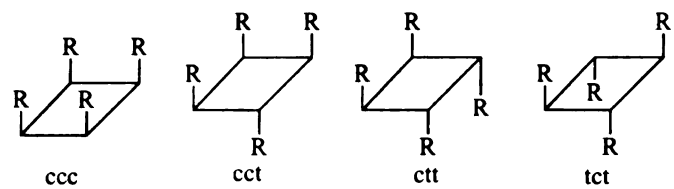
in which these conformers are formed is again dependent upon choice of the aldehyde substrate and the reaction conditions for the acid catalyzed condensation. Under homogeneous acidic conditions, the product distribution reflects the thermodynamic stability of the different isomers, as the condensation reaction is reversible. Interconversion between two conformers (boat→crown, chair→crown and diamond→crown) was observed where the rotation of aryl rings about the annulus is believed to facilitate such a process. In the case of resorcarene **107** ($R_1 = C_6H_{13}$, $R_2 = H$), the free energy $\Delta G^{\ddagger}$ for the confomational interconversion process is 18.4 kJ mol^{-1}. This is to be contrasted with the barrier for the cone to cone inversion in *p*-tert-butyl calix[4]arene which has been found to be 63-67 kJ/ mol in $CDCl_3$.

1.6.5.2 Control of relative configuration about the methylene bridges

Each of the five different conformers discussed above can differ in the relative configurations of the substituents at the methylene bridges, which would result in the formation of four stereoisomers (all-*cis* (ccc), *cis-cis-trans* (cct), *cis-trans-trans* (ctt) and *trans-cis-trans* (tct) arrangements (Figure 1.13). This nomenclature will also be adopted later for defining the relative stereochemistry at the bridges in corresponding methylene substituted calix[4]arenes in Chapter 4.

Figure 1.13 Stereoisomerism at the methylene bridges



A *cis-cis-trans* arrangement of substituents at the bridges would be expected to yield a pair of enantiomers for resorcinarenes in crown conformation and having

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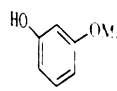
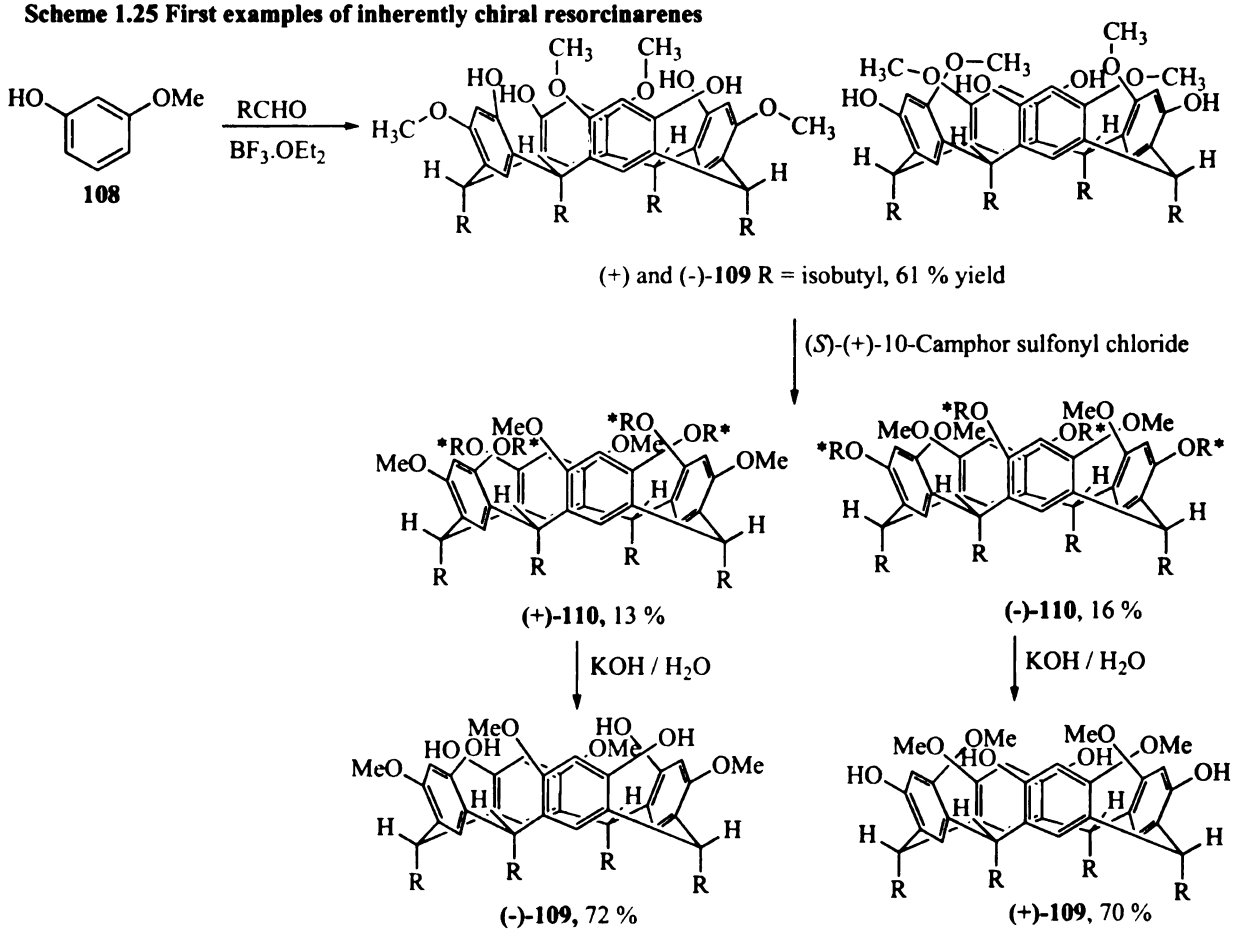


108

identical substitution patterns on the aryl rings whereas the other stereoisomers in the crown conformation would primarily result in optically inactive meso compounds.

The reduction of symmetry from C_{4v} to C_{2v} such as would be seen in unsymmetrical resorcarenes having different subsituents on the aryl rings would result in a pair of enantiomeric crown or boat conformations. The racemic macrocycles (+) and (-)-**109** were prepared by Lewis-acid mediated cyclization of resorcinol monoalkyl ether **108**. Separation of the enantiomers was then accomplished by using (*S*)-(+)-10-camphor sulfonyl chloride as the chiral auxillary to afford the diastereomeric sulfonate esters (+) and (-)-**110**, which upon saponification yielded the two enantiomers of **109** (Scheme 1.25).[57]

Scheme 1.25 First examples of inherently chiral resorcinarenes



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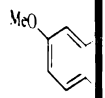

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1.7 Homoca

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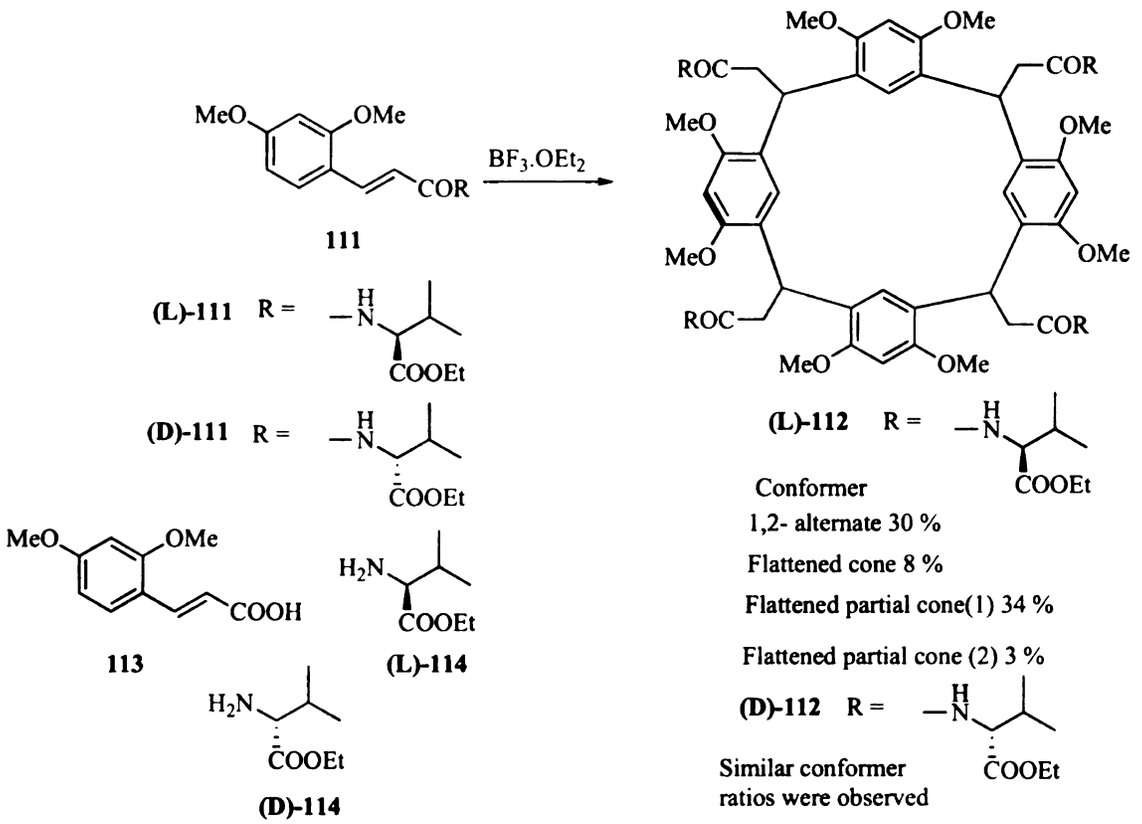
Another successful approach was reported wherein a chiral resorcinol monoalkyl ether was used for the cyclization and the two resulting diastereomers could be separated by column chromatography.

As an alternative to the use of phenols as precursors for chiral resorcarene synthesis, Lewis acid catalyzed tetramerisation of chiral 2,4-dimethoxy cinnamic acid amido derivatives **111** has been developed as an efficient route towards chiral amido[4]resorcinarenes **112**. The chiral amides **111** were obtained from 2,4-dimethoxy cinnamic acid **113** and (L) or (D)-valine **114** (Scheme 1.26).[58]

Scheme 1.26 Lewis Acid catalyzed tetramerization of 2,4-dimethoxy cinnamic acid derivatives



1.7 Homocalix[4]arenes

Homocalix[4]arenes by definition and in contrast to simple calixarenes includes all classes of [n]-metacyclophanes in which each of the four benzene rings are bridged by more than single methylene group (Figure 1.14).[59]

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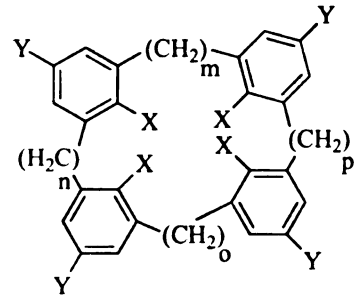
Figure 1.14 Homocalix[4]arene



X = OH, OR; Y = H, Alkyl

115

Despite the fact that a variety of methods exist for the preparation of homocalixarenes, this class of cyclophanes has been less examined due to the enhanced degree of conformational mobility introduced by the presence of a larger macrocyclic ring. Typical synthetic approaches for all carbon tethered homocalixarenes fall into two broad categories, one pot and convergent methods analogous to methods for calix[4]arene synthesis.

1.7.1 One pot methods

1.7.1.1 Müller-Röscheisen cyclization

The reaction of 1,3-(bis-bromomethyl)-benzene **116** or **117** with sodium tetraphenylethene in THF at –80°C under free radical conditions has been successful in the preparation of homocalix[4]arenes **120** and **121** with both *exo* and *endo* directed hydroxy groups. The yields of the cyclization step are typically lower than those observed for the calix[4]arenes and *endo* directed substituents favor the formation of large macrocyclic ring systems (Scheme 1.27).[60]

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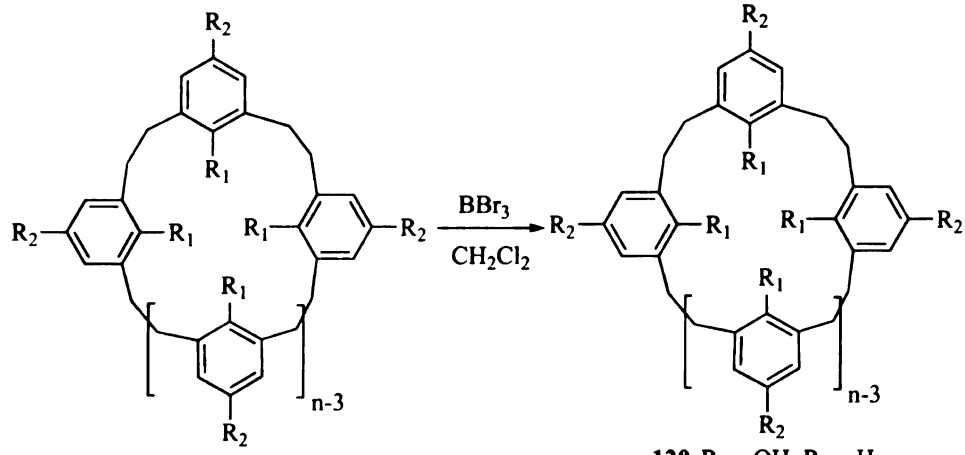
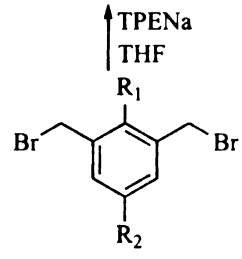
Scheme 1.27 Müller röscheisen cyclization to homocalix[4]arenes 120 and 121



118 R_1 = OMe, R_2 = H
n = 5-8, 2-8 % yields
119 R_1 = H, R_2 = OMe
n = 3-6, 2-21 % yields

120 R_1 = OH, R_2 = H
n = 5-8, 67-93 % yields
121 R_1 = H, R_2 = OH
n = 3-6, 87-99 % yields

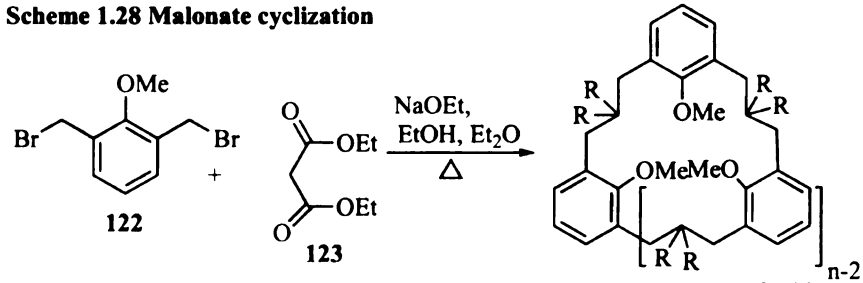


116 R_1 = OMe, R_2 = H
117 R_1 = H, R_2 = OMe

1.7.1.2 Malonate cyclization

Homocalix[n]arenes **124** can also be synthesized in low yields by the reaction of bis-(bromomethyl) arene **122** and the sodium salt of diethyl malonate **123** (Scheme 1.28).[61]

Scheme 1.28 Malonate cyclization



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R = CO_2Et **124** (n = 3) 6 %
(n = 4) 4 %

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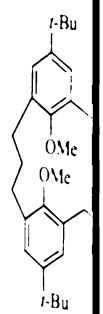

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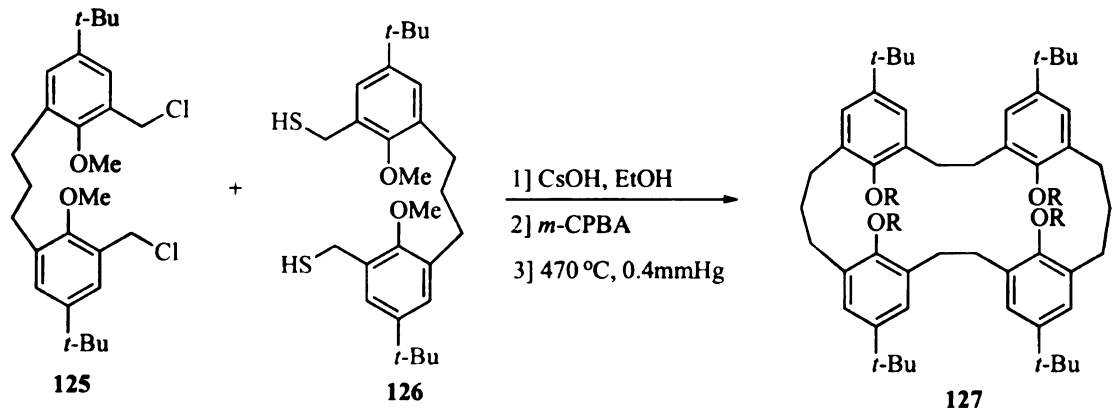
1.7.2 Convergent methods

1.7.2.1 Sulfur dioxide extrusion

Unsymmetrical homocalix[4]arene **127** was obtained by a method related to the [2+2] fragment condensation in calix[4]arene synthesis wherein bis-(chloromethyl)arene **125** was condensed with dithiol **126** in the presence of cesium hydroxide as the base followed by oxidation of the sulfide to sulfate and thermal extrusion of sulfur dioxide (Scheme 1.29).[62]

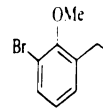
Scheme 1.29 Sulfur extrusion approach to unsymmetrical homocalixarene 127



1.7.2.2 Cross-coupling with organometallic reagents

The reaction of dibromo arene **128** with *tert*-butyl lithium generated the dianion which upon coupling with bis-alkyl halide **129** yielded the bis-homocalix[4]arene **130** along with several linear by-products (Scheme 1.30).[63] This method suffers from the tedious purification procedure using analytical HPLC that has to be employed to separate the desired [3.3.3.3]metacyclophane from a mixture of undesired by-products. The strategy is convergent as both the starting materials **128** and **129** were prepared from 2-bromo anisole in six and eight steps respectively.

Scheme 1.30 C



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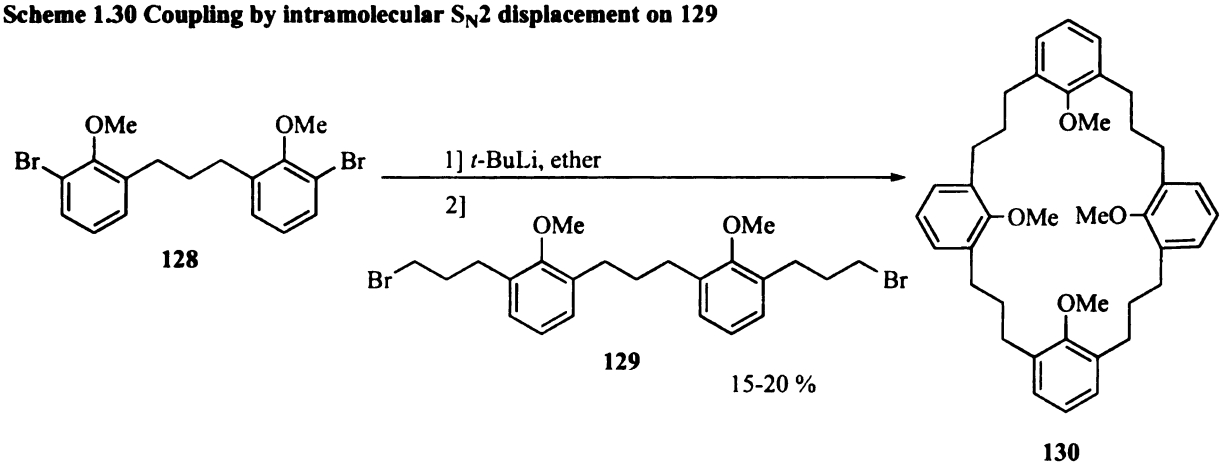
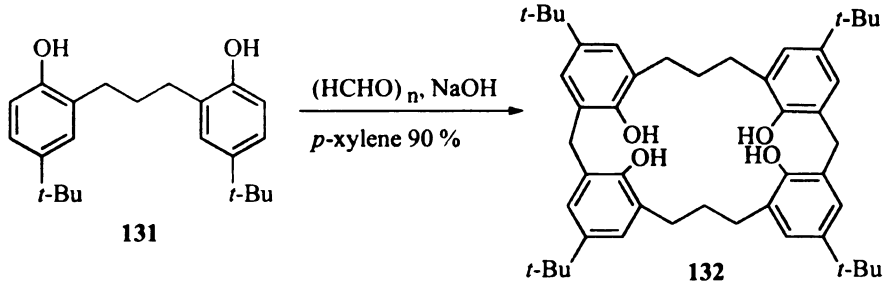
Scheme 1.30 Coupling by intramolecular S_N2 displacement on 129



1.7.2.3 Base catalyzed condensation with aldehydes

The condensation of phenol **131** with formaldehyde in the presence of a base has been utilized in the synthesis of an unsymmetrical homocalix[4]arene **132** in excellent yields (Scheme 1.31).[64]

Scheme 1.31 Base catalyzed phenol formaldehyde condensation in synthesis of 132



1.7.3 Structure and Conformational properties

Homocalix[4]arenes with identical bridges display conformational isomerism analogous to simple calix[4]arenes as cone, partial-cone, 1,2-alternate and 1,3-alternate isomers are possible. For unsymmetrical homocalix[4]arenes with varying bridges, two inequivalent 1,2-alternate conformers are known to exist depending upon the location of the symmetry plane. Conformers with the symmetry plane parallel to the longer and shorter bridge have been defined as 1,2-alternate and 1,4-alternate respectively. The net

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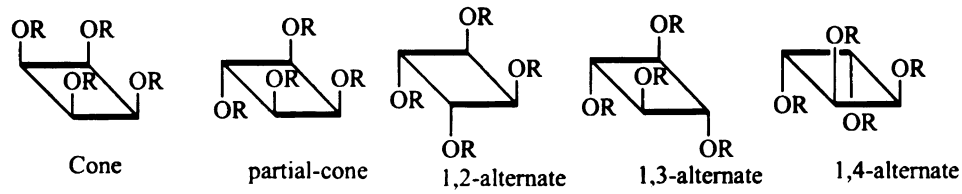
result is a minimum of five different conformers for a homocalixarene, which are illustrated below (Figure 1.15).

Figure 1.15 Conformers of homocalix[4]arenes



In contrast to intramolecular hydrogen-bonding which rigidifies the skeleton of calix[4]arenes, homocalixarenes are much more conformationally flexible owing to the weaker hydrogen-bonds. The steric bulk of the oxygen substituent again dictates the interconversion process in homocalix[4]arenes via the oxygen-through-the-annulus rotation wherein rotation is completely inhibited with butyl or benzoyl groups.

1.8 Summary and Future directions

In summary, the synthesis as well as conformational properties of calix[4]arenes, chiral calix[4]arenes and homocalix[4]arenes have been thoroughly elaborated in detail. While there are numerous reports on the preparation and applications of calix[4]arenes over the past few decades, chiral calix[4]arenes have been only of recent interest in molecular recognition and in bioorganic chemistry. Furthermore, the lack of any examples of calix[4]arenes that are chiral as a result of substitution at the methylene bridges offer a challenging avenue for further research in exploring methods aimed at their synthesis and designing new applications of these macrocycles. Homocalixarenes are another important class of metacyclophanes, which seem to be promising building blocks for development of supramolecular assemblies. The presence of a larger cavity that can be properly adjusted by varying the length of the bridges and the possibility of

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building in restraints to restrict the conformation represent some attractive incentives for developing synthetic methods towards these macrocycles.

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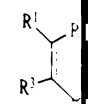


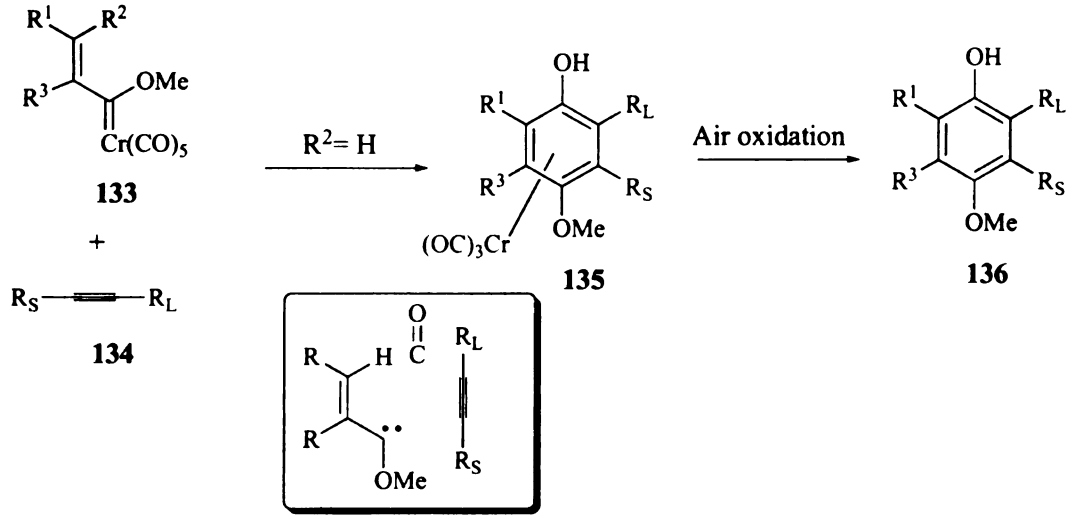
CHAPTER TWO

INTRODUCTION TO THE INTER AND INTRAMOLECULAR BENZANNULATION REACTIONS

2.1 Intermolecular benzannulation (Dötz-Wulff reaction)

Since the initial discovery by Dötz in 1975, the benzannulation reaction of an α, β-unsaturated carbene complex and an alkyne has been one of the most extensively investigated reactions of Fischer carbene complexes.[65] This is due to its mechanistic complexity and to the fact that it is one of the most synthetically useful reactions for the preparation of a wide variety of aromatic compounds. The overall process leading to product formation can be perceived as occurring via incorporation of the organic fragment of the carbene complex **133**, the alkyne **134** and a carbon monoxide ligand from the metal. The metal center acts as the template in the assembly of the three fragments thereby furnishing highly functionalized hydroquinone arene complexes **135** as the initial product. Demetalation by exposure to air subsequently affords the free phenols **136** (Scheme 2.1).

Scheme 2.1 Reaction pathway of the intermolecular benzannulation



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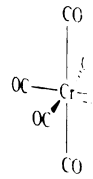

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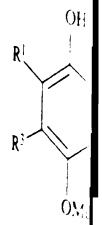

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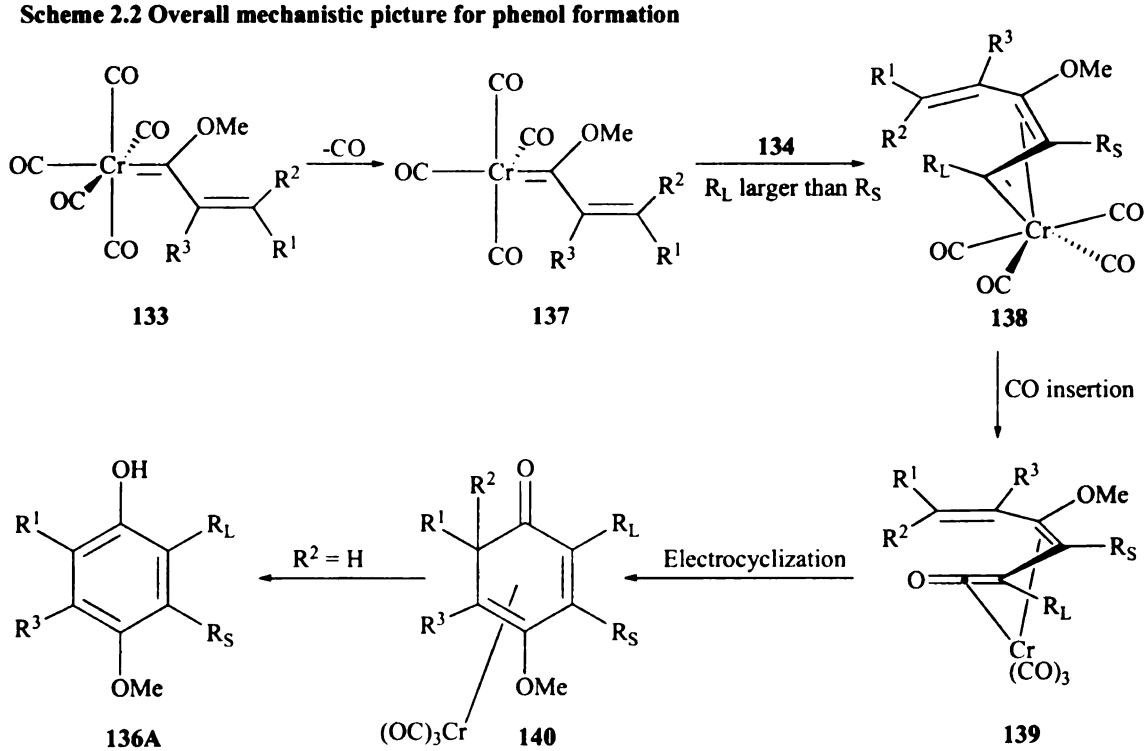
The following discussion will serve as an introduction to the methodology developed around the benzannulation reaction and will be brief since several comprehensive reviews on this topic have appeared in the past few years.

2.1.1 Mechanistic considerations

The mechanism for the formation of 4-alkoxy phenols from the reaction of Fischer carbene complexes and alkynes is not completely understood as there have been various mechanisms proposed by several researchers. The differences exist in the order of the steps and the nature of intermediates in the reaction sequence. Uncertainties also exist in the reversible nature of certain steps and in the location of the branch points for the formation of the various side products. A simplified current mechanistic understanding is illustrated below (Scheme 2.2).[66]

Scheme 2.2 Overall mechanistic picture for phenol formation



Based on kinetic studies, the first and rate limiting step of the reaction was proposed by Dötz in 1982 to be loss of a CO ligand from the coordinatively saturated 18

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electron chromium carbene complex **133** to form the 16 electron unsaturated complex **137**, thereby resulting in a vacant coordination site for association of alkyne **134**. Alkyne coordination to the vacant site followed by insertion results in the formation of η^1:η^3-vinyl carbene complex **138**. The next step is the insertion of the carbon monoxide ligand in intermediate **138**, which provides the η^4-vinyl ketene complex **139** and this is usually an irreversible step. Complex **139** then undergoes an electrocyclization to the chromacyclohexadienone species **140**. The last step in the reaction is the tautomerization of the cyclohexadienone **140** followed by demetalation to afford the free phenol **136A**.

Internal alkynes are known to react with α, β-unsaturated carbene complexes to form a mixture of two regioisomeric phenol products **136A** and **136B**, which differ in the manner in which the alkyne is incorporated. The regioselectivity is mostly determined by the steric difference between the alkyne substituents and the major product is normally the one in which the larger substituent is introduced adjacent to the phenol functionality.[67] The reaction with terminal acetylenes is highly regioselective for the formation of a single regioisomer with selectivities in most cases as >100:1. The influence of sterics on the regiochemical outcome is believed to arise from differences in the interaction of the alkyne substituents with the CO ligand in the two regioisomeric η^1:η^3-vinyl carbene complexed intermediates **138A** and **138B** (Scheme 2.3). Based on the results of the extended Huckel calculations, it was shown that the subsituent at the 2-position of the vinyl carbene complexed intermediate is atleast one angstrom closer to its nearest CO ligand than substituent at the 1-position.[66e] Only a few examples exist wherein electronic factors predominate over steric factors in determining the regioselectivity.[68]

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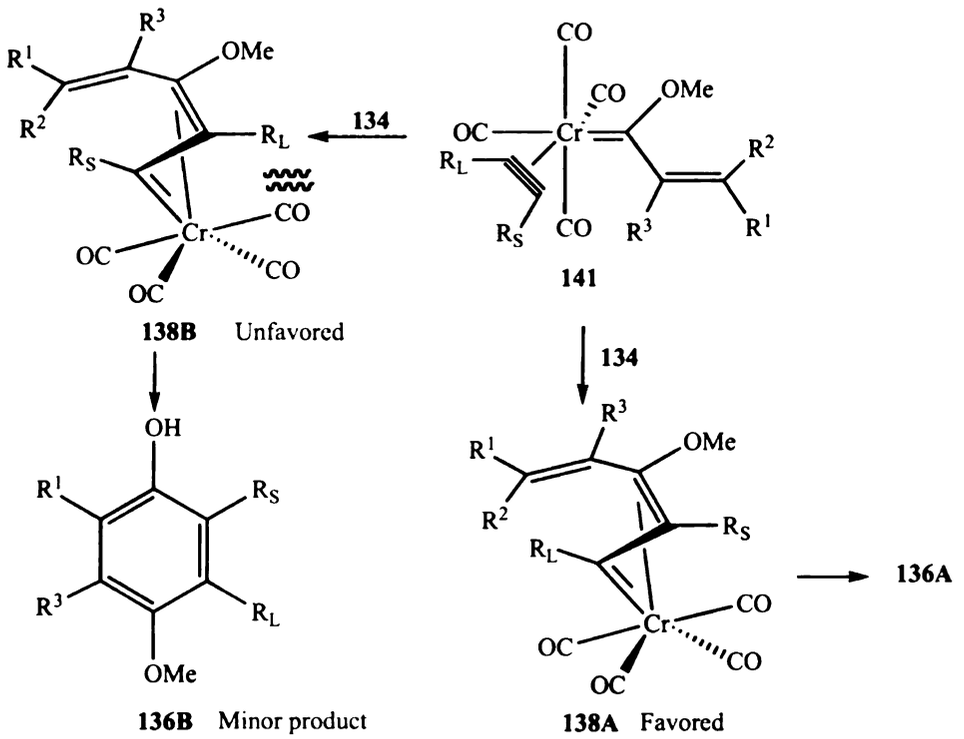
Scheme 2.3 Regioselectivity in phenol formation



2.1.2 Scope and Limitations

The benzannulation reaction is extremely sensitive to the substrate and to the reaction conditions such as the solvent, temperature and concentration. A variety of different products other than phenols are known to result as either side products or major products by the proper choice of reaction conditions or substrates. This is especially true with the reactions of aryl carbene complexes and alkynes and less so with the reactions of alkenyl carbene complexes. Higher alkyne concentration, lower temperatures and non-polar solvents favor the formation of the normal 4-alkoxy phenol products, while polar coordinating solvents, higher reaction temperatures and lower concentration result in increasing amount of indenes and in some cases as the major products.[69]

The nature of the metal and the heteroatom substituent on the carbene complex also affect the product distribution. For reactions with internal and terminal alkynes, chromium is the most suitable metal for phenol formation. Tungsten and molybdenum

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carbene complexes give increased amounts of non-CO insertion products.[70] The effect of heteroatom substituents on the carbene carbon have also been evaluated and generally it is found that alkoxy carbene complexes afford much higher yields of the corresponding phenols than do amino carbene complexes which give indenes as the predominant products depending upon the substituent on nitrogen and the solvent.[71] The greater π-electron density on nitrogen increases the electron density at the metal center and thereby strengthens the back-bonding to the CO ligand, disfavoring CO insertion from occurring in amino complexes. Consistent with this hypothesis, it was found that introduction of an electron withdrawing substituent on nitrogen results in higher yields of phenol products.[72] Amino alkenyl carbene complexes upon reaction with terminal alkynes also afford only phenols.[73]

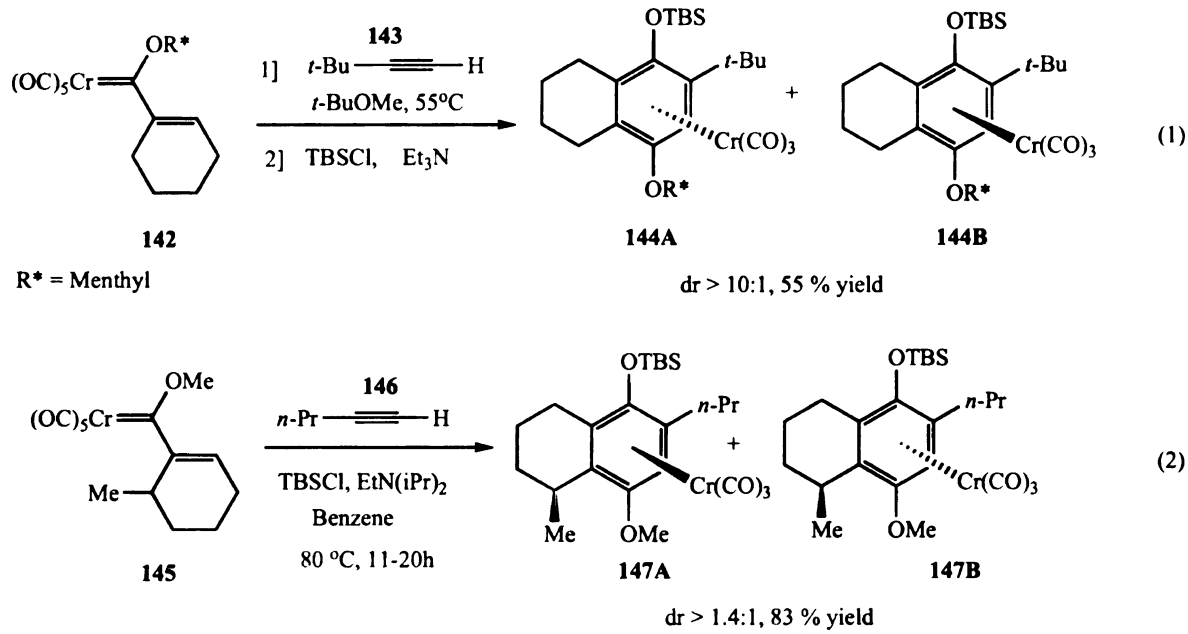
While the careful optimization of the reaction conditions has certainly contributed a great deal to the application of carbene complexes in natural product synthesis, asymmetric variants have only been a recent development. Three distinct processes have been explored which can be broadly categorized as i) Asymmetric benzannulation, ii) Stereoselective cyclohexadienone annulation and iii) Stereoselective construction of planar and axial centers of chirality.

2.1.2.1 Asymmetric benzannulation

Three successful approaches have been realized over the past decade for preparing diastereomerically pure planar arene chromium tricarbonyl complexes from the benzannulation reaction of α, β-unsaturated vinyl carbene complexes with alkynes. Among these methods, the reaction of alkynes with carbene complexes having a chiral

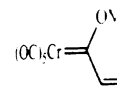
auxillary on the heteroatom substituent or a stereogenic center on the carbon substituent have resulted in only modest selectivities in the formation of planar chirality in the arene complexes via chirality transfer (Scheme 2.4).[74]

Scheme 2.4 Asymmetric benzannulation with chiral center on heteroatom and carbon substituents



On the other hand, reactions of carbene complexes with chiral propargyl ethers provided the first general method for obtaining chiral arene chromium tricarbonyl complexes in good yields and diastereoselectivities.[75] The asymmetric induction seen in this reaction is dependent on the size of the propargylic oxygen substituent. Higher diastereoselectivities were observed for larger substituents such as trityl ethers and triisopropylsilyl ethers whereas smaller substituents afforded lower diastereoselectivities (Scheme 2.5). These results indicated the absence of chelation effects in determining the stereochemical outcome and instead a stereoelectronic effect was postulated. Further experimental proof for a stereoelectronic effect was obtained when the propargylic substituent was changed from a (*p*-methoxyphenyl) dimethyl silyl group to a (pentafluorophenyl) dimethylsiloxy group.

Scheme 2.5 As



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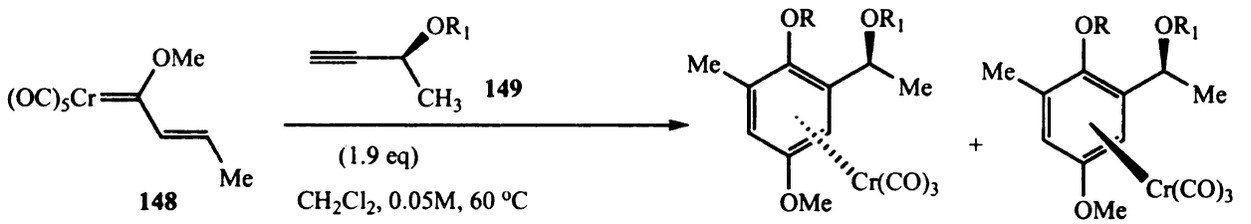
Scheme 2.5 Asymmetric benzannulation with chiral propargyl ethers



	Ratio
R = TBS, R_1 = Me	85 :15
R = TBS, R_1 = TMS	90:10
R = R_1=TBS	91:9
R = TBS, R_1 = TIPS	95 :5
R = TBS, R_1 = C(Ph)$_3$	> 96:4

The stereoselectivity of the benzannulation reaction dropped from 7.3:1 to 1.6:1. Similarly, reactions of the *trans*-propenyl complex **148** with 3,4,4-trimethyl-1-pentyne and 3-phenyl-1-butyne yielded an equal proportion of the diastereomeric arene complexes. The mechanistic rationale to account for the stereoselectivity in this benzannulation primarily is based on a proposed stereoelectronic effect that has the chromium oriented *anti* to the propargylic oxygen in the η^1: η^3 vinyl carbene complexed intermediate **151**. The two possible isomers of this intermediate are the vinyl carbene complexes **151A** and **151B** and they are likely to be in equilibrium. The stereoselectivity arises as a result of a greater stability of **151B**. The species **151A** is unfavorable due to allylic strain between the methyl group and the alkenyl substituent which is absent in **151B** (Scheme 2.6). These studies represent the first examples of central to planar chirality transfer in a benzannulation reaction.

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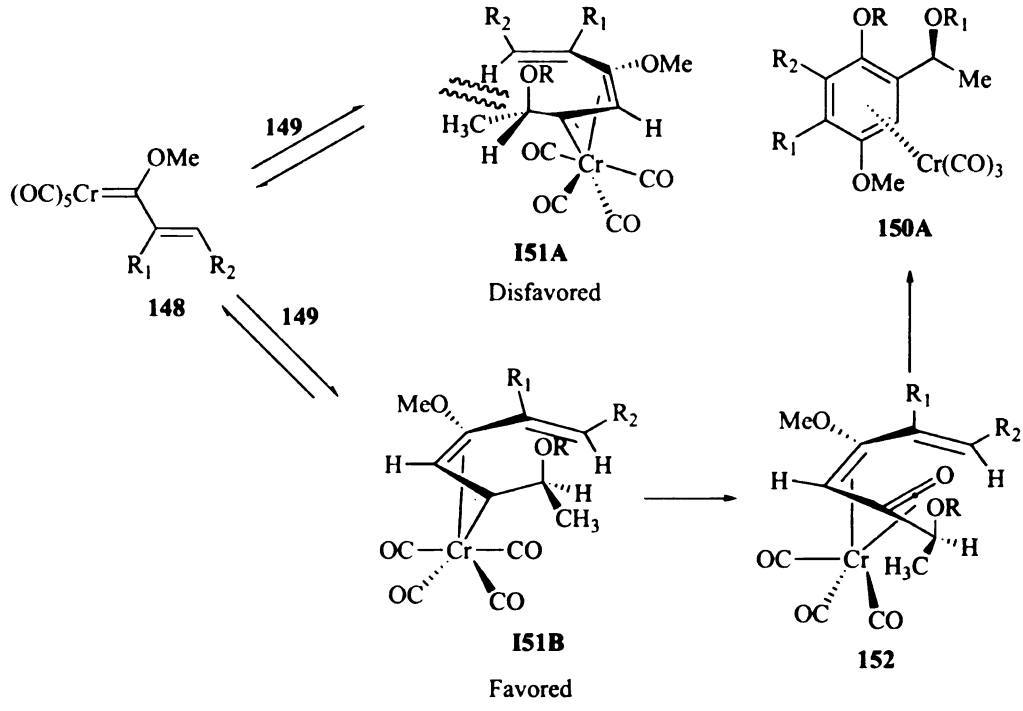
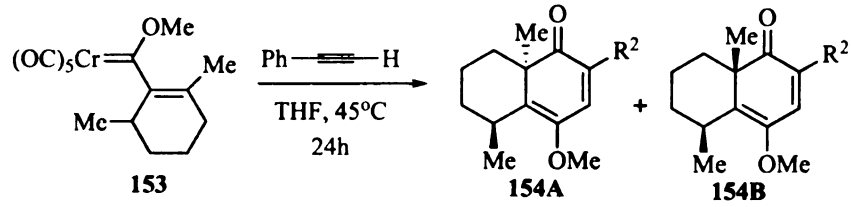
Scheme 2.6 Stereochemical model for formation of 150A



2.1.2.2 Asymmetric cyclohexadienone annulation

A new chiral center would also be created when both of the β-substituents of the carbene complex are non-hydrogen and non-identical resulting in a cyclohexadienone as the product of the reaction. The reaction of cyclohexenyl complex **153** with phenyl acetylene resulted in the formation of a single diastereomer of the cyclohexadienone **154A** in good yield (Scheme 2.7).[76]

Scheme 2.7 Asymmetric cyclohexadienone annulation with chiral center on α carbon



Similarly, the indolyl carbene complex **155** with a chiral imidazolidinone auxillary as the heteroatom substituent reacted with 1-pentyne in acetonitrile to afford the cyclohexadienone **156** as a single diastereomer in moderate yields (Scheme 2.8).

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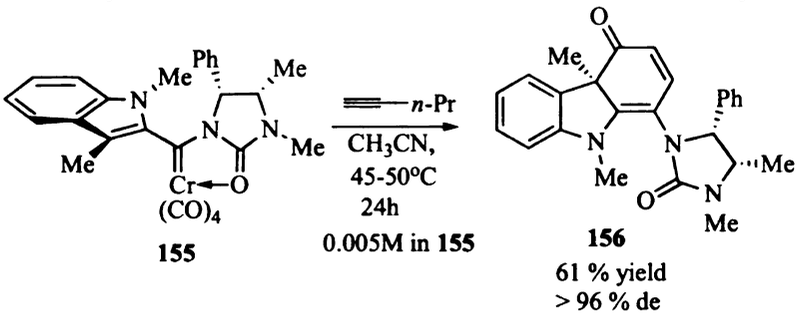
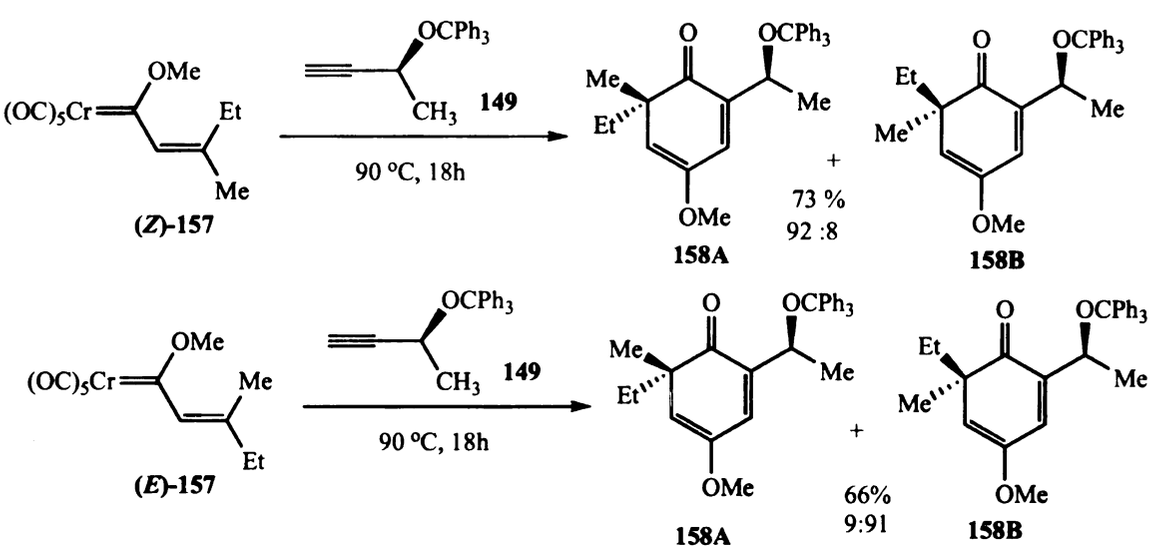
Scheme 2.8 Cyclohexadienone annulation with imidazolidinone auxillary on heteroatom



Stereoselective and stereospecific cyclohexadienone annulations were reported for the reaction of the β,β-disubstituted carbene complexes **157** with chiral propargyl ether **149** which gave either **158A** or **158B** with good diastereoselectivity depending upon the stereochemistry of the carbene complex (Scheme 2.9).[77]

Scheme 2.9 Cyclohexadienone annulation with chiral propargyl ethers



2.1.2.3 Stereoselctive construction of planar and axial centers of chirality

The reaction of alkenyl Fischer carbene complexes with aryl alkynes has been recently developed as a versatile synthetic route to atropisomerically pure biaryls. Both control of planar chirality resulting from preferential coordination of the $Cr(CO)_3$ tripod to one of the diastereotopic faces of the arene and axial chirality occurring due to restricted rotation about the biaryl bond can be accomplished with good to excellent

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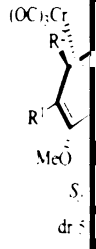
Scheme 2



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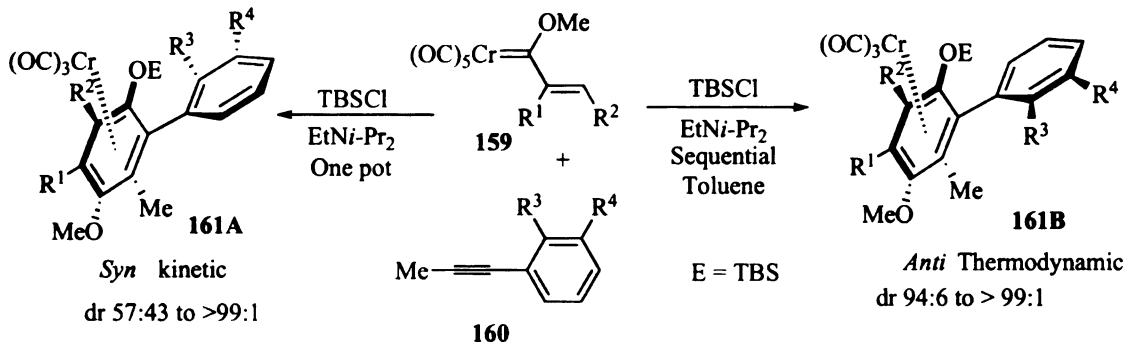
diastereoselectivities for either the *syn* or *anti* isomers depending upon the reaction conditions (Scheme 2.10).[78]

Scheme 2.10 Asymmetric benzannulation in generation of planar and axial chirality

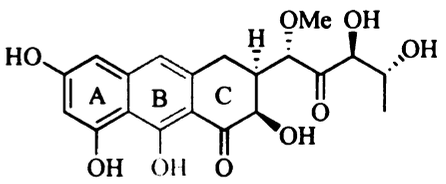


In contrast to the *anti*-products, high selectivities for the kinetic *syn*-product are only obtained for the *trans*-alkenyl carbene complexes.

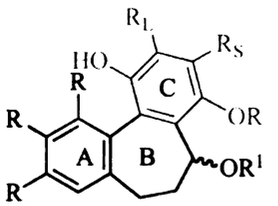
2.1.3 Synthetic applications

Despite the fact that the benzannulation reaction is stoichiometric in Cr, the mild reaction conditions and ability to tolerate a wide variety of functional groups enables the synthesis of a diverse array of aromatic ring systems. There has been a plethora of applications of the benzannulation reactions of carbene complexes with alkynes in organic synthesis. Many of these efforts have been directed towards fairly complex natural products some of which have been completed and some for which advanced intermediate has been prepared by the benzannulation methodology.[79] Besides application in natural product synthesis, some unnatural products useful as chiral ligands in asymmetric catalysis have also been synthesized by the above methodology.[80] A brief compilation of selected examples is shown below (Fig 2.1).

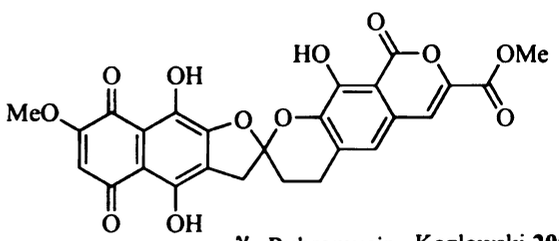
Figure 2.1 Synthetic targets of the benzannulation reaction



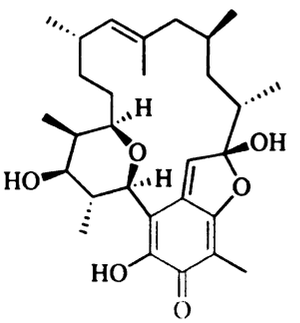
(+)-Olivin Total synthesis
Wulff **2004**



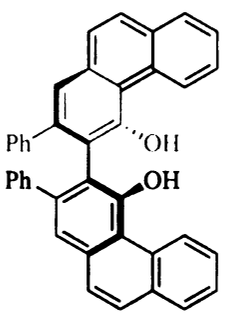
Colchicine Analogues
Wulff **2001**



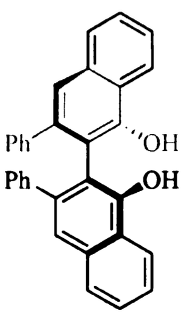
γ- Rubromycin Kozlowski **2001**
Napthazarin core



Kendomycin core
White J.D. **2005**

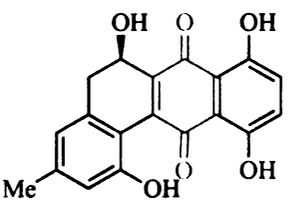


(*S*)- VAPOL



(*S*)- VANOL **25**

Highly effective Ligands for Asymmetric aziridination of Imines
Wulff **1996**



Landomycinone
Roush **2004**

2.2 Previous studies on intramolecular benzannulation

Compared to the enormous amount of work that has been done on the intermolecular benzannulation reaction, the intramolecular version has not been fully explored. While the benzannulation of an alkyne tethered to the heteroatom of the carbene complex has been studied in some detail, the analogous reaction of carbene complexes with a pendant alkyne to either the α or β carbon of the vinyl carbene complex has only been recently studied. The following discussion will briefly highlight

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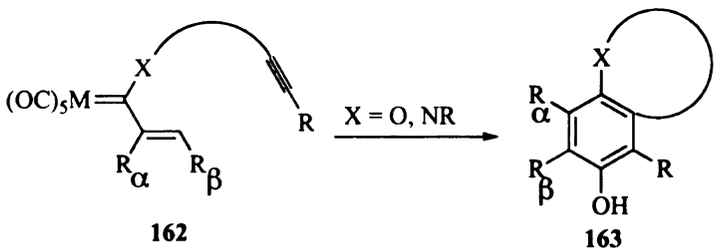
the heteroatom-tethered approach and then will focus mainly on the approach with the tether to either α or β carbon of the vinyl group.

2.2.1 Tethering the alkyne through the heteroatom of the carbene complex

Numerous examples exist in the literature wherein carbene complexes of type **162** have been prepared which have an alkyne functionality tethered through the oxygen or nitrogen heteroatom substituent. Upon thermolysis, these complexes afford only the phenol products **163** (Scheme 2.11).

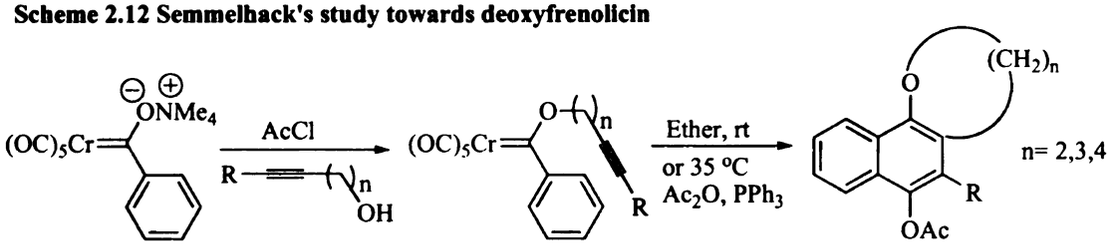
Scheme 2.11 Intramolecular benzannulation by tethering alkyne through heteroatom



162 **163**

Semmelhack reported the first example of this type of intramolecular benzannulation in 1982 in a synthetic endeavour towards deoxyfrenolicin.[81] Aryl carbene complex **165** was prepared from the tetramethylammonium salt **164** by acetylation and alcoholysis with ω-alkynol. The resultant complex upon stirring in ether at room temperature afforded the tricycle **166** as single regioisomer in good yields for internal alkynes and low yields for terminal alkyne substrates (Scheme 2.12).

Scheme 2.12 Semmelhack's study towards deoxyfrenolicin

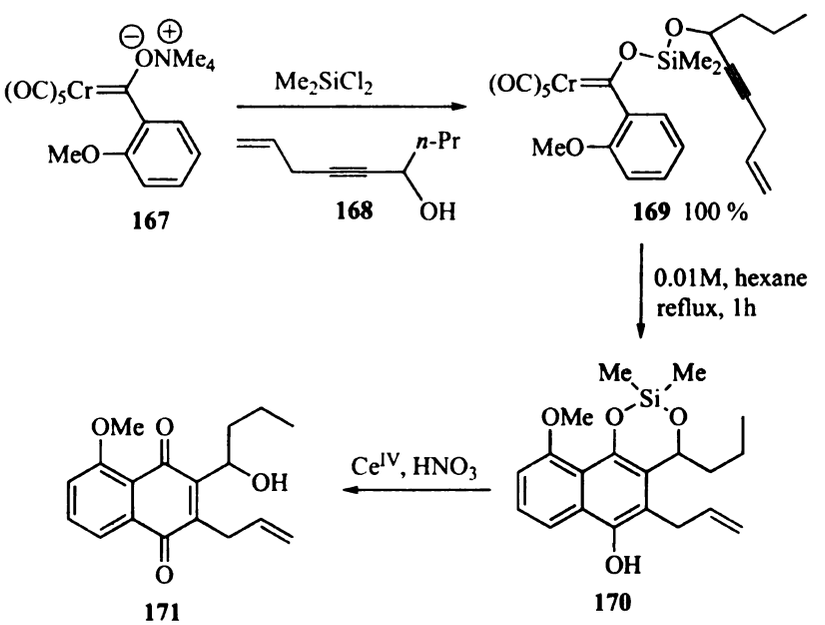


164 **165** **166**

For R = H, 16-38 %
R ≠ H, 62 - 81 %

Finn reported another approach to the same target with an intramolecular benzannulation of complex **169** wherein a silyloxy tether was introduced between the carbene fragment and the alkyne. The advantage of the silyloxy linker was that it could be easily cleaved in **170** to afford the expected regisomer of the benzannulated product **171** (Scheme 2.13).[82]

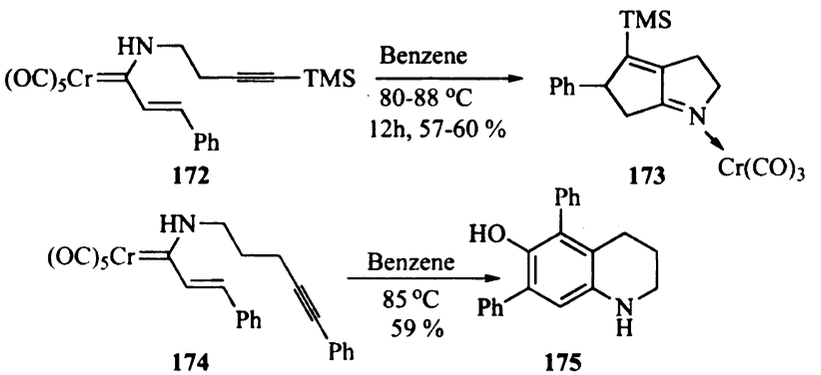
Scheme 2.13 Finn's formal synthesis of deoxyfrenolicin



167 **168** **169** 100 % **170** **171**

As a final example, the intramolecular benzannulation has also been achieved by tethering the alkyne through the nitrogen of an amino carbene complex. These reactions were found to be extremely sensitive to the substitution pattern on the carbene complex and alkyne and also on the tether length. On the basis of studies done by Wulff and Rahm, amino alkenyl carbene complexes with two carbon tethers primarily result in non-CO insertion product **173** whereas those with three carbon tethers afford the normal benzannulation product **175** (Scheme 2.14).[83]

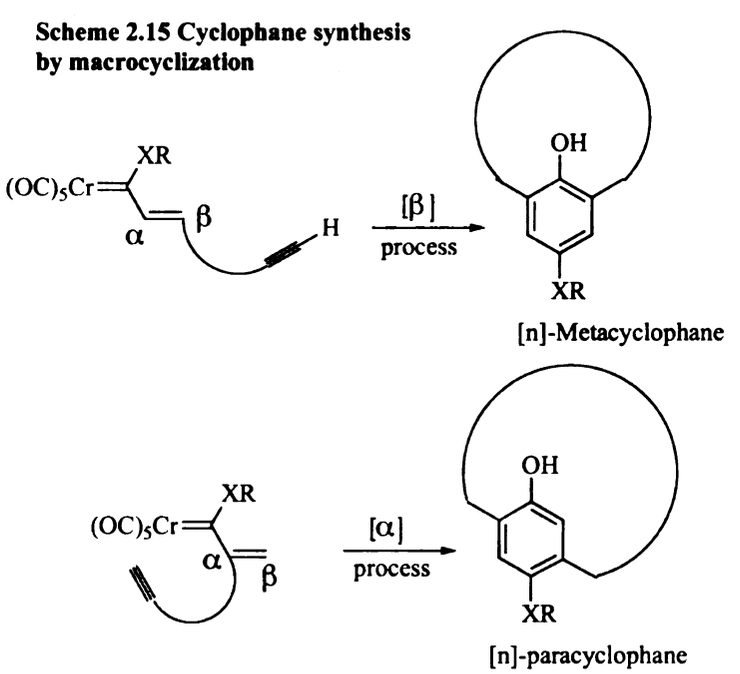
Scheme 2.14 Effect of tether length on product formation



2.2.2 Cyclophane synthesis by tethering the alkyne through carbon substituent of the carbene complex

The first examples of intramolecular benzannulation reactions involving the tethering of the alkyne to either the α or β-carbon of an alkenyl carbene complex was carried out by a former graduate student of the Wulff group, Huan Wang. He envisioned that such a process would afford a direct entry to an entire library of cyclophanes and his general synthetic strategy is depicted below (Scheme 2.15).

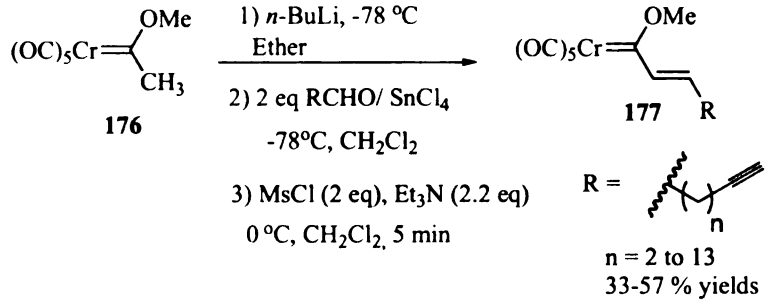
Scheme 2.15 Cyclophane synthesis by macrocyclization



2.2.2.1 [β]-Process to metacyclophanes

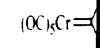
The carbene complexes required for the evaluation of this approach to *m*-cyclophanes were obtained from the aldol reaction of (methoxy)methylene pentacarbonyl chromium(0) and α,ω-alkynals (Scheme 2.16). Both tin tetrachloride and titanium tetrachloride were effective as Lewis acids in the two-step aldol reaction sequence.[84]

Scheme 2.16 Aldol methodology to form unsaturated carbene complexes



All these complexes were isolated exclusively as the *trans* isomers in modest yields. Thermolysis of carbene complex **177** (n = 6) was initially investigated and was found to yield the dimerized product [6,6]-metacyclophane **179B** in 39 % yield and the trimer **180** in 18 % yield. The effect of tether length was then studied and it was found that for complexes with tether lengths greater than six, the corresponding [n]-metacyclophanes were obtained in higher yields (Table 2.1).[85] The formation of the dimer **179B** suggested that complex **177** (n=6) doesn't have a long enough tether to permit intramolecular benzannulation perhaps because the η^1: η^3 vinyl carbene complexed intermediate **181** is too strained to form. In any event, an intermolecular process must then occur with formation of a new phenol ring in arene complex **182**, which undergoes an intramolecular benzannulation to form the [6,6]-metacyclophane **179B** as the major product (Figure 2.2).

Table 2.1



n	
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6	
8	
10	
13	

[a] Unidentified

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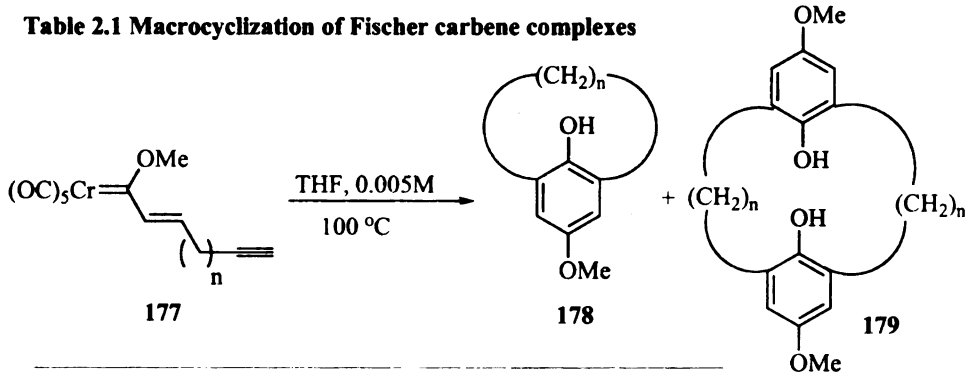
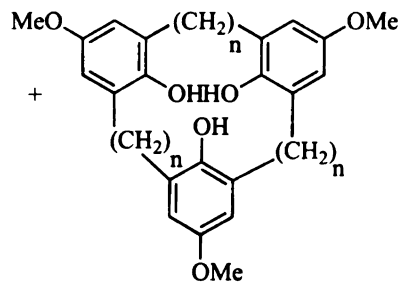
Table 2.1 Macrocyclization of Fischer carbene complexes



177 178 179

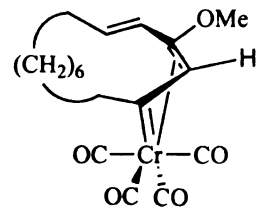
n	Series	% Yield 178	% Yield 179	%Yield 180
2[a]	A	-	-	-
6	B	-	39	18
8	C	43	15	2
10	D	58	5	-
13	E	65	-	-



180

[a] Unidentified mixtures were obtained

Figure 2.2 Possible intermediates in the intramolecular benzannulation of 177B



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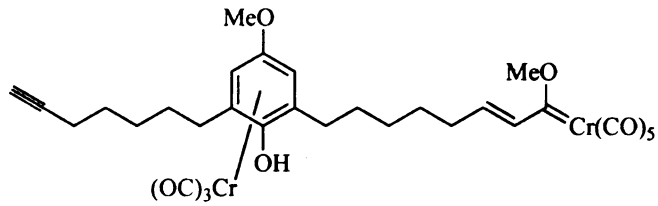


182

The intermediacy of complex **182** is also presumed in the double benzannulation of diyne **183** with bis-carbene complex **184** which afforded the same product in similar yield (Scheme 2.17). Intramolecular alkyne insertion can occur via two different modes, β-exo or β-endo processes that differ in the direction of alkyne insertion (Figure 2.3). The above cyclization process leading to **178** is an example of a β-endo process, wherein the alkyne fragment is *endo* with respect to the newly formed macrocyclic ring.

Scheme 2.17 Double benzannulation of bis-carbene complex and diyne

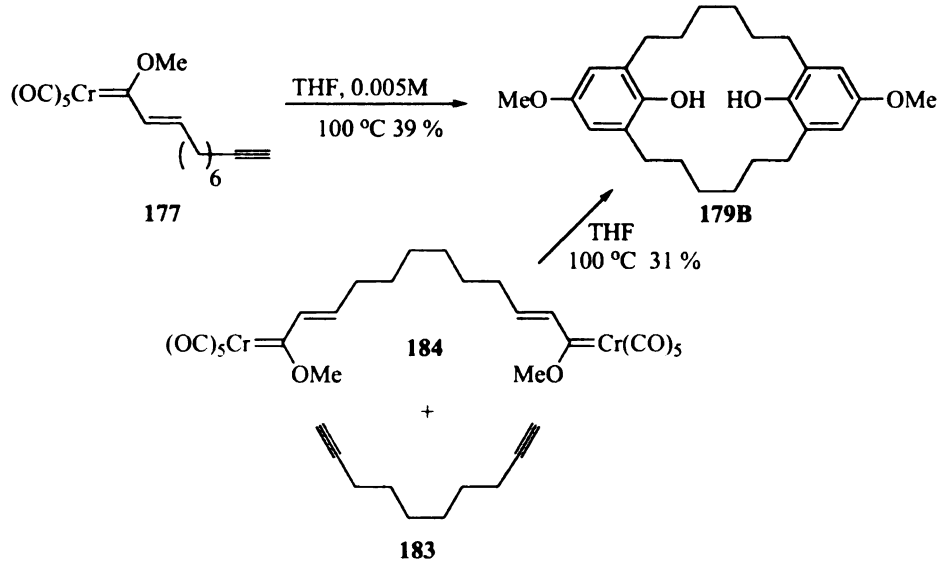
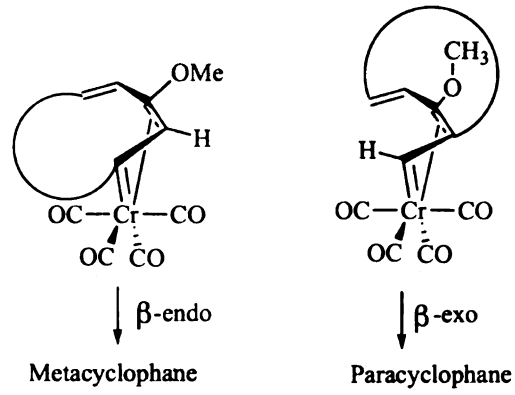
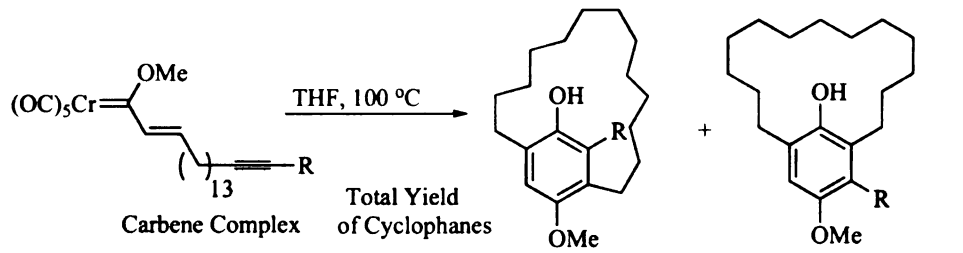


Figure 2.3 β - Endo and Exo pathways for macrocyclization



It was anticipated that if the regiochemistry of alkyne insertion were reversed then β-exo process would be favored leading to formation of paracyclophane.

Scheme 2.18 Regiochemistry switch in intramolecular benzannulation



Carbene Complex	Total Yield of Cyclophanes			
185 R = Ph	66%	**187A** R = Ph	80:20	**187B** R =Ph
186 R = $SiMe_3$	31%	a **188A** R = TMS	a	**188B** R = TMS
		189 R = H	39:61	**178** R = H
177E R = H	> 65 %	**189** R = H	<1:30	**178** R = H

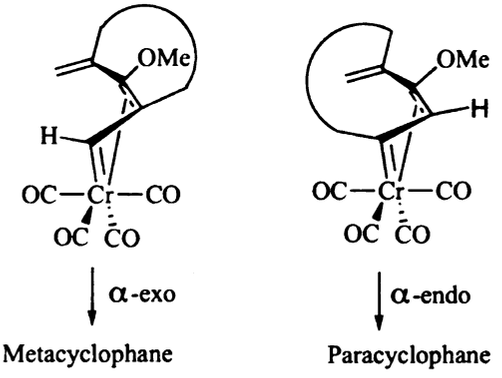
a) TFAA, rt, 0.5h

The viability of this idea was demonstrated when an internal alkyne functionality was introduced into the tether that has either a phenyl or trimethylsilyl group at the end of the alkyne as in carbene complexes **185** and **186**. The thermolysis of these complexes led to the formation of both para and metacyclophanes with modest regioselectivity (Scheme 2.18).

2.2.2.2 [α]-Process to paracyclophanes[86]

In an effort to demonstrate the versatility of the macrocyclization strategy, the direct synthesis of paracyclophanes was examined with the idea that tethering the alkyne through the α-carbon of an alkenyl carbene complex would lead to paracyclophane if an α-endo process would be operative (Fig 2.4). The normal regiochemical factors would be expected to favor an α-endo process since the larger substituent would prefer to be introduced on the newly formed carbene carbon of the vinyl carbene complexed intermediate (See Section 2.1.1).

Figure 2.4 α- Exo and Endo pathways For macrocyclization



The required carbene complexes for the investigation of this strategy were prepared by the dianion approach. The vinyl bromides **191** were prepared by monobromoboration of dialkynes **190**. In each case, the reaction gave a statistical mixture of the dibromide, monobromide **191** and unreacted dialkyne **190** from which the monobromide was readily separated. The dianion was generated from the monobromide

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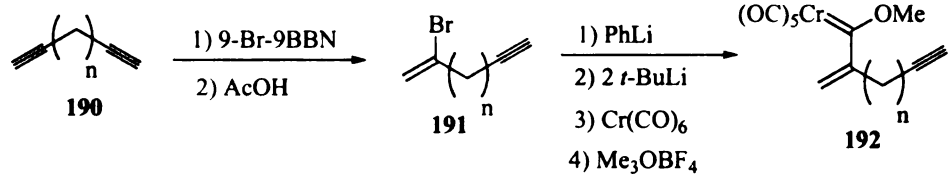
by sequential treatment with phenyl lithium to deprotonate the terminal alkyne followed by *tert*-butyl lithium to effect the halogen metal exchange. Chemoselective nucleophilic attack of the vinylic carbanion on chromium hexacarbonyl followed by methylation using Meerwein's salt resulted in the formation of carbene complexes **192** in modest yields (Table 2.2).

Table 2.2 Preparation of alkenyl complexes 192



Entry	n	Series	%Yield **191**	% Yield **192**
1	6	A	54	44
2	10	B	47	43
3	13	C	51	48
4	16	D	45	41

The cyclization of the carbene complex **192B** was first examined and it was found that in addition to the formation of the expected [10]-paracyclophane **193B** and the [10,10]-paracyclophane **194B**, this reaction produced the [10]-metacyclophane **178D** and bicyclo[3.1.0]hexenone **195B** (Scheme 2.19). Furthermore, these two unexpected products were produced as the major products. The formation of the metacyclophane **178D** involves an α-exo process and as discussed above was not expected on the basis of the normal regiochemical outcome observed for the benzannulation reaction. Hence, it was extremely intriguing to ascertain the mechanistic pathway that led to its formation.

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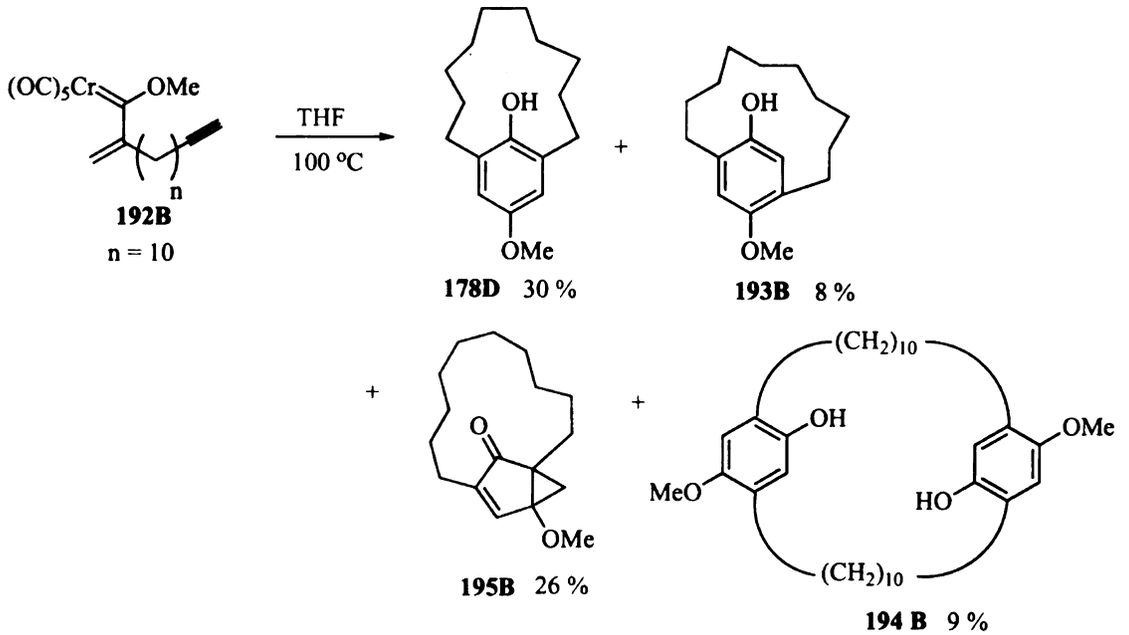
Scheme 2.19 Unexpected formation of metacyclophane 178D from cyclization of 192B



Furthermore, the formation of bicyclo[3.1.0]hexenone **195B** was quite fascinating as such a product type had never been observed before for the benzannulation reaction. Based on the similar structural connectivity in **195B** and in metacyclophane **178D**, it was hypothesized that the formation of metacyclophane might have occurred by cleavage of cyclopropane bond in **195B**. Subsequently, it was proven that this interconversion results from the exposure of **195B** to either heat or acid catalysis.

Based on a comprehensive study to determine the effect of tether length on product distribution, it was determined that carbene complexes **192** with short tethers (n=6) afforded mixtures of dimers and trimers. Those with medium tether lengths (n=10, 13) gave the metacyclophane **178** along with bicyclohexenone **195** whereas the complex with the longest tether (n=16) studied gave paracyclophanes **193** with very high selectivity (Table 2.3). The reaction profile is thus completely dependent upon the tether length between the alkyne and the vinyl carbene complex.

Table 2.3 Macrocyclization of complexes 192 as function of tether length[a]

Entry	Series	n	Time (h)	Yield **178**	Yield **193**	Yield **194**	Yield **195**
1	A	6	2			36[b]	
2	B	10	10	30	7	9	26
3	C	13	20	16	3	10	38
4	D	16	12	1	56	10	2

[a] Reaction performed at 100 °C in 0.002M of **192**

[b] 13 % yield of the trimer was also isolated

Wang and Wulff proposed a mechanism to account for the influence of tether length on formation of bicyclohexenone **195** and metacyclophane **178**. The expected normal course of events would involve intramolecular alkyne insertion in the carbene complex **192** to give an η^1: η^3 vinyl carbene complex, which would undergo CO insertion to give the η^4-vinyl ketene complex **196**. Electrocyclization of **196** to the cyclohexadienone species **197** followed by tautomerization would yield paracyclophane **193** as the expected product of the reaction. This process indeed occurs for carbene complex **192D** (n=16), which forms the corresponding [16]-paracyclophane in good yields. It was proposed that for complexes with tether lengths of n=10 (**192B**) and n=13 (**192C**) that the strain in the η^4-vinyl ketene complex **196** could be partially relieved by isomerization to the *s*-cis, *s*-trans configuration in **198**. Cyclization to form the metallabicyclo[4.1.0]heptenone **199** followed by reductive elimination then result in **195**. C-C bond cleavage of the cyclopropane unit perhaps by acid catalysis would then give metacyclophane **178**. Finally, it was proposed that for complex **192A**, the very large strain expected for the vinyl ketene complex **196** causes a change to an intermolecular

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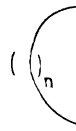

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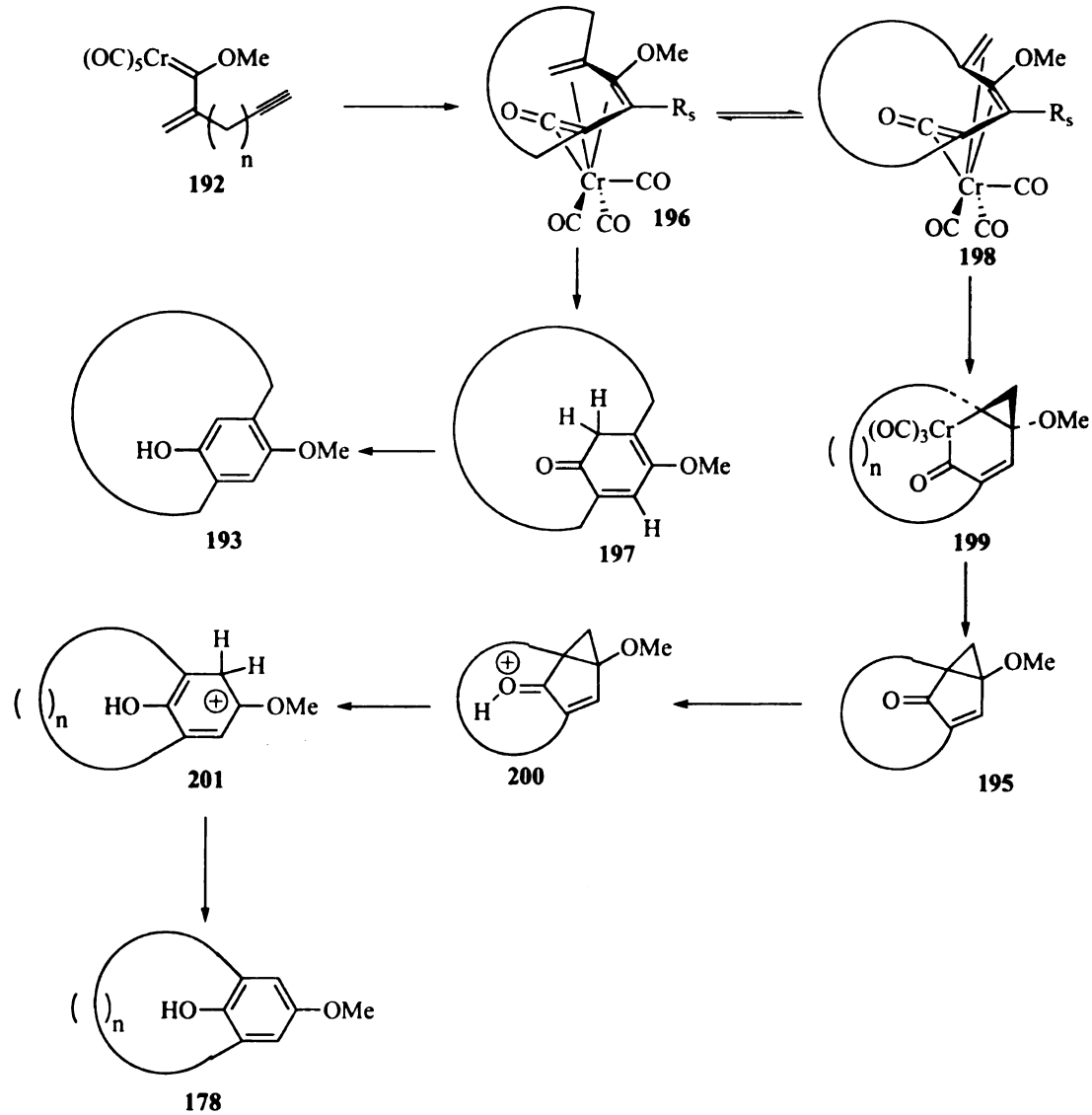
reaction of complex **192** and then leads to the formation of dimers and trimers of **193** (Scheme 2.20).

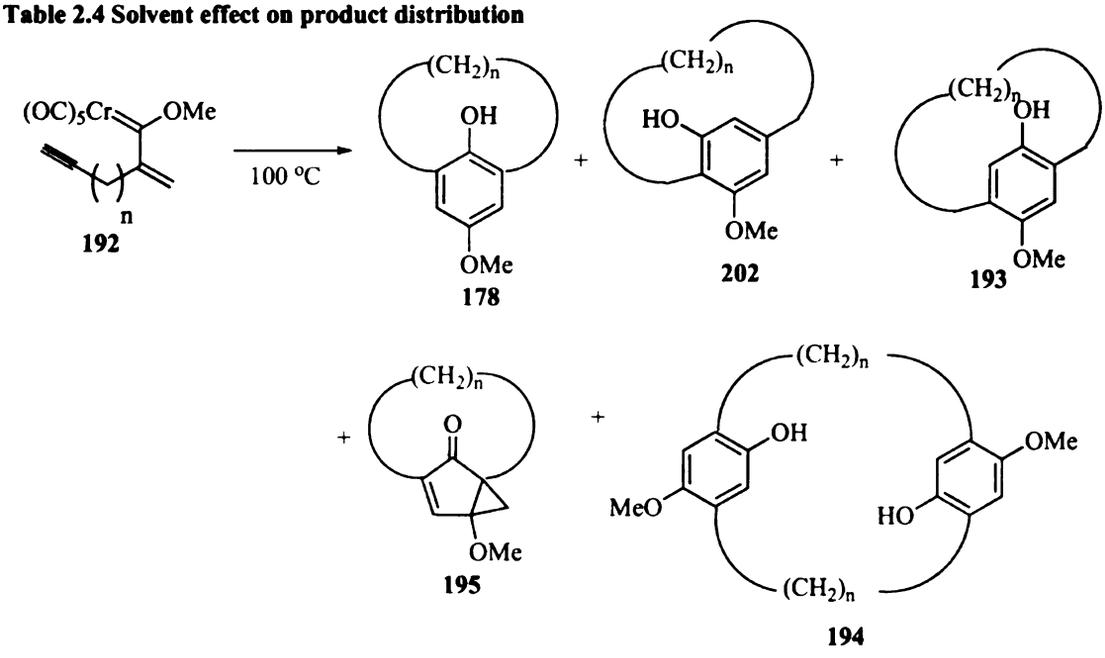
Scheme 2.20 Mechanism of intramolecular benzannulation of 192



While the above mechanism outlines a reasonable pathway for the formation of the metacyclophane **178**, the precise identity of the intermediates and sequence of steps involved could not be deduced by experimental studies. The effect of solvent on the benzannulation reaction of carbene complexes and alkynes has been well documented over the years and the sensitivity of the intramolecular process to the solvent was explored only recently. When the reaction of **192** was carried out in benzene, the *meta*-

methoxy phenol **202** was isolated as a new product.[87] It is noteworthy to point out that *meta*-methoxy phenols have never been observed before from the reaction of carbene complexes and terminal acetylenes. A solvent study was then performed to determine the product distribution for carbene complexes with varying tether lengths **192A-D** and the results are summarized in Table 2.4. For complex **192A** (n=6) only the [6,6]-paracyclophane and [6,6,6]-paracyclophane were observed as the primary products.

Table 2.4 Solvent effect on product distribution



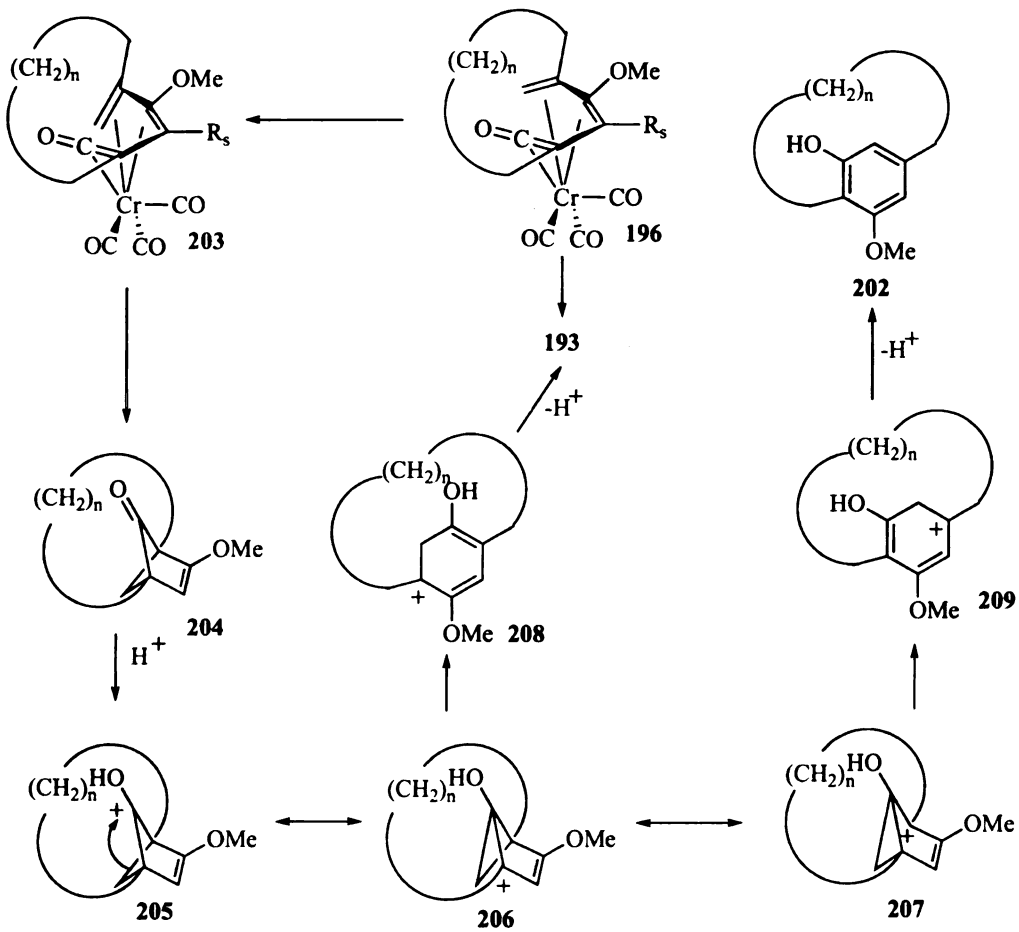
Entry	Series	n	Solvent	Yield **178**	Yield **202**	Yield **193**	Yield **195**	Yield **194**
1	A	6	THF	-	-	-	-	36 [a]
2	A	6	Benzene	-	-	-	-	28 [b]
3	B	10	THF	15	Tr	4	42	8
4	B	10	Benzene	Tr	21	40		12
5	C	13	THF	16	2	5	38	10
6	C	13	Benzene	-	18	14	-	26
7	D	16	THF	-	-	56	-	-
8	D	16	Benzene	-	2	48	-	-

[a] A 13 % yield of trimer was isolated from this reaction

[b] A 9 % yield of the trimer was also isolated

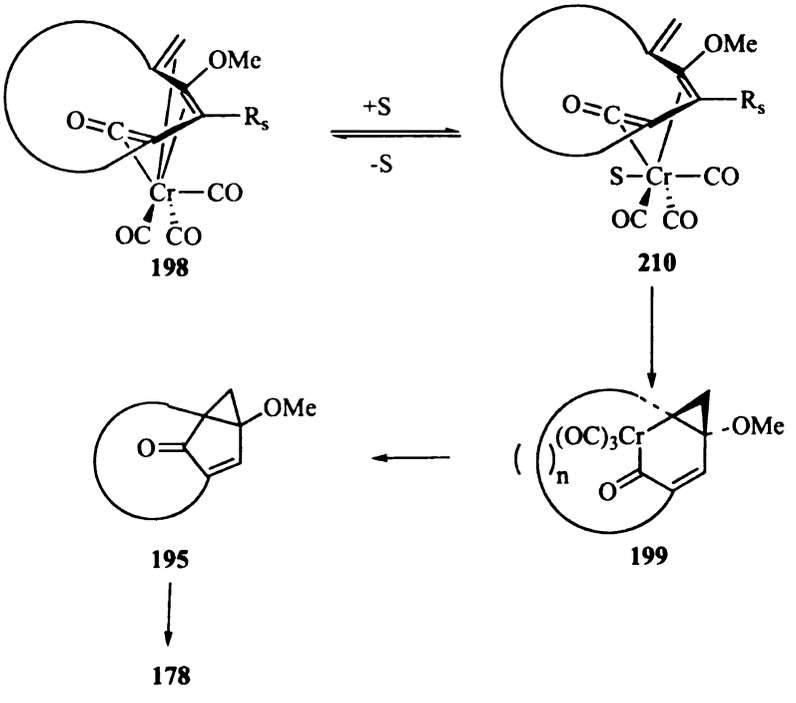
In general, products **178** and **195** were favored in coordinating solvents (i.e.,THF) whereas non-coordinating solvents (i.e., benzene) favored **202** and **193** respectively. An alternative mechanistic pathway has been proposed recently to account for the formation of these products and their solvent and tether length dependence. It is believed that the solvent dependent branch point is the vinyl ketene complex **196**. In the absence of a coordinating solvent (THF) and with medium tether lengths (n=10, 13), the vinyl ketene **196** can either cyclize directly to **193** or undergo reorganization of the olefin to form complex **203** which then undergoes a crossed [2+2] cycloaddition with the alkenyl group to form bicyclo[2.1.1]hexenone intermediate **204**.

Scheme 2.21 Mechanism of formation of meta-bridged phenol 202



The resulting benzvalenone intermediate would be expected to be susceptible to protonation affording a non-classical carbocation **205** which would have significant resonance contributions from the cyclopropyl carbinyl cations **206** and **207**. Cleavage of the internal cyclopropane bond from either of these two resonance structures would form cyclohexadienyl cations **208** or **209.** Proton loss would then yield paracyclophane **202** with a *meta*-methoxy phenol or the paracyclophane **193** (Scheme 2.21).The solvent effect was then rationalized by assuming that solvent coordination to η^4-vinyl ketene complex **198** would occur with displacement of the weakly coordinating alkenyl substituent to give a new vinyl ketene complex **210** wherein the alkenyl group would adopt an *s*-trans conformation thereby relieving strain and promoting cyclization to form the products **195** and **178** (Scheme 2.22).

Scheme 2.22 Postulated mechanism to explain solvent effect



This solvent effect is limited to the macrocyclic intermediates that exhibit ring strain (*n* =10, 13). This effect is not observed for the formation of larger macrocycles ([16]-

paracyclophane) wherein the isolated yields are the same for both benzene and tetrahydrofuran.

2.3 Triple annulation strategy towards calixarenes – A systematic investigation

At this juncture, it is very clear that the *Intramolecular Benzannulation* reaction of Fischer carbene complexes has provided a number of surprises including the formation of products not previously seen in the intramolecular reaction and a reasonable understanding of the scope of the reaction and the effects of solvent and tether now exist. This methodology has now attained significant maturity so that novel applications in supramolecular chemistry can be considered. Since the pioneering work of Cram in the early eighties,[88]cyclophanes have been ubiquitous as hosts for the inclusion of guest molecules inside its cavity but the lack of rigidity of all carbon-tethered analogs have limited their applications in host-guest chemistry. In the last decade, this science has advanced to the point where it is widely recognized as a highly mature field particularly as a result of remarkable contributions by Gutsche, Atwood and Rebek. Undoubtedly, stimulating research on calixarenes and resorcarenes became the backbone of this discipline thereby contributing to its richness as well as its diversity.

2.3.1 Design of new calixarene based templates for generation of supramolecular cavitand

Recent studies have shown that calixarenes and resorcarenes have been used in the synthesis of cavitands and other self-assembled capsules with a well-defined cavity large enough to trap organic molecules inside, thereby permitting investigation of reaction processes in such systems.[89] A simplified cartoon representation is shown below (Scheme 2.23).

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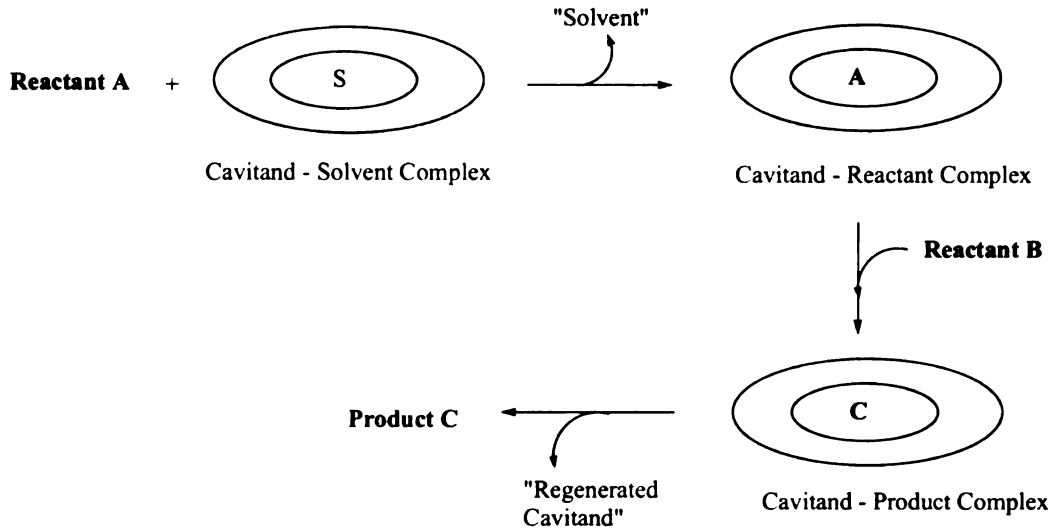
Scheme 2.23 Cartoon illustrating typical reaction sequence within a cavitand



There have been some successful examples of reactions such as palladium catalyzed allylic alkylation,[90] Diels-Alder reactions,[91] [3+2] and [2+2] cycloadditions [92]and Cope rearrangements [93] inside these molecular cavities but they are very limited to specific substrates and no asymmetric variants have been reported to date. Furthermore, the difficulty in generating these macromolecular assemblies and their restricted stability in certain organic solvents often limits the study of reactions within the cavities.

Although calix[4]arenes have been known to encapsulate metal ions, its capability to trap neutral organic molecules is much more limited due to smaller cavity size. For example, a 1:1 *p*-tert-butyl calix[4]arene : toluene complex has the methyl group of toluene directed inside the cavity rather than the aromatic group. In this respect, a general strategy was sought to access a variety of cavitands for investigation of reactions within the cavity. The criteria for host design in supramolecular chemistry is largely based on size and shape complementarities with the guest species as well as the presence of multiple identical binding sites on the host which would increase the binding constant of the host-guest complex. A larger cavity size has been known to be induced by two

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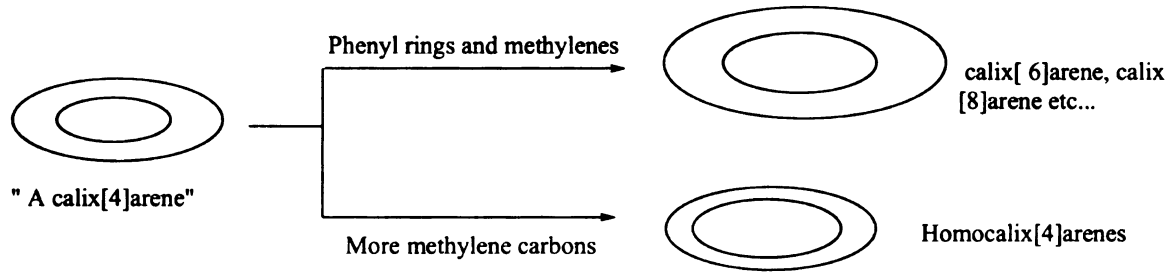
different methods, the first of which would involve either increasing the number of aryl rings and methylenes in the bridge (eg., Calix[6]arene, Calix[10]arene), whereas the latter approach would involve an increase in the tether length connecting the adjacent aromatic rings (eg., Homocalixarenes) (Figure 2.5).

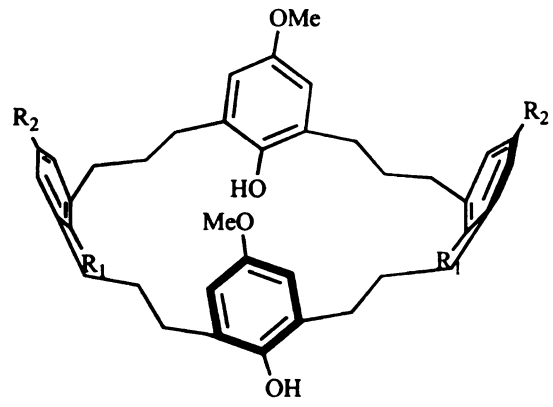
Figure 2.5 Common approaches to obtaining larger cavity sizes



While there has been numerous studies towards encapsulation of neutral organic guest molecules inside the cavity done by several research groups with Calix[6]arenes and other larger macrocycles, homocalix[4]arenes have been less examined. The design of a suitable supramolecular host based on a homocalix[4]arene has to obey certain criteria, one of them being the specific guest molecule that is targeted. Furthermore, for examining reactions within the cavity it is imperative that the reaction under investigation is slow in the absence of the host species. The extent of association of the host and guest molecules in solution measured by calculation of binding constants must be significantly large. To achieve this last requirement, the host species must have multiple binding sites (i.e.; multivalency), which are structurally similar to the guest molecule that needs to be encapsulated. Finally, the host must possess a rigid conformation for otherwise the orientation of the guest species inside the cavity would be altered thereby complicating the scenario for stereoselective reactions.

Based on a careful examination and analysis of different homocalix[4]arenes by space filling models, it was clear that a bishomocalix[4]arene **211** and its chiral analog **212** would be an ideal candidates for initial investigation (Figure 2.6). One of the most important requirements in rendering the middle carbon of the propylene tether chiral would be the adjacent arenes of the macrocycle to be diversely substituted ($R_1 \neq$ OH and $R_2 \neq$ OMe). At the outset, it was expected that this requirement would be fulfilled by an extension of the Double benzannulation strategy (See Scheme 2.17, Pg.89).

Figure 2.6 Bis-homocalix[4]arene 211 and its chiral analog 212



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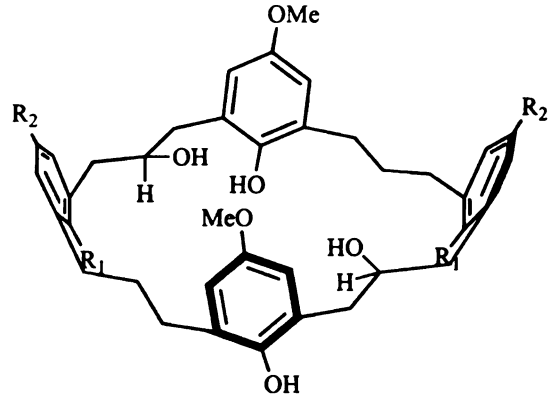
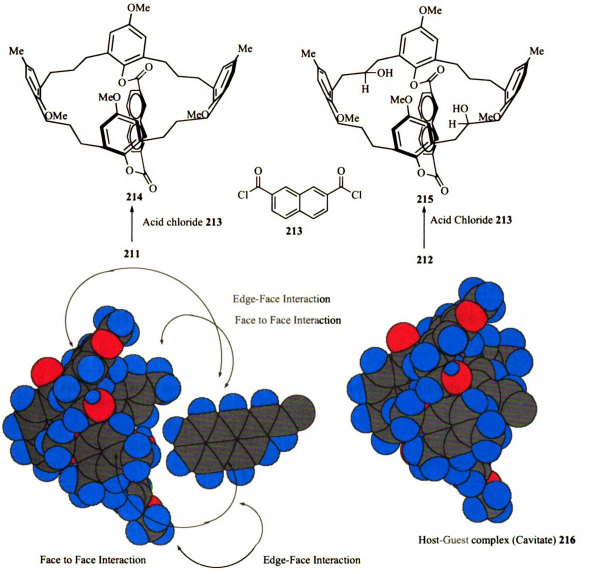


212

These supramolecules would be expected to be extremely floppy due to rapid rotation of the aryl rings about the annulus. A locked conformation would result if the opposite phenols were converted to a diester **214** and **215** (eg., R_1 = OMe and R_2 = Me) by bridging with a rigid bi-functional reagent such as 2,7-Naphthalene dicarboyl chloride **213**. The lowest energy conformation of **214** and **215** is expected to be the one shown wherein the two anisole rings would be parallel to each other and also to the naphthalene bridge at the bottom of the molecule. The two distally anchored arene rings would then be splayed outward, thereby creating a cavity large enough to permit inclusion of guest molecules. Furthermore, the distance between the two non-anchored arene rings would be 7.4 Å, exactly the right distance for the inclusion of an arene ring.

Figure 2.7 Cavitand hosts and cavitate 216



Thus, it is expected that cavitands **214**, **215** would form very stable host-guest complexes with functionalized naphthalene derivatives due to presence of several edge-face and face-face interactions between aromatic rings on the calixarene and the host arenes (Figure 2.7).

In the host-guest complex **216**, the hydroxyl group on the propylene tether would be in close proximity to the alkenyl moiety of vinyl naphthalene. Thus, it is conceivable

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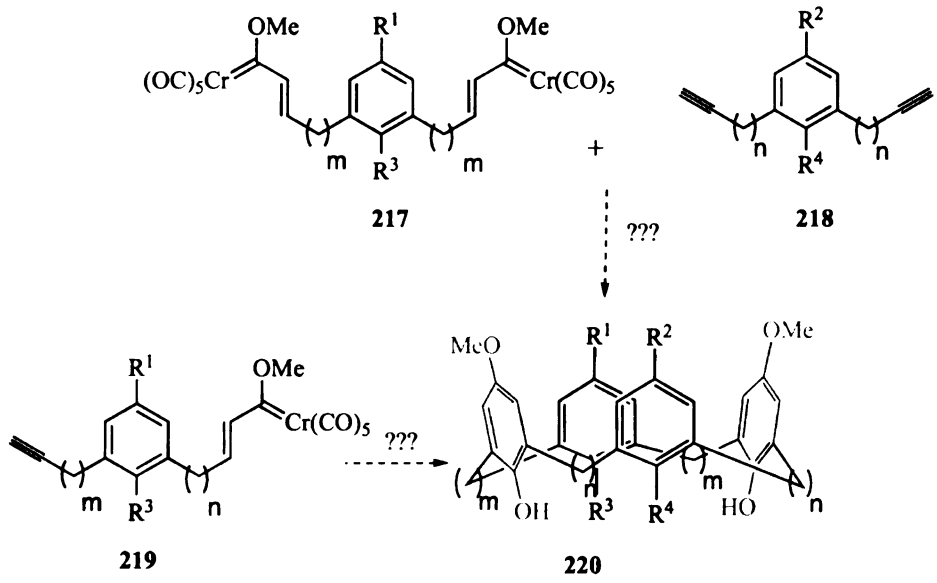
that hydroxy directed reactions such as Simmons-smith cyclopropanation and asymmetric epoxidation of unfunctionalized olefins could be examined with the cavitand **215**.[94] Chapter three will focus on the development of the triple annulation strategy for the synthesis of calix[4]arenes with C_2 or C_1 symmetry by having either two or three differently substituted arene rings (ABAB or ABAC substitution patterns). This will be followed by an examination of the feasibility of obtaining optically active calix[4]arenes with substituent(s) at the methylene bridge(s). Finally, Chapter 5 will focus upon the development of methodology for synthesis of homocalix[4]arenes. The general strategy toward all these macrocycles will involve either the reaction of bis-carbene complex **217** with a diyne **218** or the dimerization of akynyl vinyl carbene complex **219** (Scheme 2.24).

Scheme 2.24 Triple annulation strategy towards unsymmetrical calix[4]arenes and homocalixarenes



CHAPTER THREE

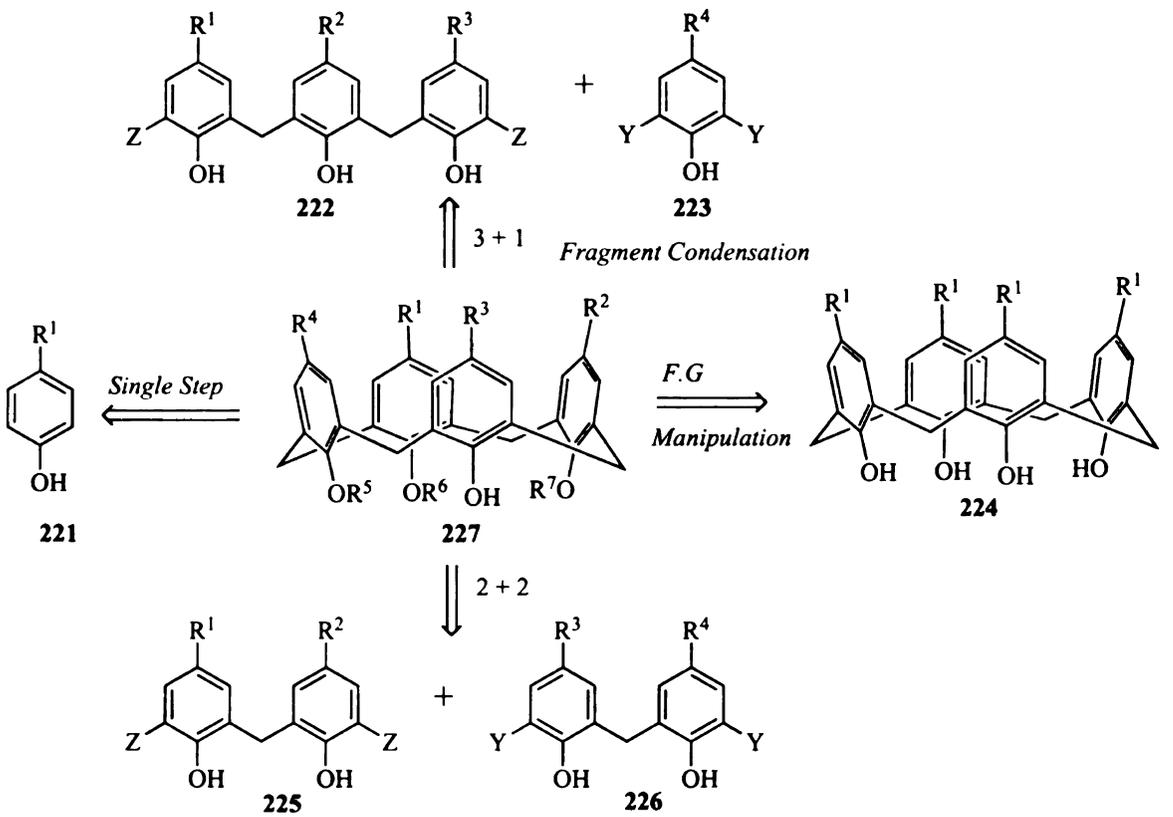
EXPLORATORY STUDIES ON SYNTHESIS OF CALIX[4]ARENES WITH C_2 AND C_1 SYMMETRY

3.1 Triple annulation approach to calix[4]arenes

The existing methods for calix[4]arene synthesis can be classified based on the symmetry introduced in the macrocycle as shown below (Fig 3.1). The most prominent method for calix[4]arene synthesis is the one developed by Gutsche, but its drawback is that only certain substituents can be introduced in the *p*-position and also calix[4]arenes with C_4 symmetry only can be obtained. The fragment condensation methods either by [3+1] or [2+2] approaches circumvents this problem because calixarenes with C_1 or C_2 symmtery can be obtained but still suffers from low overall yields in the cyclization step as well as the inability to introduce different substituents at the lower rim. Calix[4]arenes with C_1 symmetry are special class of macrocycles as they exhibit molecular asymmetry depending upon the substitution pattern (ABCD or ABAC with one inverted phenol ring) on the arene rings. Consequently, enantiomers for these calixarenes exist and synthetic strategies developed by Biali (See section 1.5.1.1) are circuitous involving sequential introduction of functionality followed by resolution with chiral reagent. Neverthless, the inherent chirality due to molecular asymmetry in such calix[4]arenes presents an attractive feature to develop synthetic applications for these scaffolds.

In this context, development of a new synthetic route to directly access calixarenes exhibiting C_2 and C_1 symmetry would represent significant advancement over existing methods.

Fig 3.1 Methods of calixarene synthesis based on symmetry classification



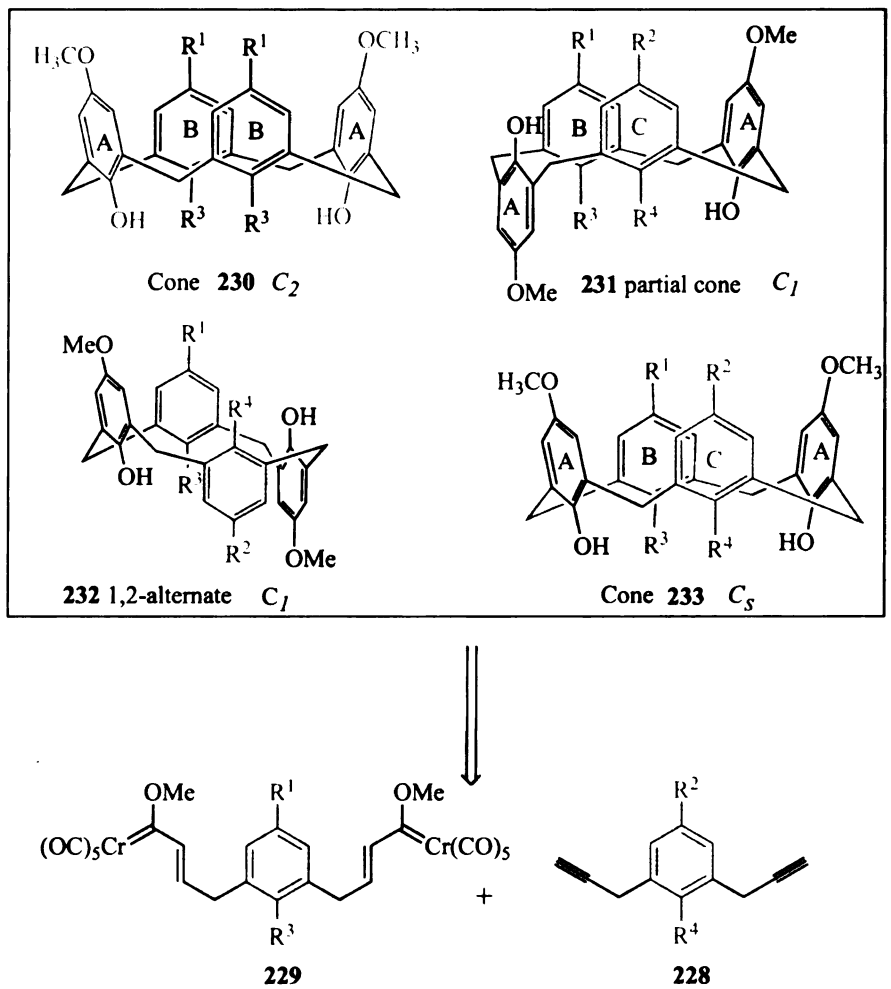
Method	Substituents	Pattern	Symmetry
Single Step [a]	$R^1 = R^2 = R^3 = R^4$	AAAA	C_4
Fragment Condensation [a]	$R^1 \neq R^2 \neq R^3 \neq R^4$	ABCD	C_1
	$R^1 = R^3$, $R^2 = R^4$	ABAB	C_2
	$R^1 = R^3$, $R^2 \neq R^4$	ABAC	C_s
Functional Group Manipulation	$R^1 = R^3$, $R^2 = R^4$ $R^5 = R^7$, $R^6 = H$	ABAB	C_2
	$R^1 = R^2 = R^3 = R^4$ $R^5 \neq R^6 \neq R^7$	ABCD	C_1

[a] Substituents $R^5 = R^6 = R^7 = H$

Thus, a novel method was envisioned based on the reaction of a bis-carbene complex **229** and diyne **228** that could enable direct access to calix[4]arenes **230** with the ABAB substitution pattern and C_2 symmetry when the substituents on the arene ring

were identical ($R^3 = R^4$ and $R^2 = R^1$). Calix[4]arenes with C_1 symmetry would exist for ABAC substitution pattern only in the case of partial-cone or 1,2-alternate conformers **231** and **232** and calix[4]arenes with C_s symmetry **233** would be expected in a cone conformation when the substituents on the arene ring were non-identical ($R^3 \neq R^4$ and $R^1 \neq R^2$). Intuitively, a general approach was conceived for these calix[4]arenes adorned with specific symmetry elements by proper choice of aryl substituents in the bis-carbene complex and the bis-propargyl arene (Scheme 3.1).

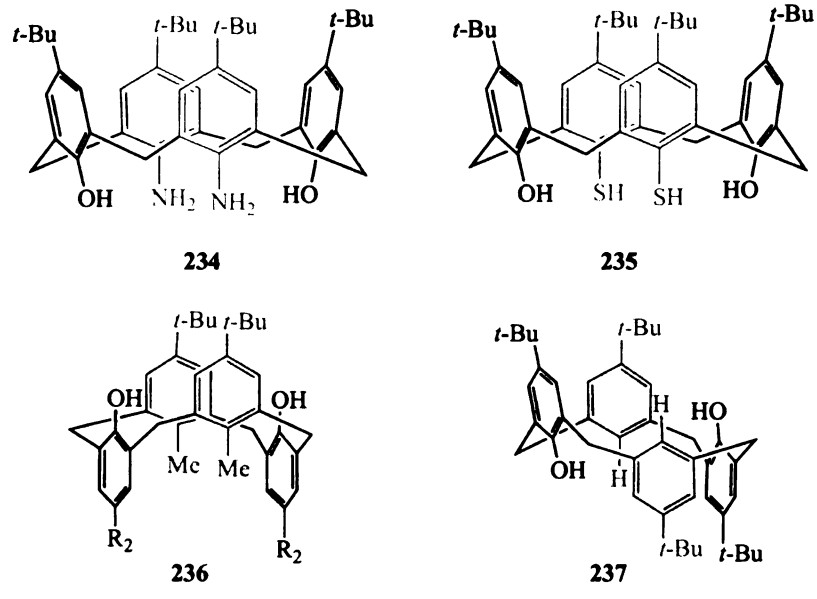
Scheme 3.1 General synthetic strategy to calix[4]arenes with specific symmetry elements



The choice of substituents was governed by factors that would either favor or disfavor the cone conformation and would thereby enable access to calix[4]arenes **230**-

233. Intramolecular hydrogen bonding is solely responsible for stability of cone conformer (See section 1.2.1). It has further been shown that replacement of hydroxyl groups by amino or thiol substituents in calix[4]arenes **234** and **235** do not disrupt the hydrogen-bonding pattern because the cone conformation is still observed in solution.[95,96] Thus, heteroatom substituents at the lower rim would enable access to ABAB calix[4]arenes **230** with C_2 symmetry. In contrast to **234** and **235**, alkyl and hydrogen substituted analogs **236, 237** were found to exist in the 1,3-alternate and 1,2-alternate conformations respectively (Fig 3.2).[97,98]

Fig 3.2 Effect of hydrogen bonding on the stability of cone conformation



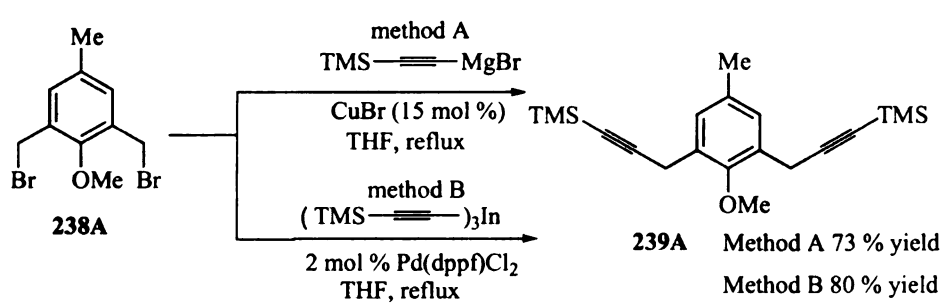
Based on these results, it was anticipated that introduction of long chain alkyl or aryl substituents ($R^3 = R^4$ = Ar (or) 1° alkyl, Scheme 3.1) at the lower rim would disfavor the cone conformation and could possibly enable access to calix[4]arenes with molecular asymmetry (C_1). These substituents were also expected to inhibit the ring-inversion process that is known to racemize such inherently chiral calix[4]arenes (See section 1.5.1.1).

3.2 Practical synthesis of bis-propargyl arenes 228

Preparative routes for bis-propargyl arene **228A** with R^4 = OMe and R^2 = Me (**239A**, Scheme 3.2) were initially investigated. After screening a wide variety of methods, two were found to be successful.

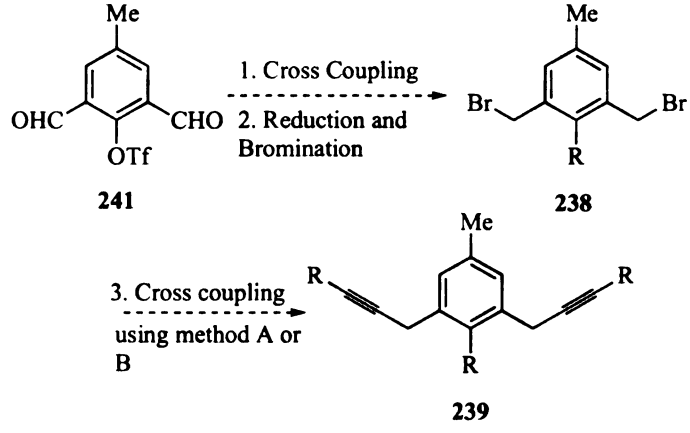
The benzyl bromide **238A** upon coupling with trimethylsilyl ethynyl Grignard reagent in the presence of catalytic amount of Cu (I)[99] or with trialkynyl indium reagent in the presence of catalytic amount of Pd (II) species[100] afforded the bis-silylsubstituted diyne **239A** in excellent yields (Scheme 3.2). While the success of both methods added greater flexibility to the desired synthetic objective, each had its own advantages and disadvantages. For example, the copper bromide catalyzed coupling had to be done with at least 8 equivalents *of the alkynyl Grignard reagent at high concentrations* as the reaction is typically slow at low concentration and with a low stoichiometric amount of the Grignard reagent. Despite this inherent problem, the low cost as well as the ease of handling of the reagents enabled this process to be the most advantageous. The palladium catalyzed coupling despite suffering from expensive Pd (II) source was still a highly atom-efficient process as an excess of the organo-indium reagent was not required for the cross coupling and all the three alkynyl groups on the indium were transferred. With a convenient route to **239A** secured, the synthesis of bis-propargyl arenes with different aryl substituents was then explored.

Scheme 3.2 Pd(II) and Cu(I) catalyzed coupling in synthesis of 239A



A Domino cross-coupling sequence was envisioned wherein the electronically activated aryl triflate **241** with formyl groups in two *ortho* positions would afford the aryl and alkyl substituted aldehydes upon the initial coupling step (Scheme 3.3). The formyl groups would then be transformed into bromomethyl groups in arene **238** and a second coupling process using either method A or B would yield a family of substituted bis-propargyl arenes of the type **239**.

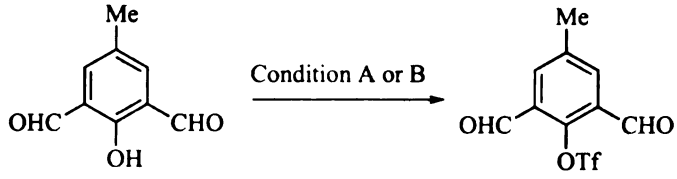
Scheme 3.3 Domino cross couping sequence to bis-propargyl arenes



241 **238** **239**

The aryl triflate **241** was prepared in good yields by two methods that differ in the source of the triflating agent. Triflation of phenol **240** using N-phenyl bis-(trifluoromethane) sulfonimide resulted in good yields of the product on a smaller scale but difficulties were encountered in its separation from the N-phenyl trifluoromethane sulfonamide by-product on a larger scale. An alternative approach was developed using triflic anhydride under biphasic conditions and potassium phosphate as the base.[101] This protocol circumvented the purification problem that was encountered in the former method and the aryl triflate could be conveniently prepared in multigram quantities in excellent yields (Scheme 3.4). The cross coupling of triflate **241** with organoboranes and organoindiums was next examined and optimized by screening a wide variety of reaction conditions.

Scheme 3.4 Preparation of aryl triflate 241



240

A. $PhNTf_2$, Et_3N
CH_2Cl_2

B. 30 % Aq.K_3PO_4, Tf_2O

83 % **241** by either Methods A or B

Recent studies by Molander and others have indicated that alkyl boronic acids are viable partners in the cross coupling reactions with aryl triflates.[102] The cross coupling of triflate **241** with *n*-hexyl boronic acid in the presence of a weak base and 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride as the catalyst resulted in only a 49 % yield of the product **242A** (Entry 1, Table 3.1). The yields were significantly lower when the stronger base cesium carbonate was employed under identical reaction conditions (Entry 2). The use of 9-hexyl-borabicyclononane resulted only in complex mixtures with two different palladium catalysts (Entries 3 and 4). Alternatively, the use of potassium hexyl trifluoroborate[103] as the alkylating reagent resulted in predominantly the hydrolysis of **241** under strongly alkaline conditions. Weaker bases such as potassium carbonate and potassium phosphate facilitated nucleophilic addition to the carbonyl of the aryl triflate **241** (Entries 5-7 &10). Finally, cross coupling with trihexyl indium reagent afforded the product **242A** in similar yields to the boronic acid (entries 8 & 9 vs entry1). In contrast to the difficulties observed in forging the formation of a sp^3-sp^2 C-C bond, Suzuki coupling of aryl triflate **241** with phenyl boronic acid using tetrakis triphenyl phosphine Pd (0) in the presence of potassium phosphate as the base resulted in formation of the biaryl **242B** in excellent yields (entry 11).[104] Both the aldehydes **242A** and **242B**

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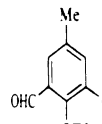
Table 3.1



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[a] Reacti

A K_2CO

D K_3PO

G K_2CO

[b] React

React

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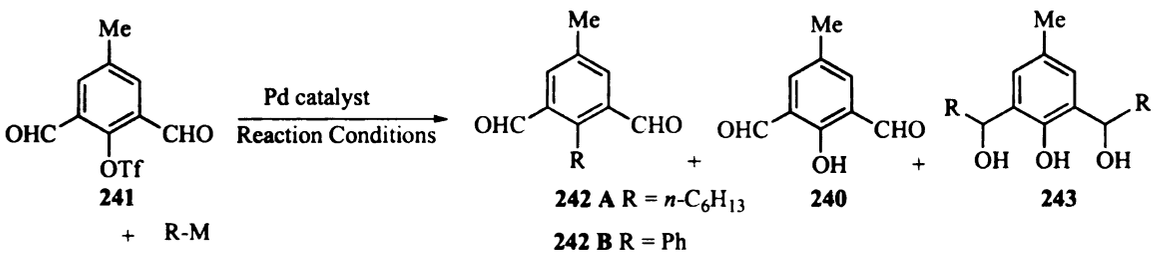
were subsequently transformed to bis-bromomethyl arenes **238B** and **238C** by reduction using sodium borohydride followed by bromination (Table 3.2).

Table 3.1 Cross coupling reactions of aryl triflate 241



S.No	R-M	Conditions[a,b]	Yield **242A / 242 B**	Yield **240 / 243**
1	$C_6H_{13}B(OH)_2$	A	49	Observed on TLC
2	"	B	17	Observed on TLC
3	C_6H_{13}9-BBN	C	-	Complex mixture of Products
4	"	D	-	Complex mixture of Products
5	$C_6H_{13}BF_3K$	E	-	Only Products
6	"	F	-	Only Products
7	"	G	Ratio **240** : **243** (>10:1) by GC/MS	
8	$(C_6H_{13})_3In$	H	47	None
9	"	I	45	None
10	$C_6H_{13}BF_3K$	J	Ratio **240** : **243** (>10:1) by GC/MS	
11	PhB $(OH)_2$	C	85	None

[a] **Reaction Conditions**

A K_2CO_3 (2.73eq), THF reflux **B** Cs_2CO_3 (3 eq), THF reflux **C** K_3PO_4 (1.5 eq), 1,4-Dioxane, 85°C

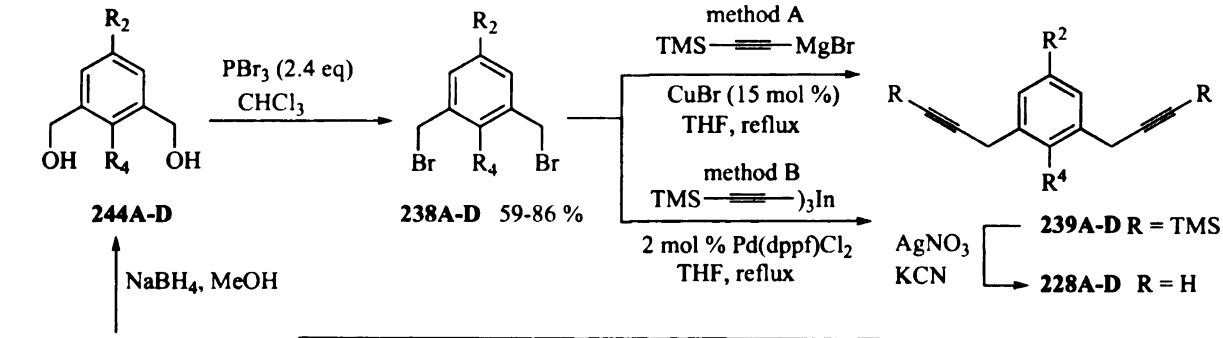
D $K_3PO_4.H_2O$, THF, reflux **E** Cs_2CO_3 (3.6 eq), THF:H_2O (10:1) reflux **F** Cs_2CO_3 (3.6 eq), THF, reflux

G K_2CO_3 (3.6 eq), K_3PO_4(3 eq) **H** THF reflux **I** THF / Dioxane (1:1), 100 °C **J** K_3PO_4(3.6 eq), THF, reflux

[b] Reactions in entries 1-3, 5-7 and 10 were carried out using 10 mol % $Pd(dppf)Cl_2$
Reaction in entry 4 was carried out using 2 mol % $Pd(OAc)_2$, 1 mol % (S)-PHOS and those in entries 8, 9 were carried out using 10 mol % $Pd(PPh_3)_2Cl_2$. Reaction in entry 11 was carried out using 2.5 mol % of Pd $(PPh_3)_4$

Bromomethyl arene **238D** could be obtained from 4-phenyl phenol in a straightforward manner and the details can be found in the experimental section. A second cross coupling of these substrates using either method A or method B yielded the bis-trimethylsilyl substituted diynes **239A-D** in high yields from which desilylation could be accomplished using silver nitrate to provide the bis-propargyl arenes **228A-D** (Table 3.2).

Table 3.2 Synthesis of bis-propargyl arenes



series	R^2	R^4	Method	Yield, % 239	228
A	Me	OMe	B	80	91
B	Me	n-C_6H_{13}	A	73	73
C	Me	Ph	A	71	77
D	Ph	OMe	B	77	90

3.3 Synthesis of bis-carbene complexes

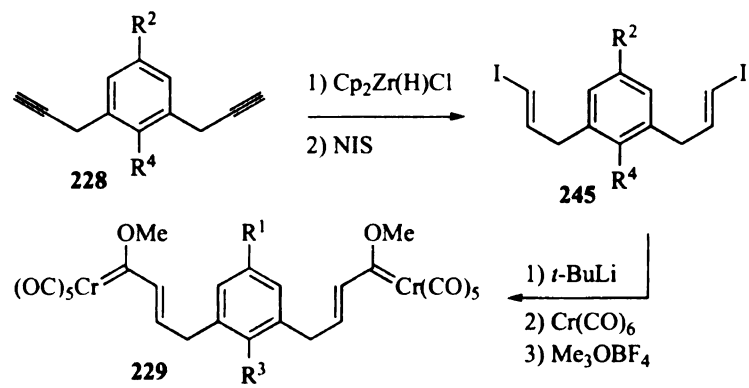


Table 3.3. Synthesis of bis-carbene complex 229

R^2	R^4	**245**	% yield **245**	R^1	R^3	**229**	% yield **229**
Me	OMe	**245A**	86	Me	OMe	**229A**	36
Me	n-C_6H_{13}	**245B**	77	Me	n-C_6H_{13}	**229B**	44
Me	Ph	**245C**	73	Me	Ph	**229C**	47
Ph	OMe	**245D**	78	Ph	OMe	**229D**	32

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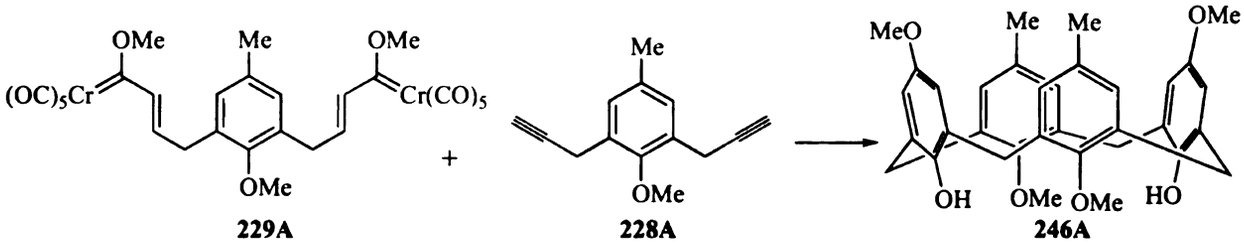
Hydrozirconation of the bis-propargyl arenes **228** using Schwartz's reagent[105] followed by iodination resulted in the formation of bis-*trans* vinyl iodides **245** in excellent yields which could be converted to the bis-carbene complexes **229** following the Fischer procedure (Table 3.3). Improved yields of the carbene complexes were not obtained by using the bis-*trans* bromo analogs.

3.4 Triple annulation: Effect of solvent, temperature and concentration

Since the efficiency of formation of phenols from the benzannulation reaction of Fischer carbene complexes and alkynes is known to be very sensitive to the reaction conditions as discussed earlier (See Section 2.2.2.2), a careful investigation of the effect of various reaction parameters on formation of ABAB calix[4]arene **246A** was undertaken in the reaction of bis-carbene complex **229A** with diyne **228A** (Table 3.4). Consistent with the general trends observed in the reactions of alkenyl carbene complexes and alkynes, only minor solvent effects were observed in this reaction as shown in entries 1-5. The non-polar non-coordinating solvent benzene afforded a lower yield (26 %) of the product compared to polar non-coordinating solvents such as ethylene dichloride (36 %). Polar coordinating solvents did not influence product yields (Entries 1 and 2). The absence of a significant solvent effect suggests that solvent coordination to the metal does not cause a shift in product distribution in the triple annulation process. This is in contrast to the observations of *p*-cyclophane formation via an intramolecular benzannulation (Scheme 2.21). No other cyclic oligomers (i.e., Calix[8]arene, Calix[12]arene etc.) were detected in any of these reactions. TLC analysis of these reactions revealed only a single mobile spot with some amount of baseline material. Analysis of the crude ^{1}H NMR of these reactions revealed only the presence of the calix[4]arene **246A**. Further studies

revealed that higher reaction temperature is optimal. Significantly lower product yields and longer reaction times were observed at lower temperatures. Since the macrocyclization involves the intramolecular benzannulation of intermediate carbene complex **248**, it is not suprising that it is sensitive to concentration. The yield drops to 16 % at 0.025M and could not be improved by adding a mixture of carbene complex and alkyne to hot 1,2-dichloroethane (Entry 11).

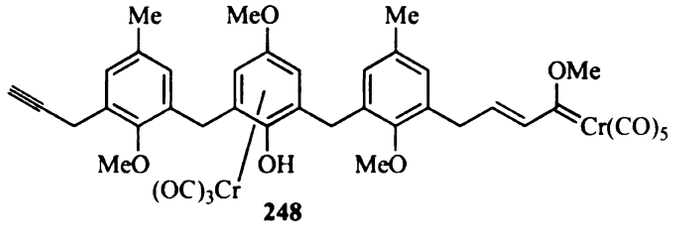
Table 3.4 Solvent, temperature and concentration effect on triple annulation



229A **228A** **246A**

			% Yield		
Entry	Solvent	Temperature (° C)	**246 A**	Concentration	Reaction time
1	Tetrahydrofuran	100	28	0.0025	50 min
2	Acetonitrile	100	29	0.0025	20 min
3	Benzene	100	26	0.0025	3h
4	1,4 - dioxane	100	30	0.0025	40 min
5	**1,2 - dichloroethane**	**100**	**36**	**0.0025**	**20 min**
6	"	83	33	0.0025	90 min
7	"	50	25	0.0025	> 2 d
8	"	83	32	0.0025 [a]	30 min
9	"	83	16	0.025	50 min
10	"	83	17	0.025 [a]	8-10 h
11	"	83	8	0.25 [a]	1h

a) Performed by syringe pump addition



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3.5 Calix[4]arenes with ABAB and ABAC substitution pattern – Exploration of substrate scope

Having determined the optimal conditions for synthesis of calix[4]arene **246A**, the reaction was screened for preparation of calixarenes with ABAB and ABAC substitution patterns by appropriate combination of the diyne **228** and bis-carbene complex **229** in the triple annulation process.

As shown in Table 3.5, the yields in all the cases range from 30-41% except in entries 2 and 7.[106] The examples in entries 3-6, 8 and 9 further illustrate the flexibility of this methodology in the preparation of either inner or outer-rim phenyl substituted calixarenes.

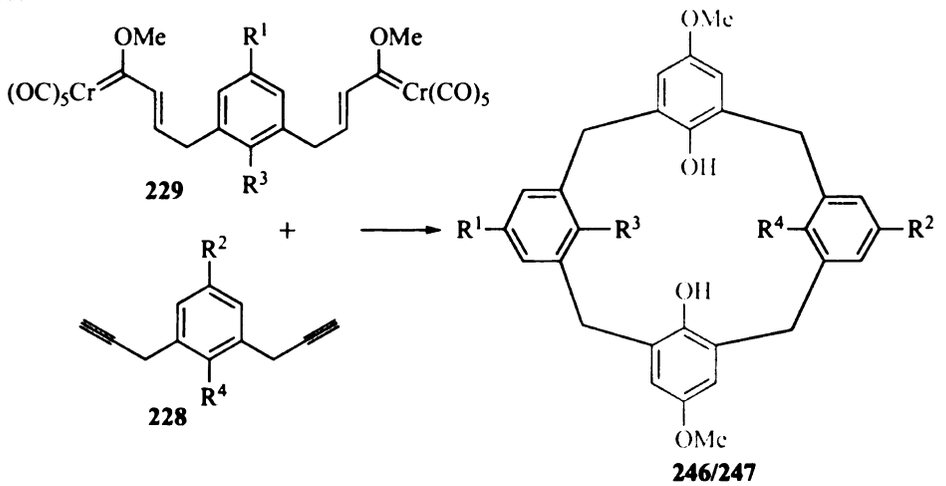

Table 3.5 Triple Benzannulation of Complex **229** and Diyne **228**.[a]

entry	complex	R^1	R^3	Arene **228**	R^2	R^4	**246/247**	% yield
1	**229A**	Me	OMe	**228A**	Me	OMe	**246A**	36
2	**229B**	Me	*n*-C_6H_{13}	**228B**	Me	*n*-C_6H_{13}	**246B**	22
3	**229C**	Me	Ph	**228C**	Me	Ph	**246C**	35 [b]
4	**229D**	Ph	OMe	**228D**	Ph	OMe	**246D**	41
5	**229A**	Me	OMe	**228C**	Me	Ph	**247A**	31 [c]
6	**229D**	Ph	OMe	**228C**	Me	Ph	**247B**	35 [d]
7	**229A**	Me	OMe	**228B**	Me	*n*-C_6H_{13}	**247C**	22 [e]
8	**229B**	Me	*n*-C_6H_{13}	**228D**	Ph	OMe	**247D**	35 [e]
9	**229A**	Me	OMe	**228D**	Ph	OMe	**247E**	40

[a]All reactions were carried out in 1,2-dichloroethane at 100 °C at 2.5 mM in **229** with 1.0 equivalent of alkyne **228** for 20 to 40 minutes. [b] Isolated as a separable 1.7 : 1 mixture of 2 conformers. [c] Isolated as a non-separable 3.8 : 1 mixture of 2 conformers. [d] Isolated as a non-separable 3.3:1 mixture of 2 conformers. [e] Isolated as a non-separable 7.9 : 1 mixture of 2 conformers

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Some of the calix[4]arenes were obtained as a mixture of different conformers and their structural elucidation will be discussed below.

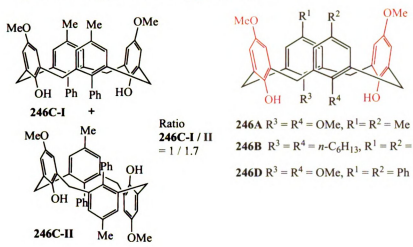
3.6 Conformation elucidation

3.6.1 Calixarenes with ABAB substitution pattern

The conformational elucidation of calixarenes was accomplished by use of X-ray crystallography and the Mendoza rule by correlating ^{13}C chemical shifts of the four known conformers (See Section 1.3). Based on a comprehensive spectroscopic examination of several symmetrical calix[4]arenes the ^{13}C chemical shifts of the corresponding methylene carbons between adjacent aryl rings that are syn to each other in the macrocylic array must be 31 ppm for cone.[29] When the adjacent aryl rings are *anti*, the chemical shift of the methylene carbons has been found to be at 37 ppm. Since the partial cone and 1,2- alternate would have two *syn* and two *anti* aryl rings, the observed ^{13}C resonances were at 31 and 37 ppm. Consistent with this rule, the ^{13}C chemical shifts of the methylene carbons in calix[4]arenes **246A, 246B, 246D** were at 31.67, 31.53 and 31.73 ppm. Based on this observation as well as the single crystal X-ray analysis of **246A** these were assigned the cone conformers with C_2 symmetry. It is intriguing to note that the conformational preferences of the macrocycle are dependent upon the size of the alkyl group as in contrast to the dihexyl substituted calix[4]arene **246B**, the dimethyl analog **236** (Fig 3.2) was reported to exist only as the 1,3-alternate conformer. The chemical shifts of the methyl groups at δ 1.3 ppm in the latter suggested that they are under the shielding effect of neighbouring aryl rings as would be expected in a 1,3-alternate conformation in contrast to the corresponding shifts of the benzylic hydrogens in the former at 2.52 ppm.

The diphenyl substituted calix[4]arene **246C** was isolated as a separable mixture of two conformers. X-ray determined the structure of each and it was found that the minor isomer **246C-I** crystallized in the cone conformation with C_2 symmetry whereas the major isomer **246C-II** crystallized in the 1,2-alternate conformation with C_i symmetry (Fig 3.3). However, inconsistent with the Mendoza rule is the observation that the chemical shifts of the methylene carbons in **246C-I** and **246C-II** resonate at 36.12 and 36.95 ppm respectively. This suggested that the 1,3-alternate conformation may be preferred in chlroform-*d* as the solvent for these compounds. Further spectral differences between **246C-I** and **246C-II** existed in the aromatic region that showed only four peaks 4, 2, 2, 2 hydrogens respectively in the former whereas the latter showed five sets of aromatic hydrogens integrating to two hydrogens each. Thus, it was conceived that rotation of the phenyl group about the biaryl axis was completely surpressed at room temperature for **246C-II** but not in **246C-I**. At this stage, NOE analysis was performed on both these compounds to determine the conformational preferences in solution. It was indeed quite surprising to note that in both the cases the same conformation was observed in solution as in the solid state. Thus, clearly inner rim phenyl substituted calix[4]arene **246C** is an exception to Mendoza rule as 1,3-alternate conformer was predicted on the basis of observed ^{13}C chemical shifts. This possibly arises due to the elongation of the $C(sp^2)$-$C(sp^3)$-$C(sp^2)$ bond angles due to the inclusion of the two phenyl rings within the smallest diameter of the macrocycle. The hydrogen bonding is completely disrupted as indicated by the ^1H NMR chemical shifts at 4.12 for **246C-I** and 4.24 ppm for **246C-II** respectively as well as by IR (3472 & 3509 cm^{-1}).

Figure 3.3 Conformations of calix[4]arenes 246A-D



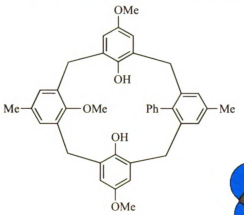
3.6.2 Conformations of calix[4]arenes with ABAC substitution pattern

3.6.2.1 Phenyl substituted Calix[4]arenes 247A and 247B

The conformation of calix[4]arene **247A** with three heteroatom substituents in the inner rim was next analyzed. The ^{1}H NMR spectra displayed a complex pattern of signals that definitely could not be assigned to a single compound. The presence of well defined sharp peaks in chloroform-*d* as solvent ruled out the possibility of rapid inter-conversion processes between conformers on NMR time scale. Careful examination of the spectra revealed that at-least two different compounds were present in $CDCl_3$ solution in a ratio of 3.8:1. These two compounds were not separable by thin-layer chromatography as well as by high-pressure liquid chromatography. The MS analysis of the mixture of these two compounds showed M+ ion at m/z 586 suggesting that they might be stereoisomers. The aromatic region for both these compounds showed a pair of doublets (J =3 Hz, i.e., meta-coupling) and a pair of singlets for a total of eight protons each. Based on this information 1,2-alternate **249** was ruled out as possible structure for either of these two compounds, as it would be expected to have eight in-equivalent aromatic hydrogens

(Figure 3.4). Intrigued by the possibility of finding a conformer with C_1 symmetry, extensive molecular modeling and examination of the ^{1}H NMR spectra was undertaken.

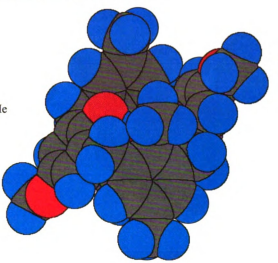
Figure 3.4 Energy minimized structure of 1,2-alternate conformer of 247A



247A

Conformers I and II

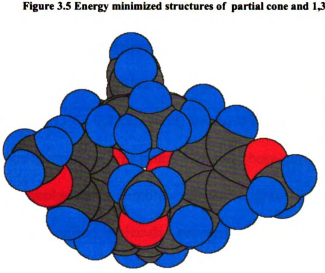
Ratio I : II = 3.8:1



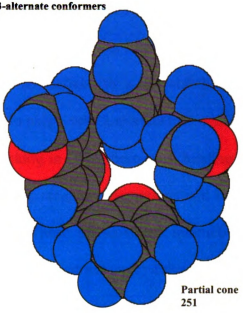
249

A careful scrutiny of the aromatic region revealed that the phenyl group showed five different hydrogens due to the hindered rotation about the biaryl bond. A rather puzzling observation was made during spectroscopic analysis when it was found that one of the *ortho*-aryl hydrogens of the phenyl group in major isomer was shifted upfield ($\delta_{\text{ortho Ar-H}} = 4.78$ ppm). Such unusual chemical shifts are observed in situations involving close edge-face association of two adjacent aromatic rings due to ring current shielding. While the 1,2-alt conformer shown above would possibly have such an interaction between the phenyl substituent and the aromatic ring of the calix backbone, it had already been ruled out as a possible structure due to its lack of symmetry. Thus, four other possible structures are proposed of which three are partial-cone conformers **250-252** differing in the aryl ring that is flipped with respect to the annulus and the last is 1,3-alternate **253** (Figure 3.5).

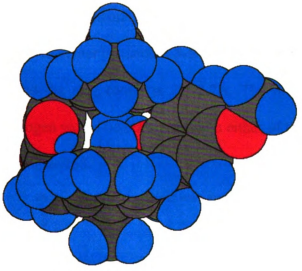
Figure 3.5 Energy minimized structures of partial cone and 1,3-alternate conformers



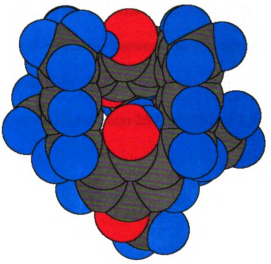
Partial cone 250



Partial cone 251



Partial cone 252



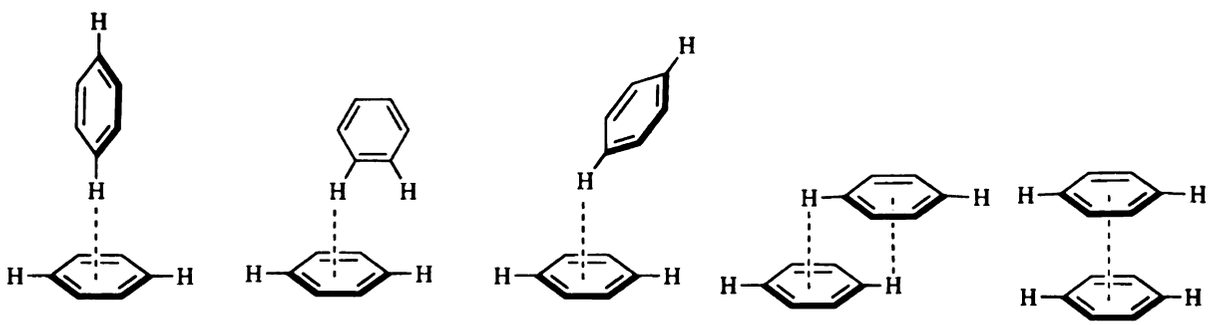
1,3-alternate 253

The chemical shifts of the methoxy groups in the *p*-alkoxy phenols (s, 6H) for the major isomer was at $\delta = 3.46$ whereas in the minor was at $\delta = 3.78$ ppm. On the other hand, the methoxy group in the anisole (s, 3H) was unaffected in both the isomers at 3.84 and 3.86 ppm respectively. This difference suggests that the two *p*-methoxy phenols are aligned parallel to each other and are under the influence of ring current shielding while

one of the other two arenes may be oriented anti-parallel. Thus, it seemed reasonable that paco **252** with C_1 symmetry was not the major conformer observed in solution.

Weak attractive aromatic interactions are often defined by a low stabilization enthalpy (1.6± 0.2 kcal/ mol) and have been known to play a very important role in many diverse areas such as protein folding, base-pair stacking in DNA, host-guest binding in supramolecular assemblies, crystal engineering, drug receptor interactions and other widely studied molecular recognition processes.[107] These non-covalent interactions typically can be classified into a) T-shaped edge to face structure b) Edge tilted T-structure c) Face tilted T-structure d) Offset parallel stacking e) Face to face (π-stacking) (Figure 3.6). Theoretical studies favor T-shaped structure for benzene dimer wherein the center-to-center distance is 5-5.2Å and the perpendicular distance between the interacting H and the ring center is 2.5-2.7Å. The observed upfield shift of the *ortho* aromatic hydrogen would be consistent with either of the three structures paco **250** and **251** or 1,3-alt isomer **253**.

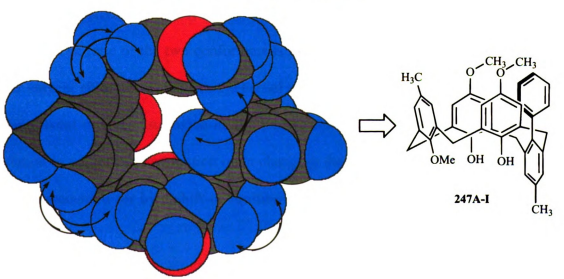
Figure 3.6 Typical modes of weak aromatic interactions



It would be reasonable to expect that the unexpected upfield chemical shifts could be explained by offset parallel π-stacking in the latter whereas edge-face interactions between opposite arene rings in the former. Neverthless, partial cone conformer (Paco

251) appeared to be the most likely candidate based on the shielding effect experienced by the two-methoxy groups. The observed chemical shift at δ 3.46 is likely an average of two chemical shifts that correspond to its *in* and *out* orientations. An *in* orientation would represent the situation when the two methyl groups are pointing into the shielding cone of the aryl ring and hence would be shifted upfield relative to an *out* orientation wherein the two methyl groups would be far away from the phenyl group to experience any shielding effect. Paco **250** with C_s symmetry is disfavored, as ring current would shield the methoxy group of the anisole ring because it is pointing inside the cavity. At this juncture, NOE studies were performed on the major conformer, which confirmed that it was indeed the paco **251** with C_s symmetry (Figure 3.7). In contrast to the major isomer, the minor isomer gave only three peaks for the phenyl group integrating to a total of five hydrogens, which indicated free rotation about the biaryl bond. The corresponding proton spectrum of the minor isomer was markedly different with all the aromatic hydrogens of the calixarene falling in the expected chemical shift range between δ 6.34 and 6.65 ppm.

Figure 3.7 NOE's observed on major isomer

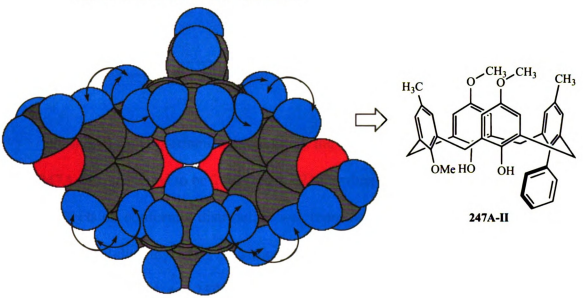


247A-I

paco-**251**

In contrast to the upfield shift observed for the *ortho*-phenyl hydrogen in the major isomer, the corresponding proton in the minor isomer was shifted extremely downfield at 7.92 ppm. Furthermore, the phenolic hydrogens were shifted upfield relative to the major isomer (5.01 vs 5.75) indicating that they might be under the shielding cone of a neighbouring aryl ring.

Figure 3.8 NOE's observed on minor isomer



254 **247A-II**

NOE analysis in $CDCl_3$ indicated that the minor conformer to be the cone **254** (Fig 3.8). The ratio of the two conformers is highly dependent on the solvent. The non-polar solvent chloroform-*d* favors the partial cone conformation **247A-I** whereas for the polar solvent dimethyl sulfoxide-d_6 the partial cone is less favored (Table 3.6). The variation in conformer distribution upon changing the solvent from $CDCl_3$ to DMSO-d_6 may be accounted for by a shift in equilibrium towards the conformer with the higher dipole.

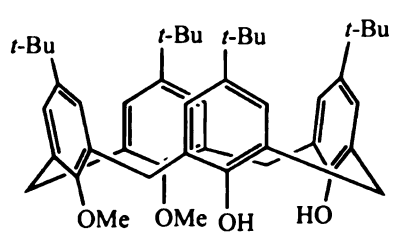
Table 3.6[a] Solvent effect on conformer distribution in 247A.

Entry	Solvent	Temperature °C	Ratio paco-I: cone-II	Dielectric constants of non-deuterated solvents
1	toluene-d_8	25	2.63:1	2.38
2	$CDCl_3$	-30	3.94 :1	4.81
		25	3.9 : 1	
		50	3.4 : 1	
3	Acetone-d_6	25	2.7: 1	20.7
4	DMSO-d_6	25	1.7:1	46.7

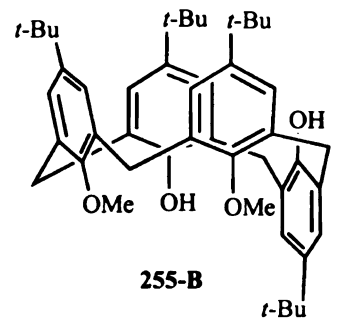
a) Ratio determined from the relative integral values of methyl hydrogens in major and minor isomer

From molecular mechanics calculations, the calculated dipole moments for **247A-I** and **247A-II** were found to be 2.54 D and 3.71 D, which validate this rationale. Similar solvent effects on conformer distribution was reported by Reinhoudt in 1992, wherein calix[4]arene 1,2-dimethyl ether was found to exist as a mixture of *syn* (cone) and *anti* (paco) conformers **255A** and **255B** the ratio of which was dependent upon the solvent: 4.3:1 (CS_2), 3.0:1 ($CDCl_3$), 2.0:1 ($CDCl_2CDCl_2$) and 1.2:1 (CCl_4) (Figure 3.9).[108]

Figure 3.9 *Syn* and *Anti* Conformations of 1,2-Dimethyl ether 255



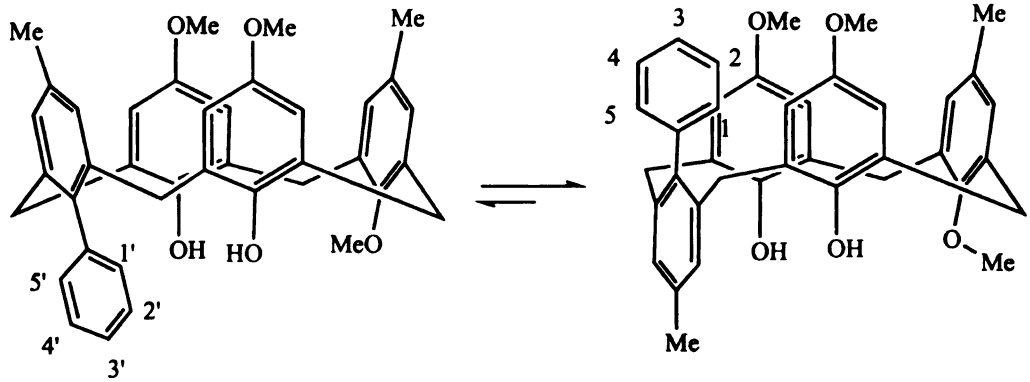
255-A



255-B

Analogous studies on the rate of conformational inter-conversion in tetrahydroxy derivatives has shown that the barrier is significantly reduced in polar solvents and such an effect has been attributed to the weakening of hydrogen bonding in calixarene. Thus, it

may be reasonable to postulate that changing the solvent to dimethyl sulfoxide results in disruption of hydrogen bonding and thereby inter-conversion between two conformers occurs to a reasonable extent to afford a new equilibrium mixture of 1.7:1. The presence of a weak hydrogen bond in either of these two conformers was shown by IR spectroscopy in dichloromethane wherein a broad signal for the hydroxyl groups were observed at higher wave numbers ~3499 cm^{-1}.



247A-II cone **247A-I** partial-cone

Table 3.7 Chemical shift of Aromatic hydrogens of **247A** in DMSO-d_6 as solvent

Proton	Chemical shift	Multiplicity
H(1)	4.68	d
H(2)	5.27	t
H(3)	ND	t
H(4)	6.99	t
H(5)	6.74-6.79	d
H (1')	7.73	d
H (2')	7.26-7.29	t
H (3')	ND	t
H (4')	6.58-6.62	t
H (5')	6.74-6.79	d

This rationale was supported by an EXSY experiment, which showed that these two conformers were inter-converting in DMSO as the solvent at 50°C. The cross peaks from

the phenyl hydrogens in both the major and the minor isomer were carefully examined. It was found that the *ortho*-phenyl hydrogen in the major isomer (δ = 4.68) displayed two cross peaks, one of which could be attributed to the other *ortho*-phenyl hydrogen (δ = 6.74-6.79) and the other to the *ortho* hydrogen in the minor isomer (δ = 7.73). Similar cross peaks were observed for the other aromatic hydrogens in both the isomers (Table 3.7 & Figure 3.9). The next issue to be addressed was which of the two conformers of **247A** was the *thermodynamic* or *kinetically* favored product. A 1.7:1 mixture of the two conformers were heated to 90°C in DMSO-d_6 and subsequently cooled to 25°C with the spectra recorded at both temperatures. Based on the identical conformer distribution that was observed prior to and after the experiment as well as the results from the solvent effect suggest that their ratio at ambient temperature depicts the equilibrium population. In order to determine the relative energies of the two conformers, molecular mechanics calculations were performed using MM94 force field. The relative energy of the cone isomer was 144.6 Kcal / mol whereas that of the partial cone isomer was 139.87 Kcal / mol indicating that the partial-cone isomer is thermodynamically more stable by 3.78 Kcal / mol. The results of the computational study are in agreement with the experimental observations described herein but clearly over-estimates the energy difference between the two compounds as this would represent a ratio of > 200:1.

Based on comparison of the chemical shifts of the methylene carbons (δ 31.33, 39.98 - major, 32.06, 36.10 - minor) with **247A**, the major and minor isomers of **247B** were deduced to be a partial cone and a cone with C_s symmetry (Ratio of paco:cone = 3.9:1).

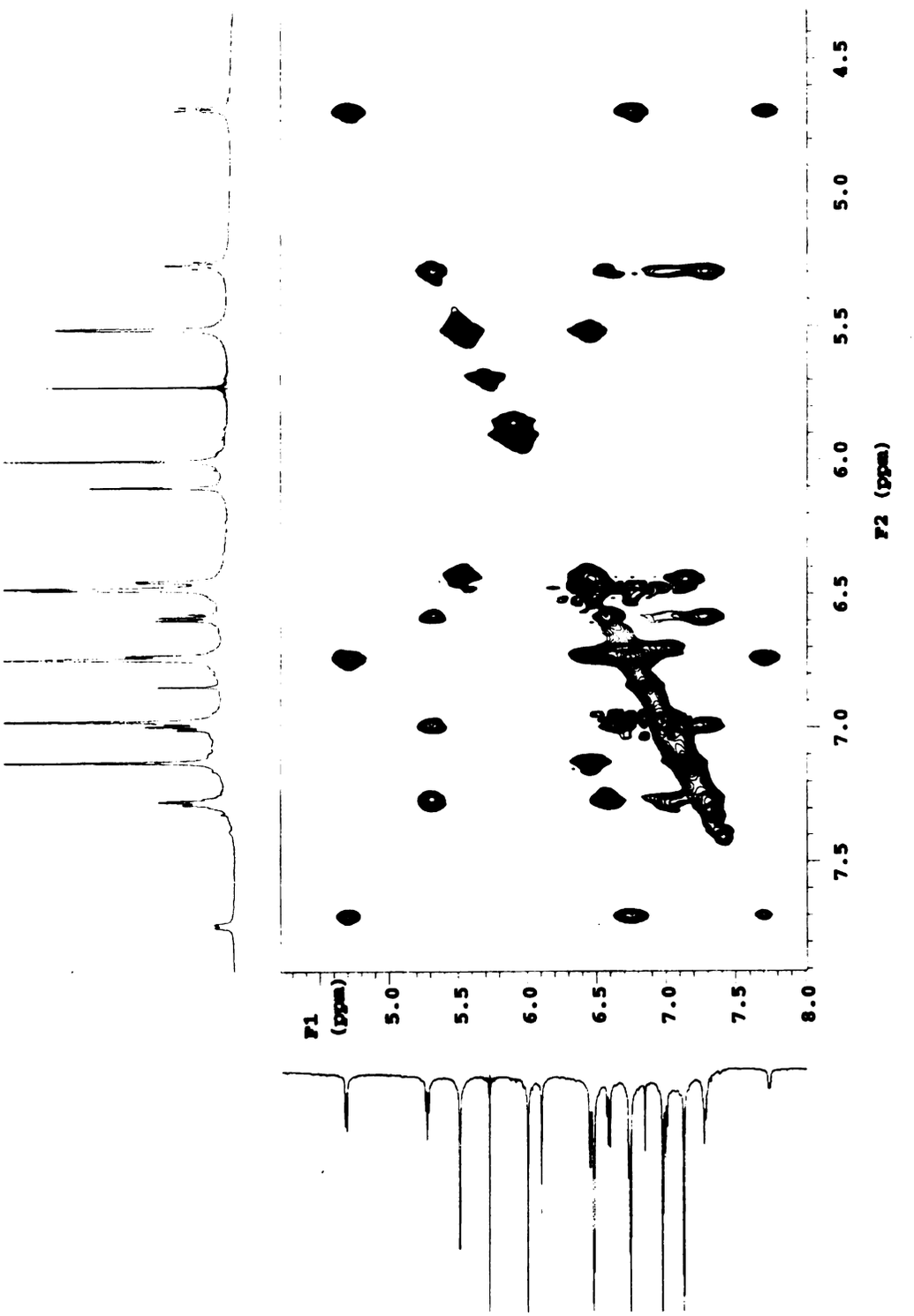


Figure 3.10 600 MHz ^{1}H EXSY spectrum (δ 4.5 – 8.0 ppm) of **247A** in DMSO-d_6 at 50 °C.

The observed chemical shifts for the minor isomer of **247B** are consistent with Mendoza rule for unsymmetrical calix[4]arenes wherein two of the methylene carbons such as in a cone conformer are magnetically inequivalent giving rise to two different chemical shifts at 30.9, 31.1. Again as observed before for calix[4]arene **247A**, the major isomer of **247B** showed the presence of five different aromatic hydrogens indicating restricted rotation about the biaryl bond whereas the minor isomer showed only three peaks. One of the *ortho* phenyl hydrogens in the major isomer was again found to be at 4.78 ppm influenced by the shielding effect of the opposite aryl ring as well as the methoxy groups (s, 6H) which were observed to resonate at 3.46 ppm.

3.6.2.2 Alkyl substituted calix[4]arenes 247C, 247D

Complete structural identification of the alkyl substituted unsymmetrical calix[4]arenes **247C** and **247D** could not be accomplished as the minor product was present in only small amounts (7.9:1). NOE analysis was again extremely valuable in deducing the structure of the predominant product as the cone for **247C** with C_s symmetry. The benzylic hydrogens were found at 3.29 and 3.35 ppm in **247C** and **247D** indicated that they are not under the shielding effect of adjacent aryl rings and the hydroxyl groups at 5.63, 5.78 ppm suggested the presence of a weak intramolecular hydrogen bond. The structure of the major conformer of **247D** was assigned by similarity of the observed chemical shifts as the cone whereas that of the minor isomer was not deduced.

3.6.2.3 Outer rim modified calix[4]arene 247E

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In contrast to the inner rim modified calix[4]arenes **247A** and **247B**, the calix[4]arene **247E** with phenyl and methyl substituents at the outer rim adopted a cone conformation in solution based on the ^{13}C NMR shifts for the methylene carbons at 31.54 and 31.72 ppm. Based on comparison of the solution structures for **246A** and **247E** as well as the examples discussed earlier, it is reasonable to postulate that the outer rim substituent does not affect the conformational preferences of the calix skeleton.

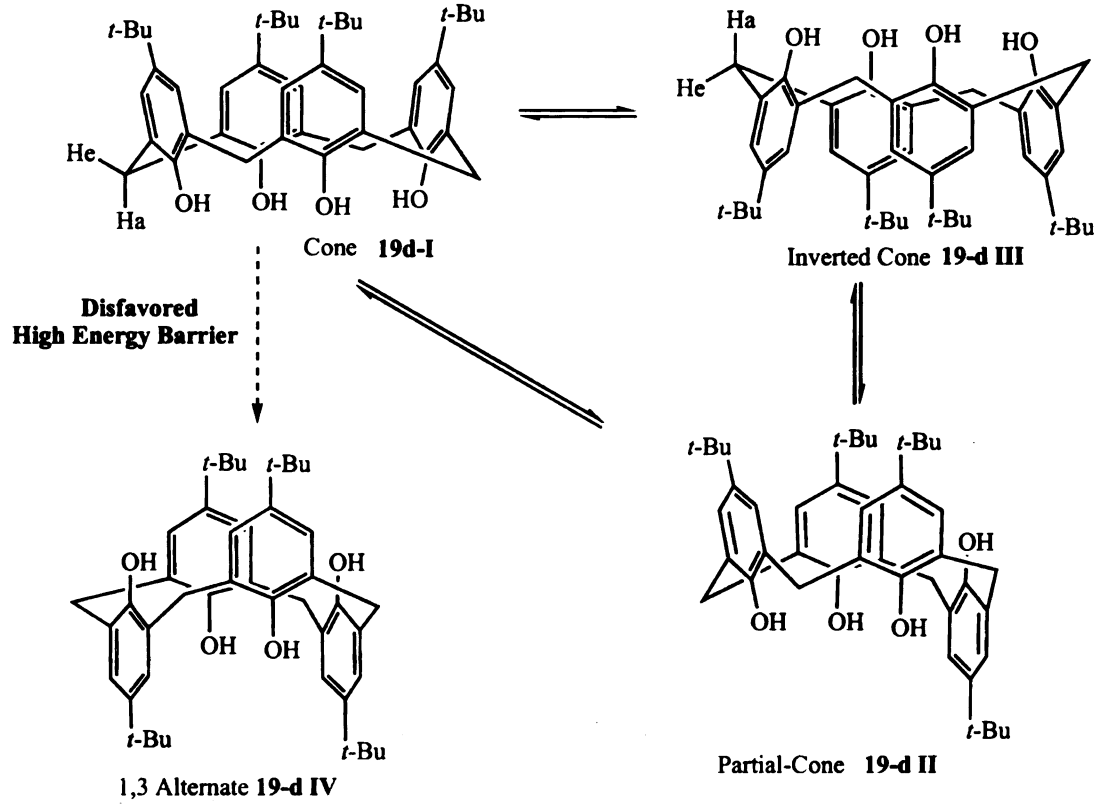
3.6.3 Mechanism of conformational interconversion

At present, two different mechanisms have been proposed for the conformational inversion in tetrahydroxy calixarenes.[23] Analysis of the intermediates and evaluation of the energetics of these proposed pathways have been accomplished over the past decade with the help of extensive theoretical studies.[109] A "continuous-chain" pathway was proposed by Gutsche to account for the cone-to-cone inversion whereby the methylene protons coalesced from a pair of doublets at low temperature to singlet at above room temperature. They postulated that the aryl groups would swing through the annulus in sequence possibly via the intermediacy of a skewed 1,2-alternate complex. Based on analysis of space filling models, it was expected that some hydrogen bond stretching or disruption of single hydrogen bond would be necessary to reach this transition state.

An alternative pathway that was invoked by Kammerer involved a stepwise rotation of the opposite or adjacent aryl group through the annulus to result either in the formation of partial cone or 1,3-alternate conformer. Either of these intermediates was then expected to revert either to the cone or the inverted-cone isomer. Now, there is significant evidence that cone to inverted-cone proceeds in a stepwise manner with the

partial cone conformer playing a key role (Figure 3.11).[110] Recently, Shinkai has also proposed similar pathways for calixarenes lacking free hydroxyl groups.[111]

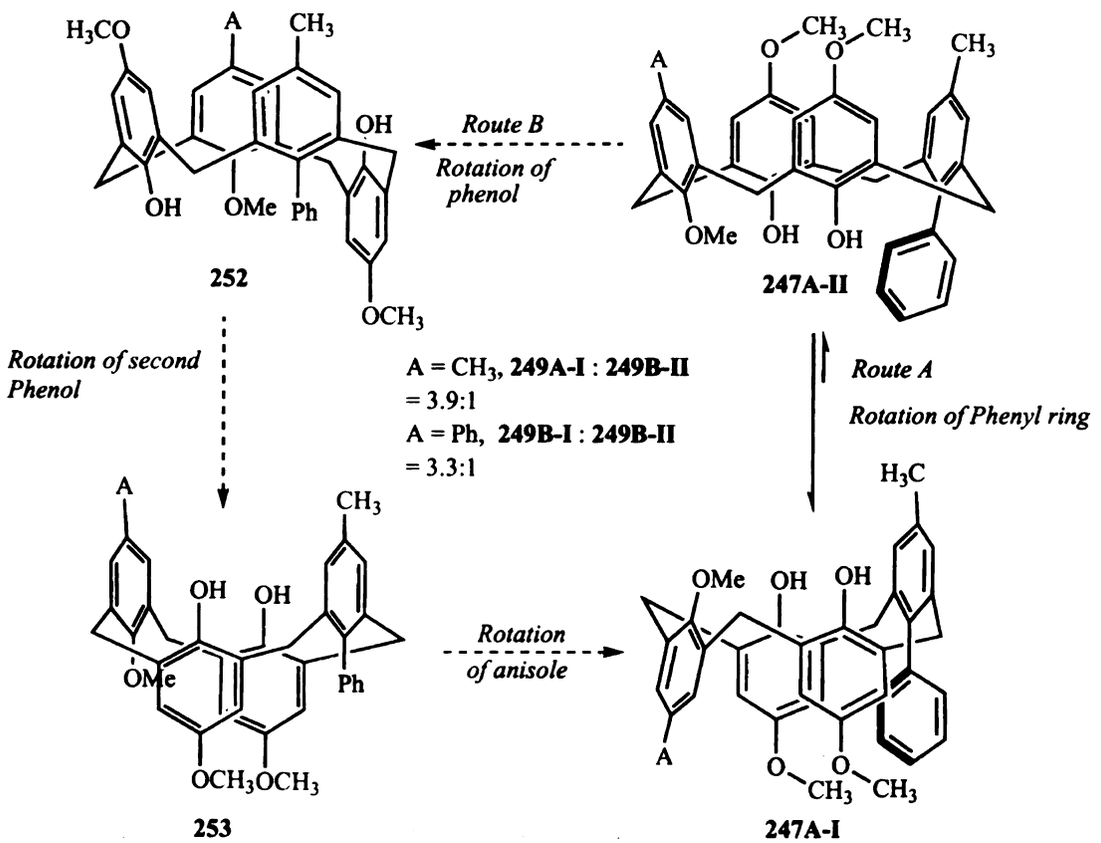
Figure 3.11 Currently accepted pathway for conformational ionversion



Analogous to these proposed mechanisms, the conformational ring flip from cone to partial cone that has been observed in the case of unsymmetrical calix[4]arene **247A** could possibly occur via at least two different pathways. The first route A would involve the direct rotation of the phenyl ring about the annulus while the second path B would be stepwise with the formation of partial cone **252** and then 1,3-alternate conformer **253** via sequential rotation of the two phenolic rings and subsequent rotation of the methoxy group of the anisole about the annulus. Considering that the rotation of methoxy group through the annulus has a high activation barrier in partially alkylated calixarenes, it is presumed that similar steric barrier would be encountered in the process involving a phenyl group. The hydroxyl moieties forming hydrogen bonds will have to make place

for the phenyl group. This will elongate the OH.....O distances and either weaken or completely disrupt the intramolecular hydrogen bonding (Scheme 3.5).

Scheme 3.5 Mechanism of conformational exchange



The ring flip of the first *p*-alkoxy phenol leading to the formation of partial cone isomer **252** would likely occur with minimal weakening of hydrogen-bonding and the barrier for the second rotation would also be significantly low. Due to the lack of hydrogen bonding in **253** caused by the protrusion of the bulky phenyl substituent in the smallest diameter of the annulus formed by the hydroxy groups, the methoxy group would encounter minimal resistance in accomplishing the desired rotation to give the observed calix[4]arene **247A-I** at room temperature. If Route A was the viable pathway, it was expected that replacement of the outer rim methyl group at the distal arene ring with a larger substituent (A= Ph) would interfere with the rotational process and thereby would likely lead to a mixture of separable cone and partial cone conformers. As the

calixarene **247B** was also found to exist as an inseparable 3.3:1 mixture of partial cone and cone conformers, Route B is believed to be operative in the inter-conversion process.

3.7 Summary

In summary, the triple annulation method has been developed as a new route for the synthesis of calix[4]arenes with C_2 symmetry. Although the objectives in this regard was to exploit the methodology for direct synthesis of calix[4]arenes with C_1 symmetry, none were found by introducing alkyl or aryl substituents in the inner rim. Alternative approaches to access these class of calix[4]arenes will be mentioned in Chapter 6. In general, the effect of introducing non-heteroatom substituents in the inner rim of calix[4]arene on the conformation was explored in detail wherein larger phenyl group introduces significant conformational rigidity to give a mixture of separable or inseparable conformers in certain cases. The overall process affords calix[4]arenes in which two of the adjacent arene rings are non-identical and the distal arene rings are identical and this inherent feature will be exploited in the synthesis of chiral calix[4]arenes which will be the subject of discussion in the following chapter.

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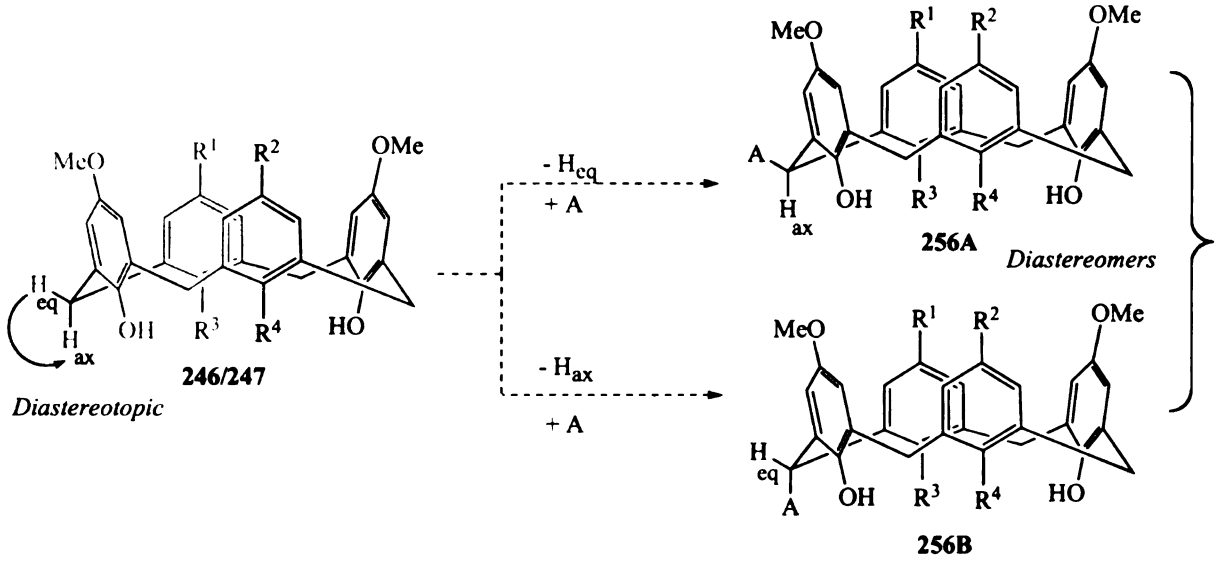
CHAPTER FOUR

CHEMO, REGIO, ENANTIO AND DIASTEREOSELECTIVE SYNTHESIS OF METHYLENE SUBSTITUTED CALIX[4]ARENES

4.1 Design of a new method for chiral calix[4]arene syntheses

In the preceding chapter it has been demonstrated that various calix[4]arenes with C_2 and C_S symmetry can be formed from the triple annulation of bis-carbene complexes and diynes. One of the most unique features of this strategy has been that the two adjacent arene rings in the macrocycle so generated are non-identical which thereby renders the methylene hydrogens diasterotopic (Figure 4.1).

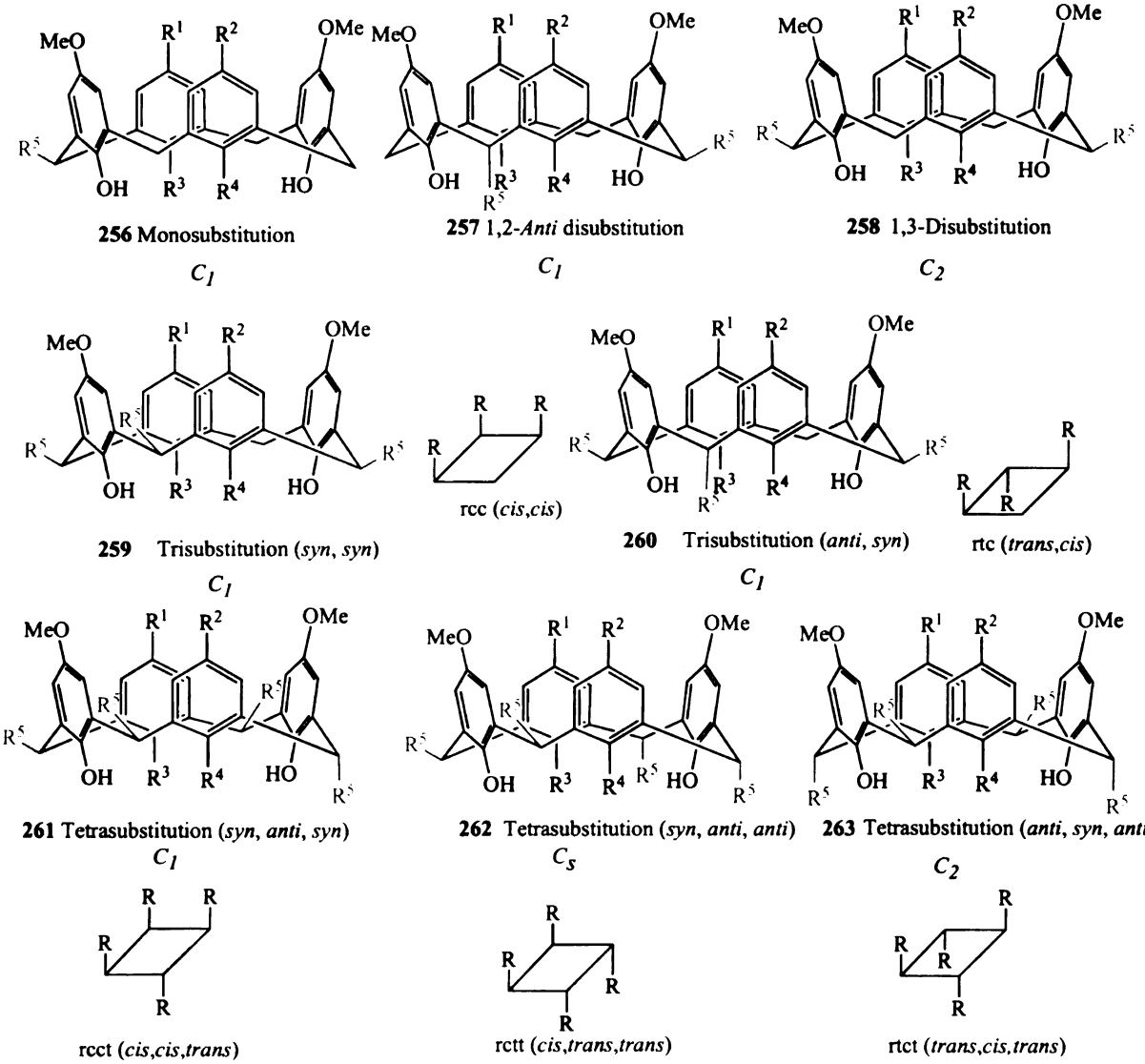
Figure 4.1 Stereoisomers resulting upon introduction of single substituent at the bridge



Thus, replacement of either the axial or the equatorial methylene hydrogens in **248/249** with a single substituent A would be expected to result in the formation of diastereomers **256A** and **256B** along with their enantiomers (not shown in the Figure). As a consequence, an increase in the degree of substitution at the methylene bridges drastically increases the number of possible stereoisomers that would result (See Section

1.6.1). Hence, the primary objectives in this regard were to not only devise an enantioselective approach but also to render the triple benzannulation process highly diastereoselective and regioselective for formation of specific stereoisomers of calix[4]arenes with different substitution patterns at the bridges. As illustrated below, introduction of a second substituent in calix[4]arene **256** would result in formation of regioisomeric calix[4]arenes **257** and **258** with 1,2-*anti* and 1,3-*syn* stereo-relationship of the substituent at the bridges possessing C_1 and C_2 symmetry.

Fig 4.2 Chiral calix[4]arenes 256-263 with C_1 and C_2 symmetry



256 Monosubstitution — C_1

257 1,2-*Anti* disubstitution — C_1

258 1,3-Disubstitution — C_2

259 Trisubstitution (*syn, syn*) — C_1

260 Trisubstitution (*anti, syn*) — C_1

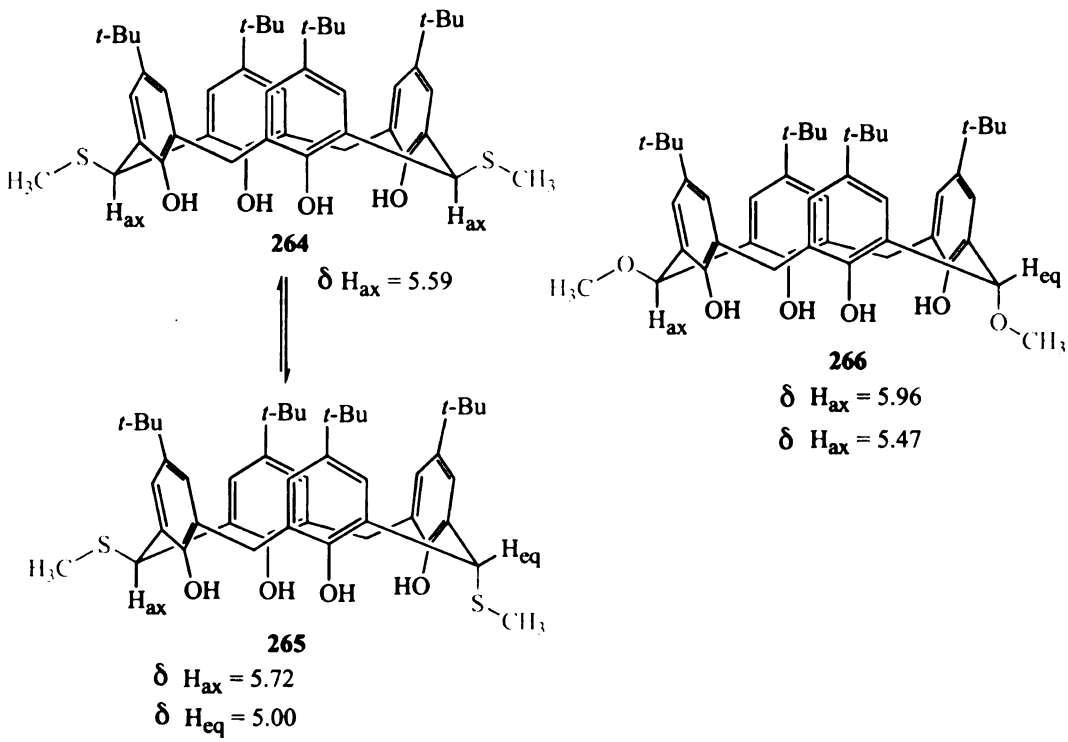
261 Tetrasubstitution (*syn, anti, syn*) — C_1

262 Tetrasubstitution (*syn, anti, anti*) — C_s

263 Tetrasubstitution (*anti, syn, anti*) — C_2

The two diastereomers of the trisubstituted analogs would be **259** and **260** with C_1 symmetry whereas those with tetrasubstitution would be **261, 262** and **263** with C_1, C_s and C_2 symmetry. The trisubstituted calix[4]arene **260** for example can be assigned either the stereochemical descriptors *anti*, *syn* or *rtc* indicating the relative *trans* and *cis* disposition of the substituents at the bridges. The relative stereochemical assignment for other methylene substituted calix[4]arenes are shown in Fig 4.2. The establishment of relative stereochemistry at the bridges was anticipated to be accomplished based on the known chemical shifts of the axial and equatorial hydrogens in alkoxy and thio substituted analogs **264-266** (Fig 4.3).[53]

Fig 4.3 Relative stereochemical assignment by correlation to thio and alkoxy substituted analogs 264-266

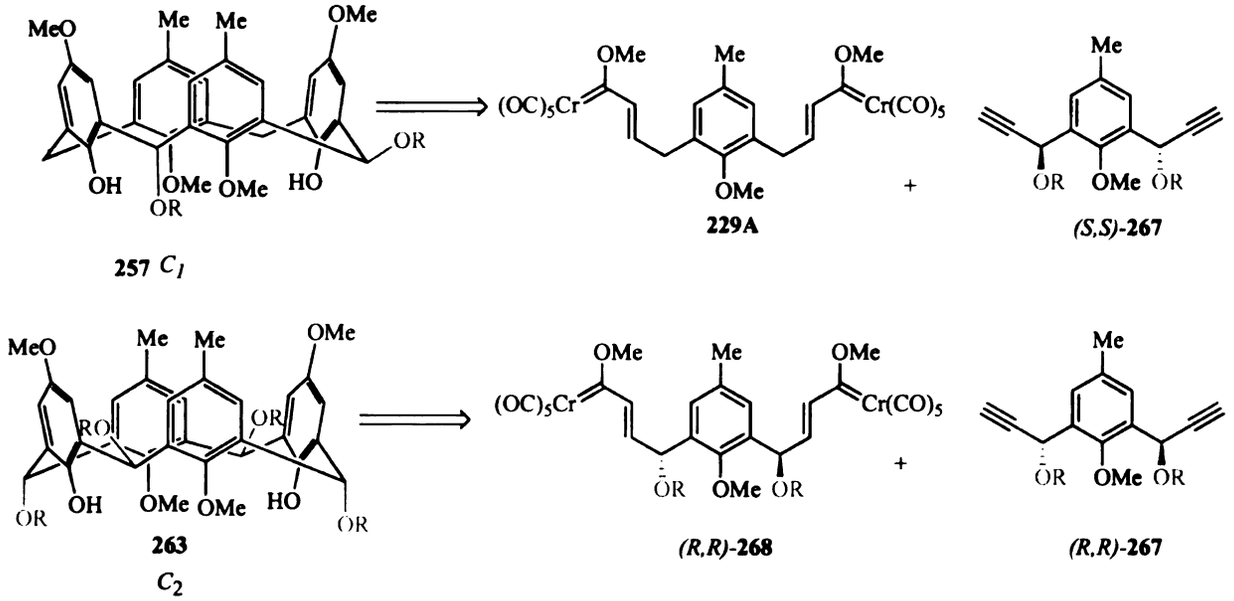


4.1.1 Triple annulation strategy towards di and tetrasubstituted Calix[4]arenes

As discussed in earlier chapters of this thesis, optically active calix[4]arenes with chiral centers at the bridges have not been previously reported. Our initial targets for this class of molecules are 1,2-dialkoxy calix[4]arene **257** and tetraalkoxy calix[4]arenes **261-**

263. The 1,2-dialkoxy calix[4]arene **257** with C_1 symmetry was envisioned to arise from the triple annulation reaction of non-chiral biscarbene complex **229A** and the C_2 symmetry element present in chiral bis-propargyl arene (*S,S*)-**267** whereas the tetrasubstituted calix[4]arene **263** with C_2 symmetry from the reaction of chiral C_2 symmetric biscarbene complex (*R,R*)-**268** with the bis-propargyl arene (*R,R*)-**267** (Scheme 4.1).

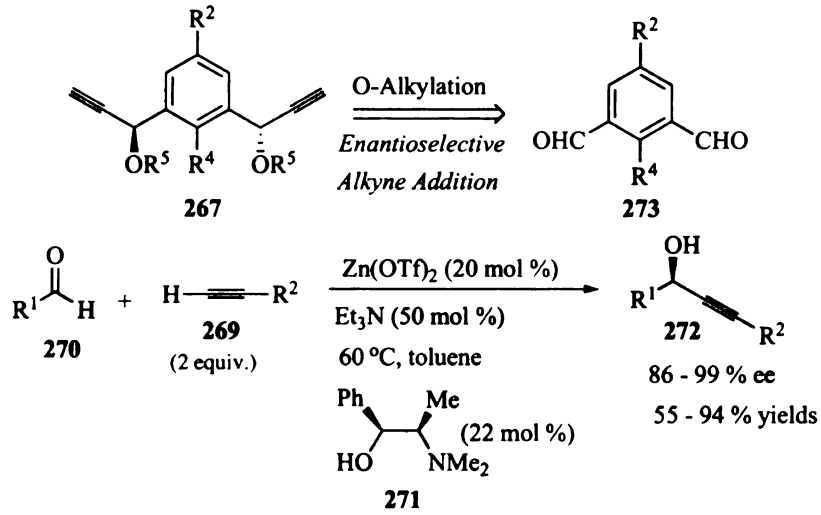
Scheme 4.1 General synthetic strategy toward 1,2-di and tetrasubstituted calix[4]arenes



4.1.1.1 Chiral bis-propargyl alcohols

The studies toward the calix[4]arenes **257**, **263** as well as the stereoisomers **261** and **262** began with devising synthetic routes toward chiral bis-propargyl alcohols. The most reasonable and practical approach in this regard was Carreira's method of asymmetric addition of alkyne **269** to aldehyde **270** in the presence of Zinc trifluromethanesulfonate as the Lewis acid and N-methyl ephedrine **271** as the chiral ligand to afford chiral propargyl alcohols **272** (Scheme 4.3).[112] Thus, asymmetric nucleophilic addition of a silyl alkyne **269** ($R^2 = SiR_3$) to aldehyde **273** followed by desilyation and alkylation was expected to furnish the required bis-propargyl ether **267**.

Scheme 4.2 Carreira's method of asymmetric alkyne addition



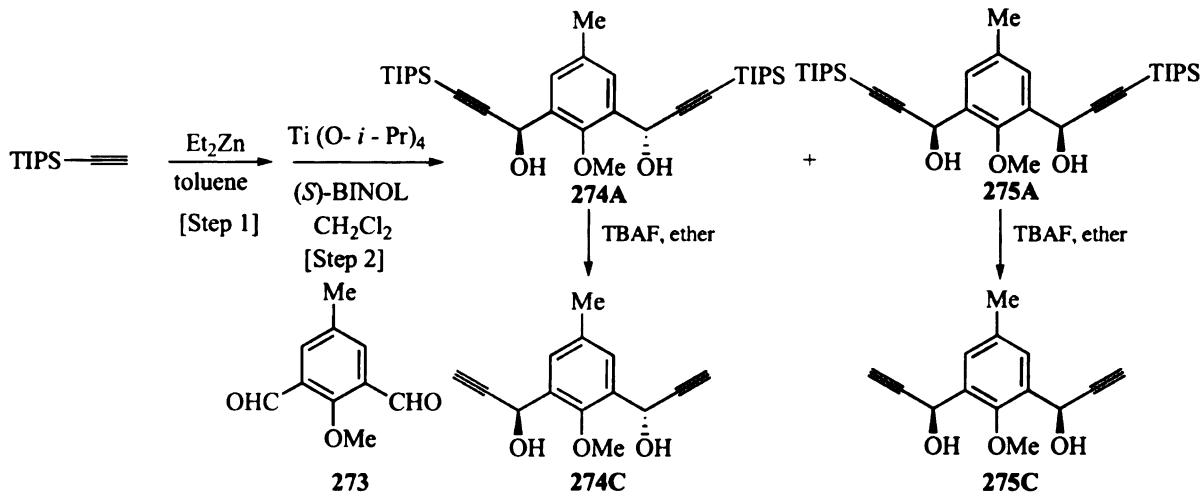
When Carreira's standard conditions were applied to the reaction of 2,6-diformyl 4-methyl anisole **273** (R^4 = OMe, R^2 = Me) with two equivalents of trimethyl silyl acetylene **269** (R^2 = $SiMe_3$), none of the product was detected and starting material was recovered. The use of higher reaction temperatures (~100°C) afforded no improvement. Also, benzoin adducts that are known to result from reactions of substituted benzaldehydes were not observed. The inertness of the aryl dialdehyde **273** to this protocol was rather unexpected but Marshall had reported similar results in his studies on alkyne addition to α-branched aldehydes.[113]

The recently developed BINOL based methodology described by Pu et.al was next examined.[114] While this method is known to work exceptionally well with aromatic aldehydes, this process had not been extended to aryl dialdehydes, which possibly could yield a mixture of diastereomers.

Hence, optimal reaction conditions were screened for aryl dialdehyde **273** and the results are shown below in Table 4.1. In general, these reactions were carried out by first deprotonating the terminal acetylene by refluxing with diethyl zinc in toluene for several hours and then sequentially adding (*S*)-BINOL, titanium isopropoxide and the aldehyde

in regular intervals. As can be seen by comparing entries 1 and 2 (Table 4.1), lower catalyst loading is detrimental to enantioselectivity of the reaction while the diastereoselectivity in formation of either the (*R,R*)-alkynol **274A** or the (*R,S*)-Alkynol **275A** is unaffected.

Table 4.1 Diastereo and Enantioselectivity in double alkyne addition to substituted isophthalaldehyde 273



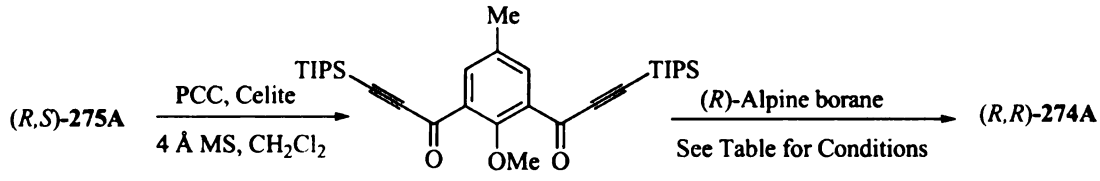
Entry	Ligand(mol%)	Ti (mol%)	Concentration[a]	Temperature[b]	dr[c]	%ee[d]
1	20	50	0.52M	25 °C	1.3:1	42
2	40	100	0.52	25	1.2:1	96.7
3	20	100	0.52	25	1:1.5	92
4	100	100	0.52	25	-	-
5[e]	40	100	0.52	25	1.2:1	99.2
6	40	100	0.72M	25	1.3:1	99.2
7	"	"	1M	25	1.3:1	99.1

[a] Concentration refers to the amount of the Alkynyl ethyl zinc reagent generated in situ by refluxing an equimolar ratio of the alkyne and diethyl zinc in toluene for 5-7 h [b] The temperature indicated refers to the reaction temperature for step 2 when the aldehyde is added to the reaction [c] The diastereomeric ratio refers to the ratio of **274A** to **275A** [d] The enantioselectivities reported are that of the terminal alkyne **274C** obtained after desilylation of **274A** [e] The reaction was carried out using 10 mmol of aldehyde **273** as compared to entries 1-4 where 2 mmol of aldehyde was used

Lower ligand loading led to lower enantiomeric excesses of the product (Entry 3 vs Entry 2). The concentration of the alkynyl zinc reagent does not affect the reaction as indicated in entries 5-7. Overall, the advantage of this approach is that a lack of facial selectivity in addition to either of the aldehyde moieties leads to the *meso* compound, which is readily separated. Either enantiomer of the terminal bis-propargyl alcohol **274C** thereby obtained is essentially enantiomerically pure (> 99 % ee) by choice of the chiral ligand and is amenable to further functional group manipulations.

Pu's method is remarkably synthetically useful as a single enantiomer of the (*R,R*)-bis-propargyl alcohol **274A** is obtained. However, the formation of a significant amount of the *meso* (*R,S*)-alcohol **275A** rendered this protocol less atom-economical, expensive and aesthetically unattractive. Henceforth, it was anticipated that if the *meso* alcohol could be transformed into optically active starting materials the overall process would meet the above-discussed critieria.

Scheme 4.3 Transformation of *meso* propargyl alcohol into optically active 274A



276A 97 %

Entry	Reagents	Reaction time	Ratio **274A** / *meso*-**275A**	% yield **274A**	%ee
1	Alpine borane [a]	26 h	1/ 1.5	38	97.84
2	Alpine borane[b]	19 h	Not determined	35	> 99.5

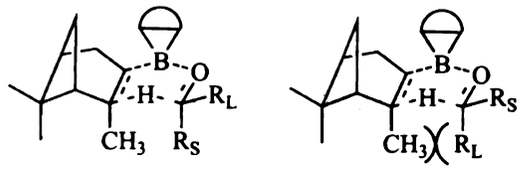
[a] (*R*)-Alpine borane generated in situ from (+)-pinene and 9-BBN in THF
[b] (*R*)-Alpine borane (0.5 M) purchased from Aldrich

The (*R,R*)-alkynol **274A** was accessible from (*R,S*)-*meso* alcohol **275A** by a two-step sequence involving oxidation by pyridinium chlorochromate to diynone **276A**

followed by reduction using (*R*)-Alpine borane [115] in overall modest yield due to the formation of significant amount of the *meso* alkynol **275A** (yield not determined) in the second step but with > 99% ee. Similar results were observed using the same borane reagent that was generated in-situ from [α]-pinene and 9-borabicyclononane. The enantiomer of the bis-propargyl alcohol thus obtained was found to be the same as that prepared by alkyne addition using (*S*)-BINOL (Scheme 4.2).

Midland et.al had postulated the mechanism for asymmetric ketone reductions with Alpine borane to involve a boat like cyclohexane structure whereby the major product arises from the intermediate **277** that has a larger group at the equatorial position rather than **278** which has the larger group at axial position (Fig 4.3).

Figure 4.4 Proposed intermediates by Midland in asymmetric ketone reduction

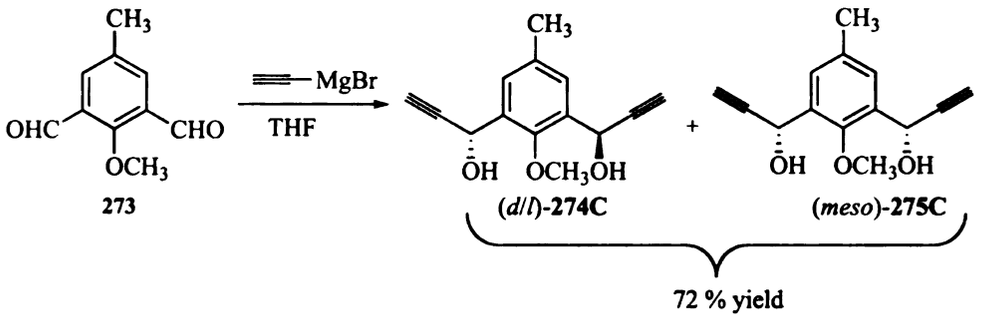


277 FAVORED **278** DISFAVORED

In general, the reduction of ketones with the Alpine borane derived from (+)-pinene led to the (*R*)-enantiomer of the alcohol, which was consistent with the proposed transition state structure **277** for the reduction step. Thus, the poor diastereoselection observed in reduction of **276A** could be attributed to two factors. The sterics of the bulky triisopropyl silyl group possibly could have a detrimental effect on the facial selectivity of the ketone reduction. The rate of decomposition of (*R*)-Alpine borane is known to be significant for ketones that are reduced slowly. As a significant amount of 9-BBN is produced by dehydroboration, this could also account for the non-selective pathway resulting in a greater amount of the *meso* diol. So, it was not that surprising to note that

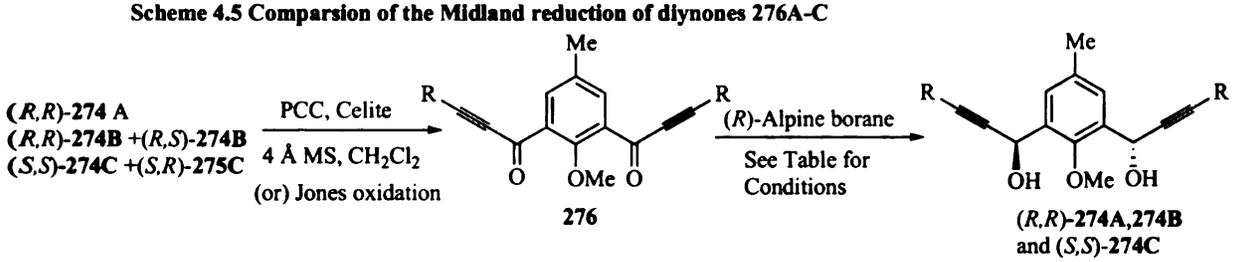
when the trimethyl silyl substituted diynone **276B** was subjected to identical reduction conditions only (*R,R*)-**274B** was isolated in 76 % yield (Scheme 4.4). None of the *meso* diastereomer (*R,S*)-**275B** could be observed by TLC. Moreover, the enantiomeric enrichment of (*S,S*)-**274C** was greater than 99.5 %.

Scheme 4.4 Addition of ethynyl Grignard to aldehyde 273



Although the optically active bis-propargyl alcohol **274C** could be obtained as single diastereomer by the use of this two-step sequence, the need for a practical and highly efficient synthesis of chiral calix[4]arenes necessitated the investigation of alternative routes that would avoid the desilylation step. To this extent, it was found that simple addition of ethynyl Grignard reagent to the dialdehyde **273** afforded **274C** and **275C** as inseparable mixture (Scheme 4.4). Jones oxidation of the mixture afforded the terminal diynone **276C** in 82 % yield. The reduction of the terminal diynone under standard conditions resulted in the formation of a single diastereomer of **274C** albeit in moderate chemical yield and purity (Scheme 4.4). However, the enantiomeric purity was still greater than 99.5 % indicating complete control of stereoselectivity in the reduction process exhibited by the organoborane reagent. With the chiral and *meso* bis-propargylic alcohols in hand, the preparation of the (*R,R*) and *meso*-bis-carbene complexes **268** was next examined.

Scheme 4.5 Comparsion of the Midland reduction of diynones 276A-C



Entry	R	Series	% Yield **276**	Reaction time for Reduction	Ratio **274/ 275** [b]	% yield **274**	%ee [c]
1	TIPS	A	97	19 h	Not determined	35	> 99.5
2	TMS	B	67	12 h	> 20:1	76	> 99.5
3	H	C	82	3h	> 20.1	56	> 99.5

[a] (*R*)-Alpine borane (0.5 M) purchased from Aldrich

[b] The ratio refers to the diastereomeric ratio after Midland reduction

[c] % ee refers to the enantiomeric purity of (*S,S*)-**274C** obtained by desilylation

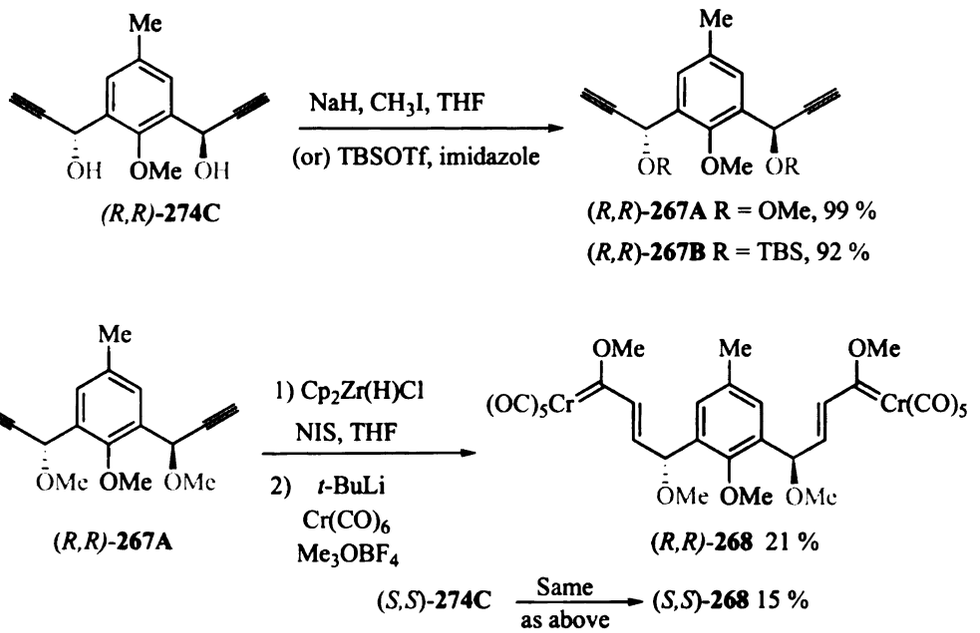
4.1.1.2 Chiral and *meso* bis-carbene complexes 268, 284

The bis-propargyl alcohol (*R,R*)-**274C** was converted to the bis-propargyl methyl ether (*R,R*)-**267A** in excellent yield . The bis-propargyl TBS ether (*R,R*)-**267B** can be also obtained similarly using *tert*-butyl dimethyl silyl trifluoromethanesulfonate and imidazole. Hydrozirconation of the terminal alkyne in (*R,R*)-**267A** followed by iodination resulted in the formation of bis-*trans* vinyl iodide (*S,S*)-**279** (not shown) which was subsequently converted to the chiral bis-carbene complex (*R,R*)-**268** in modest yields following a similar procedure reported earlier for preparation of bis-carbene complex **229** (Scheme 4.6).

The *meso* bis-propargyl alcohol **275C** was transformed via a similar sequence to the *meso* bis-*trans* vinyl iodide **283** in 50 % yield. Upon subjecting the resultant vinyl iodide to the routine conditions for carbene complex formation, it was puzzling to note that none of the carbene complex had formed. During the initial metalation step upon

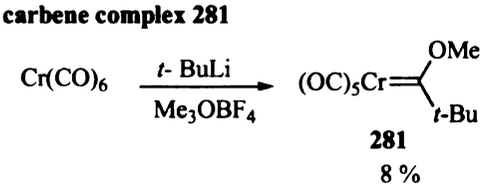
addition of *tert*-butyl lithium, the color of the solution changed from deep red to light yellow within a few minutes.

Scheme 4.6 Preparation of chiral bis-carbene complexes (*R,R*) and (*S,S*)-268



It is conceivable that the dianion **280** was not stable even at –78°C and decomposed prior to reaction with chromium hexacarbonyl as the color of the solution faded from deep red upon addition of *tert*-butyl lithium to light yellow in a few seconds. It is known that 3° alkyl lithiums will not undergo nucleophilic addition to chromium carbonyl and the maximum isolated yield for the pentacarbonyl *t*-butyl carbene complex **281** is only 8% (Scheme 4.12).[119]

Scheme 4.7 Synthesis of pentacarbonyl methoxy *t*-butyl carbene complex 281



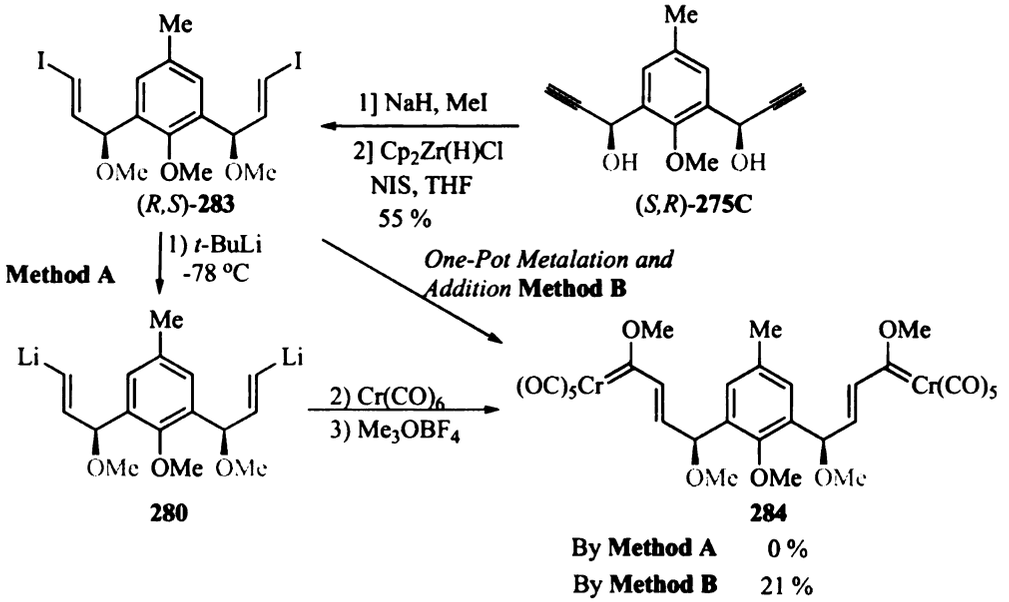
281

8 %

Thus, it was hypothesized that if$Cr(CO)_6$ were to present in the same reaction flask when the dianion is generated, the decomposition could be avoided and the carbene

complex would be prepared. Indeed, this slight change in the procedure afforded the (*S,R*) bis-carbene complex **284** in 21 % yield (Scheme 4.8).

Scheme 4.8 (*S,R*) Bis-carbene complex 284

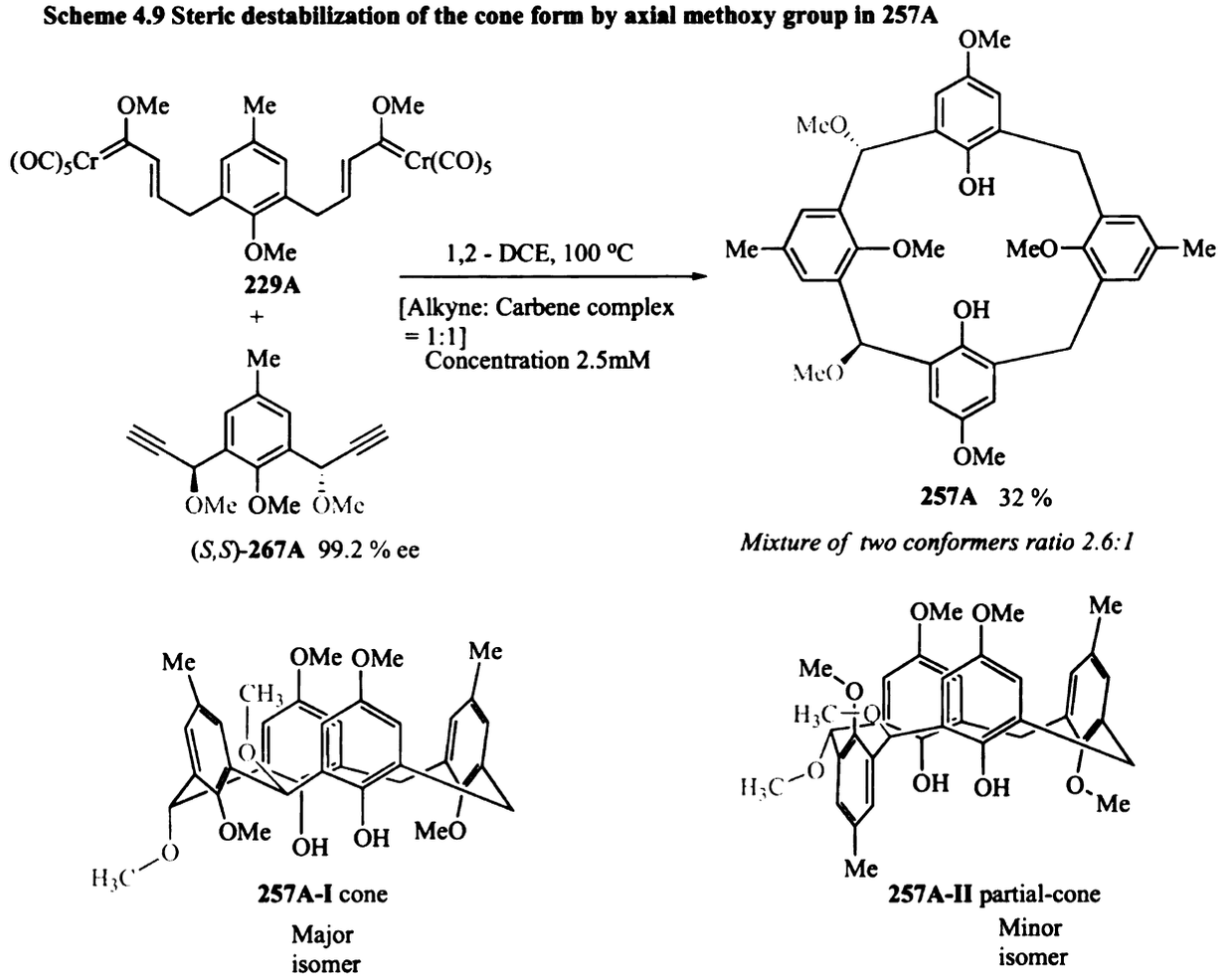


Under these newly developed conditions, the yield of the (*S,S*)-bis carbene complex **268** was found to be 24 %.

4.1.1.3 1,2-Disubstituted calix[4]arenes 257

With the chiral bis-carbene complexes and bis-propargyl arenes in hand, the formation of the 1,2-disubstituted calixarenes was next investigated. Thermolysis of the complex **229A** with chiral bis-propargyl arene (*S,S*)-**267A** resulted in the formation of 1,2-dimethyl ether **257A** in 32 % yield as a mixture of two inseparable conformers in a ratio of 2.6:1 (Scheme 4.9). The structures of the major and minor isomes of **257A** were deduced by NOESY-1D and NOESY experiments to be the cone and the partial cone with C_1 symmetry. The corresponding chemical shifts for the axial and equatorial methine hydrogens were located at 6.01 and 5.06 ppm in the cone conformer whereas those in the minor partial cone conformer were at 6.35 and 5.13 ppm respectively.

Scheme 4.9 Steric destabilization of the cone form by axial methoxy group in 257A

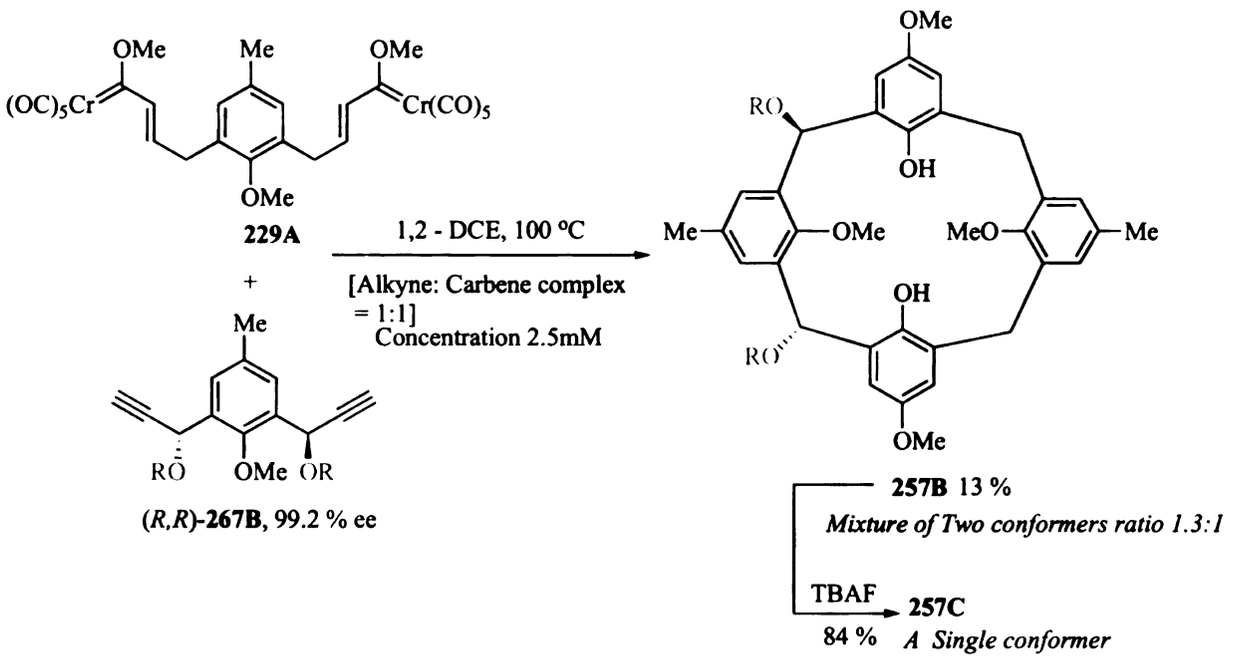


In contrast to **246A** which exists as cone conformer, the formation of significant amount of partial cone conformer in the above case suggests that the introduction of second substituent in the proximal axial position destabilizes the cone conformation due to steric repulsion between the methoxy group attached to the bridge and the adjacent hydroxy as well as methoxy groups. Apparently, the steric congestion is relieved by rotation of the methoxy group through the annulus to provide the conformer **257A-II**. To validate this hypothesis, introduction of a larger substituent at the axial position was next examined.

It was not surprising to note that the reaction of the same carbene complex **229A** with chiral bis-propargyl arene (*R,R*)-**267B** resulted only in 13 % yield of the product

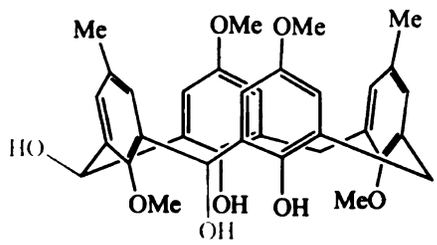
257B, which was again obtained as mixture of two inseparable conformers in a ratio of 1.3:1. Although the structures of the two conformers were not identified by NOE experiments, it is likely that partial cone and cone conformers of **257B** were again present in solution. Furthermore, the mixture of these two unidentified conformers could be transformed to a single conformer of **257C** upon desilylation (Scheme 4.10).

Scheme 4.10 Steric effect on triple annulation and conformer distribution



The equatorial and axial methine hydrogens in **257C** were observed in the ^{1}H NMR at 5.55 and 6.32 ppm. It is also of interest to note that the equatorial hydrogen was split into a doublet by the hydroxylgroup whereas the axial hydrogen appeared only as a singlet as evidenced by D_2O exchange experiment wherein the coupling between H_{eq} and OH disappeared and a singlet was observed at 5.56 ppm. The corresponding ^{13}C chemical shift for the methine carbon bearing the equatorial hydroxy group was located at 79.64 ppm whereas that with the axial hydroxy group could not be located. The conformation of the calix[4]arene **257C** was deduced to be the cone based on NOESY experiment (Fig 4.4).

Fig 4.5 Conformation of tetrahydroxy calix[4]arene 257C

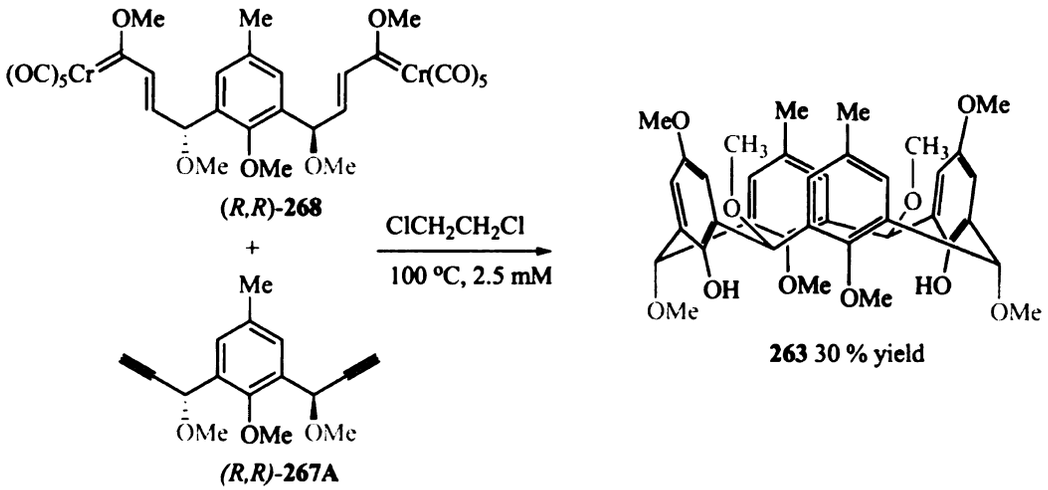


Cone-**257C**

4.1.1.4 Tetramethoxy calix[4]arene 263 (*rtct* isomer) by reaction of (*R,R*)-268 and (*R,R*)-267A

The preparation of the tetrasubstituted calix[4]arene **263** with *anti, syn, anti* (relative *trans*, *cis*, *trans*) arrangement of the substituents at the methylene bridges and C_2 symmetry was next studied. The cyclization of the bis-carbene complex (*R,R*)-**268** (99.2 % ee) with the bis-propargyl methyl ether (*R,R*)-**267A** (99.2 % ee) proceeded uneventfully to give the calix[4]arene tetramethyl ether **263** in 30 % yield (Scheme 4.11).

Scheme 4.11 Tetramethoxy calix[4]arene 263 by reaction of chiral bis-carbene complex (*R,R*)-268 and chiral diyne (*R,R*)-267A



263 30 % yield

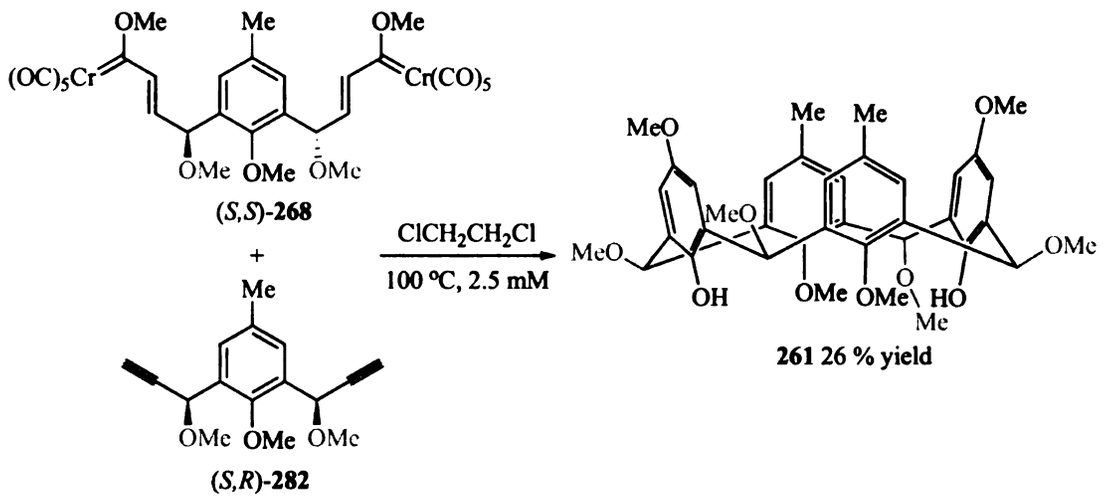
No other higher oligomers were detectable either by TLC, proton spectra of the crude compound or by mass spectra of the purified sample. The structure of the chiral calix[4]arene **263** was determined to be the cone with an *trans,cis,trans* orientation of the methoxy substituents at the bridges. The specific rotation was found to be +25.4°. The

stereochemical arrangement of the methoxy substituents at the bridges is also discernible by the ^{1}H NMR spectra, which displayed a pair of singlets (δ 5.05, 2H and δ 6.08, 2H). These protons could be attributed to the pair of axial and equatorial hydrogens in **263**. The aromatic region revealed the presence of a pair of singlets and a pair of doublets integrating to a total of eight protons. The C_2 axis of symmetry results in the splitting of the aromatic hydrogens of the *p*-alkoxy phenol to the observed doublet pattern with a coupling constant of 3Hz.

4.1.1.5 Tetramethoxy calix[4]arene 261 (*rcct*-isomer) by reaction of (*S,S*)-268 and (*S,R*)-282

The diastereomeric tetramethoxy calix[4]arene **261** (*relative cis, trans, cis*) was synthesized in 26 % yield from the reaction of the chiral bis-carbene complex (*S,S*)-**268** (94 % ee) and bis propargyl methyl ether (*S,R*)-**282** (Scheme 4.12).

Scheme 4.12 Tetramethoxy calix[4]arene (rcct isomer) 261 by reaction of chiral bis-carbene complex *(S,S)*-268 and diyne (*S,R*)-282



The proton and carbon spectral data obtained was consistent with cone conformation in solution. The three axial methine hydrogens were observed at 5.71, 5.94 and 5.96 ppm whereas the equatorial methine hydrogen was located at 5.04 ppm suggesting the presence of three equatorial and one axial methoxy groups. The resultant macrocycle had

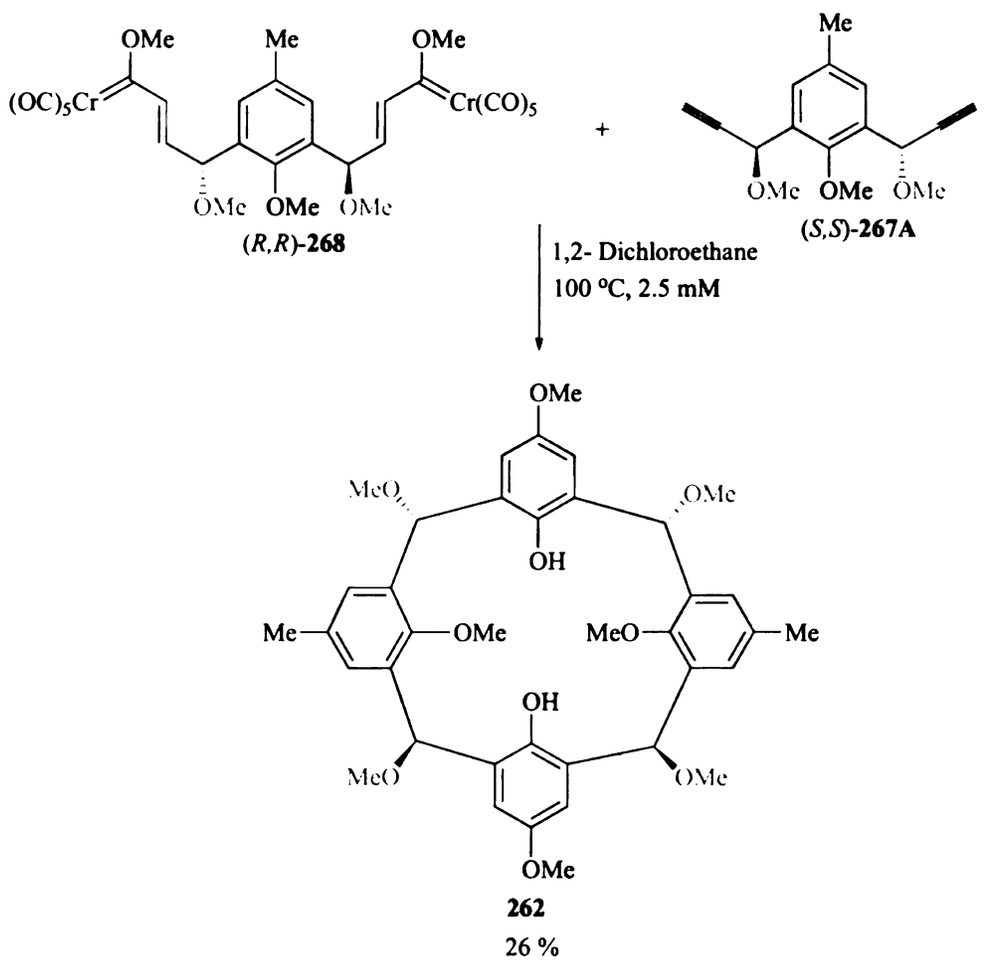
a specific rotation of −15.4° in chloroform. Mass spectral data also confirmed only the presence of tetramer as no other high molecular weight compounds were seen.

4.1.1.6 Tetramethoxy calix[4]arene (*rctt* isomer) 262 by reaction of (*R,R*)-268 and (*S,S*)-267A

It must be noted that reaction of the matched pair i.e., biscarbene complex (*R,R*)-**268** with the bispropargyl methyl ether (*R,R*)-**267A** gave the tetramethoxy calix[4]arene **263** in 30 % yield as single enantiomer. The reaction of bis carbene complex (*R,R*)-**268** (88 % ee) with the diyne (*S,S*)-**267A** (94 % ee) was next examined to probe mismatched selectivity in the triple annulation process. The resultant calix[4]arene would be a *meso* compound with relative stereochemistry at the bridges being *cis*, *trans*, *cis* and therefore was expected to be optically inactive. The reaction afforded the desired calix[4]arene in 26 % yield (Scheme 4.13). None of the higher cyclic oligomers were observable either by TLC/ crude ^{1}H NMR or by mass spectra. The proton spectra of **262** exhibited rather unique features. Two extra singlets were observed at 3.83 and 3.87 ppm integrating to 1.4 hydrogens each. Besides these anomalous peaks, only seven methoxy groups were identified in the proton spectra of the pure compound. The carbon spectra on the other hand showed signals corresponding to nine methoxy groups between 55.62 and 63.84 ppm respectively. The peak intensities for two methoxy carbons were less compared to the other seven and DEPT analysis confirmed that these two chemical shifts were indicative only of methoxy groups. By the use of an HMQC experiment, it was confirmed that the two extra singlets in proton spectra that were observed indeed corresponded to the carbons that had chemical shifts of 55.62 and 55.82 ppm.

At this stage, it was hypothesized that a mixture of two inseparable conformers were present in 1:1 ratio in solution. NOESY and 1D-NOE experiments could not elucidate the structures of these two conformers.

Scheme 4.13 Calix[4]arene 262 from reaction of (*R,R*)-268 and (*S,S*)-267A



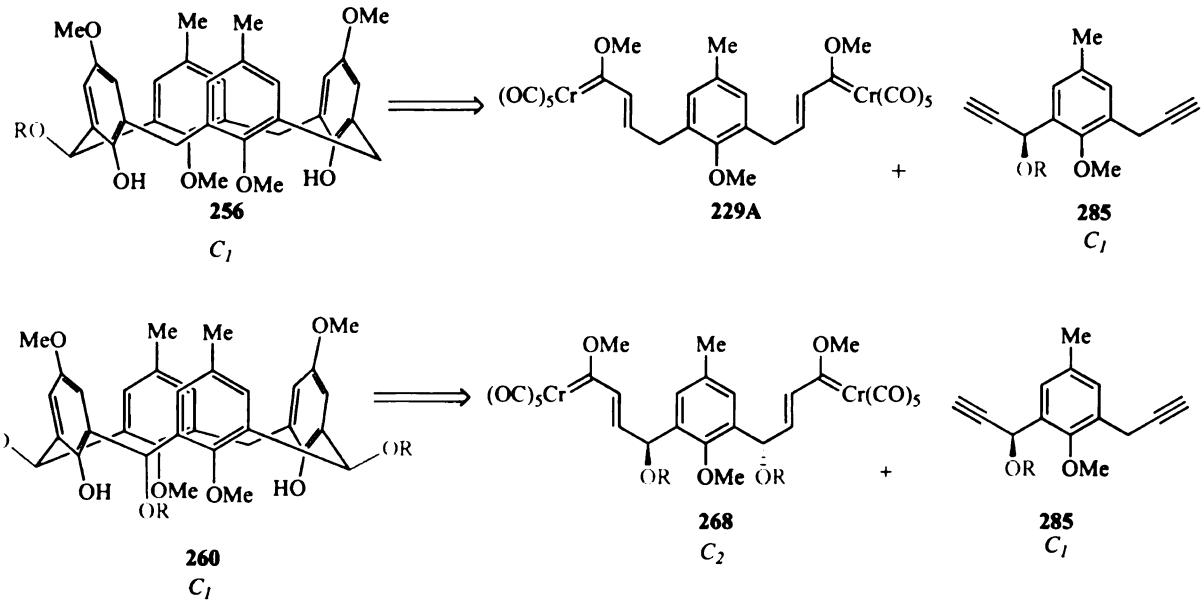
262

26 %

4.1.2 Triple annulation strategy towards mono and trisubstituted calix[4]arenes

Having demonstrated the feasibility of the methodology for synthesis of di and tetrasubstituted calix[4]arenes, mono and trisubstituted calix[4]arenes were chosen as the next targets. The C_1 symmetry element present in monoalkoxy calix[4]arene **256** and trialkoxy calix[4]arene **260** were anticipated to arise from the C_1 symmetry present in the mono-chiral propargyl arene (*S*)-**285** and its reaction with either non-chiral bis-carbene complex **229A** or the C_2 symmetric bis-carbene complex (*S,S*)-**268** (Scheme 4.14).

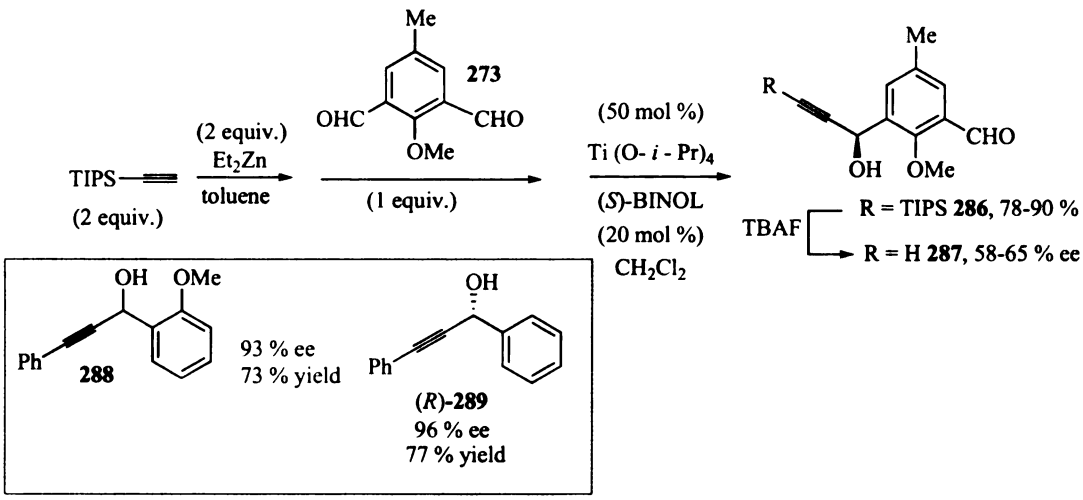
Scheme 4.14 General strategy towards mono and trisubstituted calix[4]arenes



4.1.2.1 Synthesis of monochiral bis-propargyl alcohol 287

The synthesis of the coupling partner **285** that would be necessary for introduction of C_1 symmetry in either **256, 259** or **260** was next examined. During the course of the optimization studies in alkyne additions, it was accidentally found that a reduction in the stoichiometry of the alkynyl zinc reagent, titanium isopropoxide and 1,1'-binaphthol by factor of two resulted in exclusive formation of mono-alkynol (*R*)-**286** as the only product in excellent yield. Desilylation of (*R*)-**286** to (*S*)-**287** and analysis by HPLC by comparison of the retention times of an authentic racemic sample of **287** revealed an induction of only 65 %. The modest level of enantioselectivity obtained is in contrast to that observed for phenyl acetylene addition to *o*-methoxy benzaldehyde, wherein 93 % ee was observed for the adduct **288** under identical conditions (Scheme 4.15). The enantiomeric excess and yield of the alkynol (*S*)-**287** obtained by desilylation of (*R*)-**286** was dependent upon the purity of the BINOL and quality of the diethyl zinc used for the alkyne additions.

Scheme 4.15 Chemoselective alkyne addition to dialdehyde 273

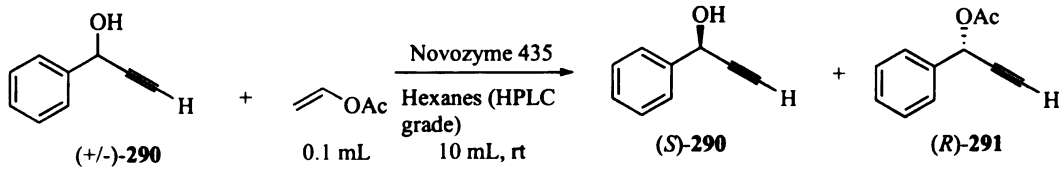


Re-use of the recovered bi-naphthol under the above-mentioned conditions afforded (*S*)-**287** in only 58 % ee. An alternative procedure for alkyne addition was recently reported by Pu, which involved the use of hexamethyl phosphoramide as an additive.[116] According to this procedure, (*S*)-BINOL in dichloromethane is mixed with HMPA, alkyne and diethyl zinc in one pot. Titanium isopropoxide and the aldehyde were then added in one-hour intervals and the reaction was complete in 3-4 h. Under these new conditions, (*R*)-1,3-diphenylprop-2-yn-1-ol **289** was obtained in 72 % yield and 93 % ee. Although this protocol resulted in lower enantiomeric excess for **289** compared to the one without HMPA, the asymmetric addition to dialdehyde **273** was neverthless examined under these conditions in an effort to improve the enantioselectivity of **287**. However, analysis of the crude proton NMR of the product using these conditions indicated that the reaction did not proceed to completion with the ratio of starting material **273** and mono-adduct **286** being 1.6:1.

Next, it was anticipated that the enantiomeric purity of alkynol **287** could be improved by chemical separation of the two enantiomers using enzymatic kinetic

resolution. Recently, Porto had demonstrated that racemic terminal propargyl alcohols such as **290** could be resolved by lipase (Novozyme 435) to give the chiral propargyl alcohols (*S*)-**290** and propargyl acetate (*R*)-**291** in high enantiomeric purity (Scheme 4.6). The enzyme preferentially reacts only with the (*R*)-enantiomer of the propargyl alcohol and hence the unreacted (*S*)-enantiomer is also obtained optically pure.[117]

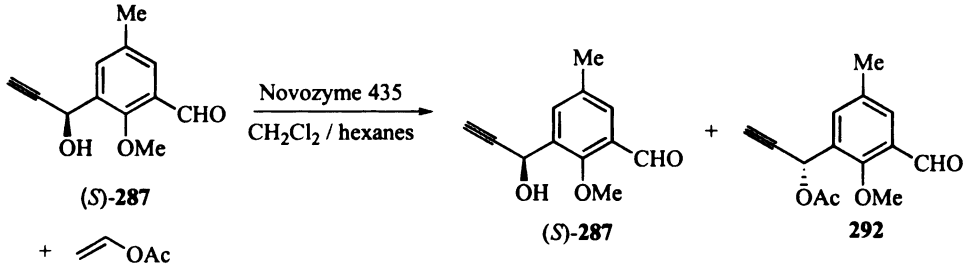
Scheme 4.16 Kinetic resolution of terminal propargyl alcohol (*S*)-290



Enzymatic resolution of the enantiomers of **286** / **287** was next examined by screening a wide variety of reaction conditions and the results can be found below in Table 4.2. Consistent with the results reported by Porto, the kinetic resolution doesn't work on the silylated alkyne **286** (entry 1). In contrast, the terminal propargyl alcohol **287** can be resolved either in a mixture of dichloromethane and hexanes or in hexanes (compare entries 5 and 3). As the enzyme is immobilized on acrylic resin, rigorous stirring of the contents of the flask can accelerate the heterogeneous reaction. Longer reaction times are often necessary to attain complete kinetic resolution of the enantiomers in a single cycle (entry 7 vs entry 1). The results obtained here are consistent with the general observation made by Porto as only the (*R*)-alcohol **287** reacts to form the propargyl acetate **292** although the selectivity obtained is not quite as high (two cycles are necessary for achieving high enantiomeric purity of **287**). Based on the results obtained in the enzymatic resolution, it would be a reasonable assumption that the absolute configuration

of the chiral alkynol **287** resulting from alkyne addition process using (*S*)-BINOL as the chiral ligand would be (*R*).

Table 4.2 Enzymatic resolution on 287 : Optimization studies



Entry	No of. cycles	Solvent ratio	% ee of **287**[b]	Reaction Time	% Yield **287**	% Yield **292**	% ee of **287**[c]
1	1st cycle	1/ 2	57.5	4 h	77	6	71
2	2nd cycle	1/ 3	71	12 h	81	ND	98.5
3	1st cycle	1/ 6	56.5	12 h	77	17	84.7
4	2nd cycle	1/ 6	84.7	"	92	5.4	96.3
5	1st cycle	0 / 1[a]	63.47	13 h	82	12.2	84.97
6	2nd cycle	0 /1	84.97	"	75	6.5	93.7
7	1st cycle	1/ 3	70	20 h	83	10.6	93.4

[a] The allkynol **287** was insoluble in hexanes and hence added directly to solution of vinyl acetate and Novozyme 435 in hexanes

[b] The % ee refers to the enantiomeric purity prior to enzymatic resolution

[c] The % ee refers to the enantiomeric purity after enzymatic resolution

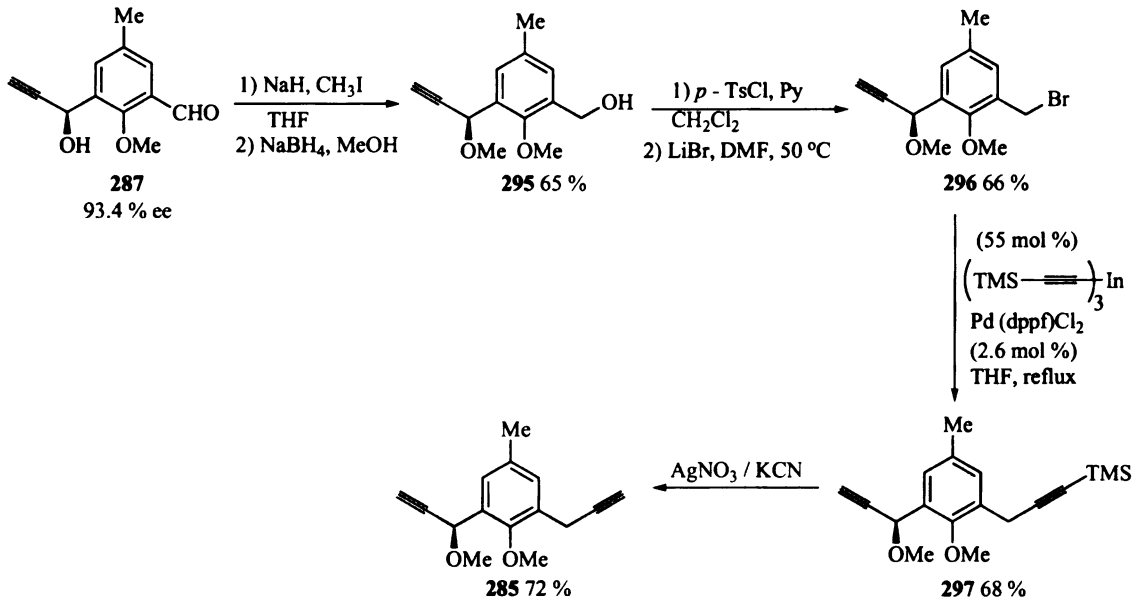
Lin Pu had reported that alkyne addition to benzaldehyde using (*S*)-BINOL gave the (*R*) enantiomer of 1,3-diphenylprop-2-yn-1-ol **289**, whereas the absolute configuration of the propargyl alcohol **288** resulting from similar addition to *o*-anisaldehyde was not proven. As the assignment of absolute configuration for these substrates principally relied on comparison of the observed optical rotation values to literature ones, it was reasoned that similar approach could not be pursued for deducing the stereochemistry in **274C** and **287** because of the disparity in the direction of the observed rotation for alcohols **288** and **289**. In general, the difficulty in unambiguous assignement of configuration in propargyl alcohols arises due to the scarcity of available

methods and the only known example involves the use of circular dichroism studies on propargyl benzoates.[118] Hence, significant amount of effort was expended to unambiguously deduce the absolute configuration in chiral alkynols **274C** and **287**. Finally, Horeau's method was used to establish the absolute configuration as (*R,R*)-**274A** and (*R*)-**286** by preparation of the 2-phenyl butyrate ester **293** and the necessary information can be found in the experimental section.

4.1.2.2 Chiral monomethoxy calix[4]arene 256

The chiral propargyl alcohol (*S*)-**287** obtained by enzymatic resolution in 93.4 % ee could be transformed to the unsymmetrical diyne (*S*)-**285** in six steps in good overall yield Methylation of the propargyl alcohol followed by reduction afforded the benzyl alcohol **295** which could then be transformed to the benzyl bromide **296** by a two step sequence with the intermediacy of benzyl tosylate.

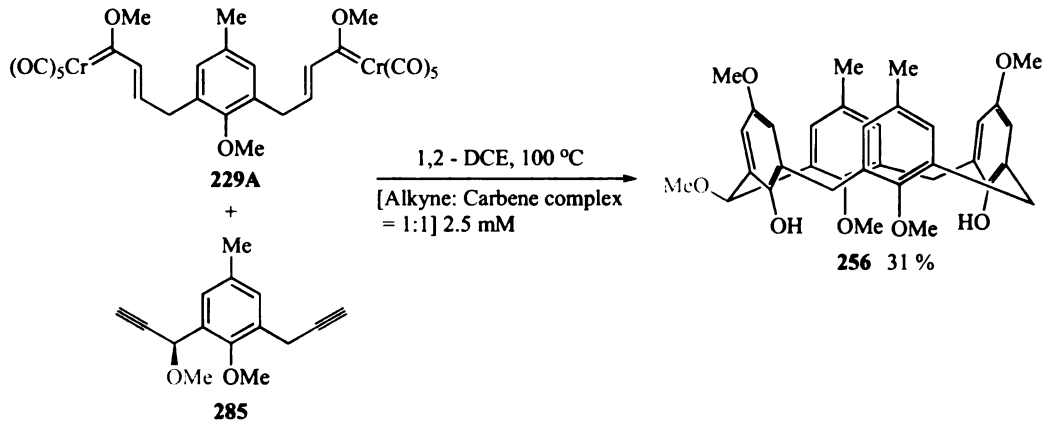
Scheme 4.17 Synthesis of chiral unsymmetrical diyne 285



Palladium catalyzed coupling with tris-trimethylsilyl ethynyl indium reagent followed by desilylation gave the diyne **285** in 21 % yield from (*S*)-**287** (Scheme 4.17). The reaction

of the non-chiral bis-carbene complex **229A** and chiral diyne (*S*)-**285** was next examined. The chiral monomethoxy calix[4]arene **256** with C_1 symmetry could be isolated in 31 % yield (Scheme 4.18).

Scheme 4.18 Monomethoxy calix[4]arene 256 by triple annulation of complex 229A and diyne 285



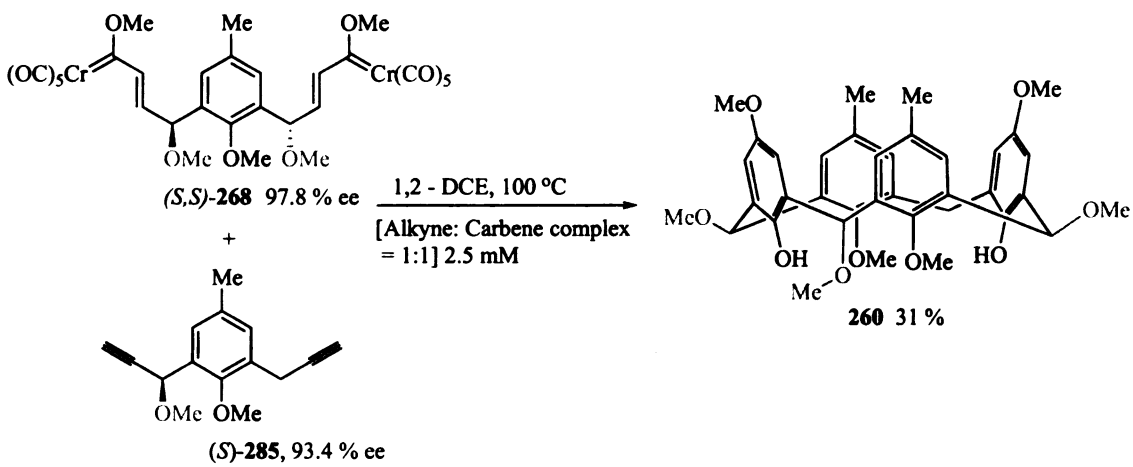
Analysis of the ^{1}H NMR spectrum of **256** showed the axial methine hydrogen at 5.98 ppm as a singlet indicating that methoxy group preferred to occupy the equatorial position of the macrocycle. Also, in agreement with the ^{13}C chemical shifts for equatorially substituted calix[4]arenes was the chemical shift of the methine signal of **256** at 73.83 ppm.

4.1.2.3 Trimethoxy calix[4]arene (*rtc* isomer) 260

Macrocyclization of chiral bis-carbene complex (*S,S*)-**268** (97.8 % ee) with the diyne (*S*)-**285** (93.4 % ee) afforded the trimethoxy derivative **260** with C_1 symmetry in 31 % yield as a cone conformer (Scheme 4.19). The relative stereochemistry at the bridges in **260** is defined by the stereochemical descriptor *rtc* (*relative trans cis*). Analysis of the mass spectra revealed that indeed the tetramer was only formed and none of the octamer was present. Notably, this represents the first synthesis of a calix[4]arene resulting from substitution at three different methylene bridges. Examination of the ^{1}H NMR spectrum

revealed similar features observed for other methylene substituted calix[4]arenes. Three distinct singlets were observed for the methine hydrogens on the benzylic carbon bearing the methoxy substituents. Two of the methine hydrogens were observed at 5.99 and 6.04 ppm indicating these correspond to axial hydrogens on the calix scaffold whereas the equatorial hydrogen was observed at 5.04 ppm respectively. The observed specific rotation of the trimethyl ether of calix[4]arene was found to be –16.2°.

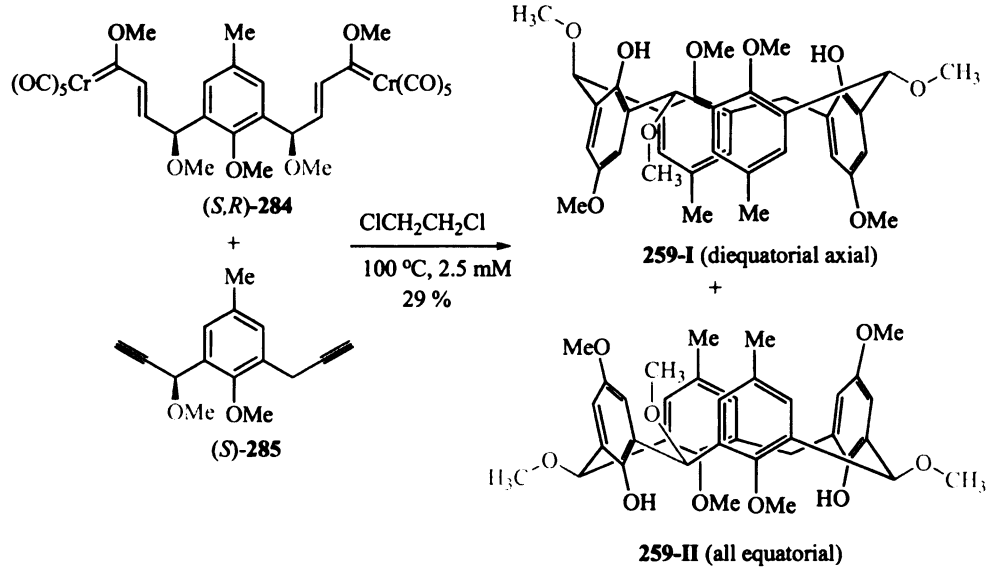
Scheme 4.19 Trimethoxy calix[4]arene 260 by triple annulation of complex 268 and diyne 285



4.1.2.4 Trimethoxy calix[4]arene (*rcc* isomer) 259

Next, cyclization of the (*S,R*) bis-carbene complex **284** with the diyne (*S*)-**285** (93.4 % ee) was probed under optimal conditions for the formation of the chiral calix[4]arene **259** (Scheme 4.20). This reaction was anticipated to afford a mixture of diastereomers, either with an all *syn* or *syn,anti* relative stereochemical disposition of the substituents at the bridges. Although the TLC analysis of the crude indicated a broad streak, the presence of only one mobile spot was evident. Chromatographic purification gave a product that exhibited a very complicated proton and carbon NMR spectra. Careful examination of the proton spectra revealed the presence of four methyl groups, fourteen methoxy groups and six methine hydrogens.

Scheme 4.20 Trimethoxy calix[4]arene 259 by reaction of *meso* bis-carbene complex 284 and chiral diyne 285

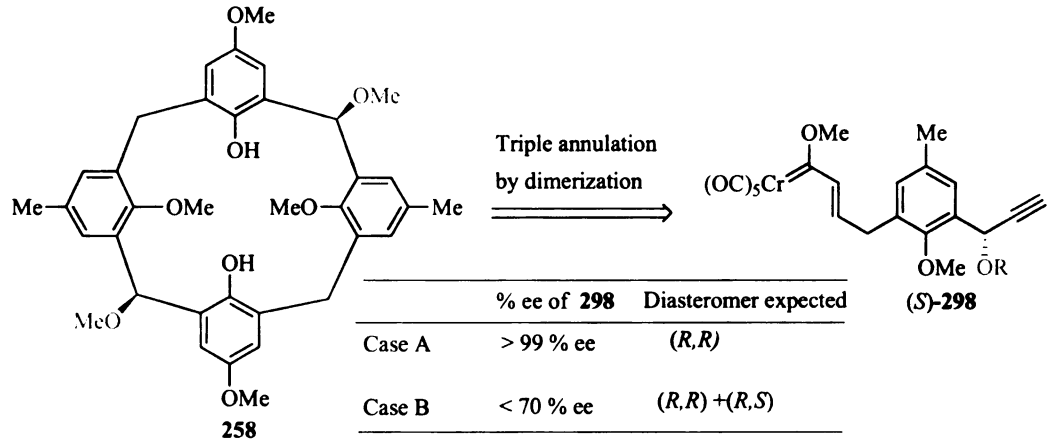


The methine protons appeared as distinct singlets at 5.05, 5.70, 5.81, 5.92 and 5.94 ppm. Furthermore, sixteen aromatic protons and four hydroxyl groups were also evident in the region between 6.58 and 7.82 ppm. The carbon spectra was much more complex embedded with alteast seventy different carbons. Again, four methyl carbons corresponding to the *p*-methyl anisole fragment were in the chemical shift range 20.77-21.26 ppm respectively. Also, the presence of thirty aromatic carbon resonances required the existence of atleast eight aryl rings in the macrocyclic framework which possibly could indicate the presence of either calix[8]arene or a mixture of two conformers of calix[4]arenes in roughly 1:1 ratio. HPLC Analysis confirmed that there were indeed two compounds (ratio 1.36:1) and mass spectra of the mixture also suggested them to be isomeric (*m/z* 630 only observed). The exact structure of these two isomeric compounds could not be deduced but tentatively these are assigned as the diastereomers **259-I** and **259-II** based on the chemical shifts of 5.05 and 5.80 in the former compared to 5.69, 5.91 and 5.93 ppm in the latter.

4.1.3 1,3- Disubstituted chiral calix[4]arene

The preparation of the 1,3-disubstituted analog **258** (See Scheme 4.1, R^5 = OMe) was expected to be accomplished by the triple annulation via dimerization of alkynyl carbene complex **298**. This strategy was anticipated to be extremely useful as direct examination of matched / mismatched selectivity could possibly be accomplished using the alkynyl carbene complex of specific enantiomeric purity (Scheme 4.21).

Scheme 4.21 Triple annulation by dimerization of complex 298



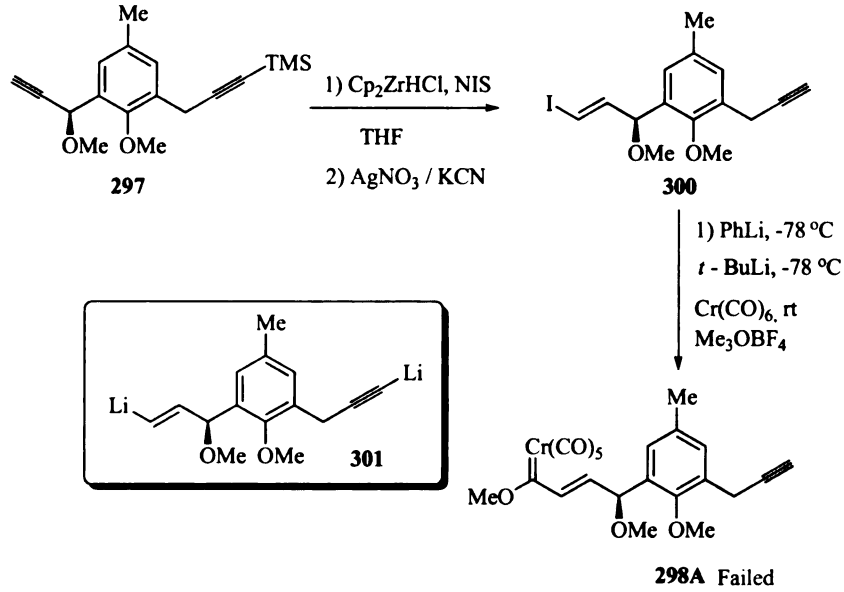
	% ee of **298**	Diasteromer expected
Case A	> 99 % ee	(*R,R*)
Case B	< 70 % ee	(*R,R*) +(*R,S*)

4.1.5.1 Case A: Attempted preparation of enantiomerically pure complex (*S*)-298 and regioisomer (*S*)-298A

The synthesis commenced with the chemoselective hydrozirconation of the terminal alkyne in **297** followed by iodination to afford the mono-vinyl iodide which was subsequently desilylated to afford the ω-alkynyl vinyl iodide **300** in good overall yield. Deprotonation of the terminal alkyne in **300** with phenyl lithium and subsequent halogen-metal exchange afforded the presumed intermediate dianion **301** which upon attempted reaction with chromium hexacarbonyl followed by methylation afforded none of the

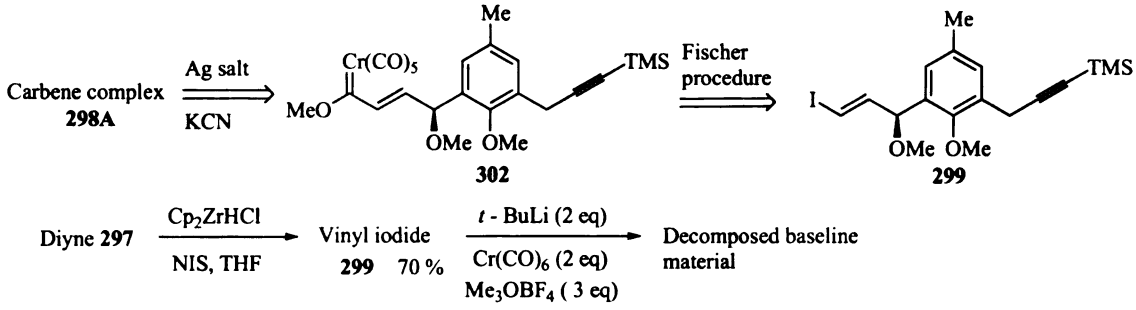
carbene complex **298A** and a significant amount of immobile baseline material was observed by TLC (Scheme 4.22).

Scheme 4.22 Attempted synthesis of the alkynyl carbene complex 298A



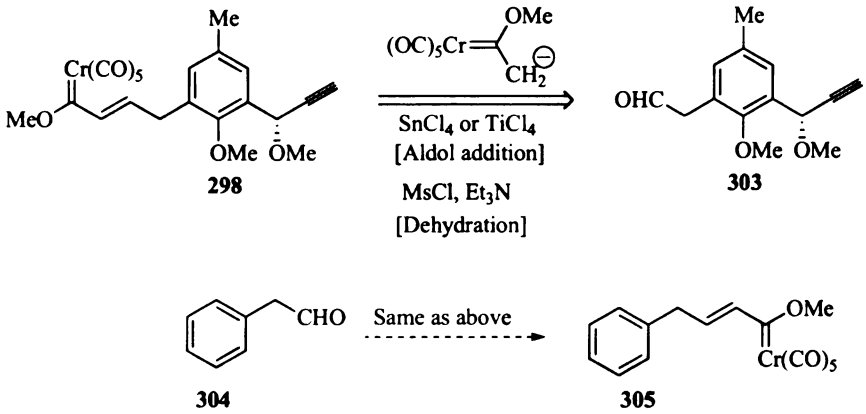
An alternate approach was then envisioned which involved desilylation as the last step in the preparation of carbene complex **298A**. The diyne **297** was subjected to hydrozirconation / iodination sequence using Schwartz reagent to afford the mono-vinyl iodide **299** in 70 % yield. The reaction of the vinyl iodide with *tert*-butyl lithium to facilitate halogen-metal exchange followed by nucleophilic addition of the vinylic carbanion on chromium hexacarbonyl did not yield the carbene complex **302** either (Scheme 4.23). The difficulty in preparation of carbene complexes **298A** and **302** might be attributed to the instability of the intermediate vinylic carbanions with respect to decomposition even when the reaction is conducted at very low temperatures (-78°C) or the instability of these complexes with respect to air oxidation.

Scheme 4.23 Alternative approach to alkynyl carbene complex 298A with desilylation as the last step



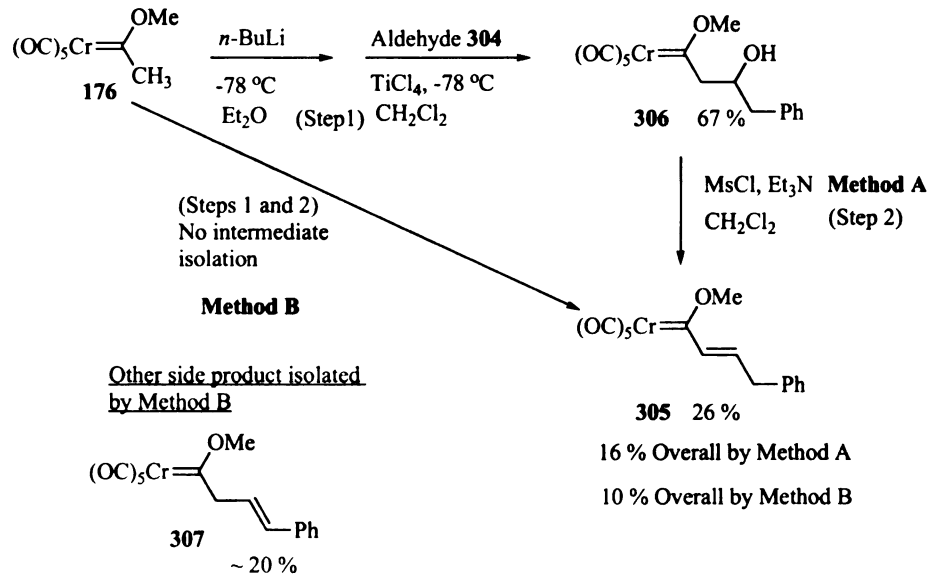
To examine the reasons for the stability of these carbene complexes, a different route was explored that avoided the generation and reaction of vinylic carbanions such as those mentioned earlier. More specifically, the aldol reaction between the enolate of pentacarbonyl methoxy methyl chromium carbene complex **176** and enolizable aldehyde **303** was expected to furnish the carbene complex **298**. Although complex **298** is a structural isomer of complex **298A**, it was still anticipated to afford the chiral 1,3-dimethoxy calixarene by macrocyclization. Aldehydic substrates similar to **303** are expected to be extremely sensitive to polymerization and hence the initial studies were examined with phenyl acetaldehyde **304** for the preparation of analogous complex **305** (Scheme 4.24). The aldol methodology was probed using titanium tetrachloride as the Lewis acid. Deprotonation of **176** in ether to generate the enolate as shown above followed by addition to the phenyl acetaldehyde-titanium tetrachloride complex in dichloromethane afforded the aldol adduct **306** in 67 % yield. Upon purification by a silica gel column and removal of the solvent, the aldol adduct was found to be extremely unstable with respect to decomposition. Treatment of **306** with methanesulfonyl chloride and triethylamine yielded the complex **305** in 26 % yield.

Scheme 4.24 Aldol methodology to carbene complexes 298 and 305



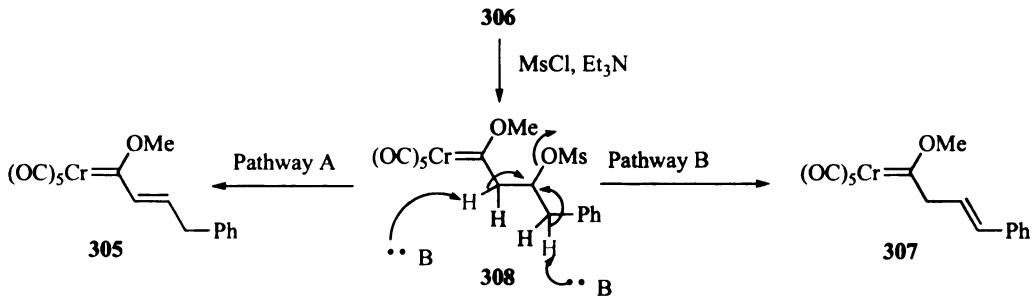
It is noteworthy to mention that no other side products were observed as mobile spots on the TLC plate by this sequential method whereas **307** was the minor product in one step method that was carried out without the purification of the intermediate **306** (Scheme 4.25).

Scheme 4.25 Aldol reactions with phenyl acetaldehyde



The formation of **305** occurs by elimination via pathway A whereas **307** presumably is formed by elimination via pathway B (Scheme 4.26).

Scheme 4.26 Mechanism of elimination of mesylate 308

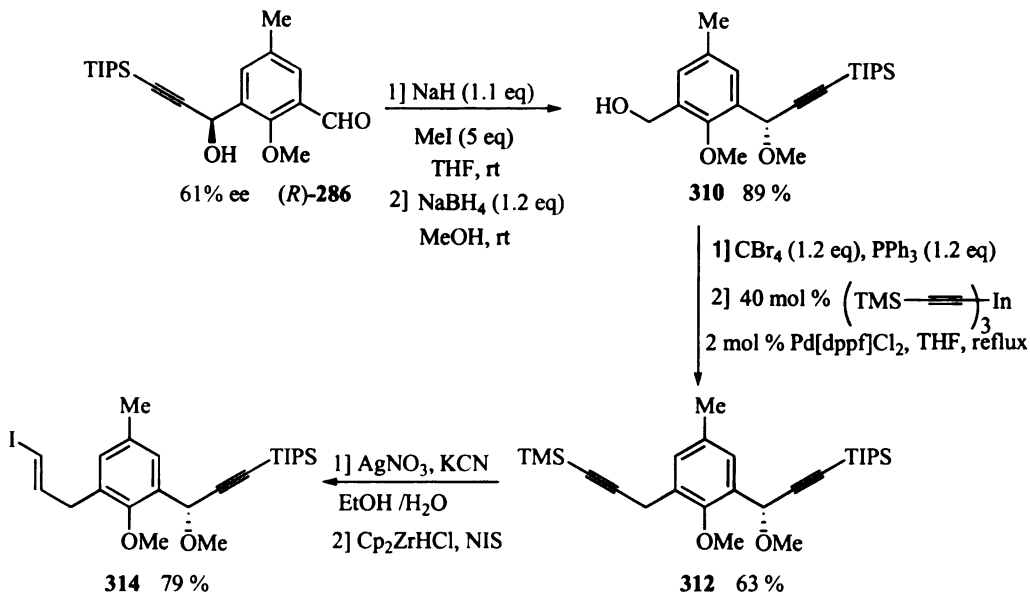


Although, it is surprising to note that a slight difference in the procedures resulted in varied product distributions in favor of either regioisomer, this methodology again suffered from poor yields of the desired complex **305**. Since the energetics of the elimination process would be expected to be relatively similar due to the presence of extended conjugation both in **305** and **307**, the aldol approach had to be abandoned at this stage.

4.1.5.2 Case B: Preparation of carbene complex (*S*)-298 with low enantiomeric purity

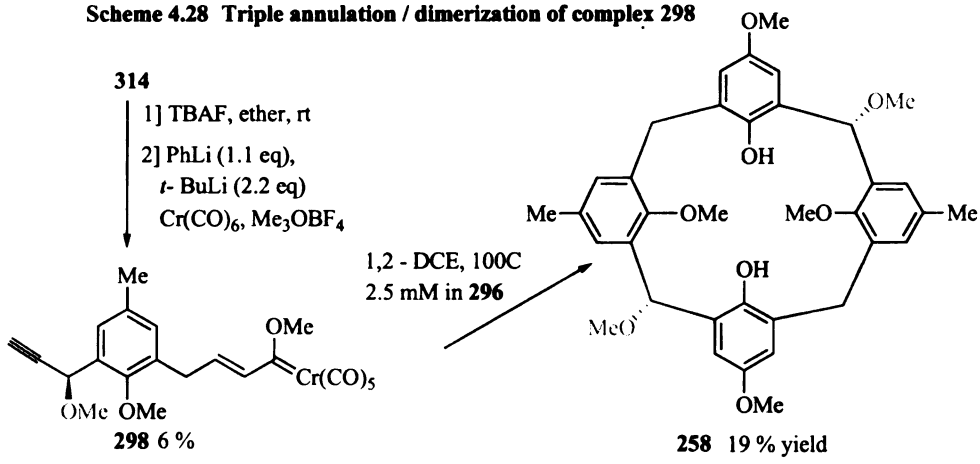
The preparation of the alkynyl carbene complex **298** in low enantiomeric purity could be accomplished by the dianion approach in very low yield by a different sequence. First, the chiral propargyl alcohol (*R*)-**286** (61 % ee) was methylated and then reduced to the benzylic alcohol **310**. Bromination using carbon tetrabromide and triphenyl phosphine afforded the benzyl bromide, which was then subjected to palladium catalyzed coupling with trialkynyl indium reagent to give the unsymmetrical diyne **312** in 63 % yield. The diyne **312** was then converted to the vinyl iodide (*R*)-**314** in two steps (Scheme 4.27).

Scheme 4.27 Preparation of chiral vinyl iodide 314



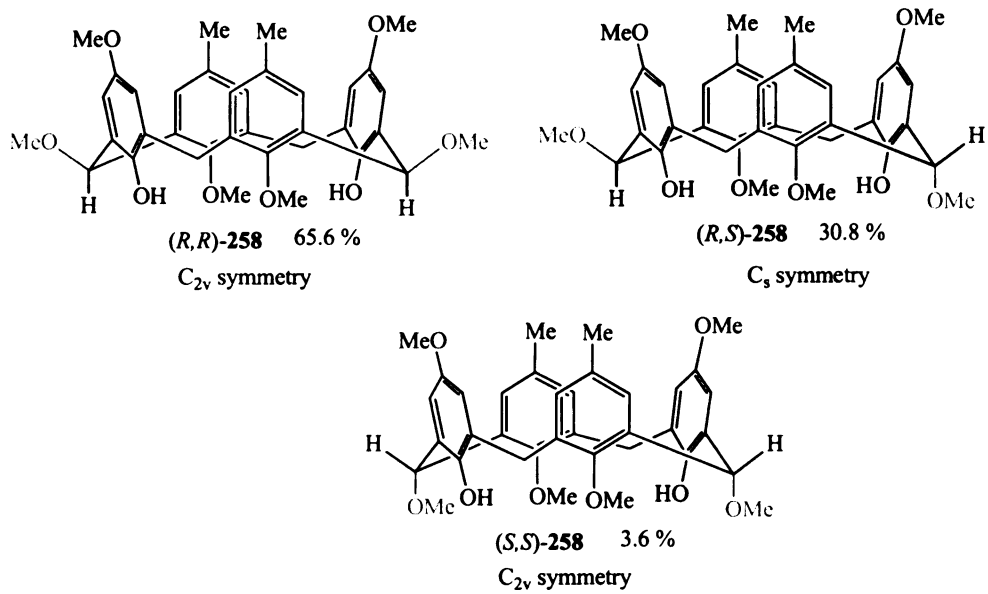
The vinyl iodide **314** was next subjected to desilylation and then exposed to the standard conditions for carbene complex formation as described earlier in an attempted preparation of **298A**. Gratifyingly, the carbene complex (*S*)-**298** could be isolated in pure form albeit in only 8 % yield. Cyclization of complex (*S*)-**298** (61 % ee) under the optimized conditions at a concentration of 2.5 mM resulted in a smooth cyclization to yield only the (*R,R*)-1,3-dimethoxy substituted calix[4]arene **258** in 19 % yield. No other mobile spots were seen on the crude TLC plate as well as by crude ^{1}H NMR (Scheme 4.28). This result is surprising considering the fact that the starting material was enriched in the (*S*)-enantiomer to only 61% ee. It was expected that a mixture of diastereomers would result from the triple annulation / dimerization sequence with the statistical distribution being in favor of the (*R,R*)-**258** than (*R,S*)-**258** in a ratio of 2.24:1.

Scheme 4.28 Triple annulation / dimerization of complex 298



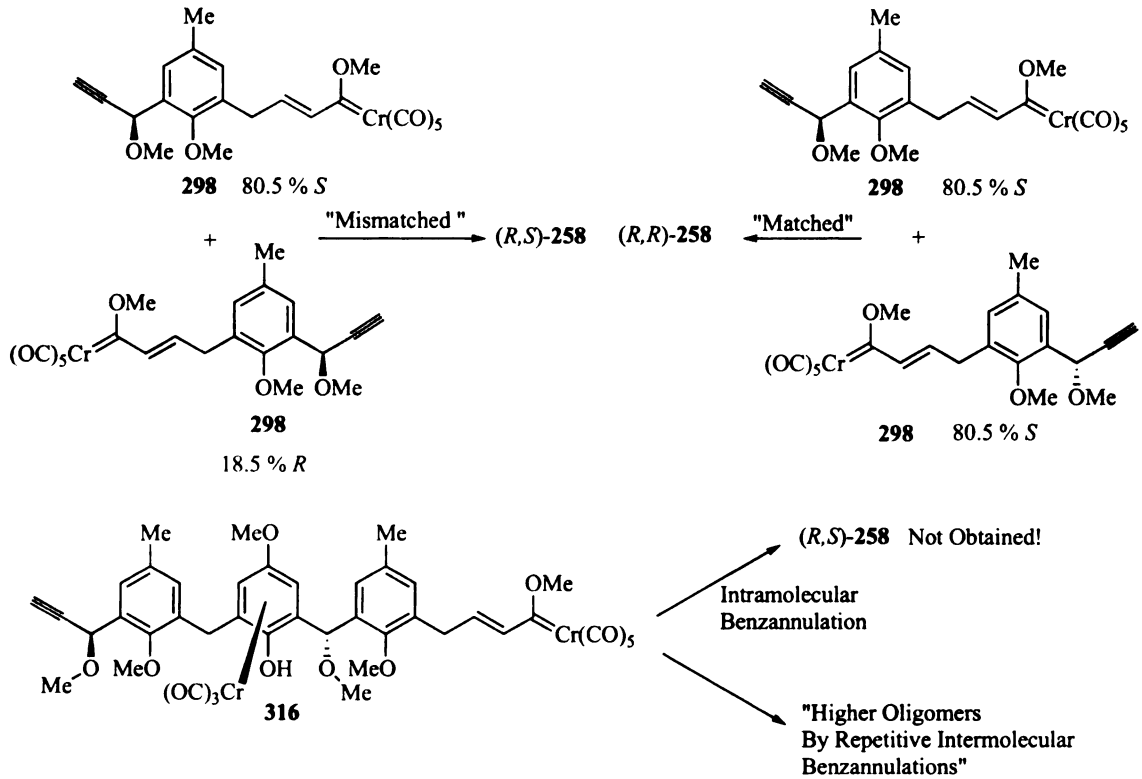
While certainly a small amount of the minor diastereomer (*R,S*)-**258** could have possibly formed that perhaps escaped detection by either TLC or crude proton spectra, there definitely exists a clear preference for the matched (*R,R*)-isomer. The calix[4]arene obtained was unambiguously determined to be the (*R,R*)-diastereomer by examination of proton spectra, optical rotation measurement and NOESY data. The (*R,S*)-diastereomer would have C_s symmetry with a *trans* relationship of the substituents at the methine bridges thereby would be achiral whereas the (*R,R*)-diasteromer would have C_{2v} symmetry in the cone conformation and therefore would be chiral. The proton NMR spectra indicated that both the methine hydrogens appeared downfield at 5.98 ppm indicating that the two-methoxy groups must occupy equatorial positions. Furthermore, it was found that the 1,3-dimethoxy substituted calix[4]arene had an optical rotation of -3.8° in chloroform and the diastereomeric assignment was further confirmed by NOESY experiment (See Experimental section for Details) (Figure 4.6). The origin of the selectivity in the macrocyclization is not well understood. Two hypothetical scenarios emerge wherein a] matched vs mismatched selectivity might contribute to only the formation of the observed (*R,R*)-diastereomer b] the intermediate alkynyl carbene complex **316** does not undergo the macrocyclization event (Scheme 4.29).

Figure 4.6 Theoretical product distribution in cyclization of 298



It is also possible that the planar chirality present in η^6-Chromium tricarbonyl arene complex **316** interferes with the cyclization step as it is expected that the mode of coordination of the chromium tricarbonyl tripod is the one wherein the metal center is *anti* to the neighbouring methoxy substituent based on studies done by Hsung (See section 2.1.2.1 Pg.55), and *syn* to the methoxy substituent at the propargylic position. In the event of alkyne terminus approaching the carbene fragment in **316** to form the η^1:η^3 vinyl carbene complex, it is anticipated that the CO ligands on the metal would be in close vicinity to the propargylic methoxy group and thereby would result in an unfavorable steric interaction prohibiting the alkyne insertion step. The net result would then be subsequent intermolecular benzannulation event leading to oligomerization (Scheme 4.29).

Scheme 4.29 Possible explanations for observed diastereoselectivity



4.2 Summary

In summary, the triple annulation approach has been established as a unique synthetic approach towards methylene substituted chiral calix[4]arenes. This methodology provides for a versatile synthesis of specific stereo and regioisomers with varying substitution patterns at the methylene bridges.

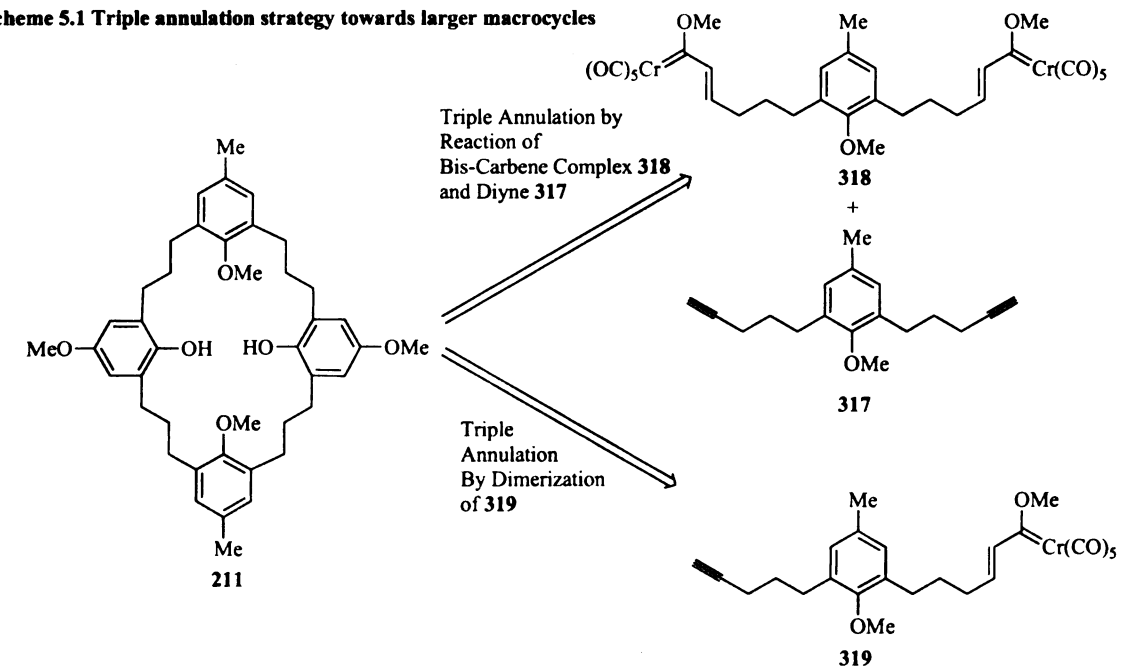
CHAPTER FIVE

MODEL STUDY TOWARDS LARGER MACROCYCLES WITH DEEPER CAVITIES- SYNTHESIS OF A BISHOMOCALIX[4]ARENE CAVITAND

5.1 Homocalix[4]arenes by triple annulation strategy

The preceding chapter demonstrated the utility of the triple annulation methodology in the synthesis of calix[4]arenes that are chiral as a result of substitution at the methylene bridges and also by the presence of adjacent aryl rings that are non-identical. In this chapter, the synthesis of bis-homocalix[4]arene model substrate **211** by reaction of bis-carbene complex **318** and diyne **317** as well as some initial studies examining the feasibility of the triple annulation / dimerization strategy of carbene complex **319** will be discussed (Scheme 5.1).

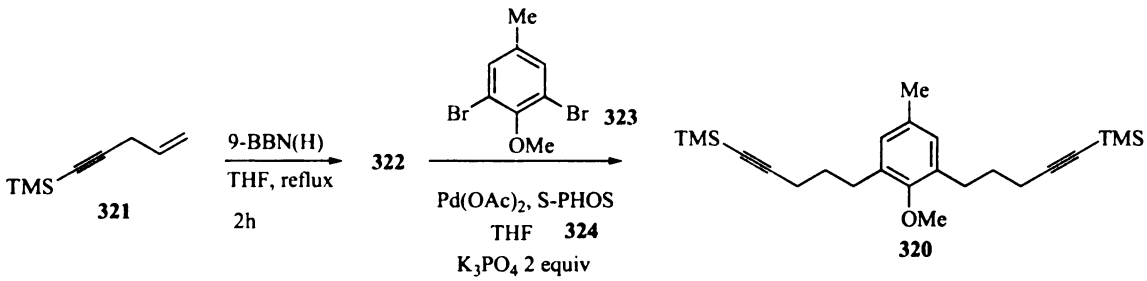
Scheme 5.1 Triple annulation strategy towards larger macrocycles



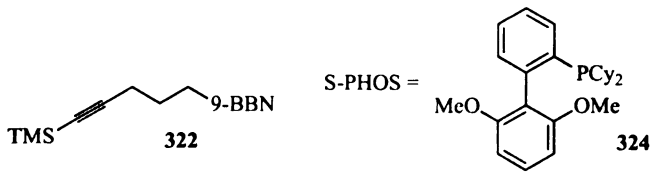
5.2 Preparation of diyne 320

The study begins with the targeted synthesis of diyne **317**. After examination of a number of different strategies towards this substrate, only one viable approach was found. This involved the palladium catalyzed Suzuki coupling of an alkyl borane **322** that was in turn obtained by hydroboration of the skipped enyne **321** with 2,6-dibromo-4-methyl anisole **323**.[120] This Suzuki coupling involves the use of the biaryl phosphine ligand S-PHOS **324** recently introduced by Buchwald.[121]The reaction works extremely well to provide the bis-trimethyl silyl substituted diyne **320** in excellent yield. Although the ligand is quite expensive, the reaction can basically be carried out using only 2 mol % of ligand with no significant drop-off in isolated chemical yields even at room temperature (Table 5.1).

Table 5.1 Suzuki coupling with Buchwald's ligand as an efficient route to 320



Entry	Catalyst Loading	Amt. of Ligand	Temperature	Time	% Yield
1	1 mol %	2 mol %	25°C	24h	76
2	2 mol %	4 mol %	75°C	9h	79

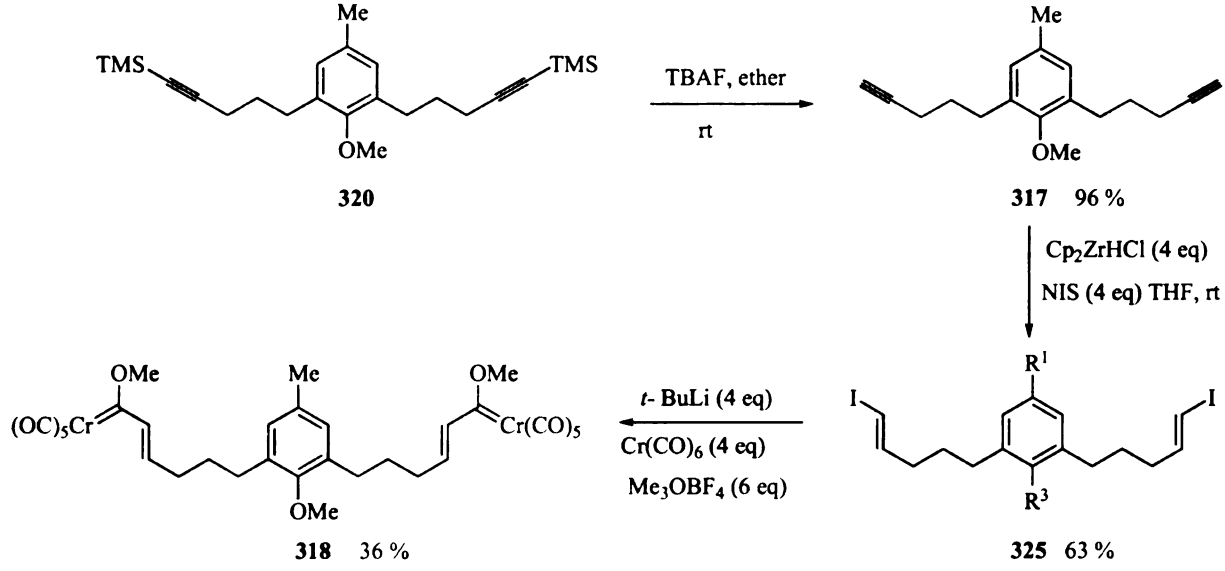


5.3 Synthesis of bis-carbene complex 318

With the diyne **320** in hand, the bis-carbene complex **318** could be prepared conveniently in three steps. Desilylation of **320** provided the terminal diyne **317**, which

was subjected to hydrozirconation/ iodination protocol to give the bis-*trans* vinyl iodide **325** in good overall yields. The vinyl iodide in turn could be transformed into the bis-carbene complex **316** in 36 % yield (Scheme 5.2).

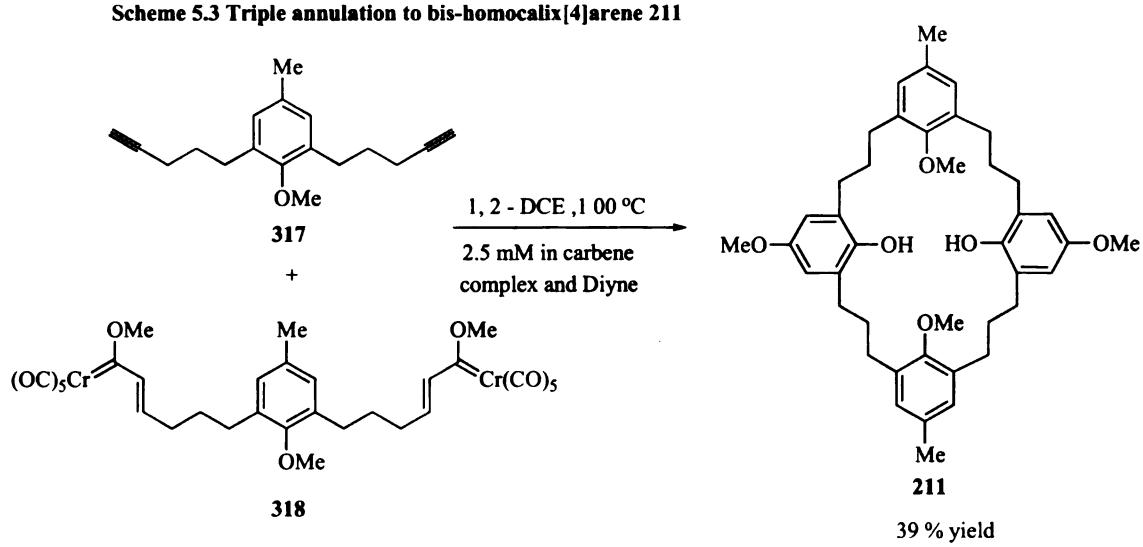
Scheme 5.2 Synthesis of bis-carbene complex 318



5.4 Bishomocalix[4]arene by triple annulation of bis-carbene complex 318 and diyne 317

Cyclization of the bis-carbene complex **318** with the diyne **317** was then investigated under optimal conditions in 1,2-dichloroethane as the solvent. Quite fascinatingly, the reaction afforded the bis-homocalix[4]arene **211** in 39 % yield (Scheme 5.3). Interestingly, there is no drop in the yield compared to the synthesis of an analogous calix[4]arene **246A** (See section 3.4 and 3.5), which has eight less atoms in the macrocycle.

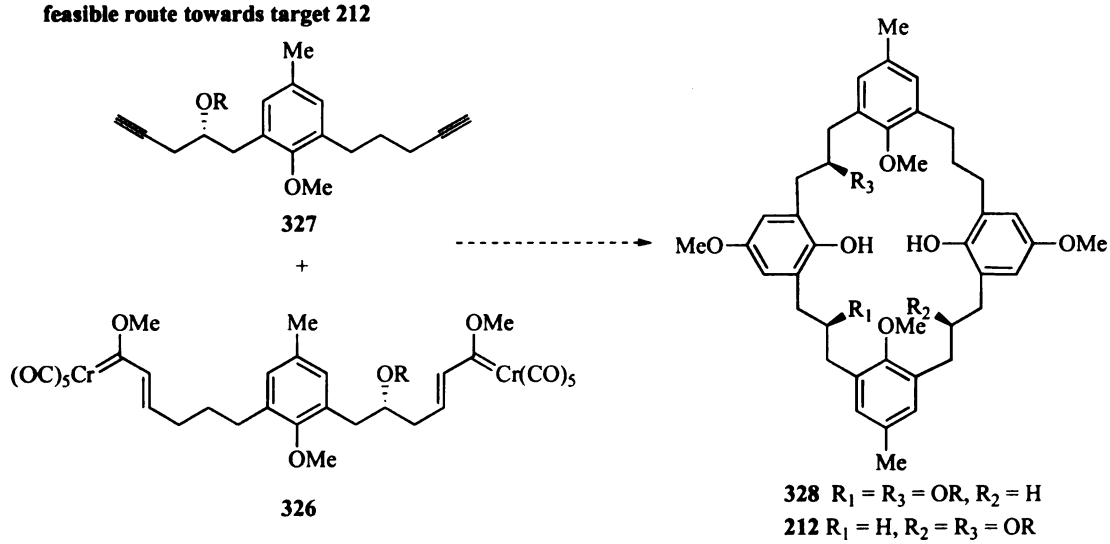
Scheme 5.3 Triple annulation to bis-homocalix[4]arene 211



5.5 Triple annulation by dimerization of 319

One of the primary reasons for pursuing the synthesis of this family of larger macrocyles was to examine the possibility of preparing chiral bis-homocalixarene cavitand **215** (See Section 2.3.1) for its intended use as a chiral ligand in asymmetric reactions.

Scheme 5.4 Triple annulation of complex 327 and diyne 326 - Not a feasible route towards target 212

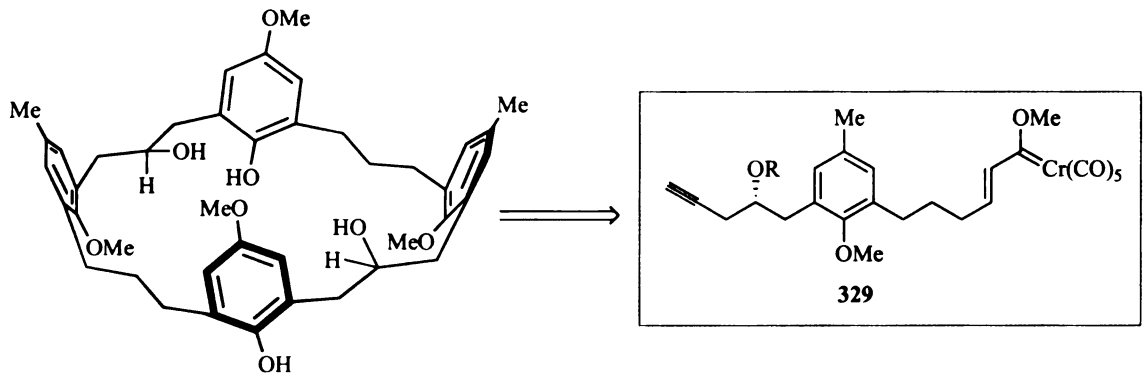


Thus, it could be perceived that the above strategy in Scheme 5.3 would not be directly useful in obtaining the chiral macrocycle **212** as it would require the cyclization of mono-

chiral carbene complex **326** with mono-chiral diyne **327** (Scheme 5.4). Such a process would be inefficient as a mixture of adjacent and distal propylene functionalized bis-homo calix[4]arenes **328** and **212** would result upon deprotection.

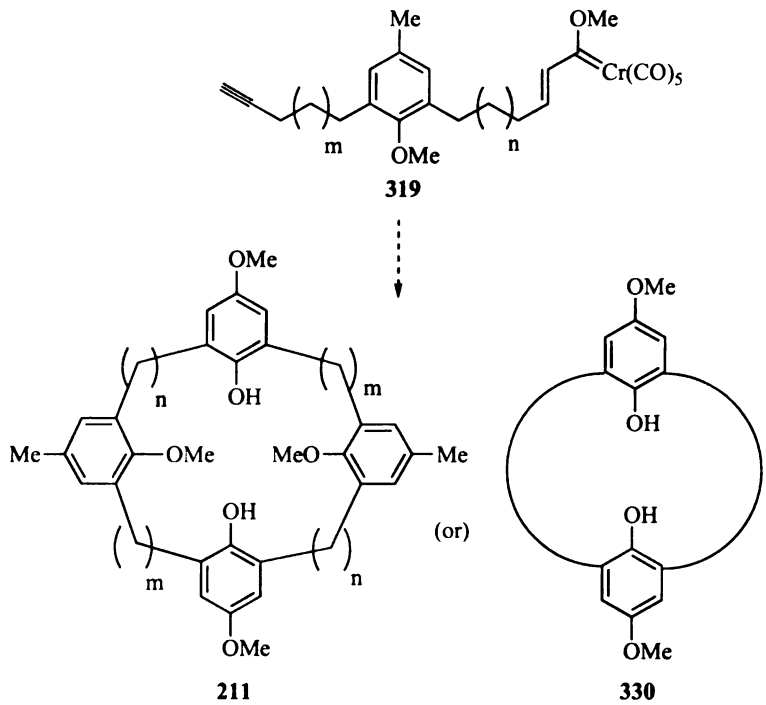
An alternative strategy would then involve cyclization of alkynyl carbene complex **329** to form the bis-homocalix[4]arene **212** (Scheme 5.5).

Scheme 5.5 Triple annulation by dimerization of complex 329 to chiral bis-homocalix[4]arene 212



In this regard, the examination of the dimerization of carbene complex **319** was considered extremely crucial for the targeted chiral macrocycle **212**. Also, it was anticipated to provide an opportunity to examine the effect of tether length on intra vs inter-molecular benzannulation of carbene complexes. Based on the results obtained in intramolecular benzannulation as function of tether lengths (See section 2.2.2.1), it was expected that thermolysis of complex **317** would give only the desired bis-homocalix[4]arene **211**. As the tether length is increased, intramolecular benzannulation was anticipated to compete with the dimerization process leading to [n,n]-metacyclophane **330** (Scheme 5.6).

Scheme 5.6 Inter vs Intramolecular benzannulations leading to 211 or 330

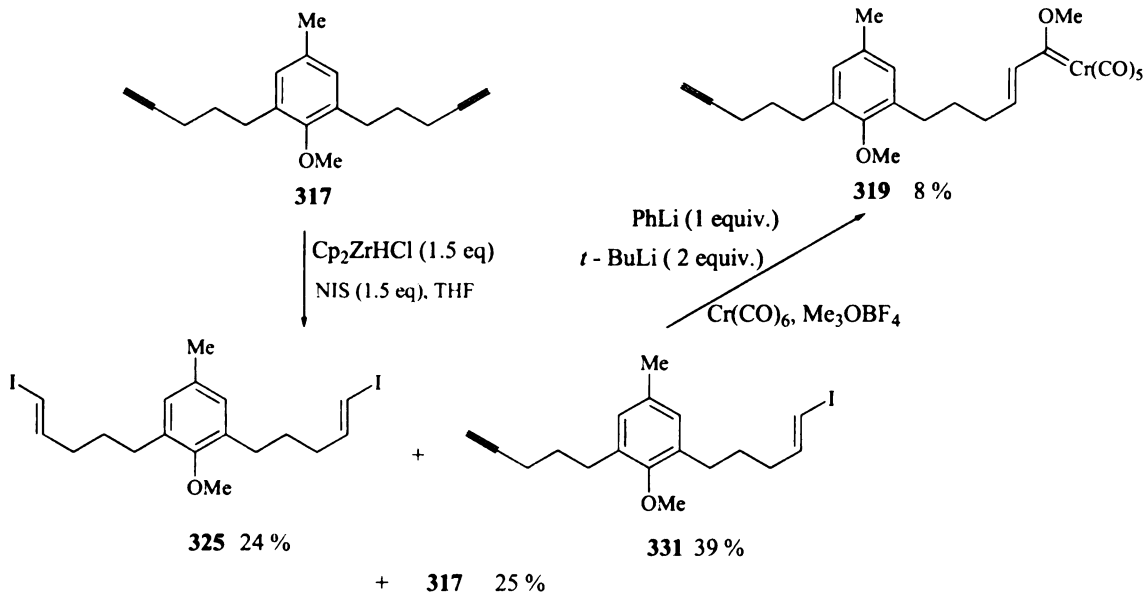


5.6 Synthesis of alkynyl carbene complex 319

5.6.1 The dianion approach

Preparation of the carbene complex **319** was initially examined by the dianion methodology developed by a former graduate student in the Wulff group.[86] In this regard, the diyne **317** was subjected to hydrozirconation / iodination sequence using only 1.5 equivalents of the Schwartz reagent. The reaction afforded a mixture of mono-vinyl iodide **331**, bis-trans vinyl iodide **325** and starting material roughly as a statistical mixture from which **331** was isolable in 39 % yield. The vinyl iodide **331** was then subjected to similar sequence of reaction conditions that were used in the synthesis of **298** (Scheme 4.22) to give only 8 % of the desired carbene complex **319** (Scheme 5.7).

Scheme 5.7 Dianion approach to carbene complex formation

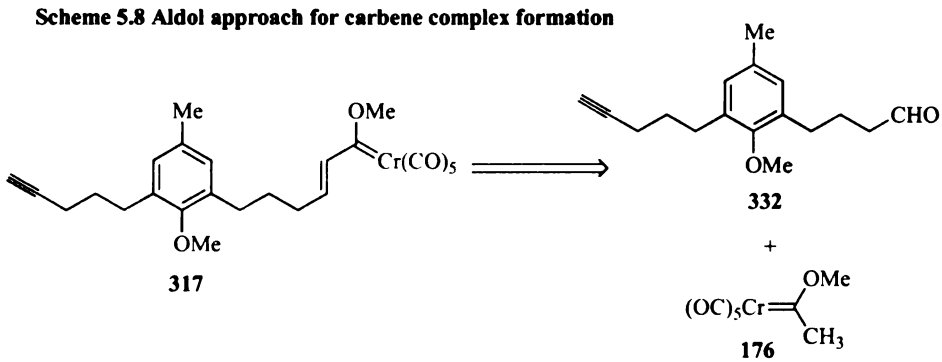


The isolated carbene complex was not of sufficient purity to allow an examination of the dimerization approach. Based on prior studies done in the Wulff group, it has been well established that aldol reactions of pentacarbonyl methoxymethyl chromium carbene complex **176** with enolizable aldehydes (See scheme 2.16) afford alkenyl carbene complexes in good yields. Hence, the aldol approach was next examined for the synthesis of complex **319**.

5.6.2 Aldol approach for carbene complex formation

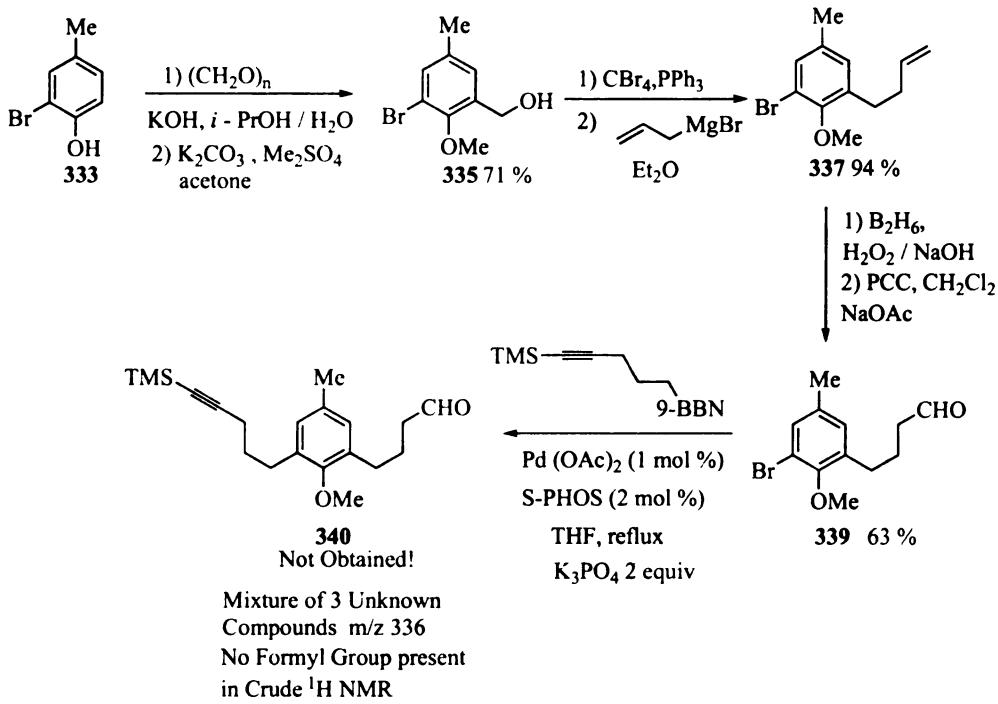
The synthesis of complex **319** was envisaged to arise from the aldol reaction/ dehydration of carbene complex **176** and enolizable aldehyde **332** (Scheme 5.8).

Scheme 5.8 Aldol approach for carbene complex formation



Commercially available 2-bromo-4-methyl-phenol **333** was converted into 2-bromo-6-hydroxymethyl-4-methylanisole **335** following literature procedure. Bromination of the benzyl alcohol using carbon tetrabromide and chain extension using allyl magnesium bromide gave the terminal alkene **337** in 94 % yield over two steps.

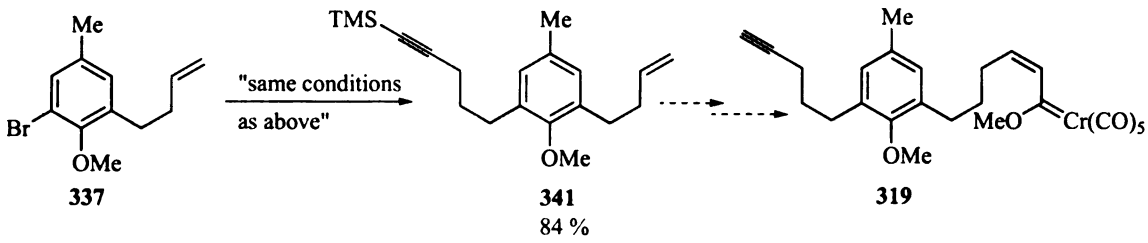
Scheme 5.9 Attempted preparation of aldehyde 340



Hydroboration of olefin **337** followed by oxidation of the intermediate alkyl borane resulted in the formation of alcohol, which was oxidized to the aldehyde **339** in good yields. The aldehyde **339** was then subjected to the Suzuki coupling conditions using S-PHOS ligand but unfortunately none of the desired coupled product was detected by TLC / crude ^{1}H NMR or mass spectroscopic analysis. The proton spectra showed that the formyl group had disappeared indicating that such reactive functionality may not be suitable under the Suzuki coupling conditions (Scheme 5.9). An alternative method that would prevent interference of the formyl group was examined wherein the coupling step preceded the installation of the reactive aldehyde functionality (Scheme 5.10). The cross

coupling of bromide **337** with the alkyl borane under identical conditions led to the formation of the desired product **341** in 84 % yield.

Scheme 5.10 Alternative approach to carbene complex 319



5.7 Summary

This chapter examines the feasibility of construction of larger macrocycles by reaction of carbene complexes and alkynes. A representative example is the synthesis of bis-homo calix[4]arene in 39 % yield from the reaction of bis-carbene complex **318** and diyne **317**. An advanced intermediate for exploration of the dimerization strategy has also been prepared by using Suzuki cross coupling as the key step.

CHAPTER SIX

CONCLUSIONS AND

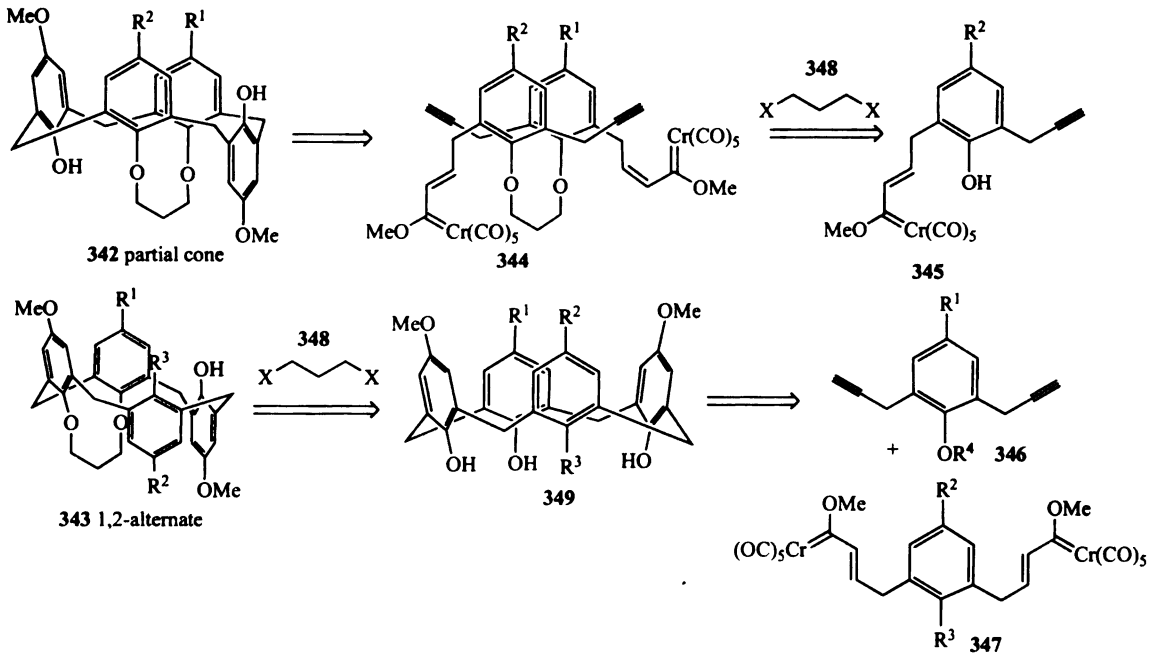
FUTURE DIRECTIONS

A versatile and expedient methodology has been described that affords access to calix[4]arenes, chiral calix[4]arenes and bis-homocalix[4]arene adorned with specific symmetry elements from the triple annulation reactions of carbene complexes and alkynes. Further advancements in methodology can arise in several different ways and this chapter is intended to provide an insight into some of the avenues for further exploration.

6.1 Calix[4]arenes with molecular asymmetry

One of the direct ways to gain access to calix[4]arenes with C_1 symmetry would be to tether either the distal arene rings or the proximal arene rings at the lower rim as in calix[4]arenes **342** and **343**. It is expected that cone conformation would not be preferred in solution for either of these compounds due to disruption of intramolecular hydrogen bonding and thereby the only preferred conformers in solution would be the partial cone and 1,2-alternate. The intramolecular triple annulation process of **344** wherein two equivalents of alkynyl carbene complex **345** are tethered by using bifunctional reagent **348** prior to the cyclization event can possibly accomplish the synthesis of **342**. Alternatively, calix[4]arene **343** should be directly accessible from the reaction of bis-carbene complex **346** with bis-propargyl arene **347** bearing different substituents on the arene rings followed by deprotection to give **349** and selective 1,2-alkylation at the lower rim halide **348** (Scheme 6.1).

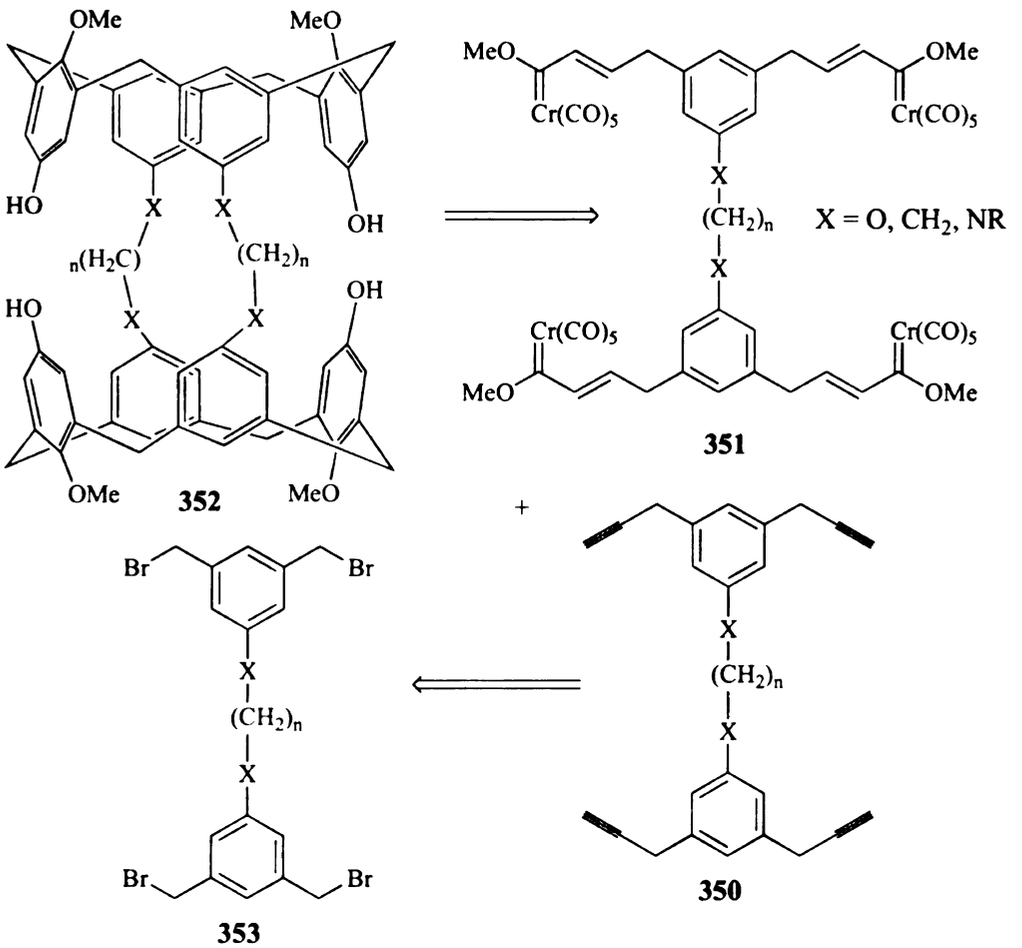
Scheme 6.1 Synthetic strategy to conformationally locked macrocycles in partial cone and 1,2-alternate conformation



6.2 Double calix[4]arenes by tandem heptannulation

Double calix[4]arenes wherein two of the cavities formed by calix[4]arenes are linked together can also be accessed by the triple annulation of carbene complexes and alkynes. More specifically, the reaction of tetrakis-carbene complex **351** and tetrayne **350** would be expected to furnish the double calix[4]arene **352** by a formal heptannulation process (Scheme 6.2). Despite their potential synthetic utility, this class of clathrand has been less popular due to the difficulty in their preparation. It has been known for example that quartenary ammonium ions can be held inside the cavity and thereby presents an attractive feature for examining reactions that generate such species in its vicinity. The tetrayne should be readily accessible from the known tetrabromide **353**[135] by Pd-catalyzed coupling with alkynyl indium reagent. The conversion of the tetrayne **350** to the tetrakis-carbene complex **351** would then follow a similar route as mentioned in this thesis earlier.

Scheme 6.2 Double calix[4]arene by heptannulation

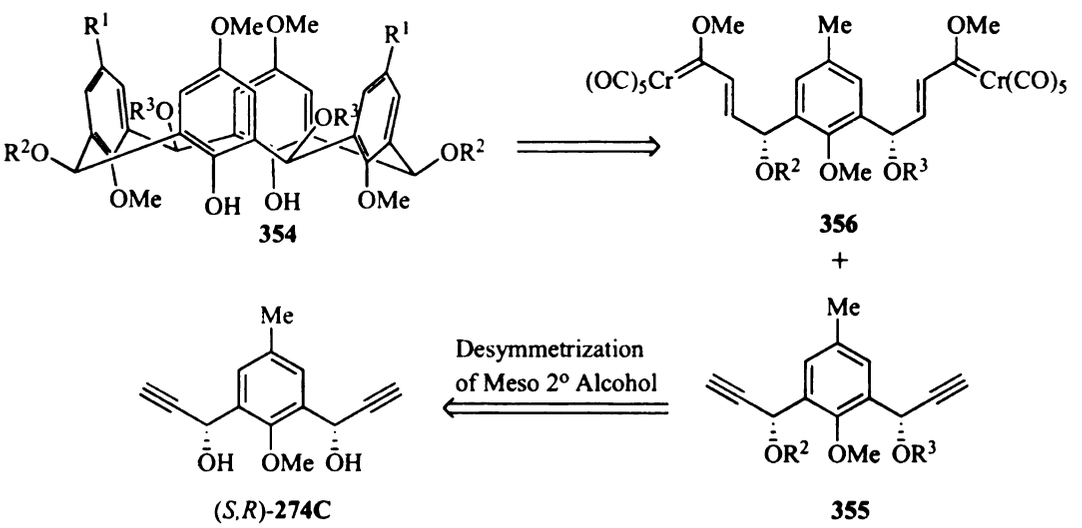


6.3 Equatorially substituted chiral calix[4]arenes with C_2 symmetry by desymmetrization of *meso* bis-propargyl arene

It is well known that resorcinarenes in crown conformation adopt axial orientation of the substituents at the bridges. This intrinsic feature has enabled development of several supramolecular cavitands based on resorcinarene framework by covalently linking the *endo* hydroxy groups by rigid tethers. Analogously, it is postulated that calix[4]arenes **354** would exhibit superior synthetic utility as they would be chiral by virtue of the presence of non-identical substituents at the adjacent positions and identical substituents at the distal positions on the methylene bridges. Such class of calix[4]arenes would be attainable by the reaction of bis-carbene complex **356** and bis-propargyl arene

355. The bis-propargyl arene with C_1 symmetry in turn can be obtained by desymmetrization of the bis-propargyl alcohol (*S,R*)-**274C** with C_s symmetry (Schemem 6.3).

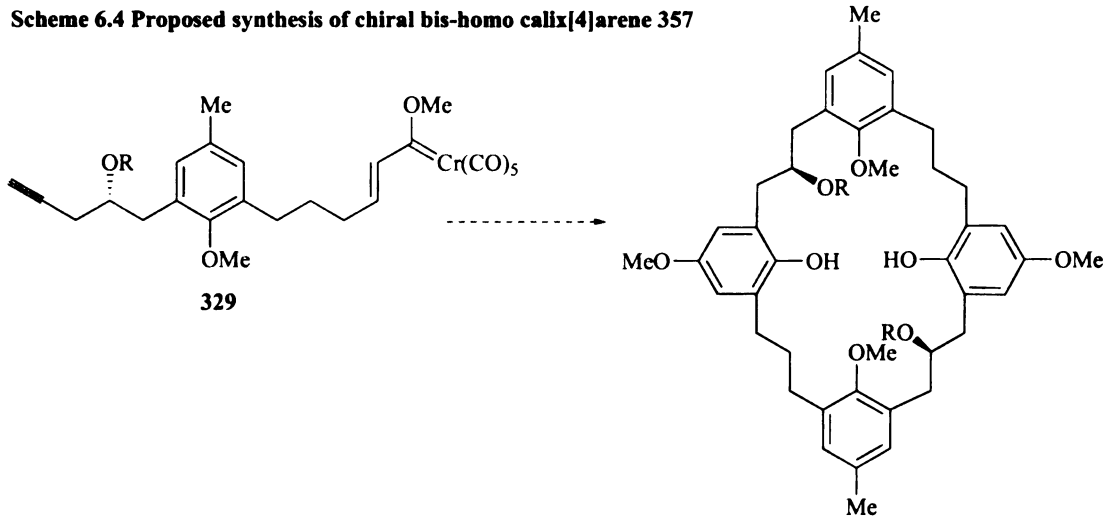
Scheme 6.3 Triple annulation approach towards equatorially substituted calix[4]arene 354



6.4 Chiral bishomocalix[4]arenes and synthesis of conformationally locked cavitand 215

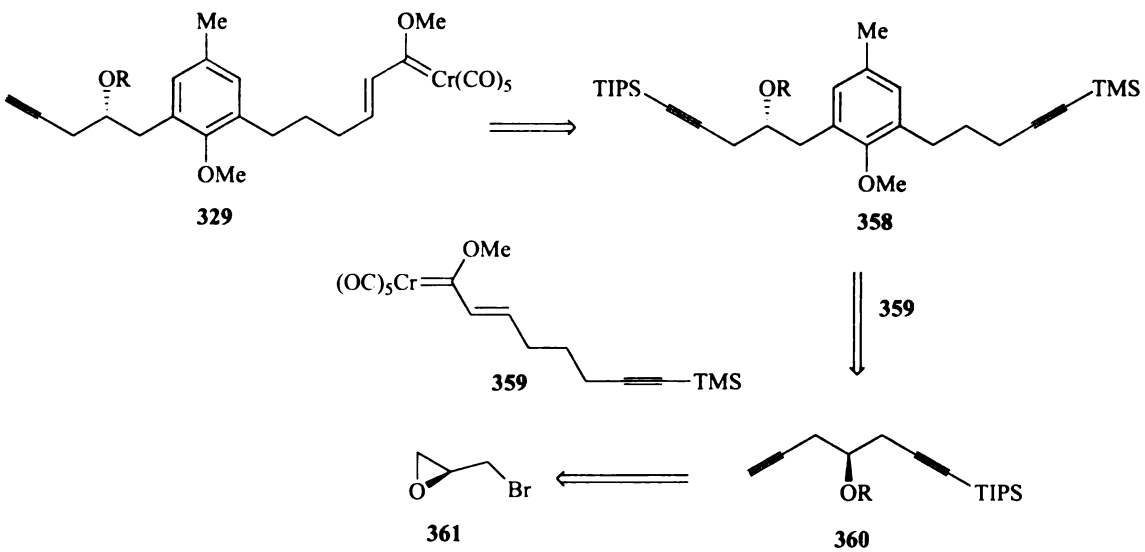
One of the possible applications of this chemistry is in the synthesis and development of chiral bis-homocalixarene cavitand **215** as a chiral ligand for asymmetric reactions. The feasibility of triple annulation by dimerization of alkynyl carbene complex **319** will solely determine the applicability of this strategy towards the target chiral cavitand **212**. Hence, the dimerization of complexes **319** will have to be examined carefully in favor of either homocalix[4]arenes **211** or *m*-cyclophanes **330** by varying the tether length and concentration (See Scheme 5.6). If the cyclization to form **211** can be optimized by adjusting the reaction conditions, it would be reasonable to expect that the macrocyclization of chiral carbene complex **329** would yield **357** (Scheme 6.4).

Scheme 6.4 Proposed synthesis of chiral bis-homo calix[4]arene 357



The alkynyl carbene complex **329** could be prepared from 2-(bromomethyl)oxirane **361** in a relatively straightforward sequence as shown in Scheme 6.5.

Scheme 6.5 Synthetic strategy for chiral alkynyl carbene complex 329



The transformation of the chiral bishomocalix[4]arene **357** into the chiral cavitand **215** could then be accomplished by ester formation as discussed earlier(Section 2.3.1). The potential utility of the chiral bis-homocalix[4]arene **215** has been discussed already in chapter 2.

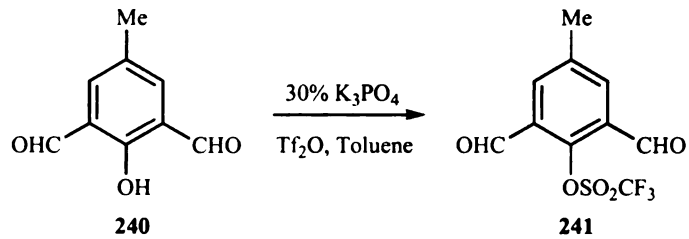
CHAPTER SEVEN

EXPERIMENTAL SECTION

General Experimental

All reactions were run using either oven-dried or flame-dried glassware under an inert atmosphere of argon. Chemicals used were reagent grade and used as supplied except where noted. The following solvents were distilled from the listed drying agents: Tetrahydrofuran (Na, benzophenone), diethyl ether (Na, benzophenone), toluene (Na), dichloromethane (CaH_2). Anhydrous 1,2-dichloroethane was purchased from Aldrich and used under atmosphere of argon. Silver nitrate (99.9995 % Ag) was purchased from Strem chemicals. Chromatographic purifications were performed on Merck silica gel grade (230-400 mesh) and TLC's were performed on silica coated plastic baked TLC plates from Silicycle. The general solvent systems used were either a combination of ethyl acetate / hexanes or dichloromethane / hexanes unless otherwise specified. Compounds were visualized by dipping the plate into a solution of $KMnO_4$ followed by heating with a heat-gun. ^1H NMR data obtained either on a Varian 300 MHz or 500 MHz instrument are reported in parts per million (δ) relative to tetramethyl silane (0.00 ppm) or chloroform (7.24 ppm) for spectra run in $CDCl_3$ and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets) and br (broad). ^{13}C NMR data were obtained on the Varian 300 MHz or 500 MHz instruments respectively and are reported in δ relative to $CDCl_3$ (77 ppm). Infrared spectra were recorded on Perkin Elmer FT IR instrument and the peaks are reported in cm^{-1}. 1-D NOE experiments and NOESY experiments were performed on a Varian 600

MHz NMR instrument. Mass spectral data and elemental analysis were obtained from Michigan State University Biochemistry Mass spectrometry facility and in-house facility. The mass spectra were obtained using direct probe EI (Electron impact) using chloroform as solvent on JEOL AX-505 double focusing mass spectometer, FAB (Fast atom bombardment) conditions using 2-nitrobenzyl alcohol as solvent on JEOL HX-110 double focusing mass spectrometer in the positive ionization mode. Data are reported in the form of m/z (intensity relative to base peak = 100). Organolithium reagents were purchased from Aldrich and titrated by the Watson-Eastham procedure[122] in benzene as the solvent whereas Grignard reagents purchased from Strem Chemicals and titrated to a known concentration following the procedure developed by Paquette et.al.[122] The indicated reaction temperatures are of the oil bath temperature monitored by a digital temperature controller. The reactions were often monitored for completion by quenching an aliquot of the reaction mixture in ether/water and then the ethereal layer was subjected to GC/MS analyses on Saturn 2000R mass spectrometer and 3800 GC using chrome-pack capillary column. Melting points (uncorrected) were recorded on a Thomas Hoover capillary melting point apparatus using 1.5-1.8×90 mm capillary tubes. Substrate **244A** (R_4 = OMe, R_2 = Me) was prepared in two steps from 2,6-bis-hydroxy-methyl-*p*-cresol in 73% overall yield following a literature procedure.[123] Compound **244D** (R_4 = OMe, R_2 = Ph) is also a known compound but a slightly different procedure was used for its preparation.[124] Optical rotation measurements were made on a Perkin Elmer 141 polarimeter at 589 nm (Sodium D Line) using 1dm cells. Specific rotations are reported in degrees per decimeter at 25°C and the concentration is given in grams per 100 mL. For rotation measurements, zero error correction was taken into account.

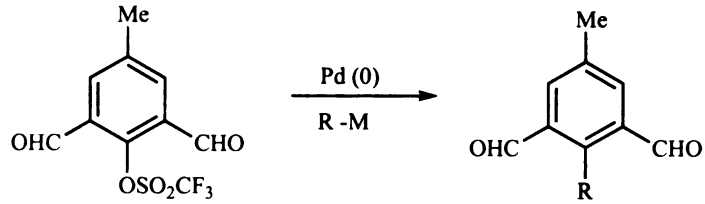


240 **241**

*Trifluoromethanesulfonic acid 2,6-diformyl-4-methyl-phenyl ester **241**:*

2-Hydroxy-5-methyl-benzene-1,3-dicarbaldehyde was either purchased from Trans-World Chemicals or obtained by manganese dioxide oxidation of 2,6-bis-hydroxymethyl-*p*-cresol just prior to use following the literature procedure.[125] The following procedure for preparation of the aryl triflate **241** was modified from that reported recently.[98] The phenol **240** (6.1 g, 37.2 mmol) was dissolved in 30 % aqueous solution of potassium phosphate (150 mL) and toluene (75 mL) was added. The resulting solution was red-orange in color and was stirred at ambient temperature for 15 min. Triflic anhydride (11.2 mL) was added dropwise at 0 °C with vigorous stirring and the resulting solution was warmed to room temperature and was stirred overnight. The reaction was subjected to an aqueous workup by washing with water (2 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. Purification by column chromatography yielded 64 % (7.05 g) of the desired compound as a white flaky solid. The phenol **240** was recovered by eluting with ethyl acetate and re-subjected to the reaction conditions and the overall yield of the triflate **241** could be improved to 83% (9.09 g, 30.73 mmol). R_f = 0.15 (10 % EtOAc / hexanes). Mp = 57-59 °C. Spectral data for **241**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.49 (s, 3H), 8.02 (s, 2H), 10.22 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.79, 118.55 (q, J = 319 Hz), 129.53, 135.91, 140.26, 147.24, 185.55; IR (CH_2Cl_2) 3063, 2893, 1699, 1597, 1466,

1435, 1389, 1292, 1248, 1203, 1122 cm^{-1}. Anal calcd for $C_{10}H_7F_3O_5S$: C, 40.55; H, 2.38. Found: C, 40.64; H, 2.30.



241 242

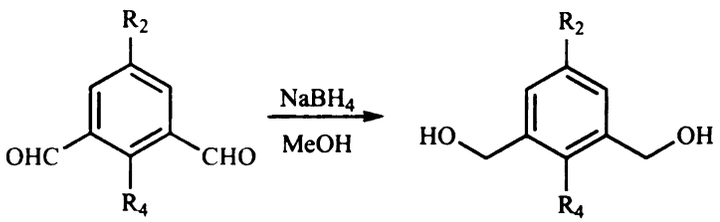
Palladium catalyzed Cross Coupling in the Preparation of the Dialdehyde 242.

*2-Hexyl-5-methyl-1,3-benzenedicarbaldehyde (R = C_6H_{13}) **242A**:* Aryl triflate **241** (4.13 g, 15.18 mmol) and dichlorobis(triphenylphosphine)palladium II (490 mg, 5 mol %) were transferred to a 100 mL three necked round bottomed flask and 50 mL of 1,4-dioxane was added. To another flask was added indium (III) chloride (1.122 g, 5.06 mmol), which was dried under vacuum with a heat gun. Tetrahydrofuran 45 mL was then added. Hexyl lithium (2.3M, 15.18 mmol) was subsequently added to the flask at –78 °C. The reaction mixture was then stirred at this temperature for 30 min and then warmed up to ambient temperature. The resulting trihexyl indium reagent generated in situ was added to the reaction mixture containing aryl triflate **241** and the catalyst in refluxing tetrahydrofuran under argon. The reaction was continued till the disappearance of the starting material was indicated by GC/MS. A few drops of methanol were added to quench the reaction. The mixture was concentrated in vacuo and ether (100 mL) was added. The organic phase was washed with aqueous hydrochloric acid (10 %, 50 × 2 mL), saturated aqueous sodium bicarbonate (60 × 2 mL), and saturated aqueous sodium chloride (60 × 2 mL), and then dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (5 % ethyl acetate / hexanes) to afford, after concentration and drying under high vacuum, 1.65 g (47 %, 7.14

mmol) of the cross-coupled product as an yellow oil. R_f (hexanes/ethyl acetate 19/1) = 0.25. Spectral data for **242A**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.90 (t, 3 H, J = 6.3 Hz), 1.32-1.65 (m, 8 H), 2.46 (s, 3 H), 3.42 (t, 2 H, J = 6.9 Hz), 7.90 (s, 2 H), 10.39 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.95, 20.54, 22.49, 25.64, 29.29, 31.45, 33.49, 134.69, 136.40, 136.56, 145.15, 191.16; IR (neat) 2959, 2928, 2857, 2756, 2731, 1689, 1608, 1570, 1462, 1396, 1281, 1234, 1107 cm^{-1}; mass spectrum *m/z* (% rel. intensity) 232 M^+ (20), 175 (25), 84 (100), HRMS calcd for $C_{15}H_{20}O_2$ *m/z* 232.1463, measd 232.1464.

4- Methylbiphenyl-2,6-dicarbaldehyde (R = Ph) ***242B*****:** Aryl triflate **241** (6.22 g, 21 mmol), phenyl boronic acid (282 mg, 23.1 mmol), tetrakis(triphenylphosphine)palladium (0) (606 mg, 2.5 mol %), and anhydrous potassium phosphate (6.69 g, 31.5 mol) were placed in a 250 mL Schlenk flask under Argon atmosphere. Degassed 1,4-dioxane (100 mL) was added. The resulting mixture was deoxygenated by the freeze-thaw method (-196 to 25°C, 2 cycles), backfilled with argon and subsequently stirred at 85 ° C till the conversion was > 95 % as estimated by GC / MS. The mixture was diluted with benzene (200 mL) and treated with 30 % aqueous basic hydrogen peroxide. The product was extracted with ether (200 mL) and subsequent removal of solvent under reduced pressure afforded the crude material. Purification by column chromatography on silica gel 5 % to 10 % ethyl acetate/hexanes yielded (4.0 g, 5.29 mmol, 85 %) of the desired compound **242B** as a white solid. Mp = 124 °C; R_f (hexanes/ethyl acetate 9/1) = 0.35. Spectral data for **242B**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.49 (s, 3H), 7.30-7.49 (m, 5H), 8.03 (s, 2H), 9.77 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.84, 128.32, 128.74, 130.87, 132.42, 132.82, 134.56, 138.46, 145.56, 190.95; IR (CH_2Cl_2) 3053, 3034, 2893, 2868, 2762, 1687, 1560, 1450, 1397, 1230 cm^{-1}; mass

spectrum *m/z* (% rel intensity) 224 M^+ (100), 195 (93), 181 (43), 165 (60), 152 (55), HRMS calcd for $C_{15}H_{12}O_2$ *m/z* 224.0837, measd 224.0836. Anal Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.08; H, 5.20.



242 **244**

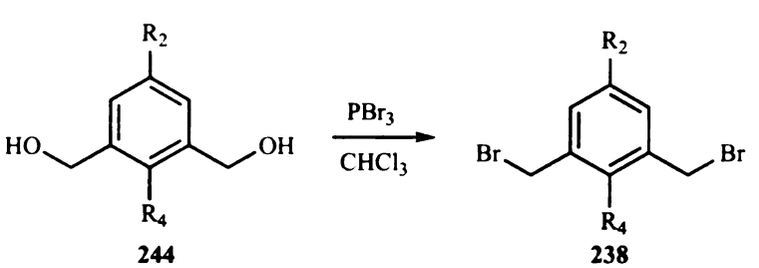
Reduction of the Dialdehyde 242 to the bis-Hydroxymethylarene 244.

(2-Hexyl-3-hydroxymethyl-5methylphenyl)methanol (R_4 = C_6H_{13}, R_2 = Me) ***244B****:* The aldehyde **242A** (0.74 g, 3.2 mmol) was dissolved in 25 mL of methanol in a 50 mL three necked round bottomed flask and sodium borohydride was added at 0°C. The resultant clear solution was left stirring for 30 min at this temperature and then warmed to room temperature upon which further stirring was continued for 1 h. The reaction was quenched by addition of water and then the organic layer was extracted into ether (100 mL). Drying over anhydrous magnesium sulfate followed by removal of the solvent under reduced pressure yielded the product **244B** in 91 % yield (0.69 g, 2.92 mmol). Mp = 78-80 °C. Spectral data for **244B**: R_f = 0.19 (hexanes/ethyl acetate 3/1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, 3 H, *J* = 6.9 Hz), 1.30-1.51 (m, 10 H), 2.32 (s, 3 H), 2.67 (t, 2 H, *J* = 6.6 Hz), 4.70 (s, 4 H), 7.17 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.08, 20.96, 22.65, 27.97, 29.94 31.63, 31.79, 63.18, 128.83, 135.85, 136.09, 138.84; IR (CH_2Cl_2) 3350, 3260, 2953, 2920, 2870, 1469, 1265 cm^{-1}. Anal calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.89; H, 10.43.

(6-Hydroxymethyl-4-methylbiphenyl-2-yl)methanol (R_4 = Ph, R_2 = Me) ***244C*** : Following the above procedure, the aldehyde **242B** (3.68 g, 16.42 mmol) afforded upon

workup **244C** as a white solid in 95 % yield (3.55 g, 15.6 mmol). Mp = 131-133 °C. Spectral data for **244C**: R_f = 0.16 (hexanes/ethyl acetate 3/1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3 H), 3.85 (t, 2 H, *J* = 5.2 Hz), 4.26 (d, 4 H, *J* = 5.4 Hz), 7.17 (d, 2 H, *J* = 7.0 Hz), 7.348 (s, 2 H), 7.352 (t, 1 H, *J* = 7.5 Hz), 7.41 (t, 2 H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.84, 61.95, 126.34, 127.11, 128.33, 129.67, 135.78, 136.65, 138.89, 139.70; IR (CH_2Cl_2) 3424, 2926, 1645, 1221 cm^{-1}; mass spectrum *m/z* (% rel. intensity) 228 M^+ (100), 210 (97), 192 (93), 181 (97), 165 (97), HRMS calcd for $C_{15}H_{16}O_2$ *m/z* 228.1150, measd 228.1154. Anal calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.58; H, 6.99.

3,5-bis-hydroxymethyl-4-methoxybiphenyl (R_4 = OMe, R_2 = Ph) ***244D***: 2,6-bis-(hydroxymethyl)-4-phenylphenol was prepared in 90 % yield by formylation of 4-phenyl phenol under basic conditions.[126] The phenol was then converted to **244D** following Cram's procedure for the methylation of 2,6-bis-(hydroxymethyl)-*p*-cresol in 87% yield.[123] R_f = 0.21 (hexanes/ ethyl acetate = 1/1). Mp = 96-98 °C. Spectral data for **244D**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.07 (s, 2 H), 3.87 (s, 3 H), 4.78 (s, 4 H), 7.32 (t, 1 H, *J* = 7.5 Hz), 7.41 (t, 2 H, *J* = 8.0 Hz), 7.546 (s, 2 H), 7.55 (d, 2 H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 61.10, 61.25, 126.99, 127.27, 127.57, 128.76, 134.25, 137.79, 140.29, 155.59.



244 **238**

Conversion of the bis-Hydroxymethylarenes 244 to the bis-Bromomethylarenes 238.

1,3- Bis-bromomethyl-2-hexyl-5-methylbenzene (R_4 = C_6H_{13}, R_2 = Me) ***238B*****:** The alcohol **244B** (0.64 g, 2.71 mmol) was dissolved in 20 mL of chloroform and phosphorus tribromide (1M in dichloromethane, 5.6 mL) was added dropwise and the mixture was stirred at ambient temperature until complete conversion to the product had occurred. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (50 mL) and the organic layer washed once with water (100 mL). Concentration of the solvent under vacuum gave the desired product as yellow oil. Purification by silica gel chromatography (10 % dichloromethane/hexanes) gave the bromide **238B** as a white solid in 59 % yield (0.52 g, 1.59 mmol). Mp = 47-49 °C. R_f = 0.44 (hexanes/dichloromethane = 9/1). Spectral data for **238B**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3 H, J = 7.1 Hz), 1.33 (m, 4 H), 1.52 (m, 2 H), 1.64 (m, 2 H), 2.28 (s, 3 H), 2.80 (t, 2 H, J = 8.1 Hz), 4.50 (s, 4 H), 7.13 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.07, 20.62, 22.61, 28.45, 29.89, 31.33, 31.55, 31.69, 132.31, 136.31, 136.39, 137.91; IR (CH_2Cl_2) 3049, 2955, 2926, 2860, 1479, 1462, 1265, 1209 cm^{-1}; mass spectrum *m/z* (% rel. intensity) 360.01 M^+ (^{79}Br, ^{79}Br, 51), 362.01 M^+ (^{79}Br, ^{81}Br, 100), 364.01 M^+ (^{81}Br, ^{81}Br, 50), 281 (15), 211 (100), 132 (43), 91 (13), HRMS calcd for $C_{15}H_{22}Br_2$ *m/z* 360.0088, measd 360.0089. Anal calcd for $C_{15}H_{22}Br_2$: C, 49.75; H, 6.12. Found: C, 49.86; H, 6.44.

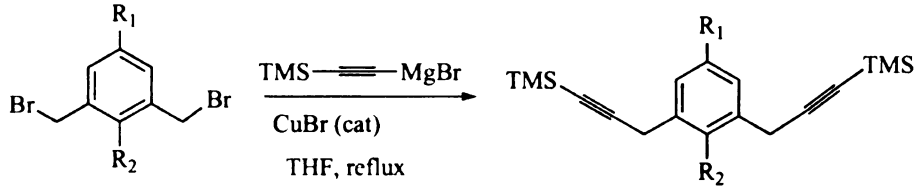
2,6-bis-bromomethyl-4-methylbiphenyl (R_4 = Ph, R_2 = Me) ***238C***: Following the procedure mentioned above for synthesis of 240A, the alcohol **244C** (3.55 g, 15.57 mmol) was transformed into **238C** as a white solid in 86 % yield (4.74 g, 13.39 mmol). Mp = 101-103 °C. R_f = 0.34 (hexanes/dichloromethane = 9/1) Spectral data for **238C**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 4.16 (s, 4H), 7.27 (s, 2H), 7.32-7.42 (m, 5H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.96, 31.96, 127.87, 128.27, 129.49, 131.32, 136.54, 136.56, 138.27, 139.02; IR (CH_2Cl_2) 3053, 2982, 1614, 1458, 1442, 1285, 1213 cm^{-1}; mass spectrum *m/z* (% rel intensity) 351.94 M^+ (^{79}Br, ^{79}Br, 6.6), 353.94 M^+ (^{79}Br, ^{81}Br,13), 355.94 M^+ (^{81}Br, ^{81}Br, 6.5), 193 (100), 178 (35), 83 (60), HRMS calcd for $C_{15}H_{14}Br_2$ *m/z* 351.9462, measd 351.9441. Anal calcd for $C_{15}H_{14}Br_2$: C, 50.88; H, 3.99. Found: C, 50.98; H, 3.90.

3,5-Bis-bromomethyl-4-methoxybiphenyl (R_4 = OMe, R_2 = Ph) ***238D***: The procedure above for **238B** was followed and the alcohol **244D** (3.66 g, 15 mmol) gave 4.38 g (11.85 mmol, 79 %) of **238D** as white solid. Mp = 100-103 °C. Spectral data for **238D**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.93 (s, 3 H), 4.48 (s, 4 H), 7.23 (t, 1 H, *J* = 6.9 Hz), 7.31 (t, 2 H, *J* = 7.2 Hz), 7.42 (d, 2 H, *J* = 7.2 Hz), 7.46 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.56, 62.36, 126.94, 127.62, 128.86, 130.84, 132.19, 138.19, 139.45, 155.91; mass spectrum *m/z* (% rel intensity) 372 M^+ (^{81}Br, ^{81}Br, 50), 370 M^+ (^{79}Br, ^{81}Br, 100), 368 M^+ (^{79}Br, ^{79}Br, 51), 291 (93), 289 (094), 182 (45), 181 (100).

Preparation of the Silyl Substituted Diynes 239.

Method A

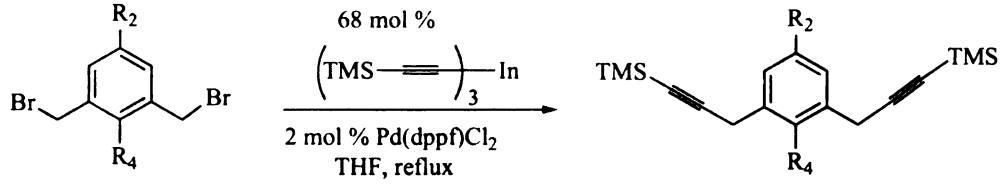


238 **239**

Trimethylsilylethynylmagnesium bromide[127] (8 eq) was generated in situ by the addition of ethylmagnesium bromide (3 M solution in THF, 8 eq) to ethynyltrimethylsilane (8 eq) in tetrahydrofuran (*c* = 1.6-2.4 M) at 0 °C followed by stirring at this temperature for 30 min. The resulting slurry was stirred at room

temperature over 0.5 h. Copper (I) bromide (15 mol %) was added and stirred for another 0.5 h. Benzyl halides **238** (1 mmol) were subsequently added and then the reaction mixture was refluxed until disappearance of the starting material was indicated by thin-layer chromatography or GC / MS. Saturated ammonium chloride (40 mL) was then added to quench the reaction and the organic layer was separated and extracted with ether (2 x 50 mL). The combined organic layer was washed once with water (equal volume) and then dried over anhydrous magnesium sulfate. The resultant organic layer was filtered through a silica gel pad and stripped of solvent under reduced pressure to give the crude compound **239**. For consistency in yields, it is highly important that the starting benzyl halides are purified and the reagents are either freshly prepared or titrated to verify concentration.

Method B



Trimethylsilylethynyllithium[127] (19.2 mmol) was prepared by addition of *n*-butyllithium (12 mL, 19.2 mmol) to trimethylsilylacetylene (3 mL, 21.22 mmol) in tetrahydrofuran (20 mL) in a 100 mL flame-dried round bottom flask under argon at –78 °C. The resulting solution was allowed to warm to room temperature for 10 to 15 min. Indium (III) chloride (1.42 g, 6.4 mmol) was added to a three-necked 100 mL round bottom flask and dried under vacuum with a heat gun. Positive argon pressure was then established and THF (30 mL) was added. The resulting solution was cooled to –78 °C and trimethylsilylethynyllithium was added drop-wise via syringe. The mixture was

subsequently warmed to room temperature. The bis-benzyl halide **238** (8 mmol) and $Pd(dppf)Cl_2$ (131 mg, 0.16 mmol) were introduced into a flame-dried three-necked 200 mL round-bottomed flask and THF (32 mL) was added. The solution of trialkynylindium reagent was added to this flask under refluxing conditions and the reaction was continued until the disappearance of the starting material was determined as monitored by GC/mass spec. The reaction was then quenched by the addition of 50 mL of methanol and the solvent was removed under vacuum. Ether (200 mL) was added and the organic layer was washed with 10 % hydrochloric acid (2 x 100 mL), saturated sodium bicarbonate (2 x 100 mL) and saturated sodium chloride solution (2 x 100 mL). The resulting solution was filtered through a pad of silica gel to remove any inorganic impurities and upon concentration under reduced pressure the crude product was obtained. Indium trichloride is extremely moisture sensitive and therefore needs to be handled carefully in order to obtain the best results.

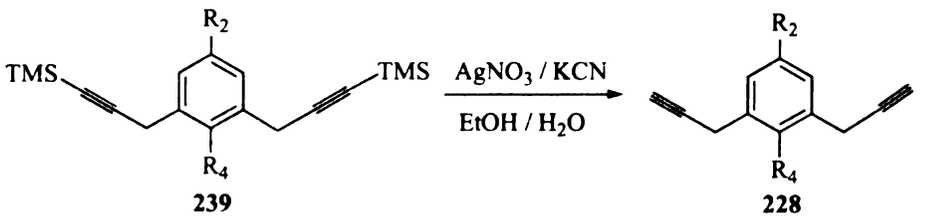
*2-Methoxy-5-methyl-1,3-bis-[3-(trimethylsilanyl)prop-2-ynyl]benzene (R_4 = OCH_3, R_2 = CH_3) **239A**:* Following method B, the bromide **238A** (2.46 g, 8 mmol) gave upon purification by silica gel chromatography (20 % dichloromethane/hexanes) diyne **239A** as an yellow oil in 80 % yield (2.19 g, 6.4 mmol). R_f = 0.36 (hexanes/dichloromethane = 4/1). Spectral data for **239A**: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.22 (s, 18 H), 2.37 (s, 3 H), 3.65 (s, 4 H), 3.79 (s, 3 H), 7.23 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.04, 20.47, 20.91, 61.02, 86.49, 104.64, 128.98, 129.16, 133.82, 153.05; IR (neat) 2961, 2901, 2832, 2178, 1482, 1250 cm^{-1}; mass spectrum *m/z* (% rel intensity) 342 M^+ (100), 327 (80), 239 (50), 156 (35), 73 (90), HRMS calcd for $C_{20}H_{30}OSi_2$ *m/z* 342.1835, measd 342.1835.

*2- Hexyl-5-methyl-1,3-bis-[3-(trimethylsilanyl)prop-2-ynyl]benzene (R_4 = C_6H_{13}, R_2 = CH_3) **239B*** : Following method A, the bromide **238B** (2.79 g, 7.5 mmol) gave upon purification by silica gel chromatography with 15 % dichloromethane/hexanes the diyne **239B** as a yellow oil in 66 % yield (1.95 g, 4.95 mmol). The average yield for three runs using varied amounts of the benzyl bromide was found to be 73 %. R_f (dichloromethane/hexanes = 15/85) = 0.49. Spectral data for **239B**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.19 (s, 18 H), 0.95 (t, 3 H, J = 6.5 Hz), 1.36-1.53 (m, 8 H), 2.35 (s, 3 H), 2.64 (t, 2 H, J = 8.0 Hz), 3.62 (s, 4 H), 7.23 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.04, 14.10, 20.96, 22.72, 24.04, 28.55, 29.73, 29.97, 31.61, 86.79, 104.85, 128.56, 134.37, 135.45, 135.52; IR (neat) 2989, 2176, 1614, 1468, 1410, 1250 cm^{-1}; HRMS calcd for $C_{25}H_{40}Si_2$ *m/z* 396.2669, measd 396.2664. Anal calcd for $C_{25}H_{40}Si_2$: C, 75.68; H, 10.16. Found: C, 75.76; H, 9.87.

*4-Methyl-2,6-bis-[(3-(trimethylsilanyl)prop-2-ynyl]biphenyl (R_4 = Ph, R_2 = Me) **239C*** : Following method A, the bromide **238C** (3.79 g, 10.78 mmol) gave the diyne **239C** in 71 % yield (2.9 g, 7.66 mmol) as a yellow oil after purification by silica gel chromatography (15 % dichloromethane/hexanes). Following method B, an 81 % yield of **239C** was obtained. The resulting oil if left in the freezer at -20°C became a light yellow solid. Mp= 55-58°C .R_f (hexanes/dichloromethane 85/15) = 0.45. Spectral data for **239C**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 18 H), 2.41 (s, 3 H), 3.23 (s, 4 H), 7.12 (d, 2 H, J = 7.3 Hz), 7.3-7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.14, 21.32, 24.90, 86.69, 104.94, 127.22, 127.59, 128.54, 129.39, 134.42, 137.44, 137.59, 138.57; IR (neat) 2959, 2899, 2176, 1466, 1410, 1250 cm^{-1}; mass spectrum *m/z* (% rel intensity) 388 M^+

(8), 315 (18), 285 (15), 179 (17), 83 (100), calcd for $C_{15}H_{22}Si_2$ *m/z* 388.2043, measd 388.2044.

*4-Methoxy-3,5-bis-[3-(trimethylsilanyl)prop-2-ynyl]biphenyl (R_4 = OCH_3, R_2 = Ph) **239D**:* Following method B, bromide **238D** (2.85 g, 7.7 mmol) gave upon purification in 20 % dichloromethane/hexanes **239D** in 77 % yield (2.39 g, 5.93 mmol) as a white solid. Mp = 72-74 °C. R_f = 0.31 (hexanes/dichloromethane 4/1). Spectral data for **239D**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 18 H), 3.59 (s, 4 H), 3.69 (s, 3 H), 7.21 (t, 1 H, *J* = 7.2 Hz), 7.32 (t, 2 H, *J* = 7.5 Hz), 7.49 (d, 2 H, *J* = 7.2 Hz), 7.57 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.05, 20.75, 60.89, 87.12, 104.34, 126.85, 127.08, 127.13, 128.73, 129.87, 137.19, 140.64, 154.86; IR (neat) 3130, 3100, 2957, 2899, 2178, 1690, 1590, 1456, 1404, 1248 cm^{-1}. Anal calcd for $C_{25}H_{32}OSi_2$: C, 74.20; H, 7.97. Found: C, 74.51; H, 7.89.



Preparation of the Diynes 228 by Desilylation of 239.

A solution of the diyne **239** (1 mmol) in ethanol (4.5 mL) was added to a 12 mL aqueous ethanol solution (ethanol / water = 2.3 / 1 v/v) of silver nitrate (3 eq) whereupon a milky white precipitate appeared immediately upon addition indicating the presence of silver acetylide. The resulting slurry was stirred shielded from light at ambient temperature for 5 h or overnight. A solution of potassium cyanide (8 eq) in 1 mL of water was then added. The mixture was stirred for another hour and then the solution was diluted with 100 mL ether. The organic layer was washed with water (4 × 25 mL), brine

(4 × 25 mL), dried over anhydrous magnesium sulfate and concentrated under vacuum. Purification was either achieved by column chromatography on silica gel or by crystallization.

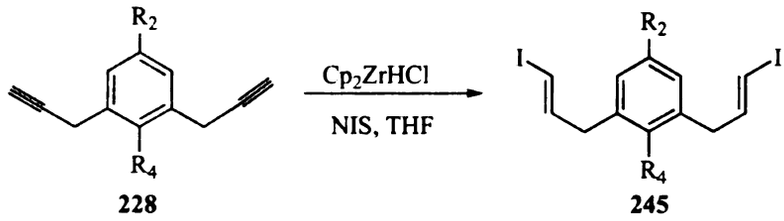
2-Methoxy-5-methyl-1,3-diprop-2-ynylbenzene (R_4 = OMe, R_2= Me) ***228A*****:** The diyne **239A** (2.28 g, 6.66 mmol) upon desilylation following the general procedure and purification by crystallization from hexanes at 0 °C gave **228A** as a white solid in 91 % yield (1.2 g, 6.06 mmol). Mp = 40-42 °C. R_f = 0.25 (20 % CH_2Cl_2/hexanes). Spectral data for **228A**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.21 (t, 2 H, *J* = 2.7 Hz), 2.37 (s, 3 H), 3.63 (d, 4 H, *J* = 2.7 Hz), 3.81 (s, 3 H), 7.26 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.05, 20.79, 61.03, 70.06, 82.16, 129.06, 134.17, 152.99 (1 aryl carbon not observed); IR (CH_2Cl_2) 3294, 2943, 2830, 2150, 1653, 1479, 1223 cm^{-1}. Anal calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.84; H, 6.94.

2-Hexyl-5-methyl-1,3-diprop-2-ynylbenzene (R_4 = C_6H_{13}, R_2= Me) ***228B****:* The diyne **239B** (1.81 g, 4.55 mmol) upon desilylation and purification by silica gel chromatography (hexanes) in gave **228B** in 69 % yield (0.79 g, 3.14 mmol) as colorless oil. The average yield for three runs with varying amounts of **239B** in this case was found to be 73 %. R_f (hexanes) = 0.32. Spectral data for **228B**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3 H, *J* = 6.6 Hz), 1.37-1.49 (m, 8 H), 2.21-2.24 (m, 2 H), 2.37 (s, 3 H), 2.67 (t, 2 H, *J* = 6.6 Hz), 3.59 (s, 4 H), 7.26 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.06, 20.92, 22.54, 22.62, 28.54, 29.89, 29.96, 31.58, 70.53, 82.36, 128.56, 134.24, 135.29, 135.82; IR (neat) 3304, 2926, 2856, 2120, 1684, 1466 cm^{-1}; mass spectrum *m/z* (% rel intensity) 252 M^+ (70), 181 (100), 165 (100), 141 (75), 128 (65), 115 (50), calcd for

$C_{19}H_{24}$ *m/z* 252.1878, measd 252.1880. Anal calcd for $C_{19}H_{24}$: C, 90.42; H, 9.58. Found: C, 90.03; H, 9.82.

4-Methyl-2,6-diprop-2-ynylbiphenyl (R_4 = Ph, R_2= Me) ***228C***: The diyne **239C** (1.03 g, 2.66 mmol) upon desilylation and purification by silica gel chromatography (10 % dichloromethane in hexanes) afforded **228C** as a white solid in 77 % yield (0.50 g, 2.05 mmol). [Note: This compound is light sensitive; the white solid turns orange over a few weeks]. Mp = 36-39 °C. R_f = 0.28 (dichloromethane/hexanes = 1/9). Spectral data for **228C**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 2 H), 2.48 (s, 3 H), 3.26 (s, 4 H), 7.19 (d, 2 H, *J* = 7.8 Hz), 7.43-7.48 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.26, 23.34, 70.39, 82.45, 127.39, 127.59, 128.71, 129.37, 134.33, 137.45, 137.77, 138.60; IR (CH_2Cl_2) 3300, 2918, 2849, 2120, 1736, 1464, 1246 cm^{-1}; mass spectrum *m/z* (% rel intensity) 244 M^+ (80), 229 (100), 205 (55), 189 (40), 101 (30), calcd for $C_{19}H_{16}$ *m/z* 244.1252, measd 244.1256.

4-Methoxy-3,5-prop-2-ynylbiphenyl (R_4 = OMe, R_2 = Ph) ***228D*****:** The diyne **239D** (2.69 g, 6.66 mmol) upon and purification by crystallization from hexanes at 0 °C gave **228D** as a white solid in 90 % yield (1.55 g, 5.94 mmol). Mp = 64-67 °C. R_f = 0.21 (20 % CH_2Cl_2/ hexanes). Spectral data for **228D**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (t, 2 H, *J* = 2.7 Hz), 3.67 (d, 4 H, *J* = 2.7 Hz), 3.82 (s, 3 H), 7.32 (t, 1 H, *J* = 7.4 Hz), 7.40-7.45 (t, 2 H, *J* = 7.4 Hz), 7.58 (d, 2 H, *J* = 7.4 Hz), 7.64 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.35, 61.12, 70.51, 81.88, 127.09, 127.32, 128.72, 129.77, 137.66, 140.54, 154.76, 156.99; IR (CH_2Cl_2) 3294, 2941, 2831, 2120, 1686, 1473, 1240 cm^{-1}. Anal calcd for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.27; H, 6.36.



228 245

Synthesis of the bis-(*E*)-Vinyl Iodides 245 by Hydrozirconation.

Schwartz's reagent was prepared following a literature procedure:[105] a solution of bis-cyclopentadienylzirconium dichloride (4 eq) in tetrahydrofuran (c = 0.12-0.15 M) was treated with Super Hydride (4 eq) and subsequently stirred for 1 h shielded from light. To this freshly prepared Schwartz reagent was added the diyne (1 mmol) and the mixture was stirred at room temperature for 1 h. N-Iodosuccinimide (4 eq) was subsequently added and stirring continued for 4 h. The reaction was quenched by pouring it into saturated sodium bicarbonate solution (40 mL). A solution of 10 % ethyl acetate/hexanes (100 mL) was added and the organic layer separated and washed with brine (40 mL), dried over anhydrous magnesium sulfate. After filtration through a bed of Celite atop a short plug of silica gel with 10 % ethyl acetate/hexanes the solvents were removed to give the crude compound as a oil. Purification by column chromatography on silica gel afforded the desired product as a clear oily liquid.

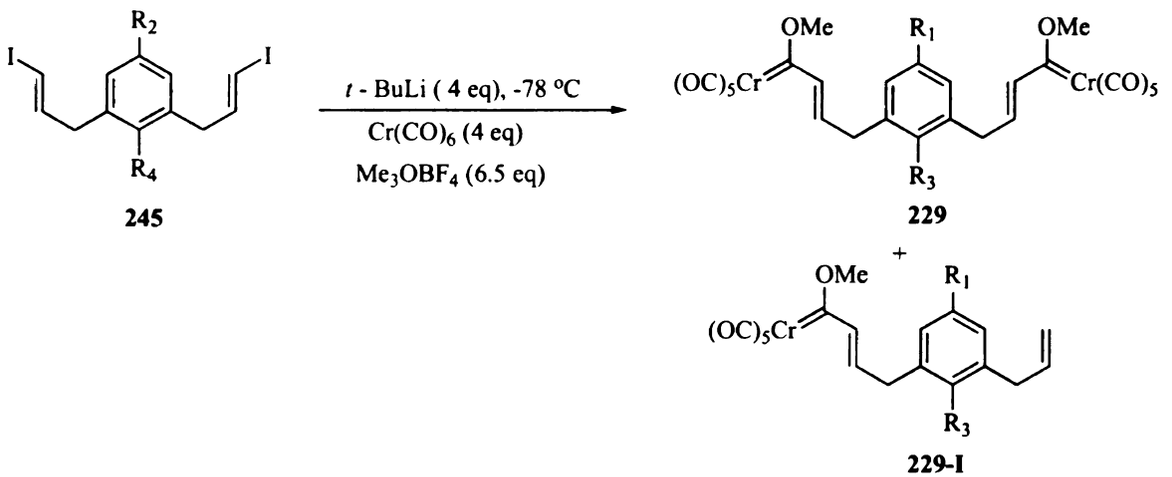
1,3-Bis-(3-iodoallyl)-2-methoxy-5-methylbenzene (R_4=OMe, R_2=Me) ***245A*****:** The diyne **228A** (0.297 g, 1.5 mmol) was subjected to hydrozirconation/iodination following the general procedure and vinyl iodide **245A** was obtained by silica gel chromatography (20 % dichloromethane/hexanes) in 86 % yield as colorless oil (0.59 g, 1.29 mmol). R_f = 0.43 (hexanes/dichloromethane 4/1). Spectral data for **245A**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 3.35 (d, 4H, J = 6.9 Hz), 3.65 (s, 3 H), 6.06 (dt, 2 H, J = 14.0, 1.5 Hz), 6.62-6.67 (m, 2 H), 6.88 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.76,

36.16, 61.48, 76.14, 129.53, 131.02, 133.94, 144.49, 153.88; IR (neat) 3045, 2931, 2828, 1604, 1478, 1232, 1209 cm^{-1}; mass spectrum *m/z* (% rel intensity) 454 M^+ (85), 307 (36), 200 (30), 154 (100), calcd for $C_{14}H_{16}I_2O$ *m/z* 453.9291, measd 453.9291.

2-Hexyl-1,3-bis-(3-iodoallyl)-5-methylbenzene (R_4=C_6H_{13},R_2=Me) ***245B***: The product was purified by silica gel chromatography (hexanes) and obtained in 77 % yield as a colorless oil. R_f (hexanes) = 0.24. Spectral data for **245B**: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92-0.96 (t, 3 H, *J* = 6.4 Hz), 1.34-1.42 (m, 8 H), 2.31 (s, 3 H), 2.53 (t, 2 H, *J* = 7.3 Hz), 3.38 (d, 4 H, *J* = 6.6 Hz), 6.02 (d, 2 H, *J* = 14.5 Hz), 6.63-6.78 (m, 2 H), 6.87 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.04, 20.86, 22.68, 28.77, 29.92, 30.94, 31.68, 39.55, 75.92, 129.25, 135.68, 136.18, 136.31, 145.08; IR (neat) 3045, 2955, 2924, 2870, 1610, 1466, 1202 cm^{-1}; mass spectrum *m/z* (% rel intensity) 508 M^+ (100), 381 (8), 310 (8), 297 (5), 254 (55), 183 (40), 155 (20), 143 (50), 128 (30).

2,6-Bis-(3-iodoallyl)-4-methylbiphenyl (R_4=Ph, R_2=Me) ***245C***: The diyne **228C** (0.366 g, 1.5 mmol) was subjected to the general procedure and upon purification by silica gel chromatography in 15 % dichloromethane/hexanes gave the vinyl iodide **245C** in 73 % yield (0.554 g, 1.1 mmol) as a colorless oil. R_f (hexanes/dichloromethane 85/15) = 0.4. Spectral data for **245C**: ^1H NMR ($CDCl_3$, 500 MHz) δ 2.36 (s, 3 H), 3.02 (d, 4 H, *J* = 6.9 Hz), 5.68 (d, 2 H, *J* = 13.5 Hz), 6.36-6.45 (m, 2 H), 6.95 (s, 2 H), 7.05 (d, 2 H, *J* = 6.5 Hz), 7.33 (t, 1 H, *J* = 7.0 Hz), 7.38 (t, 2 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.12, 40.26, 75.96, 127.22, 128.26, 128.36, 129.61, 136.46, 137.52, 138.64, 139.06, 144.59; IR (neat) 3053, 3020, 2918, 2853, 1611, 1466, 1441, 1209 cm^{-1}; mass spectrum *m/z* (% rel intensity) 500 M^+ (30), 374 (100), 247 (65), 206 (80), 85 (55), calcd for $C_{19}H_{18}I_2$ *m/z* 499.9498, measd 499.9499.

3,5-Bis-(3-iodoallyl)-4-methoxybiphenyl (R_4 = OMe, R_2 = Ph) ***245D*****:** Following the general procedure, diyne **228D** (0.686 g, 2.64 mmol) gave vinyl iodide **245D** in 78 % yield (1.06 g, 2.06 mmol) upon purification by silica gel chromatography 20 % dichloromethane/hexanes as white solid. Mp = 69-71 °C. R_f = 0.33 (hexanes/dichloromethane 4/1). Spectral data for **245D**: ^{1}H NMR ($CDCl_3$, 300 MHz) 3.32 (d, 4 H, J = 6.9 Hz), 3.59 (s, 3 H), 5.98 (d, 2 H, J = 14.5 Hz), 6.52-6.59 (m, 2 H), 7.11 (s, 2 H), 7.19 (t, 1 H, J = 6.9 Hz), 7.28 (t, 2 H, J = 7.5 Hz), 7.37 (d, 2 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.46, 61.59, 76.35, 127.04, 127.26, 127.81, 128.78, 131.82, 137.71, 140.49, 144.29, 155.79; IR (CH_2Cl_2) 3053, 2943, 2828, 1603, 1472, 1242 cm^{-1}; mass spectrum *m/z* (% rel intensity) 516 M^+ (100), 404 (8), 390 (5), 373 (20), 262 (35), 222 (100), 207 (30). Anal. Calcd for $C_{19}H_{18}I_2O$: C, 44.21; H, 3.52. Found: C, 44.51; H, 3.79.



Preparation of the Bis-Carbene complexes 229.

To a solution of vinyl iodide **245** (1 mmol) in tetrahydrofuran (c = 0.05 M) at –78 °C was added *t* -Butyllithium (4 eq, 1.7 M in pentane) and the reaction mixture was stirred at –78 °C for 30 min. Chromium hexacarbonyl (4 eq) was dissolved in 45 mL of tetrahydrofuran and then transferred via cannula to the organolithium solution under

argon at –78 °C. The resulting deep red solution was warmed to room temperature and stirred for 3 h. The solvent was evaporated under vacuum and water/ dichloromethane (1:1, 50 mL) was added and then trimethyl oxonium tetrafluoroborate (6.5 eq) was added and the mixture stirred for 30 min. The organic layer (150 mL) was washed with water (2 x 50 mL) and dried over anhydrous magnesium sulfate. After filtration the solvent was removed and crude product was purified by silica gel chromatography to give carbene complex as a red oil. In each case a small amount of a less polar product is formed that is tentatively identified by ^{1}H NMR as the mono-carbene complex **229-I** (5-10 %).

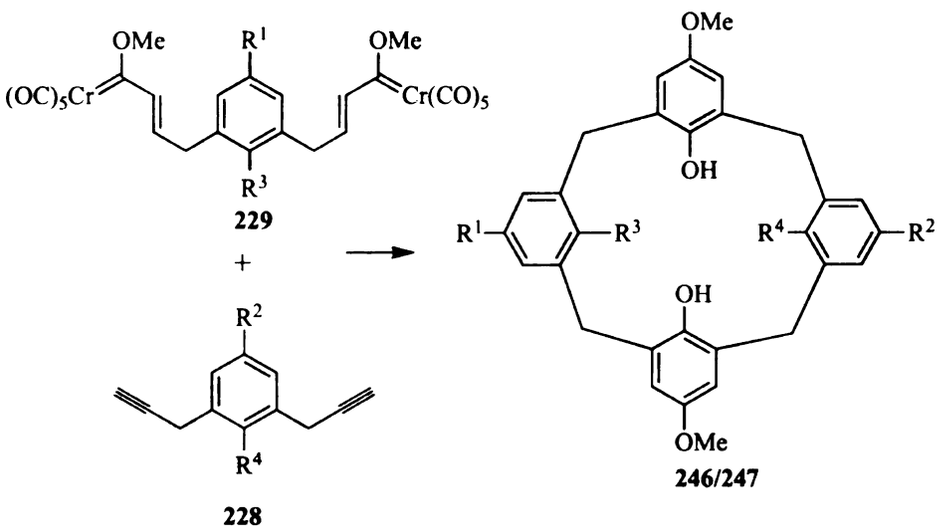
1,3-bis-[2'-propenyl(methoxy)methylene pentacarbonylchromium (0)]-2-methoxy-5-methylbenzene (R_3 = OMe , R_1 = Me) ***229A***: The vinyl iodide **245A** (0.454 g, 1.05 mmol) following the general procedure gave upon purification by silica gel chromatography in 20 % dichloromethane/hexanes **229A** in 36 % yield (0.253 g, 0.378 mmol) as a reddish oil. R_f = 0.34 (hexanes/dichloromethane 4/1). Spectral data for **229A**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 3 H), 3.47 (d, 4 H, J = 6.0 Hz), 3.67 (s, 3 H), 4.72 (s, 6 H), 6.33 (dt, 2 H, J = 14.0, 6.5 Hz), 6.85 (s, 2 H), 7.32 (d, 2 H, J = 14.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.60, 32.59, 61.59, 66.47, 130.22, 130.74, 133.26, 134.39, 144.77, 154.25, 216.61, 223.92, 335.96; IR (CH_2Cl_2) 2959, 2255, 2088, 1934, 1603, 1479, 1452, 1228 cm^{-1}; mass spectrum (FAB) *m/z* (% rel intensity) 670 M^+ (1), 530 (8), 446 (7), 418 (8), 390 (14), HRMS calcd for $C_{28}H_{22}Cr_2O_{13}$ *m/z* 669.9871, measd 669.9874.

1,3-bis-[2'-propenyl(methoxy)methylene pentacarbonylchromium (0)]-2-hexyl-5-methylbenzene (R_3= C_6H_{13} , R_1 = Me) ***229B***: Following the general procedure

described above the vinyl iodide **245B** (0.341 g, 0.67 mmol) gave the carbene complex **229B** in 44 % yield (0.213 g, 0.295 mmol) as a reddish oil after purification by silica gel chromatography in hexanes. R_f (hexanes) = 0.30. Spectral data for **229B**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, 3 H, *J* = 7.0 Hz), 1.34 (m, 8 H), 2.23 (s, 3 H), 2.49 (t, 2 H, *J* = 7.2 Hz), 3.44 (d, 4 H, *J* = 6.0 Hz), 4.75 (s, 6 H), 6.31 (dt, 2 H, *J* = 15.5, 6.5 Hz), 6.84 (s, 2 H), 7.23 (d, 2 H, *J* = 15.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.02, 22.62, 28.86, 29.78, 31.21, 31.58, 35.96, 66.44, 129.87, 133.56, 136.07, 136.14, 136.59, 144.63, 216.59, 223.93, 336.02; IR (CH_2Cl_2) 2959, 2928, 2856, 2060, 1925, 1599, 1425, 1228 cm^{-1}; mass spectrum (FAB) m/z (% rel intensity) 724 M^+ (3), 668 (1), 640 (15), 584 (7), 500 (3), 472 (2), 444 (100), HRMS calcd for $C_{33}H_{32}Cr_2O_{12}$ *m/z* 724.0704, measd 724.0707.

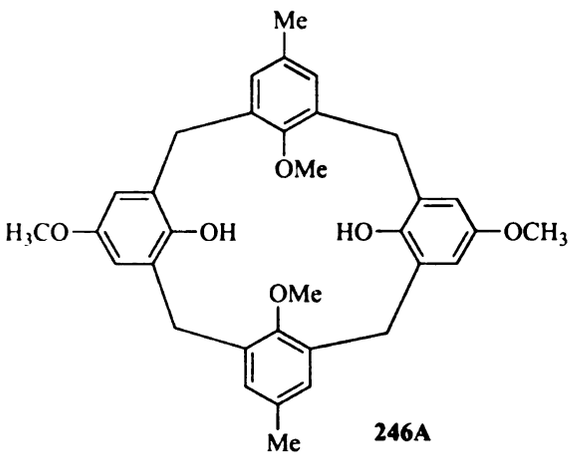
2,6-bis-[2'-propenyl(methoxy)methylene pentacarbonylchromium (0)]-4-methylbiphenyl (R_3 = Ph, R_1 = Me) ***229C*****:** Following the above procedure, the vinyl iodide **245C** (0.334 g, 0.64 mmol) gave the carbene complex **229C** in 47 % yield (0.21 g, 0.30 mmol) as a reddish oil. R_f (hexanes) = 0.24. Spectral data for **229C**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.33 (s, 3 H), 3.15-3.17 (d, 4 H, *J* = 6.3 Hz), 4.69 (s, 6 H), 6.15 (dt, 2 H, *J* = 15.0, 7.0 Hz), 6.97 (s, 2 H), 7.05 (d, 2 H, *J* = 15.0 Hz), 7.09 (d, 2 H, *J* = 6.5 Hz), 7.33-7.38 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.93, 36.95, 55.36, 127.48, 128.50, 128.95, 129.46, 134.05, 136.27, 137.87, 138.92, 139.08, 144.45, 216.62, 223.92, 335.86; IR (CH_2Cl_2) 3022, 2959, 2924, 2058, 1921, 1599, 1452, 1226 cm^{-1}; mass spectrum (FAB) *m/z* (% rel intensity) 716 M^+ (60), 660 (2), 632 (3), 604 (30), 576 (8), 548 (4), 492 (20), 464 (25), 436 (100), HRMS calcd for $C_{33}H_{24}Cr_2O_{12}$ *m/z* 716.0078, measd 716.0077.

3,5-bis-[2'-propenyl(methoxy)methylene pentacarbonylchromium (0)]-4-methoxybiphenyl (R_3 = OMe , R_1 = Ph) ***229D***: Following the general procedure as described above the vinyl iodide **245D** (0.67 g, 1.3 mmol) gave carbene complex **229D** in 32 % yield (0.30 g, 0.42 mmol) as a reddish oil after purification by silica gel chromatography in 20 % dichloromethane/hexanes. R_f = 0.23 (hexanes/dichloromethane = 4/1). Spectral data for **229D**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.56 (d, 4 H, *J* = 7.0 Hz), 3.61 (s, 3 H), 4.66 (s, 6 H), 6.37 (dt, 2 H, *J* = 15.0, 7.0 Hz), 7.26 (s, 2 H), 7.31 (t, 1 H, *J* = 7.5 Hz), 7.36 (d, 2 H, *J* = 15.0 Hz), 7.39 (t, 2 H, *J* = 7.5 Hz), 7.48 (d, 2 H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.86, 61.64, 66.49, 126.99, 127.31, 128.38, 128.75, 131.56, 132.98, 138.03, 140.21, 144.77, 156.01, 216.61, 223.89, 336.02; IR (CH_2Cl_2) 2959, 2926, 2060, 1921, 1603, 1473, 1425, 1233 cm^{-1}; mass spectrum (FAB) *m/z* (% rel intensity) 732 M^+ (8), 648 (25), 592 (1), 460 (6), 452 (2), HRMS calcd for $C_{33}H_{24}Cr_2O_{13}$ 732.0027, measd 732.0038.



Calixarene Formation by the Triple Annulation of Bis-Carbene Complex 229 with diyne 228.

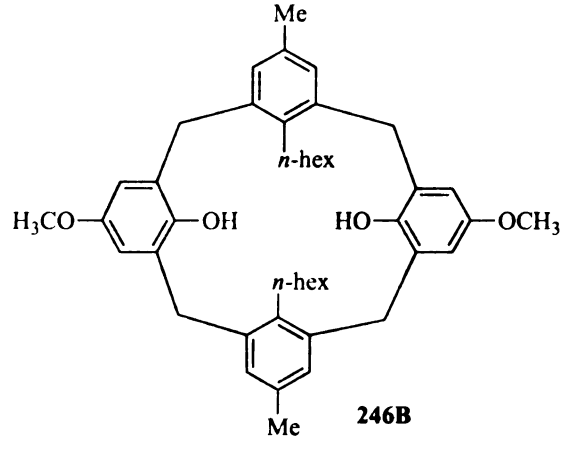
The bis-carbene complex **229** and the diyne **228** (1:1 molar ratio) were dissolved in 1,2-dichloroethane (2.5 mM) in a flame dried 100 mL or 250 mL Schlenk flask under Argon. The solution was deoxygenated by the freeze pump thaw method in three cycles (-196 to 25 °C) and then backfilled with argon at ambient temperature. The flask was sealed with a threaded high-vacuum Teflon stopcock and heated to 100 °C for 20-40 min during which time the deep red solution turned yellow. The yellow solution was stirred overnight exposed to air to facilitate demetalation of the arenechromium tricarbonyl complex. The solvent was removed under vacuum and the residue dissolved in ethyl acetate (50 mL) and then filtered through a short pad of silica gel. Further washing of the SiO_2 pad with ethyl acetate and evaporation of the solvent gave the crude calixarene which was purified by flash chromatography on silica gel.



246A

5,17-dimethyl-11,23,26,28-dimethoxy-25,27-dihydroxycalix(4)arene ***246A***: The bis-carbene complex **229A** (0.188 g, 0.28 mmol) and diyne **228A** (0.055 g, 0.28 mmol) were dissolved in 112 mL of 1,2-dichloroethane and subjected to the reaction conditions described above which gave the calixarene **246A** in 36 % yield (0.054 g, 0.101 mmol) as a white solid and as a single conformer after purification by silica gel chromatography (25 % ethyl acetate/hexanes). This compound was crystallized from acetonitrile and

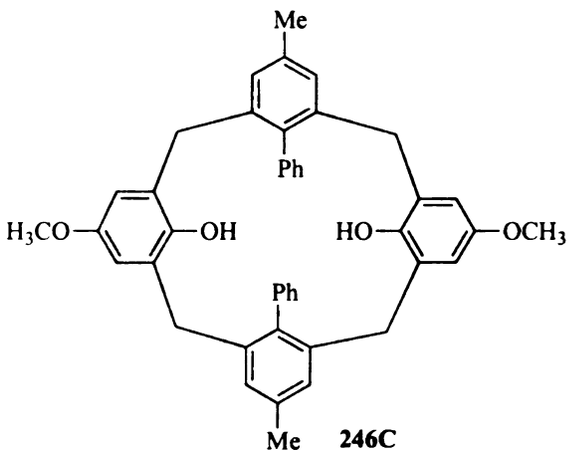
subjected to single crystal X-ray diffraction analyses, which revealed it to be the cone conformer of **246A**. Mp = > 298 °C with decomposition. R_f = 0.32 (hexanes/ ethyl acetate = 3/1). Spectral data for **246A**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03 (s, 6 H), 3.27 (d, 4 H, J = 13.2 Hz), 3.74 (s, 6 H), 3.93 (s, 6 H), 4.27 (d, 4 H, J = 12.9 Hz), 6.61 (s, 4 H), 6.72 (s, 4 H), 7.59 (s, 2 H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.86, 31.53, 55.78, 63.49, 113.72, 129.12, 129.69, 132.74, 134.32, 146.91, 151.30, 152.19; IR (CH_2Cl_2) 3297br, 3055w, 2988, 2937, 2835, 1600, 1481, 1433, 1285, 1228, 1124, 1055, 1009 cm^{-1}; HRMS calcd for $C_{34}H_{36}O_6$ *m/z* 540.2512, measd 540.2512. Anal calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.62; H, 6.60.



246B

*5,17-dimethyl-11,23-dimethoxy-25,27-dihydroxy-26,28-dihexylcalix(4)arene **246B**:* A solution of the bis-carbene complex **229B** (0.221 g, 0.306 mmol) and diyne **228B** (0.082 g, 0.32 mmol) in 120 mL of 1,2-dichloroethane was subjected to the reaction conditions described above and the resulting calixarene **246B** was purified by silica gel chromatography (5 % ethyl acetate/hexanes) to give a 22 % yield (0.044 g, 0.067 mmol) of **246B** as white solid and as a single conformation, whose structure was assigned as the cone based on Mendoza rule.[29] R_f = 0.39 (hexanes / ethyl acetate = 19/1) Mp = 158-160 °C. Spectral data for **246B**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82 (t, 6 H, J = 7.3 Hz),

1.15-1.23 (m, 16 H), 2.21 (s, 6 H), 2.52 (t, 4 H, J = 7.5 Hz), 3.62 (d, 4 H, J = 15.0 Hz), 3.81(s, 6 H), 3.91(s, 2 H), 4.05 (d, 4 H, J = 15.0 Hz), 6.66 (s, 4 H), 6.96 (s, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.04, 20.89, 22.59, 27.73, 29.29, 31.67, 31.81, 36.86, 55.69, 113.86, 128.53, 130.32, 135.57, 137.87, 138.63, 147.49, 152.66; IR (CH_2Cl_2) 3499, 2924, 2855, 1606, 1466, 1377, 1246, 1147, 1059 cm^{-1}.

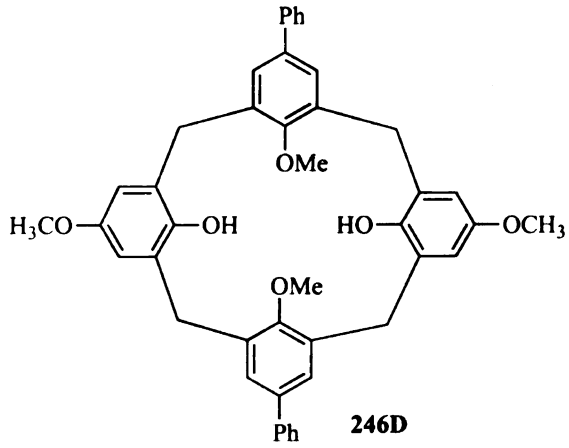


246C

5,17-dimethyl-11,23-dimethoxy-25,27-dihydroxy-26,28-diphenylcalix(4)arene

246C: The bis-carbene complex **229C** (0.121 g, 0.165 mmol) and diyne **228C** (0.0403 g, 0.165 mmol) were subjected to the benzannulation reaction in 66 mL of 1,2-dichloroethane following the general procedure and afforded a separable 1.0 : 1.7 mixture of two conformers **246C-I** and **246C-II** that were separated by silica gel chromatography (10 % ethyl acetate / hexanes) and obtained as solids in 13 % yield (0.0135 g, 0.021 mmol) and 22 % yield (0.023 g, 0.036 mmol) respectively. Each was crystallized from dichloromethane/hexanes to give single crystals, which upon X-ray diffraction analysis, revealed that the minor isomer **246C-I** exists as a pinched cone conformation and the major isomer **246C-II** exists as a pinched 1,2-alternate conformation. The following physical and spectral data were collected for the two conformers. **Conformer 246C-I**:

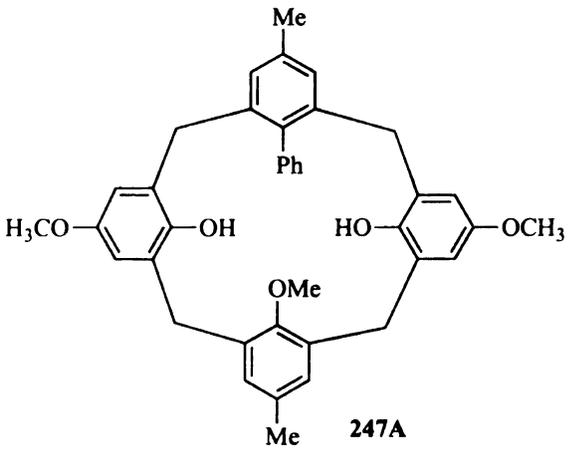
R_f = 0.37 (hexanes/ ethyl acetate = 9/1) Mp = 221-224 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.01 (s, 6 H), 3.33 (d, 4 H, J = 14.5 Hz), 3.74 (d, 4 H, *J* = 15.5 Hz), 3.77 (s, 6 H), 4.24 (s, 2 H, OH), 6.51 (s, 4 H), 6.55 (s, 4 H), 6.98 (d, 2 H, *J* = 6.5 Hz), 7.35-7.38 (m, 4 H), 7.50-7.52 (m, 2 H), 8.14 (d, 2 H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.89, 36.12, 55.68, 114.44, 126.99, 128.14, 130.32, 131.73, 132.15, 136.89, 138.15, 138.87, 139.27, 146.78, 152.72; IR (CH_2Cl_2) 3472, 3056, 2988, 1635, 1610, 1479, 1412, 1265, 1145 cm^{-1}; mass spectrum *m/z* (% rel intensity) 632 M^+ (100), 315 (30), 193 (10), 179 (15), 149 (20), calcd for $C_{44}H_{40}O_4$ *m/z* 632.2927, measd 632.2924. **Conformer 246C-II**: R_f = 0.45 (hexanes/ ethyl acetate = 9/1) Mp = 260-262 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.36 (s, 6 H), 3.53 (d, 4 H, *J* = 15.0 Hz), 3.61 (d, 4 H, *J* = 14.5 Hz), 3.66 (s, 6 H), 4.12 (s, 2 H, OH), 6.26 (d, 2 H, *J* = 7.5 Hz), 6.35 (s, 4 H), 6.82 (t, 2 H, *J* = 7.8 Hz), 6.97 (d, 2 H, *J* = 7.5 Hz), 7.10 (s, 4 H), 7.16 (t, 2 H, *J* = 7.3 Hz), 7.25 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.02, 36.95, 55.59, 113.76, 126.48, 127.15, 128.87, 129.24, 130.00, 130.78, 137.28, 138.83, 139.70, 147.34, 152.16; IR (CH_2Cl_2) 3509, 3052, 3005, 2918, 2837, 1590, 1481, 1441, 1244, 1149, 1057 cm^{-1}.



246D

5,17-diphenyl-11,23,26,28-tetramethoxy-25,27-dihydroxycalix(4)arene ***246D****:* A solution of the bis-carbene complex **229D** (0.105 g, 0.145 mmol) and diyne **228D** (0.038

g, 0.145 mmol) in 58 mL of 1,2-dichloroethane was subjected to the benzannulation conditions described above and the calixarene **246D** was isolated as a white solid in 41 % yield (0.039 g, 0.059 mmol) as a single conformation after purification by silica gel chromatography (25 % EtOAc/hexanes). Mp = 276-279 °C with decomposition. R_f= 0.25 (hexanes/ethylacetate = 3/1). The conformation of **246D** was assigned as the cone conformation based on the chemical shift of the phenol hydrogens (δ = 7.36) and again by the Mendoza rule (carbon chemical shift of the methylene hydrogen δ = 31.73). The chemical shift of the phenol protons of **246D** (cone conformer) is δ = 7.59, whereas, the chemical shift of the phenol protons of the partial cone of **247A** is δ = 5.75. The chemical shifts of the phenol hydrogens of a 1,3-alternate conformer of a related calixarene is δ = 4.01.[128] Spectral data for **246D**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.39 (d, 4 H, *J* = 13.0 Hz), 3.73 (s, 6 H), 4.01 (s, 6 H), 4.38 (d, 4 H, *J* = 13.0 Hz), 5.28 (s, 2 H), 6.66 (s, 4 H), 7.09 (s, 4 H), 7.16-7.21 (m, 3 H), 7.24-7.25 (m, 5 H), 7.36 (s, 2 H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.73, 55.85, 63.54, 113.93, 126.86, 126.95, 127.85, 128.45, 129.09, 133.41, 137.96, 140.56, 146.9, 152.48, 153.25; IR (CH_2Cl_2) 3327, 2934, 2829, 1483, 1431, 1234, 1138, 1003, 906 cm^{-1}; mass spectrum *m/z* (% rel intensity) 664 (100), 633 (5), 602 (40), 332 (15), 301 (10); HRMS calcd for $C_{44}H_{40}O_6$ *m/z* 664.2825, measd 664.2825.

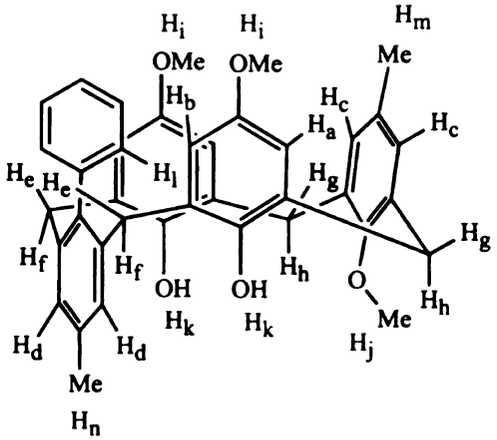


247A

*5,17-dimethyl-11,23,26-trimethoxy-25,27-dihydroxy-28phenylcalix(4)arene **247A***: The bis-carbene complex **229A** (0.124 g, 0.185 mmol) and diyne **228C** (0.045 g, 0.185 mmol) in 74 mL of 1,2-dichloroethane were reacted according to the procedure described above to give the calixarene **247A** as a 3.8:1 mixture of inseparable conformers in 31 % yield (0.034 g, 0.058 mmol) as a white solid after purification by silica gel chromatography (25 % EtOAc/hexanes). Mp = 240-242 °C. R_f (hexanes/ethylacetate 3/1) = 0.44. HPLC analysis showed the presence of a single peak at 10.19 min upon gradient elution with a hexane/iso-propanol mixture of that was varied from 99.5/0.5 to 97/3 over 40 min at a flow rate of 1mL/min using a silica gel column (R0086100C5). The ^{1}H NMR in $CDCl_3$ showed the presence of two conformers in a ratio of 3.8:1 as measured by integration of the peaks at δ = 2.02 and 2.45. The different ratio of isomers in different solvents shows that these conformers do equilibrate rapidly but not on the NMR time scale (Table 3). Also, variable temperature ^{1}H NMR was recorded from 25 to 95 °C in DMSO-d_6 but no coalescence of peaks was observed. EXSY experiments at 50 °C (t mix = 0.75s, ni = 64, nt = 256, threefold forward linear prediction along F1 dimension) reveal that rotation about the phenyl group and interconversion between conformers is rapid but not on the NMR time scale (See Figure 3.10, Pg.104). On the

basis of NOE experiments the major conformer was assigned as a partial cone and the minor as the cone conformation. The mass spectrum of **247A** shows a trace peak at m/z = 1172 (0.13). This is attributed to a trace of a calix[8]arene that can not be detected by ^{1}H NMR. The two conformers observed by ^{1}H NMR are shown to be interconverting by the solvent experiments and EXSY experiments shown below. A calix[8]arene would not be expected to exists as conformers that could be observed on the ^{1}H NMR time scale. The following spectral data were obtained on a mixture of the two conformers. Spectral data for **247A**: ^{1}H NMR ($CDCl_3$, 500 MHz) **major**; δ 2.25 (s, 3 H), 2.43 (s, 3 H), 3.25 (d, 2 H, *J* = 13.5 Hz) 3.46 (s, 6 H), 3.49 (d, 2 H, *J* = 13.0 Hz), 3.84 (s, 3 H), 3.88 (d, 2 H, *J* = 13 Hz overlapping with peak at δ 3.84), 4.11 (d, 2 H, *J* = 13.0 Hz), 4.78 (d, 1 H, *J* = 7.5 Hz), 5.51 (t, 1 H, *J* = 7.5 Hz), 5.64 (d, 2 H, *J* = 3.0 Hz), 5.75 (s, 2 H, OH), 6.48 (d, 2 H, *J* = 3.5 Hz), 6.67 (t, 1 H, *J* = 6.5 Hz), 6.83 (d, 1 H, *J* = 7.5 Hz), 6.90 (s, 2 H), 7.03 (t, 1 H, *J* = 7.5 Hz), 7.23 (s, 2 H); **minor**; δ 1.81 (s, 3 H), 2.02 (s, 3 H), 3.29 (d, 2 H, *J* = 13.5 Hz overlapping with peak at δ 3.26 of major isomer), 3.35 (d, 2 H, J = 14.0 Hz), 3.73 (d, 2 H, *J* = 14.0 Hz), 3.78 (s, 6 H), 3.86 (s, 3 H), 4.11(d, 2 H, *J* = 14.0 Hz), 5.01 (s, 2 H), 6.34 (s, 2 H), 6.51 (d, 2 H, *J* = 2.5 Hz), 6.58 (s, 2 H), 6.65 (d, 2 H, *J* = 3 Hz), 7.29-7.33 (m, 1 H), 7.41 (t, 2 H, *J* = 7.5 Hz), 7.92 (d, 2 H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) **major**; δ 20.86, 21.15, 31.12, 40.10, 55.32, 63.16, 113.03, 113.99, 125.19, 125.97, 126.61, 126.90, 128.12, 129.61, 129.96, 130.06, 130.40, 133.54, 134.78, 137.51, 138.59, 139.34, 146.61, 152.56, **minor**; δ 25.60, 29.50, 32.04, 36.24, 55.69, 63.02, 113.78, 114.50, 127.52, 127.70, 127.83, 129.49, 130.92, 131.15, 132.06, 132.11, 134.10, 136.20, 138.90, 139.01, 139.60, 147.11, 151.81, 152.40; IR (CH_2Cl_2) 3499, 3055, 2988, 1606, 1481, 1468, 1421, 1265, 1055 cm^{-1}; mass spectrum (FAB MS in 4-nitrobenzyl alcohol]

m/z (% rel intensity) 586 M^+ (100), 307 (10), 154 (37), 137 (26), 77 (6), HRMS calcd for $C_{39}H_{38}O_5$ *m/z* 586.2719, measd 586.2715. Anal calcd for $C_{39}H_{38}O_5$: C, 79.84; H, 6.53. Found: C, 80.04; H, 6.22.

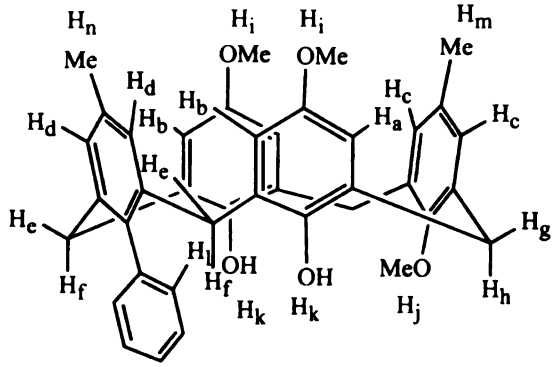


247A Partial Cone conformation

Chemical Shifts For H_a - H_n Major δ ppm	
H_a = 5.64(d)	H_j = 3.84(s)
H_b = 6.49(d)	H_k = 5.75(s)
H_c = 7.23(s)	H_l = 4.78(d)
H_d = 6.90(s)	H_m = 2.43(s)
H_e = 3.25(d)	H_n = 2.25(s)
H_f = 4.11(d)	
H_g = 3.49(d)	
H_h = 3.88(d)	
H_i = 3.46(s)	

Table 7.1 Results of Homonuclear ^1H-^1H NOE experiments on Major isomer of **247A** (Partial cone).

Nuclei Irradiated	Adjacent H	Enhancement	Nuclei irradiated	Adjacent H	Enhancement
5.64 (H_a)	H_g	y	4.11 (H_f)	H_e	y
	H_i	y		H_k	y
6.49 (H_b)	H_d	y	3.49 (H_g)	H_h	y
	H_i	y		H_a	y
	H_e	y		H_j	y
7.23(H_c)	H_h	y	3.88 (H_h)	H_g	y
	H_m	y		H_c	y
	H_k	y	3.46 (H_i)	H_a	y
6.90(H_d)	H_b	y	3.84 (H_j)	H_g	y
	H_e	y	5.75 (H_k)	H_f	y
	H_n	y		H_h	y
3.25 (H_e)	H_f	y		H_l	y
	H_d	y	4.78 (H_l)	H_c	y
	H_b	y		H_k	y
				Meta (Ar-H)	y



247A Cone Conformation

Chemical Shifts For H_a - H_m Minor

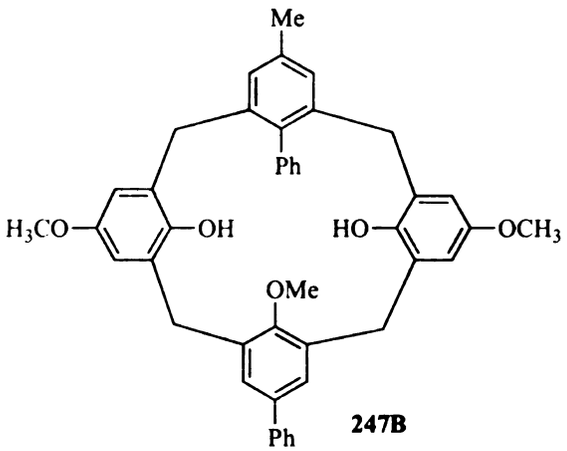
δ ppm

H_a = 6.51(d)	H_j = 3.86(s)
H_b = 6.66(d)	H_k = 5.01(s)
H_c = 6.34(s)	H_l = 7.92(d)
H_d = 6.58(s)	H_m = 2.02(s)
H_e = 3.29(d)	H_n = 1.81(s)
H_f = 3.73(d)	
H_g = 3.35(d)	
H_h = 4.11(d)	
H_i = 3.78(s)	

Table 7.2 Results of Homonuclear ^1H-^1H NOE experiments on Minor Isomer of **247A** (Cone).

Nuclei irradiated	Adjacent H	Enhancement	Nuclei irradiated	Adjacent H	Enhancement
6.51 (H_a)	H_j	y	3.35(H_g)	H_h	y
	H_e	y		H_b	y
	H_c	y		H_d	y
6.65 (H_b)	H_j	y	4.11 (H_h)	H_g	y
	H_g	y		H_k	y
6.34(H_c)	H_a	y		H_i	y
	H_e	y	3.78 (H_i)	H_a	y
	H_m	y		H_b	y
6.58(H_d)	H_b	y	3.86 (H_j) obscured by major isomer		
	H_g	y			
	H_l	y	5.01 (H_k)	H_f	y
3.29 (H_e)	H_f	y	7.92 (H_l)	No NOE Enhancements	
	H_a	y	1.81(H_m)	H_c	y
	H_c	y	2.02(H_n)	H_d	y
3.73 (H_f)	H_e	y			
	H_i	y			

An EXSY experiment revealed that these two conformers were inter-converting but not on the NMR time scale. For the results of EXSY experiment see Chapter 3, Pg 126-127.

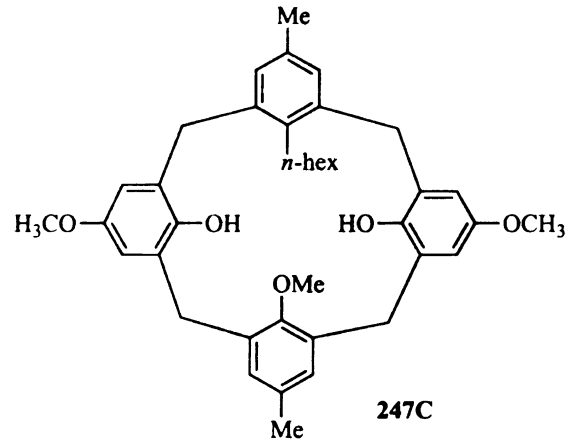


247B

5-methyl-17,28-diphenyl-11,23,26-trimethoxy-25,27-dihydroxycalix(4)arene

247B: The bis-carbene complex **229D** (0.109 g, 0.149 mmol) and diyne **228C** (0.037 g, 0.149 mmol) were dissolved in 60 mL of 1,2-dichloroethane and reacted according to the general procedure to give calixarene **247B** as an inseparable 3.3:1 mixture of conformers in 35 % total yield (0.034 g, 0.052 mmol) as a white solid after purification by silica gel chromatography (25 % ethyl acetate/hexanes). R_f = 0.45 (hexanes/ ethyl acetate = 3/1). HPLC analysis showed the presence of single peak at 4.02 min upon gradient elution with mixtures of hexane/iso-propanol varying from 99.5/0.5 to 97/3 over 40 min at a flow rate of 1 mL/min using a silica gel column (R0086100C5). However, the ^{1}H NMR reveals a mixture of two conformers in a 3.3: 1 ratio. The assignment of the major isomer as a partial cone conformer and minor as cone was made on the basis of the similarity of the proton spectra with that of **247A**. The product was further purified by crystallization from hexanes/dichloromethane and the following spectral data was recorded on the mixture of the two conformers. The mass spectrum of **247B** shows a trace peak at *m/z* = 1297 (0.13). This is attributed to a trace of a calix[8]arene that can

not be detected by ^{1}H NMR. A calix[8]arene would not be expected to exists as conformers that could be observed on the ^{1}H NMR time scale. Mp = 243-245 °C. Spectral data for **247B**: ^{1}H NMR ($CDCl_3$, 500 MHz) **major**; δ 2.43 (s, 3 H), 3.37 (d, 2 H, *J* = 13.0 Hz), 3.46 (s, 6 H), 3.50 (d, 2 H, *J* = 16.0 Hz), 3.86 (d, 2 H, *J* = 16.0 Hz), 3.90 (s, 3 H), 4.18 (d, 2 H, *J* = 13.0 Hz), 4.86 (d, 1 H, *J* = 7.5 Hz), 5.50 (t, 1 H, *J* = 7.7 Hz), 5.66 (d, 2 H, *J* = 3.0 Hz), 5.77 (s, 2 H), 6.53 (d, 2 H, *J* = 3.0 Hz), 6.61 (t, 1 H, *J* = 7.5 Hz), 6.83 (d, 1 H, *J* = 7.5 Hz), 7.01 (t, 1 H, *J* = 7.5 Hz), 7.24 (s, 2 H), 7.30 (s, 2 H), 7.33 (m, 1 H), 7.42 (t, 2 H, *J* = 7.5 Hz), 7.48 (d, 2 H, *J* = 7.0 Hz), **minor**; 1.60 (s, 3 H), 3.27 (d, 2 H, *J* = 14.0 Hz), 3.43 (d, 2 H, *J* = 14.0 Hz), 3.74 (d, 2 H, *J* = 14.0 Hz), 4.21 (d, 2 H, *J* = 14.5 Hz), 5.02 (s, 2 H), 6.28 (s, 2 H), 6.69 (d, 2 H, *J* = 3.0 Hz), 6.91 (d, 1 H, *J* = 7.5 Hz), 6.96 (s, 2 H). The remaining 11 Ar-H's of the minor conformer overlap with the peak resonances of the major isomer and hence their positions could not be precisely assigned. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.54, 21.19, 31.33, 32.06, 36.10, 39.98, 55.33, 55.68, 63.18, 63.31, 113.11, 113.67, 113.92, 114.64, 125.35, 126.15, 126.65, 126.91, 126.95, 127.03, 127.19, 127.66, 127.74, 127.79, 127.91, 128.47, 128.79, 129.53, 129.74, 130.11, 130.72, 131.28, 132.09, 132.84, 133.52, 133.60, 134.22, 136.48, 136.80, 137.71, 138.38, 138.50, 138.53, 139.01, 139.26, 139.57, 140.56, 140.64, 146.61, 147.01, 152.47, 152.54, 153.52, 153.70; IR (CH_2Cl_2) 3493, 3055, 2988, 1653, 1609, 1481, 1421, 1265, 1147 cm^{-1}; mass spectrium (FAB MS in 4-nitrobenzyl alcohol) *m/z* (% rel intensity) 648 M^+ (100), 307 (30), 154 (100), 136 (60), 107 (20), 77 (20), HRMS calcd for $C_{44}H_{40}O_5$ *m/z* 648.2876, measd 648.2874.

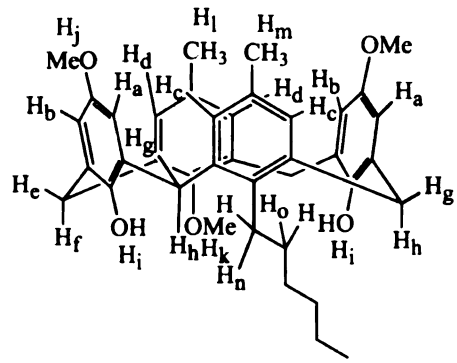


247C

5,17-dimethyl-11,23,26-trimethoxy-25,27-dihydroxy-28-hexylcalix(4)arene ***247C***: A solution of the bis-carbene complex **229A** (0.207 g, 0.31 mmol) and diyne **228B** (0.077 g, 0.307 mmol) in 122 mL of 1,2-dichloroethane was allowed to react according to the general procedure described above. The product of this reaction was purified by silica gel chromatography (hexanes/ethyl acetate = 85/15) to give calixarene **247C** in 22 % yield (0.04 g, 0.068 mmol) as an off-white solid and as a inseparable 7.9:1 mixture of conformers. R_f = 0.31 (15 % EtOAc / hexanes). Mp = 172-174 °C. HPLC analysis showed the presence of single peak at 6.02 min under gradient elution with a mixture of hexane/iso-propanol starting at 99.5/0.5 and decreasing to 97/3 over 40 min at a flow rate of 1 mL/min on a silica gel column (R0086100C5). The ^{1}H NMR indicates the presence of a 7.9:1 mixture of conformers as measured by integration of the peaks at δ = 1.91 and 2.16. The major isomer was assigned as the cone conformer on the basis of NOE and NOESY experiments (see below). The minor isomer was not assigned. NOESY experiment on **247C**: Tm = 0.5 sec, nt = 256, ni = 64, linear prediction along F1 dimension.

The following spectral data were obtained on a mixture of the conformers. The mass spectrum of **247C** shows a trace peak at m/z = 1189 (0.20). This is attributed to a

trace of a calix[8]arene that can not be detected by ^{1}H NMR. A calix[8]arene would not be expected to exists as conformers that could be observed on the ^{1}H NMR time scale. Spectral data for **247C**: ^{1}H NMR ($CDCl_3$, 500 MHz) **major**; δ 0.74 (t, 3 H, *J* = 7.2 Hz), 1.31 (m, 4 H), 1.39 (m, 4 H), 1.91 (s, 3 H), 2.04 (s, 3 H), 3.29 (t, 2 H, *J* = 7.3 Hz), 3.39 (d, 2 H, *J* = 14.0 Hz), 3.40 (d, 2 H, *J* = 14.0 Hz), 3.79 (s, 6 H), 3.88 (s, 3 H), 4.00 (d, 2 H, *J* = 14.0 Hz), 4.21 (d, 2 H, *J* = 13.5 Hz), 5.78 (s, 2 H), 6.54 (s, 2 H), 6.63 (d, 2 H, *J* = 3.0 Hz), 6.69 (s, 2 H), 6.71 (d, 2 H, *J* = 2.5 Hz), **minor**; 0.88 (t, 3 H, *J* = 7.2 Hz), 1.24 (bs, 4 H), 1.48 (bs, 4 H), 2.16 (s, 3 H), 2.35 (s, 3 H), 3.23 (d, 2 H, *J* = 12.5 Hz), 3.69 (s, 6 H), 3.77 (s, 3 H), 3.91 (d, 2 H, *J* = 12.5 Hz), 3.99 (d, 2 H, *J* = 12.5 Hz), 4.08 (d, 2 H, *J* = 12.5 Hz), 5.75 (s, 2 H), 6.52 (d, 2 H, *J* = 3.0 Hz), 6.58 (d, 2 H, *J* = 3.5 Hz), 6.87 (s, 2 H), 7.14 (s, 2 H) (2 benzylic hydrogens not observed); ^{13}C NMR ($CDCl_3$, 125 MHz) **major**; δ 14.11, 20.71, 20.72, 22.72, 28.48, 29.56, 31.96, 32.34, 32.87, 35.68, 55.77, 63.38, 113.35, 114.4, 128.37, 128.98, 129.95, 131.58, 132.16, 134.01, 134.99, 137.27, 137.73, 147.10, 150.72, 152.58; IR (CH_2Cl_2) 3437, 2924, 2855, 1605, 1482, 1225, 1145, 1053 cm^{-1}; mass spectrum *m/z* (% rel intensity) 594 M^+ (100), 307 (10), 154 (35), 136 (20), calcd for calculated for $C_{39}H_{46}O_5$ *m/z* 594.3345, measd 594.3344.



247C Major Isomer (Cone Conformer)

Chemical Shifts For H_a - H_n Major Isomer of 247C

ppm

H_a = 6.63 (d)	H_j = 3.80(s)
H_b = 6.71 (d)	H_k = 3.88(s)
H_c = 6.69 (s)	H_l = 1.92(s)
H_d = 6.54 (s)	H_m = 2.04(s)
H_e = 3.39 (d)	H_n = 3.29(t)
H_f = 4.00 (d)	
H_g = 3.40 (d)	
H_h = 4.21(d)	
H_i = 5.78 (s)	

Table 7.3 Results of Homonuclear ^1H-^1H NOE Experiments on the major conformer of 247C

Nuclei irradiated	Adjacent H	Enhancement	Nuclei irradiated	Adjacent H	enhancement
6.63 (H_a)	H_g	y	3.40 (H_g) or H_e	H_h	y
	H_j	y		H_c	y
6.71 (H_b)	H_j	y		H_a	y
	H_e (or) H_g	n	4.21 (H_h)	H_g	y
6.69(H_c)	H_g (or) H_e	y		H_n	y
	H_m	y		H_k	n
6.54(H_d)	H_l	y	5.78(H_i)		NO NOE
	H_e	n	3.80 (H_j)	H_a	y
3.39 (H_e) or (H_g)	H_f	y		H_b	y
	H_b	y	3.88 (H_k)	H_f	y
	H_d	y	1.91 (H_l)	H_d	y
4.00(H_f)	H_i	y	2.04 (H_m)	H_c	y
	H_e	y	3.29 (H_n)	H_h	y
	H_k	y		H_o	y

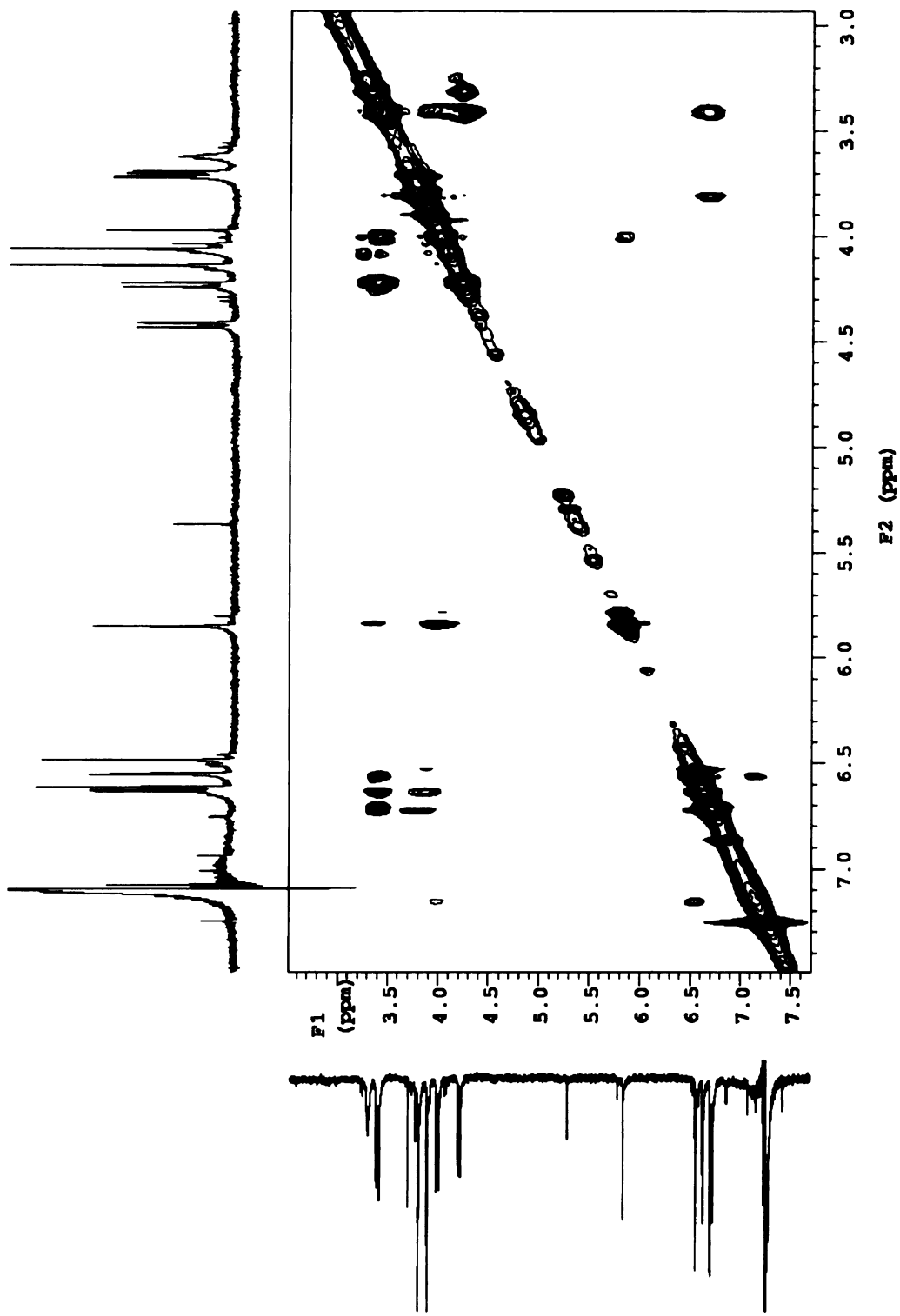
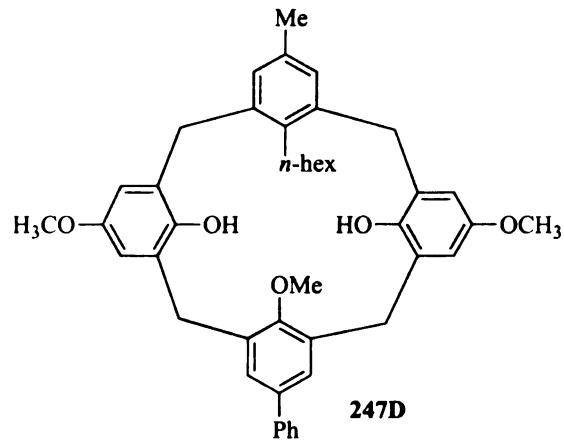


Figure 2. Expanded region of the 600 MHz NOESY spectrum of **247C** in $CDCl_3$ at 25 °C.

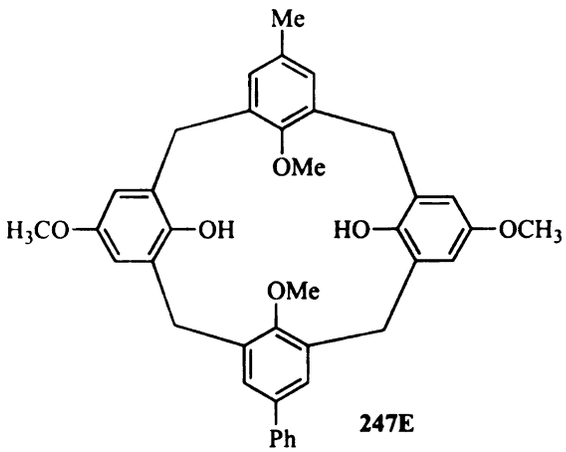


247D

5-phenyl-17-methyl-11,23,26-trimethoxy-25,27-dihydrox-28-hexylcalix(4)arene

247D: The reaction of the bis-carbene complex **229B** (0.103 g, 0.142 mmol) and diyne **228D** (0.037 g, 0.142 mmol) in 56 mL of 1,2-dichloroethane was carried out according to the general procedure. The calixarene **247D** was obtained as an inseparable 7.9:1 mixture of conformers in 35 % yield (0.032 g, 0.05 mmol) as an off-white solid after purification by silica gel chromatography (25 % EtOAc / hexanes). R_f = 0.38 (25 % EtOAc / hexanes). The resulting product was further purified by crystallization from dichlormethane/hexanes (mp = 170-172 °C). HPLC analysis showed the presence of single peak at 4.08 min with gradient elution with hexane/iso-propanol from 99.5/0.5 to 97/3 over 40 min at a flow rate of 1 mL/min on a silica gel column (R0086100C5). The structure of neither conformer was assigned. The following spectral data was taken on the mixture of conformers of **247D**: ^{1}H NMR ($CDCl_3$, 500 MHz) **major**; δ 0.95 (t, 3 H, *J* = 7.2 Hz), 1.38 (m, 4 H), 1.46 (m, 4 H), 1.89 (s, 3 H), 3.35 (t, 2 H, *J* = 7.5 Hz), 3.49 (d, 2 H, *J* = 14.0 Hz), 3.56 (d, 2 H, *J* = 14.0 Hz), 3.87 (s, 6 H), 4.00 (s, 3 H), 4.18 (d, 2 H, *J* = 14.0 Hz), 4.28 (d, 2 H, *J* = 14.0 Hz), 5.63 (s, 2 H), 6.58 (s, 2 H), 6.74 (d, 2 H, *J* = 2.5 Hz), 6.79 (d, 2 H, *J* = 3 Hz), 7.12 (s, 2 H), 7.30-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) **major + minor**; δ 13.75, 14.11, 20.65, 20.92, 22.48, 22.72, 28.44, 28.66, 29.38, 29.53,

29.82, 31.27, 31.61, 31.91, 32.38, 32.76, 35.59, 40.42, 55.51, 55.76, 63.01, 63.39, 113.39, 113.83, 114.44, 126.94, 127.07, 127.63, 127.99, 128.54, 128.57, 128.61, 128.87, 128.98, 130.68, 131.35, 131.60, 132.88, 134.29, 134.34, 136.92, 137.72, 138.29, 139.41, 140.41, 147.07, 152.64, 152.75, 152.82 (9 carbons not located); IR (CH_2Cl_2) 3485, 2926, 2855, 2836, 1605, 1481, 1236, 1146, 1055 cm^{-1}. Anal calcd for $C_{44}H_{48}O_5$: C, 80.46; H, 7.37. Found: C, 80.50; H, 7.32.



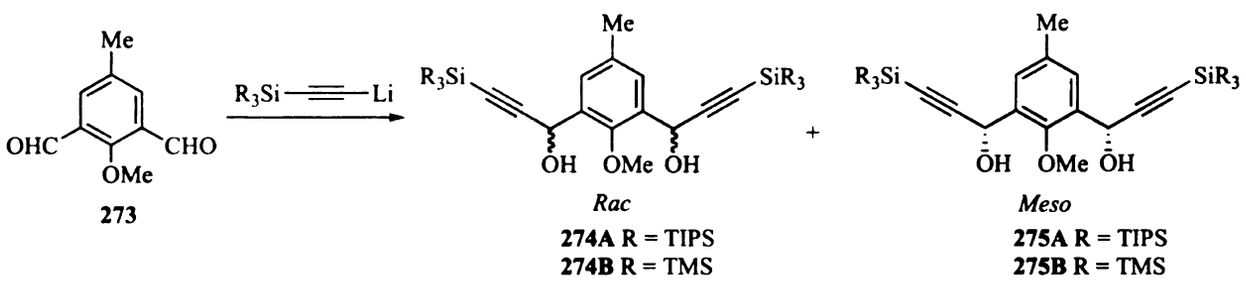
247E

5-phenyl-17-methyl-11,23,26,28-tetramethoxy-25,27-dihydroxycalix(4)arene

247E: The reaction of the bis-carbene complex **229D** (0.105 g, 0.143 mmol) and diyne **228A** (0.029 g, 0.145 mmol) was performed as described in the general procedure to give, after purification by silica gel chromatography (25 % EtOAc / hexanes), the calixarene **247E** as a single conformer in 40 % yield (0.035 g, 0.057 mmol). The conformation of the calixarene was assigned as the cone conformer. The resultant product was further purified by crystallization from hexanes/dichloromethane to afford shiny white crystals of **247E**. Mp = 236-239 ° C. R_f = 0.37 (hexanes / ethyl acetate = 3/1). Spectral data for **247E**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.02 (s, 3 H), 3.31 (d, 2 H, *J* = 13.0 Hz), 3.41 (d, 2 H, *J* = 13.0 Hz), 3.76 (s, 6 H), 3.97 (s, 3 H), 4.02 (s, 3 H), 4.29 (d, 2 H, *J* = 13.0 Hz), 4.39 (d, 2 H, *J* = 13.0 Hz), 6.64 (d, 2 H, *J* = 3.0 Hz), 6.68 (d, 2 H, *J* =

3.0 Hz), 6.71 (s, 2 H), 7.13 (s, 2 H), 7.23 (m, 1 H), 7.31 (s, 2 H), 7.32 (s, 2 H), 7.42 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.82, 31.54, 31.72, 55.85, 55.89, 63.52, 113.85, 113.93, 126.89, 127.80, 128.54, 129.08, 129.21, 129.74, 132.64, 133.49, 134.41, 137.72, 140.62, 146.96, 151.35, 152.39, 153.39 (1 aryl carbon not located); IR (CH_2Cl_2) 3354, 2930, 2829, 1599, 1483, 1435, 1244, 1142, 1053 cm^{-1}; mass spectrum EI *m/z* (% rel intensity) 602 M^+ (100), 571 (5), 539 (8), 301 (10), HRMS calcd for $C_{39}H_{38}O_6$ *m/z* 602.2668, measd 602.2668.

Synthesis of the racemic bis-propargyl alcohols *274* and Meso-*275*



To a flame dried 50 mL round bottomed flask was added triisopropyl silyl acetylene (1 mL, 4.45 mmol) and 20 mL of tetrahydrofuran as the solvent. *n*-butyl lithium (2.5 M in hexanes, 2.8 mL, 4.48 mmol) was dispensed via syringe at -78°C and the resulting solution was warmed to room temperature with stirring for another 1h. The aldehyde **273**[129](0.356 g, 2 mmol) was added at 0°C and the mixture was left to stir at room temperature for 12 h. Water (40-50 mL) was added and the organic layer extracted with methylene chloride (50 mL). After drying over anhydrous magnesium sulfate, the solvent was removed under vacuum and the crude product purified to afford **274A** (0.197 g, 0.365 mmol, 18 %) and **275A** (0.67 g, 1.24 mmol, 62 %) as white solids in a combined 80 % yield. Similarly, the addition of trimethyl silyl ethynyl lithium to aldehyde **273**

(1.78 g, 10 mmol) afforded **274B** (1.09 g, 2.91 mmol, 29 %) and **275B** (2.18 g, 5.82 mmol, 58 %) by silica-gel chromatography in a combined 87 % yield as white solids.

*(±)-2,6-bis(-3-hydroxy-1-triisopropylsilylpropynyl)-4-methylanisole **274A***

Mp = 78-81°C. R_f = 0.56 (hexanes/ ethyl acetate = 85/15). Spectral data for **274A**: ^{1}HNMR ($CDCl_3$, 300MHz) δ 1.06 (s, 42H), 2.29 (s, 3H), 2.67 (d, 2H, *J* = 5.7 Hz), 3.93 (s, 3H), 5.72 (d, 2H, *J* = 5.7 Hz), 7.49 (s, 2H); ^{13}CNMR ($CDCl_3$, 125MHz): δ 11.16, 18.56, 20.88, 60.33, 63.77, 87.89, 107.01, 129.52, 133.84, 134.53 (One of aryl carbons not seen); IR (CH_2Cl_2) 3434, 2944, 2892, 2866, 2172, 1482, 1464, 1383, 1215 cm^{-1}. Anal calcd for $C_{32}H_{54}O_3Si_2$: C, 70.79; H, 10.02. Found: C, 70.43; H, 9.76

*(±)-2,6-bis(-3-hydroxy-1-trimethylsilylpropynyl)-4-methyl-anisole **274B***

Mp = 97-100°C. R_f (hexanes/ ethylacetate = 3/1) = 0.40. Spectral data for **274B**: ^{1}HNMR ($CDCl_3$, 300MHz) δ 0.15 (s, 18H), 2.34 (s, 3H), 2.66 (d, 2H, *J* = 6.3Hz), 3.99 (s, 3H), 5.64 (d, 2H, *J* = 6.3 Hz), 7.37 (s, 2H); ^{13}CNMR ($CDCl_3$, 125MHz): δ -0.25, 20.97, 60.58, 63.77, 91.31, 105.26, 129.34, 133.84, 134.72 (One aryl carbon missing); IR ($CDCl_3$) 3393, 2961, 2901, 2837, 2174, 1481, 1437, 1408, 1250 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 374 (M^+, 28), 357 (100), 73 (36), HRMS calcd for $C_{20}H_{30}O_3Si_2$ *m/z* 374.1734, measd 374.1736.

*(Meso)-2,6-bis(-3-hydroxy-1-triisopropylsilylpropynyl)-4-methylanisole **275A***

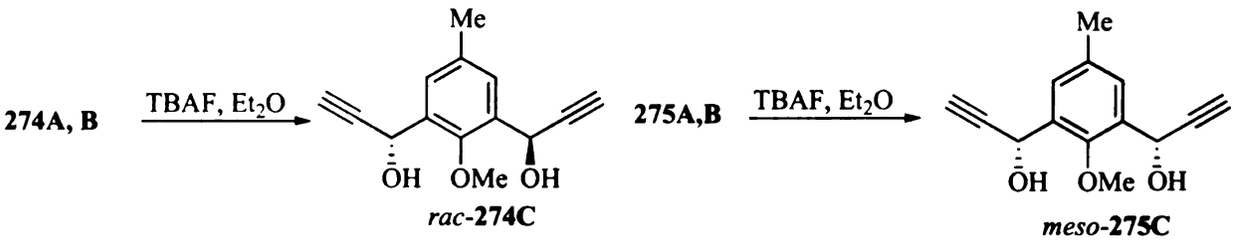
Mp = 96-98°C. R_f = 0.40 (hexanes/ ethyl acetate = 85/15). Spectral data for **275A**: ^{1}HNMR ($CDCl_3$, 300MHz) δ 1.059 (s, 42H), 2.304 (s, 3H), 2.56 (d, 2H, *J* = 6.0 Hz), 3.96 (s, 3H), 5.70 (d, 2H, *J* = 5.7 Hz), 7.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 11.17, 18.56, 20.86, 60.49, 63.87, 87.86, 107.14, 129.53, 133.91, 134.46, 153.09; IR (CH_2Cl_2)

3379, 2946, 2867, 2170, 1645, 1464, 1383, 1265 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 542 (M^+, 10), 525 (100), 165 (16), 115 (28), 87 (36), 75 (70), 59 (84), HRMS calcd for $C_{32}H_{54}O_3Si_2$ *m/z* 542.3612, measd 542.3608.

(Meso)-2,6-bis(-3-hydroxy-1-trimethylsilylpropynyl)-4-methylanisole ***275B***

Mp = 103-105°C. R_f (hexanes/ ethylacetate = 3/1) = 0.30. Spectral data for **275B**: ^{1}HNMR ($CDCl_3$, 300MHz) δ 0.15 (s, 18H), 2.34 (s, 3H), 2.66 (d, 2H, *J* = 6.0 Hz), 3.95 (s, 3H), 5.65 (d, 2H, *J* = 6.0 Hz), 7.38 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) δ -0.25, 20.97, 60.53, 63.66, 91.33, 105.20, 129.28, 133.87, 134.75 (One aryl carbon missing); IR ($CDCl_3$) 3405, 2961, 2174, 1481, 1437, 1250 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 374 (M^+, 28), 357 (100), 154 (16), 136 (16), 73 (40), HRMS calcd for $C_{20}H_{30}O_3Si_2$ *m/z* 374.1734, measd 374.1736.

2,6-bis-(3-hydroxy-1-propynyl)-4-methylanisole ***274C, 275C***



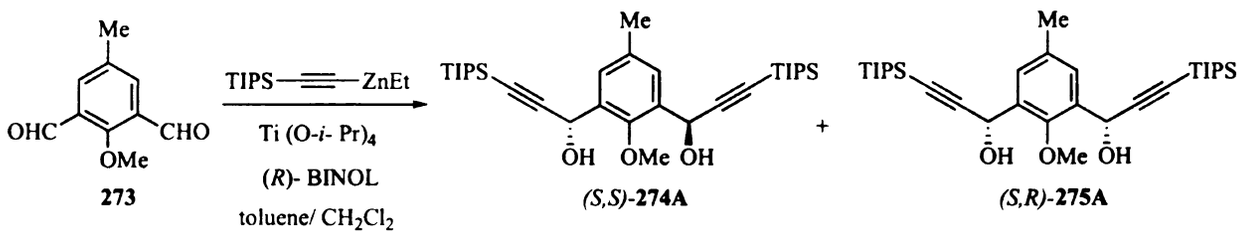
To 1 mmol (0.542 g) of (±)-**274A** or 2.9 mmol (1.09 g) of **274B** was added 5 equiv. of tetrabutyl ammonium fluoride (1M in tetrahydrofuran) followed by anhydrous ether (10 or 30 mL) and the reaction mixture was stirred at room temperature until consumption of the starting material as observed by TLC. Aqueous workup followed by removal of solvent and purification by silica gel chromatography (50 % ethyl acetate/hexanes) afforded the racemic alkynol **274C** (0.207 g, 0.9 mmol, 90 %) from **274A** and (0.48 g,

2.09 mmol, 72 %) from **274B**. The desilylation of *meso*-**275A** (2.3 g, 4.24 mmol) or **275B** (2.17 g, 5.8 mmol) using 5 equiv of tetrabutyl ammonium fluoride afforded (0.87 g, 3.78 mmol, 89 %) or (1.33 g, 5.78 mmol, 99.6 %) of *meso*-**275C** as white solid.

R_f = 0.53 (hexanes / ethylacetate = 1/1). Mp = 145-147°C. Spectral data for *rac*-**274C**: ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.34 (s, 3H), 2.58 (d, 2H, J = 5.7 Hz), 2.63 (d, 2H, J = 1.3 Hz), 3.94 (s, 3H), 5.68 (d, 2H, J = 5.4 Hz), 7.42 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 20.94, 59.76, 63.77, 74.65, 83.61, 129.26, 133.58, 135.02, 152.78; IR ($CHCl_3$) 3350, 3289, 2925, 2800, 2090, 1481 cm^{-1}. Anal calcd $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.08; H, 6.33.

R_f = 0.50 (50 % EtOAc / hexanes). Mp = 103-105°C. Spectral data for *meso*-**275C**: ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.35 (s, 3H), 2.62 (brs, 2H), 2.63 (d, 2H, J = 4.0 Hz), 3.96 (s, 3H), 5.68 (d, 2H, J = 3.5 Hz), 7.42 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) : δ 20.94, 59.76, 63.77, 74.65, 83.61, 129.26, 133.58, 135.02, 152.78; IR ($CHCl_3$) 3299, 3200, 2920, 2840, 2080, 1481 cm^{-1}. Anal calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: 73.07; H, 5.94.

Asymmetric Alkyne Addition using (*R*) or (*S*)-Binaphthol and Ti(O-i-Pr)$_4$



2,6-bis((R)-3-hydroxy-1-triisopropylsilylpropynyl)-4-methylanisole 274A

The following procedure was modified from that reported recently by Pu et.al[114] so as to avoid the use of extremely pyrophoric neat diethyl zinc. Diethyl zinc [1.1M in toluene] was purchased from Sigma-Aldrich and used under an atmosphere of dry argon.

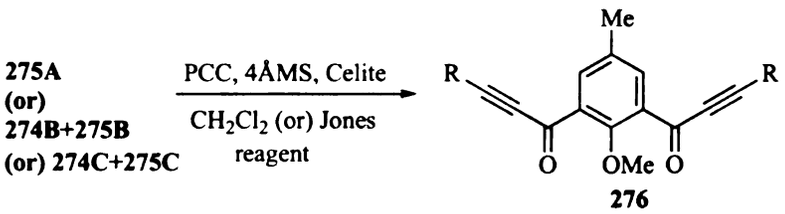
Into a clean flame dried three necked round bottomed flask fitted with a reflux condenser was added triisopropylsilyl acetylene (9.9 mL, 44 mmol) under argon. Toluene (18 mL) and diethyl zinc (1.1M in toluene, 36mL) were added and the resulting solution was refluxed for 6h upon which time the resulting solution turned grey in color. (*R*)-BINOL (1.14 g, 4 mmoL) in dichloromethane (40 mL), predried over anhydrous 4Å molecular sieves, was added to this grey solution and stirred for 15 min. Titanium isopropoxide (3 mL, 10 mmol) was then transferred to the flask via syringe. The solution turned deep red and stirring was continued for another 1h. Aldehyde **273** (1.78 g, 10 mmoL) in dichloromethane (40 mL) was added and the reaction was monitored by thin-layer chromatography for completion. Saturated ammonium chloride (50 mL) was added to quench the reaction. Extraction with dichloromethane (60 mL), drying over anhydrous magnesium sulfate, and evaporation of the solvent resulted in an yellow oil that was purified by column chromatography (5 % to 15 % ethylacetate / hexanes) to afford the major diastereomer (**274A**, 3.03 g, 5.6 mmol, 56 %) and the minor diastereomer (**275A**, 2.28 g, 4.2 mmol, 42 %). α_D for **274A** = -22.7 (c = 1.06 in $CHCl_3$)

(*R,R*)-**274A** was prepared accordingly using the (*S*)-enantiomer of 1,1'-Binaphthol. The assignment of the stereochemistry of **274A** as either the (*S,S*) or (*R,R*) enantiomer was made on the basis of the stereochemical assignment of the mono addition product **289** via derivative **293** (See page 210).

Following the procedure described earlier for synthesis of **274C**, (*R,R*)-**274A** (3.03 g, 5.6 mmol) was subjected to desilylation and subsequent purification by silica-gel chromatography (10 % to 50 % ethylacetate/ hexanes) afforded (*S,S*)-**274C** (1.07 g, 4.65 mmol, 83 %) as a crystalline white solid. The optical purity was determined to be 99.2 %

ee by HPLC analysis by comparison of retention times with that of the racemic **274C** (Chiralcel OD Column, 94:6 hexane: *i*-PrOH to 85:15 hexane : *i*-PrOH, 254 nm), Retention time: t_{major} = 47.60 min, t_{minor} = 53.79 min. α_D for (*S,S*)-**274C** = -20.5 (*c* = 0.66 in $CHCl_3$).

Oxidation / Reduction Sequence Using (*R*)-Alpine Borane to Optically Active Bis-Propargyl Alcohols



276

*Diynone **276A** (R = TIPS)*

To a solution of the bis-propargyl alcohol (*R,S*)-**275A** (2.71 g, 5 mmol) in 60 mL of dichloromethane was added 4Å MS (2.7 g) and celite (2.7 g) followed by slow addition of pyridinium chlorochromate (2.71 g) and the resultant dark brown slurry stirred at rt for 12 h. Filtration of the reaction mixture over a pad of silica-gel and removal of the solvent under reduced pressure afforded the diynone **276A** (2.69 g, 5 mmol, 100 %) as an orange-yellow oil. The crude product was of sufficient purity to be taken on directly to the next step. R_f (hexanes / ethylacetate = 95/5) = 0.39. Spectral data for **276A**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.12 (s, 42H), 2.36 (s, 3H), 3.91 (s, 3H), 8.00 (s, 2H); ^{13} CNMR ($CDCl_3$, 125MHz) δ 11.13, 18.53, 20.50, 64.19, 97.68, 104.67, 132.10, 133.09, 137.57, 158.56, 175.98; IR (neat) 2946, 2893, 2868, 2145, 1655, 1570, 1471 cm^{-1}; mass spectrum FAB in NBA *m/z* (% rel.intensity) 539 (M^++1, 100), 495 (36), 357 (28), HRMS calcd for $C_{32}H_{51}O_3Si_2$ (M^++1) *m/z* 539.3377, measd 539.3374.

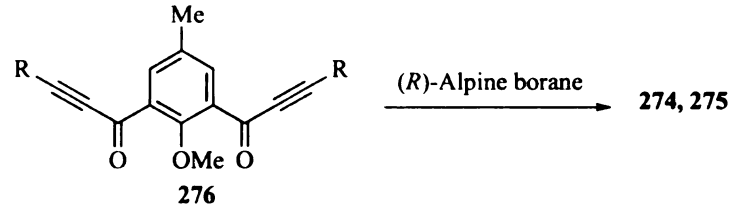
*Diynone **276B** (R = TMS)*

A mixture of bis-propargyl alcohols (*d/l*-**274B** and *meso*-**275B**, 7.42 g, 20 mmol) was subjected to oxidation following the above procedure and gave **276B** (6.46 g, 17.4 mmol, 87 %) as an yellow oil. R_f (hexanes / ethyl acetate = 95/5) = 0.20. Spectral data for **276B**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 0.27 (s, 18H), 2.37 (s, 3H), 3.90 (s, 3H), 7.91 (s, 2H); ^{13}CNMR ($CDCl_3$, 125MHz) δ 0.75, 20.59, 64.10, 100.07, 102.64, 131.75, 133.37, 137.35, 158.82, 176.08; IR ($CDCl_3$) 2963, 2151, 1653, 1570, 1472, 1421, 1307 cm^{-1}; mass spectrum FAB in NBA *m/z* (% rel.intensity) 371 (M^++1, 60), 307 (28), 273 (20), 154 (100), 136 (72), 107 (20), HRMS calcd for $C_{20}H_{27}O_3Si_2$ *m/z* 371.1499, measd 371.1501.

*Diynone **276C** (R = H)*

A mixture of the alkynols *(d/l)*-**274C** and *meso*-**275C** (0.575 g, 2.5 mmol) was dissolved in 15 mL of acetone in a 50 mL round bottomed flask and freshly prepared Jones reagent was added until the red color indicative of the excess Cr(VI) salts persisted. The reaction was quenched by addition of excess isopropanol and the insoluble Cr(III) salts were removed by filtration through a celite pad. The filtrate was diluted with ether (100 mL) and washed sequentially with satd aq $NaHCO_3$ solution (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate. Filtration followed by removal of the solvent under reduced pressure afforded the crude material that was purified by silica-gel chromatography (25 % ethyl acetate/ hexanes) to yield **276C** (0.466 g, 2.05 mmol, 82 %) as a light yellow solid. Mp = 98-100°C. R_f (hexanes / ethyl acetate = 3/1) = 0.23. Spectral data for **276C**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.05 (s,

3H), 3.45 (s, 2H), 3.93 (s, 3H), 7.98 (s, 2H); ^{13} CNMR ($CDCl_3$, 125MHz) δ 20.57, 64.30, 80.42, 81.86, 131.38, 133.76, 137.80, 158.99, 175.59; IR (neat) 3271, 3250, 2957, 2094, 1667, 1630, 1570, 1472, 1419 cm^{-1}; mass spectrum FAB in NBA *m/z* (% rel.intensity) 227 (M^++1,100), 154 (52), 136 (36), HRMS calcd for $C_{14}H_{11}O_3$ *m/z* 227.0707, measd 227.0708.



276

General Procedure For Midland Reductions of Acetylenic Ketones 276

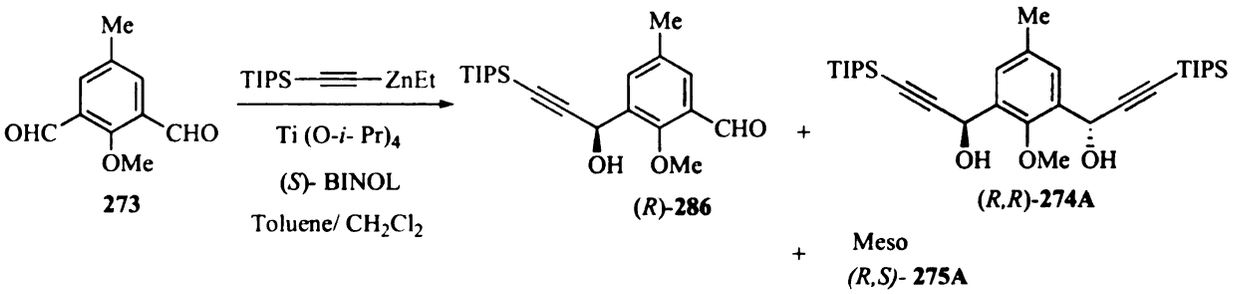
To one equiv. of the diynone **276** in tetrahydrofuran (1.1 M) was added (*R*)-Alpine borane (4 equiv, 0.5 M in tetrahydrofuran prepared from (+)-α-pinene) and the resultant solution was stirred at ambient temperature for the times specified below. After the indicated time period, solvent was removed under reduced pressure by applying a water aspirator. The resultant mixture was heated to 40°C for 20 min to afford thick reddish oil, which was subsequently dissolved in anhydrous ether (10-15 mL). Ethanolamine (2-3 mL) was added dropwise at 0°C to facilitate the formation of the borane-ethanolamine adduct that precipitates as a light yellow solid. This residue was then filtered over a medium porosity glass fritted funnel and the solid was repeatedly washed with ether (50 mL). Removal of the solvent under reduced pressure afforded the crude alkynol that was purified by silica-gel chromatography to afford the pure alkynol in the diastereomeric ratio specified. The reduction of diynone **276C** (R = H) under these conditions gave impure alcohol **274C** (> 99 % ee) after chromatographic purification while the reduction of the silylated diynones gave the corresponding alcohols **274A** and **274B** of high purity.

2,6-bis((R)-3-hydroxy-1-triisopropylsilylpropynyl)-4-methylanisole) ***274A***

Diynone **276A** (2.69 g, 5 mmol) upon subjecting to the reduction according to the general procedure afforded (*R,R*)-**274A** in 35 % yield (0.95 g, 1.75 mmol). The amount of *meso*-**275A** could not be determined as it could not be isolated pure. The enantiomeric purity of (*R,R*)-**274A** was determined upon desilylation to (*S,S*)-**274C** as > 99.5 % ee [(*R,R*)-**274C** not seen in the HPLC trace].

2,6-bis((R)-3-hydroxy-1-trimethylsilylpropynyl)-4-methylanisole ***274B***

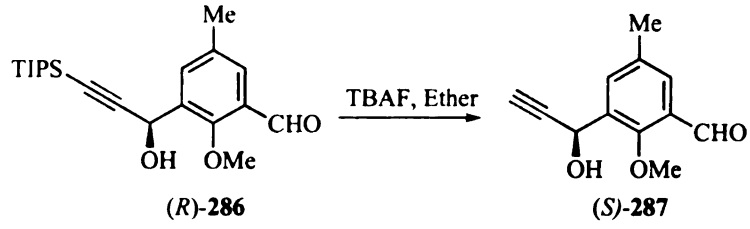
Upon subjecting diynone **276B** (2.05 g, 5.5 mmol) to the reduction according to the general procedure (*R,R*)-**274B** was obtained exclusively in 76 % yield (1.55 g, 4.18 mmol). None of the (*R,S*)-**275B** was observed by TLC. The enantiomeric enrichment of (*R,R*)-**274B** was determined upon desilylation to (*S,S*)-**274C** as > 99.5 % ee [(*R,R*)-**274C** not seen in the HPLC trace].



(R)-3-(1-hydroxy-3-(triisopropylsilyl)prop-2-ynyl)-2-methoxy-5-methylbenzaldehyde ***286***

Into a clean flame dried three necked round bottomed flask was added triisopropyl silyl acetylene (4.5 mL, 20 mmol) under argon. Toluene (10 mL) and diethyl zinc [1.1M in toluene, 18 mL) were added and the resulting solution was refluxed for 5h upon which time the resulting solution turned grey in color. (*S*)-BINOL (0.572 g, 2 mmoL) in 20 mL of dichloromethane, predried over anhydrous 4Å molecular sieves, was added to this grey solution and after stirring for 15 min, titanium isopropoxide (1.5 mL, 5 mmol) was added

via syringe. The solution turned deep red and stirring was continued for another 1h. Aldehyde **273** (1.78 g, 10 mmoL) in dichloromethane (20 mL) was added and the reaction was monitored by GC/MS for completion. Saturated ammonium chloride (80 mL) was added to quench the reaction. Extraction with dichloromethane (100 mL), drying over anhydrous magnesium sulfate, and evaporation of the solvent resulted in an yellow oil which was purified by column chromatography (5% to 15 % ethylacetate / hexanes) to afford 3.0 g (8.2 mmol, 82 %) of the alkynol (*R*)-**286** as an yellow oil along with 0.63 g (1.16 mmol, 11.6 %) of the bis-alkynol **274A**. The (*R,S*)-isomer **275A** co-eluted with (*R*)-BINOL and hence its yield could not be determined accurately. R_f (hexanes / ethylacetate = 85/15) = 0.34. Spectral data for (*R*)-**286** : ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.06 (s, 21H), 2.35 (s, 3H), 2.52 (d, 1H, *J* = 5.5 Hz), 3.99 (s, 3H), 5.78 (d, 1H, *J* = 6.0 Hz), 7.62 (d, 1H, *J* = 2.5 Hz), 7.78 (d, 1H, *J* = 2.0 Hz), 10.31 (s, 1H); ^{13}CNMR ($CDCl_3$, 125MHz) δ 11.19, 18.59, 20.72, 63.68, 65.73, 90.76, 103.34, 128.90, 129.67, 132.93, 134.48, 136.95, 159.15, 189.82; IR (neat) 3429, 2943, 2988, 2172, 1689, 1606, 1587, 1477 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 360 M^+ (2), 343 (47), 318 (100), 303 (30), 288 (50), 260 (13). Anal calcd for $C_{21}H_{32}O_3Si$: C, 69.95; H, 8.95. Found: C, 69.49; H, 9.11. Racemic alkynol **286** was prepared in an analogous manner by using (+/-)-BINOL instead of (*S*)-BINOL.

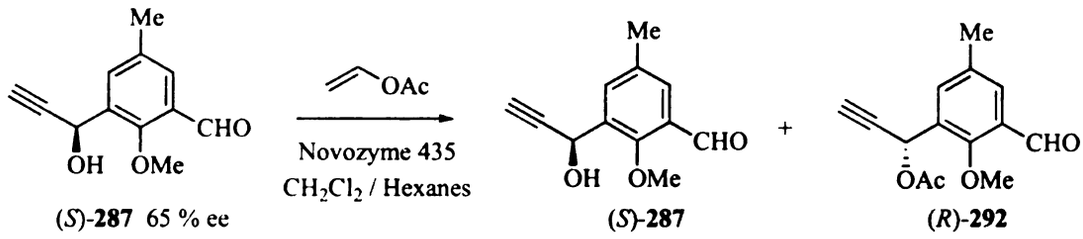


(*R*)-**286** (*S*)-**287**

(S)-3-(1-hydroxyprop-2-ynyl)-2-methoxy-5-methylbenzaldehyde ***287***

To a clean flame dried 100mL flask was added 2.95 g (8.2 mmol) of (*R*)-**286** and 35 mL of ether followed by dropwise addition of 5 equiv. of tetra-butyl ammonium fluoride (1M in tetrahydrofuran). The resultant solution was stirred for 4 h at room temperature. Aqueous workup followed by removal of solvent afforded the crude product which was purified by silica-gel chromatography (50 % ethylacetate / hexanes) to afford 1.54 g (7.5 mmol, 92 %) of *(S)*-**287** as an yellow oil. R_f (hexanes / ethylacetate = 1/1) = 0.69. Mp of *(S)*-**287** = 60-62 °C. Spectral data for (*S*)-**287** : ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.36 (s, 3H), 2.65 (d, 1H, J = 2.1 Hz), 2.74 (s, 1H), 3.98 (s, 3H), 5.72 (dd, 1H, *J* = 3.6, 2.4 Hz), 7.62 (d, 1H, *J* = 2.1 Hz), 7.66 (d, 1H, *J* = 2.4 Hz), 10.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 20.97, 59.73, 65.85, 75.14, 83.61, 129.24, 130.37, 134.64, 135.06, 135.20, 189.71 (One aryl carbon missing); IR (neat) 3425, 3289, 2910, 2875, 2100, 1088, 1609, 1479 cm^{-1}; mass spectrum FAB in NBA *m/z* (% rel.intensity) 204 (M^+, not found) 187 (94), 173 (20), 115 (15), 93 (40), HRMS calcd for $C_{12}H_{12}O_3$ (M^+-17) *m/z* 187.0759, measd 187.076.

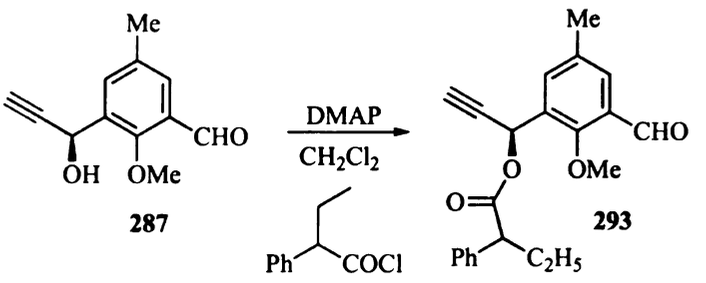
Similarly, racemic alkynol **287** was prepared by desilylation of racemic **286**. HPLC Analysis of (*S*)-**287** revealed the enantiomeric excess to be 65.4 % (Chiralpak AS column, 94:6 hexane: *i*–PrOH to 85 :15 hexane : *i* –PrOH, 254 nm, Flow rate 0.5 mL / min) Retention time t_{major} = 47.09, t_{minor} = 42.99. The major enantiomer was assigned as (*S*) based on Horeau's method via derivative **293**.



Enzymatic resolution of enantiomers of 287

To 1.54 g (7.54 mmol) of (*S*)-**287** of 65 % ee in a round-bottomed flask was added dichloromethane and hexanes (1/3 ratio, 45 mL) followed by the addition of 1.5 mL of vinyl acetate. Novozyme 435 (300 mg) was sequentially added with vigorous stirring and the reaction mixture was left at room temperature for overnight. Filtration of the resin and evaporation of the solvent under reduced pressure afforded the crude product from which upon purification by silica-gel chromatography afforded 1.27 g (6.26 mmol, 83 %) of (S)-**287** in 93.4 % ee as a light-yellow solid and 0.196 g (0.80 mmol, 10.6 %) of (*R*)-**292** as white solid. Mp = 52-54°C. The enantiomeric purity of the (*R*)-**292** was not determined. The % ee of (*S*)-**287** was determined as described in the previous experiment. R_f (hexanes / ethylacetate = 3/1) of (*R*)-**292** = 0.41. Spectral data for (*R*)-**292**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.10 (s, 3H), 2.37 (s, 3H), 2.63 (d, 1H, J = 2.5 Hz), 3.92 (s, 3H), 6.72 (d, 1H, J = 2.0 Hz), 7.65 (d, 1H, J = 2.5 Hz), 7.69 (d, 1H, J = 2.5 Hz), 10.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 125MHz) 20.70, 20.91, 59.40, 65.40, 75.39, 80.04, 128.95, 130.48, 130.96, 134.79, 135.68, 158.48, 169.32, 189.29; IR (neat) 3292, 2938, 2861, 2753, 2257, 2125, 1745, 1686, 1606, 1481 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 246 M^+ (3), 231 (14), 187 (100), 115 (12). Anal calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C; 68.19, H; 5.68. Specific rotation of (*S*)-**287** α_D = -5.0 (c = 1.02 in *i* -PrOH).

Application of Horeau's Method of Partial Kinetic Resolution For Determination of Absolute Configuration of Chiral Propargylic alcohol 287



The Alcohol **287** (93.4 % ee, 0.204 g, 1 mmol) and N,N-dimethyl amino pyridine (25 mg, 0.20 mmol) were transferred to a 25 mL three necked round bottomed flask and pyridine (2 mL) was added. To this solution was added 2-phenyl butyryl chloride (0.35 mL, 2 mmol) and the resultant mixture stirred at ambient temperature for 15 h. After 15 h, pyridine was removed under high vacuum and the residue was dissolved in dichloromethane (50 mL) and the organic layer was washed with saturated sodium bicarbonate (100 mL). Removal of the solvent under reduced pressure afforded the ester as an oil in a 2.26 : 1 mixture of inseparable diastereomers of **293** in 96 % yield (0.336 g, 0.96 mmol). The aqueous layer was acidified to pH ~ 3 and then extracted with dichloromethane (4×50 mL). Drying the organic layer over anhydrous magnesium sulfate followed by removal of the solvent afforded the 2-phenyl butanoic acid (26 mg, 0.16 mmol, 16 %) as oil. Further acidification followed by extraction with dichloromethane did not afford any more carboxylic acid. The specific rotation of the acid was recorded in two different solvents and the results are tabulated below.

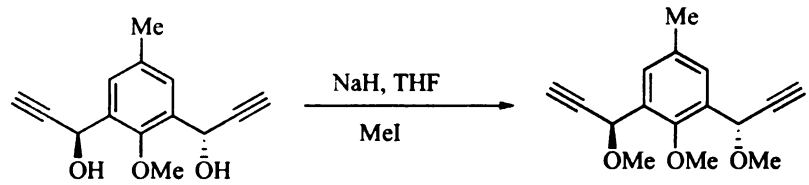
Table 7.4. Optical Rotations of Isolated 2-Phenyl Butanoic Acid

Solvent	Concentration c	Specific rotation	Literature value of Optically pure (/)-2-phenyl butanoic acid	Optical Purity
Toluene	0.9	-15.1 °	-93 °	16.34 %
Chloroform	1.0	-11.4°	-74.8 °	15.3 %

Based on the sign of the optical rotation of the isolated carboxylic acid and adopting Horeau's rule, the absolute configuration of the propargylic alcohol **287** can be deduced to be the (*S*)-isomer.[130]

*(S)-1-(3-formyl-2-methoxy-5-methylphenyl)prop-2-ynyl 2-phenylbutanoate **293***:

R_f (hexanes / ethylacetate = 85 / 15) = 0.32. Spectral data for (2.2:1) mixture of diastereomers of **293**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 0.86-0.91 (m, 4H), 1.76-1.84 (m, 2H), 2.07-2.14 (m, 2H), 2.20 (s, 3H), 2.33 (s, 1.4 H), 2.54 (d, 0.4 H, *J* = 2.0 Hz), 2.61 (d, 0.9 H, *J* = 2.0 Hz), 3.50 (t, 0.45 H, *J* = 8.0 Hz), 3.51 (t, 0.9 H, *J* =7.5 Hz), 3.70 (s, 3H), 3.84 (s, 1.41H), 6.67 (d, 0.9H, *J* = 2.5 Hz), 6.70 (d, 0.41 H, *J* = 2.5 Hz), 7.19-7.23 (m, 4H), 7.25 (d, 0.71 H, *J* = 1.5 Hz), 7.26 (d, 0.32 H, *J* = 2.0 Hz), 7.28–7.29 (m, 2H), 7.30 (d, 0.58 H, *J* = 2.0 Hz), 7.56-7.58 (m, 1.3H), 7.64 (d, 0.4 H, *J* = 2.5 Hz),10.23 (s, 0.9 H), 10.29 (s, 0.39 H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 12.04 , 12.07, 20.64, 20.71, 26.49, 26.58, 53.08, 53.31, 59.67, 59.72, 65.19, 65.34, 75.39, 75.45, 79.73, 80.04, 127.32, 127.36, 128.02, 128.55, 128.78, 128.91, 129.97, 130.26, 131.01, 131.06, 134.62, 134.72, 134.96, 135.53, 138.17, 138.25, 158.39, 158.51, 172.29, 172.33, 189.37 (3 aryl carbons not seen); IR (neat) 3285, 2967, 2936, 2876, 1741, 1891, 1604, 1589, 1479 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 350 M^+ (10), 320 (20), 203 (20), 187 (40), 119 (55), 91 (100), HRMS calcd for $C_{22}H_{22}O_4$ *m/z* 350.1518, measd 350.1517.



(*S,S*)-**274C** (*S,S*)-**267A**

*2-Methoxy-1,3-bis-((S)-1-methoxy-prop-2-ynyl)-5-methylbenzene (S,S)-**267A***

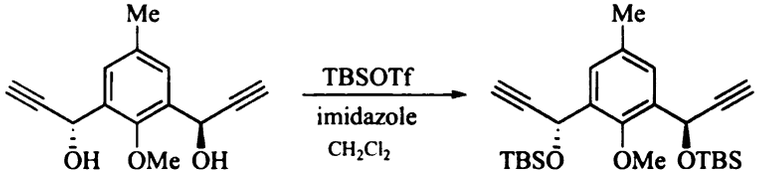
To a preweighed flame dried three necked 100 mL round bottomed flask was added 350 mg (14.6 mmol) sodium hydride (60 % dispersion in oil) and pentane (10 mL). The resulting slurry was stirred at ambient temperature for 15 minutes. Pentane was then extracted using a syringe and the residual solvent was removed under vacuum to afford 210 mg of sodium hydride. Tetrahydrofuran (30 mL) was added to this flask under argon and then the (*S,S*)- alkynol **274C** (0.782 g, 3.4 mmol) was slowly added over 5 minutes. Upon completion of the addition, the yellow slurry was stirred for another 45 min. Iodomethane (0.7 mL) was added and the reaction was left to stir overnight. Ether (25 mL) was added and the reaction was worked up by addition of saturated ammonium chloride solution (15 mL). The product was extracted with ether (100 mL) and the organic layer was washed with water (100 mL). Drying over anhydrous magnesium sulfate, removal of ether under reduced pressure, and purification by silica gel chromatography (15 % ethylacetate / hexanes) afforded 0.87 g (3.36 mmol, 99 %) of (*S,S*)-**267A** as white oil. R_f = 0.37 (hexanes / ethyl acetate = 85 / 15). Spectral data for (*S,S*)-**267A**: ^{1}HNMR ($CDCl_3$, 500MHz) δ 2.33 (s, 3H), 2.58 (d, 2H, J = 2.5 Hz), 3.44 (s, 6H), 3.83 (s, 3H), 5.34 (d, 2H, J = 2.5 Hz), 7.44 (s, 2H); ^{13}CNMR ($CDCl_3$, 125MHz) δ 20.92, 56.35, 63.60, 67.05, 75.14, 81.68, 129.93, 131.40, 134.59, 153.19; IR (CH_2Cl_2) 3297, 3053, 2992, 2939, 2903, 2824, 2114, 1662, 1593, 1481, 1435, 1331, 1261. α_D = +16.8 (c = 0.5 in $CHCl_3$); mass spectrum FAB in NBA *m/z* (% rel.intensity) 258 M^+ (60),

227 (100), 154.1 (100), 136.1 (100), 107 (35), 77 (30), HRMS calcd for $C_{16}H_{18}O_3$ *m/z* 258.1256, measd 258.1257.

(*S,R*)-**275C** (*S,R*)-**282**

*2-Methoxy-3-((S)-1-methoxyprop-2-ynyl)-1-((R)-1-methoxyprop-2-ynyl)-5-methyl-benzene (S,R)-**282***

Following the general procedure as described above for the preparation of (*S,S*)-**267A**, the diastereomer (*S,R*)-**282** could be obtained in 70 % yield (0.46 g, 1.82 mmol) from (*S,R*)-**275C** (0.598 g, 2.6 mmol). R_f = 0.37 (hexanes / ethyl acetate = 85 / 15). Spectral data for (*S,R*)-**282:** ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.34 (s, 3H), 2.58 (d, 2H, *J* = 2.5 Hz), 3.44 (s, 6H), 3.84 (s, 3H), 5.35 (d, 2H, *J* = 2.0 Hz), 7.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 20.93, 56.28, 63.57, 67.01, 75.12, 81.74, 129.85, 131.42, 134.60, 153.16; IR (neat) 3290, 2990, 2939, 2903, 2824, 2114, 1664, 1591, 1481 cm^{-1}; mass spectrum FAB in NBA *m/z* (% rel.intensity) 258 (M^+, 50), 227 (100), 154 (100), 136 (60), HRMS calcd for $C_{16}H_{18}O_3$ *m/z* 258.1256, measd 258.1257.

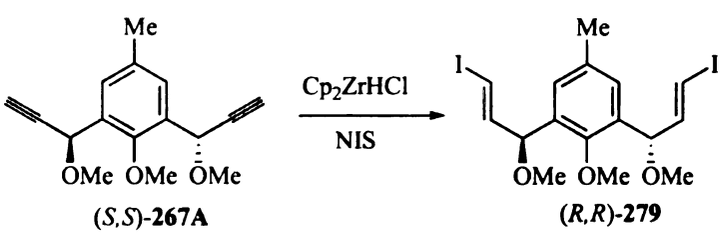


(*R,R*)-**274C** (*R,R*)-**267B**

2-Methoxy-1,3-bis-((R)-1-(tert-butyldimethylsilyloxy)prop-2-ynyl-5-methyl-benzene **267B**

To a solution of the alkynol **274C** (99.2 % ee, 0.735 g, 3.2 mmol) in 35 mL of dichloromethane was added imidazole (0.522 g, 7.7 mmol) followed by TBSOTf (1.6 mL, 7.04 mmol) at 0°C. The reaction mixture was subsequently warmed to room

temperature and stirred for 24 h. Addition of water (50 mL), extraction of the organic layer with dichloromethane and removal of the solvent under reduced pressure afforded the bis-propargyl TBS ether **267B** in 92 % yield (1.35 g, 2.92 mmol) as a white solid. Mp = 124-126°C. Spectral data for (*R,R*)-**267B**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 0.08 (s, 6H), 0.16 (s, 6H), 0.88 (s, 18H), 2.32 (s, 3H), 2.47 (d, 2H, J = 2.4 Hz), 3.82 (s, 3H), 5.71 (d, 2H, J = 2.1 Hz), 7.39 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) δ -4.90, -4.57, 18.23, 21.32, 25.77, 58.93, 63.03, 72.95, 82.57, 128.34, 134.38, 134.47; IR (neat) 3436, 3277, 2951, 2928, 2899, 2859, 2112, 1644, 1473, 1252 cm^{-1}. mass spectrum *m/z* (% rel.intensity) 458 (M^+ not found), 443 (M^+-CH_3 , 2), 401 (100), 330 (9), 256 (17). Specific rotation α_D of **267B** prepared from (*R,R*)-**274C** (99.2 % ee) = +1°(c = 1.57 in $CHCl_3$)

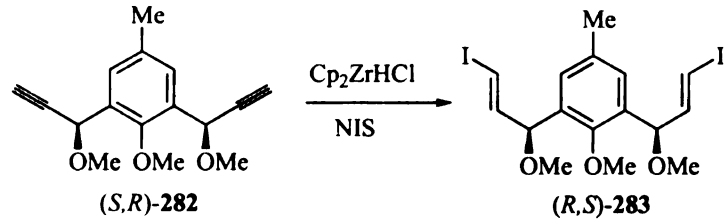


(*S,S*)-**267A** (*R,R*)-**279**

1,3-Bis-((R,E)-3-iodo-1-methoxyallyl)-2-methoxy-5-methyl-benzene 279

Following the procedure described earlier for the synthesis of **245**, the diyne (*S,S*)-**267A** (0.69 g, 2.66 mmol) gave upon purification by column chromatography on silica gel (5 % ethyl acetate / hexanes) the vinyl iodide (*R,R*)-**279** in 76 % yield (1.02 g, 2.02 mmol) as an orange oily liquid. R_f (ethyl acetate / hexanes = 19/1) = 0.35. Spectral data for (*R,R*)-**279**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.31 (s, 3H), 3.30 (s, 6H), 3.69 (s, 3H), 4.98 (d, 2H, *J* = 6.5 Hz), 6.41 (d, 2H, *J* = 14.5 Hz), 6.65 (dd, 2H, *J* = 14.5, 6.5 Hz), 7.11 (s, 2H); ^{13}CNMR ($CDCl_3$, 125MHz) δ 21.04, 56.66, 62.86, 78.71, 78.19, 128.34, 132.24, 134.99, 145.38, 153.43; IR (CH_2Cl_2) 2982, 2930, 2822, 1605, 1478, 1431, 1340, 1277, 1091 cm^{-1}; mass spectrum FAB in NBA *m/z* (% rel.intensity) 514 (16), 483 (44), 387 (52), 361 (36),

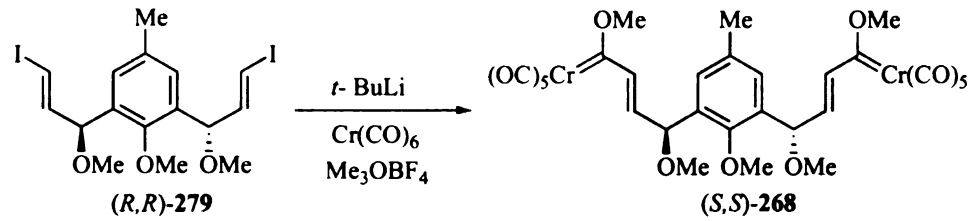
197 (100), HRMS calcd for $C_{16}H_{20}O_3Si_2$ *m/z* 513.9503, measd 513.9504. α_D = -93.7 (c = 1.49 in $CHCl_3$)



(*S,R*)-**282** (*R,S*)-**283**

*3-((R,E)-3-Iodo-1-methoxyallyl)-1-((S,E)-3-Iodo-1-methoxyallyl)-2-methoxy-5-methyol-benzene **283***

Following the procedure described earlier for synthesis of **245**, the diastereomeric vinyl iodide (*R,S*)-**283** was obtained in 72 % yield (0.93 g, 1.8 mmol) as light-yellow solid from (*S,R*)-**282** (0.575 g, 2.5 mmol). Mp = 104-106°C. Spectral data for (*R,S*)-**283**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.30 (s, 3H), 3.29 (s, 6H), 3.68 (s, 3H), 4.91 (d, 2H, *J* = 6.5 Hz), 6.42 (d, 2H, *J* = 14.5 Hz), 6.65 (dd, 2H, *J* = 14.5, 6.5 Hz), 7.11 (s, 2H); ^{13} C NMR ($CDCl_3$, 125MHz) δ 21.04, 56.59, 62.93, 78.79, 79.20, 128.34, 132.25, 135.03, 145.35, 153.48; IR (neat) 2982, 2930, 2822, 1605, 1477, 1432, 1338, 1277 cm^{-1}. Anal calcd for $C_{16}H_{20}I_2O_3$: C, 37.38; H, 3.92. Found: C, 37.55; H, 3.88.



(*R,R*)-**279** (*S,S*)-**268**

*Chiral Bis-Carbene complex (S,S)-**268***

Procedure A:

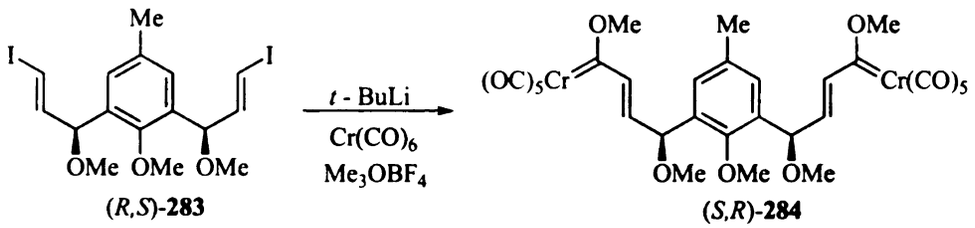
To a solution of vinyl iodide **14** (0.92 mmol) in tetrahydrofuran (20 mL) at –78 °C was added *t* -Butyllithium (4 eq, 1.7 M in pentane) and the reaction mixture was stirred at –78 °C for 30 min. Chromium hexacarbonyl (0.81 g, 3.68 mmol) was dissolved in 40 mL of

tetrahydrofuran and then transferred via cannula to the organolithium solution under argon at –78 °C. The resulting deep red solution was warmed to room temperature and stirred for 3 h. The solvent was evaporated under vacuum and water/ dichloromethane (1:1, 50 mL) was added and then trimethyl oxonium tetrafluoroborate (6.5 eq) was added and the mixture stirred for 30 min. The organic layer (150 mL) was washed with water (2 x 50 mL) and dried over anhydrous magnesium sulfate. After filtration the solvent was removed and crude product was purified by silica gel chromatography (10 % ethyl acetate / hexanes) to give carbene complex in 24 % yield (0.162 g, 0.22 mmol) as red oil.

Procedure B:

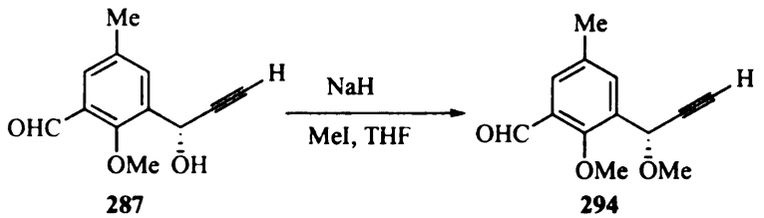
To a solution of vinyl iodide **279** (99.5 % ee, 0.651 g, 1.26 mmol) and chromium hexacarbonyl (5.04 mmol, 1.11 g) in 55 mL of tetrahydrofuran at –78 °C was added *t*-butyllithium (4 equiv, 1.7 M in pentane) and the reaction mixture was stirred at this temperature for 30 min. The resulting deep red solution was then warmed to room temperature and stirred for 3 h. The solvent was evaporated under vacuum and water/ dichloromethane (1:1, 50 mL) was added and then trimethyl oxonium tetrafluoroborate (6.5 eq) was added and the mixture stirred for 30 min. The organic layer (150 mL) was washed with water (2 x 50 mL) and dried over anhydrous magnesium sulfate. After filtration the solvent was removed and crude product was purified by silica gel chromatography (10 % ethyl acetate / hexanes) to give carbene complex **268** in 24 % yield (0.224 g, 0.31 mmol) as red oil. R_f (hexanes / ethyl acetate = 9/1) = 0.4. Spectral data for (*S,S*)-**268**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.26 (s, 3H), 3.33 (s, 6H), 3.76 (s, 3H), 4.73 (s, 6H), 5.09 (s, 2H), 6.11 (d, 2H, J = 11.5 Hz), 7.10 (s, 2H), 7.54 (d, 2H, J = 14.5 Hz); ^{13}CNMR ($CDCl_3$, 125MHz) 20.85, 56.95, 63.06, 66.58, 76.22, 129.08, 131.13,

132.09, 135.34, 142.12, 153.68, 216.43, 223.98, 337.19; IR (neat) 2934, 2828, 2060, 1927, 1605, 1452, 1226 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 730 M^+ (10), 699 (10), 590 (45), 450 (100), 154 (80), HRMS calcd for $C_{30}H_{26}Cr_2O_{15}$ *m/z* 730.0082, measd 730.0084. Specific rotation of (*S,S*)-**268** prepared from (*S,S*)-**274C** (99.5 % ee) α_D = -69 °(c = 1.22 in $CHCl_3$).



*Achiral Bis-Carbene complex (S,R)-**284***

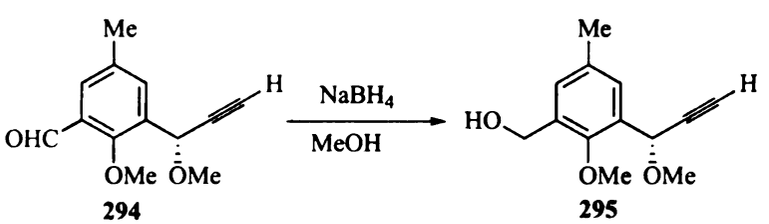
Following procedure A described above for the synthesis of (*S,S*)-**284**, the diastereomer (*R,S*)-vinyl iodide **283** gave none of the diastereomeric bis-carbene complex (*S,R*)-**284**. On the other hand, by applying procedure B, (*R,S*)-**283** (0.91 g, 1.77 mmol) gave 0.275 g (0.38 mmol, 21 %) of the bis-carbene complex (*S,R*)-**284** as deep-red oil upon workup and purification by silica-gel chromatography in 15 % ethyl acetate / hexanes. R_f (ethyl acetate / hexanes = 85/15) = 0.30. Spectral data for (*S,R*)-**284** : ^1H NMR ($CDCl_3$, 300MHz) δ 2.25 (s, 3H), 3.34 (s, 6H), 3.76 (s, 3H), 4.71 (s, 6H), 5.08 (d, 2H, *J* = 5.1 Hz), 6.07 (dd, 2H, *J* = 15.0, 5.7 Hz), 7.10 (s, 2H), 7.52 (d, 2H, *J* = 15.0 Hz); ^{13} CNMR ($CDCl_3$, 125MHz) 20.87, 56.98, 62.96, 66.57, 76.18, 128.90, 130.84, 132.10, 135.39, 141.96, 153.46, 216.41, 223.98, 337.01; IR (neat) 2934, 2828, 2060, 1917, 1605, 1477, 1452, 1275, 1228 cm^{-1} ; mass spectrum *m/z* (% rel.intensity) 730 (M^+, 2.8), 699 (3.5), 590 (64), 450.0 (100), 418.9 (28), 179.1 (40), HRMS calcd for $C_{30}H_{26}Cr_2O_{15}$ *m/z* 730.0082, measd 730.0080.



287 294

(S)-2-Methoxy-3-(1-methoxyprop-2-ynyl)-5-methylbenzaldehyde ***292***

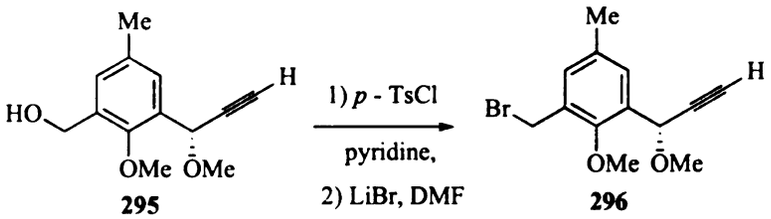
Following the procedure described above for the preparation of (*S,S*)-**267A**, (2.10 g, 10.31 mmol, 94.1 % ee) of (*S*)-**287**, 1.3 equiv. of sodium hydride and excess of iodomethane afforded upon purification by silica-gel chromatography (15 % ethylacetate / hexanes) 1.51 g (6.91 mmol, 67 %) of (*S*)-**294** as colorless oil. R_f(hexanes / ethylacetate = 85/15) = 0.43. Spectral data for (*S*)-**294**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.37 (s, 3H), 2.65 (d, 1H, *J* = 2.5 Hz), 3.49 (s, 3H), 3.94 (s, 3H), 5.40 (d, 1H, *J* = 2.0 Hz), 7.64 (s, 1H), 7.73 (s, 1H), 10.32 (s, 1H); ^{13} CNMR ($CDCl_3$, 125MHz) δ 20.64, 56.42, 65.38, 66.39, 75.60, 81.05, 128.76, 129.77, 132.56, 134.63, 135.56, 158.62, 189.52; IR (neat) 3285, 2938, 2826, 2753, 2114, 1693, 1589, 1479 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 219 (M^++1, 22), 218 (M^+, 33), 203 (36), 187 (100), 140 (44), 123 (36), HRMS calcd for $C_{13}H_{15}O_3$ (M^++1) *m/z* 219.1021, measd 219.1020. The above alkylation step was performed several times to optimize the yield of (*S*)-**294** and the rotation was recorded on material that was obtained from (*S*)-**287** (93.4 % ee). Specific rotation α_D of (*S*)-**294** prepared from (*S*)-**287** (93.4 % ee) = + 15.4 °(*c* = 1.06 in $CHCl_3$)



294 295

(S)-(2-Methoxy-3-(1-methoxyprop-2-ynyl)-5-methylphenyl)-methanol ***295***

The aryl aldehyde **294** (1.52 g, 6.94 mmol, 94.1 % ee) was dissolved in methanol (*c* = 0.22M) and transferred to a clean 100 mL round-bottomed flask. Sodium borohydride (1.1 eq) was added portion-wise to allow the exothermic reaction to subside and the resultant mixture was stirred at room temperature for 3-4 h. Aqueous workup followed by three-fold extraction with ether and removal of solvent under reduced pressure afforded 1.41 g (6.38 mmol, 92 %) of the benzyl alcohol (*S*)-**295** as an oil. R_f(hexanes / ethylacetate = 1/1) = 0.44. Spectral data for (*S*)-**295**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.31 (s, 3H), 2.59 (d, 1H, *J* = 2.5 Hz), 3.46 (s, 3H), 3.91 (s, 3H), 4.52 (s, 2H), 5.32 (d, 1H, *J* = 2.0 Hz), 7.19 (d, 1H, *J* = 2.5 Hz), 7.40 (d, 1H, *J* = 2.0 Hz); ^{13} CNMR ($CDCl_3$, 125MHz) δ 20.43, 27.49, 56.11, 62.58, 66.66, 74.90, 81.24, 129.73, 130.69, 131.54, 132.30, 134.33, 153.50; IR (neat) 3431, 3287, 2937, 2828, 2114, 1595, 1481 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 220 (M^+, 68) 203 (44), 189 (100), 159 (26), HRMS calcd for $C_{13}H_{16}O_3$ 220.1099, measd 220.1098. The above reduction step was carried out several times to optimize yield of (*S*)-**295** but the rotation was recorded on material obtained from (*S*)-**287** (93.7 % ee). Specific rotation α_D of (*S*)-**295** prepared from (*S*)-**287** (93.7 % ee) = + 20.6 (c = 0.58 in $CHCl_3$)

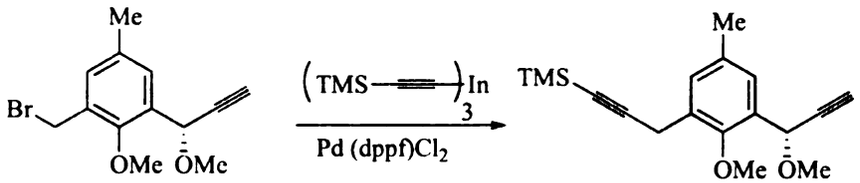


(S)-1-(Bromomethyl)-2-methoxy-3-(1-methoxyprop-2-ynyl)-5-methylbenzene ***296***

The benzyl alcohol **295** (1.4 g, 6.36 mmol, 94.1 % ee) was dissolved in 40 mL of dichloromethane in a 100 mL three necked round bottomed flask and *p*-toluene sulfonyl chloride (1.82 g, 9.54 mmol) was added followed by pyridine (0.77 mL, 9.54 mmol). The

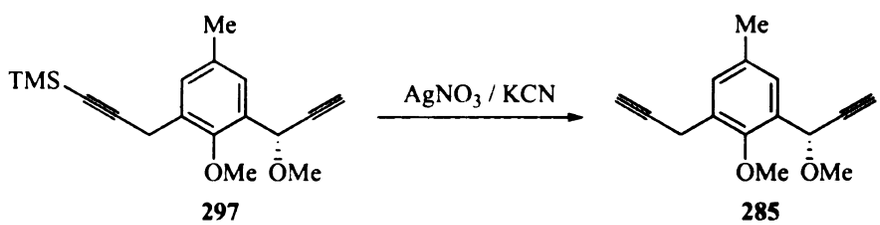
reaction was monitored for completion by TLC and excess dichloromethane (100 mL) was added. The organic layer was washed with 2N HCl (100 mL) followed by saturated sodium bicarbonate and brine solution (100 mL each). Drying over anhydrous magnesium sulfate followed by removal of the solvent under reduced pressure afforded the crude tosylate as a solid that was immediately taken to the next step.

The crude benzyl tosylate was dissolved in N,N-dimethyl formamide (40 mL) in a 100 mL flask and anhydrous lithium bromide (0.66 g, 7.55 mmol) was added. The resultant mixture was heated to 50 °C and stirred for 3-4 h. The reaction mixture was poured into water (100 mL) and then extracted with ether (100 mL). Drying over anhydrous magnesium sulfate followed by removal of the solvent afforded the crude product which was purified by silica-gel chromatography (10 % ethylacetate / hexanes) to afford 57 % (1.0 g, 3.55 mmol) of the bromide (*S*)-**296** as colorless oil. R_f(hexanes / ethylacetate = 9/1) = 0.39. Spectral data for (*S*)-**296**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.31 (s, 3H), 2.59 (d, 1H, J = 2.1 Hz), 3.45 (s, 3H), 3.82 (s, 3H), 4.68 (s, 2H), 5.34 (d, 1H, J = 2.4 Hz), 7.16 (d, 1H, J = 2.4 Hz), 7.39 (d, 1H, J = 2.1 Hz); ^{13} CNMR ($CDCl_3$, 125MHz) δ 20.87, 56.38, 61.10, 62.85, 66.99, 75.13, 81.72, 128.79, 130.48, 131.41, 133.62, 134.49, 153.40; IR (neat) 3290, 2942, 2824, 2114, 1591, 1483, 1435 cm^{-1}. mass spectrum *m/z* (% rel. intensity) 284 M^+ +2 (11, ^{81}Br), 282 M^+ (12, ^{79}Br), 260 (12,^{81}Br), 258 (45, ^{79}Br), 240 (32, ^{81}Br), 238 (85, ^{79}Br), 203 (90), 171 (100), 128 (65), 69 (45), HRMS calcd for $C_{13}H_{15}{}^{79}BrO_2$ *m/z* 282.0255, measd 282.0254. The bromination sequence was subjected to several attempts to optimize the yield of (*S*)-**296** but the rotation was recorded on material obtained from (*S*)-**287** (91 % ee). Specific rotation α_D of (*S*)-**296** prepared from (*S*)-**287** (91 % ee) = + 8.6° (c = 0.62 in $CHCl_3$).



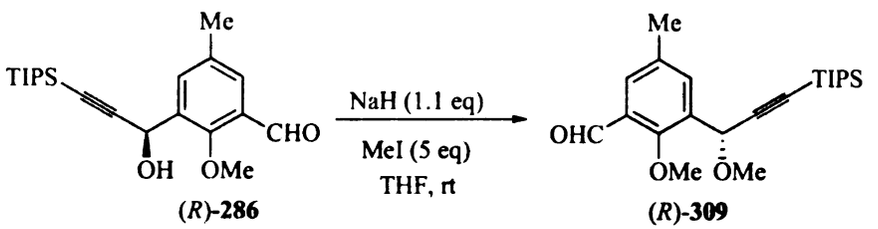
(S)-(3-(2-Methoxy-3-(1-methoxyprop-2-ynyl)-5-methylphenyl)prop-1-ynyl)trimethylsilane ***297***

By following the procedure discussed earlier for the preparation of **239** and reducing the reagent stoichiometry by a factor of two, the benzyl halide **296** (1.0 g, 3.55 mmol, 94.1 % ee) afforded the diyne **297** in 98 % yield (1.04 g, 3.46 mmol) as yellow oil. R_f(hexanes / dichloromethane = 19/1) = 0.42. Spectral data for (*S*)-**297**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.13 (s, 9H), 2.31 (s, 3H), 2.58 (d, 1H, *J* = 2.5 Hz), 3.44 (s, 3H), 3.60 (s, 2H), 3.77 (s, 3H), 5.32 (d, 1H, *J* = 2.1 Hz), 7.28 (s, 1H), 7.33 (s, 1H); ^{13} CNMR ($CDCl_3$, 125MHz) δ 0.29, 20.71, 21.19, 56.63, 62.53, 67.43, 75.27, 82.11, 87.00, 104.67, 128.03, 129.79, 131.33, 134.52, 153.34 (one aryl carbon missing); IR (neat) 3289, 2959, 2899, 2822, 2175, 1482, 1435 cm^{-1}. Anal calcd for $C_{18}H_{24}O_2Si$: C, 71.95; H, 8.05. Found: C, 72.19; H, 8.06. The cross coupling step was subjected to several attempts to optimize the yield of (*S*)-**297** but the rotation was recorded on material that was obtained from (*S*)-**287** (93.4 % ee). Specific rotation α_D of (*S*)-**297** prepared from (*S*)-**287** (93.4 % ee) = +13.1°(c = 0.45 in $CHCl_3$)



(S)-2-Methoxy-1(-methoxyprop-2-ynyl)-5-methyl-3-(prop-2-ynyl)benzene ***285***

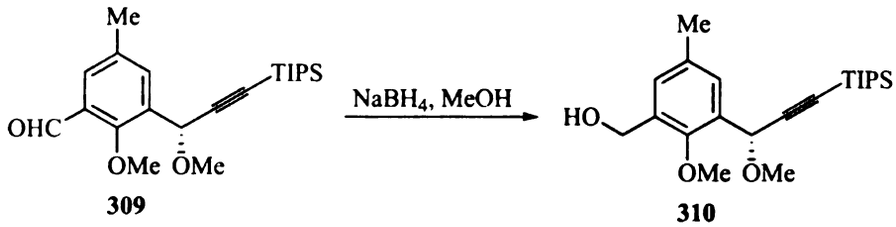
By following the procedure reported earlier for the synthesis of **228**, the diyne **297** (1.04 g, 3.48 mmol, 94.1 % ee) upon desilylation and purification by silica-gel chromatography (5 % Ethyl acetate / hexanes) afforded 0.633 g (2.78 mmol, 80 %) of diyne **285** as an oil. R_f (hexanes / ethyl acetate = 19 / 1) = 0.23. Spectral data for (*S*)-**285**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.14 (t, 1H, *J* = 2.7 Hz), 2.32 (s, 3H), 2.58 (d, 1H, *J* = 2.1 Hz), 3.45 (s, 3H), 3.58 (d, 2H, J = 2.7 Hz), 3.79 (s, 3H), 5.33 (d, 1H, *J* = 2.4 Hz), 7.29 (s, 1H), 7.34 (s, 1H); ^{13}CNMR ($CDCl_3$, 125MHz) δ 19.04, 20.91, 56.37, 62.72, 67.15, 70.24, 75.07, 81.79, 81.98, 127.95, 129.23, 130.93, 131.19, 134.41, 153.04; IR ($CDCl_3$) 3292, 2946, 2826, 2118, 1479, 1433 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 228 (M^+, 30), 197 (50), 154 (100), 136 (60), HRMS calcd for $C_{15}H_{16}O_2$ 228.1150, measd 228.1151. Specific rotation of (*S*)-**285** α_D obtained from (*S*)-**287** (93.4 % ee) = + 3.5°(c = 0.43 in $CHCl_3$)



(R)-2-Methoxy-3-(1-methoxy-3-(triisopropylsilyl)prop-2-ynyl)-5-methylbenzaldehyde ***309***

Following a similar procedure to that described for the preparation of **294**, the propargyl methyl ether **309** was obtained from (*R*)-**286** (61 % ee, 2.74 g, 7.6 mmol) in 92 % yield (2.62 g, 6.99 mmol) upon purification by silica-gel chromatography (5 % ethyl acetate / hexanes) as colorless oil. R_f (hexanes / ethylacetate = 85/15) = 0.61. Spectral data for (*R*)-**309**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.07 (s, 21H), 2.34 (s, 3H), 3.49 (s, 3H), 3.93 (s, 3H), 5.43 (s, 1H), 7.62 (d, 1H, *J* = 2.5 Hz), 7.80 (d, 1H, *J* = 2.5 Hz), 10.31 (s, 1H); ^{13} CNMR ($CDCl_3$, 125MHz) δ 11.16, 18.55, 20.66, 56.14, 65.46, 67.13, 89.40, 104.25, 128.87, 129.58, 133.11, 134.46, 136.33, 158.97, 189.73; IR (neat) 2944, 2866, 2820, 2170, 1694,

1605, 1589, 1479 cm $^{-1}$; mass spectrum *m/z* (% rel.intensity) 373 (M^+-1,40) 359 (40), 343 (100), 331(32), 89 (32), 73 (36), HRMS calcd for $C_{22}H_{33}O_3Si$ *m/z* 373.2199, measd 373.2196. Specific rotation of (*R*)-**309** obtained from (*R*)-**286** (61 % ee) α_D = -11.2°(c = 2.86 in $CHCl_3$)

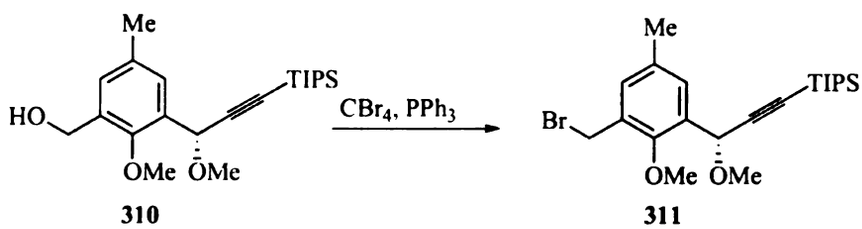


309 **310**

(R)-(2-methoxy-3-(1-methoxy-3-(triisopropylsilyl)prop-2-ynyl)-5-methylphenyl)methanol

310

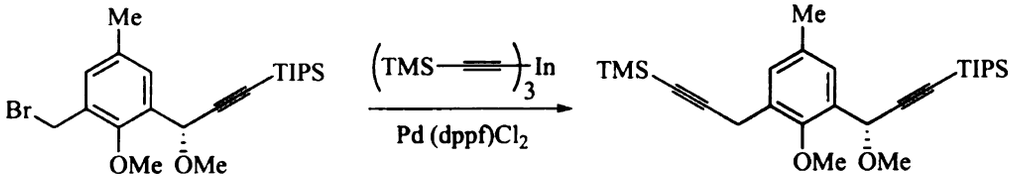
Following the procedure described earlier for the synthesis of **295**, the aldehyde **309** (2.52 g, 6.73 mmol) was reduced to the benzyl alcohol (*R*)-**310** in 97 % yield (2.45 g, 6.53 mmol) as colorless oil. R_f (hexanes / ethyl acetate = 1/1) = 0.71. Spectral data for (*R*)-**310**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.07 (s, 21H), 2.29 (s, 3H), 3.47 (s, 3H), 3.82 (s, 3H), 4.71 (s, 2H), 5.39 (s, 1H), 7.14 (d, 1H, *J* = 2.0 Hz), 7.48 (d, 1H, *J* = 2.0 Hz) (hydroxyl group not observed); ^{13} CNMR ($CDCl_3$, 125MHz) δ 11.17, 18.56, 20.86, 60.50, 63.87, 87.86, 107.14, 129.53, 133.91, 134.46, 153.10 (two aryl carbons, benzylic and propargylic carbons missing); IR (neat) 3416, 2944, 2867, 2170, 1646, 1433, 1382, 1327 cm^{-1}. mass spectrum *m/z* (% rel.intensity) 376 (M^+, 32), 359 (35), 345 (100), 259 (20), 141 (26), HRMS calcd for $C_{22}H_{36}O_3Si$ *m/z* 376.2434, measd 376.2432. Specific rotation of (*R*)-**310** obtained from (*R*)-**286** (61 % ee) α_D = -9°(c = 0.58 in $CHCl_3$)



310 **311**

(R)-(3-(3-(bromomethyl)-2-methoxy-5-methylphenyl)-3-methoxyprop-1-ynyl)triisopropylsilane ***311***

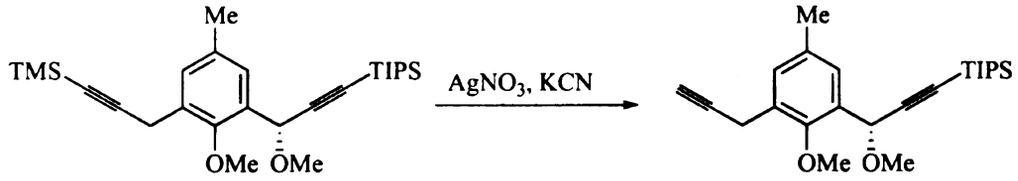
The alcohol **310** (61 % ee, 2.25 g, 5.99 mmol) was dissolved in dichloromethane (30 mL) and triphenylphosphine (1.88 g, 7.18 mmol) was added at room temperature. Carbon tetrabromide (2.38 g, 7.18 mmol) was slowly added to the solution at room temperature and the resultant mixture was stirred for 5 h. The solution was concentrated to 20 % of the total volume and diluted with ether (40 mL). The white precipitate was filtered and the filtrate was concentrated. The residue was then purified by silica-gel chromatography (5 % ethyl acetate / hexanes) to afford the benzyl bromide **311** (2.15 g, 4.91 mmol, 82 %) as colorless oil. R_f (hexanes / ethyl acetate = 19/1)= 0.56. Spectral data for (*R*)-**311**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.07 (s, 21H), 2.28 (s, 3H), 3.47 (s, 3H), 3.91 (s, 3H), 4.53 (s, 2H), 5.37 (s, 1H), 7.17 (d, 1H, J = 2.4 Hz), 7.49 (d, 1H, J = 2.1 Hz); ^{13} CNMR ($CDCl_3$, 125MHz) δ 10.82, 18.23, 20.37, 27.67, 55.69, 62.64, 67.36, 88.53, 100.20, 104.48, 130.54, 131.95, 132.07, 133.98 (one aryl carbon missing); IR (neat) 2946, 2891, 2866, 2820, 2170, 1693, 1591, 1481, 1464, 1435 cm^{-1}. Specific rotation α_D of (*R*)-**311** obtained from (*R*)-**286** 61 % ee = -6.45 °(c = 4.5 in $CHCl_3$)



(R)-2-methoxy-1-(1-methoxy-3-(triisopropylsilyl)prop-2-ynyl)-5-methyl-3-(3-(trimethylsilyl)prop-2-ynyl)benzene ***312***

Following the same procedure as reported earlier for the synthesis of **239** and reducing the reagent stoichiometry by a factor of two, benzyl bromide **311** (2.08 g, 4.91 mmol, 61

% ee) gave **312** in 77 % yield (1.63 g, 3.78 mmol) upon purification by silica-gel chromatography (20 % dichloromethane/ hexanes) as an yellow oil. R_f (hexanes / dichloromethane = 4/1) = 0.32. Spectral data for (*R*)-**312**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.15 (s, 9H), 1.06 (s, 21H), 2.29 (s, 3H), 3.45 (s, 3H), 3.60 (s, 2H), 3.77 (s, 3H), 5.37 (s, 1H), 7.27 (d, 1H, *J* = 2.0 Hz), 7.42 (d, 1H, *J* = 3.0 Hz); ^{13} CNMR ($CDCl_3$, 125MHz) δ 0.04, 11.19, 18.58, 20.48, 55.94, 62.30, 67.85, 86.72, 88.55, 104.54, 105.14, 128.59, 129.33, 130.81, 131.46, 133.91, 153.28 (one methine carbon missing); IR (neat) 2944, 2895, 2867, 2818, 2175, 1693, 1479, 1435, 1280 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 455 (M^+-1, 32), 207 (16), 147 (30), 73 (100), HRMS calcd for $C_{27}H_{43}O_2Si_2$ *m/z* 455.2802, measd 455.2805. Specific rotation α_D of (*R*)-**312** obtained from (*R*)-**286** = -2.4°(c = 2 in $CHCl_3$)

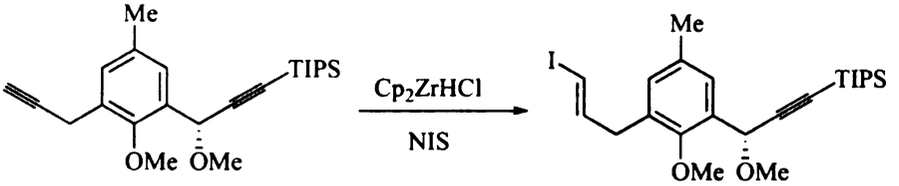


312 **313**

*(R)-triisopropyl(3-methoxy-5-methyl-3-(prop-2-ynyl)phenyl)prop-1-ynyl)silane **313***

Following the procedure reported earlier for the synthesis of **228**, desilylation of diyne **312** (1.62 g, 3.55 mmol, 61 % ee) afforded **313** in 90 % yield (1.22 g, 3.20 mmol) upon purification by silica-gel chromatography (5 % ethyl acetate / hexanes) as an yellow oil. R_f (hexanes / ethylacetate = 19/1) = 0.56. Spectral data for (*R*)-**313**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.07 (s, 21H), 2.13 (t, 1H, *J* = 3.0 Hz), 2.30 (s, 3H), 3.46 (s, 3H), 3.58 (t, 2H, *J* = 2.5 Hz), 3.79 (s, 3H), 5.39 (s, 1H), 7.27 (d, 1H, *J* = 2.5 Hz), 7.43 (d, 1H, *J* = 2.0 Hz); ^{13} CNMR ($CDCl_3$, 125MHz) δ 11.20, 18.58, 19.05, 20.85, 55.91, 62.32, 67.83, 70.16, 82.11, 88.61, 105.09, 128.79, 129.05, 130.70, 131.61, 134.06, 153.26; IR (neat) 3314,

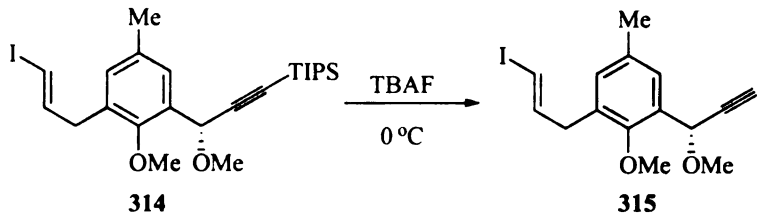
2943, 2886, 2820, 2170, 1479, 1464, 1435, 1280 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 383 (M^+-1, 20), 141 (76), 89 (88), 73 (96), 59 (100), HRMS calcd for $C_{24}H_{35}O_2Si$ *m/z* 383.2406, measd 383.2408. Specific rotation of (*R*)-**313** obtained from (*R*)-**286** (61 % ee) α_D = -6°(c = 0.88 in $CHCl_3$).



313 **314**

*(R,E)-(3-(3-iodoallyl)-2-methoxy-5-methylphenyl)-3-methoxyprop-1-ynyl)triisopropylsilane **314***

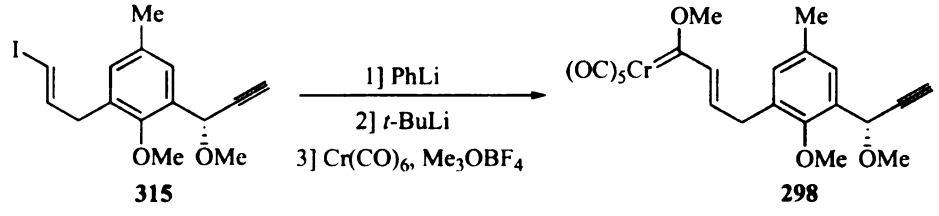
Following the procedure discussed earlier for the synthesis of (*R,R*)-**279**, the alkyne **313** (1.36 g, 3.55 mmol, 61 % ee) was reacted with only 1.6 equiv. of the Schwartz reagent and N-iodosuccinimide to give the vinyl iodide **314** in 88 % yield (1.44 g, 3.12 mmol) as an orange oil upon purification by silica-gel chromatography (5 % ethyl acetate / hexanes). R_f (hexanes / ethylacetate = 19/1)= 0.55. Spectral data for (*R*)-**314**: ^1H NMR ($CDCl_3$, 500MHz) δ 1.07 (s, 21H), 2.27 (s, 3H), 3.35-3.37 (m, 2H), 3.47 (s, 3H), 3.74 (s, 3H), 5.38 (s, 1H), 6.05 (d, 1H, *J* = 14.0 Hz), 6.63 (dt, 1H, *J* = 14.5, 6.5 Hz), 6.92 (d, 1H, *J* = 1.0 Hz), 7.42 (d, 1H, *J* = 1.5 Hz); ^{13} CNMR ($CDCl_3$, 125MHz) δ 11.45, 18.85, 21.07, 36.29, 56.23, 62.79, 68.17, 76.49, 88.87, 105.35, 128.85, 130.96, 131.67, 132.16, 134.20, 144.68, 153.90; IR (neat) 2944, 2891, 2868, 2251, 2170, 1478, 1468 cm^{-1}; mass spectrum *m/z* (% rel.intensity) 512 (M+, 20), 497 (100), 481 (68), 315 (46), 59 (80), HRMS calcd for $C_{24}H_{37}IO_2Si$ *m/z* 512.1608, measd 512.1605.



314 **315**

*(S,E)-1-(3-iodoallyl)-2-methoxy-3-(1-methoxyprop2-ynyl)-5-methylbenzene **315***

To a solution of the vinyl iodide **314** (1.28 g, 2.51 mmol) in ether at 0°C was added tetrabutyl ammonium fluoride (3.8 mL, 1.5 equiv) dropwise via a syringe and after addition stirring at this temperature was continued for 30 min. Addition of water (50 mL), extraction with ether (100 mL) followed by drying the organic layer over anhydrous magnesium sulfate and removal of the solvent afforded the crude product that was purified by silica-gel chromatography (30 % dichloromethane / hexanes) to give 0.71 g (2.01 mmol, 80 %) of the iodide **315** as yellow oil. R_f (hexanes / dichloromethane = 70/30)= 0.34. Spectral data for (*S*)-**315**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.29 (s, 3H), 2.58 (d, 1H, *J* = 2.5 Hz), 3.36 (d, 2H, *J* = 7.0 Hz), 3.46 (s, 3H), 3.74 (s, 3H), 5.34 (d, 1H, *J* = 2.5 Hz), 6.07 (d, 1H, *J* = 14.0 Hz), 6.64 (dt, 1H, *J* = 14.0, 7.0 Hz), 6.94 (d, 1H, *J* = 2.0 Hz), 7.33 (d, 1H, *J* = 2.0 Hz); ^{13} CNMR ($CDCl_3$, 125MHz) δ 21.12, 36.24, 56.67, 62.76, 67.47, 75.33, 76.59, 82.08, 127.06, 128.04, 131.11, 131.78, 134.56, 144.56, 153.71; IR (neat) 3298, 2942, 2865, 1479, 1464, 1433 cm^{-1}. mass spectrum *m/z* (% rel.intensity) 356 (56), 325 (100), 197 (36), 159 (36), 115 (40), 69 (52), HRMS calcd for $C_{15}H_{17}O_2I$ *m/z* 356.0274, measd 356.274.



315 **298**

*Carbene Complex **298***

To a solution of the vinyl iodide **315** (0.71 g, 2 mmol) in 20 mL of dry tetrahydrofuran was added phenyl lithium (1.1 equiv, 1.9 M in cyclohexane) at –78°C and the resulting solution was stirred at this temperature for another 30 min. *t*-Butyl lithium (2.4 mL, 2 equiv, 1.7 M in pentane) was added at this temperature and the resultant mixture was stirred for another 45 min. Chromium hexacarbonyl (0.88 g, 2 equiv) was then added and then upon warming to room temperature the deep red solution turned purple. The reaction was continued for another 3 h after which solvent was removed under reduced pressure. The residue was redissolved in a 1:1 mixture of dichloromethane and water (60 mL) followed by addition of trimethyl oxonium tetrafluoroborate (0.89 g, 6 mmol), which caused the solution to turn brown. Extraction with dichloromethane (100 mL), drying the organic layer over magnesium sulfate, and removal of solvent afforded the crude product which was purified by silica-gel chromatography (15 % ethylacetate / hexanes) to yield the carbene complex **298** as an deep-red oil in 8 % yield (0.074 g, 0.16 mmol). R_f (hexanes / ethylacetate = 85/15)= 0.38. Spectral data for (*S*)-**298**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.32 (s, 3H), 2.62 (s, 1H), 3.49 (broad s, 5H), 3.78 (s, 3H), 4.75 (s, 3H), 5.38 (s, 1H), 6.28 (s, 1H), 6.97 (s, 1H), 7.39 (s, 2H) (It appears that two benzylic hydrogens overlap with methoxy singlet at 3.49); ^{13} CNMR ($CDCl_3$, 125MHz) δ 20.76, 31.57, 56.31, 62.49, 66.46, 67.27, 75.07, 82.34, 128.15, 130.51, 131.90, 133.18, 134.47, 144.80, 153.72, 216.61, 223.91, 336.17 (One vinyl carbon missing).

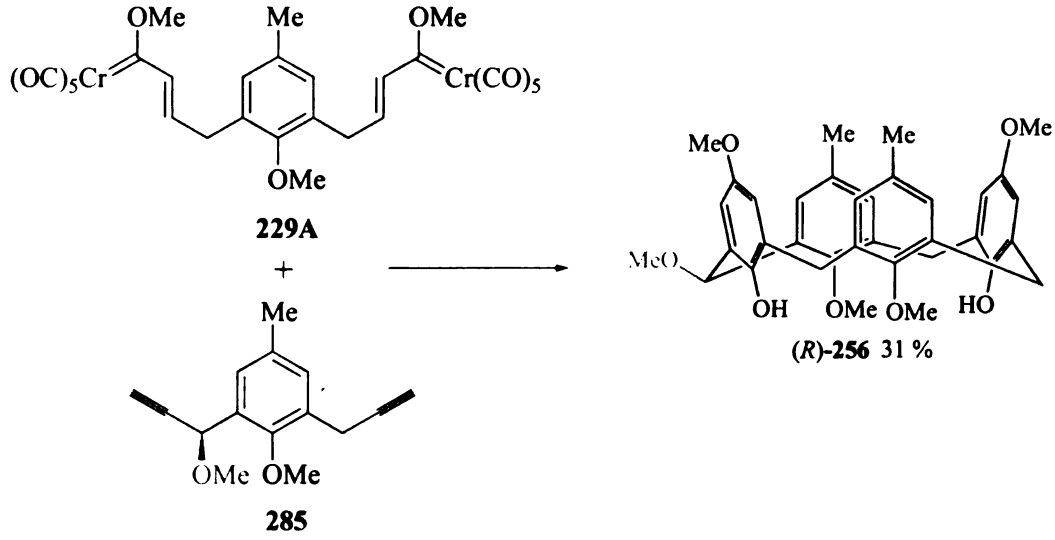
Chiral Calixarenes by Triple Annulation

General Procedure

Unless otherwise specified, the bis-carbene complex and the diyne (1:1 molar ratio) were dissolved in 1,2-dichloroethane (2.5 mM) in a flame dried 100 mL or 250 mL

Schlenk flask under argon. The solution was deoxygenated by freeze pump thaw method in three cycles (-196 to 25 °C) and then backfilled with argon at ambient temperature. The flask was sealed with a threaded high-vacuum Teflon stopcock and heated to 100 °C for 20-40 min during which time the deep red solution turned yellow. The yellow solution was stirred overnight exposed to air to facilitate demetalation of the arenechromium tricarbonyl complex. The solvent was removed under vacuum and the residue dissolved in ethyl acetate (50 mL) and then filtered through a short pad of silica gel. Further washing of the SiO_2 pad with ethyl acetate and evaporation of the solvent gave the crude calixarene, which was purified by flash chromatography on silica gel. The amount of dimer formed in all of the reactions was either none or in negligible amounts based on mass spectra of the purified calixarenes.

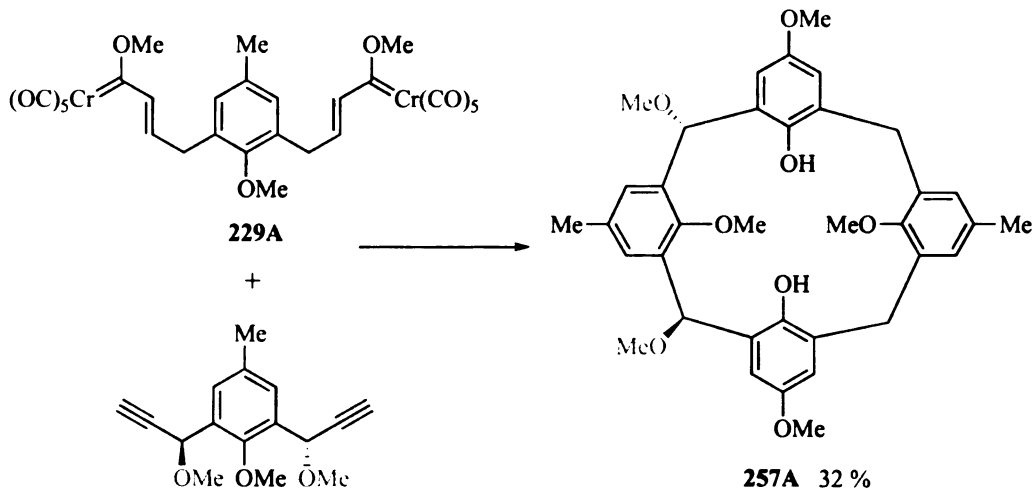
5,17-dimethyl-2(R),11, 23, 26, 28-pentamethoxy- 25,27-dihydroxycalix[4]arene **256**



A mixture of the bis-carbene complex **229A** (0.122 g, 0.183 mmol) and diyne (*S*)-**285** (93 % ee, 0.043 g, 0.183 mmol) in 72 mL of 1,2-dichloroethane was subjected to three freeze-pump thaw cycles and heated to 100 °C for 20-40 min. TLC analysis of the crude material revealed only one spot that was mobile on the TLC plate and examination of the

crude ^{1}H NMR indicated no other side products. Purification by silica-gel chromatography (50 % ethylacetate / hexanes) afforded the calix[4]arene pentamethyl ether in 31 % yield (0.032 g, 0.057 mmol) as an off-white solid. Mp = 270-273 °C. Spectral data for (*R*)-**256**: 2.03 (s, 6H), 3.22 (d, 1H, *J* = 12.6 Hz), 3.32 (d, 2H, J = 13.2 Hz), 3.44 (s, 3H), 3.72 (s, 3H), 3.74 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 4.11 (d, 1H, *J* = 12.3 Hz), 4.14 (d, 1H, *J* = 13.2 Hz), 4.35 (d, 1H, *J* = 12.9 Hz), 5.94 (s, 1H), 6.58 (d, 1H, *J* = 3.0 Hz), 6.60 (d, 1H, *J* = 3.0 Hz), 6.65 (d, 1H, *J* = 3.0 Hz), 6.72 (s, 1H), 6.75 (d, 2H, *J* = 5.5 Hz), 6.90 (d, 1H, *J* = 2.0 Hz), 6.96 (d, 1H, *J* = 3.0 Hz), 7.59 (s, 1H), 7.69 (s, 1H); ^{13} CNMR ($CDCl_3$, 125MHz) δ 20.86, 21.02, 31.03, 31.82, 31.95, 55.78, 55.81, 57.36, 63.51, 63.74, 73.83, 108.12, 113.42, 114.00, 114.32, 126.87, 128.36, 128.73, 129.41, 129.63, 130.06, 130.49, 130.92, 132.07, 132.37, 133.22, 134.36, 134.56, 134.88, 145.79, 146.78, 150.87, 151.04, 152.25, 152.91; IR (CH_2Cl_2) 3333, 2943, 2829, 1603, 1461, 1433, 1346 cm^{-1}.mass spectrum *m/z* (% rel.intensity) 570 (100), 539 (60), 507 (92), 475 (52), 154 (64), HRMS calcd for $C_{35}H_{38}O_7$ *m/z* 570.2616, measd 570.2618. Specific rotation α_D of **256** isolated by silica gel chromatography and obtained from (*S*)-**287** (93.4 % ee) = -5.4 (c = 0.91 in $CHCl_3$)

*5,17-dimethyl-2(R),8(R),11,23,26,28-hexamethoxy-25,27-dihydroxycalix[4]arene **257A***



A mixture of carbene complex **229A** (0.161 g, 0.24 mmol) and diyne **267A** (0.082 g, 0.32 mmol, 99.2 % ee), in 96 mL of 1,2- dichloroethane was subjected to thermolysis following the generic procedure and upon purification by silica-gel chromatography (25 % ethylacetate / hexanes) afforded 46 mg (32 %) of 2.6 / 1 inseparable mixture of conformers of **257A** as a light-yellow solid. TLC analysis of the crude material revealed only one mobile spot present on the TLC plate when developed with $KMnO_4$ and examination of the crude ^1H NMR indicated no other side products. Mp = > 320°C with decomposition. R_f = 0.22 (hexanes / ethyl acetate = 3/1) Spectral data for **257A**: Major conformer : ^1H NMR ($CDCl_3$, 600MHz) δ 2.10 (s, 3H), 2.12 (s, 3H), 3.35 (d, 2H, *J* = 13.5 Hz), 3.41 (s, 3H), 3.47 (s, 3H), 3.78 (s, 6H), 3.94 (s, 3H), 3.99 (s, 3H), 4.10 (d, 1H, *J* = 13.0 Hz), 4.39 (d, 1H, *J* = 13.0 Hz), 5.06 (s, 1H), 6.01 (s, 1H), 6.61 (d, 1H, *J* = 3.0 Hz), 6.65 (d, 1H, *J* = 2.0 Hz), 6.73 (s, 1H), 6.77 (s, 2H), 6.85 (s, 1H), 6.93 (s, 1H), 6.97 (d, 1H, *J* = 2.5 Hz), 7.07 (s, 1H), 7.78 (s, 1H); Minor conformer: ^1H NMR ($CDCl_3$, 600MHz) δ 2.31 (s, 3H), 2.38 (s, 3H), 3.34 (s, 3H), 3.36 (s, 3H), 3.38 (s, 3H), 3.43 (s, 3H), 3.52 (s, 3H), 4.12 (d, 1H, *J* = 11.5 Hz), 5.13 (s, 1H), 6.35 (s, 1H), 6.64 (1H overlapping with Ar-

H's of major), 6.87 (s, 1H), 7.09 (s, 1H), 7.16 (d, 1H, J = 2.0 Hz), 7.40 (s, 1H), 7.59 (broad peak undefined no. of H), Three of the methylene hydrogens, one methoxy, two aromatic hydrogens from the minor conformer are not seen. ^{13}C NMR (125MHz) data reported is on a mixture of the two conformers. δ 20.85, 20.89, 20.92, 21.20, 29.68, 31.44, 31.71, 32.05, 37.78, 55.71, 55.74, 55.78, 57.16, 57.28, 57.30, 57.75, 60.99, 62.96, 63.66, 64.26, 73.33, 81.73, 87.93, 107.68, 108.32, 109.84, 112.78, 113.49, 114.14, 114.89, 115.52, 126.30, 127.01, 128.35, 128.46, 128.83, 128.91, 129.31, 129.45, 129.96, 130.01, 130.06, 130.11, 130.18, 130.94, 131.20, 132.34, 132.63, 132.85, 133.10, 133.38, 133.45, 134.13, 134.46, 134.59, 134.74, 135.46, 136.55, 144.41, 145.89, 146.04, 146.30, 151.33, 151.71, 151.76, 151.80, 152.62, 152.93, 153.01, 153.24 (one aryl and methoxy carbon not located) ; IR (CH_2Cl_2) 3328, 2936, 2829, 2247, 1607, 1461, 1435 cm^{-1}. mass spectrum *m/z* (% rel.intensity) 600 (M^+, 40), 569 (18), 537 (35), 505 (60), 307 (36), 154 (100), HRMS calc'd for $C_{36}H_{40}O_8$ *m/z* 600.2720, measd 600.2730. Specific rotation α_D of the material isolated by silica gel chromatography = - 11.6 (c = 0.94 in $CHCl_3$). From an extensive analysis of the 1D-NOE and NOESY experiments, the major and minor isomers were deduced to be the cone and partial cone conformations. Exchange peaks from major isomer were observed in the NOE spectra of the minor isomer indicating that the minor conformer was inter-converting to the major conformer by a process involving rotation through the annulus but was not fast enough on the NMR time scale to give an average spectrum of the two conformers. HPLC analysis revealed the presence of only one peak (99.5:0.5 hexanes: *i*-PrOH to 95:5 hexanes: *i* -PrOH, flow rate 0.5 mL/min, 254 nm, retention time = 38.62 min).

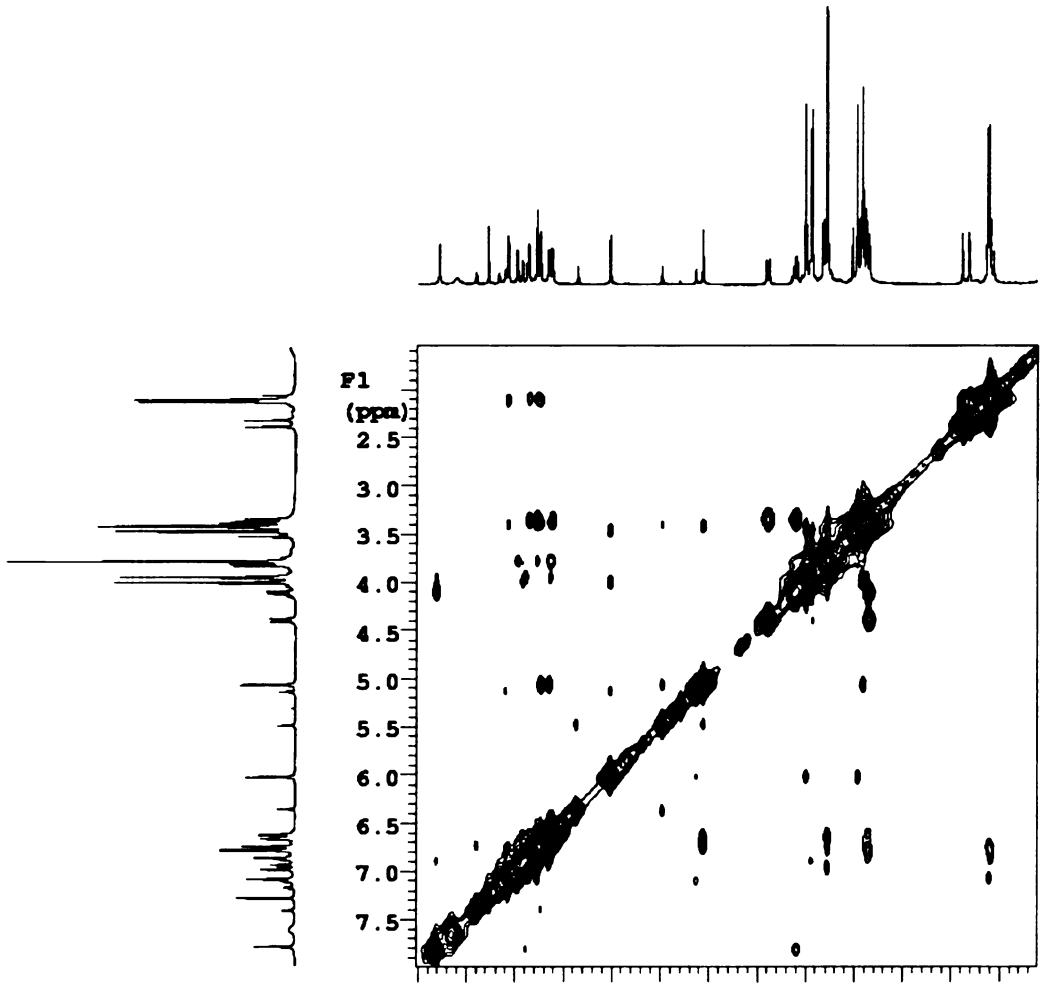
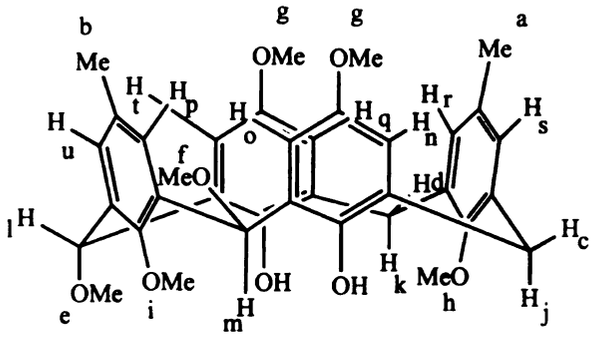


Fig 1. NOESY of mixture of major and minor conformers of **257A** in $CDCl_3$ at 25°C



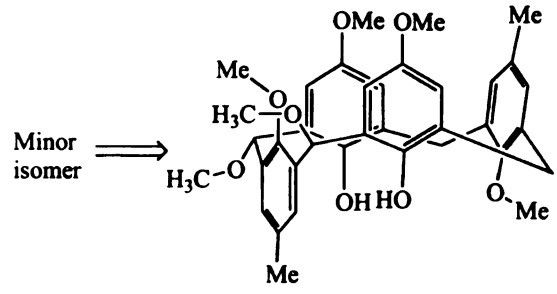
257A-I - Major Isomer

Table 7.5 Results of 1D-NOE Experiment on the Major Conformer of **257A-I**[a]

Chemical Shift	Proton Irradiated	NOE Observed	Chemical Shift	Nuclei Irradiated	NOE Observed
2.08 (s)	a	r, s	5.03 (s)	l	e,p,s
2.10 (s)	b	u, p	5.98 (s)	m	f, i
3.31 (d)	c	---	6.58 (d)	n	c, g
3.35 (d)	d	---	6.64 (d)	o	l
3.38 (s)	e	---	6.71 (s)	p	b, l
3.44 (s)	f	---	6.74 (s)	q	d,g
3.75 (s)	g	NR	6.74 (s)	r	a, d
3.91(s)	h	NR	6.82 (s)	s	a
3.97 (s)	i	m	6.94 (d)	t	g
4.11(d)	j	c, -OH	7.05 (s)	u	b
4.34 (d)	k	d			

[a] The closeness of the chemical shifts of the methylene hydrogens and overlap with those from the minor isomer does not permit accurate assignments of NOE effects

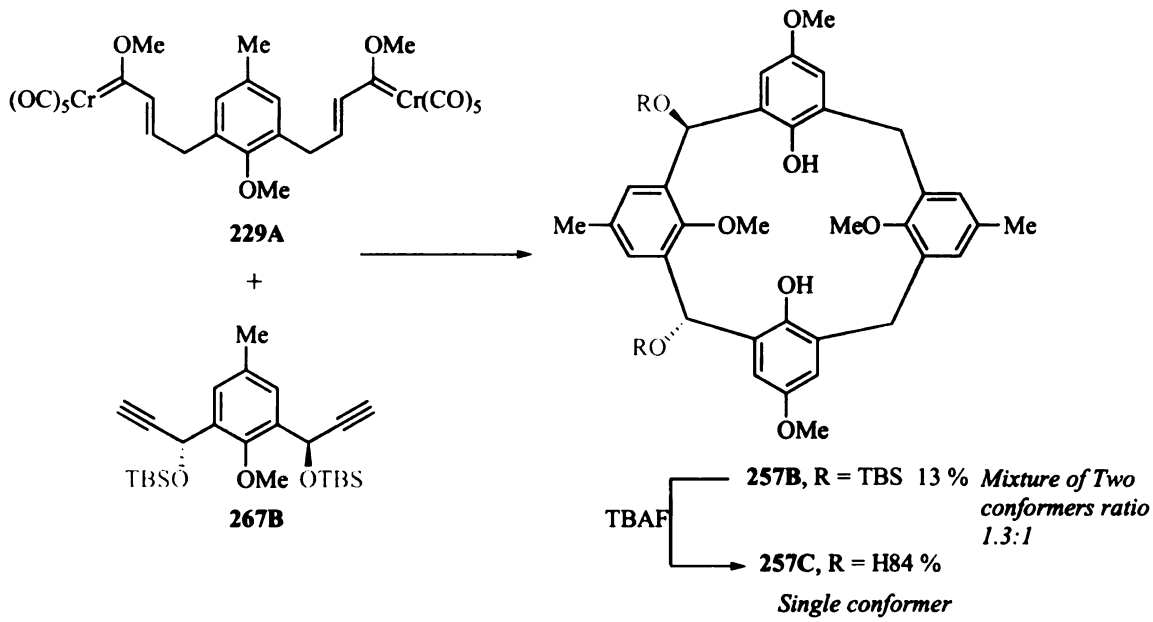
Although a precise assignment of all the protons and their through space interactions with the neighbouring ones could not be made either by NOE or by NOESY, the tentative assignment for the minor conformer based on some of the results in the 1D-NOE experiment is the partial cone (Fig.1).



257A partial-cone

Fig.2 Structure of Minor isomer of **257A-II**

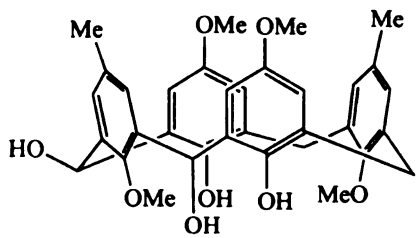
5,17-dimethyl-11,23,26,28-tetramethoxy-2(S),8(S)-tert-butyldimethylsilyloxy-25,27-dihydroxycalixarene ***257B*** *and 5,17-dimethyl-11,23,26,28-tetramethoxy-2(S),8(S),25,27-tetrahydroxycalixarene* ***257C***



Following the general procedure, a mixture of carbene complex **229A** (0.21 g, 0.23 mmol) and diyne (*R,R*)-**267B** (99.2 % ee, 0.059 g, 0.23 mmol) in 90 mL of 1,2-dichloroethane as solvent afforded upon purification in 15 % ethyl acetate / hexanes the chiral calixarene **257B** as 1.3:1 mixture of two inseparable conformers in 13 % yield (0.038 g, 0.0498 mmol). R_f (hexanes / ethylacetate = 85 / 15) = 0.39. Complete spectral data and structure elucidation was carried out on the desilylated derivative **257C** . The

chiral calix[4]arene **257B** (0.024g, 0.28 mmol) was dissolved in 10 mL of anhydrous ether and tetrabutyl ammonium fluoride (0.5 mL, 0.5 mmol) was added. The resulting slurry was stirred at ambient temperature for 3-4 h. Aqueous workup, drying the organic layer over anhydrous magnesium sulfate and concentration under vacuum afforded the crude product which was purified on a silica-gel column by elution with 50 % ethyl acetate / hexanes to give 56 % (0.015 g, 0.0265 mmol) of **257C** as a single conformer as an oil. The structure of this conformer was ascertained by NOESY as the cone. R_f (hexanes / ethylacetate = 1/1) = 0.3. Spectral data for **257C** : ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.04 (s, 3H), 2.07 (s, 3H), 3.29 (d, 1H, *J* = 13.0 Hz), 3.37 (d, 1H, *J* = 14.0 Hz), 3.74 (s, 3H), 3.77 (s, 3H), 3.98 (s, 3H), 4.04 (s, 3H), 4.05 (d, 1H, *J* = 13.5 Hz), 4.31 (d, 1H, *J* = 12.5 Hz), 5.55 (dd, 2H, *J* = 24.0, 11.0 Hz), 6.32 (s, 1H), 6.57 (d, 1H, *J* = 2.0 Hz), 6.62 (s, 2H), 6.67 (d, 1H, *J* = 3.0 Hz), 6.74 (d, 1H, *J* = 2.0 Hz), 6.81 (d, 1H, *J* = 2.0 Hz), 6.98 (d, 1H, *J* = 2.0 Hz), 7.05 (d, 1H, *J* = 3.5 Hz), 7.32 (s, 1H), 7.76 (s, 1H) (OH proton not located); ^{13}C NMR (125MHz) δ 20.90, 20.97, 30.78, 31.93, 55.79, 55.83, 63.84, 64.53, 65.16, 79.64, 106.94, 112.64, 114.49, 114.54, 126.65, 128.56, 129.41, 129.54, 129.57, 130.31, 131.86, 132.09, 132.43, 133.14, 133.56, 134.41, 135.17, 136.49, 144.65, 146.39, 150.41, 151.03, 152.37, 153.00 ; IR (neat) 3360, 2924, 2850, 1650, 1590, 1481 cm^{-1}; mass spectrum *m/z* (% rel.intensity) FAB in NBA 572 (M^+, 0.2), 460 (8.4), 307 (76),107 (36), HRMS calcd for $C_{34}H_{36}O_8$ *m/z* 572.2410, measd 572.2408. Specific rotation α_D = +2.7 (c = 0.34 in $CHCl_3$)

Structure Elucidation by NOESY in $CDCl_3$



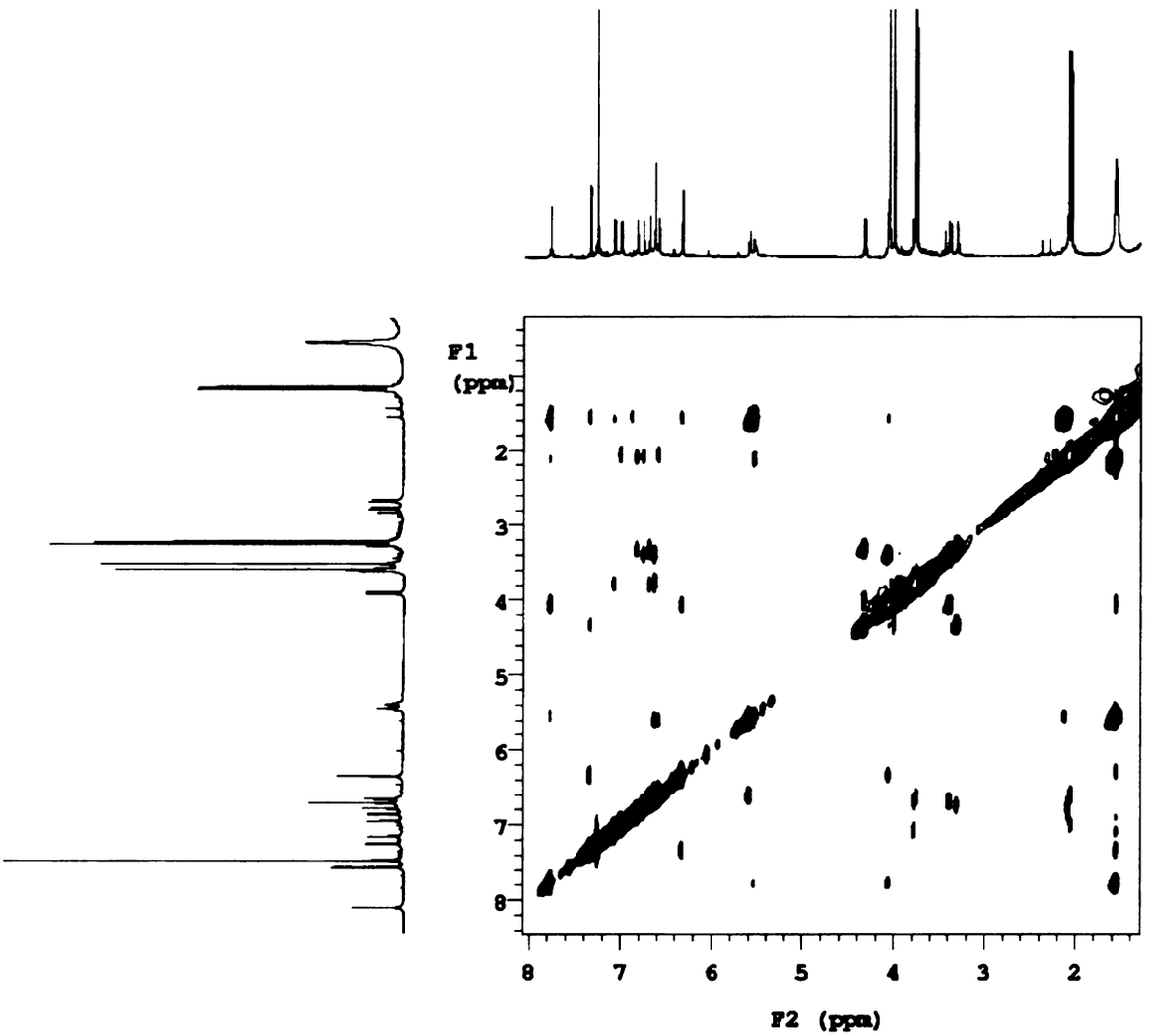
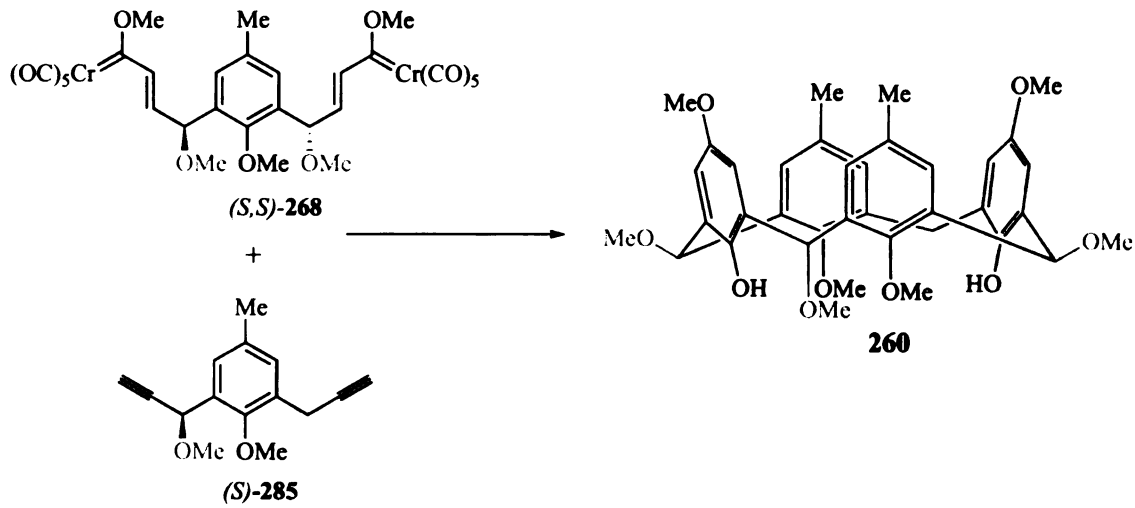


Fig 3. NOESY of **257C** in $CDCl_3$ at 25 °C

5,17-Dimethyl-2(R),8(R),14(R),11,23,26,28-heptamethoxy-25,27dihydroxycalix[4]arene-

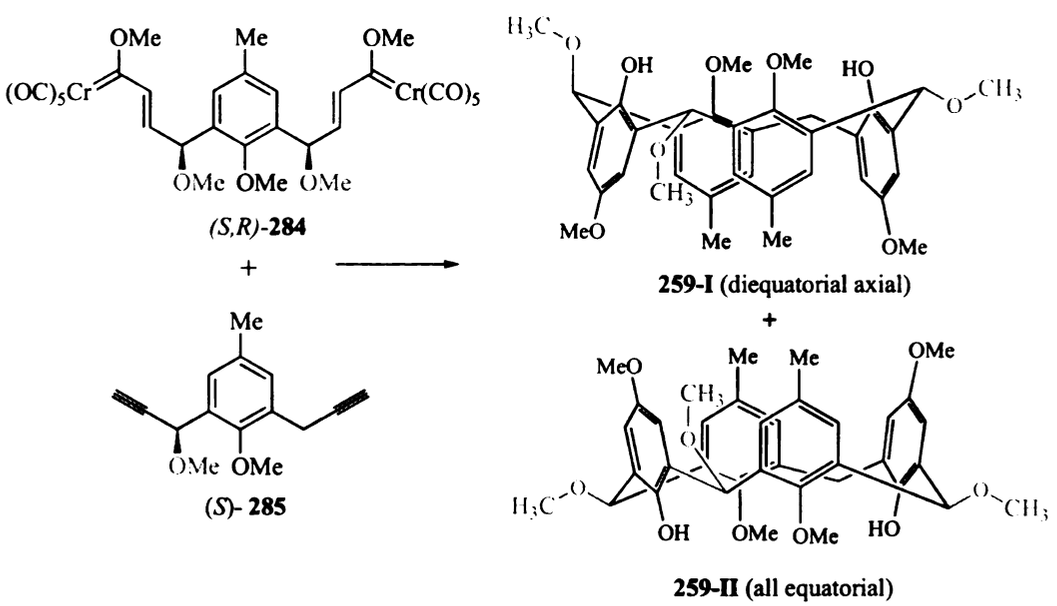
260



A mixture of chiral bis-carbene complex (*S*,*S*)-**268** (0.216 g, 0.29 mmol, 97.8 % ee) and chiral alkyne (*S*)-**285** (0.11 g, 0.48 mmol, 93.4 % ee) in 118 mL of 1,2-dichloroethane was subjected to the freeze-thaw deoxygenated according to the general procedure. The reaction mixture was then heated at 100°C for 8 h. Work up according to the general procedure followed by purification on silica gel with 25 % ethylacetate / hexanes afforded the heptamethyl ether **260** in 32 % yield (0.058 g, 0.093 mmol) as white solid and as a single cone conformer. TLC analysis of the crude material revealed the presence of only one spot when developed with $KMnO_4$ and examination of the crude ^1H NMR indicated no other side products. Mp = 105-108°C . R_f (hexanes / ethylacetate = 1/1) = 0.30. Spectral data for **260** : ^1H NMR ($CDCl_3$, 500MHz) δ 2.07 (s, 6H), 3.35 (d, 1H, J = 13.0 Hz), 3.38 (s, 3H), 3.43 (s, 3H), 3.44 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 4.09 (d, 1H, *J* = 13.0 Hz), 5.04 (s, 1H), 6.00 (s, 1H), 6.05 (s, 1H), 6.53 (d, 1H, *J* = 2.5 Hz), 6.57 (d, 1H , *J* = 3.0 Hz), 6.66 (d, 1H , *J* = 2.0 Hz), 6.78 (d, 1H, *J* = 2.0 Hz), 6.92 (d, 1H, *J* = 3.0 Hz), 6.99 (d, 1H, *J* = 2.0 Hz), 7.01 (d, 1H, *J* = 3.0 Hz), 7.08 (d,

1H, J = 2.0 Hz), 7.81 (s, 2H); ^{13}C NMR (125MHz) δ 20.96, 21.08, 29.69, 32.10, 55.76, 55.81, 57.16, 57.25, 57.41, 63.64, 64.42, 73.18, 108.45, 110.45, 114.11, 114.59, 126.36, 126.78, 128.14, 128.99, 129.54, 130.34, 131.03, 131.33, 132.31, 132.52, 134.46, 134.49, 135.01, 136.74, 145.82, 145.91, 150.88, 151.05, 152.10, 153.03 (One methoxy carbon not located); IR (neat) 3312, 2934, 2826, 1607, 1482, 1435, 1236 cm^{-1}. mass spectrum FAB in NBA (m/z, % rel.intensity) 630 (M^+, 20), 567 (40), 535 (90), 294 (80), 263 (100), HRMS calcd for $C_{37}H_{42}O_9$ m/z 630.2829, measd 630.2832. Specific rotation α_D of the material isolated by silica-gel chromatography = - 16.2 (c = 1.61 in $CHCl_3$). The enantiomeric purity of the calix[4]arene was judged to be beyond detection limits by HPLC analysis (Chiralcel OD column, 99.5:0.5 hexanes : *i*-PrOH to 95:5 hexanes : *i*-PrOH, retention time = 8.35 min). Analyses using several other chiral HPLC columns did not show the presence of any other small peaks due to the enantiomer.

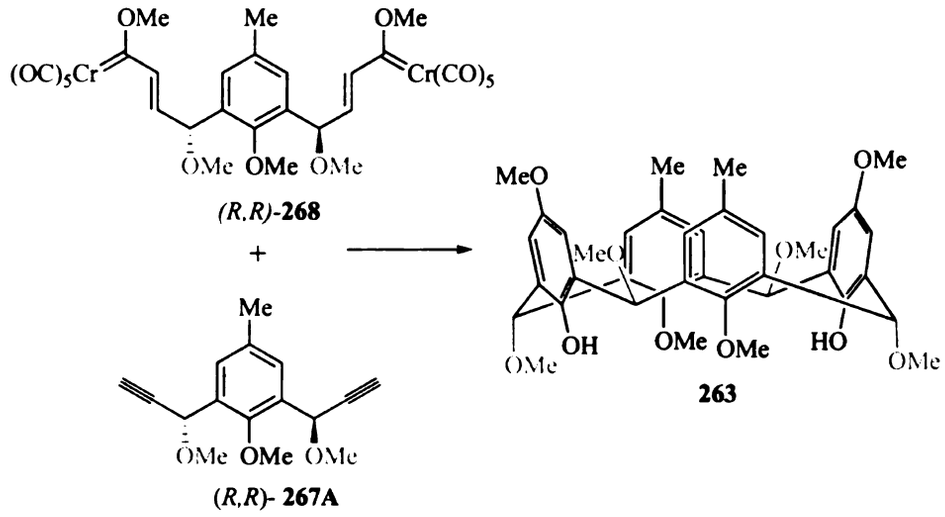
5,17-dimethyl-2(R), 8(R), 11, 14(S), 23, 26, 28-heptamethoxy-25,27-dihydroxy calixarene and5,17-dimethyl-2(R),8(S),11,14(R),23,26,28-heptamethoxy-25,27-dihydroxy calixarene – ***259-I*** and ***259-II***



A mixture of *meso* bis-carbene complex (*S,R*)-**284** (0.137 g, 0.188 mmol) and chiral alkyne (*S*)-**285** (0.048 g, 0.211 mmol, 93.4 % ee) in 118 mL of 1,2-dichloroethane was subjected to the freeze-thaw deoxygenation according to the general procedure. The reaction mixture was then heated at 100°C for 8 h. Workup according to the general procedure followed by purification on silica-gel with 25 % ethylacetate / hexanes afforded the calix[4]arene **259** in 29 % yield (0.034 g, 0.055 mmol) as light yellow solid and as a 1.4:1.0 mixture of diastereomers **259-I** and **259-II**. Both diastereomers had the same R_f value. TLC analysis of the crude material revealed the presence of only one spot as revealed by development with $KMnO_4$ and examination of the crude ^1H NMR indicated no other side products. Mp of mixture = 165-168°C. Analysis by HPLC indicated the presence of a mixture of compounds **259-I** and **259-II** in a ratio of 1.36:1 (R001086C5 Silica column, 254 nm, hexanes / *i*-PrOH 99.5/ 0.5 to 95/ 5, flow rate 0.5 mL/min, retention time for **259-I** = 46.15 min and **259-II** = 55.13 min). The mixture was purified again by gradient elution (5 % ethyl acetate / hexanes to 25 % ethyl acetate / hexanes) and thereby **259-I** could be obtained in a pure form and **259-II** was obtained as an enriched mixture (ratio 4.1:1). R_f (hexanes / ethylacetate = 1/1) = 0.62. Spectral data for **259-I**: ^1H NMR ($CDCl_3$, 500MHz) δ 2.03 (s, 3H), 2.09 (s, 3H), 3.29 (d, 1H, J = 13.0 Hz), 3.38 (s, 3H), 3.44 (s, 3H), 3.46 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 3.93 (s, 6H), 4.09 (d, 1H, J = 12.5 Hz), 5.05 (s, 1H), 5.80 (s, 2H), 6.60 (d, 1H, J = 3.0 Hz), 6.69 (s, 2H), 6.79 (s, 1H), 6.86 (s, 1H), 6.93 (s, 1H), 6.99 (d, 1H, J = 2.7 Hz), 7.10 (s, 1H) (two OH protons not located); ^{13}C NMR (125MHz) (mixture) δ 14.16, 20.71, 21.05, 21.26, 29.67, 30.74, 31.56, 31.75, 55.74, 56.98, 57.12, 57.33, 57.53, 60.38, 63.35, 63.71, 63.87, 64.32, 73.44, 73.60, 73.86, 74.15, 107.61, 108.17, 108.39, 109.15, 114.16, 114.32, 126.62,

127.64, 128.55, 130.44, 130.75, 130.79, 131.31, 131.38, 131.58, 132.25, 132.77, 133.79, 133.86, 134.35, 134.52, 134.64, 135.37, 135.69, 144.27, 145.41, 145.57, 149.94, 150.25, 150.74, 151.96, 152.39, 152.88, 153.02, 153.81 (**259-I**) 20.71, 21.05, 29.67, 30.74, 55.74, 57.12, 57.33, 57.53, 64.32, 74.15, 107.61, 114.16, 127.64, 131.31, 132.77, 133.86, 134.52, 145.41, 151.96, 152.39, 152.88 (two methoxy groups not located); Spectral data for **259-II**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.07 (s, 3H), 2.08 (s, 3H), 3.42 (s, 3H), 3.43 (s, 3H), 3.72 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 3.99 (s, 3H), 4.04 (s, 3H), 5.69 (s, 1H), 5.91 (s, 1H), 5.93 (s, 1H), 6.58 (d, 1H, J = 3.0 Hz), 6.75 (s, 1H), 6.86 (s, 1H), 6.91 (s, 1H), 6.92 (s, 1H), 6.96 (s, 2H), 6.98 (s, 1H), 7.40 (s, 1H), 7.81 (s, 1H) (two methylene hydrogens not located); ^{13}C NMR (125MHz) δ 14.16, 21.26, 31.56, 31.75, 56.98, 60.38, 63.35, 63.71, 63.87, 73.44, 73.60, 73.86, 108.17, 108.39, 109.15, 114.32, 126.62, 128.55, 130.44, 130.75, 130.79, 131.38, 131.58, 132.25, 133.80, 134.35, 134.64, 135.37, 135.69, 144.27, 145.57, 149.94, 150.25, 150.74, 153.02, 153.81 (two methoxy groups not located). IR of mixture (neat) 3350, 2932, 2828, 1604, 1491, 1435, 1346, 1234 cm^{-1}. mass spectrum of mixture FAB in NBA *m/z* (% rel.intensity) 630 (10), 567 (16), 535 (40), 197 (30), 135 (72) HRMS calcd for $C_{37}H_{42}O_9$ *m/z* 630.2829, measd 630.2832. Specific rotation α_D of the 1.36:1 mixture of diastereomers prepared from (*S*)-**287** (93 % ee) = - 3.2° (c = 1.7 in $CHCl_3$). The structures of the two conformers are assigned as the diequatorial axial **259-I** and all equatorial **259-II** respectively based on the chemical shifts of the methine hydrogens. The equatorial methine proton and the two axial protons are located at 5.05 ppm and 5.80 ppm respectively in **259-I** whereas the axial protons in **259-II** are observed at 5.69, 5.91 and 5.93 ppm.

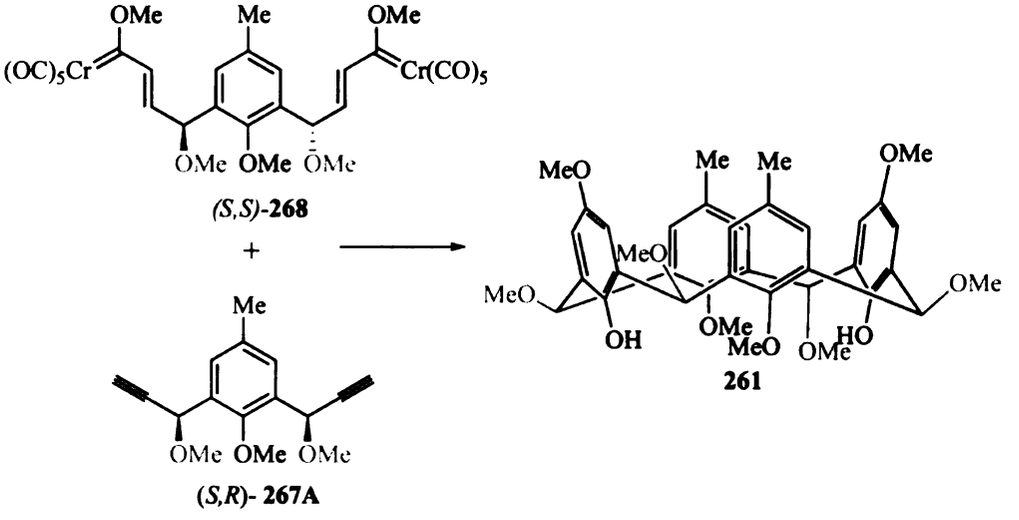
*5,17-dimethyl-2(S), 8(S), 11, 14(S), 20(S), 23, 26, 28-octamethoxy-25,27-dihydroxy calixarene –**263***



The bis carbene complex (*R*,*R*)-**268** (0.158 g, 0.216 mmol, 99.2 % ee) and the diyne (*R*,*R*)-**267A** (0.056g, 0.216 mmol, 99.2 % ee) were dissolved in 86 mL of 1,2-dichloroethane in a flame dried 250 mL Schlenk flask under argon and subjected to freeze-thaw deoxygenation according to the general procedure. The reaction mixture was then heated to 100°C for 30 min. Workup according to the general procedure gave the crude calixarene which was purified by flash chromatography on silica gel with 5 % to 25 % ethyl acetate / hexanes to give **263** in 30 % yield (0.043 g, 0.065 mmol) as powdery white solid. This compound was a single conformer as judged by ^{1}H NMR and is tentatively assigned as the cone. TLC analysis of the crude material revealed the presence of only one spot upon development with $KMnO_4$ and examination of the crude ^{1}H NMR indicated no other side products. Mp = 83-86 °C. R_f = 0.32 (hexanes / ethyl acetate = 3/1). Spectral data for **263**: ^{1}H NMR ($CDCl_3$, 600MHz) δ 2.12 (s, 6H), 3.40 (s, 6H), 3.43 (s, 6H), 3.67 (s, 6H), 3.99 (s, 6H), 5.05 (s, 2H), 6.08 (s, 2H), 6.39 (d, 2H, *J* = 3.0 Hz), 6.69 (s, 2H), 6.87 (d, 2H, *J* = 3.0 Hz), 7.15 (s, 2H) (2 OH protons not located); ^{13}C NMR

(125MHz) 20.99, 29.69, 55.78, 57.03, 57.49, 64.18, 72.89, 89.39, 110.61, 114.49, 126.28, 127.89, 129.44, 131.21, 132.85, 134.17, 136.91, 146.41, 152.02; IR ($CHCl_3$) 3343, 2930, 2826, 1609, 1483, 1345 cm^{-1}; mass spectra *m/z* (% rel.intensity) FAB in NBA 660 (M^+, 56), 629 (20), 597 (60), 565 (100), 535 (20), 149 (60), HRMS calcd for $C_{38}H_{44}O_{10}$ *m/z* 660.2929, measd 660.2934. Anal.calcd for $C_{38}H_{44}O_{10}$: C, 69.07; H, 6.71. Found: C, 69.43; H, 7.14. α_D = + 25.1 (c= 0.695 in $CDCl_3$)

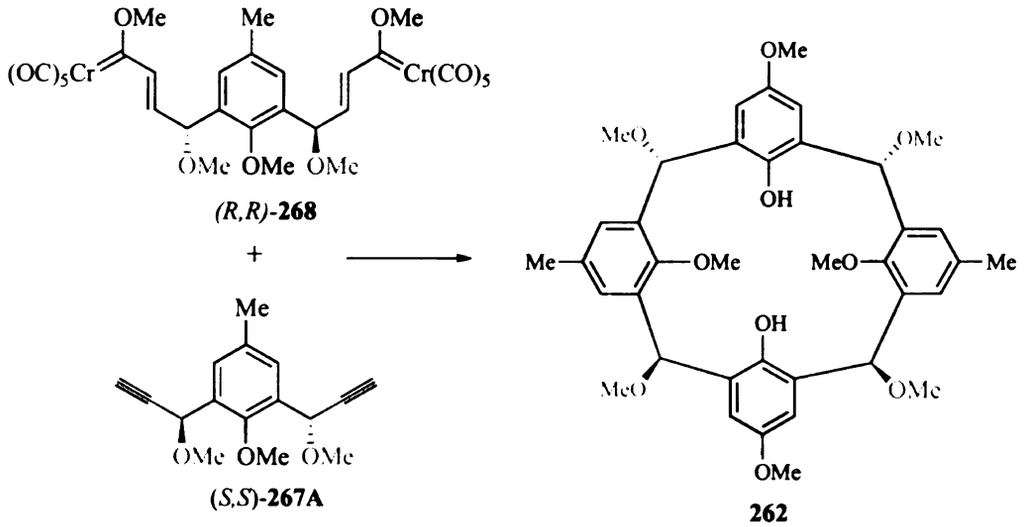
*5,17-dimethyl-2(R), 8(S), 11, 14(R), 20(R), 23, 26, 28- octamethoxy-25,27-dihydroxy calix[4]arene-**261***



A mixture of chiral bis-carbene complex (*S,S*)-**268** (0.206 g, 0.24 mmol, 94 % ee) and meso alkyne (*S,R*)-**267A** (0.073 g, 0.24 mmol) in 96 mL of 1,2-dichloroethane was subjected to the freeze-thaw deoxygenation according to the general procedure. The reaction mixture was then heated at 100°C for 8 h. Purification by silica-gel chromatography (50 % ethyl acetate / hexanes) afforded the desired calix[4]arene **261** in 26 % yield (0.04 g, 0.061 mmol) as off-white solid and exclusively as the cone conformer. TLC analysis of the crude material revealed the presence of only one spot

upon development with $KMnO_4$ and examination of the crude ^1H NMR indicated no other side products. R_f = 0.34 (hexanes / ethyl acetate = 1/1). Mp = 137-140°C . Spectral data for **261**: ^1H NMR ($CDCl_3$, 500MHz) δ 2.08 (s, 6H), 3.38 (s, 3H), 3.42 (s, 3H), 3.44 (s, 3H), 3.45 (s, 3H), 3.74 (s, 6H), 4.00 (s, 3H), 4.01 (s, 3H), 5.05 (s, 1H), 5.72 (s, 1H), 5.94 (s, 1H), 5.95 (s, 1H), 6.55 (s, 1H), 6.67 (s, 1H), 6.88 (d, 1H, *J* = 1.8 Hz), 6.90 (d, 1H, *J* = 1.9 Hz), 6.96 (s, 1H), 7.00 (d, 2H, *J* = 2.7 Hz), 7.11 (s, 1H) (2 OH protons not located); ^{13}C NMR ($CDCl_3$, 125MHz) 21.02, 21.32, 55.75, 55.81, 57.14, 57.23, 57.43, 63.62, 64.38, 73.00, 74.04, 108.35, 109.23, 114.29, 126.62, 127.28, 127.93, 130.20, 131.64, 132.49, 134.08, 134.18, 134.79, 135.11, 136.67, 144.32, 145.73, 149.35, 150.73, 150.84, 152.18, 153.93 (3 aryl carbons, one methoxy group and two methine carbons missing); IR (CH_2Cl_2) 3349, 2984, 2936, 2824,1607, 1481, 1433, 1345, 1311 cm^{-1}. mass spectrum *m/z* (% rel.intensity) FAB in NBA 660 (M+, 9), 565 (20), 307 (40), 154 (100), HRMS calcd for $C_{38}H_{44}O_{10}$ *m/z* 660.2937, measd 660.2940. Specific rotation of the material isolated by silica-gel chromatography α_D = -14.6 (c = 1.43 in $CHCl_3$)

*5,17-dimethyl-2(R), 8(R), 11, 14(S), 20(S), 23, 26, 28- octamethoxy-25,27-dihydroxy calix[4]arene -**262***



A mixture of chiral bis-carbene complex (*R*,*R*)-**268** (0.081 g, 0.11 mmol, 88 % ee) and alkyne (*S*,*S*)-**267A** (0.035 g, 0.13 mmol, 94 % ee) in 44 mL of 1,2-dichloroethane was subjected to the freeze-thaw degassing according to the general procedure. The reaction mixture was then heated at 100°C for 8h. Purification by silica-gel chromatography (50 % ethyl acetate / hexanes) afforded the calix[4]arene in 26 % yield (0.018 g, 0.028 mmol) as white solid and as mixture of two conformers in 1:1 ratio. TLC analysis of the crude material revealed the presence of only one spot upon development with $KMnO_4$ and examination of the crude ^1H NMR indicated no other side products. R_f = 0.62 (Hexanes / ethyl acetate = 1/1). Mp = > 284 ° with decomposition . Spectral data for **262** on a 1:1 mixture of the two conformers: ^1H NMR ($CDCl_3$, 500MHz) δ 2.14 (s, 3H), 2.36 (s, 3H), 3.34 (s, 3H), 3.39 (s, 3H), 3.40 (s, 3H), 3.42 (s, 3H), 3.47 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.82 (s, 1.5H), 3.88 (s, 1.5H), 4.98 (s, 1H), 5.06 (s, 1H), 5.47 (s, 1H), 5.49 (s, 1H), 6.28 (s, 1H, OH), 6.64 (s, 0.5H, OH), 6.89 (d, 1H, J = 3.0 Hz), 6.93 (s, 1H), 6.95 (s, 1H), 6.99 (s, 1H), 7.04 (d, 1H, J = 2.0 Hz), 7.15 (d, 1H, J = 2.5 Hz), 7.27 (s, 1H), 7.42 (d, 1H, J = 2.0 Hz) (1 OH group of one of the conformers not seen); ^{13}C NMR ($CDCl_3$, 125MHz) δ 20.85, 21.22, 29.69, 55.63, 55.75, 55.82, 56.96, 57.12, 57.55, 57.72, 63.73,

63.82, 72.94, 73.35, 81.42, 81.58, 108.07, 108.34, 109.88, 110.01, 126.02, 129.26, 129.68, 129.96, 130.66, 131.04, 131.21, 132.28, 132.35, 132.81, 134.07, 134.91, 135.59, 135.72, 143.69, 151.28, 153.25, 153.82; IR ($CHCl_3$) 3345, 2928, 2826, 1774, 1605, 1481, 1465, 1433 cm^{-1}; mass spectrum FAB in NPOE (m/z, % rel.intensity) 660 (M^+, 10), 565 (20), 486 (15), 252 (95), 140 (100), 57 (64), HRMS calcd for $C_{38}H_{44}O_{10}$ *m/z* 660.2934, measd 660.2932. Optical rotation of **262** in chloroform as the solvent indicated no rotation of the plane-polarized light. α_D = 0.0 (c = 0.834 in $CHCl_3$). Based on DEPT and HMQC experiments, the calix[4]arene **262** was determined to exist as a (1:1) mixture of two conformers in solution which were not assigned. The parameters that were used for the HMQC experiment are ni = 128, nt=16 and the NOESY experiment are ni= 64, t_{mix} = 0.7s, nt=32 and linear prediction along the F1 dimension.

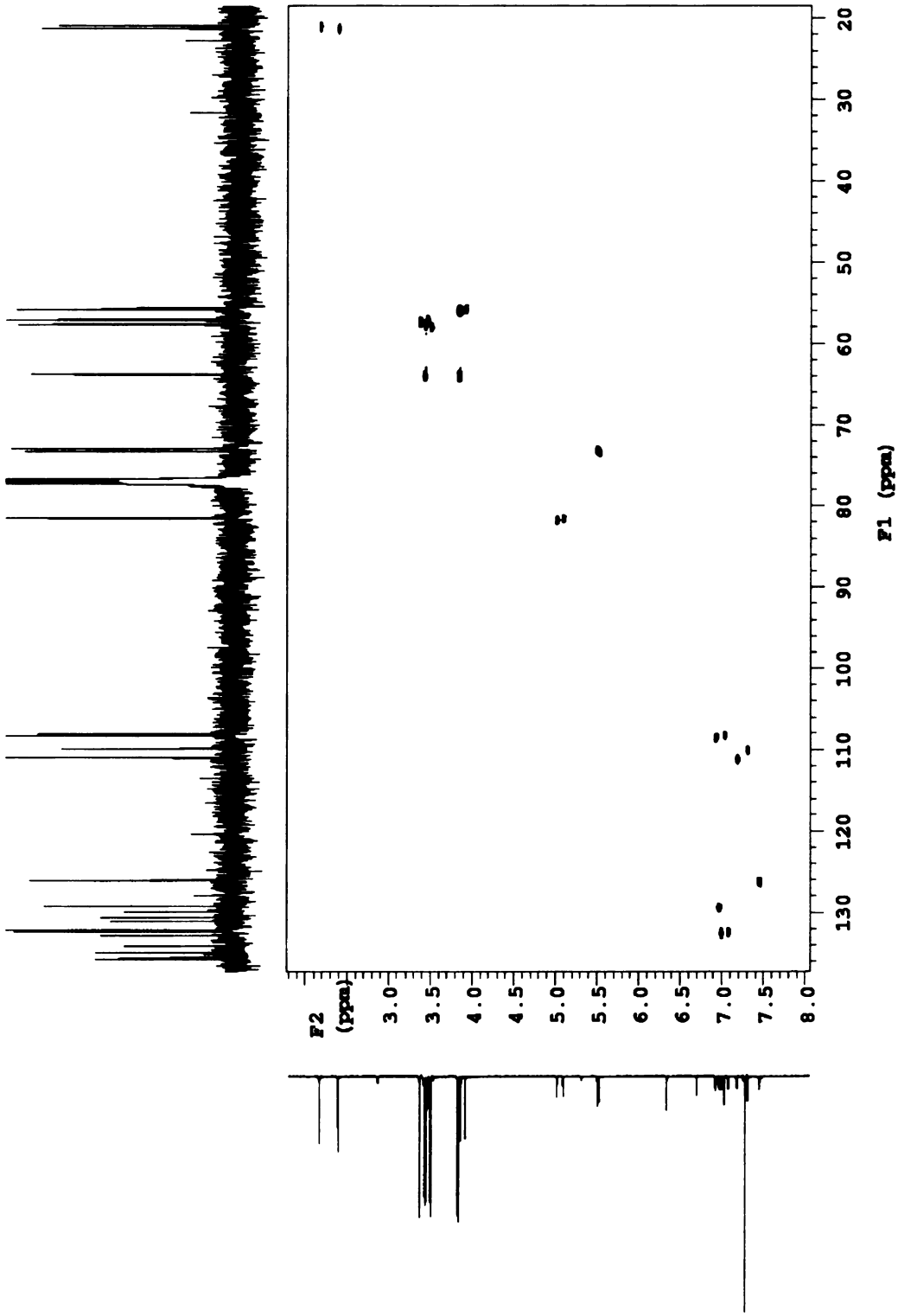


Fig 6. HMQC of **262** in $CDCl_3$ at 25°C

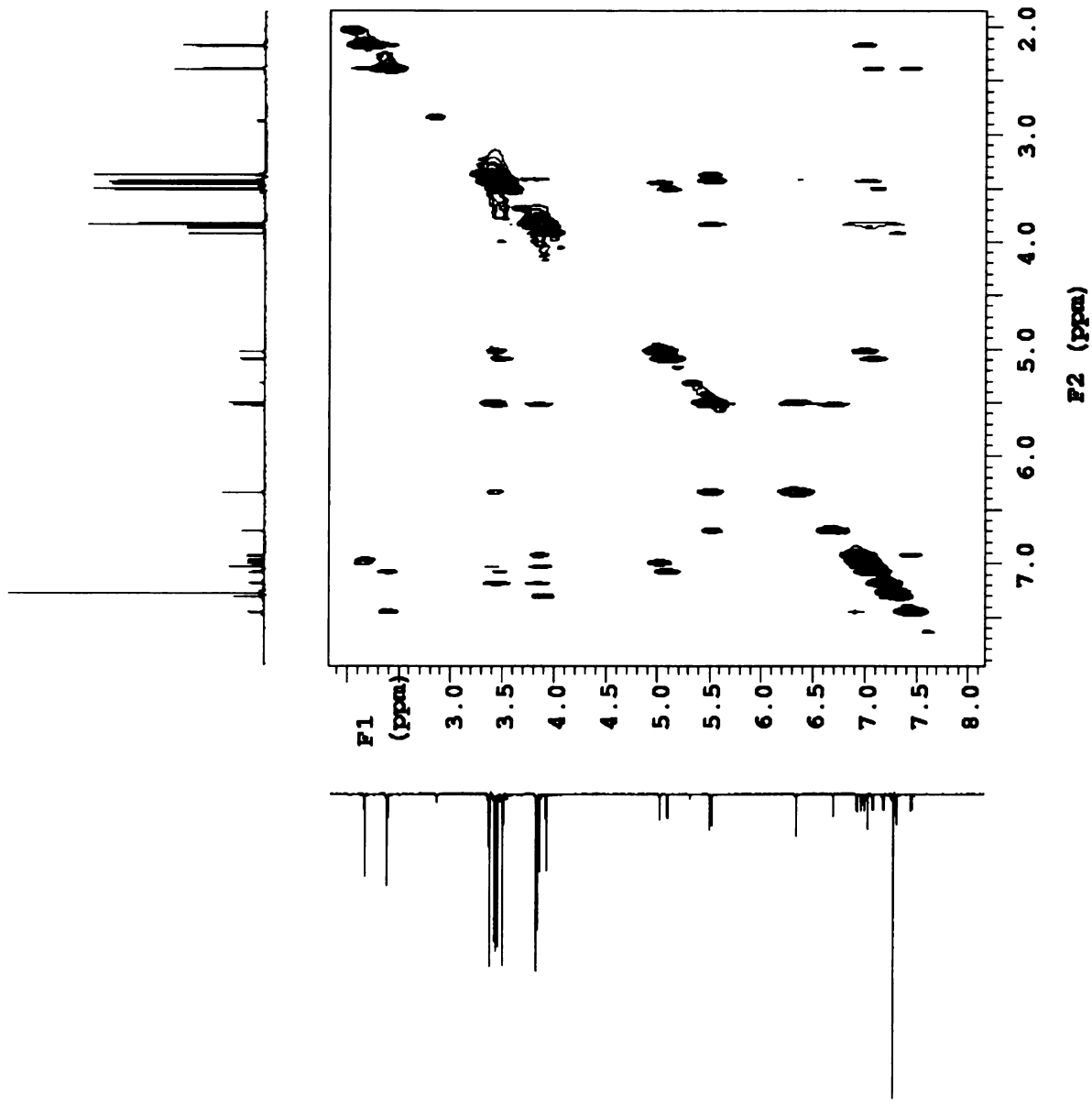


Fig.7 NOESY of **262** in $CDCl_3$ at 25°C

The structures of the two isomers could not be elucidated by either 1D-NOE or NOESY experiments but the chemical shifts corresponding to both the isomers could be defined (See Table 2 below).

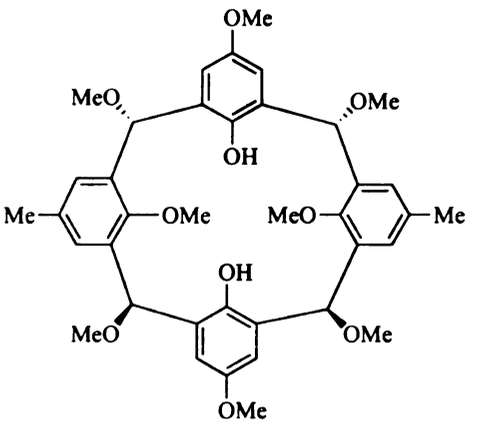


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Table 7.6 Results from the 1D-NOE / NOESY experiments **Unknown Conformer 262-A**

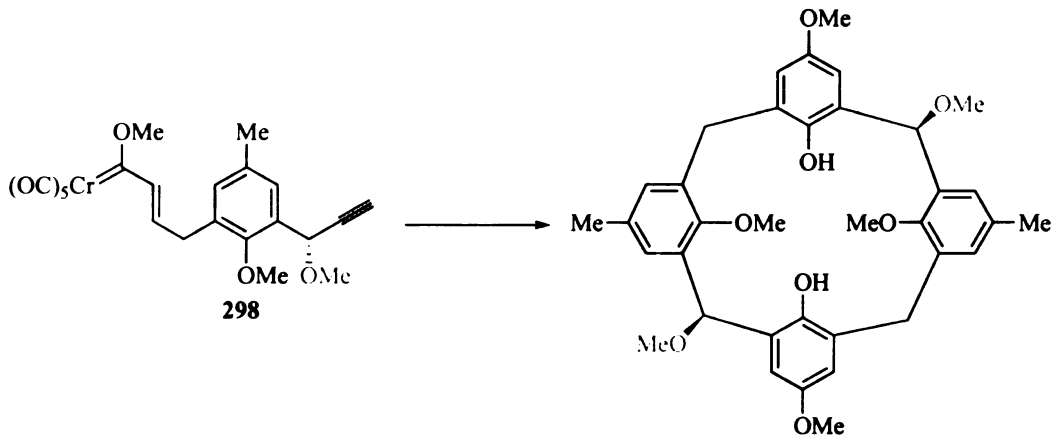
Chemical Shift	Number of Protons	NOE Observed	Chemical Shift	No.of protons	NOE Observed
2.14 (s)	6H	ND	4.98 (s)	2H	6.96, 3.422
3.403 (s)	6H	ND	5.49 (s)	2H	6.66, 3.804, 3.403
3.42 (s)	6H	ND	6.66 (s)	2H	5.49
3.804 (s)	6H	ND	6.93 (s)	2H	No NOE
3.89 (s)	3H	7.27	6.96 (s)	2H	4.99, 2.14
3.83 (s)	3H	6.99	6.996 (s)	2H	3.83, 3.403
			7.27 (s)	2H	3.89, 3.803

Unknown Conformer 262-B

Chemical Shift	Number of Protons	NOE Observed	Chemical Shift	No.of protons	NOE Observed
2.36 (s)	6H	ND	5.06 (s)	2H	7.045, 3.47
3.34 (s)	6H	ND	5.47 (s)	2H	6.30, 3.39, 3.34
3.395 (s)	6H	ND	6.30 (s)	2H	5.47, 3.39
3.47 (s)	6H	ND	6.89 (s)	2H	7.41, 3.800
3.800 (s)	6H	ND	7.046 (s)	2H	5.06, 3.47, 2.36
			7.16 (s)	2H	3.80, 3.47, 3.39
			7.41 (s)	2H	6.89, 2.36

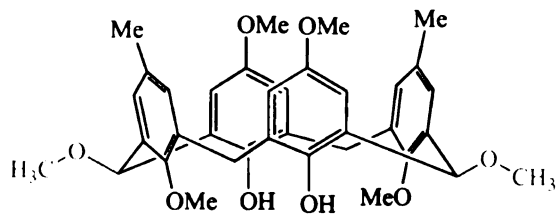
Triple annulation by dimerization of complex 298

5,17-dimethyl-2(S),14(S),11,23,26,28-hexamethoxy-25,27-dihydroxycalix[4]arene ***258***



The alkynyl carbene complex (*S*)-**298** (61 % ee, 0.074 g, 0.16 mmol) was dissolved in 64 mL of 1,2-dichloroethane and subjected to freeze-thaw deoxygenation according to the general procedure described for the reaction of bis-carbene complex and diyne (See pg 216). After thermolysis at 100°C for 30 min, the mixture was opened to air and stirred for overnight. Removal of the solvent and purification by silica-gel chromatography (25 % ethyl acetate / hexanes) afforded 18 mg (19 %, 0.03 mmol) of calix[4]arene **258** as an yellow oil. No other mobile spots were observed on TLC plate and in the ^{1}H NMR spectra of the crude compound. R_f (hexanes / ethylacetate = 3/1) = 0.25. Spectral data for **258**: ^{1}H NMR ($CDCl_3$, 600MHz) δ 2.06 (s, 6H), 3.36 (d, 2H, *J* = 13.8Hz), 3.44 (s, 6H), 3.74 (s, 6H), 4.00 (s, 6H), 4.07 (d, 2H, *J* = 13.8Hz), 6.01 (s, 2H), 6.60 (d, 2H, *J* = 4.2Hz), 6.79 (d, 2H, *J* = 2.4Hz), 6.97 (d, 2H, *J* = 1.8Hz), 6.98 (d, 2H, *J* = 4.2Hz), 7.83 (s, 2H); ^{3}C NMR (125MHz) δ 21.05, 32.05, 55.86, 57.32, 63.76, 73.73, 108.51, 114.34, 127.21, 128.27, 130.41, 131.24, 131.95, 134.65, 135.12, 145.89, 150.85, 153.03; IR ($CHCl_3$) 3339, 2926, 2890, 1665, 1611, 1480 cm^{-1}; mass spectrum *m/z* (% rel.intensity) FAB in NBA 600.2 (M^+, 2), 460 (7), 307 (56), 289 (32), 252 (16), HRMS calcd for $C_{36}H_{40}O_8$

m/z 600.2723, measd 600.2720. None of the calix[8]arene was observed by mass spectra. Specific rotation of (*R,R*)-**258** prepared from (*S*)-**287** (61% ee) = -3.8 (c = 1.0 in $CHCl_3$). The conformation of (*R,R*)-**258** was deduced to be the cone based on NOESY experiment (ni = 64, t_m = 0.7s, three fold forward linear prediction along the F1 dimension, See Fig 4 below).



258

Fig.4 Structure of 1,3-Dimethoxy Calix[4]arene

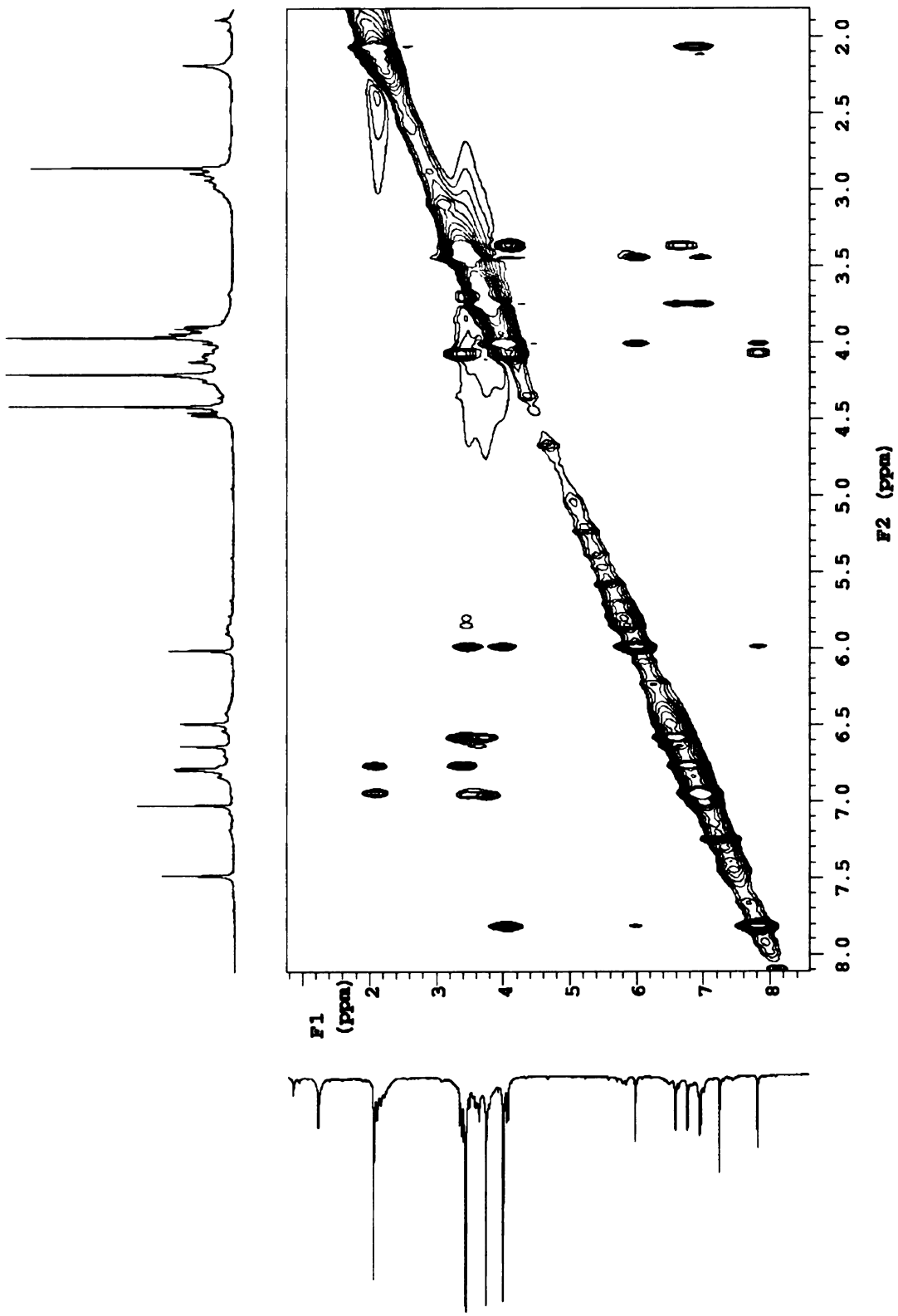
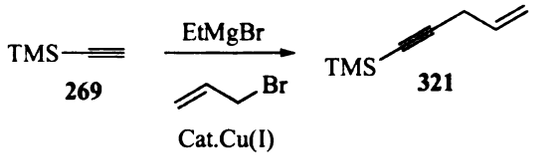
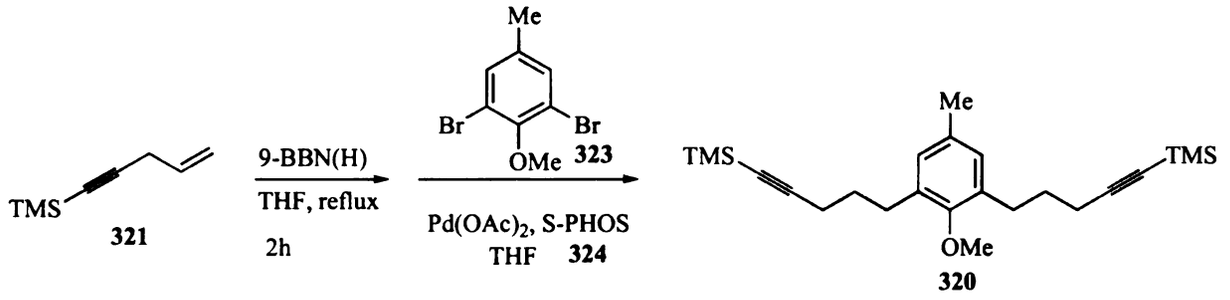


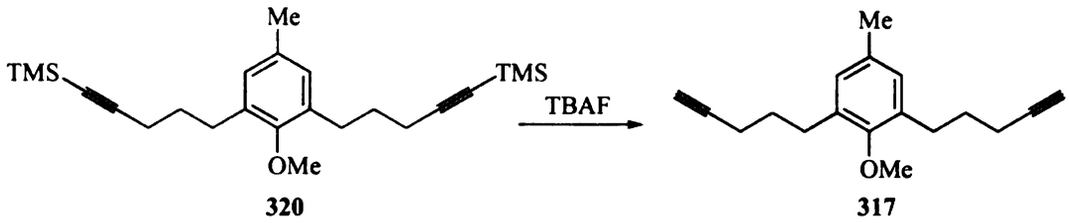
Fig 5. NOESY of **258** in $CDCl_3$ at 25°C



trimethyl(pent-4-en-1-ynyl)silane[132]**321**: Into a clean dry three necked 500 mL round bottomed flask was added sequentially trimethyl silyl acetylene (40 mL, 178 mmol) and 170 mL of tetrahydrofuran under argon. The mixture was cooled to -78°C and ethyl magnesium bromide (3M in diethyl ether, 70 mL, 210 mmol) was added dropwise. After stirring for 30 min at this temperature, copper (I) chloride (1.32 g, 7.5 mol %) was then added and stirring was continued for another 30 min at room temperature. Allyl bromide (30 mL, 350 mmol) was then added to the light brown colored slurry at 0°C dropwise to minimize exothermicity of the reaction. The reaction was continued for another 2 h before it was quenched by the addition of saturated ammonium chloride (100 mL). The organic layer was then extracted with ether (200 mL) and then concentrated under reduced pressure to yield the crude enyne **321**. The crude product was then distilled at 60°C (1 mm Hg) to afford 22.11 g (160.2 mmol, 90 %) of the enyne as a white oil. Spectral data for **321**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.14 (s, 9H), 2.98-3.00 (m, 2H), 5.08-5.12 (m, 1H), 5.28-5.34 (m, 1H), 5.75-5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.06, 24.13, 53.84, 116.21, 132.13 (1 sp carbon not located).

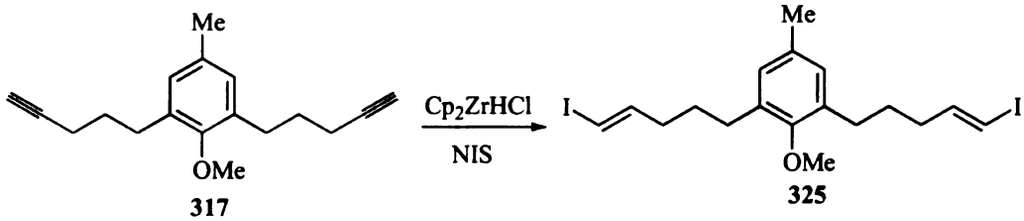


2-Methoxy-5-methyl-1,3-bis(5-trimethylsilyl)pent-4-ynyl-benzene ***320***: Into a clean three necked 100 mL flask fitted with a 14/20 reflux condenser was added 9-borabicyclononane (44 mL, 22 mmol, 0.5M in tetrahydrofuran) followed by trimethyl(4-penten-1-ynyl)silane (2.76 g, 20 mmol) at room temperature. The reaction mixture was then heated to reflux for 2 h after which the solution of the organoborane was transferred by a syringe under argon into a schlenk flask containing the aryl bromide **323**[127] (2.24 g, 8 mmol), potassium phosphate monohydrate (3.68 g, 16 mmol), palladium (II) acetate (36 mg, 2 mol %) and S-PHOS ligand [121] (132 mg, 4 mol %) in 40 mL of tetrahydrofuran. The resultant mixture was deoxygenated by freeze-pump thaw method (three cycles) after which the Schlenk flask was back-filled with argon. At room temperature, the flask was sealed and then heated to 75°C for 9 h. The contents of the flask were then poured over a Celite pad and the pad was rinsed repeatedly with 25 mL of ether (4 times). The solvent was then removed under vacuum to give the crude material, which was purified by silica-gel chromatography (20 % dichloromethane / hexanes) to afford 2.52 g (6.32 mmol, 79 %) of **320** as a yellow oil. R_f = 0.62 (Hexanes / ethyl acetate = 1/1). Spectral data for **320**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.17 (s, 18H), 1.81-1.86 (m, 4H), 2.27 (s, 3H), 2.29 (t, 4H, *J* = 7.0 Hz), 2.70 (t, 4H, *J* = 7.5 Hz), 3.74 (s, 3H), 6.86 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 0.18, 19.87, 20.82, 29.07, 29.65, 61.26, 84.81, 107.33, 128.74, 133.22, 134.39, 154.51; IR (neat) 2959, 2901, 2864, 2828, 2174, 1477, 1429, 1258, 1223 cm^{-1}; mass spectrum FAB in $CHCl_3$ *m/z* (% rel.intensity) 398 (M+, 8%), 383 (5), 89 (15), 73 (100), HRMS calcd for $C_{24}H_{38}OSi_2$ *m/z* 398.2461, measd 298.2463.



320 **317**

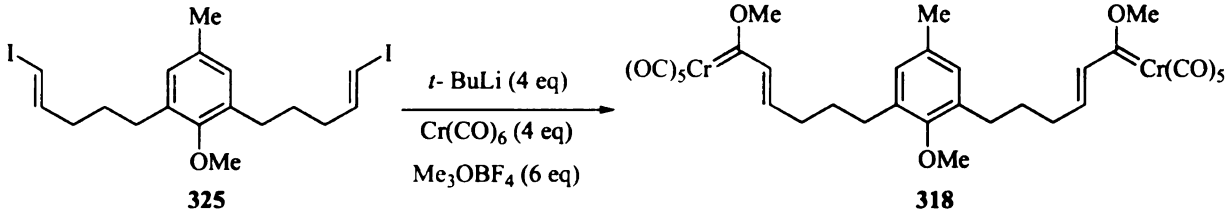
*2-methoxy-5-methyl-1,3-di(pent-4-ynyl)benzene **317*** : To a solution of the diyne **320** (2.52 g, 6.32 mmol) in 40 mL of ether was added tetrabutyl ammonium fluoride (1M in tetrahydrofuran, 32 mL, 5 equiv) and the resulting mixture was stirred at room temperature for 3 h. Water (50 mL) was then added and the organic layer was extracted with ether (100 mL). The organic layer was then dried over $MgSO_4$ and the solvent removed under vacuum to afford the crude product. Purification by silica-gel chromatography (5 % ethyl acetate / hexanes) gave the pure diyne **317** (1.57 g, 6.19 mmol, 98 %) as a yellow oil. R_f = 0.55 (hexanes / ethyl acetate = 19/1). Spectral data for **317**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.78-1.86 (m, 4H), 1.97 (t, 2H, *J* = 2.7Hz), 2.20 (t, 2H, *J* = 2.7 Hz), 2.23 (t, 2H, *J* = 6.9 Hz), 2.25 (s, 3H), 2.69 (t, 4H, *J* = 7.5 Hz), 3.70 (s, 3H), 6.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 18.33, 20.79, 28.91, 29.44, 61.27, 68.49, 84.35, 128.71, 133.28, 134.22, 154.42; IR (neat) 3300, 2939, 2864, 2828, 2118, 1607, 1498, 1478, 1431, 1286 cm^{-1}. mass spectrum *m/z* (% rel.intensity) 254 (100), 201 (52), 73 (90), HRMS calcd for $C_{18}H_{22}O$ *m/z* 254.1671, measd 254.1672.



317 **325**

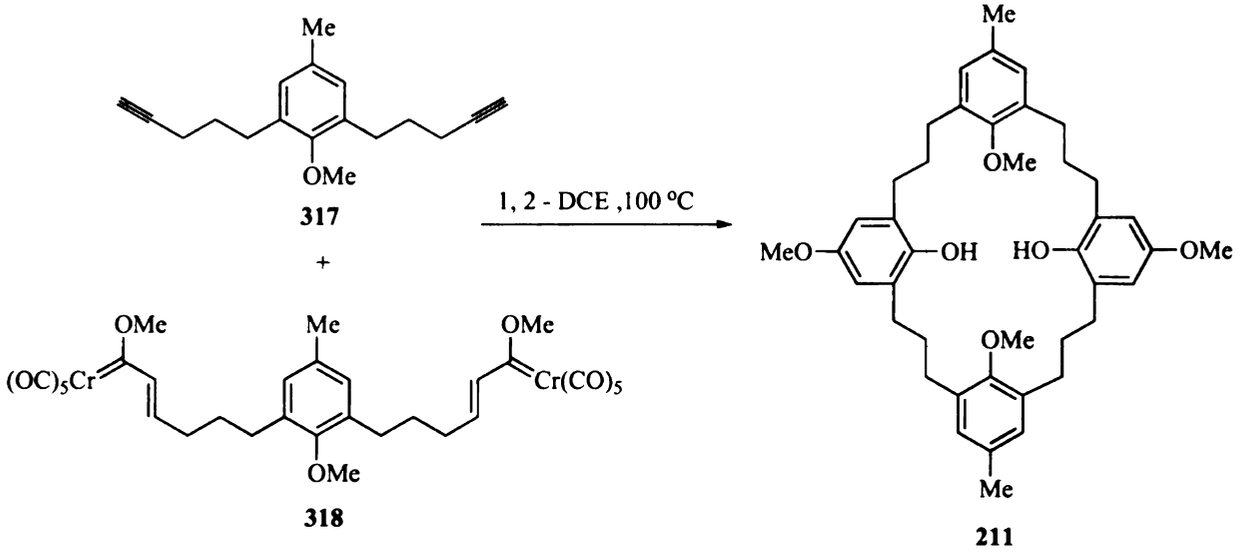
*1,3-bis((E)-5-iodopent-4-enyl)-2-methoxy-5-methylbenzene **325**:* Following the same procedure as reported earlier for the synthesis of (*S,S*)-**279**, the vinyl iodide **325** (0.97 g, 1.89 mmol) could be obtained as yellow oil from **317** (0.76 g, 3 mmol) in 63 % yield. R_f

= 0.57 (hexanes / ethyl acetate = 19 / 1). Spectral data for **325**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.66-1.72 (m, 4H), 2.08-2.12 (m, 4H), 2.24 (s, 3H), 2.56 (t, 4H, *J* = 8.0 Hz), 3.67 (s, 3H), 6.01 (d, 2H, *J* = 14.5 Hz), 6.54 (dt, 2H, *J* = 14.0, 6.5 Hz), 6.80 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.84, 29.09, 29.34, 35.86, 61.25, 128.54, 133.33, 134.50, 146.26, 154.25 (1 sp^2 carbon not located); IR (neat) 3405, 2930, 2859, 1605, 1477, 1458, 1219 cm^{-1}. mass spectrum *m/z* (% rel.intensity) 510 (M+, 42), 329 (20), 307 (40), 289 (20), 154 (100), 136 (96), HRMS calcd for $C_{18}H_{24}I_2O$ *m/z* 509.9917, measd 509.9918.



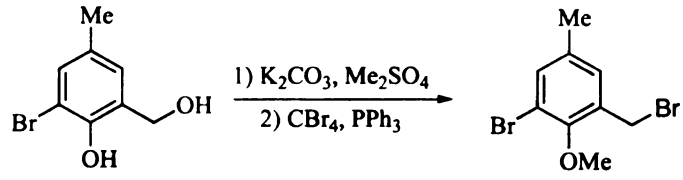
*Bis-carbene complex **318**:* To a solution of the vinyl iodide **325** (0.66 g, 1.3 mmol) in 25 mL of tetrahydrofuran was added *tert*-butyl lithium (4 equiv, 1.7 M in pentane) at -78°C and the resulting mixture was stirred for 30 min. Chromium hexacarbonyl (1.14 g, 4 equiv) was dissolved in tetrahydrofuran (40 mL) and transferred to the above solution. The resultant slurry was then warmed to room temperature and stirred for 3h. The general workup procedure described earlier for (*S,S*)-**268** was employed upon purification by silica-gel chromatography (5 % ethyl acetate / hexanes) to afford 0.339 g (36 %, 0.47 mmol) of **318** as a deep-red oil. R_f (hexanes / ethyl acetate = 19/1) = 0.25. Spectral data for **318**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.78 (t, 4H, *J* = 7.5 Hz), 2.24 (t, 4H, *J* = 7.0 Hz), 2.25 (s, 3H), 2.62 (t, 4H, J = 7.0 Hz), 3.66 (s, 3H), 4.72 (s, 6H), 6.31-6.37 (m, 2H), 6.83 (s, 2H), 7.29 (d, 2H, *J* = 14.5 Hz); ^{13}C NMR ($CDCl_3$, 125MHz) δ 20.83, 29.33, 29.43, 32.27, 61.27, 66.34, 128.69, 133.49, 134.36, 137.18, 144.50, 154.32, 216.75, 223.94, 335.89; IR (neat) 2932, 2863, 2829, 2058, 1932, 1477, 1452, 1230 cm^{-1}; mass spectrum

m/z (% rel.intensity) 726 (3.2), 586 (16), 446 (60), 351 (100), 332 (66), HRMS calcd for $C_{32}H_{30}Cr_2O_{13}$ *m/z* 726.0497, measd 726.0495.



Bis-homocalix[4]arene **211**: The following is a representative procedure for large scale synthesis. Into a 500 mL Schlenk flask under an atmosphere of argon was added the bis-carbene complex **318** (0.361 g, 0.497 mmol), the diyne **317** (0.126 g, 0.497 mmol) and 200 mL of 1,2-dichloroethane. The resultant solution was subjected to freeze-thaw degassing according to the general procedure described in Pg 216. The reaction mixture was then heated to 100°C for 30 min during which time the deep-red colored solution turned yellow. Work up and purification by silica-gel chromatography (25 % ethyl acetate / hexanes) afforded the macrocycle **211** in 39 % yield (0.125 g, 0.194 mmol) as a white solid. R_f (hexanes / ethyl acetate = 3/1) = 0.33. Spectral data for **211**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 1.88-1.94 (m, 8H), 2.23 (s, 6H), 2.51 (t, 8H, *J* = 8.5Hz), 2.64 (t, 8H, *J* = 7Hz), 3.56 (s, 6H), 3.73 (s, 6H), 5.99 (s, 2H), 6.53 (s, 4H), 6.82 (s, 4H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 20.78, 29.52, 29.78, 31.12, 48.06, 53.84, 55.58, 61.00, 112.54, 129.21, 130.59, 133.90, 134.71, 146.05, 153.12, 154.05 (1 sp^3 carbon not located); IR (neat) 3414, 2930, 2860, 2832, 1605, 1478, 1318, 1196 cm^{-1}; mass spectrum *m/z* (%

rel.intensity) 652 (M^+, 66), 386 (10), 307 (30), 154 (100), 136 (60), 117 (74), HRMS calcd for $C_{42}H_{52}O_6$ *m/z* 652.3764, measd 652.3767.

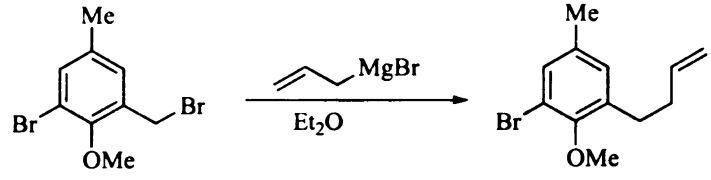


334 336

1-Bromo-3-(bromomethyl)-2-methoxy-5-methylbenzene **336**: The intermediate methyl ether **335** is known in the literature[133] but a different procedure was used for its preparation. 2-Bromo-6-hydroxymethyl-*p*-cresol **334** was obtained following the procedure reported by Cram in 95 % yield.[134] The alcohol **334** (9.71 g, 44.94 mmol) was dissolved in 220 mL of acetone and potassium carbonate (9.07 g, 65.61 mmol) was then added. The resultant slurry was stirred for a few minutes after which dimethyl sulfate (4.7 mL, 49.43 mmol) was added dropwise with constant stirring. The reaction was continued for 24 h and the insoluble residue was filtered through a fritted glass funnel. The filtrate was concentrated under reduced pressure and purified by silica-gel chromatography (50 % ethyl acetate/ hexanes) to afford 8.16 g (35.5 mmol, 79 %) of the title compound as white oil.

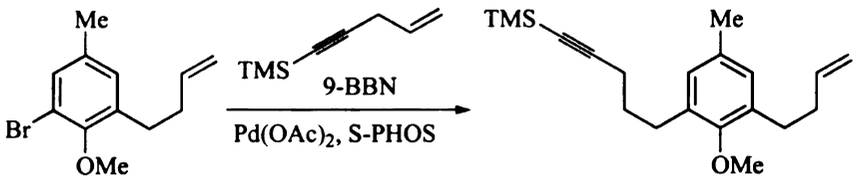
The alcohol **335** (8.16 g, 35.5 mmol) was dissolved in dichloromethane (200 mL) and triphenyl phosphine (11.17 g, 42.6 mmol) was then added. Carbon tetrabromide (14.13 g, 42.6 mmol) was added in portions carefully and the resulting mixture was stirred for 4 h. The solvent was removed and the crude material was purified by silica-gel chromatography (5 % ethyl acetate/ hexanes) to give 9.6 g (32.66 mmol, 92 % yield) of bromide **336** as white oil. R_f (hexanes / ethylacetate = 19/1) = 0.49. Spectral data for **336**:

^{1}H NMR ($CDCl_3$, 300MHz) δ 2.27 (s, 3H), 3.93 (s, 3H), 4.51 (s, 2H), 7.12 (d, 1H, J = 1.5 Hz), 7.30 (d, 1H, J = 1.8 Hz).



336 **337**

*1-Bromo-3-(but-enyl)-2-methoxy-5-methylbenzene **337***: The bromide **336** 3.44 g (11.7 mmol) was transferred into a 100 mL three-necked round-bottomed flask. Ether (20 mL) was added followed by allyl magnesium bromide (1M in ether, 1.3 equiv) at room temperature and the reaction mixture was stirred overnight. The reaction mixture was poured into water (50 mL) and extracted with ether (100 mL). The organic layer was then concentrated under reduced pressure to afford the crude material, which was then purified by silica-gel chromatography (5 % ethyl acetate / hexanes) to give 2.79 g (11.04 mmol, 94 %) of **337** as white oil. R_f (hexanes / ethyl acetate = 19/1) = 0.68. Spectral data for **337**: ^{1}H NMR ($CDCl_3$, 500MHz) δ 2.25 (s, 3H), 2.29-2.37 (m, 2H), 2.69 (t, 2H, J = 8.1 Hz), 3.78 (s, 3H), 4.95-5.07 (m, 2H), 5.80-5.87 (m, 1H), 6.91 (d, 1H, J = 1.5 Hz), 7.19 (d, 1H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 125MHz) δ 20.51, 29.83, 34.65, 60.94, 115.02, 116.89, 130.04, 131.54, 134.98, 136.39, 137.95, 152.85; IR (neat) 3077, 2928, 2867, 2828, 1642, 1476, 1450 cm^{-1}; mass spectrum *m/z* (% rel.intensity) NBA in FAB 256 M^++2 (Br^{81}, 21), 254 M^+ (Br^{79}, 19), 215 (Br^{81}, 100), 213 (Br^{79}, 99), 174.1 (20), 135.1 (44), 105 (44), 81(56), 55(68), HRMS calcd for $C_{12}H_{15}OBr^{79}$ *m/z* 254.0306, measd 254.0307



337 341

*(5-(3-but-3-enyl)-2-methoxy-5-methylphenyl)pent-1-ynyl)trimethylsilane **341***:

Following the procedure described earlier for the synthesis of **320**, the aryl bromide **337** (5.58 g, 22 mmol) was converted into the cross-coupled product **341** in 83 % yield (5.73 g, 18.3 mmol) after purification by silica-gel chromatography (15 % dichloromethane / hexanes). R_f (hexanes / dichloromethane = 85/15) = 0.43. Spectral data for **341**: ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.14 (s, 9H), 1.76-1.85 (m, 2H), 2.25 (s, 3H), 2.27 (t, 2H, J = 6.9 Hz), 2.31-2.38 (m, 2H), 2.64-2.70 (m, 4H), 3.74 (s, 3H), 4.94-5.09 (m, 2H), 5.81-5.95 (m, 1H), 6.84 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 0.17, 19.84, 20.86, 29.01, 29.27, 29.61, 34.81, 61.28, 84.76, 107.31, 114.64, 128.52, 128.64, 133.22, 134.29, 134.50, 138.49, 154.31; IR (neat) 3078, 2975, 2862, 2174, 1641, 1477, 1452, 1429 cm^{-1}; mass spectrum FAB in NPOE *m/z* (% rel.intensity) 314 (M^+, 88), 273 (44), 252 (24), 73 (100), HRMS cacld for $C_{20}H_{30}OSi$ *m/z* 314.2066, measd 314.2065.

APPENDIX-I

Crystallographic Data of Selected Compounds

246A, 246C-I and 246C-II

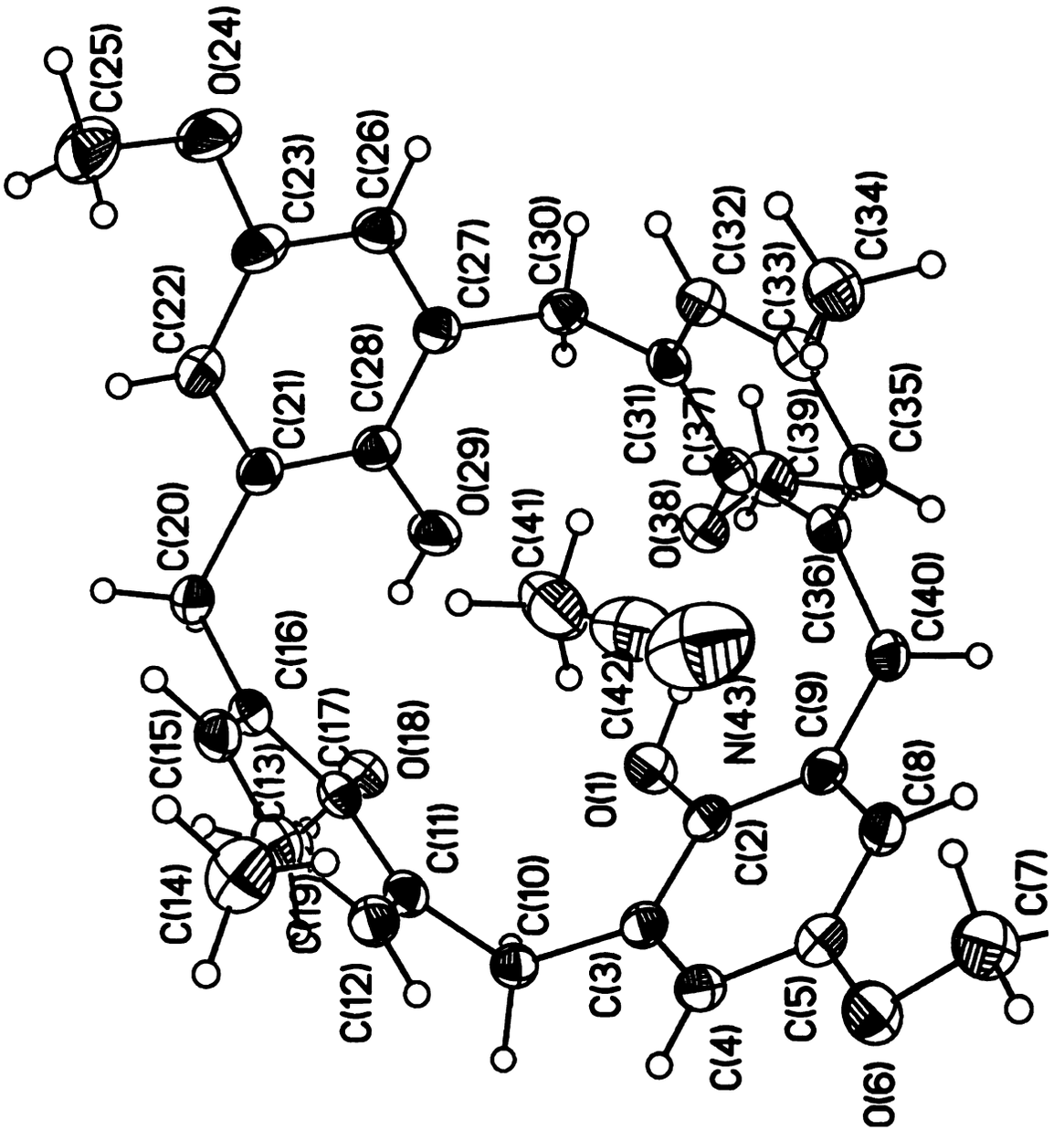


Fig A.1 ORTEP Diagram of Calix[4]arene 246A

Table A.3.1. Crystal data and structure refinement for 246A.

Identification code	223c
Empirical formula	C36 H39 N O6
Formula weight	581.68
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.817(2) A
	b = 10.839(2) A
	c = 13.945(3) A
	alpha = 104.68(3) deg.
	beta = 101.53(3) deg.
	gamma = 92.22(3) deg.
Volume	1542.7(5) A^3
Z	2
Density (calculated)	1.252 Mg/m^3
Absorption coefficient	0.085 mm^-1
F(000)	620
Crystal size	0.8 x 0.8 x 0.2 mm
Theta range for data collection	1.55 to 28.27 deg.
Index ranges	-13<=h<=12, -13<=k<=10, -13<=l<=18
Reflections collected / unique	9671/6813 [R(int) =0.0190]
Completeness to theta = 28.27	89.0%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6813 / 0 / 396
Goodness-of-fit on F^2	1.189
Final R indices [I>2sigma(I)]	R1 = 0.0499, wR2 = 0.1618
R indices (all data)	R1 = 0.0603, wR2 = 0.1671
Largest diff. peak and hole	0.440 and -0.325 e.A^-3

Table A.3.2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for 246A.

	x	y	z	U(eq)	Occ.
O(1)	7639(1)	9450(1)	4209(1)	29(1)	1
C(2)	8243(2)	9423(1)	3424(1)	22(1)	1
C(3)	7636(2)	9969(1)	2656(1)	23(1)	1
C(4)	8215(2)	9978(2)	1849(1)	25(1)	1
C(5)	9348(2)	9423(2)	1770(1)	26(1)	1
O(6)	9801(1)	9460(1)	920(1)	36(1)	1
C(7)	10781(2)	8652(2)	696(2)	40(1)	1
C(8)	9936(2)	8883(2)	2529(1)	25(1)	1
C(9)	9397(1)	8888(1)	3367(1)	23(1)	1
C(10)	6324(2)	10429(1)	2661(1)	23(1)	1
C(11)	5300(2)	9338(1)	2070(1)	22(1)	1
C(12)	5128(2)	8867(2)	1016(1)	25(1)	1
C(13)	4300(2)	7787(2)	460(1)	27(1)	1
C(14)	4170(2)	7299(2)	-677(1)	40(1)	1
C(15)	3646(2)	7146(2)	989(1)	26(1)	1
C(16)	3766(1)	7588(1)	2039(1)	22(1)	1
C(17)	4564(1)	8716(1)	2560(1)	22(1)	1
O(18)	4655(1)	9188(1)	3606(1)	24(1)	1
C(19)	3771(2)	10127(2)	3851(1)	31(1)	1
C(20)	3081(2)	6828(2)	2597(1)	25(1)	1
C(21)	3775(2)	5707(2)	2842(1)	23(1)	1
C(22)	3304(2)	4447(2)	2278(1)	27(1)	1
C(23)	3906(2)	3409(2)	2512(1)	28(1)	1
O(24)	3515(1)	2132(1)	2018(1)	38(1)	1
C(25)	2522(2)	1859(2)	1133(2)	43(1)	1
C(26)	4981(2)	3620(2)	3295(1)	26(1)	1
C(27)	5487(2)	4855(2)	3843(1)	24(1)	1
C(28)	4865(2)	5903(1)	3623(1)	23(1)	1
O(29)	5377(1)	7088(1)	4234(1)	33(1)	1
C(30)	6728(2)	5075(2)	4633(1)	25(1)	1
C(31)	7838(2)	5356(2)	4170(1)	23(1)	1
C(32)	8182(2)	4404(2)	3404(1)	25(1)	1
C(33)	9122(2)	4650(2)	2900(1)	25(1)	1
C(34)	9426(2)	3640(2)	2026(1)	32(1)	1
C(35)	9741(2)	5889(2)	3183(1)	25(1)	1
C(36)	9433(2)	6867(2)	3947(1)	24(1)	1
C(37)	8495(2)	6574(2)	4438(1)	22(1)	1
O(38)	8173(1)	7566(1)	5187(1)	25(1)	1
C(39)	8841(2)	7610(2)	6199(1)	35(1)	1
C(40)	10038(2)	8233(2)	4160(1)	25(1)	1
C(41)	6823(2)	6350(2)	1746(2)	52(1)	1
C(42)	7616(3)	6116(2)	1012(2)	54(1)	1
N(43)	8244(3)	5905(3)	420(2)	79(1)	1

U(eq) is defined as one third of the trace of the orthogonalized
Uij tensor.

Table A.3.3. Bond lengths [A] and angles [deg] for 246A.

O(1)-C(2)	1.378(2)
C(2)-C(9)	1.405(2)
C(2)-C(3)	1.414(2)
C(3)-C(4)	1.394(2)
C(3)-C(10)	1.524(2)
C(4)-C(5)	1.399(2)
C(5)-O(6)	1.379(2)
C(5)-C(8)	1.393(2)
O(6)-C(7)	1.433(2)
C(8)-C(9)	1.404(2)
C(9)-C(40)	1.529(2)
C(10)-C(11)	1.530(2)
C(11)-C(12)	1.400(2)
C(11)-C(17)	1.402(2)
C(12)-C(13)	1.397(2)
C(13)-C(15)	1.399(2)
C(13)-C(14)	1.515(2)
C(15)-C(16)	1.398(2)
C(16)-C(17)	1.408(2)
C(16)-C(20)	1.530(2)
C(17)-O(18)	1.4001(19)
O(18)-C(19)	1.4480(19)
C(20)-C(21)	1.529(2)
C(21)-C(28)	1.404(2)
C(21)-C(22)	1.408(2)
C(22)-C(23)	1.398(2)
C(23)-O(24)	1.387(2)
C(23)-C(26)	1.394(2)
O(24)-C(25)	1.422(2)
C(26)-C(27)	1.390(2)
C(27)-C(28)	1.410(2)
C(27)-C(30)	1.524(2)
C(28)-O(29)	1.373(2)
C(30)-C(31)	1.527(2)
C(31)-C(37)	1.399(2)
C(31)-C(32)	1.405(2)
C(32)-C(33)	1.399(2)
C(33)-C(35)	1.401(2)
C(33)-C(34)	1.517(2)
C(35)-C(36)	1.402(2)
C(36)-C(37)	1.402(2)

C(36)-C(40)	1.527(2)
C(37)-O(38)	1.4048(19)
O(38)-C(39)	1.440(2)
C(41)-C(42)	1.444(4)
C(42)-N(43)	1.156(4)

O(1)-C(2)-C(9)	123.12(14)
O(1)-C(2)-C(3)	116.34(14)
C(9)-C(2)-C(3)	120.54(15)
C(4)-C(3)-C(2)	118.61(14)
C(4)-C(3)-C(10)	120.59(14)
C(2)-C(3)-C(10)	120.57(14)
C(3)-C(4)-C(5)	121.47(15)
O(6)-C(5)-C(8)	124.82(15)
O(6)-C(5)-C(4)	115.78(15)
C(8)-C(5)-C(4)	119.41(15)
C(5)-O(6)-C(7)	116.79(14)
C(5)-C(8)-C(9)	120.62(15)
C(8)-C(9)-C(2)	119.30(15)
C(8)-C(9)-C(40)	119.05(14)
C(2)-C(9)-C(40)	121.54(14)
C(3)-C(10)-C(11)	110.22(12)
C(12)-C(11)-C(17)	117.37(15)
C(12)-C(11)-C(10)	120.53(15)
C(17)-C(11)-C(10)	121.96(14)
C(13)-C(12)-C(11)	122.46(16)
C(12)-C(13)-C(15)	118.19(15)
C(12)-C(13)-C(14)	120.37(16)
C(15)-C(13)-C(14)	121.39(15)
C(13)-C(15)-C(16)	121.70(15)
C(15)-C(16)-C(17)	118.05(15)
C(15)-C(16)-C(20)	120.16(14)
C(17)-C(16)-C(20)	121.75(14)
O(18)-C(17)-C(11)	119.59(14)
O(18)-C(17)-C(16)	118.39(14)
C(11)-C(17)-C(16)	121.96(14)
C(17)-O(18)-C(19)	113.01(12)
C(21)-C(20)-C(16)	113.81(13)
C(28)-C(21)-C(22)	119.19(15)
C(28)-C(21)-C(20)	121.49(14)
C(22)-C(21)-C(20)	119.31(14)
C(23)-C(22)-C(21)	120.03(16)
O(24)-C(23)-C(26)	115.08(15)
O(24)-C(23)-C(22)	124.90(16)
C(26)-C(23)-C(22)	120.02(15)
C(23)-O(24)-C(25)	117.60(15)
C(27)-C(26)-C(23)	121.07(15)
C(26)-C(27)-C(28)	118.94(15)

C(26)-C(27)-C(30)	120.49(14)
C(28)-C(27)-C(30)	120.50(14)
O(29)-C(28)-C(21)	123.66(14)
O(29)-C(28)-C(27)	115.63(14)
C(21)-C(28)-C(27)	120.69(14)
C(27)-C(30)-C(31)	110.36(13)
C(37)-C(31)-C(32)	117.51(15)
C(37)-C(31)-C(30)	122.00(14)
C(32)-C(31)-C(30)	120.37(14)
C(33)-C(32)-C(31)	122.26(15)
C(32)-C(33)-C(35)	118.22(15)
C(32)-C(33)-C(34)	121.82(15)
C(35)-C(33)-C(34)	119.87(16)
C(33)-C(35)-C(36)	121.55(15)
C(37)-C(36)-C(35)	118.24(15)
C(37)-C(36)-C(40)	121.82(14)
C(35)-C(36)-C(40)	119.75(15)
C(31)-C(37)-C(36)	122.19(14)
C(31)-C(37)-O(38)	119.84(14)
C(36)-C(37)-O(38)	117.88(14)
C(37)-O(38)-C(39)	113.08(13)
C(36)-C(40)-C(9)	111.01(13)
N(43)-C(42)-C(41)	178.7(3)

Symmetry transformations used to generate equivalent atoms:

Table A.3.4. Anisotropic displacement parameters (A^2 x 10^3) for 246A

	U11	U22	U33	U23	U13	U12
O(1)	31(1)	34(1)	28(1)	12(1)	11(1)	9(1)
C(2)	24(1)	20(1)	22(1)	3(1)	4(1)	-2(1)
C(3)	23(1)	17(1)	26(1)	2(1)	4(1)	0(1)
C(4)	26(1)	23(1)	27(1)	9(1)	4(1)	1(1)
C(5)	26(1)	26(1)	26(1)	6(1)	7(1)	-2(1)
O(6)	33(1)	48(1)	35(1)	20(1)	16(1)	13(1)
C(7)	42(1)	45(1)	43(1)	17(1)	23(1)	15(1)
C(8)	20(1)	25(1)	30(1)	6(1)	4(1)	0(1)
C(9)	22(1)	20(1)	24(1)	4(1)	2(1)	3(1)
C(10)	24(1)	19(1)	25(1)	5(1)	5(1)	3(1)
C(11)	21(1)	20(1)	25(1)	6(1)	4(1)	6(1)
C(12)	24(1)	28(1)	26(1)	9(1)	6(1)	3(1)
C(13)	26(1)	31(1)	23(1)	6(1)	3(1)	6(1)
C(14)	46(1)	47(1)	24(1)	4(1)	4(1)	5(1)
C(15)	22(1)	24(1)	27(1)	4(1)	1(1)	2(1)
C(16)	19(1)	22(1)	27(1)	7(1)	5(1)	5(1)
C(17)	20(1)	22(1)	22(1)	5(1)	4(1)	7(1)
O(18)	27(1)	24(1)	22(1)	4(1)	7(1)	6(1)
C(19)	31(1)	28(1)	33(1)	2(1)	12(1)	8(1)
C(20)	19(1)	26(1)	30(1)	8(1)	6(1)	2(1)
C(21)	22(1)	24(1)	26(1)	7(1)	9(1)	1(1)
C(22)	24(1)	26(1)	28(1)	6(1)	7(1)	1(1)
C(23)	32(1)	19(1)	32(1)	2(1)	11(1)	2(1)
O(24)	45(1)	21(1)	41(1)	2(1)	4(1)	3(1)
C(25)	43(1)	32(1)	43(1)	-2(1)	3(1)	-5(1)
C(26)	29(1)	22(1)	31(1)	8(1)	12(1)	5(1)
C(27)	24(1)	24(1)	26(1)	9(1)	10(1)	3(1)
C(28)	24(1)	22(1)	24(1)	6(1)	8(1)	1(1)
O(29)	36(1)	20(1)	37(1)	6(1)	-5(1)	2(1)
C(30)	27(1)	27(1)	26(1)	11(1)	8(1)	3(1)
C(31)	21(1)	27(1)	23(1)	11(1)	3(1)	5(1)
C(32)	24(1)	24(1)	27(1)	8(1)	4(1)	3(1)
C(33)	23(1)	28(1)	25(1)	7(1)	4(1)	7(1)
C(34)	33(1)	33(1)	32(1)	5(1)	10(1)	9(1)
C(35)	21(1)	30(1)	27(1)	10(1)	7(1)	5(1)
C(36)	20(1)	26(1)	24(1)	9(1)	1(1)	2(1)
C(37)	22(1)	26(1)	20(1)	7(1)	2(1)	5(1)
O(38)	28(1)	27(1)	19(1)	5(1)	3(1)	5(1)
C(39)	42(1)	39(1)	21(1)	7(1)	1(1)	6(1)
C(40)	20(1)	28(1)	25(1)	6(1)	1(1)	0(1)
C(41)	49(1)	36(1)	59(1)	6(1)	-12(1)	11(1)
C(42)	71(2)	34(1)	42(1)	9(1)	-16(1)	4(1)
N(43)	106(2)	66(2)	56(2)	13(1)	2(1)	-13(1)

The anisotropic displacement factor exponent takes the

form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table A.3.5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for 246A.

	x	y	z	U(eq)	Occ.
H(1)	7930(30)	8860(30)	4540(20)	58(7)	1
H(4)	7838	10362	1352	30	1
H(7A)	11025	8762	96	60	1
H(7B)	10473	7774	587	60	1
H(7C)	11501	8879	1256	60	1
H(8)	10692	8517	2481	31	1
H(10A)	6232	11139	2354	28	1
H(10B)	6223	10729	3355	28	1
H(12)	5581	9288	672	30	1
H(14A)	3559	6563	-938	61	1
H(14B)	4974	7067	-820	61	1
H(14C)	3893	7959	-995	61	1
H(15)	3117	6407	632	31	1
H(19A)	3879	10423	4575	46	1
H(19B)	2920	9742	3557	46	1
H(19C)	3926	10837	3584	46	1
H(20A)	2973	7404	3225	30	1
H(20B)	2244	6502	2182	30	1
H(22)	2593	4306	1750	32	1
H(25A)	2339	949	867	64	1
H(25B)	2780	2214	632	64	1
H(25C)	1778	2231	1305	64	1
H(26)	5367	2924	3454	31	1
H(29)	5020(20)	7600(20)	4066(19)	48(7)	1
H(30A)	6855	4320	4881	30	1
H(30B)	6688	5791	5204	30	1
H(32)	7771	3583	3225	30	1
H(34A)	8923	2851	1929	49	1
H(34B)	10309	3509	2180	49	1
H(34C)	9239	3921	1418	49	1
H(35)	10371	6066	2858	30	1
H(39A)	8586	8304	6677	52	1
H(39B)	9737	7739	6247	52	1
H(39C)	8646	6817	6349	52	1
H(40A)	10932	8213	4152	30	1
H(40B)	9966	8721	4829	30	1
H(41A)	5951	6125	1402	79	1

H(41B)	6942	7240	2110	79	1
H(41C)	7048	5840	2214	79	1

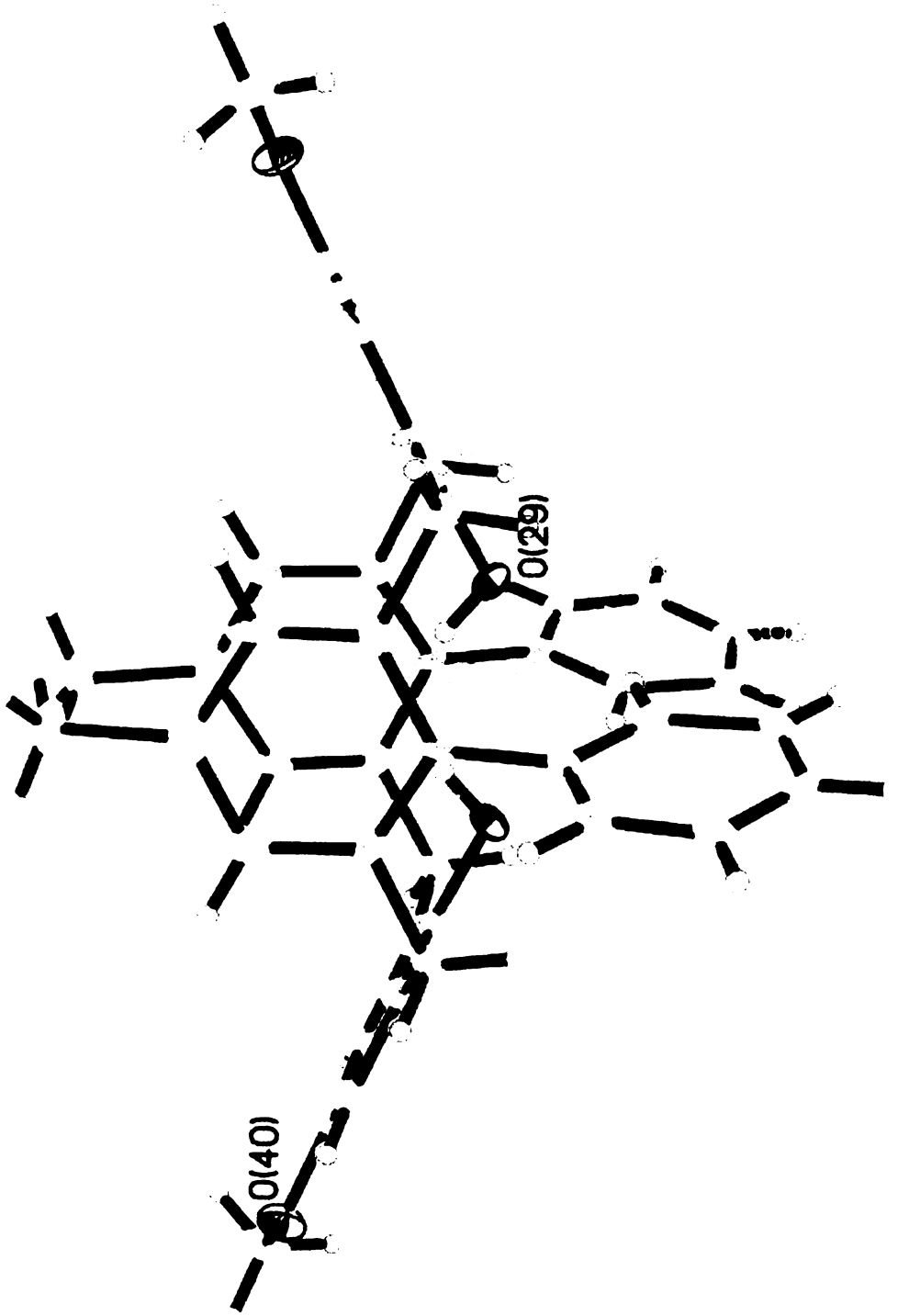


Fig A.2 Calix[4]arene 246C-I in the Cone Conformation

Table A.1.1. Crystal data and structure refinement for 246C-I

Identification code	223a-I
Empirical formula	C44 H40 O4
Formula weight	xx640.74
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	tetragonal
Space group	P 4(1)2(1)2
Unit cell dimensions	a = 15.699(2) A b = 15.699(2) A c = 16.214(3) A alpha = 90 deg. beta = 90 deg. gamma = 90 deg.
Volume	3996.2(11) A^3
Z	4
Density (calculated)	xx1.065 Mg/m^3
Absorption coefficient	xx0.070 mm^-1
F(000)	xx1360
Crystal size	0.22 x 0.20 x 0.14 mm
Theta range for data collection	1.81 to 28.24 deg.
Index ranges	-20<=h<=20, -20<=k<=20, -20<=l<=21
Reflections collected / unique	47415 / 4877 [R(int) = 0.7337]
Completeness to theta = 28.24	99.2%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4877 / 0 / 237
Goodness-of-fit on F^2	1.493
Final R indices [I>2sigma(I)]	R1 = 0.1875, wR2 = 0.3515
R indices (all data)	R1 = 0.4414, wR2 = 0.4137
Absolute structure parameter	2(8)
Largest diff. peak and hole	0.995 and -0.440 e.A^-3

Table A.1.2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for 246C-I

	x	y	z	U(eq)	Occ.
O(1)	7575(4)	8381(6)	697(5)	41(2)	1
O(2)	8632(5)	5081(6)	-3104(5)	59(3)	1
C(3)	6084(7)	8615(7)	-390(7)	33(3)	1
C(4)	7513(8)	7887(8)	-2176(6)	47(3)	1
C(5)	8090(8)	6471(8)	-2678(8)	46(3)	1
C(6)	5016(9)	6410(9)	-790(10)	69(4)	1
C(7)	6187(8)	8836(7)	1130(7)	39(3)	1
C(8)	6666(7)	8690(8)	-1021(6)	33(3)	1
C(9)	6783(7)	7957(8)	-1537(7)	38(3)	1
C(10)	7890(13)	11012(9)	-1537(8)	62(4)	1
C(11)	7959(10)	9579(9)	-1051(8)	53(4)	1
C(12)	5626(9)	7247(9)	-832(10)	59(4)	1
C(13)	6036(8)	9269(7)	277(6)	34(3)	1
C(14)	5563(8)	8910(7)	1749(8)	45(3)	1
C(15)	6910(8)	8422(7)	1295(7)	35(3)	1
C(16)	5553(9)	7922(9)	-287(8)	50(4)	1
C(17)	8397(11)	10336(10)	-1224(8)	64(4)	1
C(18)	6276(8)	7283(8)	-1469(7)	42(3)	1
C(19)	8267(12)	5212(10)	-3927(8)	75(5)	1
C(20)	7061(10)	10933(9)	-1628(7)	49(4)	1
C(21)	6687(9)	10183(10)	-1469(7)	46(4)	1
C(22)	8033(8)	7093(8)	-2031(7)	43(3)	1
C(23)	8526(8)	5732(8)	-2537(8)	48(3)	1
C(24)	7122(8)	9498(8)	-1170(6)	34(3)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table A.1.3. Bond lengths [A] and angles [deg] for 246C-I

O(1)-C(15)	1.426(13)
O(1)-H(1)	0.8200
O(2)-C(23)	1.385(13)
O(2)-C(19)	1.467(13)
C(3)-C(16)	1.380(16)
C(3)-C(8)	1.377(14)
C(3)-C(13)	1.494(14)
C(4)-C(22)	1.508(15)
C(4)-C(9)	1.548(15)
C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700
C(5)-C(23)	1.366(16)
C(5)-C(22)	1.436(16)
C(5)-H(5)	0.9300
C(6)-C(12)	1.628(17)
C(6)-H(6A)	0.9600
C(6)-H(6B)	0.9600
C(6)-H(6C)	0.9600
C(7)-C(15)	1.335(15)
C(7)-C(14)	1.407(15)
C(7)-C(13)	1.561(13)
C(8)-C(9)	1.435(16)
C(8)-C(24)	1.476(15)
C(9)-C(18)	1.328(16)
C(10)-C(20)	1.315(18)
C(10)-C(17)	1.42(2)
C(10)-H(10)	0.9300
C(11)-C(24)	1.334(16)
C(11)-C(17)	1.402(16)
C(11)-H(11)	0.9300
C(12)-C(16)	1.385(17)
C(12)-C(18)	1.453(17)
C(13)-H(13A)	0.9700
C(13)-H(13B)	0.9700
C(14)-C(23)#1	1.438(15)
C(14)-H(14)	0.9300
C(15)-C(22)#1	1.371(15)
C(16)-H(16)	0.9300
C(17)-H(17)	0.9300
C(18)-H(18)	0.9300
C(19)-H(19A)	0.9600
C(19)-H(19B)	0.9600
C(19)-H(19C)	0.9600

C(20)-C(21)	1.342(16)
C(20)-H(20)	0.9300
C(21)-C(24)	1.363(15)
C(21)-H(21)	0.9300
C(22)-C(15)#1	1.371(15)
C(23)-C(14)#1	1.438(15)

C(15)-O(1)-H(1)	109.5
C(23)-O(2)-C(19)	117.0(10)
C(16)-C(3)-C(8)	124.0(11)
C(16)-C(3)-C(13)	115.0(11)
C(8)-C(3)-C(13)	120.9(11)
C(22)-C(4)-C(9)	110.8(9)
C(22)-C(4)-H(4A)	109.5
C(9)-C(4)-H(4A)	109.5
C(22)-C(4)-H(4B)	109.5
C(9)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	108.1
C(23)-C(5)-C(22)	119.1(12)
C(23)-C(5)-H(5)	120.4
C(22)-C(5)-H(5)	120.5
C(12)-C(6)-H(6A)	109.5
C(12)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5
C(12)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(15)-C(7)-C(14)	119.3(11)
C(15)-C(7)-C(13)	121.3(11)
C(14)-C(7)-C(13)	119.3(12)
C(3)-C(8)-C(9)	116.7(11)
C(3)-C(8)-C(24)	121.1(10)
C(9)-C(8)-C(24)	122.2(10)
C(18)-C(9)-C(8)	121.0(11)
C(18)-C(9)-C(4)	116.2(12)
C(8)-C(9)-C(4)	122.8(11)
C(20)-C(10)-C(17)	121.6(14)
C(20)-C(10)-H(10)	119.3
C(17)-C(10)-H(10)	119.2
C(24)-C(11)-C(17)	122.3(15)
C(24)-C(11)-H(11)	118.8
C(17)-C(11)-H(11)	118.8
C(16)-C(12)-C(18)	118.8(12)
C(16)-C(12)-C(6)	122.9(15)
C(18)-C(12)-C(6)	118.3(14)
C(3)-C(13)-C(7)	109.5(9)
C(3)-C(13)-H(13A)	109.8
C(7)-C(13)-H(13A)	109.8

C(3)-C(13)-H(13B)	109.8
C(7)-C(13)-H(13B)	109.7
H(13A)-C(13)-H(13B)	108.2
C(7)-C(14)-C(23)#1	118.1(12)
C(7)-C(14)-H(14)	121.0
C(23)#1-C(14)-H(14)	121.0
C(7)-C(15)-C(22)#1	124.7(12)
C(7)-C(15)-O(1)	120.5(10)
C(22)#1-C(15)-O(1)	114.8(10)
C(3)-C(16)-C(12)	118.4(13)
C(3)-C(16)-H(16)	120.8
C(12)-C(16)-H(16)	120.8
C(11)-C(17)-C(10)	115.5(15)
C(11)-C(17)-H(17)	122.2
C(10)-C(17)-H(17)	122.3
C(9)-C(18)-C(12)	120.7(12)
C(9)-C(18)-H(18)	119.7
C(12)-C(18)-H(18)	119.7
O(2)-C(19)-H(19A)	109.5
O(2)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
O(2)-C(19)-H(19C)	109.4
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(10)-C(20)-C(21)	119.6(14)
C(10)-C(20)-H(20)	120.2
C(21)-C(20)-H(20)	120.2
C(20)-C(21)-C(24)	122.9(13)
C(20)-C(21)-H(21)	118.6
C(24)-C(21)-H(21)	118.6
C(15)#1-C(22)-C(5)	117.8(11)
C(15)#1-C(22)-C(4)	123.3(11)
C(5)-C(22)-C(4)	118.8(11)
C(5)-C(23)-O(2)	125.2(12)
C(5)-C(23)-C(14)#1	121.0(12)
O(2)-C(23)-C(14)#1	113.8(12)
C(11)-C(24)-C(21)	118.0(13)
C(11)-C(24)-C(8)	122.4(12)
C(21)-C(24)-C(8)	119.5(12)

Symmetry transformations used to generate equivalent atoms: #1 y,x,-z

Table A.1.4. Anisotropic displacement parameters (A^2 x 10^3) for 246C-I

	U11	U22	U33	U23	U13	U12
O(1)	25(5)	56(6)	43(4)	11(5)	3(4)	5(4)
O(2)	67(6)	66(7)	44(5)	-22(5)	-15(5)	14(5)
C(3)	35(8)	32(8)	34(7)	-5(6)	-10(6)	5(7)
C(4)	73(10)	47(9)	19(7)	-4(6)	-11(7)	5(8)
C(5)	41(8)	50(9)	46(8)	14(7)	-6(7)	7(7)
C(6)	56(10)	75(12)	76(11)	-7(9)	-20(11)	-25(8)
C(7)	51(9)	39(8)	28(7)	-3(6)	2(7)	-4(7)
C(8)	29(7)	43(8)	27(6)	-10(6)	7(6)	8(6)
C(9)	38(8)	36(8)	39(8)	13(7)	-1(6)	6(7)
C(10)	121(15)	20(8)	45(9)	-5(7)	36(10)	-3(10)
C(11)	81(11)	35(9)	44(9)	0(7)	-1(9)	5(9)
C(12)	57(10)	61(11)	61(10)	39(9)	-29(8)	3(8)
C(13)	26(8)	50(8)	27(7)	6(6)	-6(5)	-9(7)
C(14)	40(9)	31(8)	64(9)	6(7)	0(8)	4(7)
C(15)	44(8)	23(7)	39(7)	0(6)	5(7)	11(6)
C(16)	55(10)	50(10)	45(9)	-5(8)	0(8)	16(8)
C(17)	70(12)	69(12)	54(9)	-10(9)	33(8)	-13(10)
C(18)	47(9)	49(9)	30(7)	-12(7)	-4(7)	21(7)
C(19)	100(16)	80(14)	44(9)	-27(10)	-20(9)	15(11)
C(20)	51(9)	58(11)	39(8)	15(7)	3(8)	8(10)
C(21)	42(9)	65(11)	30(7)	0(7)	-2(7)	-2(8)
C(22)	55(9)	38(8)	37(8)	-3(7)	4(7)	18(7)
C(23)	52(9)	45(9)	47(9)	-4(8)	14(8)	0(8)
C(24)	37(8)	48(9)	17(6)	-1(6)	0(6)	0(8)

The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table A.1.5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for 246C-I

	x	y	z	U(eq)	Occ.
H(1)	7486	7983	382	250(130)	1
H(4A)	7274	7873	-2727	40(30)	1
H(4B)	7877	8384	-2134	50(40)	1
H(5)	7834	6570	-3186	340(140)	1
H(6A)	4619	6470	-344	150(80)	1
H(6B)	5360	5912	-702	700(400)	1
H(6C)	4711	6352	-1300	30(30)	1
H(10)	8150	11523	-1682	40(30)	1
H(11)	8263	9116	-846	120(70)	1
H(13A)	5480	9539	270	50(40)	1
H(13B)	6463	9705	185	0(20)	1
H(14)	5056	9199	1651	80(50)	1
H(16)	5157	7909	139	10(30)	1
H(17)	8980	10393	-1139	40(40)	1
H(18)	6338	6830	-1834	0(20)	1
H(19A)	8392	4728	-4269	80(50)	1
H(19B)	8509	5715	-4170	100(60)	1
H(19C)	7661	5278	-3883	80(50)	1
H(20)	6736	11395	-1801	0(20)	1
H(21)	6106	10127	-1567	160(80)	1

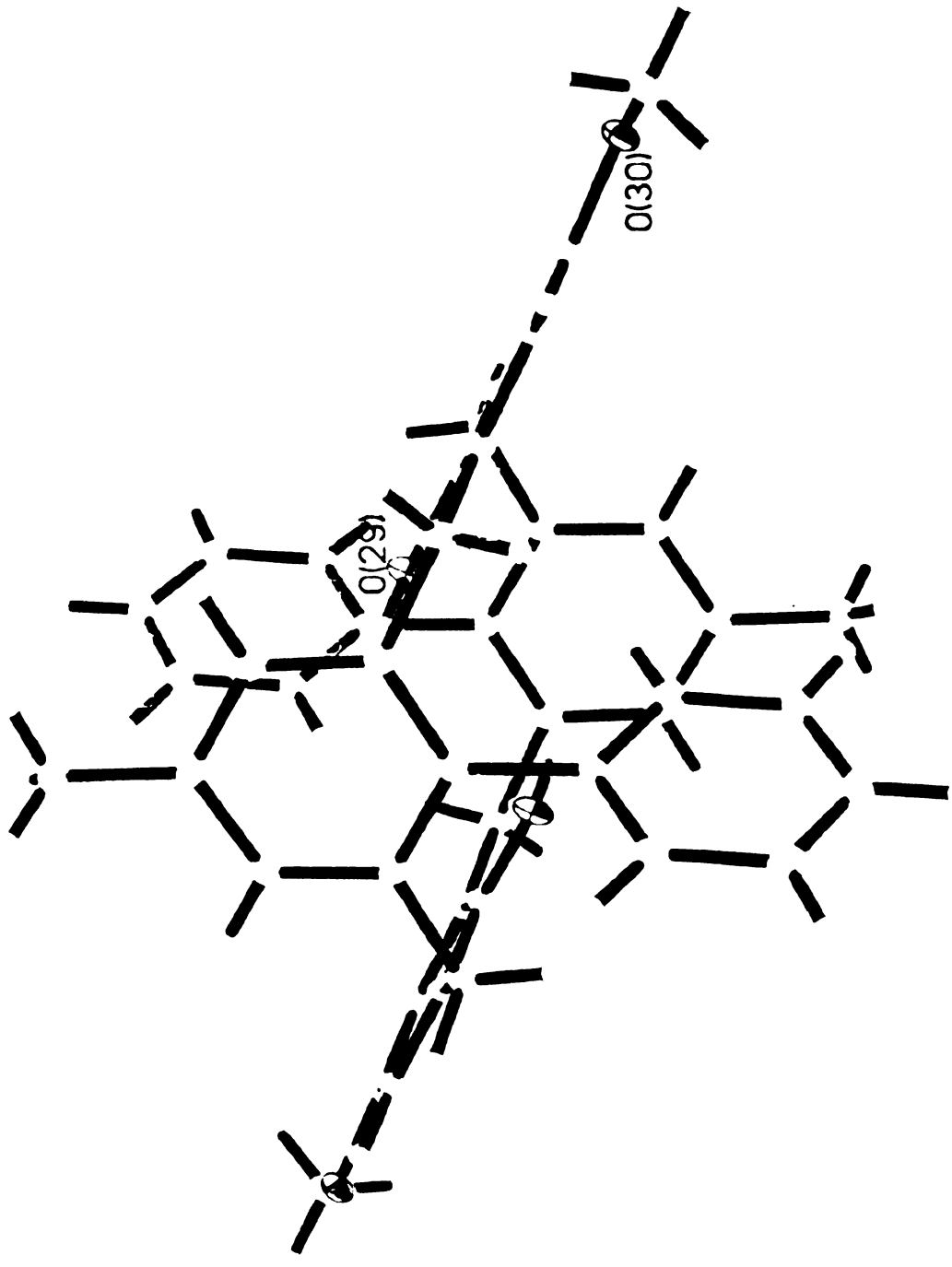


Fig A.3 Structure of 246C-II – 1,2 Alternate

Table A.2.1. Crystal data and structure refinement for 246C-II

Identification code	3a-II
Empirical formula	C44 H40 O4
Formula weight	632.76
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 12.899(3) A b = 16.405(3) A c = 15.888(3) A alpha = 90 deg. beta = 97.61(3) deg. gamma = 90 deg.
Volume	3332.3(12) A^3
Z	4
Density (calculated)	1.261 Mg/m^3
Absorption coefficient	0.079 mm^-1
F(000)	1344
Crystal size	0.45 x 0.40 x 0.35 mm
Theta range for data collection	2.02 to 28.34 deg.
Index ranges	-16<=h<=17, -21<=k<=21, -21<=l<=20
Reflections collected / unique [R(int) = 0.0892]	37057 / 7755
Completeness to theta = 28.34	93.3%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7755 / 0 / 537
Goodness-of-fit on F^2	0.858
Final R indices [I>2sigma(I)]	R1 = 0.0551, wR2 = 0.1228
R indices (all data)	R1 = 0.1379, wR2 = 0.1660
Extinction coefficient	0.0026(6)
Largest diff. peak and hole	0.239 and -0.225 e.A^-3

Table A.2.2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for 246C-II

	x	y	z	U(eq)	Occ.
O(1)	5573(1)	844(1)	2(1)	33(1)	1
O(2)	9287(1)	1472(1)	-1223(1)	34(1)	1
C(5)	7459(2)	1385(1)	-1379(2)	25(1)	1
C(6)	8408(2)	1268(1)	-863(2)	25(1)	1
C(8)	4836(2)	605(1)	-1765(1)	22(1)	1
C(9)	6548(2)	947(1)	-236(2)	24(1)	1
C(10)	6168(2)	886(2)	2005(2)	31(1)	1
C(11)	5477(2)	1379(1)	-1602(2)	24(1)	1
C(12)	6622(2)	278(2)	1566(1)	27(1)	1
C(16)	6528(2)	1232(1)	-1070(1)	22(1)	1
C(17)	7488(2)	800(1)	282(2)	25(1)	1
C(21)	7608(2)	473(2)	1188(2)	33(1)	1
C(22)	8416(2)	973(1)	-50(2)	26(1)	1
C(23)	3863(2)	495(1)	-1469(1)	24(1)	1
C(27)	3369(2)	1181(1)	-1043(2)	26(1)	1
C(31)	5267(2)	-28(2)	-2187(1)	28(1)	1
C(34)	5233(2)	771(2)	2331(2)	32(1)	1
C(35)	10272(2)	1349(2)	-721(2)	41(1)	1
C(40)	3292(2)	1178(2)	-179(2)	32(1)	1
C(41)	4767(4)	1437(2)	2816(3)	52(1)	1
C(43)	2566(2)	2525(2)	-266(2)	45(1)	1
C(45)	2895(2)	1845(2)	205(2)	41(1)	1
C(46)	2612(2)	2529(2)	-1124(2)	44(1)	1
C(47)	3012(2)	1864(2)	-1513(2)	35(1)	1
O(3)	340(1)	1519(1)	4828(1)	35(1)	1
O(4)	-3130(1)	2181(1)	6399(1)	41(1)	1
C(7)	1971(2)	159(1)	5857(2)	26(1)	1
C(13)	-572(2)	1649(1)	5169(2)	26(1)	1
C(14)	-1547(2)	1713(1)	4675(2)	25(1)	1
C(15)	-2412(2)	1893(1)	5082(2)	28(1)	1
C(18)	1158(2)	-71(1)	6408(1)	24(1)	1
C(19)	-2308(2)	1998(2)	5954(2)	31(1)	1
C(20)	-1338(2)	1891(2)	6437(2)	31(1)	1
C(24)	1052(2)	-903(1)	6611(1)	26(1)	1
C(25)	526(2)	502(1)	6757(1)	26(1)	1

C(26)	551(2)	1421(1)	6573(2)	29(1)	1
C(28)	-184(2)	235(2)	7284(2)	28(1)	1
C(29)	2974(2)	360(2)	6221(2)	35(1)	1
C(30)	1772(2)	114(2)	4973(2)	32(1)	1
C(32)	-296(2)	-576(2)	7492(2)	30(1)	1
C(33)	330(2)	-1137(2)	7146(2)	29(1)	1
C(36)	-469(2)	1690(1)	6054(2)	28(1)	1
C(37)	-1713(2)	1564(2)	3725(2)	30(1)	1
C(38)	3559(2)	422(2)	4854(2)	48(1)	1
C(39)	3759(2)	487(2)	5723(2)	48(1)	1
C(42)	-4146(2)	2175(2)	5927(2)	45(1)	1
C(44)	-1071(3)	-842(2)	8075(2)	42(1)	1
C(51)	2559(2)	242(2)	4479(2)	41(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table A.2.3. Bond lengths [A] and angles [deg] for 246C-II

O(1)-C(9)	1.372(3)
O(1)-H(1)	0.86(3)
O(2)-C(6)	1.377(3)
O(2)-C(35)	1.422(3)
C(5)-C(16)	1.379(3)
C(5)-C(6)	1.393(3)
C(5)-H(5A)	0.9300
C(6)-C(22)	1.378(3)
C(8)-C(31)	1.391(3)
C(8)-C(23)	1.409(3)
C(8)-C(11)	1.519(3)
C(9)-C(17)	1.392(3)
C(9)-C(16)	1.403(3)
C(10)-C(34)	1.386(3)
C(10)-C(12)	1.390(3)
C(10)-H(10A)	0.9300
C(11)-C(16)	1.520(3)
C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700
C(12)-C(23)#1	1.413(3)
C(12)-C(21)	1.510(3)
C(17)-C(22)	1.400(3)
C(17)-C(21)	1.525(3)
C(21)-H(21A)	0.97(3)
C(21)-H(21B)	0.99(3)
C(22)-H(22A)	0.9300
C(23)-C(12)#1	1.413(3)
C(23)-C(27)	1.498(3)
C(27)-C(40)	1.389(3)
C(27)-C(47)	1.391(3)
C(31)-C(34)#1	1.384(3)
C(31)-H(31A)	0.9300
C(34)-C(31)#1	1.384(3)
C(34)-C(41)	1.507(4)
C(35)-H(35A)	0.99(3)
C(35)-H(35B)	0.99(3)
C(35)-H(35C)	1.05(3)
C(40)-C(45)	1.384(4)
C(40)-H(40A)	0.9300
C(41)-H(41A)	0.89(7)
C(41)-H(41B)	0.99(7)
C(41)-H(41C)	1.09(11)

C(41)-H(41D)	1.05(5)
C(41)-H(41E)	1.04(5)
C(41)-H(41F)	0.99(7)
C(43)-C(46)	1.373(4)
C(43)-C(45)	1.378(4)
C(43)-H(43A)	0.9300
C(45)-H(45A)	0.9300
C(46)-C(47)	1.386(4)
C(46)-H(46A)	0.9300
C(47)-H(47A)	0.9300
O(3)-C(13)	1.375(3)
O(3)-H(3A)	0.8200
O(4)-C(19)	1.383(3)
O(4)-C(42)	1.420(3)
C(7)-C(29)	1.385(3)
C(7)-C(30)	1.396(3)
C(7)-C(18)	1.500(3)
C(13)-C(36)	1.397(3)
C(13)-C(14)	1.396(3)
C(14)-C(15)	1.392(3)
C(14)-C(37)	1.515(3)
C(15)-C(19)	1.386(3)
C(15)-H(15A)	0.9300
C(18)-C(25)	1.405(3)
C(18)-C(24)	1.414(3)
C(19)-C(20)	1.390(4)
C(20)-C(36)	1.384(3)
C(20)-H(20)	0.97(3)
C(24)-C(33)	1.396(3)
C(24)-C(37)#2	1.519(3)
C(25)-C(28)	1.391(3)
C(25)-C(26)	1.536(3)
C(26)-C(36)	1.522(3)
C(26)-H(26A)	0.9700
C(26)-H(26B)	0.9700
C(28)-C(32)	1.382(3)
C(28)-H(28A)	0.9300
C(29)-C(39)	1.381(4)
C(29)-H(29A)	0.9300
C(30)-C(51)	1.379(4)
C(30)-H(30A)	0.9300
C(32)-C(33)	1.385(3)
C(32)-C(44)	1.514(4)
C(33)-H(33A)	0.9300
C(37)-C(24)#2	1.519(3)
C(37)-H(37A)	0.9700
C(37)-H(37B)	0.9700
C(38)-C(51)	1.379(4)

C(38)-C(39)	1.375(4)
C(38)-H(38A)	0.9300
C(39)-H(39A)	0.9300
C(42)-H(42A)	0.9600
C(42)-H(42B)	0.9600
C(42)-H(42C)	0.9600
C(44)-H(44A)	0.99(7)
C(44)-H(44B)	0.93(8)
C(44)-H(44C)	0.99(6)
C(44)-H(44D)	1.09(5)
C(44)-H(44E)	1.00(5)
C(44)-H(44F)	1.08(6)
C(51)-H(51A)	0.9300

C(9)-O(1)-H(1)	114(2)
C(6)-O(2)-C(35)	117.2(2)
C(16)-C(5)-C(6)	120.3(2)
C(16)-C(5)-H(5A)	119.8
C(6)-C(5)-H(5A)	119.8
C(22)-C(6)-O(2)	124.7(2)
C(22)-C(6)-C(5)	119.8(2)
O(2)-C(6)-C(5)	115.5(2)
C(31)-C(8)-C(23)	119.7(2)
C(31)-C(8)-C(11)	117.6(2)
C(23)-C(8)-C(11)	122.6(2)
O(1)-C(9)-C(17)	125.1(2)
O(1)-C(9)-C(16)	113.5(2)
C(17)-C(9)-C(16)	121.4(2)
C(34)-C(10)-C(12)	122.4(2)
C(34)-C(10)-H(10A)	118.8
C(12)-C(10)-H(10A)	118.8
C(8)-C(11)-C(16)	112.79(18)
C(8)-C(11)-H(11A)	109.0
C(16)-C(11)-H(11A)	109.0
C(8)-C(11)-H(11B)	109.0
C(16)-C(11)-H(11B)	109.0
H(11A)-C(11)-H(11B)	107.8
C(10)-C(12)-C(23)#1	119.2(2)
C(10)-C(12)-C(21)	118.7(2)
C(23)#1-C(12)-C(21)	122.1(2)
C(5)-C(16)-C(9)	119.3(2)
C(5)-C(16)-C(11)	121.9(2)
C(9)-C(16)-C(11)	118.8(2)
C(9)-C(17)-C(22)	117.7(2)
C(9)-C(17)-C(21)	126.1(2)
C(22)-C(17)-C(21)	116.3(2)
C(12)-C(21)-C(17)	117.7(2)
C(12)-C(21)-H(21A)	107.8(15)

C(17)-C(21)-H(21A)	108.0(15)
C(12)-C(21)-H(21B)	108.6(15)
C(17)-C(21)-H(21B)	108.5(15)
H(21A)-C(21)-H(21B)	106(2)
C(6)-C(22)-C(17)	121.5(2)
C(6)-C(22)-H(22A)	119.2
C(17)-C(22)-H(22A)	119.2
C(8)-C(23)-C(12)#1	118.6(2)
C(8)-C(23)-C(27)	120.4(2)
C(12)#1-C(23)-C(27)	120.9(2)
C(40)-C(27)-C(47)	118.1(2)
C(40)-C(27)-C(23)	122.3(2)
C(47)-C(27)-C(23)	119.6(2)
C(34)#1-C(31)-C(8)	122.0(2)
C(34)#1-C(31)-H(31A)	119.0
C(8)-C(31)-H(31A)	119.0
C(31)#1-C(34)-C(10)	117.8(2)
C(31)#1-C(34)-C(41)	120.9(3)
C(10)-C(34)-C(41)	121.2(3)
O(2)-C(35)-H(35A)	110.6(17)
O(2)-C(35)-H(35B)	104.3(16)
H(35A)-C(35)-H(35B)	112(2)
O(2)-C(35)-H(35C)	111.8(17)
H(35A)-C(35)-H(35C)	111(2)
H(35B)-C(35)-H(35C)	108(2)
C(45)-C(40)-C(27)	120.7(3)
C(45)-C(40)-H(40A)	119.6
C(27)-C(40)-H(40A)	119.6
C(34)-C(41)-H(41A)	110(4)
C(34)-C(41)-H(41B)	114(4)
H(41A)-C(41)-H(41B)	101(6)
C(34)-C(41)-H(41C)	111(5)
H(41A)-C(41)-H(41C)	114(7)
H(41B)-C(41)-H(41C)	107(6)
C(34)-C(41)-H(41D)	112(2)
H(41A)-C(41)-H(41D)	138(5)
H(41B)-C(41)-H(41D)	61(4)
H(41C)-C(41)-H(41D)	50(6)
C(34)-C(41)-H(41E)	110(3)
H(41A)-C(41)-H(41E)	67(4)
H(41B)-C(41)-H(41E)	135(5)
H(41C)-C(41)-H(41E)	51(6)
H(41D)-C(41)-H(41E)	98(4)
C(34)-C(41)-H(41F)	111(4)
H(41A)-C(41)-H(41F)	50(5)
H(41B)-C(41)-H(41F)	54(4)
H(41C)-C(41)-H(41F)	138(6)
H(41D)-C(41)-H(41F)	111(5)

H(41E)-C(41)-H(41F)	113(5)
C(46)-C(43)-C(45)	119.5(3)
C(46)-C(43)-H(43A)	120.3
C(45)-C(43)-H(43A)	120.3
C(43)-C(45)-C(40)	120.5(3)
C(43)-C(45)-H(45A)	119.8
C(40)-C(45)-H(45A)	119.8
C(43)-C(46)-C(47)	120.4(3)
C(43)-C(46)-H(46A)	119.8
C(47)-C(46)-H(46A)	119.8
C(46)-C(47)-C(27)	120.8(3)
C(46)-C(47)-H(47A)	119.6
C(27)-C(47)-H(47A)	119.6
C(13)-O(3)-H(3A)	109.5
C(19)-O(4)-C(42)	116.5(2)
C(29)-C(7)-C(30)	118.0(2)
C(29)-C(7)-C(18)	120.2(2)
C(30)-C(7)-C(18)	121.6(2)
O(3)-C(13)-C(36)	115.5(2)
O(3)-C(13)-C(14)	123.0(2)
C(36)-C(13)-C(14)	121.5(2)
C(15)-C(14)-C(13)	118.2(2)
C(15)-C(14)-C(37)	118.7(2)
C(13)-C(14)-C(37)	123.1(2)
C(19)-C(15)-C(14)	120.9(2)
C(19)-C(15)-H(15A)	119.5
C(14)-C(15)-H(15A)	119.5
C(25)-C(18)-C(24)	118.5(2)
C(25)-C(18)-C(7)	123.3(2)
C(24)-C(18)-C(7)	118.1(2)
O(4)-C(19)-C(20)	116.1(2)
O(4)-C(19)-C(15)	124.0(2)
C(20)-C(19)-C(15)	119.8(2)
C(36)-C(20)-C(19)	120.7(2)
C(36)-C(20)-H(20)	121.1(15)
C(19)-C(20)-H(20)	118.1(15)
C(33)-C(24)-C(18)	119.8(2)
C(33)-C(24)-C(37)#2	118.0(2)
C(18)-C(24)-C(37)#2	122.2(2)
C(28)-C(25)-C(18)	119.2(2)
C(28)-C(25)-C(26)	117.1(2)
C(18)-C(25)-C(26)	123.6(2)
C(36)-C(26)-C(25)	110.42(19)
C(36)-C(26)-H(26A)	109.6
C(25)-C(26)-H(26A)	109.6
C(36)-C(26)-H(26B)	109.6
C(25)-C(26)-H(26B)	109.6
H(26A)-C(26)-H(26B)	108.1

C(32)-C(28)-C(25)	123.0(2)
C(32)-C(28)-H(28A)	118.5
C(25)-C(28)-H(28A)	118.5
C(39)-C(29)-C(7)	120.8(3)
C(39)-C(29)-H(29A)	119.6
C(7)-C(29)-H(29A)	119.6
C(51)-C(30)-C(7)	120.9(2)
C(51)-C(30)-H(30A)	119.6
C(7)-C(30)-H(30A)	119.6
C(28)-C(32)-C(33)	117.4(2)
C(28)-C(32)-C(44)	121.5(2)
C(33)-C(32)-C(44)	121.1(3)
C(32)-C(33)-C(24)	122.0(2)
C(32)-C(33)-H(33A)	119.0
C(24)-C(33)-H(33A)	119.0
C(20)-C(36)-C(13)	118.6(2)
C(20)-C(36)-C(26)	121.6(2)
C(13)-C(36)-C(26)	119.4(2)
C(14)-C(37)-C(24)#2	117.0(2)
C(14)-C(37)-H(37A)	108.0
C(24)#2-C(37)-H(37A)	108.0
C(14)-C(37)-H(37B)	108.0
C(24)#2-C(37)-H(37B)	108.0
H(37A)-C(37)-H(37B)	107.3
C(51)-C(38)-C(39)	119.3(3)
C(51)-C(38)-H(38A)	120.3
C(39)-C(38)-H(38A)	120.3
C(38)-C(39)-C(29)	120.6(3)
C(38)-C(39)-H(39A)	119.7
C(29)-C(39)-H(39A)	119.7
O(4)-C(42)-H(42A)	109.5
O(4)-C(42)-H(42B)	109.5
H(42A)-C(42)-H(42B)	109.5
O(4)-C(42)-H(42C)	109.5
H(42A)-C(42)-H(42C)	109.5
H(42B)-C(42)-H(42C)	109.5
C(32)-C(44)-H(44A)	113(4)
C(32)-C(44)-H(44B)	107(4)
H(44A)-C(44)-H(44B)	106(6)
C(32)-C(44)-H(44C)	112(3)
H(44A)-C(44)-H(44C)	102(5)
H(44B)-C(44)-H(44C)	117(6)
C(32)-C(44)-H(44D)	109(2)
H(44A)-C(44)-H(44D)	138(4)
H(44B)-C(44)-H(44D)	57(5)
H(44C)-C(44)-H(44D)	65(4)
C(32)-C(44)-H(44E)	112(3)
H(44A)-C(44)-H(44E)	53(4)

H(44B)-C(44)-H(44E)	55(5)
H(44C)-C(44)-H(44E)	135(4)
H(44D)-C(44)-H(44E)	108(4)
C(32)-C(44)-H(44F)	108(3)
H(44A)-C(44)-H(44F)	54(4)
H(44B)-C(44)-H(44F)	144(5)
H(44C)-C(44)-H(44F)	52(4)
H(44D)-C(44)-H(44F)	115(4)
H(44E)-C(44)-H(44F)	105(4)
C(38)-C(51)-C(30)	120.3(3)
C(38)-C(51)-H(51A)	119.8
C(30)-C(51)-H(51A)	119.8

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y,-z #2 -x,-y,-z+1

Table A.2.4. Anisotropic displacement parameters (A^2 x 10^3) for 246C-II

	U11	U22	U33	U23	U13	U12
O(1)	21(1)	52(1)	25(1)	10(1)	3(1)	-5(1)
O(2)	24(1)	45(1)	35(1)	-2(1)	12(1)	-4(1)
C(5)	30(1)	24(1)	22(1)	-1(1)	6(1)	-4(1)
C(6)	24(1)	22(1)	31(1)	-6(1)	10(1)	-3(1)
C(8)	24(1)	24(1)	18(1)	4(1)	-3(1)	-1(1)
C(9)	23(1)	22(1)	27(1)	0(1)	5(1)	-5(1)
C(10)	40(2)	26(1)	24(1)	2(1)	-1(1)	-9(1)
C(11)	26(1)	24(1)	22(1)	4(1)	3(1)	0(1)
C(12)	29(1)	32(1)	18(1)	6(1)	-3(1)	-2(1)
C(16)	24(1)	18(1)	24(1)	0(1)	4(1)	-3(1)
C(17)	28(1)	21(1)	26(1)	0(1)	3(1)	-4(1)
C(21)	27(1)	40(2)	29(1)	8(1)	-4(1)	-8(1)
C(22)	22(1)	26(1)	31(1)	-1(1)	2(1)	0(1)
C(23)	24(1)	28(1)	19(1)	2(1)	-1(1)	0(1)
C(27)	18(1)	29(1)	32(1)	1(1)	2(1)	0(1)
C(31)	31(1)	30(1)	24(1)	1(1)	6(1)	0(1)
C(34)	42(2)	30(1)	25(1)	-1(1)	2(1)	-2(1)
C(35)	22(2)	56(2)	45(2)	-2(2)	8(1)	-5(1)
C(40)	29(1)	35(2)	34(2)	0(1)	5(1)	1(1)
C(41)	74(3)	37(2)	50(2)	-14(2)	23(2)	7(2)
C(43)	29(2)	40(2)	68(2)	-9(2)	15(1)	3(1)
C(45)	34(2)	48(2)	42(2)	-8(1)	11(1)	1(1)
C(46)	32(2)	32(2)	69(2)	10(1)	9(1)	6(1)
C(47)	28(1)	39(2)	40(2)	9(1)	7(1)	1(1)
O(3)	26(1)	52(1)	28(1)	-3(1)	5(1)	-1(1)
O(4)	36(1)	50(1)	38(1)	-1(1)	12(1)	11(1)
C(7)	28(1)	24(1)	26(1)	2(1)	3(1)	1(1)
C(13)	27(1)	21(1)	31(1)	0(1)	6(1)	-2(1)
C(14)	31(1)	19(1)	26(1)	2(1)	6(1)	2(1)
C(15)	30(1)	25(1)	29(1)	2(1)	3(1)	3(1)
C(18)	24(1)	29(1)	19(1)	-2(1)	-2(1)	-2(1)
C(19)	34(2)	26(1)	35(2)	-1(1)	12(1)	5(1)
C(20)	40(2)	26(1)	27(1)	-3(1)	7(1)	2(1)
C(24)	27(1)	28(1)	22(1)	0(1)	1(1)	1(1)
C(25)	26(1)	28(1)	22(1)	-1(1)	-3(1)	-1(1)
C(26)	33(1)	26(1)	28(1)	-7(1)	1(1)	-3(1)

C(28)	29(1)	32(1)	24(1)	-2(1)	2(1)	4(1)
C(29)	31(2)	41(2)	32(2)	10(1)	0(1)	-2(1)
C(30)	38(2)	27(1)	30(1)	-1(1)	4(1)	-2(1)
C(32)	27(1)	38(2)	24(1)	-2(1)	3(1)	-3(1)
C(33)	31(1)	29(1)	28(1)	4(1)	1(1)	-2(1)
C(36)	33(1)	22(1)	31(1)	-3(1)	3(1)	-1(1)
C(37)	33(2)	28(1)	28(1)	4(1)	3(1)	3(1)
C(38)	44(2)	50(2)	53(2)	22(2)	23(2)	9(1)
C(39)	26(2)	63(2)	54(2)	25(2)	4(1)	-4(1)
C(42)	37(2)	54(2)	48(2)	-3(2)	16(1)	2(1)
C(44)	41(2)	50(2)	38(2)	0(2)	14(2)	-3(2)
C(51)	60(2)	36(2)	30(2)	5(1)	14(1)	6(1)

The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table A.2.5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for 246C-II

	x	y	z	U(eq)	Occ.
H(1)	5570(30)	650(20)	510(20)	72(11)	1
H(5A)	7454	1566	-1934	29(7)	1
H(10A)	6503	1387	2082	29(7)	1
H(11A)	5084	1770	-1314	26(6)	1
H(11B)	5592	1615	-2143	27(6)	1
H(22A)	9054	887	286	29(7)	1
H(31A)	5910	51	-2378	27(6)	1
H(35A)	10330(20)	1690(18)	-204(19)	51(9)	1
H(35B)	10790(20)	1507(16)	-1099(17)	41(8)	1
H(35C)	10400(20)	730(20)	-562(19)	63(10)	1
H(40A)	3510	722	145	45(8)	1
H(41A)	5200(50)	1860(40)	2890(50)	44(19)	0.50
H(41B)	4700(70)	1300(40)	3410(50)	60(20)	0.50
H(41C)	3990(90)	1600(70)	2510(70)	120(40)	0.50
H(41D)	4030(40)	1280(30)	2970(30)	15(12)	0.50
H(41E)	4540(50)	1920(30)	2420(30)	21(13)	0.50
H(41F)	5250(50)	1600(50)	3330(50)	46(19)	0.50
H(43A)	2314	2977	-4	54(9)	1
H(45A)	2851	1835	784	46(8)	1
H(46A)	2374	2981	-1447	55(9)	1
H(47A)	3042	1875	-2094	28(7)	1
H(3A)	213	1503	4309	63(11)	1
H(15A)	-3068	1942	4763	28(7)	1
H(20)	-1296(19)	1933(15)	7050(17)	34(7)	1
H(26A)	656	1720	7104	18(6)	1
H(26B)	1132	1542	6262	33(7)	1
H(28A)	-603	619	7506	35(7)	1
H(29A)	3120	410	6808	39(8)	1
H(30A)	1099	-5	4714	27(7)	1
H(33A)	267	-1687	7275	32(7)	1
H(37A)	-1581	2071	3444	24(6)	1
H(37B)	-2443	1428	3561	36(7)	1
H(38A)	4093	499	4522	55(9)	1
H(39A)	4429	617	5978	44(8)	1
H(42A)	-4653	2313	6295	49(8)	1

H(42B)	-4295	1642	5693	71(11)	1
H(42C)	-4177	2567	5476	61(10)	1
H(44A)	-1640(60)	-450(40)	8100(50)	53(19)	0.50
H(44B)	-720(60)	-860(50)	8620(50)	60(20)	0.50
H(44C)	-1460(50)	-1330(40)	7860(40)	48(17)	0.50
H(44D)	-800(30)	-1410(30)	8380(30)	11(11)	0.50
H(44E)	-1140(40)	-430(30)	8530(30)	11(11)	0.50
H(44F)	-1840(40)	-870(40)	7710(30)	29(14)	0.50
H(51A)	2415	207	3891	38(8)	1
H(21A)	8000(20)	868(16)	1553(16)	34(7)	1
H(21B)	8050(20)	-23(17)	1217(16)	41(8)	1

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