DEEP MOLECULAR BASKETS: CONVERGENT SYNTHESES OF CALIX[4]NAPHTHALENES VIA DIRECTED ortho METALLATION AND SUZUKI-MIYAURA COUPLING REACTIONS

SULTAN CHOWDHURY

Deep Molecular Baskets: Convergent Syntheses of Calix[4]naphthalenes via Directed *ortho* Metallation and Suzuki-Miyaura Coupling Reactions

by

© Sultan Chowdhury

B. Sc. University of Waterloo

Waterloo, Ontario, 1992

A thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

Memorial University of Newfoundland

St. John's, Newfoundland

Canada

September 2001

Abstract

Calix[4]naphthalenes are a new class of compounds which are analogous to the better-known calix[4]arenes, but have deeper cavities. These compounds, especially the *endo* calix[4]naphthalenes e.g., **31** can behave as "molecular baskets" in their abilities to complex with neutral guest molecules such as [60]fullerene. This thesis describes the synthesis of such deep molecular baskets.

Calix[4]naphthalene (**31**) was synthesized by self-condensation reactions of 6-*tert*-butyl-3-(hydroxymethyl)-2-naphthol (**29**). Various Lewis acids were evaluated in order to obtain **31** in higher yield. Conformational properties of **31** were studied by VT-^{1}H NMR experiments in two different deuterated solvents. Alkyl ether derivatives (**41a-41b**) of **31**, and also *tert*-butylcalix[4]naphthalene-1,3-crown **42** were synthesized, and all compounds were shown by NMR experiments to exist in *cone* conformations.

A synthetic route toward the synthesis of the C_{2v}-symmetrical "C-12" *endo* calix[4]naphthalenes e.g., **35** allowed us to evaluate the efficiency of the Suzuki-Miyaura coupling reactions for various benzylic halides and bromomethylnaphthalenes with phenyl- and naphthylboronic acids. Directed *ortho* Metallation (DoM) reactions using both *n*-butyl- and *tert*-butyllithium were evaluated for the introduction of various functional groups *ortho* to the hydroxyl group of 2-naphthol, bis(2-hydroxy-1-naphthyl)methane and their derivatives.

Synthesis of calix[4]naphthalene (**35**) was achieved using both acid- and

base-induced condensation reactions of compound **98** and aqueous formaldehyde solution. Various alkyl ether derivatives (**113a-113d**) of **35** were obtained, and their conformational properties were studied by NMR experiments. The X-ray crystal structure of **113d** revealed that it exists in a *cone* conformation as a clathrate containing two molecules of toluene located in its hydrophobic cavity.

Calix[4]naphthalene (**114**), an example of an *endo/exo*-type calixnaphthalene was synthesized using "2+2" Böhmer condensation conditions. Considerable effort was expended to synthesize *endo* calix[4]naphthalenes (**78-80**), and other calixarenes containing mixed benzene and naphthalene units (e.g., **116**) via "2+2" and/or "3+1" Böhmer conditions. Other unsuccessful attempts were made to synthesize all the possible isomers of *endo* calix[4]naphthalenes (**35a-c** and **107**) using Suzuki-Miyaura coupling reactions.

Several approaches towards modifying the lower rim of calixarenes were undertaken in order to deepen their cavities. The hydroxyl groups of **2** were derivatized to triflates **118-121** and also to nonaflate **125** in order to evaluate Suzuki-Miyaura, Stille and Pd-catalyzed carbonylative reaction conditions. The first successful syntheses aryl ether derivatives (**131-134** and **137-143**) of **2** were achieved using either Nucleophilic Aromatic Substitution (S_NAr) or Ullmann ether conditions.

Acknowledgments

I would like to extend my sincere admiration and immeasurable thanks to my supervisor, Professor Paris E. Georghiou, for his guidance, encouragement and instruction throughout the course of my research project and the writing of this thesis.

I would like to express my appreciation to Professor D. Jean Burnell, and Dr. John N. Bridson for proofreading and valuable comments and suggestions.

I would like to thank Mr. D. Miller and Dr. R. McDonald (U. of Alberta) for X-ray crystal structures determination and special thanks to Mr. Miller for variable temperature NMR experiments.

I would like to thank Ms. M. Baggs and Dr. B. Gregory for mass spectra; and also to the staff of the Chemistry Department offices and stores.

I am deeply grateful to my late father, Chowdhury Mohammad Zakariah and my mother, Zarina Chowdhury for their encouragement, love and guidance in reaching this milestone.

I am indebted to my loving wife, Afreen whose name means "happiness" for giving me happiness and also for her encouragement, support and believing in me, also grateful for accompanying me to those sleepless nights in front of the computer and helping me to complete this thesis.

I am extremely thankful to my sisters, Nazma-ara Chowdhury, Shamsa-ara Chowdhury, Moksuda Chowdhury and my brother-in-law Masihuz-zaman Chowdhury

for their sincere support and encouragement and my nephews Nazim Chowdhury, Nayeem Chowdhury and Kausar Chowdhury for their love.

Special thanks to my grandmother-in-law, Bela Ahmed, grandfather-in-law, Daliluddin Ahmed, mother-in-law, Marzina Ahmed and father-in-law, Aftabuddin Ahmed for their encouragement, love and believing in me and my brother-in-law, Arif Ahmed for his love.

I would like to extend my thanks to my friends Shahid Aziz Malik, Azeem Maherali, Jalaj Arora, Amin Assar, Dr. Malik Slassi and Dr. You Chu Wang for their support and friendship.

I would like to thank the members of the Georghiou group for their cooperation and friendship.

The financial support from Memorial University of Newfoundland, and the Chemistry Department is gratefully acknowledged.

Table of Contents

List of Figures

List of Schemes

List of Tables

Glossary of Abbreviations

Bu	*n*-butyl
bp	boiling point
calcd	calculated
conc	concentrated
COSY	correlation spectroscopy
CPK	Corey-Pauling-Koltun
d	days
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
Et	ethyl
FAB	fast atom bombardment
h	hour(s)
HMQC	hetero multiple quantum correlation
HRMS	high-resolution mass spectrum
IR	infrared
kcal	kilocalorie(s)
min	minute(s)
mm	millimeter(s)

MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance (spectroscopy)
NOED	nuclear overhauser effect difference
NR	no reaction
Pr	*n*-propyl
^{i}Pr	isopropyl
quant	Quantitative
rt	room temperature
TLC	thin layer chromatography
THF	tetrahydrofuran
THP	tetrahydropyran
TMSCl	chlorotrimethylsilane
TMS	tetramethylsilane
tert	*tertiary*
Tf	trifluoromethanesulfonyl
TFA	trifluromethanesulfonic acid

To my Loving Jaan, Afreen

my dedication to Abbajan and Ammajan

and to my family

Chapter 1

Basic Concepts of Supramolecular Chemistry and Calixarenes

1.1 Introduction

The term 'Supramolecular Chemistry' was introduced in 1978 by J. - M. Lehn with a general statement: "Just as there is a field of molecular chemistry based on a covalent bond, there is a field of supramolecular chemistry, the chemistry of molecular assemblies and of the intermolecular bond."[1] Supramolecular chemistry is the "Chemistry beyond the molecule, referring to organized structure of higher complexity which results from the association of two or more chemical species held together by intermolecular (non-covalent) interactions."[2,3]

For their pioneering research in the field of supramolecular chemistry, Lehn, along with Pedersen, and Cram were awarded the 1987 Nobel Prize in chemistry. This new field in organic chemistry has attracted an enormous amount of interest, covers a very broad area of chemical phenomena and structures, and extends to biological systems.[4] Supramolecular chemistry can be divided into two major aspects: a) the organization of molecular units into supramolecular assemblies, also called supramolecular arrays, i.e., "polymolecular species that result from the spontaneous association of a large undefined number of components;" and b) well defined to discrete oligomolecular entities that result from the intermolecular association of a few components.[2,3,4] In the solid state, both supramolecules and supramolecular arrays can associate with one another to form macroscopic

conglomerates, or a supramolecular structure of higher order.[4]

Therefore, according to the definition of supramolecular chemistry, the smallest supramolecule can be a dimer, while a polymeric aggregate can contain an infinite number of building blocks held together by non-covalent intermolecular interactions, *i.e.*, the supramolecular array. In both cases, the spatial arrangement between the individual molecular units and the type of forces which hold them together define the supramolecular architecture and determine their properties. There are a number of types of non-covalent interactions that can operate between the building blocks of a supramolecular system. They include the following: a) electrostatic forces (ion-ion, ion-dipole and dipole-dipole); b) hydrogen bonding; c) π-π stacking interactions; d) dispersion and induction forces (Van der Waals forces); e) hydrophobic or solvophobic effects; and f) metal-ion coordination. Intermolecular forces, in general, are weaker than covalent bonds, therefore supramolecular species are in general thermodynamically less stable, kinetically more labile and dynamically more flexible than molecular species. These non-covalent interactions can be used individually, or in a cooperative manner, to form an energetically stable supramolecular architecture. Thus, one can say that "supramolecules, therefore, are to molecules and their intermolecular bonds what molecules are to atoms and their covalent bonds."[1]

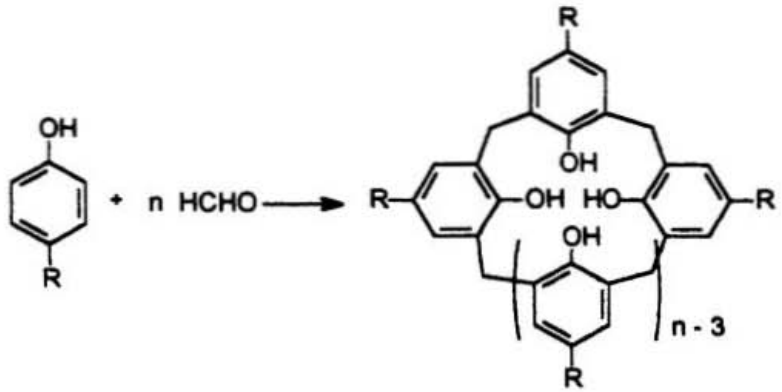
1.2 Molecular recognition and host-guest interactions

One of the aims of supramolecular chemistry is to use synthetic molecules to

mimic biological processes. The discovery of crown ethers by Pedersen[5] in 1968, showing that these macrocyclic molecules have a high affinity for the alkali metal cations has led to the emergence of molecular recognition as a discrete branch of chemistry. Molecular recognition means that the information required for the complexation process is stored in the binding sites of the interacting molecules. The binding sites are characterized by steric or geometric properties (i.e., shape, size) as well as by electronic properties of each of the interacting species. The phenomenon of molecular recognition is well-illustrated by the complexation between crown ethers and alkali metal ions.[4] More recently, the vancomycin group of antibiotics are examples of biologically active molecules,[6] which act through a relatively simple molecular recognition process. Stoddart *et al.*[7] demonstrated that weak intermolecular forces such as hydrogen bonding and π-π interactions can be used in the synthesis of supramolecules such as catenanes and rotaxanes. These new supramolecules exemplify the importance of *preorganization* in the host and *complementarity* between the host and the guest. Gutsche developed a new strategy for the synthesis of artificial receptors for specific target molecules by using calixarenes, based on the fact that molecular recognition is an important feature in bioorganic and supramolecular chemistry.

1.3 History of calixarenes

Calixarenes are [1$_n$]metacyclophanes named by Gutsche[8] from the Greek word "calix " meaning "vase". The name was adopted originally for cyclic oligomers

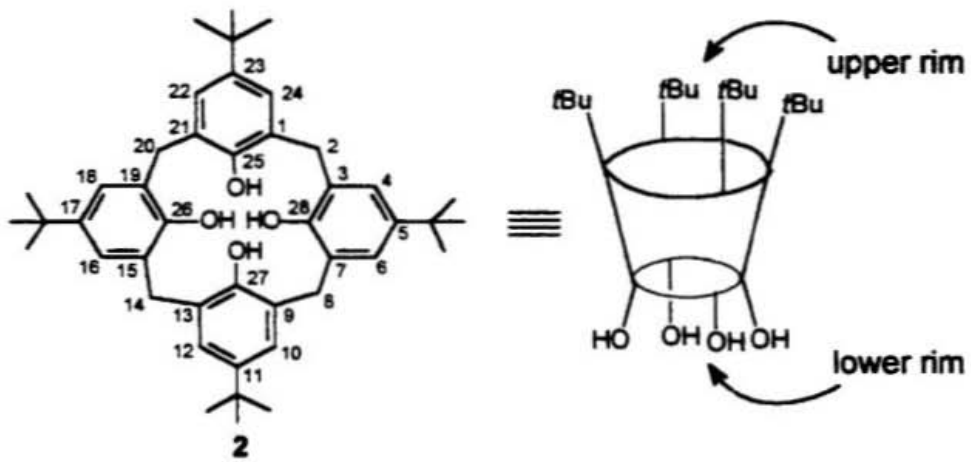


1: R = H; n = 4
2: R = *t*-Bu; n = 4
3: R = *t*-Bu; n = 6
4: R = *t*-Bu; n = 8

Scheme 1.1 Synthesis of calixarenes

obtained from the condensation of *para*-substituted phenols and formaldehyde (Scheme 1.1). The term is now applied in a more generic manner and is currently used to describe a wide variety of structurally-related types of macrocyclic molecules.[9] In the early 1940's, Zinke and coworkers[10] reported obtaining a "resinous tar," which they thought to be cyclic tetramer, from the based-induced reaction of *para*-alkylphenols with formaldehyde. Re-investigation of Zinke's work by Cornforth and coworkers[11] in the 1950's indicated that the "resinous tar" was a mixture of cyclic oligomers of the alkylphenols and formaldehyde.

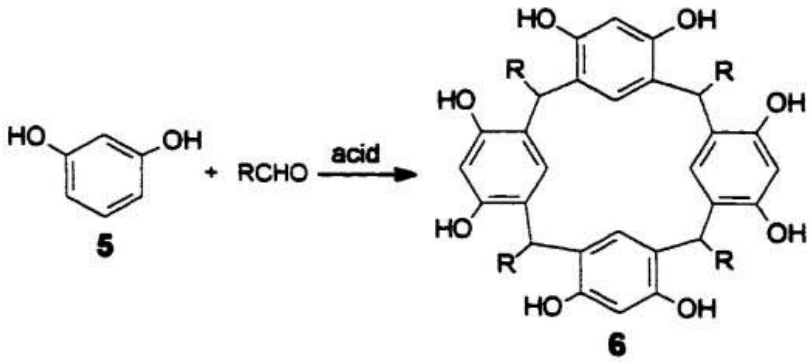
In the mid 1970's, Gutsche[5] confirmed the work of Cornforth and identified the mixture to contain a cyclic tetramer, a cyclic hexamer and a cyclic octamer. Gutsche introduced the name "calixarene" to these cyclic compounds, which were named calix[4]arene (**1**), calix[6]arene and calix[8]arene, respectively, where the bracketed



2

Figure 1.1 Nomenclature of calix[4]arene

number between "calix" and "arene" specifies the number of repeating units.[8] During the mid 1980's, Gutsche and his group[12] developed simple and reproducible one-pot procedures for the synthesis of *para-tert*-butylcalix[4]arene (**2**), *para-tert*-butylcalix[6]arene (**3**) and *para-tert*-butylcalix[8]arene (**4**) in good-to-excellent yields from less than a gram to many kilograms. In addition to these three major *para-tert*-butylcalixarenes, a number of other calixarenes (n = 5 - 20) have been obtained and fully characterized following a 'one-pot' synthesis, via either base- or acid-catalyzed reactions of *para-tert*-butylphenol and formaldehyde.[9] According to "calixarene" nomenclature, *para-tert*-butylcalix[4]arene (**2**) is named 5,11,17,23-tetra-*tert*-butylcalix[4]arene-25,26,27,28-tetrol (Figure 1.1),[8] whereas the Chemical Abstracts name for the same compound is: 5,11,17,23-tetrakis(1,1-dimethylethyl)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene.

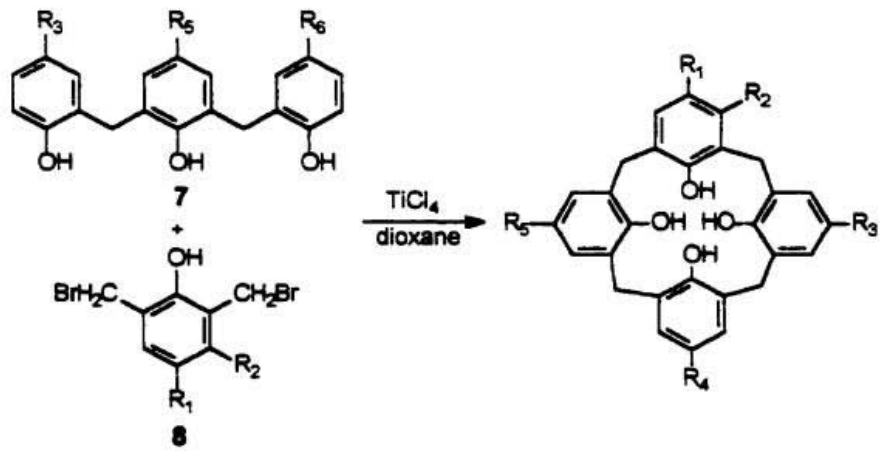


Scheme 1.2 Synthesis of calixresorcin[4]arenes

The two major classes of calixarenes[9] are (a) those derived from *para*-substituted phenols and (b) those derived from resorcinol (**5**) which are better-known as resorcin[4]arenes[12] or calixresorcin[4]arenes (**6**) (Scheme 1.2). These two classes of calixarenes can be differentiated by the orientation of the hydroxyl groups with respect to the macrocyclic ring. In general, *endo* calix[4]arenes are those which are obtained from condensation of *para*-alkylphenols and formaldehyde, and have their hydroxyl groups oriented towards the interior of the macrocyclic ring, the "annulus". Calixresorcin[4]arenes (**6**), on the other hand, are synthesized from the condensation of resorcinol (**5**) and aldehydes, and their hydroxyl groups are oriented away from the annulus, and are examples of *exo* calixarenes.

By analogy with the shape of a vase, calixarene structures are generally depicted with the aryl carbon, usually carrying an oxygen functional group, pointing downward and the aryl *para* carbon pointing upward between the methylene groups. Thus, the face bearing the *endo* hydroxyl groups is termed the 'lower rim', while the face bearing the aryl *para* substituents is termed the 'upper rim' (Figure 1.1).

The isolation of calixarenes by direct reaction of phenol and formaldehyde is unsatisfactory due to excessive formation of polymers. On the other hand, blocking the *para* position of phenol with alkyl or aryl substituents faciliates the isolation of calixarenes. Removal of the *tert*-butyl groups with $AlCl_3$ permits the parent calixarenes to be obtained in high yield.[13] However, in order to prepare diversely substituted calixarenes, stepwise synthetic approaches have been extensively studied by Böhmer and coworkers[14] and other groups.[9]

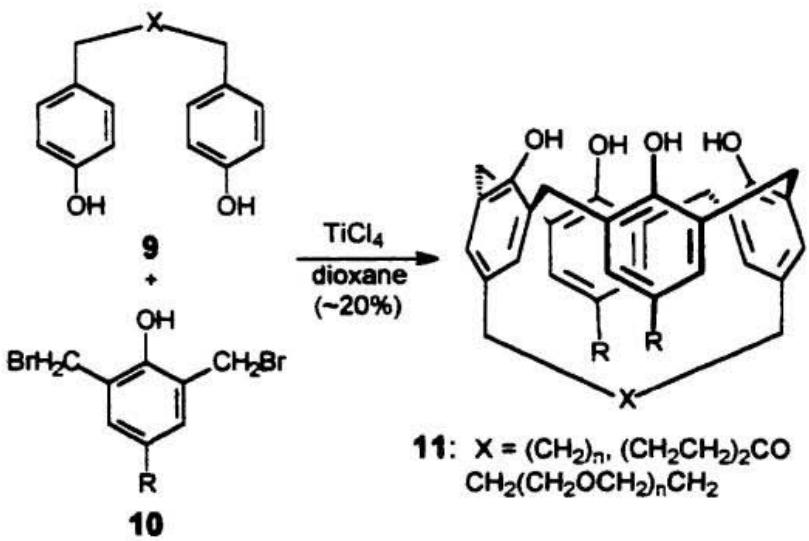


Scheme 1.3 Synthesis of calix[4]arenes via "3+1" fragment condensation

1.4 Convergent synthesis of calixarenes

In the 1950's Hayes and Hunter[15] reported the synthesis of calix[4]arenes with different substituents at the *para*-position of the aryl groups using a stepwise procedure. Later, in the 1970's, Kämmerer[16] showed the utility of such an approach to obtain calix[5]arene, calix[6]arene and calix[7]arenes, while in the early 1980's,

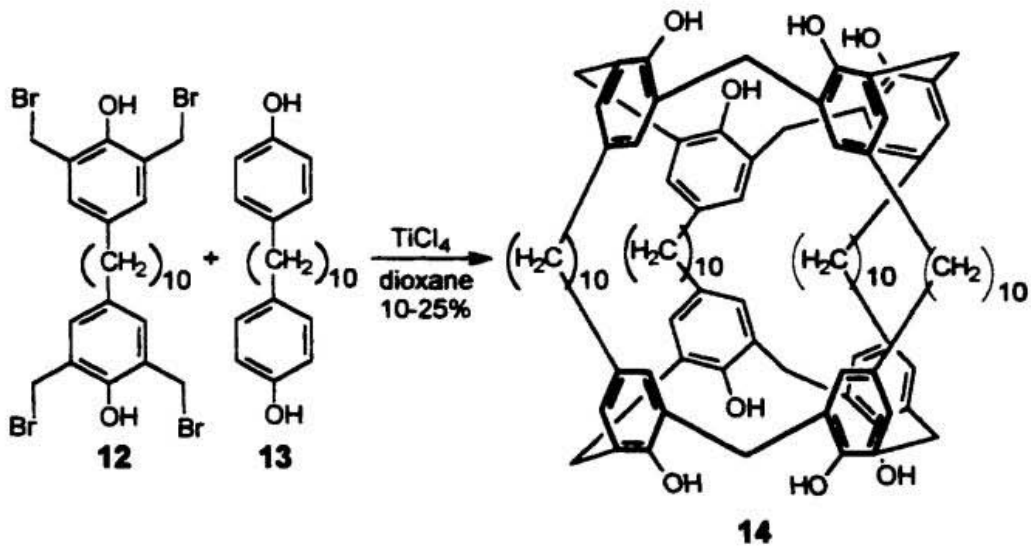
convergent "3+1" or, "2+2" fragment condensation syntheses were developed by Böhmer and coworkers.[17] Typically in the "3+1" fragment condensation,[18] a linear phenolic compound (**7**) is condensed with a bis(bromomethyl)phenol (**8**) to give the cyclic tetramer (Scheme 1.3). Alternatively, a linear phenol (**9**) can be condensed with a bis(bromomethyl)phenol (**10**) to afford **11** (Scheme 1.4).[19] A Lewis acid, notably $TiCl_4$, can be used as a catalyst to give the desired calix[4]arene derivatives, although yields are generally poor to satisfactory.



Scheme 1.4 Synthesis of calix[4]arenes via "2+2" fragment condensation

A few special calix[4]arenes such as the tetra-linked double calixarenes[20] (**14**) have been synthesized by the "2+2" fragment condensation approach by condensation of the tetra(bromomethyl)diphenol (**12**) with the diphenol (**13**) in boiling dioxane in the presence of $TiCl_4$ as a catalyst (Scheme 1.5). Other types of

interesting calixarenes are the chiral calixarenes such as dissymmetric and asymmetric calixarenes. Chiral calixarenes are synthesized either by affixing a chiral group to the upper or lower rim of an achiral calixarene, or by establishing a dissymmetric or asymmetric pattern of different substitution after the parent calixarene ring has been formed.[21]



Scheme 1.5 Synthesis of tetra-linked double calix[4]arenes

1.5 Conformational properties and nomenclature of calixarenes

Some calixarenes are highly flexible and therefore exhibit interesting conformational isomerism. Cornforth[10] originally proposed that calix[4]arenes might exist in four discrete conformations, with various numbers of aryl groups projecting upward ('u'), or downward ('d') relative to an average plane defined by the bridge of methylene groups (Figure 1.2). The proposed conformational isomers of

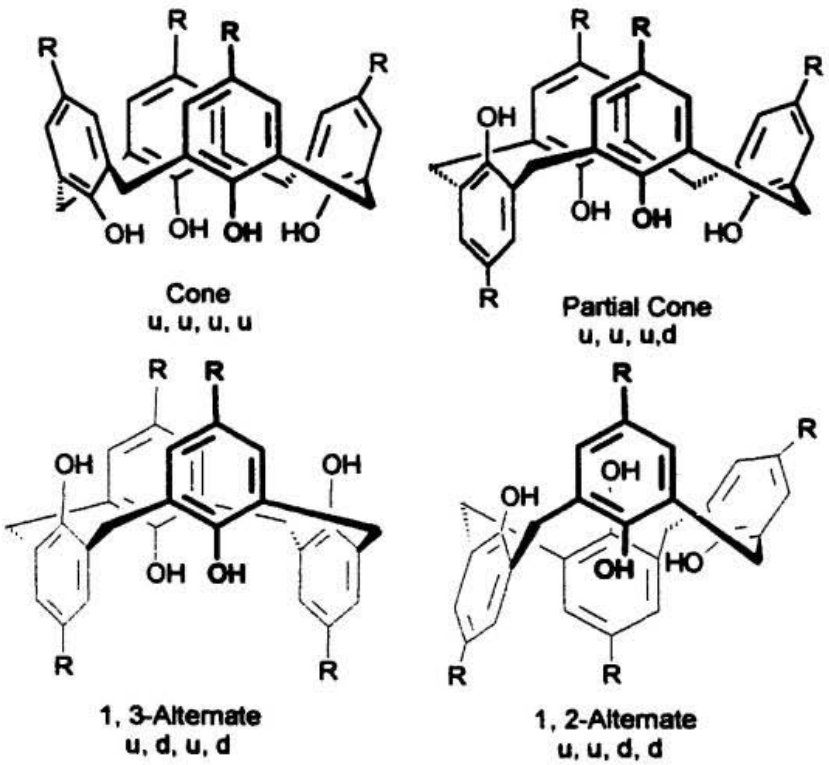
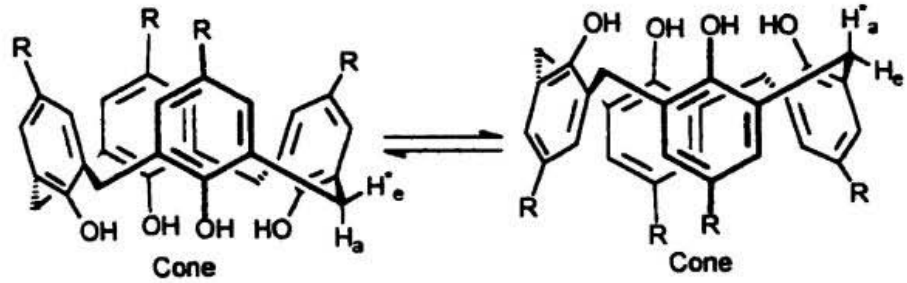


Figure 1.2 Conformation of calix[4]arenes

calix[4]arenes were later renamed by Gutsche[22] as '*cone*' (u, u, u, u), '*partial cone*' (u, u, u, d), '*1,2-alternate*' (u, u, d, d) and '*1,3-alternate*' (u, d, u, d) (Figure 1.2).

An extensive NMR study[23] of calix[4]arenes suggests that rapid interconversion occurs between two mirror-image *cone* conformations having C_4 symmetry (Scheme 1.6). This behavior has been observed by variable temperature (dynamic) ^{1}H NMR spectroscopy, in which a pair of doublets is observed at low temperature and a singlet at high temperature for the diastereotopic methylene bridge protons. A Nuclear Overhauser Effect Difference (NOED) experiment on



Scheme 1.6 Interconversion between two mirror image *cone* conformers

calix[4]arene confirmed that the low temperature spectra correspond to the *cone* conformation and that the low field doublet is due to the axial proton (H_a) whereas the high field doublet is due to the equatorial proton (H_e).[23] The chemical shifts of the OH groups in the ^{1}H NMR spectra provide valuable information about the conformation of the calix[4]arenes; they give a measure of the strength of the intramolecular hydrogen bonding: the greater the δ value, the stronger the hydrogen bond.[9] This is illustrated in *tert*-butylcalix[4]arene (**2**) and *tert*-butylcalix[6]arene (**3**), in which the hydroxyl groups exhibit δ values at 10.34 and 10.53, respectively as compared to the chemical shifts at 9.64, 9.34 and 9.60, respectively for *tert*-butyl[5]-, *tert*-butyl[7]-, and *tert*-butyl[8]arene.[24] For the larger calix[n]arenes (n = 9-20), the δ values for the hydroxyl groups appear in the range of 8.00-9.78, which is also indicative of weaker hydrogen bonding in these compounds.

The conformational behavior of calixarenes can also be influenced by the solvent. The lowest free energy ($\Delta G^{\ddagger}$) at the coalescence temperature (T_c) has been found to be 13.7 kcal mol^{-1} for *tert*-butylcalix[4]arene (**2**) in pyridine-d_5, as compared

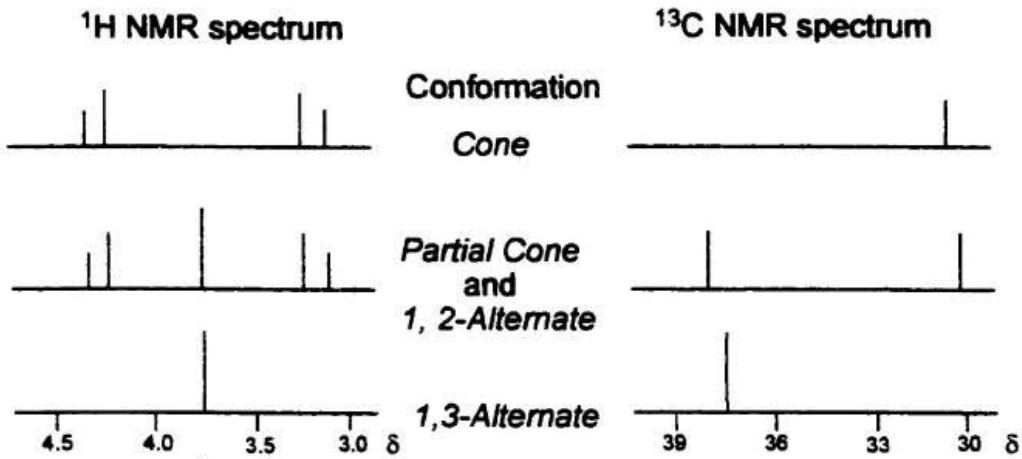


Figure 1.3 ^{1}H NMR and ^{13}C NMR spectral patterns of the methylene groups of calixarenes

to $\Delta G^{\ddagger}$ 15.7 kcal mol^{-1} in $CDCl_3$.[25] Such temperature-dependent ^{1}H NMR studies show that weaker intramolecular hydrogen bonds exist in polar solvents, thereby enhancing the rate of ring inversion in calixarene compounds.[25] In $CDCl_3$, however, the energy ($\Delta G^{\ddagger}$) for such processes is 15-16 kcal mol^{-1} for simple *para*-alkylcalix[4]arenes.[25] This difference can be explained by the fact that pyridine has the ability to competitively form hydrogen bonds with the OH group(s) of calix[4]arenes, thus disrupting the intramolecular hydrogen-bonding, whereas $CHCl_3$ cannot hydrogen-bond with the OH group(s).

A simple and useful rule has been introduced by de Mendoza and coworkers[26] for correlating both ^{1}H and ^{13}C NMR spectra of calix[4]arenes and their four different possible conformations (Figure 1.3). These four conformations can be easily identified in both the ^{1}H and ^{13}C NMR spectra by the patterns of the methylene groups, which are different for three of the four conformations. In their ^{1}H NMR

spectra, the *cone* conformation shows a pair of doublets for the methylene groups, while the *1,3-alternate* conformation shows a singlet for these protons. The less common *1,2-alternate* conformation shows a similar pattern to the *partial cone* conformation, although the two conformations can be distinguished by the signals in the aromatic regions of their ^{1}H NMR spectra. In the ^{1}H NMR spectra of the *1,2-alternate* and *partial cone* conformers, the methylene protons show a pair of doublets and a singlet. The group of de Mendoza and coworkers[26] have shown that when two adjacent aryl groups are *syn* to each other, the chemical shifts of the methylene carbon is near δ 31. The methylene carbon is near δ 38 when the two adjacent aryl groups are in *anti* to each other, as can be found in either *1,3-alternate*, *partial cone* or *1,2-alternate* conformations. These simple observations laid out by de Mendoza[26] have been applied with success to establish the conformational behavior in solution not only of calix[4]arenes, but also of calix[5]arenes[27] and calix[6]arenes.[28]

The interest in using calixarenes as molecular hosts was developed by comparison with crown ethers[5] and cyclodextrins.[29] One of the major factors contributing to the increasing interest in the synthesis and functionalization of calixarenes is their ability to act as molecular hosts, catalysts, chromatography supports, and thin films or ligands.[12] As molecular hosts, they can encapsulate neutral guest molecules and ionic guests of complementary size both in solution and in the solid state. A number of *tert*-butylcalix[4]arenes and their derivatives have been obtained as clathrates in the solid state, complexed with aromatic molecules

such as toluene[30], anisole,[31] pyridine[32] and acetonitrile[33] and, as recently demonstrated by ourselves, with non-solvent, benzophenone.[34]

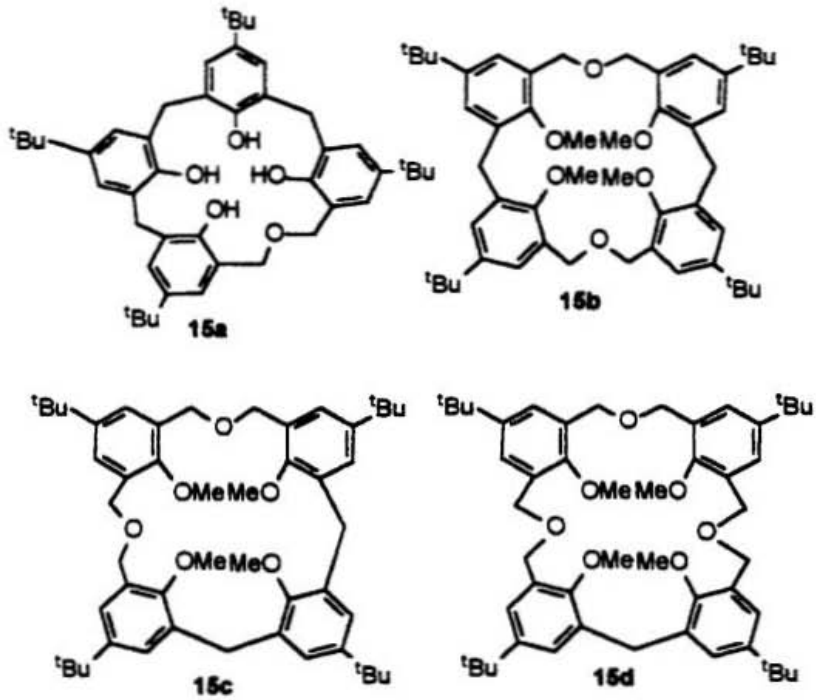


Figure 1.4 Examples of homooxacalixarenes

Both the physical and the chemical properties of calixarenes and their derivatives are dependent on the size of the baskets and on the number of hydroxyl groups. The larger calixarenes have not been as well-studied due to their higher conformational flexibility, which makes it difficult to lock these molecules into a particular conformation for the potential host. Other types of calixarenes such as homooxacalixarenes (**15a-15d**)[35] (Figure 1.4), hexahomotrioxacalix[3]arene (**16a**), hexahomotriazacalix[3]arene (**16b**),[36] octahomotetraoxacalix[4]arene (**16c**),[37]

octahomotetraazacalix[4]arene (**16d**)[38,39] (Figure 1.5) have shown selective complexation properties toward either or both, ionic and neutral molecules.

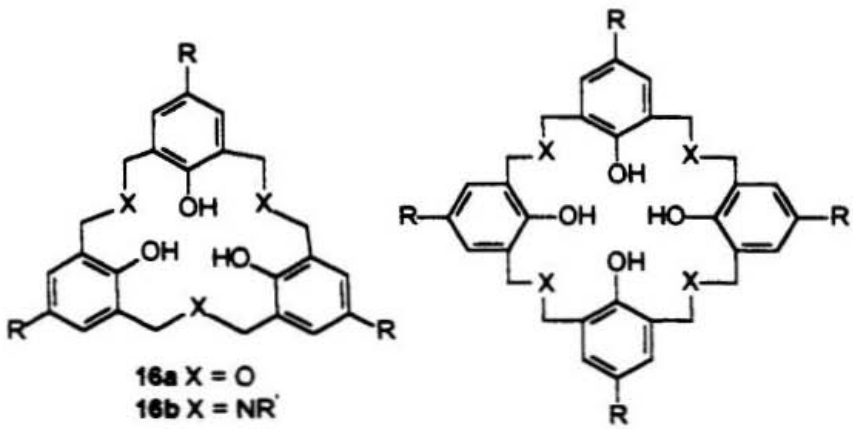
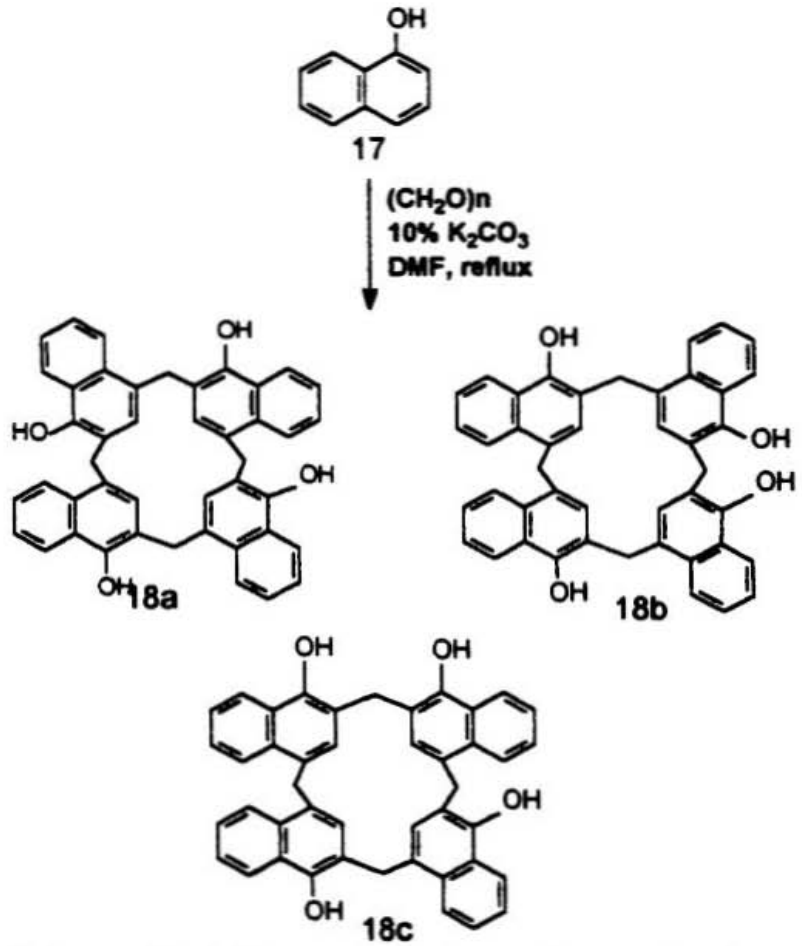


Figure 1.5 Other examples of calixarenes

1.6 Synthesis of calix[4]naphthalenes

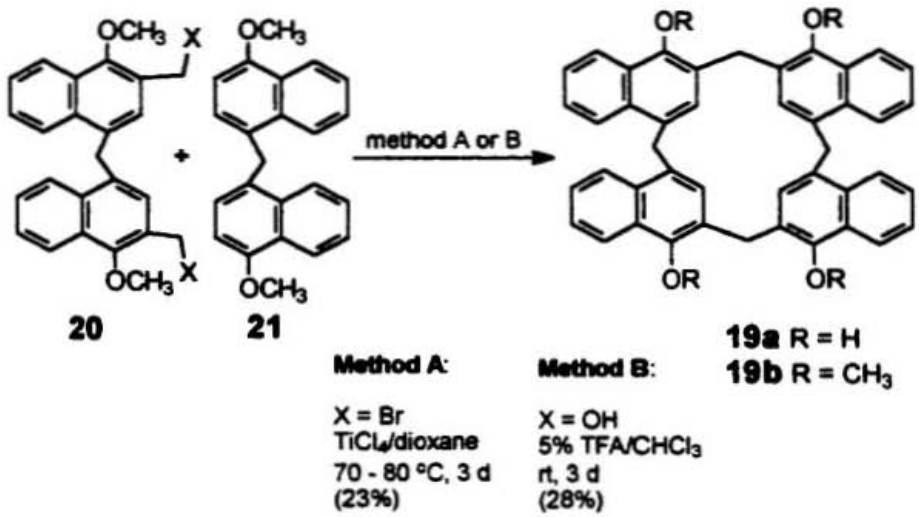
The need for diverse types of supramolecular hosts has accelerated research into designing larger calixarenes and calixarene-related compounds. A new class of supramolecular hosts having units larger than benzene rings for forming the baskets and which are also capable of having functional groups both at the lower and upper rims, were envisioned by Georghiou *et al.*[40] to be promising targets. The larger size of the naphthalene ring would result in larger, more π-electron rich cavities, than those of the corresponding calixarenes. Furthermore, the greater reactivity of the naphthalene[41] unit would potentially enable modification of the basket with suitable functional groups on the naphthalene ring.

In 1993 Georghiou and Li[40] reported that three isomeric cyclic tetrameric



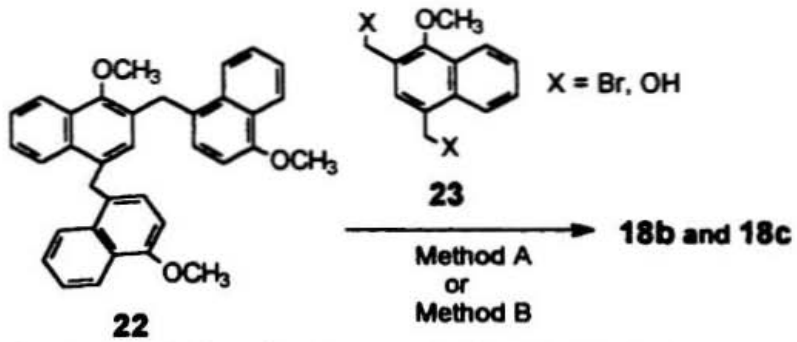
Scheme 1.7 A 'One-pot' synthesis of *exo* calix[4]-naphthalene (18a-18c)

compounds, designated as "C-11" (**18a**), "C-23" (**18b**) and "C-44" (**18c**) were formed by the direct condensation of **17** with formaldehyde in DMF (Scheme 1.7). In principle, a fourth possible tetrameric isomer (**19a**) having C_{2v} symmetry ("C-12") (Scheme 1.8) could also have been formed, but it was not detected in the reaction mixture. The four tetramers were named as calix[4]naphthalenes by analogy with



Scheme 1.8 Synthesis of *exo* calix[4]naphthalenes via "2+2" fragment condensation

the calix[4]arenes, and they were designated as "C-11", "C-12", "C-23" and "C-44" based on the respective number of expected ^{13}C NMR signals. Since the 'one-pot' synthesis of "C-11","C-23", and "C-44" from **17** gave modest yields, alternate routes to all of these cyclic isomers were developed. Recently, however the fourth isomer "C-12" (**19a**) was reported to be observed in the 'one-pot' reaction of **17** with formaldehyde.[42] Georghiou and Ashram[43] reported convergent syntheses of all these calix[4]naphthalenes, including "C-12" (**19a**) in modest yields. By adaptation of Böhmer's[15] $TiCl_4$-catalyzed "2+2" conditions (Method A), the tetra-*O*-methyl derivative of "C-12" (**19b**) was obtained in 23% yield from condensation of **20** and **21** (Scheme 1.8). The coupling of **20** and **21** to form the tetra-*O*-methyl derivative of "C-12" (**19b**) was also achieved in 28% yield by using 5% TFA in chloroform (Method B) (Scheme 1.8). An alternative method involves a "3+1" condensation of

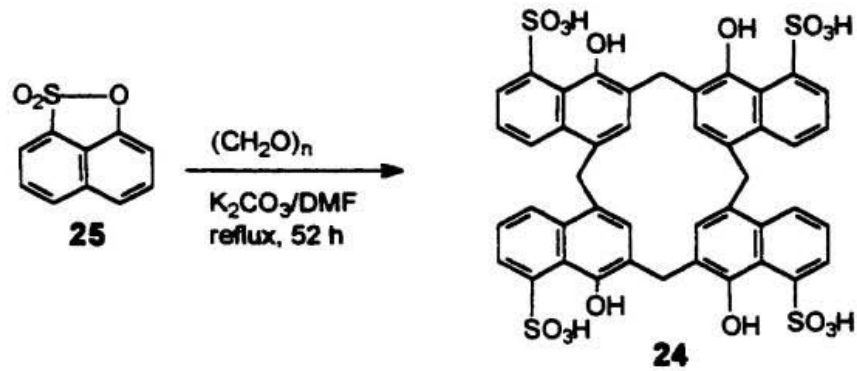


Scheme 1.9 Synthesis of 18b-18c via "3+1" fragment condensation

22 with diol **23** to obtain tetra-*O*-methyl derivatives of **18b** and **18c** using either Method A or Method B (Scheme 1.9). Overall, Method A was found to be more reproducible than Method B for the synthesis of tetra-*O*-methoxy derivatives of these calixnaphthalenes.

1.7 Synthesis of water-soluble calixnaphthalenes

Arduini and co-workers[44] reported the first water-soluble calix[4]arene, which contained the water-soluble functionality at the lower rim, while Shinkai[45] synthesized the upper rim *para*-substituted sulfonatocalixarenes. These sulfonatocalixarenes readily dissolved in water and in aqueous solution, could complex with metal and organic cations, and also showed high affinity for neutral molecules. In 1998, Georghiou and co-workers[46] reported the first synthesis of *peri*-tetrasulfonatocalix[4]naphthalene (**24**) in 15% yield from the condensation of 1,8-naphthalene sultone (**25**) and formaldehyde (Scheme1.10). These water-soluble sulfonatocalix[4]naphthalenes **24**, however, failed to show any complexation



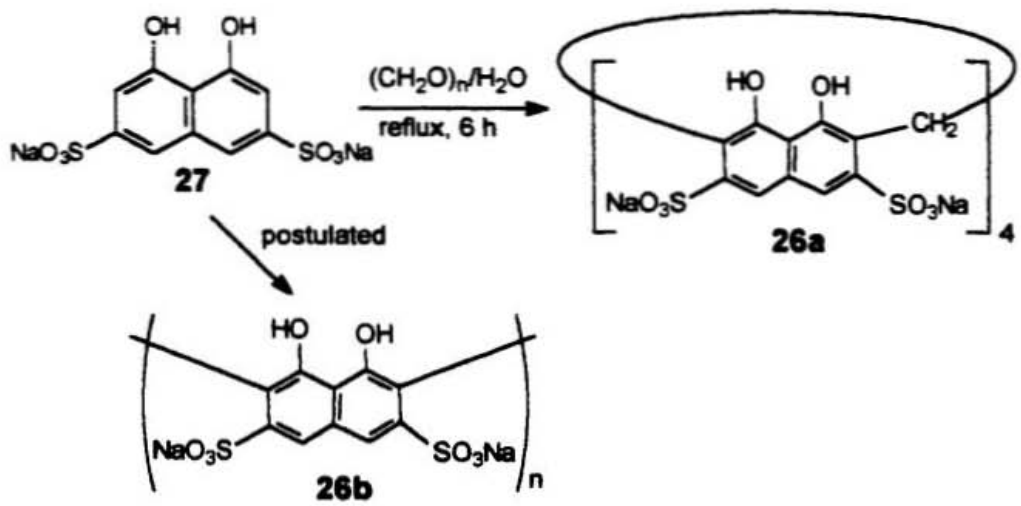
25 **24**

Scheme 1.10 **Synthesis of *peri*-tetrasulfonatocalix-[4]naphthalene (24)**

properties, although the study was rather limited. A report by Poh[47a-c] showed the synthesis of a highly water-soluble sulfonatocalix[4]naphthalene (**26**) in which the eight OH groups are all *endo* from the condensation of the disodium salt of 1,8-dihydroxy-3,6-naphthalenedisulfonic acid (**27**) (chromotropic acid) with an aqueous solution of formaldehyde (Scheme 1.11). An interesting feature of this condensation reaction is that the deactivating effect of the sulfonic acid group adjacent to the loci of condensation were seemingly outweighed by the activating effect of the hydroxyl groups in the formation of **26a**. Georghiou and Ho[47d] however disagreed with Poh's reported findings and postulated instead that linear oligomers **26b** were more likely formed.

Calix[4]naphthalenes (**18a-18c**, **19a**) have their hydroxyl groups oriented away (*exo*) from the annulus of the cavity and thus resemble calixresorcin[4]arene (**6**). The synthesis of *endo* calix[4]naphthalenes in which the hydroxyl groups are

oriented toward the lower rim of the cavity are of considerable interest.[48]

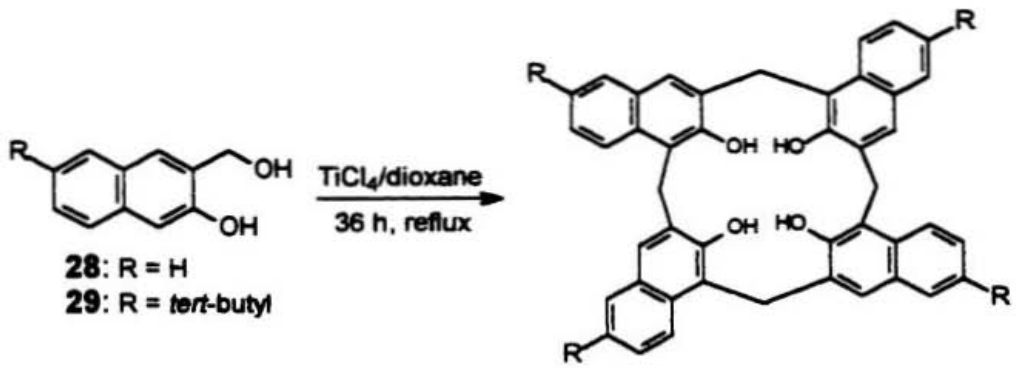


Scheme 1.11 Synthesis of sulfonatocalix[4]naphthalene (26a)

1.8 Synthesis of *endo* calix[4]naphthalenes

Georghiou and co-workers[48] reinvestigated the self-condensation of 3-hydroxymethyl-2-naphthol (**28**) by modifying an earlier method described by Böhmer[49] using $TiCl_4$/dioxane conditions to obtain the inherently chiral *endo* "C-11" (**30**) in 10-11% yield (Scheme 1.12). The related *endo* calix[4]naphthalene (**31**), was synthesized from 6-*tert*-butyl-3-(hydroxymethyl)-2-naphthol (**29**) in a similar 'one-pot' reaction using $TiCl_4$/dioxane, to afford **31** in 27-31% yields (Scheme 1.12).

In the ^{1}H NMR spectra of these *endo* calix[4]naphthalenes, the signals for the hydroxyl groups fall in the range δ 10.63-10.96. This is consistent with the presence of stronger intramolecular hydrogen bonds between the lower rim hydroxyl groups than with the corresponding hydroxyl groups of calix[4]arenes (δ 10.34-10.53).

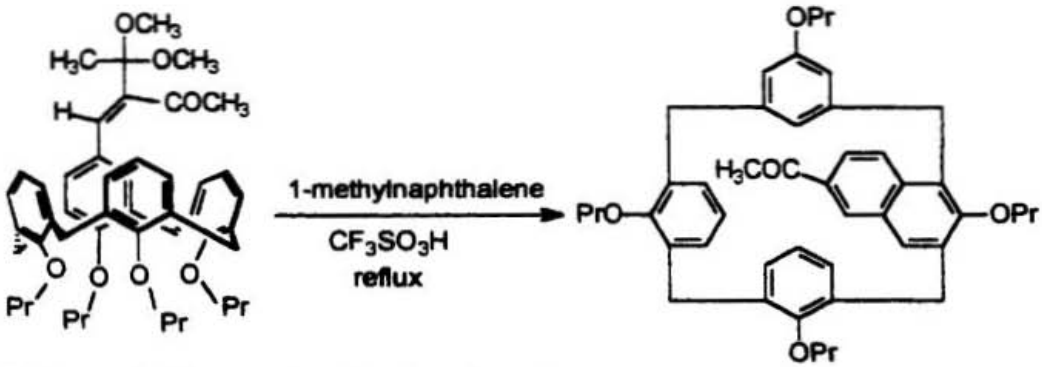


28: R = H
29: R = *tert*-butyl

30: R = H (10 -11%)
31: R = *tert*-butyl (27 - 31%)

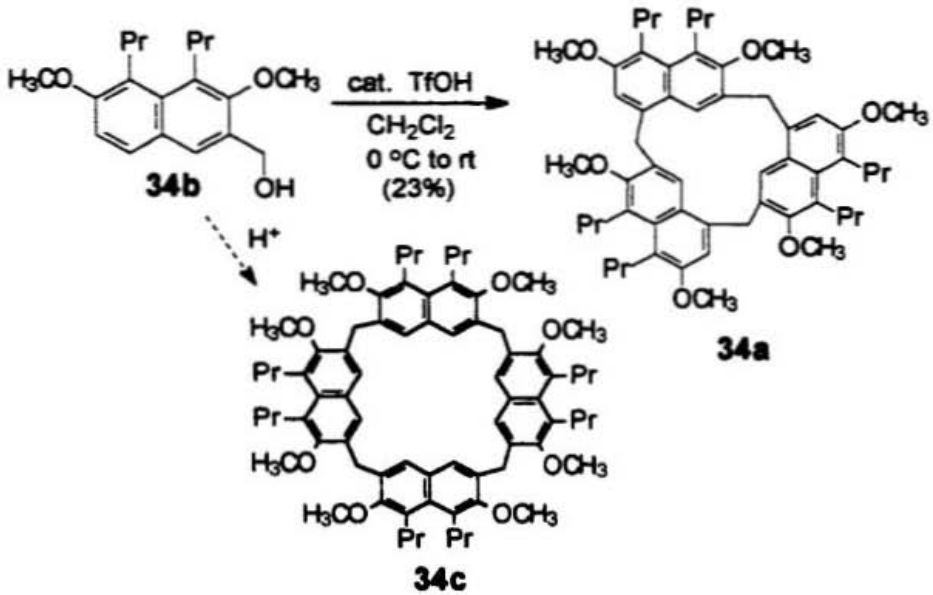
Scheme 1.12 Synthesis of *endo* calix[4]naphthalenes (30-31)

1.9 Other calixnaphthalenes or naphthalene-containing calixarenes



Scheme 1.13 Synthesis of naphthalene-containing calix[4]arene

There are only two other calixnaphthalene or naphthalene-containing calixarenes which have been reported besides those which are discussed in this chapter. In 1996 Shinkai *et al.*[50] reported the synthesis of a naphthalene-containing inherently chiral calix[4]arene (**32**) derived by an intramolecular ring closure reaction of **33** (Scheme 1.13). More recently, Glass *et al.*[51] reported the synthesis of



Scheme 1.14 **Synthesis of cyclic trimer containing naphthalene rings**

naphthalene-based calixarenes such as compound **34a** using Friedel-Crafts alkylation conditions (Scheme 1.14). These authors used carbinol **34b** and catalytic TFA to obtain cyclic trimer **34a** in 23% yield, but they did not observe the expected cyclic tetramer **34c** in this reaction mixture.

1.10 Objectives of the research described in this thesis

We were interested in obtaining all of the possible isomers of *endo* calix[4]naphthalenes (**30**, **35** and **35a-c**) (Figure 1.6). Our interest in the synthesis of "C-12" *endo* calix[4]naphthalene (**35**) grew from analysis of its conformational features. A CPK molecular model study of **35** showed that it can have C_{2v} symmetry in its cone conformation, C_2 symmetry in the *1,3-alternate* and C_i symmetry in the

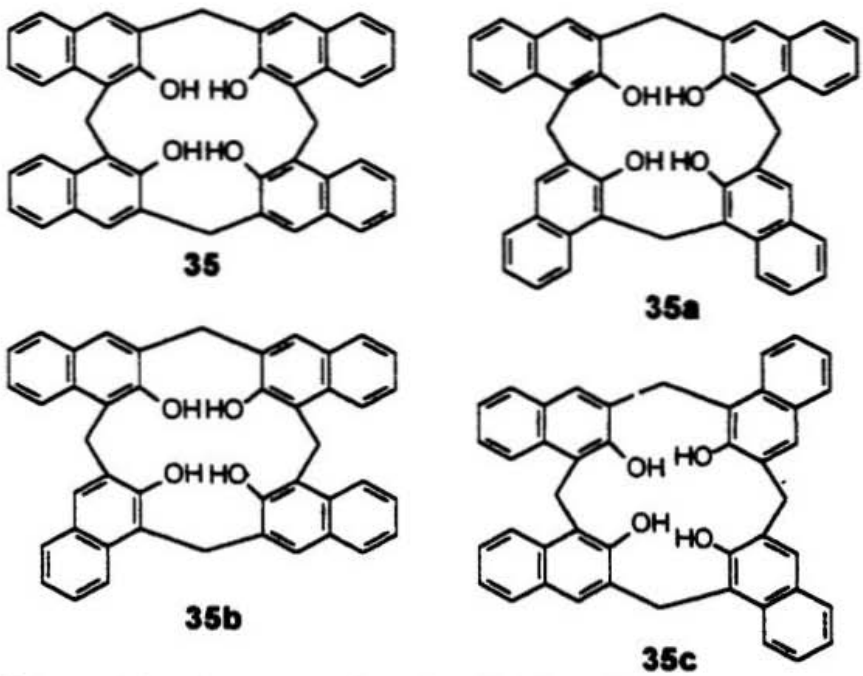
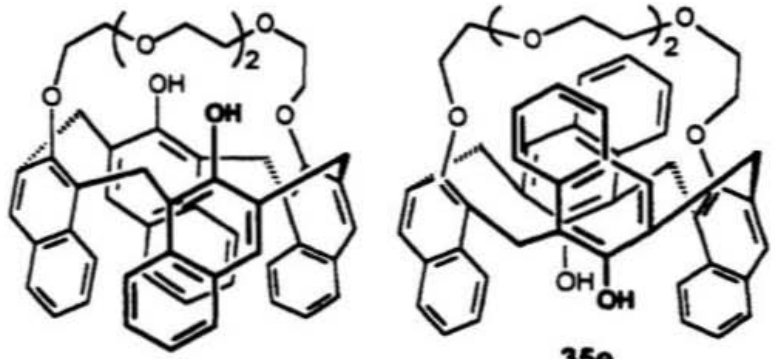


Figure 1.6 Isomers of *endo* calix[4]naphthalenes

1,2-alternate conformation. These conformational features of **35** also clearly showed the presence of deeper cavities and that they could be functionalized with polyethyleneoxy moieties on the lower rim, to produce "calixcrown" in a *cone* and *1,3-alternate* conformations, respectively (**35d** and **35e**) type structures (Figure 1.7).

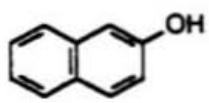
The research work in this thesis is divided into three major areas: (1) synthesis of **31** and its derivatives; (2) convergent synthesis of **35** and other types of calix[4]naphthalenes by the use of: (a) directed *ortho* metallation of 2-naphthol (**36**), bis(2-hydroxy-1-naphthyl)methane (**37**) and its derivatives such as methoxy, carbamate and methoxymethyl ether (Figure 1.8); and (b) Suzuki-Miyaura coupling of benzyl halides and bromomethylated derivatives of naphthalene with a variety of



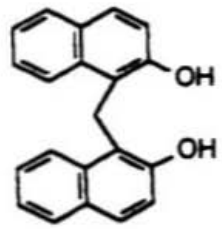
35d 35e

Figure 1.7 An example of calixcrown derivative of 35

aromatic boronic acids; (3) modification of the lower rim of *para-tert*-butylcalix[4]arene (**2**) by: (a) attempts at the direct replacement of hydroxyl groups; and (b) synthesis of aryl ether derivatives, thereby leading to other structures containing deeper cavities than the corresponding calixarenes.



36



37

Figure 1.8 2-Naphthol (36) and bis(2-hydroxy-1-naphthyl)methane (37)

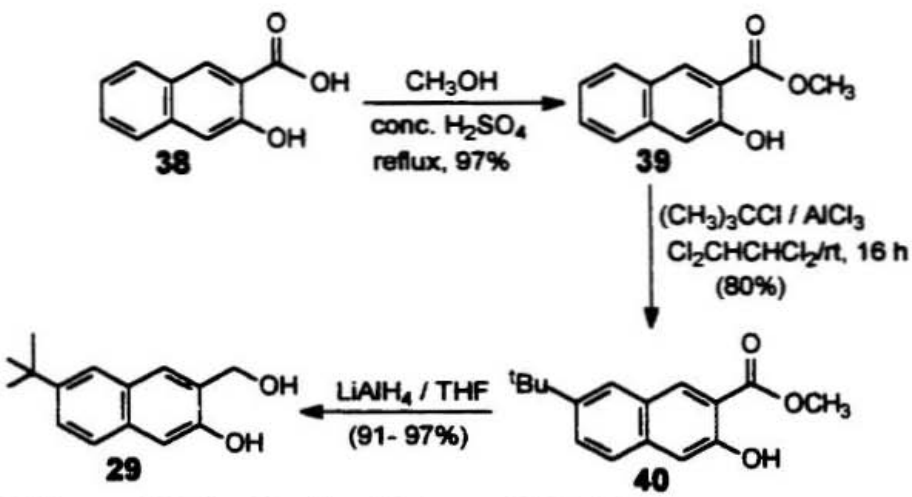
for the optimal formation of calixarene-[60]fullerene inclusion complexes. Shinkai[57a] has shown that calix[5]arene, calix[6]arene and hexahomooxacalix[3]arene all form complexes with [60]fullerene in toluene. These findings allowed Shinkai *et al.*[57b] to identify a few important requirements for the effective inclusion of [60]fullerene in solution. One of these prerequisites is that the calix[n]arene must be in a pre-organized *cone* conformation, which would form as a result of intramolecular hydrogen bonding among the hydroxyl groups. Another prerequisite is the proper inclination of the benzene rings of the calixarene host. It was also concluded that a deep inclusion of [60]fullerene in the calix[n]arene cavity, as is expected to be the case for *tert*-butylcalix[8]arene, is not a necessary prerequisite for the complex formation. Other factors to be considered as driving-forces for [60]fullerene inclusion include π-π interactions (including the charge-transfer-type interaction) and/or a solvophobic effect.[57] We reasoned that calix[4]naphthalenes having extra π-electrons due to the presence of the extra fused aromatic rings on each naphthalene as compared with calixarenes might serve as effective hosts for the inclusion of [60]fullerene and other large guest molecules.

The calix[4]naphthalenes which were first reported by Georghiou *et al.*[40] in 1993 possess deeper cavities than the corresponding calix[4]arenes. These first calix[4]naphthalenes had their hydroxyl groups located outside the cavity, and are examples of *exo* calix[4]naphthalenes. In 1993, Böhmer *et al.*[49] also reported an example of a calix[4]naphthalene (**30**), which had all four hydroxyl groups located

inside the cavity, although they did not name the compound as being a calix[4]naphthalene. Compound **30** is an example of an *endo*-type calix[4]naphthalene. This compound was synthesized in our laboratory, and it was found that in the solid state it adopts a "*pinched cone*" (*flattened cone*) conformation.[48] Its unit cell contains a pair of molecules in which a naphthalene unit of one molecule is situated within the hydrophobic cavity of the second molecule. In principle, therefore, it was reasoned that efficient inclusion could occur between [60]fullerene and **30** and also with its 6-*tert*-butylated derivative **31** (Scheme 2.2) since similar multi π-π interactions are possible.

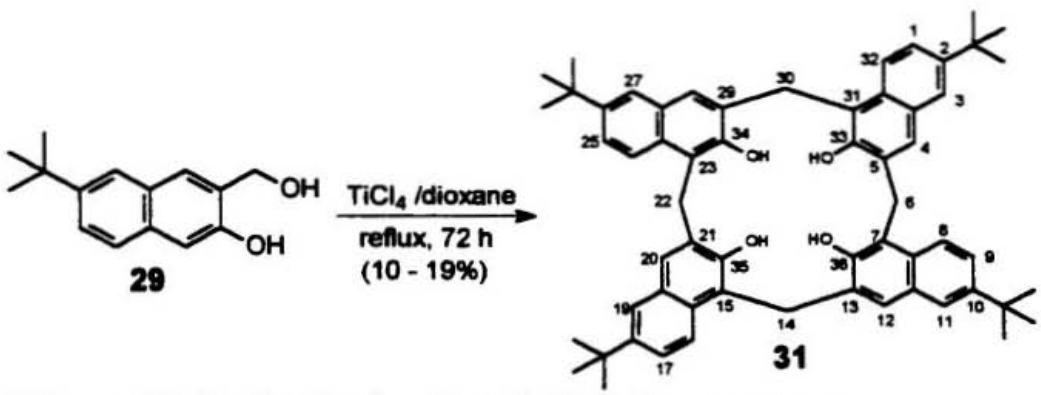
2.2 Synthesis of *tert*-butylcalix[4]naphthalene

The earlier work of Ashram[58] was repeated in order to obtain larger amounts of *tert*-butylcalix[4]naphthalene (**31**) in order to study its supramolecular interactions with [60]fullerene. The synthetic route to compound **31** was carried out as shown



Scheme 2.1 Synthesis of intermediate 29

in Scheme 2.1. Acid-catalyzed esterfication of commercially available 3-hydroxy-2-naphthoic acid (**38**) gave the ester **39** in 97% yield. This ester was subjected to Friedel-Crafts alkylation to afford methyl 7-*tert*-butyl-3-hydroxy-2-naphthoate (**40**) in 80% yield. Reduction of **40** with lithium aluminum hydride furnished in 91-97% yield the corresponding alcohol **29**, which is the essential precursor for **31**. A solution of this diol **29** in anhydrous dioxane was treated with $TiCl_4$ as a catalyst (Böhmer conditions)[15] in the crucial 'one-pot' cyclization step (Scheme 2.2). Calixnaphthalene **31** was obtained as a light tan solid in 10-19% yields in 3.0 g scale reactions.



Scheme 2.2 Synthesis of *endo* calix[4]naphthalene (31)

Although it was assumed that $TiCl_4$ acted as a template during the cyclization process, and as such would facilitate the cyclization of **29** to yield cyclic tetramer **31**, the relatively low yields obtained and the requirement for larger amounts of **31** prompted us to investigate the use of other Lewis acids. With TiI_4 in dioxane, diol **29** gave **31** in 10% yield. With $SnCl_4$, either in CH_2Cl_2 at room temperature or in boiling dioxane, **31** was obtained in yields of only 6% and 10%, respectively. Boron

trifluoride diethyl etherate failed to give any cyclized product **31** at all. Based upon these experiments, it was concluded that the best conditions to obtain **29** in a 'one-pot' procedure was the use of $TiCl_4$ as the catalyst in refluxing anhydrous dioxane.

The ^1H NMR spectrum of **31** in $CDCl_3$ or CD_2Cl_2 is very simple and is consistent with its expected structure. The phenolic protons appear as a sharp singlet at δ 10.63, indicating fast proton exchange and also suggesting the presence of stronger intramolecular hydrogen bonding present than in the corresponding calix[4]arenes, in which the phenolic protons appear at δ10.34 in $CDCl_3$.[12] The *tert*-butyl protons appear as a singlet at δ1.31 and the methylene protons also appear as a singlet at δ 4.53, which is consistent with the compound being conformationally mobile, rapidly interconverting between two *cone* conformers. The data are also consistent with a structure possessing C_4 symmetry, and its conformation is confirmed by the NOED measurements: saturation of the *tert*-butyl signal at δ 1.31 did not enhance the methylene bridge protons, whereas the signals at δ 7.51 (H-3, H-11, H-19, H-27) and 7.57 (H-1, H-9, H-17, H-25), due to the naphthalene protons, were enhanced by 8% and 7%, respectively. Also, saturation of the naphthalene proton signal at δ 7.76 (H-4, H-12, H-20, H-28) enhanced the signals at δ 7.51 (H-3, H-11, H-19, H-27) and at δ 8.27 (H-8, H-16, H-24, H-32) by 13% and 7%, respectively. The latter signals are due to the second naphthalene ring proton, which is in the proximity of the proton whose signal is at δ 7.76 (H-4, H-12, H-20, H-28). Dynamic ^1H NMR experiments on **31** in CD_2Cl_2 (Figure 2.1) over the range

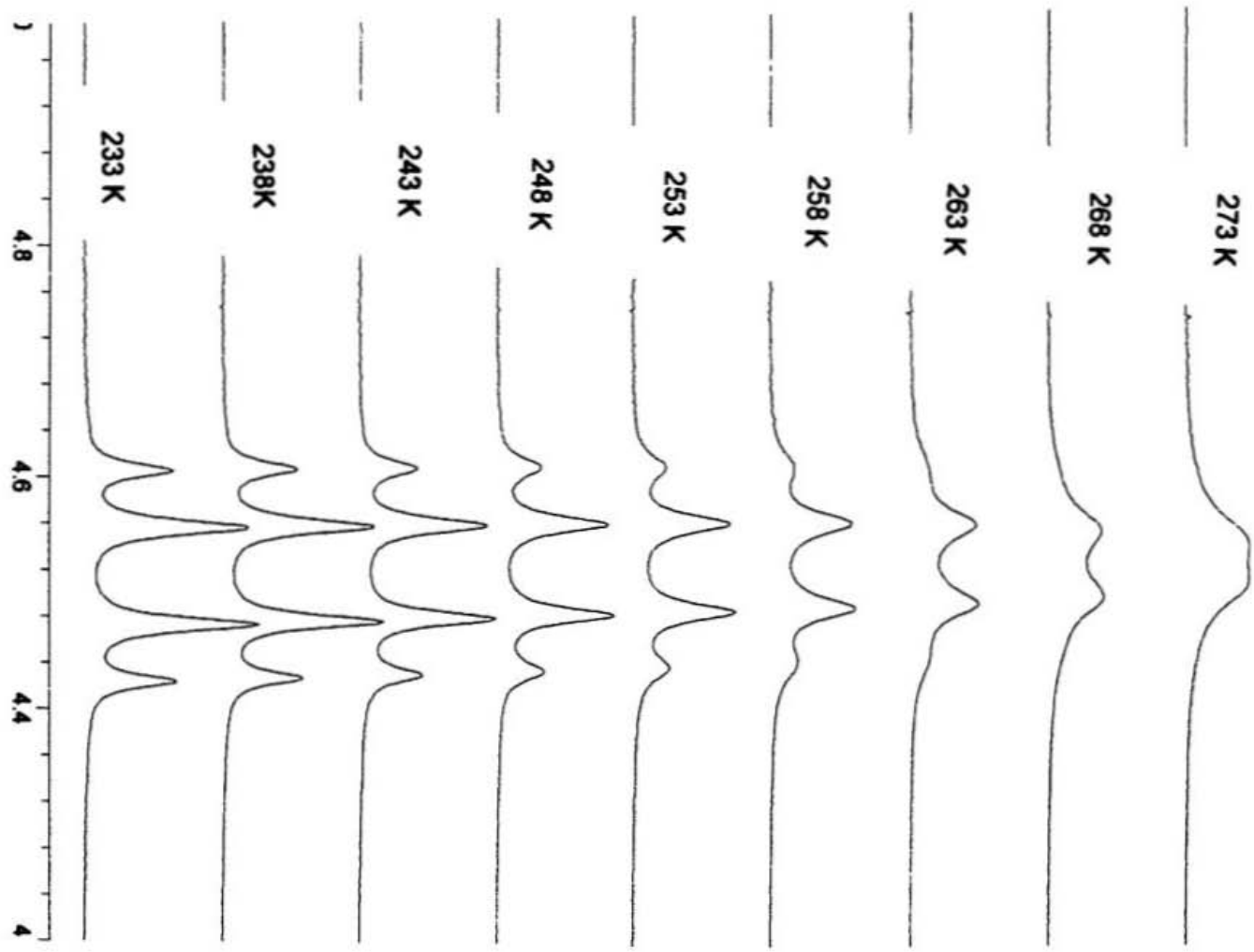


Figure 2.1 VT-^{1}H NMR spectra of compound 31 in CD_2Cl_2

from 298 to 233 K showed that, upon cooling, the sharp singlet due to the methylene protons becomes broad. The lower temperatures splits the methylene protons into a broad AB system at 258 K with geminal coupling constant J = 15 Hz at 233 K, and sharpens as the conformational mobility is reduced. This decreased mobility could also result from the inclusion of the solvent into the cavity of **31**.[59] The signal due to the phenolic protons shifts from δ 10.63 to 11.05 also suggesting the presence of stronger intramolecular hydrogen-bonding when **31** is in a fixed *cone* conformation.

Table 2.1. Solvent effect observed in ^{1}H NMR spectra on 31

Group	CD_2Cl_2 (ppm)	Pyridine-d_5 (ppm)
tert-butyl	1.34	1.14
methylene	4.53	5.01
hydroxyl group	10.63	10.85

The effect of solvent on **31** was also studied and the data is presented in Table 2.1. In pyridine-d_5, the resonances from the *tert*-butyl protons and the methylene protons appear as sharp singlets and the hydroxyl groups as a broad singlet. The methylene proton signal is found at δ 4.52 at room temperature in $CDCl_3$, at δ 4.53 in CD_2Cl_2, whereas in pyridine-d_5 it is at δ 5.01. Similarly to $CDCl_3$, the resonance for the hydroxyl groups appear at δ 10.85 in pyridine-d_5 at room temperature suggesting very strong intramolecular hydrogen bonds. These data also suggest that the compound **31** is conformationally flexible and indicate the presence of a weak interaction with pyridine-d_5.[59] Dynamic ^{1}H NMR experiments on

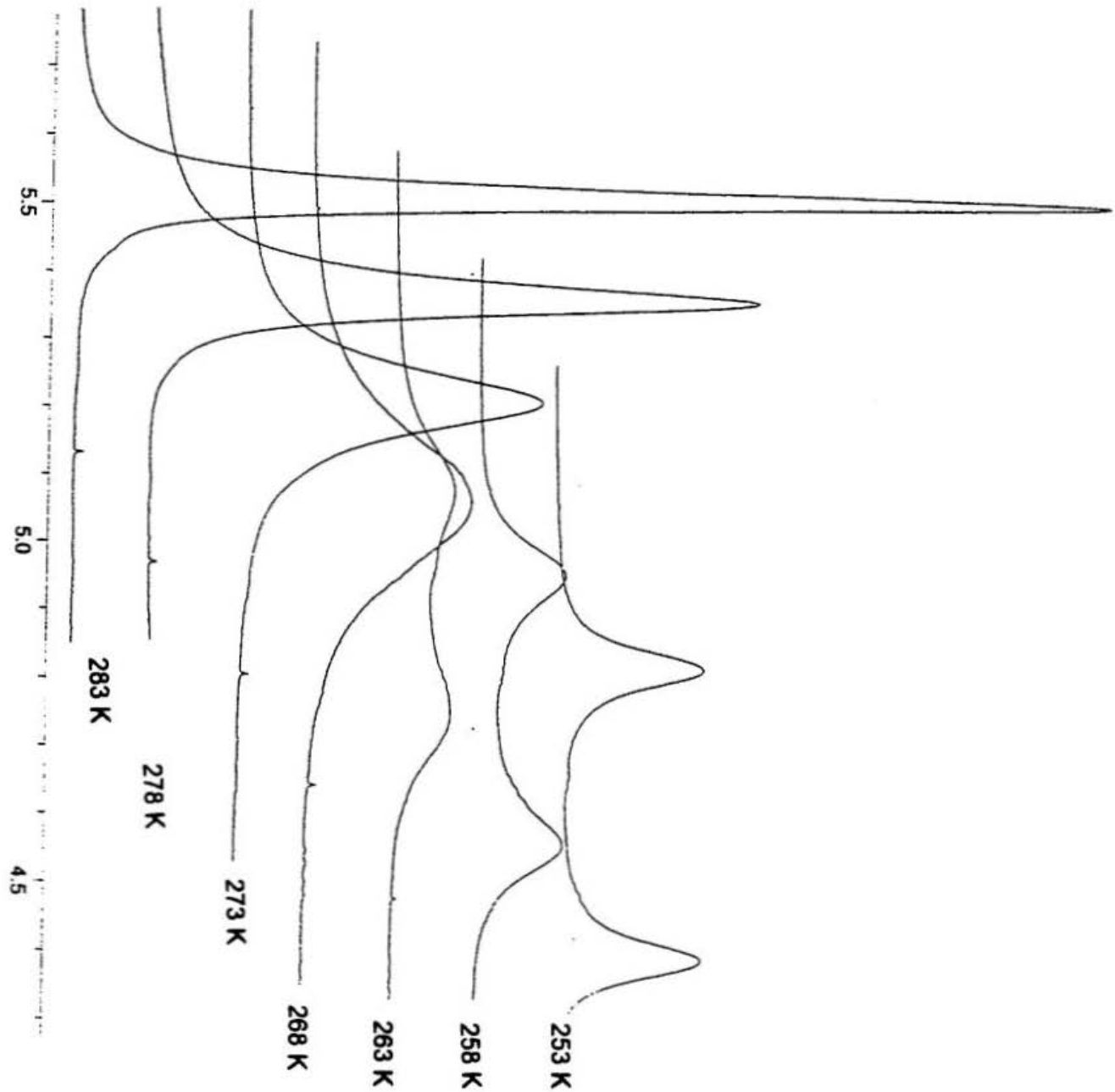


Figure 2.2 VT-^{1}H NMR spectra of compound 31 in pyridine-d_5

31 in a more polar solvent such as pyridine-d_5 (Figure 2.2) showed typical splitting of the methylene singlet into doublets upon cooling. The methylene protons broadened at 273K and split into a pair of broad singlets at 263K.

Similar changes in the ^{1}H NMR spectra of calix[4]arene have been interpreted as being due to exchange between the *cone* and the *1,3-alternate* conformations.[60] However, Shinkai *et al.*[61] have shown that this conformational exchange does not exist, and the changes observed are due to a slow inversion between two *cone* conformers on NMR time scale. The results for coalescence temperatures of compound **31**, shown in Table 2.2 are similar to those reported conformational barriers for calix[4]arenes in the *cone* conformation.[62] The approximate free-energy barriers ($\Delta G^{\ddagger}$) at the coalescence temperature were calculated from the expression:[63]

$$\Delta G^{\ddagger} = 0.004573 \times T_C (9.97 + \log T_C/\Delta\nu)$$

where T_C is the coalescence temperature, and $\Delta\nu$ is the difference in chemical shift between the centers of the two doublets arising from the methylene protons. The data in Table 2.2 for the calix[4]arenes **1** and **2** show that the barriers to inversion from *cone*-to-*cone* conformers change from the less polar to the more polar solvent. The difference in the conformational inversion free-energy barrier ($\Delta G^{\ddagger}$) between **31** and *tert*-butylcalix[4]arene (**2**) is 1.7 kcal.mol^{-1}, and with calix[4]arene (**1**) it is 0.2 kcal.mol^{-1} in pyridine-d_5. The inversion barrier for interconversion between *cone* conformations for **31** appreciably decreased in changing solvent from pyridine-d_5

Table 2.2. Coalescence temperatures and conformational barriers measured by ^{1}H NMR for the methylene protons of 31

Compound	Solvent	T_C (K)	Methylene shifts (Hz)		$\Delta G^{\ddagger}$ (kcal/mol)
			H_A	H_B	
1	pyridine-d_5	251	478	345	11.8
2	pyridine-d_5	288	472	360	13.7
31	CD_2Cl_2	258	1377	1341	12.8
31	pyridine-d_5	263	2705	2434	12.0

compared to CD_2Cl_2. These findings can be explained as pyridine disrupts the intramolecular hydrogen-bonding between the lower rim hydroxyl groups, which is the major factor for the general preference of calixarenes and related molecules to adopt the *cone* conformation. These findings are consistent with the results reported by Gutsche *et al.*[84] with various calixarenes in different solvents. In more polar solvents, such as acetone and $CHCl_3$, an appreciable decrease in the inversion free-energy barrier is observed for **2**, which becomes even greater in a basic, hydrogen-bonding solvent such as pyridine. In general, however interactions between amines and calixarenes in solution depend on the structure of the amine. If the amine is not too bulky, then it can abstract a phenolic hydrogen from the calixarene via a proton-transfer mechanism, forming an ion pair in which the guest occupies the position

inside (*endo*) the cavity.[65] Bulky amines appear to interact with the host molecule so that the amine is outside (*exo*) the cavity.[65] Gutsche's[64] studies showed that there were no interactions between the guest and the hydrogen-bonded hydroxyl groups of the host. Previous work by Gutsche *et al.*[65] revealed that pyridine guest molecules occupy positions both inside (*endo*) and outside (*exo*) the cavity of the *tert*-butylcalix[*n*]arene-pyridine complex (*n* = 7, 8) structures. The role of the CH_3(host)—π(guest) and weak hydrogen-bonding interactions for the *endo* pyridine guest has been studied with the *1,3*-crown-5-ether-bridged *tert*-butylcalix[4]arene pyridine compound. The study[66] demonstrated that the pyridine plane lies along the major axis of the ellipse defined by the free phenolic groups of the calixarene indicating the presence of a weak (1.9 kcal.mol^{-1}) CH---N hydrogen bond. Recently, extensive studies by Ripmeester *et al.*[67] on weak intermolecular interactions and molecular recognition of benzene and pyridine with **2** have shown inclusion of pyridine in the host cavity. This study established the presence of a CH---N hydrogen bonding interaction between the host and pyridine in the solid state using ^{13}C CP-MAS (cross-polarization and magic-angle spinning) NMR spectroscopy and from a single-crystal X-ray diffraction studies. On the basis of these data and results obtained from several calixarene-pyridine complexes, the conclusion can be made that it is most likely that pyridine interacts with **31** both outside (*exo*) and inside (*endo*) with respect to the host cavity. A similar finding was observed with triethylamine and **124** in Chapter 4.

With **31** being synthetically available, our group was able to study its complexation properties with fullerenes.[68] The study showed that **31** was able to bind [60]fullerene with a K_{assoc} = 6,920 dm^{-3} mol^{-1} in CS_2, a value higher than the highest value of K_{assoc} = 2,100 dm^{-3} mol^{-1} reported by Haino *et al.*[69] for a calix[5]arene in toluene solution. In a more recent paper, Haino *et al.*[70] reported higher K_{assoc} values, but the host molecules that they employed were all bridged calix[5]arenes. Thus, it can be concluded that *tert*-butylcalix[4]naphthalene (**31**) possesses a well-defined cavity that can form complexes with [60]fullerene, both in solution and possibly in the solid state, although an X-ray crystal structure has so far eluded us.[68] For the complexation of **31** with [60]fullerene, a solvophobic effect may also be occurring, in addition to the enhanced π-π interactions due to the presence of the extra aromatic rings on the naphthalene units.

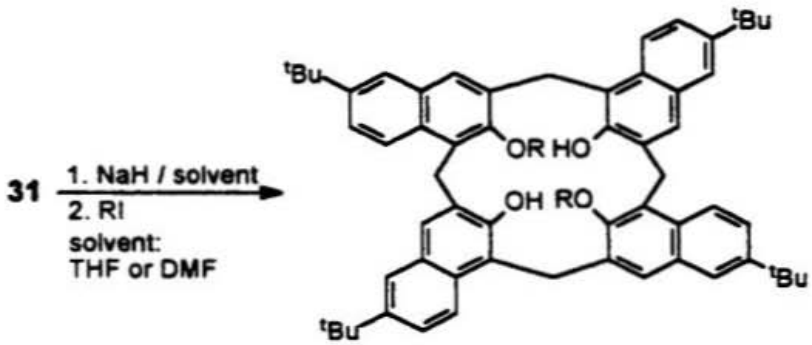
The foregoing discussion has demonstrated that a new class of calix[4]naphthalene exemplified by **31** could be synthesized in large scale, although in poor yields. These new molecules posses cavities that are sufficiently large enough to recognize large, neutral guest molecules, as demonstrated with the [60]fullerene-**31** complex formation studies.

2.3 Ether derivatives of *tert*-butylcalix[4]naphthalene

The utility of calixarenes for the majority of potential applications depends upon suitable modification on either, or both, the upper and the lower rim of the parent compounds.[12] Ethers, esters and variety of other functional groups have

been studied extensively in the calix[4]arene and calix[6]arene series. Different methods have also been developed for the selective functionalization of the hydroxyl groups of calix[4]arenes for the recognition of cations, anions and neutral molecules.[71]

The earliest examples of lower rim alkylated calix[4]arenes (**2**) studied for their complexation properties are compounds which have shown only a modest degree of cation binding ability. Surprisingly, however, the simple *n*-propyl ether of **2** in the *1,3-alternate* conformation shows strong complexation with K^+ (log K_{assoc} = 4.7) and Ag^+ (log K_{assoc} = 4.3).[72] The special ability of the *1,3-alternate* conformer to form tight complexes is due to the coordination of the cation with the ether oxygen atoms combined with π-donor participation from the aryl rings of the calixarene. We therefore reasoned that simple *n*-propyl ether derivatives of the lower rim substituted derivatives of **31** could show strong binding capacity with similar cations. By analogy with calix[4]arenes, alkylation of **31** can be effected using an alkylating agent with a base such as NaH, K_2CO_3, or CsF in different solvents. *Distal* (*i.e.*, 1,3) dialkylation of **31** was carried out under conditions similar to those leading to monoether formation in calix[4]arenes, but in our case with an excess of the alkylating agent and base. Treatment of **31** with a large excess of 1-iodopropane (13 equiv) and NaH (100 equiv) in DMF afforded 1,3-dialkoxy compound **41a** in 56% yield (Scheme 2.3). Similarly, treatment of **31** with 2-iodopropane (3 equiv) and NaH (5 equiv) in THF afforded the 1,3-dialkoxy compound **41b** in 36% yield. These



41a: R = n-propyl (56%)
41b: R = isopropyl (36%)

Scheme 2.3 Synthesis of alkyl ether derivatives of 31

findings are inconsistent with the results observed from the selective *proximal* (*i.e.*, 1,2-) dialkylation in calix[4]arenes with a weak base but can be explained by considering the stabilities of the two different monoanions (Figure 2.3b and 2.3c) which arise from the monoalkoxycalix[4]arenes.[71] The hydroxyl group in the *distal* position to the mono alkylated phenol is more acidic than that in the *proximal* position since monoalkoxycalix[4]arene gives rise to an anion (Figure 2.3b) that is stabilized by two hydrogen bonds, whereas the anion in the proximal position (Figure 2.3c) is stabilized by only one hydrogen bond. In contrast, on reaction with a strong base (NaH) monoalkoxy-dianionic species (Figure 2.3d and 2.3e) are formed, which both show a more reactive phenoxide in the proximal position. Based on the above explanations for the observation that a strong base such as NaH selectively produces *proximal* alkylation of calix[4]arenes, alkylation of **31** should also give *proximal* alkylation product. The results obtained however were selective *distal*

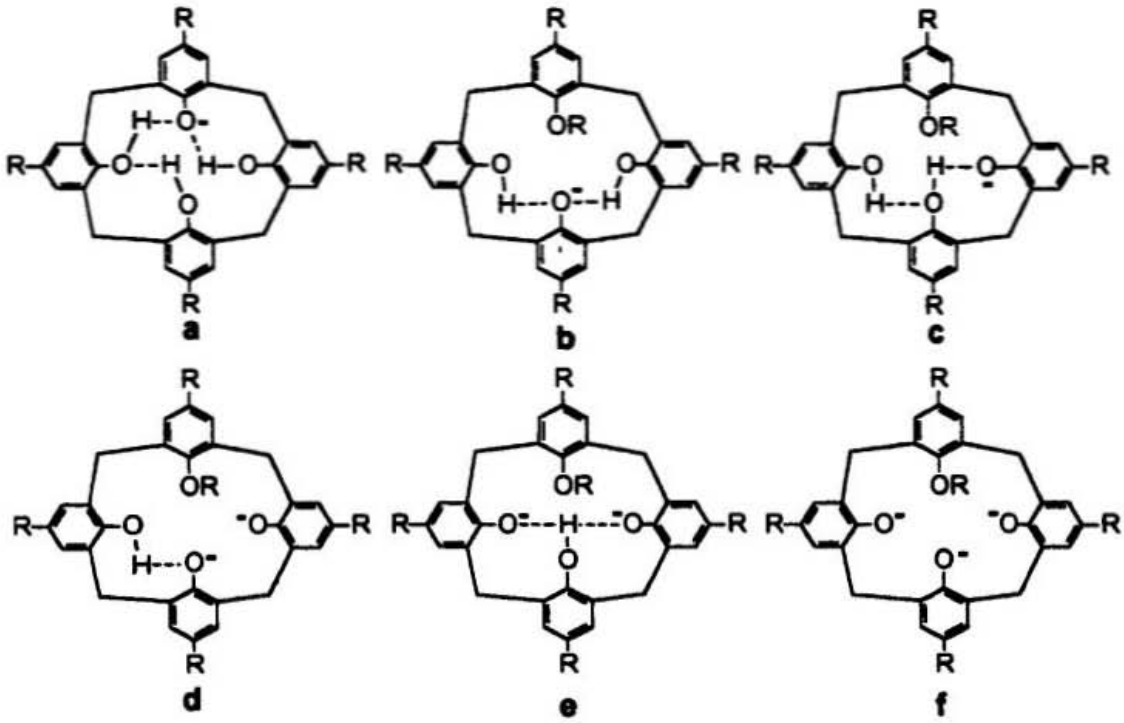


Figure 2.3 Mono, dianions and trianions of calix[4]arenes

dialkylation of **31** which can be explained by the fact that excess of base formed monoalkoxy-trianionic species which led to the formation of *distal* dialkylation. These findings are under further investigation in our laboratory.

The ^{1}H NMR spectrum of compound **41a** at ambient temperature clearly shows that *cone* to *cone* inversion is either slow on the NMR time scale or is completely suppressed. This is in agreement with results found with *n*-propyl ether(s) of **2**, wherein the *n*-propyl groups are bulky enough to inhibit inversion of compound **41a** through the annulus. The ^{1}H NMR spectrum of 1,3-di-*n*-propyl ether **41a** in $CDCl_3$ shows a pair of *tert*-butyl resonances in a 1:1 ratio at δ 1.14 and δ1.46,

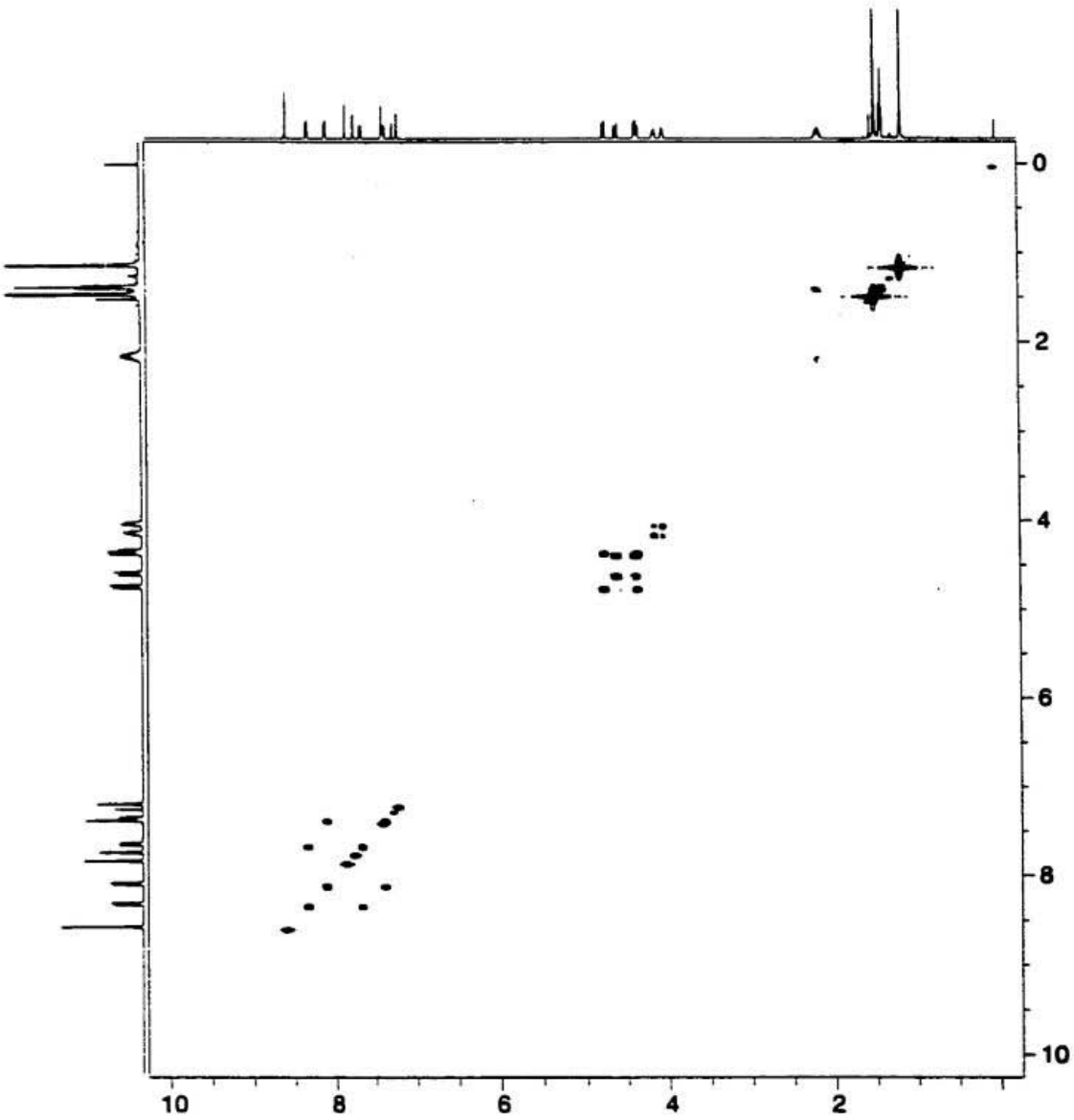


Figure 2.4 ^{1}H COSY spectrum of compound 41a

whereas there is only singlet at δ 1.31 for all four *tert*-butyl groups in the parent compound **31** providing further support that the molecule exists in a fixed conformation.

The most indicative regions of the ^{1}H NMR spectra however for the structural assignment of compounds **41a** and **41b** are the methylene regions, which show AB systems (J ~ 13 - 14 Hz) due to the bridging methylene groups between the naphthalene units. The four doublets in the ^{1}H NMR spectrum of **41a** at δ 4.33, 4.36, 4.59 and 4.73 with J = 14.0, 13.0, 14.2 and 13.4 Hz, respectively, were assigned to two different types of methylene protons. Figure 2.4 shows the COSY spectrum of **41a** which confirms the correlation of the four pairs of doublets for the two different types of methylene protons.

An interesting pattern is found for both the *n*-propyl and the isopropyl groups in **41a** and **41b**, respectively. Figure 2.4 clearly reveals two sets of signals at δ 4.00 - 4.05 and δ 4.11 - 4.16 for the pair of methylene protons α to the oxygen atom of compound **41a** indicating that these protons are diastereotopic. The methine proton of the isopropyl group in **41b** appears as a septet at δ 4.46 - 4.54 in the ^{1}H NMR spectrum indicating the proton is in a chiral environment. The doublets signal at δ 1.54 and δ1.66 (vicinal coupling with the methine proton) are assigned to the diastereotopic methyl groups in the isopropyl group (**41b**) as shown in the COSY NMR spectrum (Figure 2.5). Diastereotopicity of the protons α to the oxygen atoms in **41a** and **41b** indicates that the conformational inversion (*cone* to *cone*) of these

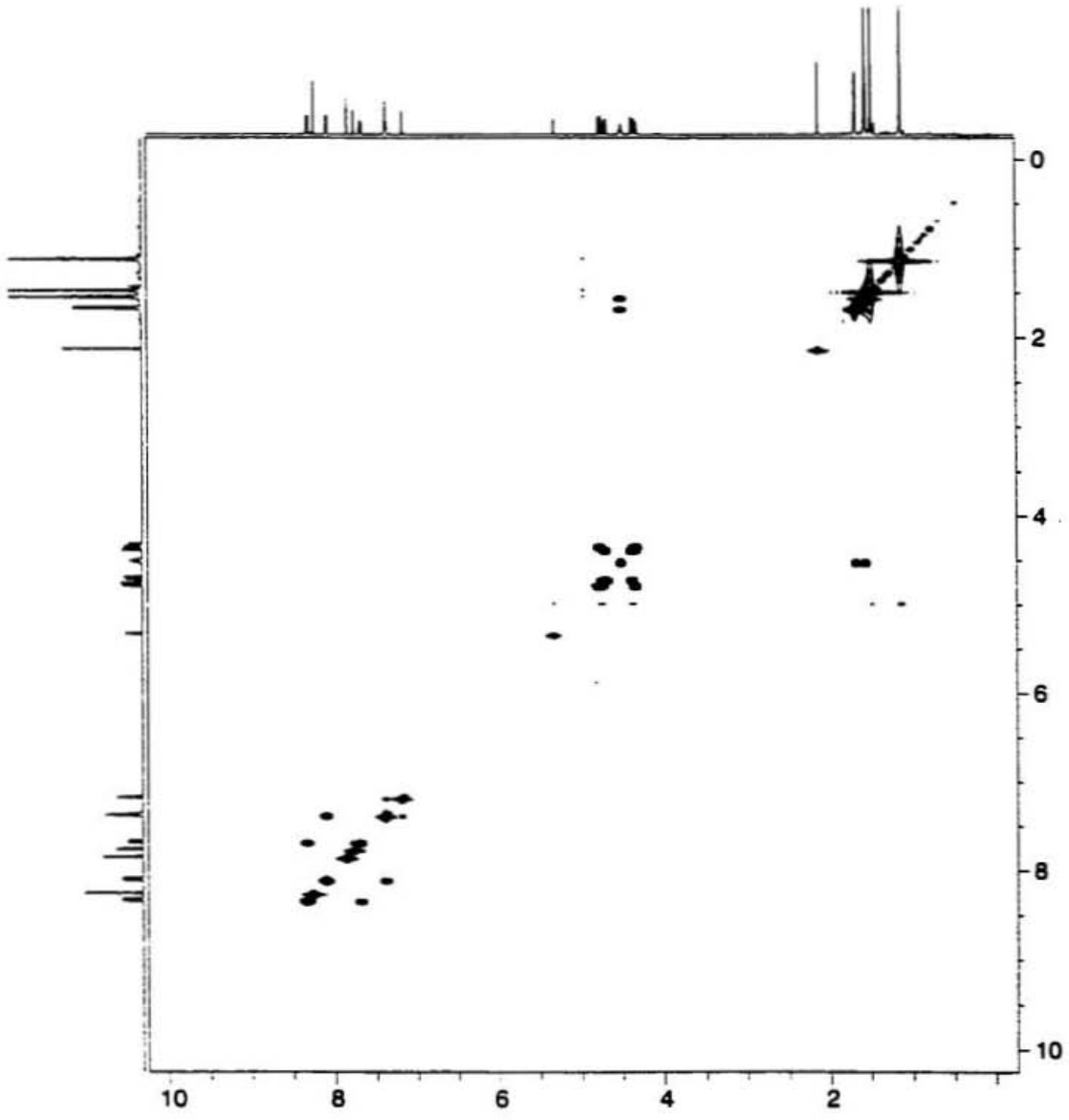


Figure 2.5 ^{1}H COSY spectrum of compound 41b

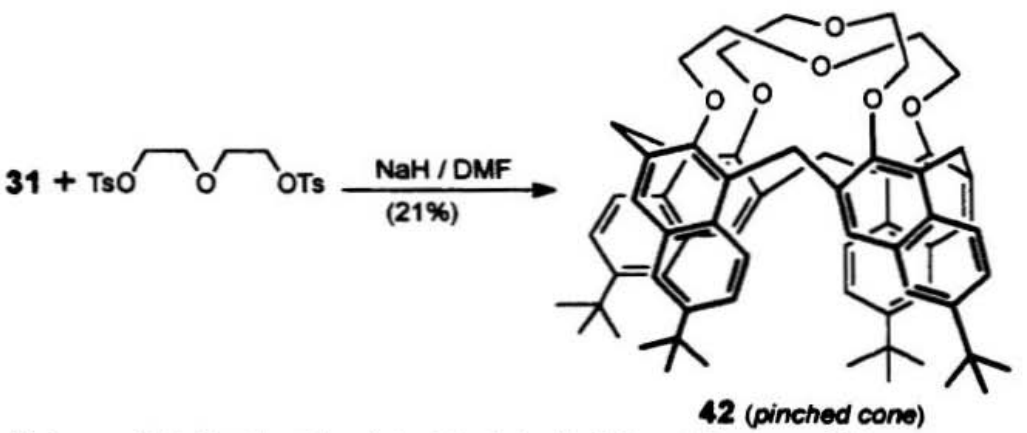
molecules at ambient temperature is either slow on NMR time scale, or non-exist out and that the conformation is fixed. These findings are consistent with the patterns observed with some ester derivatives of **31**.[58]

A NOED experiment on **41b** allowed the conclusion that **41b** was in a *cone* conformation. When the signals due to *tert*-butyl groups were irradiated, the only signals that showed NOE enhancements were those due to the naphthalene protons which are *ortho* to the *tert* butyl group, while saturation of the signals due to methyl groups of the isopropyl moiety did not enhance any signal except for the methine proton. This experiment clearly demonstrated that the molecule does not exhibit ring inversion and that it is therefore in a fixed *cone* conformation. (+)-FAB mass spectral analysis of compounds **41a** and **41b** showed the expected molecular ion peak at *m/z* 963 was the base peak. These derivatives (**41a-b**) of **31** are potential useful as hosts for metal ions of complementary sizes. Further complexation studies are currently underway in our laboratory.

2.4 Synthesis of *tert*-butylcalix[4]naphthalene-1,3-crown

Calixcrowns are a family of macropolycyclic molecules in which subunits consisting of calixarenes and crown ethers are combined through the bridging of the phenolic oxygen atoms of the calixarene units by poly(oxyethylene) chains. In 1983 Alfieri *et al.*[73] reported the synthesis of the first calixcrown. As calixcrowns possess well-preorganized structures and more rigid binding sites in comparison with calixarenes and crown ethers, they exhibited superior recognition ability towards

alkali metal cations. For example, the Na^+/K^+ selectively attainable with crown ethers[74] is of the order of 10^2 and with calixarenes the best selectivity that has been reached was in the order of $10^{3.1}$. The Na^+/K^+ selectivity of diethoxycalix[4]arene-crown-4,[74] can reach as high as $10^{5.3}$ due to the additional π-cation interaction possible, since the molecule exists in a *partial cone* conformation. Due to this degree of selectivity, much attention has been paid to the synthesis of structurally complex molecules. It was reasoned that a *tert*-butylcalix[4]naphthalene-crown **42** should have a deeper well-defined rigid cavity, and might demonstrate potentially interesting ion selectivity.



42 (*pinched cone*)

Scheme 2.4 Synthesis of *tert*-butylcalix[4]naphthalene-1,3-crown

Synthesis of the first calix[4]naphthalene-1,3-crown **42** was achieved by reaction of ditosylate and **31** as a beige solid in 21% yield (Scheme 2.4). Its structure was confirmed by its NMR (^1H, ^{13}C and COSY) spectra and its CI mass spectral analysis indicated the presence of the expected molecular ion peak.

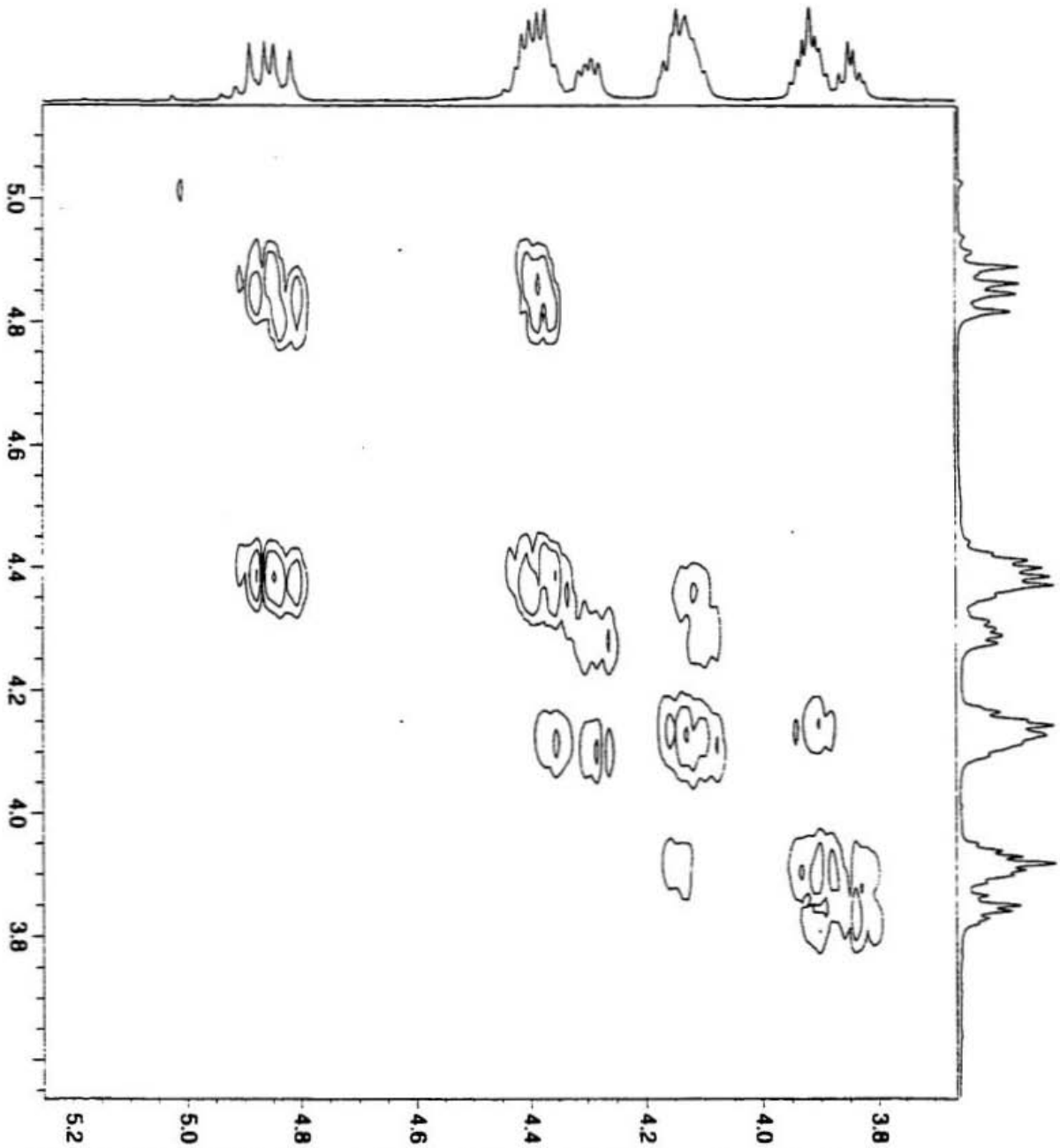


Figure 2.6 ^{1}H COSY spectrum of the methylene region of 42

1.51 in a 1:1 ratio, which are due to the two different *tert*-butyl groups. The multiple peaks between δ 3.75-4.90 can be assigned to the methylene bridges linking the naphthalene units and to the -OCH_2CH_2O- groups of the bridging crown. A COSY experiment showed that the two doublets centered at δ 4.71 and 4.75 are coupled to the doublets which are embedded in the multiplet centered at δ 4.40 (Figure 2.6). On the basis of the large coupling constant of the doublets centered at δ 4.71 and 4.75, these peaks can be assigned to the methylene bridge protons between the naphthalene units and two different *tert*-butyl groups, suggesting that compound **42** is in a fixed "*pinched cone*" conformation. The COSY experiment also shows that the multiplets centered at δ 4.40 and δ 4.30 are coupled to multiplets centered at δ 4.13. These multiplets at δ 4.13, 4.30 and 4.40 can be assigned to the -OCH_2CH_2O- protons of **42**. This is consistent with the structure of **42** since two AB systems would be expected for the methylene bridge protons, and each methylene group of the -OCH_2CH_2O- protons were expected to be diastereotopic in a manner similar to those found in **41a** and **41b**. A NOED experiment on **42** further supported the conclusion that the molecule was in a "*pinched cone*" conformation: saturation of the signals due to the protons of the methylene groups bridging the naphthalene units at δ 4.79 - 4.86 resulted in enhancements of the naphthalene (H-10, H-20, H-30, H-40) signals by 3% as well as the signal (2%) due to the methylene protons of the ethylene bridge. CI mass spectral analysis was also consistent with the expected structure since there was a molecular ion peak at *m/z* = 1007 (relative intensity, 75),

and a peak at *m/z* 951 (relative intensity, 60) which represents the loss of one *tert*-butyl group from the molecular ion peak.

In summary, it has been shown that **31** can be synthesized in relatively large amounts and that it has the ability to encapsulate [60]fullerene[68] in its cavity (not demonstrated in this thesis). Also, alkyl ether derivatives (**41a-b**) of **31** have been synthesized and, their conformational properties have been determined from ^{1}H NMR spectra. Finally the first crown derivative of **31**, which is found to exist in a *"pinched cone"* conformation, is reported.

2.5. Experimental Section

General Methods: All reactions were performed under argon unless otherwise indicated. Organic solvents were removed under reduced pressure using a rotary evaporator. Flash column chromatography was performed using MERCK silica gel 230-400 mesh. Preparative thin-layer chromatography (TLC) plates were made from Aldrich silica gel (TLC standard grade, 2-25 microns) with added 14% calcium sulphate, and also from Scientific Adsorbent Inc., silica gel (TLC standard grade 2-25 microns) with calcium sulphate as a binder. Thin-layer chromatography was performed using precoated silica gel 60 F_{254} plates (Merck).

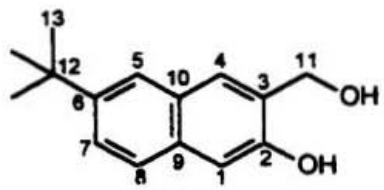
Materials: All chemical reagents and solvents whose synthesis are not described in this thesis were purchased from Aldrich or Fluka. Palladium catalysts were supplied by Alfa Aesar Matheson and by a generous gift from Dr. P. Johnson of Johnson Matthey. Anhydrous methylene chloride and benzene were obtained by

drying over calcium hydride. Anhydrous *N,N*-dimethylformamide (DMF) was obtained by drying over magnesium sulphate. Anhydrous pyridine was obtained by drying over potassium hydroxide prior to distillation. Anhydrous tetrahydrofuran (THF) was obtained prior to use by drying over sodium metal and benzophenone as an indicator under nitrogen.

Instrumentation: Infrared (IR) spectra were recorded as a liquid film or as a KBr disk on a Mattson Polaris FT instrument. Data are presented as follows: frequency of absorption (cm^{-1}), intensity (s = strong, m = medium, w = weak, br = broad), and assignment (when appropriate). Melting points (mp) were determined on a Fisher-Johns apparatus and are not corrected. Low resolution mass spectral (*ms*) data were obtained using a V.G. Micromass 7070 HS instrument. MS data are presented as follows: *m/z*, intensity, and assignment (when appropriate). Fast atom bombardment (FAB) MS were obtained using *m*-nitrobenzyl alcohol as a matrix with a Kratos MS50TC spectrometer at the Department of Chemistry, University of Manitoba, Winnipeg using the following operating conditions: Vacc = 4,000 volts; FAB gun set at 7.0 - 7.5 kV, using xenon as the FAB gas; resolution = 1500; accelerating voltage = 6 kV. "In some cases, where noted, HRMS data were conducted on a Quattro 2 with APCI in negative or positive mode." ^{1}H and ^{13}C NMR spectra unless otherwise noted were recorded in $CDCl_3$ and tetramethylsilane (TMS) was used as an internal standard at 300 MHz GE GN-300 NB or Bruker Avance 500 spectrometers, operated in Pulse mode. Data are presented as follows: chemical

shift, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, m = multiplet, sept = septet), coupling constant (*J*, Hz), integration (# of H), and assignment (when appropriate). The assignments are based on COSY, and NOED experiments. Chemical shifts in the ^{13}C NMR spectra are relative to solvent shifts (δ 77.0 for $CDCl_3$; δ 54.0 for CD_2Cl_2; δ 128.3 for C_6D_6 and δ 150.4 for pyridine-d_5).

6-*tert*-Butyl-3-(hydroxymethyl)-2-naphthol (29)

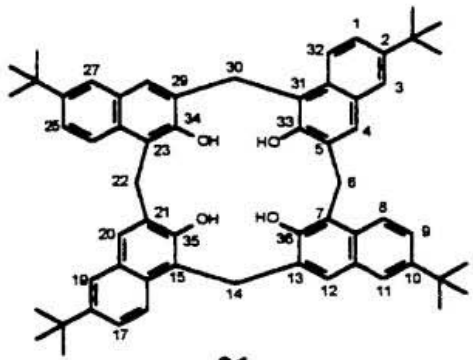


29

To a suspension of $LiAlH_4$ (1.5 g, 38 mmol) in anhydrous THF (150 mL) at 0 °C under argon was added via cannula a solution of **40** (5.0 g, 19 mmol) in anhydrous THF (25 mL). The reaction was completed in 2 h, after which time the reaction was quenched by the slow addition of aqueous 5% HCl (20 mL), and then the organic solvent was evaporated. The resulting slurry was diluted with ethyl acetate. The organic layer was washed with aqueous saturated NH_4Cl, brine and then dried over anhydrous $MgSO_4$ and filtered. After the solvent was evaporated, the yellow solid residue was crystallized from ethyl acetate-hexane to afford **29** (4.1 g, 91%): mp 153-155 °C (174-176 °C)[58]; ^1H NMR (300 MHz) δ 1.39 (s, 9H, H-13), 2.25 (br, t, *J* = 5.2 Hz, OH, D_2O exchangeable), 4.99 (d, *J* = 4.8 Hz, 2H, H-11), 7.09 (br, 1H, OH, D_2O exchangeable), 7.20 (s, 1H, H-1), 7.53 (d, *J* = 8.7 Hz, 2H, H-7, H-8), 7.62 (s,

1H, H-5), 7.65 (s, 1H, H-4).

2,10,18,26-Tetra-*tert*-butyl-6*H*,14*H*,22*H*,30*H*-5,31:7,13:15,21:23,29-tetramethanotetrabenzo[a,g,m,s]cyclotetracosene-33,34,35,36-tetrol (31)

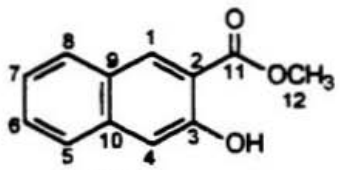


31

To a solution of **29** (3.00 g, 13.1 mmol) in dioxane (300 mL) at rt was added $TiCl_4$ (1.43 mL, 13.1 mmol). The yellow reaction mixture was heated at reflux for 72 h, cooled to rt and silica gel (~3 g) was added to the mixture, then the solvent was evaporated. The brown material was placed on the top of a column and purified by flash column chromatography eluting with 1:1 petroleum ether-CH_2Cl_2 to afford a brown solid. The solid was repeatedly washed with cold acetone to afford **31** (536 mg, 19%): mp >320 °C (mp 246-249 °C)[58]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 36H, *tert*-butyl), 4.52 (s, 8H, H-6, H-14, H-22, H-30), 7.51 (s, 4H, H-3, H-11, H-19, H-27), 7.57 (dd, J = 1.5, 7.8 Hz, 4H, H-1, H-9, H-17, H-25), 7.76 (s, 4H, H-4, H-12, H-20, H-28), 8.27 (d, J = 9.0 Hz, 4H, H-8, H-16, H-24, H-32), 10.63 (s, 4H, OH); ^{13}C NMR δ 26.0 (C-6, C-14, C-22, C-30), 31.2 ($C(\underline{C}H_3)_3$), 34.4 ($\underline{C}(CH_3)_3$), 119.3 (C-2, C-

10, C-18, C-26), 122.6 (C-8, C-16, C-24, C-32), 123.7 (C-3, C-11, C-19, C-27), 125.0 (C-1, C-9, C-17, C-25), 128.2 (C-5, C-13, C-21, C-29), 129.2 (C-4, C-12, C-20, C-28), 129.7, 129.9, 145.8 (C-7, C-15, C-23, C-31), 147.6 (C-33, C-34, C-35/36).

Methyl 3-hydroxy-2-naphthoate (39)

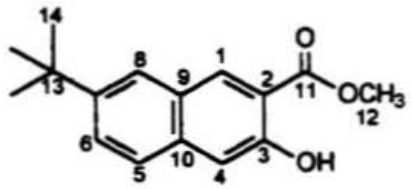


39

To a solution of 3-hydroxy-2-naphthoic acid (**38**) (29.0 g, 154 mmol) in CH_3OH (150 mL) at rt was added dropwise conc. H_2SO_4 (7.80 mL). The yellow reaction solution was then heated at reflux for 16 h. Upon cooling to room temperature, a yellow precipitate formed which was filtered, washed with aqueous 10% $NaHCO_3$, water and dried under vacuum to afford **39** (30.3 g, 97%): mp 71-72 °C (mp 69-70 °C)[58]; ^{1}H NMR (300 MHZ, $CDCl_3$) δ 4.02 (s, 3H, H-12), 7.32 (m, 2H, H-4, H-6), 7.50 (t, J = 8.4 Hz, 1H, H-7), 7.68 (d, J = 8.4 Hz, 1H, H-5), 7.80 (d, J = 8.4 Hz, 1H, H-8), 8.49 (s, 1H, H-1), 10.43 (s, 1H, OH).

Methyl 7-*tert*-butyl-3-hydroxy-2-naphthoate (40)

To a solution of **39** (12.5 g, 61.8 mmol) in 1,1,2,2-tetrachloroethane (220 mL) at 0 °C was added *tert*-butyl chloride (26.9 mL, 247 mmol). To this solution was added $AlCl_3$ (16.5 g, 124 mmol) in three portions. The mixture was stirred for 16 h, then cooled to 0 °C and quenched by the addition of water. The organic layer was

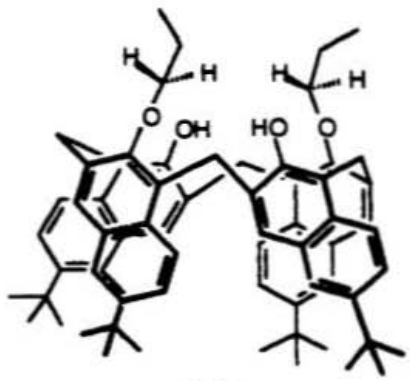


40

extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. After removing the excess 1,1,2,2-tetrachloroethane by vacuum distillation, the crude product was purified by flash column chromatography eluting with 5:95 ethyl acetate-petroleum ether to afford **40** (12.7 g, 80%) as a colourless solid: mp 90-92 °C (mp 102-103 °C)[58]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H, H-14), 4.02 (s, 3H, H-12), 7.27 (s, 1H, H-8), 7.58 - 7.64 (m, 2H, H-5, H-6), 7.71 (s, 1H, H-4), 8.47 (s, 1H, H-1), 10.37 (s, 1H, OH).

2,10,18,26-Tetrakis(1,1-dimethylethyl)-6*H*,14*H*,22*H*,30*H*-5,31:7,13:15,21:23,29-tetramethanotetrabenzo[a,g,m,s]cyclotetracosene-33,35-bis(propyloxy)-34,36-diol (41a)

To a 25 mL round-bottomed flask equipped with a stirring bar and a rubber septum was added **31** (70 mg, 0.083 mmol), and NaH (60% suspension in oil 0.32 g, 8.3 mmol). After flushing the flask with argon, anhydrous DMF (5 mL) was added. The mixture was stirred for 30 min, then 1-iodopropane (1.10 mmol) was added. The mixture was stirred at room temperature for 16 h. The residue was then diluted with ethyl acetate (15 mL) and the excess of NaH was quenched with H_2O. The organic layer was washed with aqueous 10% HCl (2x5 mL) and brine, and dried over

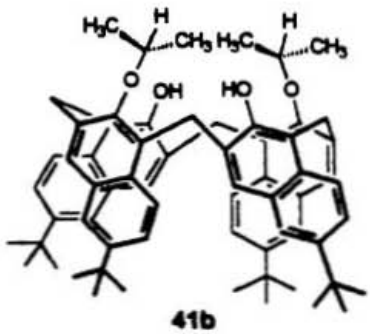


41a

anhydrous $MgSO_4$ and filtered. After the solvent was evaporated, the crude product was purified by preparative TLC using 25:75 CH_2Cl_2-petroleum ether as eluent, to afford starting material (20 mg), an minor unidentified component and **41a** (43 mg, 56%) as a colourless solid: mp 330-333 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 18H, *tert*-butyl), 1.37 (t, J = 7.5 Hz, 6H, $OCH_2CH_2C\underline{H}_3$), 1.46 (s, 18H, *tert*-butyl), 2.16 (m, 4H, $OCH_2C\underline{H}_2CH_3$), 4.03 (m, 2H, $OC\underline{H}H'CH_2CH_3$), 4.14 (m, 2H, $OCH\underline{H}'CH_2CH_3$), 4.33 (d, J = 14.0 Hz, 2H, -$C\underline{H}_2$-), 4.36 (d, J = 13.0 Hz, 2H, -$C\underline{H}_2$-), 4.59 (d, J = 14.2 Hz, 2H, -$C\underline{H}_2$-), 4.73 (d, J = 13.4 Hz, 2H, -$C\underline{H}_2$-), 7.18 (d, J = 1.8 Hz, 2H), 7.33 (d, J = 1.9 Hz, 2H), 7.35 (d, J = 1.9 Hz, 2H), 7.36 (s, 2H), 7.63 (dd, J = 1.9, 8.8 Hz, 2H), 7.73 (d, J = 1.9 Hz, 2H), 7.83 (s, 2H), 8.08 (d, J = 9.0 Hz, 2H), 8.30 (d, J = 8.8 Hz, 2H), 8.56 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0 ($OCH_2CH_2\mathbf{C}H_3$), 23.6 ($OCH_2\mathbf{C}H_2CH_3$), 23.7, 29.4, 31.0, 31.4, 34.3 (-$\mathbf{C}H_2$-), 34.5 (-$\mathbf{C}H_2$-), 78.0 ($\mathbf{O}CH_2CH_2CH_3$), 121.2, 122.6, 123.3, 124.1, 124.2, 124.8, 127.4, 128.1, 128.5, 129.2, 129.6, 129.6, 130.8, 131.5, 134.1, 144.3, 146.4, 150.7, 152.2; HRMS

(APCI -ve mode): calcd for $C_{86}H_{76}O_4$ $(M-H)^-$ 931.5661, found 931.4106.

2,10,18,26-Tetrakis(1,1-dimethylethyl)-6*H*,14*H*,22*H*,30*H*-5,31:7,13:15,21:23,29-tetramethanotetrabenzo[a,g,m,s]cyclotetracosene-33,35-bis(isopropyloxy)-34,36-diol (41b)



41b

To a solution of **31** (50 mg, 5.9 mmol) in THF (8 mL) was added NaH (60 % suspension in oil, 11 mg, 0.3 mmol). The resulting slurry was stirred at room temperature for 30 min, then 2-iodopropane (0.03 mL, 0.2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, and quenched with 10% aqueous HCl (5 mL). The solvent was evaporated and the crude product was diluted with ethyl acetate (10 mL) washed with brine, dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC eluting with 5:95 ethyl acetate-hexane to afford **41b** (20 mg, 36%): mp >300 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 1.12 (s, 18 H, *tert*-butyl), 1.47 (s, 18 H, *tert*-butyl), 1.54 (d, J = 6.1 Hz, 6 H, OCH(C$\underline{H}_3$)(CH_3')), 1.66 (d, J = 6.1 Hz, 6 H, OCH(CH_3)(C$\underline{H}_3$')), 4.32 (d, J = 13.7 Hz, 2 H, -C$\underline{H}_2$-), 4.36 (d, J

= 14.2 Hz, 2 H, -C<u>H</u>$_2$-), 4.50 (sep, 2 H, OC<u>H</u>(CH$_3$)$_2$), 4.70 (d, *J* = 14.2 Hz, 2 H, -C<u>H</u>$_2$-), 4.76 (d, *J* = 13.5 Hz, 2 H, -C<u>H</u>$_2$-), 7.16 (d, *J* = 1.9 Hz, 2 H), 7.37 (m, 4 H), 7.65 (d, *J* = 2.1 Hz, 2 H), 7.67 (d, *J* = 2.0 Hz, 2 H), 7.75 (d, *J* = 1.7 Hz, 2 H), 7.83 (s, 2 H), 8.09 (d, *J* = 9.1 Hz, 2 H), 8.24 (s, 2 H), 8.32 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR (125 MHz, CD_2Cl_2 δ 22.2 (OCH(**C**H$_3$)$_2$), 22.5 (OCH(**C**H$_3$)$_2$), 24.9, 30.5, 31.2, 31.3, 31.7, 34.8 (-**C**H$_2$-), 35.0 (-**C**H$_2$-), 79.7 (O**C**H(CH$_3$)$_2$), 121.9, 123.3, 123.8, 123.8, 123.9, 124.5, 125.5, 128.2, 128.7, 128.9, 129.1, 130.0, 131.2, 132.1, 135.7, 145.2, 147.2, 149.9, 152.6; (+)-FAB MS (*m/z*): 932 (M$^+$, 100), 848 (20), 829 (60), 811 (35), 617 (30), 407 (40).

33,35-Dihydroxy-34,36-bis(crown-3)-*tert*-butylcalix[4]naphthalene, *pinched cone* conformer (42)

42

To a solution of **31** (100 mg, 0.118 mmol) in anhydrous DMF (5 mL) at room temperature was added NaH (60% dispersion in oil, 45.3 mg, 1.18 mmol). The mixture was stirred for 45 min, then a solution of diethylene glycol *p*-ditosylate (218 mg, 0.590 mmol) in DMF (2 mL) was added over 10 min. The mixture was stirred

for another 36 h, then the excess of NaH was quenched by the slow addition of water. The organic layer was extracted with ethyl acetate (3x15 mL) and the combined organic layers dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by preparative TLC eluting with 20:80 ethyl acetate-hexane to afford **42** (24 mg, 21%) as a beige solid: mp > 300 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 1.03 (s, 18H, *tert*-butyl), 1.38 (s, 18H, *tert*-butyl), 3.70-3.74 (m, 2H), 3.76-3.83 (m, 4H), 3.97-4.04 (m, 6H), 4.15-4.19 (m, 2H), 4.23-4.32 (m, 6H), 4.71(d, J = 14.5 Hz, 2H, -C$\underline{H}_2$-), 4.75 (d, J = 13.3, 2H, -C$\underline{H}_2$-), 7.07 (s, 2H), 7.25 (m, 4H), 7.57 (dd, J = 2.0, 9.0 Hz, 2H), 7.67, (s, 2H), 7.77 (s, 2H), 7.98 (d, J = 9.0 Hz, 2H), 8.16 (s, 2H, OH), 8.23 (d, J = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 20.8 (C(**C**H$_3$)$_2$, 26.7 (C(**C**H$_3$)$_2$), 27.1 (**C**(CH$_3$)$_2$), 27.8 (**C**(CH$_3$)$_2$), 31.0 (**C**H$_2$), 31.6 (**C**H$_2$), 67.5, 68.1, 68.7, 74.2, 117.6, 119.3, 120.1, 120.3, 120.5, 121.0, 121.2, 121.4, 122.3, 126.1, 126.2, 126.8, 127.1, 128.7, 129.1, 131.1, 141.6, 142.9, 148.1, 149.8; CI MS (*m/z*): 1007 (M^++1, 75), 951 (58), 895 (10), 677 (9), 391 (100), 363 (95), 285 (78).

Chapter 3

Synthesis of "C-12" *endo* Calixnaphthalenes and Their Derivatives

3.1 Introduction

The Georghiou group has been involved in the synthesis of various calixnaphthalenes since their discovery in 1992-1993. Such molecules (**16-19**) could be formed from the 'one-pot' reaction of 1-naphthol (**15**) and formaldehyde, and later, by multi-step convergent approaches.[40,43] These initial calixnaphthalenes have their hydroxyl groups situated within the 16-membered macrocyclic array ("annulus") and are thus of the "*exo*" type. Böhmer *et al.*[49] in 1993 reported, as an aside to their main objectives, the synthesis of only *endo* calix[4]naphthalene (**30**). Such *endo* calixnaphthalenes (**30-31**) are by analogy closer in structure to the better-known calixarenes.

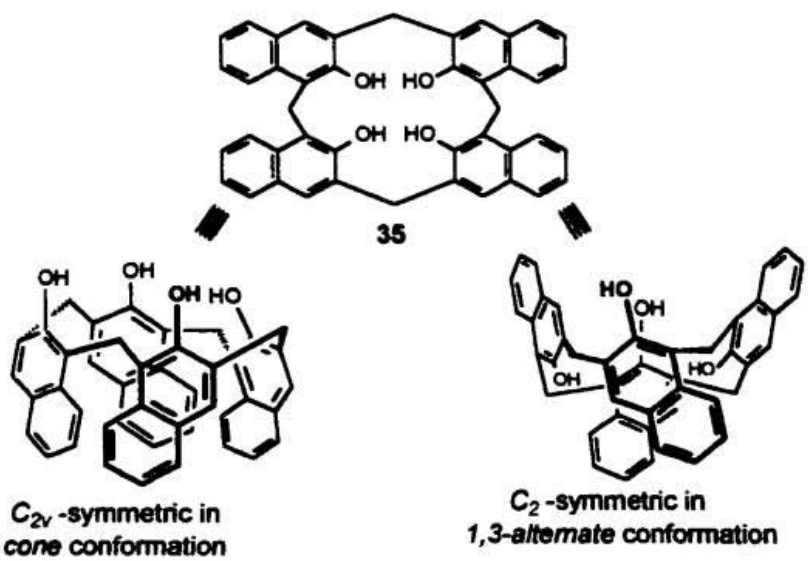
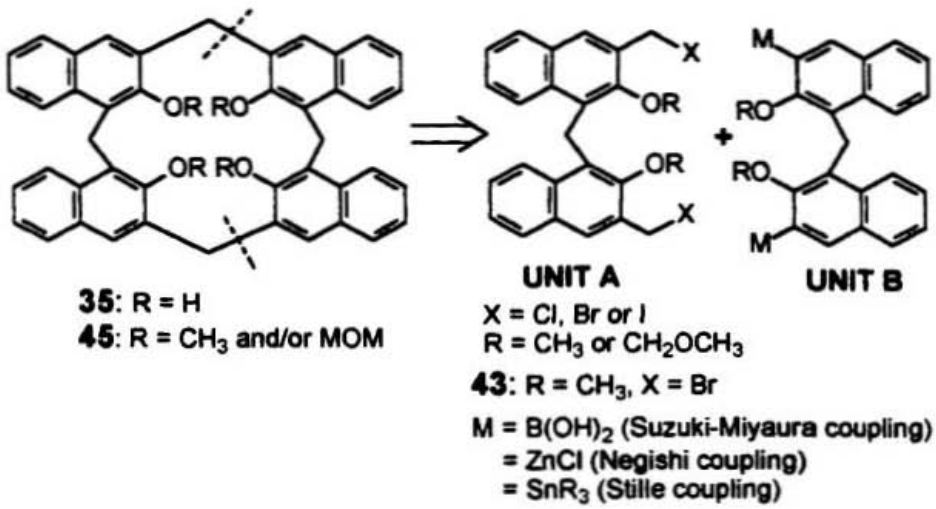
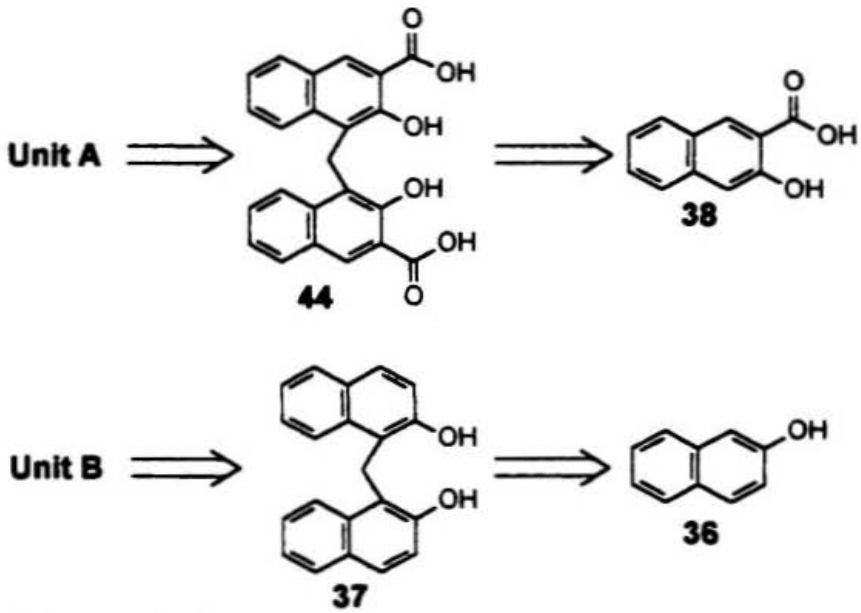


Figure 3.1 Different conformation of 35



Scheme 3.1 Retrosynthetic analysis of 35

Examination of CPK molecular models revealed that in its *cone* conformation compound **35** has C_{2v} symmetry, but that in its *1,3-alternate* conformation the molecule has C_2 symmetry (Figure 3.1). An interesting feature is that new "calixnaphthalene-crown" compounds can be envisioned for **35** in its *1,3-alternate* conformation by derivatizing the hydroxyl groups with poly(ethylene) glycol units **35e** (Figure 1.7). Such compounds could augment the metal cation-complexing ability of crown-ethers with the additional π-metal interactions that are possible as a result of the presence of the additional rings of the naphthalene units. A retrosynthetic analysis (Scheme 3.1) shows how **35** might be obtained by the coupling of two different units: Unit A and Unit B. These Units can be readily obtained from inexpensive, commercially-available 2-naphthol (**36**) and 3-hydroxy-2-naphthoic acid (**38**), respectively, as depicted in Scheme 3.2. The important features in the



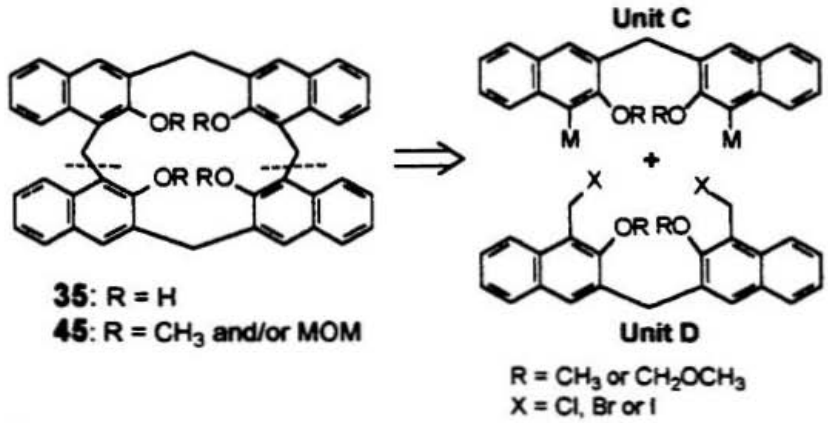
Scheme 3.2 Retrosynthetic analysis of Unit A and Unit B

retrosynthetic strategy envisioned are: (a) the palladium-catalyzed coupling reaction of the benzylic-type halides Unit A with organometallic intermediates Unit B; and (b) the double *ortho* metallation of **37** and its derivatives which produces the organometallic intermediate Unit B needed in (a). There are many established transition metal catalyzed methods used for the formation of carbon-carbon bonds.[75] Some of these are: a) Ni(0)-catalyzed aryl metal-aryl halide cross-coupling reactions to produce biaryls as reported independently by Kumada[76a] and Corriu;[76b] b) Negishi[77] coupling reactions between aryl zinc and aryl halide substrates; c) Suzuki-Miyaura[78] Pd(0)-catalyzed cross-coupling of aryl boronic acids with aryl halides; and d) Stille[79] coupling between aryl tin and aryl halides and/or aryl triflates. A wide range of aryl- and 1-alkenylborane reagents are known to undergo the Pd(0)-

catalyzed cross-coupling reactions with alkyl, allylic, 1-alkenyl, aryl and 1-alkynyl substrates.[75] However, at the onset of this work there was only one reported example in which a benzylic halide, namely 2,4-dimethoxybenzyl chloride, had been employed with Suzuki-Miyaura type conditions.[80] In this example, the benzylic chloride was coupled with 1-naphthylboronate, which was generated *in situ* from 1-bromonaphthalene in a modification of the Suzuki-Miyaura reaction conditions. Negishi[81] had earlier reported Pd(0)- and Ni(0)-catalyzed preparations of unsymmetrical diarylmethanes from the corresponding benzylic bromides or benzylmagnesium chlorides with aryl bromides or iodides. There are other instances in which Pd(0)-catalyzed coupling of benzylic halides under Stille-type conditions have been reported.[82] Brandsma *et al.*[83] evaluated benzyl-aryl cross-coupling for the syntheses of various tetrachlorobenzyltoluenes using four different transition-metal catalysts with a number of different aryl metal compounds. However, they did not employ Suzuki-Miyaura conditions.

In typical *ortho* metallation conditions,[84] a "Directing *ortho* Metallation" (DoM) group is used on a aromatic ring to direct the metallation onto the *ortho* position using an alkyllithium base. In the case of **37**, however the methylene protons linking the two naphthalene units are doubly benzylic and can be easily deprotonated by an alkylithium base such as *n*-BuLi. Therefore, it was first necessary to explore the appropriate conditions needed for the double *ortho* metallation in the presence of the methylene protons and the subsequent transition metal-catalyzed cross-coupling

reaction for effective carbon-carbon bond formation with such dinaphthylmethane systems.

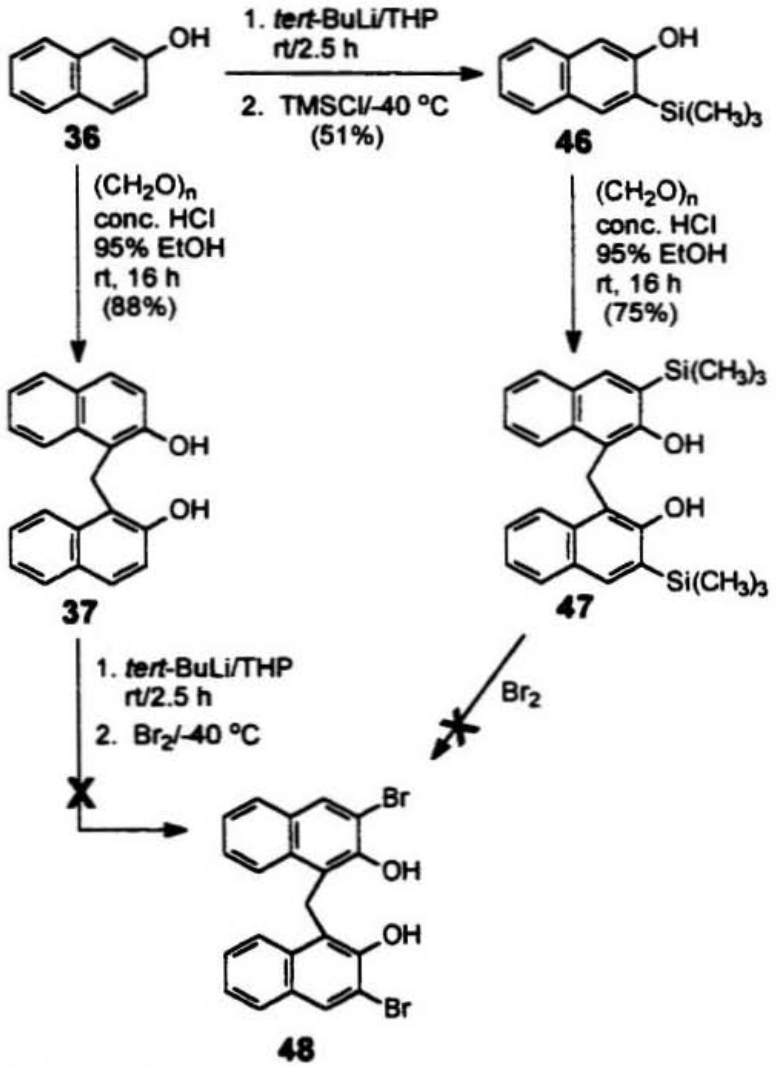


Scheme 3.3 Alternative retrosynthetic route of 35

A similar retrosynthetic approach to that of Scheme 3.1 can be envisioned to synthesize **35** from the palladium-catalyzed intermolecular coupling reactions of the alternative units, Unit C and Unit D (Scheme 3.3). This chapter will deal with the investigations of (a) the scope and limitations of the *ortho* metallation of naphthalene and bis(naphthalene) systems; and (b) the scope and limitations of Suzuki-Miyaura type cross-coupling between benzylic- and naphthylic-type halides and aromatic boronic acids. These methodologies were employed for the synthesis of "C-12" *endo* calix[4]naphthalenes (**35**) and several other types of calix[4]naphthalenes described herein.

3.2 Double *ortho* metallation of bis(2-hydroxynaphthyl)methane system

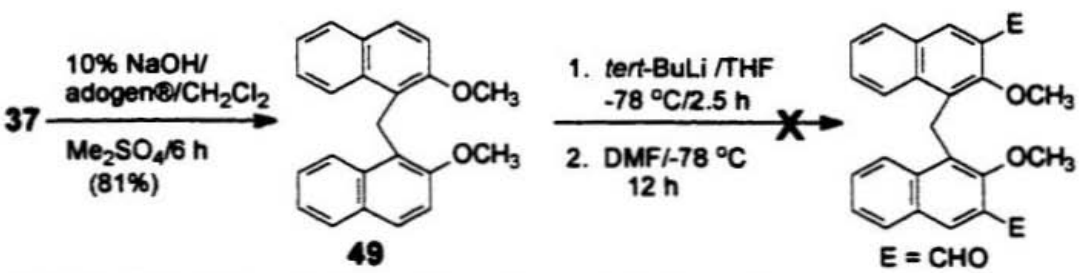
The work of Saà *et al.*[85] using 2-naphthol (**36**) was repeated in order to evaluate the efficacy of the double *ortho* metallation with methylene bridge-linked



Scheme 3.4 Attempted synthesis of compound 48

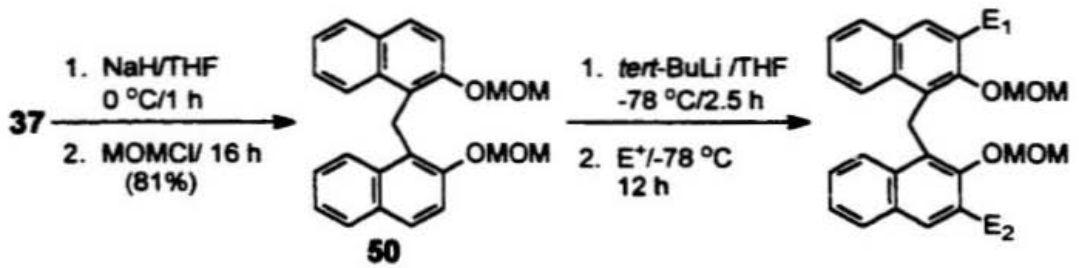
bis(naphthalene) systems such as **37**. When **36** was reacted with *tert*-BuLi in tetrahydropyran (THP) at room temperature, an exothermic reaction ensued (Scheme 3.4). The resulting brown reaction mixture was stirred for 2.5 h, and was then quenched with chlorotrimethylsilane at -40 °C to obtain 3-trimethylsilyl-2-

naphthol (**46**) in 51% yield (Scheme 3.4). When a solution of **46** in 95% ethanol was treated with aqueous 37% formaldehyde solution under acid-catalysis the corresponding dimer **47** was obtained in 75% yield (Scheme 3.4). The silyl groups on compound **47**, however, could not be replaced with electrophiles such as bromine to produce **48**. Using dimer **37** (obtained in 88% yield from **36** using aqueous 37% formaldehyde solution and conc. hydrochloric acid in 95% ethanol) with Saá's *tert*-BuLi/THP conditions, followed by the addition of bromine, also failed to produce the corresponding *ortho* substituted product. In general, phenols are known not to be good DoM groups.[84] It was therefore decided to modify the hydroxyl groups of **37** into methoxy groups which are more efficient DoM groups. Conversion of the hydroxyl groups in **37** with aqueous 10% $NaOH/Me_2SO_4$ under phase-transfer catalysis conditions in CH_2Cl_2 afforded the corresponding dimethoxy compound **49** in 81% yield (Scheme 3.5). However, under typical *ortho* metallation conditions, **49** failed to produce the required *ortho* substituted product.



Scheme 3.5 Attempted double *ortho* metallation of compound 49

Compound **37** was derivatized to form the methoxymethyl ether **50** (Scheme 3.6) and carbamate **56** (Scheme 3.8), which are "known to be better" directing

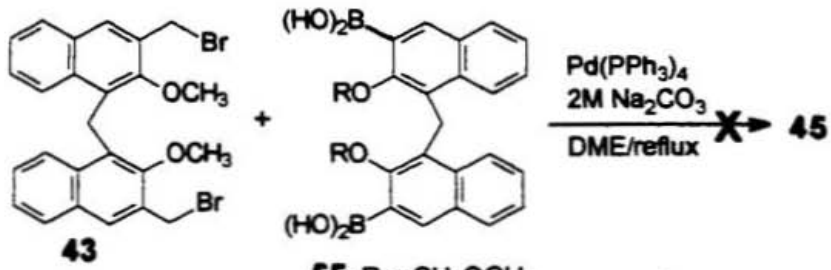


E^+ = TMSCl, **51**: $E_1 = E_2$ = TMS (37%)
E^+ = DMF, **52**: E_1 = H, E_2 = CHO (43%)
E^+ = DMF, **53**: $E_1 = E_2$ = CHO (52%)
$E^+ = I_2$, **54**: $E_1 = E_2$ = I (10%)
$E^+ = B(OCH_3)_3$, **55**: $E_1 = E_2 = B(OH)_2$ (quant.)

Scheme 3.6 Double *ortho* metallation of compound 50

groups. Treatment of **37** with NaH followed by chloromethyl methyl ether in THF gave **50** in 81% yield. After considerable experimentation, it was found that six equivalents of *tert*-BuLi on **50** at -78 °C in THF and stirring for 3 h, followed by quenching with an electrophile was needed to afford the desired *ortho* substituted product. When chlorotrimethylsilane was used as an electrophile, **51** was obtained in 37% yield. With DMF as an electrophile, both monoaldehyde **52** and dialdehyde **53** were obtained in 43% and 52% yields, respectively (Scheme 3.6). It was therefore possible to effect double *ortho* metallation of **50** by using *six* equivalents of *tert*-BuLi instead of only the stoichiometric amount of the base. Another important point to be noted here is that the use of a less bulky alkyllithium base such as *n*-BuLi did not produce the corresponding *ortho* substituted products. Other electrophiles such as iodine and trimethylborate afforded the corresponding products **54** and **55**, the former in relatively low yield (10%), and the latter in quantitative yield as the

crude product (Scheme 3.6). This compound **55**, which was a vital precursor for the coupling reaction, was not purified and was used directly in the Suzuki-Miyaura coupling reaction. However, the attempted Suzuki-Miyaura coupling reaction using **43** with **55** failed to produce the desired **45** (Scheme 3.7) and afforded **50** and a product which not could be identified.

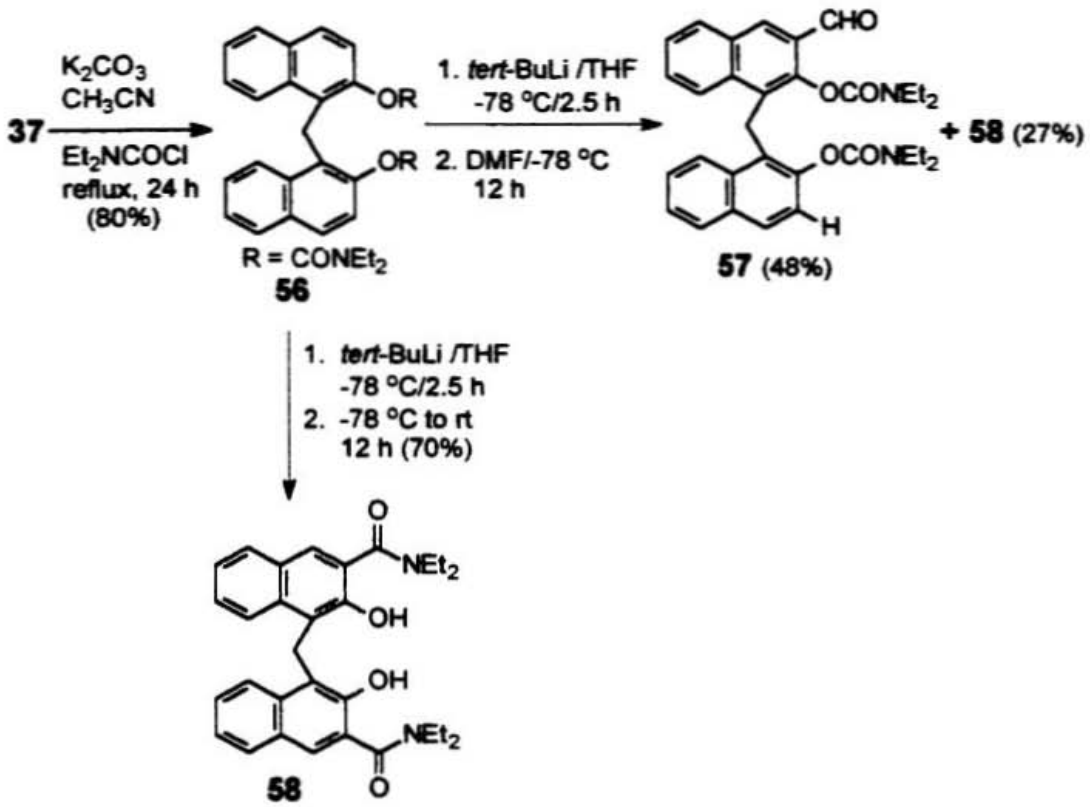


43 **55**: R = CH_2OCH_3

Scheme 3.7 Attempted cyclization of 43 and 55 using Suzuki-Miyaura Pd(0)-catalyzed conditions

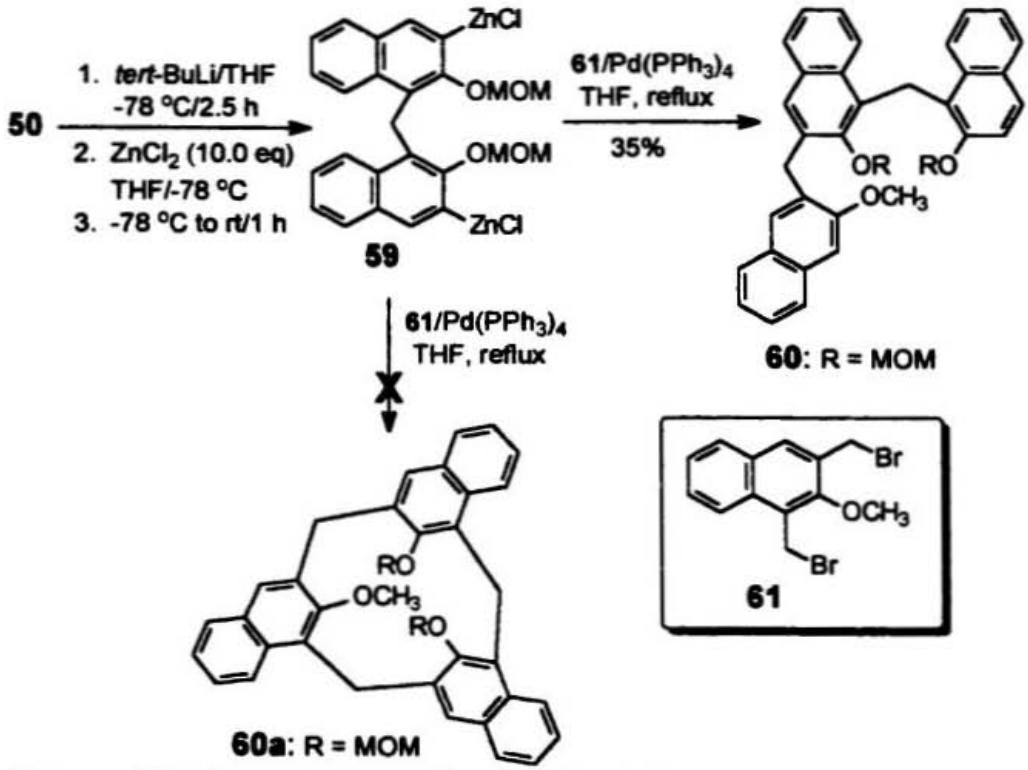
3.3 Palladium-catalyzed Negishi coupling reactions

Having failed to obtain **45** by employing the palladium-catalyzed coupling reaction conditions as shown in Scheme 3.7, it was thought that the boronic acid derivative of **50** might not have been formed during the *ortho* metallation reaction procedure. Attention was thus turned toward obtaining the pure bis(boronic acid) from the carbamate derivative **56** of bis(2-hydroxynaphthyl)methane **37**. The *ortho* metallation conditions were employed with **56** to obtain *ortho* disubstituted products **57** or **58**. Compound **56** was obtained in 80% yield from simple alkylation of **37** in acetonitrile with diethylcarbamoyl chloride in the presence of K_2CO_3 as the base (Scheme 3.8). When **56** was subjected to *ortho* metallation conditions with *tert*-BuLi



Scheme 3.8 Double *ortho* metallation of compound 56

in THF at -78 °C and stirred for 3 h, followed by the addition of DMF, both **57** and **58** were obtained in 48% and 27% yields, respectively. Similarly, compound **58** was also obtained in 70% yield from the *ortho* Fries rearrangement of compound **56** after treating it with *tert*-BuLi in THF at -78 °C, and then warming the reaction to room temperature (Scheme 3.8). The results obtained from the *ortho* metallation of both **50** and **56** provided sufficient proof that double *ortho* metallation can be accomplished, using *tert*-BuLi as the base and not necessarily requiring THP as the solvent. It was expected therefore that the corresponding boronic acid derivatives

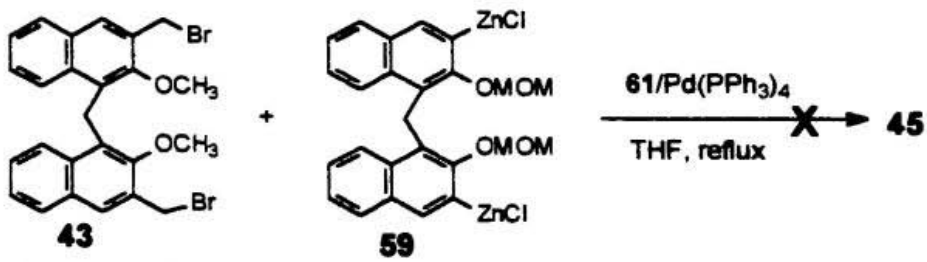


Scheme 3.9 Attempted coupling of 59 and 61 using Negishi conditions

of both **50** and **56** could be formed. Unfortunately however, when metallation conditions were employed with **50** or **56**, the corresponding boronic acids could have formed during the reactions, but could not be isolated as pure products.

It was envisioned that a Pd(0)-catalyzed Negishi-type cross-coupling reaction could be possible between **43** and the zinc derivative **59**, to furnish the target compound **35**. A model reaction between **61** and the zinc derivative **59** as shown in Scheme 3.9 was then evaluated. Treatment of **50** in THF at -78 °C with six equivalents of *tert*-BuLi and stirring for 3 h followed by the addition of $ZnCl_2$

presumably produced the corresponding organozinc species **59**, which was then added to a solution of **61** in THF with $Pd(PPh_3)_4$ as a catalyst. Compound **60** was obtained in 35% yield. The fact that the expected cyclized trimer **60a** did not form during this Negishi coupling reaction could possibly be accounted for in terms of steric factors. CPK molecular models showed the cyclized trimer to be crowded at its lower rim and therefore it is likely that coupling failed to proceed in the final reductive elimination step. A similar argument could account for why the Pd(0)-catalyzed Negishi coupling reaction of **43** and zinc intermediate **59** did not to afford the target calix[4]naphthalene **45** (Scheme 3.10).

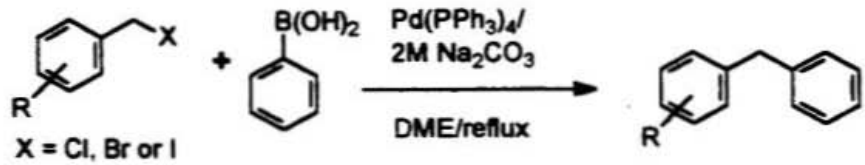


43 **59**

Scheme 3.10 **Attempted coupling of 43 and 59 using Negishi conditions**

3.4 Palladium-catalyzed coupling reaction of benzyl halides with phenylboronic acid

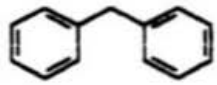
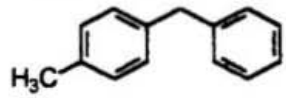
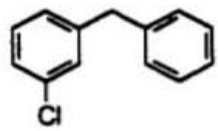
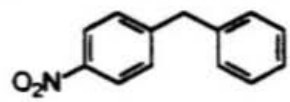
In a model study to evaluate the Pd(0)-catalyzed Suzuki-Miyaura coupling chemistry of bromomethyl-functionalized naphthalenes, preliminary investigations were carried out using benzyl bromide and several representative methyl-, chloro- or nitro-substituted benzyl bromides with phenylboronic acid itself (Scheme 3.11).[86] Aryl bromomethyl derivatives were chosen for this study mainly because they can



Scheme 3.11 **General coupling of benzyl halides and phenylboronic acid**

conveniently be prepared by a variety of methods including light-initiated bromination of methylaryls with *N*-bromosuccinimide, and direct bromomethylation of phenols or naphthols using formaldehyde and HBr in acetic acid. As summarized in Table 3.1, good yields of the mixed diarylmethanes were obtained. The yields were unaffected by the presence of either an electron-donating (Table 3.1, Entry 2) or electron-withdrawing group (Table 3.1, Entries 3 and 4) on the benzyl halide. By contrast, Miyaura *et al.*[87] reported that the presence of electron-withdrawing groups tended to diminish the yields of aryl-aryl cross-coupled products. A slightly higher yield of coupled product **63** (Table 3.1) was obtained with benzyl iodide compared to benzyl bromide (Table 3.1, Entries 2 and 5). Table 3.2 also presents the products and the respective yields of the cross-coupled products (**66-70**) obtained with benzyl halides and 3-methoxy-2-naphthylboronic acid (**72**) (Scheme 3.12). Entry 6 (Table 3.2) shows that 2,6-bis(bromomethyl)-4-*tert*-butylanisole **71** gave a relatively low yield (42%) of the coupled product **70**, a potential intermediate for a mixed calixnaphthalene-calixarene (Scheme 3.12). The relatively low yield (42%) of compound **70** could perhaps be explained in terms of the steric crowding that could

Table 3.1 Cross-coupling products of benzyl halides and phenylboronic acid, $PhB(OH)_2$.

Entry	Benzyl halide	Product	Yield (%)
1	(bromomethyl)benzene	 **62**	80
2	4-methyl-1-(bromo methyl)benzene	 **63**	75
3	3-chloro-1-(bromo methyl)benzene	 **64**	85
4	4-nitro-1-(bromo methyl)benzene	 **65**	82
5	4-methyl-1-(iodomethyl) benzene	**63**	81

occur during the oxidative step of the palladium-catalytic cycle. Furthermore, it was observed that bis(bromomethyl) compounds such as **71** could themselves undergo hydrolysis by these reaction conditions to give the corresponding diol, and thus would also lead to lower the yields of the final product.

Table 3.2 Cross-coupling products of benzyl halides and 3-methoxy-2-naphthaleneboronic acid (72).

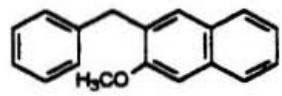
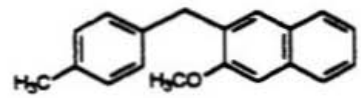
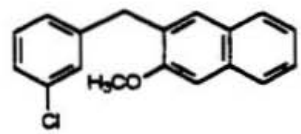
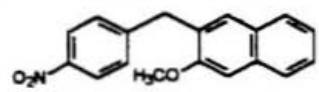
Entry	Benzyl halide	Product	Yield (%)
1	(bromomethyl)benzene	 **66**	75
2	4-methyl-1-(bromo methyl)benzene	 **67**	61
3	3-chloro-1-(bromo methyl)benzene	 **68**	70
4	4-nitro-1-(bromo methyl)benzene	 **69**	68
5	4-methyl-1-(iodomethyl) benzene	**67**	61
6	**71**	**70**	**42**

Table 3.3 Cross-coupling products of (bromomethyl)naphthalenes with phenylboronic acid ($PhB(OH)_2$) and 72.

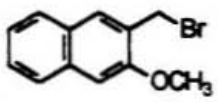
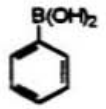
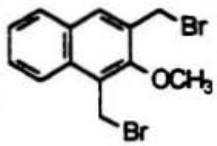
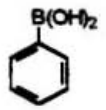
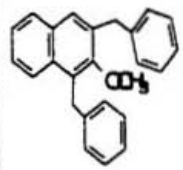
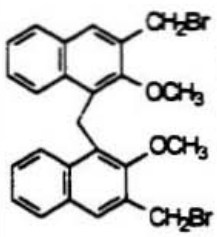
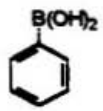
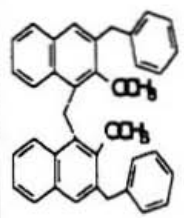
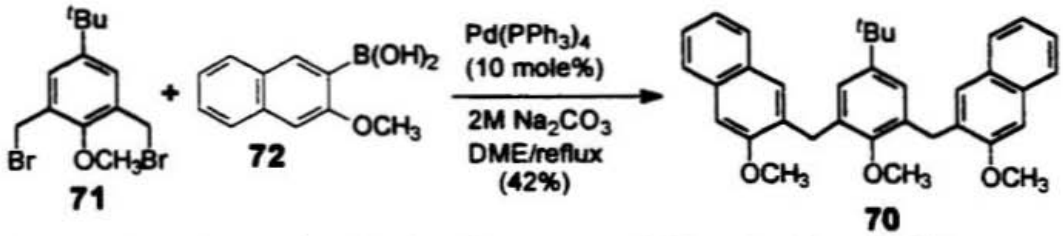
Entry	Substrate	Boronic acids	Product	Yield (%)
1	 **74**		**66**	65
2	 **61**		 **75**	35
3	**61**	**72**	**76**	66
4	 **43**		 **77**	45

Table 3.3 presents the products and the respective yields of the cross-coupled products (Entries 1-4, compounds **66**, **75-77**) obtained with bromomethylnaphthalene compounds and various naphthaleneboronic acids. The yields of the bis(bromomethyl)naphthalene compounds (Entries 2-4) were relatively low, in

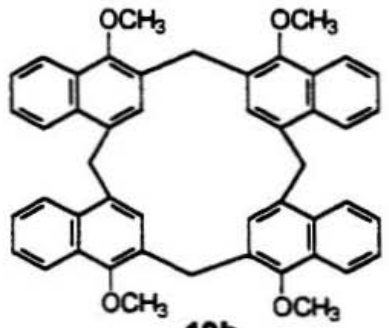


Scheme 3.12 **Synthesis of compound 70 using Suzuki-Miyaura Pd(0)-catalyzed conditions**

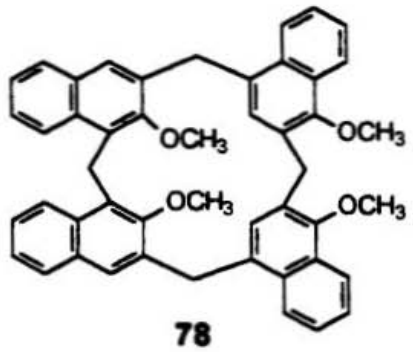
contrast to 3-(bromomethyl)-2-methoxynaphthalene (**74**) (Entry 1). Also, longer reaction times and higher catalyst loadings (10 mole%) were required for substrates containing two bromomethyl groups (Table 3.3, Entries 2-4) as compared to those which contain only one bromomethyl group (Table 3.1 and 3.2). The most convenient catalyst to use in the above reaction conditions was found to be $Pd(PPh_3)_4$, although other palladium catalysts such as $PdCl_2(dppf)$, $PdCl_2(PPh_3)_3$, $Pd_2(dba)_2$ gave similar results. These results showed that the Suzuki-Miyaura methodology could be extended to achieve cross-coupling between phenylboronic acid and the benzylic bromides, iodides or bromomethylnaphthalenes in synthetically useful yields.

3.5 Palladium-catalyzed coupling reaction of 43 with naphthylboronic acids

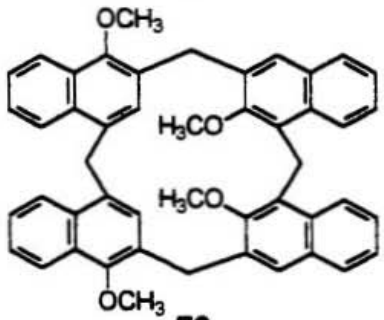
Although the palladium-catalyzed double intermolecular Suzuki-Miyaura type coupling reactions between **43** and **44** failed to give the target compound **35**, it was anticipated that such reaction conditions could still be useful for convergent syntheses of other *endo*- and *exo*-functionalized calix[4]naphthalenes such as **19b**, **78**, **79** and **80** shown in Figure 3.2. It was also envisioned that **45** could also be



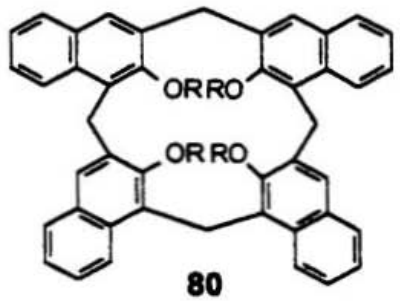
19b



78



79

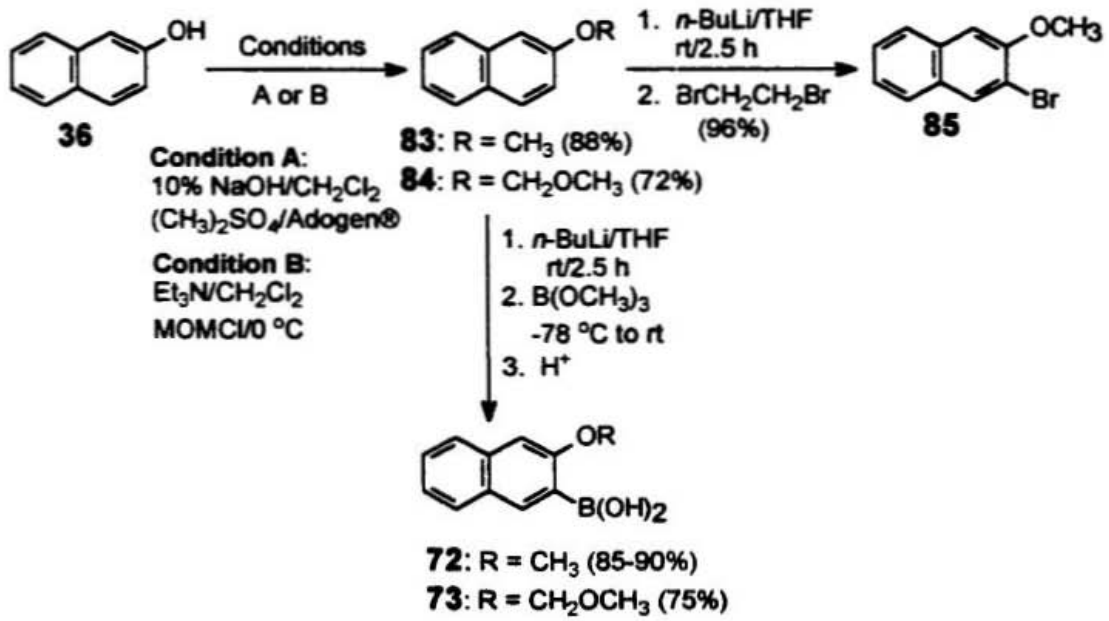


80

Figure 3.2 Different isomers of calix[4]naphthalenes (19b, 78-80)

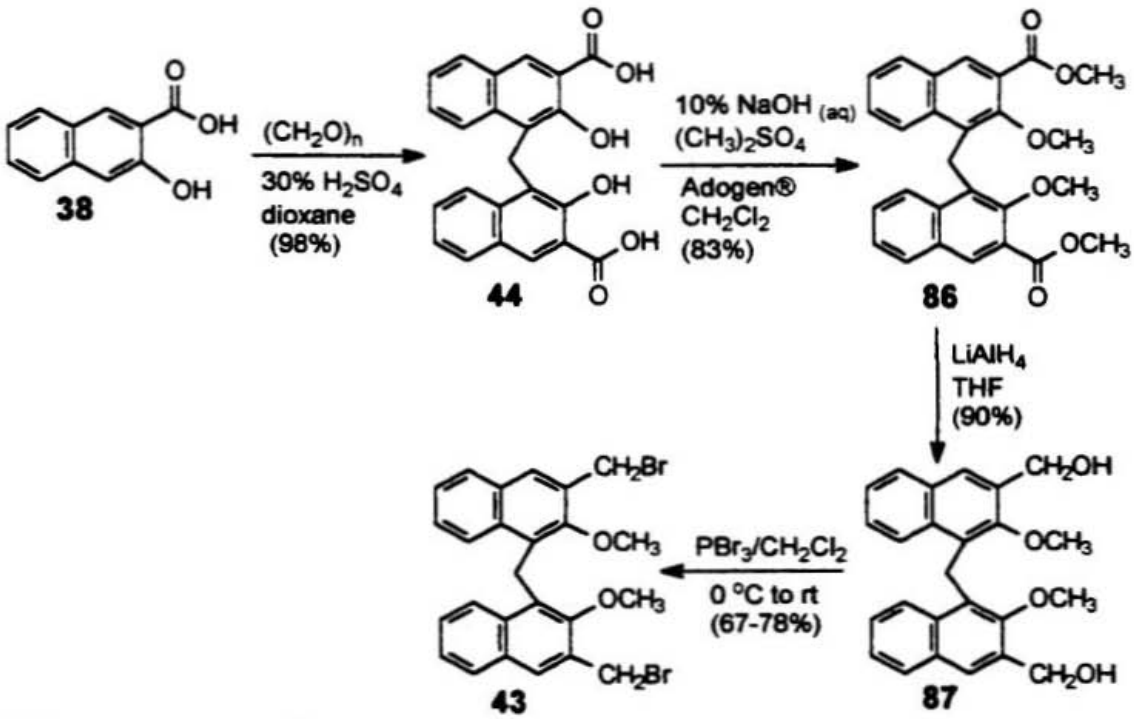
synthesized from the corresponding uncyclized tetranaphthyl compounds **81**, or **82** as depicted in Scheme 3.15 (on page 77). The synthesis of **81** was carried out using **43** and 2-methoxy-3-naphthaleneboronic acid (**72**). The key intermediate **72** for the synthesis of calixnaphthalene was prepared efficiently from 2-methoxynaphthalene **83**, obtained in 97% yield by alkylation of **36** with dimethyl sulfate and aqueous 10% NaOH solution under phase-transfer catalysis condition in CH_2Cl_2 (Scheme 3.13).

The important feature in the synthetic route (Scheme 3.13) is the *ortho* metallation of **83** or **84**. The "normal" reactive site in **36** is the C-1 position on the naphthalene ring, however, using *ortho* metallation conditions it is possible to effect



Scheme 3.13 ***Ortho* metallation of 2-naphthol derivatives (83 and 84)**

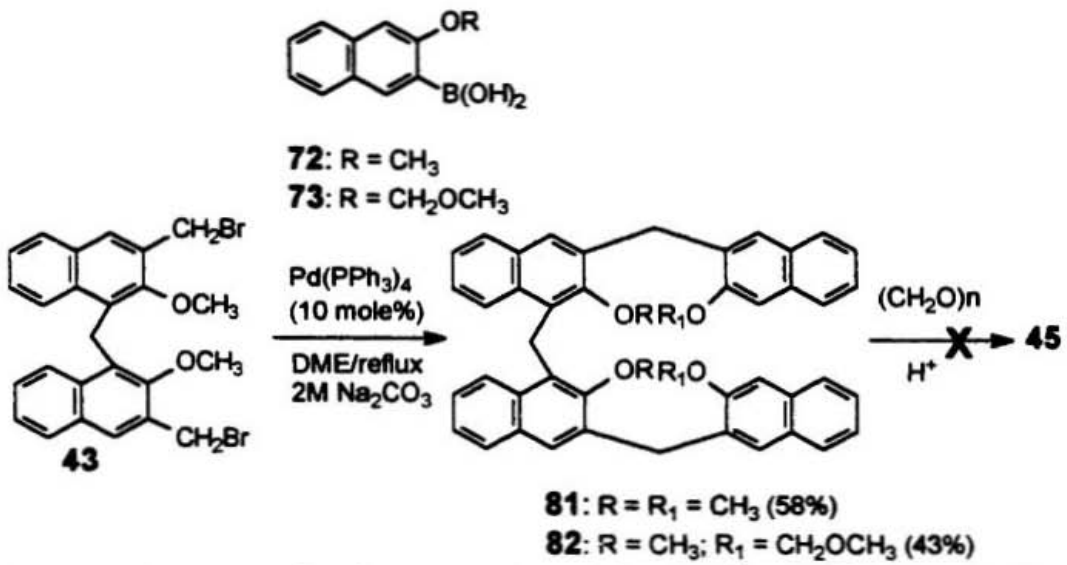
preferential substitution at the C-3 position. Biehl *et al.*[88] have shown that treating **83** with *n*-BuLi in diethyl ether followed by the addition of electrophiles DMF or TMSCl afforded *ortho* substituted products. In our hands, a more convenient approach was found by treating **83** with *n*-BuLi in THF instead of diethyl ether and stirring for 2.5 h at room temperature, followed by the addition of trimethyl borate or 1,2-dibromoethane at -78 °C to afford the *ortho* substituted (C-3) products **72** or **85**, respectively. Thus, *ortho* metallation of **83** with1.25 equivalents of *n*-BuLi and 1,2-dibromoethane in THF afforded 3-bromo-2-methoxynaphthalene **85** in 96% yield (Scheme 3.13). When the *ortho* metallation conditions were employed with either **83** or **84**, followed by treatment with trimethyl borate, the corresponding boronic acid derivatives **72** and **73** were obtained in 85-90% and 75% yields, respectively



Scheme 3.14 Synthesis of compound 43

(Scheme 3.13).

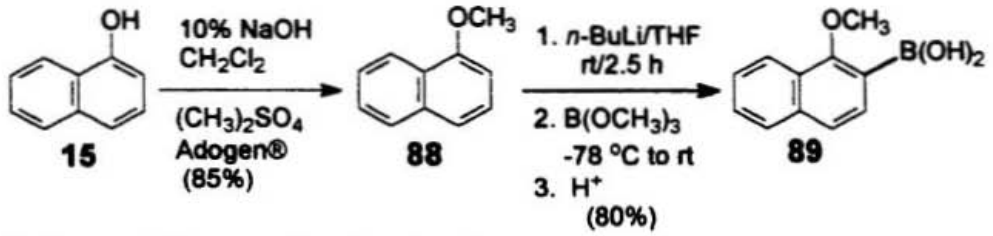
Another important precursor for the synthesis of calix[4]naphthalenes was **43** which was synthesized via the inexpensive commercially-available 3-hydroxy-2-naphthoic acid (**38**). When **38** was treated with aqueous 37% formaldehyde solution under acidic conditions, **44** was obtained in 98% yield (Scheme 3.14). The alkylated product **86** was obtained in 83% yield from **44** using dimethyl sulfate and aqueous 10% NaOH solution under Adogen phase-transfer conditions in CH_2Cl_2. The ester groups of **86** were reduced by $LiAlH_4$ to the corresponding hydroxymethyl groups to give **87** in 90% yield. Reaction of **86** with phosphorous tribromide in CH_2Cl_2 gave



Scheme 3.15 **Synthesis of 81 and 82 using Suzuki-Miyaura Pd(0)-catalyzed conditions**

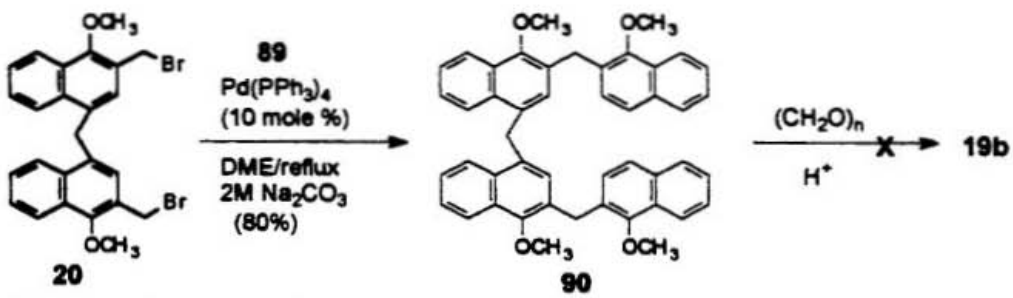
43 in 67-78% yield. Coupling of **43** and **72** proceeded smoothly in the presence of $Pd(PPh_3)_4$ in refluxing DME to afford **81** in 58% yield (Scheme 3.15). Using similar reaction conditions, **82** was obtained in 43% yield from the coupling of **43** and **73** (Scheme 3.15). The low yields of these Suzuki-Miyaura coupling reactions can be accounted for by the steric hindrance due to the methoxy group in **43** being *ortho* to the reacting site and thus preventing oxidative addition to the Pd-catalyst. When either compound **81** or **82** was reacted with aqueous 37% formaldehyde solution under acidic conditions (Scheme 3.15), the expected calix[4]naphthalene (**45**) was not obtained. Only the starting material was recovered from the reaction with **81** and from the reaction **82** a brown insoluble solid was obtained which could not be purified. The (+)-FAB mass spectrum of this brown insoluble solid however,

indicated the presence of the expected molecular ion at *m/z* = 624.

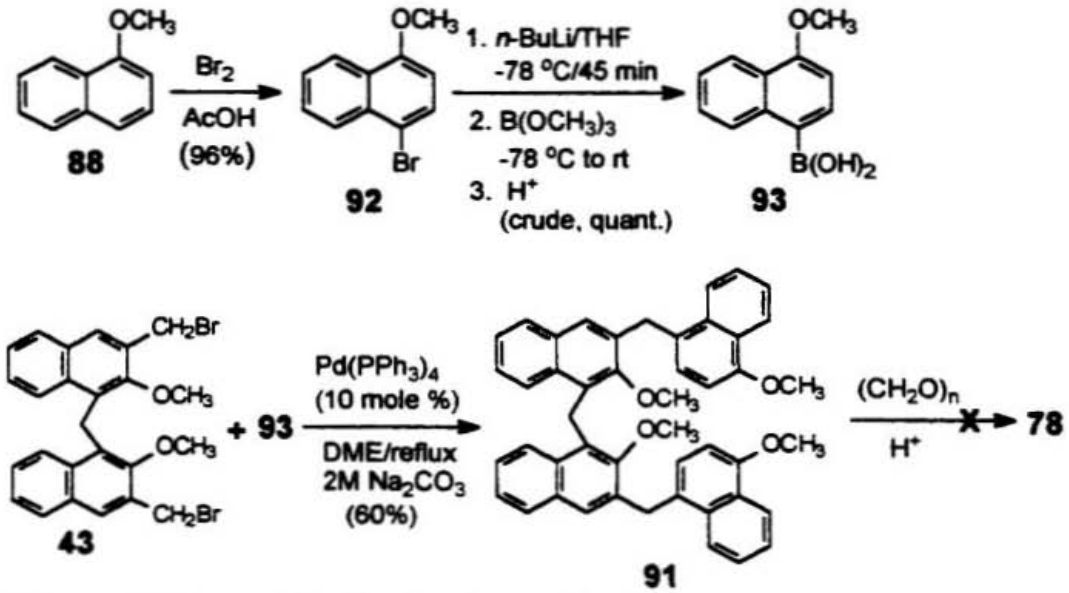


Scheme 3.16 **Synthesis of naphthylboronic acid 89 using *ortho* metallation conditions**

It was envisioned that calix[4]naphthalene **19b**, previously synthesized by Georghiou *et al.*[43] using a $TiCl_4$-mediated "2+2" condensation, could also be synthesized using the Suzuki-Miyaura coupling methodology. Scheme 3.16 outlines the synthesis of 1-methoxy-2-naphthylboronic acid (**89**) obtained in 80% yield from 1-methoxynaphthalene (**88**) using the *ortho* metallation conditions that were used previously for the synthesis of boronic acid **72**. Without further purification, **89** was used directly in the next coupling reaction (Scheme 3.17). The uncyclized tetranaphthyl compound **90**, the precursor envisioned for **19b**, was obtained in 80% yield from the coupling reaction of **20** and **89** in the presence of $Pd(PPh_3)_4$, in refluxing DME (Scheme 3.17).



Scheme 3.17 **Synthesis of uncyclized compound 90**



Scheme 3.18 **Synthesis of uncyclized tetranaphthyl compound 91**

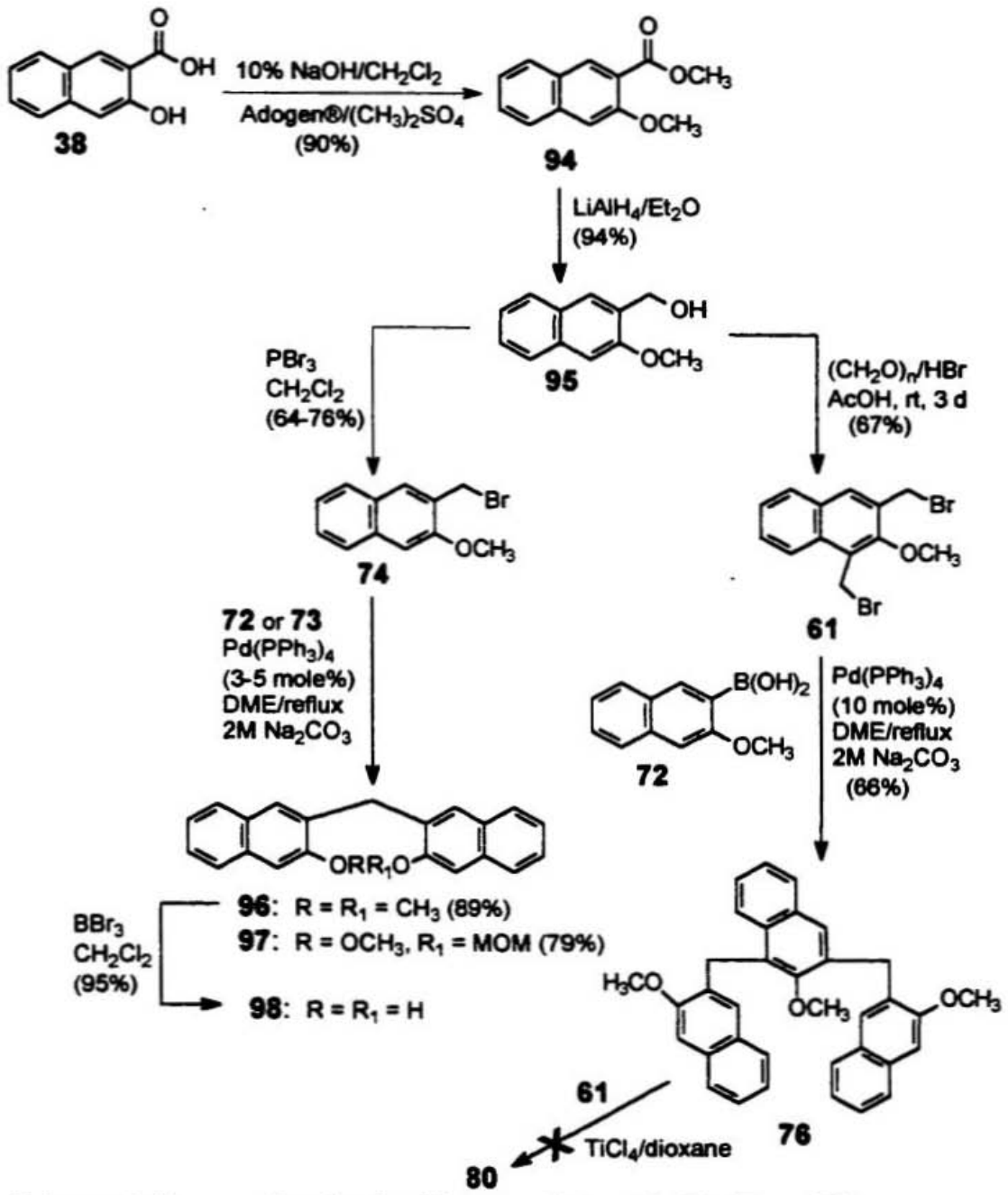
For the synthesis of **91**, the corresponding tetranaphthyl intermediate required for calix[4]naphthalene **78**, 4-bromo-1methoxynaphthalene (**92**) was readily prepared in 96% yield from 1-methoxynaphthalene (**88**) by the reaction with bromine in acetic acid. Treatment of **92** with *n*-BuLi in THF at -78 °C and trimethylborate afforded the corresponding boronic acid **93** was obtained as crude in quantitative yield. Without any purification, **93** was used with **43** employing the palladium-catalyzed coupling reaction conditions to obtain **91** in 60% yield (Scheme 3.18). Attempted cyclization of either **90** or **91**, respectively failed to produce **19b** or **78** under variety of different conditions with aqueous 37% formaldehyde solution. Failure of these reactions could again be accounted for in terms of steric hindrance present at the lower rim of calixnaphthalene. The final cyclized methoxy calixnaphthalenes are expected to be

in fixed conformations due to restricted inversion through the annulus. The presence of the methoxy groups however in the uncyclized tetranaphthyl compounds on the other hand could have prevented the two terminal naphthalene units from coming close enough to each other to allow formation of the final methylene bridge.

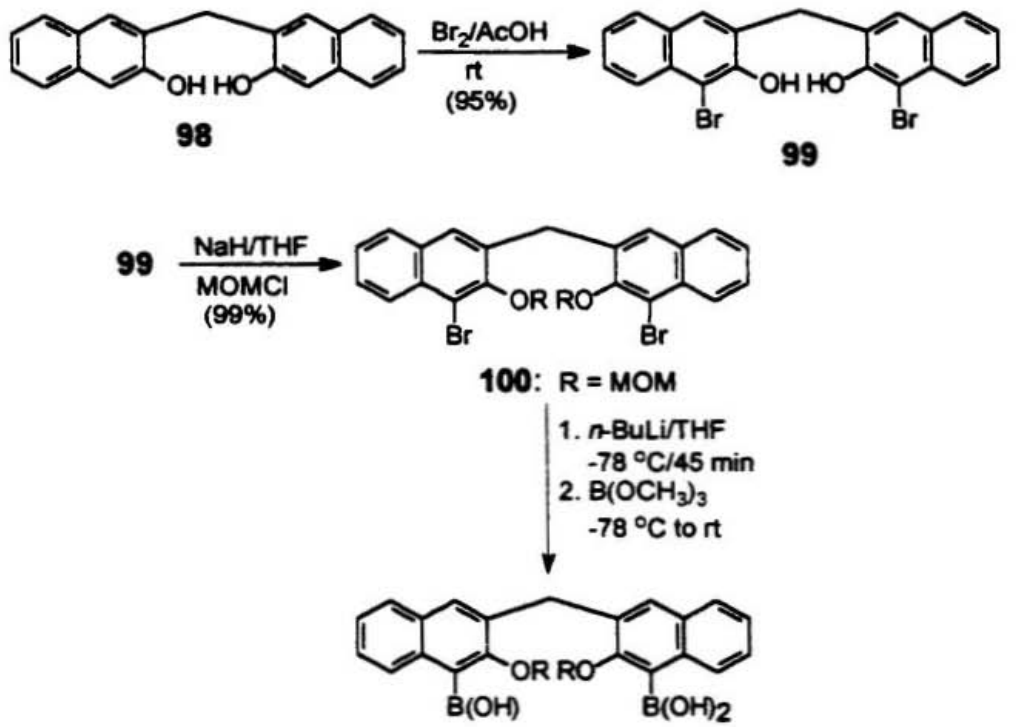
As a result of these failed experiments to obtain calixnaphthalenes, alternative routes were investigated. Scheme 3.19 shows two alternative routes for the synthesis of calix[4]naphthalene **80**. It was envisioned that **80** could be obtained by utilizing a final-step $TiCl_4$-mediated "3+1" condensation of two intermediates **61** and **76**. The series of reactions began with the synthesis of compound **94**, obtained in 90% yield by alkylation of the readily-available starting material **38** with aqueous 10% NaOH solution and dimethyl sulfate. The ester group of **94** was reduced with lithium aluminum hydride to the corresponding primary alcohol **95** in 94% yield. Treatment of **95** with aqueous 37% formaldehyde and HBr in acetic acid solution afforded **61** in 67% yield. Coupling of **61** with **72** using the Suzuki-Miyaura reaction conditions afforded in 66% yield the linear trinaphthyl compound **76**, also an important precursor for further coupling reactions toward the synthesis of a dihomooxacalix[4]naphthalene wide infra. Unfortunately, however, the $TiCl_4$-mediated "3+1" condensation conditions failed to produce the "3+1" cyclized tetramer **80** from **61** and **76**.

3.6 Synthesis of Unit C and Unit D

Having failed to obtain calixnaphthalenes either by a Pd-catalyzed coupling



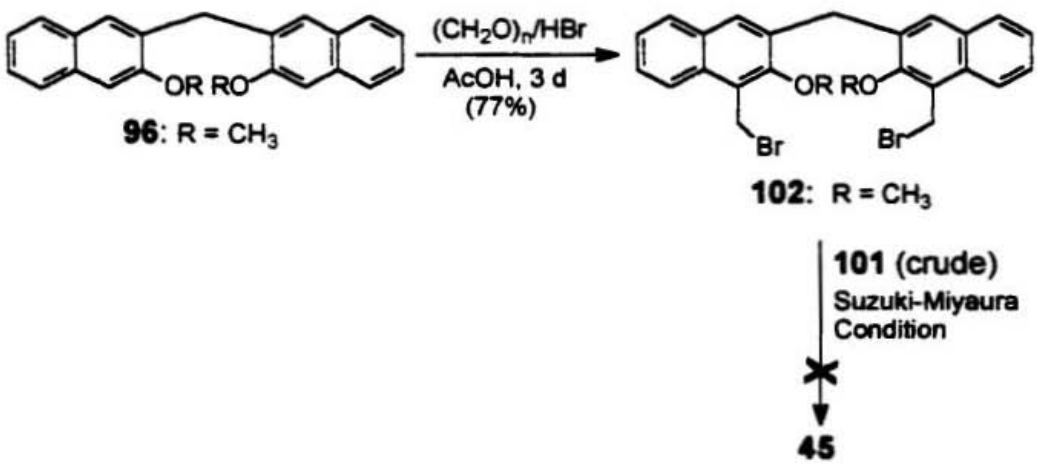
Scheme 3.19 **Synthesis of intermediates 76, 96, 97 and 98**



Scheme 3.20 **Synthesis of bis(naphthalene)boronic acid 101**

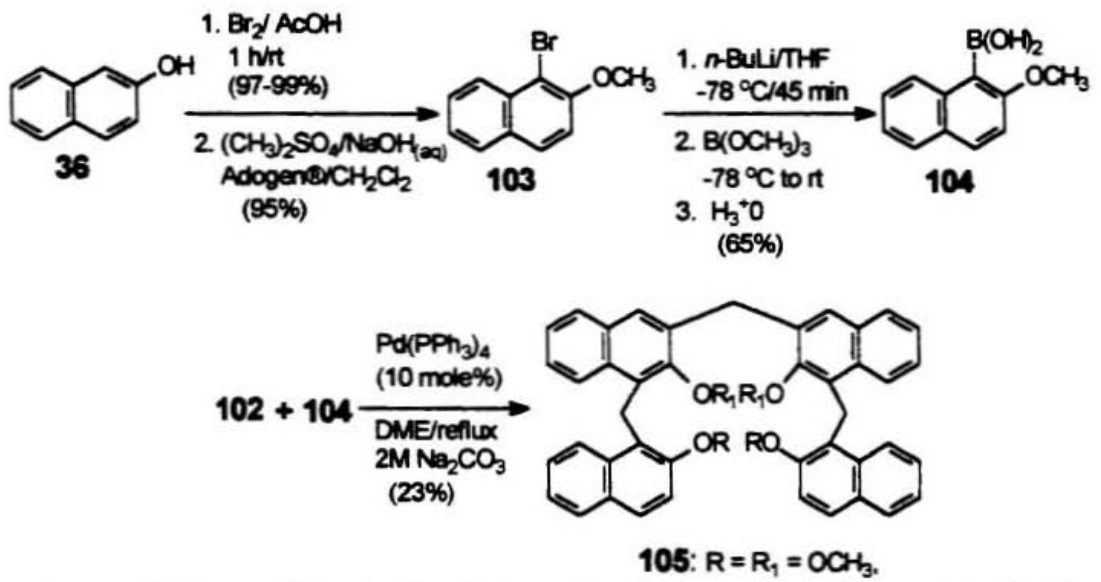
reaction or the $TiCl_4$-mediated methodology, it was necessary to evaluate the routes depicted earlier in Scheme 3.3. The alternative precursors of **35**, Unit C and Unit D, can be obtained from a common intermediate **96**, or **97** (Scheme 3.19). When a solution of **95** in CH_2Cl_2 was treated with phosphorous tribromide, **74** was obtained in 64-76% yield. In the presence of 5 mole% $Pd(PPh_3)_4$, **74** was coupled with **72** or **73** to afford **96** or **97** in 89% and 79% yields, respectively (Scheme 3.19). Bromination of **98** (obtained via de-methylation of **96** using BBr_3), with bromine in acetic acid provided **99** in 95% yield. Treatment of **99** with NaH followed by

chloromethyl methyl ether in THF gave **100** in 99% yield, which was then treated with 2.2 equivalents of *n*-BuLi in THF at -78 °C, followed by the addition of trimethyl borate to furnish **101** (Scheme 3.20). Boronic acid **101** was used without any further purification in the coupling reaction with **102**, which in turn was obtained in 77% yield from **96** using aqueous 37% formaldehyde solution in HBr-acetic acid solution. Unfortunately the Pd(0)-catalyzed coupling conditions previously described, using **101** with **102** also failed to afford the target molecule **45** (Scheme 3.21).



Scheme 3.21 **Attempted coupling of 101 and 102 using Suzuki-Miyaura Pd(0)-catalyzed conditions**

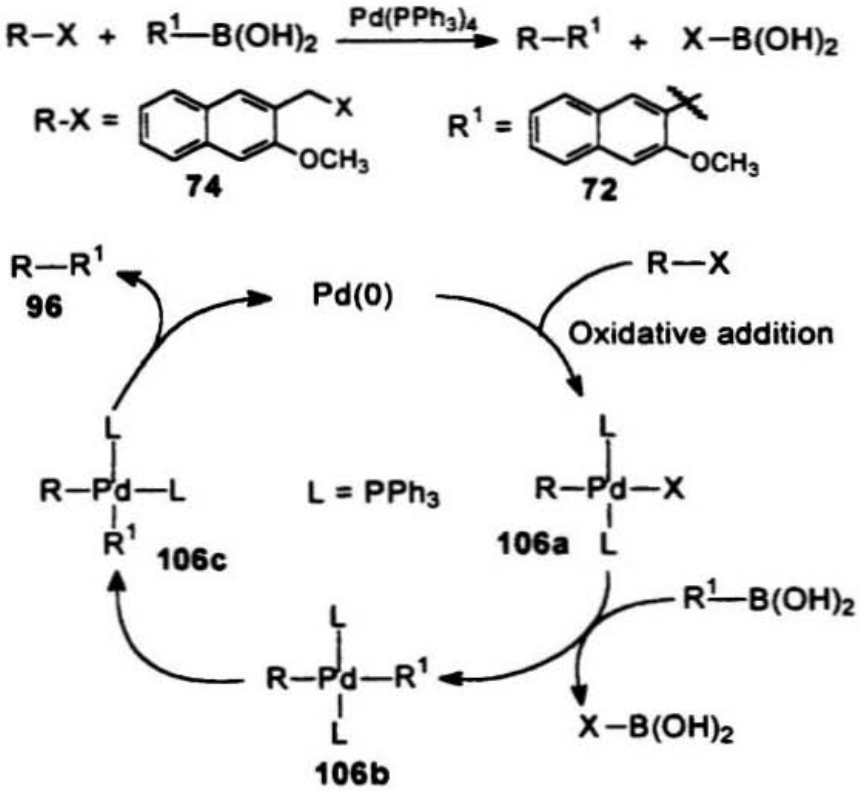
Another planned route to the target molecule is shown in Scheme 3.22. Compound **103** was obtained in high yield in two steps from **36**, by bromination with bromine in acetic acid, followed by phase-transfer alkylation with dimethyl sulfate. Using metal-halogen exchange conditions with *n*-BuLi and trimethyl borate in THF, the boronic acid **104** was obtained in 65% yield from **103**. The coupling of **102** and



Scheme 3.22 Synthesis of uncyclized tetranaphthyl compound 105

104 using Pd(0)-catalyzed conditions afforded **105** in low yield (23%) (Scheme 3.22). A possible reason for the low yield could be the instability of the palladium-intermediate formed during the oxidative addition of the halide to the Pd(0)-catalyst which resulted in de-boronation. This route was therefore abandoned.

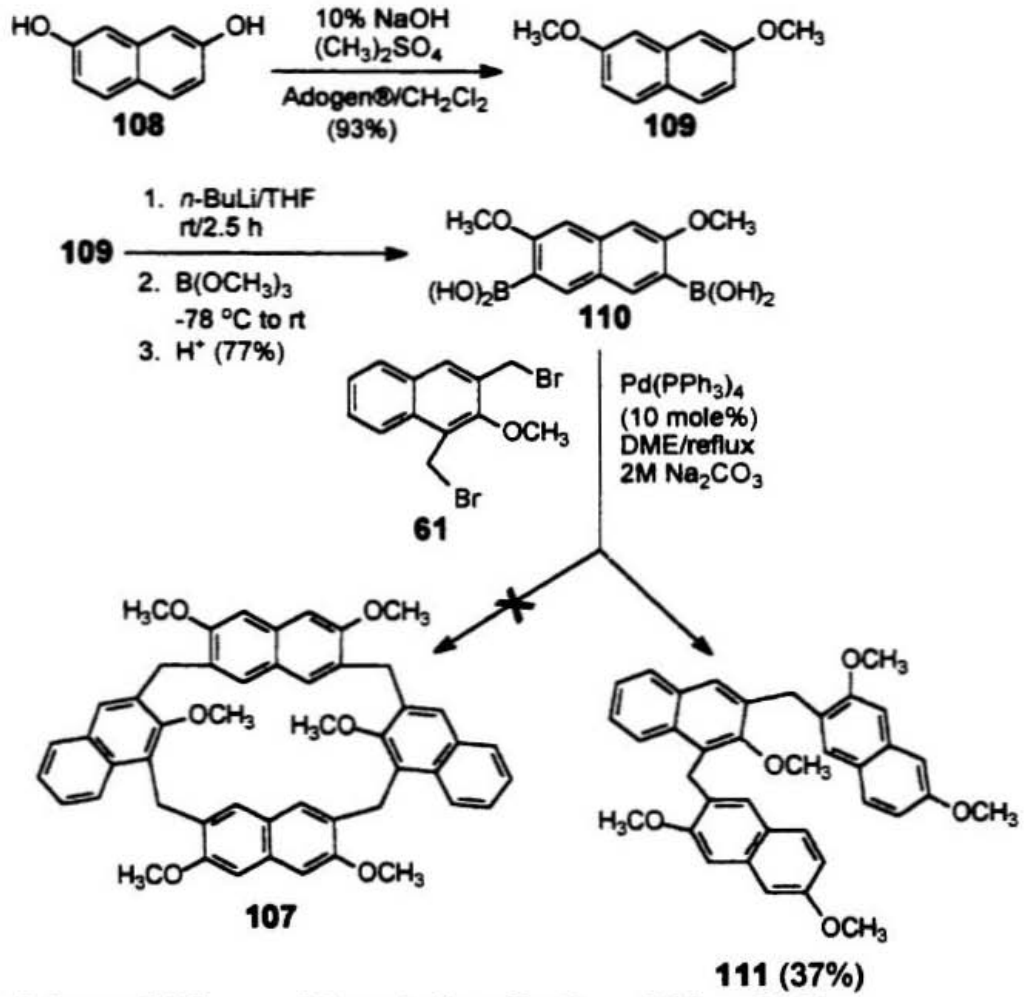
The unsuccessful attempts to use Pd(0)-catalyzed coupling reactions to form calixnaphthalenes could be due to the steric hindrance during the final stage in the palladium catalytic cycle. A proposed general synthetic mechanism for the coupling reaction of benzylic or naphthylic halide such as **74** and boronic acid such as **72** based on the catalytic cycle for the Suzuki-Miyaura coupling process,[78] is shown in Scheme 3.23. The first step in this catalytic cycle involves the oxidative addition of benzylic or naphthylic halide to the Pd(0)-catalyst to form a stable *trans*-σ-palladium(II) complex (**106a**). This complex then participates in a transmetallation



Scheme 3.23 **A proposed mechanism for the Pd(0)-catalyzed coupling of 72 and 74**

with the boronic acid to produce **106b**. After a facile *trans*-σ-palladium(II) complex isomerization to *cis*-σ-palladium(II) complex (**106c**), a reductive elimination produces the coupling product **96** and regenerates the catalytically-active Pd(0)-catalyst. The failure of the coupling reaction between Unit A and Unit B, and also between Unit C and Unit D, to form the cyclized tetramer can be explained based on this palladium

catalytic cycle. The first coupling reaction occurs smoothly between Unit A and Unit B via oxidative addition, transmetallation and reductive elimination to form the uncyclized tetranaphthyl intermediate such as **81** or **82**. The second oxidative addition could occur, followed by transmetallation, but the crucial isomerization step (**106b** to **106c**) might not proceed due to steric crowding and therefore the final reductive process to form the cyclized tetramer does not proceed.

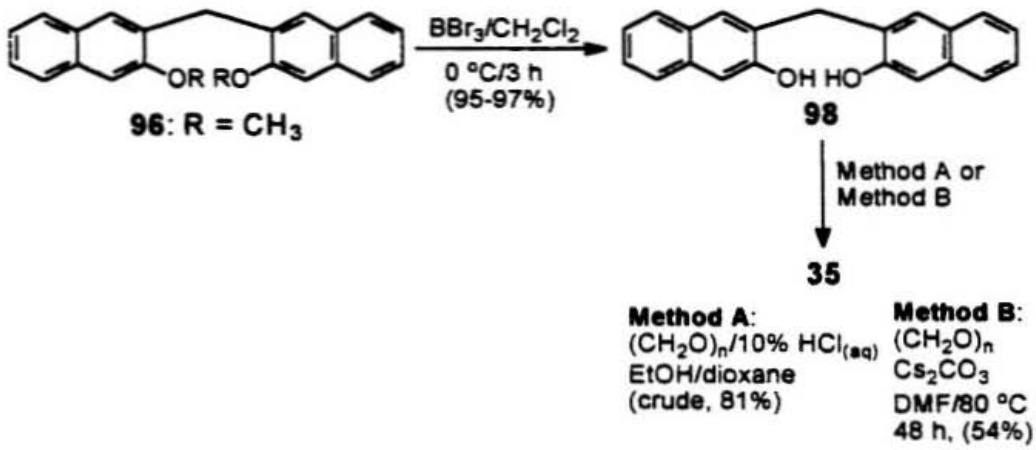


Scheme 3.24 **Attempted cyclization of 61 and 110**

It is worth pointing out in this context that the palladium-catalyzed cyclization depicted in Scheme 3.24 also failed to give the desired coupled product **107**. Treatment of commercially available 2,7-dihydroxynaphthalene (**108**) in the usual manner resulted in the formation of 2,7-dimethoxynaphthalene (**109**) in 93% yield. Under usual *ortho* metallation conditions in THF **109** afforded **110** in 77% yield. Unfortunately, treatment of the diboronic acid **110** with **61** in DME and 10 mole % of $Pd(PPh_3)_4$ gave the uncyclized trinaphthyl compound **111** rather than the expected product **107** or its unsymmetrical structural isomer (Scheme 3.24). It was therefore decided to change the basic strategy of the retrosynthetic routes discussed earlier using Scheme 3.1 and Scheme 3.3.

3.7 Synthesis of "C-12" *endo* calix[4]naphthalene (35) from Unit C

The unsuccessful attempt to link the double *ortho* metallation and double Suzuki-Miyaura cross coupling reactions to construct calix[4]naphthalenes led to the application of a simpler route. It was reasoned that the intermediate **96** was a significant intermediate towards the synthesis of **35**. To make the dimer **96** more reactive at the C-1 position on each of the naphthalene rings, it was de-methylated to afford **98** in 95-97% yields. Scheme 3.25 details the synthesis of calix[4]naphthalene **35** which was achieved by either acid-induced or based-induced condensations with aqueous 37% formaldehyde solution. The acid-catalyzed condensation of **98** with aqueous 37% formaldehyde solution was carried out in ethanol-dioxane with aqueous concentrated HCl solution to afford **35** as a brown



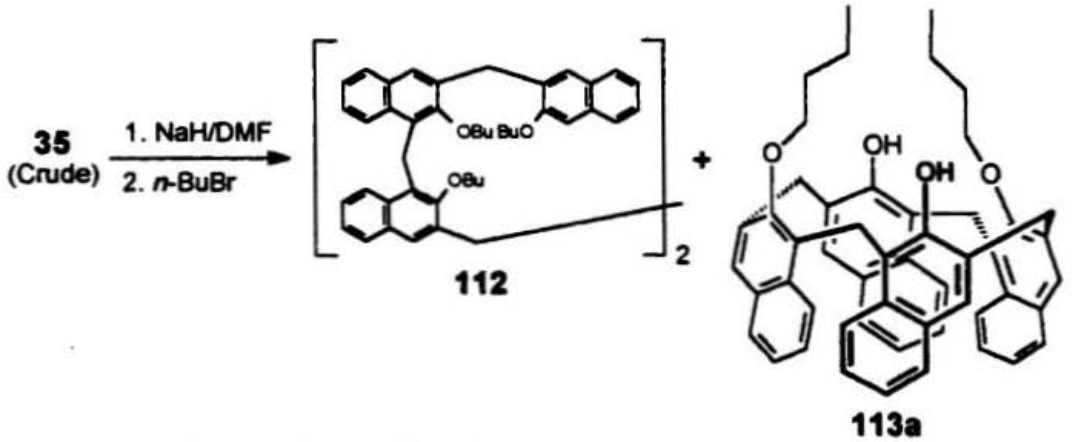
Scheme 3.25 **Synthesis of "C-12" *endo* calix[4]naphthalene 35**

solid in 81% yield. The brown solid could not be purified due to its insolubility in most of the common organic solvents except DMF and DMSO. The ^{1}H NMR spectrum of the crude brown solid in DMSO-d_6 indicated the presence of two singlets at δ 4.53 and 5.00 due to the two methylene groups in the cyclized tetramer **35**. The fact that **35** formed in the acid-induced condensation reaction of **98** with aqueous 37% formaldehyde solution was supported by the (+)-FAB MS analysis showing the presence of the expected molecular ion peak at *m/z* = 624. Similarly, pure **35** was also obtained as a brown solid, in 54% yield, from the base-induced condensation reaction of **98** with two molar equivalents of aqueous 37% formaldehyde solution in boiling DMF for 48 h in the presence of a stoichiometric amount of Cs_2CO_3 as the base (Scheme 3.25). The ^{1}H NMR spectrum of **35** in pyridine-d_5 shows two signals at δ 4.61 and 5.19, which were assigned to the two different methylene protons

present in the molecule. In the ^{13}C NMR spectrum the peaks at δ 23.3 and 34.4 correspond to the methylene carbons and correlated with the proton signals at δ 4.61 and 5.19, respectively. The molecular mass of the assigned structure **35** was also confirmed by CI MS analysis showing the expected molecular ion peak $M^{+}+1$ at *m/z* = 625. In solution, the pattern of ^{1}H and ^{13}C NMR signals indicated that the molecule exists in a *cone* conformation. Since **35** could be obtained in pure form directly from the base-induced condensation therefore, the preferred method is to use aqueous 37% formaldehyde solution and Cs_2CO_3 in DMF. This new *endo* calix[4]naphthalene can be synthesized in better yield and larger quantity than the calixnaphthalenes (**30-31**) discussed in Chapter 2.

3.8 Ether derivatives of "C-12" *endo* calix[4]naphthalene

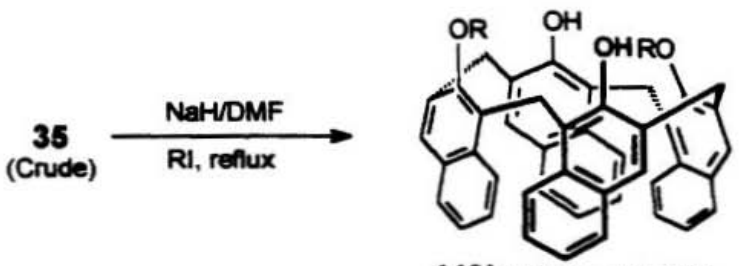
The crude product obtained from the acid-induced condensation of **98** with aqueous 37% formaldehyde solution was used in various alkylation reactions (Scheme 3.26 and Scheme 3.27) in attempts to isolate alkylated derivatives of **35**. Alkylation was effected with a solution of the crude calix[4]naphthalene (**35**) in DMF with NaH as the base and 1-bromobutane (Scheme 3.26). The reaction product was purified by preparative TLC using benzene-petroleum ether 40:60 to obtain the linear hexanaphthyl compound **112** as the major product (18%). The minor product (3%) was the *distally* substituted 1,3-di-*O*-*n*-butylcalix[4]naphthalene **113a**. Analysis of the ^{1}H NMR spectrum clearly indicates that compound **113a** is a conformationally-fixed molecule. The four doublets at δ 3.67, 4.50, 4.73, 4.90 having geminal coupling



Scheme 3.26 Synthesis of *n*-butyl ether derivative of 35

constants of J = 12.9, 15.3, 12.9, 15.2 Hz, respectively can be assigned to the methylene protons. By analogy with the ether derivatives of the *tert*-butylcalix[4]naphthalene (**31**) as described in Chapter 2, this ether derivative of **35** shows similar conformational properties. The doublets at δ 3.67 and 4.50 are due to the axial hydrogens and the others at δ 4.73 and 4.90 are due to the equatorial protons of the methylene groups. The doublets at δ 3.67 is unusually high field compared to other ether derivatives of **31** as discussed in Chapter 2. The axial hydrogen is most likely located in the shielding region of the naphthalene unit of calix[4]naphthalene. An interesting pattern for the *n*-butyl groups was found in the ^{1}H NMR spectrum of **113a** in the region between δ 4.03-4.07 and δ 4.11-4.16, which shows two sets of overlapped multiplets arising from the methylene protons of the *n*-butyl groups α to the oxygen atom. The pattern of these overlapped multiplets clearly demonstrates the diastereotopicity of these protons. The ^{13}C NMR spectrum

of **113a** which shows six aliphatic signals and twenty aromatic signals, is in good agreement with the structure proposed for **113a**. In particular, the signals at δ 21.9 and 32.2 due to the methylene carbons joining the two naphthalene units confirm that the butyl groups in **113a** are *distal* to each other, whereas three carbon signals would have been observed in the ^{13}C NMR spectrum of **113a** for *proximal* substitution of the butyl groups regardless whether the molecule is in the *cone* or in the *1,2-alternate* conformation. Likewise, the existence of only two clearly defined AB systems for the methylene protons is further support for the *distal* or 1,3-disubstitution in **113a**. NOED measurements on **113a** also confirmed that the molecule is in a *cone* conformation: saturation of the methylene signals at δ 3.67 enhanced the signals at δ 4.73, 7.08, and 7.36 by 14%, 3% and 7%, respectively, while saturation of the signal at δ 4.90 enhanced the signals at δ 4.50 and 8.48 by 18% and 12%, respectively. Finally, further support for the assigned compound **113a** was obtained from the (+)-FAB mass spectrum, which showed the expected molecular ion peak at *m/z* = 736.



113b: R = propyl (4%)
113c: R = isopropyl (6%)

Scheme 3.27 **Synthesis of propyl and isopropyl ether derivatives of 35**

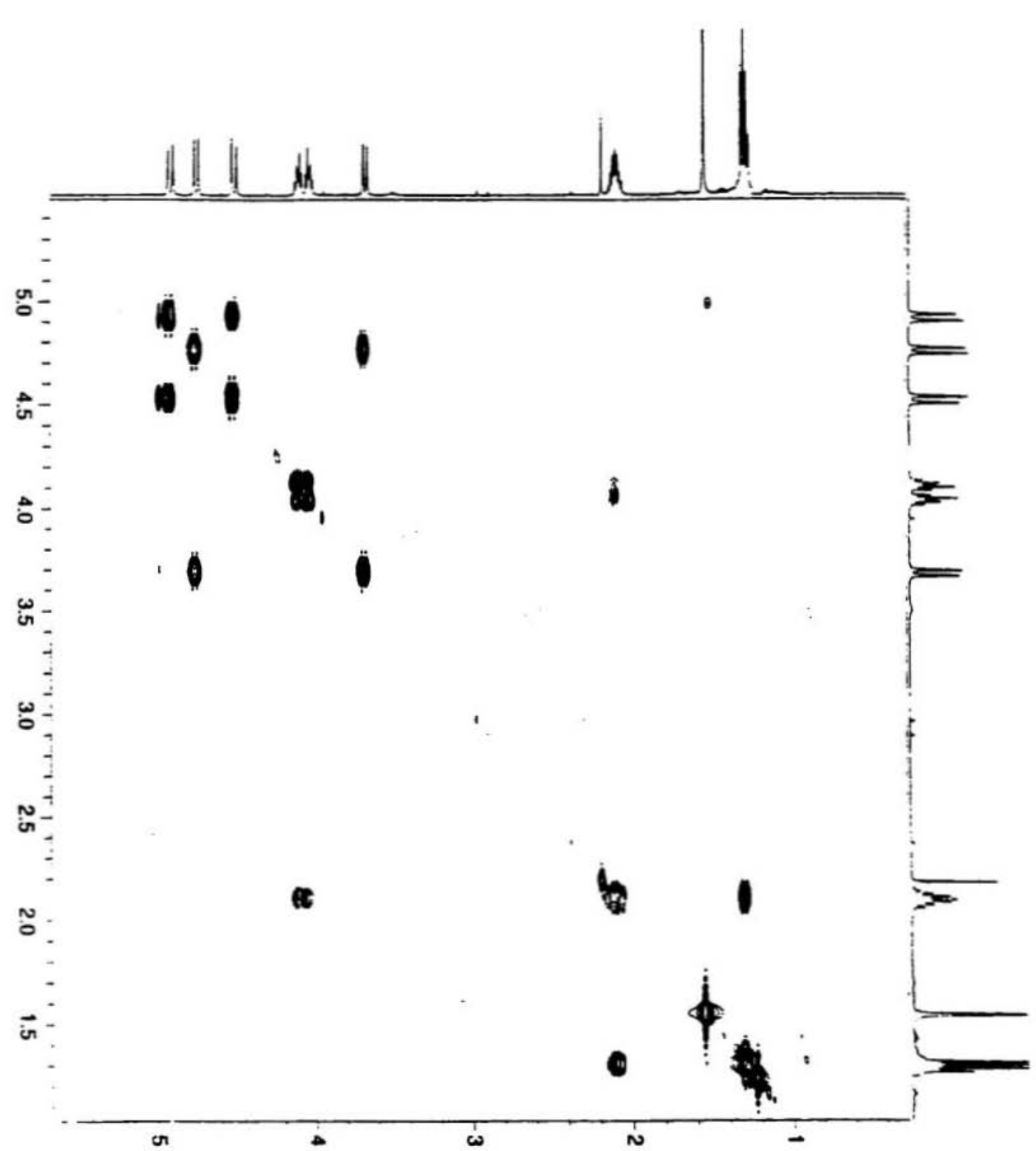


Figure 3.3 ^{1}H COSY spectrum of the methylene region of 113b

The di-*n*-propyl and diisopropyl derivatives of calix[4]naphthalene (**35**) were also obtained (Scheme 3.27) in a similar manner from the crude product obtained from the acid-mediated condensation reaction. (*Distal*) 1,3-di-*O*-propylcalix[4]naphthalene **113b** was obtained in 4% yield with 1-iodopropane. Similarly, 1,3-di-*O*-isopropylcalix[4] naphthalene **113c** was also obtained in 6% yield with 2-iodopropane (Scheme 3.27). The structures of **113b** and **113c** were determined by NMR analysis (^{1}H, ^{13}C,COSY and HMQC) and their molecular masses were confirmed by the (+)-FAB MS, each of which showed the expected molecular ion peak at *m/z* = 708. The ^{1}H NMR spectra of **113b** and **113c** show four doublets (J ~ 13-15 Hz) which were assigned to the protons of the methylene group joining the naphthalene units. The doublets at δ 3.60 and 3.66, each having geminal coupling constants of J = 12.5 Hz are due to the axial protons of the methylene groups in **113b** and **113c**, respectively. The positions of these signals are at higher fields than the doublets at δ 4.74 and 4.75 which are assigned to the equatorial protons of the methylene groups joining the two naphthalene units in **113b** and **113c**, respectively. The signals due to the axial protons of the methylene group at δ 3.60 and 3.66 for **113b** and **113c**, respectively have been shifted upfield most likely by the shielding of the naphthalene units of calix[4]naphthalene. The COSY spectra of both **113b** (Figure 3.3) and **113c** (Figure 3.4) confirmed the correlations of the four doublets due to the protons of the methylene groups. The ^{1}H NMR spectrum of **113b** clearly indicates two sets of signals at δ 4.02 - 4.05 and δ 4.08 - 4.11 for the

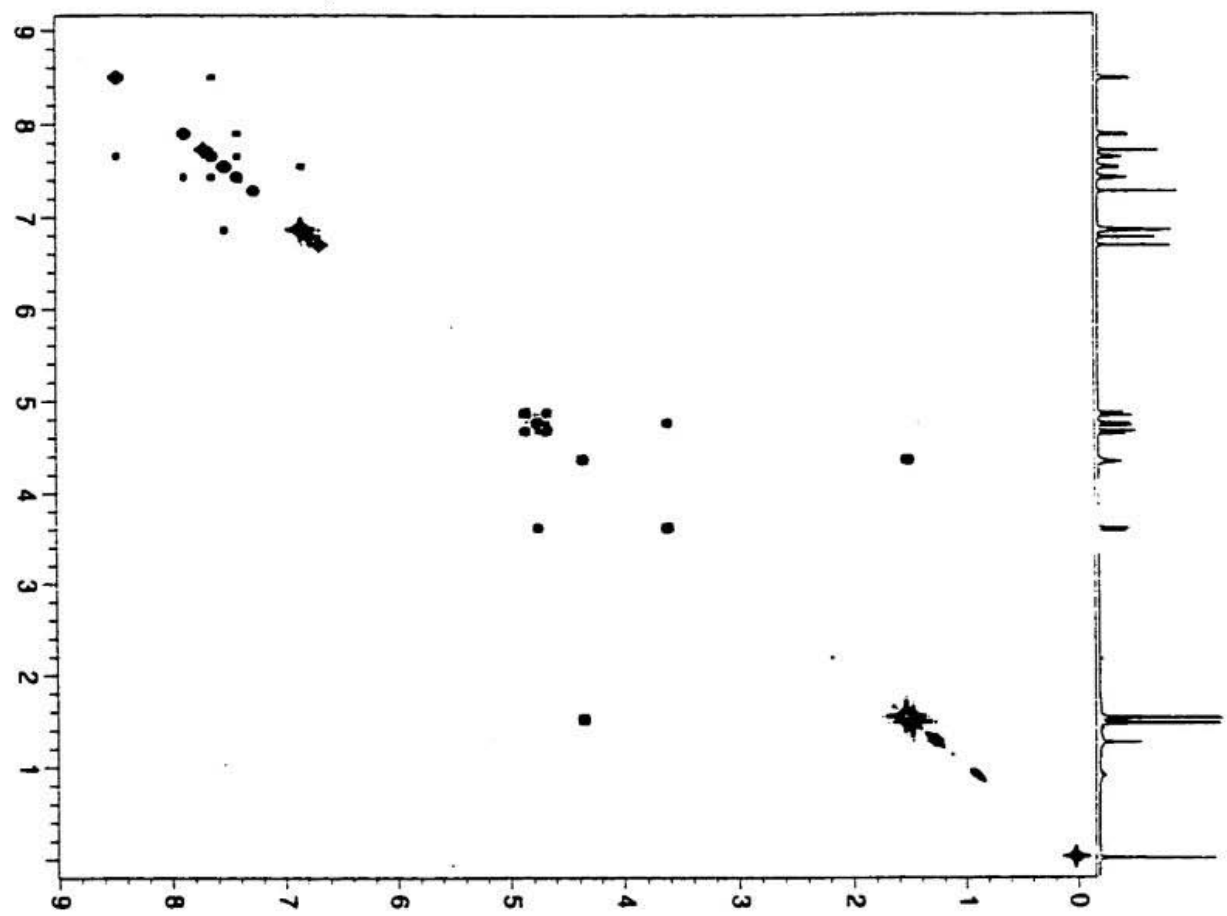
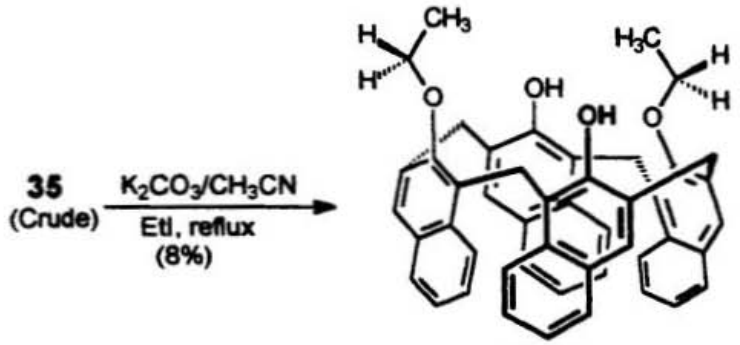


Figure 3.4 ^{1}H COSY spectrum of compound 113c

methylene protons of the propyl groups α to the oxygen atom, again demonstrating the diastereotopicity of these protons. The methine protons of the isopropyl groups in **113c** appear as a septet at δ 4.35 in the ^{1}H NMR spectrum. The two sets of doublets (vicinal coupling with the methine proton) was confirmed by the COSY spectrum, are assigned to the diastereotopic methyl groups of the isopropyl groups (**113c**). The signals in the ^{13}C NMR spectra are also consistent with the proposed structures both being in *cone* conformations. The ^{13}C NMR spectrum of **113b**, shows five aliphatic signals, of which those at δ 10.8, 23.5 and 77.9 can be assigned to the methyl and methylene carbons of the propyl groups, while the signals at δ 30.9 and 31.6 are due to the methylene carbons linking the naphthalene units. In particular, the signal at δ 30.9 can be assigned to the C-2 and C-22 of the methylene carbons which connect the two naphthalene units. Analysis of the HMQC spectrum of **113b**, revealed that the ^{13}C signals at δ 30.9 and 31.6 are correlated to the ^{1}H NMR signals at δ 4.73 and 4.90, respectively. The ^{13}C signals can be assigned to the C-12 and C-32 methylene carbons. By a similar spectral analysis, the structure of **113c** was postulated to be 1,3-*O*-alkylated and in *cone* conformation. The chemical shifts of the methylene carbons at δ 29.7 and 31.2 are supportive of the proposed structure for **113c**.

Treatment of the crude product **35** from the acid-mediated reaction referred previously with a large excess of 1-iodoethane and K_2CO_3 in CH_3CN afforded the 1,3-di-*O*-ethyl compound **113d** in 8% yield (Scheme 3.28). The ^{1}H NMR spectrum



113d

Scheme 3.28 Synthesis of ethyl ether derivatives of 35

of **113d** in $CDCl_3$, clearly shows four doublets centered at δ 3.63, 4.57, 4.73 and 4.88 (J ~ 13-15). The doublets centered at δ 3.63 and 4.73 can be assigned to the axial protons of the methylene groups, while the other set of doublets centered at δ 4.57 and 4.88 are due to the equatorial protons of the methylene groups. One of the axial methylene protons might be shielded by the naphthalene unit of calix[4]naphthalene giving rise to the high-field doublet at δ 3.67, while the second axial methylene protons are not shielded by either the ethyl group or by the *distal* naphthalene units appear as a doublet at δ 4.73. The correlation of the four doublets arising due to the protons of the methylene groups in **113d** was confirmed by COSY spectrum. The ^{1}H NMR spectrum of **113d** shows another two sets of multiplets at δ 4.07-4.17 and δ 4.19-4.25, which are due to the diastereotopic methylene protons of the ethyl groups α to the oxygen atom. The ^{13}C NMR signals of **113d** confirm that the ethyl groups are *distal* to each other at the lower rim of the molecule, showing as expected, four upfield resonances at δ 15.5, 29.7, 31.6 and

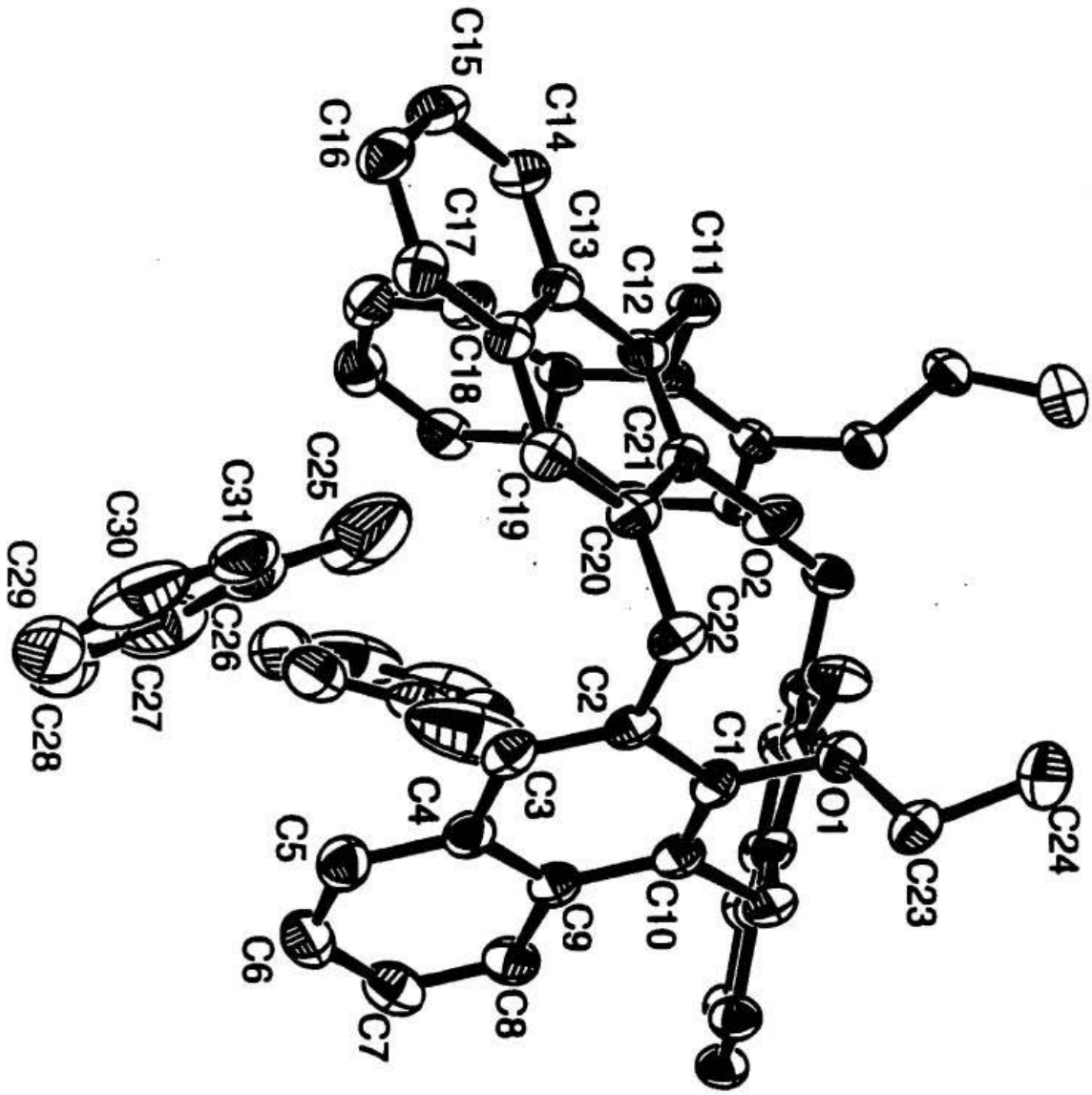
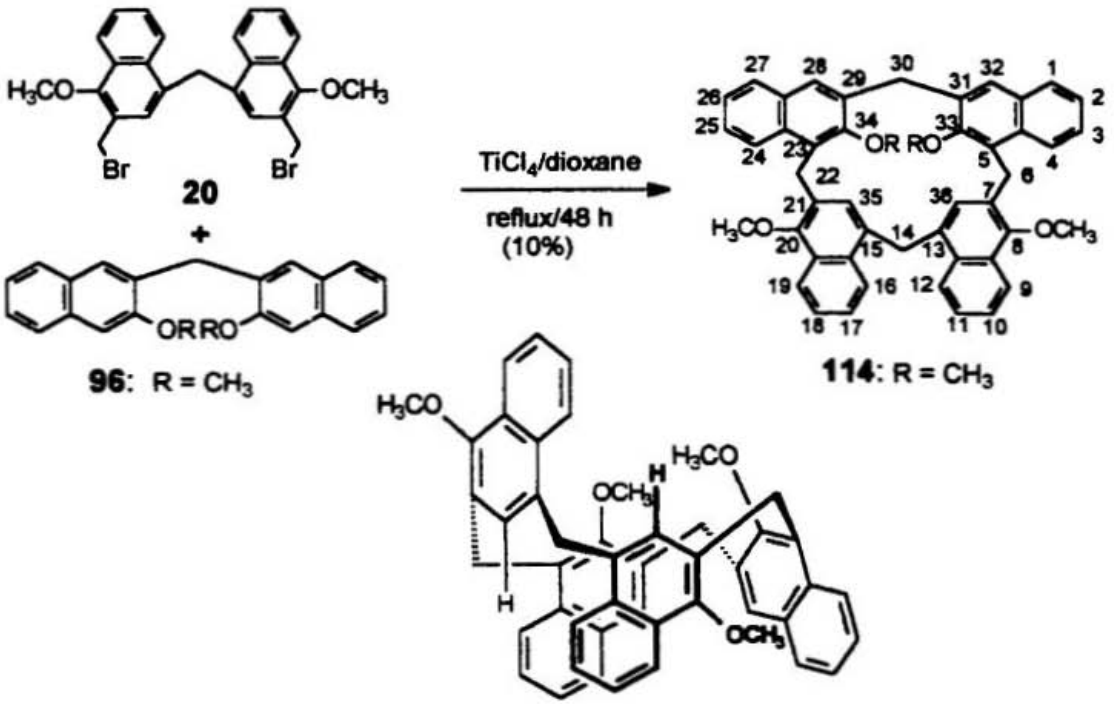


Figure 3.5 X-ray crystal structure of compound 113d

72.1. The signals at δ 15.5 and 72.1 are due to the ethyl groups, while the peaks at δ 29.7 and 31.6 can be assigned to the C-2 and C-22 methylene carbons and to the C-12 and C-32 methylene carbons, respectively. Further mass spectral support for the assigned structure of **113d** was provided by the CI MS, which showed the expected molecular ion peaks at *m/z* = 680. Unequivocal evidence for the *cone* conformation of **113d** in the solid state was provided by its single X-ray crystal structure (Figure 3.5), which showed that the two naphthalene units bearing the ethyl groups are nearly parallel to each other, while the other two naphthalene units are pushed outward to give a "*pinched cone*" *(flattened cone)* conformation. It would be interesting in the future to determine if these ether derivatives (**113a-113d**) of **35** can demonstrate an allosteric effect. The X-ray structure of **113d** clearly reveals the presence of two molecules of toluene situated within the cavity and is therefore a 1:2 clathrate with C_2 symmetry. The methyl groups of each of the two toluene molecules suggest the presence of π---CH_3 interactions with the *distal* naphthalene units having the ethyl groups on the oxygen atom of calix[4]naphthalene. Formation of a clathrate with *two* molecules of toluene appears to be unique to this *endo* calix[4]napthalene system. In general, clathrates formed with various derivatives of *tert*-butylcalix[4]arene (**2**) are usually 1:1 complexes, as discussed in Chapter 1. It would be useful to compare in future, the thermodynamic and complexation properties of **113a-d** with those previously determined with *tert*-butylcalix[4]naphthalene (**31**).



Scheme 3.29 **Synthesis of *endo/exo* calix[4]naphthalene 114**

3.9 Synthesis of *endo/exo* calix[4]naphthalene

It was anticipated that bis(2-methoxy-3-naphthyl)methane (**96**) and bis(1-methoxy-2-bromomethyl-4-naphthyl)methane (**20**) might be useful intermediates for the synthesis of an *endo/exo* calix[4]naphthalene **114** (Scheme 3.29). A solution of **20** and **96** in dioxane with $TiCl_4$ as a catalyst, was refluxed for 48 h. After the standard work-up, the crude material was purified by preparative TLC to afford **114** as a colourless solid in 10% yield. The structure of **114** was determined by NMR analysis (^1H, ^{13}C, COSY) and the mass of the assigned structure was supported by

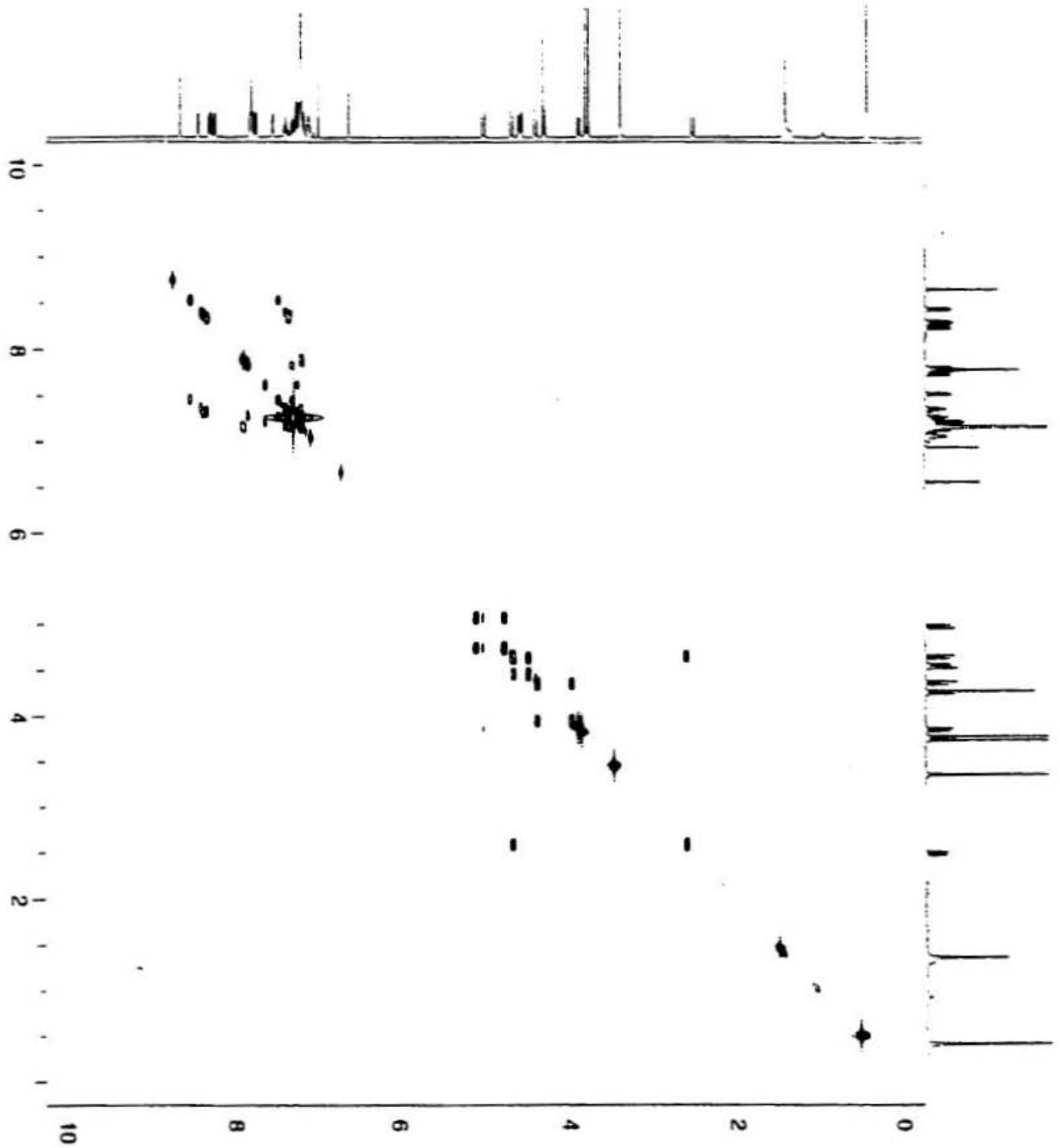
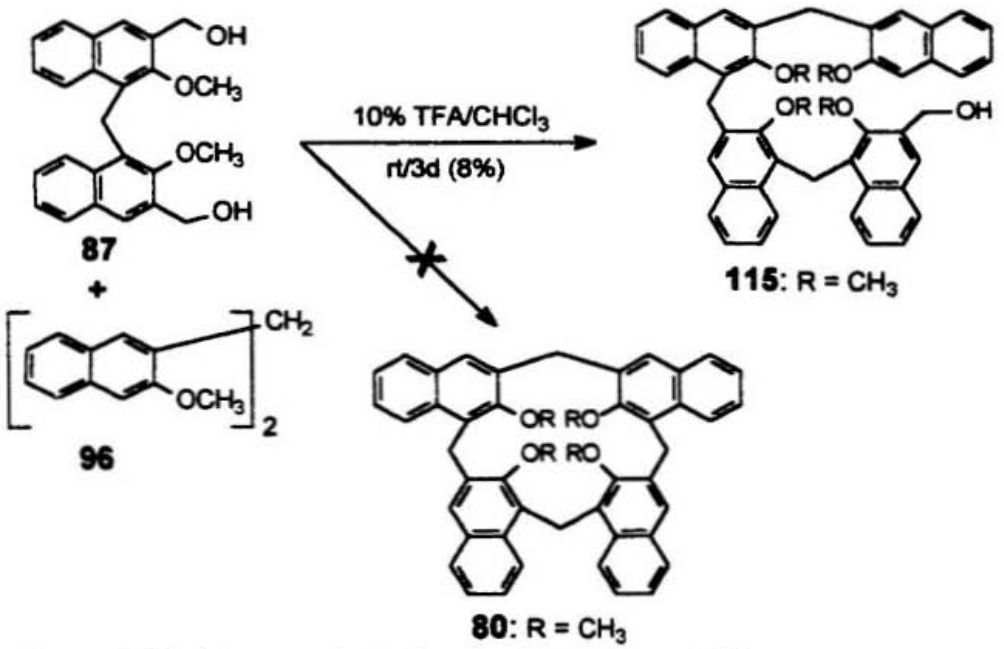


Figure 3.6 ^{1}H COSY spectrum of compound 114

mass spectral analysis. In the ^{1}H NMR spectrum of **114**, the four singlets at δ 2.95, 3.33, 3.70, 3.87 are due to the different methoxy groups. The most interesting features in ^{1}H NMR spectrum are the patterns of the protons of the methylene groups linking the naphthalene units. The methylene region displays eight doublets at δ 2.07, 3.44, 3.84, 3.96, 4.12, 4.14, 4.24 and 4.56 (H-6, H-14, H-22, H-30) having geminal coupling constants of $J \sim 13.0$-15.5 Hz, which are due to the four equatorial and four axial diastereotopic protons of the methylene groups. The exceptionally high field doublet at δ 2.07 was assigned to the axial methylene proton (H-14) linking the two naphthalene units, resulted from the shielding effect of the neighbouring naphthalene unit in a *partial cone* conformation (Scheme 3.29). Correlation of all the doublets due to the methylene protons were confirmed by a COSY NMR spectrum (Figure 3.6). The aromatic region signals are consistent with the proposed structure. The two singlets at δ 6.16 and 6.53 were assigned to the intra-annular naphthalene protons (H-35 and H-36) and their positions are supportive of a shielding effect by the proximal naphthalene units in a *partial cone* conformation. The singlets at δ 7.37 and 8.23 are due to the *peri*-hydrogens (H-28 and H-32) on the two different naphthalene units. A surprising result was obtained from the mass spectrum of **114**. A low resolution MS afforded the expected molecular ion peak at *m/z* = 680, but a high resolution MS determination failed to detect the expected molecular ion corresponding to the formula of $C_{48}H_{40}O_4$ with a calculated mass of 680.2927. Instead, an ion peak at *m/z* = 666.2579, corresponding to $C_{47}H_{38}O_4$, i.e., a loss of -

CH_2-, was obtained. At present, an explanation for this unusual finding has not been forthcoming.

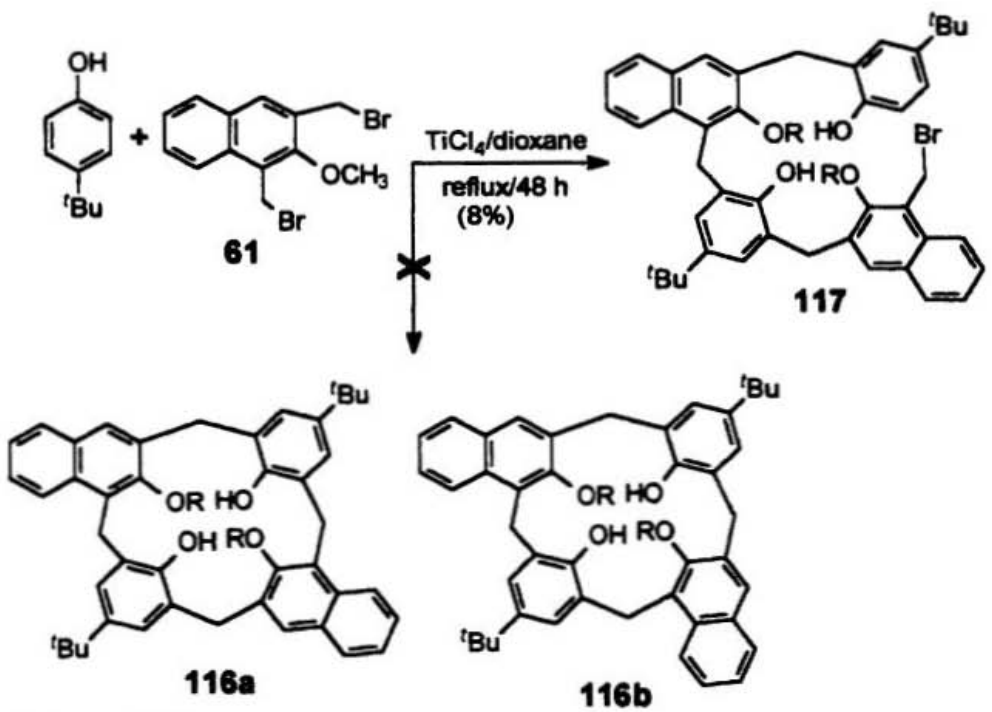


Scheme 3.30 Attempted synthesis of compound 80

3.10 Attempts at the synthesis of other types of calix[4]naphthalenes

The results obtained by the use of $TiCl_4$ as a catalyst to synthesize **114**, led to the investigation of another synthetic approach to synthesize calix[4]naphthalene **80**. Reaction of diol **87** with **96** in dry CH_2Cl_2 with 10% trifluoroacetic acid afforded a colourless product **115** in 8% yield (Scheme 3.30). The ^{1}H NMR spectrum of this product in CD_2Cl_2 displayed four different singlets in a 1:1:1:1 ratio due to four different methoxy groups. There were also four singlets at δ 4.37, 4.78, 4.82 and 5.05, which were assigned to the four different methylene protons. In the ^{1}H NMR spectrum of **115**, the absence of AB systems for the methylene protons indicate that

the product did not form. In general, AB quartets are usually observed for the methylene protons when the calixnaphthalenes are in a fixed conformation. The aromatic protons showed simple patterns, and consisted of a total of twenty-one protons in the ^{1}H NMR spectrum of **115**, further suggesting that the molecule is uncyclized. The ^{13}C NMR spectrum shows four signals at δ 23.6, 26.6, 29.9 and 31.5 due to the methylene carbons and the presence of forty aromatic signals are consistent with the uncyclized tetranaphthyl product **115**. The mass of the assigned structure of **115** was obtained from (+)FAB MS spectrum, which showed a molecular ion peak at *m/z* = 760.



Scheme 3.31 **Attempted synthesis of compound 116a-b**

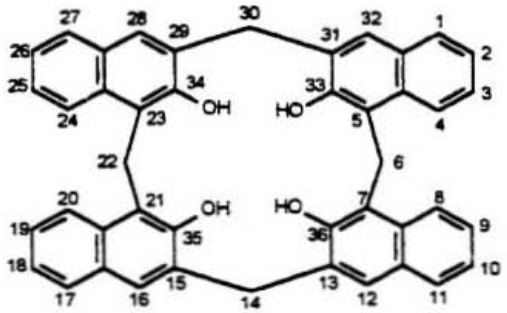
A novel cyclic molecule such as **116a** or **116b** was envisioned that could be synthesized from two simple starting materials, *p-tert*-butylphenol and **61**. The interesting feature of this structure is the presence of alternating benzene and naphthalene units. When a mixture of *p-tert*-butylphenol and **61** in boiling dioxane was treated with $TiCl_4$ a colourless product **117** was obtained in only 8% yield (Scheme 3.31). Both ^1H and ^{13}C NMR analysis suggested that the molecule is an uncyclized compound. The ^1H NMR spectrum of **117** displays five singlets at δ 4.06, 4.09, 4.37, 4.74 and 4.82 due to the protons of the two methoxy groups and the four methylene groups in a 3:3:4:2:2 ratio, respectively. The ^1H NMR spectrum reveals a total of eighteen protons, corresponding signals in the aromatic region. In particular, an AX system can be observed due to protons of the uncyclized phenolic unit at δ 6.73. Further evidence for the proposed structure was obtained from the ^{13}C NMR spectrum which showed ten aliphatic resonance signals due to the two *tert*-butyl group, four methylene units and two methoxy groups. In particular, the ^{13}C NMR signal at δ 41.7 is due to the methylene carbon connected to a bromine atom. The aromatic region of the ^{13}C NMR spectrum displays thirty-two signals, rather than fourteen expected ^{13}C NMR signals. The (+)-FAB MS spectrum shows a molecular ion peak at the expected value *m/z* = 745.

In conclusion, it has been shown that double *ortho* metallation in the presence of the methylene protons can be achieved with *six* equivalents of *tert*-butyllithium in THF at -78 °C to obtain the corresponding *ortho* substituted products. Also, it has

been shown that Suzuki-Miyaura methodology could be extended to achieve cross-coupling between aromatic boronic acids and benzylic bromides, iodides or (bromomethyl)naphthalenes to form various diarylmethane compounds in synthetically useful yields. Using the Suzuki-Miyaura coupling reactions conditions, various bisnaphthyl and tetranaphthyl compounds were synthesized. Syntheses of intermediates **96** and **98** were achieved via Suzuki-Miyaura coupling reaction conditions. These compounds could not previously be obtained by simple condensation of formaldehyde and 2-naphthol. The synthesis of "C-12" *endo* calix[4]naphthalene (**35**) was achieved in high yield and in pure form directly from the base-induced condensation reaction of intermediate **98**. Also, several alkyl ether derivatives (**113a-113d**) of **35** have been synthesized and their conformational properties have been determined from both ^{1}H and ^{13}C NMR spectra. The X-ray crystal structure of **113d** confirmed the structure of the molecule to have a *pinched cone* conformation with two molecules of toluene situated within the cavity as a 1:2 clathrate having C_2 symmetry. Also, the synthesis of *endo/exo* calix[4]naphthalene (**114**) was achieved utilizing $TiCl_4$-mediated "2+2" condensation conditions. Additional experiments are needed to find the optimal conditions for the synthesis of other *endo* calix[4]naphthalenes (**19b**, **78-80**) envisioned as a result of the successful syntheses of **35** and also of the *endo/exo* calix[4]naphthalene (**114**). Also, further experiments are needed to synthesize "C-12" *endo* calix[4]naphthalene-1,3-crowns to study their complexation properties with various metal cations.

3.11 Experimental Section For general methods, see Chapter 2.

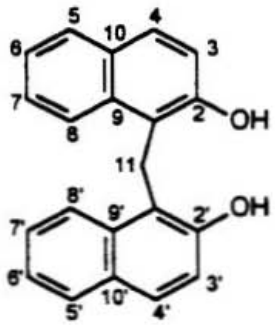
6*H*,14*H*,22*H*,30*H*-5,31:7,13:15,21:23,29-Tetramethenotetrabenzo[a,f,m,r] cyclotetracosene-33,34,35,36-tetrol[89] (*endo* calix[4]naphthalene) (35)



To a solution of bis(2-hydroxy-3-naphthyl)methane (**98**) (0.48 g, 1.6 mmol) in DMF (50 mL) was added aqueous 37% formaldehyde (0.08 mL, 2.8 mmol) and Cs_2CO_3 (0.52 g, 1.6 mmol) in H_2O (1.0 mL). The yellow solution was heated at reflux for 48 h, cooled to room temperature and the solvent was evaporated under reduced pressure. The crude material was diluted with CH_2Cl_2, washed with aqueous 10% HCl, and dried over $MgSO_4$. After the solvent was evaporated, the residue (0.45 g), was purified by flash column chromatography over silica gel eluting with ethyl acetate-hexane 20:80 to recover 30 mg of the pure product. After further eluting the column with $CHCl_3$, brown solid (0.32 g) was obtained that showed the presence of two spots on TLC. The solid was washed several times with $CHCl_3$ to afford pure **35** (0.276 g, 54%): mp >360 °C; ^{1}H NMR (500 MHz, pyridine-d_5) δ 4.61 (s, 4H), 5.19 (s, 4H), 7.04 (t, J = 7.4 Hz, 4H), 7.26 (t, J = 7.4 Hz, 4H), 7.47 (d, J = 7.9 Hz, 4H), 7.71 (s, 4H), 8.45 (br, 4H, OH), 8.49 (d, J = 8.6 Hz, 4H); ^{13}C (125 MHz, pyridine-d_5)

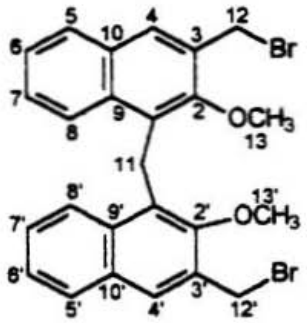
δ 23.3, 34.3, 120.2, 122.7, 126.0, 129.0, 129.7, 133.2, 133.9, 135.5, 136.3, 155.0; MS (*m/z*): 625 (M^++1, 8), 624 (M^+, 17), 606 (10), 588 (5), 437 (4), 325 (35), 312 (M/2, 100), 300 (23), 281 (8); HRMS M^+ 624.2352, calcd for $C_{44}H_{32}O_4$ 624.2300

Bis(2-hydroxy-1-naphthyl)methane (37)



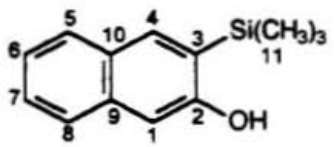
To a solution of **36** (32.0 g, 222 mmol) in 95% ethanol (140 mL) was added aqueous 37% formaldehyde (24.3 mL, 877 mmol), water (140 mL) and concentrated HCl (35 mL) at room temperature. The brown reaction solution was stirred for 16 h, during which time a white precipitate formed. The solid was filtered, washed with aqueous 10% $NaHCO_3$ and dried under vacuum to afford **37** (29 g, 88%) as a light brown solid that was sufficiently pure to use in subsequent reactions: mp 201-203 °C (lit.[58] mp 197-190 °C); ^{1}H NMR (acetone-d_6) δ 4.81 (s, 2H), 7.12 - 7.23 (m, 4H), 7.27 (d, J = 9.0 Hz, 2H), 7.63 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 8.35 (d, J = 8.4 Hz, 2H), 9.05 (br, 2H, OH); ^{13}C NMR (acetone-d_6) δ 18.0, 115.0, 115.1, 119.7, 121.3, 122.9, 125.1, 125.5, 126.9 131.4, 149.2.

Bis(3-bromomethyl-2-methoxy-1-naphthyl)methane (43)



To a solution of bis(3-hydroxymethyl-2-methoxy-1-naphthyl)methane (**87**) (10.0 g, 25.7 mmol) in CH_2Cl_2 at 0 °C was added slowly phosphorous tribromide (9.78 mL, 103 mmol). The brown reaction solution was stirred for 6 h, and then the reaction was quenched by slow addition of water at 0 °C. The organic layer was washed with saturated aqueous NH_4Cl, brine and dried over $MgSO_4$. After the solvent was evaporated, the crude product was washed with cold diethyl ether to afford **43** (8.90 g, 68%) as a colourless solid: mp 166-168 °C (lit.[58] mp 191-193 °C); ^{1}H NMR δ 4.08 (s, 6H, H-13, H-13'), 4.84 (s, 4H, H-12, H-12'), 5.01 (s, 2H, H-11), 7.29 (m, H-6, H-6', H-7, H-7'), 7.68 (m , 2H, H-5, H-5'), 7.75 (s, 2H, H-4, H-4'), 8.10 (m, 2H, H-8, H-8'); ^{13}C NMR δ 23.0 (C-11), 29.5 (C-12, C-12'), 62.5 (C-13, C-13'), 124.8 (C-8, C-8'), 125.0 (C-6, C-6'), 126.7 (C-7, C-7'), 128.2 (C-5, C-5'), 129.3 (C-1, C-1'), 130.4 (C-4, C-4'), 130.5, (C-3, C-3'), 130.9 (C-10, C-10'), 133.8 (C-9, C-9'), 153.6 (C-2, C-2'); MS (*m/z*): 515 (M^+, ^{81}Br, ^{81}Br, 20), 513 (M^+,^{79}Br, ^{79}Br, 10), 436 (5), 435 (5), 434 (5), 433 (4), 308 (13), 295 (2), 279 (4), 277 (4), 265 (49), 263 (48), HRMS M^+ 513.9938, calcd for $C_{25}H_{22}{}^{79}Br^{81}BrO_2$ 515.9946.

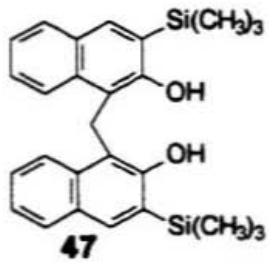
2-Hydroxy-3-trimethylsilylnaphthalene (46)



To a solution of **36** (1.73 g, 120 mmol) in tetrahydropyran (THP) (3 mL) at room temperature under argon was added *tert*-BuLi (1.7 M pentane, 20.0 mL, 27.0 mmol). The resulting brown solution became warm and a gas evolved. The mixture was stirred at room temperature for 4 h, and was cooled to -40 °C, then TMSCl (6.09 mL, 48.0 mmol) was added dropwise over 15 min. The mixture was stirred for another 16 h, then quenched by addition of H_2O (10 mL) and the organic layer was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography eluting with 15:85 ethyl acetate-hexane to afford **46** (1.32 g, 51%) as a colourless solid: mp 144-146 °C ^{1}H NMR δ 0.56 (s, 9H), 6.21 (s, 1H, OH), 6.92 (s, 1H, H-1), 7.41 (dd, *J* = 1.2, 8.1 Hz, 1H), 7.51 (dd, *J* = 1.2, 8.1 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H, H-4); ^{13}C NMR δ -0.89, 108.0, 123.2, 125.7, 126.6, 127.9, 128.6, 129.1, 135.4, 136.2, 158.2; MS (*m/z*): 216 (M^+, 36,), 200 (100), 183 (80), 141 (35).

Bis(2-hydroxy-3-trimethylsilyl-1-naphthyl)methane (47)

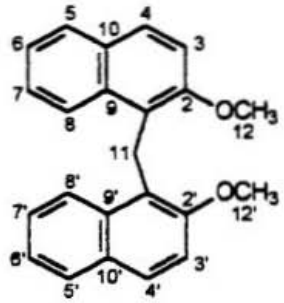
To a solution of 2-hydroxy-3-trimethylsilylnaphthalene (**46**) (780 mg, 3.61 mmol) in 95% ethanol (1.6 mL) was added aqueous 37% formaldehyde (2.5 mL), water (1.6



47

mL) and aqueous concentrated HCl (0.37 mL). The brown solution was stirred at room temperature for 16 h. The organic layer was extracted with CH_2Cl_2 (2 mL), washed with brine and dried over $MgSO_4$. After the solvent was evaporated, the residue was purified using preparative TLC eluting with 15:85 ethyl acetate-hexane to afford **47** (605 mg,75%) as a colourless solid: mp 180-181 °C; ^{1}H NMR δ 0.29 (s, 18H, H-12, H-12'), 4.79 (s, 2H, H-11), 5.77 (s, 2H, OH), 7.38 (t, J = 7.5 Hz, 2H, H-6, H-6'), 7.52 (t, J = 7.5 Hz, 2H, H-7, H-7'), 7.83 (m, 4H, H-4, H-4', H-5, H-5'), 8.18 (d, J = 8.6 Hz, 2H, H-8, H-8'); ^{13}C NMR δ 0.01, 22.7, 112.9, 122.3, 123.3, 127.4, 129.2, 129.5, 129.6, 133.8, 136.2, 157.3; HRMS M$^+$ 444.1944 calcd for $C_{27}H_{32}O_2Si_2$ 444.1941.

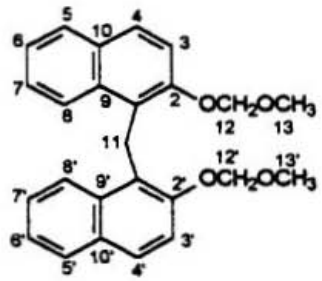
Bis(2-methoxy-1-naphthyl)methane (49)



To a solution of **37** (10.0 g, 33.3 mmol) in CH_2Cl_2 (150 mL) was added aqueous 10%

NaOH (37.5 mmol), Adogen® (5.0 mL) and dimethyl sulfate (10.0 mL, 106 mmol). The reaction mixture was stirred for 16 h, quenched with saturated aqueous NH_4Cl (10 mL) and the organic layer was extracted with CH_2Cl_2, washed with brine, and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The crude product was crystallized from ethyl acetate-hexane to afford **49** (8.9 g, 81%) as a colourless solid: mp 140-142 °C; ^1H NMR δ 3.87 (s, 6H, H-12, H-12'), 4.91 (s, 2H, H-11), 7.20-7.32 (m, 6H), 7.69 (d, J = 8.7 Hz, 4H), 8.19 (d, J = 8.7 Hz, 2H, H-8, H-8'); MS (*m/z*): 328 (M^+, 100), 314 (62), 297 (14), 281 (38), 265 (26), 252 (18); HRMS M^+ 328.1469, calcd for $C_{23}H_{20}O_2$ 328.1463.

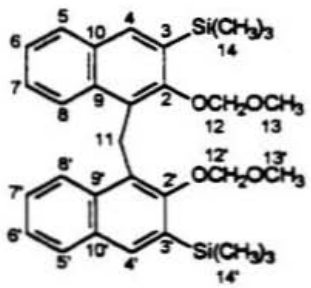
Bis(2-methoxymethoxy-1-naphthyl)methane (50)



To a suspension of NaH (60 % suspension in oil, 3.07 g, 79.9 mmol) in anhydrous THF (85 mL) was added bis(2-hydroxy-1-naphthyl)methane (**37**) (4.00 g, 13.3 mmol) in anhydrous THF (15 mL) at 0 °C. The mixture was stirred for 1 h, then chloromethyl methyl ether (8.10 mL, 106 mmol) was added dropwise. The mixture was stirred for 16 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the solvent was evaporated under reduced pressure. The residue was

dissolved with CH_2Cl_2 (50 mL), washed with brine, and dried over $MgSO_4$. The crude product was crystallized from ethyl acetate-hexane to obtain **50** (4.20 g, 81%) as colourless crystals: mp 105–106 °C; ^{1}H NMR δ 3.20 (s, 6H, H-13, H-13'), 4.93 (s, 2H, H-11), 5.05 (s, 4H, H-12, H-12'), 7.31 (t, *J* = 8.0 Hz, 4H, H-6, H-6', H-7, H-7'), 7.37 (d, *J* = 9.0 Hz, 2H, H-4, H-4'), 7.67 (d, *J* = 9.0 Hz, 2H, H-3, H-3'), 7.73 (d, *J* = 8.1 Hz, 2H, H-5, H-5'), 8.28 (d, *J* = 8.4 Hz, 2H, H-8, H-8'); ^{13}C NMR δ 22.5 (C-11), 55.8 (C-13, C-13'), 94.7 (C-12, C-12'), 115.9, 123.4, 124.2, 124.4, 125.7, 127.8, 128.3, 129.9, 130.7, 152.5; MS (*m/z*): 388 (M^+, 29) 343 (2), 312 (17), 280 (24), 265 (3), 232 (19); HRMS M^+ 388.1689, calcd for $C_{25}H_{24}O_4$ 388.1675.

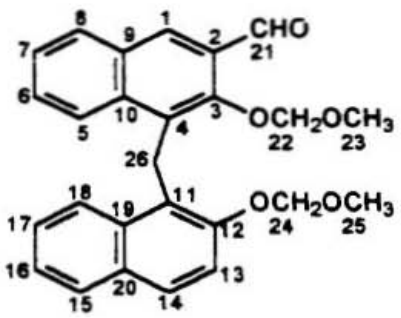
Bis(2-methoxymethoxy-3-trimethylsilyl-1-naphthyl)methane (51)



To solution of **50** (50 mg, 0.13 mmol) in dry THF (2.5 mL) at -78 °C was added dropwise *tert*-BuLi (1.7M in pentane, 0.23 mL, 0.39 mmol). The yellow mixture was stirred for 90 min and then TMSCl (0.10 mL, 0.78 mmol) was added slowly. The resulting colourless mixture was warmed to room temperature over 4 h, the reaction was quenched with saturated aqueous NH_4Cl (2 mL), and the solvent evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (10 mL), washed with

water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography eluting with 30:70 ethyl acetate-hexane to afford **51** (25 mg, 37%) as a colourless solid: mp 128-132 °C; ^{1}H NMR δ 0.50 (s, 18H, H-14, H-14'), 3.79 (s, 6H, H-13, H-13'), 5.11 (s, 2H, H-11), 5.25 (s, 4H, H-12, H-12'), 7.22-7.32 (m, 4H, H-6, H-6', H-7, H-7'), 7.65 (d, *J* = 7.5 Hz, 2H, H-5, H-5'), 7.76 (s, 2H, H-4, H-4'), 8.42 (d, *J* = 8.4 Hz, 2H, H-8, H-8'); ^{13}C NMR δ 0.10 (C-14, C-14'), 24.4 (C-11), 58.0 (C-13, C-13'), 101.5 (C-12, C-12'), 124.6, 125.4, 126.3, 128.3, 131.4, 133.4, 134.8, 135.9, 156.4; MS (*m/z*): 532 (M^+, 15), 456 (48), 425 (17), 397 (13), 383 (10), 366 (11), 213 (95).

4-Methyl-[(2'-methoxymethoxy)naphthyl]-(3-methoxymethoxy)-2-naphthaldehyde (52)

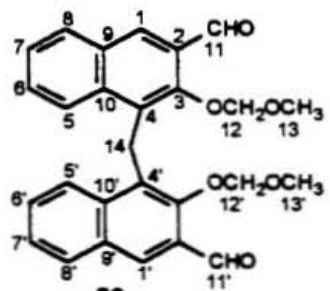


52

To a solution of **50** (777 mg, 2.00 mmol) in anhydrous THF (30 mL) at -78 °C was added *tert*-BuLi (1.7 M in pentane, 7.06 mmol, 12.0 mL). The yellow solution was stirred at -78 °C for 3 h, then DMF (1.55 mL, 20.0 mmol) was added slowly. The resulting reaction solution was warmed to room temperature over 6 h, and saturated

aqueous NH_4Cl solution (10 mL) was added, then the solvent was evaporated. The residue was diluted with CH_2Cl_2, the organic layer washed with brine, dried over $MgSO_4$, filtered, and finally the solvent was evaporated. The residue was purified by flash column chromatography eluting with 20:80 ethyl acetate-hexane to afford **52** (360 mg, 43%) as a yellow solid: mp 120-121 °C; ^{1}H NMR δ 3.36 (s, 3H), 3.57 (s, 3H), 5.01 (s, 2H, H-26), 5.07 (s, 2H), 5.17 (s, 2H), 7.26-7.44 (m, 5H), 7.72 (t, *J* = 8.6 Hz, 2H), 7.84-7.88 (m, 1H), 8.13-8.20 (m, 2H), 8.29 (s, 1H, H-1), 10.51 (s, 1H, CHO); ^{13}C NMR δ 20.3, 53.4, 55.4, 92.4, 98.9, 113.2, 117.6, 120.0, 121.0, 122.3, 122.7, 123.8, 125.7(2), 125.8, 125.9, 127.2, 127.6, 127.7, 128.0, 128.1, 130.6, 133.8, 149.6, 150.3, 188.7; MS (*m/z*): 413 (M^+-3H, 5), 367 (25), 353 (36), 337 (100), 309 (94), 281 (38), HRMS M^+ 416.1628, calcd for $C_{26}H_{24}O_5$ 416.1224; and

4,4'-Methylene bis(3-methoxymethoxy-2-naphthaldehyde) (53)

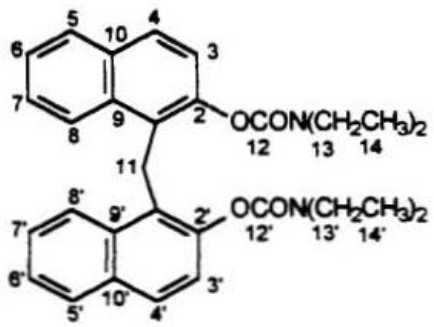


53

(446 mg, 52%) was obtained as a yellow solid: mp 117-119 °C; ^{1}H NMR δ 3.64 (s, 6H, H-13, H-13'), 5.08 (s, 2H, H-14), 5.23 (s, 4H, H-12, H-12'), 7.33-7.46 (m, 4H, H-6, H-6', H-7, H-7'), 7.85 (d, *J* = 8.1 Hz, 2H, H-8, H-8'), 8.16 (d, *J* = 8.4 Hz, 2H,H-5, H-5'), 10.48 (s, 2H, CHO); ^{13}C NMR δ 23.4 (C-14), 58.2 (C-13, C-13'),102.0 (C-12,

C-12'), 124.7,125.8, 128.4, 129.3, 129.8, 130.4, 130.5, 132.2, 136.1, 152.6, 191.0; MS (*m/z*): 444 (M^+, 10), 413 (5), 367 (25), 353 (36), 339 (23), 338 (58), 337 (100)

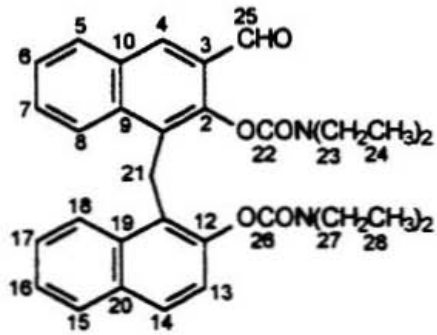
Bis(2-*N*, *N*-diethylcarbamoyloxy-1-naphthyl)methane (56)



A suspension of **37** (1.5 g, 5.0 mmol) and anhydrous K_2CO_3 (6.9 g, 50 mmol) in dry acetonitrile (50 mL) was heated at reflux for 30 min. To this suspension was added diethylcarbamoyl chloride (6.4 mL, 50 mmol) and the mixture was refluxed for 24 h. After filtration to remove K_2CO_3, the solvent was removed under reduced pressure, and the residue was diluted with CH_2Cl_2 (50 mL) and then aqueous 10% HCl (20 mL) was added. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated to afford a brown solid. The crude product was purified by flash column chromatography using 20:80 ethyl acetate-hexane to afford **56** (2.0 g, 80%) as a brown solid: mp 138-140 °C; ^{1}H NMR δ 1.06 (t, *J* = 7.0 Hz, 6H), 1.10 (t, *J* = 7.0 Hz, 6H), 3.09 (q, *J* = 7.0 Hz, 4H), 3.27 (q, *J* = 7.0 Hz, 4H), 4.80 (s, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.29 - 7.36 (m, 4H), 7.69 - 7.76 (m, 4H), 8.17 - 8.20 (m, 2H); ^{13}C NMR δ 13.2, 14.1, 24.0, 41.4. 42.1, 122.1, 124.2, 125.3, 125.9,

127.2, 125.2, 127.7, 131.7, 133.2, 146.8, 153.8; MS (*m/z*): 498 (M^+, 3), 398 (2), 308 (2), 281 (8); HRMS M^+ 498.2524, calcd for $C_{31}H_{34}N_2O_4$ 498.2517.

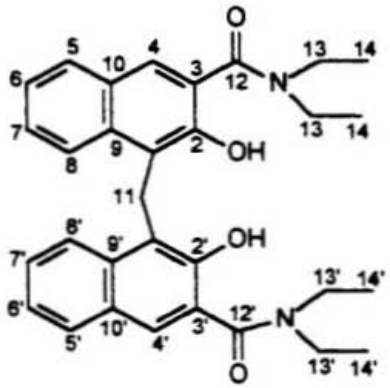
4-Methyl-[(2'-*N*,*N*-diethylnaphthylcarbamoyl)naphthyl]-(3-*N*,*N*-diethylcarbamate)-2-naphthaldehyde (57)



A solution of **56** (2.00 g, 4.01 mmol) in dry THF (40 mL) under argon was cooled to -78 °C and then *t*-BuLi (1.7 M in pentane, 14.2 mL, 24.1 mmol) was added dropwise. The resulting yellow mixture was stirred for 3 h, after which time DMF (6.21 mL, 80.2 mmol) was added dropwise. The resulting solution was allowed to warm to room temperature over 4 h, then quenched with saturated aqueous NH_4Cl (2 mL) and the solvent was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (50 mL), washed with water, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with 30:70 ethyl acetate-hexane to afford **57** (1.00 g, 47%) as a yellow solid: mp 164-166 °C; ^1H NMR 1.19 - 1.27 (m, 12H), 3.34 - 3.52 (m, 8H), 4.86 (s, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.40 (m, 3H), 7.68 (m, 2H), 7.89 (m, 1H), 8.10

(m, 2H), 8.25 (s, 1H), 9.26 (s, 1H), 10.18 (s, 1H); MS (*m/z*): 526 (M^+, 6), 453 (16), 408 (24), 381 (3), 337 (9), 309 (10); HRMS M^+ 526.2474, calcd for $C_{32}H_{34}N_2O_5$ 526.2468; and **58** (0.59 g, 26%) as a yellow solid, identical with **58** obtained by *ortho* Fries rearrangement (below).

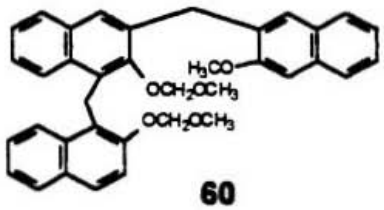
Bis(3-*N*,*N*-diethylcarbamoyl-2-hydroxy-1-naphthyl)methane (58)



To a solution of **56** (499 mg, 1.00 mmol) in anhydrous THF (17 mL) at -78 °C was added *tert*-BuLi (1.7 M in pentane, 3.53 mL, 6.00 mmol). The resulting deep blue reaction solution was stirred at -78 °C for 2 h, and then warmed to room temperature, before quenching with saturated aqueous NH_4Cl (5.0 mL). After the solvent was evaporated under reduced pressure, the yellow slurry was extracted with CH_2Cl_2, the organic solution was washed with brine, dried over Na_2SO_4 and filtered. After the solvent was evaporated, the crude product was crystallized from ethyl acetate-hexane to afford **58** (347 mg, 70%) as yellow crystals: mp 173-175 °C; ^{1}H NMR δ 1.25 (t, J = 7.0 Hz, 12H, H-14, H-14'), 3.56 (q, J = 7.0 Hz, 8H, H-13, H-13'), 4.84 (s, 2H, H-11), 7.27 (t, J = 7.8 Hz, 2H, H-6, H-6'), 7.40 (t, J = 7.6 Hz, 2H,

H-7, H-7'), 7.67 (s, 2H, H-1, H-1'), 7.70 (d, J = 7.8 Hz, 2H, H-5, H-5'), 8.24 (d, J = 8.7 Hz, 2H, H-8, H-8'), 9.66 (br, OH); ^{13}C NMR δ 13.4 (C-14, C-14'), 21.5 (C-11), 42.5 (C-13, C-13'), 121.0, 122.9, 123.4, 123.8, 126.4, 127.3, 127.8, 129.0, 134.3, 150.2, 170.9 (C-12, C-12'); MS (*m/z*): 498 (M$^+$, 3), 479 (4), 307 (5), 294 (8), 280 (5), 256 (12).

1-[1-Naphthyl-(2'-*O*-methoxymethoxy)methyl]-3-[3"-naphthyl-(2"-methoxy)methyl]-2-*O*-(methoxymethoxy)naphthalene (60)



60

To a solution of **50** (388 mg, 1.00 mmol) in anhydrous THF (15 mL) at -78 °C was added 6.0 equivalents of 1.7 M *tert*-BuLi (3.5 mL, 6.0 mmol). The yellow solution was stirred at -78 °C for 4 h, and was added via a cannula to a solution of anhydrous $ZnCl_2$ (2.3 g, 10 mmol) in anhydrous THF (5.0 mL). The resulting mixture was stirred for 1 h at rt. This organozinc reagent was added via a cannula into a mixture of **61** (388 mg, 1.00 mmol) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) in anhydrous THF (30 mL) and was stirred for 24 h at rt, and then heated at reflux for 1 h. The solvent was evaporated under reduced pressure and the black slurry was diluted with CH_2Cl_2, washed with saturated aqueous NH_4Cl, brine and dried over $MgSO_4$ and filtered. After the solvent was evaporated, the black residue was purified by column

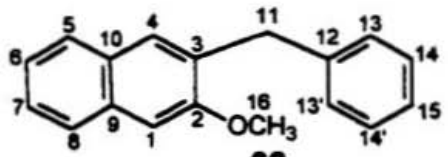
chromatography using 30:70 ethyl acetate-hexane to afford **60** (196 mg, 35%) as a colourless solid: mp 149-151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (s, 3H), 3.60 (s, 3H), 3.95 (s, 3H), 4.40 (s, 2H), 5.02 (s, 2H), 5.14 (s, 2H), 5.27 (s, 2H), 7.10 (t, *J* = 8.5 Hz, 1H), 7.18 (m, 4H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.35 - 7.46 (m, 4H), 7.56 (t, *J* = 9.0 Hz, 2H), 7.67 (dd, *J* = 1.5, *J* = 9.0 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5, 31.7, 55.4, 56.2, 57.8, 95.6, 100.6, 104.9, 116.2, 123.4, 123.6, 123.9, 124.3, 124.4, 124.9, 125.0, 125.7, 126.3, 126.4, 127.5, 127.8, 128.2, 128.3, 128.7, 128.8, 128.9, 129.6, 130.1, 131.1, 131.4, 132.6, 133.2, 133.5, 133.7, 152.0, 152.5, 156.3; MS (*m/z*): 558 (M^+, 2), 482 (7), 451 (5), 388 (14), 326 (25), 312 (18), 295 (18), 281 (38), 156 (100); HRMS M^+ 558.2406, calcd for $C_{37}H_{34}O_5$ 558.2498.

General Method of Suzuki-Miyaura Cross-Coupling Reactions

A flask equipped with a magnetic stirrer and a condenser was charged with benzyl halide or (bromomethyl)naphthalene (1.00 mmol) and $Pd(PPh_3)_4$ (5-10 mol%). The mixture was flushed with argon, and then DME (15 mL) was added. The yellow reaction solution was heated at 50 °C for 15 min, and a solution of phenyl- or naphthaleneboronic acid (1.00 mmol) in DME/ethanol (6 mL, 2:1) was added via a cannula, followed by aqueous 2M Na_2CO_3 (2 mL). The resulting yellow mixture was heated at reflux for 24 h under argon, cooled to rt, and then the organic solvent was evaporated. The resulting black suspension was diluted with ethyl acetate, and the organic layer washed twice with saturated aqueous NH_4Cl, brine, and dried over

$MgSO_4$. After filtering, the solvent was evaporated under reduced pressure. The crude product was purified by either flash column chromatography or preparative TLC eluting with ethyl acetate-hexane to afford the following products:

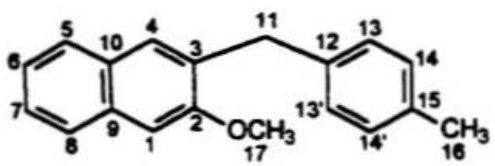
3-Benzyl-2-methoxynaphthalene (66)



66

66 was obtained in 75% yield (186 mg) as a colourless liquid from the reaction between benzyl bromide and **72** using the Suzuki-Miyaura cross-coupling procedure: ^{1}H NMR δ 3.89 (s, 3H, H-16), 4.11 (s, 2H, H-11), 7.09 (s, 1H), 7.12 - 7.38 (m, 6H), 7.47 (s, 1H), 7.58 - 7.76 (m, 3H); ^{13}C NMR δ 36.5, 55.4, 105.0, 123.6, 125.8, 126.0, 126.3, 127.3, 128.3, 128.8, 129.0, 129.1, 131.5, 133.6, 140.7, 156.4; HRMS M^+ 248.1210 calcd for $C_{18}H_{16}O$ 248.1200.

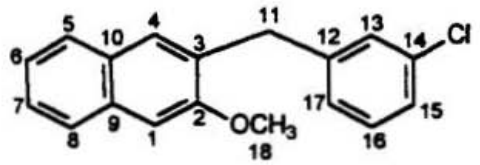
3-(4'-Methylbenzyl)-2-methoxynaphthalene (67)



67 was obtained in 57% (160 mg) as a colourless liquid from the reaction between 4-methylbenzyl bromide and **72** using the Suzuki-Miyaura cross-coupling procedure: ^{1}H NMR δ 1.47 (s, 3H), 3.93 (s, 3H), 4.05 (s, 1H), 7.15 (s, 1H), 7.30 - 7.50 (m, 4H), 7.66 - 7.83 (m, 4H), 8.05 (d, J = 8.2 Hz, 1H) ^{13}C NMR δ 36.8, 55.7, 105.4, 123.8,

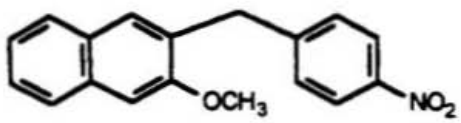
124.0, 126.2, 126.3, 126.5, 127.7, 128.8, 129.6, 129.9, 130.3, 130.4, 134.4, 156.3; MS (*m/z*): 262 (M^+, 13), 247 (2), 231 (3), 215 (3), 191 (3), 158 (96); HRMS M^+ 262.1375, calcd for $C_{19}H_{18}O$ 262.1358.

3-(3'-Chlorobenzyl)-2-methoxynaphthalene (68)



68 was obtained in 70% (185 mg) as a colourless crystals from the reaction between 3-chlorobenzyl bromide and **72** using the Suzuki-Miyaura cross-coupling procedure: mp 172-174 °C; ^{1}H NMR δ 3.95 (s, 3H, H-18), 4.14 (s, 2H, H-11), 7.04 - 7.17 (m, 4H), 7.22 (s, 1H) 7.28 (t, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.46 (s, 1H), 7.66 (t, J = 8.0 Hz, 2H); ^{13}C NMR δ 36.2 (C-11), 55.3 (C-18), 105.1, 120.2, 123.7, 125.9, 126.1, 126.3, 127.1, 127.2, 128.7, 129.0, 129.4, 130.4, 133.6, 133.9, 142.8, 156.1; MS (*m/z*): 282 (100, M^+), 267 (5), 232 (15), 231 (18), 216 (13), 215 (30); HRMS M^+ 282.0814, calcd for $C_{18}H_{15}{}^{35}ClO$ 282.0811.

3-(4'-Nitrobenzyl)-2-methoxynaphthalene (69)

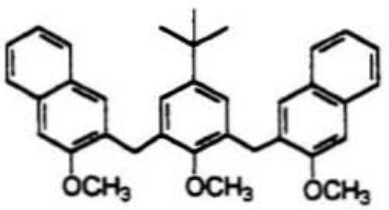


69

69 was obtained in 68% (199 mg) as a colourless liquid from the reaction between 4-nitrobenzyl bromide and **72** using the Suzuki-Miyaura cross-coupling procedure:

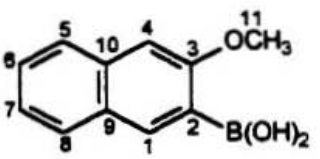
^{1}H NMR δ 3.80 (s, 3H), 4.12 (s, 2H), 7.19 (s, 1H), 7.26 - 7.49 (m, 4H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.72 (m, 3H), 8.06 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 36.7, 55.7, 105.4, 123.8, 124.0, 126.2, 126.3, 126.5, 127.7, 128.8, 129.6, 129.9, 130.3, 130.4, 134.4, 156.3.

4-*Tert*-butyl-1-methoxy-2,6-bis[3'-naphthyl-(2-methoxy)methyl]benzene (70)



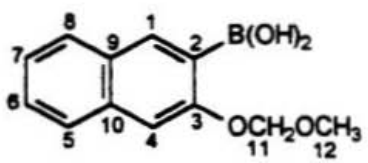
70 was obtained in 42% yield (111 mg) as colourless crystals from the reaction between **72** and 3-(bromomethyl)-2-methoxynaphthalene (**74**) using the Suzuki-Miyaura cross-coupling procedure: mp 172-174 °C; ^{1}H NMR δ 1.19 (s, 9H), 3.65 (s, 3H), 3.95 (s, 6H), 4.17 (s, 4H), 7.09 (s, 2H), 7.12 (s, 2H), 7.25 (m, 2H), 7.36 (m, 4H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR δ 30.6, 31.4, 34.2, 55.3, 61.3, 104.7, 123.4, 125.5, 126.2, 126.4, 127.3, 128.7, 128.8, 131.6, 132.2, 133.4, 146.4, 154.8, 156.5; MS (*m/z*): 504 (M^+, 17), 489 (12), 315 (17), 314 (76); HRMS M^+ 504.2682, calcd for $C_{35}H_{36}O_3$ 504.2664.

3-Methoxy-2-naphthaleneboronic acid (72)



To a solution of 2-methoxynaphthalene (**83**) (8.3 g, 53 mmol) in anhydrous THF (350 mL) at room temperature, *n*-BuLi (37.1 mL, 63.0 mmol) was added dropwise. The reaction mixture was stirred for 2.5 h, then cooled to -78 °C, and trimethylborate (4.2 mL, 76 mmol) was added dropwise over a period of 30 min. The reaction was warmed to room temperature over 6 h, then aqueous 10% HCl (50 mL) was added. The mixture was stirred at rt for another 30 min. After the solvent was evaporated, the slurry was diluted with CH_2Cl_2, washed with saturated aqueous NH_4Cl, dried over $MgSO_4$ and filtered. After the solvent was evaporated, the residue was crystallized from benzene-hexane to afford **72** (9.0 g, 85%) as colourless crystals: mp 129-130 °C; ^{1}H NMR (acetone -d_6) δ 4.04 (s, 3H), 7.19 (s, 2H), 7.34 - 7.37 (m, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.4 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR δ 52.3, 102.0, 117.6, 121.8, 124.5, 125.5, 126.1, 133.5, 135.4, 158.8; MS (*m/z*): 552 (anhydride of boronic acid, 2), 203 (13), 202 (M^+, 100), 184 (11), 159 (16), 141 (32), 126 (21), 115 (15); HRMS M^+ 202.0827, calcd for $C_{11}H_{11}BO_3$ 202.0801.

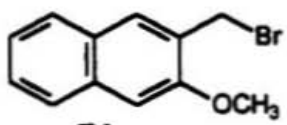
3-Methoxymethyl-2-naphthaleneboronic acid (73)



To a solution of 2-methoxymethoxynaphthalene (**84**) (1.3 g, 6.7 mmol) in anhydrous THF (50 mL) at -78 °C was added *tert*-BuLi (4.8 mL, 8.1 mmol). The yellow solution was stirred for 3 h at -78 °C, after which time trimethylborate (1.1 mL, 10 mmol) was

added slowly. The mixture was slowly warmed to room temperature and stirred overnight. After quenching the reaction with saturated aqueous NH_4Cl (20 mL), the organic solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2. The solution was washed with saturated aqueous NH_4Cl (2x25 mL), dried over $MgSO_4$ and filtered, and the solvent was evaporated. The product was crystallized from ethyl acetate-hexane to afford **73** (1.2 g, 75%) as yellow crystals: ^{1}H NMR δ 3.56 (s, 3H, H-12), 5.42 (s, 2H, H-11), 6.35 (s, 2H, OH, D_2O exchangeable), 7.38 (t, *J* = 7.5 Hz, 1H), 7.43 (s, 1H, H-4), 7.49 (t, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 8.44 (s, 1H, H-1); ^{13}C NMR δ 56.5, 94.8, 108.4, 120.3, 124.4, 126.8, 127.7, 128.6, 129.2, 136.0, 138.8, 138.9, 158.7; MS (*m/z*): 232 (M^+, 3), 214 (3), 199 (2), 184 (16), 170 (9), 156 (8).

3-Bromomethyl-2-methoxynaphthalene (74)

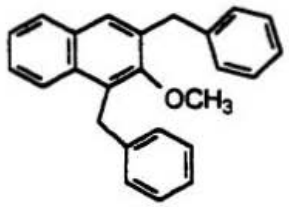


74

To a solution of 2-hydroxymethyl-3-methoxynaphthalene (**95**) (10.0 g, 53.2 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C was added phosphorous tribromide (7.6 mL, 80 mmol). The brown reaction solution was allowed to warm to room temperature over 5 h, and the reaction was then quenched by the slow addition of water. The organic layer was washed with aqueous 10% $NaHCO_3$ solution, then brine, dried over $MgSO_4$ and filtered. After the solvent was evaporated, the residue was purified

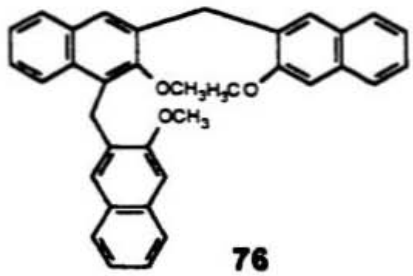
by flash column chromatography eluting with 15:85 ethyl acetate-hexane to afford **74** (8.5 g, 64%) as a colourless solid: mp 148-149 °C; ^{1}H NMR δ 3.94 (s, 3H, H-12), 4.24 (s, 2H, H-11), 7.15 (s, 1H, H-4), 7.29 (t, 7.8, 2H, H-6), 7.35 - 7.44 (m, 2H), 7.63 (d, *J* = 8.5 Hz, 1H, H-5), 7.74 (d, *J* = 8.2 Hz, 1H, H-8); MS (*m/z*): 250 (M^+, 15), 172 (13), 171 (100), 141 (86), 128 (37).

1,3-Dibenzyl-2-methoxynaphthalene (75)



75 was obtained in 35% yield (55 mg) as a colourless solid from the reaction between **61** and phenylboronic acid using the Suzuki-Miyaura cross-coupling procedure: mp 115-118 °C; ^{1}H NMR δ 3.59 (s, 3H), 4.21 (s, 2H), 4.57 (s, 2H), 7.15 - 7.36 (m, 12H), 7.54 (s, 1H), 7.69 - 7.74 (m, 1H), 7.75 - 7.79 (m, 1H).

1,3-Bis([3'-naphthyl-(2'-methoxy)methyl]-2-methoxynaphthalene (76)

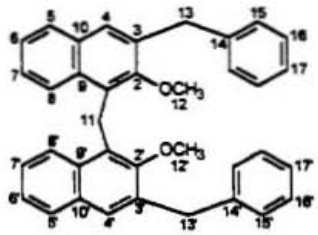


76

76 was obtained in 66% yield (0.65 g) as colourless fluffy solid from the reaction

between **61** and 3-methoxy-2-naphthaleneboronic acid (**72**) using the Suzuki-Miyaura cross-coupling procedure: mp 110-112 °C; ^{1}H NMR δ 3.71 (s, 3H), 3.94 (s, 3H), 4.10 (s, 3H), 4.37 (s, 2H), 4.60 (s, 2H), 6.96 (s, 1H), 7.14 - 7.22 (m, 3H), 7.23 -7.44 (m, 6H), 7.49 (s, 1H), 7.56 (s, 1H), 7.62 - 7.78 (m, 5H); ^{13}C NMR δ 26.0, 31.0, 55.4, 55.5, 61.8, 104.4, 105.0, 120.3, 123.3, 123.6, 124.6, 124.7, 125.5, 125.6, 125.7, 126.2, 126.3, 127.3, 127.6, 127.9, 128.7, 128.8, 129.3, 130.2, 131.2, 131.3, 132.7, 133.2, 133.6, 133.9, 156.0, 156.2, 156.5; MS (*m/z*): 498 (M^{+}, 65), 494 (100), 486 (70), 480 (75); HRMS M^{+} 498.2193, calcd for $C_{35}H_{27}O_3$ 498.2195.

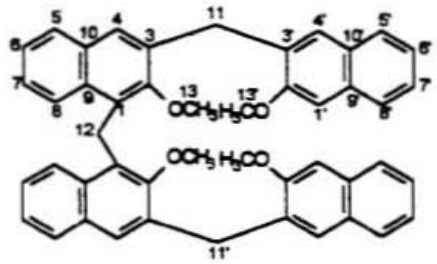
Bis(3-benzyl-2-methoxy-1-naphthyl)methane (77)



77 was obtained in 45% yield (297 mg) as colourless crystals from the reaction between **43** and phenylboronic acid using the Suzuki-Miyaura cross-coupling procedure: mp 145-147 °C; ^{1}H NMR δ 3.79 (s, 6H, H-12, H-12'), 4.21 (s, 4H, H-13, H-13'), 4.93 (s, 2H, H-11), 7.17 (m, 14H), 7.43 (s, 2H, H-4, H-4'), 7.5 (d, *J* = 8.0 Hz, 2H, H-5, H-5'), 8.11 (d, *J* = 8.5 Hz, 2H, H-8, H-8'); ^{13}C NMR δ 20.5 (C-13, C-13'), 34.5 (C-11), 59.4 (C-12, C-12'), 121.9, 122.3, 122.8, 123.4, 125.1, 125.8, 126.2, 126.3, 126.6, 128.6, 130.2, 130.8, 138.5, 151.8 (C-2, C-2'); MS (*m/z*): 508 (M^{+}, 58), 461 (13), 432 (22), 385 (14), 371 (15), 356 (16), 356(16), 326 (12), 260 (18), 231

(50); HRMS M^+ 508.2371, calcd for $C_{37}H_{32}O_2$ 508.2402.

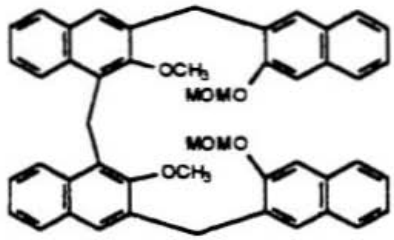
Bis{(2-methoxy)-3-[3'-naphthyl-(2'-methoxy)methyl]naphthyl}methane (81)



81 was obtained in 58% yield (193 mg) as colourless crystals from the reaction between **43** and 3-methoxy-2-naphthaleneboronic acid (**72**) using the Suzuki-Miyaura cross-coupling procedure: mp 241-244 °C; ^{1}H NMR (CD_2Cl_2) δ 3.98 (s, 6H), 3.99 (s, 6H), 4.39 (s, 4H), 5.03 (s, 2H), 6.81 (t, *J* = 7.4 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 4H), 7.24 (s, 2H), 7.33 (t, *J* = 7.4, 2H), 7.38 - 7.51 (m, 6H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.80 (s, *J* = 8.2 Hz, 2H), 8.17 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (CD_2Cl_2) δ 20.3, 28.3, 52.7, 59.4, 102.1, 117.6, 120.6, 121.6, 121.9, 122.3, 122.6, 122.9, 123.5, 124.6, 125.0, 125.9, 126.1, 128.5, 128.7, 129.8, 130.5, 130.8, 151.9, 153.6; MS (*m/z*): 668 (M^+, 32), 621 (3), 512 (4), 497 (3), 465 (3), 340 (21), 327 (33), 311 (29); HRMS M^+ 668.2936 calcd for $C_{47}H_{40}O_4$ 668.2924.

Bis{(2-methoxy)-3-[3'-naphthyl-(2'-methoxymethoxy)methyl]naphthyl}methane (82):

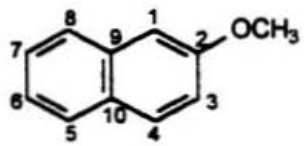
82 was obtained in 43% yield (0.54 g) as a yellow fluffy solid from the reaction between **43** and 3-methoxymethoxy-2-naphthaleneboronic acid (**73**) using the Suzuki-Miyaura cross-coupling procedure: mp 78-80 °C; ^{1}H NMR δ 3.35 (s, 6H),



82

3.90 (s, 6H), 4.40 (s, 4H), 5.01 (s, 2H), 5.3 (s, 4H), 7.00 (t, J = 7.7 Hz, 2H), 7.17 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.4 Hz, 2H), 7.37 - 744 (m, 7H), 7.57 (t, J = 9.4 Hz, 5H), 7.75 (d, J = 7.8 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 23.1, 31.4, 56.0, 62.1, 94.2, 108.5, 120.3, 123.8, 124.4, 124.8, 124.9, 125.5, 125.7, 126.6, 127.4, 127.7, 128.7, 129.2, 131.2, 131.3, 132.7, 132.9, 133.4, 153.6, 154.6; MS (*m/z*): 698 (3), 665 (10), 652 (6), 633 (4), 591 (2), 575 (5), 495 (2), 463 (2), 371 (22), 339 (30), 325 (25).

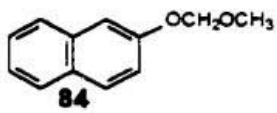
2-Methoxynaphthalene (83)



To a solution of 2-naphthol (**36**) (60.0 g, 417 mmol) in CH_2Cl_2 (330 mL) was added phase-transfer catalyst , Adogen® (10.0 mL) and aqueous 10% NaOH (336 mL, 834 mmol). The mixture was stirred vigorously for 30 min at 0 °C, and then dimethylsulfate (60.0 mL, 625 mmol) was added over a period of 30 min. The reaction solution was stirred for another 3 h, then partitioned between the organic

and aqueous layers. The organic layer was washed with aqueous 10% K_2CO_3 solution, then brine, dried over $MgSO_4$ and filtered. After the solvent was evaporated, the crude product was crystallized from petroleum ether to afford **83** 58.0 g, 88%) as colourless crystals: ^{1}H NMR δ 3.98 (s, 3H), 7.17 (m, 2H), 7.35 (t, *J* = 8.8 Hz, 1H), 7.42 (t, *J* = 8.8 Hz, 1H), 7.72 (m, 3H); ^{13}C NMR δ 52.6, 103.1, 116.1, 120.9, 123.7, 124.1, 125.0, 126.3, 126.7, 131.9, 154.9.

2-Methoxymethyoxynaphthalene (84)

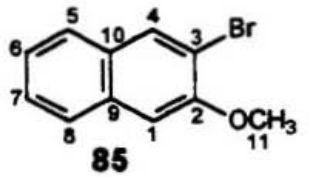


84

To a solution of **36** (10.0 g, 69.4 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added triethylamine (11.6 mL, 83.3 mmol). The brown reaction mixture was stirred for 30 min, and chloromethyl methyl ether (6.30 mL, 83.3 mmol) was added dropwise. The mixture was stirred for another 2 h. The organic solution was washed several times with water, then brine, dried over $MgSO_4$, filtered and finally the solvent was evaporated. The residue was triturated with a minimum amount of CH_2Cl_2 to afford **84** (9.50 g, 72%) as a viscous oil: ^{1}H NMR δ 3.48 (s, 3H), 5.25 (s, 2H), 7.23 (m, 1H), 7.33 (m, 1H), 7.40 (m, 2H), 7.73 (m, 3H); ^{13}C NMR δ 55.9, 94.3, 109.8, 118.8, 123.9, 126.2, 126.9, 127.5, 129.3, 134.3, 154.9; MS (*m/z*): 188.2 (M^+, 22), 158.2 (16), 127.2 (7), 115 (16).

3-Bromo-2-methoxynaphthalene (85)

To a solution of 2-methoxynaphthalene (**83**) (5.0 g, 32 mmol) in anhydrous THF (80

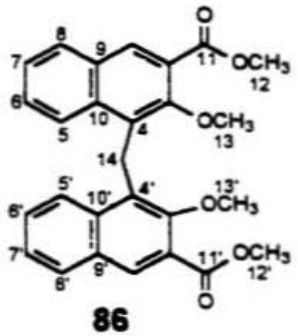


85

mL) at room temperature, *n*-BuLi (1.6 M in hexane, 24.7 mL, 39.5 mmol) was added. The reaction solution was stirred for 2.5 h, cooled to -78 °C, and then 1,2-dibromoethane (3.4 mL, 40 mmol) added dropwise over a period of 30 min. The solution was warmed to room temperature over 6 h and was stirred overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL), and the solvent was removed under reduced pressure. The slurry was diluted with CH_2Cl_2 (100 mL), washed with aqueous saturated NH_4Cl, brine, dried over $MgSO_4$ and filtered. After removal of the solvent, the residue was purified by flash column chromatography eluting with 10:90 ethyl acetate-hexane to afford **85** (7.2 g, 96%) as colourless crystals: mp 67-68 °C; ^{1}H NMR δ 3.95 (s, 3H, H-11), 7.11 (s, 1H, H-1), 7.33 (t, *J* = 8.1 Hz,1H, H-7), 7.43 (t, *J* = 8.1 Hz,1H, H-6), 7.66 (dd, *J* = 1.5, 8.5 Hz, 2H, H-5, H-8), 8.02 (s, 1H, H-4); ^{13}C NMR δ 56.1 (C-11), 106.5, 113.2, 124.4, 126.5, 129.3, 132.2, 133.4, 153.4; MS (*m/z*): 238 (98), 236 (100), 223 (13), 195 (63), 127 (22), 114 (38); HRMS M^+ 235.9863, calcd for $C_{11}H_9{}^{79}BrO$ 235.9837.

Bis(methyl 3-methoxy-2-naphthoate)methane (86)

To a solution of bis(3-hydroxy-2-naphthoic acid) (**44**) (10.0 g, 25.7 mmol) in CH_2Cl_2 (200 mL) at room temperature was added phase transfer catalyst Adogen® (5 mL) and aqueous NaOH solution (25.7 mL, 64.3 mmol). The two-phase mixture was

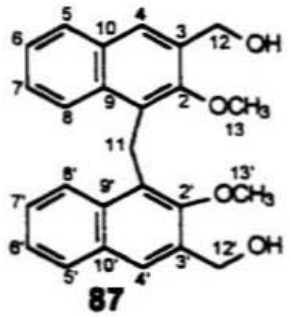


86

stirred vigorously for 15 min, then dimethyl sulfate (7.3 mL, 77 mmol) was slowly added. The mixture was stirred for 16 h, and then the two layers were separated. The organic layer was washed with aqueous 10% $NaHCO_3$, brine, dried over $MgSO_4$ and filtered. After the solvent was evaporated, the crude product was crystallized from ethyl acetate-hexane to afford **86** (9.5 g, 83%) as colourless crystals: mp 134-35 °C (lit.[58b] mp 133 °C); ^{1}H NMR δ 3.81 (s, 6H, H-13, H-13'), 3.99 (s, 6H, H-12, H-12'), 5.01 (s, 2H, H-14), 7.34 (dd, *J* = 1.5, 8.2 Hz, 2H, H-6, H-6'), 7.40 (dd, *J* = 1.5, 8.3 Hz, 2H, H-7, H-7'), 7.76 (d, *J* = 7.9 Hz, 2H, H-5, H-5'), 8.17 (d, *J* = 8.5 Hz, 2H, H-8, H-8'), 8.26 (s, 2H, H-1, H-1'); ^{13}C NMR δ 22.6 (C-14), 52.3 (C-13, C-13'), 62.3 (C-12, C-12'), 123.8, 124.7, 125.2, 128.3, 129.3, 129.8, 130.1, 132.3, 135.2, 153.6, 166.9 (C-11, C-11'); MS (*m/z*): 445 (M^++1, 18), 444 (M^+, 56), 414 (8), 413 (30), 412 (57), 397 (100), 353 (55), 337 (53), 324 (54), 280 (26).

Bis(3-hydroxymethyl-2-methoxy-1-naphthyl)methane (87)

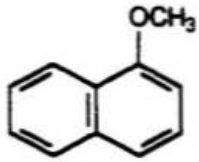
To a slurry of $LiAlH_4$ (2.1 g, 54 mmol) in anhydrous THF (100 mL) at 0 °C was added dropwise a solution of **86** (6.00 g, 13.5 mmol) in THF (50 mL). The mixture was



87

stirred for 6 h, then the reaction was quenched by the slow addition of water (20 mL) at 0 °C, and the solvent was then evaporated. The organic slurry was diluted with CH_2Cl_2 (100 mL), washed with aqueous 10% HCl, brine, dried over $MgSO_4$ and filtered. After the solvent was evaporated, the residue was crystallized from ethyl acetate-hexane to afford **86** (4.75 g, 90%) as colourless crystals: mp 95-97 °C (lit.[58b] mp 89-90 °C); ^{1}H NMR δ 2.57 (br, 2H, OH, D_2O exchangeable), 3.82 (s, 6H, H-12, H12'), 4.93 (s, 4H, H-11, H-11'), 7.25 (m, 4H, H-6, H-6', H-7, H-7') , 7.64 - 7.68 (m, 2H, H-5, H-5'), 7.69 (s, 2H, H-4, H-4'), 8.07 (m, 2H, H-8, H-8').

1-Methoxynaphthalene (88)

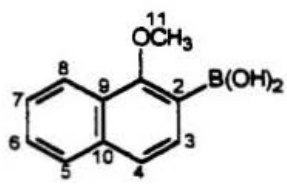


88

To a solution of 1-naphthol (**15**) (60.0 g, 417 mmol) in CH_2Cl_2 (330 mL) was added phase-transfer catalyst (Adogen®, 10.0 mL) and aqueous 10% NaOH (336 mL, 834 mmol). The reaction mixture was stirred vigorously for 30 min, then dimethylsulfate

(60.0 mL, 625 mmol) was added dropwise over a period of 30 min at 0 °C . The mixture was stirred for another 3 h. The organic layer was washed with aqueous 10% K_2CO_3, brine, dried over $MgSO_4$ and filtered. After the solvent was evaporated, the residue was purified by vacuum distillation to afford **88** (56.0 g, 85%) as a yellow liquid: bp 105-110 °C, 0.5 mm Hg; ^{1}H NMR δ 3.88 (s, 3H), 6.70 (d, J = 7.4 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.40 - 7.47 (m, 1H), 7.72 - 7.76 (m, 1H), 8.23 - 8.27 (m, 2H).

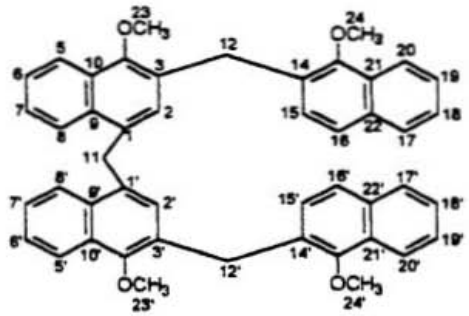
1-Methoxy-2-naphthaleneboronic acid (89)



To a solution of 1-methoxynaphthalene (**88**) (3.0 g, 19 mmol) in anhydrous THF (30 mL) at room temperature, *n*-BuLi (1.6 M in hexane, 17.8 mL, 28.5 mmol) was added dropwise. The mixture was stirred for 2.5 h, then cooled to -78 °C, and trimethyl borate (3.1 mL, 28 mmol) was added dropwise over a period of 30 min. The solution was warmed to room temperature over 6 h, then aqueous 10% HCl (20 mL) was added and the mixture was stirred at room temperature for 30 min. The THF was evaporated, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$ and filtered. After the organic solvent was evaporated **89** (3.1 g, 80%) was obtained as a gum that was directly used with **20** in the Suzuki-Miyaura cross coupling reaction (Scheme 3.17):

^{1}H NMR (crude) δ 4.02 (s, 3H), 6.09 (s, 2H, OH, D_2O exchange), 7.49 - 7.57 (m, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.79 - 7.88 (m, 2H), 8.09 - 8.12 (m, 1H).

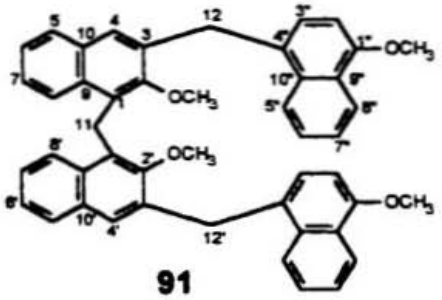
Bis(4-methoxy)-3-((1'-methoxy-2'-naphthyl)methyl)-1-naphthyl)methane (90)



90 was obtained in 80% yield (0.53 g) as a colourless solid from the reaction between **20** and 1-methoxy-2-naphthaleneboronic acid (**89**) using the Suzuki-Miyaura cross-coupling procedure: mp 143-46 °C; ^{1}H NMR δ 3.65 (s, 6H), 3.81 (s, 6H), 4.19 (s, 4H), 4.56 (s, 2H), 6.68 (s, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 7.24 - 7.34 (m, 4H), 7.35 - 7.50 (m, 6H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 7.99 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR δ 28.8, 35.1, 61.5, 61.8, 120.2, 121.9, 122.5, 123.8, 124.2, 125.4, 125.5, 125.7, 127.8, 127.9, 127.9, 128.1, 128.3, 128.7, 129.6, 131.9, 132.2, 133.7, 152.4, 153.3; MS (*m/z*): 669 (M^++1, 30), 668 (M^+, 61), 498 (31), 341 (13), 328 (36), 327 (22); HRMS M^+ 668.2958, calcd for $C_{47}H_{40}O_4$ 668.2924.

Bis{(2-methoxy)-[3-(1'-methoxy-4'-naphthyl)methyl]-1-naphthyl}methane (91)

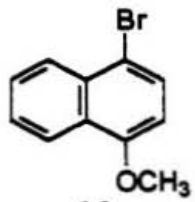
91 was obtained in 60 % yield (0.401) as a colourless solid from the reaction between **43** and 4-methoxy-1-naphthaleneboronic acid (**93**) using the Suzuki-



91

Miyaura cross-coupling procedure: mp 237-240 °C; ^{1}H NMR (CD_2Cl_2) δ 4.05 (s, 12H), 4.65 (s, 4H), 5.12 (s, 2H), 6.82 (d, *J* = 7.9 Hz, 2H), 7.24 (m, 8H), 7.48 (m, 6H), 7.98 (m, 2H), 8.32 (m, 4H); ^{13}C NMR (CD_2Cl_2) δ 20.4, 30.2, 52.7, 100.7, 117.6, 119.6, 121.3, 121.6, 122.0, 122.1, 122.4, 123.3, 123.7, 124.4, 124.9, 125.7, 125.8, 126.1, 128.5, 129.7, 130.0, 131.2, 151.6, 151.7; MS (*m/z*): 668 (M^+, 36), 556 (5), 510 (10), 352 (25); HRMS M^+ 668.2908, calcd for $C_{47}H_{40}O_4$ 668.2924.

4-Bromo-1-methoxynaphthalene (92)

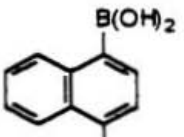


92

To a solution of 1-methoxynaphthalene (**88**) (10 g, 63 mmol) in dioxane (30 mL) at room temperature was added dioxane-dibromide (15.8 g, 633 mmol) in dioxane (50 mL). The mixture was stirred 16 h, and then the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with aqueous 10% $Na_2S_2O_3$, brine, dried over $MgSO_4$ and filtered. After the solvent was

evaporated, the residue was purified by flash column chromatography eluting with 5:95 ethyl acetate-hexane to afford **92** (14.4 g, 96%) as a liquid:[58] ^{1}H NMR δ 3.91 (s, 3H), 6.50 (d, J = 8.1 Hz, 1H), 7.45 - 7.58 (m, 3H), 8.13 (d, J = 8.1 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 55.5, 104.3, 113.1, 122.3, 125.8, 126.7, 127.6, 129.3, 132.3, 155.1.

4-Methoxy-1-naphthaleneboronic acid (93)

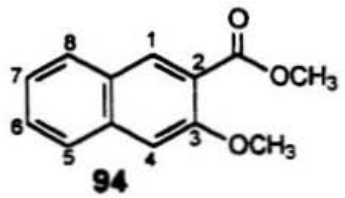


93

To a solution of 4-bromo-1-methoxynaphthalene (**92**) (2.3 g, 9.7 mmol) in anhydrous THF (24 mL) at -78 °C, was added , *n*-BuLi (1.6 M in hexane, 4.3 mL, 14.5 mmol) dropwise. The mixture was stirred for 45 min, then trimethyl borate (2.1 mL, 19 mmol) was added dropwise. The solution was warmed to room temperature over 6 h, then aqueous 10% HCl (20 mL) was added and the mixture was stirred at room temperature for 30 min. The THF was evaporated, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$ and filtered. After the organic solvent was evaporated **93** (1.9 g, crude, quantitative) was obtained as a gum that was directly used with **43** in the Suzuki-Miyaura cross coupling reaction (Scheme 3.18):

Methyl 3-methoxy-2-naphthoate (94)

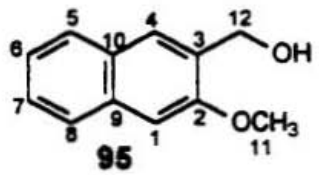
To a solution of 3-hydroxy-2-naphthoic acid (**38**) (7.8 g, 42 mmol) in CH_2Cl_2 (100 mL)



94

was added phase transfer catalyst Adogen® (2mL), and aqueous 50% NaOH solution (60 mL) at room temperature. The two-phase solution was stirred vigorously for 15 min, then dimethyl sulfate (15.0 mL, 158 mmol) was added slowly. The mixture was stirred for 6 h, and then the two layers were partitioned. The organic layer was washed with aqueous 10% $NaHCO_3$, brine, dried over $MgSO_4$ and filtered. After the solvent was evaporated, the residue was distilled under vacuum to afford **94** (8.2 g, 90%) as a golden liquid:[58] bp 135-137 °C, 0.5 mm Hg; ^{1}H NMR δ 3.95 (s, 3H), 3.99 (s, 3H), 7.20 (s, 1H), 7.37 (t, J = 7.0 Hz, 8.1 Hz, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR δ 51.9, 55.8, 106.4, 121.4, 124.1, 126.1, 127.2, 128.3, 132.4, 135.8, 155.4.

3-(Hydroxymethyl)-2-methoxynaphthalene (95)

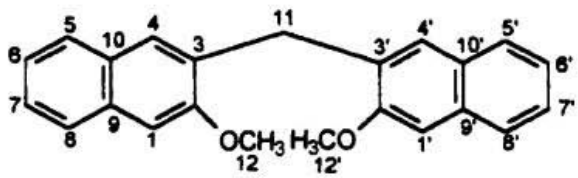


95

To a slurry of $LiAlH_4$ (0.35 g, 9.3 mmol) in diethyl ether (50 mL) at 0 °C was added a solution of **94** (1.0 g, 4.6 mmol) in diethyl ether (5 mL). The mixture was stirred at room temperature for 2 h. The reaction was quenched by the slow addition of cold

water followed by aqueous 10% HCl. The organic layer was separated, washed with brine, dried over Na_2SO_4 and filtered. After the solvent was evaporated, the residue was crystallized from ethyl acetate-hexane to afford **95** (0.81 g, 94%) as colourless crystals:[58] mp 72-73 °C; ^{1}H NMR δ 2.40 (br, 1H, OH), 3.92 (s, 3H, H-11), 7.15 (s, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.74 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 2H).

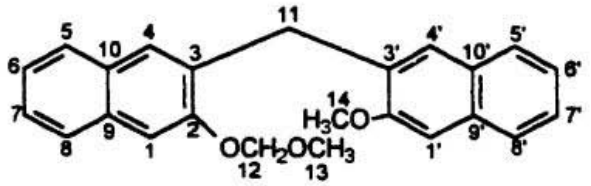
Bis(2-methoxy-3-naphthyl)methane (96)



96 was obtained in 89% yield (7.9 g) as colourless crystals from the reaction between 3-methoxy-2-naphthaleneboronic acid (**72**) and 3-(bromomethyl)-2-methoxynaphthalene (**74**) using the Suzuki-Miyaura cross-coupling procedure: mp 145-46 °C; ^{1}H NMR δ 3.88 (s, 6H, H-12, H-12'), 4.23 (s, 2H, H-11), 7.11 (s, 2H, H-4, H-4'), 7.25 (t, *J* = 7.4 Hz, 2H, H-7, H-7'), 7.36 (t, *J* = 7.5 Hz, 2H, H-6, H-6'), 7.41 (s, 2H, H-1, H-1'), 7.60 (d, *J* = 8.0 Hz, 2H, H-5, H-5'), 7.71 (d, *J* = 8.1 Hz, 2H, H-8, H-8'); ^{13}C NMR δ 30.8 (C-11), 55.3 (C-12, C-12'), 104.8, 123.4, 125.6, 126.3, 127.2, 128.8, 128.9, 130.6, 133.5, 156.6 (C-2, C-2'); MS (*m/z*): 328 (M^+, 47), 281 (7), 265 (3), 234 (100); HRMS M^+ 328.1461, calcd for $C_{23}H_{20}O_2$ 328.1463.

(2-Methoxy-3-naphthyl)-(2-methoxymethoxy-3'-naphthyl)methane (97)

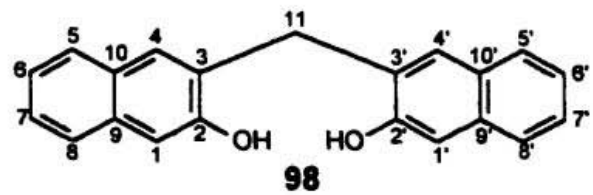
97 was obtained in 79% yield (0.72g) as a colourless solid from the reaction between



97

3-methoxymethyl ether-2-naphthaleneboronic acid (**73**) and 3-(bromomethyl)-2-methoxynaphthalene (**74**) using the Suzuki-Miyaura cross-coupling procedure: mp 101-103 °C; ^{1}H NMR δ 3.37 (s, 3H, H-13), 3.91 (s, 3H, H-14), 4.26 (s, 2H, H-11), 5.28 (s, 2H, H-12), 7.12 (s, 1H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.35 - 7.46 (m, 4H), 7.49 (s, 1H), 7.58 - 7.65 (m, 2H), 7.68 - 7.75 (m, 2H); ^{13}C NMR δ 31.0 (C-11), 55.3 (C-14), 56.0 (C-13), 94.1(C-12), 104.7, 108.5, 123.4, 123.8, 125.5(2), 125.6, 126.2, 126.6(2), 127.1, 127.2, 128.7, 129.2, 129.3, 130.6, 133.3, 133.4, 153.8, 156.5; MS (*m/z*): 359 (M^++1, 2), 358 (M^+, 11), 326 (21), 313 (14), 295 (7), 281(10), 265 (3), 253 (3), 228 (18), 197 (10), 188 (12).

Bis(2-hydroxy-3-naphthyl)methane (98)

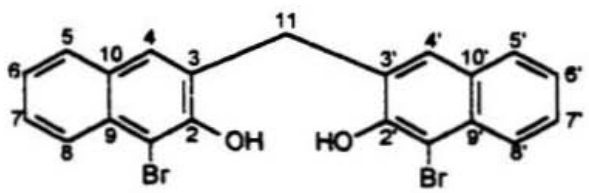


98

To a solution of **96** (0.98 g, 3.0 mmol) in anhydrous CH_2Cl_2 (15.0 mL) was added dropwise a solution of BBr_3 (1M in CH_2Cl_2, 10.5 mL, 10.5 mmol). The brown solution was stirred at room temperature for 16 h, then aqueous 10% HCl (5.0 mL) was added, and the mixture was stirred at room temperature for another 30 min. The

organic layer was washed with saturated aqueous NH_4Cl (3 x 15 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduce pressure. The brown solid was purified by flash column chromatography eluting with 30:70 ethyl acetate-hexane to afford **98** (0.86 g, 95%) as a brown solid: mp 185-87 °C; ^1H NMR (CD_3OD) δ 4.23 (s, 2H), 4.90 (s, 2H), 7.12 - 7.19 (m, 4H), 7.28 (dd, *J* = 1.9, 6.9 Hz, 2H), 7.45 (s, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (CD_3OD) δ 30.3, 108.2, 120.3, 122.3, 124.9, 125.2, 126.8, 128.6, 129.8, 133.8, 153.9; MS (*m/z*): 300 (M^+, 100), 281 (8), 252 (10), 157 (95); HRMS M^+ 300.1160, calcd for $C_{21}H_{16}O_2$ 300.1149.

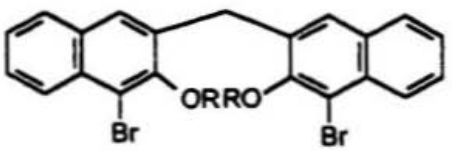
Bis(1-bromo-2-hydroxy-3-naphthyl)methane (99)



To a solution of **98** (0.90 g, 3.0 mmol) in acetic acid (20.0 mL), a solution of Br_2 (0.31 mL, 6.0 mmol) in acetic acid (5.0 mL) was added dropwise over period of 5 min. The mixture was stirred at rt for 4 h, after which time, a second equivalent of Br_2 was added and the reaction was stirred a further 16 h. The mixture was poured into water (100 mL), and the organic layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with aqueous 10% $NaHSO_3$ (20 mL), then brine (20 mL), dried over $MgSO_4$, and finally the solvent was evaporated. The

residue was washed several times with hexane to afford **99** (1.30 g, 95%) as a yellow solid was used in the next step as the compound turns brown: mp 160-163 °C; ^{1}H NMR δ 4.40 (s, 2H, H-11), 6.18 (s, 2H, OH, D_2O exchangeable), 7.35 (t, *J* = 8.1 Hz, 2H, H-6, H-6'), 7.52 (t, *J* = 8.3 Hz, 2H, H-7, H7'), 7.58 (s, 2H), 7.68 (d, *J* = 8.1 Hz, 2H, H-5, H-5'), 7.99 (d, *J* = 8.3 Hz, 2H, H-8, H-8').

Bis(1-bromo-2-methoxymethoxy-3-naphthyl)methane (100)

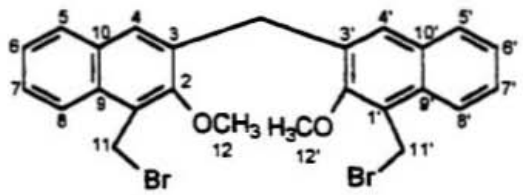


R = CH_2OCH_3

To a solution of **99** (1.30 g, 2.83 mmol) in THF (40 mL) at 0 °C, NaH (327 mg, 8.52 mmol) was added. The mixture was stirred for 30 min, chloromethyl methyl ether (0.65 mL, 8.52 mmol) was added dropwise, and the mixture was stirred for 12 h. The reaction was quenched with water, and the THF was removed under reduced pressure. The residue was diluted with ethyl acetate, washed with water, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with 20:80 ethyl acetate-hexane to afford as a viscous liquid **100** in 99% yield. This product was subjected to the usual metallation conditions using *n*-BuLi in THF. The product **101** obtained from **100** was used without purification with **102** in the Suzuki-Miyaura cross-coupling reaction conditions (Scheme 3.20): **100** ^{1}H NMR δ 3.65 (s, 6H), 4. 62 (s, 2H), 5.21 (s, 4H),

7.39 - 7.47 (m, 4H), 7.55 (dd, J = 2.1, 8.5 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H); MS (*m/z*): 546 (M^+, 1), 469 (7), 438 (2), 390 (3).

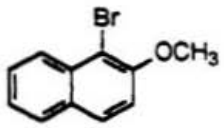
Bis(1-bromomethyl-2-methoxy-3-naphthyl)methane (102)



To a solution of **96** (984 mg, 3.00 mmol) in acetic acid (30 mL) was added aqueous 37% formaldehyde solution (0.500 mL, 15.0 mmol), and 30% HBr in acetic acid (1.20 mL, 15.0 mmol). The mixture was stirred at room temperature for 3 d, during which time a colourless precipitate was formed. The reaction was stirred for another 24 h, then the solid was filtered and washed with water to remove any acid. The residue was purified by flash column chromatography, eluting with 10:90 ethyl acetate-hexane to afford **102** (1.2 g, 77%) as a colourless solid: mp 143-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94 (s, 6H, H-12, H-12'), 4.34 (s, 2H, H-13), 5.09 (s, 4H, H-11, H-11'), 7.40 (t, J = 7.8 Hz, 2H, H-7, H-7'), 7.45 - 7.58 (m, 4H, H-4, H-4', H-6, H-6'), 7.68 (d, J = 8.1 Hz, 2H, H-5, H-5'), 8.08 (d, J = 8.4 Hz, 2H, H-8, H-8'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.3 (C-13), 30.7 (C-11, C-11'), 61.6 (C-12, C-12'), 123.3, 123.4, 124.8, 125.4, 126.5, 128.3, 131.1, 131.3, 133.3, 155.6 (C-2, C-2'); MS (*m/z*): 515 (M^+, ^{81}Br, ^{81}Br, 2), 513 (M^+, ^{79}Br, ^{79}Br, 3), 436 (12), 435 (37), 434 (12), 432 (38), 355 (27), 338 (21), 323 (12), 308 (14); HRMS M^+ 515.9945, calcd for

$C_{25}H_{22}{}^{81}Br^{81}BrO_2$ 515.9946.

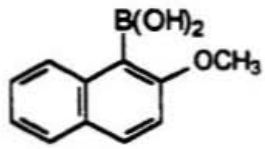
1-Bromo-2-methoxynaphthalene (103)



To a solution of **36** (10 g, 69 mmol) in acetic acid (150 mL) was added a solution of bromine (11 g, 69 mmol) in acetic acid (50 mL) over a period of 30 min. The slurry was stirred at room temperature for 2 h, then poured into ice. The organic layer was extracted with ethyl acetate, washed with water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was treated with a aqueous 10% NaOH (45 mL), dimethyl sulfate (6.6 mL, 69 mmol) and Adogen® (5 mL) in CH_2Cl_2 (100 mL). The mixture was stirred for 6 h and the organic layer was separated. The organic layer was washed successively with aqueous 10% $NaHCO_3$, brine, dried over $MgSO_4$ and filtered. After the solvent was evaporated under reduced pressure, the residue was purified by flash column chromatography eluting with 10% ethyl acetate-hexane to afford **103** (16 g, 98%) as a beige solid: mp 79-81 °C; ^{1}H NMR 4.03 (s, 3H), 7.27 (d, J = 9.0 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.78 - 7.82 (m, 2H), 8.22 (d, J = 8.4 Hz, 1H).

2-Methoxy-1-naphthaleneboronic acid (104)

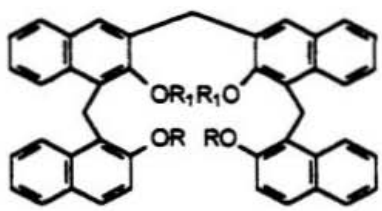
To a solution of **103** (10.0 g, 42.2 mmol) in anhydrous THF (250 mL) at -78 °C, n-BuLi (1.6 M in hexane, 29.0 mL, 46.4 mmol) was added dropwise. The reaction solution was stirred for 45 min at -78 °C, then trimethyl borate (5.80 mL, 50.6 mmol)



104

was added dropwise. The mixture was warmed to room temperature over 6 h, then aqueous 10% HCl (40 mL) was added and the mixture stirred at room temperature for another 30 min. After the solvent was evaporated, the slurry was diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous NH_4Cl, brine and dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product was crystallized from ethyl acetate-hexane to afford **104** (5.56 g, 65%) as colourless crystals: mp 109-112 °C; ^{1}H NMR (CD_3OD) δ 3.89 (s, 3H), 4.90 (s, 2H), 7.25 - 7.34 (m, 2H), 7.42 (t, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 56.7, 113.8, 124.6, 127.6, 127.7, 128.2, 129.3, 129.5, 132.0, 137.3, 160.6; MS (*m/z*): 202 (M^+, 100), 186 (5), 172 (4), 158 (63), 141 (26), 126 (25), 115 (62); HRMS M^+ 202.0796, calcd for $C_{11}H_{11}BO_3$ 202.0801.

Bis{(2-methoxy)-3-[1-naphthyl-(2'-methoxy)methyl]naphthyl}methane (105)

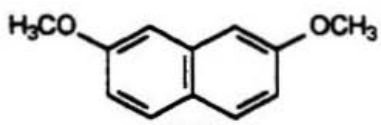


105: R = R_1 = OCH_3.

105 was obtained in 23% yield (76 mg) as a colourless solid from the reaction

between bis(1-bromomethyl-2-methoxy-3-naphthyl)methane **102** and 2-methoxy-1-naphthaleneboronic acid (**104**) using the Suzuki-Miyaura cross-coupling procedure: mp 101-103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 6H), 3.96 (s, 6H), 4.49 (s, 2H), 4.99 (s, 4H), 7.06 (t, J = 7.2 Hz, 2H), 7.14 (t, J = 7.3 Hz, 2H), 7.21 (m, 4H), 7.29 (d, J = 9.3 Hz, 2H), 7.40 (s, 2H), 7.53 (m, 2H), 7.65 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 8.12 (d, J = 2.5 Hz, 2H), 8.14 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 23.2, 32.2, 57.4, 62.5, 114.3, 123.8, 123.9, 124.9, 125.0, 125.4, 125.7, 127.0, 128.6, 128.8, 128.9, 129.2, 130.1, 130.2, 131.9, 133.5, 134.4, 154.8, 155.5; HRMS M$^+$ 668.2948, calcd for $C_{47}H_{40}O_4$ 668.2924.

2,7-Dimethoxynaphthalene (109)

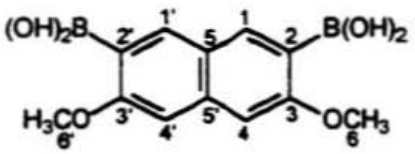


109

To a solution of 2,7-dihydroxynaphthalene (**108**) (10 g, 62 mmol) in CH_2Cl_2 (200 mL), Adogen® (5 mL), aqueous 10% NaOH (55.0 mL, 137 mmol) and dimethylsulfate (14.8 mL, 156 mmol) were added in sequence. The dark purple mixture was stirred at room temperature for 12 h. The organic layer was separated from the aqueous layer, washed with aqueous 5% NaOH (2 x 50 mL), dried over $MgSO_4$ and filtered. After the solvent was evaporated, the residue was crystallized from ethyl acetate-hexane to afford **109** (10.9 g, 93%) as beige crystals: ^{1}H NMR δ 3.87 (s, 3H), 6.98 (d, J = 8.9 Hz, 2H), 7.04 (s, 2H), 7.63 (d, J = 8.9 Hz, 2H); ^{13}C NMR δ 55.2, 105.2,

115.9, 124.2, 129.1, 135.8, 158.1.

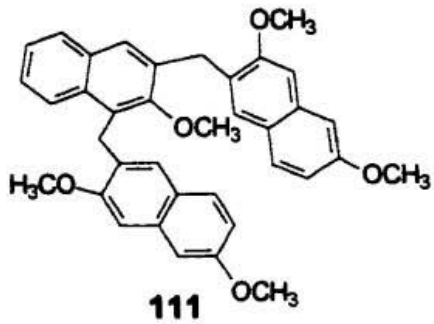
3,6-Dimethoxy-2,7-naphthalenediboronic acid (110)



To a solution of **109** (3.25 g, 17.3 mmol) in anhydrous THF (70 mL) at room temperature, *n*-BuLi (32.4 mL, 51.9 mmol) was added dropwise. The mixture was stirred for 2.5 h, cooled to -78 °C and trimethylborate (5.70 mL, 51.9 mmol) was slowly added. The reaction was warmed to rt over 6 h, then saturated aqueous NH_4Cl (10 mL) was added, and the THF was evaporated under reduced pressure. The slurry was dissolved in CH_2Cl_2, washed with saturated aqueous NH_4Cl, then brine, dried over $MgSO_4$ and filtered. After the solvent was evaporated, the residue was crystallized from benzene-hexane to afford **110** (3.67 g, 77%) as colourless crystals: mp 148-150 °C; ^{1}H NMR δ 3.90 (s, 6H), 7.19 (s, 2H), 7.80 (s, 4H), 8.02 (s, 2H); ^{13}C NMR δ 55.7, 104.2, 121.0, 123.5, 137.2, 138.8, 162.3; MS (*m/z*): 276 (M^+, 100), 233 (31), 200 (10), 188 (8), 172 (7); HRMS M^+ 276.0985, calcd for $C_{12}H_{14}B_2O_6$ 276.0976.

2-Methoxy-bis{1,3-[3'-naphthyl-(2,7-dimethoxy)methyl]}naphthalene (111):

111 was obtained in 37% yield (103 mg) as a colourless solid from the reaction between **61** and **110** using the Suzuki-Miyaura cross-coupling procedure: ^{1}H NMR δ 3.85 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 4.07 (s, 2H), 4.33 (s, 2H),

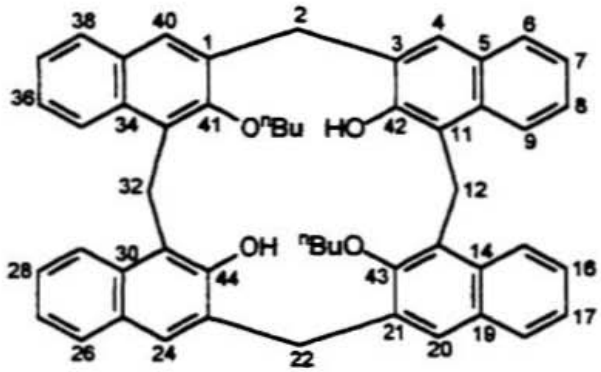


111

4.56 (s, 2H), 6.83 (dd, *J* = 2.5, 8.8 Hz, 1H), 6.88 (s, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H) 6.99 (d, *J* = 2.5 Hz, 1H), 7.01 (d, *J* = 2.5 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 7.13 (s, 1H), 7.23 - 7.31 (m, 4H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.86 (m, 3H), 7.71 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 29.7, 30.7, 55.2, 55.3, 55.4, 55.5, 61.7, 103.8, 104.4, 104.9, 105.0, 115.4, 115.8, 120.3, 123.9, 124.1, 124.5, 124.7, 125.5, 126.4, 127.3, 127.8, 128.2, 128.4, 128.6, 128.8, 129.1, 131.2, 132.7, 134.0, 134.3, 134.8, 156.0, 156.8, 157.0, 157.5, 157.7.

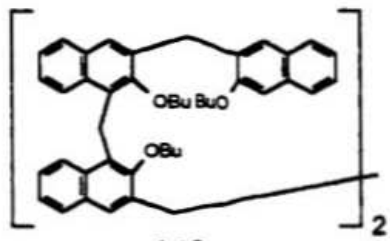
34,36-Dibutyloxy-6*H*,14*H*,22*H*,30*H*-5,31:7,13:15,21:23,29-tetramethenotetrabenzo [a,f,m,r]cyclotetracosene-33,35-diol (113a)

To a solution of the crude reaction product obtained from the acid-mediated condensation, calix[4]naphthalene (**35**) (725 mg, 1.16 mmol) in DMF (10 mL) was added NaH (60 % suspension in oil, 223 mg, 5.81 mmol). The brown solution was stirred at room temperature for 30 min, then 1-bromobutane (0.31 mL, 7.0 mmol) was added. The mixture was stirred at 80 °C for 16 h, cooled to room temperature



113a

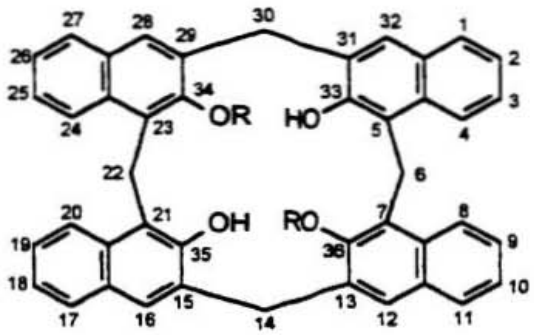
and diluted with ethyl acetate. The organic solution was washed several times with water, then with aqueous 10% HCl, brine, dried over $MgSO_4$, filtered and the solvent was evaporated to afford brown crude product, which was purified by preparative TLC using 10:90 ethyl acetate-hexane. TLC analysis of this material showed the presence of two products which were separated by preparative TLC using benzene-petroleum ether 40:60 to afford **112** (300 mg) as a yellow solid: mp>300 °C; ^{1}H NMR δ 0.93 - 1.02 (m, 18H), 1.43 - 1.69 (m, 12H), 1.81 - 2.01 (m, 12H), 4.01 - 4.16 (m, 12H), 4.37 (s, 4H), 4.51 (s, 2H), 5.02 (s, 4H), 6.94 (m, 4H), 7.10 (m, 4H), 7.16 (s, 2H), 7.27 - 7.44 (m, 12H), 7.53 (d, J = 8.7 Hz, 4H), 7.74 (d, J = 8.1 Hz, 2H), 8.28 (m, 4H); ^{13}C NMR δ 13.9, 14.1, 19.4, 19.5, 19.6, 23.3, 31.3, 31.6, 32.5, 32.6, 67.6, 74.7, 105.2, 120.3, 124.1, 124.2, 124.9, 125.0, 125.4, 125.5, 126.2, 126.3, 127.5, 127.8, 128.5, 128.6, 128.8, 128.9, 129.0, 129.1, 131.1, 131.6, 132.7, 132.8, 133.0, 133.5, 133.6, 153.4, 153.5, 155.8; and **113a** (20 mg, 3%): mp >320 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, J = 7.3 Hz, 6H), 1.71-1.83 (m, 4H), 2.01 (m, 4H), 3.67



112

(d, *J* = 12.9 Hz, 2H), 4.04 (m, 2H), 4.14 (m, 2H), 4.50 (d, *J* = 15.3 Hz, 2H), 4.73 (d, *J* = 12.9 Hz, 2H), 4.90 (d, *J* = 15.2 Hz, 2H), 6.90 (m, 4H), 7.09 - 7.12 (m, 4H), 7.36 (dd, *J* = 1.2, 7.8 Hz, 2H), 7.61 (dd, *J* = 1.2, 8.4 Hz, 2H), 7.73-7.77 (m, 4H), 7.84 (dd, *J* = 1.2, 8.0 Hz, 2H), 7.90 (s, 2H), 8.48 (d, *J* = 8.4 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 19.6, 21.9, 30.9, 31.6, 32.2, 116.5, 121.9, 122.2, 124.0, 124.1, 124.9, 125.2, 125.8, 127.5, 127.9, 128.6, 128.7, 129.5, 131.1, 131.7, 132.2, 132.6, 133.1, 152.2, 153.4; (+) FAB MS *(m/z)*: 736 (M^+, 2, 100), 677 (2), 661 (22), 605 (65), 587 (19), 325 (70), 252 (95).

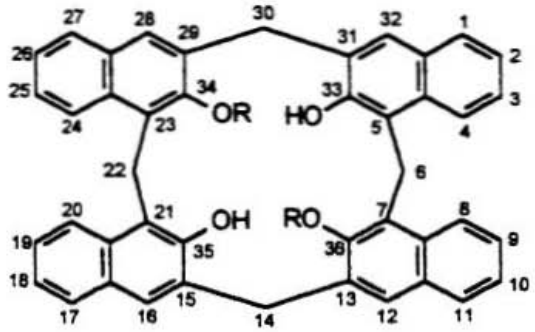
34,36-Dipropyloxy-6*H*,14*H*,22*H*,30*H*-5,31:7,13:15,21:23,29-tetramethenotetrabenzo [a,f,m,r]cyclotetracosene-33,35-diol (113b)



113b: R = n-Propyl

To a solution of the crude reaction product obtained from the acid-mediated condensation, calix[4]naphthalene (**35**) (0.485 g, 0.749 mmol) in DMF (15 mL) at room temperature was added NaH (60 % suspension in oil, 0.280 mg, 7.49 mmol). The slurry was stirred at room temperature for 30 min, then 1-iodopropane (0.40 mL, 4.49 mmol) was added. The reaction mixture was stirred for 3 d. After the DMF was removed under reduced pressure, the brown residue was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl, then brine, dried over $MgSO_4$, filtered and finally the solvent was evaporated. The crude product was purified by preparative TLC eluting with 30:70 CH_2Cl_2-petroleum ether to afford brown solid. This product was further purified by preparative TLC eluting with 90:10 benzene-hexane to afford **113b** (20 mg, 4%) as a brown solid: mp >300 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.5 Hz, 6H), 2.09 (m, 4H), 3.67 (d, *J* = 13.0 Hz, 2H), 4.03 (m, 2H), 4.10 (m, 2H), 4.50 (d, *J* = 15.5 Hz, 2H), 4.73 (d, *J* = 13.0 Hz, 2H), 4.90 (d, *J* = 15.2 Hz, 2H), 6.90 (m, 4H), 709 (d, *J* = 9.0 Hz, 4H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 2H), 7.73 (t, *J* = 9.0 Hz, 4H), 7.82 (s, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 8.48 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.8, 21.9, 23.5, 30.9, 77.9, 116.7, 121.9, 122.2, 124.0, 124.1, 124.9, 125,3, 125.8, 127.5, 127.8, 128.6, 127.7, 129.5, 131.1, 131.7, 132.3, 132.6, 133.2, 152.2, 153.4; FAB MS (*m/z*): 708 (M^+, 100), 664 (41), 605 (37), 312 (73).

34,36-Diisopropyloxy-6*H*,14*H*,22*H*,30*H*-5,31:7,13:15,21:23,29-tetramethenotetrabenzo[a,f,m,r]cyclotetracosene-33,35-diol (113c)

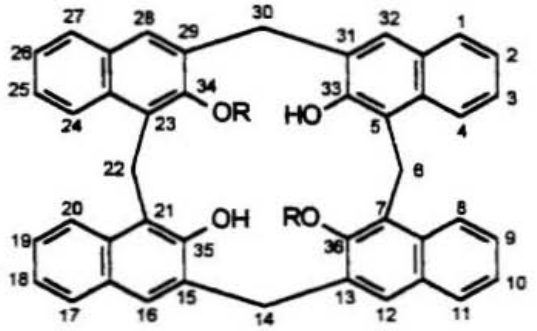


113c: R = isopropyl

To a solution of the crude reaction product obtained from the acid-mediated condensation, calix[4]naphthalene (**35**) (0.31 g, 0.50 mmol) in DMF (10 mL) at room temperature was added NaH (60% suspension in oil, 46 mg, 1.2 mmol). The slurry was stirred at room temperature for 30 min, then 2-iodopropane (0.15 mL, 1.5 mmol) was added. The mixture was stirred for 48 h. After the DMF was removed under reduced pressure, the residue was diluted with ethyl acetate, washed with aqueous 10% HCl, brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by preparative TLC eluting with 10:90 ethyl acetate-hexane to afford a brown solid (110 mg). The ^1H NMR spectrum showed the expected product signals and other signals which could not be identified. This solid was again purified by preparative TLC eluting with 10:90 dioxane-pentane to afford **113c** (20 mg, 6%): mp >320 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.47 (d, J = 6.1 Hz, 6H), 1.52 (d, J = 6.1 Hz, 6H), 3.60 (d, J = 13.6 Hz, 2H), 4.29 - 4.37 (sept, J = 6.0 Hz, 2H), 4.63 (d, J = 15.4 Hz, 2H), 4.73 (d, J = 13.5 Hz, 2H), 4.84 (d, J = 15.4 Hz, 2H), 6.74 (s, 2H), 6.79 (s, 2H), 6.84 (m, 6H), 7.40 (m, 2H), 7.54 (m, 2H), 7.64 (m, 2H),

7.69 (s, 2H), 7.86 (d, J = 8.1 Hz, 2H), 8.47 (d, J = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.1, 22.3, 22.7, 32.2, 78.6, 118.1, 121.8, 122.4, 123.9, 124.7, 125.6, 125.9, 127.4, 127.6, 128.6, 128.7, 130.8, 131.1, 132.4, 132.8, 134.2, 151.3, 152.7; FAB MS (*m/z*): 708 (M^+, 100), 664 (41), 605 (37), 312 (73).

34,36-Diethyloxy-*6H,14H,22H,30H*-5,31:7,13:15,21:23,29-tetramethenotetrabenzo [a,f,m,r]cyclotetracosene-33,35-diol (113d)

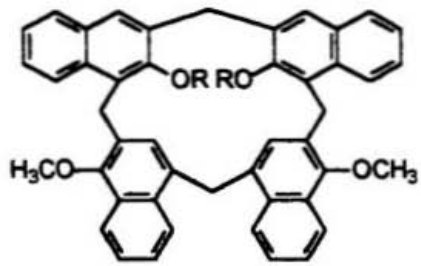


113d: R = Ethyl

A suspension of the crude reaction product obtained from the acid-mediated condensation, calix[4]naphthalene (**35**) (0.57 g, 0.91 mmol), powdered anhydrous K_2CO_3 (2.5 g, 9.1 mmol), and iodoethane (0.73 mL, 9.1 mmol) in dry CH_3CN (20 mL) was reflux for 16 h. The reaction mixture was cooled to room temperature, solid material was filtered, and the solvent was evaporated under reduce pressure. The residue was diluted with $CHCl_3$ (25 mL), washed with aqueous 10% HCl (15 mL), brine, dried over $MgSO_4$, and filtered. After the solvent was evaporated, the residue was purified by preparative TLC eluting with 30:70 benzene-hexane to afford **113d** (52 mg, 8%) as a brown solid: mp >300 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (t,

7.0 Hz, 6H), 3.63 (d, J = 13.2, Hz, 2H), 4.07 - 4.15 (m, 2H), 4.17-4.22 (m, 2H), 4.57 (d, J = 15.4 Hz, 2H), 4.73 (d, J = 13.2 Hz, 2H), 4.88 (d, J = 15.3 Hz, 2H), 6.91 (m, 2H), 7.10 (s, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.56 (d, J = 9.4 Hz, 2H), 7.63 (t, J = 7.6 Hz, 2H), 7.71 (s, 2H), 7.86 (d, J = 8.1 Hz, 2H), 8.46 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5, 29.7, 31.6, 72.1, 117.4, 120.3, 121.8, 122.4, 123.9, 124.9, 125.1, 125.9, 127.4, 127.6, 128.7, 129.1, 130.9, 131.3, 132.3, 132.7, 133.4, 152.4, 153.0; FAB MS *(m/z)*: 680 (M^+, 24), 679 (48), 633 (60), 605 (100), 587 (60).

Bis{(2-methoxy)-[3-(1'-methoxy-4'-naphthyl)methyl]naphthyl}methane (114)

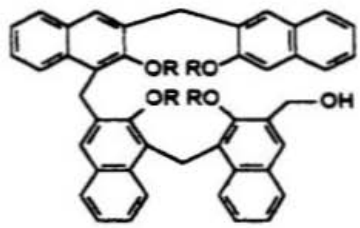


114: R = CH_3

To a solution of **20** (50 mg, 0.15 mmol) and **98** (87 mg, 0.17 mmol) in dioxane (10 mL) was added $TiCl_4$ (0.020 mL, 0.17 mmol). The resulting yellow reaction solution was reflux for 48 h, cooled to room temperature and the solvent was removed under reduced pressure. The brown material was filtered through silica with CH_2Cl_2, then the solvent was evaporated. The brown residue was purified by preparative TLC eluting with 1:1 petroleum ether-CH_2Cl_2 to afford **114** (10 mg, 10%) as a colourless solid: mp >300 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 2.09 (d, J = 15.5 Hz, 1H), 2.91 (s, 3H), 3.34 (s, 3H), 3.38 (s, 3H), 3.85 (d, J = 13.6 Hz, 1H), 3.87 (s, 3H), 3.96 d, J =

13.6 Hz, 1H), 4.12 (d, J = 15.2 Hz, 1H), 4.16 (d, J = 15.2 Hz, 1H), 4.24 (d, J = 15.3 Hz, 1H), 4.58 (d, J = 15.1 Hz, 1H), 6.56 (s, 1H), 6.14 (s, 1H), 6.52 (s, 1H), 6.62 - 6.80 (m, 6H), 6.92 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.36 - 7.41 (m, 4H), 7.72 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 8.38 (s, 1H); MS (*m/z*): 682 (M^++2, 1), 681 (M^++1, 4), 668 (11), 667 (51), 666 (100), 635 (25), 620 (5), 463 (7), 333 (12).

Compound 115

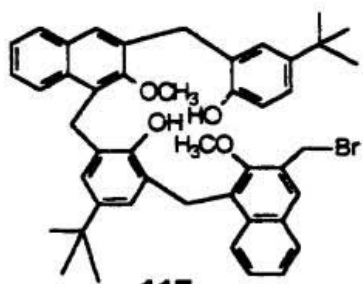


115: R = CH_3

To a solution of bis(2-hydroxymethyl-3-methoxy-1-naphthyl)methane (**86**) (194 mg, 0.500 mmol) and **98** (164 mg, 0.500 mmol) in $CHCl_3$ (10 mL), 10% TFA (1 mL in 9 mL of $CHCl_3$) was added. The reaction mixture was stirred at room temperature for 36 h, then diluted with $CHCl_3$ (25 mL). The organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered and the solvent was evaporated under reduce pressure. The residue was purified by preparative TLC eluting with 25:75 CH_2Cl_2-petroleum ether to afford **115** (50 mg, 14%) as a colourless solid: mp >300 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.94, (s, 3H), 4.07 (s, 3H), 4.09 (s, 3H), 4.37 (s, 2H), 4.78 (s, 2H), 4.83 (s, 2H), 5.05, (s, 2H), 6.98 (s, 1H), 7.09 (t, J = 7.8

Hz, 1H), 7.17 (m, 2H), 7.23 - 7.34 (m 5H), 7.40 (t, J = 8.1 Hz, 1H), 7.49 (s, 1H), 7.54 (t, 1H), 7.66 (d, J = 8.1 Hz, 3H), 7.74 (d, J = 7.6 Hz, 2H), 7.77 (s, 1H), 8.10 (d, J = 8.5 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 26.6, 29.9, 31.5, 55.9, 62.1, 62.2, 63.4, 105.5, 124.0, 124.7, 124.8, 124.9, 125.0, 125.4, 125.5, 125.8, 126.1, 126.2, 126.7, 126.8, 127.1, 127.8, 128.1, 128.3, 128.4, 128.5, 128.8, 129.1, 129.3, 129.7, 130.1, 130.7, 131.0, 131.4, 131.5, 131.6, 131.7, 132.6, 133.1, 134.1, 134.2, 134.3, 134.4, 154.2, 154.6, 156.3, 156.9; (+) FAB MS (*m/z*): 760 (M^+, 100), 680 (33), 511 (80).

Compound 117



117

To a solution of **4** (87 mg, 0.17 mmol) and **74** (50 mg, 0.15 mmol) in dioxane (10 mL) was added $TiCl_4$ (0.020 mL, 0.17 mmol). The resulting yellow reaction solution was reflux for 48 h, cooled to room temperature and the solvent was removed under reduced pressure. The brown material was filtered through silica with CH_2Cl_2, then the solvent was evaporated under reduced pressure. The brown residue was purified by preparative TLC eluting with 1:1 petroleum ether-CH_2Cl_2 to afford **117** (10 mg, 8%) as a colourless solid: ^{1}H NMR δ 1.20 (s, 9H), 1.21 (s, 9H), 4.05 (s, 3H),

4.08 (s, 3H), 4.37 (s, 4H), 4.72 (s, 2H), 4.80 (s, 2H), 6.73 (d, J = 8.4 Hz, 2H), 7.06 (dd, J = 2.4, 8.4 Hz, 2H), 7.19 (s, 1H), 7.23 (s, 1H), 7.30 (m, 2H), 7.40 (m, 2H), 7.49 (m, 2H), 7.52 (2 x d (overlapped), J = 7.5 Hz, 2H), 7.81 (d, J = 2.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 27.1 (2 x -$\underline{C}H_2$-), 28.5 (2 x -$\underline{C}H_2$-), 31.4 (2 x -C($\underline{C}H_3$)$_3$), 33.9 (2 x -C($\underline{C}H_3$)$_3$), 41.7 (-CH_2Br-), 63.2 (-O$\underline{C}H_3$), 63.5 (-O$\underline{C}H_3$), 115.6, 124.1, 124.4, 124.6, 125.4, 126.7, 126.8, 127.3, 127.8, 128.6, 128.7, 130.0, 130.3, 130.4, 130.8, 131.4, 133.2, 133.3, 142.5, 152.2, 152.3.

Chapter 4

Synthesis of Calixarene Triflates and Their Unusual Chemical Reactivity in Palladium-Catalyzed Reactions

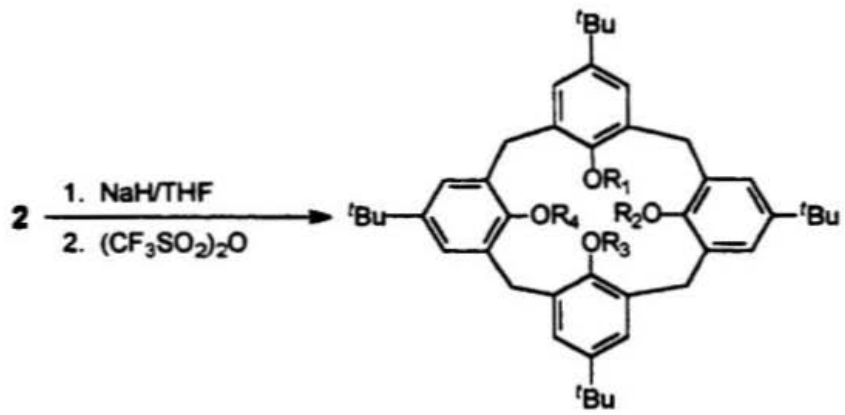
4.1 Introduction

Calixarenes continue to be the focus of considerable research activity since they are easily accessible compounds with interesting conformational, physicochemical and complexation properties.[12] There are many examples of calix[4]arenes (**1**) that have been modified, either at the "lower rim" (phenolic hydroxyl-bearing), or at the upper rim, in order to assess and enhance their selectivity in the complexation of ionic or neutral species. Modifications of the upper rim are readily accessed by the sequential or total removal of the *tert*-butyl groups of *tert*-butylcalix[4]arene (**2**).[90] The majority of modifications of the lower rim however, have involved attaching various substituents containing ether, ketone, ester and/or amide groups to the phenolic oxygen of the calix[4]arenes.[91] Lower rim hydroxyl-depleted calixarenes have been obtained by reduction of the corresponding phosphonates.[92] Recently, however, Biali *et al.*[93a] developed novel methodologies to effect modification and/or removal of the phenolic hydroxyl groups via the spirodienone calix[4]arene derivatives. Another report by Biali *et al.*[93b] describes the partial replacement of the hydroxyl groups of calixarenes by methyl groups, this was achieved by reacting spirodiene calixarene derivatives with methyllithium (CH_3Li). Gutsche *et al.*[94] employed the Newman-Kwart method for converting all of the four

hydroxyl groups of *tert*-butylcalix[4]arene to *tert*-butylcalix[4]arenethiols. Other examples of hydroxyl-group-depleted calix[4]arenes with amino[95] groups or xanthanes[96] and mercapto[97] groups have been also reported.

The Stille[80] and Suzuki-Miyaura[79] coupling methods represent two different very attractive procedures for modification of the phenolic hydroxyl groups of calixarenes. There has been only one report involving an attempted application of a Stille coupling using the 1,3-ditriflate derivative of *tert*-butylcalix[4]arene (**118**). Using typical Stille conditions, González *et al.*[98] reported an unprecedented intermolecular migration of the sulfonyl groups of **118** without observing any of the desired coupling. The only reported application of the Suzuki-Miyaura coupling methodology with **1** is that of Dondoni *et al.*[99] Their report however, described only upper rim, functionalization, resulting in the synthesis of calix[4]arenylvinylene and calix[4]arenylphenylene oligomers. More recently, Csók *et al.*[100] reported the synthesis and the dynamic NMR measurements of triflate derivatives of various de-*tert*-butylated- and *tert*-butylcalix[*n*]arenes (*n* = 4,6,8), including **2**, and **3**. They found that **118** was conformationally rigid and also that it underwent hydrolysis in the presence of $Pd(PPh_3)_4$ to yield only the monotriflate **119**. These authors however, failed to recognize or acknowledge the earlier work of González *et al.*[98] on *tert*-butylcalix[4]arene triflates.

As part of our own investigations on the chemical modification of the lower rim of calix[4]naphthalenes,[48] and calix[4]arenes, the chemistry of the triflates of the



$R_1 = R_3 = SO_2CF_3$, $R_2 = R_4 = H$ **118** (69%)
$R_1 = R_2 = R_3 = H$, $R_4 = SO_2CF_3$ **119** (72%)
$R_1 = R_2 = R_3 = SO_2CF_3$, $R_4 = H$ **120** (60%)
$R_1 = R_2 = R_3 = R_4 = SO_2CF_3$ **121** (11%)

Scheme 4.1 Synthesis of *tert*-butylcalix[4]arene triflates (118-121)

more readily accessible *tert*-butylcalix[4]arene (**2**) was first re-examined. In this chapter, the syntheses of the individual mono-, di-, tri- and tetratriflate (**118-121**) of *tert*-butylcalix[4]arene (**2**) and the unusual chemistry of these compounds will be discussed in this chapter. The reactions of these triflates are described under Suzuki-Miyaura coupling conditions and also under the de-oxygenation conditions of Snieckus *et al.*[101] The formation of an unprecedented non-solvent-containing clathrate is also reported.

4.2 Synthesis of calix[4]arene triflates

González *et al.*[98] and also Csók *et al*[100] independently reported that they were only able to synthesize directly the 1,3-ditriflate **118** but not monotriflate **119**, tritriflate **120** or tetratriflate **121** using triflic anhydride with *tert*-butylcalix[4]arene (**2**)

and a variety of bases. González obtained **119** and **120** indirectly, as the only products from the Stille reaction of **118** whereas Csók obtained **119** by the Pd(0)-mediated hydrolysis of **118**.

The synthesis the individual triflates **118** - **121** using various ratios of triflic anhydride and NaH in either CH_2Cl_2 or THF as solvent is depicted in Scheme 4.1. Thus, the ditriflate **118** was obtained in 69 % yield from the reaction of **2** with two mole equivalents of triflic anhydride and two mole equivalents of NaH. Both ^1H and ^{13}C NMR spectra of **118** were in agreement with a *cone* conformation for the molecule. The ^1H NMR spectrum of **118** shows two signals of *tert*-butyl protons, one pair of doublets centered at δ 3.55 and 4.22 (J = 14.5 and 14.4 Hz, respectively) which is an indication that the molecule is in a *cone* conformation. The ^{13}C NMR spectrum shows signal at δ 32.4 typical of 1,3-disubstituted calix[4]arenes in the *cone* conformation as shown by de Mendoza.[26] The (+)-FAB MS analysis of the assigned compound **118**, showed a molecular ion peak at the expected mass value of m/z = 913. Treatment of **2** with an excess (6 mole equivalents) of NaH, produced an easily separable mixture of tritriflate **120** and tetratriflate **121** in 60% and 11% yields, respectively. The ^1H NMR spectrum of **120** shows four doublets at δ 3.55, 3.59, 4.14 and 4.63 with coupling constant of J = 14.1, 14.5, 14.6 and 14.1 Hz, respectively, due to the methylene protons. Similarly, the ^{13}C NMR spectrum of **120** shows signals for the methylene carbons at δ 31.1 and 33.4, respectively. The ^1H NMR spectrum of **121** is very simple, showing one signal for a *tert*-butyl group at δ

1.13, two doublets centered at δ 3.58 and 4.55 with geminal coupling constant of *J* = 14.4 and 14.3 Hz, respectively and one singlet at δ 7.00 for the aromatic signal. These spectral data are typical of calix[4]arenes in the *cone* conformation.[26] Further support for the assigned structures for **120** and **121**, were provided by the (+)-FAB MS, which show molecular ion peaks, at their expected values of *m/z* = 1044 and 1176, respectively. Monotriflate **119** was synthesized directly in 72 % yield using 1.1 mole equivalents of NaH and 1.5 mole equivalents of triflic anhydride. Analysis of its ^{1}H NMR spectrum clearly indicates that it is in a *cone* conformation. The spectrum reveals two sets of AB quartets centered at δ 3.82 and 3.99 with typical geminal coupling constants of *J* = 14.2 and 14.0 Hz, respectively which are assigned to the methylene protons of the calixarene. The ^{13}C NMR spectrum is also consistent with the assigned structure and confirms that the molecule is in a *cone* conformation. This is confirmed by the ^{13}C NMR signals at δ 32.3 and 32.5 of the methylene carbons which are in good agreement with literature values.[26] The X-ray structure of **119** clearly showed a distorted C_{2v} "*pinched cone*",[102] conformation in which the plane of the triflate group on the phenyl ring is distorted into the cavity (Figure 4.1). The fact that "*pinched cone*" conformers have not yet been detected in solution[103a] has been rationalized in terms of a rapid interconversion between two equivalent C_{2v} isomers.[103b] The dihedral angle between the least-squares planes defined by the phenyl group bearing the triflate group and the distal phenyl group (Planes 1 and 3) is 6.8°. A single crystal X-ray structure of **119** also shows that the

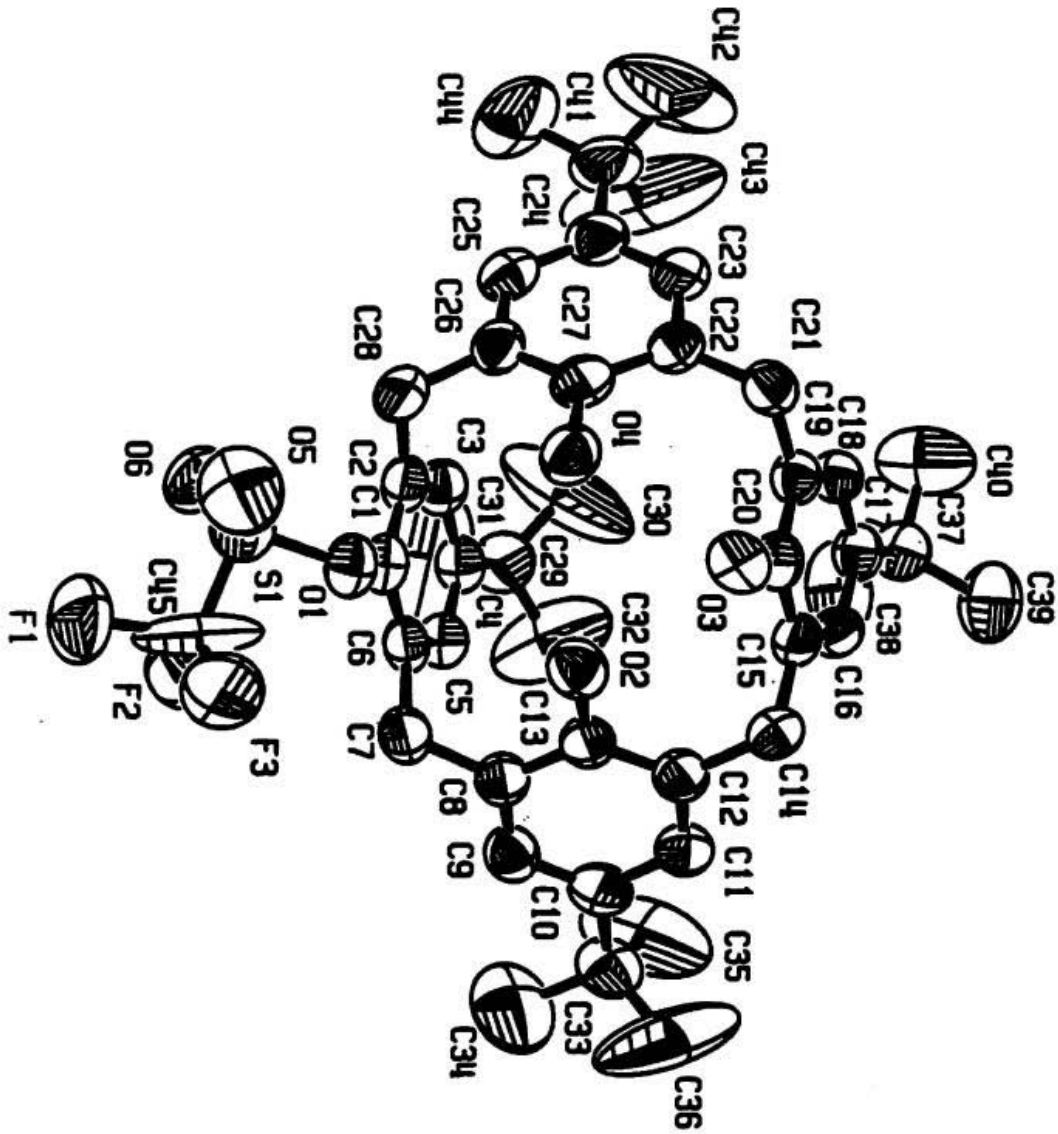


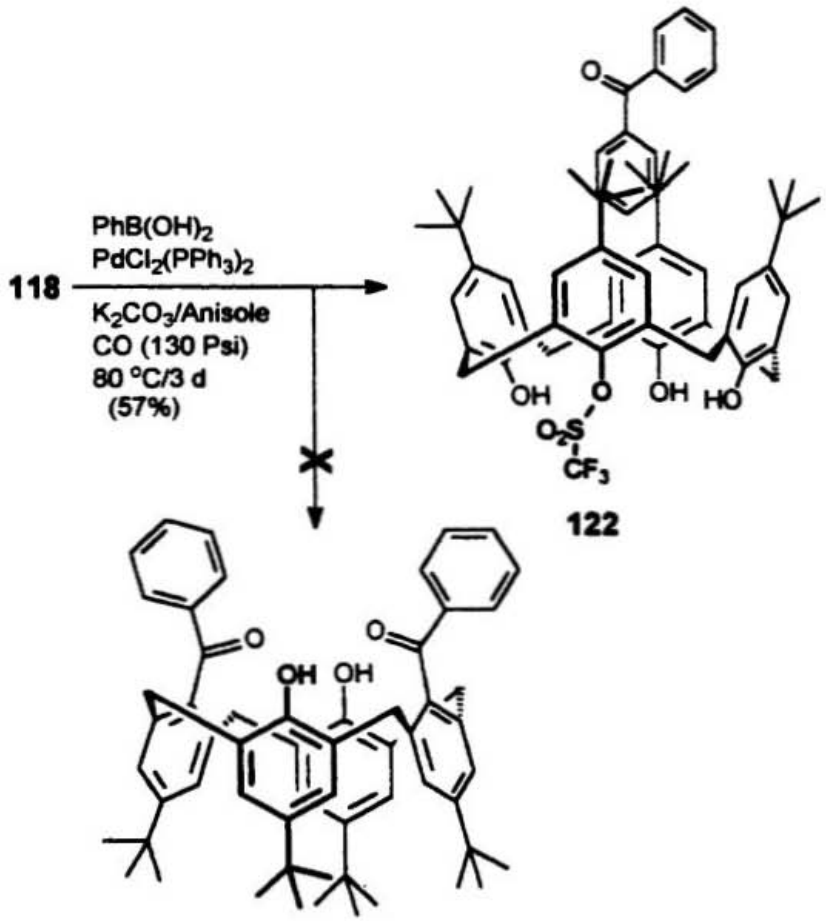
Figure 4.1 X-ray crystal structure of 119

dihedral angle between the least-square planes defined by the other two phenyl groups (planes 2 and 4) is 70.39°.

4.3 Reactions of calix[4]arene triflates

Treatment of either **118**, **120** or **121** with phenylboronic acid under Suzuki-Miyaura coupling conditions with $Pd(PPh_3)_4$, $PdCl_2(dppf)$ or $PdCl_2(PPh_3)_2$ did not produce the anticipated corresponding lower rim phenyl group-functionalized products. Instead, from the reactions of either **118** or **120**, only monotriflate **119** was obtained, while from **121**, only starting material was recovered. Thus, under these conditions, Pd-catalyzed disproportionation of **118** to **119** occurred, a reaction which is similar to the disproportionation observed by González *et al.*[98] using Stille conditions. Having failed to obtain the desired Pd-catalyzed cross-coupled products, Pd-catalyzed carbonylative coupling reactions[104] were next examined using carbon monoxide/ phenylboronic acid with **118**, **120** and **121**. Insertion of a carbonyl group between the lower rim and the phenyl group derived from an phenylboronic acid to form aryl ketones would also be a desirable lower rim functionalization of calix[4]arenes.

Reaction of **118** with phenylboronic acid under Pd-catalyzed carbonylative conditions,[104] gave a crystalline product (mp 262-264 °C), whose NMR spectra in various solvents clearly indicated additional aromatic signals (ten aromatic protons; four ^{13}C signals) as well as a carbonyl group. The ^1H NMR spectrum of this product revealed four doublets at δ 3.48, 3.57, 4.15 and 4.33, all with the same coupling



Scheme 4.2 Attempted synthesis of 122a via Pd(0)-catalyzed carbonylation reactions

constant of J = 14.1 Hz, are due to the methylene protons. The ^{1}H NMR spectrum also clearly indicates additional signals centered at δ 7.49, 7.60, 7.80 consisted with the expected extra aromatic protons from the carbonylation reaction. Similarly, in the ^{13}C NMR spectrum of the crystalline compound, the signal at δ 196.7 indicates

the presence of a carbonyl group. The IR spectrum showed, an absorption at 1661 cm^{-1} (Nujol) which is consistent with the presence of a carbonyl group. The ^{13}C NMR spectrum was also supportive that the compound is in a *cone* conformation, showing methylene carbon signals at δ 32.3 and 32.4. Thus, spectral analysis (^{1}H, ^{13}C NMR and IR) of the crystalline compound obtained from reaction between **118** and phenylboronic acid in a Pd-catalyzed carbonylation reaction seemed to be consistent with the expected product **122a** (Scheme 4.2).

Definitive structural elucidation of the crystalline compound however was obtained from its X-ray structure. As can be seen from the X-ray crystal structure shown in Figure 4.2, the product (**122**) is a 1:1 clathrate[105] formed between monotriflate **119** and benzophenone (Scheme 4.2). It has one of the phenyl groups of the benzophenone situated within the cavity of the calixarene, which is in a *pinched cone* conformation. The least-squares plane of the phenyl group of the guest benzophenone is near-parallel to the planes of the triflate-bearing phenyl group, and the *distal* phenolic group, with the dihedral angles between the respective planes being 19.8° and 22.3°. The dihedral angle between the least-squares planes defined by the phenyl groups of the other two phenolic units is 86.9°, to accommodate the enclosed phenyl group of the benzophenone. Andreetti and coworkers[105a-d] identified the *tert*-butyl groups to be of critical importance for favourable CH_3---π interactions between the methyl groups and the π-system of a guest molecule. The ^{1}H NMR spectrum of **122** in $CDCl_3$, CD_2Cl_2, or CD_3CN solution

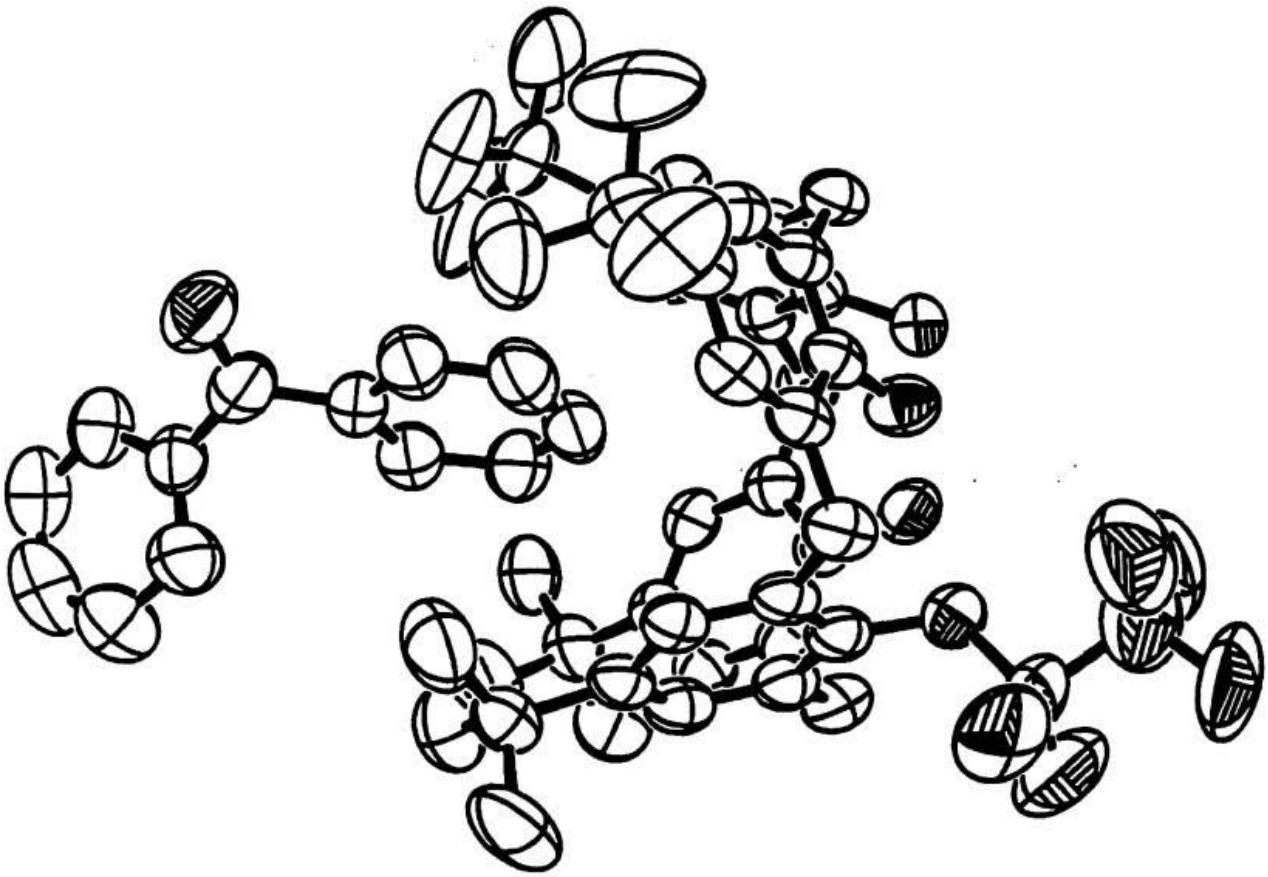
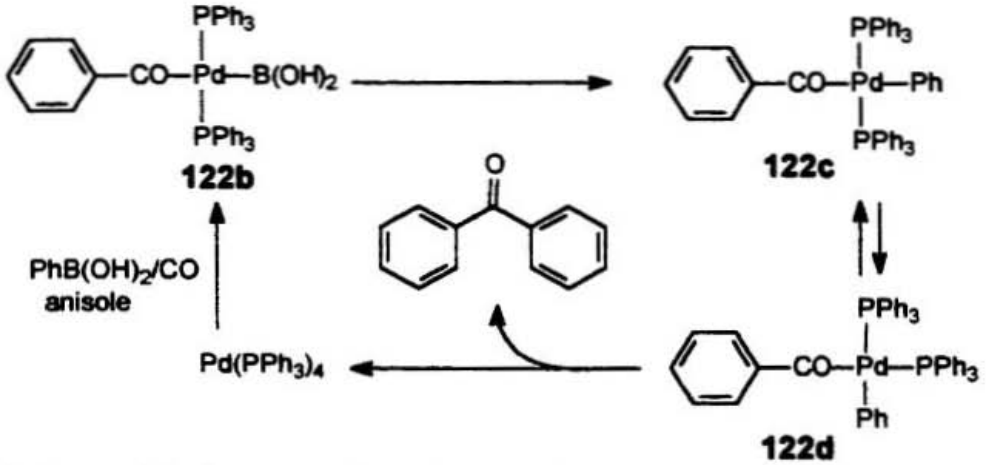


Figure 4.2 X-ray crystal structure of clathrate 122

did not reveal unequivocal evidence for the existence of the clathrate in solution. In each case, the spectra were indistinguishable from those of equimolar mixtures prepared from **119** and benzophenone. Evaporation of the deuterated solvents from the appropriate solutions containing **122** afforded residues having only a slightly lower melting point (with decomposition), whereas removal of the solvent from the equimolar mixtures of **119** and benzophenone, afforded residues having a much lower and broader range melting points than those of **122**. The melting point of the recovered single crystal which produced the X-ray structure was found to be identical with that of the bulk sample. To our knowledge, the X-ray structure reported herein is the first crystal structure of a clathrate of a calix[4]arene containing a neutral guest molecule that is not solvent-derived but is likely derived from carbonylation reactions of phenylboronic acid.

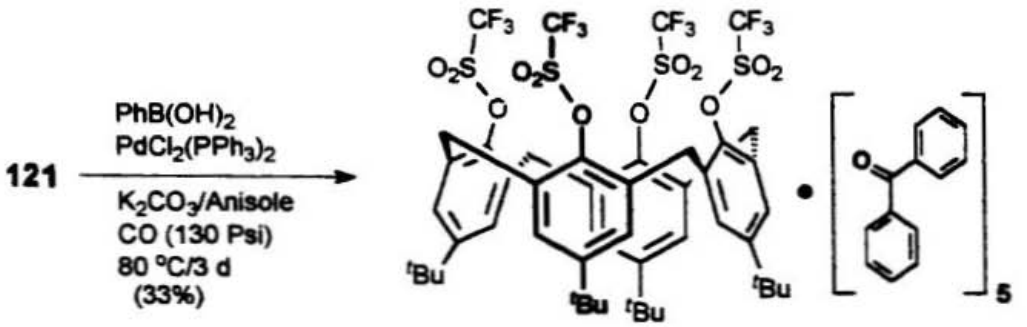
Allowing equimolar mixtures of **119** and benzophenone to crystallize slowly failed to produce **122** thereby establishing that the clathrate was not merely formed by a simple co-crystallization of its two components. When **119** and benzophenone in anisole alone were pressurized with carbon monoxide under the same conditions which were employed for the carbonylative conditions, but omitting the Pd catalyst and base, no formation of **122** was observed. The mechanism of formation of this unusual clathrate is still unclear. It can be noted however, that using the same carbonylative conditions in the presence of either **118** or **119**, phenylboronic acid produced benzophenone without any evidence of the formation of the corresponding



Scheme 4.3 A proposed mechanism for the synthesis of benzophenone during the coupling reactions of 118 and phenylboronic acid

clathrates. Furthermore, the homo-coupling of phenylboronic acid to give benzophenone itself was not reported by Ishiyama *et al.*[104] among the extensive list of biaryl ketones which they synthesized via Pd-catalyzed cross-coupling of various arylboronic acids with aryl electrophiles. Thus, the formation of benzophenone from phenylboronic acid is unusual, and its formation in our case, may be assisted by the presence of the calixarenes.[106]

The formation of biaryl from the homo-coupling of boronic acids is precedented in the literature.[107] The formation of benzophenone (Scheme 4.2) could have resulted from reductive elimination of the Ph(CO)-Pd-Ph intermediate **122c** and **122d** (Scheme 4.3) in which either a second phenylboronic acid or triphenylphosphine itself are the potential sources of the phenyl group in the PhCO-Pd-Ph intermediate. It is worth mentioning in this context that tritriflate **120** was

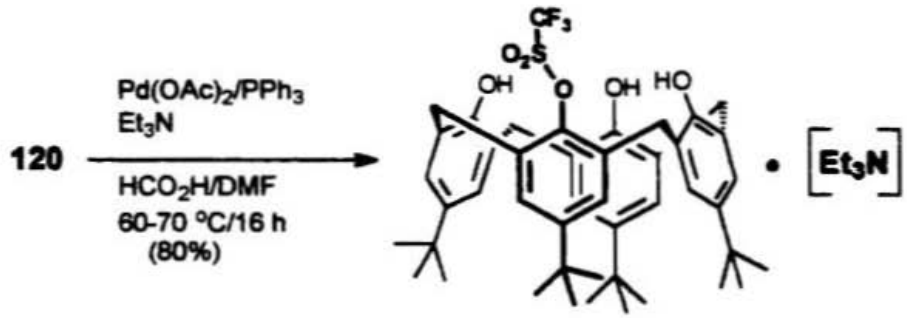


123

Scheme 4.4 Pd(0)-catalyzed carbonylation reactions between 121 and phenylboronic acid

recovered unchanged (36 h at 80 °C; carbon monoxide 130 psi) under the Pd-catalyzed carbonylative conditions used. Under the same conditions tetratriflate **121** afforded a product **123** (mp 265 - 272 °C) whose ^{1}H NMR spectrum is consistent with it being **119** having *five* included benzophenone molecules (Scheme 4.4). We have not as yet been able to obtain a single crystal suitable for X-ray structure determination.

Snieckus *et al.*[101] reported a general Pd(II)-catalyzed procedure for the deoxygenative replacement of the hydroxyl functionalities of phenols by a hydrogen atom via the corresponding triflates. This procedure was therefore examined as an alternative method for the reduction of calix[4]arene phosphonates described by Goren and Biali[82] to obtain hydroxyl-depleted calix[4]arenes. Tritriflate **120** was treated with $Pd(OAc)_2/PPh_3/Et_3N/HCO_2H$ in refluxing DME for 16 h (Scheme 4.5). After work-up and flash column chromatography, a crystalline product **124** (80 %) was obtained whose ^{1}H NMR spectral data revealed, among other signals, a well-



124

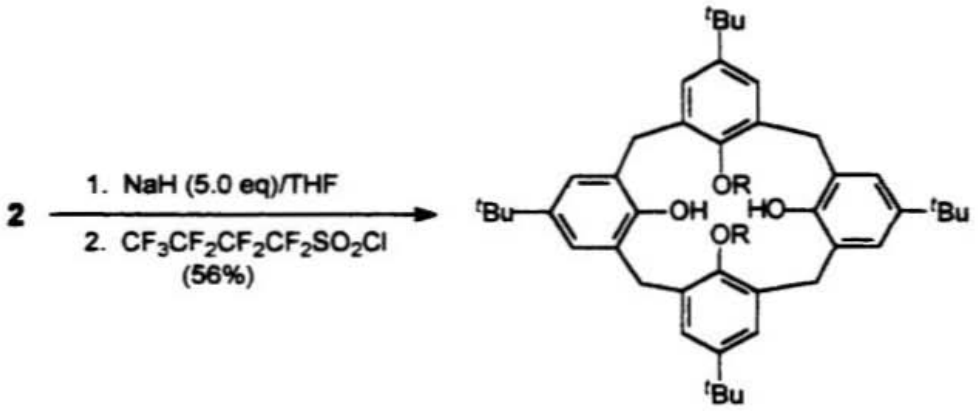
Scheme 4.5 Attempted reactions to replace triflates in 120

defined quartet centered at δ 3.14 (apparent coupling constant of J = 7.3 Hz) coupled to a well-defined triplet at δ 1.31 ppm (J = 7.3 Hz) whose integration values suggested the presence of three ethyl groups. Suitable crystals for X-ray structure determination have so far not been obtained. However, (+)-FAB mass spectrometry revealed molecular ions at *m/z* = 780 and 101, corresponding to monotriflate **119** and triethylamine respectively, suggesting that this product is a 1:1 complex of **119** and triethylamine. The ^{1}H NMR spectrum of **124** shows that the signals of the methylene and methyl groups of the complexed triethylamine are shifted 0.54 and 0.20 ppm downfield compared to those of the corresponding signals obtained from 1:1 or 1:3 mixtures of **119** itself and triethylamine. Gutsche's group has studied the interaction of *p*-allylcalix[4]arenes and amines.[108] On the basis of NOE and ^{1}H NMR spectral data Gutsche[108] concluded that *p*-allylcalix[4]arene formed an *endo*-type complex in which the amine "guests" were complexed within the cavity formed by the aryl groups of calixarene. An *exo*-type complex is also formed in which the amine

"guest" is bound to the lower rim of *p*-allylcalix[4]arene. Chemical shifts differences or T_1 differences between uncomplexed amine and 1:1 mixtures were unequivocal. In this example, when **124** was subjected to a NOE experiment, no enhancement of the signals due to either the methylene or methyl group of the triethyl amine was observed upon irradiation of the *tert*-butyl methyl signals. Since there is only one set of amine resonance appearing on the ^{1}H NMR spectrum of **124**, there is obviously a fast exchange between "free" and "guest" triethylamine. This was tested by a titration experiment of **119** and triethylamine which showed that the triethylamine signals are shifted upfield compared with the signals which appear with the amine as the guest in **124**. On the basis of these experiments, it can be concluded that **124** is an *exo*-type complex.

4.4 Reactions of calix[4]arene nonaflates

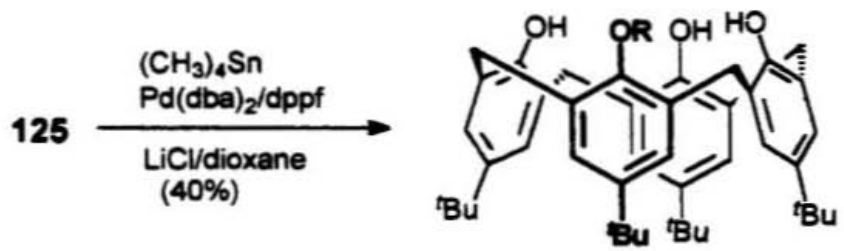
While the work described above was in progress, Lipshutz *et al.*[109] reported that aryl triflates and nonaflates could be reductively deoxygenated efficiently using Pd(0)-catalyzed reaction with dimethylamine•borane. These same reductive conditions were examined using **118** but again, only **119** and **120** were obtained as the major products, with no evidence for reductive deoxygenation. Finally, di(nonaflate) **125** was prepared in 56% yield using perfluoro-1-butanesulfonyl chloride with **2** and NaH as a base in THF as a solvent (Scheme 4.6). For compound **125**, the *cone* conformation was deduced from its ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum shows two doublets centered at δ 3.52 and 4.25



125: R = $CF_3CF_2CF_2CF_2SO_2$

Scheme 4.6 Synthesis of *tert*-butylcalix[4]arene nonaflates (125)

with geminal coupling constants of J = 14.5 and 14.3 Hz, respectively, while the ^{13}C NMR chemical shifts at δ 34.0 and 34.1 were in good agreement with a *cone* conformation as previously shown in the literature.[26] When **125** was subjected to typical Stille-coupling conditions[82] with tetramethylstannane, only monononaflate **126**, which is analogous to **119**, was obtained as shown in Scheme 4.7.



126: R = $SO_2(CF_2)_3CF_3$

Scheme 4.7 Attempted reactions to replace nonaflates in 125

From the results which were obtained, it is possible that the oxidative addition step[78] requiring a square-planar intermediate[110] which was presumed to form in the

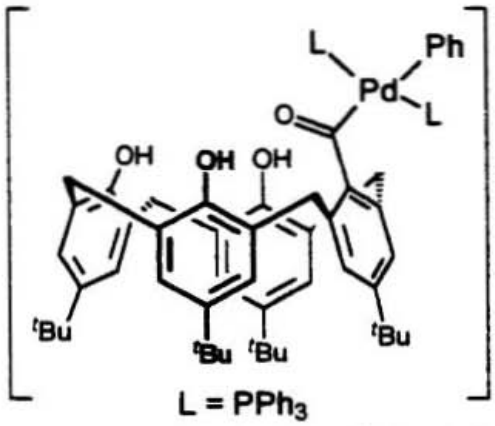


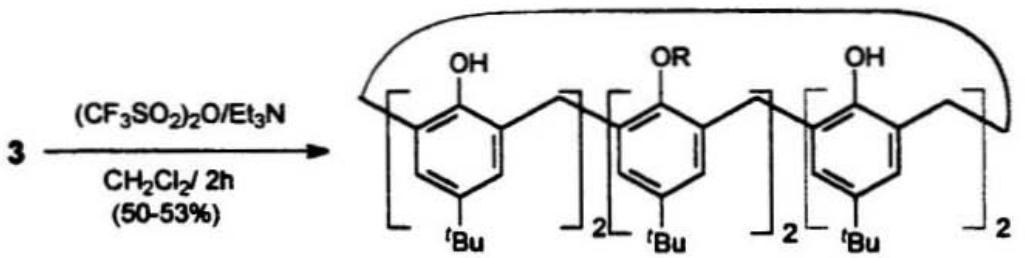
Figure 4.3 A putative square-planar intermediate during carbonylation reactions of calixarene triflate and phenylboronic acid

Pd(0)- Pd(II) catalytic cycle, might not be occurring in the case of these calix[4]arene triflates, likely due to a prohibitively large steric encumberance in the lower rim of calixarene (Figure 4.3).

4.5 Synthesis and reaction of calix[6]arene triflates

As discussed in the previous sections, both Suzuki-Miyaura coupling and carbonylation of *tert*-butylcalix[4]arene triflates failed to give lower rim-substituted derivatives of **2**, and instead, gave the hydrolysis product of **118** and the benzophenone clathrate **122**. To be able to use Pd-catalytic chemistry with *tert*-butylcalix[6]arene (**3**) to replace its phenolic groups would be a valuable addition to their chemistry.

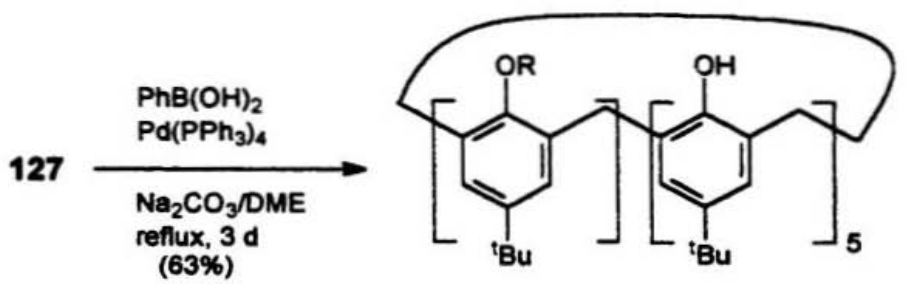
To test this possibility, *tert*-butylcalix[6](OTf)$_2$(OH)$_4$ **127** was prepared. Csók *et al.*[100] showed that compound **127** can be readily obtained from **3** using pyridine and trifilic anhydride. In our hands, when **3** was treated with an equimolar amount



127: R = SO_2CF_3

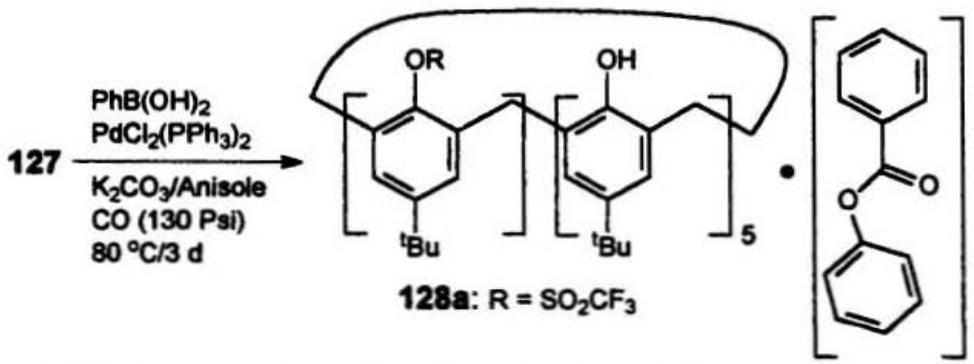
Scheme 4.8 Synthesis of *tert*-butylcalix[6]arene triflates (127)

of triethylamine then with triflic anhydride, the ditriflate **127** was obtained in 50-53 % yield (Scheme 4.8). The spectral data (^1H and ^{13}C NMR) of compound **127** were consistent with the expected product being in a *cone* conformation. Further support of the assigned structure for compound **127** was provided by the (+)-FAB mass spectrum, which shows a molecular ion peak at the expected value of *m/z* M^+ = 1236. In the presence of 2 mole % of Pd $(PPh_3)_4$ in refluxing DME the reaction of **127** with phenylboronic acid afforded only the *tert*-butylcalix[6](OTf)$(OH)_5$ **128** in 63% yield (Scheme 4.9). Both the ^1H and ^{13}C NMR spectral data are consistent with the



128: R = SO_2CF_3

Scheme 4.9 Attempted reactions to replace triflates in 127



Scheme 4.10 **Pd(0)-catalyzed carbonylation reactions between 127 and phenylboronic acid**

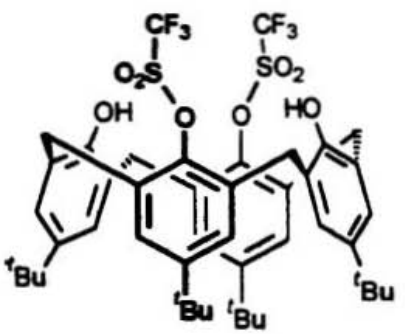
structure of compound **128** being in a *cone* conformation. Finally, the (+)-FAB mass spectrum of compound **128** showed molecular ions peak at *m/z* M^+ = 1105 in agreement with its expected mass. This finding was consistent with our results obtained with *tert*-butylcalix[4]arene triflates. It is noteworthy to mention that the carbonylation reaction of **127** with phenylboronic acid did not result in carbonylation of the calix[6]arene but instead showed the presence of a molecule of phenyl benzoate, presumably as a complex **128a** (Scheme 4.10). This too is an unusual finding for which at present we do not have any definitive explanation.

In conclusion, we have demonstrated that each of the four calix[4]arene triflates and calix[6]arene triflates can be easily synthesized and characterized. However, possibly because of steric restrictions, oxidative addition does not appear to occur with any of these triflates to form Pd(II) intermediates. These intermediates are required for effective Pd(0)-catalyzed Suzuki-Miyaura coupling, carbonylative

coupling or deoxygenation. Instead, in the Suzuki-Miyaura coupling reaction, hydrolysis of triflate or nonaflate groups occurred. In the case of Pd(0)-catalyzed carbonylative coupling using ditriflate **118**, an unprecedented non-solvent-molecule-derived 1:1 clathrate **122** was formed. From the Pd(II)-catalyzed deoxygenation reaction with **118**, a 1:1 clathrate **124** was formed. We also showed that Pd(0)-catalyzed carbonylative coupling using ditriflate **127**, another unprecedented non-solvent molecule-derived 1:1 clathrate **128a** was formed.

4.6 Experimental Section For general methods, see Chapter 2.

***tert*-Butylcalix[4]arene 1,3-ditriflate (118)**

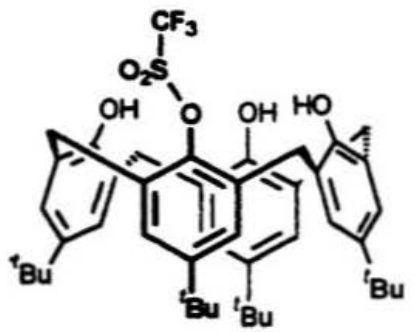


118

To a solution of *tert*-butylcalix[4]arene (**2**) (2.59 g, 4.00 mmol) in THF (120 mL) at 0 °C was added in two portions, with stirring, NaH (60% suspension in oil, 317 mg, 8.00 mmol). The mixture was stirred for a further 30 min at 0 °C and then trifluromethanesulfonic anhydride (1.33 mL, 8.00 mmol) was added slowly. The reaction mixture was stirred overnight at room temperature. It was quenched by the addition of an aqueous saturated NH_4Cl (20 mL). The solvent was removed under

reduced pressure. The residue was diluted with CH_2Cl_2 (2 x 30 mL), washed with brine, dried $MgSO_4$, and filtered. After the solvent was evaporated, the crude product was triturated with hexane to afford **118** (2.50 g, 69%) as a colourless solid: mp 285-287 °C, (305 °C from methanol - benzene,[98] 255 °C from $CHCl_3$[100]) whose spectral characteristics were identical with those reported:[98, 100] ^{1}H NMR δ 0.92 (s, 18 H), 1.36 (s, 18 H), 3.55 (d, *J* = 14.5 Hz, 4H), 4.13 (s, 2H, OH), 4.22 (d, *J* = 14.4 Hz, 4H), 6.81 (s, 4H), 7.20 (s, 4H); ^{13}C NMR δ 30.7, 31.6, 32.4, 34.0, 34.1, 120.3 (2C, q), 125.8, 126.8, 127.6, 132.6, 141.3, 143.4, 149.7, 150.8; (+)-FAB MS (*m/z*): 913 (M^+, 100), 900 (42), 858 (20), 781 (48), 765 (38), 649 (78), 612 (82).

tert-Butylcalix[4]arene triflate (119)

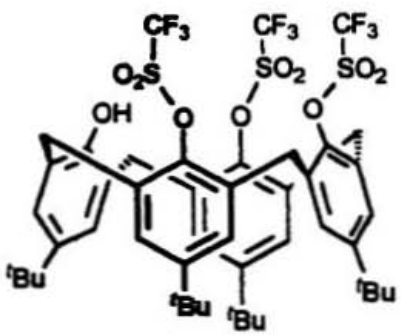


119

To a solution of **2** (2.59 g, 4.00 mmol) in THF (120 mL) at 0 °C was added with stirring, NaH (60% suspension in oil, 175 mg, 4.40 mmol). The mixture was stirred for a further 30 min at 0 °C and then trifluromethanesulfonic anhydride (1.0 mL, 6.00 mmol) was added slowly. The reaction was carried out and worked up as described for **118** to afford a yellow product which was purified by flash chromatography (5:95

ethyl acetate - hexane) to afford **119** as colourless crystals (2.25 g, 72%): mp 234-236 °C (228-230 °C from hexane[98], 225 °C from $CHCl_3$[100]) whose spectral characteristics, apart from singlets at δ 6.81 (2H) and 8.34 (1H) which are D_2O - exchangeable, were identical with those reported.[10,12] IR (cm^{-1}) 3392, 2963, 1469, 1424, 1212; ^1H NMR δ 0.99 (s, 9H), 1.14 (s, 9H), 1.27 (s, 18H), 3.48 (d, *J* = 14.2 Hz, 2H), 3.57 (d, *J* = 14.2 Hz, 2H), 4.15 (d, *J* = 14.0 Hz, 2H), 4.32 (d, *J* = 14.0 Hz, 2H), 6.81 (s, 2H), 6.94 (s, 2H), 6.96 (s, 2H), 7.09 (d, *J* = 2.0 Hz, 2H), 7.13 (d, *J* = 2.0 Hz, 2H), 8.34 (s, 1H); ^{13}C NMR δ 30.7, 31.3, 31.5, 32.3, 32.5, 33.9, 34.0, 34.2, 120.3 (1 C, q), 125.6, 126.0, 127.0, 127.1, 127.3, 127.4, 127.6, 133.0, 140.9, 143.6, 144.1, 146.5, 148.9, 151.1; MS (*m/z*): 687 (5), 686 (11), 671 (3), 648 (3), 612 (2), 396 (8).

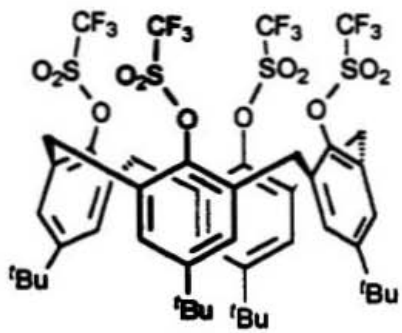
***tert*-Butylcalix[4]arene tritriflate (120) and *tert*-butylcalix[4]arene tetratriflate (121)**



120

To a solution of **2** (2.59 g, 4.00 mmol) in THF (120 mL) at 0 °C was added in 4-5 portions with stirring, NaH (60% suspension in oil, 955 mg, 24.0 mmol). The mixture was stirred for a further 30 min at 0 °C and then trifluromethanesulfonic anhydride

(3.36 mL, 20.0 mmol) was added slowly. The reaction was carried out and worked up as described for **119** to afford a yellow product which was purified by flash chromatography (5:95 ethyl acetate-hexane) to give **120** (2.51 g, 60%): mp 248-250 °C (239-240 °C from hexane[98]); ^{1}H NMR δ 0.92 (s, 18H), 1.33 (s, 9H), 1.41 (s, 9H), 3.56 (d, *J* = 14.2 Hz, 2H), 3.59 (d, *J* = 14.4 Hz, 2H), 3.76 (s, 1H, OH), 4.15 (d, *J* = 14.4 Hz, 2H), 4.62 (d, *J* = 14.2 Hz, 2H), 6.70 (d, *J* = 2.3 Hz, 2H), 6.76 (d, *J* = 2.3 Hz, 2H), 7.20 (s, 2H), 7.39 (s, 2H); and

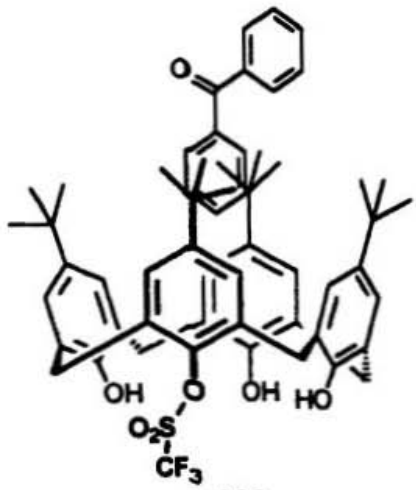


121

121 (517 mg, 11%) was obtained as a colourless solid: mp 260-262 °C; ^{1}H NMR δ 1.13 (s, 36H), 3.58 (d, *J* = 14.4 Hz, 4H), 4.55 (d, *J* = 14.3 Hz, 4H), 7.00 (s, 8H); ^{13}C NMR δ 31.2, 34.4, 116.5, 120.8 (4 C, q), 126.9, 133.5, 141.4, 150.6; (+)-FAB MS (*m/z*): 1176 (M^+, 3), 1044 (25, -SO_2CF_3), 912 (18, -2xSO_2CF_3), 645 (10), 611 (20), 550 (32), 522 (37), 154 (100).

***tert*-Butylcalix[4]arene triflate:benzophenone clathrate (122)**

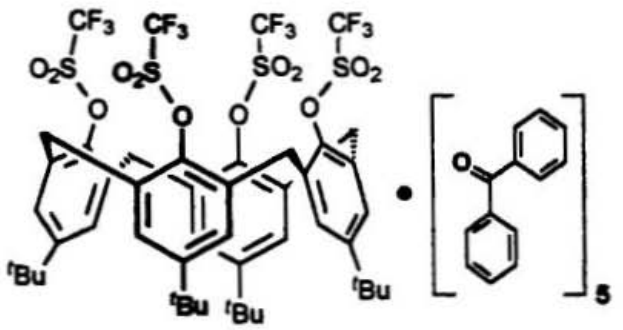
A mixture of **118** (150 mg, 0.164 mmol), phenylboronic acid (44 mg, 0.36 mmol), $PdCl_2(PPh_3)_2$ (23 mg, 20 mol%), K_2CO_3 (68 mg, 0.49 mmol) and anisole (15 mL)



122

were placed in a stainless steel high-pressure reaction vessel. The reaction was flushed once and then charged with CO (130 Psi) and heated at 80 °C for 3 d. After releasing the unreacted carbon monooxide, the crude mixture was partitioned between water (15 mL) and ethyl acetate (3x15 mL). The organic layer was dried ($MgSO_4$) and evaporated to afford a product, which was purified by preparative TLC eluting with 1:5 benzene - hexane to give **122** (90 mg, 57%) as a colourless solid: mp 262-264 °C; IR (cm^{-1}) 1661; ^1H NMR δ 0.99 (s, 9H), 1.14 (s, 9H), 1.27 (s, 18H), 3.48 (d, J = 14.1 Hz, 2H), 3.57 (d, J = 14.1 Hz, 2H), 4.15 (s, J = 14.1 Hz, 2H), 4.33 (s, J = 14.1 Hz, 2H), 6.81 (s, 2H), 6.94 (s, 2H), 6.96 (s, 2H, OH), 7.09 (d, J = 2.2 Hz, 2H), 7.13 (d, J = 2.3 Hz, 2H), 7.49 (t, J = 7.6 Hz, 4H), 7.60 (t, J = 7.4 Hz, 2H), 7.80 (m, 4H), 8.33 (s, 1H, OH); ^{13}C NMR δ 30.7, 31.2, 31.5, 32.3, 32.4, 33.9, 34.0, 34.2, 120.9 (1 C, q), 125.7, 125.9, 127.1, 127.3, 127.5, 128.2, 128.5, 129.4, 130.0, 133.5, 137.5, 141.0, 143.6, 144.1, 146.5, 148.9, 151.0, 196.7.

***tert*-Butylcalix[4]arene tetratriflate:benzophenone clathrate (123)**

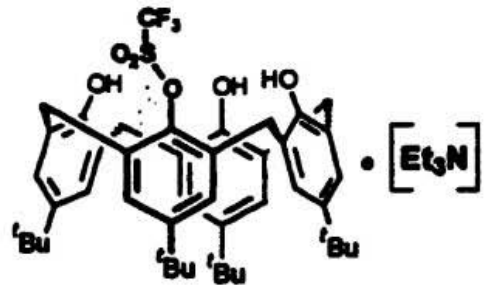


123

A mixture of **121** (26 mg, 0.022 mmol), phenylboronic acid (22 mg, 0.175 mmol), $PdCl_2(PPh_3)_2$ (1.54 mg, 0.018 mmol), K_2CO_3 (18 mg, 0.131 mmol) and anisole (2 mL) were placed in stainless steel high-pressure reaction vessel. The reaction was carried out and worked up as described for **122** to afford a crude product which was purified by preparative TLC eluting with 1:5 benzene-hexane to give **123** (10 mg) as a colourless solid: mp 265-272 ^{0}C; IR (cm^{-1}) 1659; ^{1}H NMR δ 1.13 (s, 36H), 3.59 (d, J = 14.3 Hz, 4H), 4.56 (d, J = 14.3 Hz, 4H), 7.01 (s, 8H), 7.51 (m, 21H), 7.61 (m, 10H), 7.81 (m, 19H); ^{13}C NMR δ 31.2, 34.4, 120.3 (4 C, q), 126.9, 128.3, 130.1, 132.4, 133.5, 137.6, 141.5, 150.6, 196.8.

***tert*-Butylcalix[4]arene triflate:triethylamine complex (124)**

A mixture of **120** (522 mg, 0.500 mmol), $Pd(OAc)_2$ (13 mg, 0.060 mmol), PPh_3 (31 mg, 0.12 mmol), formic acid (0.11 mL, 3.0 mmol), Et_3N (1.3 mL, 9.0 mmol) and DMF (10 mL) were heated at 60 - 70 °C for 16 h. The mixture was washed with H_2O (3x10 mL) and the organic layer was extracted with ethyl acetate (3x15 mL), dried

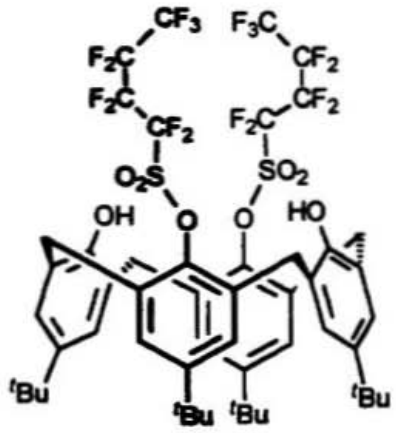


124

($MgSO_4$) and evaporated to afford a product which was purified by preparative TLC (5:95 ethyl acetate-hexane) to give 124 (350 mg, 80%) as a colourless solid: mp 194-196 °C; ^{1}H NMR δ 1.03 (s, 9H), 1.19 (s, 9H), 1.24 (s, 18H), 1.31 (t, J = 7.3 Hz, 9H), 3.14 (q, J = 7.3Hz, 6H), 3.34 (d, J =13.1 Hz, 2H), 3.37 (d, J = 13.0 Hz, 2H), 4.12 (d, J = 13.0 Hz, 2H), 4.43 (d, J = 12.9 Hz, 2H), 6.91 (s, 4H), 6.96 (d, J = 2.4 Hz, 2H), 6.98 (2, 2H), 7.07 (d, J = 2.4 Hz, 2H); ^{13}C NMR δ 30.9, 31.3, 31.5, 31.7, 32.4, 33.8, 34.1, 34.6, 45.7, 120.3 (1 C, q), 125.0, 125.2, 125.3, 126.8, 129.6, 132.9, 139.9, 141.2, 142.8, 144.1, 149.3, 151.5, 152.7; (+)-FAB MS *m/z*: 881 (M^+), 780, 101.

***tert*-Butylcalix[4]arene 1,3-bis(nonaflate) (125)**

To a solution of 2 (0.648 g, 1.00 mmol) in THF (40 mL) at 0 °C was added in two portions, with stirring, NaH (60% suspension in oil, 192 mg, 5.00 mmol). The mixture was stirred for a further 45 min at 0 °C and then perfluoro-1-butanesulfonyl chloride (0.9 mL, 5.00 mmol) was added slowly. The reaction was carried out and worked up as described for 118 to afford a yellow product which was purified by

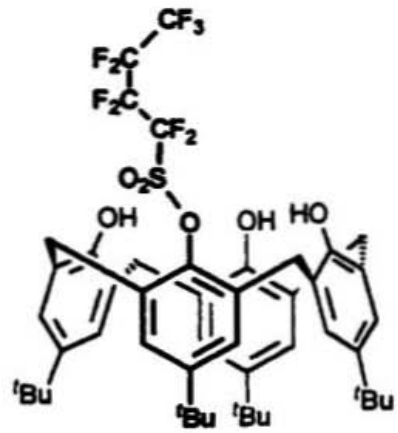


125

flash chromatography (10:90 ethyl acetate - hexane) to give the bisnonaflate **125** as a colourless crystalline solid (0.68 g, 56%): mp 277-279 °C; ^{1}H NMR δ 0.88 (s, 18H), 1.34 (s, 18H), 3.52 (d, *J* = 14.5 Hz, 4H), 4.19 (s, 2H, OH), 4.25 (d, *J* = 14.3 Hz, 4H), 6.76 (s, 4H), 7.17 (s, 4H); ^{13}C NMR δ 30.6, 30.7, 31.5, 31.6, 31.7, 31.8, 32.1, 32.1, 34.0, 34.1, 120.3 (2 C, q), 125.7, 126.9, 127.9, 132.8, 140.4, 143.5, 149.7, 150.9; (+)-FAB MS *m/z*: 1212 (M^+, 60), 1156 (-*tert*-butyl, 52), 1100 (-*tert*-butyl, 48), 930 (97), 649 (100).

tert-Butylcalix[4]arene nonaflate (126)

To a mixture of **125** (121 mg, 0.10 mmol), $Pd(dba)_2$ (3 mg, 5 mole %), dppf (3 mg, 2 mole %), LiCl (21 mg, 0.50 mmol), tetramethylstannane (0.04 mL, 0.3 mmol) under argon was added dioxane (5 mL). The mixture was heated at reflux for 2 days. After cooling to room temperature, the organic layer was poured into saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3x15 mL), dried over

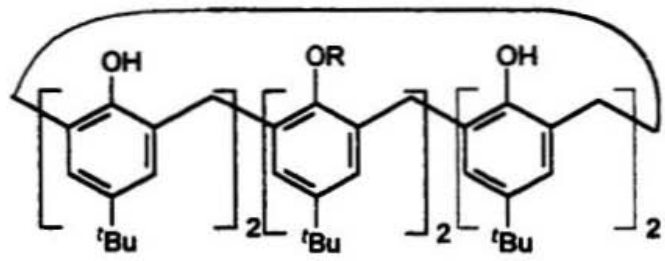


126

$MgSO_4$, filtered and the solvent was evaporated. The product was purified by preparative TLC to afford **125** (60 mg) and **126** (30 mg, 40%) as a colourless solid: ^{1}H NMR δ 0.96 (s, 9H), 1.13 (s, 9H), 1.28 (s, 18H), 3.46 (d, *J* = 14.2 Hz, 2H), 3.56 (d, *J* = 14.2 Hz, 2H), 3.71 (2H), 4.11 (d, *J* = 14.0 Hz, 2H), 4.34 (d, *J* = 14.0 Hz), 6.75 (s, 2H, OH), 6.90 (s, 2H), 6.94 (s, 2H), 7.09 (d, *J* = 3.4 Hz, 2H), 7.13 (d, *J* = 3.4 Hz); ^{13}C NMR δ 29.7, 30.7, 31.2, 31.4, 31.5, 32.1, 32.4, 33.9, 34.2, 67.1, 120.3 (1 C, q), 125.6, 125.9, 127.0, 127.1, 127.3, 127.4, 127.6, 133.0, 140.7, 143.6, 144.1, 146.4, 148.9, 151.0; (+)-FAB MS *m/z*: 929 (M^+, 60), 873 (30), 649 (100).

tert-Butylcalix[6]arene ditriflate (127)

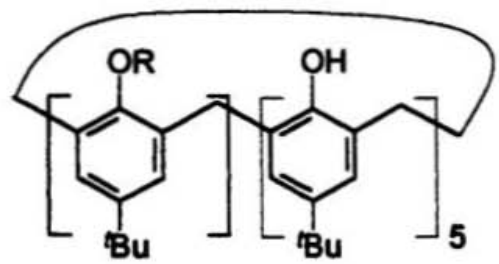
To a solution of *tert*-butylcalix[6]arene (**3**) (0.973 g, 1.00 mmol) in CH_2Cl_2 (70 mL) at room temperature under argon was added triethyl amine (0.31 mL, 2.2 mmol). The mixture was stirred at room temperature for 2 h and trifluromethanesulfonic anhydride (0.34 mL, 2.0 mmol) was added 5 min. The resulting yellow solution was



127: R = SO_2CF_3

stirred for 12 h, then aqueous saturated NH_4Cl (5 mL) was added. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated. The product was triturated with warm hexane to afford **127** (0.614 g, 50%) as a colourless solid: mp 296-298 °C (decomposition); ^1H NMR δ 1.02 (s, 18H, *tert*-butyl), 1.30 (s, 36H, *tert*-butyl), 3.25 - 4.65 (br, 12H, CH_2), 6.50 (br, 4H, OH), 6.95 (s, 4H, ArH), 7.19 (s, 8H, ArH); ^{13}C NMR ($CDCl_3$) δ 30.9, 31.9, 32.5, 32.6, 34.0, 34.3, 116.6, 120.3 (2 C, q), 125.8, 125.9, 126.9, 128.7, 132.7, 141.3, 144.7, 148.2, 151.1; (+)-FAB MS m/z: 1236 (M^+, 85), 1173 (45), 1103 (70), 1089 (85), 1021 (58), 989 (55), 968 (48), 954 (99), 938 (100).

***tert*-Butylcalix[6]arene monotriflate (128)**



128: R = SO_2CF_3

A solution of **127** (124 mg, 0.010 mmol), $Pd(PPh_3)_4$ (2 mole %) in DME (2mL) at

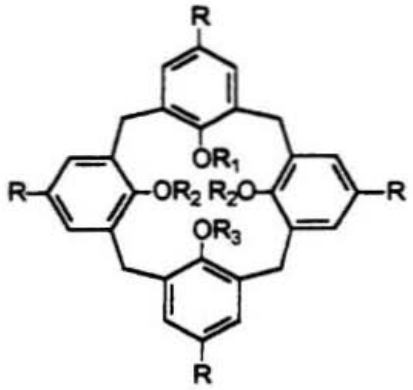
room temperature was stirred for 15 min. To this solution was added a solution of phenylboronic acid (49 mg, 0.03 mmol) in DME/ethanol (2:1, 2 mL). The yellow mixture was stirred for 3 d and diluted with ethyl acetate. The organic later was washed with saturated aqueous NH_4Cl and brine, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was subjected to preparative TLC eluting with 2:98 ethyl acetate-hexane to afford **128** (70 mg, 63%) as a colourless solid: mp >300 °C; ^{1}H NMR δ 1.07 (s, 9H), 1.20 (s, 9H), 1.28 (s, 18H), 1.30 (s, 18H), 3.42 (d, *J* = 14.1 Hz, 2H), 3.52 (d, *J* = 13.8 Hz, 2H), 3.65 (d, *J* = 14.7 Hz, 2H), 3.97 (d, *J* = 13.8 Hz, 2H), 4.24 (d, *J* = 14.1 Hz, 2H), 4.53 (d, *J* = 14.1 Hz, 2H), 7.69 (s, 2H), 7.07 (s, 2H), 7.12 (d, *J* = 2.4 Hz, 2H), 7.16 (m, 4H), 7.21 (m, 2H), 9.72 (br, 4H); ^{13}C NMR δ 30.9, 31.4, 31.5, 31.6, 32.4, 32.9, 33.0, 34.0, 34.1, 34.4, 113.8, 116.7, 120.3, 120.6, 121.0, 125.8, 126.1, 126.4, 126.8, 127.2, 127.5, 128.6, 129.4, 130.0, 133.0, 141.5, 144.0, 144.5, 145.0, 146.1, 147.8, 148.0, 151.3; (+)-FAB MS *m/z* (%): 1105 (M^+, 100), 1085 (19), 1049 (22), 972 (23), 954 (72), 935 (52).

Chapter 5

Lower rim Substituted Aryl Ethers of *para-tert*-Butylcalix[4]arene

5.1 Introduction

In recent years, much attention has been devoted to the synthesis and to the study of the properties of functionalized calix[4]arenes, due to their potential utility as supramolecular hosts for neutral guest molecules such as [60]fullerene and as selective ionophores for cations or anions.[12] Calix[4]arenes can be readily functionalized at either their lower and/or upper rim by the introduction of various substituents. These functional groups, which include amides, esters, polyethylene glycol units, alkyl and benzyl ethers, are most often introduced at the lower rim of the calix[4]arene scaffold.[111] However, lower rim calix[4]arene-aryl ethers such as **129** have never been reported, although such derivatives might be useful lower rim cavitands in which the aryl pendant functionalities might define an additional hydrophilic cavity. A single publication by Gutsche[112] exists in which is reported the lower rim functionalized mono-, di- and hexa-2,4-dinitro-ether derivatives of *tert*-butylcalix[8]arenes. To our knowledge, this is the only published report of any lower-rim aryl ether derivatives of a calixarene. Whereas mono-, di-, tri- and tetra-*O*-alkylated- and *O*-benzylated calix[4]arenes are easily formed by simple Williamson-type nucleophilic substitution reactions of the corresponding calixarenes with alkyl or benzyl halides, the synthesis of analogous *O*-aryl ethers such as **129** (Figure 5.1) has not been reported. This chapter will discuss the first synthesis of lower rim



R = *tert*-butyl; R_1 = aryl;
R_2 = R_3 = H *and/or* aryl

129

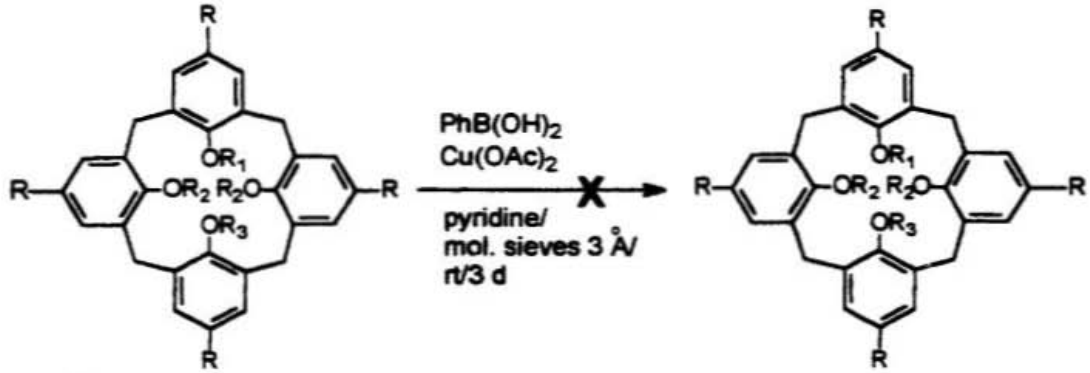
Figure 5.1 Lower rim aryl ether derivatives of calixarenes

substituted aryl ethers (*O*-arylation) of *tert*-butylcalix[4]arene (**2**) in order to create new molecular architectures.[113]

5.2 Synthesis of *O*-aryl ethers of *para-tert*-butylcalix[4]arene

The endeavors required for the synthesis and study of the vancomycin group of antibiotics have necessitated the development of mild methods for macrocylization of the 16-membered ring system in vancomycin.[114] This macrocyclization step is essentially one in which a diaryl ether is formed. Recently Chan[115a] and Evans[115b] reported methods for relatively mild Cu(II) acetate-promoted arylation of phenols with arylboronic acids. However, the use of their methodology with **2** and phenylboronic acid in our hands failed to produce any of the corresponding phenyl ethers such as **129**, affording only unreacted starting materials (Scheme 5.1).

In this regard, the finding was consistent with our earlier observations that attempted lower rim Suzuki-Miyaura coupling reactions with phenylboronic acid and



2: R = *tert*-butyl;
$R_1 = R_2 = R_3 = R_4 = H$

129 R = *tert*-butyl; R_1 = aryl;
$R_2 = R_3 = H$ ***and/or*** aryl

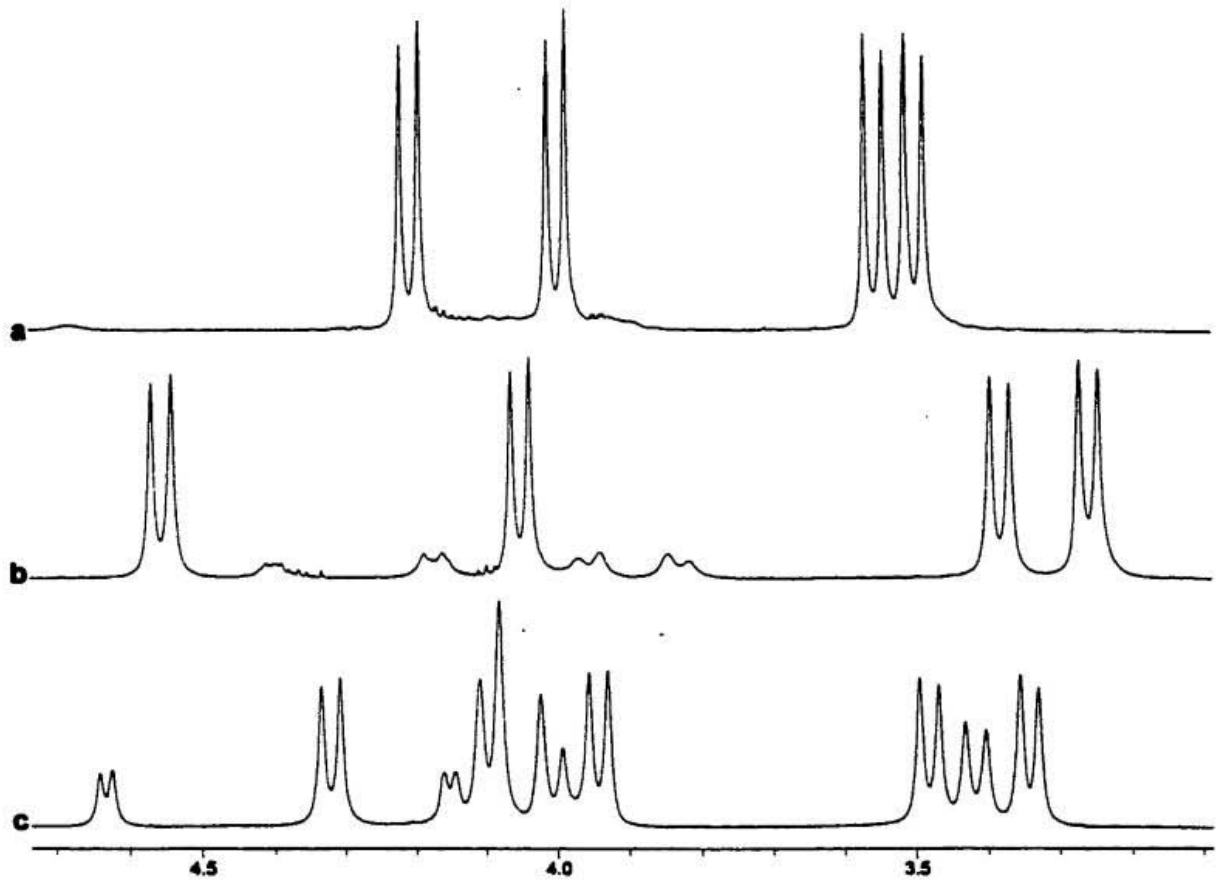
Scheme 5.1 Attempts to form phenyl ethers using Cu(II)acetate-promoted conditions

tert-butylcalix[4]arene triflates (**118-121**) proved also to be unsuccessful. This was presumably due to the steric crowding of the putative intermediates that would have led to the product.[34] When a nucleophilic aromatic substitution (S_NAr-based) reaction of **2** was employed with two molar equivalents of 4-fluoro-3-nitrobenzaldehyde (**130**) in the presence of K_2CO_3/DMF, the *tert*-butylcalix[4]arene monoaryl ether **131** was formed in 58% yield (Scheme 5.2).

130

131

Scheme 5.2 Synthesis of monoaryl ether compound 131



a) ^{1}H NMR spectrum of the methylene region in $CDCl_3$

b) ^{1}H NMR spectrum of the methylene region in C_6D_6

c) ^{1}H NMR spectrum of the methylene region in acetone-d_6

Figure 5.2 ^{1}H NMR spectra of the methylene region of compound 131

It was not immediately apparent from the ^{1}H NMR spectrum in $CDCl_3$ of chromatographically purified and crystalline **131** that it was indeed a single product. As shown in Figure 5.2a, the product appeared to be a mixture of conformers, as evidenced by the number of methylene proton signals in the ^{1}H NMR spectrum. A spectrum of the same sample recovered simply by evaporating the $CDCl_3$ and redissolving it in C_6D_6 (Figure 5.2b), showed a simpler pattern of signals. Nevertheless, the number of methylene signals still suggested that this was a mixture of conformers. The deuterated solvent was evaporated again, and this time the crystalline product was redissolved in acetone-d_6 to reveal an even simpler pattern of signals for the methylene protons (Figure 5.2c). The ^{1}H NMR spectrum of **131** in acetone-d_6 now revealed four distinct doublets centered at δ 3.53, 3.59, 4.04 and 4.25 with geminal coupling constants of J = 13.2, 13.7, 13.2 and 13.7 Hz respectively, suggesting that only a single compound existed in acetone-d_6 solution. The pattern of the methylene proton signals is consistent with that of a lower rim substituted *tert*-butylcalix[4]arene (**2**) existing in a *cone* conformation in the acetone-d_6 solution.[25] NOED experiments on **131** in C_6D_6 and in acetone-d_6 were also consistent for this assignment. The X-ray crystal structure of **131**, crystallized from benzene solution, clearly reveals its *cone* conformation in the solid state (Figure 5.3) and also reveals that the compound is a clathrate with three molecules of benzene contained in the lattice. One of the benzene molecules is situated within the cavity (or basket) of **131** and the other two are situated outside the cavity.

The ^{1}H NMR spectra of **131** both in $CDCl_3$ and C_6D_6 solutions suggest that the

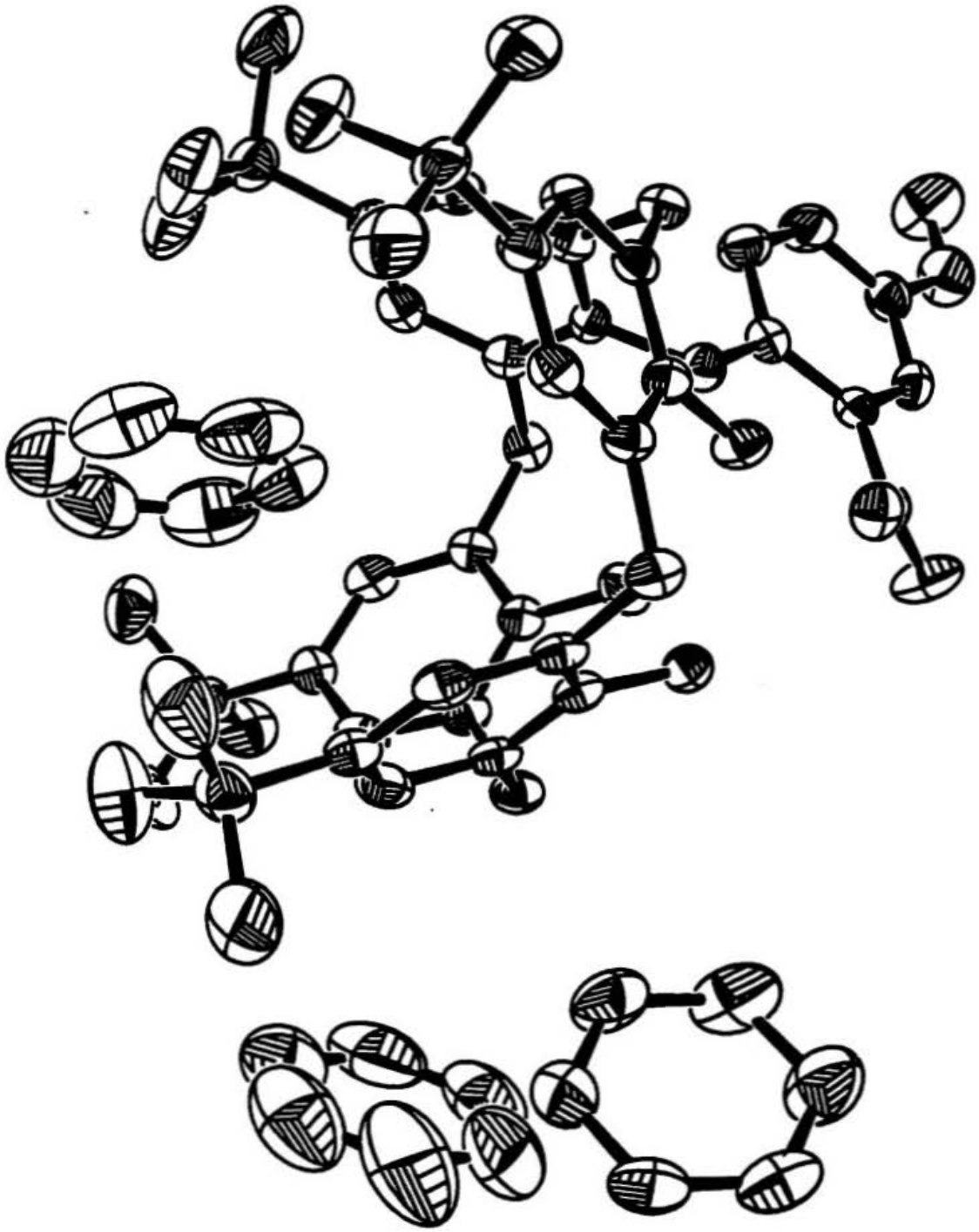
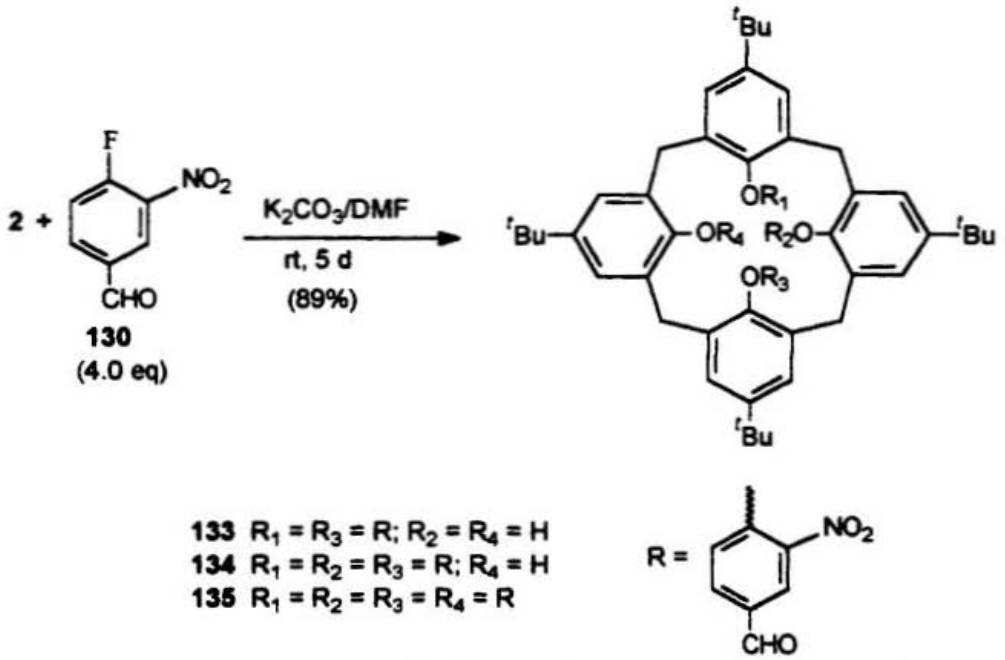


Figure 5.3 X-ray crystal structure of 131

molecule exists as a mixture of two conformers or possibly two atropisomers which could be due to the restricted rotation of the aryl group on the lower rim of **2**. The ^{1}H NMR spectrum of **131** in acetone-d_6 shows that only one conformation of the molecule is present in the solution. Variable-temperature ^{1}H NMR experiments on **131** in DMSO-d_6 over the temperature range of 223 to 323 K revealed only that the relative concentration of the minor component increased with increasing temperature, but the spectra did not provide an unequivocal answer as to the exact origin of the extra methylene proton signals in the ^{1}H NMR spectrum of **131**. The fact that a similar phenomenon was not observed with the corresponding hydroxymethyl compound (**132**) (see structure **132** in Scheme 5.8, p 205), suggested that the minor component is probably not an atropisomer.

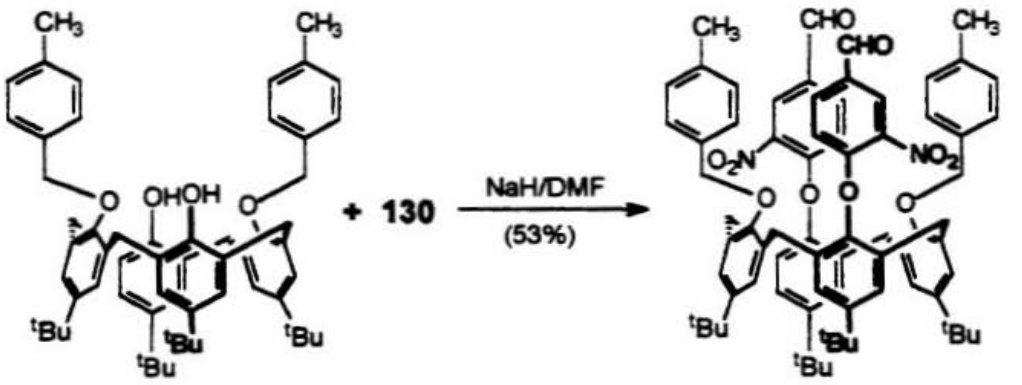
Examination of CPK molecular models revealed an interesting tetra-*O*-arylether-calix[4]arene structure with two π-electron-rich cavities: the "normal" calix[4]arene cavity (the "upper rim"), and another cavity which can be formed on the lower rim as a result of the aryl ether formation. An attempt to obtain the tetra-*O*-aryl ether of **2** using the S_NAr methodology was therefore undertaken by reacting **2** with four molar equivalents of **130** in the presence of K_2CO_3/DMF. The products obtained in 89% combined yield were the di- (**133**), tri- (**134**) but not tetra-*O*-aryl ethers (**135**) (Scheme 5.3). The mixture of **133** and **134** could not be completely resolved using flash column chromatography. The (+)-FAB mass spectrum of the mixture however indicated the presence of molecular ions, most likely due to **133** and **134**. Table 5.1



Scheme 5.3 Attempts to form tetra-O-aryl ether derivatives of 2

lists several other aryl halide substrates, some of which contain electron-withdrawing substituents and which were evaluated for their reactivities with **2** and its derivative. With the exception of aryl halides listed in Entries 3, 4 and 5, all were capable of forming the corresponding ethers with **2** and its derivative. In order to ascertain whether or not the potential steric crowding by having four aryl groups on the lower rim of the calixarene could have been a factor inhibiting the formation of the tri- or tetra-*O*-aryl ethers, 1,3-di-*O*-benzyl-*tert*-butylcalix[4]arene[9] (**136**) was treated with **130** using NaH in DMF (Entry 2). The reaction successfully afforded the 1,3-di-*O*-benzyl-2,4-di-*O*-aryl ether **137** in 53% yield (Scheme 5.4). In the ^{1}H NMR spectrum, the two doublets due the methylene protons clearly defined AB systems centered at δ 2.86 and 3.98 (J = 14.1 and 12.9 Hz, respectively) and a signal at δ 31.3 in the ^{13}C

NMR spectrum established that the compound exists in a *cone* conformation.[12, 26]

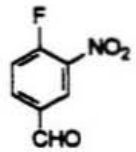
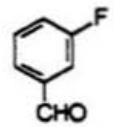
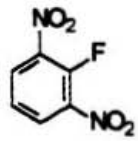
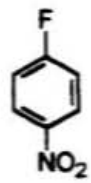


136 **137**

Scheme 5.4 Synthesis of di-*O*-benzyl-di-*O*-aryl compound 137

An interesting feature in the ^{1}H NMR spectrum of **137** is the large upfield shift for the axial and equatorial protons of the methylene group in the calixarene ring. The chemical shifts observed for the axial and equatorial protons are at δ 3.20 and 4.22 in the starting calixarene **136**, and are shifted to δ 2.86 and 3.98, respectively, in compound **137**. In the 1,3-di-*O*-benzyl-2,4-di-*O*-aryl ether derivative **137**, the aryl ether groups are most likely oriented in "*pinched cone*" conformation, and the methylene groups are therefore in the proximity of the shielding region of the neighboring aryl rings. When the signal at δ 2.86 (equatorial methylene proton) was irradiated in an NOED experiment, the signals at δ 3.98, 6.39 (proton *meta* to the nitro group in the *O*-aryl pendant) and 6.97 (proton *ortho* to the benzyl methylene) were enhanced by 12%, 4% and 7%, respectively. The NOED experiment confirms that the aryl ether groups are in the proximity of the methylene protons, therefore the

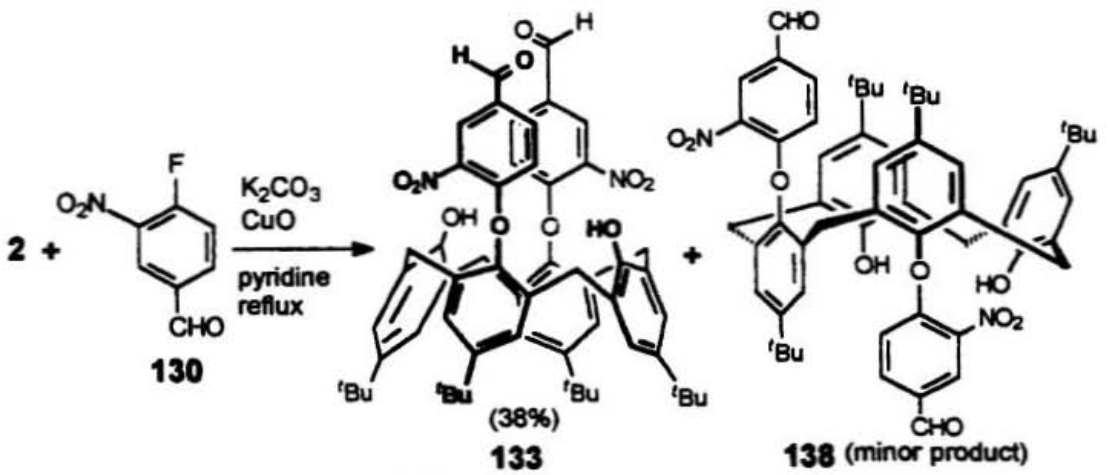
Table 5.1. Reactions of aryl halides with 2 and 136

Entry	Substrates	Conditions*	Product(s)
1	**2** +  **130**	A or B	**131, 133, 134,138**
2	**130 + 136**	C	**137**
3	**2** + 	A	**NR**
4	**2** + 	A	**NR**
5	**2** + 	A	**NR**
6	**2 + 141**	B	**139, 140**
7		B	**142, 143**

Conditions* A: ArF (2 equiv for entry 1 and excess for entries 3, 4 and 5)/K_2CO_3/DMF; B: ArF (excess)/K_2CO_3/CuO/pyridine; C: ArF (4.5 equiv)/NaH/DMF

π-electrons of the aryl ether groups shield these protons causing the signal to be upfield. Similarly, irradiation of the signal at δ 3.98 (axial methylene proton) enhanced the signals at δ 2.86, 5.47 (benzylic protons) and 6.99 (calixarene aromatic proton) by 10%, 6% and 3%, respectively. The downfield shift for the benzylic protons from δ 5.00 to 5.47 can be explained by the deshielding effect from the presence of strong electron-withdrawing nitro groups on aryl ether ring in proximity of the benzylic group. The *1,3-alternate* structure would not likely have resulted in the observed downfield shift. Furthermore, the single ^{13}C signal due to the methylene bridges at δ 31.3 ("de Mendoza Rule" [12,26]) supports the assignment of a *cone* conformation. It is thus possible to functionalize the lower rim of **2** with two aryl ether and two benzyl ether pendants using S_NAr type reaction conditions. This experiment suggested that steric crowding therefore, should not be a factor inhibiting potential tetra-O-arylation. The use of Ullman[116] ether forming conditions with **2** and the aryl halides were then evaluated.

When three molar equivalents of **130** were reacted with **2** using Ullman conditions (K_2CO_3/CuO/pyridine, reflux), mono- and di-O-aryl ethers **131** and **133** were each obtained in 38% yields (Entry 1) after facile separation by flash column chromatography (Scheme 5.5). The ^1H NMR spectrum of **133** revealed two doublets centered at δ 3.22 and 4.00 with geminal coupling constant J = 13.6 Hz due to the methylene protons of the calixarene ring. The ^{13}C NMR spectrum shows the corresponding methylene carbons at δ 31.0 and 31.5, respectively which, according to the de Mendoza Rule is typical for 1,3-disubstituted calix[4]arenes in the *cone*



Scheme 5.5 Synthesis of di-*O*-aryl compound 133 and 138 using Ullmann aryl ether-forming conditions

conformation in solution. A single crystal X-ray structure however showed it to be a *proximally* (i.e., 1,2-) disubstituted compound in a *partial cone* conformation (**138**) (Figure 5.4). The X-ray structure shows that the two aryl ether groups are situated *trans* to each other, with one being "sandwiched" between two adjacent *tert*-butyl-bearing phenyl rings, within the calixarene basket. The other aryl ether group is twisted outside of the cavity or basket. The *partial cone* 1,2-disubstituted structure for **138** does not fit with the ^{1}H and ^{13}C NMR spectra of bulk isolated product discussed above. Therefore, one possible explanation for the X-ray crystal structure is that it is due to a minor product **138**, which formed during the reaction between **2** and **130** but was not detected in either the ^{1}H and ^{13}C NMR spectra.

Ullman aryl ether-forming conditions[116] were also employed using two molar equivalents of ethyl-4-fluoro-3-nitrobenzoate (**141**) with **2** to afford mono-*O*-aryl and di-*O*-aryl ether products, **139** and **140** in 57% and 19% yields, respectively (Table

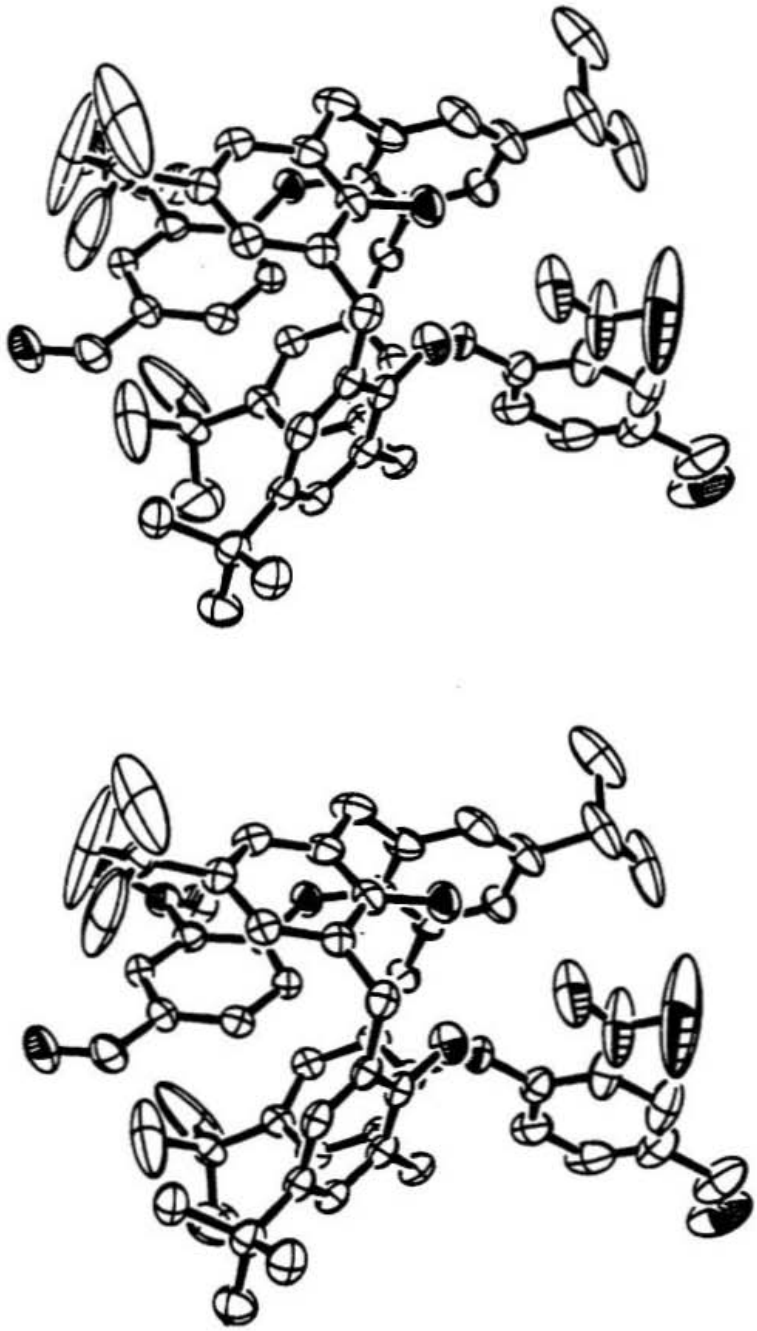
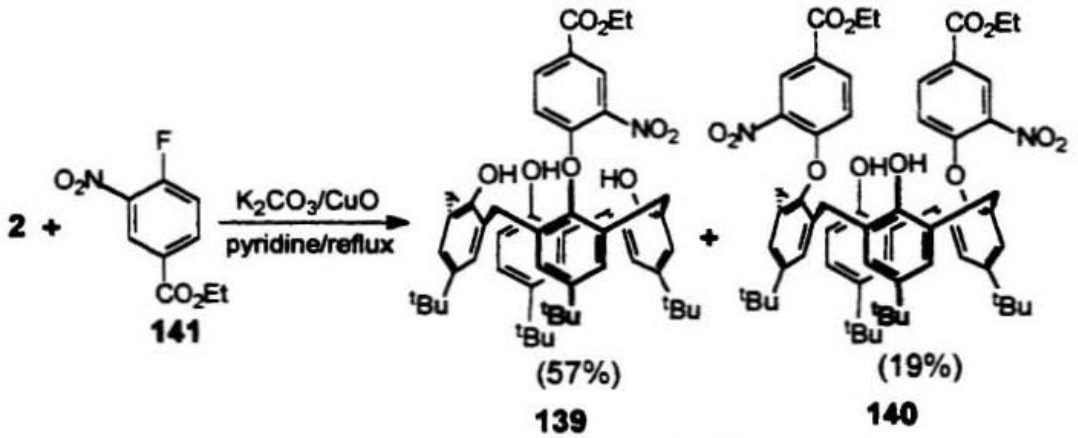


Figure 5.4 Stereoview X-ray crystal structure of compound 138

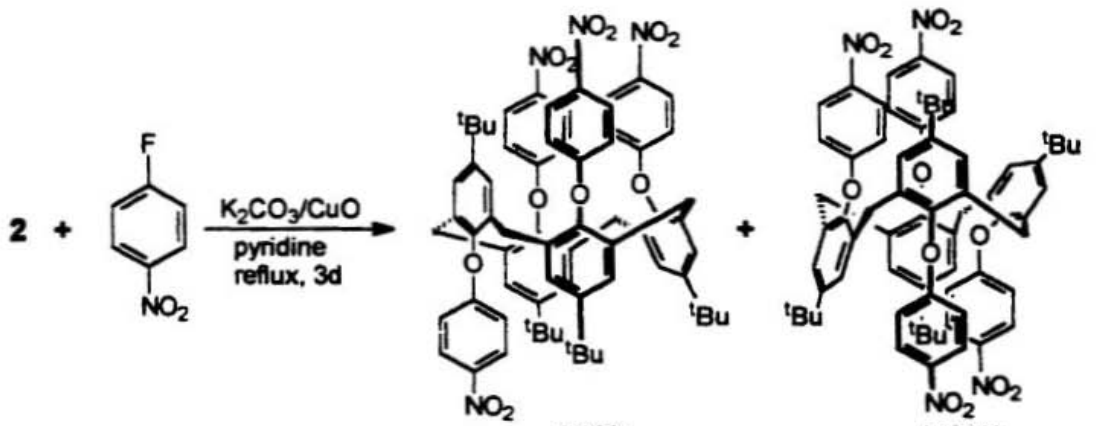


Scheme 5.6 Synthesis of compounds 139 and 140

5.1, Entry 6). Analysis of the ^{1}H NMR and ^{13}C NMR spectra of **139** and **140** indicate that both products exist in *cone* conformations in solution (Scheme 5.6). With four molar equivalents of **141**, only **139** and **140** were obtained, this time in 73% and 21% yields respectively, with no evidence of tri- or tetra- substituted aryl ethers having being formed. Overall, however, the work-up of reaction products obtained from the Ullmann procedure was generally more convenient than that from the K_2CO_3/DMF procedure.

5.3 Synthesis of tetra-*O*-aryl ether derivatives of *para-tert*-butylcalix[4]arene

To obtain tetrasubstituted *O*-aryl ethers of **2**, the efficacy of both Ullmann coupling and S_NAr conditions was evaluated. Reaction of **2** with four molar equivalents of 1-fluoro-4-nitrobenzene gave **142** as the major product in 46% yield and another minor product, **143** in 16% yield (Scheme 5.7). The structure of compound **142** was unambiguously confirmed by NMR analysis (^{1}H, ^{13}C and 2D NMR) and mass spectrometry to be the expected tetra-*O*-aryl ether derivative of **2**,



Scheme 5.7 Synthesis of tetra-*O*-aryl compounds 142 and 143 using Ullmann aryl ether-forming conditions

and found to be in a *partial cone* conformation. The assignments of the ^{1}H and ^{13}C NMR spectra were based upon the cross-peak correlations in the COSY spectrum shown in Figure 5.5, and by analysis of the HMQC spectrum, which shows the correlations of directly bonded ^{1}H and ^{13}C nuclei. The ^{1}H NMR spectrum of **142** in CD_2Cl_2 includes three signals at δ 1.14,1.44 and 1.63 in a 1:2:1 ratio, which can be assigned to the three different *tert*-butyl groups. The doublets due to the methylene protons clearly defines AB systems centered at δ 3.10, 3.30, 3.38 and 3.40 with geminal coupling constants of J = 15.0 and 13.0 Hz, respectively. The ^{13}C NMR spectrum shows a pattern that is consistent for that of calix[4]arene in a *partial cone* conformation,[12,26] and shows eight upfield resonances due to the quaternary carbons (δ 34.7, 36.1 and 35.4), the methyl carbons of the *tert*-butyl groups (δ 31.7, 31.9 and 32.5) and the methylene carbons (δ 31.0 and 37.4). The methylene carbon signals at δ 31.0 and 37.4 deviate only slightly from the positions typically found at δ 31.1

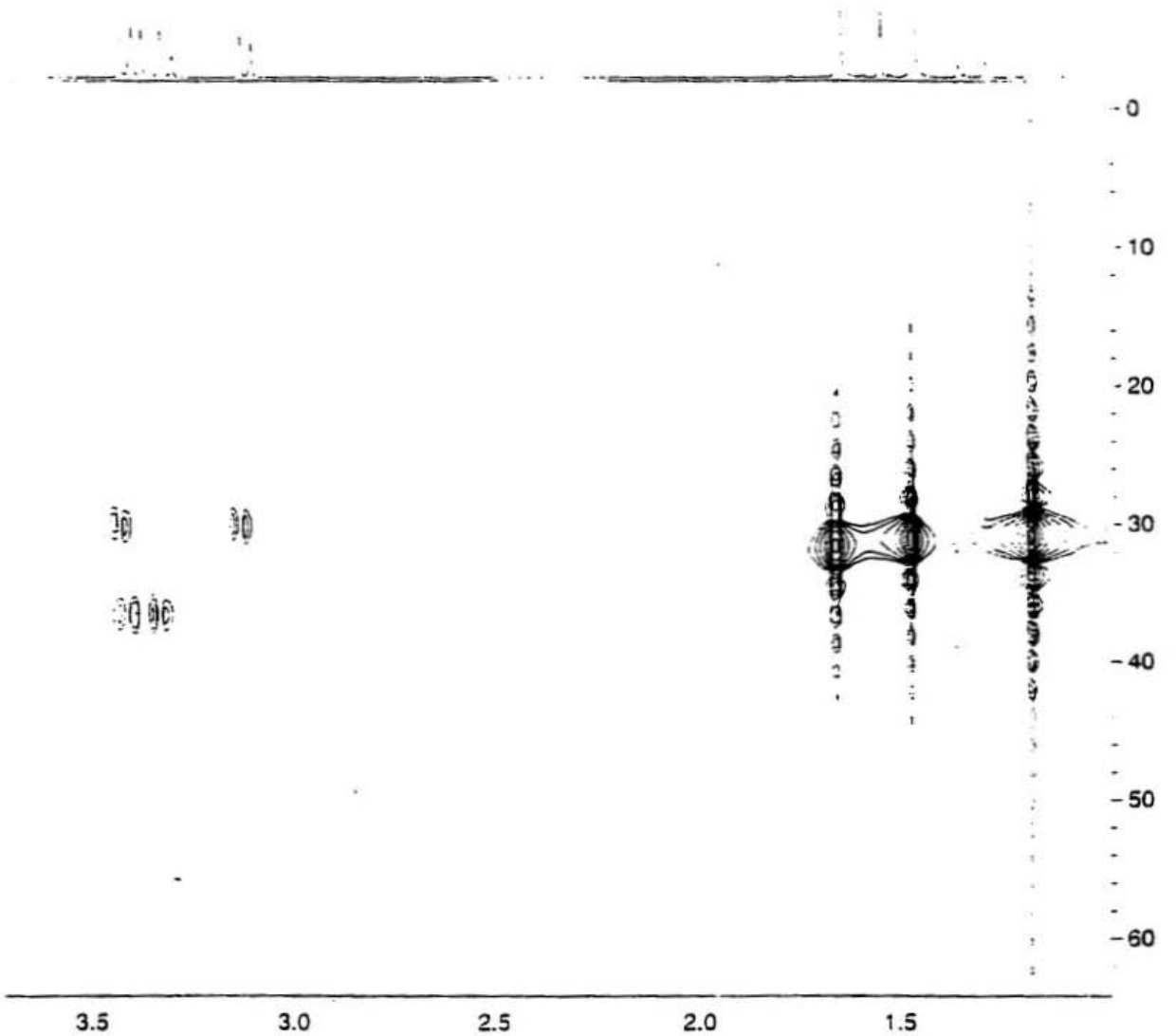


Figure 5.5 **^{1}H COSY spectrum of the methylene region of compound 142**

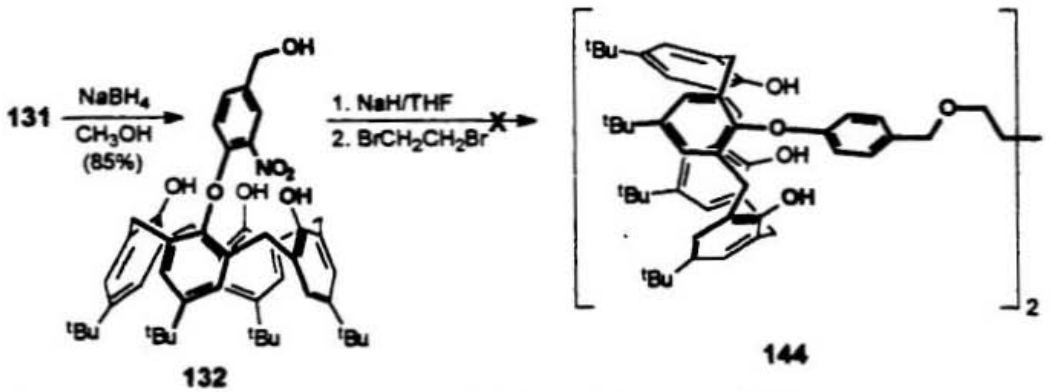
and 37.0 as described by de Mendoza *et al.*[12,26] for calix[4]arenes in the *partial cone* (*paco*) conformation. The downfield resonances, consisting of 22 signals arising from the aromatic carbons, are in agreement with the predicted structure. Finally, additional support for the structure proposed was obtained by CI MS analysis, which showed a molecular ion peak at the expected value of *m/z* = 1132. The minor product **143** is also a tetra-*O*-aryl ether derivative of **2**. It exists in the *1,2-alternate* conformation in solution. Its structure was determined by NMR analysis (^{1}H, ^{13}C and 2D NMR), and its molecular mass was confirmed by CI MS measurements. The ^{1}H NMR spectrum of **143** in CD_2Cl_2 was very simple. A singlet at δ 1.25 due to the *tert*-butyl protons, the pair of doublets centered at δ 3.20 and 3.57 having geminal coupling constant of J = 12.5 Hz, and a singlet at δ 3.40 for the methylene protons strongly suggested that **143** has C_2 symmetry and is in a 1,2-*alternate* conformation (Scheme 5.7). The aromatic signals at δ 5.98 with coupling constant of J = 8.0 Hz can be assigned to the protons on the aryl ether groups that are *ortho* to the oxygen atom. The doublet at δ 5.98 is due to the aryl ether group which is located inside the basket in a 1,2-*alternate* conformation and which is thus being shielded by the *distal* calixarene aromatic units. The proton which is *ortho* to the strongly electron-withdrawing nitro group on the aryl ether pendant appears as a doublet at δ 7.83 with a coupling constant of J = 9.0 Hz. A proton *ortho* to a strongly electron-withdrawing group such as a nitro group, would be expected to appear further downfield than δ 7.83 compared to δ 8.1 for *p*-nitroanisole,[117] but in this case, it is assumed that the proton is located in the shielding region of the aromatic rings of

calixarene and therefore appears upfield. The ^{13}C NMR spectrum of **143** exhibits signals at δ 30.4 and 38.5 due to the methylene carbons while the signals at δ 31.9 and 34.9 are due to the methyl and quaternary carbons of the *tert*-butyl groups, respectively. The chemical shifts of the methylene carbons are consistent for calixarenes having a *1,2-alternate* conformation in solution.[12, 28] CI MS analysis of compound **143** showed a molecular ion peak at the expected *m/z* = 1132.

It has thus been demonstrated that either Ullmann or S_NAr conditions can be employed to synthesize for the first time, mono- to tetra-*O*-aryl ether derivatives of *tert*-butylcalix[4]arene (**2**) in good yields.

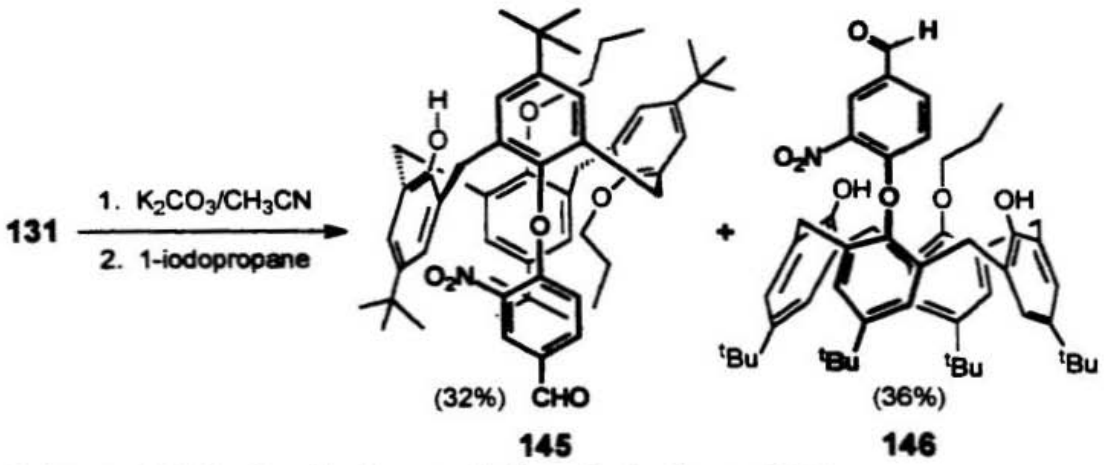
5.4 Attempts at the synthesis of double calix[4]arenes

During the past decade, several double (or multiple) calixarenes have been prepared as examples of higher order molecular architectures.[12] These molecules have calixarene units linked either at their upper or at their lower rims through one or more "spacer" (units or groups). The spacers that have been used generally include alkyl, alkenyl, and alkynyl chains, diesters, diamides, ethers, polyethers, anisyl, pyridyl, bipyridyl and metallocenyl groups linked at the lower rim of the calixarenes.[12] Recently, Neri *et al.*[117] reported the synthesis of 5,5'-bis(calix[4]arene), an example of a double calixarene of the "head-to-head" type with a direct *para-para* linkage, via Pummerer's conditions[118] using $FeCl_3.6H_2O$ in CH_3CN. These double calixarenes are of interest due to their higher level of potential host properties, such as allostery and cooperativity. Since mono-*O*-aryl ether derivatives of **2** have been successfully synthesized using either Ullmann or S_NAr conditions, the



Scheme 5.8 Attempts to form double calixarenes 144

focus now was to synthesize double calixarenes such as **144**, linked at the lower rim with an aryl ether group serving as a spacer. Compound **131** was thus subjected to $NaBH_4$ reduction to afford the corresponding alcohol **132**, which would serve as the direct precursor towards **144** in 85% yield as outlined in Scheme 5.8. The structure of **132** was determined by NMR analysis (^1H, ^{13}C and 2D NMR). The ^1H NMR spectrum shows four doublets corresponding to the methylene protons centered at δ 3.26, 3.43, 3.98 and 4.31 and having coupling constants of J = 13.0, 13.5, 13.0 and 13.5 Hz, respectively. The ^{13}C NMR spectrum of compound **132** contains nine aliphatic signals along with twenty aromatic signals in the low-field region which are in good agreement with the structure depicted. In particular, ^{13}C NMR chemical signals at δ 32.6 and 33.3 due to the methylene bridge carbon atoms indicate that **132** is in a *cone* conformation. Attempted coupling of **132** with 1,2-dibromoethane in the presence of NaH in THF, however, did not afford the expected double calix[4]arene product **144** (Scheme 5.8). The ^1H and ^{13}C NMR spectra of the



Scheme 5.9 Synthesis of propyl ether derivatives of 131

product did not provide conclusive evidence to allow for the determination of its structure. It was presumed that the free phenolic groups of **131** could interfere in the coupling reactions and also that 1,2-dibromoethane might not be a suitable 'spacer' molecule. The free hydroxyl groups in **131** were therefore first protected before attempting the coupling reactions with excess 1-iodopropane in the presence of K_2CO_3 in acetonitrile, the mono-*O*-aryl-dipropyloxy-*tert*-butylcalix[4]arene **145** and the mono-*O*-aryl-propyloxy-*tert*-butylcalix[4]arene **146** were formed in 32% and 36% yields, respectively (Scheme 5.9). The structures of **145** and **146** were determined in the usual manner, by NMR analysis (^1H and ^{13}C and 2D NMR) and were corroborated by their CI mass spectra, which showed molecular ion peaks at their expected values *m/z* = 882 and 840, respectively. The eight methylene protons of structure **145** appear as a set of six doublets due to three clearly defined AB systems and a singlet (in a 1:1:1:1:2:2 ratio). These doublets are centered at δ 2.99, 3.36, 3.53, 3.86 and 3.97 (the later consisting of a pair of overlapping doublets) with

typical geminal coupling constants (J ~ 13 to 15.5 Hz), and a two-proton sharp singlet at δ 3.94. The signal at δ 3.97 is most probably due to the equatorial proton(s) of the methylene groups. The equatorial proton (the signal at δ 3.97) is positioned *trans* with respect to the pair of propyloxy-bearing aromatic ring of the calixarene. As such, the methylene protons (the signal at δ 3.97) would therefore be *pseudo*-axial and *pseudo*-equatorial and thus would be expected to have a relatively small chemical shift difference. Compound **145** is therefore most likely *proximally* dipropyloxy-substituted in a *1,2-alternate* conformation. The presence of cross-peaks in the COSY spectrum (Figure 5.6) between the methylene protons (δ 2.99 and 3.97, 3.36 and 3.94, 3.53 and 3.86) are in agreement with the assigned structure. There are signals at δ 31.3, 32.9, 39.1 and 39.6 that can be assigned to the methylene bridges, their positions being consistent with the ^{13}C NMR signal patterns identified by de Mendoza *et al.*[26] to be typically that of a calix[4]arene in the *1,2-alternate* conformation. The ^{13}C NMR signals at δ 39.1 and 39.6 are more deshielded than the generally reported values for such a *1,2-alternate* conformation.[26] The ^{1}H NMR spectrum of **145** also reveals a strong upfield shift for the methyl protons of one of the propyloxy groups, which is most likely located in the shielding region (cavity) of the calixarene (Scheme 5.9). The triplet centered at the exceptionally high field position at δ 0.04 (J = 7.3 Hz), coupled to the multiplet at δ 0.92 (J = 7.3 Hz) are assigned to the methyl protons adjacent to the central methylene protons ($H_3C\underline{C}H_2CH_2O$) of the propyloxy group. Interestingly, the OCH_2 signals of one of the propyloxy group ($H_3CCH_2\underline{C}H_2O$) centered at δ 3.60 and 4.11,

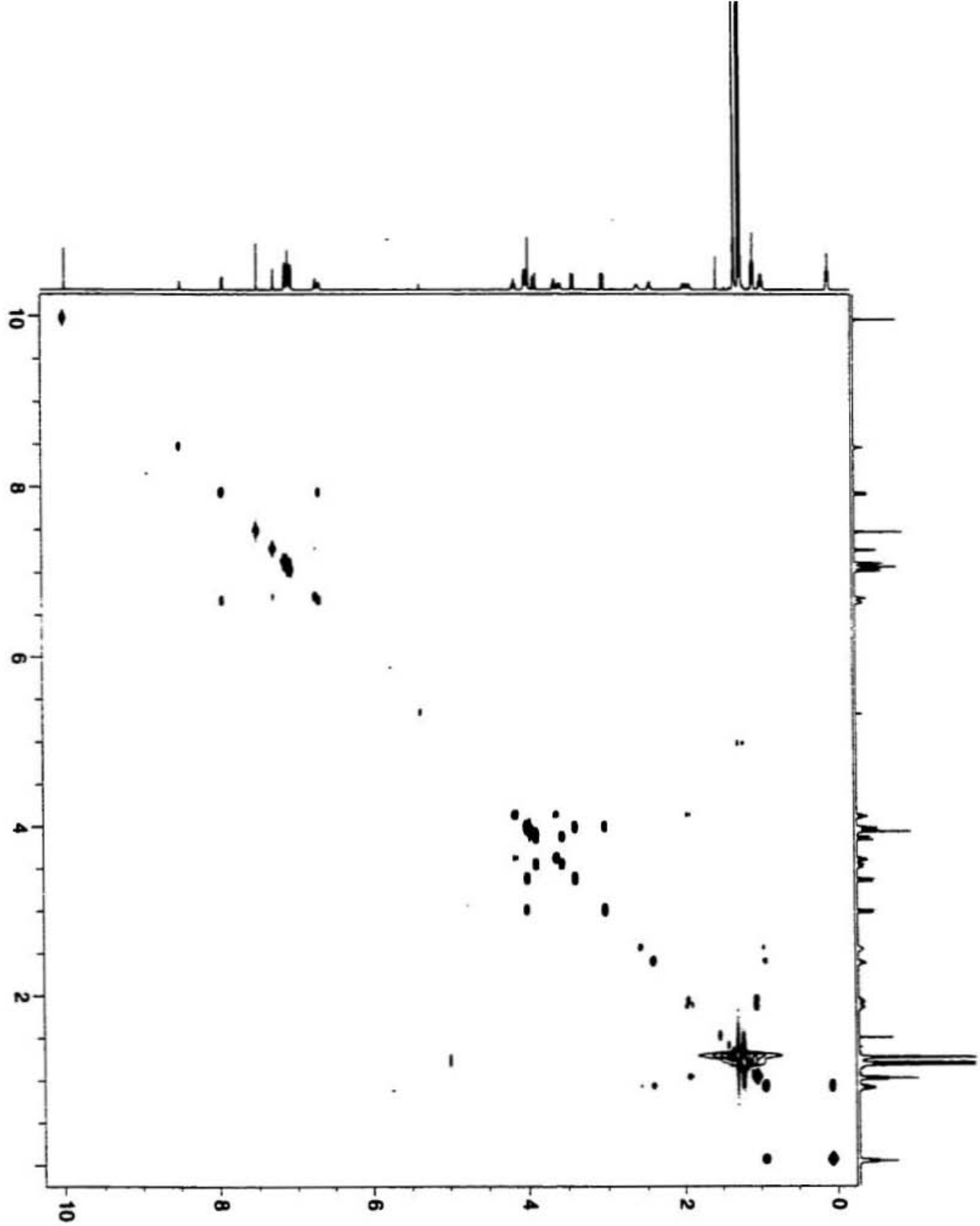


Figure 5.6 ^{1}H COSY spectrum of compound 145

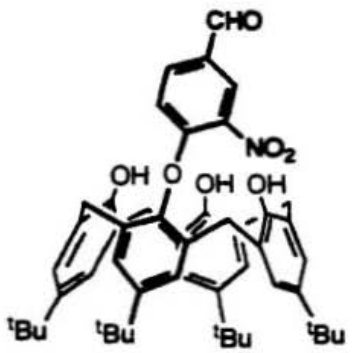
while for the other propyloxy group they are upfield, at δ 2.39 and 2.55. These signals clearly indicate that these methylene protons are diastereotopic. No similar diastereotopicity for the protons of simple propyloxy-bearing calix[4]arenes have been noted by others. Both ^{1}H and ^{13}C NMR spectra of compound **146** is consistent with the proposed structure. Compound **146**is *distally* substituted and exists in a *cone* conformation. These findings are consistent with the results reported earlier for the diastereotopicity observed with the propyloxy derivatives of *tert*-butylcalix[4]naphthalene (**31**) and calix[4]naphthalene (**35**) (Chapter 2 and Chapter 3).

In conclusion, both S_NAr or Ullmann ether conditions can be used to functionalize the lower rim of *tert*-butylcalix[4]arene (**2**). It has been shown that one or more free hydroxyl groups of **2** can be selectively derivatized with readily-available aryl fluorides containing electron-withdrawing groups. The ^{1}H NMR spectrum of **131** was most intriguing, revealing one or more conformers to be present in $CDCl_3$ and in benzene-d_6 solution, but only one to be present in acetone-d_6 and that one being the *cone* conformation. The X-ray crystal structure of **131** confirmed the molecule having a *cone* conformation. Other interesting structural features appeared in the ^{1}H and ^{13}C NMR spectra of **145**, which show a very strong upfield signal at δ 0.04 for the methyl group of a propyl ether on the molecule, and that the molecule exits in an *1,2-alternate* conformation under the conditions examined. The most significant result found overall is that compounds **142** and **143** could be produced,

showing that all the hydroxyl groups can be functionalized, thus opening up many possibilities for calixarene structural modifications. Furthermore, these prototype tetra-*O*-aryl ethers can be shown to exist as two different stable conformers, compound **142** existing in the *partial cone* conformation, and **143** in a *1,2-alternate* conformation.

5.5 Experimental Section: For general methods, see Chapter 2.

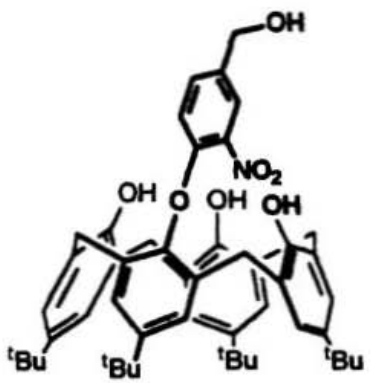
5, 11, 17, 23-Tetra-*tert*-butyl-25-mono-(4-formyl-2-nitrophenoxy)calix[4]arene-26, 27, 28-triol (*cone* conformer) (131).



A mixture of **2** (1.01 g, 1.57 mmol), 4-fluoro-3-nitrobenzaldehyde (**130**) (0.53 g, 3.13 mmol), and powdered anhydrous K_2CO_3 (1.73 g, 12.5 mmol) in anhydrous DMF (15.7 mL) was stirred at room temperature under argon for 5 days. The black mixture was diluted with ethyl acetate (50 mL), and the precipitate was removed by filtration. The organic layer was washed with aqueous 10% HCl (2 x 10 mL), with brine (15 mL), dried over anhydrous $MgSO_4$ and filtered. The organic solvent was evaporated and the residue was purified by flash column chromatography eluting with ethyl acetate-hexane 20:80 to afford **131** (0.97 g, 58%) as a light yellow solid:

mp 178-80 °C; ^{1}H NMR (500 MHz, acetone -d_6) δ 1.20 (s, 9H), 1.14 (s, 9H), 1.23 (s, 18H), 3.53 (d, J = 13.3 Hz, 2H), 3.59 (d, J = 14.7 Hz, 2H), 4.04 (d, J = 13.1 Hz, 2H), 4.25 (d, 13.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 1H), 7.21 (s, 2H), 7.27 (d, J = 1.9 Hz, 2H), 7.32 (d, J = 1.9 Hz, 2H), 7.44 (s, 2H), 8.19 (dd, J = 1.8, 8.7 H, 1H), 8.42 (s, 2H, OH), 8.74 (d, J = 1.8 Hz, 1H), 10.11 (s, 1H); ^{13}C NMR (125 MHz, acetone -d_6) δ 30.9, 31.4, 31.6, 32.0, 32.3, 32.4, 33.3, 33.9, 34.3, 34.5, 117.1, 121.0, 125.8, 126.6, 127.0, 127.8, 129.6, 131.2, 132.8, 133.6, 139.9, 143.4, 144.2, 144.9, 147.1, 150.3, 156.4, 188.2; (+)-FAB MS (*m/z*), relative intensity (%): 797 (100, M$^+$), 782 (20), 740 (15), 630 (72), 611 (25).

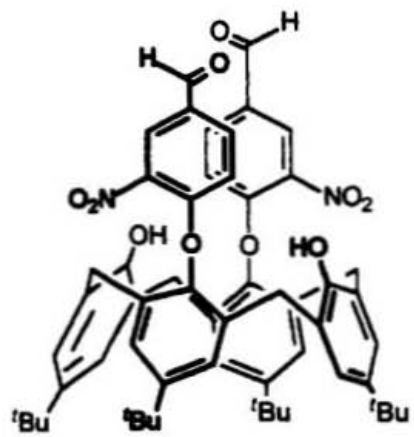
5,11,17,23-Tetra-*tert*-butyl-25-(4-hydroxymethyl-2-nitrophenoxy)calix[4]arene-26,27,28-triol (*cone* conformer) (132).



To a solution of **131** (258 mg, 0.33 mmol) in methanol (10 mL) was added in one portion $NaBH_4$ (65 mg). The reaction slurry was stirred at room temperature for 2 h, the solvent was evaporated on a rotary evaporator, the residue diluted with CH_2Cl_2 (25 mL), and the resulting solution washed with saturated aqueous NH_4Cl

(3x10 mL). The organic solution was dried over anhydrous $MgSO_4$ and filtered. After the solvent was evaporated, the yellow residue was purified by flash chromatography, eluting with ethyl acetate-hexane 30:70, to afford **132** (0.23 g, 85%): mp 160-162 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 0.90 (s, 18H), 1.00 (s, 18H), 1.25 (s, 1H), 3.36 (d, *J* = 13.3 Hz, 2H), 3.46 (d, *J* = 13.8 Hz, 2H), 4.17 (s, 2H), 4.29 (d, *J* = 13.3 Hz, 2H), 4.66 (d, *J* = 13.8 Hz, 2H), 6.60 (d, *J* = 8.6 Hz, 1H), 6.95 (m, 3H), 7.29 (m, 6H), 7.84 (s, 1H). 9.24 (s, 2H, OH), 10.01 (s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 31.0, 31.5, 32.6, 33.3, 33.9, 34.3, 34.5, 62.5, 116.5, 125.1, 125.9, 126.5, 126.8, 127.5, 127.7, 128.5, 128.8, 132.8, 133.3, 136.5, 140.0, 143.2, 144.2, 145.2, 147.2, 149.8, 150.4, 151.9; (+)-FAB MS *(m/z)*, relative intensity (%): 799 (M^+, 100), 798 (75), 781 (5), 764 (15), 743 (12), 708 (8).

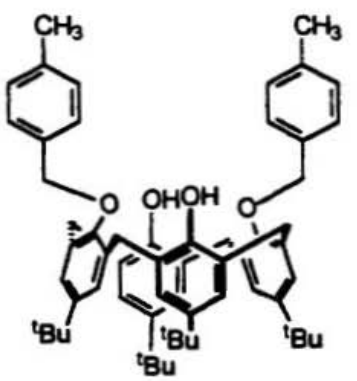
5,11,17,23-Tetra-*tert*-butyl-25,26-di-(4-formyl-2-nitrophenoxy]calix[4]arene-27,28-diol (*cone* conformer) (133)



A mixture of **2** (324 mg, 0.50 mmol), **130** (169 mg, 1.00 mmol), K_2CO_3 (278 mg, 1.00 mmol), CuO (158 mg, 1.00 mmol) in anhydrous pyridine (10 mL) under argon was

heated at reflux for 24 h. TLC showed the presence of the mono-aryl ether product **131**, so an additional equivalent of **130** was added and the reaction was refluxed for a further 24 h. The mixture was then cooled to room temperature and the precipitate was removed by filtration. The organic layer was diluted with CH_2Cl_2 (50 mL), washed with aqueous 10% $NaHSO_4$, then with water, dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate-hexane 20:80 to afford **131** (0.15 g, 38%) and **133** (0.19 g, 38%): mp 252-254 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (s, 18H), 1.31 (s, 18H), 3.22 (d, *J* = 13.6 Hz, 4H), 4.00 (d, *J* = 13.6 Hz, 4H), 5.90 (s, H), 6.79 (s, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.06 (s, 4H), 7.98 (dd, *J* = 1.9, 8.8 Hz, 2H), 8.95 (d, *J* = 1.9 Hz, 2H), 9.99 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.9, 31.0, 31.5, 34.8, 125.2, 126.3, 127.3, 129.0, 130.1, 131.6, 134.0, 139.9, 142.0, 144.5, 149.1, 150.1, 150.4, 156.7, 188.8; (+)-FAB MS (*m/z*), relative intensity (%): 946 (M^+, 100), 931 (28), 874 (20).

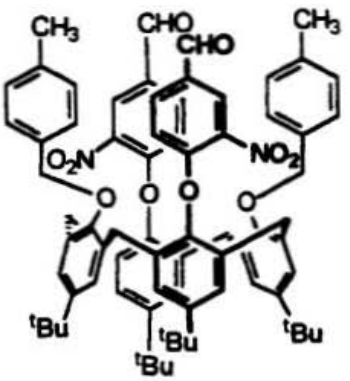
5,11,17,23-Tetra-*tert*-butyl-25,27-di-(4-methylbenzyl)calix[4]arene-26,28-diol (*cone* conformation) (136)



136

A mixture of **2** (1.00 g, 1.35 mmol), 4-methylbenzyl bromide (1.14 g, 6.16 mmol) and K_2CO_3 (2.13 g, 15.4 mmol) in acetone (25 mL) was refluxed for 6 h. After cooling, the reaction mixture was diluted with H_2O, and the organic layer was extracted with $CHCl_3$, dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by column chromatography eluting with ethyl acetate-hexane 15:85 to afford **136** (0.86 g, 74%) as a colourless solid: ^{1}H NMR δ 0.95 (s, 18H), 1.28 (s, 18H), 2.41 (s, 6H), 3.25 (d, *J* = 13.2 Hz, 4H), 4.27 (d, *J* = 13.0 Hz, 4H), 5.01 (s, 4H), 6.78 (s, 4H), 7.03 (s, 4H), 7.17 (d, *J* = 7.9 Hz, 4H), 7.36 (s, 2H), 7.52 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR δ 21.3, 31.0, 31.7, 33.8, 33.9, 77.9, 124.9, 125.4, 126.2, 127.5, 127.7, 129.2, 132.6, 134.2, 137.3, 141.2, 146.8, 149.8, 150.8; (+)-FAB MS (*m/z*): 857 (M^+, 18), 801 (21), 734 (25), 612 (40), 428 (38), 337 (77), 175 (100).

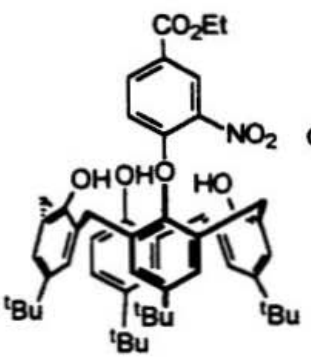
5,11,17,23-Tetra-*tert*-butyl-25,27-di-(4-formyl-2-nitrophenoxy)-26,28-di-[(4-methylbenzyl)oxy]calix[4]arene (*cone* conformer) (137)



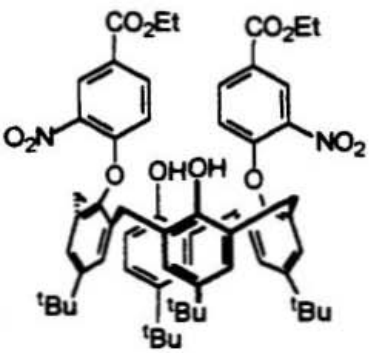
A mixture of **136** (373 mg, 0.43 mmol), **130** (333 mg, 1.97 mmol) and NaH (60% suspension in oil, 114 mg, 2.96 mmol) in DMF (5 mL) was stirred at room temperature for 3 d. The dark reaction mixture was diluted with ethyl acetate, washed with two portion of water, saturated aqueous NH_4Cl, and dried over

anhydrous $MgSO_4$ and filtered. After the solvent was evaporated, the residue was purified by preparative TLC, eluting with ethyl acetate-hexane 20:80, to afford **137** (264 mg, 53%) as a colourless solid: mp 275-277 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 18H), 1.29 (s, 18H), 2.18 (s, 6H), 2.86 (d, *J* = 14.1 Hz, 4H), 3.98 (d, *J* = 12.9 Hz, 4H), 5.46 (s, 4H), 6.39 (d, *J* = 8.9 Hz, 2H), 6.53 (s, 4H), 6.81 (d, *J* = 7.8 Hz, 4H), 6.97 (s, 4H), 6.99 (d, *J* = 8.9 Hz, 4H), 7.77 (dd, *J* = 1.8, 8.4 Hz, 2H), 8.45 (d, *J* = 1.8 Hz, 2H), 9.95 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 31.1, 31.3, 31.7, 33.9, 34.0, 74.6, 125.6, 125.7, 127.9, 128.1, 129.4, 130.4, 131.9, 133.7, 134.3, 135.3, 137.0, 139.7, 145.2, 146.0, 147.4, 151.7, 157.6, 188.8; MS CI (*m/z*), relative intensity (%): 1153 (M^+-1, 30), 1099 (92), 1042 (31), 992 (15), 958 (78), 902 (45), 900 (30).

5,11,17,23-Tetra-*tert*-butyl-25-[4-(ethylcarboxy)-2-nitrophenoxy]calix[4]-arene-26,27,28-triol (*cone* conformer) (139) and 5,11,17,23-tetra-*tert*-butyl-25,27-di-(4-ethylformate-2-nitrophenoxy)calix[4]arene-26,28-diol (*cone* conformer) (140).



139



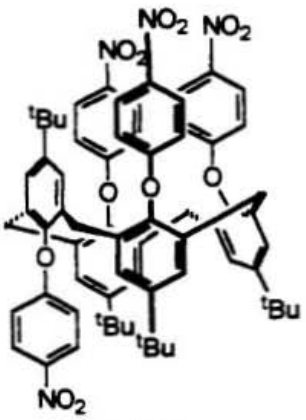
140

A flask containing **2** (0.32 g, 0.5 mmol), ethyl 4-fluoro-3-nitrobenzoate (**141**) (0.21 g, 1.00 mmol), K_2CO_3 (0.56 g, 4.0 mmol) and CuO (0.32 g,4.0 mmol) was flushed with

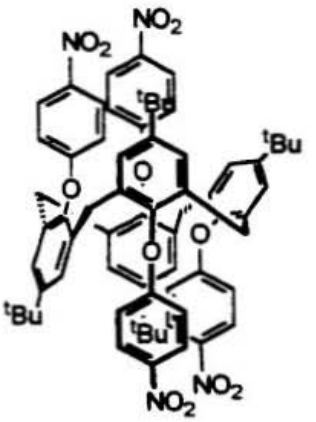
argon and then anhydrous pyridine (10 mL) was added. The resulting black mixture was refluxed for 24 h. After checking the mixture by TLC it was decided to continue refluxing the mixture for another 24 h, after which time TLC showed no further change. The reaction mixture was cooled to room temperature, and the solid filtered off. The organic layer was diluted with ethyl acetate (25 mL) and washed with aqueous 10% $NaHSO_4$, then with water, dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated and the crude product was subjected to flash column chromatography eluting with ethyl acetate-hexane 20:80 to afford **139** (243 mg, 57%) as a colourless solid: mp 199-201 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (s, 9H, *tert*-butyl), 1.22 (s, 27 H, *tert*-butyl), 1.40 (t, J = 7.1 Hz, 3H, -OCH_2**CH_3**), 3.30 (d, J = 13.3 Hz, 2H, -**CH_2**-), 3.45 (d, J = 13.8 Hz, 2H, -**CH_2**-), 3.94 (d, J = 13.3 Hz, 2H, -**CH_2**-), 4.32 (d, J = 13.8 Hz, 2H, -**CH_2**-), 4.41 (q, J = 7.1 Hz, 2H, -**OCH_2**CH_3), 6.67 (d, J = 8.8 Hz, 1H), 7.01 (s, 2H), 7.02 (s, 2H), 7.04 (s, 2H), 7.12 (s, 2H), 8.15 (d, J = 8.7 Hz, 1H), 8.37 (s, 2H, OH), 8.78 (s, 1H), 9.83 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 31.1, 31.4, 31.5, 32.8, 33.9, 34.0, 34.4, 61.7, 116.4, 124.8, 125.3, 125.7, 126.1, 126.5, 126.9, 127.4, 128.2, 132.6, 135.6, 138.8, 143.0, 143.3, 147.6, 147.6, 148.6, 150.0, 155.5, 164.7; **140** (101 mg, 19%) was obtained as a light yellow solid: mp 270-272 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 18H, *tert*-butyl), 1.30 (s, 18H, *tert*-butyl), 1.41 (t, J = 7.2 Hz, 6H, -OCH_2**CH_3**), 3.20 (d, J = 13.6 Hz, 4H, -**CH_2**-), 4.01 (d, J = 13.6 Hz, 4H, -**CH_2**-), 4.39 - 4.43 (q, J = 7.2 Hz, 4H, -**OCH_2**CH_3), 5.97 (s, 2H, OH), 6.76 (d, J = 8.8 Hz, 2H), 6.78 (s, 4H), 7.05 (s, 4H), 8.10 (dd, J = 2.1, J = 8.8 Hz, 2H), 8.75 (d, J = 2.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 30.9, 31.3,

31.7, 33.8, 33.9, 61.6, 124.0, 125.2, 126.2, 127.4, 131.7, 135.2, 138.5, 141.7, 144.6, 150.5, 155.7, 164.5; MS CI (*m/z*), relative intensity (%): 1036 (M^++2, 60), 1035 (M^++1, 100), 1034 (M^+, 78, calcd for $C_{62}H_{70}N_2O_{12}$ 1034.4929), 391 (75), 279 (38).

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetra-(4-nitrophenoxy)calix[4]arene (*partial cone* conformer) (142) and 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetra-(4-nitrophenoxy)calix[4]arene (*1,2-alternate* conformer) (143).



142



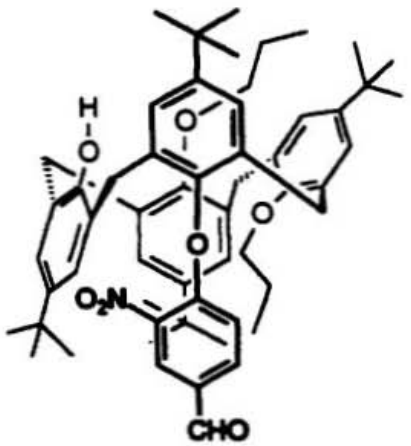
143

A mixture of **2** (324 mg, 0.50 mmol) and 1-fluoro-4-nitrobenzene (0.21 mL, 2.00 mmol), K_2CO_3 (278 mg, 2.00 mmol), and CuO (159 mg, 2.00 mmol) in pyridine was refluxed for 3 d. After the reaction mixture was cooled to room temperature, the mixture was filtered, and the organic layer was partitioned between ethyl acetate and 10% aqueous Na_2HPO_4. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered and the solvent was removed under reduced pressure. The crude product was by purified preparative TLC, eluting with hexane-benzene 5:95. The yellow product was purified again by preparative TLC using the same solvent mixture to afford **142** (159 mg, 46%) as the major product: mp >360

°C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 1.14 (s, 18H), 1.44 (s, 9 H), 1.63 (s, 9 H), 3.10 (d, *J* = 15.0 Hz, 2H), 3.30 (d, *J* = 15.0 Hz, 2H), 3.38 (d, *J* = 15.0 Hz, 2H), 3.40 (d, *J* = 13.0 Hz, 2H), 6.47 (d, *J* = 9.0 Hz, 4H), 6.53 (br, 2H), 6.64 (d, *J* = 2.0 Hz, 2H), 7.02 (d, *J* = 2.0 Hz, 2H), 7.26 (s, 2H), 7.39 (s, 2H), 8.05 (d, *J* = 9.5 Hz, 4H), 8.19 (br, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 31.0, 31.7, 31.9, 32.5, 34.7, 35.1, 35.4, 37.4, 115.2, 126.5, 126.9, 128.0, 128.1, 132.4, 132.9, 134.5, 135.4, 142.5, 142.6, 142.8, 147.1, 147.6, 148.1, 149.3, 150.4, 162.1, 163.9, 164.1; MS CI (*m/z*), relative intensity(%): 1133 (M^++1, 40), 431 (28), 391 (100); **143** (90 mg, 16%) was obtained as a light yellow solid: mp >300 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 1.25 (s, 36H), 3.20 (d, *J* = 12.5 Hz, 2H), 3.40 (s, 4H), 3.57 (d, *J* = 12.5 Hz, 2H), 5.98 (d, *J* = 8.0 Hz, 8H), 6.60 (d, *J* = 2.0 Hz, 4H), 7.74 (d, *J* = 2.0 Hz, 4H), 7.83 (d, *J* = 9.0 Hz, 8H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 30.4, 31.9, 34.9, 38.5,126.1, 127.1, 127.4, 131.8, 134.3, 142.2, 147.6, 148.9, 163.2; MS CI (*m/z*), relative intensity (%): 1132 (M^+, 60), 391 (100).

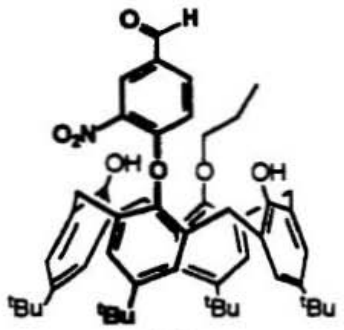
5,11,17,23-Tetra-*tert*-butyl-25-(4-formyl-2-nitrophenoxy)-26,27-dipropyloxy-calix[4]arene-28-ol (*1,2-alternate* conformer) (145) and 5,11,17,23-tetra-*tert*-butyl-25-(4-formyl-2-nitrophenoxy)-27-propyloxy-calix[4]arene-26,28-diol (*cone* conformer) (146).

A mixture of **131** (459 mg, 0.576 mmol), 1-iodopropane (0.22 mL, 2.30 mmol) and K_2CO_3 (640 mg, 4.60 mmol) in CH_3CN (25 mL) was refluxed for 28 h. The reaction mixture was cooled to room temperature, filtered, and then the solvent was evaporated under reduced pressure. The organic layer was extracted with CH_2Cl_2, washed with saturated aqueous NH_4Cl, dried over anhydrous $MgSO_4$ and filtered.



145

After the solvent was evaporated, the residue was purified by silica gel flash column chromatography using ethyl acetate-hexane 10:90 to afford **145** (156 mg, 36%): mp 202-204 °C; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 0.04 (t, *J* = 7.3 Hz, 3H), 0.89 - 0.95 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H), 1.18 (s, 9H), 1.20 (s, 9H), 1.27 (s, 18H), 1.81 - 1.98 (m, 2H), 2.39 (q, *J* = 8.3 Hz, 1H), 2.55 (q, *J* = 7.8 Hz, 1H), 2.99 (d, *J* = 12.3 Hz, 1H), 3.36 (d, *J* = 13.5 Hz, 1H), 3.53 (d, *J* = 15.4 Hz, 1H), 3.60 (q, *J* = 9.0 Hz, 1H), 3.86 (d, *J* = 15.5 Hz, 1H), 3.94 (s, 2H), 3.97 (d, *J* = 13.5 Hz, 2H), 4.08 - 4.15 (m, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 7.04 (s, 1H), 7.06 (d, *J* = 2.3 Hz, 2H), 7.10 (d, *J* = 3.6 Hz, 2H), 7.25 (d, *J* = 2.2 Hz, 1H), 7.47 (s, 1H), 7.90 (dd, *J* = 2.2, 8.7 Hz, 1H), 8.45 (br, s, 1H), 9.94 (s, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 9.8, 10.2, 24.2, 24.3, 31.3, 31.5, 31.6, 31.8, 32.0, 32.9, 34.3, 34.4, 34.6, 34.7, 39.1, 39.6, 125.5, 126.3, 126.8, 127.1, 128.0, 128.1, 128.2, 128.4, 128.5, 129.1, 129.9, 133.3, 133.5, 133.8, 133.9, 134.0, 134.6, 139.8, 141.9, 145.3, 147.2, 147.8, 148.4, 151.1, 151.8, 154.9, 157.3, 189.9; MS CI (*m/z*), relative intensity (%): 883 (M^++1, 38), 882 (M^+, 75), 880 (M^+-2, 100,), 879 (95), 849 (30), 838 (28), 732 (30), 647 (60); and **146**



146

(175 mg, 32%) was obtained as colourless solid: mp 151-153 °C; ^{1}H NMR δ 0.84 (s, 9H), 1.00 (s, 9H), 1.29 (s, 21H), 2.15 - 2.22 (m, 2H), 3.12 (d, *J* = 13.0 Hz, 2H), 3.40 (d, *J* = 13.6 Hz, 2H), 4.01 - 4.12 (m, 6H), 6.72 (s, 2H), 6.80 (s, 1H), 6.82 (s, 2H), 6.87 (s, 2H), 7.05 (s, 2H), 7.92 (dd, *J* = 2.0, 8.7 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 23.3, 30.8, 31.0, 31.2, 31.7, 33.8, 33.9, 34.0, 79.3, 116.6, 124.8, 125.1, 125.7, 126.2, 126.4, 127.9, 129.3, 131.9, 132.3, 133.9, 139.6, 141.5, 146.4, 147.7, 147.9, 148.5, 150.5, 157.4, 188.9; MS CI (*m/z*) relative intensity (%): 838 (M^+-2, 27), 732 (30), 647 (62).

References

1. (a) Lehn, J.-M. *Pure Appl. Chem.* **1978**, *50*, 871. (b) Lehn, J.-M. *Acc. Chem. Res.* **1978**, *11*, 49. (c) Lehn, J.-M. *Science.* **1985**, 227, 849.
2. (a) Lehn, J.-M. (NOBEL Lecture) *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89. (b) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1304.
3. (a) Cram, D. J. (NOBEL Lecture) *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009.
4. (a) Gokel, G. W., Ed. *Molecular Recognition Receptors for Cationic Guests.* In *Comprehensive Supramolecular Chemistry*, Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F.; Lehn, J.-M., Eds., Pergamon Press: Oxford, U. K., **1996**; Vol. 1. (b) Vögtle, F. *Molecular Recognition Receptors for Molecular Guests.* In *Comprehensive Supramolecular Chemistry*, Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F.; Lehn, J.-M., Eds., Pergamon Press: Oxford, U. K., **1996**; Vol. 2. (c) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991.
5. (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 153. (b) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017. (c) Pedersen, C. J. (NOBEL Lecture) *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021.
6. Frish, L.; Sansone, F.; Casnati, A.; Ungaro, R.; Cohen, Y. *J. Org. Chem.* **2000**, *65*, 5026.
7. Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643.

8. (a) Gutsche, C. D.; Kung, T. C.; Hsu, M.-L. Abstracts of 11th Midwest Regional Mtg. of Am. Chem. Soc., Carbondale, IL, **1975**, no. 517. (b) Muthukrishnan, R.; Gutsche, C. D. *J. Org. Chem.* **1979**, *44*, 3962. (c) Gutsche, C. D.; Muthukrishnan, R. *J. Org. Chem.* **1978**, *43*, 4905.

9. (a) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234. (b) Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1990**, *68*, 238. (c) Gutsche, C. D. *Calixarenes*, In *Monographs in Supramolecular Chemistry;* Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge and London, **1989**.

10. (a) Zinke, A.; Ziegler, E. *Chem. Ber.* **1941**, *B74*, 1729. (b) Zinke, A.; Kertz, R.; Leggewie, E.; Hössinger, K.; Hoffman, G. *Chem. Ber.* **1952**, *83*, 1213.

11. (a) Cornforth, J. W.; D'Arcy Hart, P.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Br. J. Pharmacol.* **1955**, *10*, 73. (b) Cornforth, J. W.; Morgan, E. D.; Potts, K. T.; Rees, R. J. W. *Tetrahedron* **1973**, *29*, 1659.

12. (a) Gutsche, C. D. *Calixarenes Revisited*, In *Monographs in Supramolecular Chemistry;* Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, **1998**. (b) '*Calixarenes*, A *Versatile Class of Macrocyclic compounds*', Vicens, J.; Böhmer, V. Eds.; Kluwer: Dorderecht; **1991**. (c) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713. (d) '*Calixarenes in Action*' Mandolini, L.; Ungaro, R., Eds.: World Scientific Publishing: River Edge, NJ, **2000**.

13. (a) Hogberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498. (b) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.;

14. (a) Böhmer, V.; Chhim, Ph.; Kämmerer, H. *Makromol. Chem.* **1979**, *180*, 2503. (b) Böhmer, V.; Marschollek, F., Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.

15. Hayes, B. T.; Hunter, R. F. *J. Appl. Chem.* **1958**, *8*, 743.

16. Kämmerer, H.; Happel, G.; Ceaser, F. *Makromol. Chem.* **1972**, *162*, 179.

17. (a) Böhmer, V.; Goldman, H.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1985**, 667. (b) Böhmer, V.; Goldman, H.; Kaptein, R. *J. Chem. Soc., Chem. Commun.* **1987**, 1358. (c) Paulus, E.; Böhmer, V.; Goldman, H.; Vogt, W. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1609. (d) Goldman, H.; Vogt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811. (e) Böhmer, V.; Goldman, H.; Vogt, W.; Paulus, E.; Tobiason, F. L.; Thielman, M. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1769.

18. (a) Casabianca, H.; Royer, J.; Satrallah, A.; Taty,-C. A.; Vicens, J. *Tetrahedron Lett.* **1987**, *28*, 6595. (b) Shinkai, A.; Arimura, T.; Kabawata, H.; Iwamoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2429.

19. Böhmer, V.; Goldman, H.; Vogt, W.; Vicens, J.; Asfari, Z. *Tetrahedron Lett.* **1989**, *30*, 1391.

20. Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.

21. Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 17.

22. Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J.

Tetrahedron **1983**, *39*, 409.

23. Kämmerer, H.; Happel, G.; Mathiasch, B. *Makromol. Chem.* **1981**, *182*, 1685.

24. Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. It.* **1989**, *119*, 335.

25. Shinkai, S. *Tetrahedron*, **1993**, *49*, 8933.

26. Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. D.; Sânchez, C. *J. Org. Chem.* **1991**, *56*, 3372.

27. Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 586.

28. Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1994**, *59*, 3871.

29. (a) French, D.; Levine, M. L.; Pazur, J. H.; Norberg, E. *J. Am. Chem. Soc.* **1949**, *71*, 353. (b) d'Alessandro, F.; Gulino, F. G.; Impellizzeri, G.; Pappalardo, S.; Rizzarelli, E.; Ungaro, R. *Tetrahedron Lett.* **1997**, *38*, 4685.

30. Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005.

31. Perrin, M.; Gharnati, F.; Oehler, D.; Perrin, R.; Lecocq, S. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *14*, 257.

32. (a) Brouwer, E. B.; Enright, G. D.; Ripmeester, J. A.; *Supramol. Chem.* **1996**, *7*, 7. (b) Brouwer, E. B.; Enright, G. D.; Ripmeester, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 5404.

33. Arduini, A.; McGregor, W. M.; Paganuzzi, D.; Pochini, A.; Ugozzoli, F.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1996**, 839.

34. Chowdhury, S.; Bridson, J. N.; Georghiou, P. E. *J. Org. Chem.* **2000**, *65*, 3299.

35. (a) Masci, B. *J. Org. Chem.* **2001**, *66*, 1497. (b) Masci, B.; Finelli, M.; Varrone, M. *Chem. Eur. J.* **1998**, *4*, 2018.

36. (a) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48*, 1536. (b) Bavoux, C.; Vocanson, F.; Perrin, M.; Lamartine, R. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, *22*, 119. (c) Hampton, P. D.; Bencze, Z.; Tong, W.; Diatch, C. E. *J. Org. Chem.* **1994**, *59*, 4838. (d) Hampton, P. D.; Diatch, C. E.; Duesler, E. N. *New J. Chem.* **1996**, *20*, 427.

37. (a) Iki, N.; Kumagai, H.; Morohashi, N.; Ejima, K.; Hasegawa, M.; Miyanari, S.; Miyano, S. *Tetrahedron Lett.* **1998**, *39*, 7559. (b) Akdas, H.; Graf, E.; Hosseini, M. W.; Cian, A. De.; Harrowfield, J. McB. *Chem. Commun.* **2000**, 2219.

38. (a) Takemura, H.; Yoshimura, K.; Khan, I. U.; Shinmyozu, T.; Inazu, T. *Tetrahedron Lett.* **1992**, *33*, 5775. (b) Khan, I. U.; Takemura, H.; Suenaga, M.; Shinmyozu, T.; Inazu, T. *J. Org. Chem.* **1993**, *58*, 3158. (c) Takemura, H.; Shinmyozu, T.; Miura, H.; Khan, I. U.; Inazu, T. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 193.

39. (a) König, B.; Rödel, M.; Bubenitschek, P.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 661.

40. (a) Georghiou, P. E.; Li, Z. *Tetrahedron Lett.* **1993**, *34*, 2887. (b) Georghiou,

P. E.; Li, Z. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 55.

41. Badger, G. M. The *Structure & Reactions of the Aromatic Compounds*, The University Press, Cambridge, **1957**.

42. Ferla, M. University of Padua, **2000** (Personal communication).

43. Georghiou, P. E.; Ashram, M.; Li, Z.; Chaulk, S. G. *J. Org. Chem.* **1995**, *60*, 7284.

44. Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, *45*, 2177.

45. (a) Shinkai, S.; Mori, S.; Tsubaki, T.; Sone, T.; Manabe, O. *Tetrahedron Lett.* **1984**, *25*, 5315. (b) Shinkai, S. *Pure Appl. Chem.* **1986**, *58*, 1523.

46. (a) Georghiou, P. E.; Li, Z.; Ashram, M. *J. Org. Chem.* **1998**, *63*, 3748.

47. (a) Poh, B. L.; Lim, C. S.; Khoo, K. S. *Tetrahedron Lett.* **1989**, *30*, 1005. (b) Poh, B. L.; Lim, C. S. *Tetrahedron* **1990**, *46*, 3651. (c) Poh, B. L.; Tan, C. M. *ibid.* **1993**, *49*, 3849.

48. Georghiou, P. E.; Ashram, M.; Clase, H. J.; Bridson, J. N. *J. Org. Chem.* **1998**, *63*, 1819.

49. Andreetti, G. D.; Böhmer, V.; Jordon, J. G.; Tabatabai, M.; Ugozzoli, F.; Vogt, W.; Wolff, A. *J. Org. Chem.* **1993**, *58*, 4023.

50. Ikeda, A.; Yoshimura, M.; Lhotak, P.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1945.

51. Shorthill, B. J.; Glass, T. E. *Org. Lett.* **2000**, *2*, 577.

52. (a) Sansone, F.; Barboso, S.; Casnati, A.; Fabbi, A.; Pochini, A.; Ugozzoli, F.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 897. (b) Casnati, A.; Fabbi, M.; Pelizzi, N.; Pochini, A.; Sansone, F.; Ungaro, R.; Di Modugno, E.; Tarzia, G. *Bioorg. & Med. Chem. Lett.* **1996**, *6*, 2699. (c) Hamuro, Y.; Calama, M. C.; Perk, H. S.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2680.

53. Atwood, J. L.; Koutsantonis, G. A.; Raston, C. L. *Nature (London),* **1994**, *368*, 229.

54. Suzuki, T.; Nakashima, K.; Shinkai, S. *Chem.* Lett. **1994**, 699.

55. (a) MacGillivray, L. R.; Atwood, J. L. *Nature (London),* **1997**, *389*, 469. (b) Atwood, J. L.; Barbour, L. J.; Raston, C. L.; Sudria, I. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 981.

56. (a) Chiang, L.Y.; Swirezewski, J. W.; Liang, K.; Miller, J. *Chem. Lett.* **1994**, 981. (b) Steed, J. W.; Junk, P. C.; Atwood, J. L.; Barnes, M. J.; Raston, C. L. *J. Am. Chem. Soc.* **1994**, *116*, 10346.

57. (a) Shinkai, S.; Ikeda, A. *Gazz. Chim. It.* **1997**, *127*, 657. (b) Ikeda, A.; Suzuki, Y.; Yoshimura, M.; Shinkai, S. *Tetrahedron* **1998**, *54*, 2497.

58. Ashram, M. Ph.D. Thesis, Memorial University of Newfoundland, **1997**.

59. Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

60. Sun, Y.-P.; Bunker, C. E.; Ma, B. *J. Am. Chem. Soc.* **1994**, *116*, 9692.

61. Ikeda, A.; Fukuhara, C.; Shinkai, S. *Chem. Lett.* **1997**, 407.

62. Raston, C. L.; Atwood, J. L.; Nichols, P. J.; Sudria, I. B. N. *J. Chem. Soc.*,

Chem. Commun. **1996**, 2615.

63. Kurland, R. S.; Rubin, N. B.; Wise, W. B. *J. Chem. Phys.* **1964**, *40*, 2426.

64. Bauer, L. J.; Gutsche, C. D. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

65. Gutsche, C. D.; Iqbal. M.; Alam, I. *J. Am. Chem. Soc.* **1987**, *109*, 4314.

66. Brouwer, E. B.; Kostantin, A.; Udachin, K. A.; Enright, G. D.; Ripmeester, J. A. *Chem. Commun.* **2000**, 1905.

67. (a) Brouwer, E. B.; Enright, G. D.; Ratcliffe, C. I.; Facey, G. A.; Ripmeester, J. A. *J. Phys. Chem. B.* **1999**, *103*, 10604. (b) Brouwer, E. B.; Enright, G. D.; Ratcliffe, C. I.; Ripmeester, J. A. *Supramol. Chem.* **1996**, *7*, 79.

68. Georghiou, P. E.; Mizyed, S.; Chowdhury, S. *Tetrahedron Lett.* **1999**, *40*, 611.

69. Haino, T.; Yanase, M.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 259.

70. Haino, T.; Yanase, M.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 997.

71. Casnati, A. *Gazz. Chim. It.* **1997**, *127*, 637.

72. Ikeda, A.; Shinkai, S. *Tetrahedron Lett.* **1992**, *33*, 7385.

73. Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R.; Eretti, G. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1075.

74. (a) Ungaro, R.; Casnati, A.; Ugozzoli, F.; Pochini, A.; Dozol, J.-F.; Hill, C.; Rouquette, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1506. (b) Arnaud-Neu, F.; Caccamese, S.; Fuangswasdi, S.; Pappalardo, S.; Parisi, M. F.; Petringa,

A.; Principato, G. *J. Org. Chem.* **1997**, *62*, 8041. (c) Asfari, Z.; Lamare, V.; Dozol, J.-F.; Vicens, J. *Tetrahedron Lett.* **1999**, *40*, 691. (d) Casnati, A.; Pochini, A.; Ungaro, R.; Bocchi, C.; Ugozzoli, F.; Egberink, R. J. M.; Struijk, H.; Lugtenberg, R.; de Jong, F.; Reinhout, D. N. *Chem. Eur. J.* **1996**, *2*, 436. (e) Yamamoto, H.; Shinkai, S. *Chem. Lett.* **1994**, 1115.

75. Diederich, F.; Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH: Weinheim, Germany, **1997**.

76. (a) Tamao, K.; Sumutani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.

77. Nigishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

78. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

79. Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.

80. Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501.

81. Negishi, E.; Matsushita, H.; Okukado *Tetrahedron Lett.* **1981**, *22*, 2715.

82. (a) Stille, J. K. *Angew. Chem.* **1986**, *98*, 483. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Farina, V. In *Comprehensive Organometallic Chemistry II* (Eds.: Abel, E. W.; Stone, F. G. A.; Wilkinson, G), Pergamon, Oxford, **195**, Vol. 12, p.200. (d) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73.

83. de Lang, R.-J.; van Hooijdonl, M. G. C. M.; Brandsma, L. *Tetrahedron* **1998**, *54*, 2953.

84. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

85. (a) Coll, G.; Morey, J.; Costa, A.; Saá, J. M. *J. Org. Chem.* **1988**, *53*, 5345. (b) Suner, G. A.; Deya, P. M.; Saá, J. M. *J.* Am. *Chem. Soc.* **1990**, *112*, 1467. (c) Narasimhan, N. S.; Mali, R. S. *Tetrahedron* **1974**, *31*, 1005.

86. Chowdhury, S.; Georghiou, P. E. *Tetrahedron Lett.* **1999**, *40*, 7599.

87. Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993.

88. Biehl, E. R.; Deshmukh, A. R.; Dutta, M. *Synthesis* **1993**, 885.

89. (a) Powell, W. H. *Pure Appl. Chem.* **1995**, *67*, 1307. (b) Powell, W. H. *Pure Appl. Chem.* **1998**, *70*, 1513.

90. Rha, S. G.; Chang, S.-K. *J. Org. Chem.* **1998**, *63*, 2357.

91. Gutsche, C. D.; Levine, J. A.; Sujeeth, P. K. *J. Org. Chem.* **1985**, *50*, 5802.

92. Goren, Z.; Biali, S. E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1484.

93. (a) Van Gelder, J. M.; Aleksuik, O.; Biali, S. E. *J. Org. Chem.* **1996**, *61*, 8419. (b) Aleksuik, O.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1995**, *117*, 9645.

94. Gibbs, C. G.; Sujeeth, P. K.; Rogers, J. S.; Stanley, G. G.; Krawiec, M.; Watson, W. H.; Gutsche, C. D. *J. Org. Chem.* **1995**, *60*, 8394.

95. Ohseto, F.; Murakami, H.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1992**, *33*, 1217.

96. Ting, Y.; Verboom, W.; Groenen, L.C.; van Loon, J.-D.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1990**, 1432.

97. Gibbs, C. G.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 5338.

98. González, J. J.; Nieto, P. M. ; Prados, P.; Echavarren, A. M.; de Mendoza, J. *J. Org. Chem.* **1995**, *60*, 7419.

99. Dondini, A.; Ghiglione, C.; Marra, A.; Scoponi, M. *J. Org. Chem.* **1998**, *63*, 9535.

100. Csók, Z.; Szalontai, G.; Czira, G.; Kollár, L. *Supramol. Chem.* **1998**, *10*, 69.

101. Chowdhury, S.; Zhao. B.; Snieckus, V. *J. Polycyclic Aromatic Hydrocarbons* **1994**, *5*, 27.

102. (a) Conner, M.; Janout, V.; Regen, S. *J. Am. Chem. Soc.* **1991**, *113*, 9670. (b) Grootenhius, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhout, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165.

103. (a) Ungaro, R.; Pochini, A.; Andreetti, G. D. *J. Inclusion Phenom.* **1984**, *2*, 199. (b) McKervery, M. A.; Seward, E. M.; Ferguson, G.; Ruhl, B.; Harris, S. J. *J. Chem. Soc., Chem.* Comun. **1985**, 388. (c) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R.; Andreetti, G. D.; Ugozzoli, F. *Tetrahedron* **1986**, *42*, 2089. (d) Ferguson, G.; Kaitner, B.; McKervery, M. A.; Seward, E. M. *J. Chem. Soc., Chem. Comun.* **1987**, 584. (e) Calestani, G.; Ugozzoli, F.; Arduini, A.; Ghidini, E.; Ungaro, R. *J. Chem. Soc., Chem. Comun.* **1987**, 344.

104. Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726.

105. (a) Andreetti, G. D.; Ugozzoli, F.; Ungaro, R.; Pochini, A. In *Inclusion*

Compounds, Vol. 4 (Eds.: Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.), Oxford University Press, Oxford, **1991**, pp. 64. (b) Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Comun.* **1979**, 1005. (c) Coruzzi, M.; Andreetti, G. D.; Bocchi, V.; Pochini, A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1133. (d) Andreetti, G. D.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1773. (e) Rizzoli, C.; Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Mol. Struct.* **1982**, *82*, 133.

106. Schatz J.; Schildbach, R.; Baur, M. in Abstracts of The Fifth International Conference on Calixarene Chemistry, 19-23 September, **1999**, Perth, Australia.

107. Moreno-Manas, M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *64*, 2346.

108. (a) Bauer, L. J.; Gutsche, C. D. *J. Am. Chem. Soc.* **1985**, *107*, 6063. (b) Gutsche, C. D.; Iqbal, M.; Alam, I. *J. Am. Chem. Soc.* **1987**, *109*, 4314.

109. Lipshutz, B. H.; Buzard, D. J.; Vivian, R. W. *Tetrahedron Lett.* **1999**, *40*, 6871.

110. Cotter, W. D.; Barbour, L.; McNamara, K. L.; Hechter, R.; Lachicotte, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 11016.

111. Tucci, F. C.; Rudkevich, D. M.; Rebek, J. Jr. *J. Org. Chem.* **1999**, *64*, 4555.

112. Muthukrishnan, R.; Gutsche, D. C. *J. Org. Chem.* **1979**, *44*, 3962.

113. Chowdhury, S.; Georghiou, P. E. *J. Org. Chem.* **2001**, *66*, 6257.

114. (a) Rama Rao, A. V.; Gurjar, M. K.; Reddy, L.; Srinivasa Rao, A. *Chem. Rev.*

1995, 95, 2135. (b) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed. Eng.* **1999**, *38*, 2096.

115. (a) Chan, D. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (b) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.

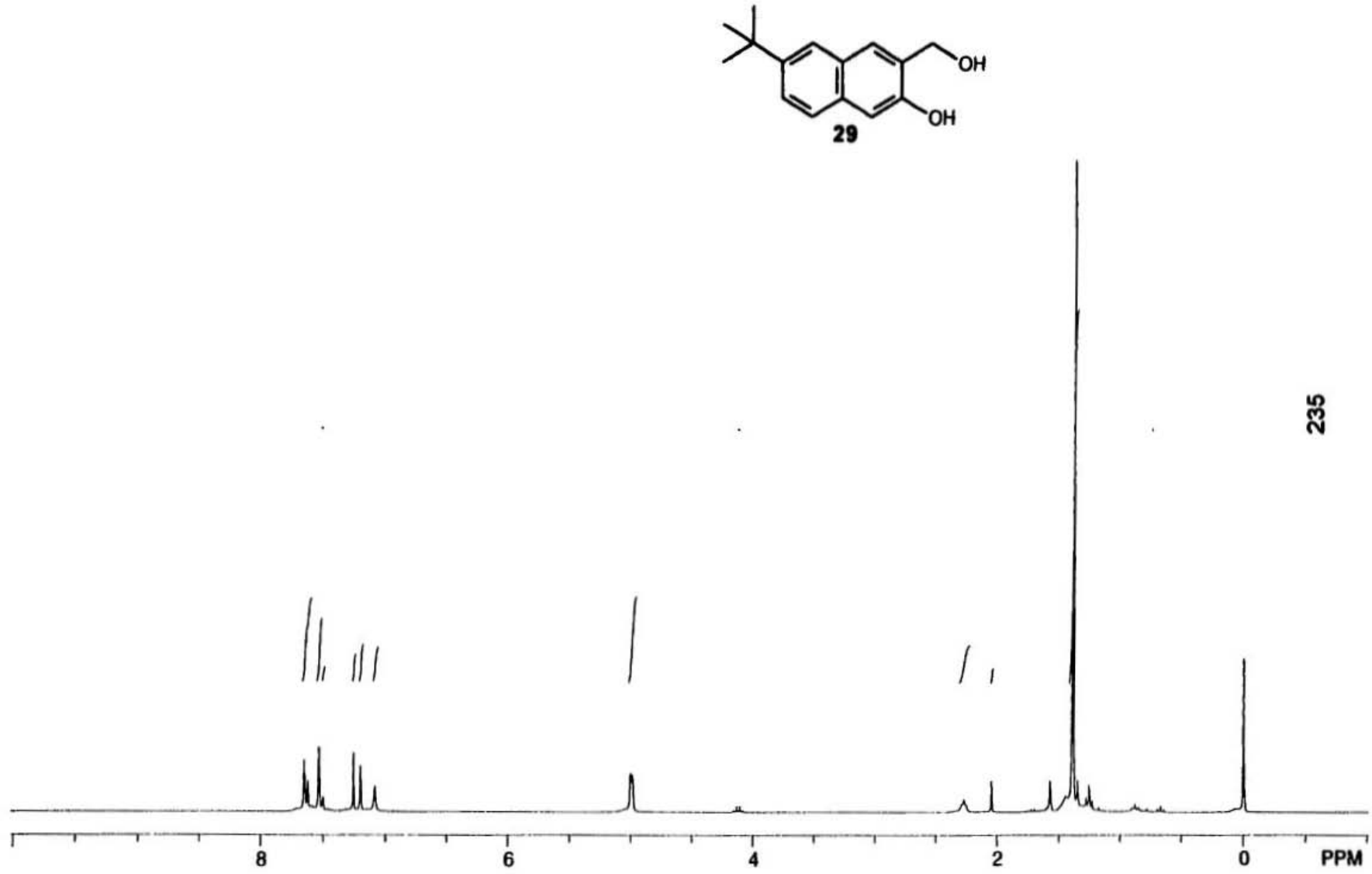
116. a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853. b) Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211.

117. Neri, P.; Bottino, A.; Cunsolo, F.; Piattelli, M.; Gavuzzo, E. *Angew. Chem., Int. Ed.* **1998**, *37*, 166.

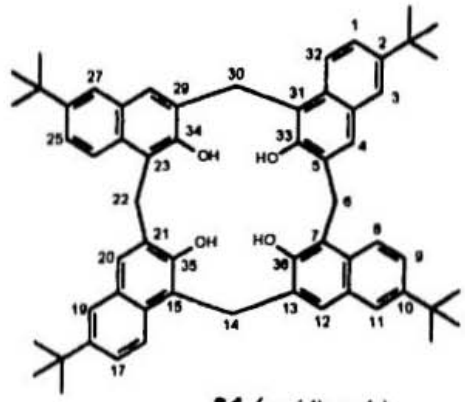
118. Pummerer, E. P.; Rieche, A. *Ber. Dtsch. Chem. Ges. B* **1926**, *59*, 2159.

Appendix A

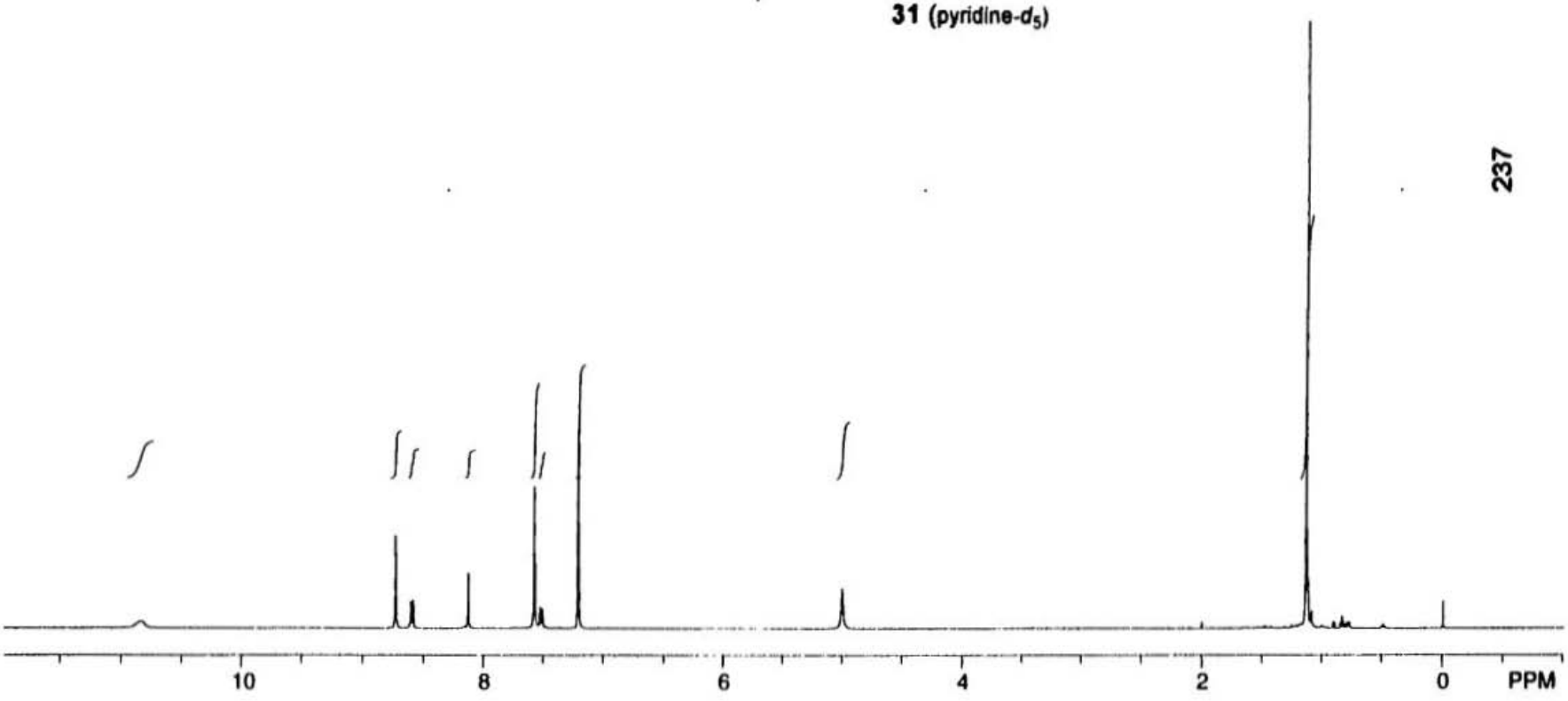
Spectra for synthesized compounds in numerical order

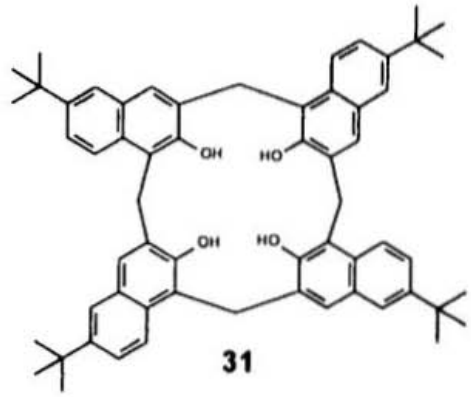

OH
OH
29
235
8
6
4
2
0
PPM

31



31 (pyridine-d_5)

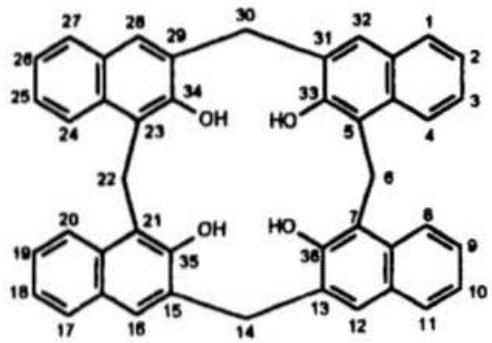




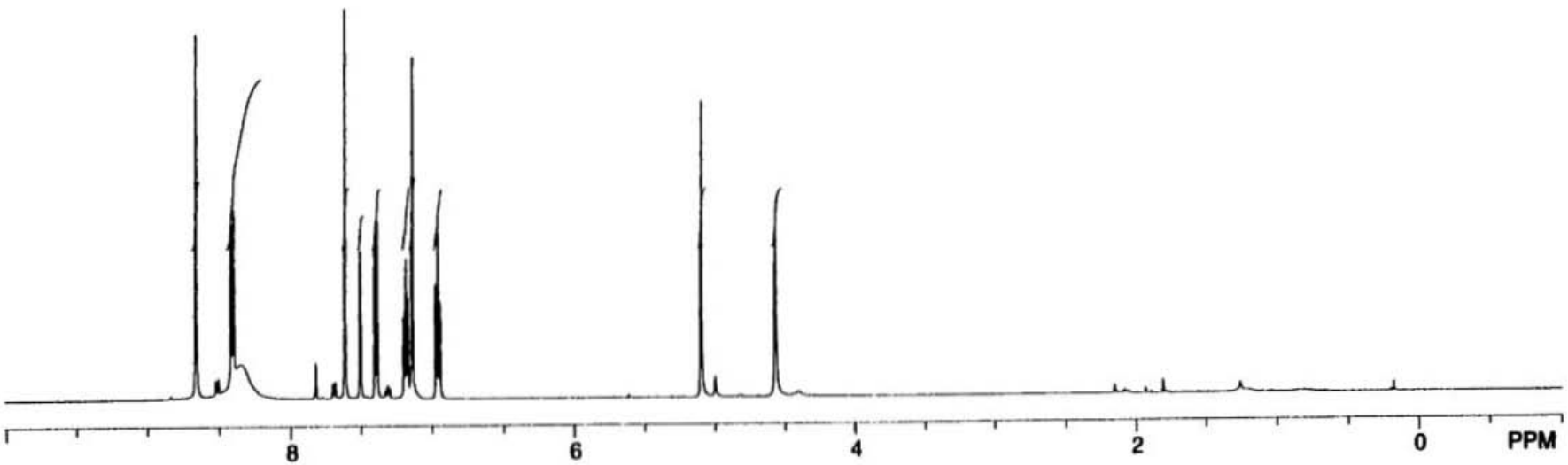
31

238

160 140 120 100 80 60 40 20 0 ppm


27
28
29
30
31
32
1
26
2
25
34
33
3
OH
HO
24
23
5
4
22
6
20
21
OH
HO
7
8
19
35
36
9
18
10
17
16
15
14
13
12
11

35


8
6
4
2
0
PPM

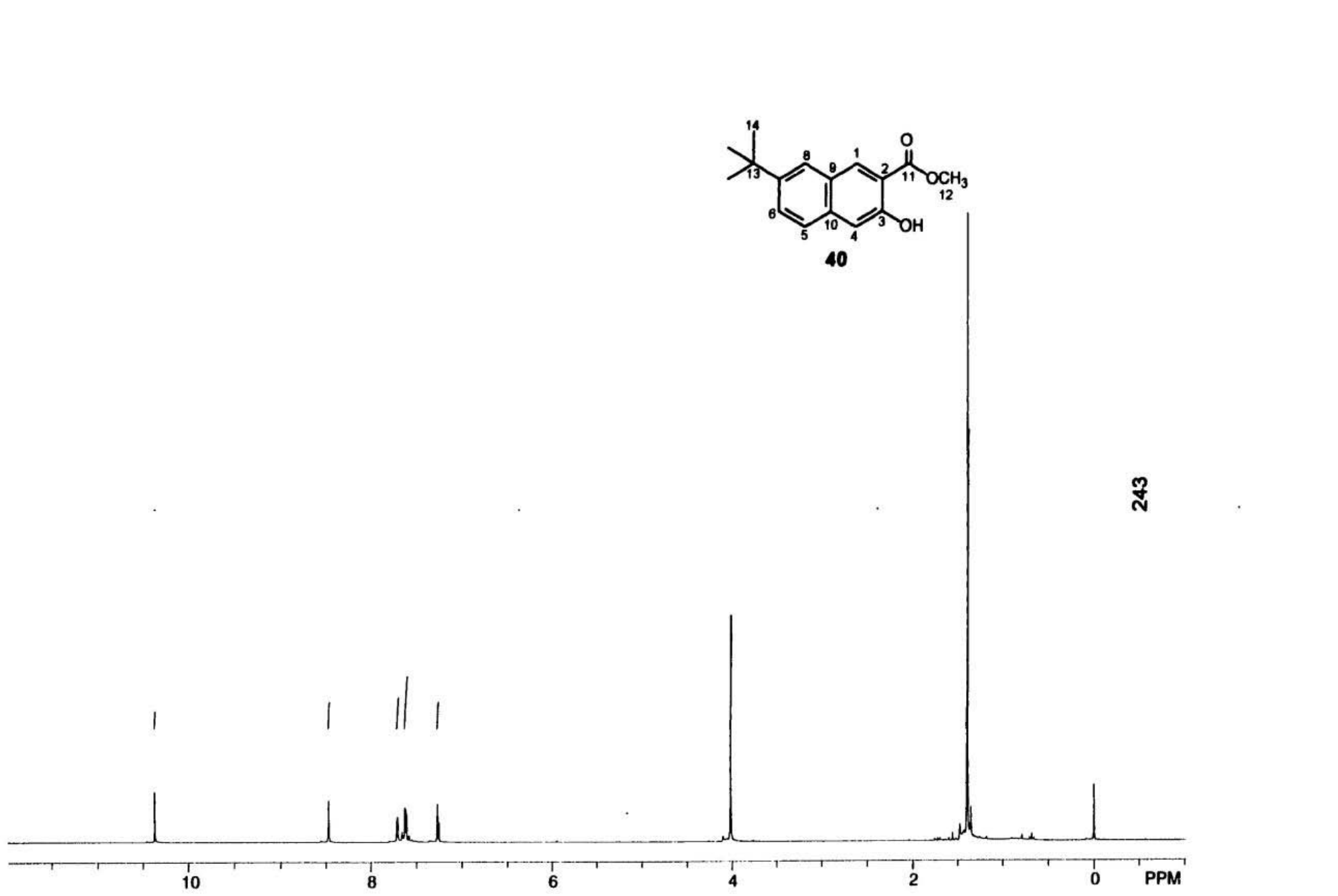
240

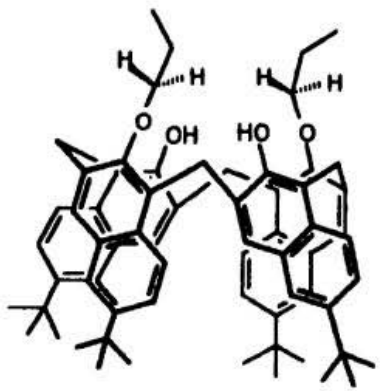
160
140
120
100
80
60
40
20
0
ppm

37
OH
OH

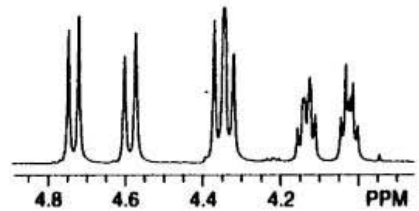
10
8
6
4
2
0
PPM

39
OH
OCH3
12
11


14
13
8
9
1
2
11
O
OCH3
12
6
10
5
4
3
OH
40
243
10
8
6
4
2
0
PPM

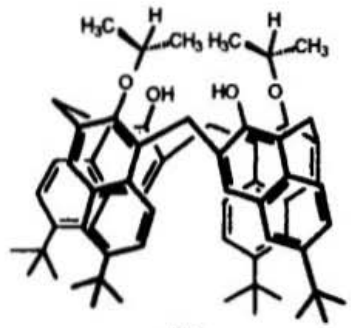


41a

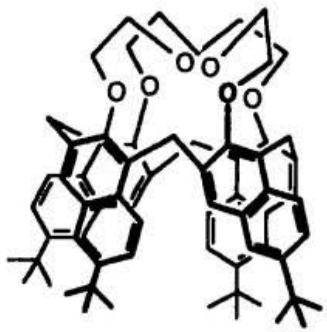


244

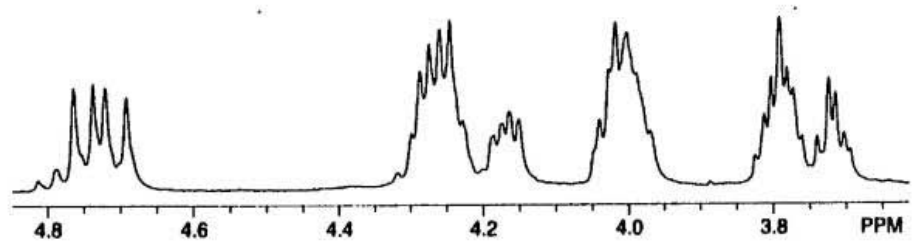
41a



41b

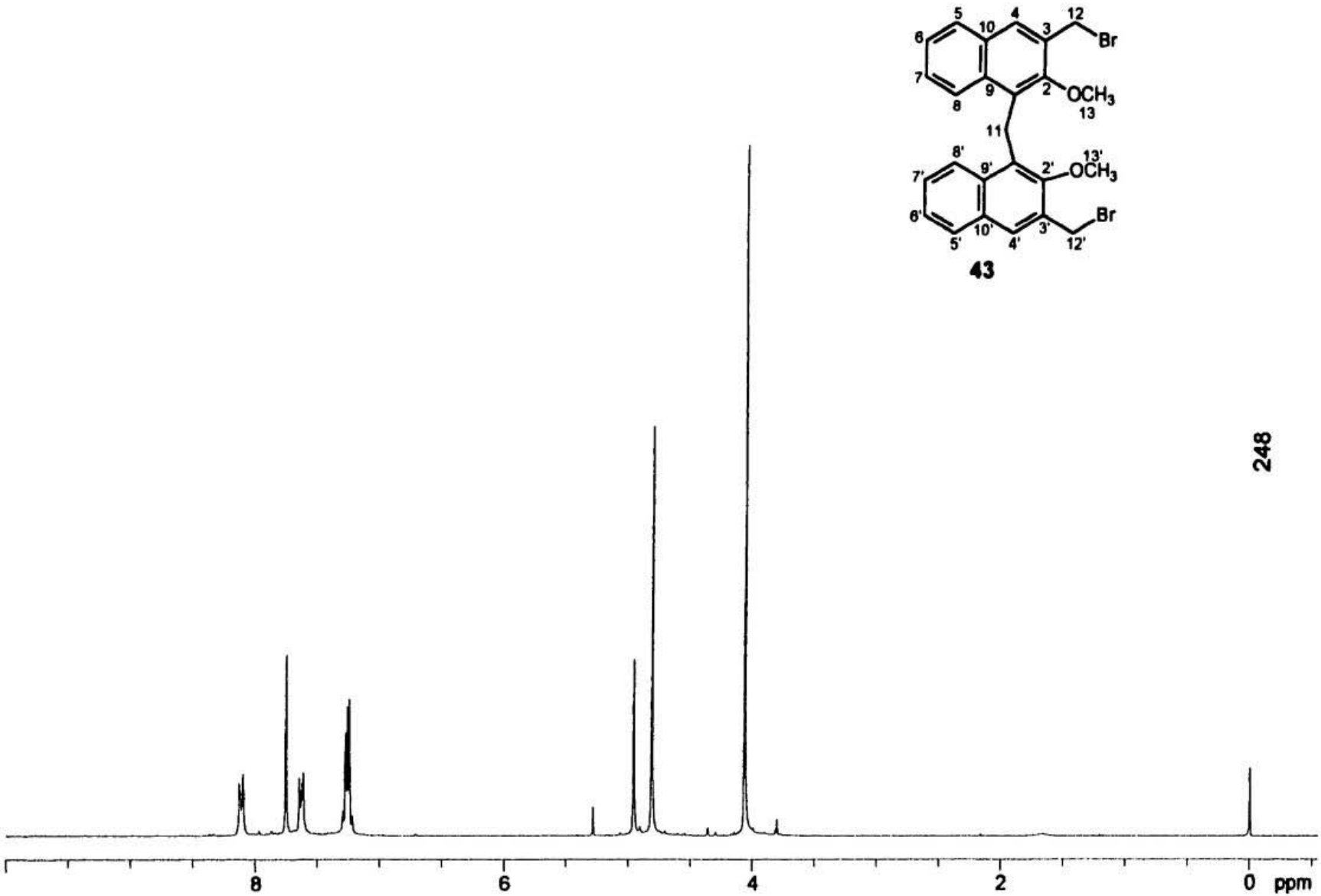


42 (*pinchedcone*)



247

8
6
4
2
0
PPM


Br
OCH3
13
11
13'
OCH3
Br
12'
43
248
8
6
4
2
0
ppm

8
6
4
2
0
ppm

OH
Si(CH3)3
11
46

46

250

8
6
4
2
0
ppm

47
OH
OH
Si(CH3)3
Si(CH3)3

47

8
6
4
2
0
ppm

49
OCH3
12
OCH3
12'

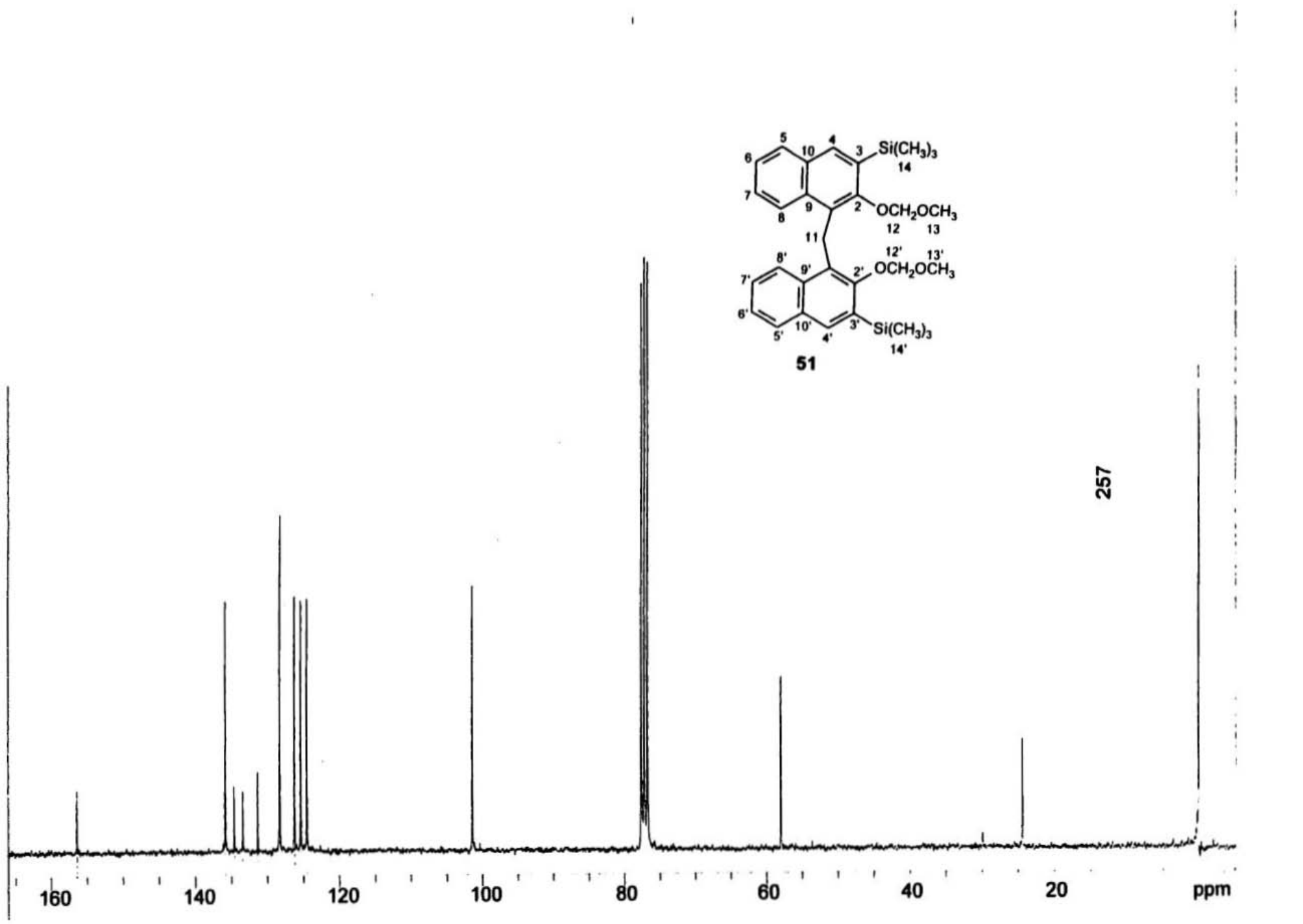
8
6
4
2
0 ppm

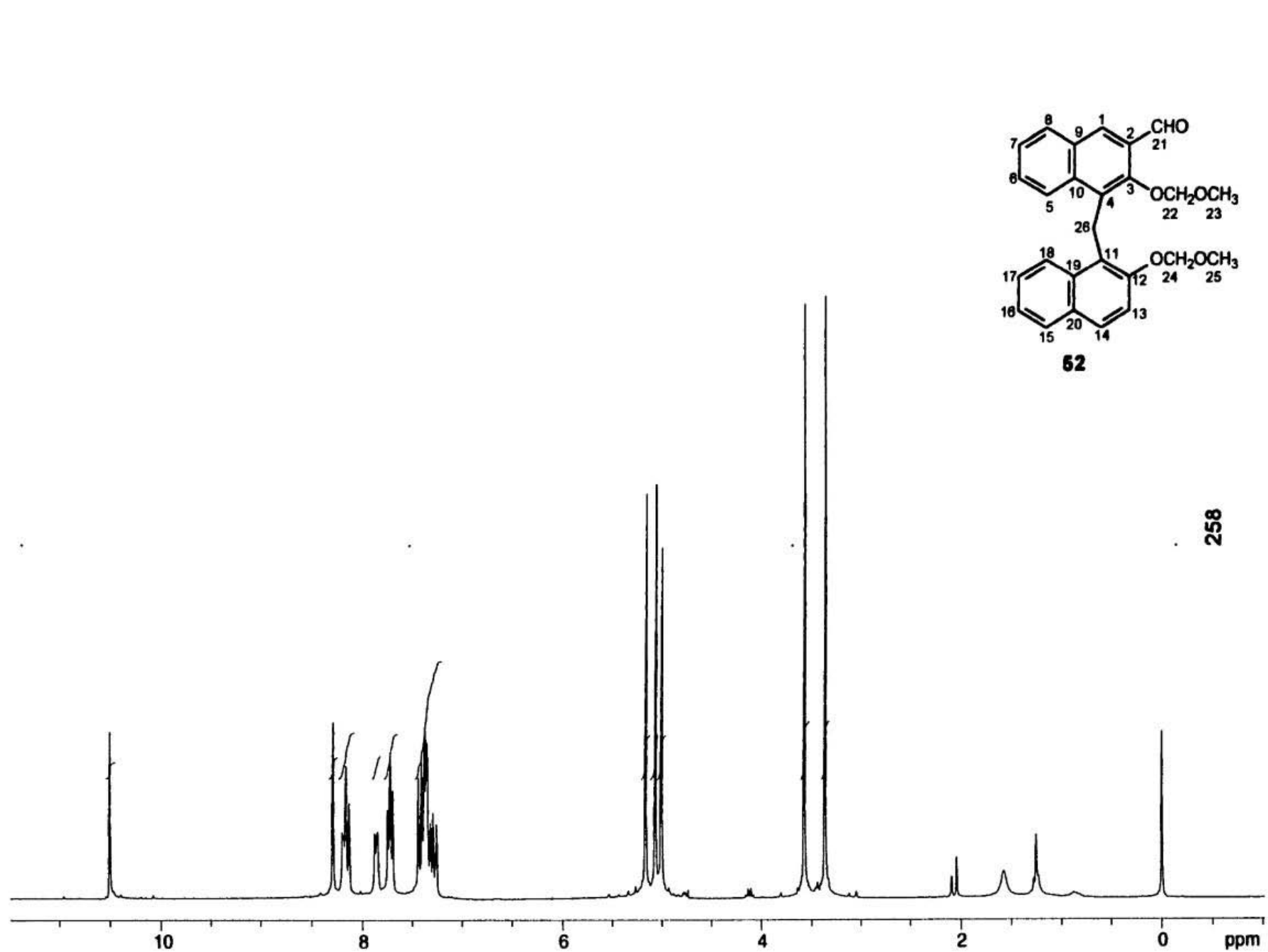
50
OCH2OCH3
OCH2OCH3

160
140
120
100
80
60
40
20
0
ppm

50
OCH2OCH3
OCH2OCH3

61

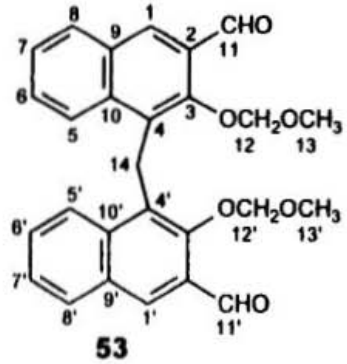

Si(CH3)3
14
OCH2OCH3
12
13
11
12'
13'
OCH2OCH3
Si(CH3)3
14'
51
257
160
140
120
100
80
60
40
20
ppm


CHO
21
OCH2OCH3
22 23
26
OCH2OCH3
24 25
52
258
10
8
6
4
2
0
ppm

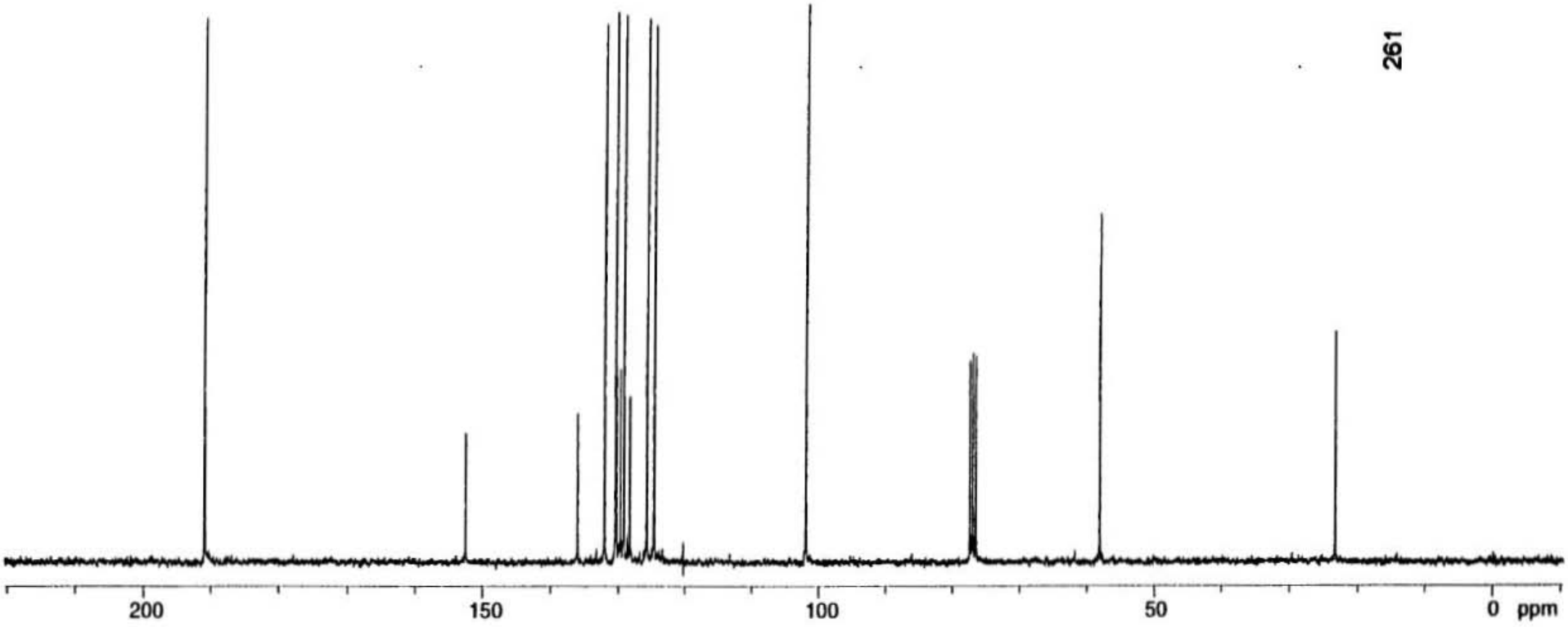
52

10
8
6
4
2
0
ppm

63
CHO
OCH2OCH3
OCH2OCH3
CHO


8
9
1
2
CHO
11
7
6
10
3
OCH2OCH3
12
13
5
4
14
5'
10'
4'
OCH2OCH3
12'
13'
6'
7'
9'
1'
CHO
11'
8'

53


261
200
150
100
50
0 ppm

56

263

56

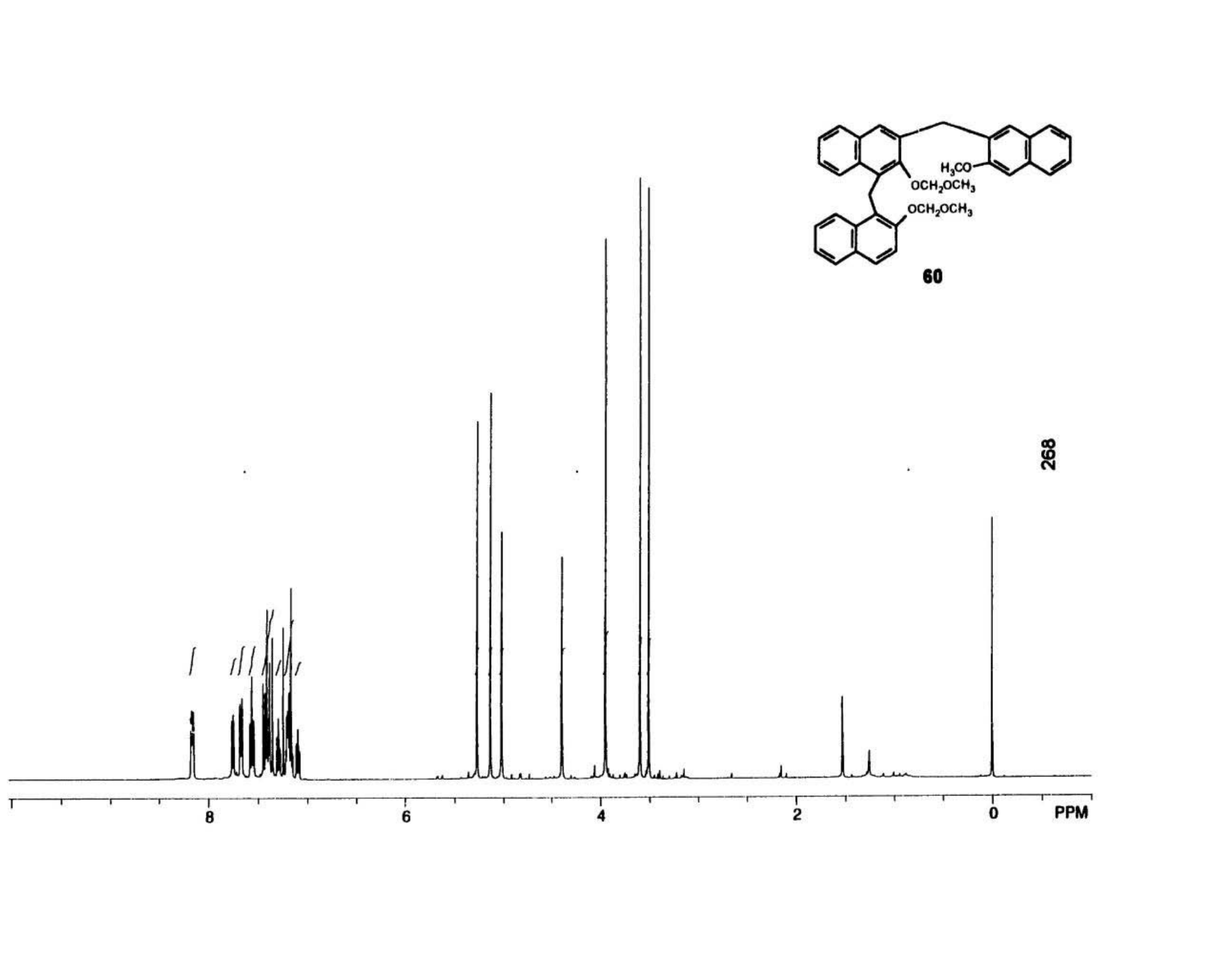
67

57

266

150
100
50
0
ppm

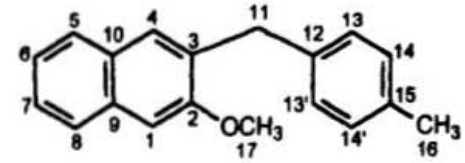
58
OH
OH
O
N
O
N


H3CO
OCH2OCH3
OCH2OCH3
60
268
8
6
4
2
0
PPM

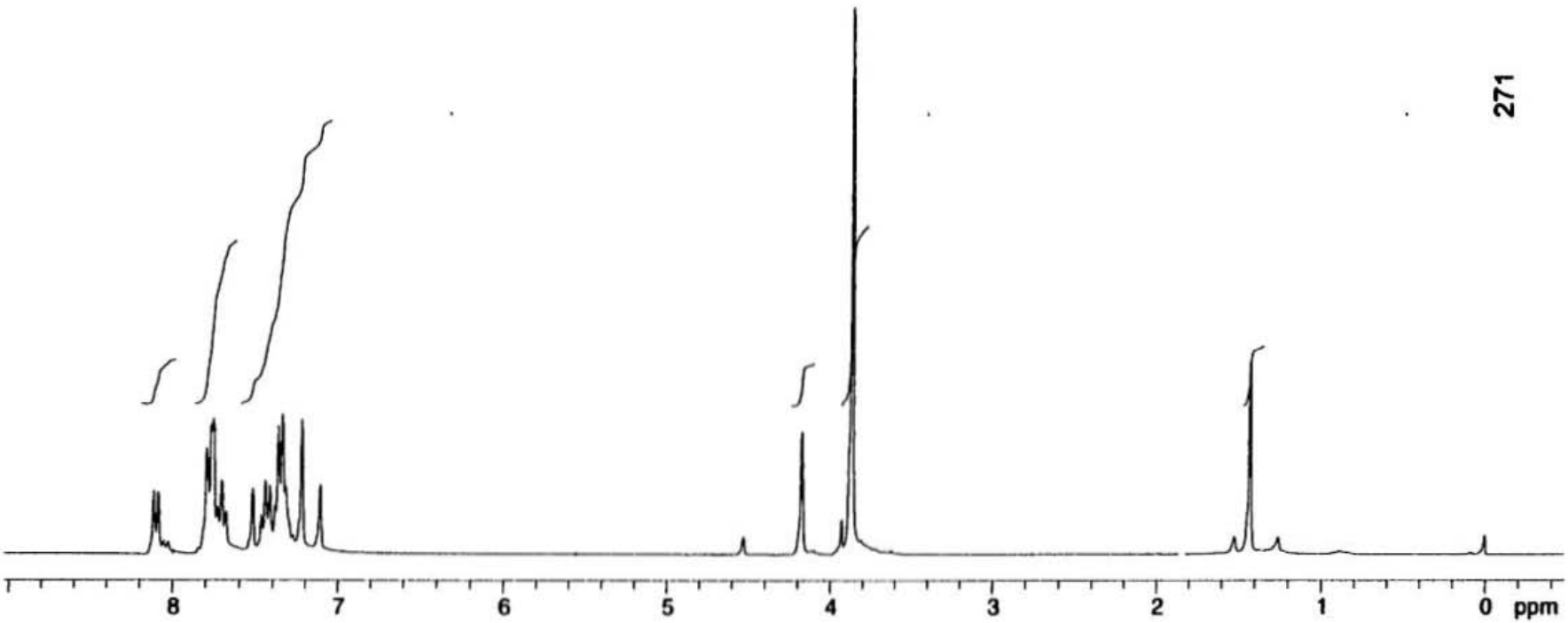
8
7
6
5
4
3
2
1
0 ppm

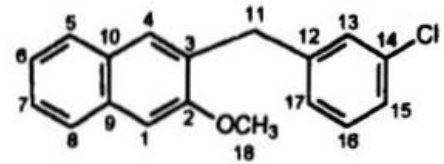
OCH3
66

66

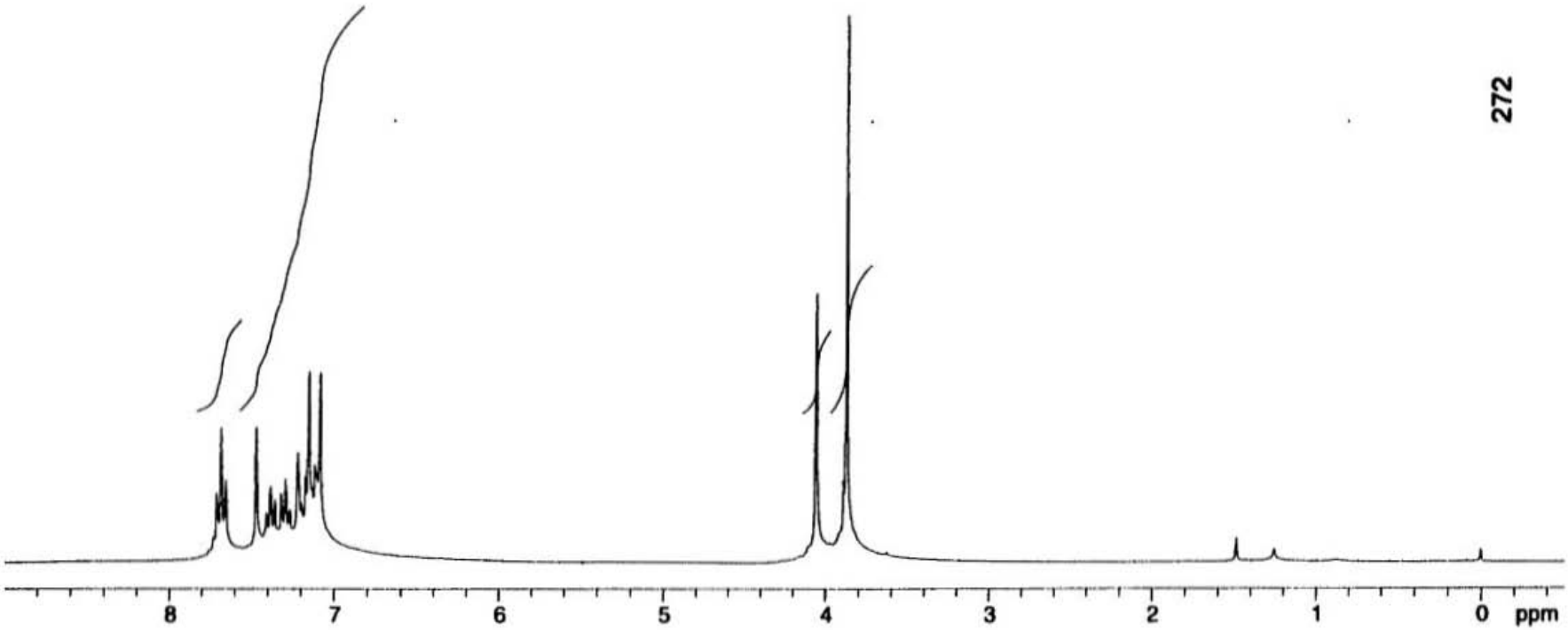

5
10
4
11
12
13
6
3
14
7
13'
15
2
OCH3
17
9
CH3
8
1
14'
16

67

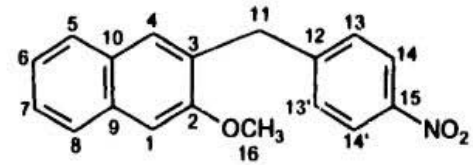

271
8
7
6
5
4
3
2
1
0
ppm



68



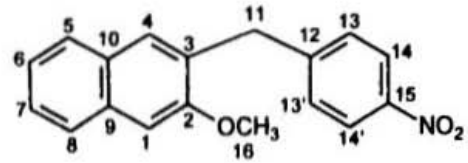
68



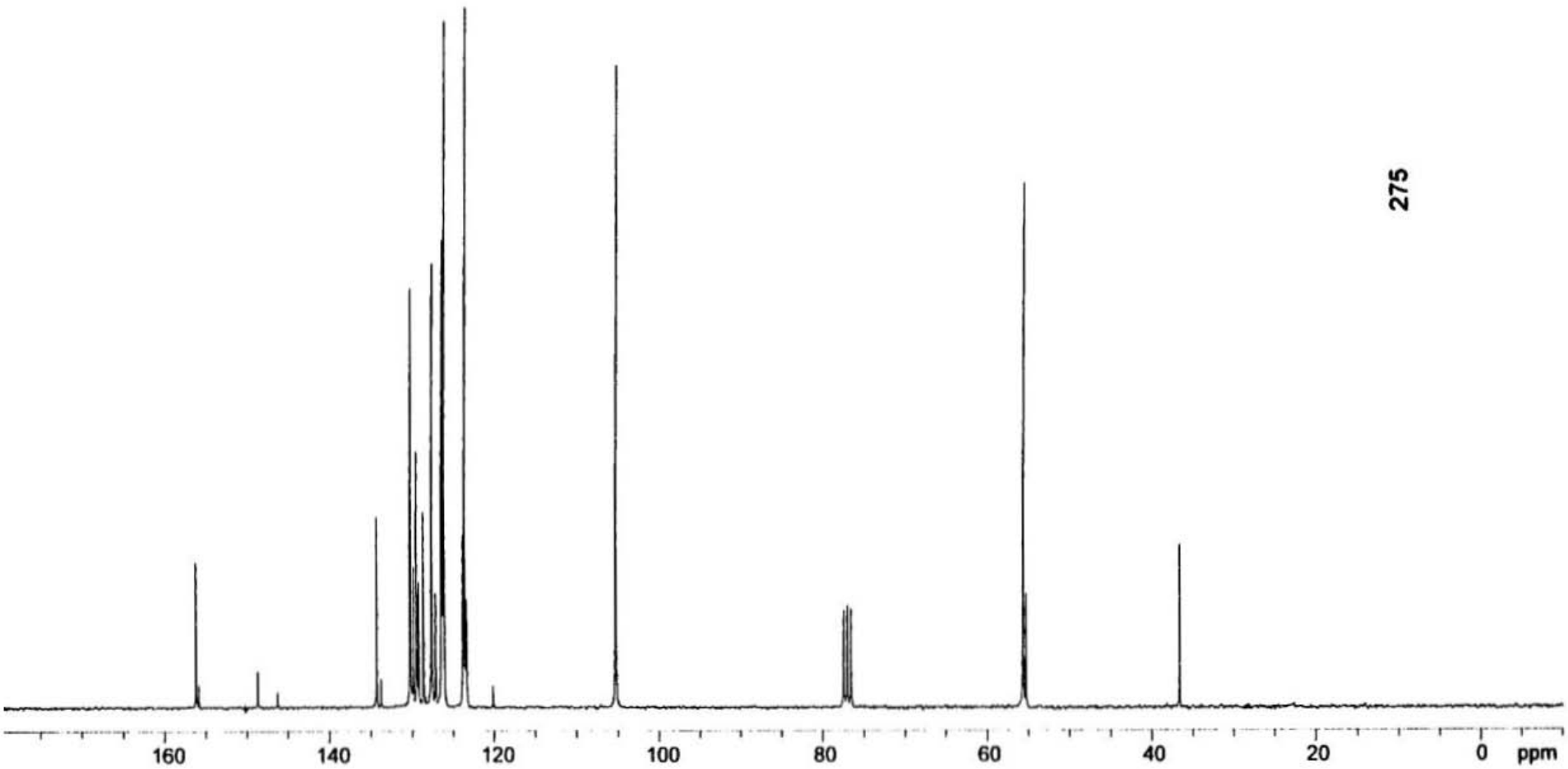
69

274

8 6 4 2 0 ppm


5
10
4
3
11
12
13
14
6
15
7
13'
2
OCH_3
9
1
16
14'
NO_2
8

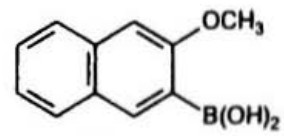
69


275
160
140
120
100
80
60
40
20
0
ppm

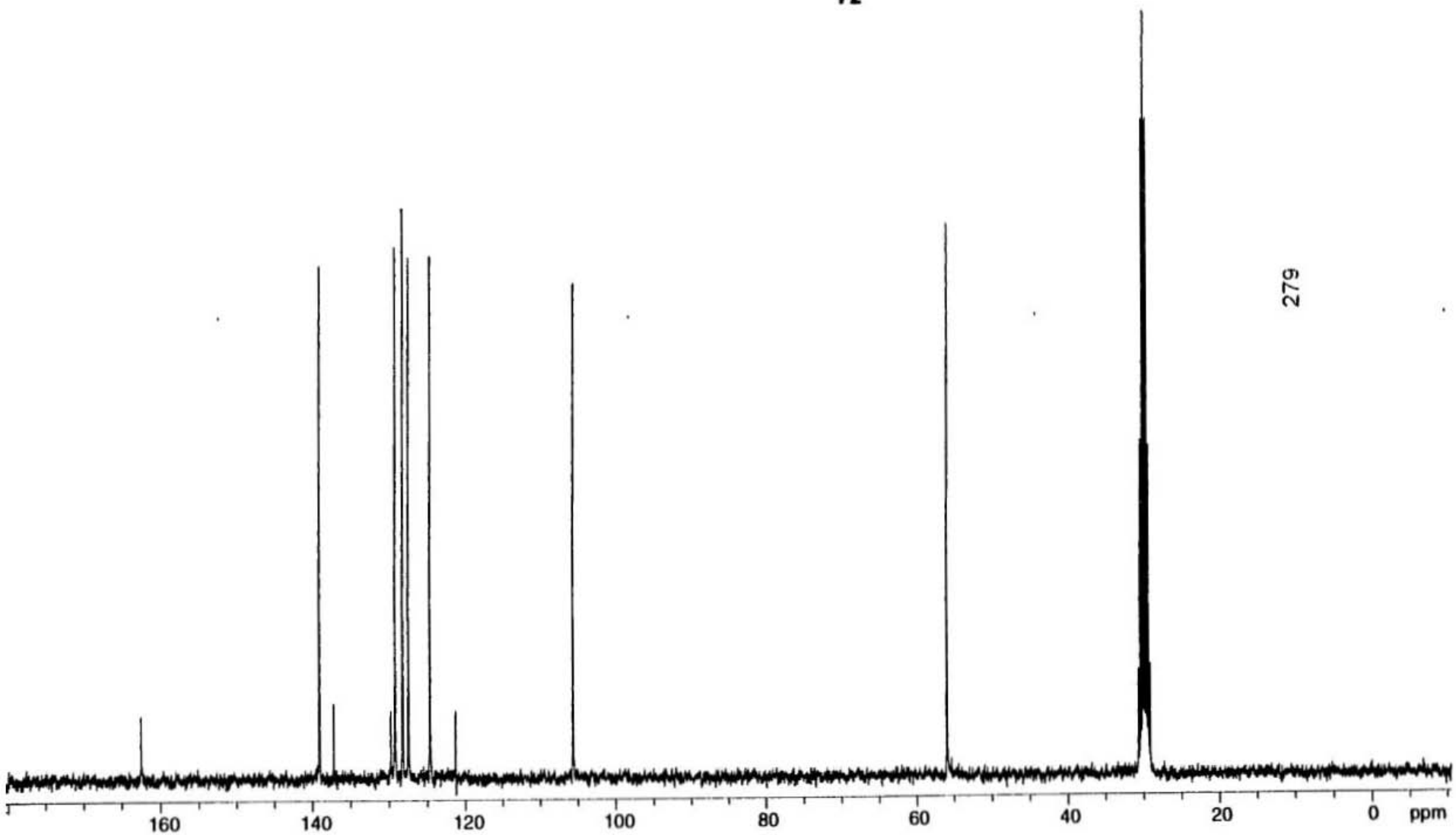
70

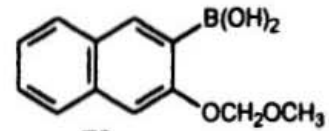
70

72

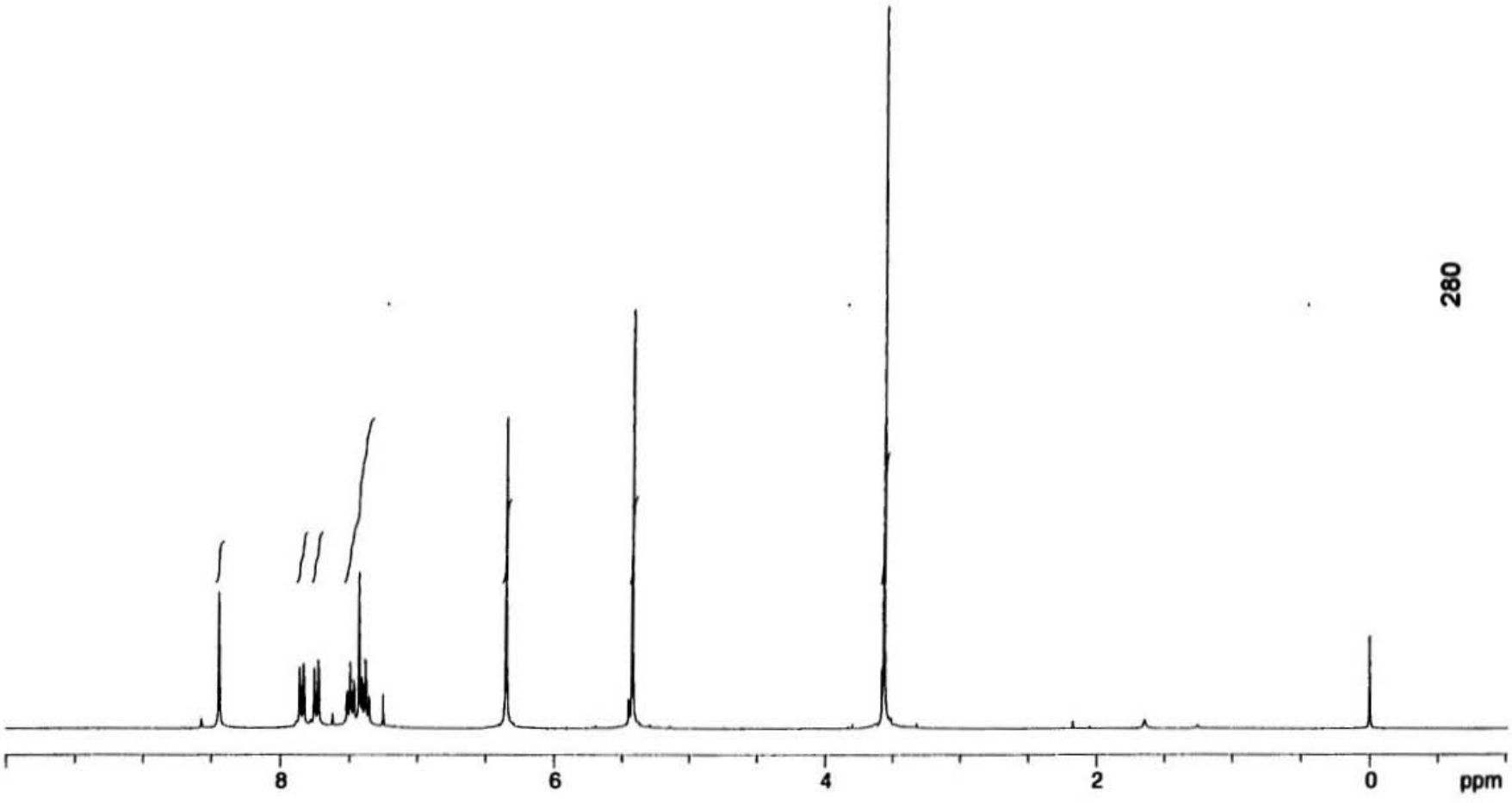


72

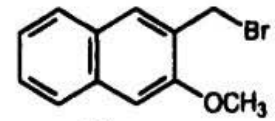




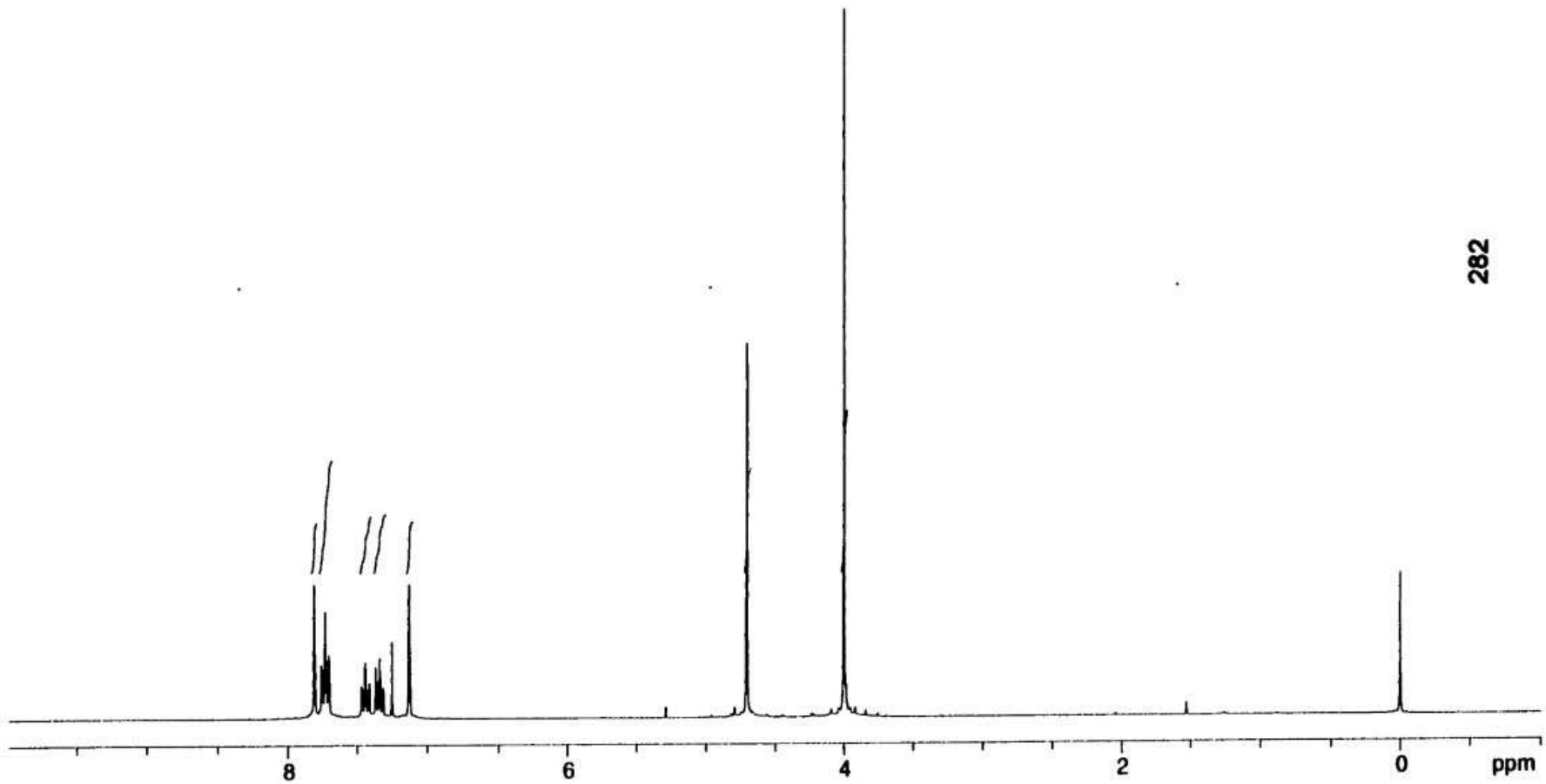
73



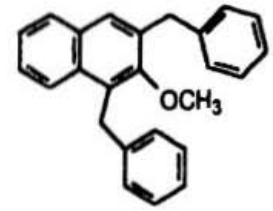
73



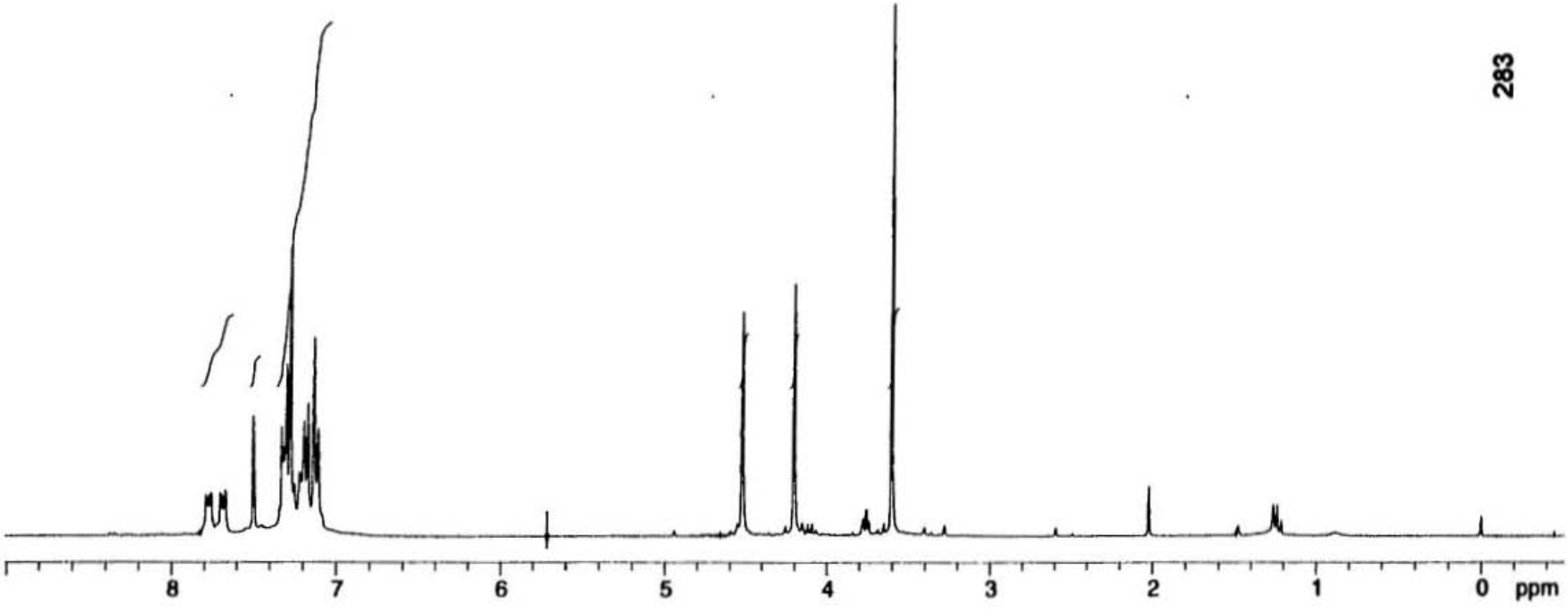
74



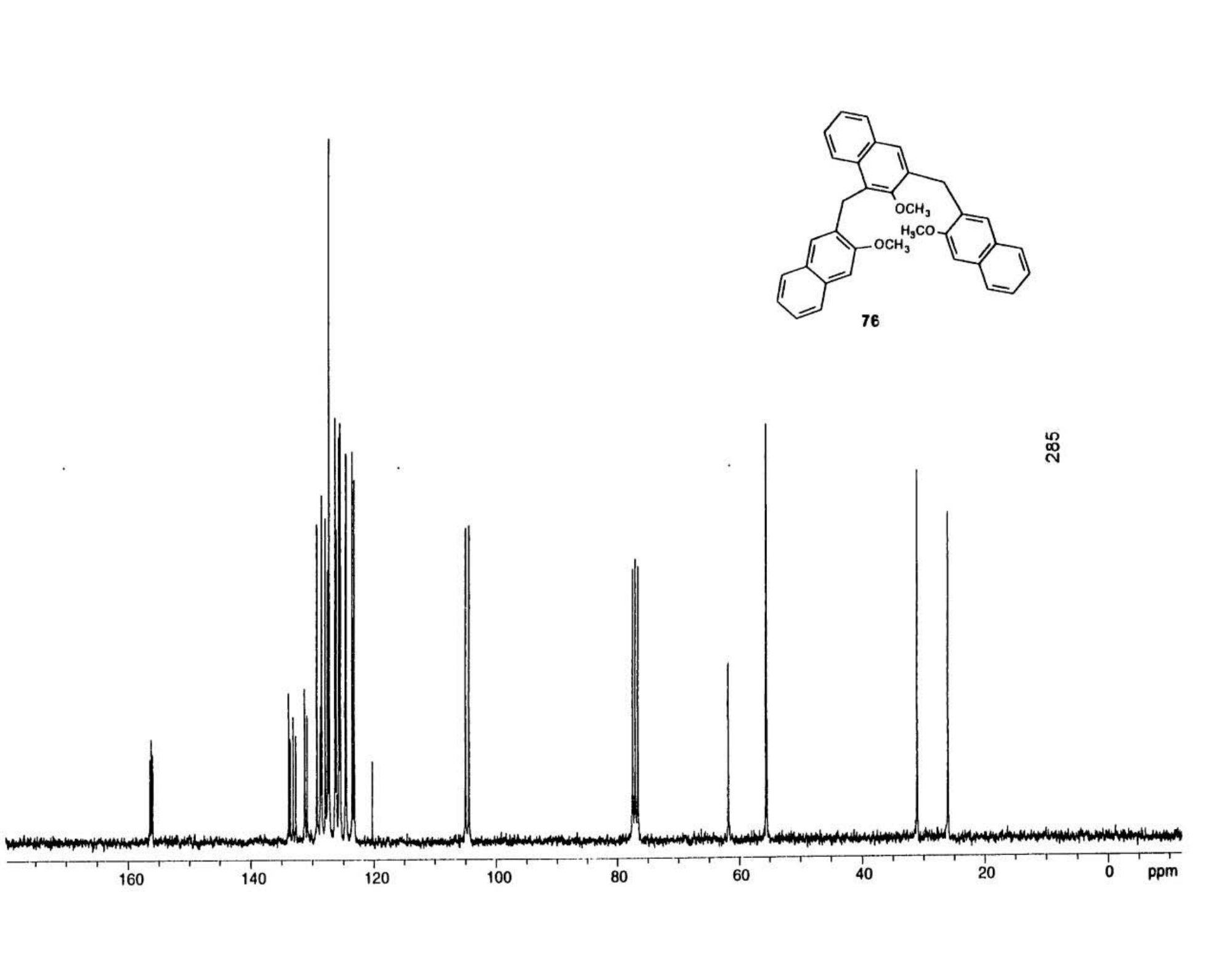
282



75

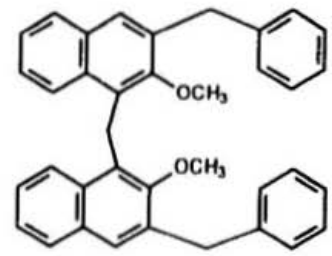


76


OCH3
H3CO
OCH3
76
285
160
140
120
100
80
60
40
20
0
ppm

286

77



77

287

160 140 120 100 80 60 40 20 0 ppm

81

288

289

61

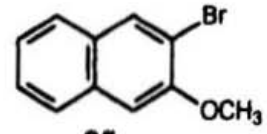
82

291

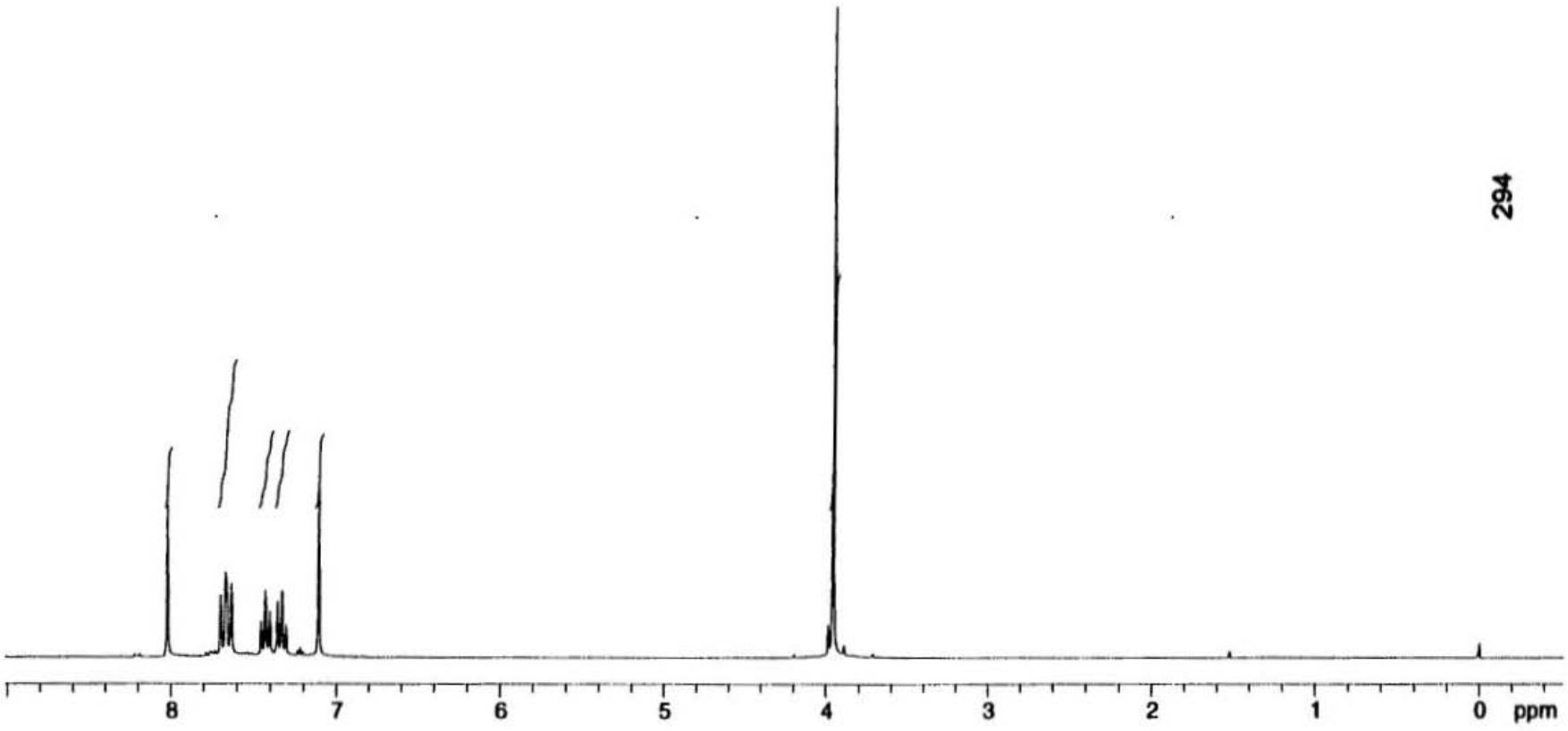
82

83

84

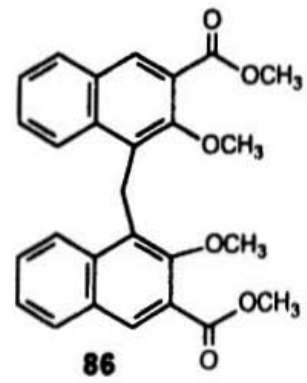


85

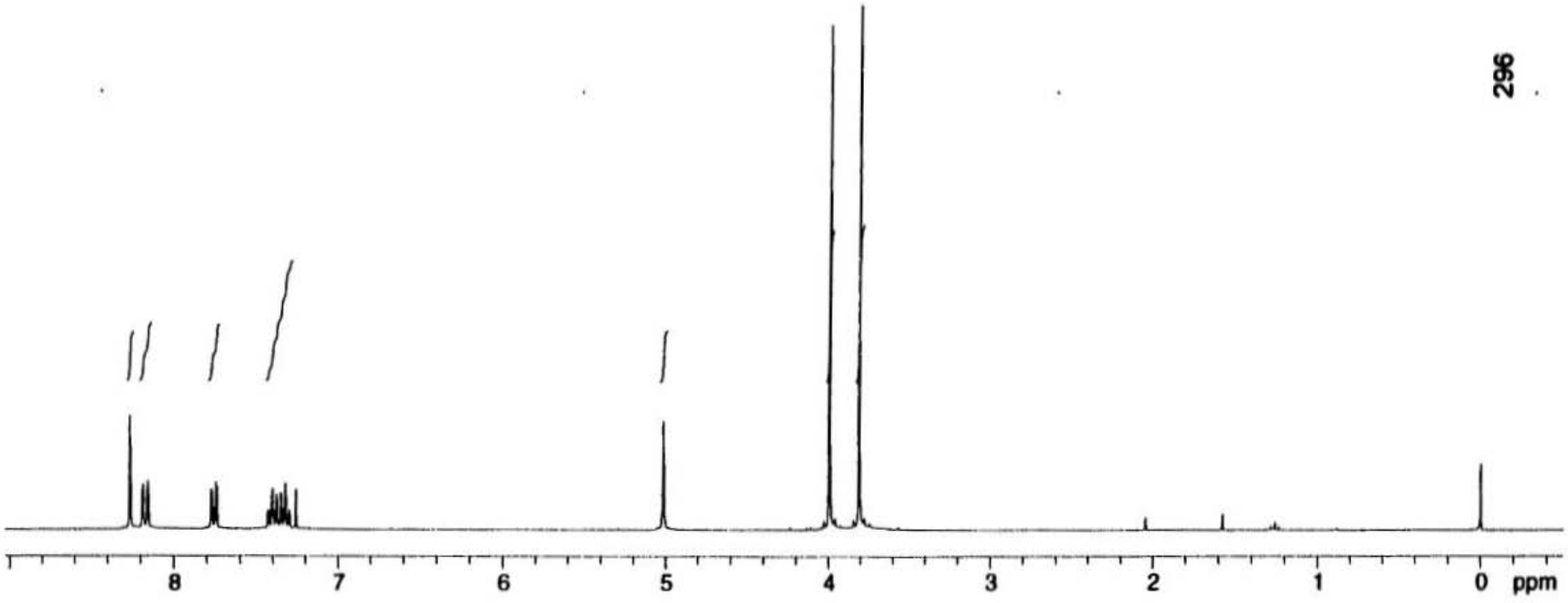


294

86

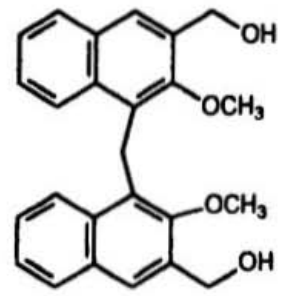


86

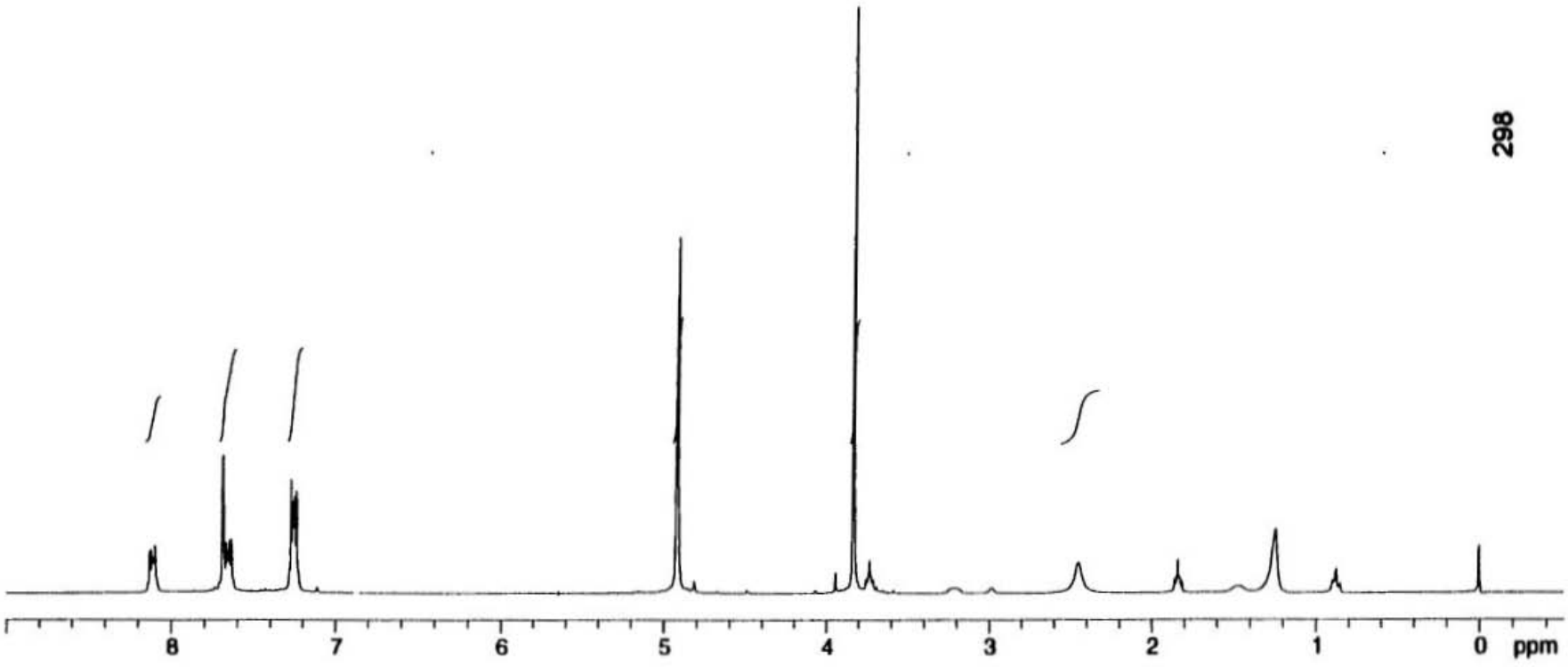


86

297



87



88

89

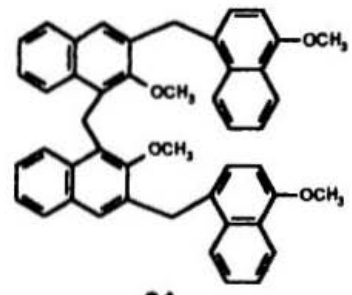
300

301

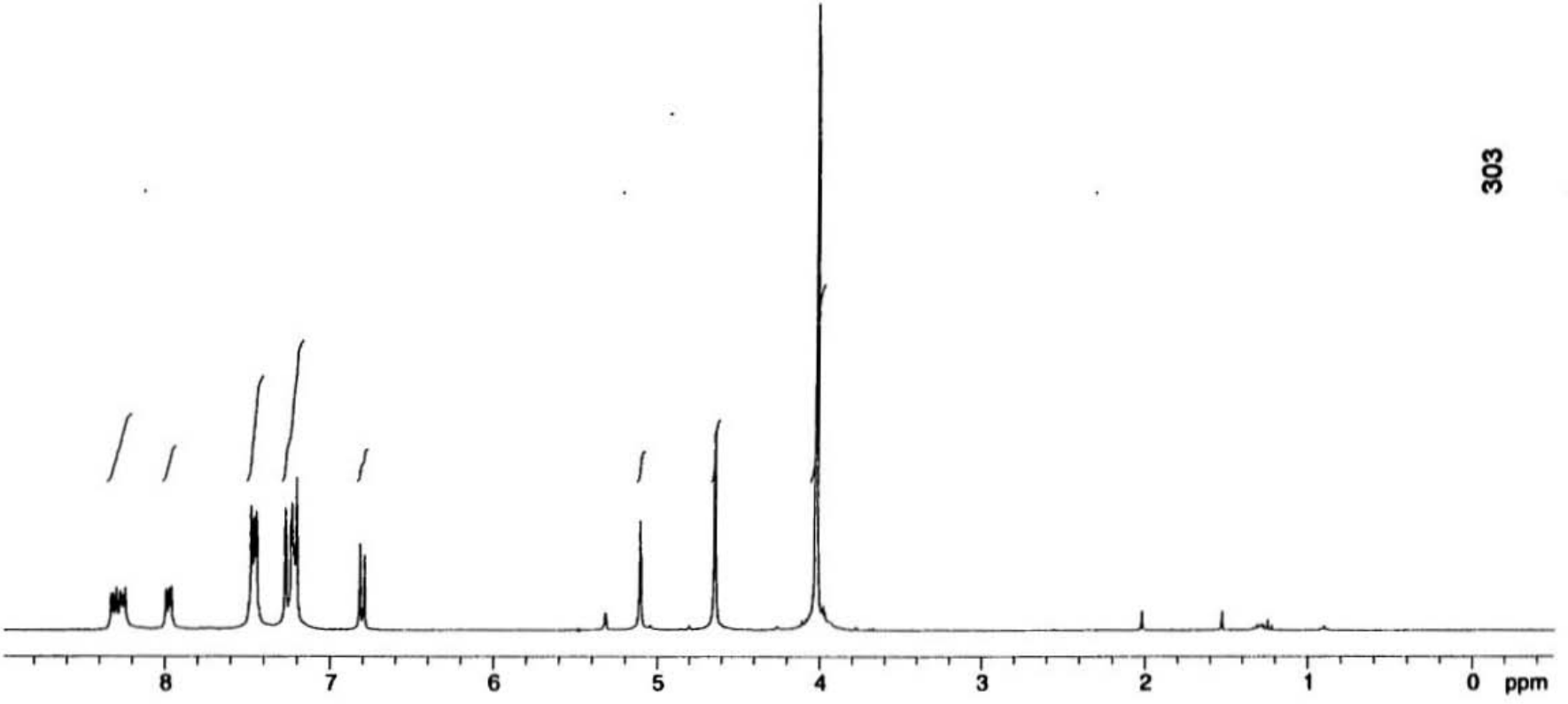
90

90

302



91



91

92

92

8
6
4
2
0
ppm

94
OCH3
O
OCH3

96

96

96

97

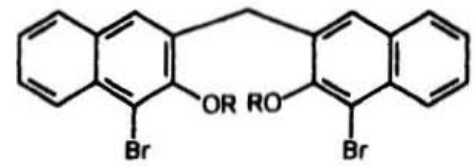
97

98

98

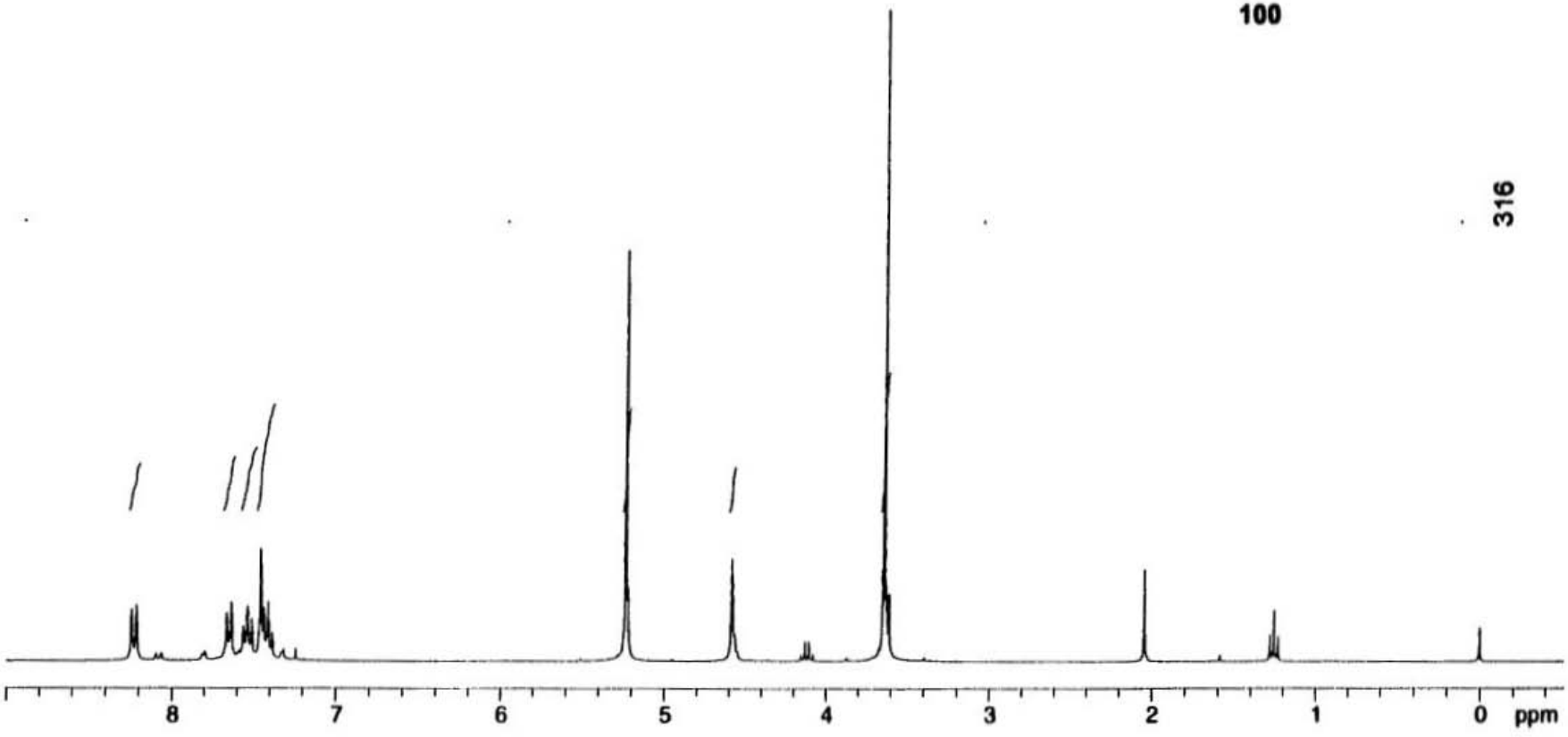
315

99

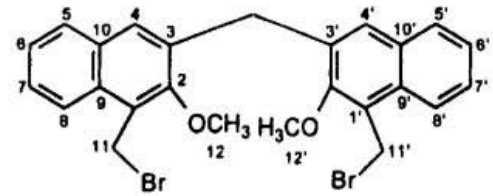


$R = CH_2OCH_3$

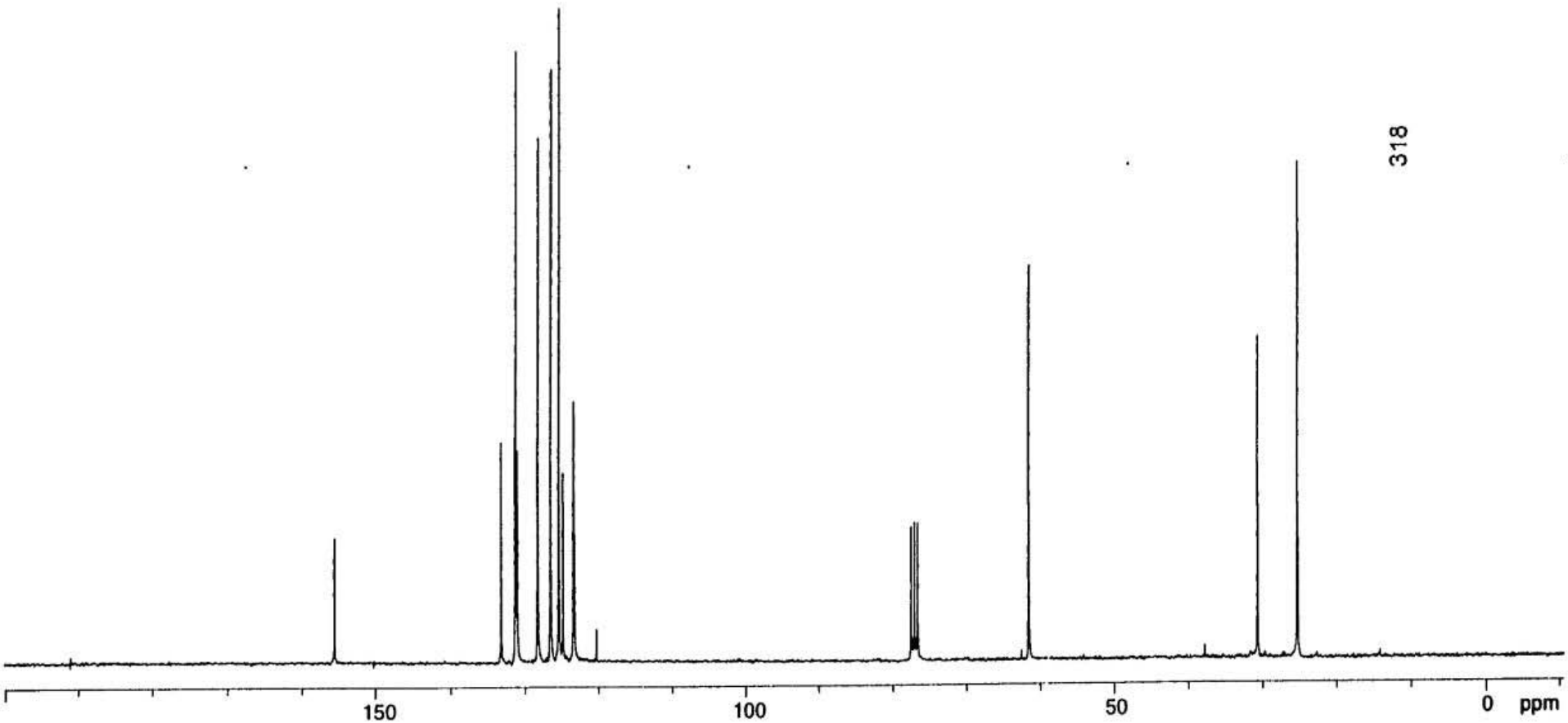
100



102



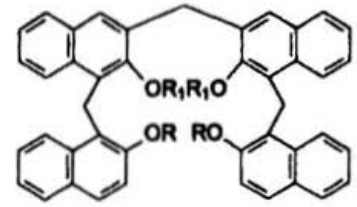
102



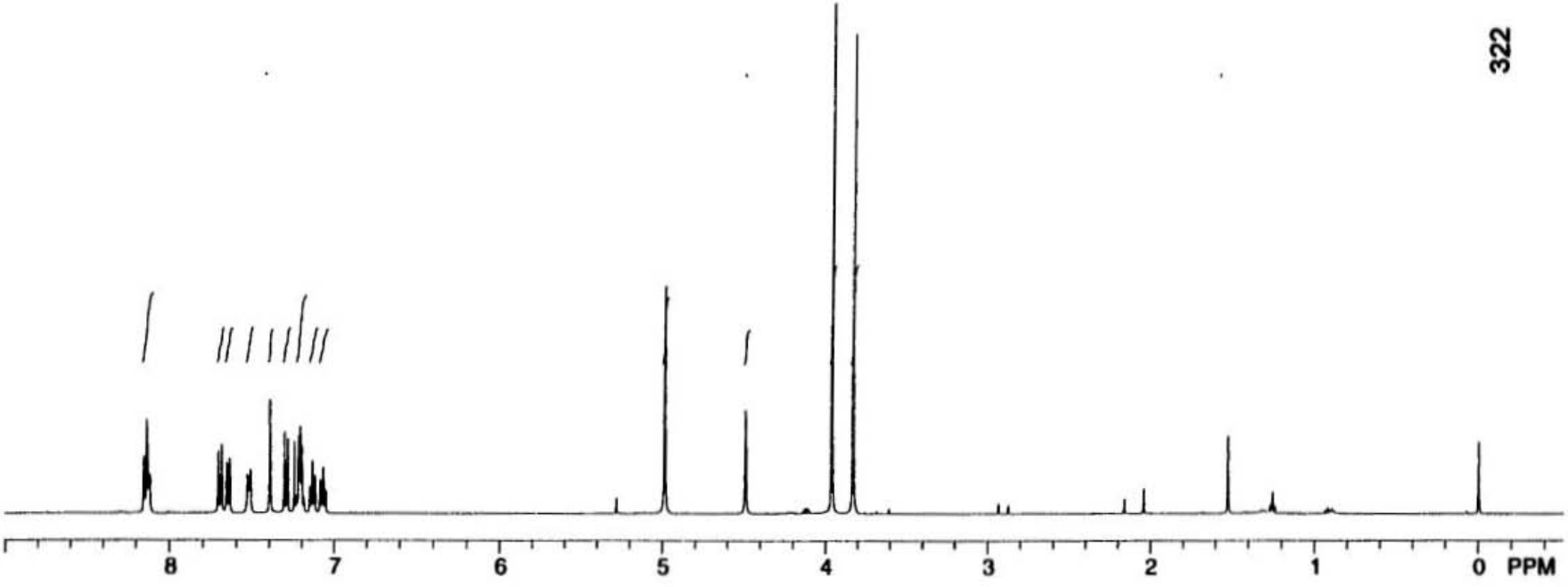
103

104

104



105: R = R_1 = OCH_3.



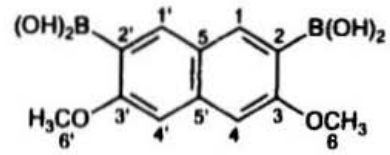
109

323

109

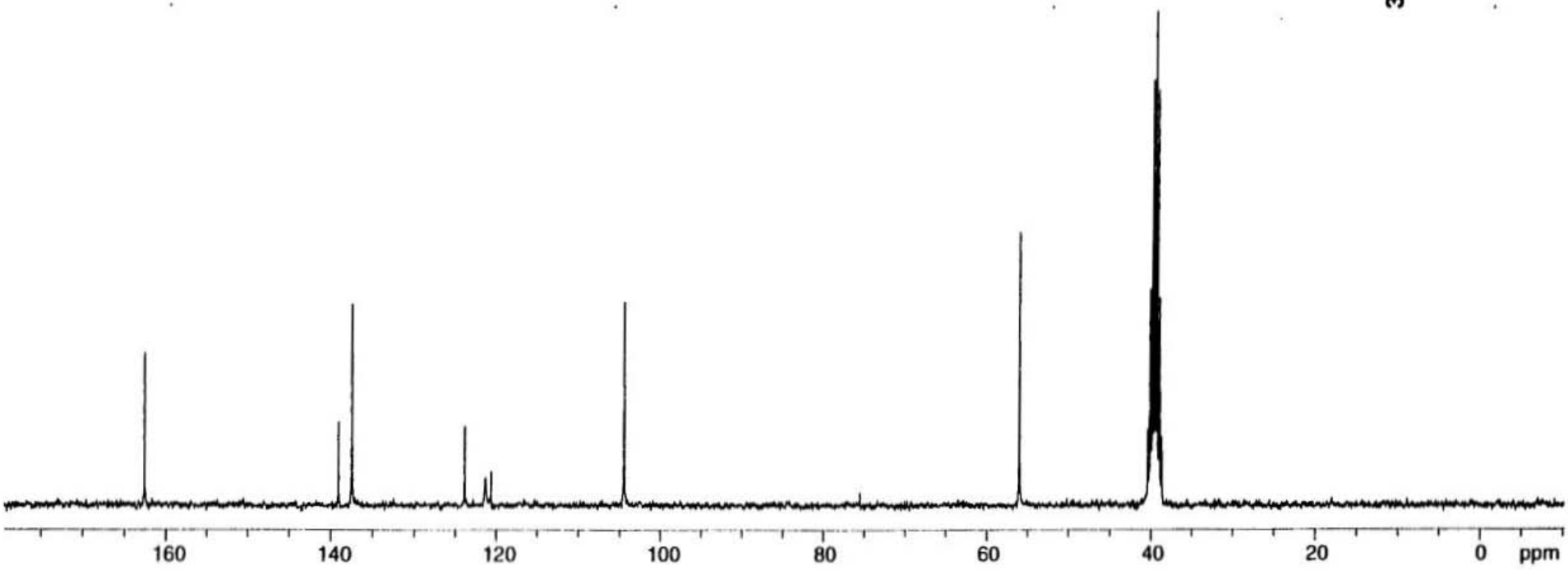
324

110


(OH)2B
B(OH)2
H3CO
OCH3
1'
1
2'
5
2
3'
5'
3
4'
4
6'
6

110

326


160
140
120
100
80
60
40
20
0
ppm

111

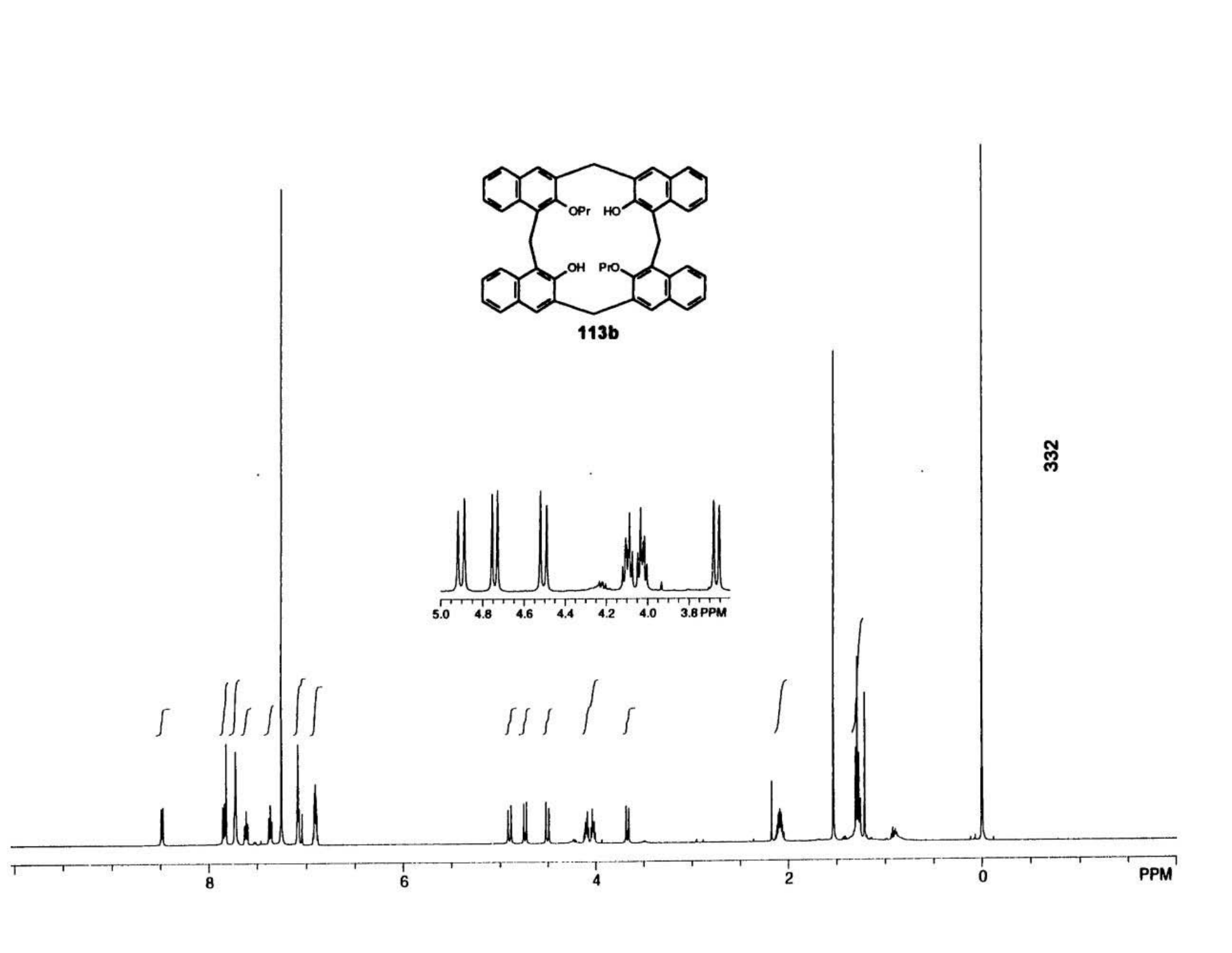
PPM
8
6
4
2
0
328
112
OBu
OBu BuO
2

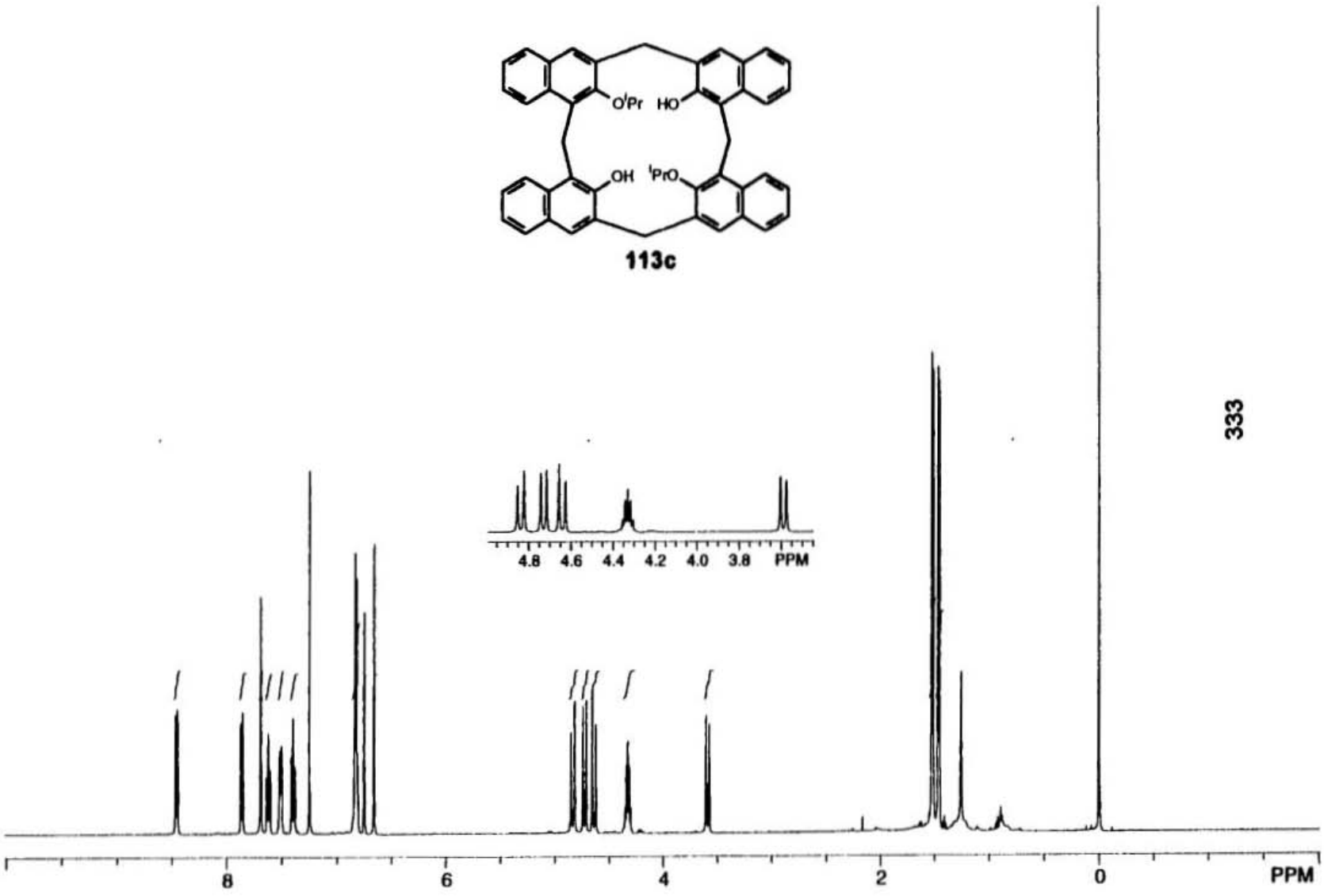
150
100
50
0
ppm
329

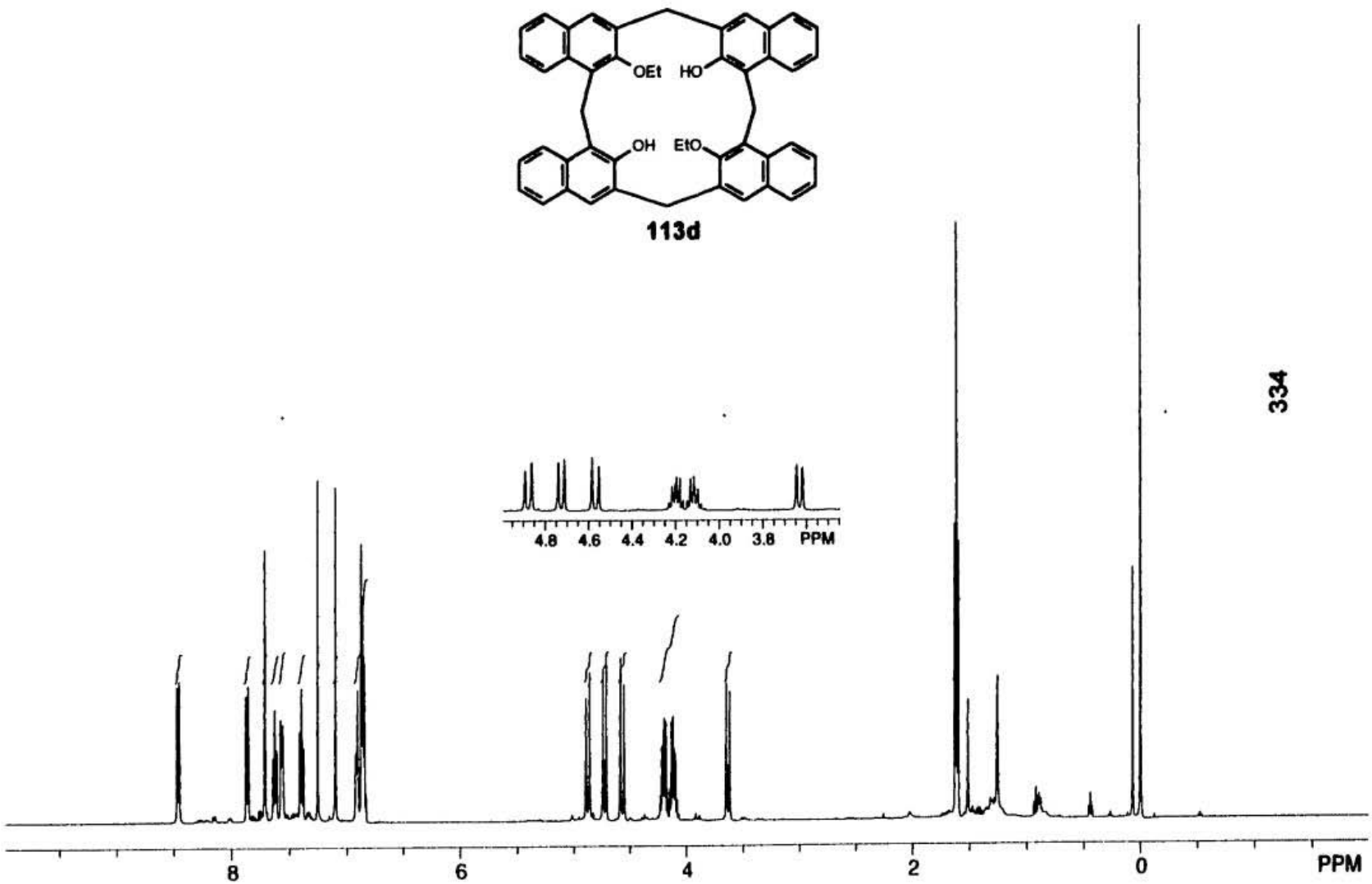
OBu
OBu BuO
112
2

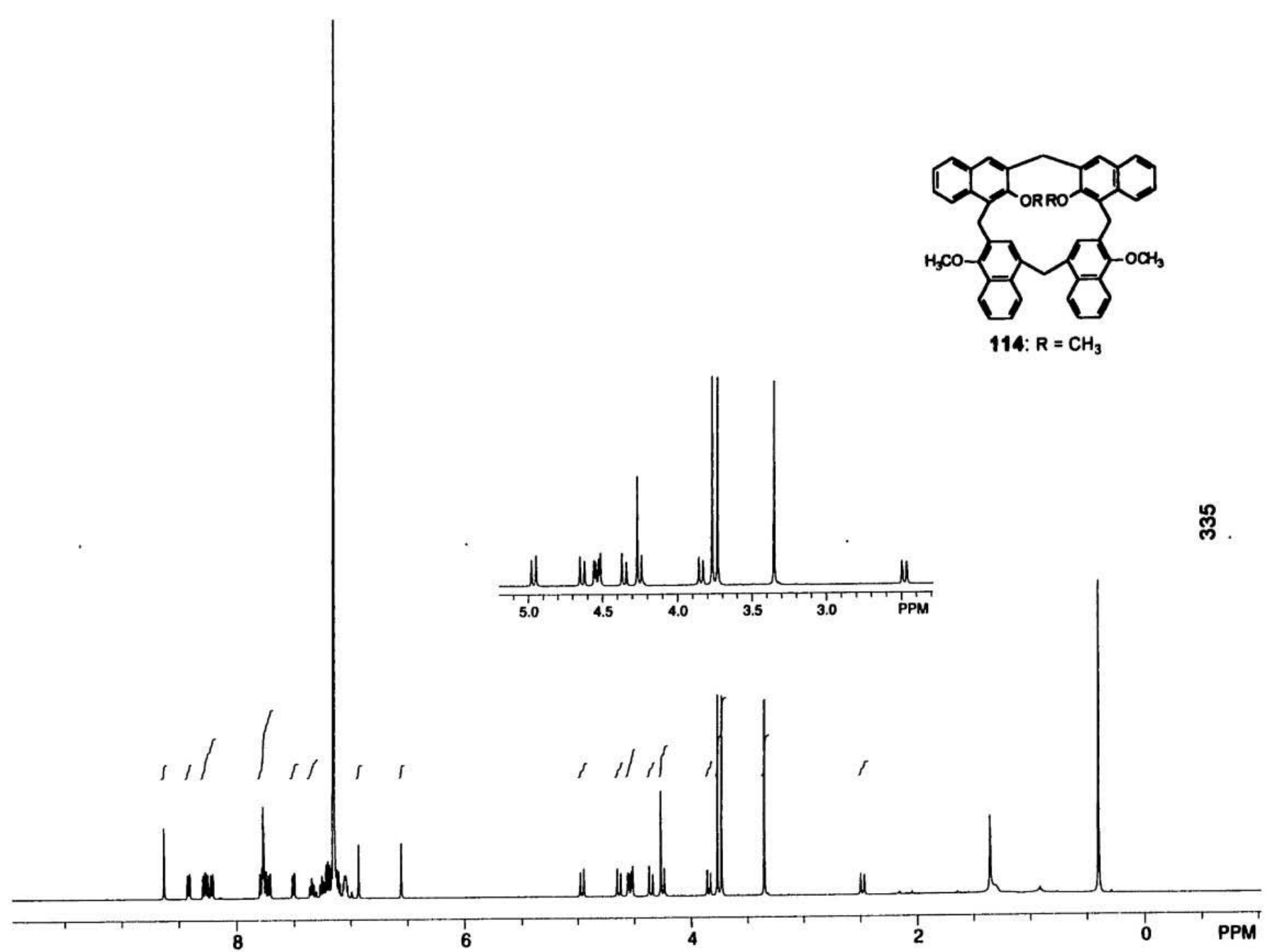
113a

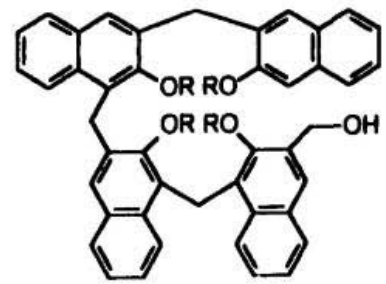
113a


OPr
HO
OH
PrO
113b
332
5.0
4.8
4.6
4.4
4.2
4.0
3.8 PPM
8
6
4
2
0
PPM

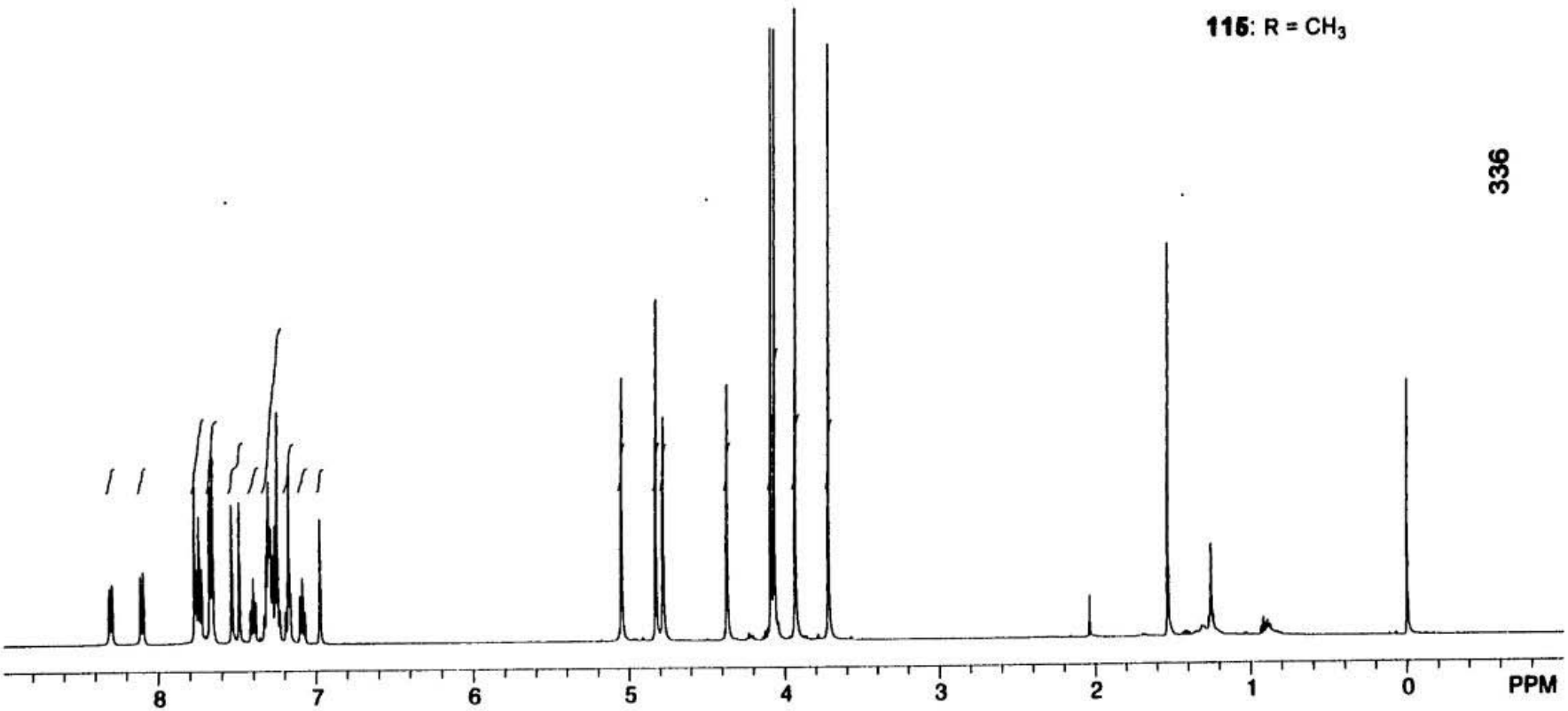

O^{i}Pr
HO
OH
^{i}PrO
113c
333
4.8
4.6
4.4
4.2
4.0
3.8
PPM
8
6
4
2
0
PPM


OEt
HO
OH
EtO
113d
4.8
4.6
4.4
4.2
4.0
3.8
PPM
8
6
4
2
0
PPM
334


OR RO
H3CO
OCH3
114: R = CH3
5.0
4.5
4.0
3.5
3.0
PPM
8
6
4
2
0
PPM

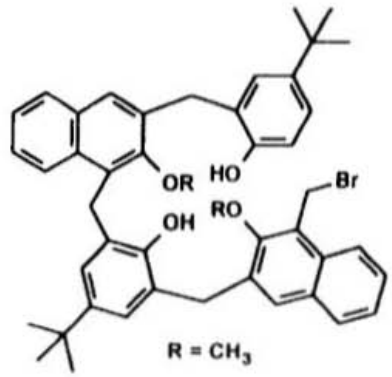


115: R = CH_3



336

117



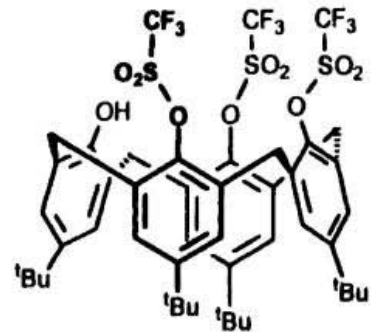
117

338

160 140 120 100 80 60 40 20 0 ppm

118

119


CF3
CF3
CF3
O2S
SO2
SO2
OH
O
O
O
tBu
tBu
tBu
tBu

120

341
8
7
6
5
4
3
2
1
0
ppm

121

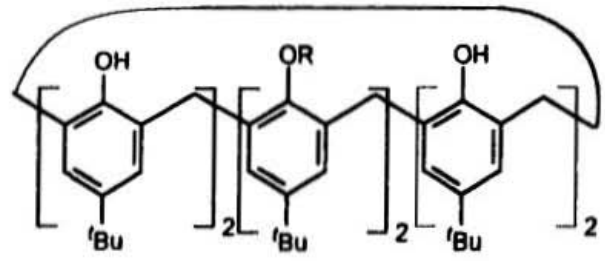
122

123

124

125

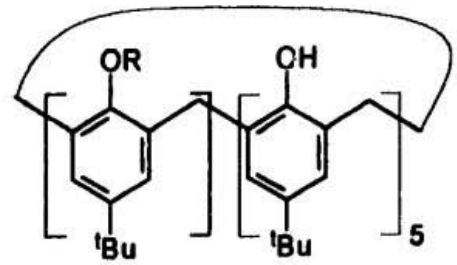
126



127: R = SO_2CF_3

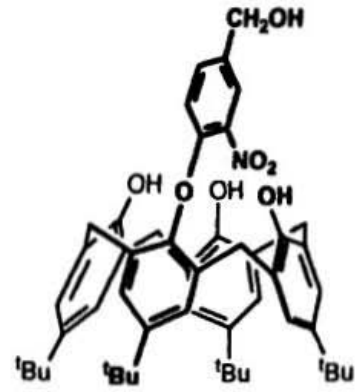
348

8 7 6 5 4 3 2 1 0 ppm

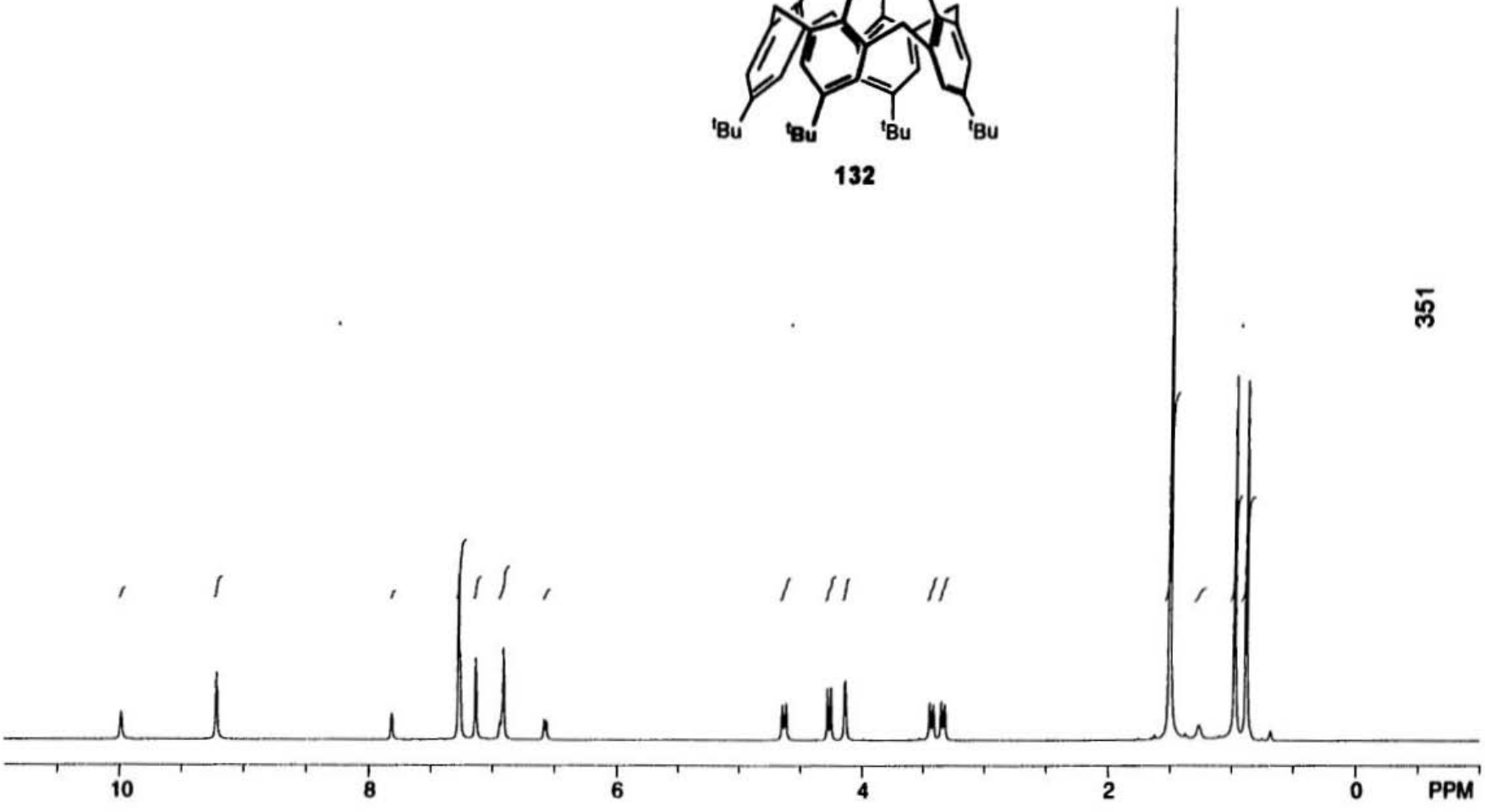


128: R = SO_2CF_3

131 (acetone-d_6)

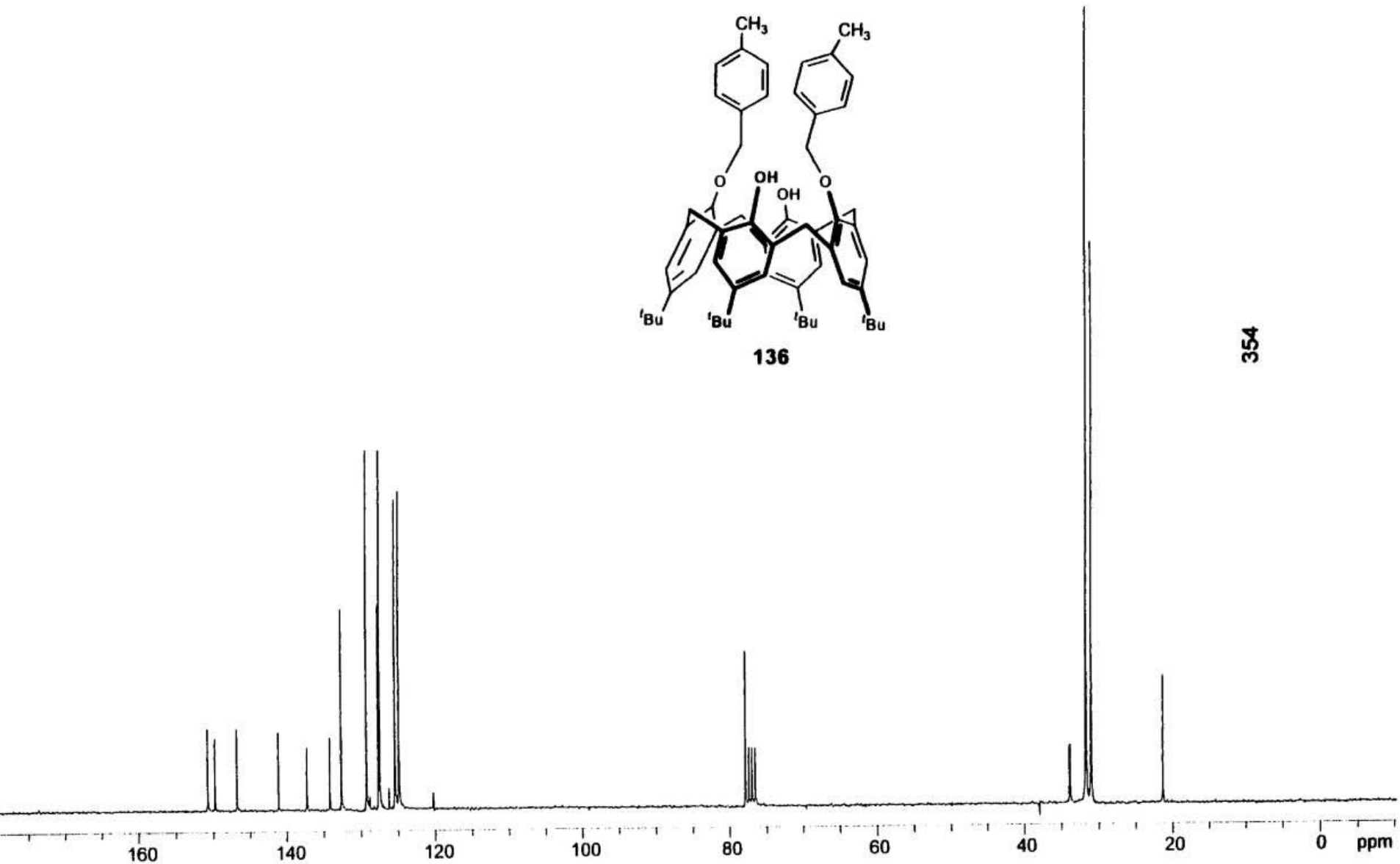


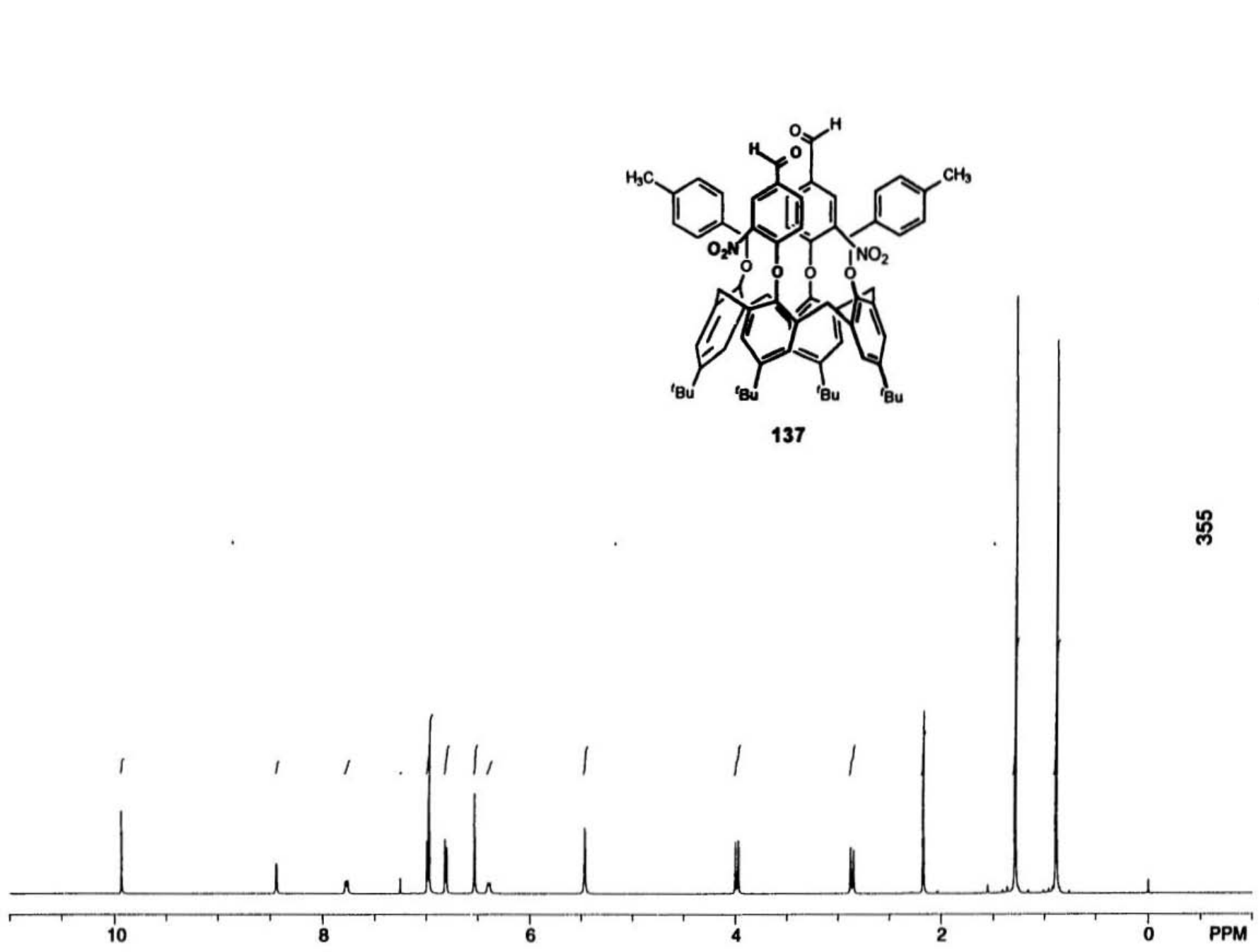
132

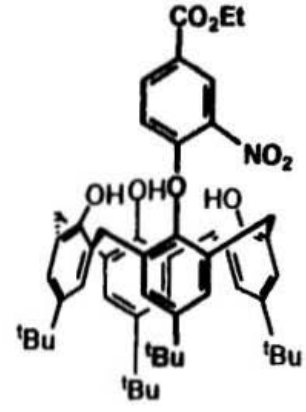


133

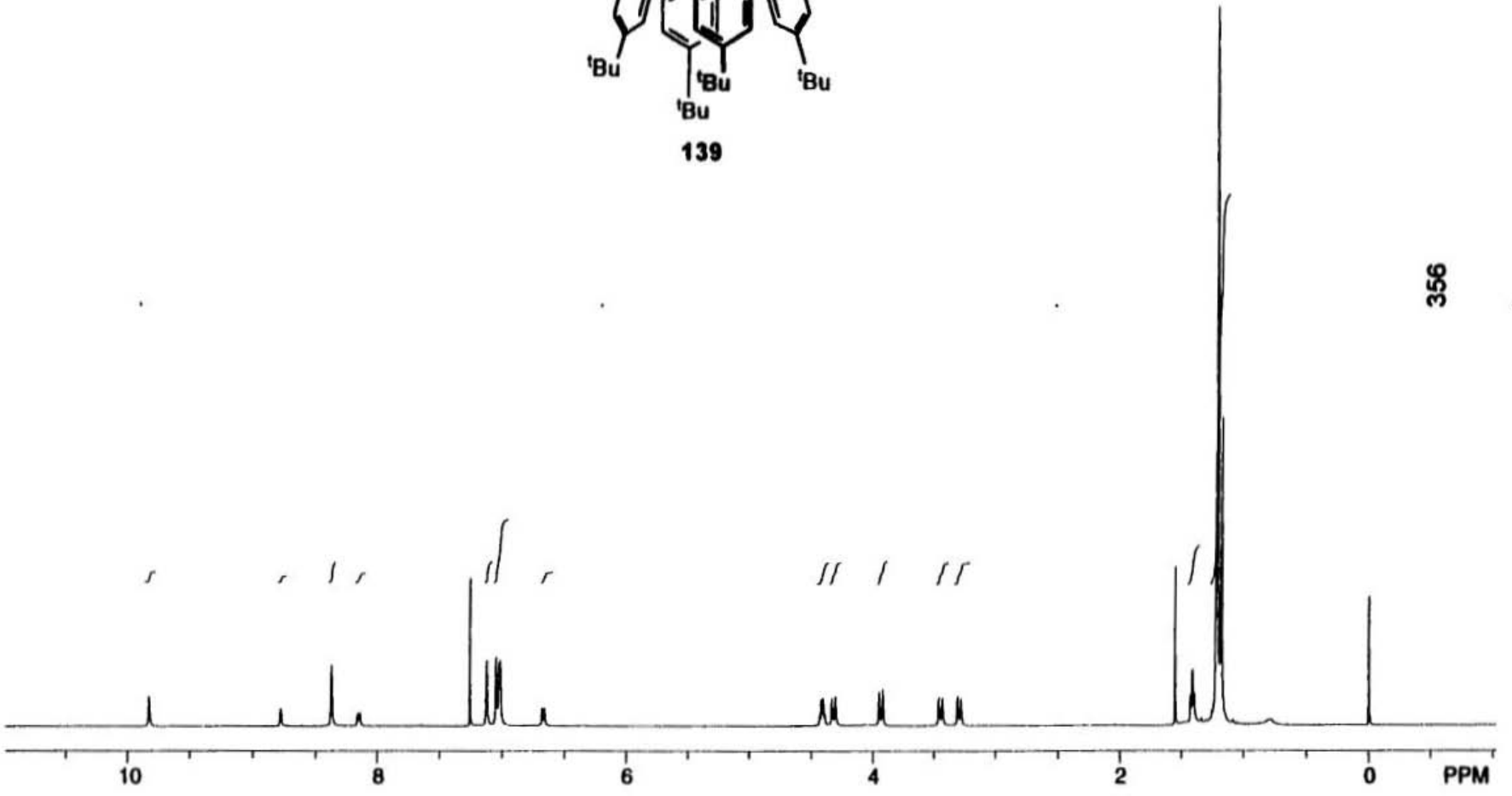
136


CH3
CH3
O
OH
OH
O
tBu
tBu
tBu
tBu
136
354
160
140
120
100
80
60
40
20
0
ppm


H
O
H
O
H3C
CH3
O2N
NO2
O
O
O
O
tBu
tBu
tBu
tBu
137
355
10
8
6
4
2
0
PPM

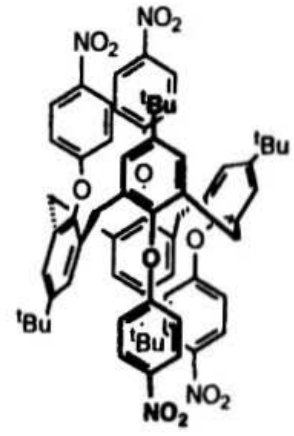


139



140

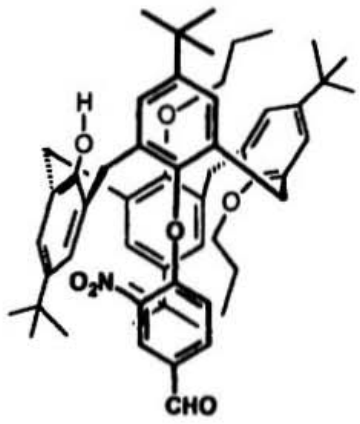
142



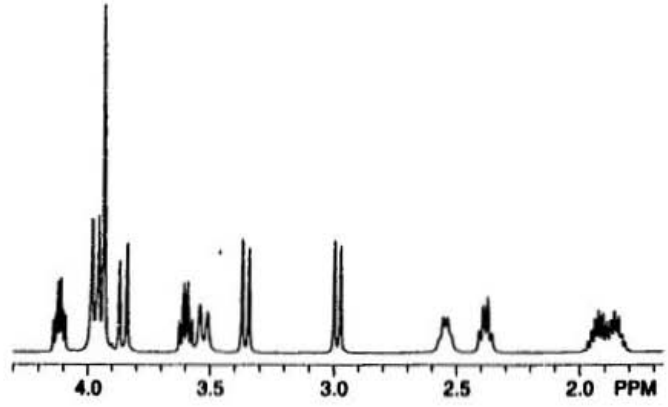
143

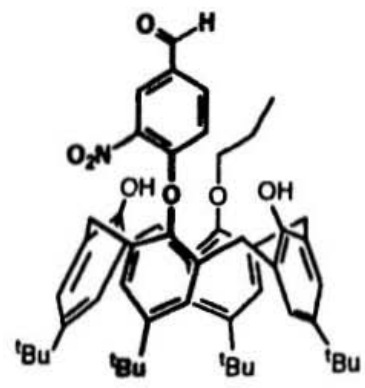
359

8 7 6 5 4 3 2 1 0 PPM



145





146

Appendix B

X-ray data for all compounds in numerical order

X-ray crystal data for 113d: (toluene) $C_{48}H_{40}O_4.2C_{14}H_{16}$; monoclinic, space group C2/c (#15), Z value = 4, a = 13.840(1) Å , b = 17.001(1) Å, c = 20.287(2) Å, β = 103.090(2)°, V = 4649.4(6) Å^3, D_{calc} = 1.236 g/cm^3, F_{000} = 1840.00, μ(MoKα = 0.75 cm^{-1}, crystal dimension = 0.45 x 0.25 x 0.14 mm. Intensity data were measured at 193 K on a Bruker P4/CCD diffractometer with graphite monochromated Mo-Kα (l = 0.71073 Å) radiation to $2q_{max}$ (deg) = -80±1°C; 11374 reflections which were collected, 4776 were unique (R_{int} = 0.044) with I > 2.00σ(I); Final R1 and wR2 values were 0.055 and 0.154, respectively, gof = 1.03.

X-ray crystal data for 119: (ethyl acetate-hexane) (mp 234 - 236 °C) $C_{45}H_{55}F_3O_8S$, monoclinic, space group $P2_1$ (#14), a = 12.382(4) Å, b = 16.795(2) Å, c = 21.825(2) Å, β = 105.31(1)°, V = 4378(1) Å^3, Z = 4, D_{calc} = 1.185 g/cm^3, crystal size = 0.25 x 0.25 x 0.40 mm. Intensity data were measured at 299.1 K on a Rigaku AFC6S diffractometer with graphite monochromated Cu-Kα radiation to $2\theta_{max}$(deg) = 120.2°; 6758 unique reflections converged to a final R = 0.084 for 4155 reflections with I > 2.00$\sigma(I)$; R_w = 0.084, gof = 3.86.

X-ray crystal data for 122: (hexane-cyclohexane) (mp 262 - 264 °C decomp.) $C_{58}H_{65}F_3O_7S$, triclinic, space group $P1$ (#2), a = 12.5828(9) Å, b = 17.514(2) Å, c = 12.474(1) Å, a = 98.015(8)°, b = 101.715(7)°, g = 92.392(7)°, V = 2658.6(4) Å^3, Z = 2, D_{calc} = 1.203 g/cm^3, crystal size = 0.30 x 0.30 x 0.20 mm. Intensity data were measured at 299.1 K on a Rigaku AFC6S diffractometer with graphite monochromated Cu-Kα radiation to $2\theta_{max}$ (deg) = 120.2°; 7916 unique reflections

converged to a final $R = 0.069$ for 5558 reflections with $I > 2.00\sigma(I)$; $R_w = 0.075$, gof = 3.21.

X-ray crystal data for 131: (benzene) mp 178 - 180 °C. $C_{89}H_{77}O_7N$; monoclinic, space group $P2_1/c$ (#14), Z = 4, a = 19.281 (1), b = 15.153(1), c = 20.866(1) Å, b =101.249(2)o,V = 3414 Å, Dcalc = 1.147 g/cm^3, crystal size = 0.35 x 0.24 x 0.07 mm. Intensity data were measured at 183 K on a Bruker P4/CCD diffractometer with graphite monochromated Mo-Ka (l = 0.71073 Å) radiation to 2qmax (deg) = 52.9o; 34213 reflections converged to a final $R_{int} = 0.102$ for 12254 reflections with I > 2.00 s (I); Final R1 and wR2 values were 0.073 and 0.210 respectively, gof = 0.90.

X-ray crystal data for 138: (benzene) mp 252 - 254 °C. $C_{58}H_{68}O_{13}N_2$; triclinic, space group P-1 (#2), $Z = 2$, a = 10.9363(7), b = 12.6808(8), c = 20.501(1) Å, α = 89.837(1)°, β = 83.837(1)°, γ = 78.003(1)°, $V = 2764.4(3)$ Å, $D_{calc} = 1.203$ g/ cm^3, crystal size = 0.60 x 0.44 x 0.14 mm. Intensity data were measured at 183 K on a Bruker P4/CCD diffractometer with graphite monochromated Mo-Kα (l = 0.71073 Å) radiation to $2q_{max}$ (deg) = -80±1°C; 15875 reflections converged to a final $R_{int} = 0.026$ for 11133 reflections with $I > 2.00\sigma(I)$; Final R1 and wR2 values were 0.098 and 0.324, respectively, gof = 1.05.