SYNTHESIS OF NEW CALIX[4]ARENES AND CALIX[4]NAPHTHALENES VIA SONOGASHIRA REACTIONS, PHOTOCHEMICALLY-INDUCED REACTIONS AND [2+2] FRAGMENT CONDENSATION REACTIONS

HASSAN AL-SARAIERH

NOTE TO USERS

Your file Votre référence
ISBN: 978-0-494-33467-6
Our file Notre référence
ISBN: 978-0-494-33467-6

Synthesis of New Calix[4]arenes and Calix[4]naphthalenes via Sonogashira Reactions, Photochemically-Induced Reactions and [2+2] Fragment Condensation Reactions

By

Hassan Al-Saraierh
B. Sc., M. Sc. (2001), Mutah University
Karak, Jordan

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

2007

Abstract

Calixarenes are macrocyclic compounds which can be produced with different sizes and functionalities. They are mainly synthesized by 'one-pot' base-induced condensation reactions of the corresponding phenol(s) with *para*-formaldehyde. For example, the most accessible and commonly-used calixarene, tetra-*p-tert*-butylcalix[4]arene is produced by such a reaction, of *p-tert*-butylphenol with *para*-formaldehyde. The well-defined "calix"- or "cup"-like shape in most of these compounds have made them attractive targets for host-guest and/or supramolecular studies and many other applications.

The work described in this thesis concerns the synthesis and a study of the properties of some new modified calix[4]arenes and calix[4]naphthalenes which were synthesized using different methods. Among the topics dealt with are the following: (a) An attempt to develop a new methodology for the wide-rim modification of calix[4]naphthalene by using a suitably pre-functionalized precursor. (b) The synthesis of a new thiophene-based calix[4]arene using [2+2] fragment condensation reactions. (c) The synthesis of a new member of the homooxacalix[4]naphthalene family using [2+2] fragment condensation reactions. (d) The ability to modify the dimensions of the cavity of a calix[4]naphthalene by extending the bridging units with ($-CH_2-CH_2-$) and/or ($-CH_2-O-CH_2-$) groups.

The narrow-rim hydroxyl groups of calixarenes are known to be resistant to substitution displacement. The Sonogashira coupling reaction with trimethylsilylacetylene and phenylacetylene, however, has now been extended to

trimethylsilylacetylene and phenylacetylene, however, has now been extended to the bistriflate of *p-tert*-butylcalix[4]arene, previously known to be resistant to Stille, Neigishi, or Suzuki-Miyaura reactions. Under some of the reaction conditions investigated, the previously unknown narrow-rim mono- and diiodo-*p-tert*-butylcalix[4]arene products were also produced, in addition to the targeted narrow-rim mono- and dialkynyl products. Homocoupling of the narrow rim monoethynyl-*p-tert*-butyl-calix[4]arene produced a new narrow-rim rigid butadiyne-linked bis-*p-tert*-butylcalix[4]arene.

Some of the narrow-rim 1,3-bis(phenylethynyl)-*p-tert*-butylcalix[4]arenes which were synthesized using modified Sonogashira coupling conditions, were found to be photolabile, and produced unprecedented 7-membered oxacycle systems formed via 7-*exo*-dig cyclizations, as well as a new [3.2.1]bicyclic system via postulated 1,8-H shifts. The calixarene provided a scaffold for these unprecedented photochemical reactions to occur.

Finally, the syntheses of several new donor-acceptor narrow-rim functionalized alkynylcalix[4]arenes, and their potential in nonlinear optical materials are described.

Acknowledgments

I would like express my deep gratitude to Dr. Paris E. Georghiou for his supervision, guidance and patience. I would like also to thank him for providing support and a great learning environment.

I would like also to thank the members of my research committee, Dr. Peter Pickup and Dr. Laurence Thompson, for their advice, suggestions and helping comments to this work. Thanks also to David Miller and Julie Collins for the X-ray structures and NMR spectra, and thanks to Linda Winsor for mass spectra.

Special thanks to my parents, my wife and parents, for their love and support. Thanks also extended to the entire organic group and the staff in the Chemistry Department for their help, friendship and encouragement.

The financial support from the Department of Chemistry, the School of Graduate Studies, Memorial University of Newfoundland and NSERC were greatly appreciated.

Table of Contents

List of Figures

List of Figures: Chapter 1

List of Figures: Chapter 2

List of Figures: Chapter 3

List of Figures: Chapter 4

List of Figures: Chapter 5

List of Figures: Chapter 6

List of Figures: Chapter 7

List of Tables

Glossary of Abbreviations

Ar	Argon
APCI	Atmospheric pressure chemical ionization
t-Bu	*Tertiary*-Butyl
n-BuLi	Butyl lithium
^{13}C NMR	Carbon Nuclear Magnetic resonance
CPK models	Corey-Pauling-Koltun space-filling models
DBU	1,5-Diazabicyclo[5.4.0]undec-5-ene
DMF	Dimethylformamide
D–π–A	Electron-donating group-π-electron-accepting group
ESIPT	Exited state intramolecular proton transfer
ESIET	Excited state intramolecular electron transfer
HMBC	Heternuclear correlation emphasizing long range couplings
HMQC	Heteronuclear Multiple-Quantum Correlation
^{1}H NMR	Proton Nuclear Magnetic resonance
LAH	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
MCPBA	Meta-chloroperbenzoic acid
Me	Methyl
MS	Mass spectrometry
NLO	Non-linear optics
NOED	Nuclear Overhauser effect difference
[Pd]	Palladium catalyst
PLC	Preparative thin layer chromatography
Pr or *n*-Pr	*n*-Propyl
i-Pr or *i*-Propyl	*iso*-Propyl
PTMATB	Phenyltrimethylammonium tribromide
rt	Room temperature
SHG	Second Harmonic Generation
TBAF	Tetrabutylammonium floride
p-tert	*Para*-tertiary
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMSA	Trimethylsilylacetylene
TMS	Trimethylsilyl
TMACl	Tetramethylammonium chloride
TPE	Tetraphenylethene
U.V.	Ultraviolet
β	Second-order Hyperpolarization

This thesis dedicated to:
My wife and my son Hamza
and my parents

Chapter 1
Introduction

1.1. Supramolecular Chemistry

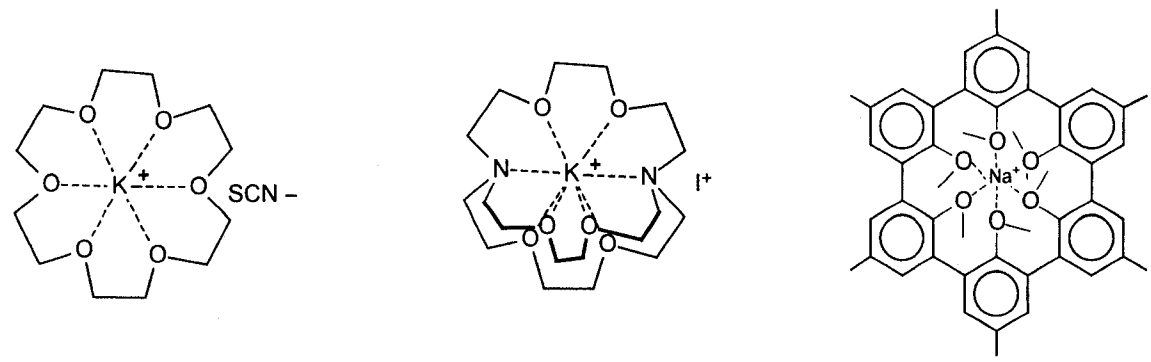
Supramolecular chemistry is a multidisciplinary science which covers the chemical, physical, and biological properties of particular systems that are produced as a result of noncovalent bonding interactions between different component molecules. In contrast to typical covalent bonding in which bond energies are relatively high, those in noncovalent bonding are lower. The chemical species in noncovalent bonding are held together and are organized by relatively weak interactions such as hydrogen bonding and van der Waals forces.[1] Even though these intermolecular non-bonding interactions are weaker than those involved in typical covalent bonding, they can change the molecular properties of supramolecular assemblies when they are combined and summed.

Supramolecular chemistry was first recognized by the chemical community at large when the 1987 Chemistry Nobel Prize was awarded jointly to Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen for their research in this area. In particular they were recognized for their studies on artificial "host-guest" systems mimicking those in living species which execute many biological activities employing noncovalent interactions. For example, enzymes can recognize their particular substrates, as a consequence of non-bonding interactions with them, and perform specific reactions on these substrates, for example, only L-amino acids and not the D-amino acids are produced in cells.[2] Another example where supramolecular interactions occur in living species can

be found in cell membranes, which have channels within self-assembled structures. The channels can execute complicated non-covalent functions such as selective ion transportation through the cell.[3]

The synthesis of targeted novel molecules that are able to mimic biological systems is one of the main goals of supramolecular chemistry, in particular, the study of their "host-guest", or "molecular recognition", or "inclusion" chemistry. This fascinating area of chemistry was pioneered by Pederesen.[4,5] He discovered of crown ethers in 1968 and found out that these compounds have remarkable abilities to recognize and selectively bind to specific metal cations in complex mixtures, as in complex **X** where 18-Crown-6 ether binds selectively with K^+ (Figure 1.1).

In 1969, based upon Pedersen's discovery, Lehn developed a new class of bycyclic compound from crown ethers which have become known as "cryptands". These compounds show even higher selectivity when they form complexes, e.g. "Complex **Y**. Cram has also designed new host molecules that form complexes of very high selectivity, for example the host in "Complex **Z**" binds sodium ions 420,000 times stronger than lithium ions (Figure 1.1).[6]



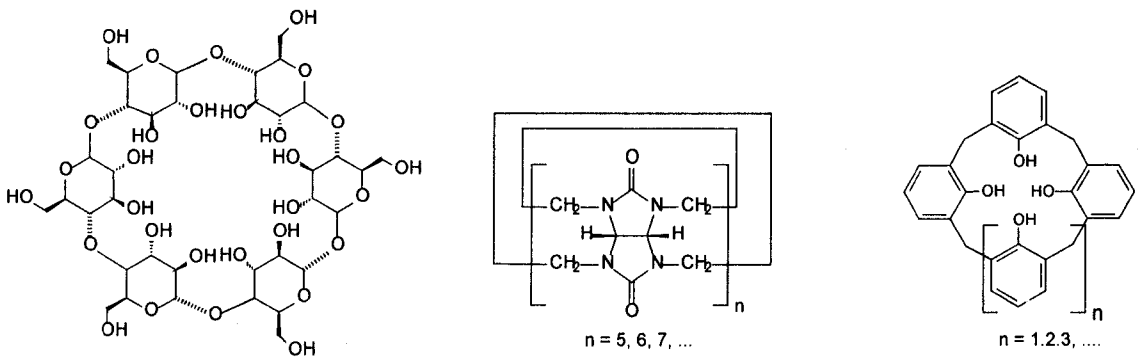
X Crown ether complex (Pedersen)

Y Cryptate (Lehn)

Z host-guest complex (Cram)

Figure 1.1 Examples of supramolecular complexes **X**, **Y** and **Z**.

Following Pedersen's, Lehn's and Cram's work, research on the synthesis and study of supramolecular properties has accelerated rapidly, and new generations of macrocyclic host molecules such as cyclodextrins,[7] cucurbiturils,[8] and calixarenes[9] have been developed (Figure 1.2). These molecules are subjects of extensive current research by many groups, but in the following paragraphs calixarenes only will be reviewed.



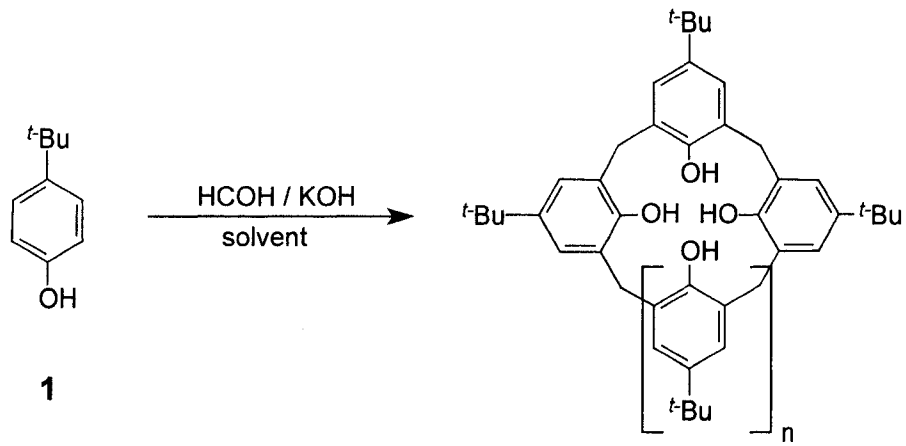
cyclodextrins cucurbiturils calixarenes

Figure 1.2 Different generations of macrocyclic host molecules.

1.2. Calixarenes

Calixarenes are macrocyclic compounds whose structures can be considered to be examples of [1_n]metacyclophanes. The first example was accidentally produced by Zinke and Ziegler in the 1940s,[10] when they reported that the base-induced reaction of some *para*-alkylated phenols with formaldehyde, under similar reaction conditions that Baeyer had conducted in 1872,[11] produced "resinous tar" which produced crystalline products that decomposed above 300 °C. After several years of investigations, Ziegler concluded that these products were "cyclic oligomers".[12]

The same reaction was reinvestigated by Gutsche and co-workers[13] in the 1970s, as a part of their studies of enzyme catalysis. Gutsche was able to synthesize and fully characterize these cyclic oligomers in good and reproducible yields. Different cyclic oligomers can be obtained as the major products depending on the conditions of the condensation reaction; the tetramer, calix[4]arene **2**, is obtained as the major product of the reaction of *p-tert*-butyl phenol (**1**) and formaldehyde when diphenyl ether and KOH are used, the octamer calix[8]arene **4**, is obtained when xylene and trace amounts of KOH are employed, while with a larger amount of KOH in xylene the hexameric calix[6]arene **3** becomes the major product (Scheme 1.1). Gutsche's pioneering work thus led to easy one–step reactions of making calixarenes.

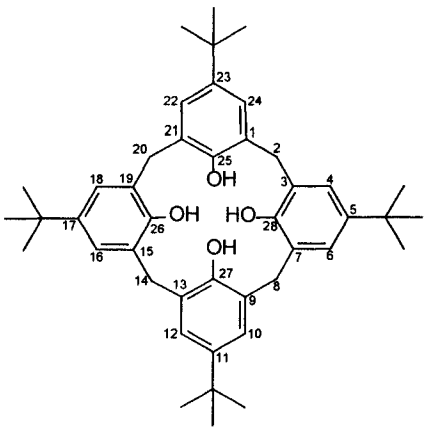


Scheme 1.1 Different cyclic oligomers are obtained using different reaction conditions.

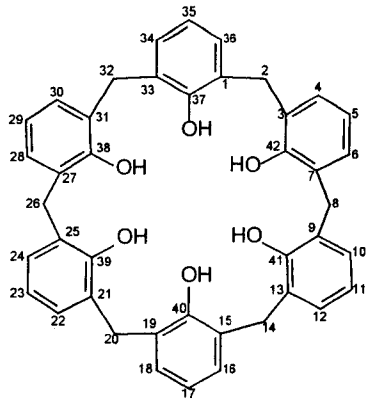
1.2.a. Calixarene Nomenclature:

Several different ways have been used for naming calixarenes. Zinke[12] named the cyclic tetramer **2**, produced from the condensation of *p-tert*-butylphenol and formaldehyde as a "cyclischen benzylene". The Chemical Abstracts name for this compound is complicated and inconvenient. On the other hand, the more convenient name "calixarenes" was introduced by Gutsche,[3] because of the vase-like structure resemblance of these compounds. Thus, the cyclic tetramer above was named more fully as *p-tert*-butylcalix[4]arene (**2**), where "calix" is the *Greek* word for a type of vase, and "arene" refers to the incorporated aromatic rings. In most cases these arenes are oriented in such a way that each of them constructs a well-defined "cavity". The bracketed number

between "calix" and "arene" indicates the ring size of the macrocyclic compound, and the prefixes represent the positions of the substituent units on the aromatic rings.[3] The same compound can be named in a more systematic way as 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-calix[4]arene (**2**). This is also the method used to describe hetero-substituted calixarenes, i.e. calixarenes with different functional groups (Figure 1.3).



5,11,17,23-tetra-*tert*-butylcalix[4]arene-25,26,27,28-tetrol
or
p-tert-butylcalix[4]arene (**2**)



Calix[6]arene-37,38,39,40,41,42-tetrol
or
Calix[6]arene

Figure 1.3 Nomenclature of calixarenes

Calixarenes have two major regions where most of their derivatizations take place; the first is the phenolic hydroxyl group region which is named the "narrow-rim", or the "upper-rim". The second region is represented by the *para*-position on the phenolic rings, which is named the "wide-rim" or the "lower-rim". The terms "proximal" and "distal" are also used to designate the adjacent and opposite phenyl groups, respectively (Figure 1.4).

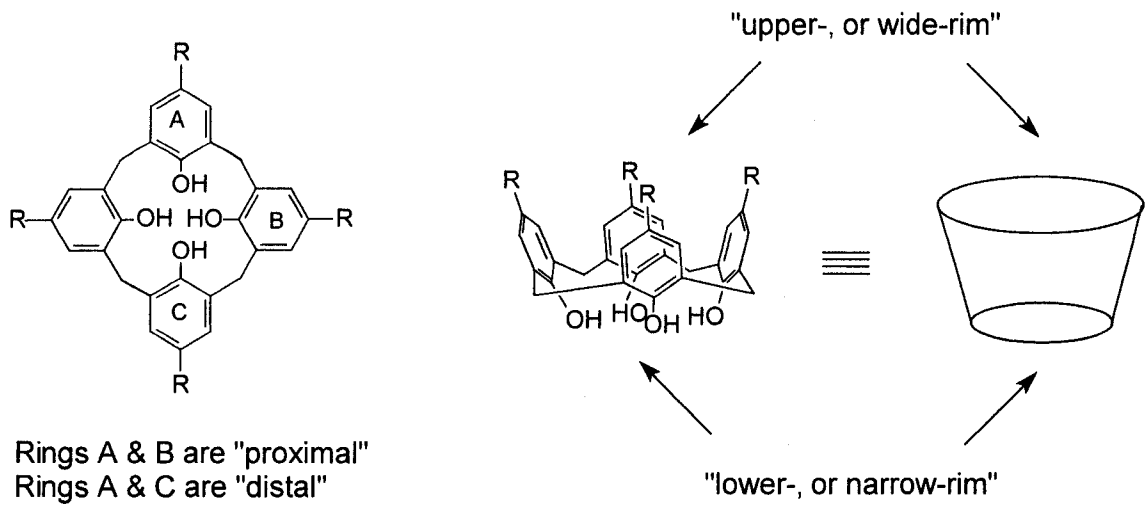


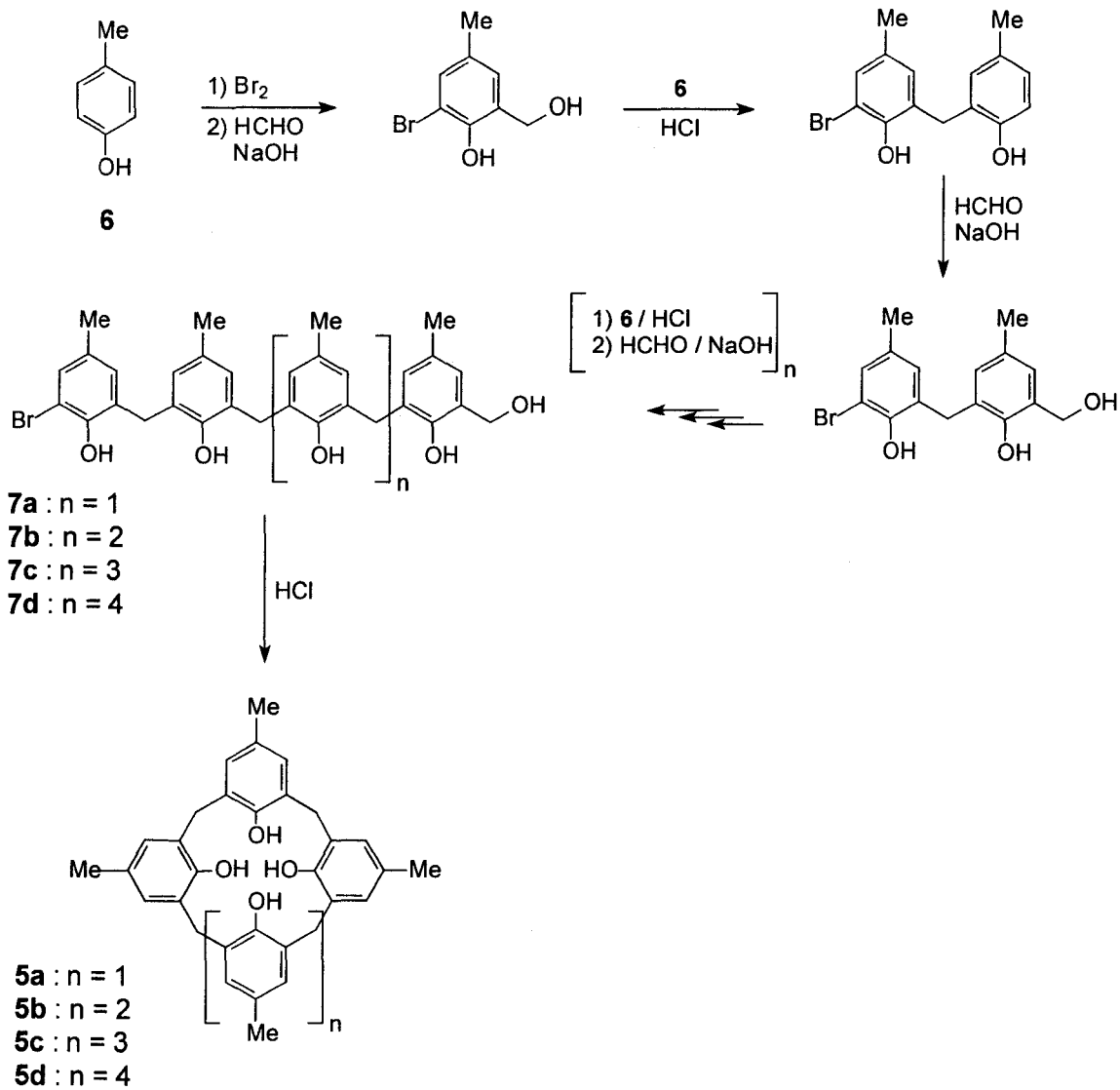
Figure 1.4 Representation of calix[4]arenes

1.2.b. Total Synthesis of Calixarenes:

Although the one-step syntheses of calixarenes via acid- or base-mediated condensation provides these materials in high yields and in synthetically useful large scales from cheap starting materials, these methods produce only symmetrical calixarenes in which the phenolic groups have the same degree of functionality. On the other hand, asymmetrical calixarenes can be obtained via multi-step syntheses in which different functional groups can also be introduced at different stages of the syntheses.

The first total multi-step convergent synthesis of *para*-methylcalix[4]arene **5a** was accomplished in 1956 by Hayes and Hunter.[15] Using the same methodology from *p*-methylphenol (**6**), Kämmerer *et al*[16] were able to extend the

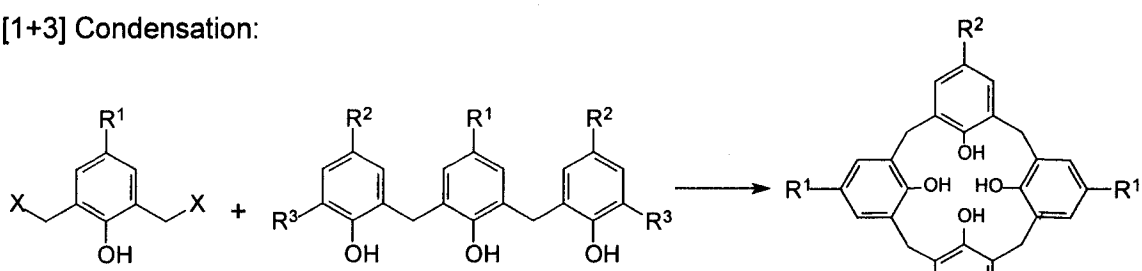
Hayes and Hunter synthesis to obtain calix[5]arene **5b**, calix[6]arene **5c** and calix[7]arene **5d** via the corresponding linear oligomers **7a-d** (Scheme 1.2).



Scheme 1.2 The first total multi-step synthesis of calixarenes **5a-d**.

In 1979 Böhmer and coworkers improved the step-wise synthesis of calixarenes by introducing a new approach known as "fragment condensation". Applying this approach they were able to synthesize various calix[4]arenes **8** and **9** using [3+1] [16] or [2+2][17] condensations, respectively (Scheme 1.3).

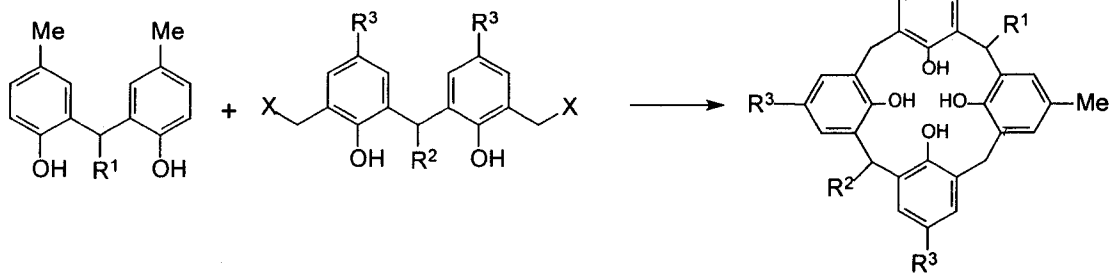
[1+3] Condensation:



R^1= *t*-Butyl, Cl, CO_2Et, NO_2
R^2= Me, Et, *i*-Pr, *t*-Bu, *p*-Ar
R^3= H or CH_2X

8

[2+2] Condensation:



R^1 and/or R^2 = Me, Et, *i*-Pr, *t*-Bu, *p*-Ar
R^3 = H, Alkyl, etc..

9

Scheme 1.3 Multi-step synthesis of calix[4]arenes via [3+1] or [2+2] condensations.

1.2.c. Conformations of Calixarenes

There are two possible rotational modes in calixarenes which involve the relative movements of the phenolic rings. The first one is that in which one or more of the phenolic hydroxy groups rotate through the cavity. The other results when one or more of the *para*-substituent groups instead, rotate through the cavity. This flexibility produces different conformers or atropisomers. The flexibility and the number of these conformers depend on the size of the calixarene cavity, and the number and nature of the groups on either the narrow- or the wide-rims.

For example, in *p-tert*-butylcalix[4]arene (**2**) there are up to four different conformers which can be observed and have been characterized. They are named: *cone*, *partial-cone, 1,2-alternate*, and *1,3-alternate* (Figure 1.5).[18] In most cases the *cone* conformer has been found to be the most thermodynamically stable conformer in **2**. This stability can be accounted for by the intramolecular hydrogen bonding between the phenolic hydroxyl groups in the narrow-rim, which prevent rotation of the phenolic units. It is found that modification of the narrow-rim substituents of *p-tert*-butylcalix[4]arene (**2**) will change its conformational behavior. For example, attaching propyl groups at the narrow-rim will block the calixarene in one conformation, because these groups are bulky enough to prevent rotation of the phenolic units through the cavity,[19] while attachment of relatively small groups such as methyl groups does not affect the phenolic rotation.[20]

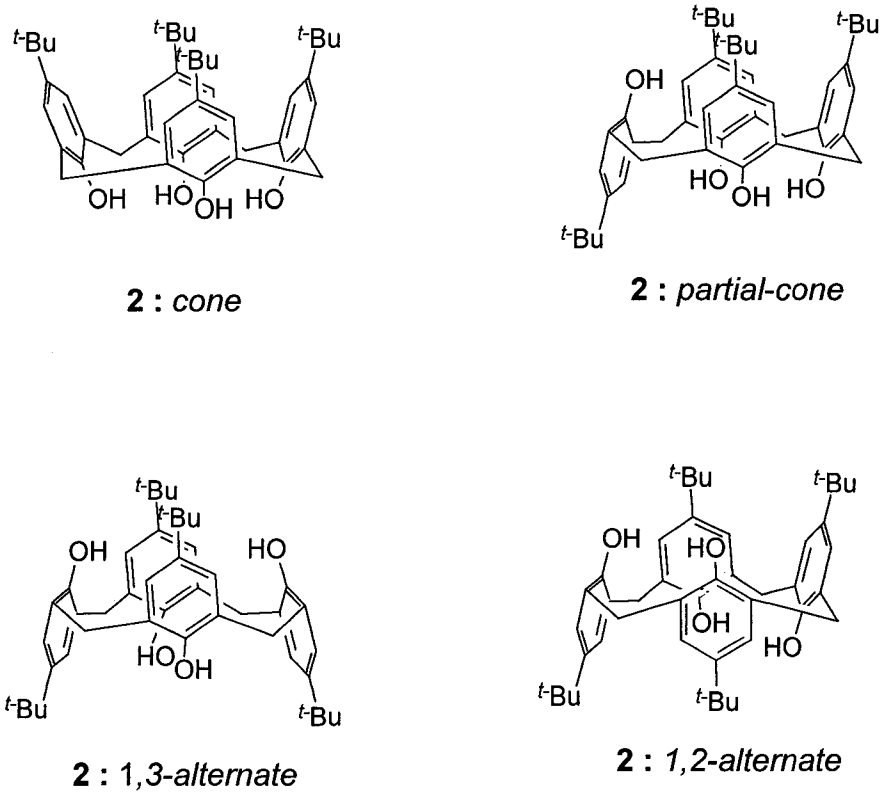
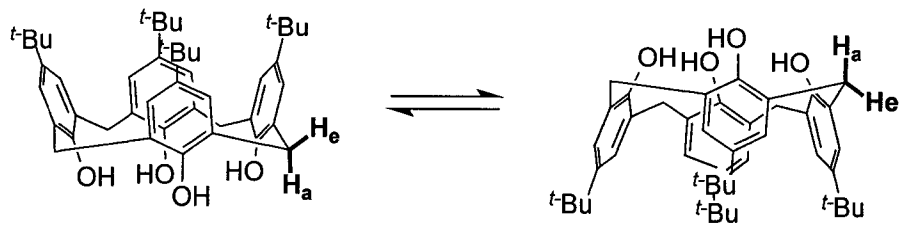


Figure 1.5 Conformations of *p-tert*-butylcalix[4]arene (**1**).

Calix[4]arene conformers can be distinguished relatively easily by ^{13}C- or ^{1}H-NMR spectroscopy by application of the so-called "de Mendoza rules", [21] According to these rules, the conformation for any calix[4]arene can be determined mainly by the chemical shift of its bridged carbons. de Mendoza found that the chemical shift of each bridge carbon clearly depends upon the orientation of the adjacent phenolic rings. In the case of the *cone* conformer in which all the adjacent rings are *syn* to one another, the bridge carbons resonate at a relatively high field, i.e. at $\delta \approx 30$ ppm. In the *1,3-alternate* conformation adjacent rings are in an *anti* orientation, and the bridge carbons resonate at a lower field, i.e. $\delta \approx 37$ ppm. In the *1,2-* and the *partial cone* conformers, the

phenyl rings have both *syn* and *anti* orientations with respect one to one another and as expected, the bridging carbons resonate at both $\delta \approx 30$ and 37 ppm. The latter two conformers can only be further distinguished by ^{1}H NMR spectroscopy, by observing the aromatic proton resonances. The de Mendoza rule has also been successfully applied to larger calixarenes, such as calix[5]arenes[22] and calix[6]arenes.[23]

Although the *cone* conformation is the most stable conformer, *cone*-to-*cone* interconversion can occur. The rate of this interconversion depends on both the temperature and the solvent. The activation energy for such dynamic interconversion phenomena, which can be also observed for the other conformers, can be measured by variable temperature ^{1}H NMR spectroscopy (VT-NMR), by observing the resonance signals of the two non-equivalent methylene protons H_{axial} (**H_a**) and $H_{equatorial}$ (**H_e**) for example, in *p-tert*-butylcalix[4]arene (**2**) (Figure 1.6). Kämmerer and co-workers[24] have demonstrated that for a solution of **2** in $CDCl_3$ at 16 °C or at lower temperatures, the methylene hydrogens appear as a pair of doublets, because the rate of interconversion is slow enough to be observed by ^{1}H NMR. As the temperature is increased, the rate of interconversion increases. At 59 °C or above, the two signals merge to appear as one signal. This temperature is known as the "coalescence temperature" and gives a measure of the activation energy barrier to the interconversion.[25]



2: *cone* **2:** *cone*

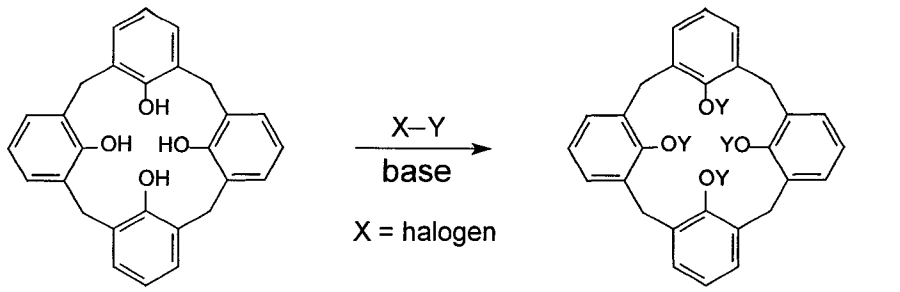
Figure 1.6 *Cone-to-cone* interconversion of *p-tert*-butylcalix[4]arene (**2**).

1.3. Calixarenes Modification

Much research has been conducted to modify calixarenes by synthesizing new derivatives which would have unique chemical and physical properties. The great majority of the modifications have involved lower- or narrow-rim functionalization of the phenolic hydroxy groups or, to a lesser extent, upper- or wide-rim modifications.

1.3.a. Modification of the phenolic hydroxy groups (narrow-rim)

This type of modification, which has been carried out for example on calix[4]arene (**10**) is the most common type, and usually, involves *O*-alkylation,[26] *O*-arylatio,[27] *O*-acylation,[28] *O*-amidation[29] and *O*-thioamidation[29] to give the corresponding calixarenes **11a-e**, respectively (Scheme 1.4).



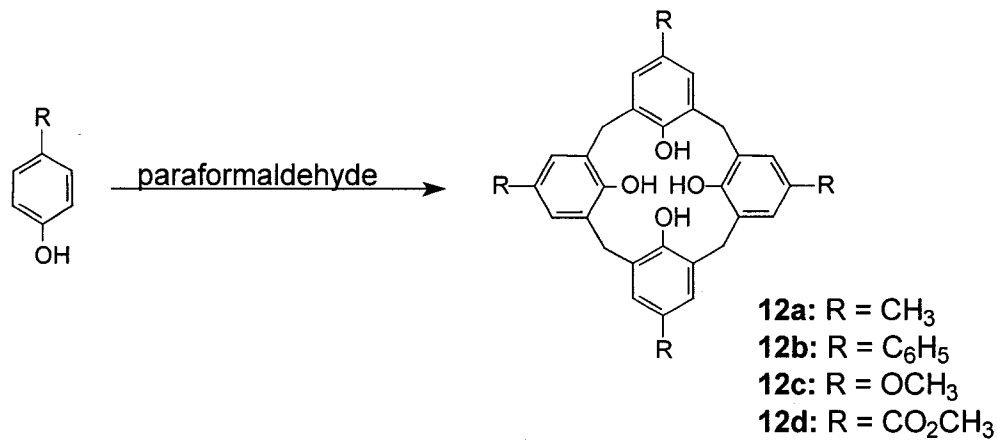
10

11a : Y = Alkyl
11b : Y = Aryl
11c : Y = –CO–R
11d : Y = $CH_2CO–NR_2$
11e : Y = $CH_2CS–NR_2$

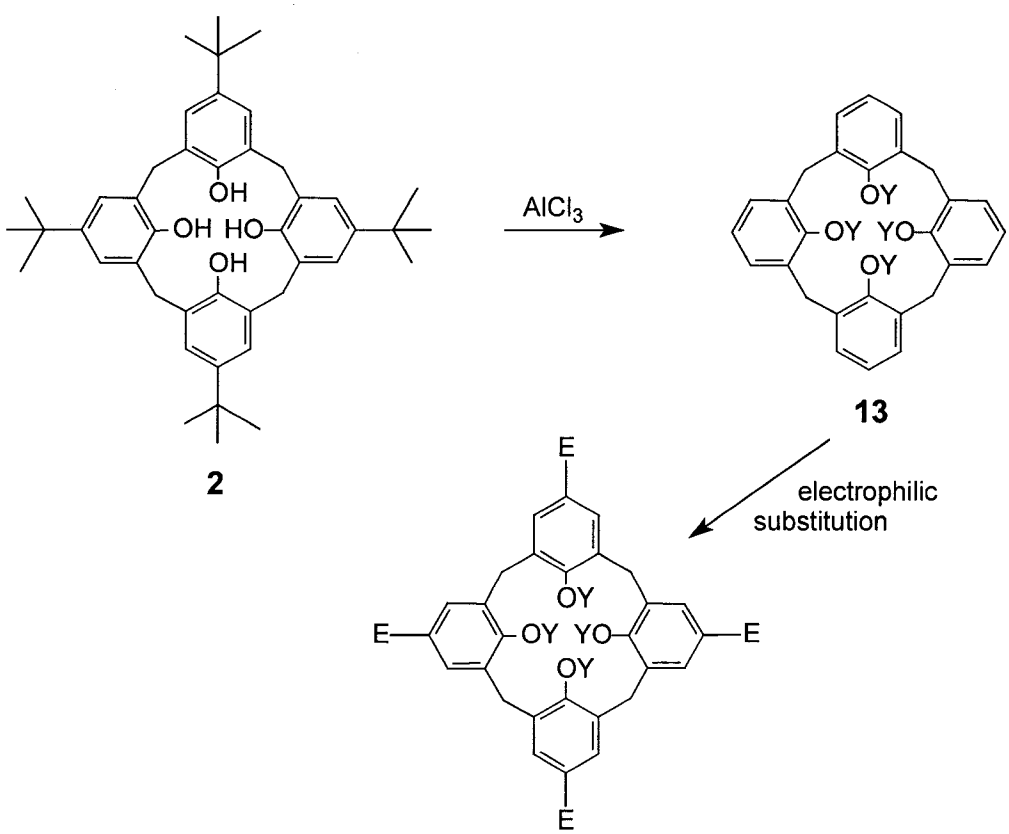
Scheme 1.4 Modification of calix[4]arene (**10**) on the narrow-rim.

1.3.b. Modification of the aromatic rings (wide-rim)

Modification of the wide-rim of calixarenes, particularly at the *para*-position, can be conducted in at least two different ways: (a) before the cyclization step: this can be achieved by condensing a suitable *para*-substituted phenol with formaldehyde to give the corresponding *para*-substituted calixarenes **12a-d** (Scheme 1.5a)[30]; or (b) by selectively removing one or more of the *tert*-butyl groups from the parent tetra-*p*-*tert*-butyl calixarene (**2**),[31] followed by reacting the de-*tert*-butylated calix[4]arene **13**, for example, with different electrophiles to give the corresponding *para*-substituted calix[4]arenes (**14**). In the literature there are many examples describing this strategy involving, for example, halogenations,[32] nitration,[33] cyanation[34] and/or sulfonation[35] (Scheme 1.5b).

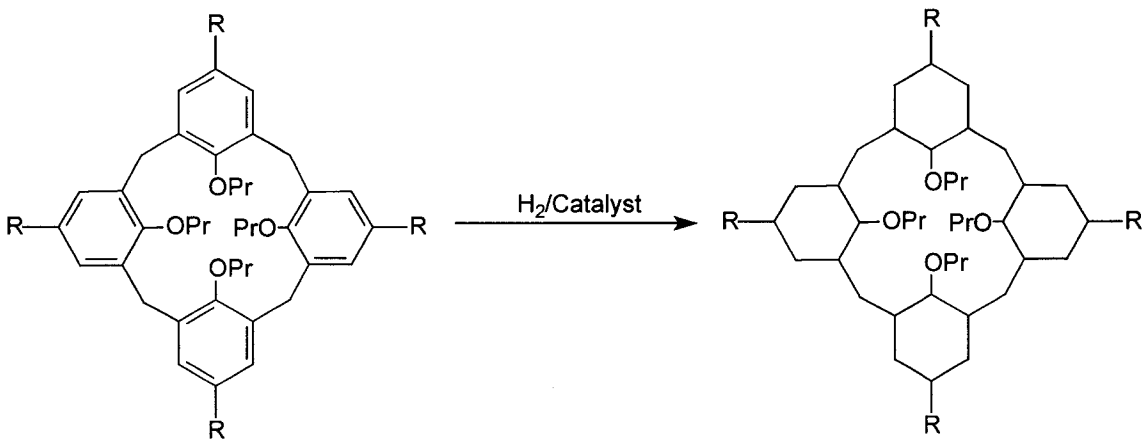


Scheme 1.5a Wide-rim modification of calix[4]arene



Scheme 1.5b Wide-rim modification of calix[4]arene

The *para* position of the phenolic ring is not the only position where calixarenes can be modified. Complete hydrogenation of the phenolic rings themselves has been reported, resulting in the formation of a new class of saturated host molecules. For example, catalytic hydrogenation of calixarenes **15a-b** gives the saturated calixarenes **16a-b** (Scheme 1.6).[36]

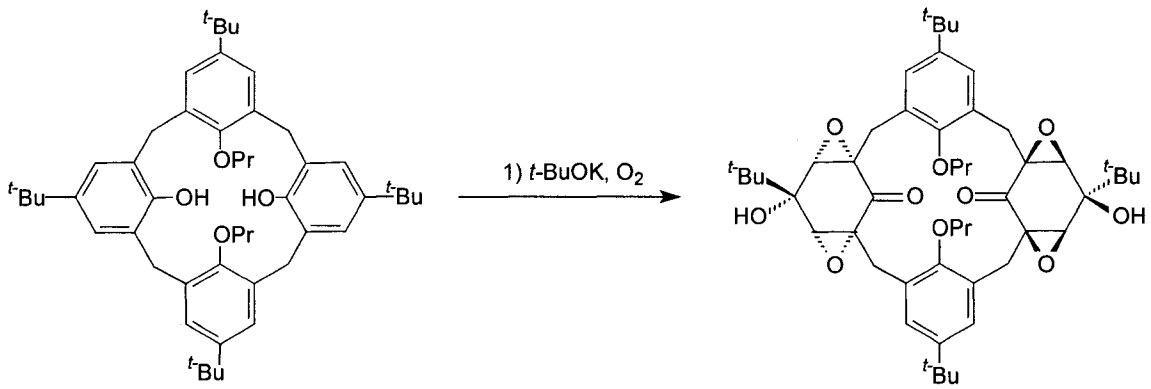


15a : R = H
15b : R = *tert*-butyl

16a : R = H
16b : R = *tert*-butyl

Scheme 1.6 Modification the phenolic rings of calix[4]arene by hydrogenaton

Oxygenation of calixarene is also possible, whereby oxygen atoms are added directly to the aromatic double bonds, for example, of calixarene **17**, to give the corresponding epoxy-*p*-quinol-calixarene **18** (Scheme 1.7).[37]

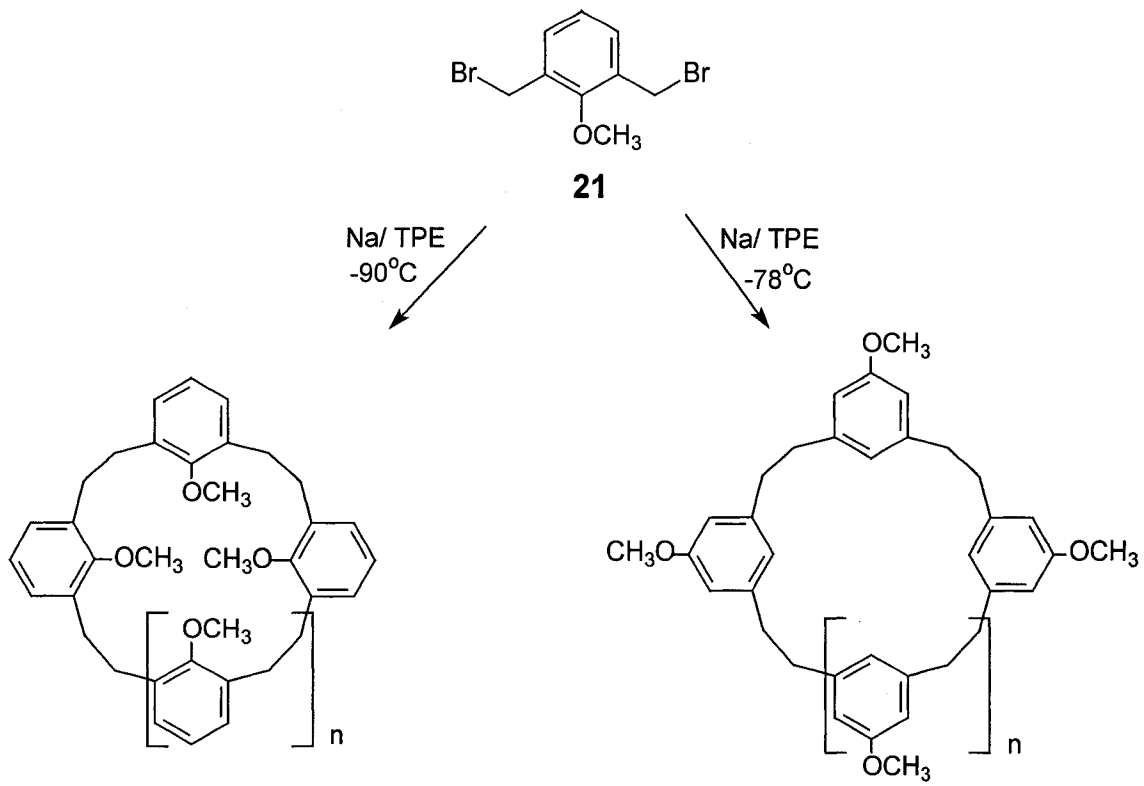


17 **18**

Scheme 1.7 Modification the phenolic rings of calix[4]arene by oxidation

1.4. Homocalixarenes

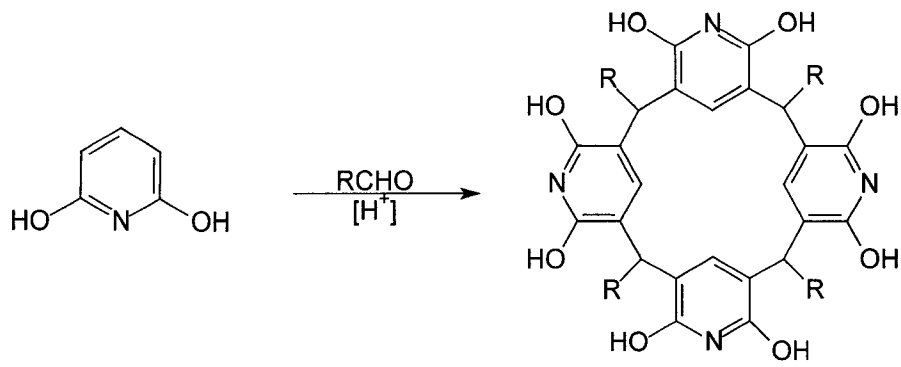
The cavity size in a calixarene can be controlled by (a) changing the number of the phenolic rings, or (b) extending the number of methylene groups in the bridges to produce "homocalixarenes".[40] For example, *all*-homocalixarenes **19a-l** and **20a-h** can be obtained by using a Müller-Röscheisen-type of cyclization,[41] using 2,6-bis(bromomethyl)methoxy benzene (**21**) with sodium powder and tetraphenylethene (TPE) to obtain the corresponding products (Scheme 1.8).



Scheme 1.8 The syntheses of *all*-homocalixarenes **19a-l**, and **20a-h** by using Müller-Röscheisen-type cyclization.

1.5. Heterocalixarenes

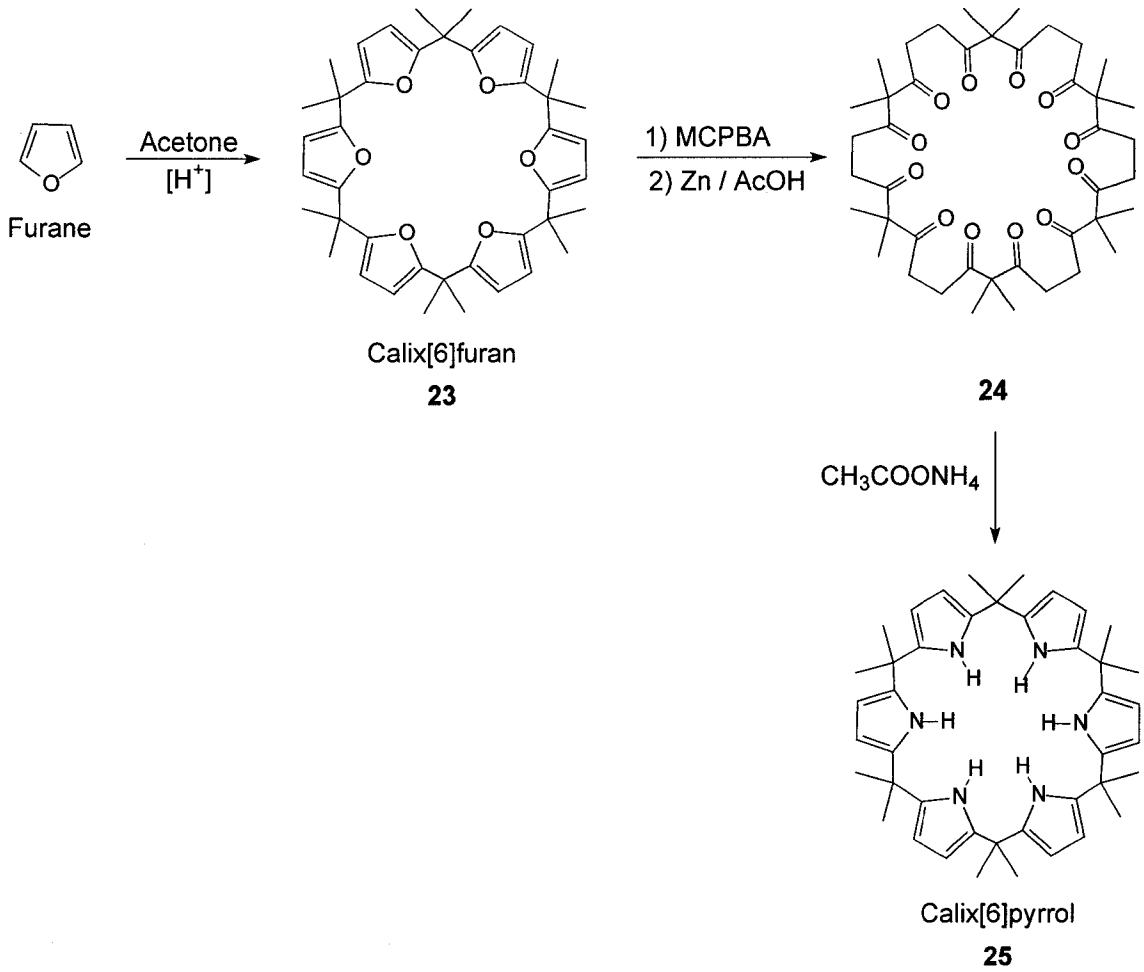
Heterocalixarenes are formed by the replacement of one or more of the calixarene phenolic rings with a heterocyclic moiety (such as pyridine, pyrrole, thiophene, etc). For example, pyridine-based calixarenes **22a-e**[40] are produced from the reaction of 2,6-dihydroxypyridine with different aldehydes in acidic medium (Scheme 1.9).



22a : R = *n*-Butyl
22b : R = *iso*-Butyl
22c : R = *n*-pentyl
22d : R = Phenyl
22e : R = 2'-Thienyl

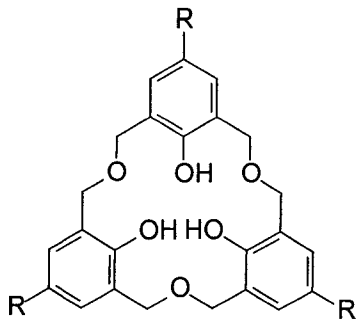
Scheme 1.9 Acid-catalyzed synthesis of the pyridine-based calixarenes **22a-e**

The furan-based calix[6]furan **23**[43] is synthesized by the direct condensation of furan with acetone. Calix[6]furan can be converted to another heterocyclic-based calixarene by first oxidizing it with MCPBA, followed by the reduction of the olefinic double bonds which give the dodecaketone **24**, which is converted to calix[6]pyrrole **25** after reacting it with $CH_3CO_2NH_4$ (Scheme 1.10).[44]



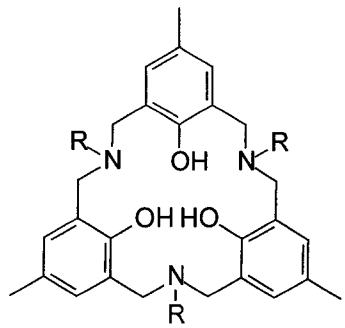
Scheme 1.10 The syntheses of calix[6]furan **23** and its conversion to calix[6]pyrrole **25**.

Another class of heterocyclic calixarenes can be obtained by replacement of one or more of the methylene bridges with $-CH_2-X-CH_2-$ groups, where X = O or N, to give the corresponding oxa-,[45] or aza-,[46] calixarenes, e.g. **26** and **27**, respectively (Figure 1.7).



R = *tert*-butyl

Oxacalix[3]arenes
26



R = $CH_2CO_2CH_3$

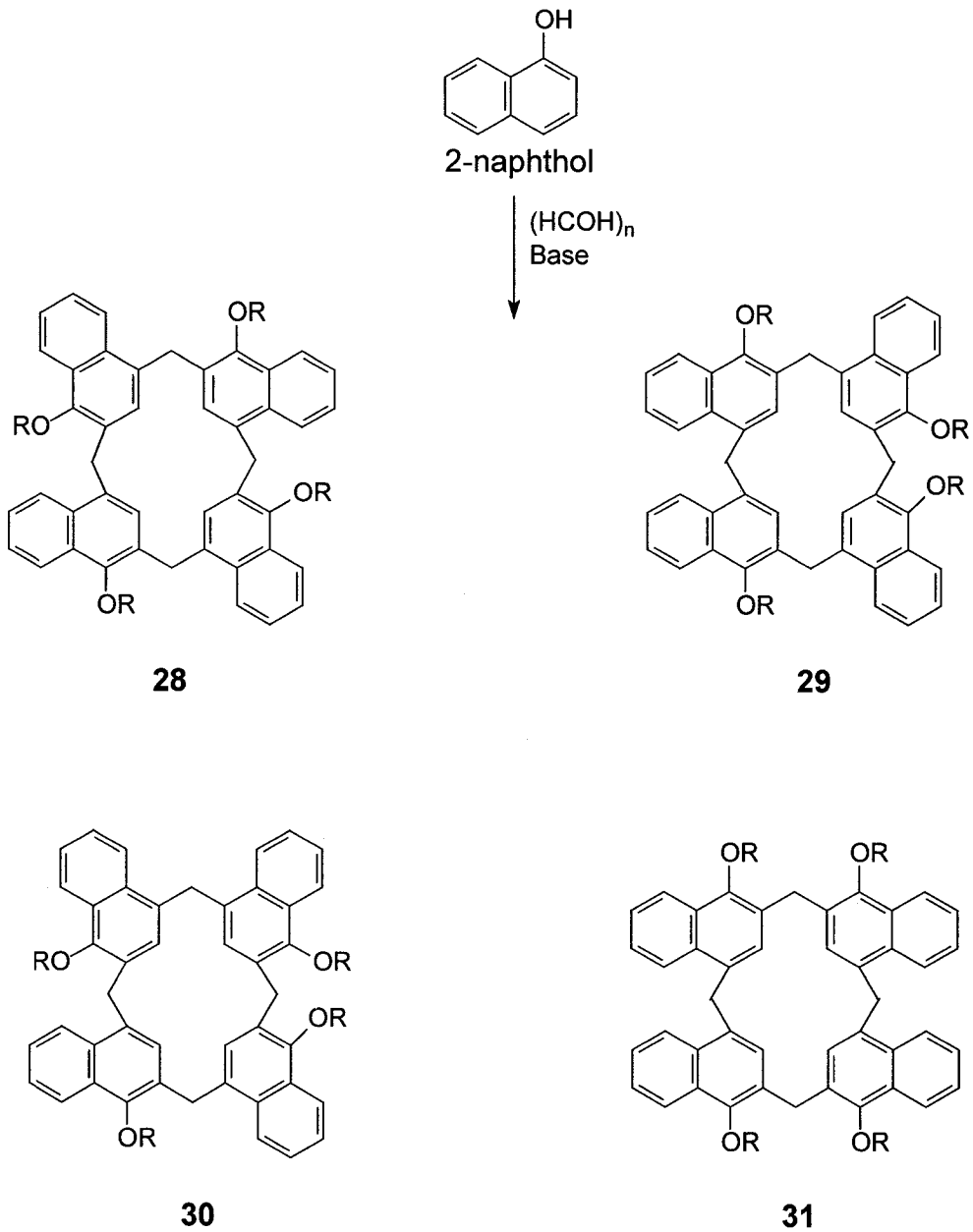
Azacalix[3]arene
27

Figure 1.7 Hexahomooxacalix[3]arene (**26**) and azacalix[3]arene (**27**).

1.6. Calix[4]naphthalenes

Incorporating naphthalene rings in the construction of macrocyclic compounds is a useful method to produce compounds which may have deeper, wider and more electron-rich cavities. The first members of these types of compounds, **28-30** were reported in 1993 by Georghiou and Li (Scheme 1.11)[45] who named these as calix[4]naphthalenes by analogy with the phenyl-ring based calix[*n*]arenes. Synthesis of these compounds was initially achieved by the one-pot condensation of 1-naphthol with formaldehyde. Although there are in principle four different regioisomeric products which could be produced from this reaction, only three, **28**, **29**, and **30** were isolated (Scheme 1.11).[46] These compounds are examples of *exo*-type calix[4]naphthalenes, since the hydroxyl groups are situated on the outside of the annulus, or cavity.

By using different convergent approaches Georghiou and Ashram[47] were able to synthesize all four of the isomeric calix[4]naphthalenes **28-31** (Scheme 1.11) separately and in acceptable yields, based on either "2+2", or "3+1" fragment-type condensations.

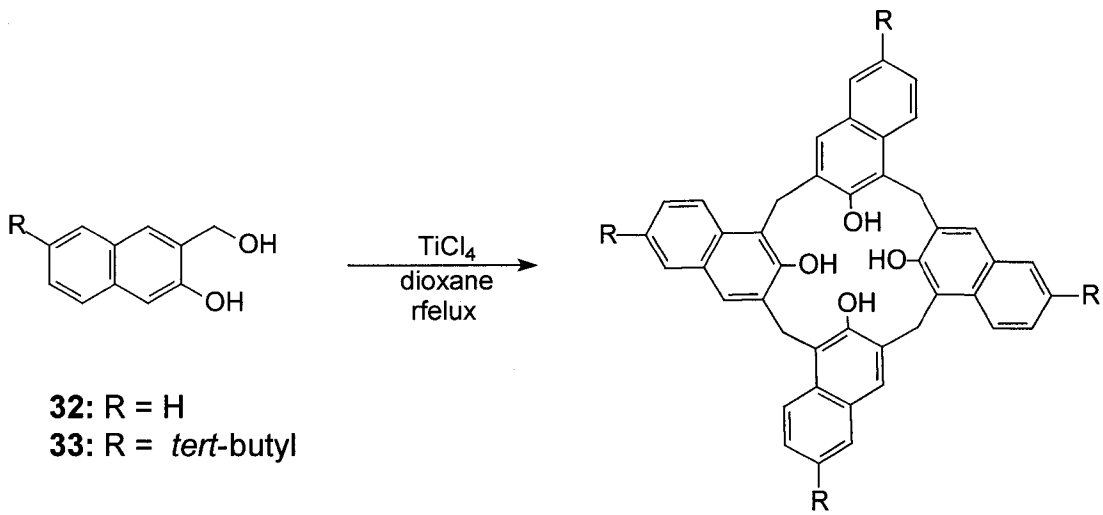


28 **29**

30 **31**

Scheme 1.11 Syntheses of the *exo*-calix[4]naphthalenes **28-31**.

Coincidentally, also in 1993 Andreetti et al.[48] reported the synthesis of compound **34** (Scheme 1.12), an "*endo*-type" calix[4]naphthalene, in which the hydroxy group is situated within the cavity. This compound was prepared in a relatively poor yield (5%) by the condensation of 3-hydroxymethyl-2-naphthol (**32**) in the presence of $TiCl_4$. Subsequent attempts at the optimization of the reaction conditions by Georghiou et al[49] increased the yield up to 11%. They were able to increase the yield to ~30% of the corresponding *tert*-butyl derivative **35** when 7-*tert*-butyl-3-hydroxymethyl-2-naphthol (**33**) was used instead of **32**.



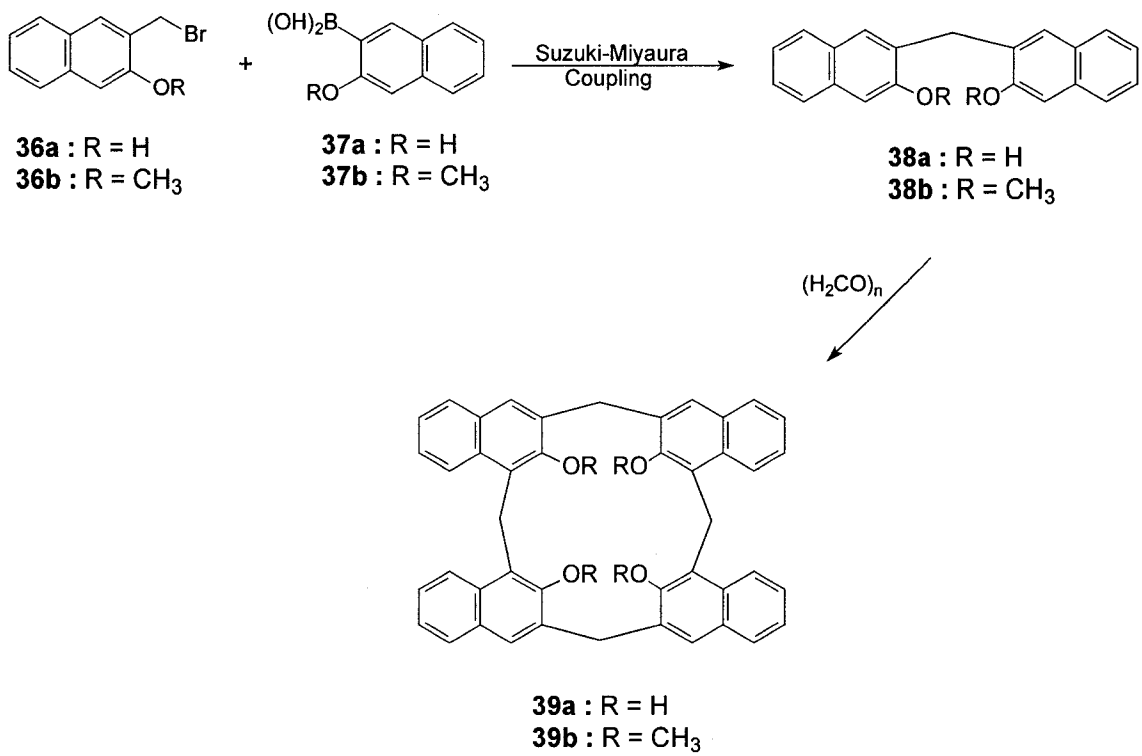
32: R = H
33: R = *tert*-butyl

34 : R = H
35 : R = *tert*-butyl

Scheme 1.12 Synthesis of the *endo*-calix[4]naphthalenes **34** and **35**.

The C_2-symmetrical *endo*-calix[4]naphthalenes **39a-b** have also been reported by Georghiou *et al.*[50] The key intermediates **38a-b** were first synthesized using a modified Suzuki-Miyaura cross-coupling reaction of

compounds **36a-b** and **37a-b**. Intermediates **38a-b** were then subjected to cyclocondensation reaction conditions with paraformaldehyde to give **39a-b** (Scheme 1.13).



36a : R = H
36b : R = CH_3

37a : R = H
37b : R = CH_3

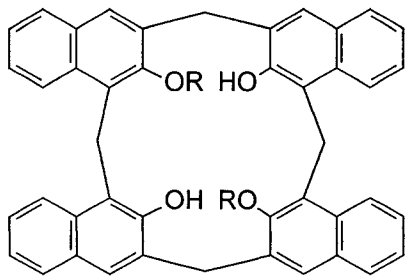
38a : R = H
38b : R = CH_3

39a : R = H
39b : R = CH_3

Scheme 1.13 Syntheses of the C_2-symmetrical *endo*-calix[4]naphthalenes **39a-b** via a modified Suzuki-Miyaura cross-coupling reaction.

In order to synthesize new macrocyclic compounds which would have unique properties, different modifications, including the cavity sizes and the attached functional groups have been performed on calixnaphthalenes. The first example involved narrow-rim modifications in which different groups such as

ethyl, propyl, *iso*-propyl and butyl are introduced on the narrow-rim to give corresponding calix[4]naphthalenes **40a-d**, respectively (Figure 1.8).[52]



40a : R = Ethyl
40b : R = Propyl
40c : R = *i*-Propyl
40d : R = Butyl

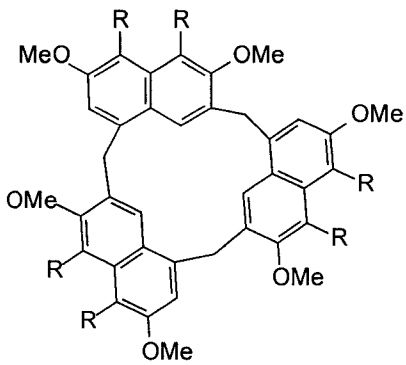
Figure 1.8 Derivatives **40a-d** of the *endo*-calix[4]naphthalenes.

The size of calixnaphthalenes can be expanded by changing the linkage positions on the naphthalene rings; for example, Glass et al[51] reported the synthesis of compound **41** (Figure 1.10) in which the naphthalene rings are linked by the 3,5-positions.

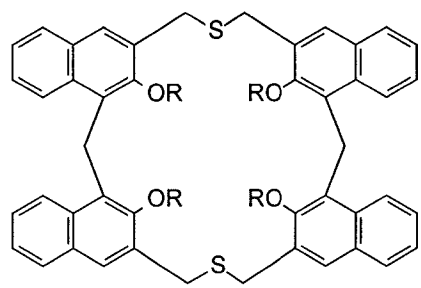
As with calixarenes, homocalixnaphthalenes are also accessible by homologation of the methylene bridges. Several homocalixnaphthalenes have been synthesized, mainly by Georghiou's group.[52] For example, the dihomocalix[4]naphthalenes **42** and **43** (Figure 1.9) have been synthesized in

acceptable yields, and these compounds have been found to bind with different metal ions.

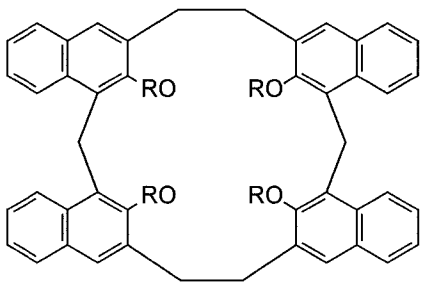
The hexahomotrioxacalix[3]naphthalenes **44a** and **44b** which are calix[3]naphthalenes having one or more of the methylene bridges replaced by CH_2OCH_2 have also been reported[27] (Figure 1.10). Only **44b** formed a stable complex and the X-ray structure of a 2:1 complex of **44b** with C_{60} was successfully solved.[53]



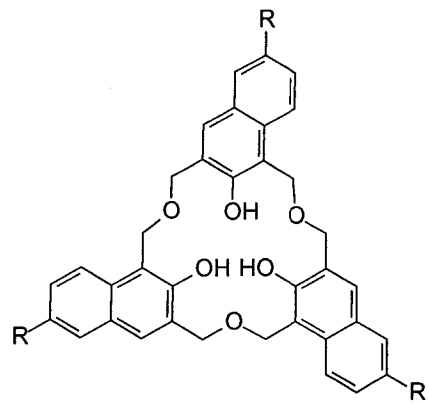
41



42



43



44a : R = H
44b : R = *tert*-butyl

Figure 1.9 Some examples on the homo-, homooxa- and homothia-calixnaphthalene **41-44**.

Recently, Georghiou and Tran[54] prepared the calixnaphthalene-like compounds **45a-d** and **46a-d** in which the naphthalene ring units are joined via their 1,4-positions (Scheme 1.14). These compounds were derived from 2,3-dialkoxy-substituted naphthalenes. The structure of **45b**, as indicated by X-ray crystallography, was found to be a *flattened partial cone* conformation. In this conformation, three naphthalene rings adopt a tripodal orientation (Figure 1.10).

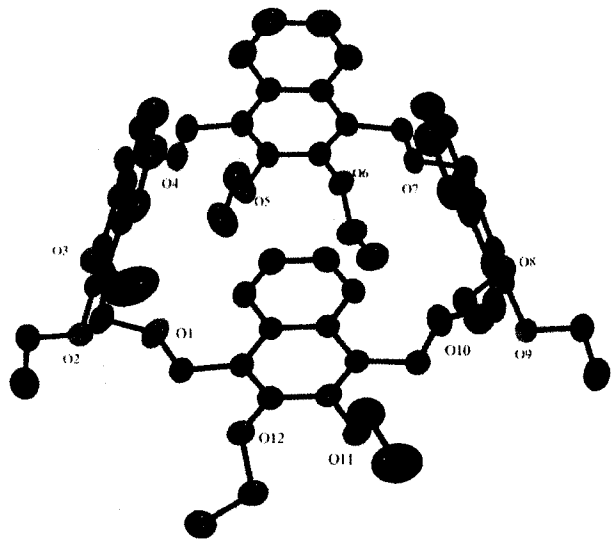
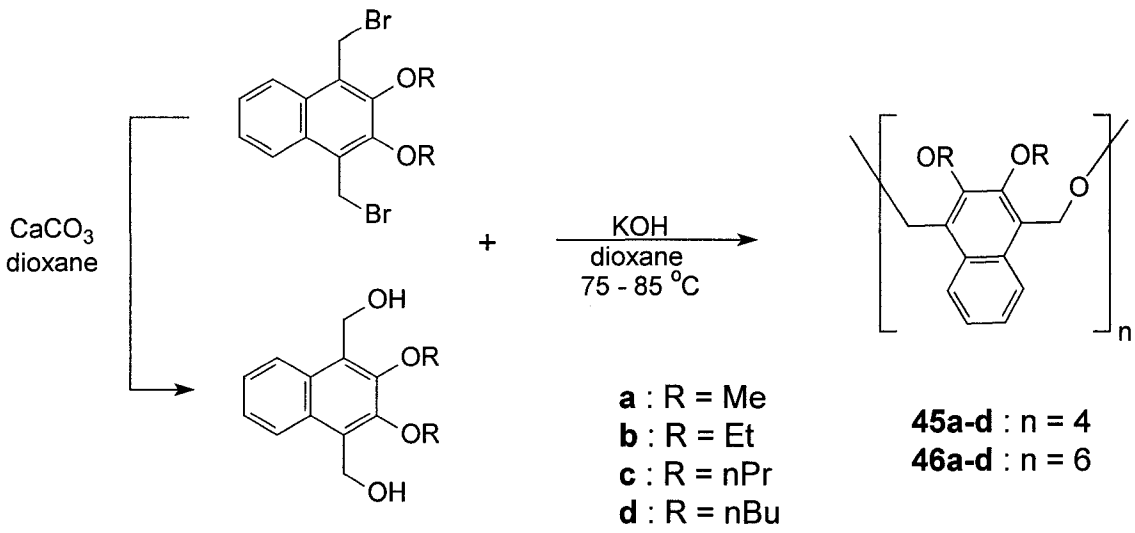


Figure 1.10 X-ray of **45b** showing its *flattened partial cone* conformation.

Although theoretically, as suggested by molecular modeling,[55] these compounds were considered to be ideal hosts for C_{60} and C_{70}, experimentally no complexation was observed. However, they were found to form fairly stable complexes with TMACl.



Scheme 1.14 The syntheses of 1,4-linkage calixnaphthalene-like compounds **45a-d** and **46a-d**.

1.7. Summary

In Chapter (2) of this thesis, a new methodology for the wide-rim modification of calix[4]naphthalene by using a suitably pre-functionalized bromo precursor is described.

In Chapter (3), we have described the synthesis of the thiophene-based calix[4]arene (**12**), by employing a [2+2] fragment condensation reaction. The structure of **12** as been determined by X-ray analysis, revealed that this compound adopts, the *1,3-alternate* conformation in the solid state.

In Chapter (4) a new member of the homooxacalix[4]naphthalene family also synthesized by employing also [2+2] fragment condensation reaction. In this particular chapter the ability to increase the cavity size of the calix[4]naphthalene

by extending the bridging units with ($-CH_2-CH_2-$) and ($-CH_2-O-CH_2-$) is described.

In Chapter (5), the first Pd-catalysed Sonogashira reaction of the narrow rim of calix[4]arene is described. Reasonably useful synthetic yields of the narrow-rim alkynyl derivatives have been obtained using this methodology. In this chapter, the first example of a biscalix[4]arene is reported, which was formed by directly linking two calixarenes at their narrow rims via potentially modifiable hydrocarbon groups.

In Chapter (6), different potentially narrow rim functionalized alkynylcalix[4]arenes containing donor-acceptor tolanes, which have been synthesized via Sonogashira coupling, are described. These compounds are currently under investigation, to study their nonlinear optical properties as well as their conformational behaviors.

In chapter (7), the fact that the narrow-rim 1,3-bis(arylethynyl)-*p-tert*-butylcalix[4]arenes are photo-labile is described. Upon photoirradiation, these compounds undergo facile cyclization-rearrangement reactions. A mechanism is proposed to account for the observed results. These findings further expand the versatility of functionalized calixarenes, especially, with respect to their photochemical behavior. In this chapter, the first examples on an intramolecular cyclizations of such *O*-phenylethynyl calixarenes via *7-exo-dig* photochemically-mediated cyclizations is demonstrated.

1.7. References

1. *Supramolecular Chemistry,* Lehn, J. M.; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F. Comprehensive Eds., Pergamon, Oxford, **1996**.

2. Cram, D. J.; Cram, J. M.; *Container Molecules and Their Guests, Monographs in Supramolecular Chemistry*, J. F. Stoddart. Ed., The Royal Society of Chemistry, Cambridge, United Kingdom, **1994**.

3. Dodziuk, Helena. *Introduction to Supramolecular Chemistry*. Hingham, MA, USA: Kluwer Academic Publishers, **2001**. 102.

4. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 153.

5. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

6. Cram, D. J.; R. Carmack, A.; deGrandpre, M. P.; Lein, G. M. Goldberg, I.; C.; Knobler, B.; Maverick, E. F.; Trueblood, K. N. *J. Am. Chem.* Soc. **1987**, *109,* 7068.

7. (a) Villiers, A. *Compt. Rend.* **1891**, *112*, 536. (b) Szejtli, J. *Chem. Rev.* **1998,** *98,* 1743.

8. (a) Behrend, R.; Meyer, E.; Rusche, F.; *Justus Liebigs Ann. Chem.* **1905**, *339*, 1. (b) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367.

9. Gutsche, C.D. Calixarenes in '*Monographs in Supramolecular Chemistry*'; Stoddart, J. F., Ed.; Royal Society: **1989**.

10. Zinke, A.; Ziegler, E. *Ber.* **1941**, *B74*, 1729.

11. Baeyer, A. *Ber.,* **1872**, *5*, 1094

12. Zinke, A.; Kretz, R.; Leggewie, E.; Hössinger, K. *Monastsh*, **1952**, *83*, 1213.

13. (a) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782 (b) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234. (c) Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1990**, *68*, 243. (d) Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1990**, *68*, 238. (e) Stewart, D. R.; Gutsche, C. D. *Org. Prep. Proc. Int.* **1993**, *25*, 137.

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

15. Kämmerer, H.; Happel, G.; Ceasser, F. *Makromol. Chem.* **1972**, *162*, 179.

16. Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.

17. Biali, S. E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938.

18. Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron,* **1983**, *39*, 409.

19. Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955.

20. Blixt, J.; Detellier, C. *J. Am. Chem. Soc.* ***1994,116,*** 11957.

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

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

23. Kanamathareddy, S.; Gutshe, C. D. *J. Org. Chem.* **1994**, *59,* 3871.

24. Happel, G.; Mathiasch, B.; Kammerer, H. Ibid. **1975,** *176,* 3317.

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

26. Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron*, **1991**, *47*, 4325.

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

28. Gutsche, C.D. *Calixarenes in Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society: **1989**.

29. Arena, G.; Contino, A.; Longo, E.; Sciotto, D.; Spoto, G. *J. Chem. Soc., Perkin Trans. 2*, **2001**, 2287.

30. Gutsche, C. D.; Pagoria, P. F. *J. Org. Chem.* **1985**, *50*, 5795.

31. Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652.

32. van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reindhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639.

33. Van Loon, J. D.; Heida, J. F.; Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas,* **1992**, *111*, 353.

34. Vreekap, R. H.; Veerbom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas,* **1995**, *115*, 363.

35. Shinkai, S.; Arkai, K.; Tsubaki, T.; Sone, T.; Manab, O. *Tetrahedron Lett.* **1985**, *26,* 3343.

36. Columbus, I.; Haj-Zaroubi, M.; Siegel, J. S.; Biali, S. E. *J. Org. Chem.* **1998**, *63,* 9148.

37. Gaeta, C.; Troisi, F.; Martino, M.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2004**, *6,* 3027.

38. Ibach,S.; Prautzsch,V.; VöGtle, F. *Acc. Chem. Res.* **1999,** *32*, 729.

39. Müller, E.; Röscheisen, G. *Chem. Ber.* **1957**, *90*, 543.

40. Gerkensmeier, T.; Mattay, J.; Näther, C. *Chem. Eur. J.,* **2001**, *7*, 465.

41. Cafeo,G.; Giannetto,M.; Kohnke, F. N.; La Torre,G. L.; Parisi, M. F.; Menzer, S.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.*, **1999**, *5,* 356.

42. Cafeo, G.; Kohnke, F. H.; La Torre, G. L.; White, A. P.; Williams, D. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 1496.

43. Miah, M.; Romanov, N. N.; P. Cragg, J. *J. Org. Chem.* ***2002****, 67, 3124.*

44. Niikura, K.; Anslyn, E. V. *J. Chem. Soc., Perkin Trans. 2*, **1999**, 2769.

45. (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.

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

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

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

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

50. Chowdhury, S.; Georghiou, P. E. *J. Org. Chem.* **2002**, *67*, 6808.

51. Shorthill, B. J.; Granucci, R. G.; Powell, D. R.; Glass, T. E. *J. Org. Chem.* **2002**, *67*, 904.

52. Georghiou, P. E.; Li, Z.; Ashram, M.; Miller, D. O.; *J. Org. Chem.* **1996**, *61,* 3865

53. Mizyed, S.; Ashram, M.; Miller, D. O.; Georghiou, P. E. *J. Chem. Soc., Perkin Trans. 2*, **2001**, 1916.

54. Tran, A. H.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem.* **2005**, *70*, 1115.

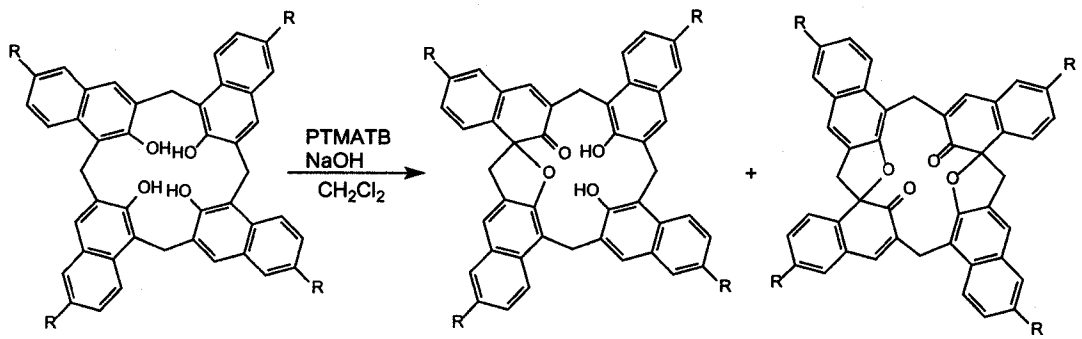
55. Molecular modeling was conducted using Spartan '06 Molecular Modeling Software from Wave-function Inc.: Irvine, CA.

Chapter 2

A limited study of Wide-Rim Modification of Calix[4]naphthalenes Derived from 2-Naphthol

2.1- Introduction

Calixnaphthalenes are similar to calixarenes, in the sense that there are two main sites where they can be modified: on either, or both, of their narrow- or wide-rims. In 1998, the Georghiou group[1] reported the first examples of narrow-rim modifications of calix[4]naphthalenes. They reported the synthesis of the bis(spirodienone) **5** which was obtained from the oxidation of the *endo*-type calix[4]naphthalene **1** with phenyltrimethylammonium tribromide (PTMATB) in basic solution. Using similar reaction conditions, spirodienone **4** and bis(spirodienone) **6** were obtained from the oxidation of calix[4]naphthalene (**2**) (Scheme 2.1).



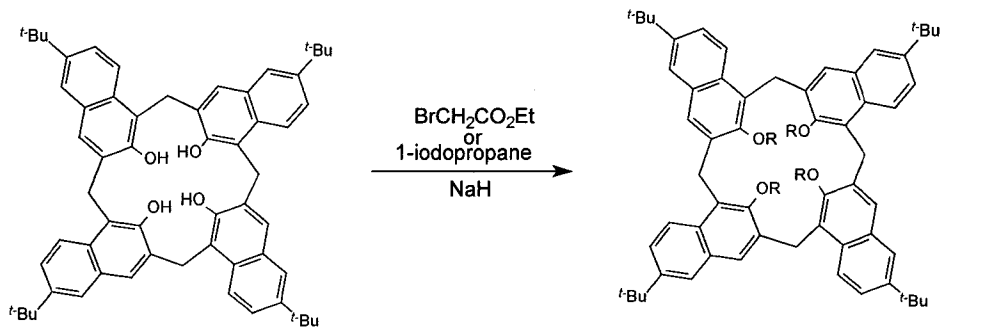
1 : R = H
2 : R = $C(CH_3)_3$

3 : R = H(did not form)
4 : R = $C(CH_3)_3$

5 : R = H
6 : R = $C(CH_3)_3$

Scheme 2.1 Spirodienone **4** and bis(spirodienone) **5-6** derivatives obtained from the oxidation of corresponding calix[4]naphthalenes **1** and **2**.

Among the first examples also, of narrow-rim modifications of calix[4]naphthalenes were the *O*-(ethoxycarbonyl)methoxy derivatives **7** and **8** which had been prepared by Ashram.[2] These derivatives were obtained by treating the calix[4]naphthalene (**2**) with an excess of ethyl bromoacetate and NaH. These compounds were targeted initially in order to improve their solubility and to simplify their purification (Scheme 2.2).



2

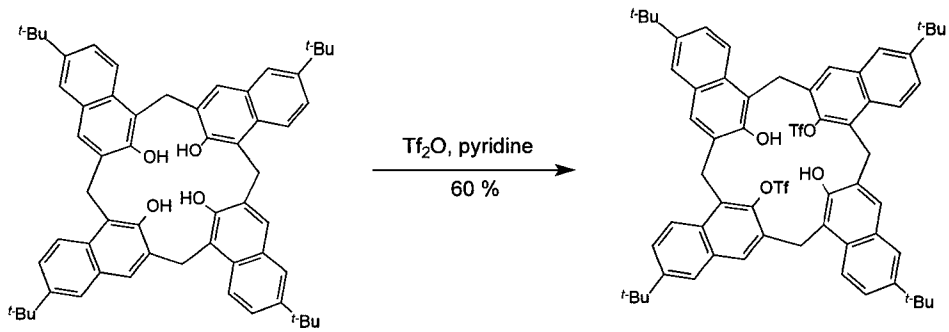
7 : R = CH_2CO_2Et (*cone*)
8 : R = CH_2CO_2Et (*partial-cone*)
9 : R = *n*-propyl (*cone*)

Scheme 2.2 Some narrow-rim modifications of calix[4]naphthalene **2**

Conformational analysis showed **7** and **8** are locked in *cone* and *partial-cone* conformations, respectively, which therefore indicated that such narrow-rim modifications in calix[4]naphthalenes could control their conformations. Similar observations have been made with calix[4]arenes, as described in the introduction to this thesis (Chapter 1).

Narrow-rim functionalization of calix[4]naphthalenes can also be achieved by modification of the hydroxy groups with different alkyl groups. For example, the calix[4]naphthalene tetra-*n*-propoxy ether **9** was obtained by treating **2** with a large excess of 1-iodopropane and NaH (Scheme 2.2). This type of modification was first conducted in our labs by Chowdhury.[3] As expected, the conformation of **9** was locked in a *cone* conformation as confirmed by ^{1}H NMR and NOESY experiments.

Recently, Tran[4] has been able to synthesize the *p-tert*-butylcalix[4]naphthalene bistriflate (**10**) in good yield, by reacting **2** with triflic anhydride (Scheme 2.3). Initial attempts at further modification of **10** by Sonogashira coupling with phenylacetylene, however, were not successful. This work is nevertheless still currently under investigation by the Georghiou group.



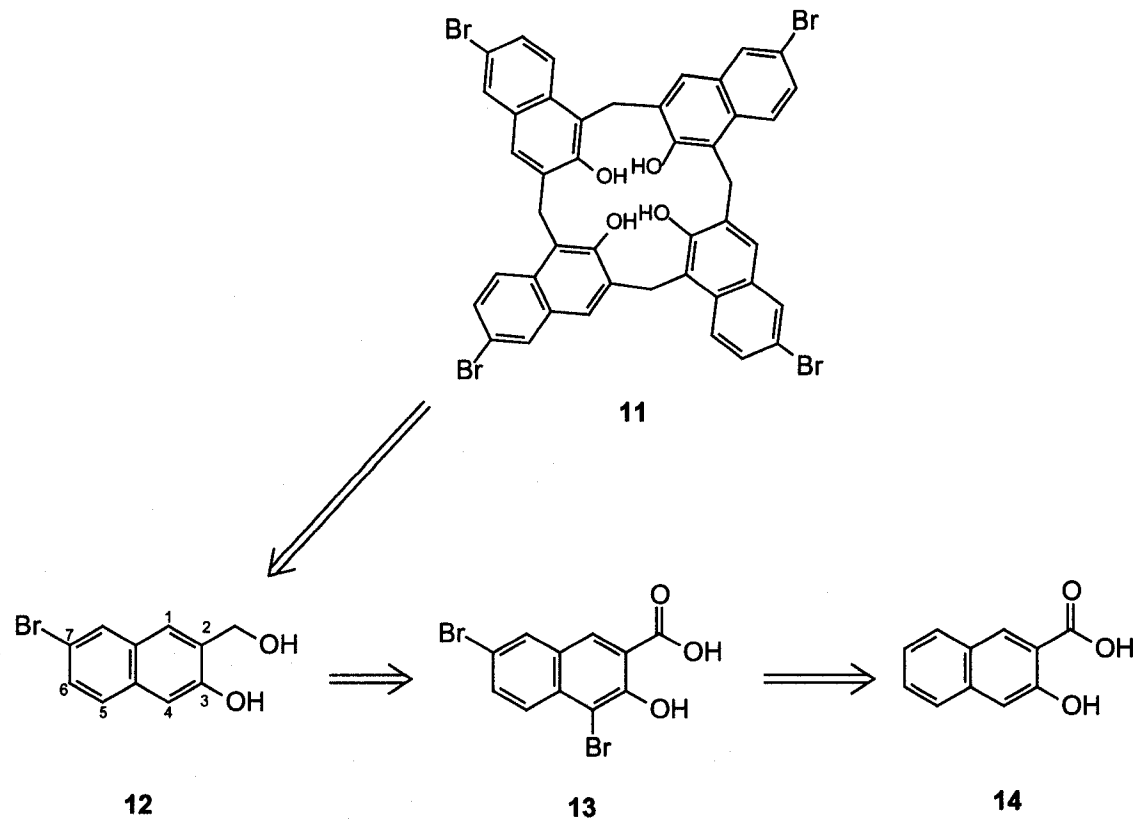
2 **10**

Scheme 2.3 Synthesis of the bistriflate **10** from the naphthalene **2**

While narrow-rim modifications of calix[4]naphthalenes **1** or **2** generally influence some of their conformational properties as described above, wide-rim modifications are also important. Such modifications can be used to synthesize new calix[4]naphthalene derivatives having deeper and wider cavities and which could lead to enhanced complexation properties. Initial attempts by previous members of the Georghiou group involved direct sulfonation of **1** in order to produce water-soluble derivatives, but these attempts did not meet with success.

Our methodology for the wide-rim modification of calix[4]naphthalene was based on the introduction of a halogen atom (such as bromine) regioselectively, in order to synthesize the targeted molecule **11**. The halide could then, in principle, be substituted by another group via, for example, a C-C bond forming reaction (*e.g.* Sonogashira, Stille, and/or Suzuki, etc. coupling) to give the corresponding wide-rim modified derivatives. This methodology required functionalized naphthalene precursors **12** and **13** for example, as key intermediates for the synthesis (Scheme 2.4).

It was presumed that direct wide-rim halogenation of calix[4]naphthalene **1** by, for example, bromination would be problematic since these types of reactions are not regioselective. This problem is even further complicated because of the relatively low yield of **1**, which could only be obtained in a maximum 11% yield. Although, the *tert*-butyl analogue **2** could be produced in a relatively higher yield (31 %), the need for an extra step to remove the *tert*-butyl groups before the desired bromination can negates this higher yield advantage.



Scheme 2.4 Retrosynthetic approach for the wide-rim modified calix[4]naphthalene (**11**)

Whether **1** or **2** is used as starting material for the wide-rim modification, the products from their direct bromination would be expected to produce complex mixtures because prior studies in our lab by Ashram[5] have shown that there are three reactive positions on each naphthalene ring. By way of contrast, this is not the case in calix[4]arenes, in which there only one reactive position for the electrophilic substitution to occur (Figure 2.1).[6]

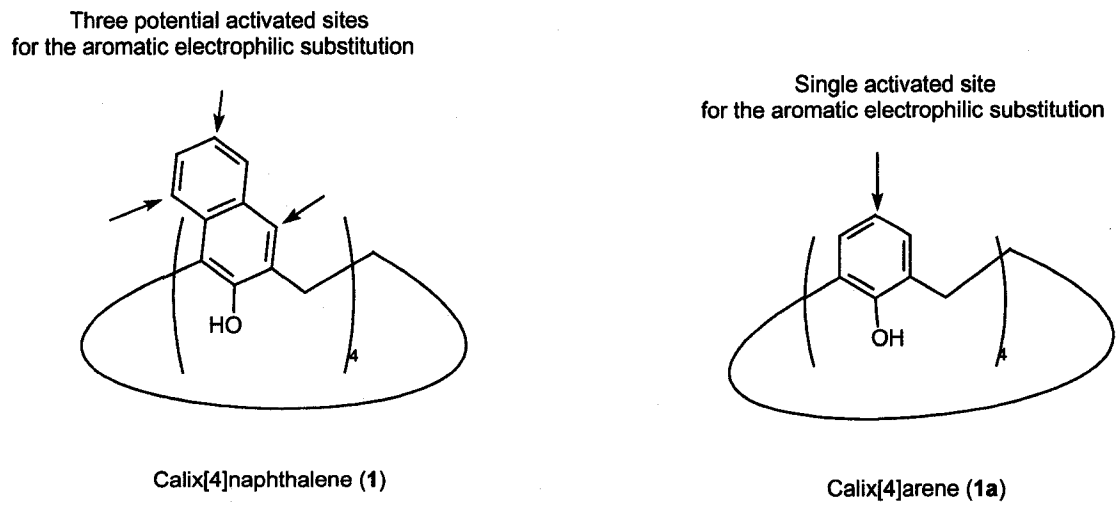


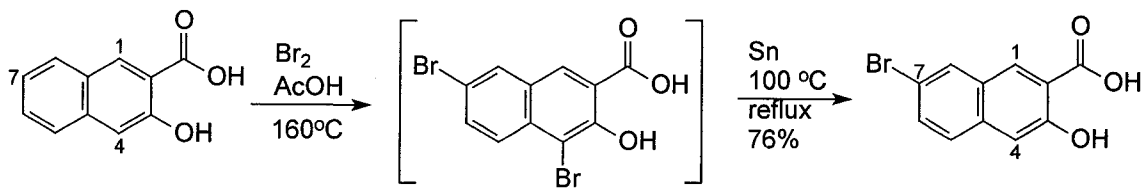
Figure 2.1 The activated positions on calix[4]naphthalene (**1**) compared with that of calix[4]arene (**1a**).

The approach undertaken during this author's research, for the wide-rim modified calix[4]naphthalene **11**, is depicted in Scheme 2.4. The key step in this approach, required the important precursor, 7-bromo-2-(hydroxymethyl)-3-naphthol (**12**), which could be obtained via several steps starting from the commercially-available 3-hydroxymethy-2-naphthoic acid (**14**). As proposed, these steps could be conducted by bromination of **14**, which forms the corresponding dibromonaphthoic acid **13**. In **13** the bromine atoms were expected to be on C-4 and C-7. Selective de-bromination[7] would give the desired 7-bromo-3-hydroxy-2-naphthoic acid (**15**). Esterification, followed by reduction would give **12** which, by analogy with **1**, could result from a $TiCl_4$-mediated cyclization.

2.2- Synthesis

Bromination of 3-hydroxy-2-naphthoic acid (**14**) using a solution of Br_2 in acetic acid gave the corresponding 4,7-dibromo-3-hydroxy-2-naphthoic acid (**13**). Selective *in situ* metal-assisted debromination of **13** was achieved by addition of Sn metal directly to the reaction mixture at reflux temperature to produce **15** in useful yields (Scheme 2.5).

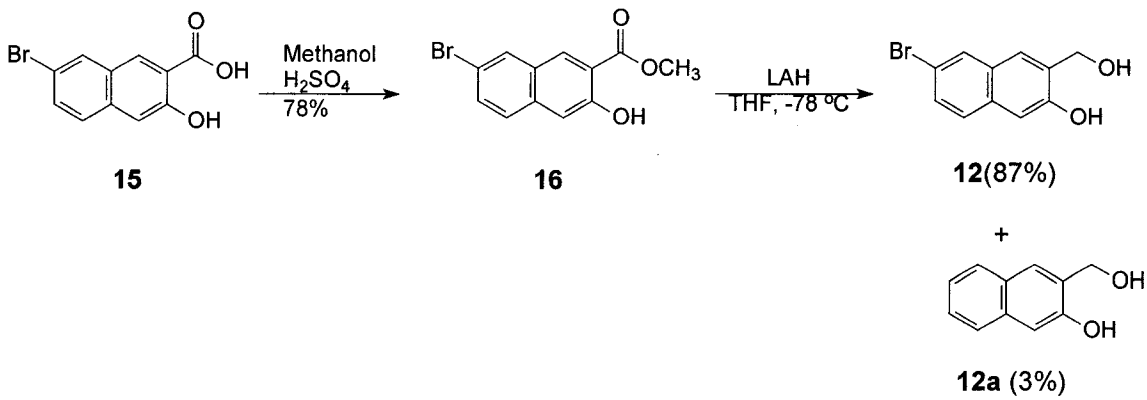
Selective de-bromination of **13** with different reducing agents such as $LiAlH_4$, or Super-Hydride® was unsuccessful and resulted in the removal of both bromine atoms at C-7 and/or C-4. The selectivity of tin metal toward the reduction of the bromine on C-4 could be explained by the fact that the bromine at C-4 is *ortho* to the naphthalene hydroxyl group, so that chelation between the hydroxyl group and tin could play an important role. (Analogous "directed ortho-metallation" ("DOM") reactions are well-known in synthetic organic chemistry). In addition, Sn is known to be a milder reducing agent when compared with the other reducing agents described above.



14 **13** **15**

Scheme 2.5 Synthesis of the 7-bromo-3-hydroxy-2-naphthoic acid (**15**)

Esterification of **15** was conducted by stirring a solution of **15** in the presence of a catalytic amount of H_2SO_4 in methanol, at room temperature. Methyl 7-bromo-3-hydroxy-2-naphthoate (**16**) was produced in good yield (78 %). Selective reduction of the ester moiety in **16** was achieved using LAH, to give the 6-bromo-3-hydroxymethyl-2-naphthol (**12**) in 87% yield. The use of a specific amount of LAH (0.5 equiv) was critical for this step, as was the temperature of the reaction which should be in the range of -78 to 0°C to avoid any undesired de-bromination. Despite these precautions, a small amount of the undesired de-dibrominated product **12a** was always produced (~ 3%) (Scheme 2.6), which could be only removed by fractional crystallization from methanol.



Scheme 2.6 Synthesis of 6-bromo-3-hydroxymethyl-2-naphthol (**12**)

The ^1H NMR spectrum of **12** was not equivocal as to the position of the bromine atom. However, a suitable crystal for the X-ray analysis for precursor **12**

was obtained which revealed that the bromine atom was indeed inserted in the desired position at C-7 (Figure 2.2).

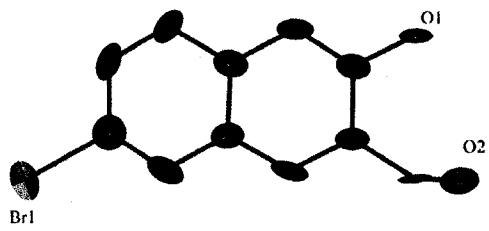
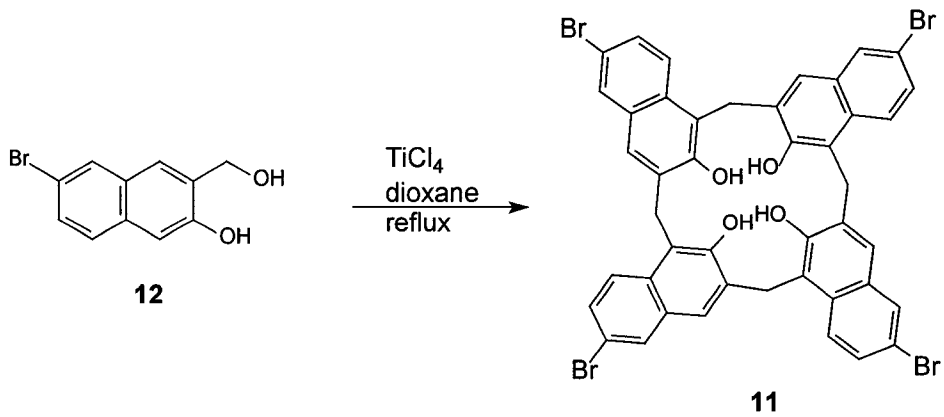


Figure 2.2 X-ray single-crystal ORTEP structural representation of compound **12** (all of the H atoms have been removed for clarity).

Treatment of a solution of **12** in dioxane with $TiCl_4$ (whose role can be considered to be either as catalyst and/or possibly as a templating agent)[8] formed a product which is presumed to be the bromo-calix[4]naphthalene **11** (Scheme 2.7). Analysis of the crude product by mass spectroscopy suggested the formation of the desired product since there is a strong peak at *m/z* 936.8 ($APCI^-$) while the calculated exact mass is 935.9 (Figure 2.3a).

The ^1H NMR spectrum for the crude product also indicated that there is a significant amount of the targeted product present in the mixture with no sign for any starting material remaining. The ^1H NMR spectrum revealed signals at $\delta \sim$ 5.2 - 5.0 ppm, one of which is a characteristic signal for the bridging methylenes in comparision to calix[4]naphthalenes **1** and **2**. Similar observations could be made for two doublet signals which appeared in the aromatic region at $\delta \sim 7.5$ and 8.2 ppm (Figure 2.3b).

Although the NMR and mass analyses strongly suggested that the desired product might have been formed, attempts to purify the crude product by chromatography (column or PLC) or by crystallization have thus far been unsuccessful.



Scheme 2.7 Attempted synthesis of *p*-bromo-calix[4]naphthalene (**11**).

Attempted purification of the desired product by treatment of the crude mixture directly after the reaction with excess NaH and 1-iodopropane, in order to form the corresponding ether derivative, failed to give any defined product and afforded only an inseparable mixture. An attempt to produce the corresponding thiophenyl derivative by reacting the crude mixture with 2-thiophene boronic acid under Suzuki-Miyaura conditions was also unsuccessful (Scheme 2.8). Further research efforts are clearly required to isolate and characterize this very important wide-rim substituted derivative which could serve as a potential precursor for many other wide-rim functionalized derivatives.

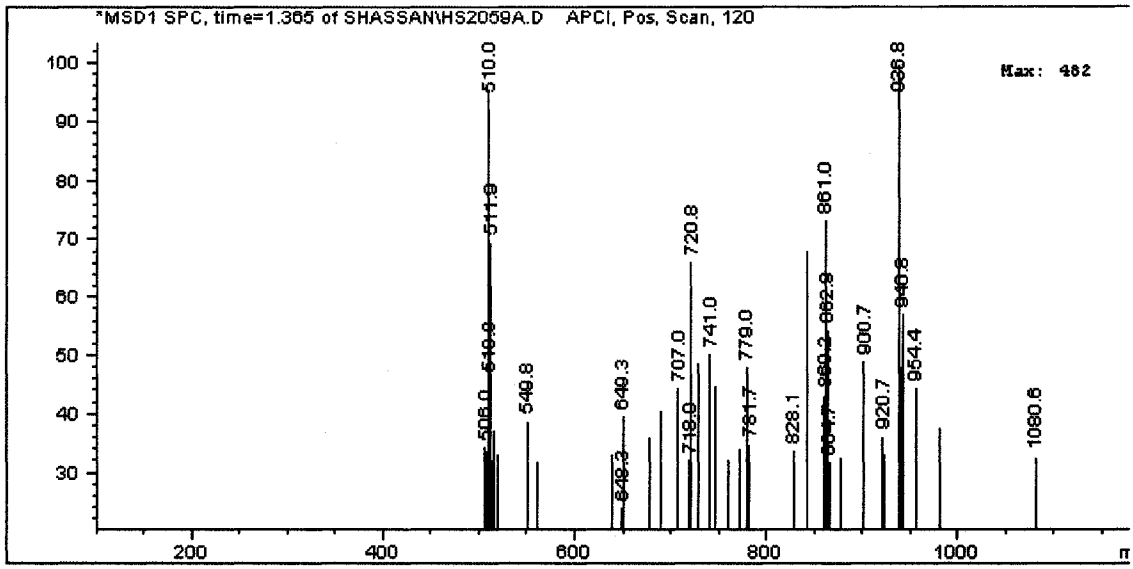


Figure 2.3a Mass spectruum of crude product containing *p*-bromo-calix[4]naphthalene (**11**).

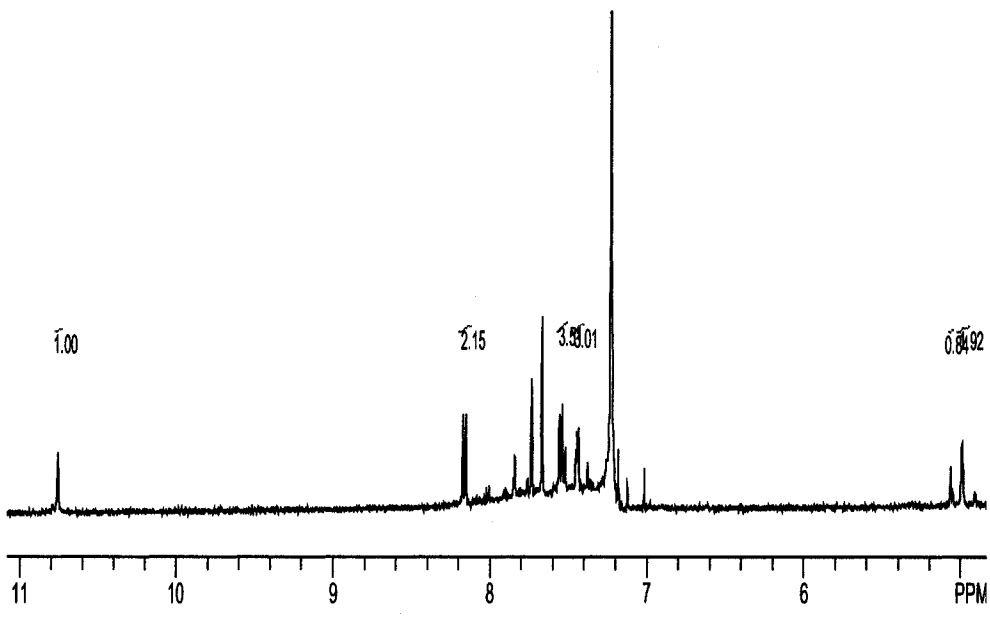
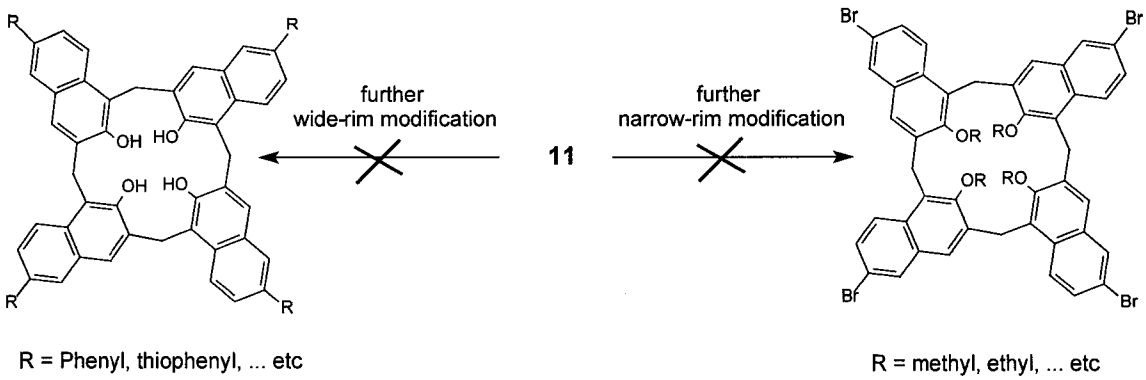


Figure 2.3b ^{1}H NMR spectra of crude product containing *p*-bromo-calix[4]naphthalene (**11**).



Scheme 2.8 Attempts for wide- and narrow-rim modifications of **11**.

2.3- Conclusions

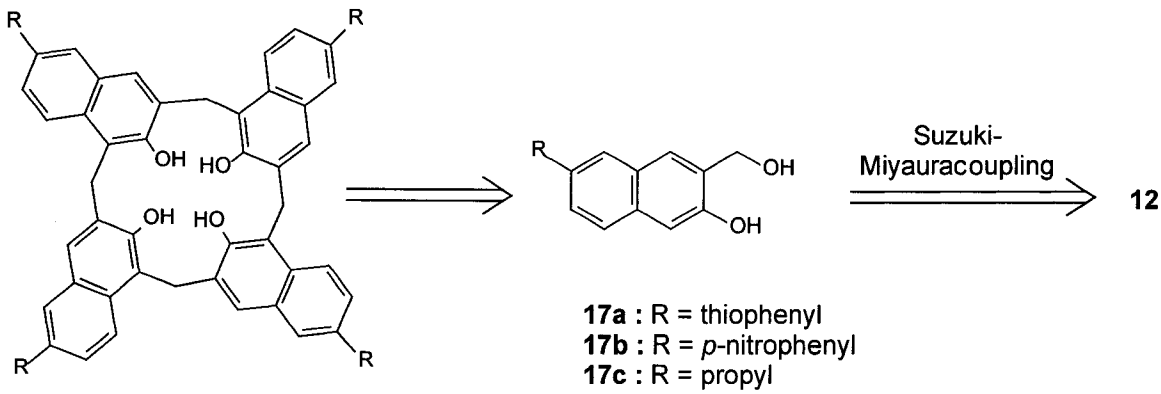
Although the targeted intermediate product **11** has not as yet been fully purified and characterized, an attempt was undertaken to develop a new methodology for the wide-rim modification of calix[4]naphthalene by using a suitably pre-functionalized precursor. Further work is needed to fully explore this approach.

2.4- Suggestions for Future Work

Because there were problems found with respect the complete isolation and identification of **11**, as the precursor for further wide-rim modifications, the following experiments are suggested in order to try to overcome some of the problems encountered.

It is suggested that, for example, instead of using the precursor **12** as starting material for the cyclization step (final step), that more stable starting materials which can be derived from **12** itself be used. For example, the

thiophenyl derivative **17a** could be obtained by coupling **12** with the 2-thiopheneboronic acid. The final step can then be attempted as before, by refluxing a solution of **17a** and $TiCl_4$ in dioxane to try to produce the desired product **18a** (Scheme 2.9). By following the same methodology, different groups such as various aryl groups, heterocyclic rings or aliphatic groups, etc., could be attached on the wide-rim of the calix[4]naphthalene.



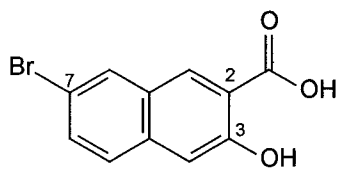
Scheme 2.9 Proposed experiments for the production of different wide-rim modified calix[4]naphthalenes **18a-c**.

2.5- Experimental

General experimental information

All chemical reagents and solvents were purchased from Aldrich, or Fluka, or Fisher. Organic solvents were dried, if needed, by using standard methods. Sensitive reactions were conducted under dry Argon. Column chromatography was performed on SAI silica gel, particle size 32-63 μm, pore size 60 Å.

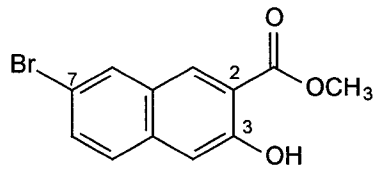
Preparative thin-layer chromatography (PLC) was performed by SAI F-254 silica gel particle size 5 – 15 μm. ^{1}H and ^{13}C NMR spectra were conducted on Bruker Avance 500 MHz using $CDCl_3$ as a solvent and TMS as an internal standard at 0.00 ppm for the ^{1}H NMR, while the chemical shift in the ^{13}C NMR are relative to δ 77.23 ppm for $CDCl_3$ and 29.92 for acetone-d_6. Mass spectra were obtained by GCMS (HP 5972 series II®), LCMS (HP series 1100). Melting points were measured on MEL-TEMP II® apparatus and were not corrected.



15

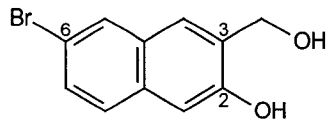
7-Bromo-3-hydroxy-2-naphthoic acid (15): In a three-neck round-bottomed flask fitted with a dropping funnel and a condenser, were placed 3-hydroxy-2-naphthoic acid (**14**) (15.0 g, 79.7 mmol) and glacial acetic acid (30 mL). Through the dropping funnel another solution of bromine (25.5 g, 159 mmol) in glacial acetic acid (15 mL) was added dropwise over 30 min. After the bromine solution was added, H_2O (20 mL) was added in one portion and the reaction was heated to 100°C. Granules of Sn (12.0 g, 101 mmol) were then added to the mixture with vigorous stirring. The reaction mixture was heated at reflux for an additional 3h, and was then filtered while hot. The filtrate was cooled to room temperature and diluted with water (50 mL) to form a yellow precipitate, which was filtered,

washed with water (3 X 50 mL) and air-dried to give **15** as a yellow solid (32.4 g, 76%): mp 247- 250 °C; ^{1}H NMR (acetone-d_6) δ 7.37 (s, 1H), 7.66 (d, J = 15.0 Hz, 1H), 7.76 (d, J = 15.0 Hz, 1H), 8.23 (s, 1H), 8.63 (s, 1H), 10.89 (s, 1H, OH); ^{13}C NMR (acetone-d_6) δ 112.4, 116.3, 117.7, 129.1, 129.2, 132.0, 133.0, 133.1, 137.4, 158.4, 172.4; GC-MS *m/z* calcd for $C_{11}H_7BrO_3$ 265.96/267.96, found 264.92/266.92 (M^+).



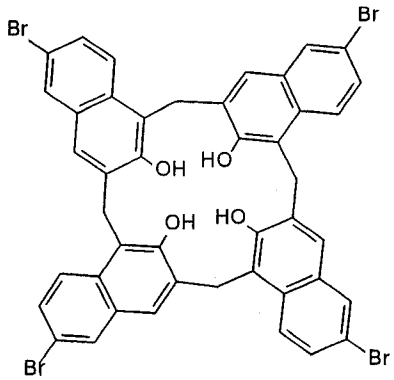
16

Methyl 7-bromo-3-hydroxy-2-naphthoate (16): A solution of 7-bromo-3-hydroxy-2-naphthoic acid (**15**) (8.0 g, 30 mmol) in methanol (30 mL) and sulfuric acid (1.2 mL) was heated at reflux temperature for 24 hours. The reaction mixture was then cooled to room temperature after which it formed a yellow precipitate which was filtered and washed with aqueous 5% sodium bicarbonate (10 mL), water (3x5 mL) and air-dried to give **16** (6.57g, 78 %): mp 147- 149 °C; ^{1}H NMR (acetone-d_6) δ 4.07 (s, 3H), 7.38 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 8.21 (s, 1H), 8.58 (s, 1H); ^{13}C NMR (acetone-d_6) δ 60.8, 109.3, 116.3, 116.4, 125.5, 128.3, 129.0, 129.8, 130.1, 132.8, 133.0, 154.6; MS (APCI-) *m/z* calcd for $C_{12}H_9BrO_3$ 279.97/281.97, found 279.11/281.11 (M^-).



12

6-Bromo-3-hydroxymethyl-2-naphthol (12): To a solution of methyl 7-bromo-3-hydroxy-2-naphthoate (**16**) (12.0 g, 42.7 mmol) in dry THF (100 mL) was added at -78 °C suspension of LAH (0.80 g, 21.4 mmol) over 20 min, After addition was completed, the reaction mixture was stirred for 12 h at room temperature, then poured into cold wet diethyl ether, and the mixture was acidified by addition of 10% hydrochloric acid. The ether layer was separated and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to give **12** (9.3 g, 86%) as pale yellow solid: mp 194 - 195 °C; ^{1}H NMR (acetone-d_6) δ 2.90 (t, 1H, OH), 4.89 (d, *J*= 8 Hz, 2H), 7.20 (s, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.83 (s, 1H), 8.98 (s, 1H), 8.92 (b, 1H, OH); ^{13}C NMR (acetone-d_6) δ 61.3, 109.9, 116.8, 126.1, 128.8, 129.6, 130.3, 130.7, 133.3, 133.6, 155.2; MS (APCI-) *m/z* calcd for $C_{11}H_9BrO_2$ 251.98/253.98, found 251.45/253.45 (M^-).



11

***p*-Bromo-calix[4]naphthalene (11):** To a solution of 6-bromo-3-hydroxymethyl-2-naphthol (**12**) (0.20 g, 0.79 mmol) in anhydrous dioxane (40 mL) at 60 °C under argon was added $TiCl_4$ (0.09 mL, 0.8 mmol), dropwise. The reaction mixture was then heated to reflux temperature for 48 h. After cooling to room temperature, the solvent was evaporated *in vacuo.* MS (APCI-) *m/z* calcd for $C_{44}H_{28}Br_4O_4$ 935.9, found 936.8 (M^-).

2.6- References

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

2. Ashram, M. *Ph.D. Dissertation*; Memorial University of Newfoundland: Newfoundland and Labrador, Canada, **1999**. pp.103.

3. Chowdhury, S. *Ph.D. Dissertation*: Memorial University of Newfoundland: Newfoundland and Labrador, Canada, **1999**.

4. Tran, H. *Ph.D. Dissertation*; Memorial University of Newfoundland: Newfoundland and Labrador, Canada, **2007**. pp. 70.

5. Murphy, R. A.; Kung, H. F.; Kung, M. –P.; Billings, J. *J. Med. Chem.* **1990**, *33*, 171.

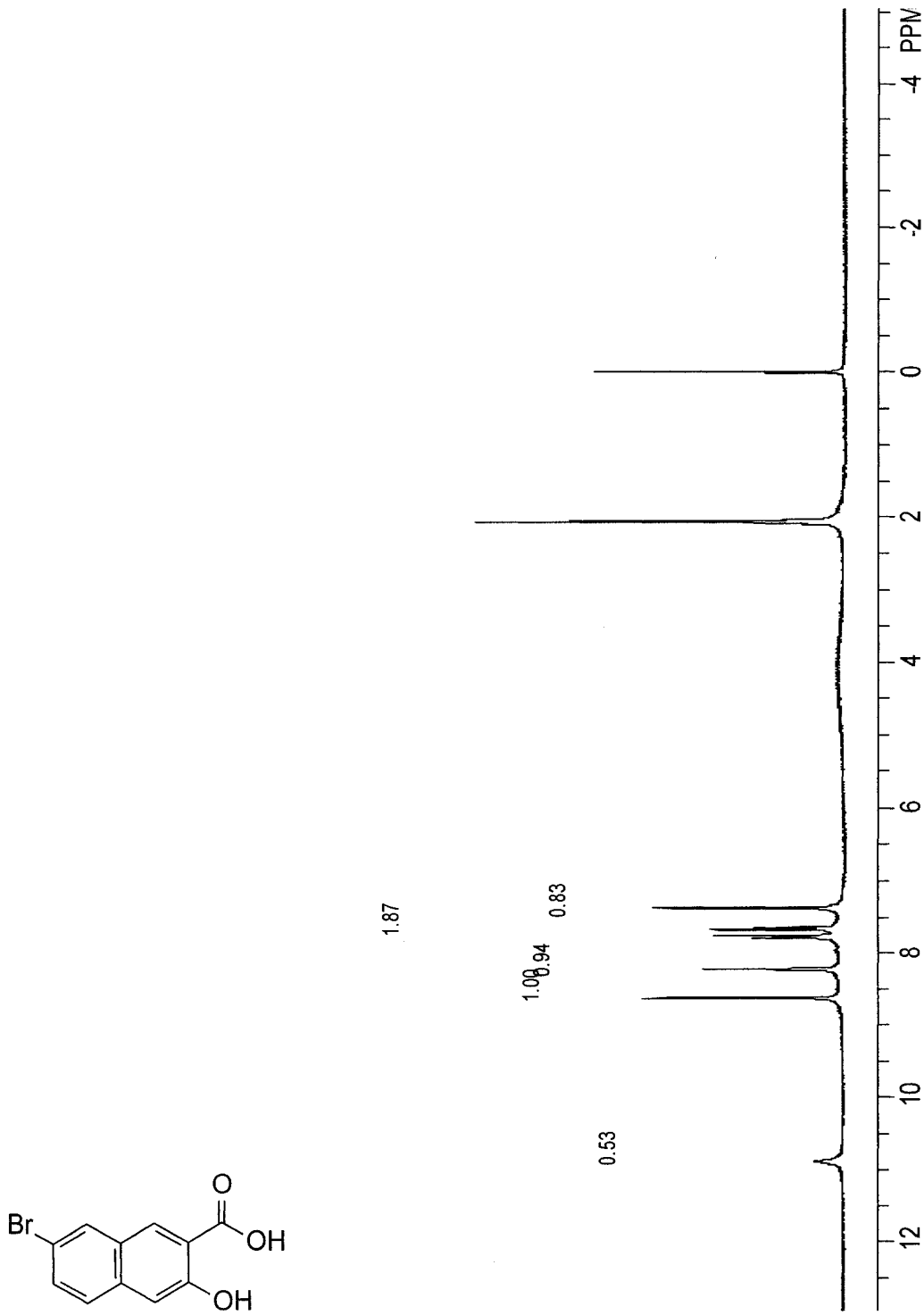
6. Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2652.

7. Murphy, R. A.; Kung, H. F.; Kung, M. P.; Billings, J. *Journal of Medicinal Chemistry,* **1990**, *33,* 171.

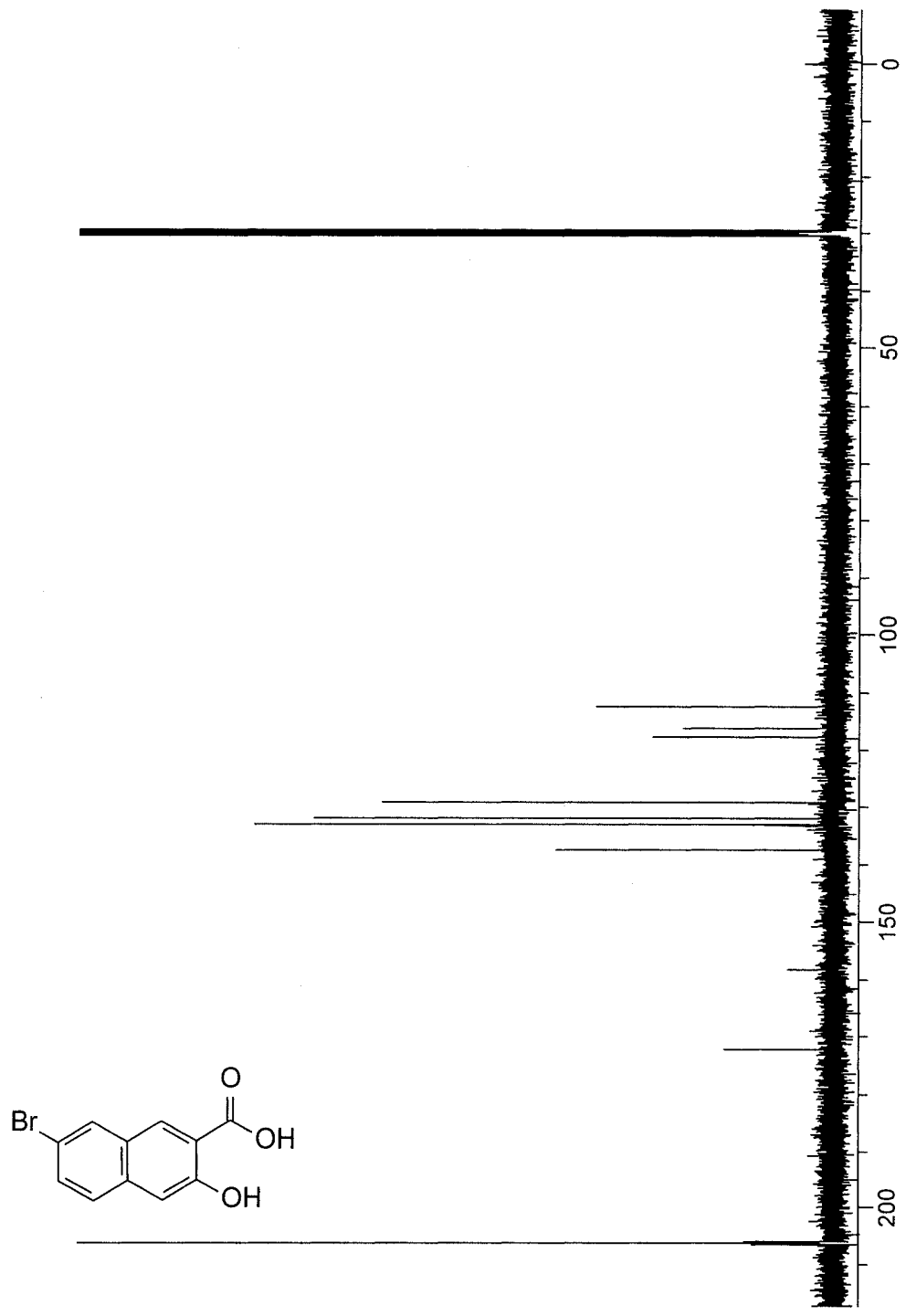
8. Andreetti, G. D.; Böhmer, V.; Jordon, J. G.; Tabatabai, M.; Ugozzoli, F.; Vogt, W.; Wolff, W. *J. Org. Chem.* **1993**, *58*, 4023.

Appendix: Chapter 2

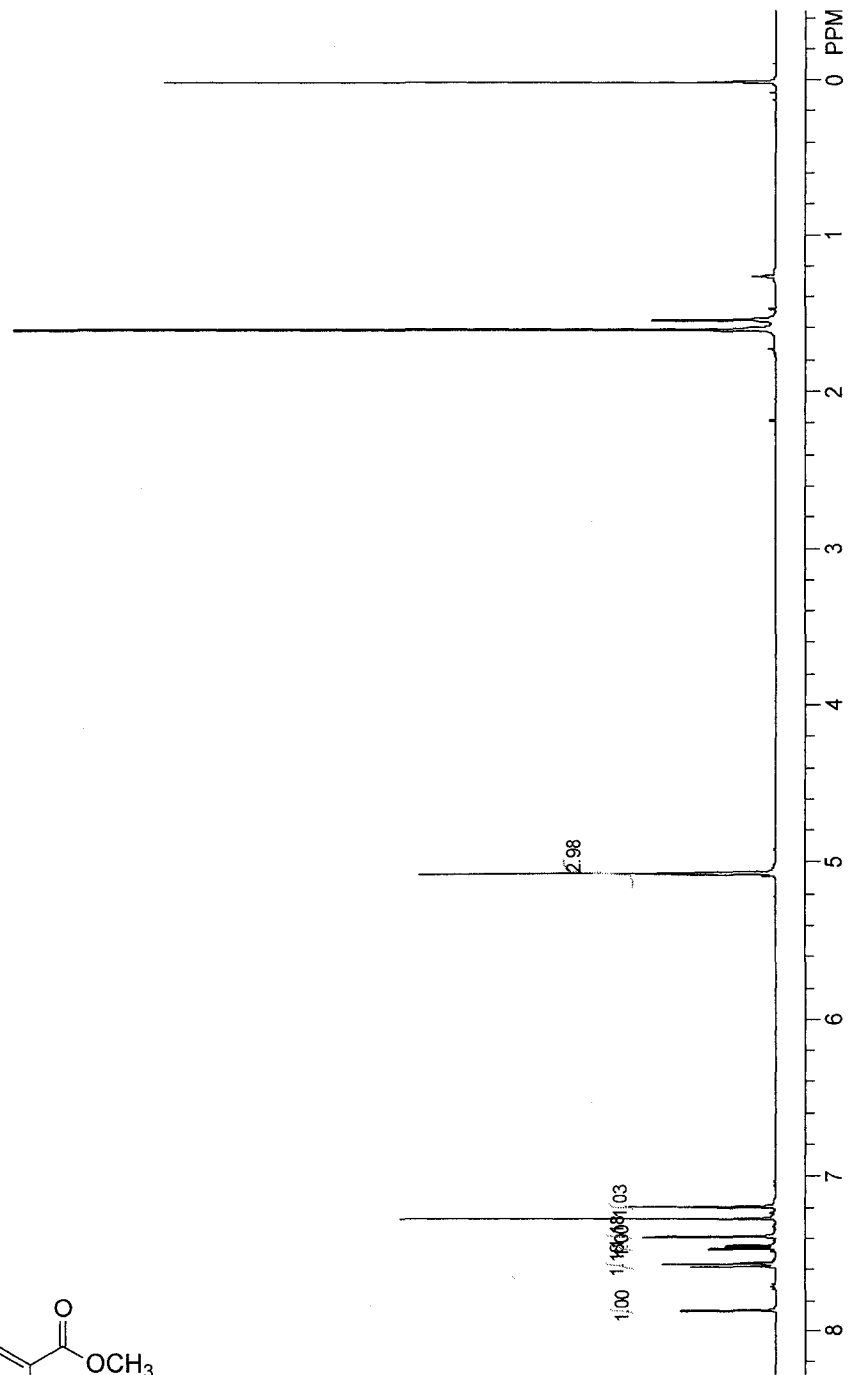
X-ray crystal data for 12: Colourless crystal ($MeOH/CHCl_3$), $C_{11}H_9O_2Br$, monoclinic, space group $P2_1/c$ (#14), Z = 4, a = 21.191(2) Å, b = 5.583(6) Å, c = 8.183(6) Å, β= 98.47(2)°. V = 957.5(9) $Å^3$, $D_{Calcd.}$ = 1.76 g cm^{-3}, crystal size = 0.40 x 0.30 x 0.40 mm. Intensity data were measured on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα (λ = 0.71069 Å) radiation $2\theta_{max}$ = 55.2°; 2602 reflections converged to a final R_{int} of 0.061 for 2437 unique reflections and 150 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0.072 and 0.079, respectively, and GoF = 3.93.

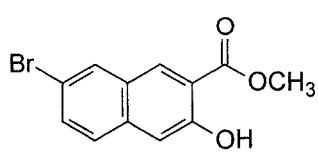


^{1}H NMR spectrum for compound **15**

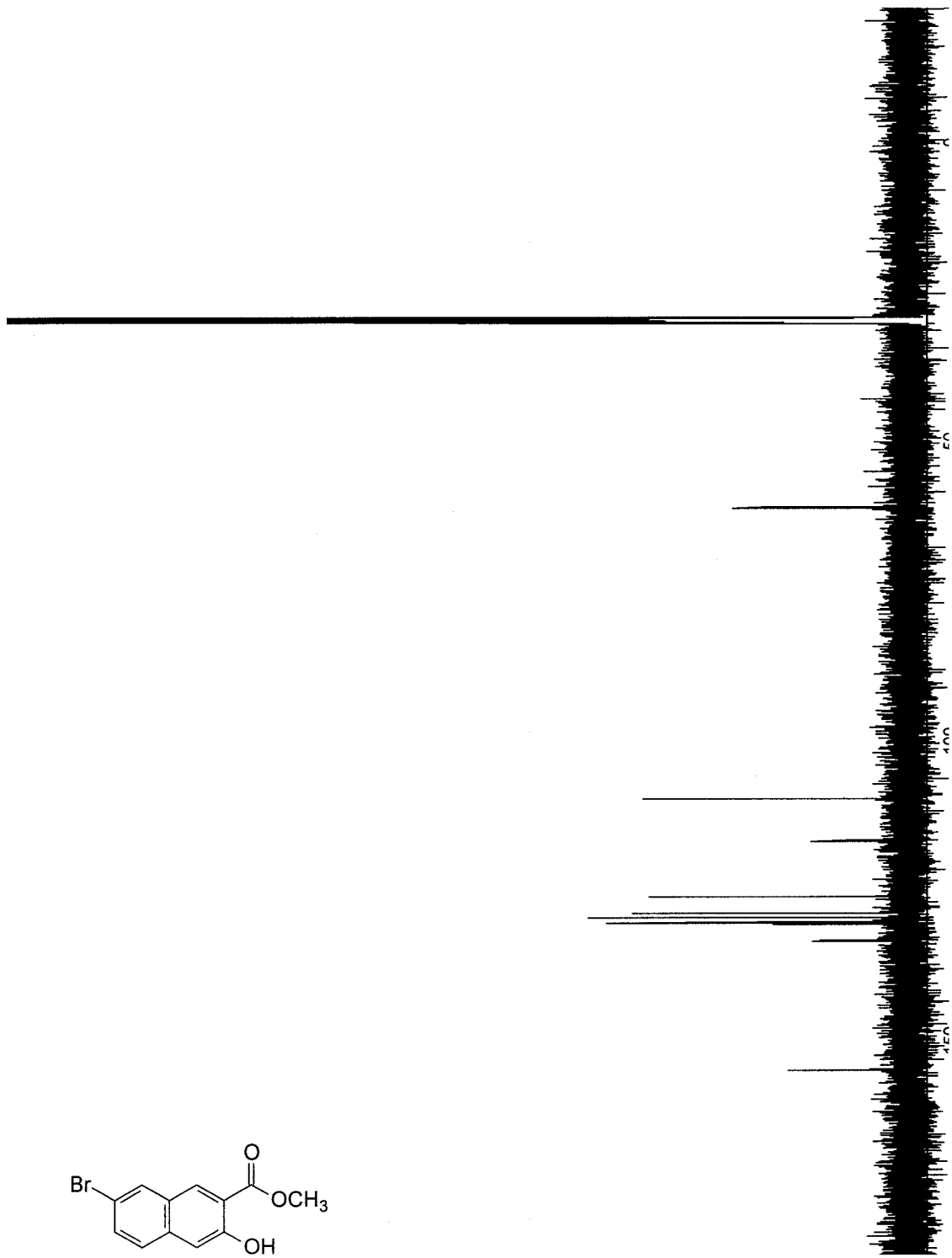


^{13}C NMR spectrum for compound **15**

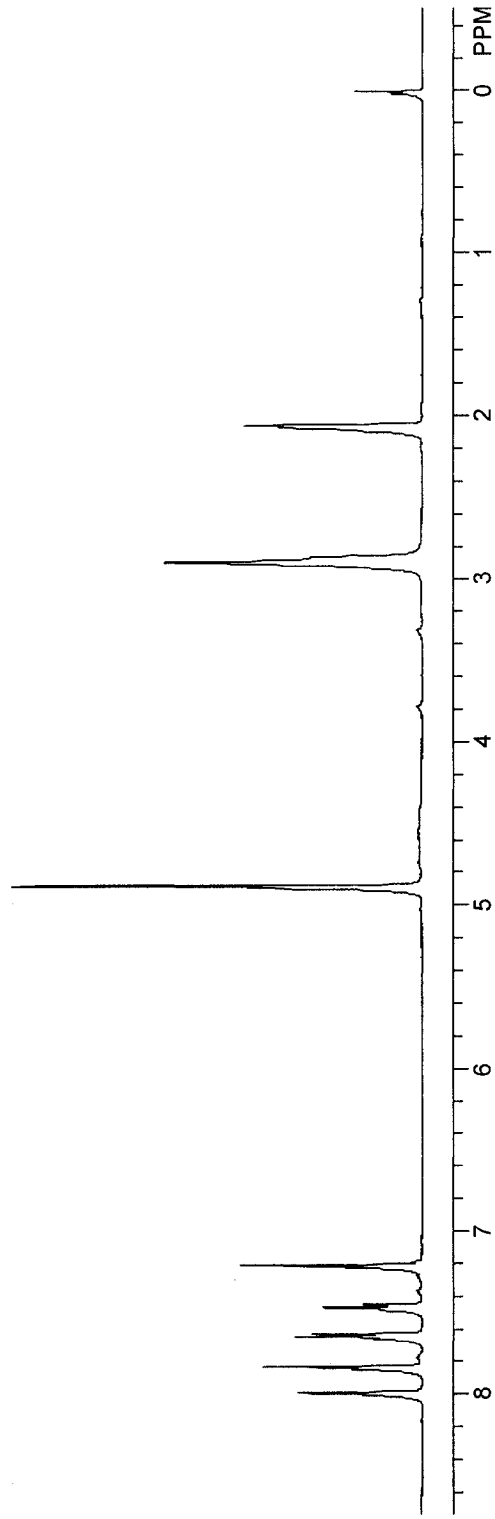


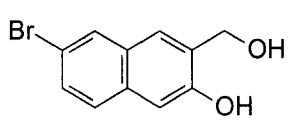


^{1}H NMR spectrum for compound **16**

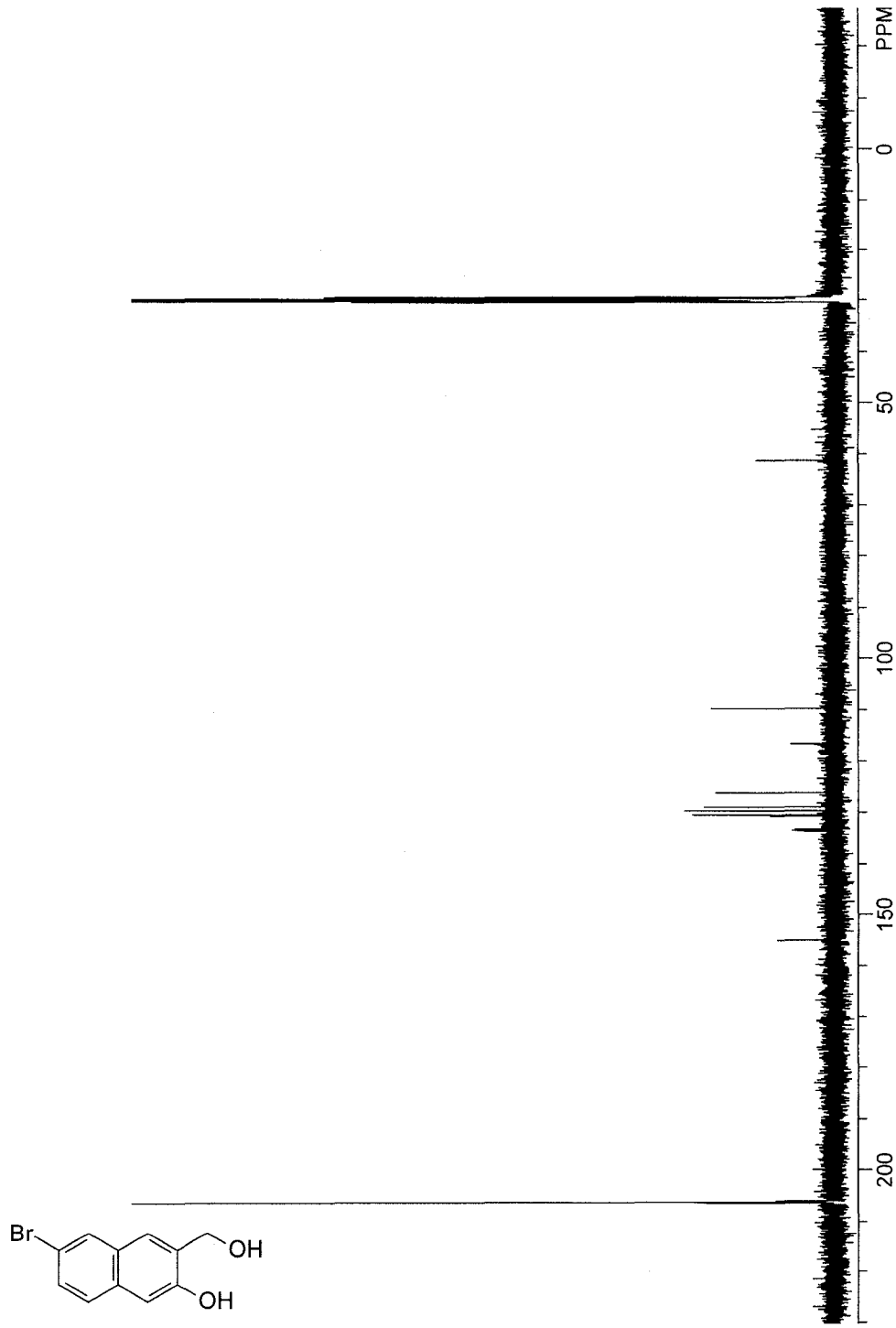


^{13}C NMR spectrum for compound **16**





^{1}H NMR spectrum for compound **12**



^{13}C NMR spectrum for compound **12**

Chapter 3

Thiophene-Based Homooxa-Calix[4]arenes

3.1-Introduction

Heterocycle-based calixarenes incorporate different heterocyclic units instead of the conventional phenolic units in the construction of the macrocyclic compound. For example, incorporating pyridine, furan, thiophene, indole or pyrrole units produces compounds **1**,[1] **2**,[2] **3**,[3] **4**[4] and **5**,[5] respectively (Figure 3.1). In some cases, more than one type of heterocyclic unit have been used, as in calix[2]bipyrrole[2]furan (**6**) and calix[2]bipyrrole[2]thiophene (**7**) (Figure 3.2).

Due to their potentially useful chemical properties and their applications; such heterocyclic-based calixarenes have gained considerable attention from many research groups. For example, the mixed heterocycle-containing compounds **6** and **7** have been shown by Sessler et al.[6] to selectively bind with specific anions, such as acetate and benzoate, with high binding constant values

Other mixed heterocalixarenes such as **8–11** containing imidazolium units within the frameworks of the calixarene have also been synthesized. These compounds were found to be good anion receptors. For example, compound **8** (Figure 3.3), in particular, displays high affinity for acetate ions, as concluded from the complexation-induced ^{1}H NMR chemical shifts of the imidazolium ring protons which moved downfield.[7]

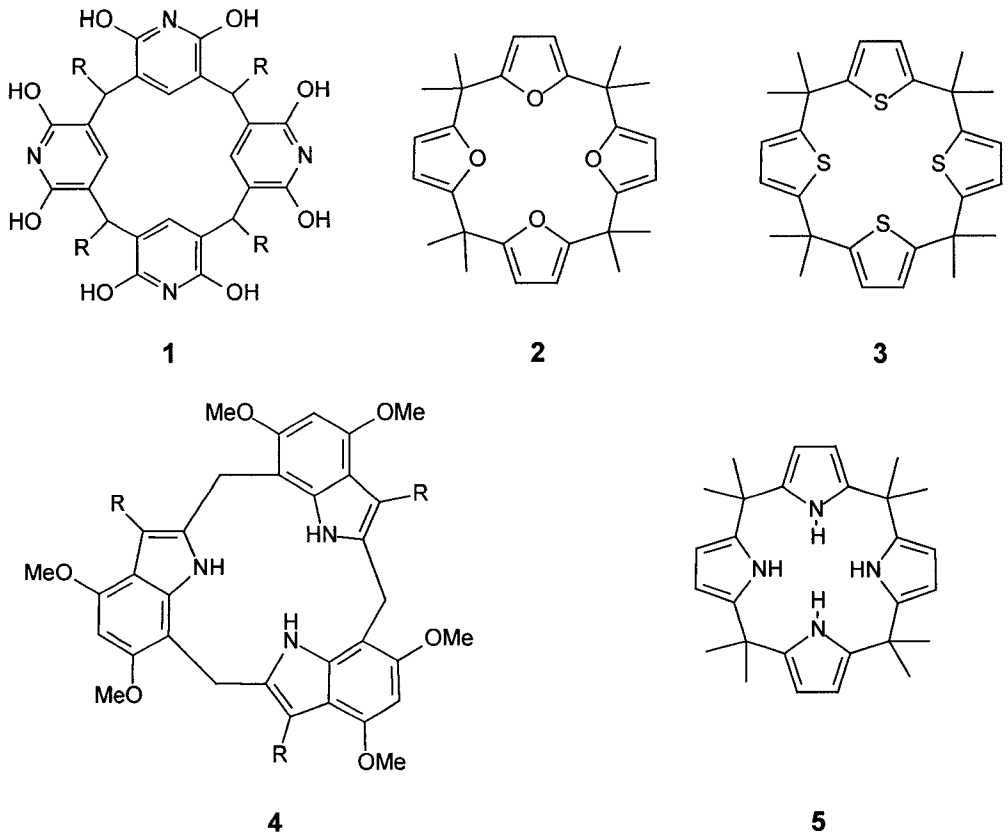


Figure 3.1 Heterocyclic-based calixarenes **1-5**.

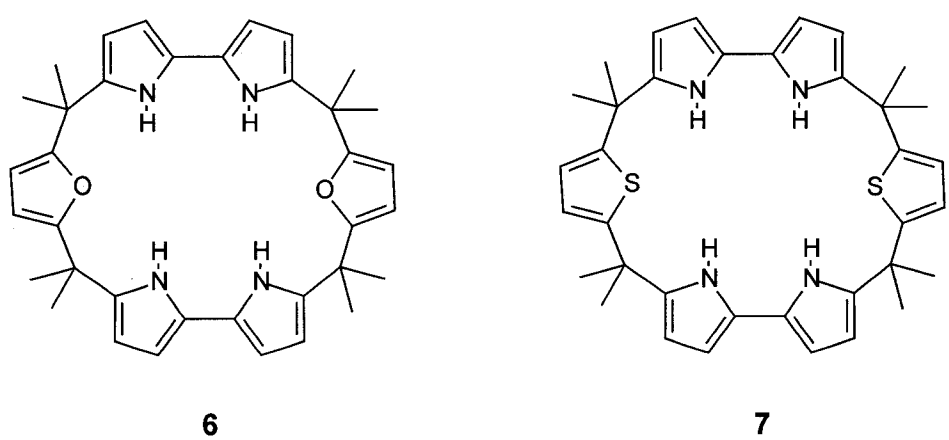
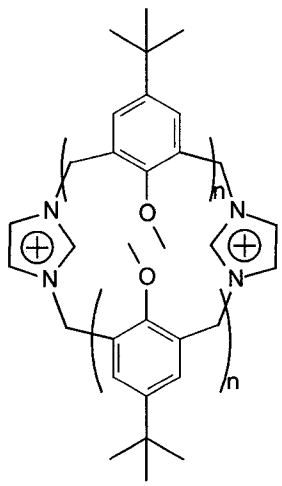
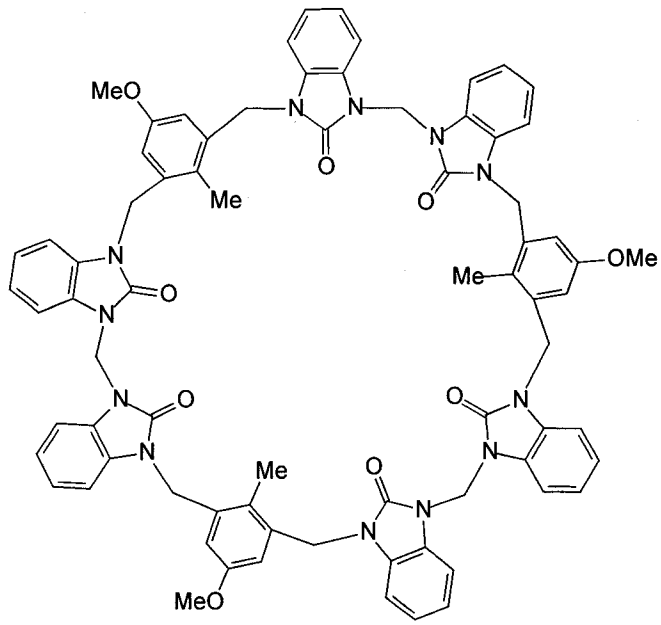


Figure 3.2 Heterocyclic-based calixarenes **6** and **7**.

Larger heterocyclic calixarenes such as the calix-benzimidazolone **11,** are other examples in which benzimidazolone units are used to construct larger macrocyclic compounds (Figure 3.3). Complexation studies revealed that compound **11** had the ability to bind with several guest compounds; for example, a single molecule of **11** can bind with two acetone molecules and also with two dichloromethane molecules to form (1:2:2) complex as shown by X-ray crystallography. The driving forces for the formation of such complexes were attributed to the presence of the benzimidazolone units. These results were confirmed by the X-ray analysis of the complex, which also revealed that this compound forms a cage-like structure (Figure 3.4).[8]



8 : n = 1
9 : n = 2
10 : n = 3



11

Figure 3.3 Mixed heterocalixarenes **8–11**

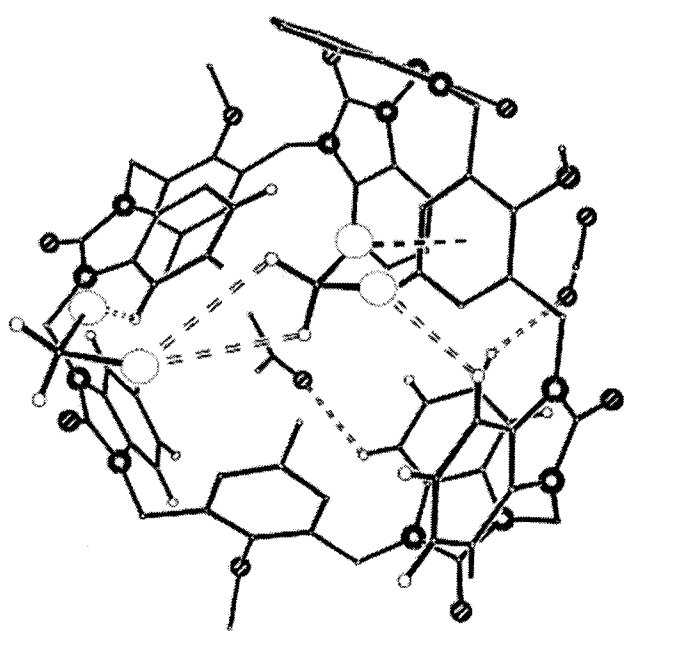
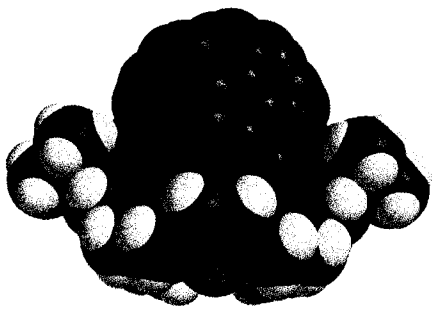
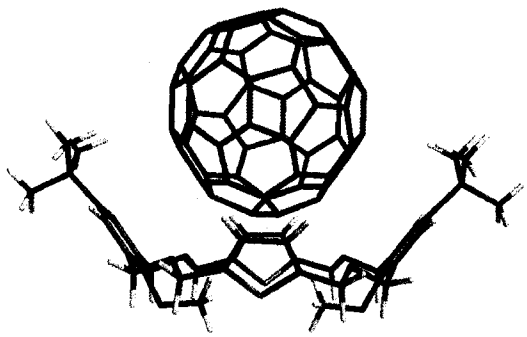


Figure 3.4 View of the inclusion complex **11**:acetone:dichloromethane (1:2:2).

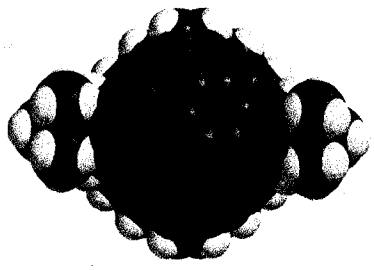
We anticipated that the replacement of one or two of the benzene rings in calix[4]arene with thiophene rings, to form new derivatives such as "**12**" (Scheme 3.1) might produce a potential new host for C_{60} or C_{70} fullerene (Figure 3.5). Although it would have a large degree of rotational flexibility due to the presence of four ether units ($-CH_2-O-CH_2-$) linking the aromatic units (phenyl and thiophenyl units) together, model studies indicated that this compound could have a very well-defined cavity. Indeed, the presence of four oxygen atoms and two sulfur atoms within the cavity could play an important role and could potentially enhance its complexation ability based on previous work.[9] Modeling studies using Spartan '06 also suggested that the tetramethyl ammonium ("TMA") cation could be a potential guest.[9]



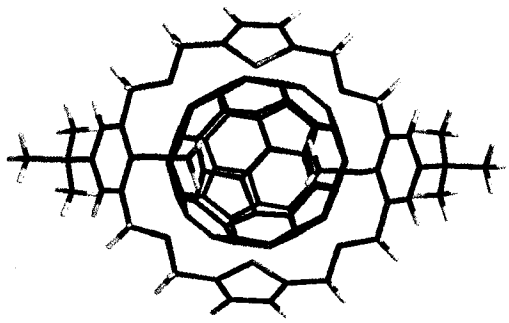
Space-filling model (side view)



Tube model (side view)



Space-filling model (top view)



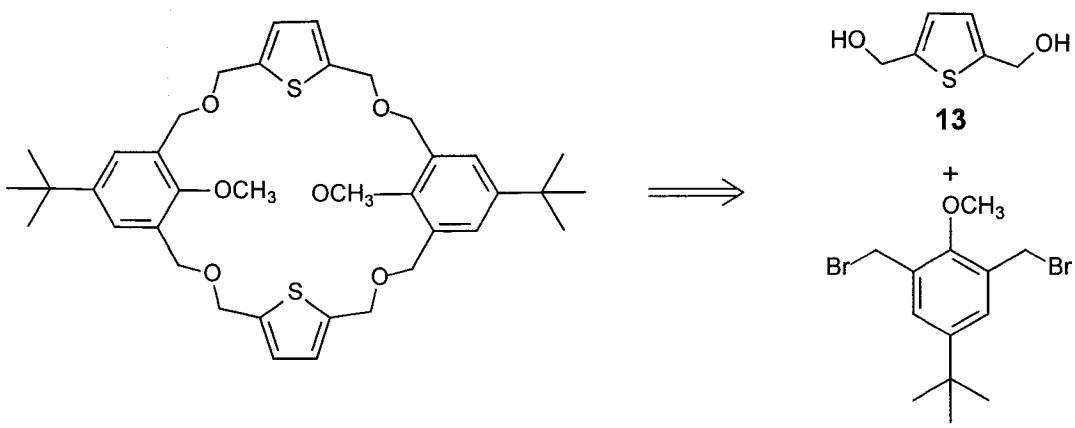
Tube model (top view)

Figure 3.5 Spartan '06-generated 1:1 supramolecular complex of C_{60} with **12**

In this chapter, the synthesis and some properties of the thiophene unit-containing calixarene **12** is described. The synthesis could be achieved by condensation of the corresponding thiophene precursors 2,5-

bis(hydroxymethyl)thiophene (**13**) with the 2,6-bis(bromomethyl)-4-*tert*-butylanisole (**14**) for example, as outlined in Scheme 3.1.

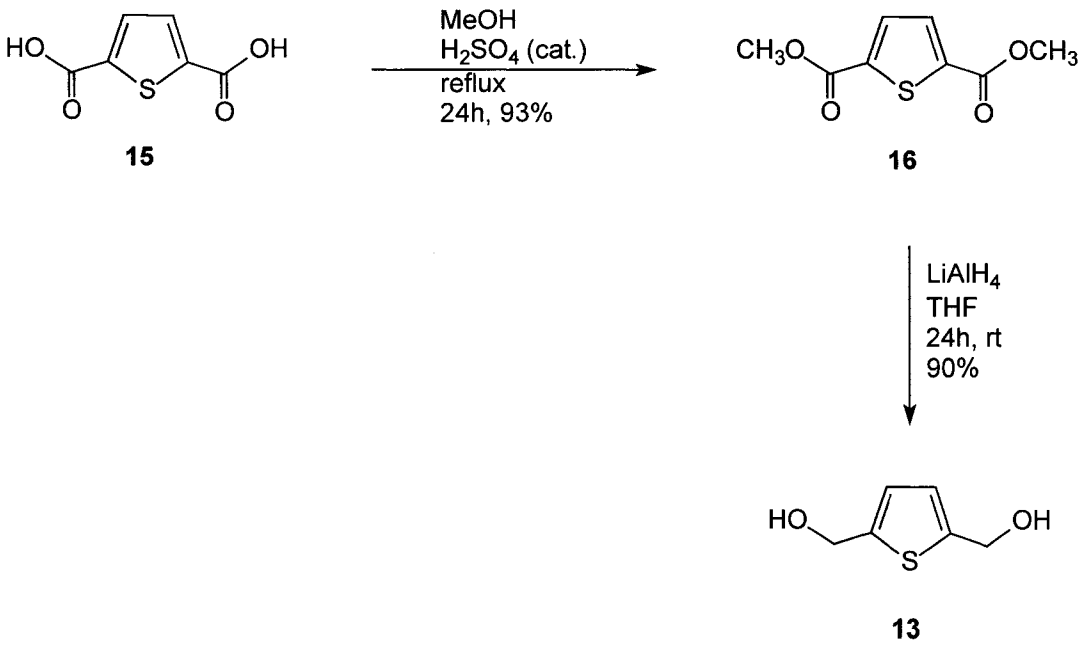
It was estimated that both precursors **13** and **14** could be obtained from relatively inexpensive starting materials. Thiophene **13** could be prepared via two steps from 2,5-thiophene dicarboxylic acid (**15**). The first step requires esterification which is then followed by LAH reduction, to give **13**. Precursor **14** could be also obtained in two steps, starting from *p*-*tert*-butylphenol (**17**), via protection of the phenolic hydroxyl group, followed by the bromomethylation step.



Scheme 3.1 Retrosynthetic approach for the thiophene-based calix[4]arene **12**.

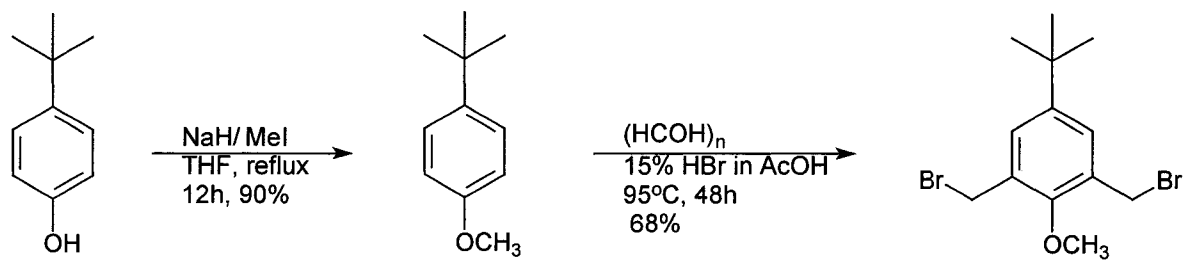
3.2- Synthesis

The synthesis of **13** commenced with the esterification of commercially available 2,5-thiophene carboxylic acid (**15**). This step was conducted by refluxing a mixture of **15** in methanol containing a catalytic amount of concentrated sulfuric acid, for 24 h, to give the dimethyl thiophene-2,5-dicarboxylate (**16**) in 93 % yield. Reduction of **16** was achieved by room temperature LAH reduction in THF, to furnish the thiophene precursor **13** in 90 % yield (Scheme 3.2).



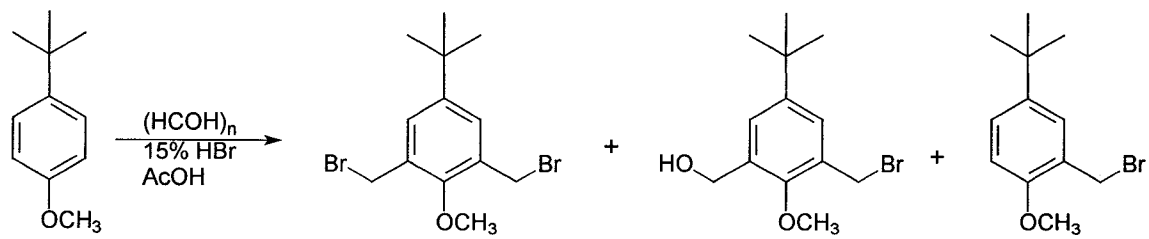
Scheme 3.2 Synthesis of 2,5-bis(hydroxymethyl)thiophene (**13**)

The bromomethyl intermediate **14** was prepared[10] in two steps, starting from commercially-available *p-tert*-butylphenol (**17**). The first step included the protection of the phenolic hydroxyl group by treating a solution of **17** in THF with NaH and MeI at reflux to give *p-tert*-butylanisole (**18**) in 90% yield. Bromomethylation of **18** using a mixture of paraformaldehyde and HBr in acetic acid (15 % solution) produced bromomethyl **14** in 68 % yield. The low yield which was observed in the synthesis of **14** was due to the formation of the undesired products **19** and **20**, as concluded from the GC-MS analysis (Scheme 3.4).



17 **18** **14**

Scheme 3.3 Synthesis 2,6-bis(bromomethyl)-4-*tert*-butylanisole (**14**)

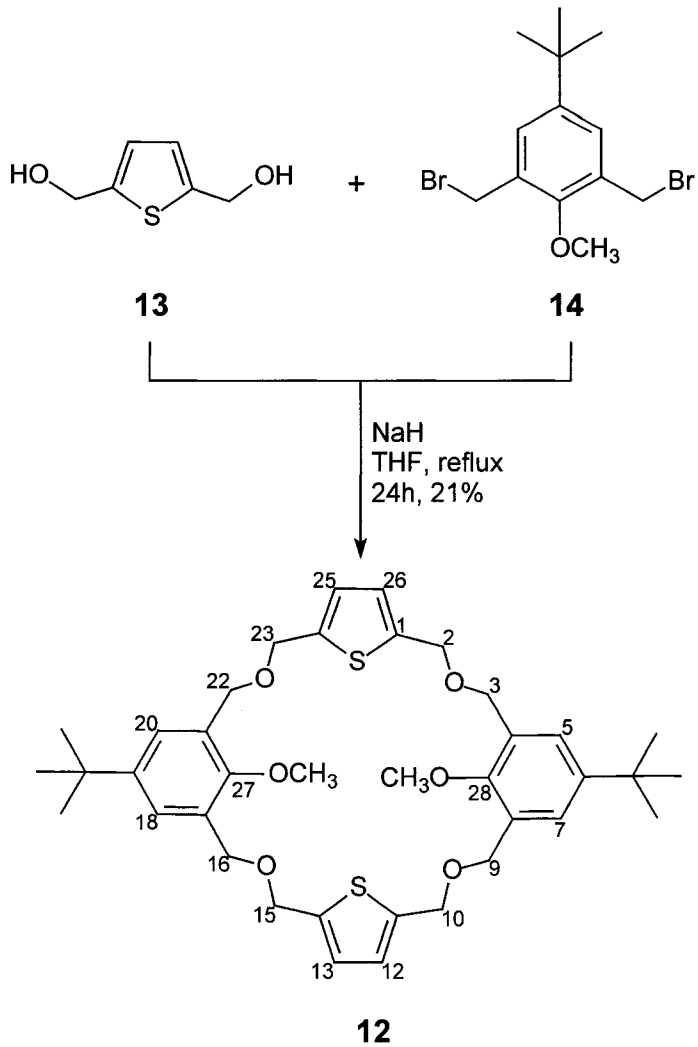


18 **14** **19** **20**

~68% ~10% ~20%

Scheme 3.4 Mixture of products obtained from the bromomethylation of **18**

The last step in this synthesis was accomplished by the condensation reaction between **13** and **14** in the presence of base, to give the corresponding thiophene-based calix[4]arene **12** in 21 % yield. The reaction was conducted by slowly adding an equimolar solution of **13** and **14** in THF to a mixture of NaH in THF at reflux temperature.



12

Scheme 3.3: Synthesis of the thiophene-based calix[4]arene **12**

The ^{1}H and ^{13}C NMR spectra of **12** were in agreement with the expected product and its simplicity indicated that this compound is highly symmetrical. The ^{1}H NMR spectrum shows two signals at low field, one corresponding to the protons of the aryl units (at C5, 7, 18 and 20) and the other for the protons of the thiophenyl units (at C12, 13, 25 and 26) (Figure 3.6a).The ^{13}C NMR spectrum shows only six carbon signals at the low field region corresponding to the aryl and thiophenyl carbons, and five signals at higher field for the remaining carbon atoms in the molecule (Figure 3.6b).

The bridging methylene protons appeared as two sharp singlet signals, one at δ ~ 4.51 and one at ~ 4.75 ppm in the ^{1}H NMR spectrum, showing that this compound is highly flexible at, or above, room temperature. This confirms the hypothesis stated earlier in this chapter, that this flexibility is likely due to the presence of four ether bridges which link the aryl and thiophenyl units.

Colorless twinned crystals for **12** (Figure 3.7a-b) were obtained from a methanol / dichloromethane solution. The crystals obtained were suitable for X-ray diffraction analysis which was in general agreement with the ^{1}H and ^{13}C NMR spectroscopic interpretation. The X-ray structure revealed that compound **12** in the solid state adopts the *1,3-alternate* conformation. In this conformation, the two phenolic rings are almost completely antiparallel to each other. One of the thiophene rings is tilted inwards towards the cavity, and is nearly orthogonal with respect to the other thiophene ring. In the other molecule, the thiophene rings

have a different orientation in which both rings are tilted inward, toward the interior of the cavity, the angle between the two ring planes being less than 90°.

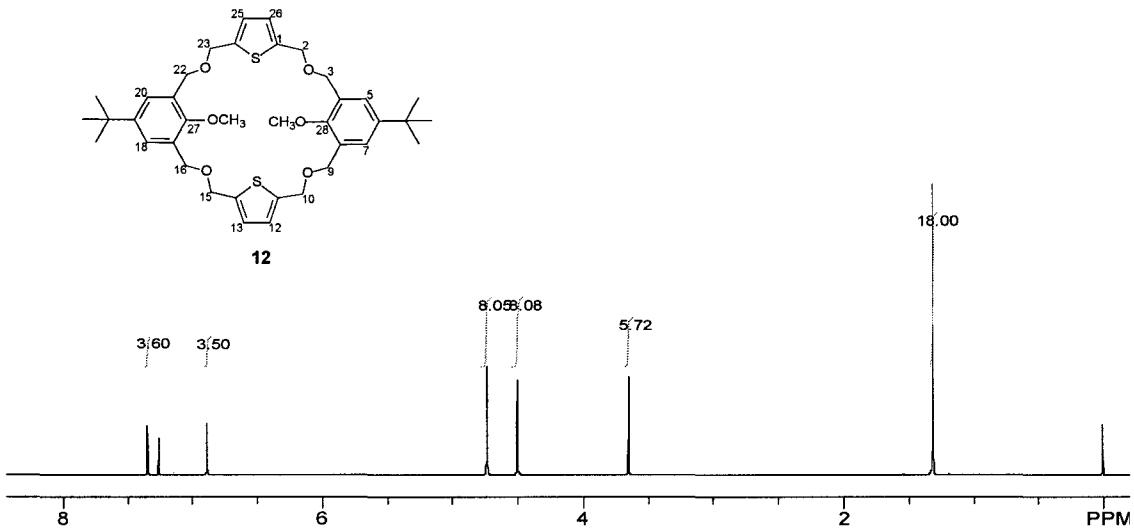


Figure 3.6a ^{1}H NMR spectrum for **12**

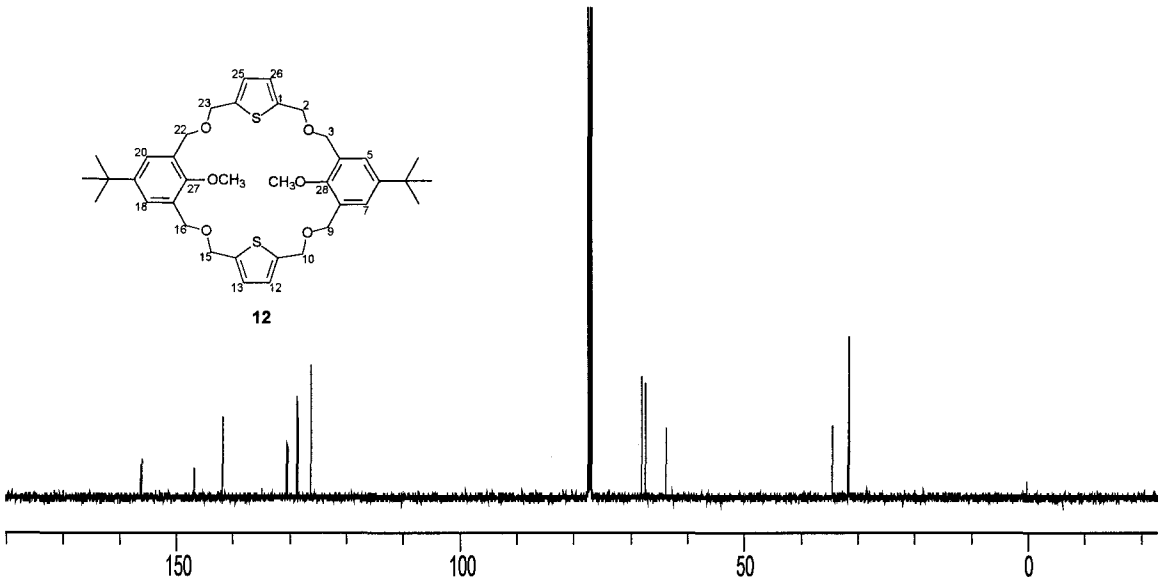


Figure 3.6b ^{13}C NMR spectrum for **12**

The X-ray structure (Figure 3.7a-b) indicates that the two molecules in the unit cell are packed in such a way that one of the *tert*-butyl groups of each molecule is situated within the cavity of the second molecule. Figure 3.7b is a Spartan'06 rendered structure from the x-ray coordinates. The *tert*-butyl groups are situated above a phenyl ring of the second molecule in such a way as to suggest π-CH_3 interactions. A similar supramolecular solid state "dimer" which is not very common in calixarenes in general, was previously observed with calix[4]naphthalene **7**.[11]

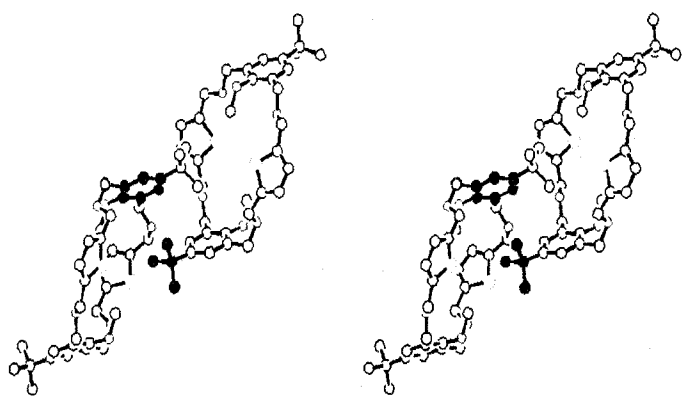


Figure 3.7a Twinned crystal PLUTO X-ray stereoview of **12** (hydrogen atoms have been omitted for clarity), two molecules in the unit cell are packed in such way that one of the phenol units is situated within the hydrophobic cavity of the second molecule. The blue-colored atoms show the proximity of a *tert*-butyl group with the phenyl ring of the other twin.

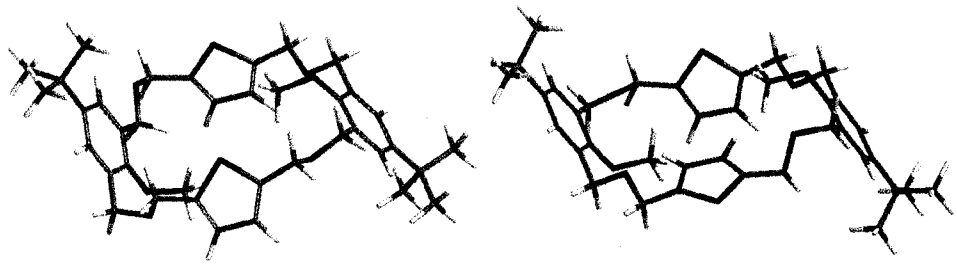


Figure 3.7b Spartan '06-rendered structures of the two individual molecules present in the unit cell of the X-ray structure of **12**. The structures were generated directly from the *cif* data obtained from the single-crystal X-ray crystallography. The left-hand structure shows the *"partial cone"* conformation in which the two thiophene units and one of the phenolic units are *syn*. The left-hand structure shows the *"1,2-alternate"* conformation in which the two thiophene units are *anti*.

3.3- Conclusion

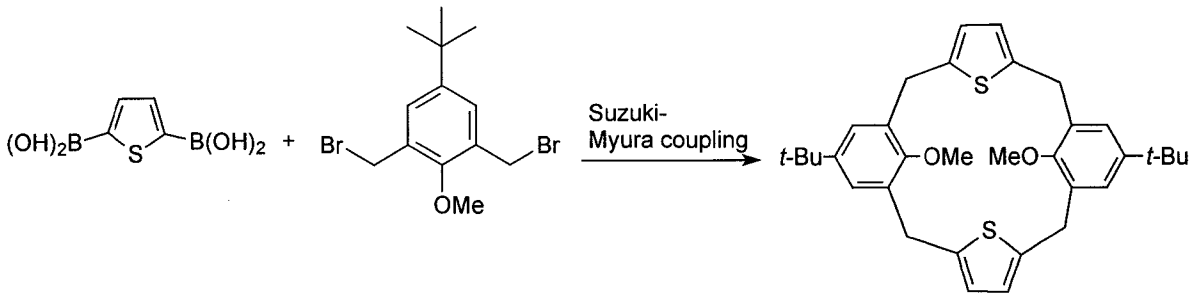
In this work we have described the synthesis of the thiophene-based calix[4]arene **12,** by employing the [2+2] fragment condensation reactions. An x-ray crystal for **12** has been obtained, which revealed that this compound in the solid state adopts the *1,3-alternate* conformation.

3.4- Suggestions for Future Work

The following objectives are suggested:

1. Complexation properties of the newly-synthesized Thiophene-based calix[4]arene **12** with potential neutral guests such as C_{60} and C_{70}, or with cations such as quaternary ammonium salts, etc. should be studied.

2. Based on the results obtained in this chapter, it is worth synthesizing the thiophene-based calix[4]arene **21** which showed a more defined cavity compared to **12** as proven by conducted a molding study (Scheme 3.4):

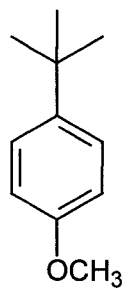


21

Scheme 3.4 The proposed synthesis for a thiophene-based calix[4]arene **21** as a targeted product for a future work

3.4- Experimental

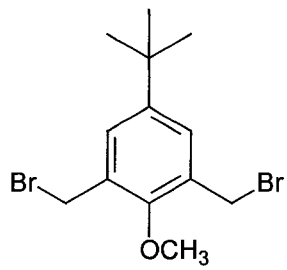
For general experimental information see Chapter 2 page 46



18

4-*tert*-Butylanisole (18): To a stirred solution of 4-*tert*-butylphenol (**17**) (2.00 g, 13.3 mmol) and methyl iodide (7.56 g, 53.2 mmol) in anhydrous THF (50 mL) at room temperature, NaH (0.48 g, 20.0 mmol) was added slowly. The reaction

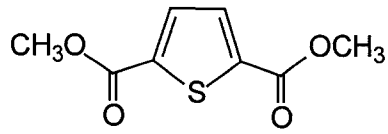
mixture was heated at reflux for 12h, then was cooled, and quenched with aqueous 1M HCl (15 mL). The resulting mixture was concentrated rotary evaporator and then extracted with diethyl ether (2 x 25 mL). The combined organic layers was washed with brine (15 mL), dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (1:9 ethyl acetate /hexanes) to give **18** (1.97 g, 90 %) as a colorless oil whose spectral data were in agreement with those published.[12]



14

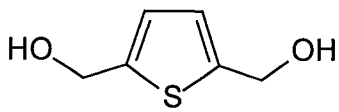
2,6-Bis(bromomethyl)-4-*tert*-butylanisole (14): To a mixture of 4-*tert*-butylanisole (**18**) (1.0 g, 2.9 mmol) and paraformaldehyde (0.34 g, 11 mmol) in glacial acetic acid (20 mL) at room temperature under argon was added a solution of HBr (15%, 4.7 mL) in acetic acid (10 mL) over 2 h. The reaction mixture was heated at reflux for 48 h, then cooled to room temperature, diluted with ethyl acetate (30 mL) and washed with water (2 x 20 mL) followed by aqueous saturated Na_2CO_3 solution. The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography (1:9 ethyl acetate/hexanes)

to give **14** (0.69 g, 68 %) as a colorless oil, whose spectral data were in agreement with those published.[10]



16

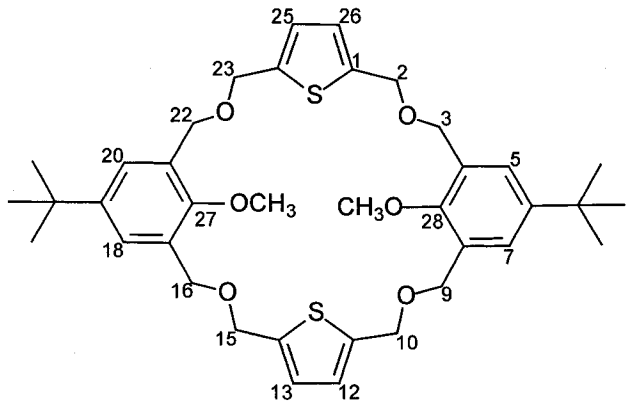
Dimethyl thiophene-2,5-dicarboxylate (16): To a solution of 2,5-thiophene carboxylic acid (**15**) (1.00 g, 5.81 mmol) in methanol (20 mL) was added a catalytic amount of conc. H_2SO_4 (~0.2 mL). The reaction mixture was then heated at reflux for 24 h. The reaction was cooled to room temperature, and quenched with aqueous 10% $NaHCO_3$ solution (10 mL). The colorless precipitate was separated, washed with water (2 x 15 mL) and air-dried to give **16** (1.08 g, 93 %) as a colorless solid, whose spectral data were in agreement with those published.[13]



13

2,5-Bis(hydroxymethyl)-thiophene (13): To a mixture of $LiAlH_4$ (0.61 g, 16.0 mmol) in anhydrous THF (40 mL) at 0°C was added a solution of dimethyl thiophene-2,5-dicarboxylate (**16**) (0.80 g, 4.0 mmol) in anhydrous THF (10 mL) over 10 min. The reaction mixture was stirred for an additional 24 h at room temperature, quenched by pouring it into a cooled solution of ether and aqueous10% HCl. The organic layer was separated and washed with water (2 x

20 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated on a rotary evaporator and the residue was purified by column chromatography (2:8 ethyl acetate/hexanes) to give **13** (0.52 g, 90 %) as a colorless oil, whose spectral data was in agreement with that published.[14]



12

Thiophene-based calix[4]arene (12): To a mixture of NaH (51.4 mg, 2.14 mmol) in anhydrous THF (30 mL) at reflux was added a solution of 2,5-bis(hydroxymethyl)thiophene (**13**) (100.0 mg, 0.69 mmol) and 2,6-bis(bromomethyl)-4-*tert*-butylanisole (**14**) (241.0 mg, 0.69 mmol) in anhydrous THF (50 mL) by syringe-pump over 3 h. The reaction mixture was stirred at reflux temperature for an additional 24 h. The reaction mixture was then cooled to room temperature and washed with water (2 x 25 ml). The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated on a rotary evaporator and the residue was purified by PLC (1:4 ethyl acetate/hexanes) to give **7** (91.7 mg, 21 %) as a colorless solid: mp 253 - 255 °C; ^{1}H NMR δ 1.35 (s, 18H), 3.66 (s, 6H), 4.51(s, 8H), 4.75 (s, 8H), 6.90 (s, 4H),

^{13}C NMR δ 31.7, 34.5, 63.8, 67.4, 68.1, 126.3, 128.7, 130.5, 141.9, 146.7, 156.2.

MS (APCI+) *m/z* calcd for $C_{38}H_{48}NaO_6S_2$ 687.3, found 687.2 $(M+Na)^+$.

3.5- References

1. Gerkensmeier, J.; Mattay, T.; Näther, C. *Chem. Eur. J.*, **2001**, *7*, 465.

2. Ackman, R. G.; Brown, W. H.; Wright, G. F. *J. Org. Chem.*, **1955**, *20*, 1147.

3. Ahmed, M.; Meth-Cohn, O. *Tetrahedron Letters*, **1969**, *19*, 1493.

4. Black, D. S.; Craig, D. C.; Kumar, N. *Tetrahedron Letters*, **1995**, *36*, 8075.

5. Arumugam, N.; Jang, Y. S.; Lee, C. H. *Organic Letters*, **2000**, *2*, 3115.

6. Sessler, J. L.; An, D.; Cho, W. S.; Lynch, V. *J. Am. Chem. Soc.* **2003**, *125*, 13646.

7. Qin, D. B.; Xu, F. B.; Li, Q. S.; Song, H. B.; Zhang, Z. Z. *Synlett.* **2005**, *19*, 2987.

8. Trepte, J.; Czugler, M.; Gloea, K.; Weber, E. *Chem. Commun.*, **1997**, 1461.

9. Tran, A. H.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem.* **2005**, *70*, 1115.

10. Zee-Cheng, R. K. Y.; Podrebarac, E. *G.;* Menon, C. S.; Cheng, C. C. *J. Med. Chem.* **1979**, *22*, 501

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

12. Bauer, A.; Gajewiak, J. *Synthesis*, **2004**, 20.

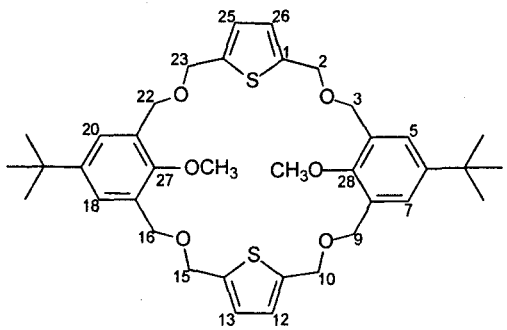
13. Zee-Cheng, R. K. Y.; Podrebarac, E. *G.;* Menon, C. S.; Cheng, C. C. *J. Med. Chem.* **1979**, *22*, 501.

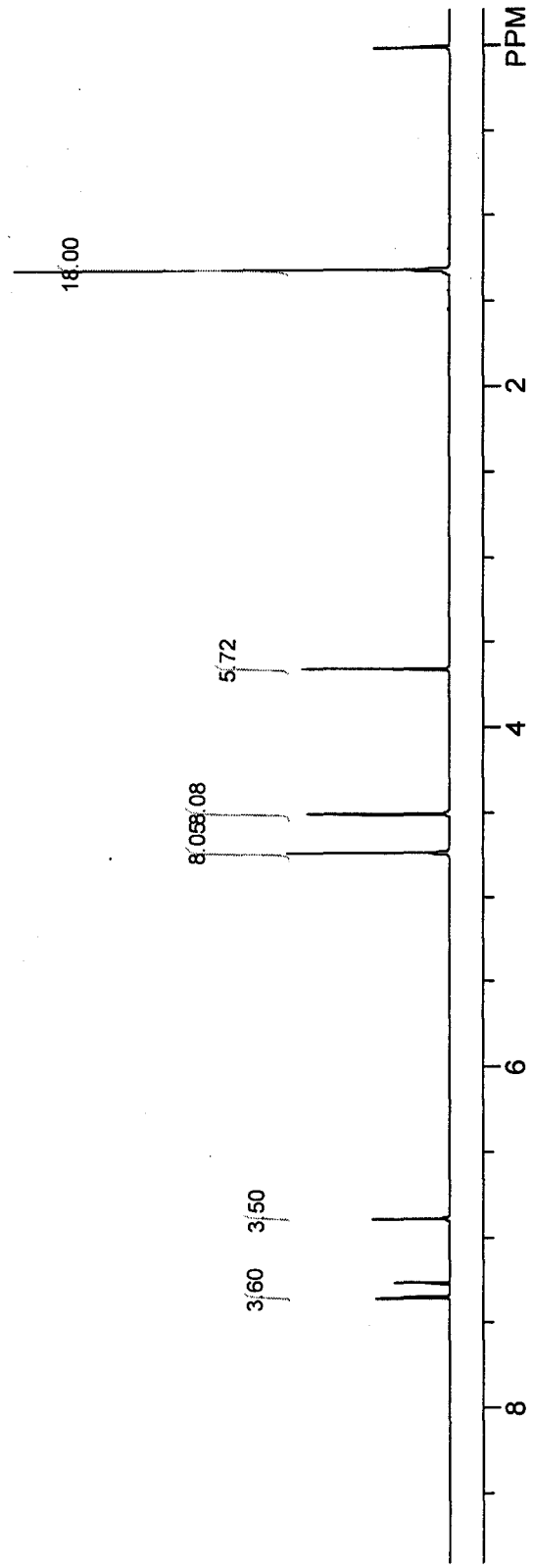
14. Yamato, T.; Tsuchihashi, K.; Nakamura, N.; Hirahara, M.; Tanaka, K. *Can. J. Chem.* **2002**, *80*, 510.

15. Block, E.; Page, J.; Toscano, J. P.; Wang, C.-X.; Zhang, X.; DeOrazio, R.; Guo, C.; Sheridan, R. S.; Towers G. H. *J. Am. Chem. Soc.* **1996**, *118*, 4719.

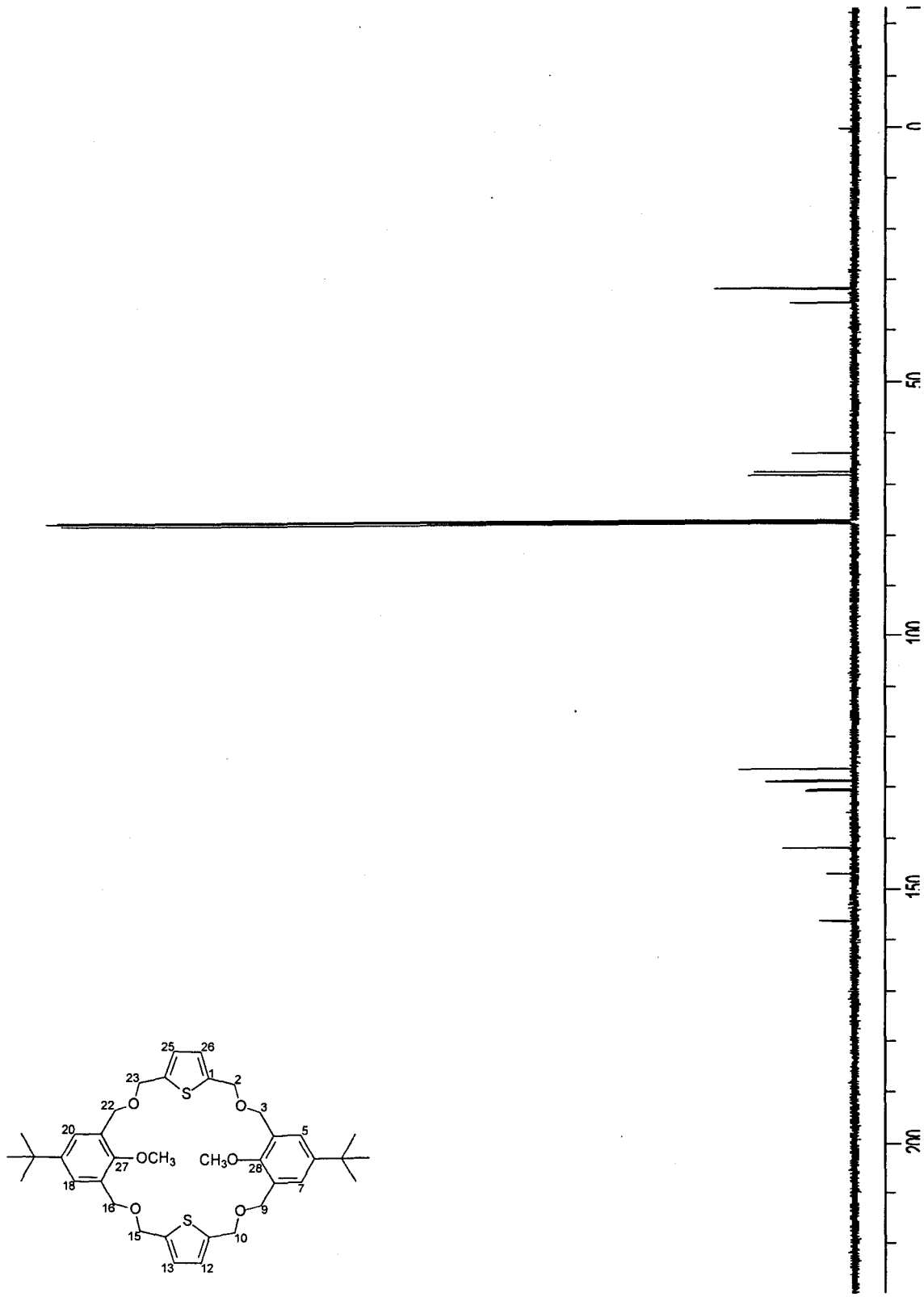
Appendix Chapter 3

X-ray Crystal Data for 12: X-ray crystal data for 12: Colourless crystal ($MeOH/CHCl_3$), $C_{38}H_{48}O_6S_2$, monoclinic, space group $P2_1/c$ (#14), Z = 4, a = 41.256(3) Å, b = 10.1714(5) Å, c = 17.4177(10) Å, β= 105.5160(10)°. V = 7042.7(7) $Å^3$, $D_{Calcd.}$ = 1.254 g cm^{-3}, crystal size = 0.60 x 0.40 x 0.10 mm. Intensity data were measured at -100 ± 1 C° on a Rigaku AFC8 diffractometer with graphite monochromated Mo-Kα (λ = 0.71070 Å) radiation $2\theta_{max}$ = 54.3°; 19346 reflections converged to a final R_{int} of 0.014 for 9860 unique reflections and 830 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0.0391 and 0.1057, respectively, and GoF = 1.040.





^{1}H NMR spectrum for compound **12**



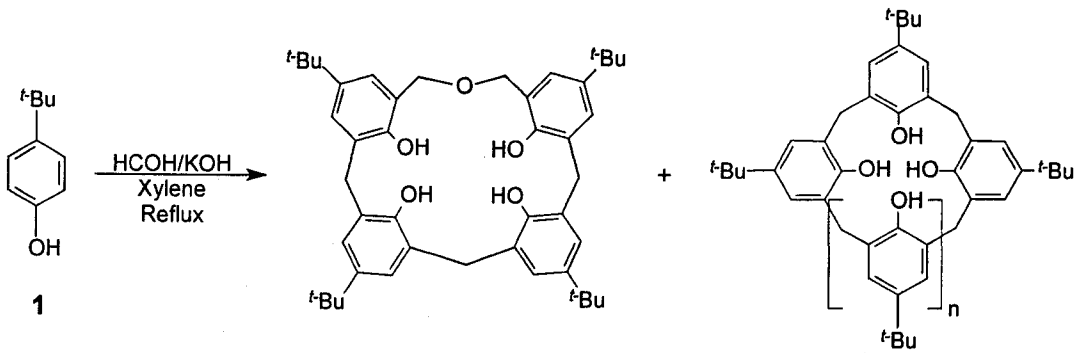
^{13}C NMR spectrum for compound **12**

Chapter 4

Homooxacalix[4]naphthalene

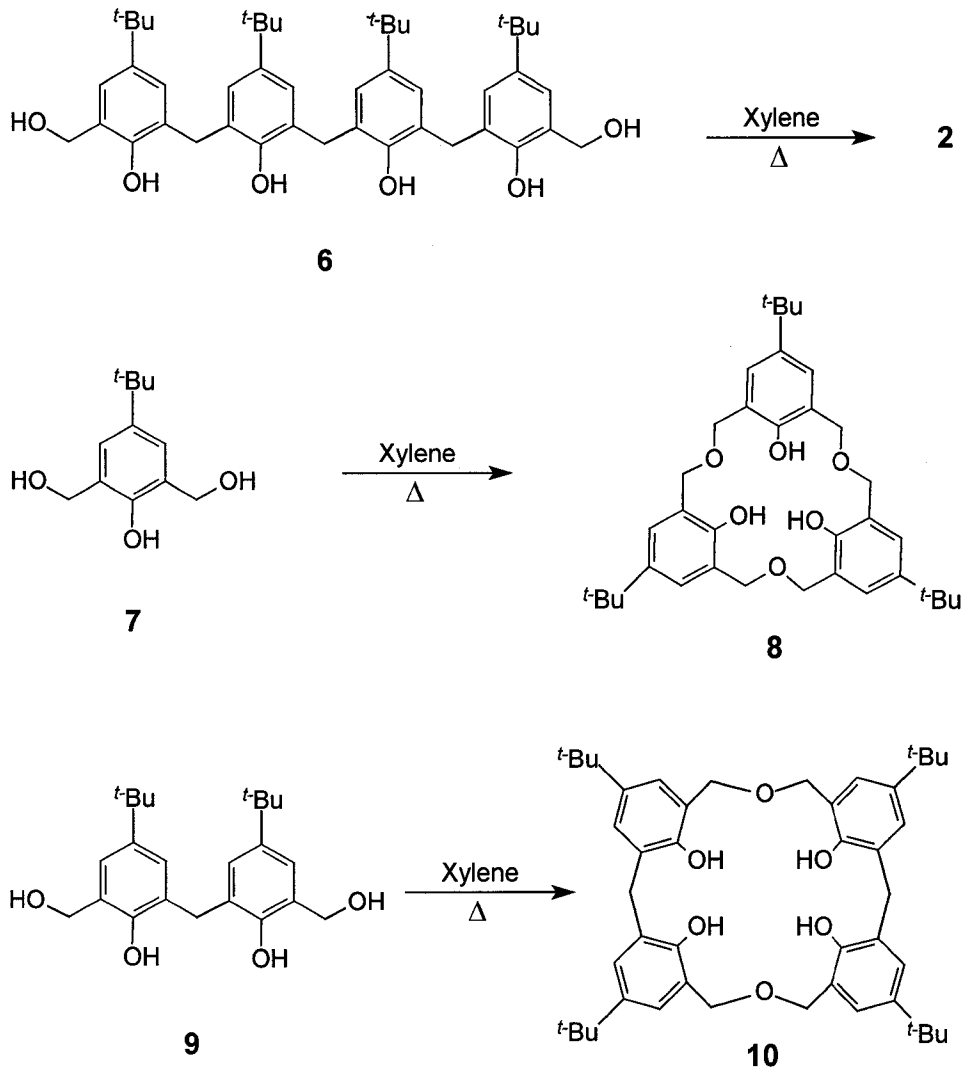
4.1- Introduction

Homooxacalix[4]arenes are a different class of macrocyclic compounds which are produced when one or more of the bridging methylenes in the parent calixarene are replaced by (-CH_2-O-CH_2-) linkages. It has been demonstrated[1] that the presence of these ethereal groups provides an additional opportunity to modify the cavity size, conformation, and/or binding properties of the macrocyclic compound. The first example of such compounds was the *p-tert*-butyldihomooxacalix[4]arene (**2**) which was reported in 1979 by Gutsche.[2] Compound **2** was obtained unexpectedly as a by-product from a reaction conducted originally to produce calixarenes **3**, **4** and **5**, by heating a mixture of *p-tert*-butylphenol, paraformaldehyde and KOH at reflux temperature in xylene (Scheme 4.1).



Scheme 4.1: Synthesis of the dihomoxacalix[4]arene **2** and calixarenes **3-5**.

In 1983 Dhawan and Gutsche[3] synthesized the homooxacalixarenes **2**, **8** and **10** via an alternative route, which involved condensation reactions of the corresponding bis(hydroxymethyl) precursors **6**, **7** and **9**, respectively (Scheme 4.2).



Scheme 4.2 Synthesis of homooxacalixarenes **2**, **8** and **10** via the condensation reactions of the corresponding bis(hydroxymethyl) precursors.

In comparison to calix[4]arenes, the ether linkage oxygens in homooxacalix[4]arenes may act cooperatively with the phenolic oxygens upon the binding of different guests. Fujita et al.[4] and Stang et al.[5] have shown that the presence of the coordination bond is useful for the construction of self-assembling supramolecular structures. Masci[6] reported that homooxacalixarenes **2**, **8** and **10** complexed with different quaternary ammonium salts. For example, he showed that the homooxacalixarene **8** has a relatively high binding constant value ($K = 64\ M^{-1}$) compared to **2** ($K = 13\ M^{-1}$) and **10** ($K = 11\ M^{-}$) when complexed with trimethylethyl ammonium salt. Shinkai and co-workers[7] demonstrated the first example of a supramolecular inclusion of C_{60} in a capsule-like cage molecule, which was formed from two molecules of **8**.

In 2001 the Georghiou group[8] reported the synthesis of homooxanaphthalene-based analogues (compounds **44a-b**, Figure 1.9, Chapter 1). Although the hexahomotrioxacalix[3]naphthalene **44a** and its *tert*-butylated analogue **44b** showed a weak complexation abilities with alkali-metal cations, these compounds showed stronger complexing abilities with C_{60}. An X-ray structure of a supramolecular complex formed between C_{60} and **44b** has been obtained and is shown in Figure 4.1.[8]

The Georghiou[9] group has also been able to synthesize the *endo*- and *exo*-dihomooxacalix[4]naphthalenes **15** and **16**, from the reaction of the corresponding intermediates (**11** with **13**) and (**12** with **14**), respectively (Scheme 4.3).

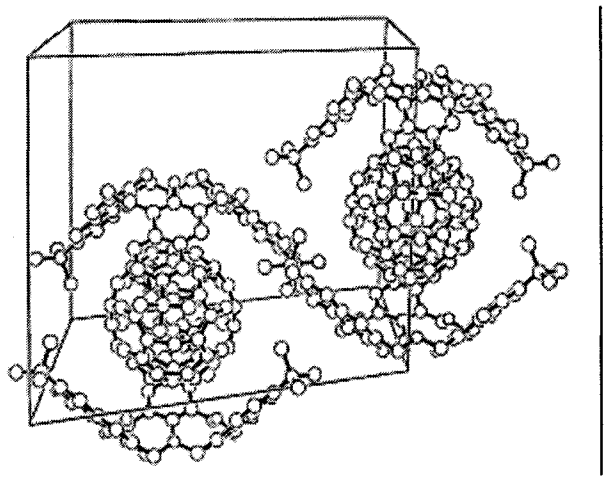
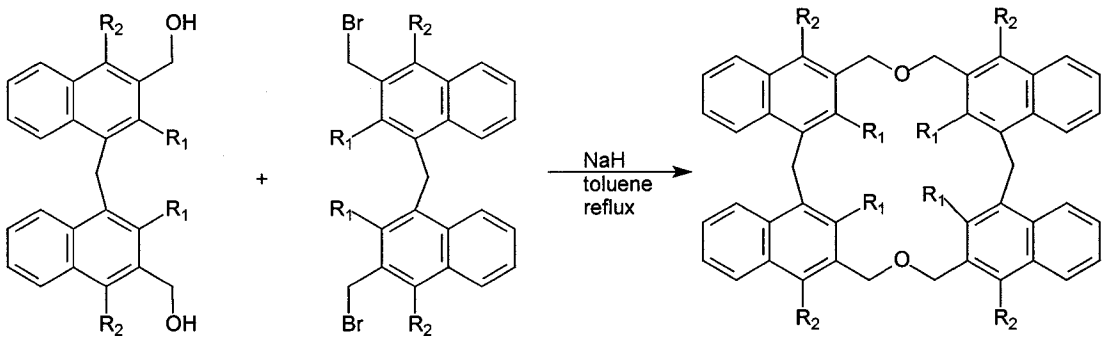


Figure 4.1 X-ray partial packing diagram for a supramolecular complex formed between C_{60} and **44b**



11 : $R_1 = OCH_3$, $R_2 = H$
12 : $R_1 = H$, $R_2 = OCH_3$

13 : $R_1 = OCH_3$, $R_2 = H$
14 : $R_1 = H$, $R_2 = OCH_3$

15 : $R_1 = OCH_3$, $R_2 = H$ (*endo*)
16 : $R_1 = H$, $R_2 = OCH_3$ (*exo*)

Scheme 4.3 Synthesis of the *endo*- and *exo*-homooxacalix[4]naphthalenes **15** and **16**

Using a similar approach to that used by the Georghiou group as shown in Scheme 4.4, the synthesis of the tetrahomodioxacalix[4]naphthalene (**24**) as a new member of the homooxacalix[4]naphthalene family is reported herein.

It was anticipated that the targeted compound **24**, would have a relatively larger cavity size due to the presence of two new bridging units; the ethylene units (–CH_2CH_2-) and the ether units (-CH_2-O-CH_2-). Although it would appear that **24** could have a high degree of conformational flexibility due to the presence of these flexible linkages, its CPK molecular model revealed that this compound has a well-defined cavity (Figure 4.2). This suggested further that this compound could potentially be used as a host molecule for different neutral organic potential guests such as $C_{60,}$ and C_{70}.

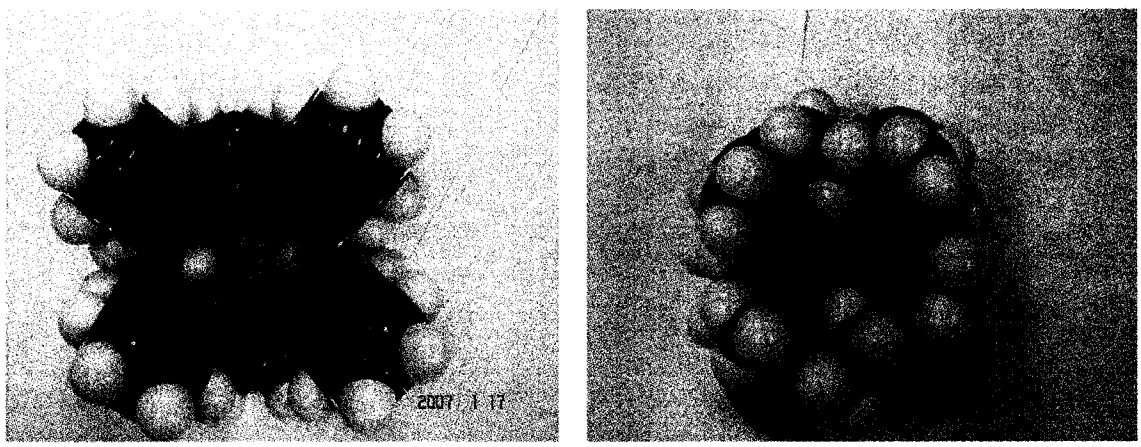
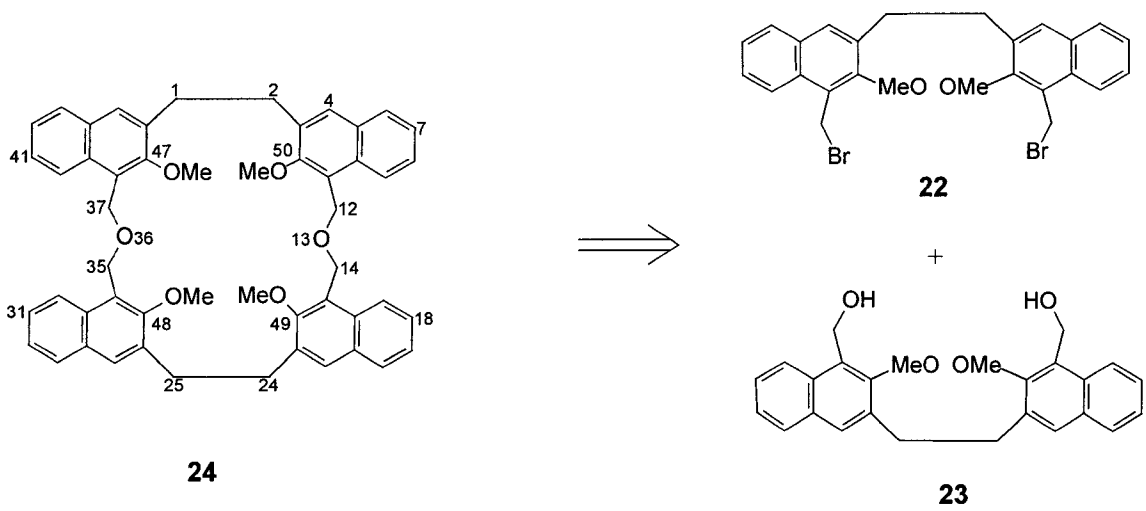


Figure 4.2 CPK model for tetrahomodioxacalix[4]naphthalene (**24**), *left* picture shows the wide-rim view while the *right* one shows the narrow-rim view.

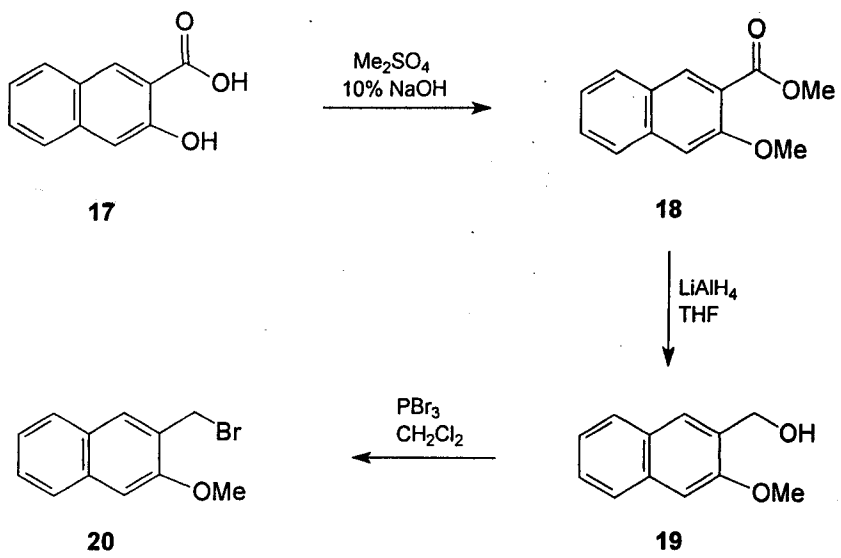
The key step in the synthesis of **24** was based on a [2+2] fragment condensation reaction via the base-mediated coupling reaction of the corresponding precursors **22** and **23**, as outlined in Scheme 4.4.



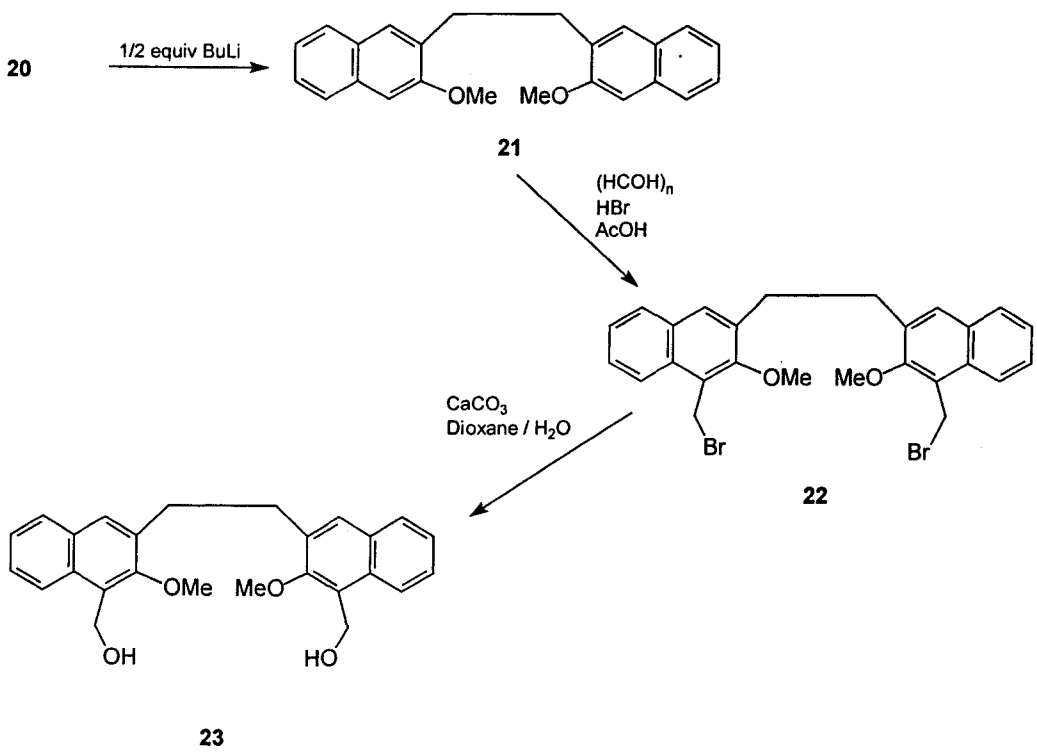
Scheme 4.4 Retrosynthetic approach for the homooxacalix[4]naphthalene **24**

Schemes 4.5 and 4.6 respectively show the syntheses of **20** and **23**. In Scheme 4.5, 3-hydroxymethyl-2-naphthoic acid (**17**) is used as the starting material for the synthesis of **20**. Esterification of **17**, followed by reduction produced the corresponding hydroxymethyl precursor, **19** which was converted to the corresponding bromomethyl compound **20** by treatment with PBr_3.

As shown in Scheme 4.6, synthesis of the bisnaphthyl compound **21** was achieved by reaction of **20** with 0.5 equiv. of *n*-BuLi. Bisbromomethyl **22** was obtained by selective bromomethylation of **21** using a solution of Br_2 in acetic acid. Hydrolysis of **22** in basic solution afforded the corresponding bishydroxymethyl precursor, **23**.



Scheme 4.5 Convergent approach for intermediates **18 – 20**.



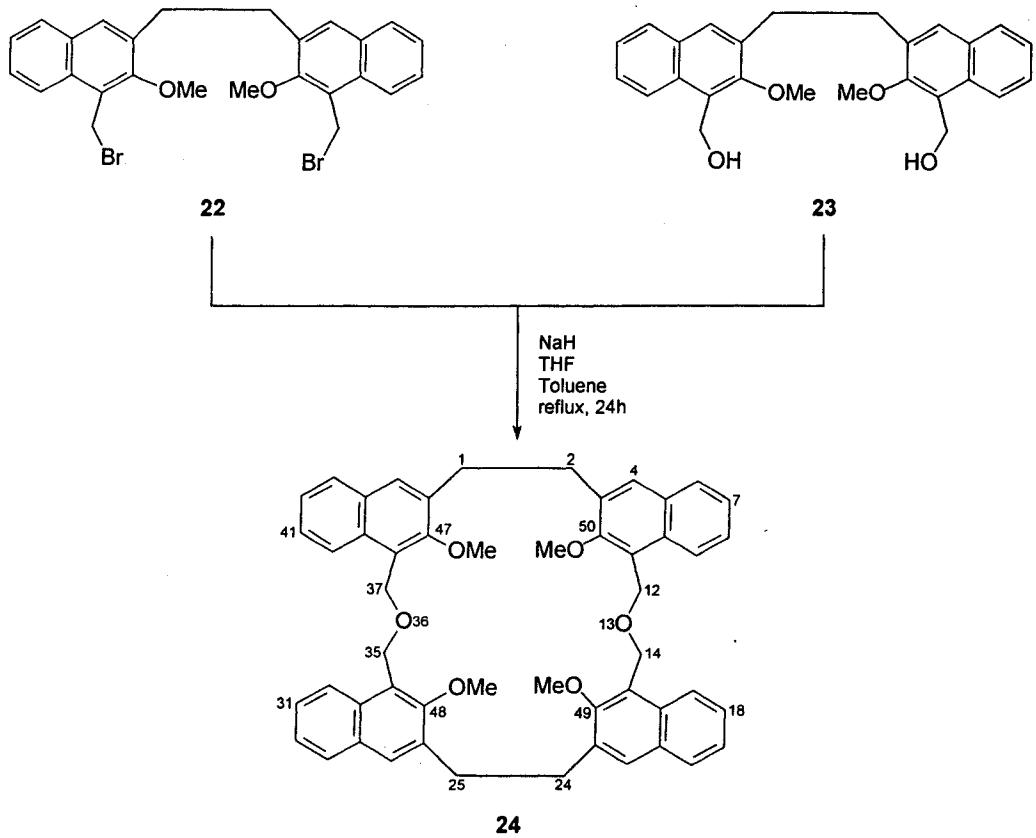
Scheme 4.6 Convergent approach for intermediates **21 – 23**.

4.2-Synthesis

The synthesis of **24** was commenced by first protecting the hydroxyl and acidic moieties. This was conducted in one step by treating the commercially available 3-hydroxymethyl-2-naphthoic acid (**17**) with dimethylsulfate and aqueous 10% NaOH to give the methyl 3-methoxy-2-naphthoate (**18**) in 92 % yield. Reduction of the corresponding ester **18** was achieved by LAH reduction in THF at room temperature to furnish the 3-(hydroxymethyl)-2-methoxynaphthalene (**19**) in 91% yield. The bromomethyl intermediate **20** was obtained in 61 % yield, by treating **19** with a solution of PBr_3 in CH_2Cl_2 (Scheme 4.5).

Dimerization of **20** was achieved by adding a solution of *n*-BuLi in THF to another solution of **22** in THF -78 °C to give the 1,2-bis(2-methoxy-3-naphthyl)ethane (**21**) in 93 % yield. Bromomethylation of **21** was conducted selectively by using a mixture of paraformaldehyde in glacial acetic acid, followed by the addition of HBr (30 % solution) in acetic acid, to give the corresponding bisbromomethyl precursor **22** in 98% yield. The hydrolysis of **22** was achieved by heating a mixture of **22** and $CaCO_3$ in a mixed solvent system (dioxane and water) at reflux temperature, which gave the corresponding hydroxymethyl precursor **23** in a good yield (75%) (Scheme 4.6). The synthesis of the targeted compound, the tetrahomodioxacalix[4]naphthalene **24**, was achieved in acceptable yield (15%) by the base-mediated coupling of the corresponding precursors **22** and **23**. This reaction was conducted by slowly adding a solution

of **22** and **23** (1:1) in anhydrous THF to a mixture of NaH and anhydrous toluene at reflux temperature (Scheme 4.7).



Scheme 4.7 Convergent approach for tetrahomodioxacalix[4]naphthalene (**24**)

The ^{1}H NMR spectrum for **24** revealed that this compound could have C_{2v}-symmetry. The four methoxy group proton signals appeared as one sharp signal at 3.27 ppm. In addition, the signal patterns of the aromatic region, methylene and the ether bridging protons are also in agreement with the proposed symmetry (Figure 4.3).

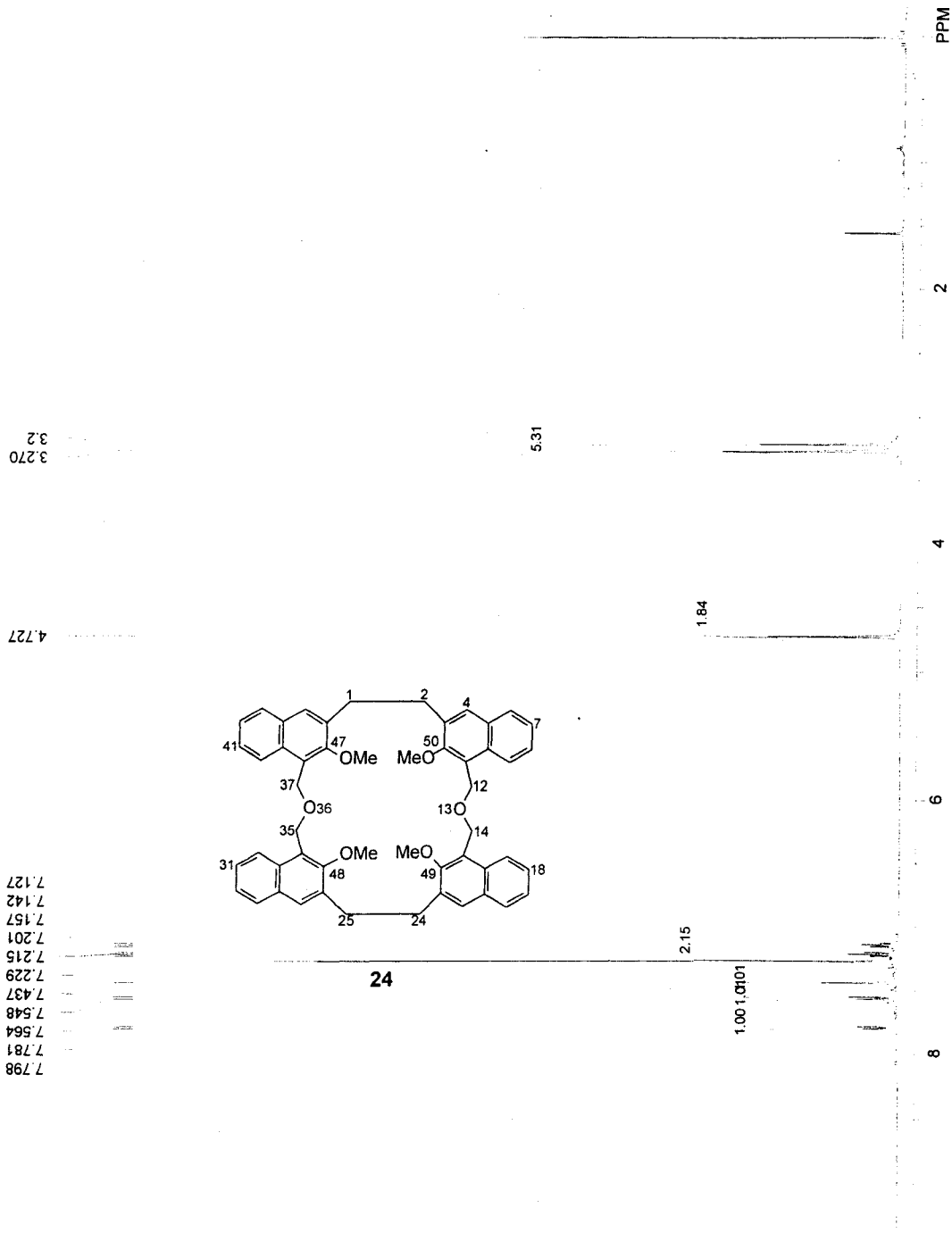


Figure 4.3 ^{1}H NMR spectrum for tetrahomo-dioxacalix[4]naphthalene (**24**)

The mass spectrum (APCI$^+$) for **24** did not show the expected M^+ signal. Instead, it shows different signals which probably resulted from the fragmentations of the methyl groups. For example, the M^+- (CH_3) signal appeared at 753.3 which is in a good agreement with the calculated values 753.3, respectively (Figure 4.4).

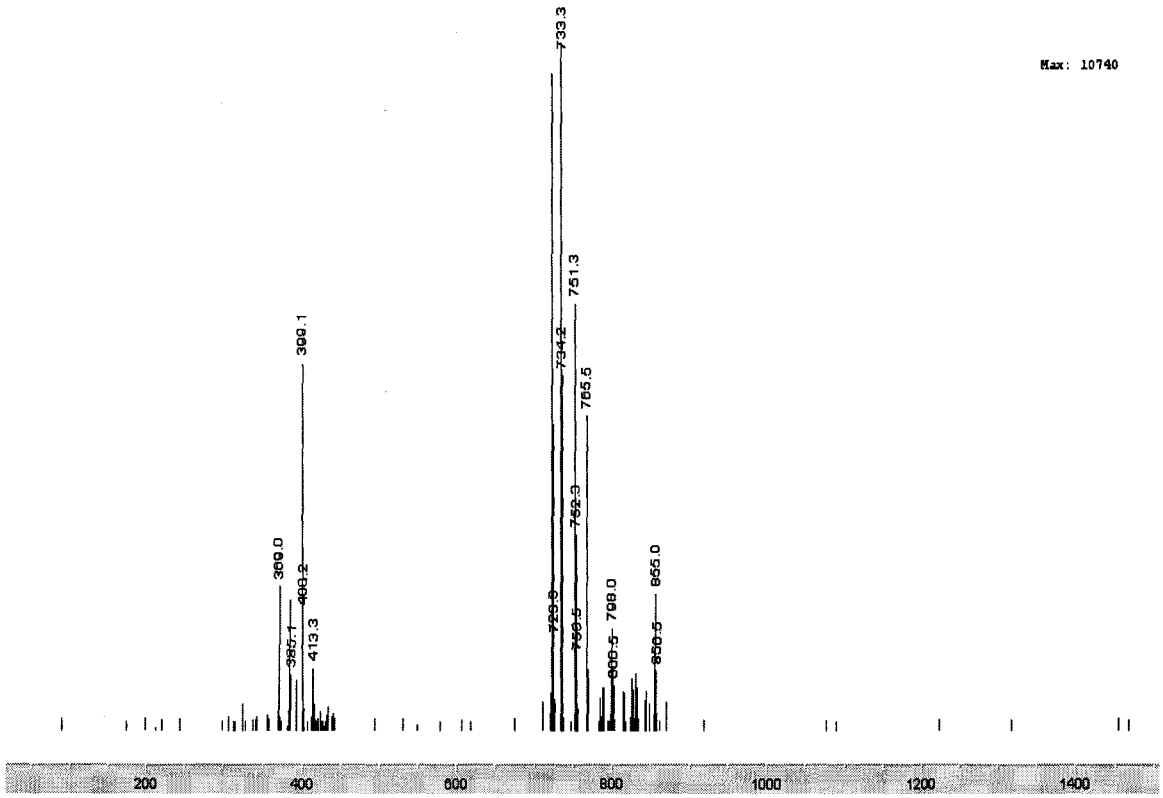


Figure 4.4 Mass spectrum of tetrahomo-dioxacalix[4]naphthalene (**24**)

4.3- Conclusion

A new member of the homooxacalix[4]naphthalene family has been prepared by using [2+2] fragment condensation reactions. In this work the ability

to change the cavity size of a calix[4]naphthalene by extending the bridging units with ($-CH_2-CH_2-$) and ($-CH_2-O-CH_2-$) has been demonstrated. However, the bindings or complexation properties of **24** could not be determined, due to the time limitations.

4.4- Suggestions for future work

The following objectives are suggested:

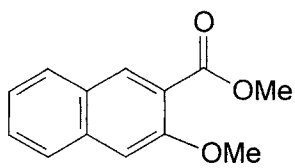
1. The complexation properties of the newly-synthesized homooxa-calix[4]naphthalene **24** with potential neutral guests such as C_{60} and C_{70}, or with cations such as quaternary ammonium salts, etc. should be studied.

2. Different *O*-alkylated derivatives could be obtained from **24** using alkyl groups (such as ethyl, *n*-propyl, *n*-butyl ... etc). which could influence their conformational flexibilities and their resultant complexation abilities.

3. It is worth synthesizing the deprotected analogue of **24** and to study its complexation properties in order to examine the effect that intramolecular hydrogen bonding by the intranular hydroxy groups have, if any, on their properties.

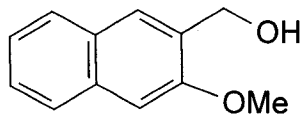
4.5- Experimental

For general experimental information see Chapter 2, page 46



18

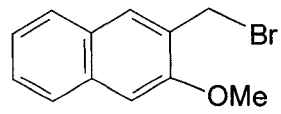
Methyl 3-methoxy-2-naphthoate (18): To a stirred solution of 3-hydroxymethyl-2-naphthoic acid (**17**) (3.9 g, 20.7 mmol) in CH_2Cl_2 (50 mL) at room temperature was added phase transfer catalyst Adogen® (0.5 mL) and aqueous 50% NaOH solution (30 mL). The reaction mixture was stirred for 10 min, then dimethyl sulfate (7.5 mL, 79 mmol) was added dropwise over 30 min. The resulting reaction mixture stirred for an additional 8 h at room temperature. The organic layer was separated and quenched with aqueous 10% $NaHCO_3$ (30 mL), brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the residue was purified by column chromatography (1:9 diethyl ether/hexanes) to give **18** (4.12 g, 92%) as yellow oil, whose spectral data were in agreement with that published.[9]



19

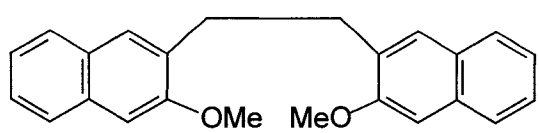
3-Hydroxymethyl-2-methoxynaphthalene (19): To a stirred solution of 3-(hydroxymethyl)-2-methoxynaphthalene (**18**) (4.00 g, 0.02 mol) in anhydrous CH_2Cl_2 (20 mL) at -78 °C was added over 15 min a suspension of LAH (3.20 g, 27.74 mmol). The reaction mixture was stirred for 3 h at room temperature. The reaction mixture poured into cold wet diethyl ether (20 mL), and then acidified by aqueous 10% hydrochloric acid. The organic layer was separated and washed

with water (2x15 mL), brine (15 mL), dried over $MgSO_4$ and filtered. The solvent was removed under vacuum and the residue was crystallized from ethyl acetate-hexanes to give **19** (2.4 g, 91%) as a white solid, whose spectral data were in agreement with that published.[9]



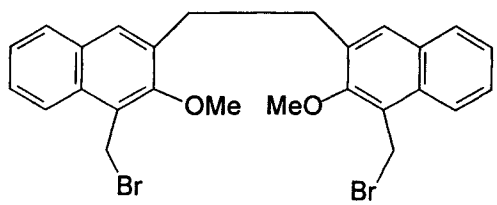
20

3-Bromomethyl-2-methoxynaphthalene (20): To a stirred solution of 3-Hydroxymethyl-2-methoxynaphthalene (**19**) (3.00 g, 15.94 mmol) in anhydrous CH_2Cl_2 (70 mL) at 0 °C was added PBr_3 (2.5 g, 23.97 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for 5 h at the same temperature. The reaction mixture was quenched with iced-water (80 mL), and then the organic layer separated and washed with aqueous 10% $NaHCO_3$ (60 mL), brine (60 mL), dried over $MgSO_4$ and filtered. The solvent was removed under vacuum, and then the residue was purified by column chromatography (2:8 ethyl acetate / hexanes) to give **20** (2.4 g, 61%) as a colorless solid, whose spectral data were in agreement with those published.[11]



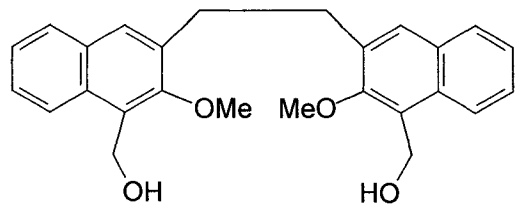
21

1,2-Bis(2-methoxy-3-naphthyl)ethane (21): To a stirred solution of 3-(bromomethyl)-2-methoxynaphthalene (**20**) (0.50 g, 1.99 mmol) in anhydrous THF (5 ml) at -78 °C was added n-BuLi (0.81 mL, 1.02 mmol). The reaction was stirred for 3 h. The reaction mixture diluted with $CHCl_3$ (20 mL) and then washed with water (2x15 mL). The organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum to give **21** (0.32 g, 93%) as a colorless solid, whose spectral data were in agreement with that published.[12]



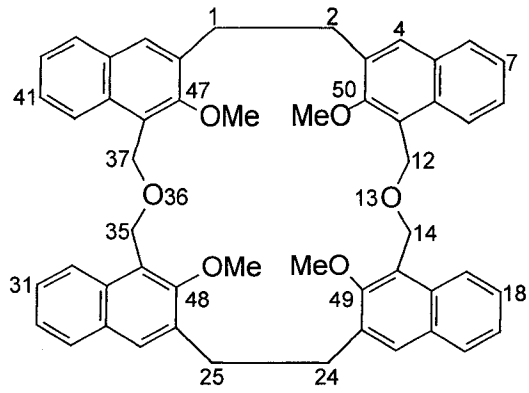
22

1,2-Bis(1-bromomethyl-2-methoxy-3-naphthyl)ethane (22): To a stirred mixture of 1,2-bis(2-methoxy-3-naphthyl)ethane (**21**) (0.15 g, 0.44 mmol) and paraformaldehyde in glacial acetic acid (3 mL) at room temperature was added over 2 h a solution of 30% HBr in acetic acid (1.36 mL). The resulting reaction mixture was then stirred for three days to form a yellow precipitate. The precipitate was filtered and washed with petroleum ethers (3x5 mL) and then air dried to give **22** (0.23 g, 98%) as a colorless solid, whose spectral data were in agreement with that published.[13]



23

1,2-Bis(1-hydroxymethyl-2-methoxy-3-naphthyl)ethane (23): To a stirred solution of 1,2-bis(1-bromomethyl-2-methoxy-3-naphthyl)ethane (**22**) (0.20 g, 0.38 mmol) in (1:1 dioxane/water) (5 mL) at room temperature was added $CaCO_3$ (0.15 g, 1.52 mmol). The resulting reaction mixture was stirred at reflux temperature for 4 h. The solvent was removed under vacuum and the residue dissolved in ethyl acetate and washed with aqueous 10% HCl (5 mL), water (5 mL), dried over $MgSO_4$. The solvent was removed under vacuum to give **23** (0.12 g, 75%) as a white solid: mp 192-194 °C; ^{1}H NMR δ 3.21 (s, 4H), 3.72 (s, 6H), 3.96(s, 4H), 5.24 - 7.44 (m, 2H), 7.52 (m, 2H), 7.76 (s, 2H), 7.80 (d, *J* = 7.5 Hz, 2H), 8.15 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 32.1, 56.8, 67.3, 123.7, 125.3, 126.4, 127.3, 128.2, 129.8, 131.5, 132.1, 135.0, 156.0. MS (APCI+) *m/z*, calcd for $C_{26}H_{25}NaO_4$ 424.16, found 425.20 (M^++Na).



24

Tetrahomodioxacalix[4]naphthalene (24): To mixture of NaH (0.10 g, 4.17 mmol) in anhydrous toluene (30 mL) at reflux temperature was added, via syringe pump and over a period of 2 h, a solution of 2-bis(1-bromomethyl-2-methoxy-3-naphthyl)ethane (**22**) (0.40 g, 0.76 mmol) and 1,2-bis(1-hydroxymethyl-2-methoxy-3-naphthyl)ethane (**23**) (0.30 g, 0.76 mmol) in anhydrous THF (15 mL). The reaction mixture was cooled to room temperature and the reaction was quenched with aqueous 10% HCl (5 mL) and organic layer were extracted with $CHCl_3$ (3x15 mL). The combined organic layers dried over $MgSO_4$, filtered, and the solvent was removed under vacuum. The residue was purified by PLC (3:7 ethyl acetate / hexanes) to give **24** (43.8 mg, 15%) as a white solid: m.p. 288-290 °C; ^{1}H NMR δ 3.22 (s, 8H), 3.27 (s, 12H), 4.73 (s, 8H), 7.14 (m, 4H), 7.22 (m, 4H), 7.44 (s, 4H), 7.55 (d, *J* = 8.0 Hz, 4H), 7.78 (d, *J* = 8.5 Hz, 4H); ^{13}C NMR δ 31.73, 62.47, 62.68, 124.59, 124.69, 125.50, 127.81, 130.44, 130.47, 131.17, 132.87, 134.03. MS (APCI-) *m/z* calcd for $C_{51}H_{45}O_6$ 753.3, found 753.5 (M^+-CH_3).

4.6- References

1. Araki, K.; Hashimoto, N.; Otsuka, H.; Shinkai, S. *J. Org. Chem. 58*, **1993**, 5958.

2. (a) Gutsche, C. D.; Muthukrishnan, R.; No, K. H. *Tetrahedron Lett.* **1979,** 2213.

3. (b) Dhawan, B.; Gutsche, C. D. *J. Org. Chem.* **1983**, *48,* 1536.

4. (a) Fujita, M.; Yazaki, J.; Ogura, K. *J. Am. Chem. Soc.* **1990**, *112*, 5645. (b) Fujita, M.; Nagao, S.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 1649.

5. (a) Stang, P. J.; Cao, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4981. (b) Stang, P. J.; Cao, D. H.; Saito, S.; Arif, A. M. *J. Am. Chem. Soc.* **1995**, *117*, 6273.

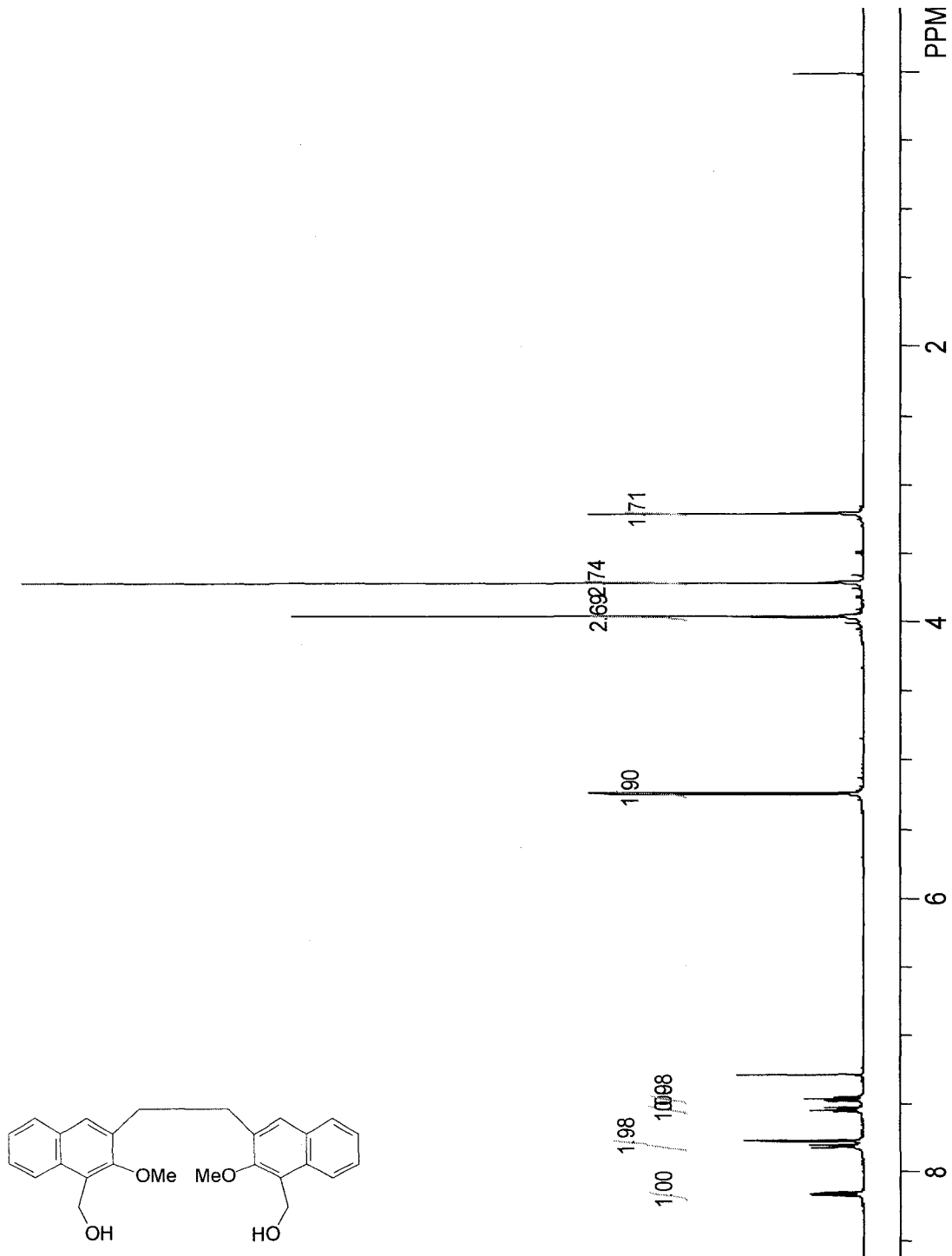
6. Masci, B. *Tetrahedron,* **1995**, *51*, 5459.

7. Ikeda, A.; Suzuki, Y.; Yoshimura, M.; Shinkai, S. *Tetrahedron*, **1998**, *54*, 2497.

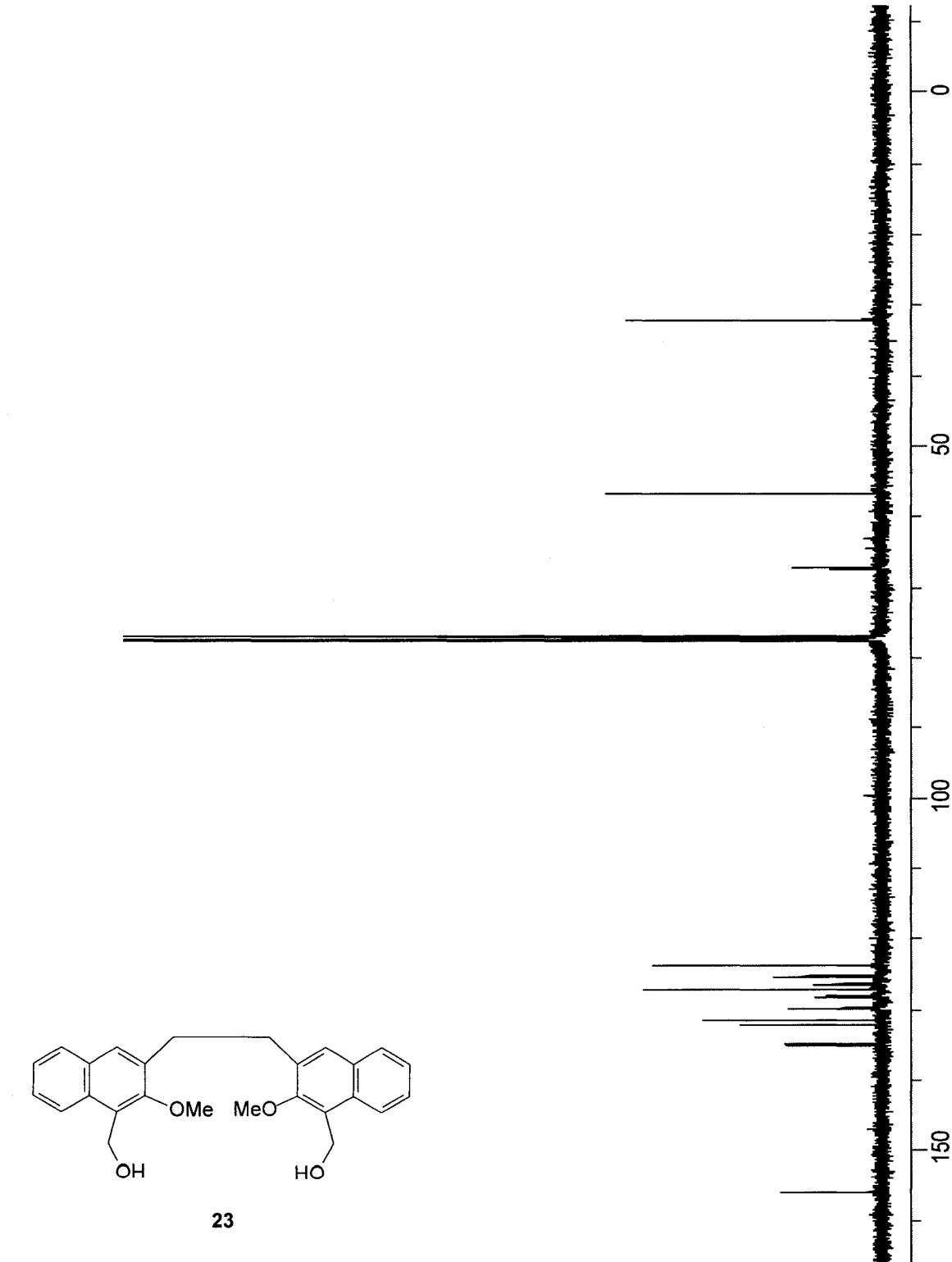
8. Ashram, M.; Mizyed, S.; Georghiou, P. E. *J. Org. Chem.*, **2001**, *66*, 1473.

9. Ashram, M. Ph.D. *Dissertation*, Memorial University of Newfoundland, **1999**.

Appendix: Chapter 4

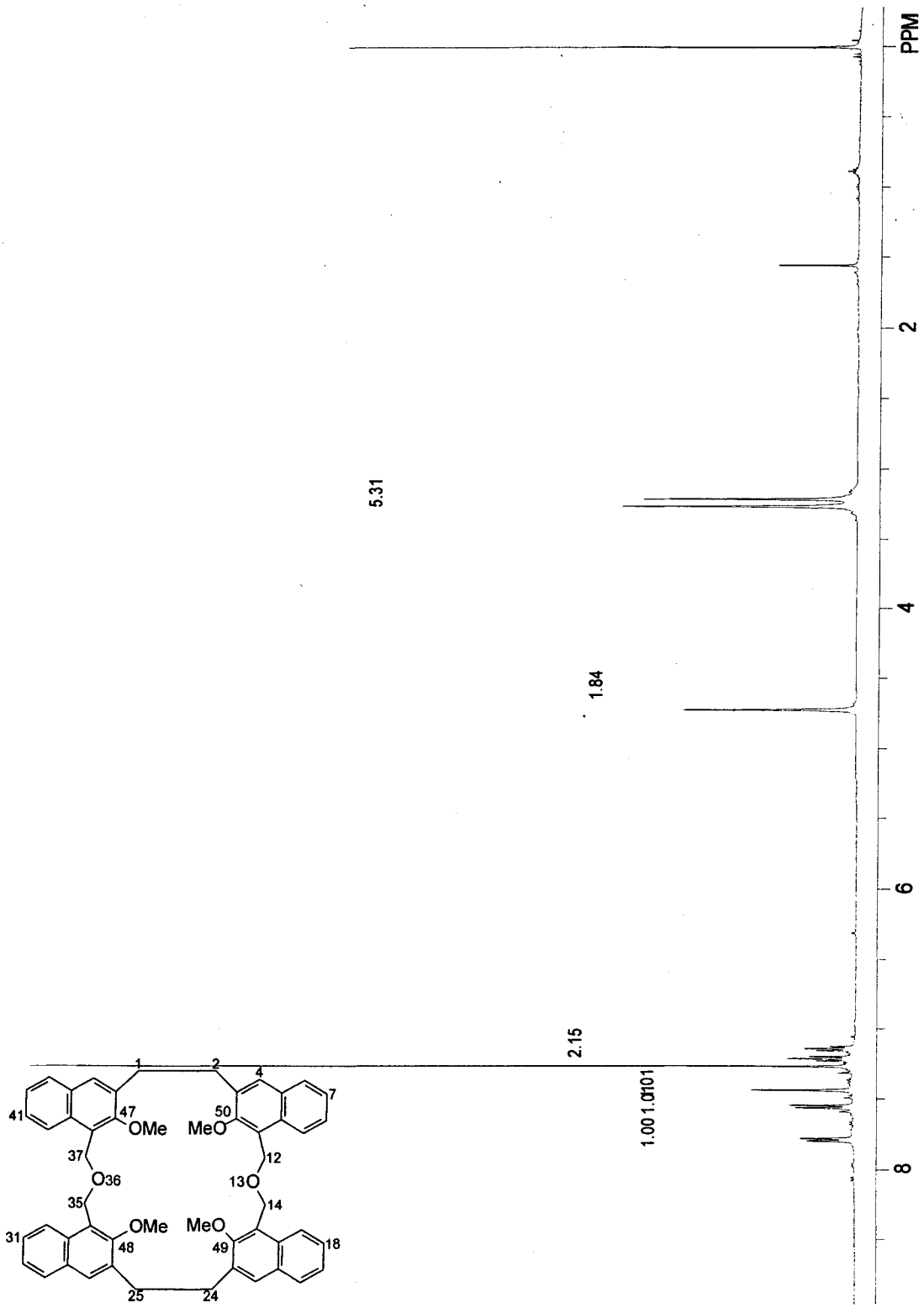


^{1}H NMR spectrum for compound **23**

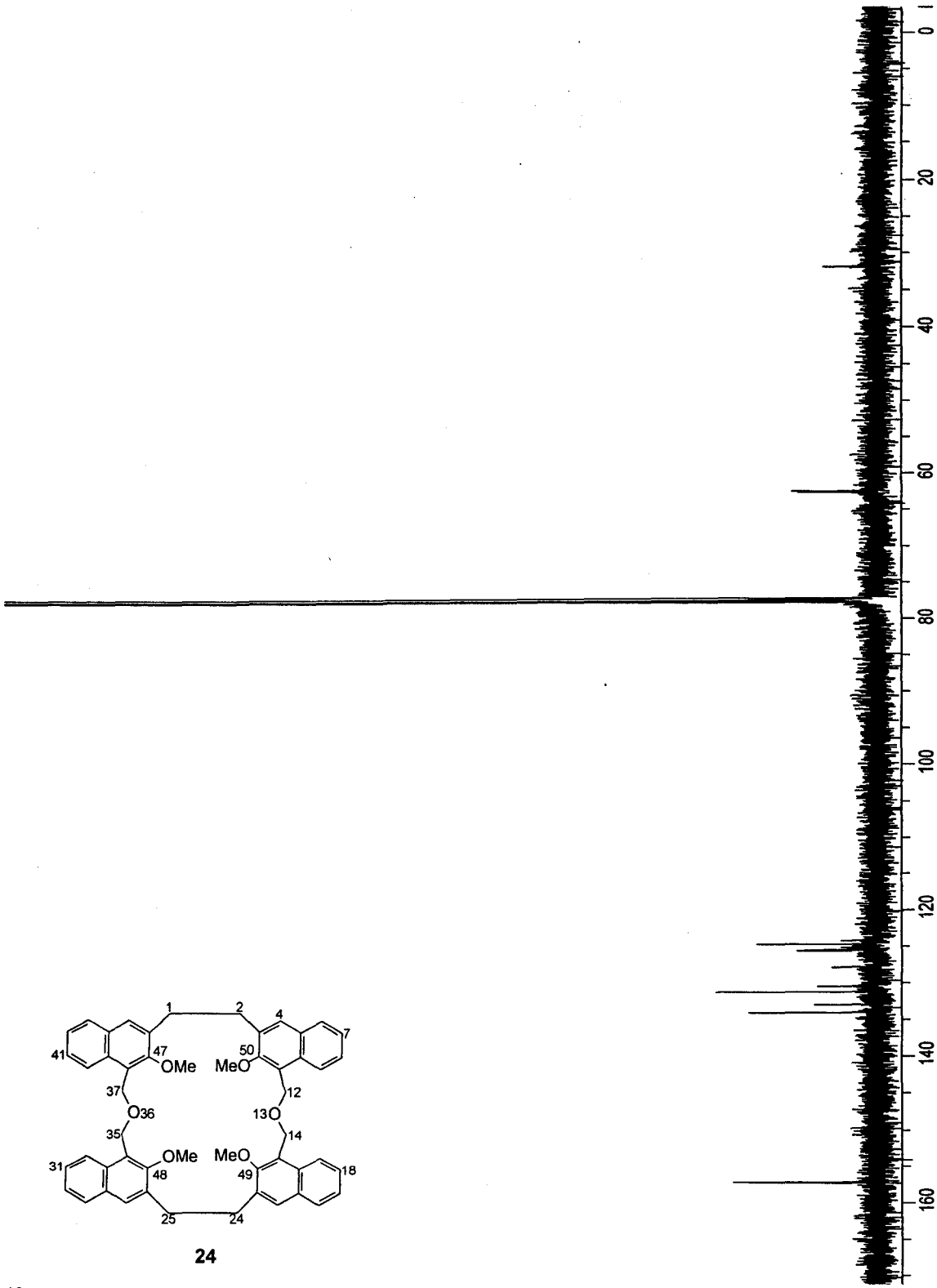


23

^{13}C NMR spectrum for compound **23**



^{1}H NMR spectrum for compound **24**



24

^{13}C NMR spectrum for compound **24**

Chapter 5

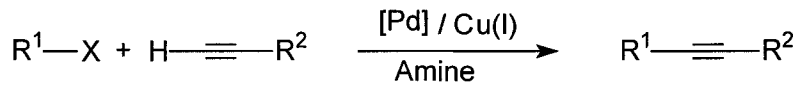
Narrow-Rim Functionalization of Calix[4]arenes via Sonogashira Coupling Reactions

5.1- Introduction

5.1.a. Sonogashira Coupling Reactions

The Sonogashira[1] cross-coupling reaction in recent years has become one of the most important metal-catalysed reactions for the construction of carbon-carbon bonds. In particular, this particular type of Pd-catalysed reaction has proven to be a powerful method for the construction of alkyne-containing compounds, and has also been applied in the synthesis of numerous natural products, bioactive compounds,[2] molecular electronic devices,[3] dendrimers[4] and polymers.[5]

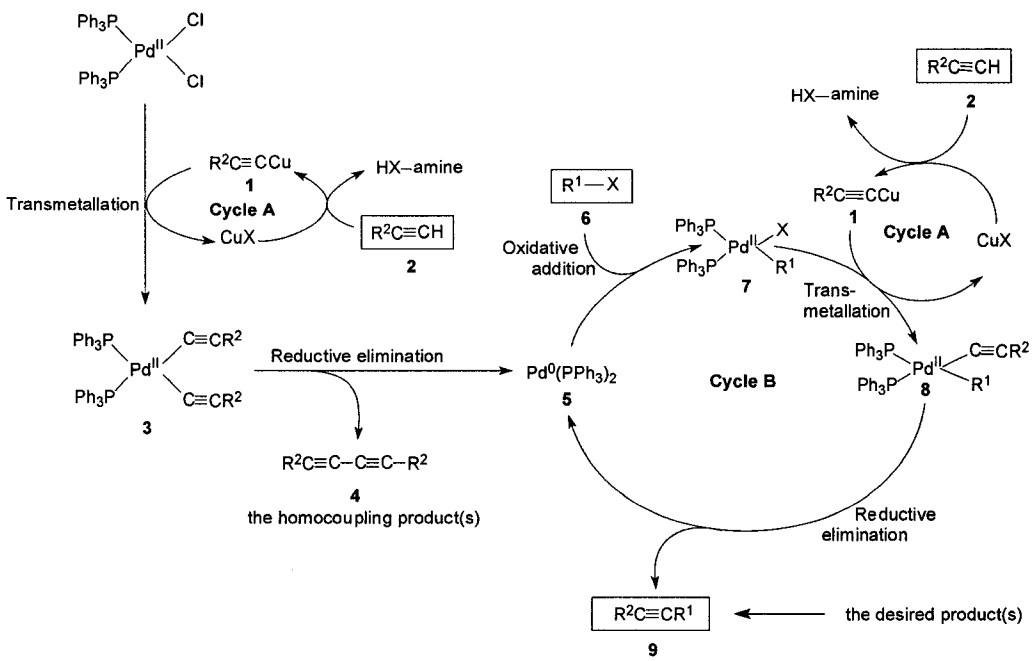
A typical Sonogashira reaction is usually conducted by coupling terminal alkynes with aryl or vinyl halides, in the presence of a catalyst and a base (Scheme 5.1). Pd is the most commonly used catalyst for such transformations, and it can be used in different forms such as $PdCl_2(PPh_3)_2$, $PdCl_2/PPh_3$, $Pd(OAc)_2$, or $Pd(PPh_3)_4$. Amines are the most common bases which have been used and in some cases they are used in large amounts as the solvents or cosolvents of the reactions. Cu(I) is also used as a cocatalyst.[6]



R = aryl, alkenyl
X = Cl, Br, I , OTf

Scheme 5.1 The Pd-catalysed coupling of terminal alkyne with sp^2-carbon halides

The reaction mechanism proposed initially for the Pd-catalysed reaction of a terminal alkyne with sp^2-carbon halides is depicted in Scheme 5.2[7] and included two different cycles: cycles "**A**" and "**B**". In cycle **A**, the Cu(I)-acetylide (**1**) is generated from the terminal alkyne **2** in the presence of Cu(I), and an amine. In this cycle, the catalyst source, $PdCl_2(PPh_3)_2$ in this case, undergoes a transmetallation reaction with **1** to generate the Pd-acetylide complex **3**. Reductive elimination of **3** produces the catalytically-active catalyst $Pd^0(PPh_3)_2$ (**5**), which is necessary for cycle **B** (in which the desired coupling is carried out).



Scheme 5.2 Pd-catalysed cross-coupling reaction of terminal alkynes with sp^2-halides.[7]

Although the last step is necessary for generating the active catalyst, this step consumes variable amounts of the terminal alkynes, which are relatively

expensive starting materials, and converts them to the corresponding homo-coupled product **4**. These are common by-products in such reactions and result in lowering the efficiency of the desired coupling. In cycle **B**, the catalyst **5** undergoes an oxidative addition reaction with the arylhalide **6** to give the corresponding Pd-complex **7**.

The copper acetylide **1**, which is produced from cycle **A** undergoes a transmetallation reaction with complex **7** to generate the Pd-complex **8**. The last step in this cycle includes the reductive elimination reaction of **8** to give the desired product(s) **9**.

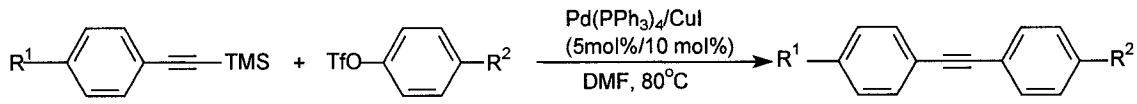
Although the typical Sonogashira coupling reaction is conducted using the Pd/phosphine/CuI/amine systems described above, these typical conditions have some limitations and difficulties: (i) In some cases, excellent yields are only obtained if highly purified starting materials are used, which demands more effort in their purification. (ii) The need for the strict exclusion of oxygen from the reaction, in order to avoid the decomposition of the phosphene ligands[8] and to avoid homocoupling of the alkyne to the corresponding symmetrical diyne (known as Glaser coupling),[9] can reduce the practical value of the desired coupling. (iii) The reactivity of aryl chlorides and bromides is often low which means that harsh conditions are sometimes needed; on the other hand, the more reactive aryl iodide is expensive and/or difficult to prepare. (iv) The presence of CuI, as proposed in the proposed mechanism above, can result in the formation of Cu(I)-acetylides which can undergo oxidative homocoupling.[10] (v) The need for

large amounts of amine (as a base and/or as a solvent) is not favored from an environmental and industrial standpoint, particularly for large scale reactions.

Due to the above difficulties and limitations; considerable attention has been directed in developing new and efficient palladium catalytic systems for the Sonogashira reaction. In the following paragraphs, a few representative examples of some procedures are described for which satisfactory results for the desired Pd-catalysed coupling reactions have been achieved.

In Sonogashira coupling, the terminal alkyne often possesses a trimethylsilyl (TMS) protecting group which allowed modification on the other end of the alkyne. The TMS group would in principle be required to be removed before the desired coupling at the terminal end is carried out. In 1997, Nishihara et al.[11] reported a much more convenient process in which direct coupling of the alkynyltrimethylsilane with aryl triflate can be effected, without the need for prior removal of the TMS group. As shown in Scheme 5.3, the Cu(I)/Pd(0)-catalysed system has been used to couple alkynyltrimethylsilanes (**10a-15a**) with the aryl triflates (**10b-15b**) to give the corresponding tolane products **10-15**.

In 1998 Krause and Thorand[12] developed a reliable and practical procedure to prepare **16a-h** from the coupling of aryl bromides **17a-h** with terminal alkynes **18a-h** via Pd-catalysed coupling using THF instead of amine as a solvent (Scheme 5.4). They found that the crude product contained only trace amounts of the undesired homocoupling products. The work-up of the reaction is simple and the crude product, in general, can be used without further purification.

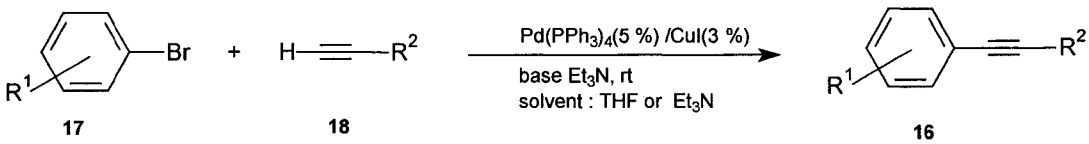


10a : R^1 = H
11a : R^1 = MeO
12a : R^1 = NC
13a : R^1 = MeO
14a : R^1 = MeO
15a : R^1 = TBSO

10b : R^2 = COMe
11b : R^2 = ^{t}-Butyl
12b : R^2 = COMe
13b : R^2 = CN
14b : R^2 = COMe
15b : R^2 = CN

10 : R^1 = H, R^2 = COMe (89%)
11 : R^1 = MeO, R^2 = ^{t}-Butyl (90%)
12 : R^1 = NC, R^2 = COMe (52%)
13 : R^1 = MeO, R^2 = CN (51%)
14 : R^1 = MeO, R^2 = COMe (65%)
15 : R^1 = TBSO, R^2 = CN (71%)

Scheme 5.3 Cu/Pd-catalysed cross-coupling reaction of alkynylsilanes (**10a-15a**) with aryl triflates (**10b-15b**).



17 **18** **16**

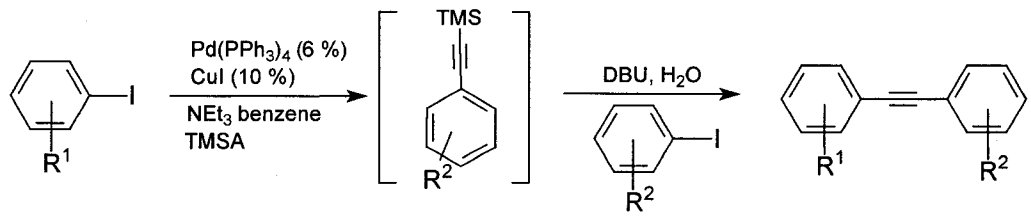
alkyle bromide	terminal alkyne	product	in THF	in Et_3N
17a : R^1 = 4-CHO	**18a** : R^2 = Me_3Si	**16a** : R^1 = 4-CHO, R^2 = Me_3Si	99 % (25 °C, 1 h)	99 % (reflux, 1 h)
17b : R^1 = 4-COMe	**18b** : R^2 = Me_3Si	**16b** : R^1 = 4-COMe, R^2 = Me_3Si	92 % (25 °C, 1 h)	80 % (25 °C, 1 h)
17c : R^1 = 2-CO_2Me	**18c** : R^2 = Me_3Si	**16c** : R^1 = 2-CO_2Me, R^2 = Me_3Si	88 % (25 °C, 16 h)	81 % (80 °C, 1 h)
17d : R^1 = 3-CO_2Me	**18d** : R^2 = Me_3Si	**16d** : R^1 = 3-CO_2Me, R^2 = Me_3Si	87 % (25 °C, 16 h)	70 % (100 °C, 1 h)
17e : R^1 = 4-CO_2Me	**18e** : R^2 = Me_3Si	**16e** : R^1 = 4-CO_2Me, R^2 = Me_3Si	88 % (25 °C, 16 h)	69 % (100 °C, 1 h)
17f : R^1 = 4-COMe	**18f** : R^2 = *n*-Bu	**16f** : R^1 = 4-COMe, R^2 = *n*-Bu	91 % (25 °C, 16 h)	73 % (140 °C, 1 h)
17g : R^1 = 4-COMe	**18g** : R^2 = Ph	**16g** : R^1 = 4-COMe, R^2 = Ph	87 % (25 °C, 16 h)	83 % (reflux, 1 h)
17h : R^1 = 4-CHO	**18h** : R^2 = Ph	**16h** : R^1 = 4-CHO, R^2 = Ph	82 % (25 °C, 16 h)	66 % (100°C, 1 h)

Scheme 5.4 Cu/Pd-catalysed cross-coupling reaction of alkylbromides (**17a-h**) with terminal alkynes (**18a-h**) in THF compared to ones in Et_3N.

A "one-pot" modified Sonogashira coupling reaction was reported in 2002 by Grieco et al.,[13] in which symmetrical and unsymmetrical bisarylethynes were synthesized by employing an amidine base, a sub-stoichiometric amount of water, Pd^0 (6 mol %) and CuI (10 mol %) (Scheme 5.5). These conditions were found to be efficient for the synthesis of wide range of bisarylethynyls **19a-f** which

can be used in the construction of supramolecular self-assembly systems via Co-mediated [2+2] annulation of these alkynes.

Mori et al.[14] found that diluted aqueous ammonia served as an efficient additive for the Sonogashira coupling reaction. The reaction was found to be sensitive to the ammonia concentration, and the highest yields were observed when aqueous 0.5 M, or less concentrated ammonia solutions, are used. For example, the aryl alkynes **22a-b** were obtained from the coupling of terminal alkynes **23a-b** with aryl iodide **24** in the presence of ammonia (Scheme 5.6).



20

20a : R^1 = 2-F
20b : R^1 = 3-Cl
20c : R^1 = 4-Br
20d : R^1 = 3-Br
20e : R^1 = 3-Br
20f : R^1 = 4-OMe

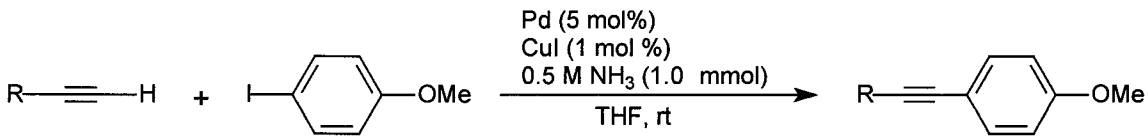
21

21a : R^2 = 2-F
21b : R^2 = 3-Cl
21c : R^2 = 3-Br
21d : R^2 = 4-Cl
21e : R^2 = 3-Cl
21f : R^2 = 4-COOMe

19

19a : R^1 = 2-F, R^2 = 2-F (93 %)
19b : R^1 = 3-Cl, R^2 = 3-Cl (93 %)
19c : R^1 = 4-Br, R^2 = 3-Br (89 %)
19d : R^1 = 3-Br, R^2 = 4-Cl (90 %)
19e : R^1 = 3-Br, R^2 = 3-Cl (79 %)
19f : R^1 = 4-OMe, R^2 = 4-COOMe (71 %)

Scheme 5.5 One-pot Cu/Pd-catalysed cross-coupling reaction of aryliodides **20a-f** and alkyliodide **21a-f** with terminal TMS-protected alkynes to give the corresponding bisarylethynylenes **19a-f**.



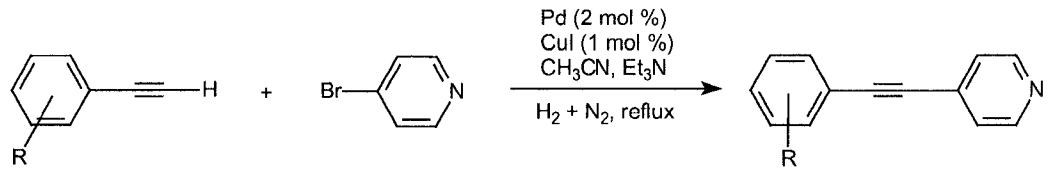
23a: R = Ph
23b: R = Me_3Si (0.6 mmol)

24 (0.5 mmol)

22a: R = Ph (96 %)
22b: R = Me_3Si (83 %)

Scheme 5.6 Cu/Pd-catalysed cross-coupling reaction of terminal alkynes **23a-b** with the aryliodide **24** in a solution of dilute aqueous ammonia.

Ho et al.[15] presented a method using a reducing atmosphere, of hydrogen gas diluted with nitrogen, or argon to diminish alkyne homocoupling and enhance the desired cross-coupling. For example, the homocoupling of terminal alkynes **26a-f** under these conditions were reduced to about 2 % (Scheme 5.7).

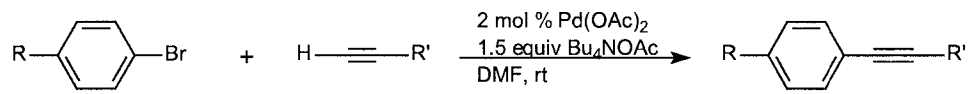


26a : R = 2,4-dimethyl
26b : R = 4-OMe
26c : R = 4-NMe_2
26d : R = 4-NEt_2
26e : R = 4-H
26f : R = 4-Me

25a : R = 2,4-dimethyl (89 %)
25b : R = 4-OMe (91 %)
25c : R = 4-NMe_2 (94 %)
25d : R = 4-NEt_2 (95 %)
25e : R = 4-H (88 %)
25f : R = 4-Me (85 %)

Scheme 5.7 Synthesis of alkynes **25a-f** under reducing atmospheric conditions using hydrogen diluted with nitrogen or argon.

In 2004, Verkade et al.[16] reported the coupling of aryl iodides and bromides with different terminal alkynes using PPh_3 ligand-, copper- and amine-free reactions. Using $Pd(OAc)_2$- or $Pd_2(dba)_3$ compounds **27a-f** were formed by reaction of the alkyl bromides **28a-f** with terminal alkynes **29a-f** (Scheme 5.8).



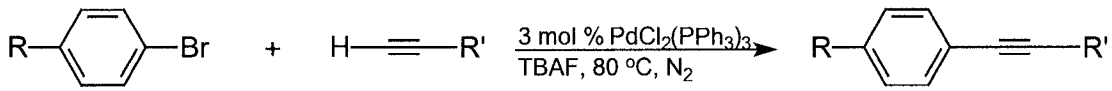
28a : R = NO_2
28b : R = NO_2
28c : R = NO_2
28d : R = CHO
28e : R = NC
28f : R = NC

29a : R' = Ph
29b : R' = -$(CH_2)_4OH$
29c : R' = -$(CH_2)_5Me$
29d : R' = -$(CH_2)_5Me$
29e : R' = -$(CH_2)_4OH$
29f : R' = TIPS

27a : R = NO_2, R' = Ph (86 %)
27b : R = NO_2, R' = -$(CH_2)_4OH$ (92 %)
27c : R = NO_2, R' = -$(CH_2)_5Me$ (91 %)
27d :R = CHO, R' = -$(CH_2)_5Me$ (90 %)
27e :R = NC, R' = -$(CH_2)_4OH$ (94 %)
27f : R = NC, R' = TIPS (89 %)

Scheme 5.8 PPh_3 ligand-, copper- and amine-free Sonogashira couplings of aryl bromides **28a-f** with terminal alkynes **29a-f**.

Li et al.[17] also reported a Pd-catalysed coupling reaction under solvent-copper-, and amine-free conditions. For example, the corresponding products **30a-f** were obtained from the coupling of the alkyl bromides **28a-f** with terminal alkynes **29a-f** by employing $PdCl_2(PPh_3)_2$ combined with TBAF (Scheme 5.9).



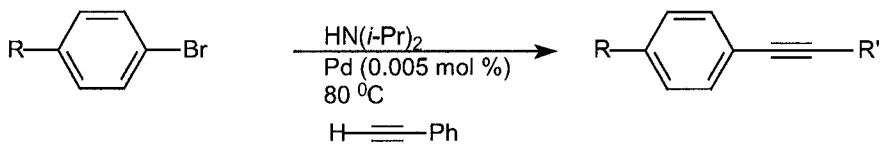
31a : R = H
31b : R = NO_2
31c : R = NO_2
31d : R = CHO
31e : R = MeO
31f : R = MeO

32a : R' = Ph
32b : R' = Ph
32c : R' = $-(CH_2)_5Me$
32d : R' = Ph
32e : R' = C_8H_{17}
32f : R' = CH_2OH

30a : R = H, R' = Ph (98 %)
30b : R = NO_2, R' = Ph (98 %)
30c : R = NO_2, R' = $-(CH_2)_5Me$ (91 %)
30d : R = CHO, R' = Ph (99 %)
30e : R = MeO, R' = C_8H_{17} (98 %)
30f : R = MeO, R' = CH_2OH (80 %)

Scheme 5.9 Copper-, amine-, and solvent-free Sonogashira couplings of aryl bromides **31a-f** with terminal alkynes **32a-f**.

A convenient high activity catalyst for the cross-coupling of aryl bromides was reported by Plenio et al,[18] using a 4:3:8 mixture of Na_2PdCl_4, CuI and $(t\text{-}Bu)_3PH^+BF_4^-$ in $H_2N(i\text{-}Pr)_2^+Br^-$ can be employed as a single catalyst. This catalyst has been found to be a very active catalyst, even at low ratios (0.005 mol %), for the production of **33a-f** from **34a-f** with phenyl alkyne (Scheme 5.10).



34a : R = NO_2
34b : R = CH_3CO
34c : R = COOEt
34d : R = Cl
34e : R = Me
34f : R = MeO

33a : R = NO_2 (96 %)
33b : R = CH_3CO (94 %)
33c : R = COOEt (98 %)
33d : R = Cl (93 %)
33e : R = Me (94 %)
33f : R = MeO (92 %)

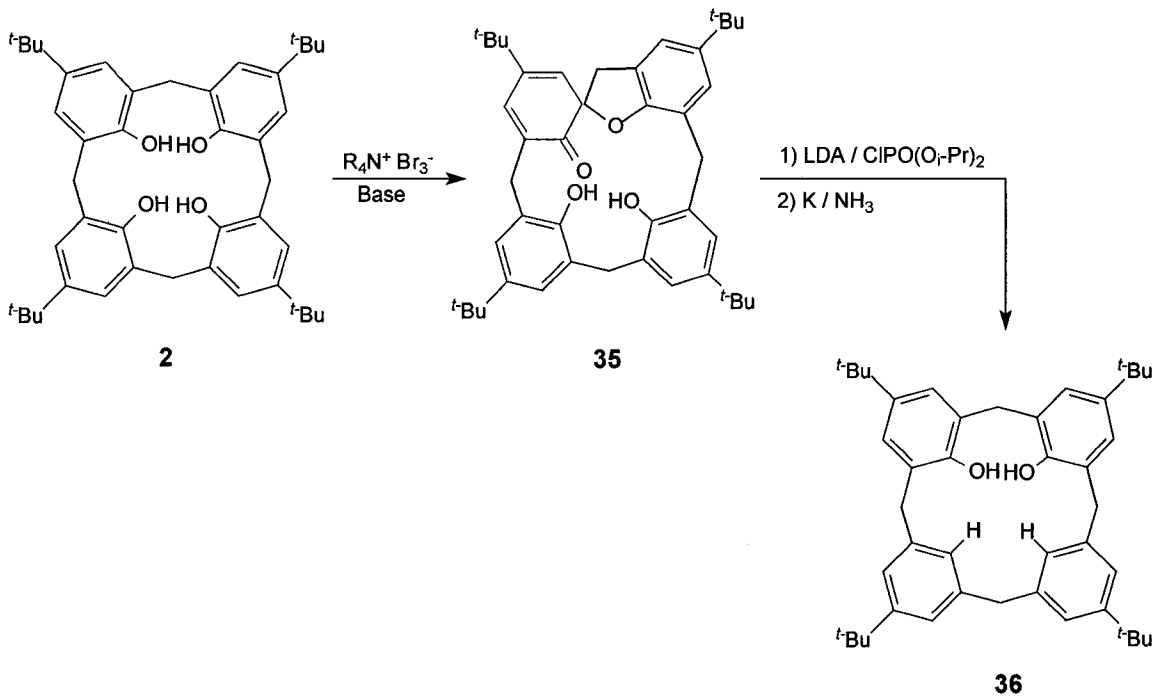
Scheme 5.10 Sonogashira couplings of aryl bromides **34a-f** with phenylacetylene using Plenio's conditions.

5.1.b. Narrow-rim Modification of Calix[4]arenes

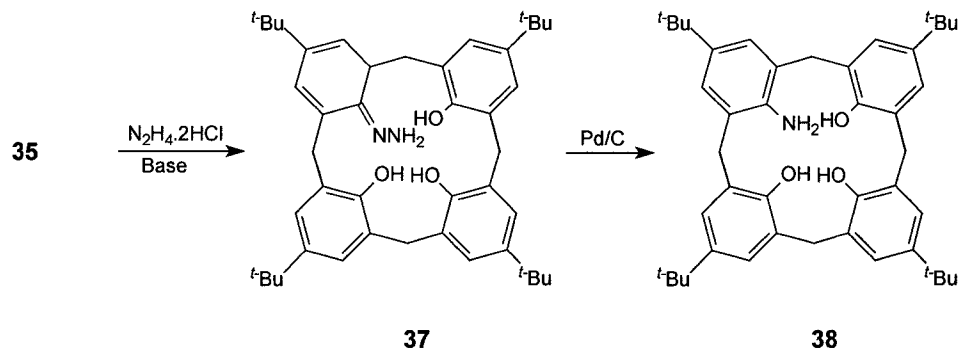
As stated in the introduction of this thesis (Chapter 1), structural modifications of calixarenes in general, can lead to significant changes in their chemical and physical properties. This has resulted in much synthetic effort by many research groups being directed toward producing analogues and derivatives of these versatile molecules. The great majority of the modifications have involved narrow (or "lower")-rim functionalization of the phenolic hydroxy groups or, to a lesser extent, wide (or "upper")-rim modifications. Modifications of the narrow rim of calixarenes have primarily involved aliphatic mono- to tetra-*O*-alkylation or mono- to tetra-*O*-esterification and *O*-arylation (*see* e.g. Scheme 1.4, Chapter 1).

There are only a limited number of reported examples of narrow-rim modification of *p-tert*-butylcalix[4]arene (**2**) by substitution of either one, or more of the phenolic hydroxyl groups with different functional groups or atoms. These examples include hydrogen atoms (Scheme 5.11),[19] amino groups (Scheme 5.12),[20] or sulfhydryl groups (Scheme 5.13).[21]

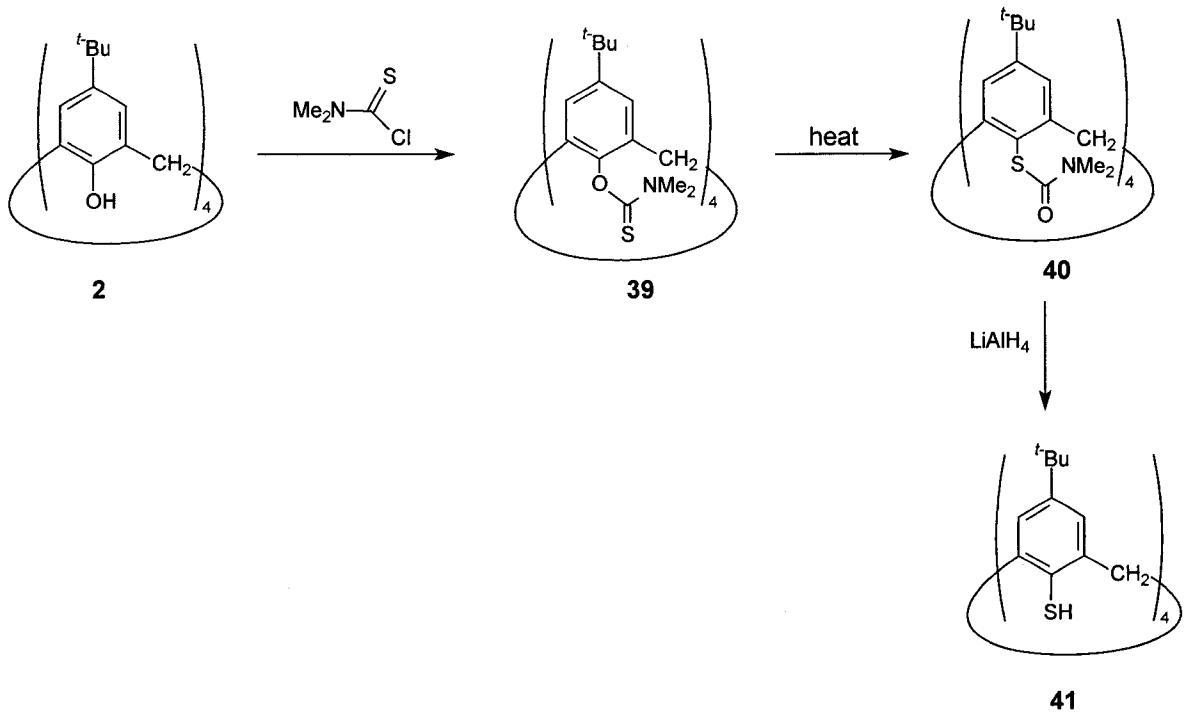
Other narrow-rim modifications could, in principle, also be achieved using metal-assisted coupling reactions such as the Stille,[22] or Suzuki-Miyaura[23] reactions, reactions which our group has been interested in for some time. The following is a summary of some such attempts which have been reported to date.



Scheme 5.11 Narrow-rim modification of *p-tert*-butylcalix[4]arene (**2**) by substitution of one or more of the phenolic hydroxyl groups by hydrogen toms.



Scheme 5.12 Narow-rim modification of *p-tert*-butylcalix[4]arene (**2**) by substitution of one of the phenolic hydroxyl groups by an amine group.

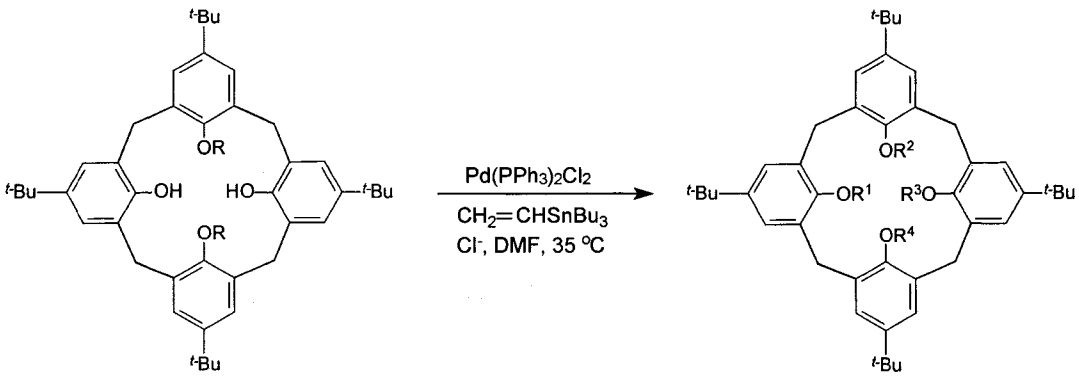


Scheme 5.13 Narrow-rim modification of *p-tert*-butylcalix[4]arene (**2**) by substitution of the phenolic hydroxyl groups with sulfhydryl groups.

The first attempts of metal-assisted coupling reactions of calix[4]arenes on the narrow rim, were reported by González et al.[24] in 1995. They found that under their Pd-catalysed Stille reaction conditions using 1,3-bistriflate **42** or 1,3-bis-mesylate **43** the desired couplings were unsuccessful, and instead of the expected narrow-rim substitution they observed an intramolecular migration, or hydrolysis of the sulfonyl groups as in calix[4]arenes **44-48** (Scheme 5.14).

The Georghiou group has also been interested in the potential of functionalizing the narrow rim of calix[4]arenes using calix[4]arene triflate **42** or the mesylate **43**. They previously reported that Suzuki-Miyaura reactions of the

mono- to tetrakistriflates of **2**, however, failed to afford any of the desired products, affording only unexpected products. For example, Chowdhury *et al.*[25] reported that the Pd-catalysed carbonylation[26] with the 1,3-bistriflate **42** and phenylboronic acid (**49**) resulted only in the formation of an unprecedented stable 1:1 supramolecular complex of benzophenone and the monotriflate **45**, with no evidence for triflate displacement (Scheme 5.15).



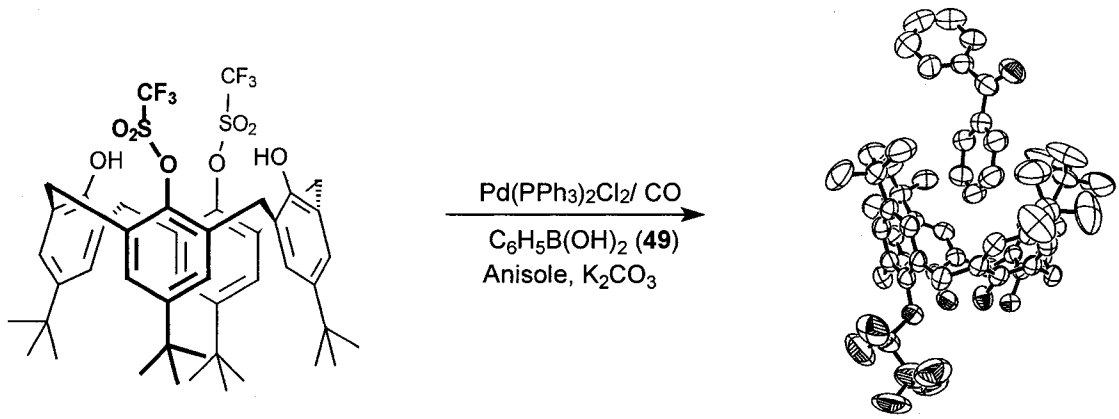
42 : R = Tf
43 : R = Ms

44 : $R^1 = R^2 = R^3$ = Tf, R^4 = H
45 : R^1 = Tf, $R^2 = R^3 = R^4$ = H
46 : $R^1 = R^2$ = Tf, $R^3 = R^4$ = H
47 : $R^1 = R^2 = R^3$ = Ms, R^4 = H
48 : R^1 = Ms, $R^2 = R^3 = R^4$ = H

Scheme 5.14 Palladium-catalysed intermolecular migration of sulfonyl groups of the 1,3-bistriflate **42** or 1,3-bismesylate **43.**

Another attempt was carried out by Chowdhury[27] to deoxygenate the monotriflate **44** by employing Snieckus' Pd-catalysed conditions with formic acid. These conditions however also failed to give any of the desired products and

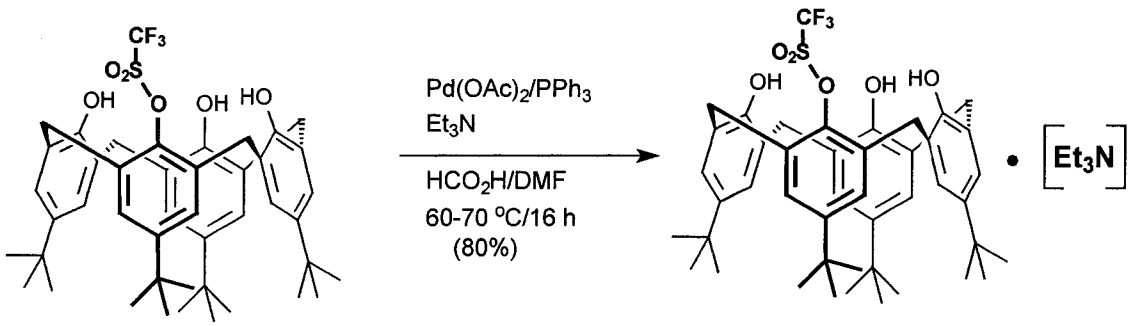
instead gave a different 1:1 supramolecular complex between triethylamine and **45** (Scheme 5.16).[25]



42

45 • benzophenone (1:1) complex

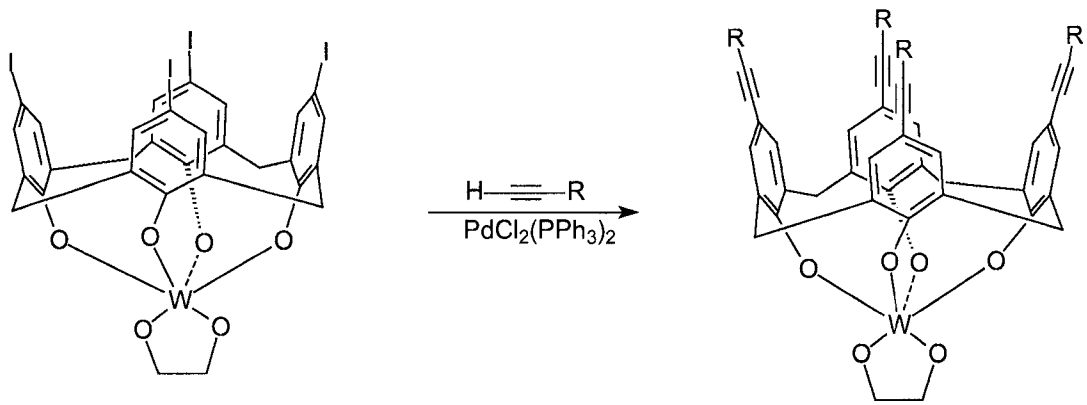
Scheme 5.15 Attempted Pd-catalysed carbonylative Suzuki-Miyaura-type reaction with the 1,3-bistriflate **42** and phenylboronic acid (**49**)



44 **45**

Scheme 5.16 Attempted Snieckus Pd-catalysed coupling with the triflate **44**

To the best of our knowledge, there are only few published reports in which the Sonogashira reaction has been employed with calixarenes, and these reports have all involved functionalization of the wide-rim. For example, Swager et al.[29] reported the wide-rim modification of the tungsten-calix[4]arene derivative **50** by the Sonogashira coupling with different terminal alkynes to give the corresponding calix[4]arenes **51-52** (Scheme 5.17).

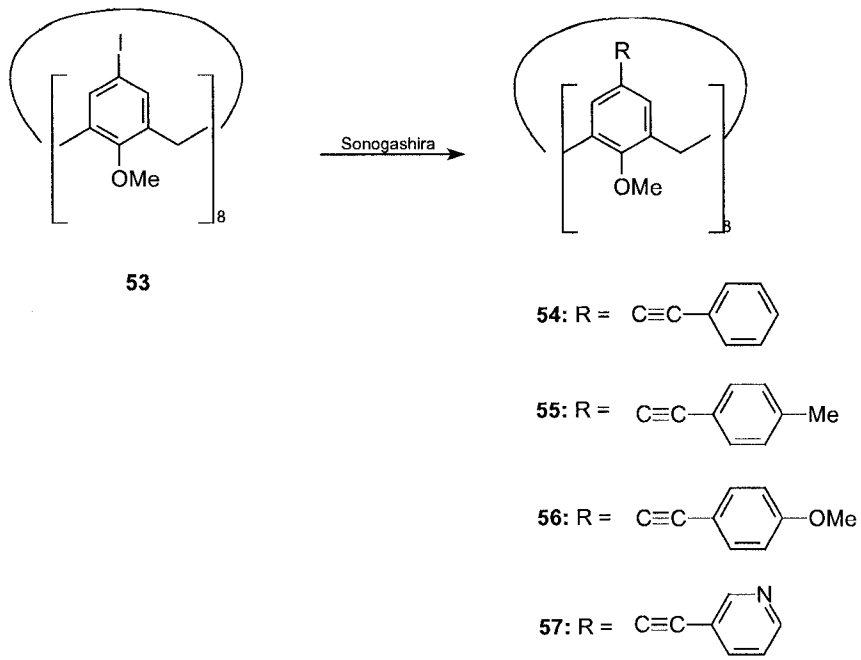


50

51 : R = $ArOC_4H_9$
52 : R = C_4H_9

Scheme 5.17 Wide-rim modification of calix[4]arene **50** by Sonogashira coupling reactions with different terminal alkynes

Extending calix[8]arene's cavity has been reported by Böhmer et al.[30] who described the use of a Sonogashira reaction to couple calix[8]arene **53** with different terminal alkynes to produce the corresponding calix[8]arenes **54-57** (Scheme 5.18).

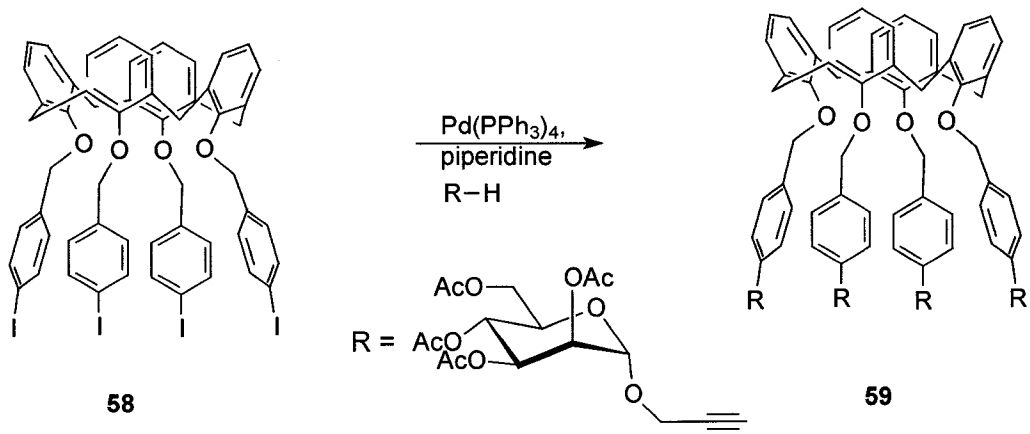


Scheme 5.18 Extending the cavity of calix[8]arene's by Sonogashira coupling

There are also other reports describing the introduction of porphyrins[31] and π-conjugated chromophores[32] to the wide rim of calix[4]arene using Sonogashira coupling. González et al[33] also used Sonogashira coupling conditions to prepare sugar-based calix[4]arenes, via the conversion of tetrakis-*p*-iodobenzyloxy-calix[4]arene (**58**) to form the corresponding tetrakis-*p*-(mannopyranosyl)benzyl-oxycalix[4]arene (**59**) (Scheme 5.19).

Although the reactions described above were based on Sonogashira reactions, none involved displacement of the phenolic oxygen atoms on the narrow-rim. In 2005, however, we reported that Pd-catalysed reactions of **42** under modified Sonogashira conditions,[34] using different terminal alkynes, produced the desired narrow-rim substitution. We also found that under certain

conditions an unusual aromatic substitution of the narrow-rim triflates by iodide occurred. In this chapter, the research on these first successful Sonogashira reaction-mediated narrow-rim functionalizations of a calix[4]arene will be described.



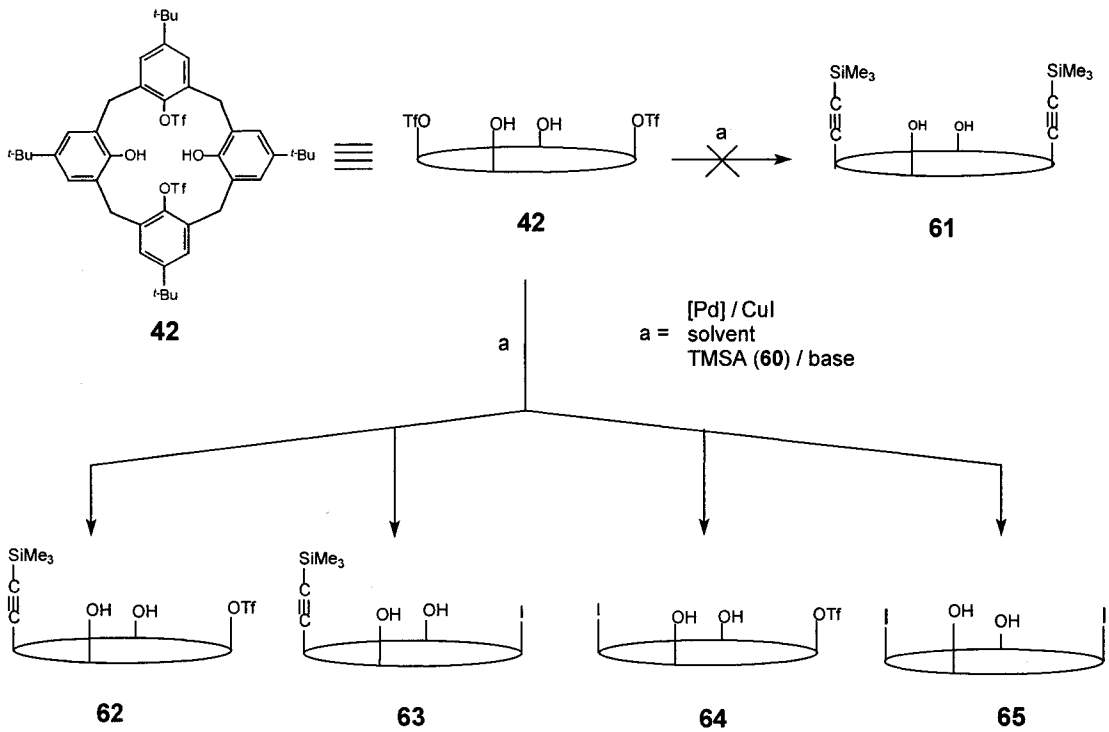
58 59

Scheme 5.19 Synthesis of the calix-sugar–based calix[4]arene (**59**) via Sonogashira reaction

5.2- Synthesis

The first experiments with the Sonogashira reaction by this author were conducted by reacting bistriflate **42**[34] with trimethylsilylacetylene (TMSA, **60**) (Scheme 5.20) using different reaction conditions (Table 5.1). During these experiments, several different bases, for example, triethylamine, pyrrolidine, 2,6-lutidine, ammonium hydroxide, and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), and also different solvents, for example, benzene, THF, dioxane, DMF, water, acetonitrile and toluene, were evaluated.

DBU and toluene was found to be the best base and solvent combination to use in our cases (for example see entries: 17, 18, 21 and 22 and in Table 5.1).



Scheme 5.20 Pd-coupling of the 1,3-bistriflate calix[4]arene (**42**) with TMSA (**60**)

It was also found to be necessary to use refluxing temperatures to get an optimum yield for any reaction between **42** and **60**. The desired product, **61**, in which both of the triflates are substituted by TMSA was not produced from these reactions. The mono-coupled product **62** however, was obtained along with three new, unexpected, products (**63-65**) which were apparently formed by the unprecedented substitutions of the triflate(s) by iodide (s).

The structures of compounds **62**, **63** and **65** were established by NMR and single-crystal X-ray crystallography, to be the narrow-rim functionalized

monotrimethylsilylethynyl-substituted monotriflate **62**, the iodo- and trimethylsilylethynyl-substituted calix[4]arene **63**, and the diiodosubstituted calix[4]arene **65**.

Table 5.1 Some typical reaction conditions employed for the Pd-catalysed reactions of bistriflate **42** with TMSA

entry	base / molar equiv	catalyst /mol%	solvent /temp	CuI mol%	time (h)	% yield 62	63	64	65
1	Et_3N/4	$Pd(PPh_3)_2Cl_2$/ 10	THF/25	20	24	0	0	0	0
2	DBU/3	$Pd(PPh_3)_2Cl_2$/ 10	THF/25	20	24	0	0	0	0
3	NH_3/ excess	$Pd(PPh_3)_2Cl_2$/ 20	THF/25	Excess	24	0	0	0	0
4	Et_3N/4	$Pd(PPh_3)_2Cl_2$/ 10	THF/60	20	12	0	0	0	0
5	DBU/3	$Pd(PPh_3)_2Cl_2$/ 10	THF/60	20	24	0	0	0	0
6	NH_3/ excess	$Pd(PPh_3)_2Cl_2$/ 20	THF/60	Excess	24	0	0	0	0
7	DBU/10	$Pd(PPh_3)_2Cl_2$/ 10	Dioxane/25	10	12	0	0	0	0
8	DBU/10	$Pd(PPh_3)_2Cl_2$/ 10	Dioxane/100	10	12	0	0	0	0
9	2,6-lutidine/10	$Pd(PPh_3)_2Cl_2$/ 2	Dioxane/100	10	24	0	0	0	0
10	DBU/24	$Pd(PPh_3)_2Cl_2$/ 10	H_2O/100	2.2	18	0	0	0	0
11	DBU/4	$Pd(PPh_3)_2Cl_2$/ 5	Acetonitrile/80	10	24	0	0	0	0
12	DBU/4	$Pd(PPh_3)_2Cl_2$/ 10	H_2O /60	10	24	0	0	0	0
13	DBU/4	$Pd(PPh_3)_2Cl_2$/ 5	Benzene/25	10	12	0	0	4	6
14	DBU/4	$Pd(PPh_3)_2Cl_2$/5	Benzene/80	10	24	*	0	0	*
15	DBU/4	$Pd(PPh_3)_2Cl_2$/10	Benzene/80	260	0.5	*	*	25	55
16	DBU/4	$Pd(PPh_3)_2Cl_2$/10	Toluene/25	500	4	0	0	*	*
17	DBU/4	$Pd(PPh_3)_2Cl_2$/10	Toluene/110	500	1.5	12	19	8	25
18	DBU/2	$Pd(PPh_3)_2Cl_2$/10	Toluene/110	200	0.5	*	8	10	53
19	DBU/2	$Pd(OAc)_2$ /10	Toluene/25	50	3	0	0	0	0
20	DBU/4	$Pd(OAc)_2$ /10	Toluene/110	50	3	*	*	0	0
21	DBU/4	$Pd(PPh_3)_2Cl_2$/1	Toluene/110	200	1	44	43	*	*
22	DBU/4	$Pd(PPh_3)_2Cl_2$/1	Toluene/110	1	1	51	*	0	*
23◊	DBU/2	$Pd(PPh_3)_2Cl_2$/10	Toluene/25	600	4	-	-	14	64

* = traces amounts only obtained
◊ = the reaction conducted without TMSA

The X-ray structure of **62** (Figure 5.1) which has two molecules in the asymmetric unit, reveals it to be in a *pinched-cone* conformation, in which the two distal aryl rings bearing the triflate and trimethylsilylethynyl groups are parallel to each other.

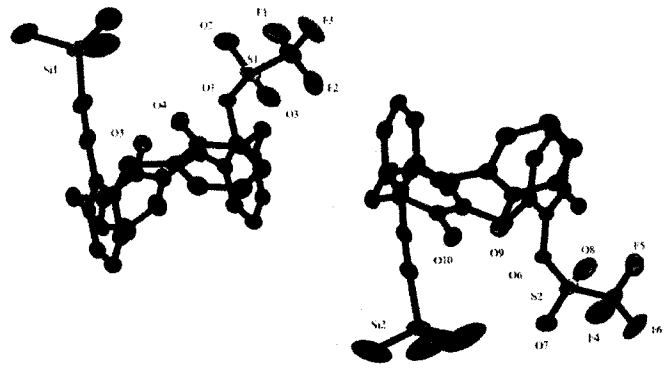


Figure 5.1 X-ray single-crystal ORTEP structural representation of two molecules of **62** in the unit cell, in which one is in an anti-parallel orientation to the other. Both molecules are in *pinched-cone* conformations (all of the *p-tert*-butyl groups and H atoms have been removed for clarity)

The X-ray structure of **63** (Figure 5.2) reveals it to be in a similar *pinched-cone* conformation in which the two distal aryl rings containing the iodo and the trimethylsilylethynyl groups are parallel to each other, by analogy with the structure of **62**. The X-ray structure of **65** on the other hand, reveals it to be in a *1,2-alternate* conformation, which is not a very commonly encountered conformation in calix[4]arenes in general (Figure 5.3).

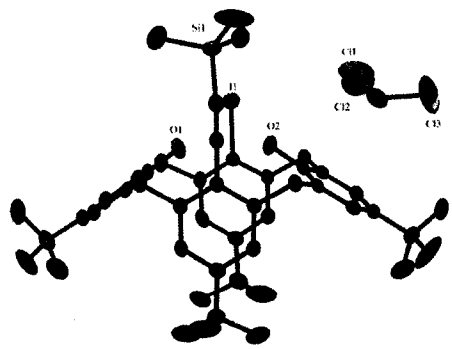


Figure 5.2 X-ray single-crystal ORTEP structural representation of **63** and a molecule of $CHCl_3$ (all of the H atoms have been removed for clarity).

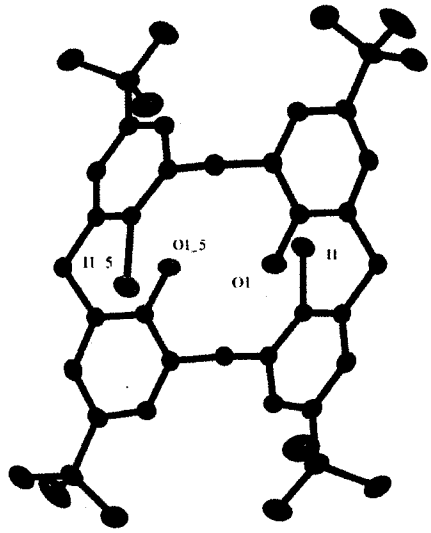


Figure 5.3 X-ray single-crystal ORTEP structural representation of **65** in a *1,2-alternate* conformation (all of the H atoms have been removed for clarity)

Although a crystal of **65** suitable for X-ray analysis revealed that this compound adopts a *1,2-alternate* conformation, its NMR spectrum at ambient temperature indicated that it adopts a *cone* conformation when predicted using de Mendoza's criteria.[36] The ^{1}H NMR spectrum of a freshly prepared $CDCl_3$ solution using a crystal had taken from the same X-ray batch however, showed a different ^{1}H NMR pattern. This spectrum was consistent with a *1,2-alternate* conformer, in agreement with the X-ray structure. Heating this solution for 1 h at 50 °C resulted in the conformation changing from the *1,2-alternate* to the *cone* conformation as revealed by their ^{1}H NMR spectra shown in Figure 5.4. These results therefore suggest that **65** adopts a *1,2-alternate* conformation in the solid state, while in solutions at, or above, room temperature it adopts, the *cone* conformation.

These incorporations of the trimethylsilylethynyl groups onto the narrow rim of the calix[4]arene scaffold in **62** and **63** are the first examples to be reported of a *metal-assisted* direct coupling of an alkyne (or for that matter, any hydrocarbon) moiety, by displacement of the phenolic functionality on the narrow rim of a calixarene. The presence of the iodine atoms in **63**, **64**, and **65**, however, was unexpected and these are also the first examples to be reported of direct substitutions by a halide on the narrow rim of a calix[4]arene.

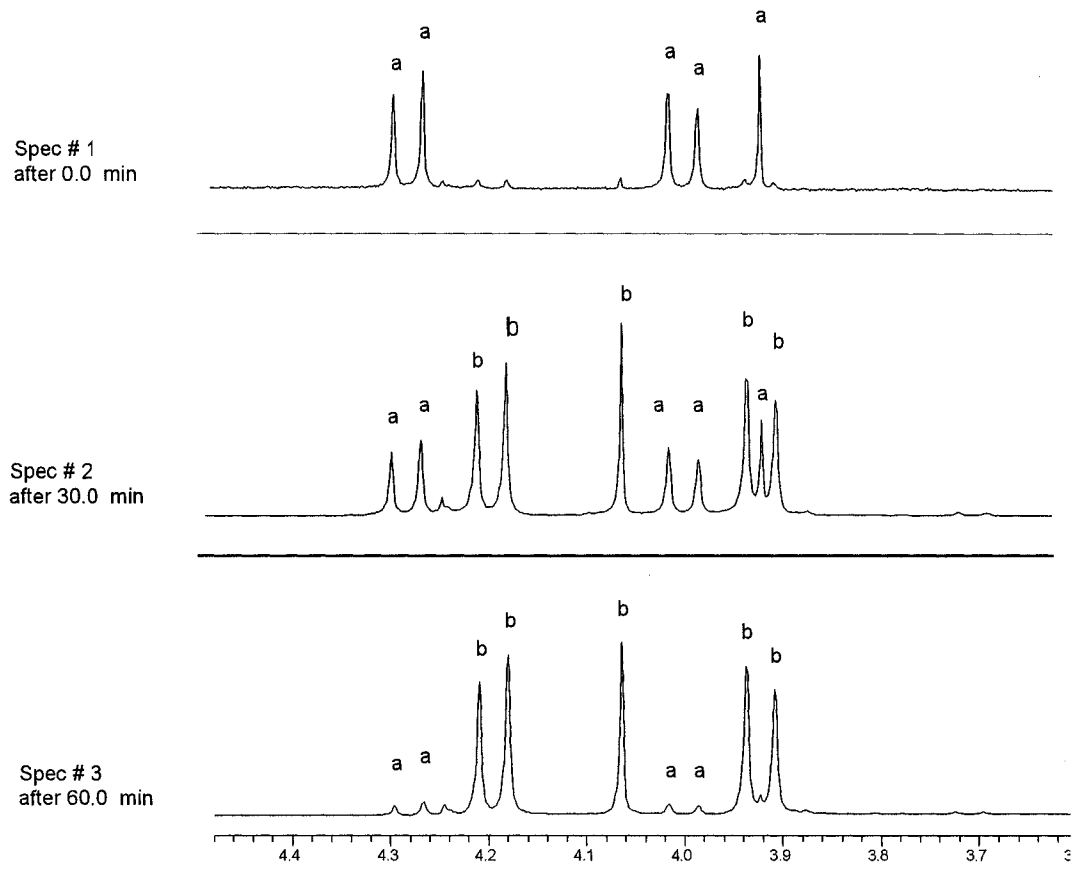
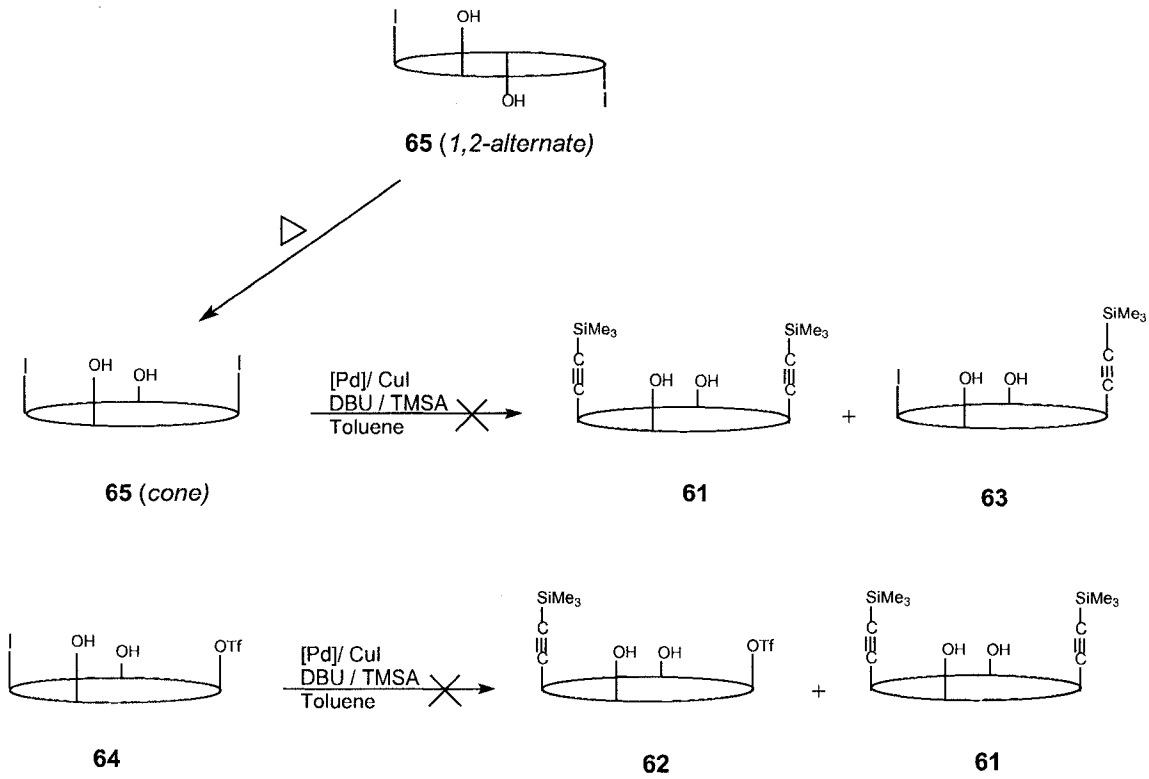


Figure 5.4 Combined partial ^{1}H NMR spectra from the heating at 50 °C of a solution of **65** in $CDCl_3$. *Labels*: ***a***: Compound **65** (*1,3-alternate conformation*); ***b***: Compound **65** (*cone conformation*).

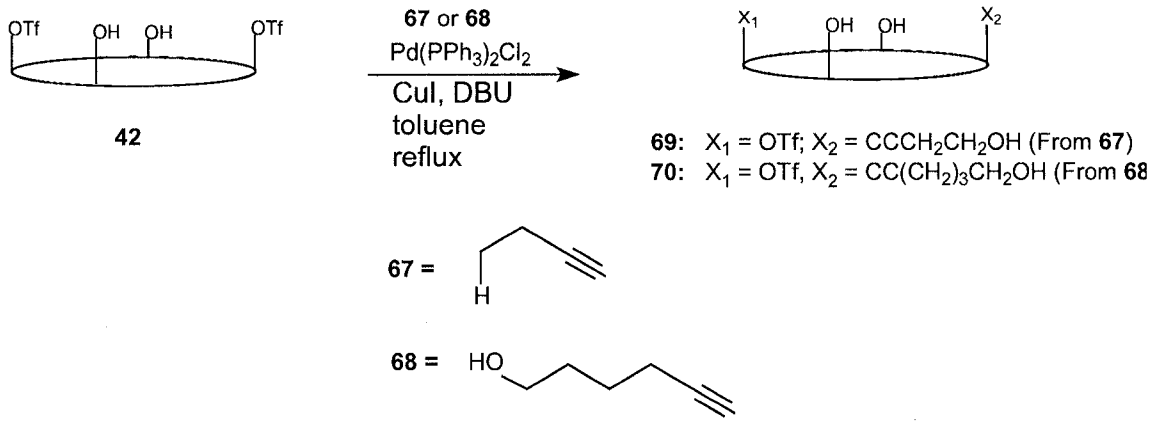
To determine whether the iodo compounds were formed as intermediates or by-products of the reaction, conditions were first evaluated in order to optimize the yields of these iodo products. Using similar Pd-catalysed conditions as that used above, but excluding the terminal alkynes which were employed in this study, it was found that the monoiodo- and diiodocalixarenes **64** and **65**, respectively, were formed in reproducible and synthetically useful yields of 14 % and 64 %, respectively (Table 5.1, entry 23). However, with both **64** and **65** in hand, attempts to effect the coupling reaction of TMSA directly on either of these compounds, under the same Sonogashira reaction conditions used previously, failed to produce any TMSA-coupled products. Only 1,4-bis(trimethylsilyl)-1,3-butadiyne (produced from the homocoupling of TMSA itself) and unreacted starting material were recovered (Scheme 5.21). These results suggest that the iodo compounds were therefore not formed as intermediates in the reactions of **42** with TMSA that produced **62** and/or **63** but that they were instead formed as by-products.

The optimal conditions which were found for synthesizing **62** (in 51% isolated yields) required 1 mol % of both the Pd catalyst and the CuI cocatalyst, and 4 molar equivalents of DBU, in refluxing toluene (Table 5.1, entry 22). However, when a higher molar ratio of CuI was used, together with a more concentrated solution of reactants (Table 5.1, entry 21), a mixture containing both **62** and **63** in 44% and 43% yield, respectively, was obtained.



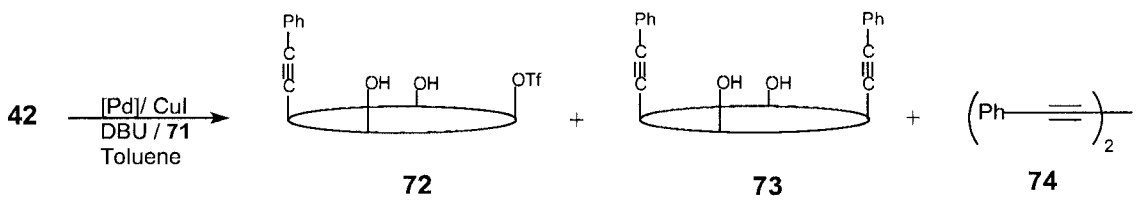
Scheme 5.21 Attempted Pd-coupling reactions for **64** or **65** with TMSA

To test the generality of these reaction conditions for other potential narrow-rim substitutions, **42** was reacted with some other readily-available terminal alkynes. The reactions of **42** with, for example, 3-butyn-1-ol (**67**) or 5-hexyn-1-ol (**68**), under the optimal conditions found for TMSA, gave the corresponding monosubstituted products **69** and **70** in 32 and 20 % yields, respectively. However, as was also found with the reactions of **42** with TMSA, none of the corresponding disubstituted products were obtained (Scheme 5.22).



Scheme 5.22 Pd-coupling reaction of **42** with different terminal alkynes **67** and **68** to give the corresponding calixarenes **69** and **70**, respectively.

With phenylacetylene (**71**), on the other hand, Pd-catalysed coupling with **42** afforded both the expected mono- *and* 1,3-bis(phenylethynyl)calix[4]arenes **72** and **73**, respectively in addition to significant amounts of the homocoupling by-product, **74** (Scheme 5.23).



Scheme 5.23 Pd-coupling of the bistriflate **42** with phenylacetylene (**71**)

A single-crystal X-ray determination of **73** (Figure 5.5) revealed that the two aryl groups which bear the phenylethynyl groups are parallel to each other, in a *pinched-cone* conformation, analogous to those conformations previously

observed with **62** and **63**. The conformation of **73** is similar to that of a wide-rim-substituted tetrakis-*p*-nitrophenylethynylcalix[4]arene recently described by Hennrich and co-workers.[37] As determined by X-ray crystallography, the two pendant-type *p*-nitrophenylethynyl groups in their compound and in our narrow-rim-substituted **73** are similarly oriented, having approximate "edge-to-face" types of interactions, in which the twist angles in **73** are 80.8°, compared with the approximately 60° angle in their compound.

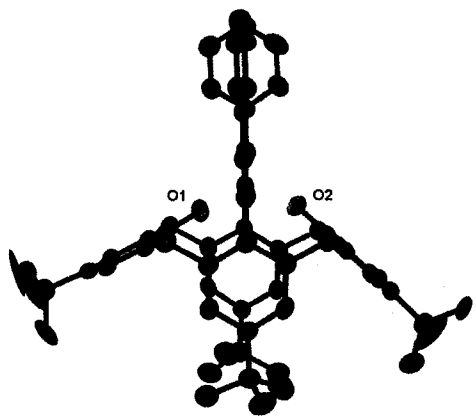
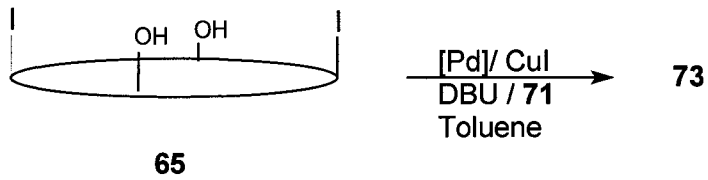


Figure 5.5 X-ray single-crystal ORTEP structural representation of **73** (all of the Hatoms have been removed for clarity).

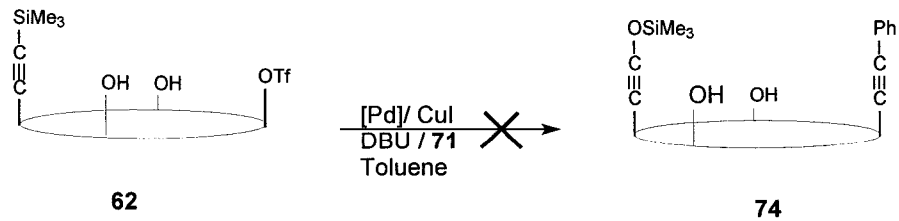
The best yields of **72** and **73** (11% and 64%, respectively) that we obtained required the use of 5 mol % of both the Pd catalyst and the cocatalyst CuI, with 3 molar equiv of DBU, in refluxing toluene. When several other reaction condition modifications recently described by others[38] were tried with bistriflate **42** and **71**, they all failed to produce any of the desired calixarene coupling products, affording instead only 1,4-diphenyl-1,3-butadiyne and recovered unreacted

starting material **42**. However, in contrast to the reactions of TMSA or **67** or **68** with diiodo **65**, phenylacetylene did produce **73** as the major product with 1,3-diiodo calix[4]arene **65** under the coupling conditions (Scheme 5.24).



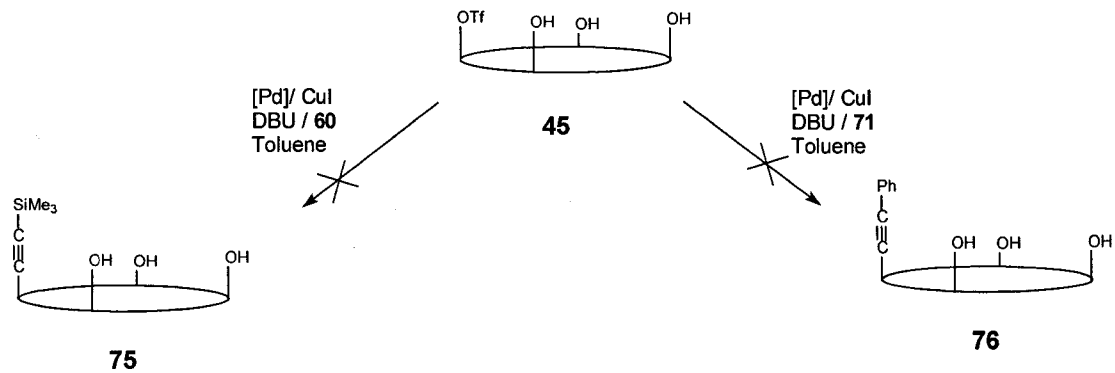
Scheme 5.24 Pd-coupling reaction of **65** with phenylacetylene (**71**)

Pd-CuI-catalysed coupling of **63** with phenylacetylene produced the corresponding mixed bisethynyl product **74** in 54% yield. When the same conditions were used with **62** the expected product **74** was not formed, affording only 1,4-diphenyl-1,3-butadiyne and unreacted **62**. The reasons for this result can only be conjectured at this stage, but a possible explanation is that the steric hindrance due to the presence of both the bulky TMS with the triflate groups on the same calyx[4]arene substrate inhibits the formation of an intermediate in the Sonogashira catalytic cycle,[1] which leads to the formation of **74** in this case (Scheme 5.25).



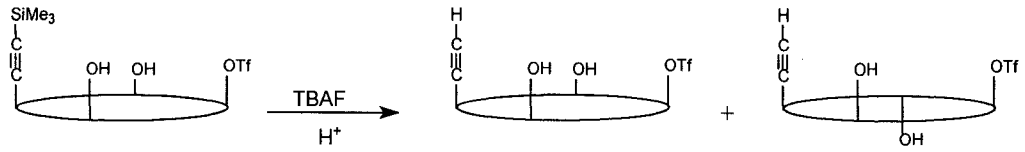
Scheme 5.25 Attempted Pd-coupling of **62** with phenylacetylene

When the monotriflate **45**, instead, was employed to effect the same Pd-assisted Sonogashira coupling with TMSA, none of the desired monocoupling product **75** was obtained, and only 1,4 bis(trimethylsilyl)-1,3-butadiyne and **2** were produced. With **45** and phenylacetylene, only 1,4-diphenyl-1,3-butadiyne and **36** were formed, with none of the expected monophenylethynyl product **76** being detected. As a result of these findings, subsequent narrow-rim transformations were carried out via the synthetically more-accessible bistriflate **44** (Scheme 5.26).



Scheme 5.26 Attempts for the Pd-coupling of **45** with TMSA or phenylacetylene

With synthetically useful amounts of **62** available, removal of the TMS group was easily achieved using one equivalent of tetrabutylammonium fluoride (TBAF), followed by mild acid workup, to afford **77** (Scheme 5.27).



62 **77** major (*pinched-cone*) **78** minor (*partial cone*)

Scheme 5.27 Removal of the TMS group in **62** by treating it with TBAF

The ^{1}H NMR spectrum of **77** revealed, in addition to other signals due to a minor component (see discussion below), two sets of AB quartets centered at δ 3.87 and 4.02 ppm due to the bridging methylene groups and three singlets at δ 0.90, 0.98 and 1.35 in a ratio of 1:1:2, respectively, due to the *tert*-butyl groups. This is consistent with a structure that is in a similar *pinched-cone* conformation to those observed for **62**, **63**, and **73**.

A single-crystal X-ray structure, however, showed a distinct unusual *partial-cone* (*paco*) conformation (Figure 5.6). The ^{1}H NMR spectrum of this compound would be expected to have revealed four singlets for the *tert*-butyl groups, which is not the case. It is therefore possible that **77** crystallizes out in a different conformation (i.e., *paco*-**78**) than that which predominantly exists in solution (a similar behavior was observed for **64** which was described earlier in this chapter). To support this hypothesis it has been calculated that difference in computed (MMFF)[37] free energies between the *paco* and *pinched-cone* conformations is only 1.2 kcal mol^{-1}. The mass and NMR spectra of a trace minor component

formed along with **77** is consistent with the presence of the 1,3-*alternate* conformational isomer, **78**.

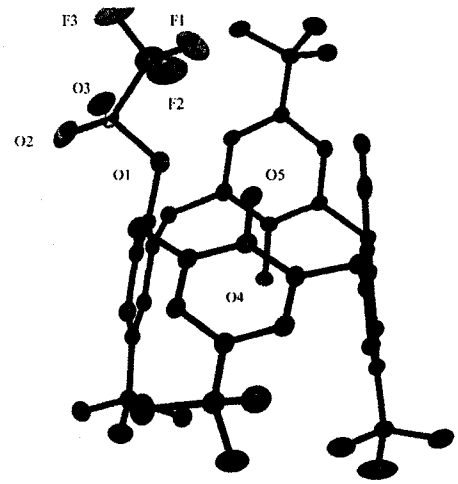
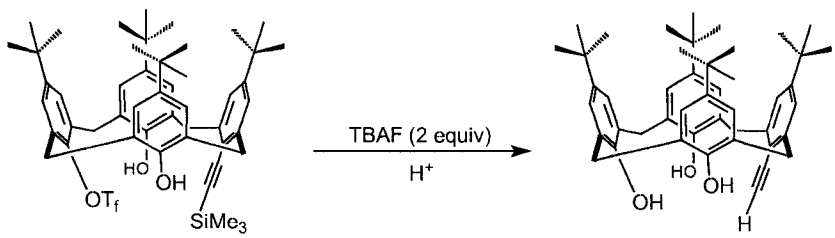


Figure 5.6 X-ray single-crystal ORTEP structural representation of *paco*-**78** in *a partial cone* conformation

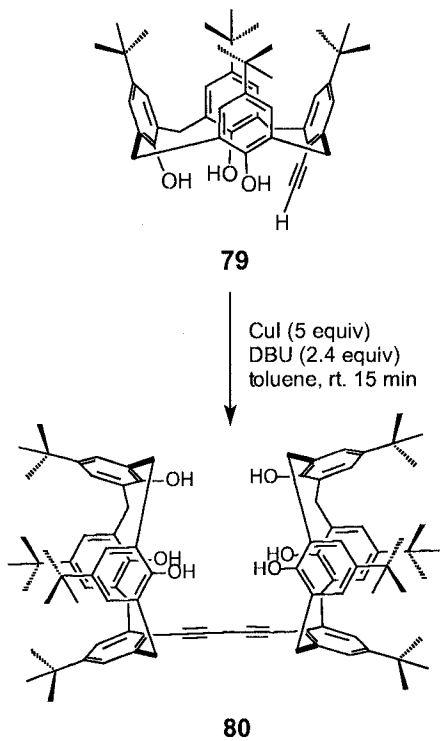
Treatment of **62** with 2 equiv of TBAF, followed by mild acid workup, resulted in both the removal of the TMS group and cleavage of the triflate group to afford the trihydroxy-ethynyl calixarene **79** (Scheme 5.28). The ^{1}H NMR spectrum of **79** showed similarities to those of all of the other major products formed in this study; however, no crystals suitable for X-ray analysis could be obtained.

Compound **79** was next subjected to Glaser homocoupling conditions[41] in order to produce the desired narrow-rim monobutadiyne-bridged biscalix[4]arene **80**. The spectroscopic and mass properties of **80** are consistent with the proposed structure (Scheme 5.29).



62 79

Scheme 5.28 Removal of TMS and triflate groups in compound **62**



Scheme 5.29 Synthesis of the bis-calix[4]arene **80**

The ^{1}H NMR spectrum of **80** reveals signals that are consistent for each calixarene unit being in a *cone*-like conformation. The lowest energy conformation predicted by MMFF molecular modeling calculations[42] is one in

which the two calixarenes, each of which is in a *pinched-cone* conformation, are situated directly above (eclipse) each other, most likely as a result of hydrogen-bonding that can occur between the hydroxy groups of each calixarene unit. The *intra*calixarene O---H bond distances are 1.67 and 1.73 Å, with the closest O---H and O---O bond distances between the two calixarene units being 2.53 and 2.84 Å, respectively. The rigid butadiyne linkage provides a linear "spine" connecting the two calixarene units (Figure 5.7).

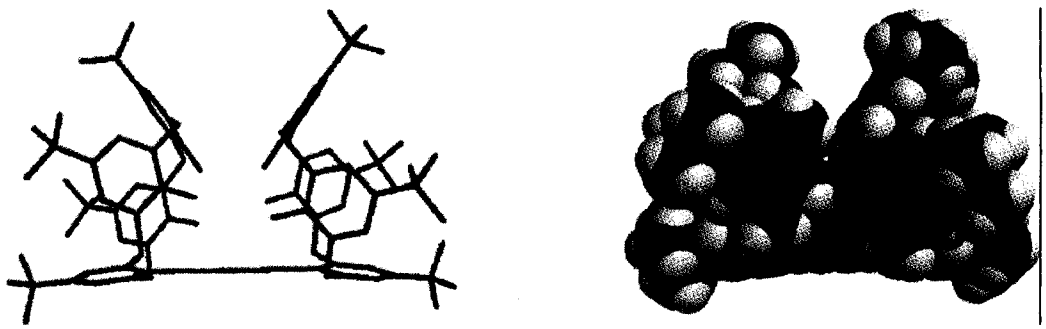
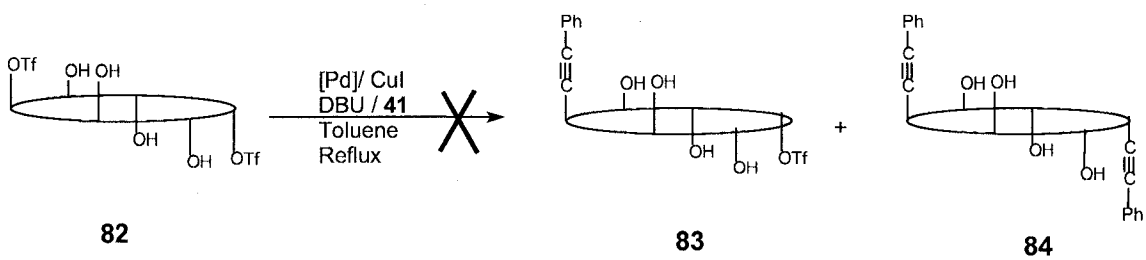


Figure 5.7 Computer-generated (MMFF-minimized) structure of butadiyne-bridged biscalix[4]arene **80** showing the relative orientation of the two calixarene units which are joined by the butadiyne backbone. *Left*: H atoms have been omitted from the structure for clarity. *Right*: space-filling representation of the same minimized structure

In order to examine the Pd-catalytic chemistry on higher calixarenes, such as *p-tert*-butyl calix[6]arene (**81**) the 1,3,5-tristriflate *p-tert*-butylcalix[6]arene (**82**) was prepared according to a procedure used previously by the Georghiou[43]

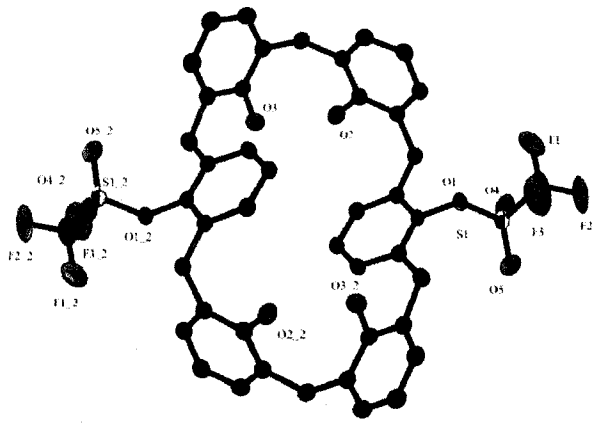
group, by reacting **81** with a mixture of triethylamine and trifluromethanesulfonic anhydride in CH_2Cl_2 at room temperature. This procedure was found to be more convenient than that of Csók et al.[44] who used pyridine instead of triethylamine as the base. Although **82** had been reported previously, no X-ray data were available for this compound. During the course of this research however, an X-ray crystal structure of this compound was solved, and is shown in Figure 5.8 This structure showed that **82** adopts an "uudduudd" or *1,2,3-alternate-like* conformation in the solid sate in which the two *distal* triflates are *anti* to each other.

When coupling of **82** with phenylacetylene (**41**) was attempted by employing the same reaction conditions that were used to produce **64** and **65**, none of the desired coupling products **83** or **84** were detected. Only 1,4-bis(trimethylsilyl)-1,3-butadiyne and recovered **82** was obtained (Scheme 5.30).



82 **83** **84**

Scheme 5.30 Pd-coupling of the bistriflate **82** with phenylacetylene (**71**)



82

Figure 5.8 X-ray single-crystal ORTEP structural representation of **82**, showing it to be in an "uudduudd" or *1,2,3-alternate-like* conformation

5.3- Complexation Studies

Preliminary complexation tests with **80** were conducted individually with NaI, KI, RbI, or $HgCl_2$ in 1:1 methanol-d_4 / $CDCl_3$; with tetramethylammonium chloride or CF_3CO_2Ag in neat $CDCl_3$; with $AgBF_4$ or $AgClO_4$ in $CDCl_3$/acetone-d_6; with CD_3CN or hexamethylbenzene in $CDCl_3$; or with C_{60} in CS_2 or toluene-d_8 solutions. As determined by ^1H NMR spectroscopy, no significant complexation was discerned with any of these cationic or neutral guests.

5.4- Conclusions

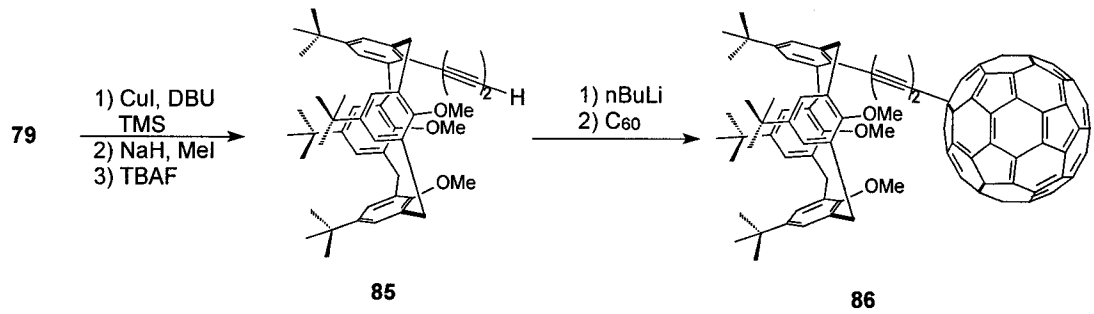
The results described in this chapter have shown for the first time that the Pd-catalysed Sonogashira reaction can now be extended to the direct functionalization of the narrow rim of a calix[4]arene. While undoubtedly modifications in the future might lead to better synthetic yields, the reactions demonstrated in this chapter show that reasonably useful synthetic yields of the

narrow-rim alkynyl derivatives can indeed be obtained. Phenylacetylene is clearly the most reactive of the terminal alkynes examined in this study and also appears to be the most robust under the reaction conditions. Preliminary studies have thus far failed to reveal any significant complexation properties for a new biscalix[4]arene. This compound represents the first example of a biscalixarene which has been formed by directly linking two calixarenes at their narrow rims via potentially modifiable hydrocarbon groups. Thus, the molecular architectures of calixarenes can now be further elaborated using the synthetic routes which have described in this chapter.

5.5- Suggestions for Future Work

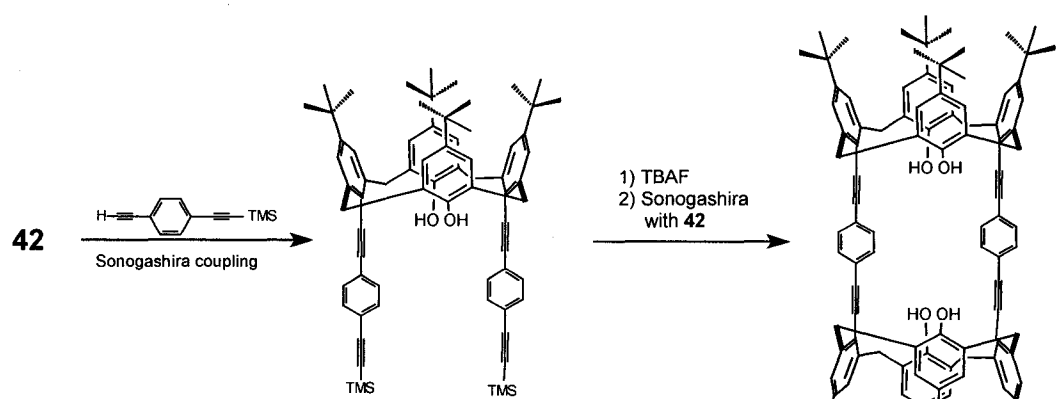
The following are suggestions for future work which builds upon the findings described in this chapter:

1. The Sonogashira coupling reactions should be extended to the higher calix[n]arene analogues (n = 6 and 8).
2. Further elaborations on some of the derivatives described in this chapter could be useful. For example, the mono alkynyl-substituted compound **79** can be extended or modified and then reacted with C_{60} to give the corresponding functionalized fullerene-calixarene as shown below in Scheme 5.31.
3. A double-linked biscalix[4]arene **88** which can be obtained from **87** may be attempted using the same methodology described in this chapter starting from **42** as shown in Scheme 5.32.



85 86

Scheme 5.31 The proposed synthesis for a functionalized fullerene-calixarene **86** as a targeted product for a future work.

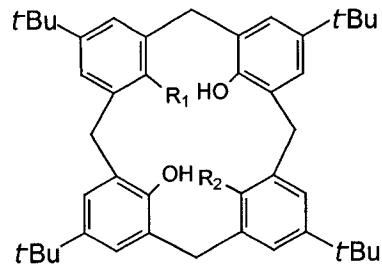


87 88

Scheme 5.32 The proposed synthesis for double-linked biscalix[4]arene **88** as a targeted product for a future work.

5.6- Experimental

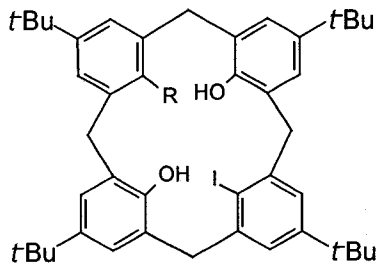
For general experimental information see Chapter 2, page 46.



62: R_1 = C≡C–Si$(CH_3)_3$, R_2 = OTf
63: R_1 = C≡C–Si$(CH_3)_3$, R_2 = I

(Trimethylsilyl)ethynyl *tert*-butylcalix[4]arene triflate 62 and (trimethylsilyl)ethynyl *tert*-butylcalix[4]arene iodide 63. To a mixture of $PdCl_2(PPh_3)_2$ (0.77 mg, 0.0011 mmol), CuI (42 mg, 0.22 mmol), and **42** (100 mg, 0.11 mmol) heated at reflux in toluene (10 mL) and with stirring was added a solution of DBU (30 mg, 0.20 mmol) and **60** (26 mg, 0.26 mmol) in toluene (5 mL). The reaction mixture was stirred for a further 0.5 h at the reflux temperature. The solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (20 mL), washed with aqueous saturated NH_4Cl (10 mL) and then with water (10 mL). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator. The crude product was purified by PLC (1:9 acetonitrile/hexanes) to give the following compounds: **62** (41 mg, 44 %); ^1H NMR: δ 0.39 (s, 9H), 0.78 (s, 9H), 0.93 (s, 9H),1.35 (s, 18H), 3.40 (d, J = 13.5 Hz, 2H), 3.64 (d, J = 14.0 Hz, 2H), 4.36 (d, J

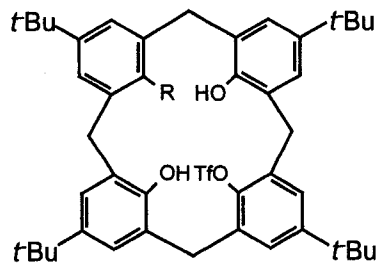
= 13.5 Hz, 2H), 4.42 (d, *J* = 14.0 Hz, 2H), 5.42 (s, 2H, OH), 6.62 (s, 2H), 6.80 (s, 2H), 7.14 (s, 4H), 7.14 (s, 2H); ^{13}C NMR δ -0.01, 14.2, 21.3, 30.8, 30.9, 31.9, 34.1, 34.6, 36.7, 60.6, 103.2, 106.1, 117.1, 124.4, 125.6, 125.6, 126.5, 127.1, 129.1, 132.9, 141.4, 142.5, 142.7, 149.3, 150.77, 152.4; MS (APCI+) *m/z* calcd for $C_{50}H_{63}O_5SiF_3S$ 861.1, found 861.3 (M+). **63** (40 mg, 43%): ^{1}H NMR δ 0.42 (s, 9H), 0.78 (s, 9H), 0.99 (s, 9H), 1.39 (s, 18H), 3.60 (d, *J* = 14.0 Hz, 2H) 3.71 (d, *J* = 14.0 Hz, 2H), 4.53 (d, *J* = 13.5, Hz, 2H), 4.55 (d, *J* = 13.5, Hz, 2H), 5.23 (s, 2H, OH), 6.55 (s, 2H), 6.81 (s, 2H), 7.17 (s, 4H); ^{13}C NMR δ 0.04, 14.4, 30.9, 31.9, 33.8, 34.2, 34.5, 37.0, 44.5, 103.5, 104.5, 105.9, 118.3, 124.1, 125.5, 125.6, 125.8, 128.0, 130.0, 137.5 141.6, 142.5, 143.3, 149.4, 151.6; MS (APCI+) *m/z* calcd for $C_{49}H_{63}O_2ISi$ 839.03, found 839.3 (M+).



64: R = OTf
65: R = I

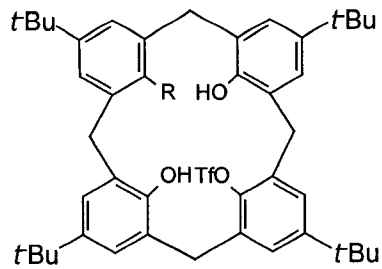
Iodo-*p*-*tert*-butylcalix[4]-arene triflate 64 and diiodo-*p*-*tert*-butylcalix[4]-arene 65. To a stirred mixture of $PdCl_2(PPh_3)$ (0.008 g, 0.011 mmol), CuI (0.12 g, 0.63 mmol), and DBU (0.03 g, 0.20 mmol) in toluene (25 mL) was added a solution of **3** (0.10 g, 0.11 mmol) in toluene (15 mL) over a period of 1.0 h. The reaction mixture was then stirred for a further 3.0 h at room

temperature. The solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (40 mL) and washed with aqueous saturated NH_4Cl (15 mL) and then with water (20 mL). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator. The crude product was purified by PLC (1:9 acetonitrile / hexanes) to give the following compounds: **64** (14 mg, 14 %): mp 298-300 °C; ^{1}H NMR δ 0.92 (s, 9H), 0.99 (s, 9H), 1.33 (s, 18H), 3.52 (d, *J* =14.0 Hz, 2H), 3.84 (d, *J* = 14.5 Hz, 2H), 4.07 (s, 2H, OH), 4.22 (d, *J* =14.0 Hz, 2H), 4.32 (d, *J* = 14.5 Hz, 2H), 6.77 (s, 2H), 6.85 (s, 2H), 7.19 (s, 2H), 7.20 (s, 2H); ^{13}C NMR δ 30.9, 31.1, 31.85, 33.4, 34.1, 34.2, 34.4, 45.1, 104.1, 125.9, 126.2, 127.2, 127.5, 127.9, 128.2, 132.2, 133.3, 142.2, 143.0, 143.3, 150.6, 150.7, 151.0; MS (APCI+) *m/z* calcd for $C_{44}H_{54}F_3IO_5S$ 890.9, found 890.3 (M+). **65** (60 mg, 64%): mp 235-238 °C; ^{1}H NMR δ 1.06 (s, 18H), 1.34 (s, 18H), 3.89 (d, *J* = 13.5 Hz, 4H), 4.03 (s, 2H, OH), 4.16 (d, *J* = 13.5 Hz, 4H), 6.93 (s, 4H), 7.21 (s, 4H); ^{13}C NMR δ 31.1, 31.9, 34.2, 45.6, 103.0, 126.4, 127.4, 128.6, 142.0, 143.9, 150.5, 151.8; MS (APCI+) *m/z* calcd for $C_{44}H_{54}O_2I_2$ 868.7, found 868.0 (M+).



69: R = C≡C–CH_2CH_2OH

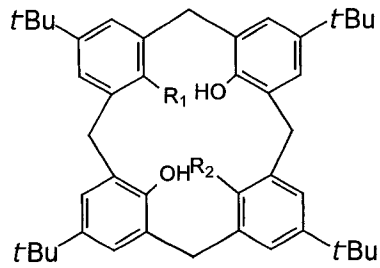
4-Hydroxybutynyl-*p-tert*-butylcalix[4]arene triflate 69. To a stirred mixture of **42** (0.050 mg, 0.055 mmol), CuI (0.520 mg, 0.003 mmol), and $PdCl_2(PPh_3)_2$ (0.770 mg, 0.001 mmol) in toluene (5 mL) was added a solution of 3-butyn-1-ol (**67**) (8.4 mg, 0.12 mmol) and DBU (0.03 mg, 0.20 mmol) in toluene (5 mL) at reflux temperature in toluene (5 mL). The reaction mixture was stirred for a further 2 h at the reflux temperature. The solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (10 mL) and washed with aqueous saturated NH_4Cl (5 mL) and then with water (5 mL). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude product was purified by PLC (6:1 petroleum ether / THF) to give **69** (14.5 mg, 32 %): mp 206-209 °C; ^{1}H NMR δ 0.82 (s, 9H), 0.95 (s, 9H), 1.35 (s, 18H), 2.84-2.81 (m, 2H), 3.00 (s, 1H, OH), 3.45 (d, *J* = 13.5 Hz, 2H), 3.64 (d, *J* = 13.5 Hz, 2H), 3.95-3.94 (m, 2H), 4.30 (d, *J* = 14.5 Hz, 2H), 4.45 (d, *J* = 14.5 Hz, 2H), 5.10 (s, 2H, OH), 6.68 (s, 2H), 6.82 (s, 2H), 7.15 (s, 2H), 7.17 (s, 2H); ^{13}C NMR δ 24.6, 30.9, 30.9, 31.9, 31.9, 32.5, 34.2, 37.1, 34.5, 61.3, 80.0, 98.9, 117.7, 125.7, 126.0, 126.9, 128.3, 129.3, 133.0, 133.3, 141.4, 142.6, 143.6, 149.8, 150.3, 151.7 (one missing carbon from the aromatic region); MS (APCI+) *m/z* calcd for $C_{49}H_{59}O_6F_3S$ 833.1, found 833.2 (M+).



70: R = $-C{\equiv}C-(CH_2)_3CH_2OH$

6-Hydroxyhexynyl-*p-tert*-butylcalix[4]arene triflate 70. To a stirred mixture of **42** (0.050 g, 0.055 mmol), CuI (0.52 mg, 0.27 mmol), and $PdCl_2(PPh_3)_2$ (0.770 mg, 0.001 mmol) in toluene (5 mL) was added a solution of hexyn-1-ol (**68**) (11.8 mg, 0.120 mmol) and DBU (0.03 g, 0.20 mmol) in toluene (5 mL) at reflux temperature in toluene (5 mL). The reaction mixture was stirred for a further 2 h at the reflux temperature. The solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (10 mL) and washed with aqueous saturated NH_4Cl (5 mL) and with water (5 mL). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude product was purified by PLC (9:1 petroleum ether / THF) to give **70** (9.5 mg, 20 %): mp 193-195 °C; ^{1}H NMR δ 0.79 (s, 9H), 1.04 (s,9H), 1.32 (s, 18H), 2.01-1.91 (m, 2H), 2.23-2.21 (m, 2H), 2.40-2.39 (m, 2H), 3.37 (d, *J* = 13.0 Hz, 2H), 3.49 (d, *J* = 14.5 Hz, 2H), 3.95 (d, *J* = 14.5 Hz, 2H), 4.18-4.15 (m, 2H), 4.41 (d, *J* = 13.0 Hz, 2H), 6.65 (s, 2H), 6.66 (s, 2H), 6.92 (s, 2H, OH), 7.06 (s, 2H), 7.16 (s, 2H); ^{13}C NMR δ 18.4, 21.3, 24.9, 29.0, 30.9, 31.2, 31.9, 32.2, 32.3; 34.1, 34.4, 69.4, 84.10,117.9, 120.4, 125.0, 125.7, 126.0, 126.4,

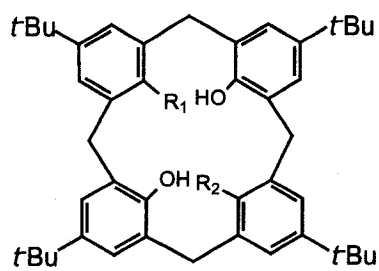
126.5, 129.1, 132.3, 133.3, 142.3, 148.0, 149.1, 150.5 MS (APCI+) *m/z* calcd for $C_{51}H_{63}F_3O_6S$ 861.4, found 861.3 (M+).



72: R_1 = OTf, R_2 = $-C{\equiv}C-C_6H_5$
73: $R_1 = R_2 = -C{\equiv}C-C_6H_5$

Phenylethynyl-*p-tert*-butylcalix[4]arene triflate 72 and bis(phenylethynyl) *p-tert*-butylcalix[4]arene 73. To a stirred mixture of $PdCl_2(PPh_3)_2$ (8.0 mg, 0.01 mmol), CuI (0.10 g, 0.53 mmol) and **42** (0.10 mg, 0.11 mmol) in toluene (30 mL) was added a solution of DBU (0.07 g, 0.46 mmol) and phenylacetylene (**71**) (26 mg, 0.26 mmol) in toluene (10 mL) at reflux temperature. The reaction mixture was stirred for a further 4 h at the reflux temperature. The solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (40 mL) and washed with aqueous saturated NH_4Cl (15 mL) and then with water (20 mL). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude product was purified by PLC (3:7 CH_2Cl_2 / petroleum ether) to give the following compounds: **72** (13 mg, 14%): mp >310 °C; ^{1}H NMR δ 0.92 (s, 9H), 1.02 (s, 9H), 1.28(s, 18H), 3.58 (d, *J* =14.0 Hz, 2H), 3.68 (d, *J* = 14.5 Hz, 2H), 4.39 (d, *J* = 14.0 Hz, 2H),

4.47 (d, *J* = 14.5 Hz, 2H), 4.92 (s, 2H, OH), 6.79 (s, 2H), 6.90 (s, 2H), 7.13 (s, 2H), 7.14 (s, 2H), 7.36-7.35 (m, 3H), 7.56-7.54 (m, 2H), ^{13}C NMR δ 31.0, 31.1, 31.7, 31.8, 34.1, 34.54, 36.6, 37.7, 86.8, 98.4, 118.6, 123.3, 123.4, 124.7, 126.0, 126.4, 126.5, 127.8, 128.4, 128.6, 130.7, 131.9, 137.8, 142.0, 142.4, 148.5, 151.2, 151.4; MS (APCI+) *m/z* calcd for $C_{53}H_{59}F_3O_5S$ 865.10, found 865.4 (M+). **73** (60.0 mg, 67%): mp 241-244 °C; ^{1}H NMR δ 0.92 (s, 18H), 1.33 (s, 18H), 3.61(d, *J* = 14.0 Hz, 4H), 4.64 (d, *J* = 14.0 Hz, 4H), 5.51 (s, 2H, OH), 6.76 (s, 4H), 7.12-7.09 (m, 4H), 7.16 (s, 4H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR 30.9, 32.0, 34.2, 34.4, 37.1, 87.3, 97.6, 119.0, 123.5, 124.4, 125.7, 128.2, 128.4, 128.6, 131.7; 141.7, 142.4, 151.0, 151.4 MS (APCI+) *m/z* calcd for $C_{60}H_{64}O_2$ 817.2, found 817.5 (M+).

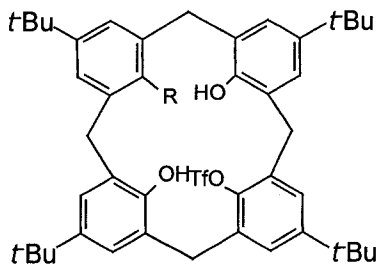


74

R_1 = –C≡C–Si$(CH_3)_3$, R_2 = –C≡C–C_6H_5

(Trimethylsilyl)ethynyl-phenylethynyl-*p-tert*-butylcalix[4]arene 74. To a mixture of $PdCl_2(PPh_3)_2$ (1.7 mg, 2.4 μmol), CuI (0.45 mg, 2.4 μmol), and **63** (0.040 g, 0.048 mmol) heated at reflux in toluene (3.0 mL) and with stirring was

added a solution of DBU (14.6 mL, 0.096 mmol) and **71** (6.0 mL, 55 μmol) in toluene (2.0 mL). The reaction mixture was stirred for a further 3.0 h at the reflux temperature. The solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (5.0 mL) and washed with aqueous saturated NH_4Cl (5.0 mL) and then with water (5.0 mL). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent was removed under vaccum. The crude product was purified by PLC (CH_2Cl_2 / petroleum ether 3:7) to give **74** (21 mg, 54 %): ^{1}H NMR δ 0.04 (s, 9H), 0.84 (s, 9H), 0.86 (s, 9H), 1.36 (s, 18H), 1.55 (s, 18H), 3.51 (d, *J* = 13.5 Hz, 2H), 3.59 (d, *J* = 13.5 Hz, 2H), 4.57 (d, *J* = 13.5, 2H), 4.74 (d, *J* = 13.5, 2H), 5.46 (s, 2H, OH), 6.66 (s, 2H), 6.66 (s, 2H), 7.13 (s, 2H), 7.16 (s, 2H), 7.34-7.32. (m, 3H), 7.63-7.61 (m, 2H); ^{13}C NMR δ 0.2, 30.9, 32.0, 34.2, 34.3, 34.4, 36.7, 87.5, 97.4, 103.3, 119.0, 119.1, 124.0, 124.1, 124.2, 125.52, 128.2, 128.5, 128.9, 131.8, 139.8, 141.4, 141.6, 142.3, 150.8, 151.0, 151.4 ; MS (APCI+) *m/z* calcd for $C_{57}H_{68}O_2Si$ 813.3, found 813.6 (M+).

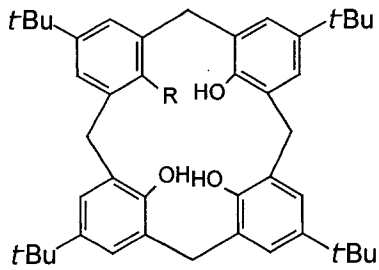


77: R = −C≡C−H (*pinched-cone*)
78: R = −C≡C−H (1,3-*alternate*)

Ethynyl-*p-tert*-butylcalix[4]arene triflates 77 and 78.

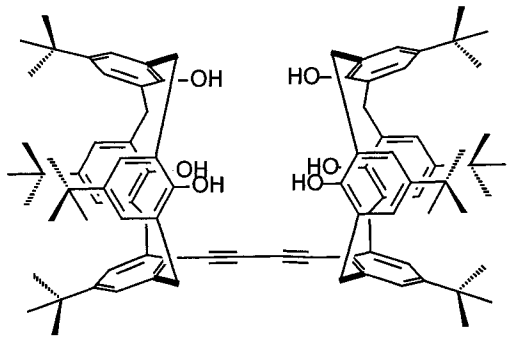
Ethynyl-*p-tert*-butylcalix[4]arene triflates 77 and 78.

To a stirred solution of **80** (0.020 mg, 0.023 mmol) in THF (2.0 mL) was added Bu_4NF (6.00 mg, 0.023 mmol), and the reaction mixture stirred, in a flask open to the air, for a further 15 min at room temperature. The solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (10 mL) and washed with aqueous 10% HCl (5 mL) and then with water (5 mL). The organic solvent was separated and dried over $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator. The crude product was purified by PLC (3:7 CH_2Cl_2 / petroleum ether) to give the following compounds: **77** (9.0 mg, 49%): mp 156-157 °C; ^{1}H NMR δ 0.89 (s, 9H), 0.98 (s, 9H), 1.35 (s, 18H), 3.48 (d, *J* = 14.5 Hz, 2H), 3.67 (d, *J* = 14.5 Hz, 2H), 3.69 (s, 1H), 4.26 (d, *J* = 14.0 Hz, 2H), 4.37 (d, *J* = 14.0 Hz, 2H), 4.66 (s, 2H, OH), 6.76 (s, 2H), 6.86 (s, 2H), 7.17 (s, 2H), 7.18 (s, 2H); ^{13}C NMR δ 30.9, 31.0, 31.1, 31.9, 33.1, 34.2, 34.6, 37.3, 81.2, 87.3, 116.9, 120.1, 124.7, 125.9, 126.7, 127.0, 127.4, 128.3, 133.2, 142.3, 142.6, 142.8, 150.0, 150.7, 152.3; MS (APCI+) *m/z* calcd for $C_{47}H_{55}F_3O_5S$ 789.01, found 789.3 (M+). **78** (traces): ^{1}H NMR δ 0.89 (s, 9H), 1.02 (s, 9H), 1.35 (s, 18H), 3.56 (s, 1H), 3.65 (d, *J* = 14.5 Hz, 2H), 3.77 (d, *J* = 14.0 Hz, 2H), 4.34 (d, *J* = 14 Hz, 2H), 4.35 (d, *J* = 14 Hz, 2H), 4.59 (s, 2H, OH), 6.72 (s, 2H), 6.87 (s, 2H), 7.14 (s, 2H), 7.19 (s, 2H); ^{13}C NMR δ 31.0, 31.0, 31.9, 34.0, 34.2, 34.6, 37.7, 44.8, 57.6, 81.4, 9.76, 104.9, 117.1, 124.7, 125.9, 126.6, 127.2, 128.7, 142.2, 142.5,143.6, 150.0, 151.5, 151.7; MS (APCI+) *m/z* calcd for $C_{47}H_{55}F_3O_5S$ 789.0, found 789.5 (M+).



79: R = –C≡C–H

Ethynyl-*p-tert*-butylcalix[4]arene 79. To a stirred solution of **62** (20.0 mg, 0.023 mmol) in THF (5 mL) was added Bu_4NF (12.2 mg, 0.047 mmol) and the reaction stirred for a further 15 min at room temperature in a flask open to the air. The solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (10 mL) and washed with 10% HCl (5 mL) and then with water (10 mL). The organic solvent was separated and dried over $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator. The crude product was purified by PLC (3:7 CH_2Cl_2 / petroleum ether) to give **79** (13 mg, 85%): mp 215-217 °C; ^{1}H NMR δ 1.08 (s, 9H), 1.19 (s, 9H), 1.26 (s, 18H), 3.49 (d, *J* = 14.0 Hz, 2H), 3.67 (d, *J* = 13.5 Hz, 2H), 3.79 (s, 1H, OH), 4.18 (d, *J* = 14.0 Hz, 2H), 4.61 (d, *J* = 13.5 Hz, 2H), 7.00 (s, 2H), 7.01 (s, 4H), 7.13 (s, 2H), 7.83 (bs, 2H, OH); ^{13}C NMR δ 30.9, 31.6, 31.8, 32.8, 34.2, 34.3, 34.7, 36.6, 83.2, 85.2, 116.2, 125.1, 125.7, 125.9, 126.2, 126.9, 127.9, 128.2; 143.2, 143.4, 143.8, 147.3, 149.3, ,152.3; MS (APCI+) *m/z* calcd for $C_{46}H_{56}O_3$ 657.0, found 657.3 (M+).



80

Biscalix[4]arene 80. To a stirred solution of **79** (0.025 mg, 0.038 mmol) and CuI (0.03 mg, 0.16 mmol) in toluene (10 mL) was added a solution of DBU (0.014 mg, 0.091 mmol) in toluene (2 mL) at room temperature. The reaction mixture was stirred for a further 15 min at room temperature. The solvent was evaporated on a rotary evaporator and the resulting crude product was dissolved in CH_2Cl_2 (15 mL) and washed with aqueous 10% HCl (5 mL) and with water (5 mL). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator. The crude product was purified by PLC (1:1 CH_2Cl_2/petroleum ether) to give **80** (17 mg, 68 %): mp 161-164 °C. ^{1}H NMR δ 1.11 (s, 18H), 1.19 (s, 18H), 1.26 (s, 36H), 3.41 (d, *J* = 13.0 Hz, 4H), 3.71 (d, *J* = 13.0 Hz, 4H), 4.29 (d, *J* = 13.0 Hz, 4H), 4.76 (d, *J* = 13.0 Hz, 4H), 7.00 (s, 4H), 7.05 (s, 4H), 7.15 (s, 4H), 8.11(s, 4H, OH), 9.55 (s, 2H, OH); ^{13}C NMR δ 30.9, 31.6, 31.8, 32.9, 34.2, 34.19, 34.9, 36.7, 81.1, 83.4, 116.3, 125.2, 125.8, 126.0, 126.1, 127.2, 128.1, 128.1, 133.9, 143.4, 144.5, 147.6, 149.3, 152.8; MS (APCI+) *m/z* calcd for $C_{92}H_{110}O_6$ 1311.9, found 1312.7 (M+).

5.7- References

1. (a) Sonogashira, K.; Todha, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) For a general review, see: Sonogashira, K. In *Metal Catalysed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 5.

2. Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004,** *104,* 3079.

3. Tour, J. M. *Acc. Chem. Res.* **2000**, *33*, 791.

4. Pugh, V. J.; Hu, Q. –S.; Zuo, X.; Lewis, F. D.; Pu, L. *J. Org. Chem.* **2001,** *66,* 6136.

5. Bunz, U. H. F. *Chem. Rev.* **2000,** *100,* 1605.

6. (a) *Metal-Catalysed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J. Eds.; Wiley-VCH: Weinheim, **1998**; p 203. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (c) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (d) Negishi, E. *Chem. Rev.* **2003**, *103*, 1979.

7. a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**,*16*, 4467. b) Doucet, H.; Hierso, J. C. *Angew. Chem. Int. Ed.* **2007**, *46,* 834.

8. Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280.

9. (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422. (b) Glaser, C. *Ann. Chem. Pharm.* **1870**, *154*, 137.

10. Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.

11. Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chemistry Letters*, **1997**, 1233.

12. Krause, N.; Thorand, S. *J. Org. Chem.* **1998**, *63*, 8551.

13. Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco P. A. *Org. Lett.,* **2002,** *4,* 3199.

14. Mori, A.; Ahmed, M.; Sekitoshi, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, 756.

15. Elangovan, A.; Wang, Y-H.; Ho, T-I. *Org. Lett.* **2003**, *5,* 1841.

16. Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69,* 5752.

17. Liang, Y.; Xie, Y-. X.; Li, J-. H. *J. Org. Chem.* **2006,** *71*, 379.

18. Köllhofer, A.; Plenio, H. *Adv. Synth. Catal.* **2005,** *347*, 1295.

19. Biali, S. E. *Synlett*, **2003**, *1*

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

21. 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

22. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508

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

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

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

26. Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63,* 4726

27. Chowdhury, S.; Zhao, B.; Snieckus, V. *J. Polycyclic Aromat. Compd.* **1994**, *5*, 27

28. Xu, B.; Miao, Y.-J.; Swager T. M. *J. Org. Chem.* **1998**, *63*, 8561.

29. Böhmer, V.; Brusko, V.; Rissanen, K. *Synthesis*, **2002**, 1898.

30. Jokic, D.; Asfari, Z.; Weiss, J. *Org. Lett.* **2002**, *4*, 2129.

31. (a) Armaroli, N.; Accorsi, G.; Rio, Y.; Ceroni, P.; Vicinelli, V.; Welter, R.; Gu, T.; Saddik, M.; Holler, M.; Nierengarten, J.-F. *New J. Chem.* **2004**, *28*, 1627. (b) Hennrich, G.; Murillo, M. T.; Prados, P.; Song, K.; Asselberghs, I.; Clays, K.; Persoons, A.; Benet-Buchholz, J.; de Mendoza, *J. Chem. Commun.* **2005**, 2747. (c) Hennrich, G.; Murillo, M. T.; Prados, P.; Song, K.; Asselberghs, I.; Clays, K.; Persoons, A.; Benet-Buchholzc, J.; de Mendoza J. *Chem. Commun.*, **2005**, 2747.

32. Perez-Balderas, F.; Santoyo-González, F. *Synlett,* **2001**, 1699.

33. Al-Saraierh, H.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem.* **2005**, *70*, 8273.

34. Csók, Z.; Szalontai, G.; Czira, G.; Kollar, L. *Supramol. Chem.***1998**, *10*, 69

35. Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sánchez, C. *J. Org. Chem.* **1991**, *56*, 3372

36. (a) See ref. 15 (b) Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733. (c) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391.

37. Molecular modeling calculations were performed using Spartan '04 for Windows.

38. (a) See ref. 9a (b) Glaser, C. *Ann. Chem. Pharm.* **1870**, *154*, 137.

39. Chowdhury, S. *Ph.D. Dissertation*; Memorial University of Newfoundland: Newfoundland and Labrador, Canada, **2001**, pp. 185.

Appendix: Chapter 5

X-ray Crystal Data for 62: Colourless crystal ($MeOH/CHCl_3$), $C_{50}H_{63}O_5SiF_3S$, monoclinic, space group P-1 (#2), Z = 4, a = 13.218(1) Å, b = 18.086(1) Å, c = 22.432(2) Å, β= 90.743(1)°. V = 5033.1(6) $Å^3$, $D_{Calcd.}$ = 1.136 g cm^{-3}, crystal size = 0.42 X 0.21 X 0.19 mm. Intensity data were measured at -80 ± 1 C° on a Bruker P4/CCD diffractometer with graphite monochromated Mo-Kα (λ = 0.71073 Å) radiation $2\theta_{max}$ = 52.8°; 39051 reflections converged to a final R_{int} of 0.048 for 20502 unique reflections and 1108 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0.070 and 0.221, respectively, and GoF = 1.03.

X-ray Crystal Data for 63: A colorless plate crystal ($MeOH/CHCl_3$) of $C_{50}H_{64}O_2ISiCl_3$, triclinic, space group P-1 (#2), Z = 2, a = 13.1511(9) Å, b = 14.402(1) Å, c = 15.419(1) Å, β= 76.823(1)°. V = 2526.3(3) $Å^3$, $D_{Calcd.}$ = 1.260 g cm^{-3}, crystal size = 0.60 X 0.28 X 0.05 mm. Intensity data were measured at -80 ± 1 C° on a Bruker P4/CCD diffractometer with graphite monochromated Mo-Kα (λ = 0.71073 Å) radiation $2\theta_{max}$ = 52.8°; 17987 reflections converged to a final R_{int} of 0.035 for 10245 unique reflections and 514 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0.064 and 0.180, respectively, and GoF = 1.04.

X-ray Crystal Data for 65: A colorless prism crystal ($MeOH/CHCl_3$) of $C_{44}H_{54}I_2O_2$ of orthorhombic, space group Pcca (#54), Z = 4, a = 18.6685(11) Å,

b = 12.6676(7) Å, c = 17.1276(9) Å, β= 76.823(1)°, V = 4050.4(4) Å^3, $D_{Calcd.}$ = 1.424 g cm^{-3}, crystal size = 0.43 X 0.39 X 0.20 mm. Intensity data were measured on a Rigaku AFC8 diffractometer with graphite monochromated Mo-Kα (λ = 0.71070 Å) radiation $2\theta_{max}$ = 61.6°; 27832 reflections converged to a final R_{int} of 0.024 for 5754 unique reflections and 219 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0.0325 and 0.0810, respectively, and GoF = 1.130.

Prepared by: David O. Miller, Memorial University, Chemistry Department.

X-ray Crystal Data for 73: A colorless prism crystal (MeOH/$CHCl_3$) of $C_{60}H_{64}O_2$ of monoclinic, space group Ia (#9), Z = 4, a = 11.757(4) Å, b = 46.19(1) Å, c = 9.611(3) Å, β= 106.585(5)°, V =5002(2)Å^3, $D_{Calcd.}$ = 1. 085 g cm^{-3}, crystal size = 0.56 x 0.52 x 0.17 mm. Intensity data were measured -80 ± 1 °C on a Bruker P4/CCD diffractometer with graphite monochromated Mo-Kα (λ = 0.71073 Å) radiation $2\theta_{max}$ = 53.5°; 19123 reflections converged to a final R_{int} of 0.062 for 10209 unique reflections and 613 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0.0325 and 0.0810, respectively, and GoF = 1.02.

Prepared by: David O. Miller, Memorial University, Chemistry Department.

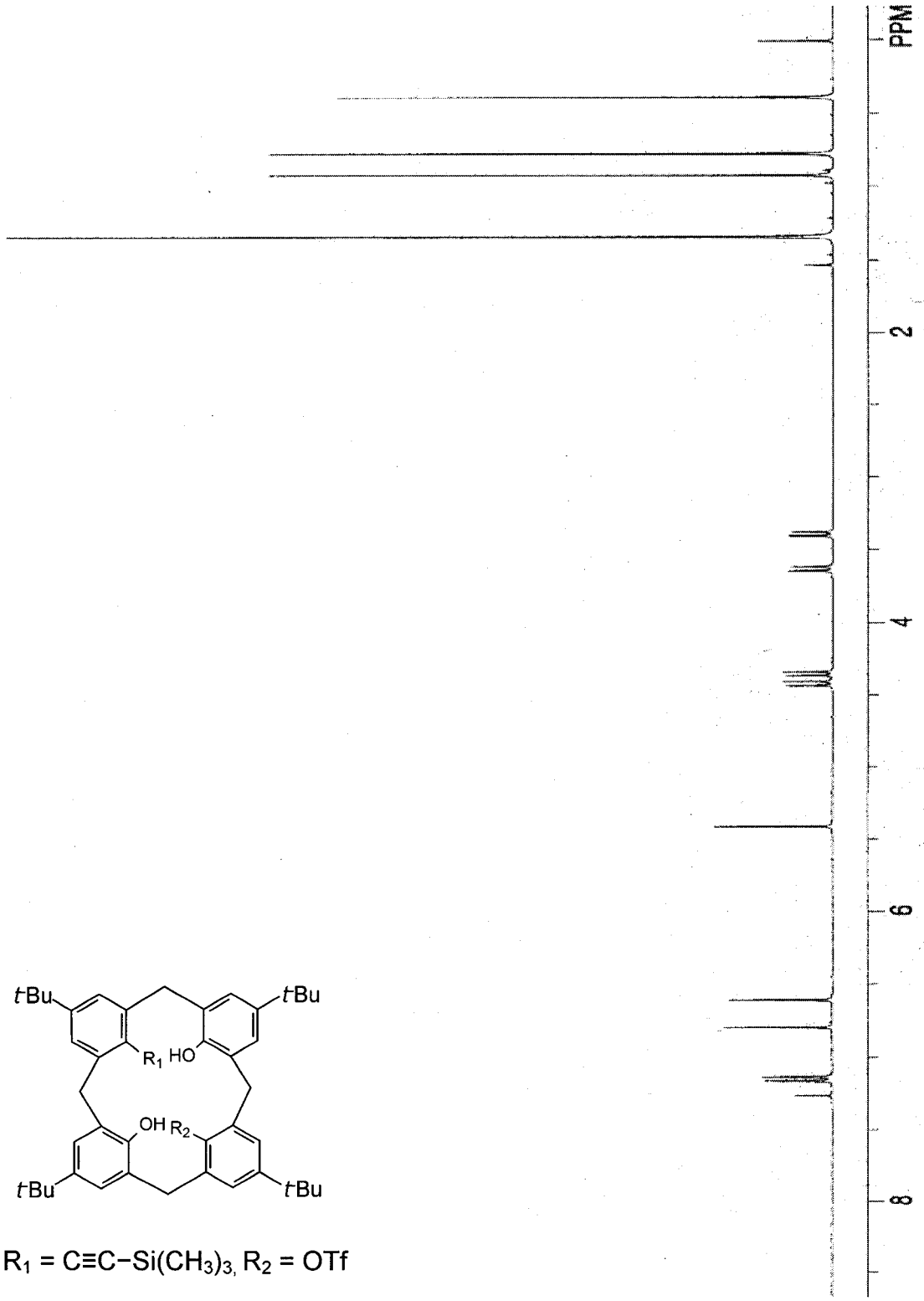
X-ray Crystal Data for *paco*-78: A colorless plate crystal of $C_{47}H_{55}O_5F_3S$ of monoclinic, space group $P2_1/c$ (#14), Z = 4, a = 14.056(1) Å, b = 24.827(2) Å, c =

12.300(1) Å, β= 106.585(5)°, V = 4288.6(6) Å^3, $D_{Calcd.}$ = 1. 222 g cm^{-3}, crystal size = 0.34 X 0.34 X 0.16 mm. Intensity data were measured -80 ± 1 °C on a Bruker P4/CCD diffractometer with graphite monochromated Mo-Kα (λ = 0.71073 Å) radiation $2\theta_{max}$ = 52.9°; 30523 reflections converged to a final R_{int} of 0. 058 for 8789 unique reflections and 509 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0. 106 and 0.294, respectively, and GoF = 1. 13.

Prepared by: David O. Miller, Memorial University, Chemistry Department.

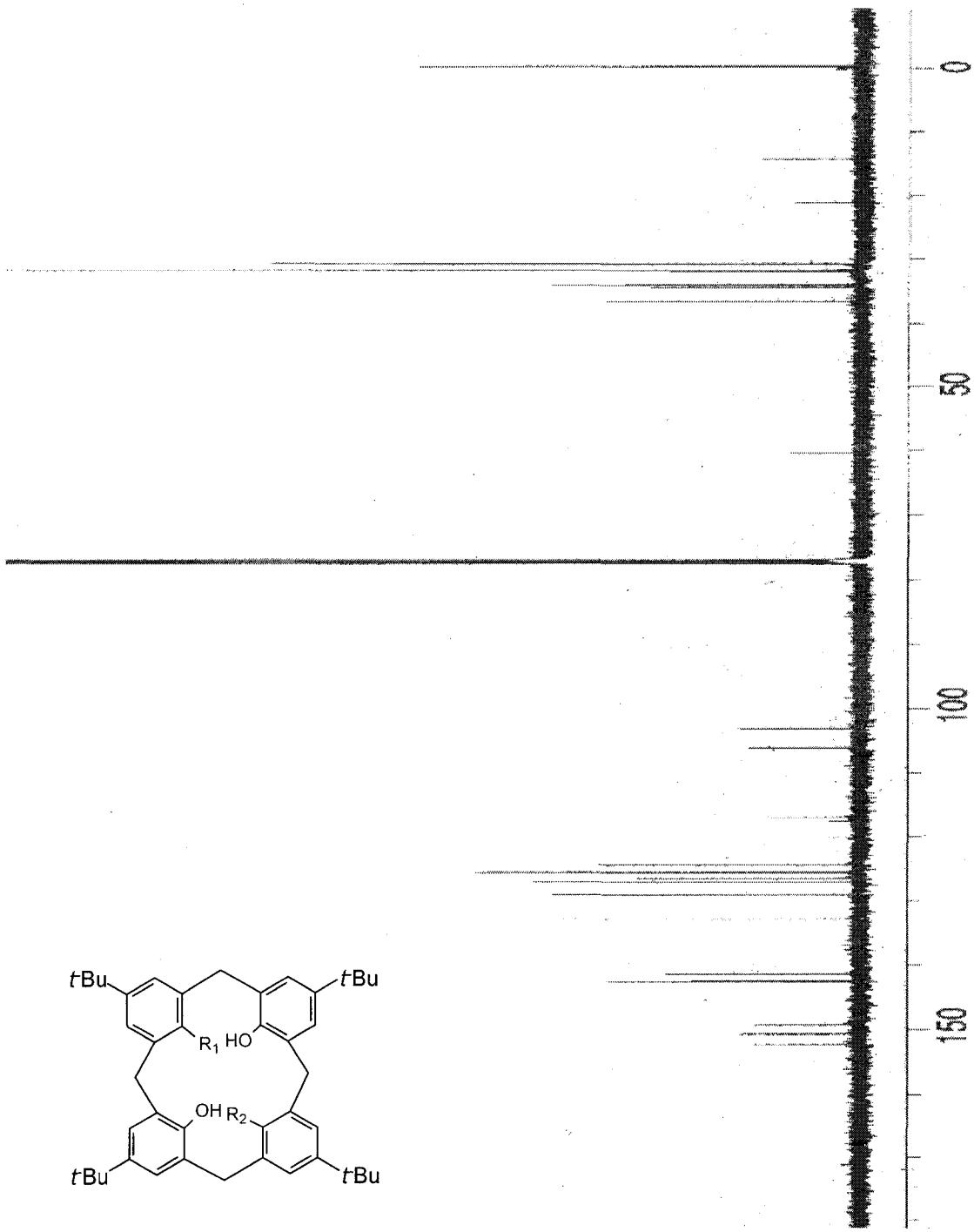
X-ray Crystal Data for 82: A colourless fragment crystal of $C_{74}H_{94}O_{12}S_2F_6$ of primitive triclinic, space group P-1 (#2), Z = 1, a = 14.056(1) Å, b = 12.376(1) Å, c = 13.152(1) Å, β= 84.156(2)°, V =1806.7(3) Å^3, $D_{Calcd.}$ = 1.244 g cm^{-3}, crystal size = 0.34 X 0.34 X 0.16 mm. Intensity data were measured -80 ± 1 °C on a Bruker P4/CCD diffractometer with graphite monochromated Mo-Kα (λ = 0.71073 Å) radiation $2\theta_{max}$ = 52.9°; 30523 reflections converged to a final R_{int} of 0. 058 for 8789 unique reflections and 509 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0. 106 and 0.294, respectively, and GoF = 1. 13.

Prepared by: David O. Miller, Memorial University, Chemistry Department.



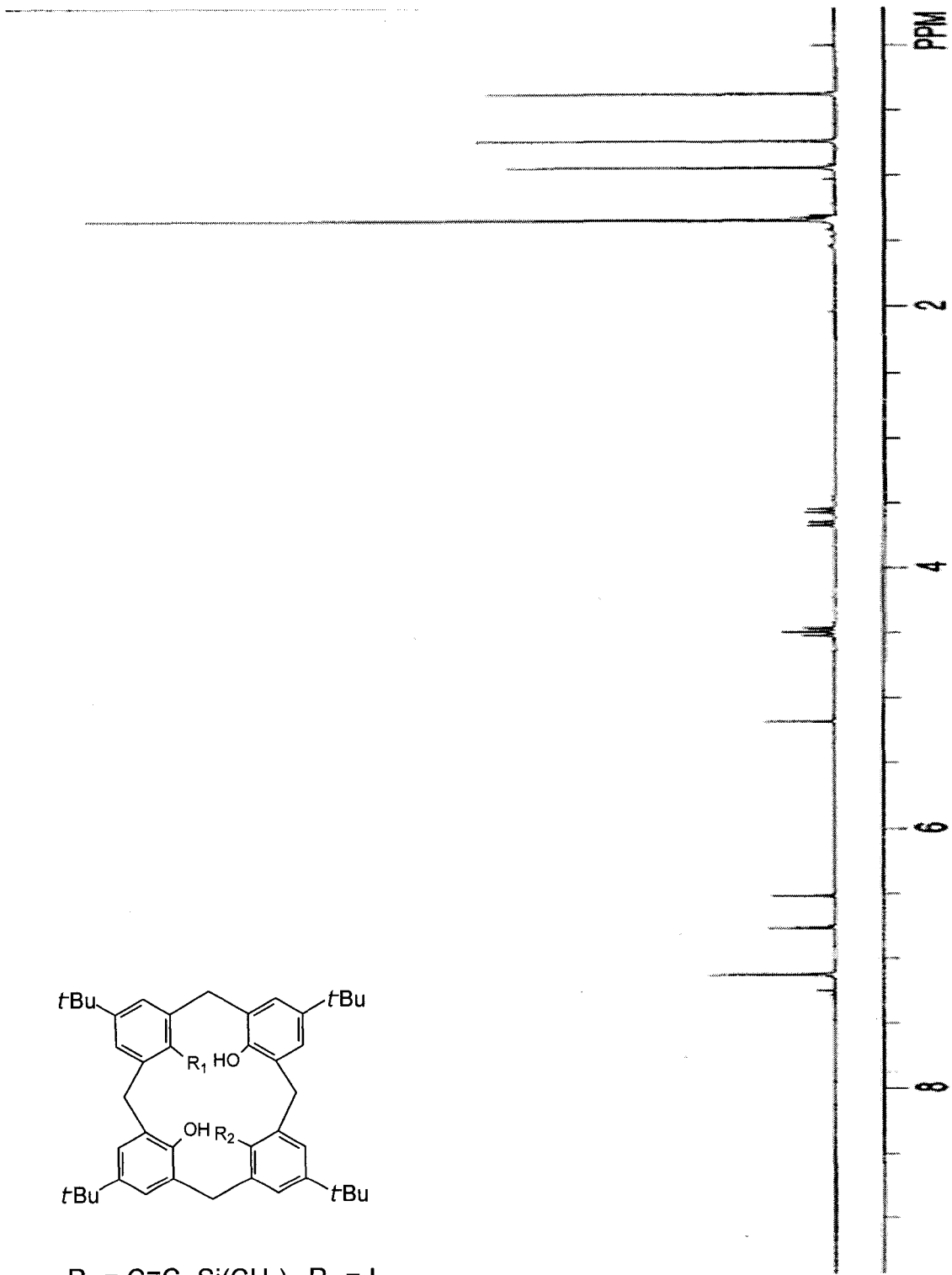
R_1 = C≡C−Si$(CH_3)_3$, R_2 = OTf

^{1}H NMR spectrum for compound **62**



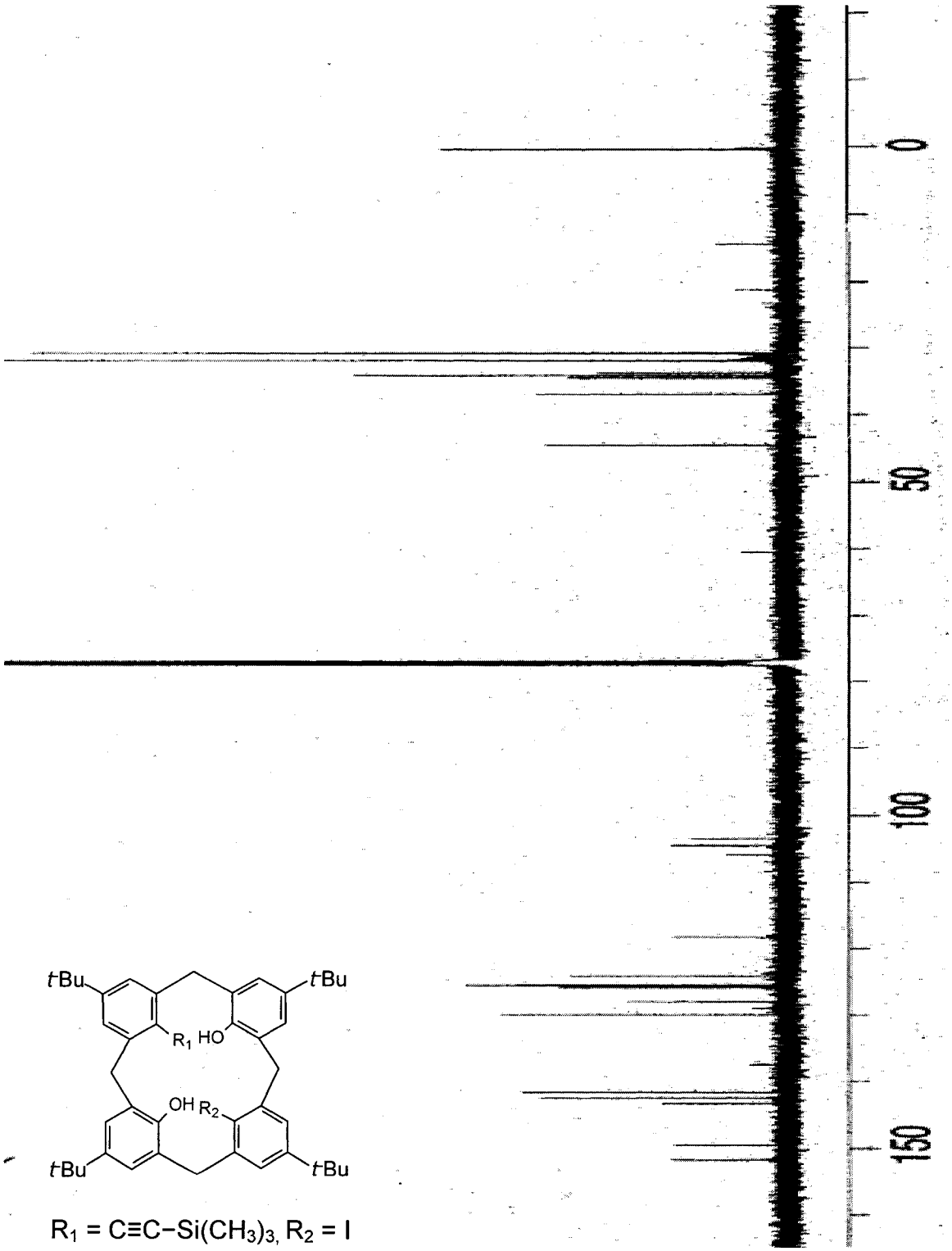
R_1 = C≡C−Si$(CH_3)_3$, R_2 = OTf

^{13}C NMR spectrum for compound **62**



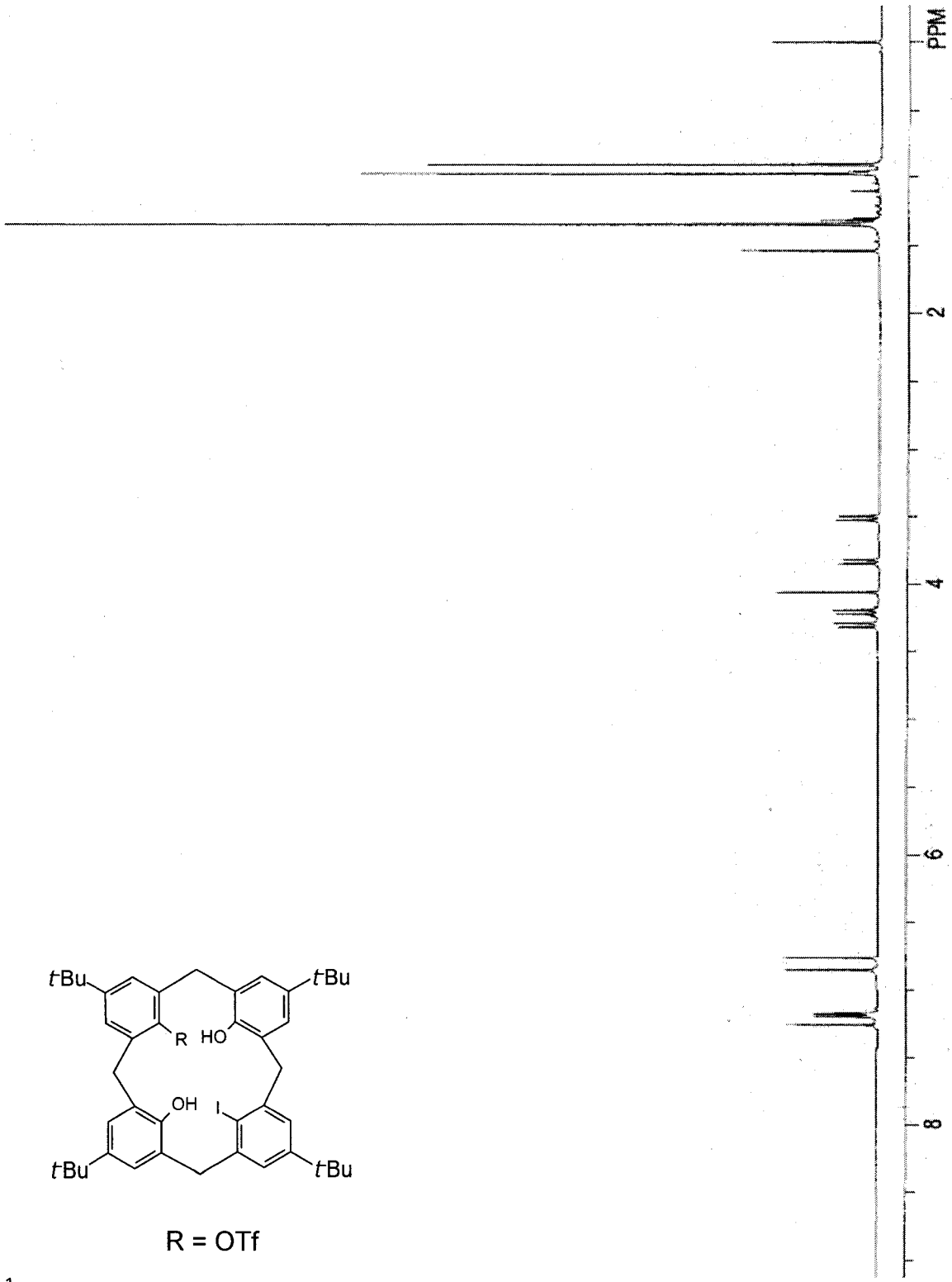
R_1 = C≡C−Si$(CH_3)_3$, R_2 = I

^{1}H NMR spectrum for compound **63**



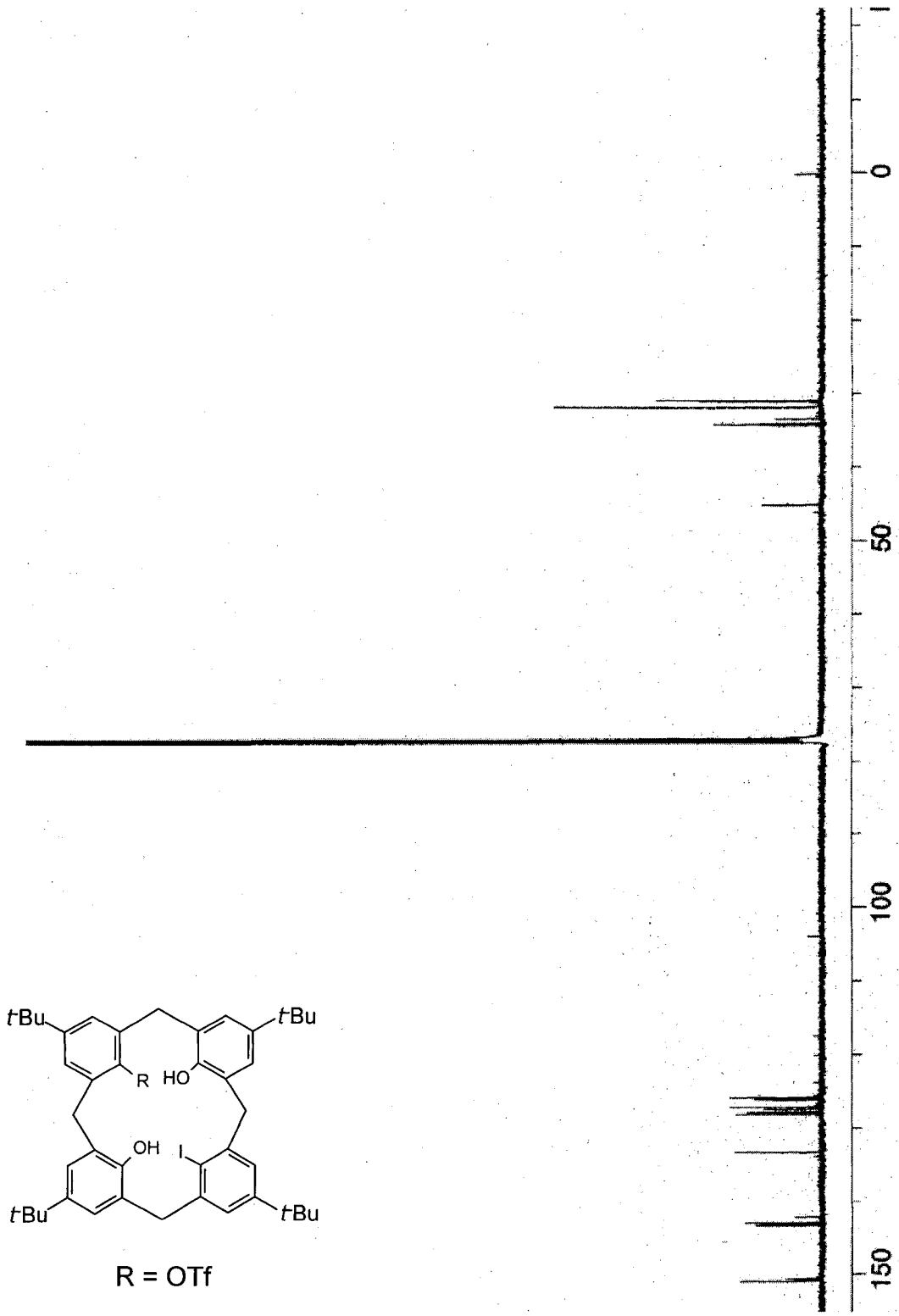
R_1 = C≡C−Si$(CH_3)_3$, R_2 = I

^{13}C NMR spectrum for compound **63**



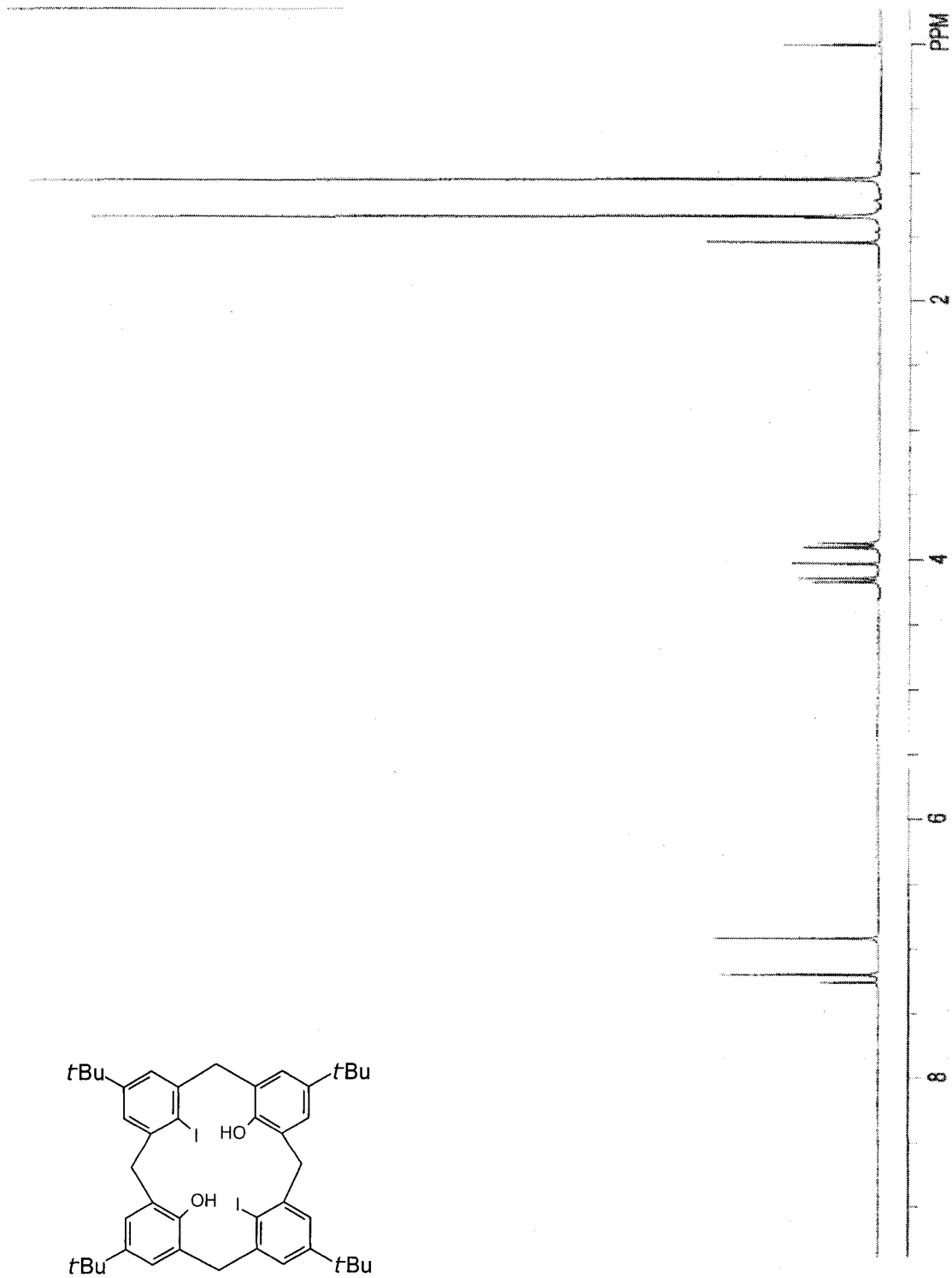
R = OTf

^{1}H NMR spectrum for compound **64**

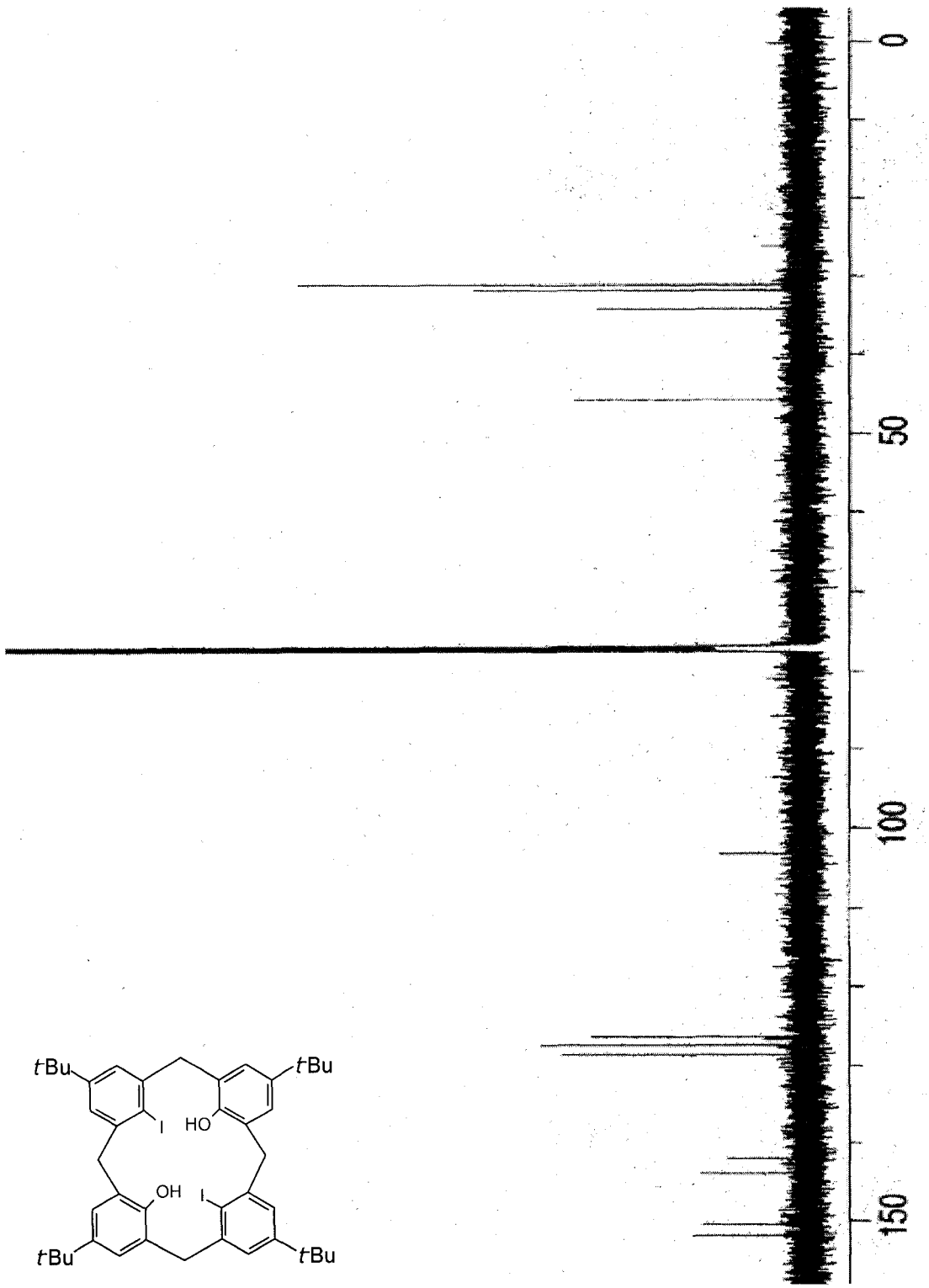


R = OTf

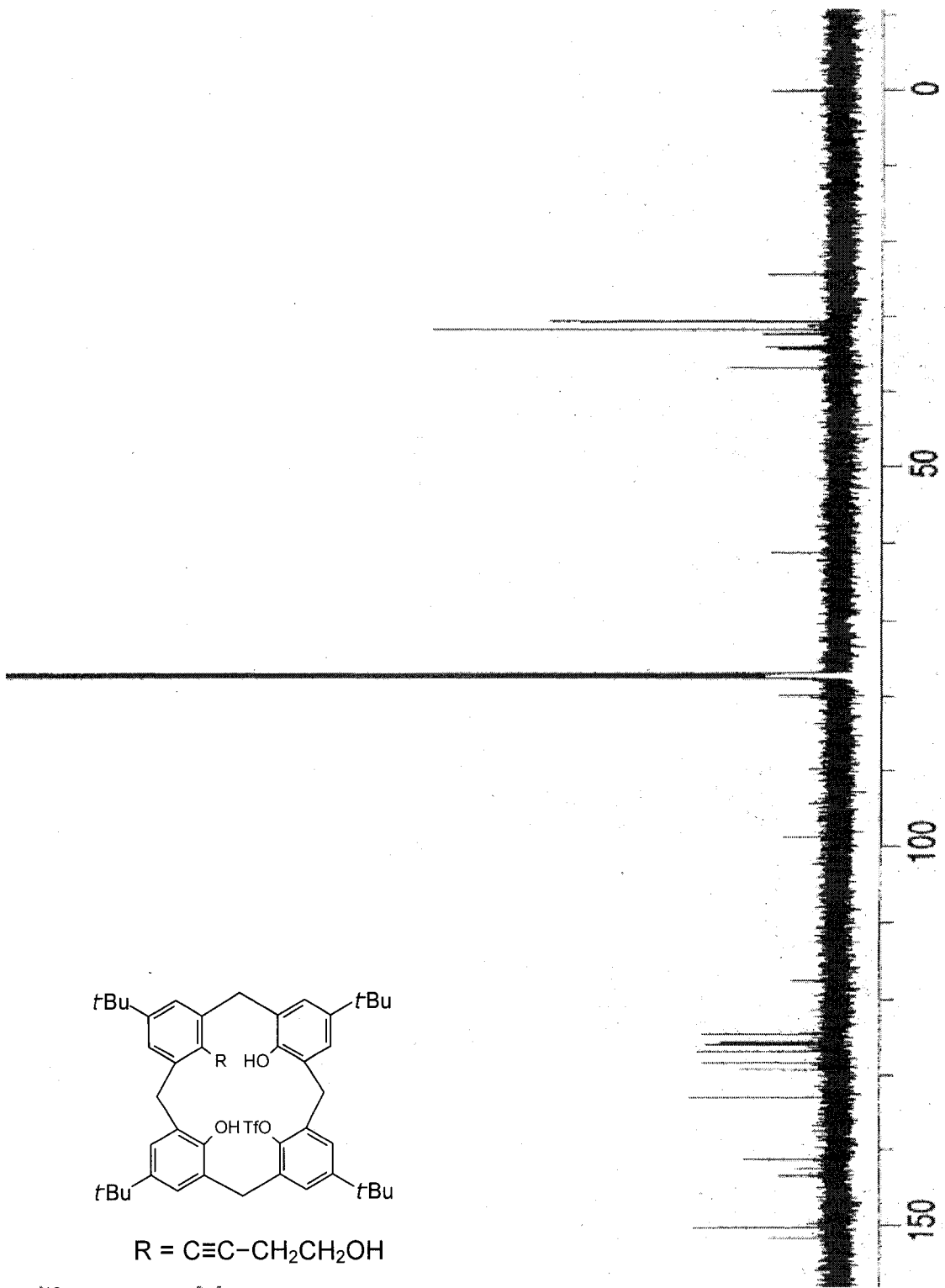
^{13}C NMR spectrum for compound **64**



^{1}H NMR spectrum for compound **65**

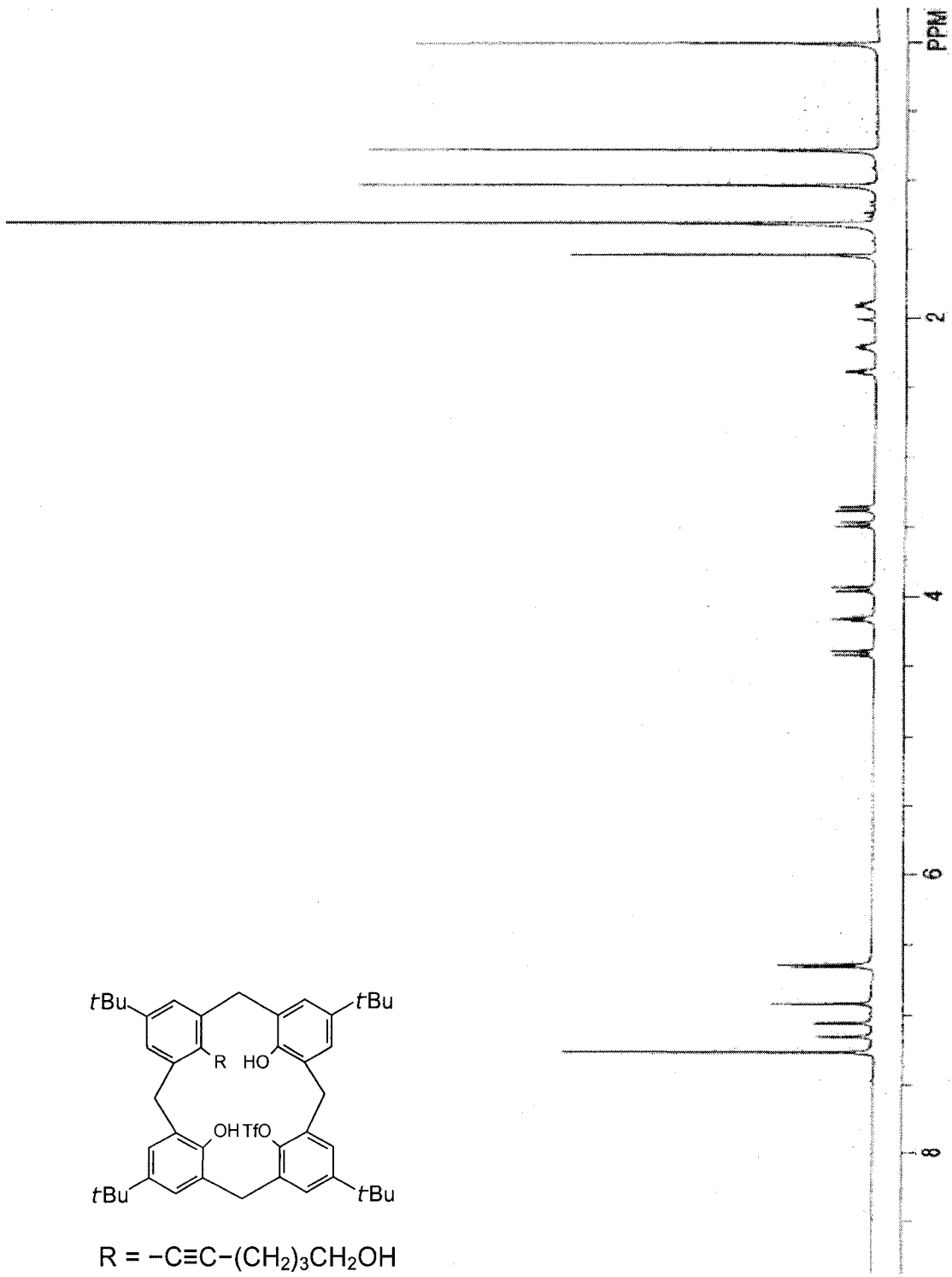


^{1}H NMR spectrum for compound **65**



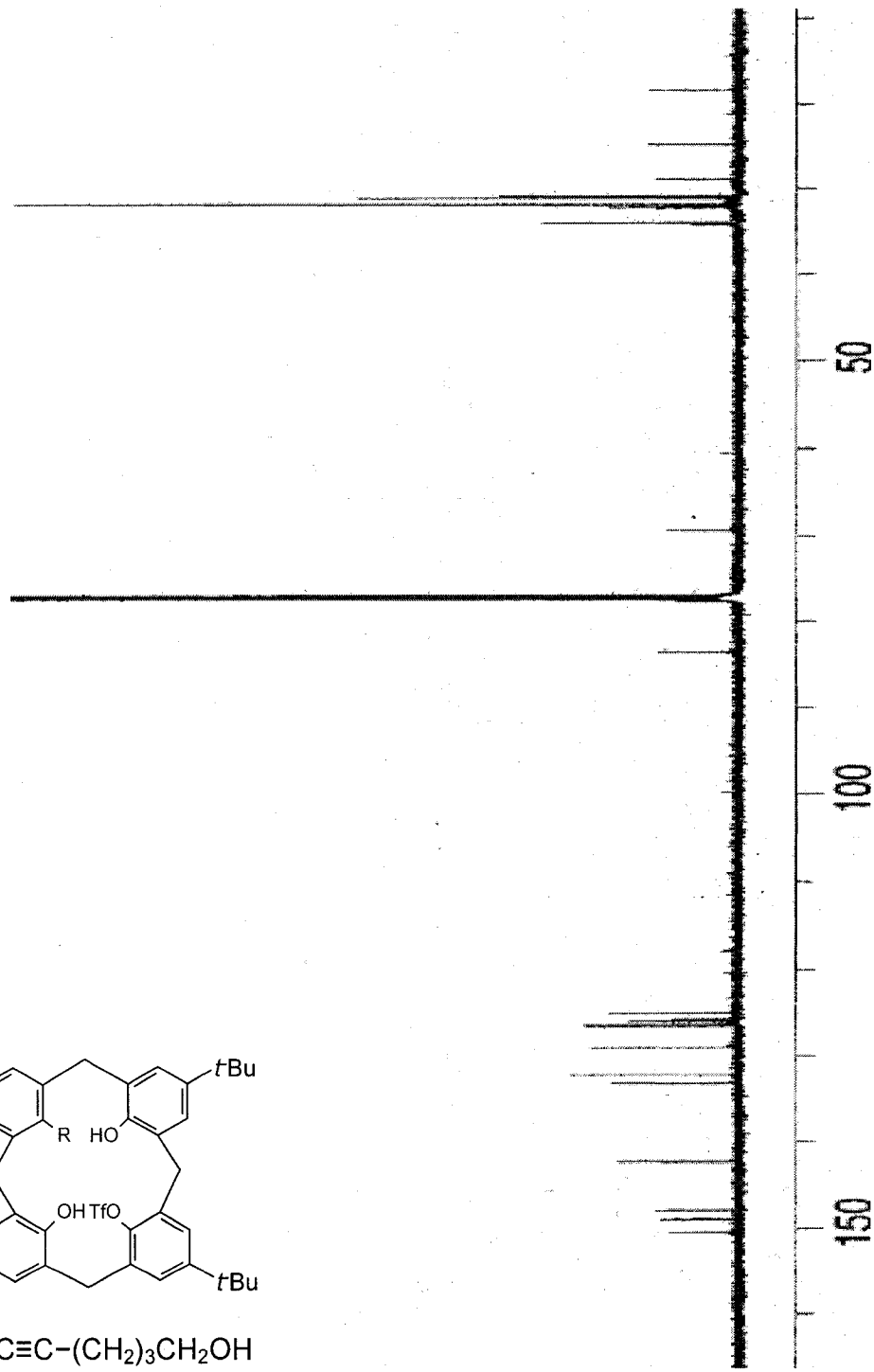
R = C≡C–CH_2CH_2OH

^{13}C NMR spectrum for compound **69**



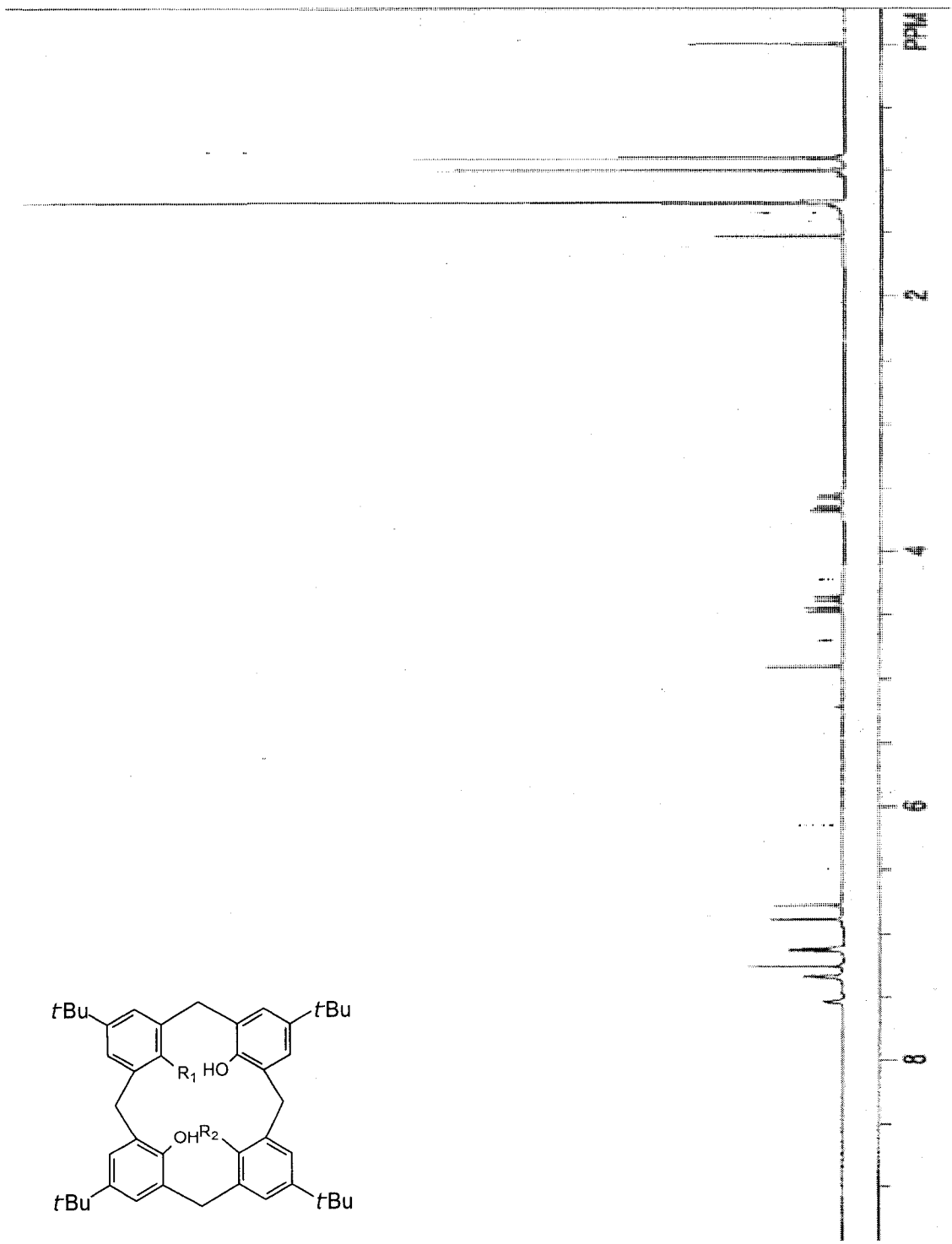
R = $-C\equiv C-(CH_2)_3CH_2OH$

^{1}H NMR spectrum for compound **70**



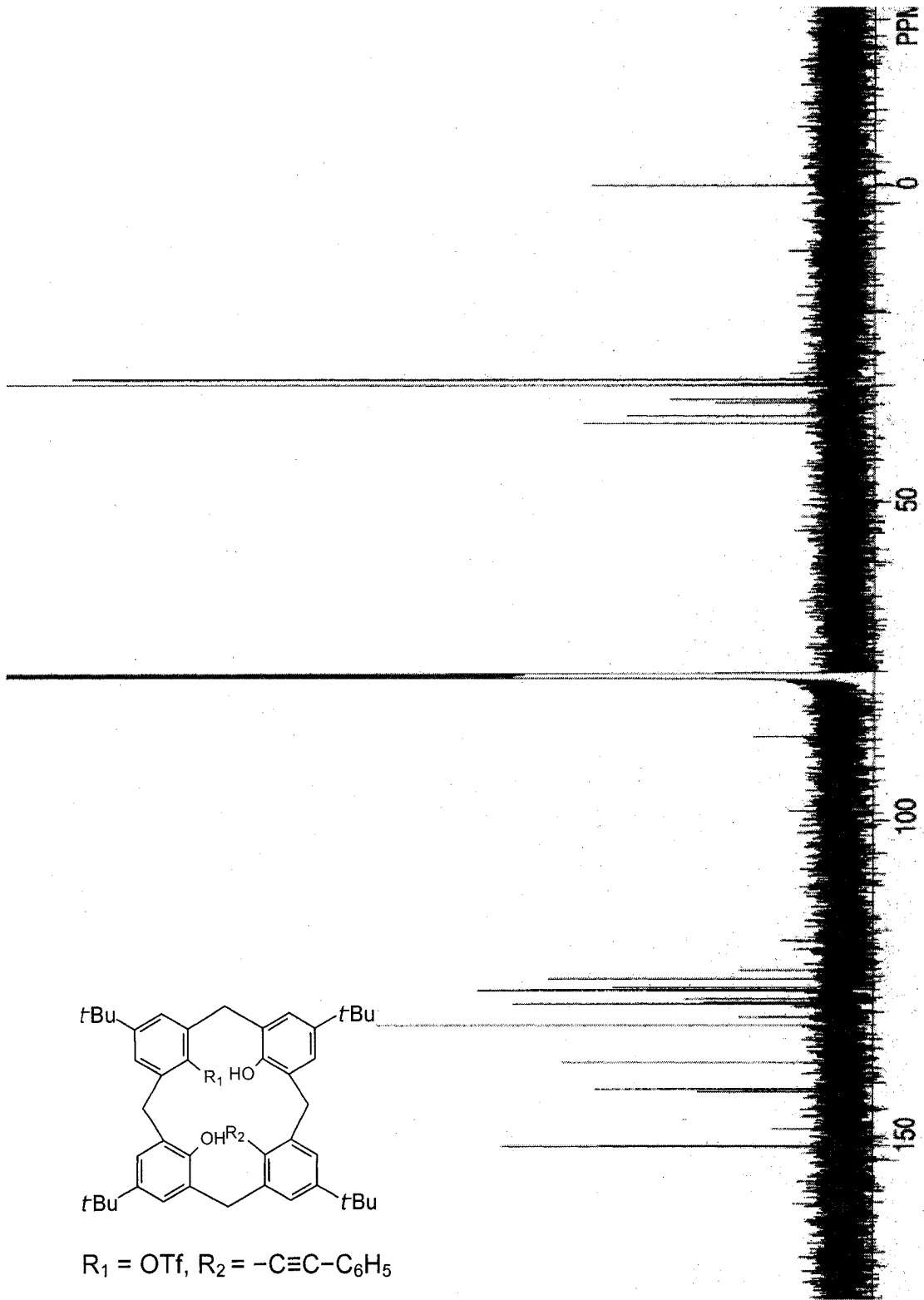
R = $-C\equiv C-(CH_2)_3CH_2OH$

^{13}C NMR spectrum for compound **70**



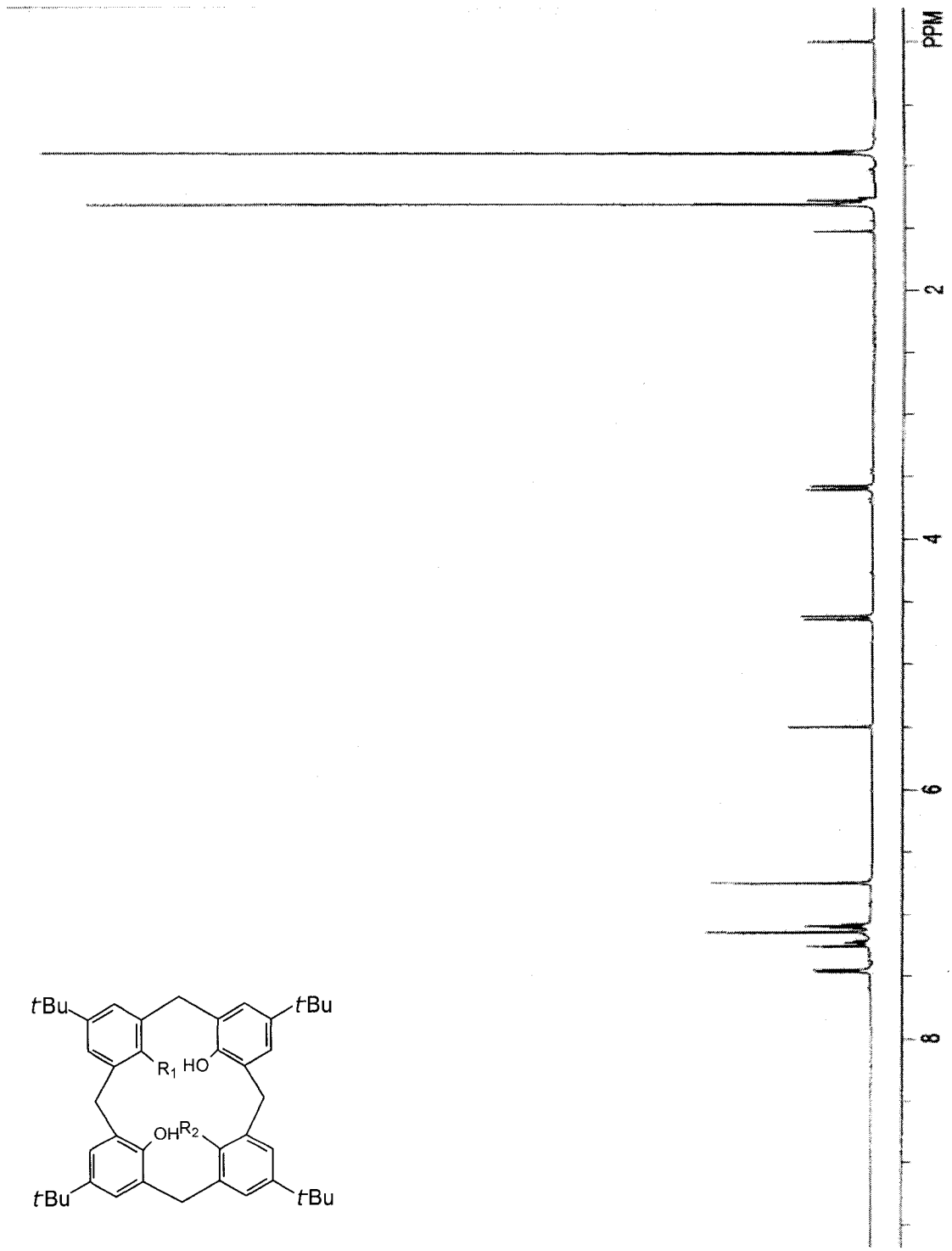
R_1 = OTf, R_2 = $-C{\equiv}C-C_6H_5$

^{1}H NMR spectrum for compound **72**



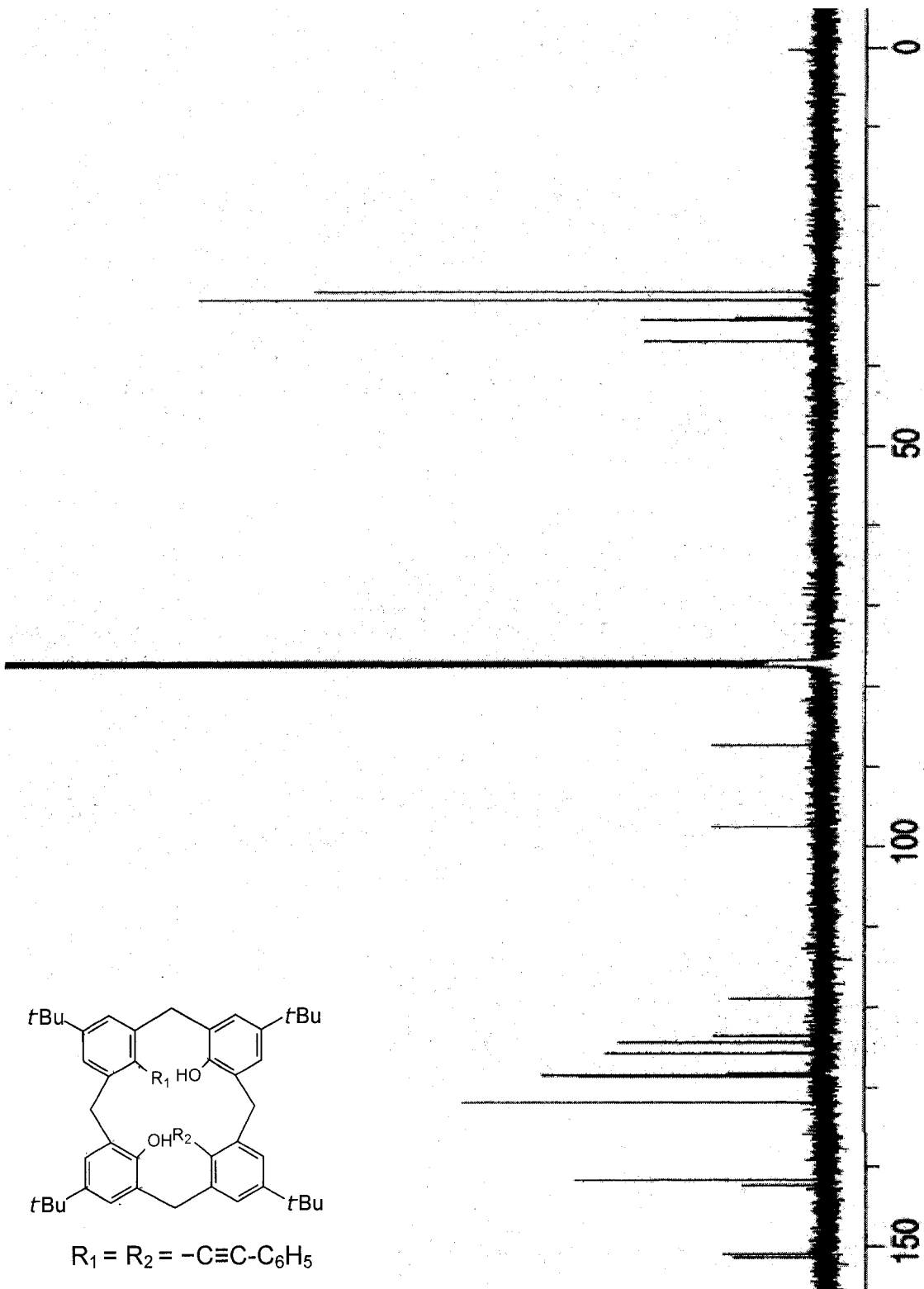
R_1 = OTf, R_2 = $-C{\equiv}C-C_6H_5$

^{1}H NMR spectrum for compound **72**



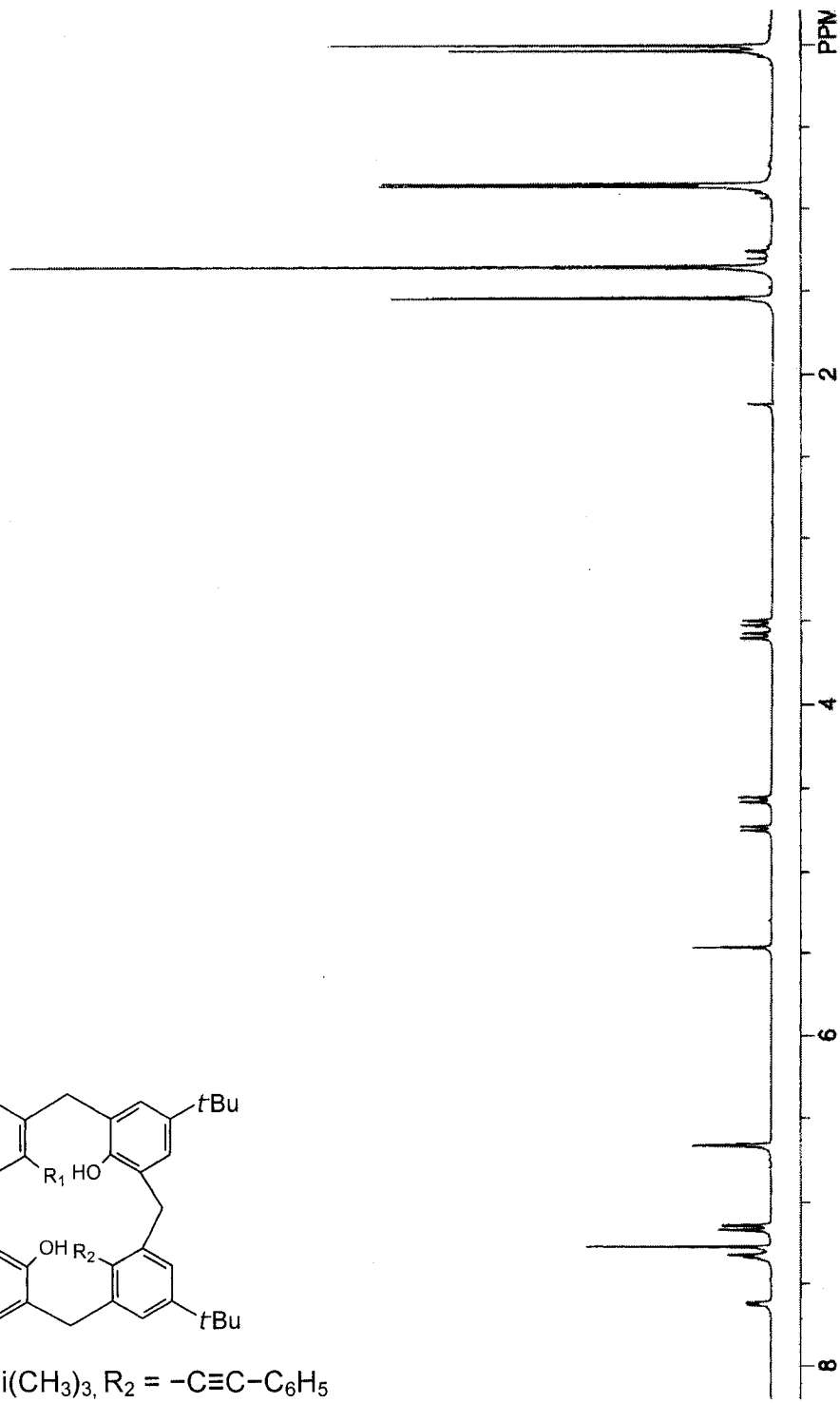
$R_1 = R_2 = -C\equiv C\text{-}C_6H_5$

^{1}H NMR spectrum for compound **73**



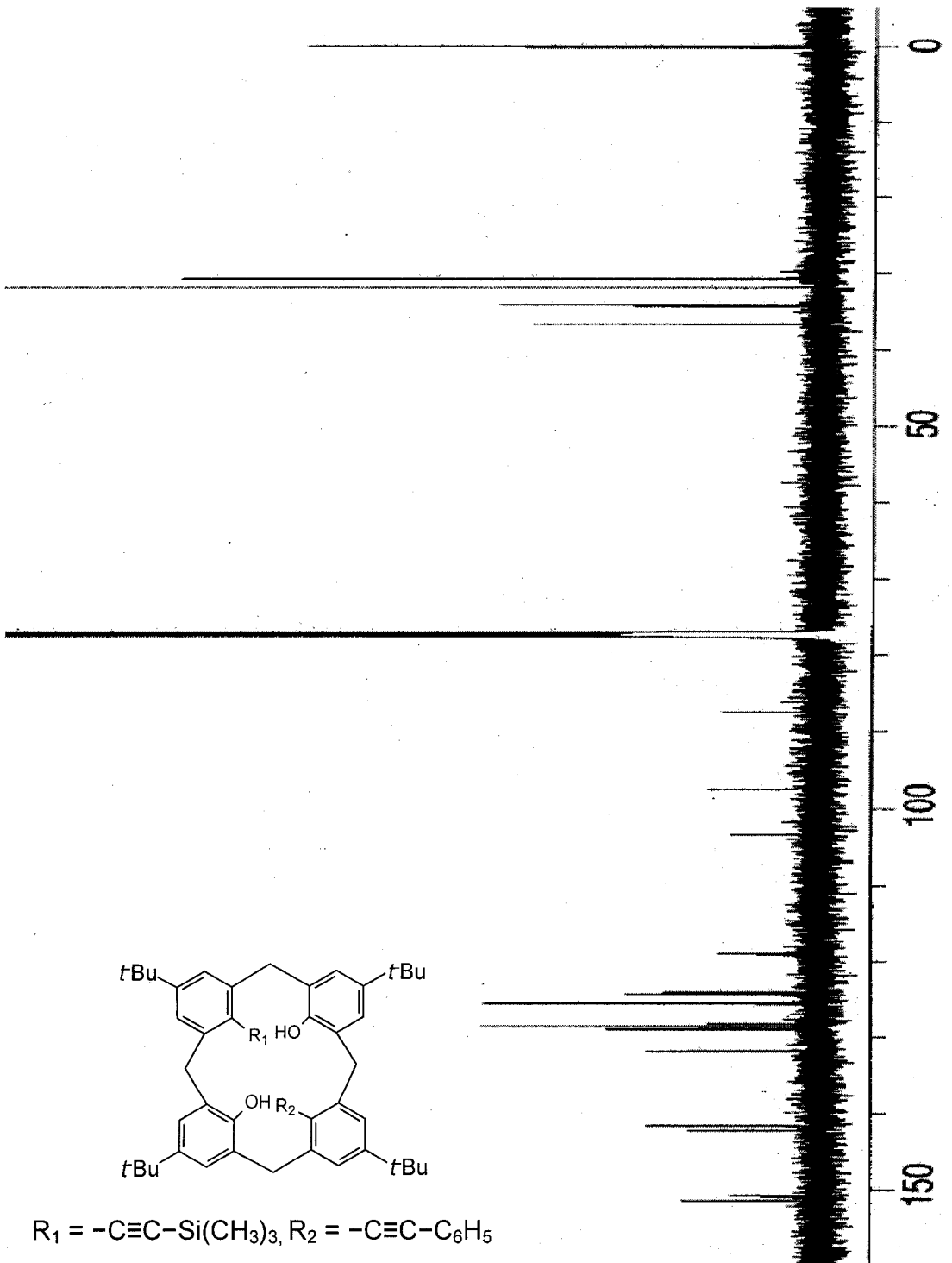
$R_1 = R_2 = -C\equiv C\text{-}C_6H_5$

^{13}C NMR spectrum for compound **73**



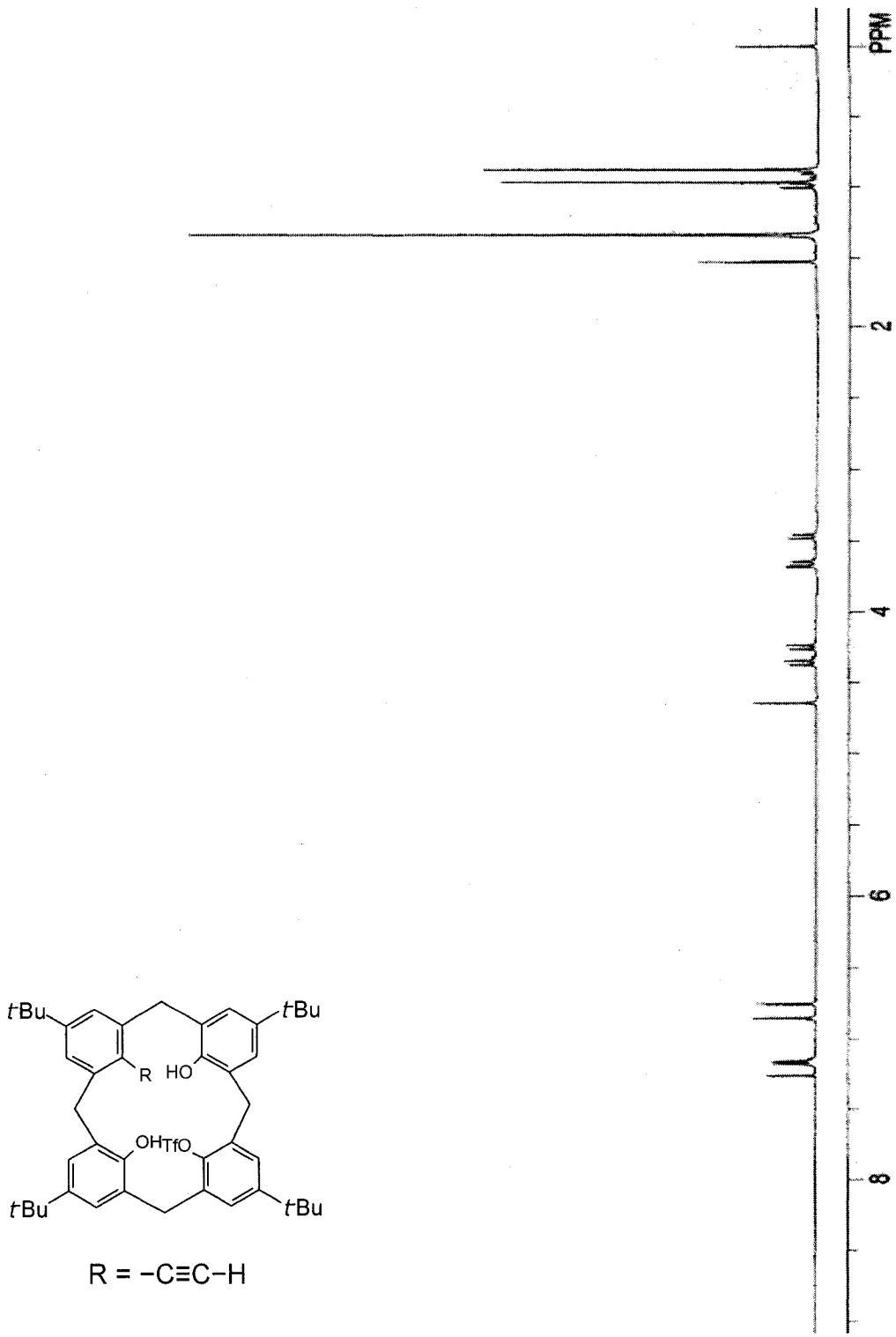
R_1 = −C≡C−Si$(CH_3)_3$, R_2 = −C≡C−C_6H_5

^{1}H NMR spectrum for compound **74**



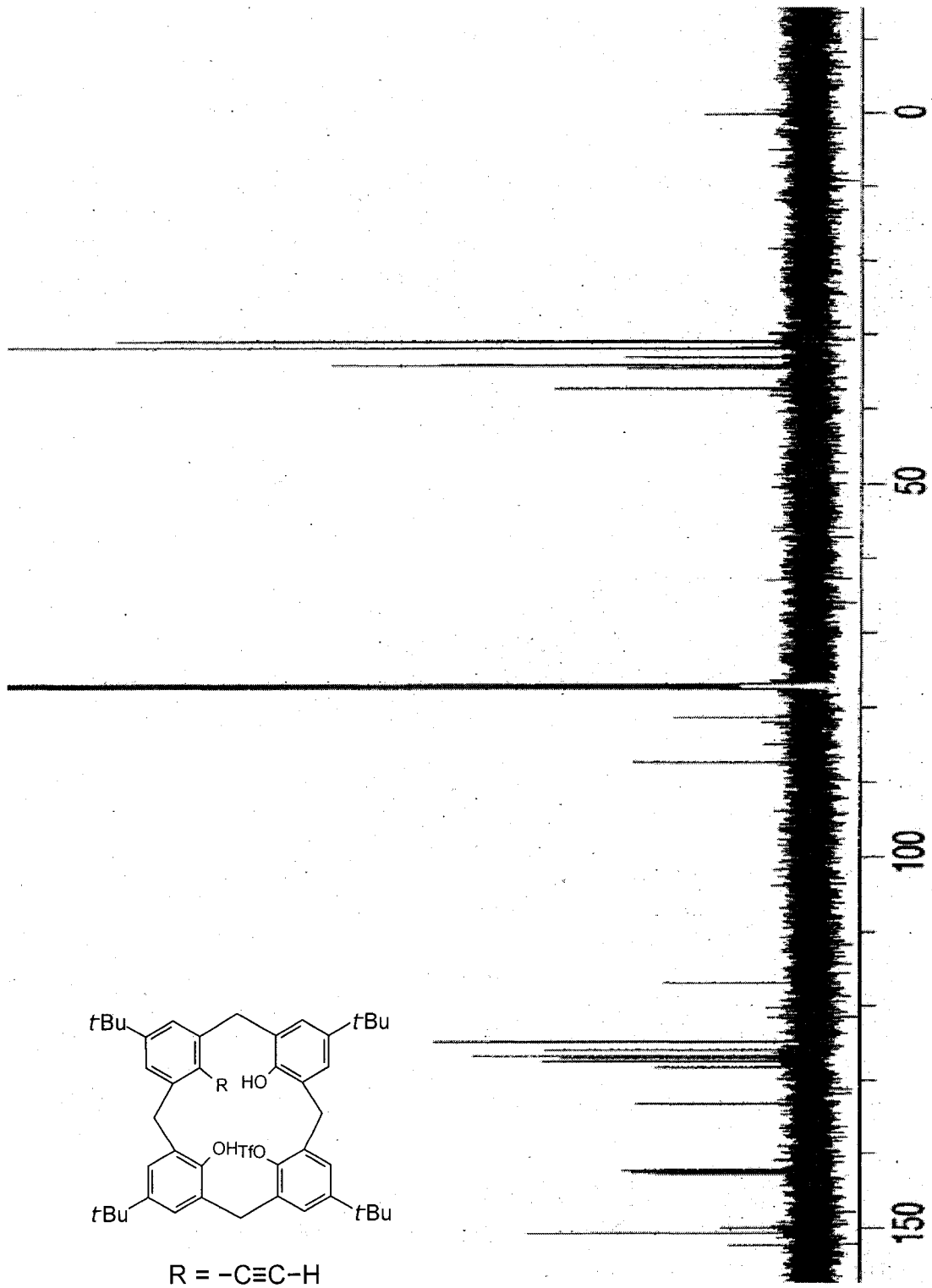
R_1 = −C≡C−Si$(CH_3)_3$, R_2 = −C≡C−C_6H_5

^{13}C NMR spectrum for compound **74**



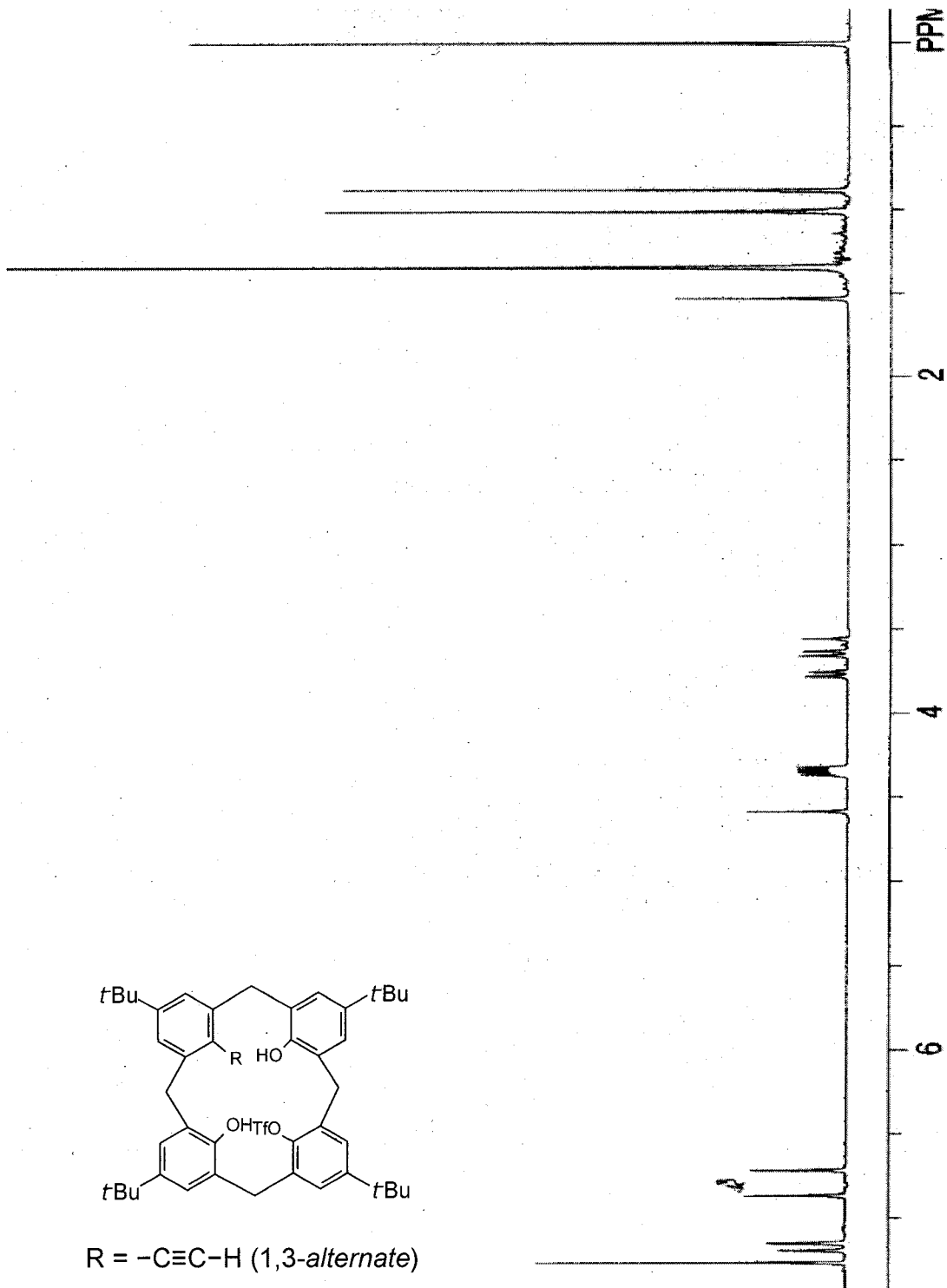
R = −C≡C−H

^{1}H NMR spectrum for compound **77**



R = −C≡C−H

^{13}C NMR spectrum for compound **77**

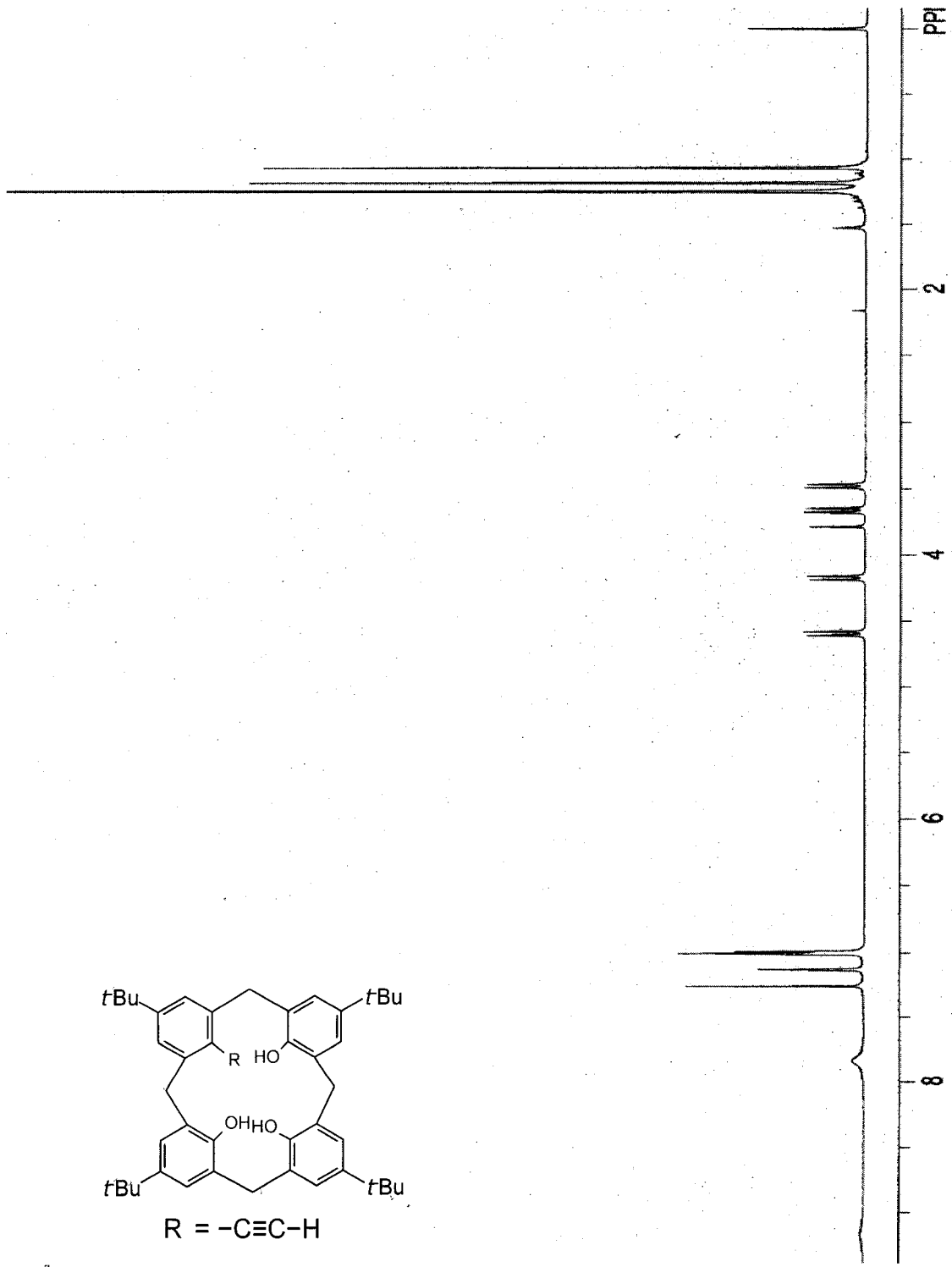


R = −C≡C−H (1,3-*alternate*)

^{1}H NMR spectrum for compound **78**

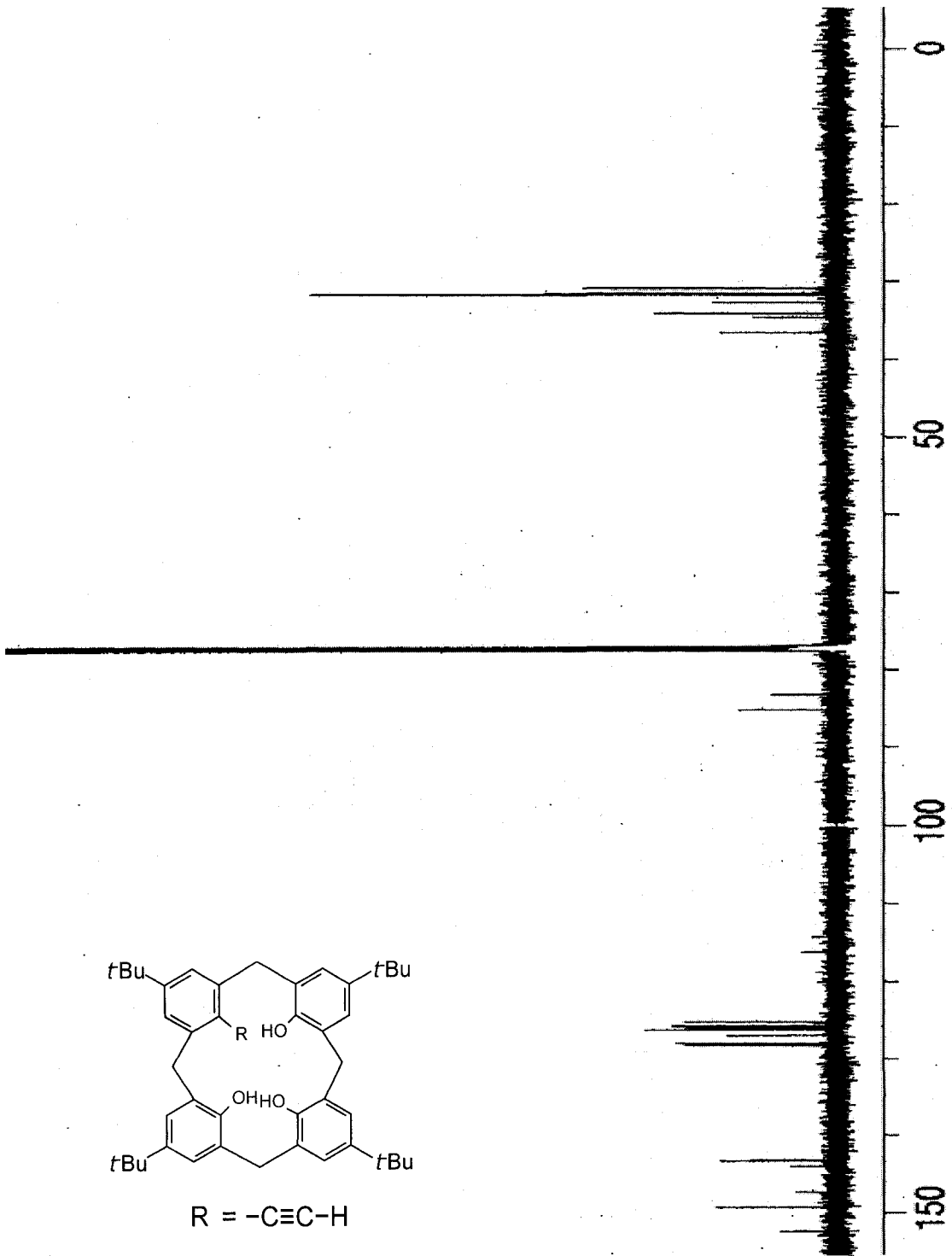
R = −C≡C−H (1,3-*alternate*)

^{13}C NMR spectrum for compound **78**



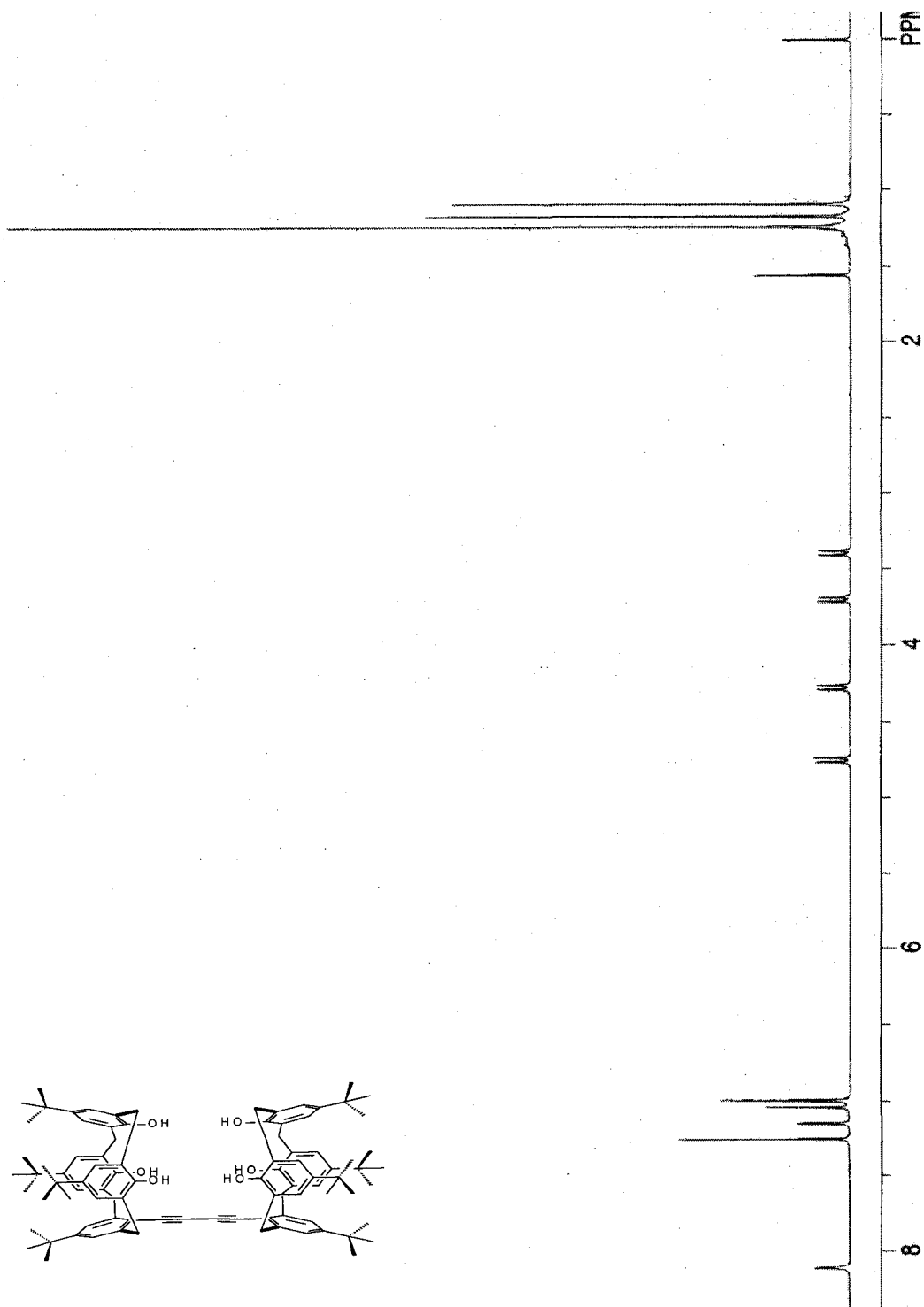
R = −C≡C−H

^{1}H NMR spectrum for compound **79**

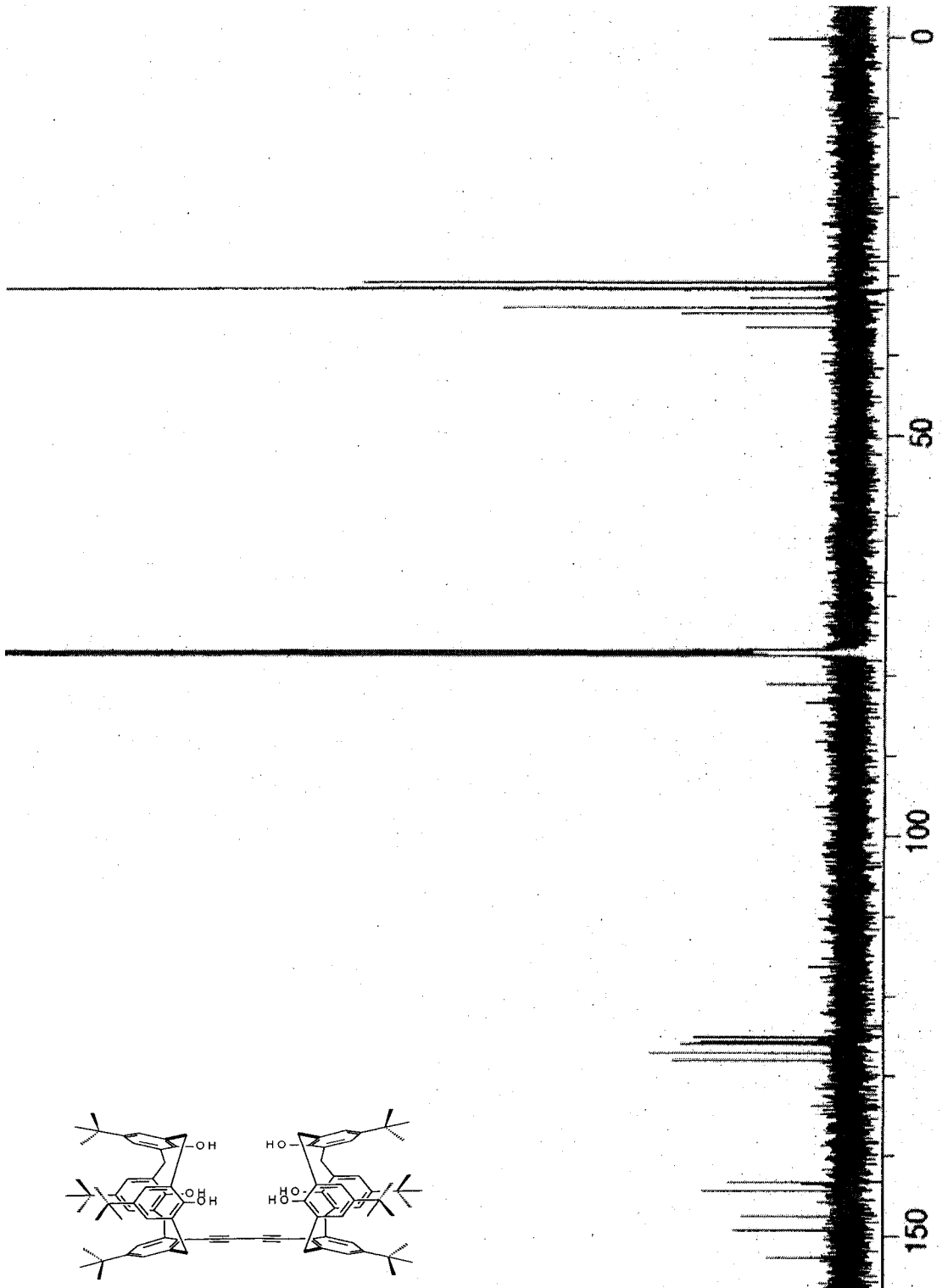


R = −C≡C−H

^{13}C NMR spectrum for compound **79**



^{1}H NMR spectrum for compound **80**



^{13}C NMR spectrum for compound **80**

Chapter 6

Narrow-rim modified Donor-Acceptor Calix[4]arenes as New Nonlinear Optical Materials

6.1- Introduction

During the last few decades **N**on-**L**inear **O**ptical (NLO) materials have acquired much interest around the world due to their promising applications in optical communication, optical computing, optical information processing, optical switches, optical disk data storage, color displays, medical diagnostics, and frequency doubling, etc.[1]

It is well-known that the response of matter to incident light has both linear and nonlinear components. With respect to first-order linear responses, the polarization induced by the light is proportional to the applied electric field. When the responses are not proportional in a linear way to the applied electric field, the materials which are subjected to the incident light are known as NLO materials.

Although NLO properties were first observed with inorganic compounds, such as $LiNbO_3$,[2] most of these materials have either low NLO responses (e.g. as semiconductors) or are difficult to process into thin films to be used with, or for micro-optoelectronic devices. By the mid 1980s, organic materials appeared as competitive materials for NLO applications,[3] because they have large and fast nonlinear responses and also because most of these materials are relatively easy to process and incorporate into optical devices. In addition, their NLO properties can be easily adjusted by conducting selective chemical modifications.

Furthermore, these materials are the best choice with which to produce photonic devices on the molecular level.[4]

For an organic compound to be a second-order NLO-active material, it should have within its framework an electron-donating group (D) and an electron-accepting group (A) connected via π-conjugated linkers ("D–π–A" or "push–pull" units). Figure 6.1 shows a template structure example **"T"** for a typical NLO-active material. Such compounds usually have strong visible electronic transitions and a high degree of charge-transfer character (CT) which are responsible for both their linear and non-linear responses. D–π–A units generate the required asymmetric polarizability in the molecule which is produced from the asymmetric delocalization of the conjugated π-electrons. This polarization is found to be responsible for the non-linearity behavior for these types of compounds.[5]

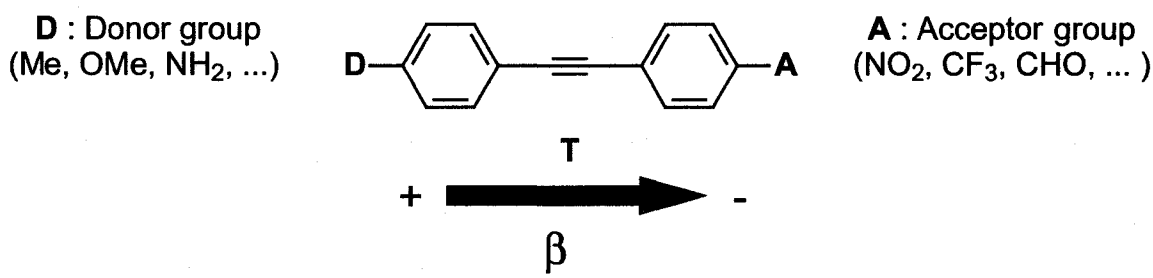
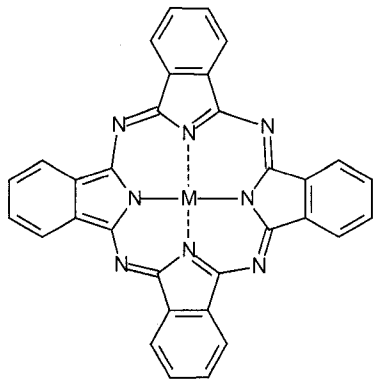


Figure 6.1: Typical models for an NLO-active organic compound.

Phthalocyanines **1**, are organic compounds which fulfill the requirements to be NLO-active materials. The presence of 18 delocalizable π-electrons accounts for the high NLO responses for such compounds (Figure 6. 2).[7]



M : Metal (Cu, Co, Ni, etc)

1

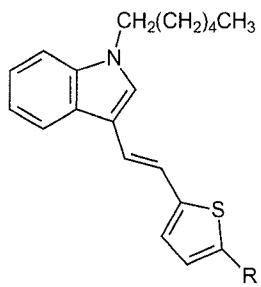
Figure 6. 2 Phthalocyanines **1** as examples of organic NLO-active materials.

In 2006 Gong et al.[8] reported the synthesis of push-pull indole-containing NLO chromophores **2a-d,** with different acceptor and π-conjugated moieties, and for which they demonstrated that these compounds have high optical non-linear responses (Figure 6.3).

On the other hand, relatively smaller organic compounds can also be used as NLO-active materials. Srinivasan et al.[9] for example, obtained good quality crystals for 2,4,6-trinitrophenol by a slow solution cooling growth technique, and they found that these crystals exhibited high NLO efficiency.

6.2- Calixarenes as NLO materials

Although calixarenes are widely studied for their host-guest properties, there is growing interest for their potential applications as NLO materials on account of their relatively high stabilities, versatility and processibilities. The huge variety of substituents which can be attached to a calixarene on its narrow- or on its wide-rim can alter the electronic structure of the macrocyclic core, and therefore, enable the potential for adjusting their non-linear responses.



2a-d

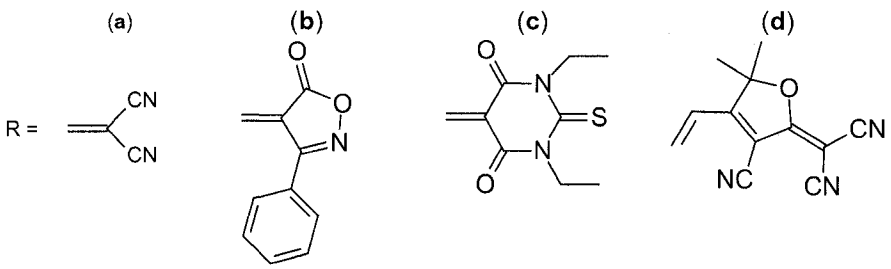
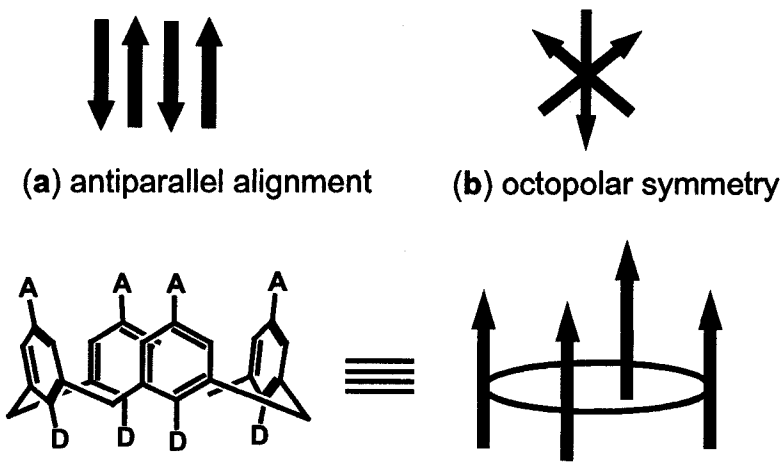


Figure 6.3 Indole-containing chromophores **2a-d** as NLO materials

With calixarenes, it is possible to have more than one D−π−A unit covalently fixed by the calixarene scaffold. The combination of more than one

D–π–A unit has the advantage of having a high dipole moment to combine with a high β and maximize the NLO response, as can be illustrated, for example, in the case of "**c**" compared to cases "**a**" and "**b**" in Figure 6.4, where the dipole moment of the bulk is decreased due to their non-favoured alignments.[10]

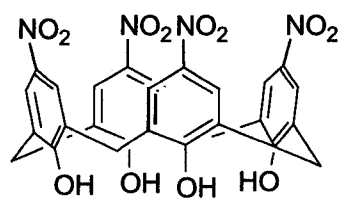


(**a**) antiparallel alignment (**b**) octopolar symmetry

(**c**) covalent fixation in calix[4]arenes

Figure 6.4 D–π–A systems in **a** and **b** are free in bulk, while in **c** they are covalently fixed by the calix[4]arene scaffold.

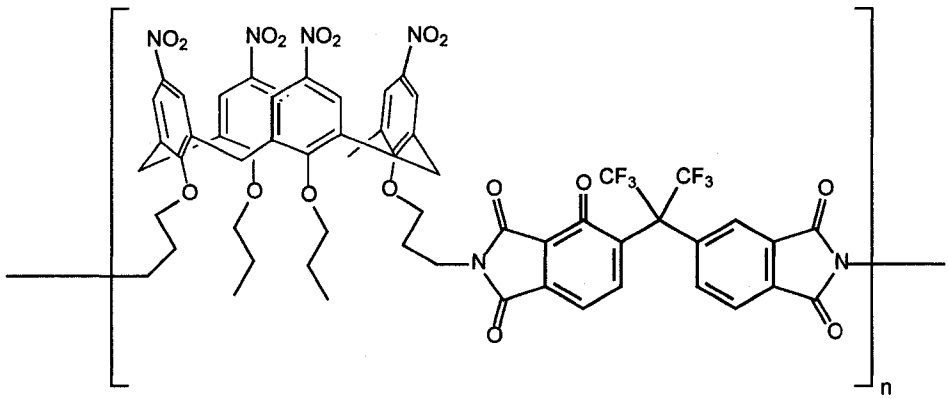
Tetra-*p*-nitrocalix[4]arene (**4**) reported by Reinhoudt[11] was the first practical example of a calixarene to be studied as an NLO chromophore[12] (Figure 6.5). In such compounds the determination of the relative orientation of the subunits to one another i.e. the conformation, is an important consideration for NLO studies.



Tetra-*p*-nitrocalix[4]calixarene (**4**)

Figure 6.5 Tetra-*p*-nitrocalix[4]arene (**4**) as NLO-active material.

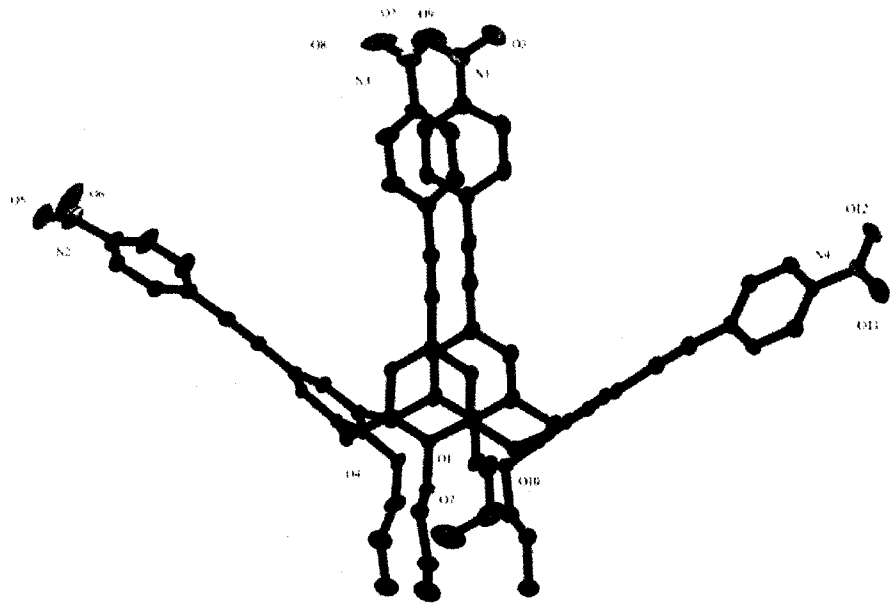
In 1997, another report by Reinhoudt et al.[12] described the synthesis of calix[4]arene-based polyimides **5** and their NLO applications (Figure 6.6). They found that spin-coating these materials generated polymeric films that are highly transparent and have very high, NLO responses and thermal stability. They also demonstrated, that these materials were very suitable for frequency-doubling applications in the UV- region.



5

Figure 6. 6 Calix[4]arene-based polyimides **5** prepared by Reinhoudt et al. and found to be suitable NLO-active material for frequency doubling in the UV-region.

In 2005, Hennrich et al.[13] reported the synthesis of rigid, highly conjugated wide rim-modified tetraalkynyl-calix[4]arenes via Sonogashira coupling from the corresponding tetraiodocalix[4]arenes. They demonstrated for example, that **6** had improved hyperpolarizability (β) values from which they have shown hyper-Rayleigh scattering to be a useful tool to determine the inter-dipolar angle or "opening angle" in tetraalkynyl-calix[4]arene **6**, in solution (Figure 6. 7).



6

Figure 6.7 X-ray structure of tetraalkynyl calix[4]arene **6**

As an extension of our previous work on the narrow-rim modification of calix[4]arene via Sonogashira coupling (Chapter 5), and as a result of an on-going collaborative study with the groups of Dr. G. Hennrich at U.A.M., Madrid, Spain.[15] Dr. K. Clays at the Katholieke Universiteit, Leuven, Belgium[16] and Dr. D. W. Thompson at Memorial University, a series of second-order NLO-active expanded "**A-**" and "**B**"-Type calix[4]arenes and the equivalent tolanes "**C**" were designed and synthesized in which the calixarene platform is substituted on either, the wide- or the narrow rim by a pair of arylethynyl moieties (Figure 6. 8).

Hennrich's group synthesized the Type-**A** calixarenes (*Note:* some of the data reported herein has been taken from a draft manuscript which is currently

being co-authored by Hennrich, Clays, Thompson and ourselves[17]). The synthesis of the wide-rim alkynylated calixarenes **7–9** were achieved in good yields via Sonogashira coupling of the diiodo precursor **9a** with different arylethynyls (Scheme 6. 1). The syntheses of the Type-**B** calixarenes **10–12** and their equivalent Type-**C** tolanes were synthesized by this author as part of our contribution to this work.

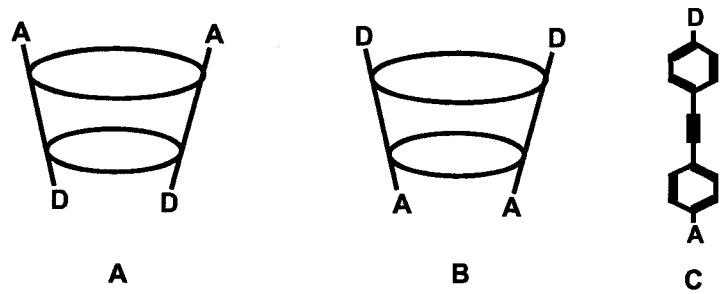
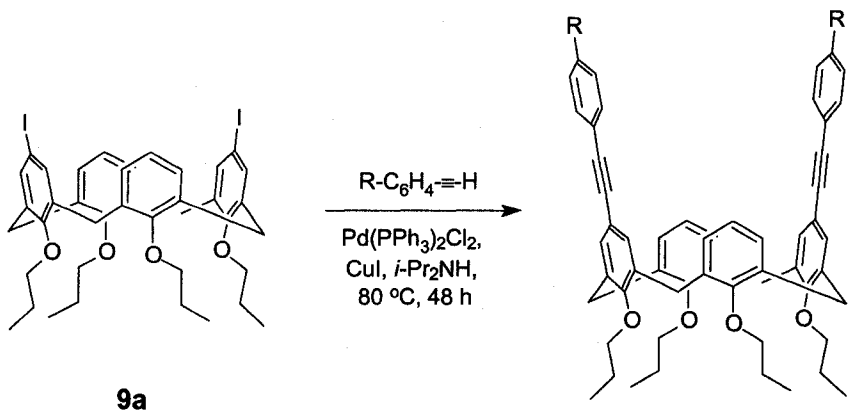


Figure 6.8 Schematic depiction of different D-A substituted calix[4]arenes "**A**" and "**B**" and their equivalent tolanes, "**C**".

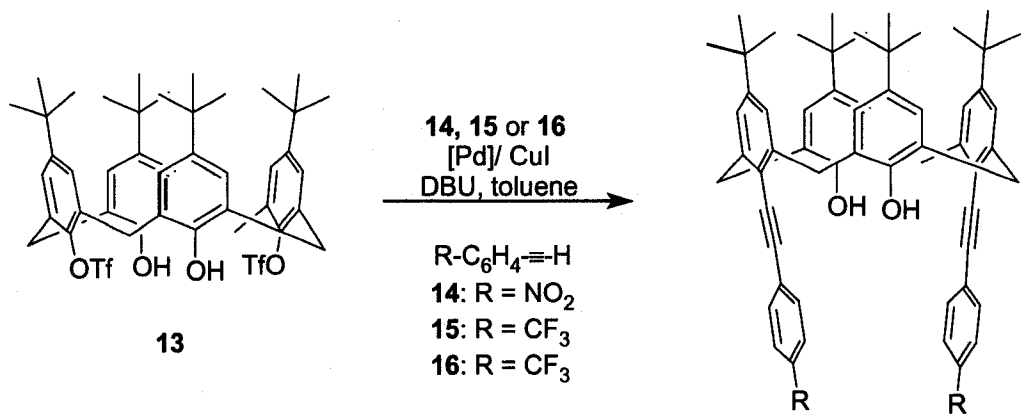


7: R = NO_2; 62%
8: R = CF_3; 60%
9: R = H; 76%

Scheme 6.1 Synthesis of the tetraalkynylcalix[4]arenes **7 – 9** by Hennrich et al.[17]

6.3- Results and discussion

The syntheses of calix[4]arenes **10** and **11** were achieved via the Sonogashira coupling of the bistriflate **13** with 1-ethynyl-4-nitrobenzene (**14**) and 4-ethynyl-α,α,α-trifluorotoluene (**15**), respectively as shown in Scheme 6.2, while the synthesis of compound **12** is reported in Chapter 5 .



Scheme 6.2 Synthesis of the narrow-rim functionalized bisarylalkynyl-calix[4]arenes **10** and **11**.

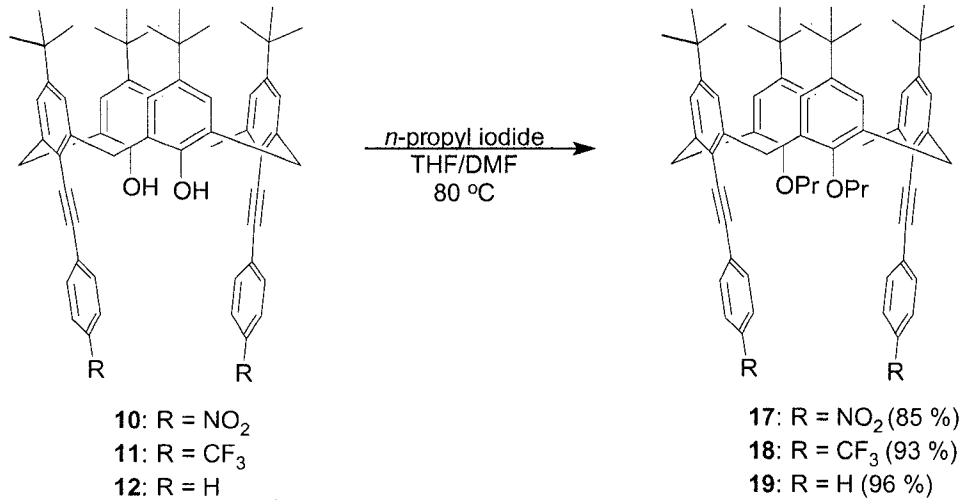
The syntheses of the two new narrow-rim modified calix[4]arenes **11** and **12** was found to be less efficient, (isolated yields were 27 % for **10** and 33 % for **11**) than that of the diphenyl analogue **12** which was achieved in 60 % yield. Analysis of the crude mixture obtained from the synthesis of compound **10**, indicated that ~75 % of the terminal alkyne **14** had been converted to the homocoupled by-product. A similar observation was made for **11**, except in this

except in this case the amount of the undesired homocoupling of alkyne **15** was lower (~60 %). These results suggest that under the reaction conditions described above, homocoupling of the terminal alkynes is faster than the desired coupling, particularly when deactivated terminal alkynes such as **14** and **15** are used. An attempt to improve the reaction yield by increasing the mole ratio of the alkyne failed, and only resulted in increasing the amounts of homocoupling products. The isolation of **10** and **11** was achieved by PLC, with the nitro derivative **10** being more difficult to purify than the trifluoromethyl analogue **11**, and this might have been a factor for the relatively lower yield obtained .

The ^{1}H NMR spectra of **10** and **11** revealed that each of these compounds are symmetrical (for example, the ^{1}H NMR spectrum of compound **10** has only two AB signals at ~ 3.7 and 4.6 ppm and two *tert*-butyl signals at ~ 0.9 and 1.3 ppm). The ^{13}C NMR spectra of calixarenes **10** and **11** showed that both of the methylene bridging carbons resonated at ~ 37 ppm, indicating that these two compounds are present in the *cone* conformation in solution.

Compounds **10-12** were each converted to the corresponding *O*-propylated derivative **17-19,** respectively, (Scheme 6.3) for two reasons: first, we found that calixarenes **10-12** were photo-labile and underwent changes during the measurement of their UV-visible spectral properties and that the hydroxyl groups reacted with the neighboring alkyne moieties, as described in detail in Chapter 7. Secondly, the *O*-propylated derivatives were required in order to directly compare

the NLO properties of the Type-**B** calixarenes **5-7** with those of the Type-**A** calixarenes, **7-9**.



10: R = NO_2
11: R = CF_3
12: R = H

17: R = NO_2 (85 %)
18: R = CF_3 (93 %)
19: R = H (96 %)

Scheme 6. 3 Synthesis of the narrow-rim functionalized calix[4]arenes **17-19**.

The *O*-propylation step was achieved only after several reaction conditions which failed to give the desired products were evaluated. The desired *O*-propylated analogues **17-19**, however, were eventually synthesized by reacting the corresponding starting materials **10-12**, with excess 1-iodopropane and NaH in a mixed solvent system of DMF and THF. The ^{1}H- and ^{13}C- NMR spectra of **17-19** are consistent with the expected structures, which also reveal that they have the expected *pinched-cone* conformation in solutions. A single-crystal X-ray analysis of **19** was conducted, confirming the structure to be in a *pinched-cone* conformation (Figure 6.9). At this point it is worth noting that the degree of flattening in calixarene **12** (according to its X-ray in Chapter 5) is larger than that in the *O*-propylated analogue **19,** likely due to the differences in the

intramolecular hydrogen-bonding possible with these two compounds. It is also evident that the triple bond of the arylalkynyl moieties in **19** are bent with dihedral angle = 25.7°.

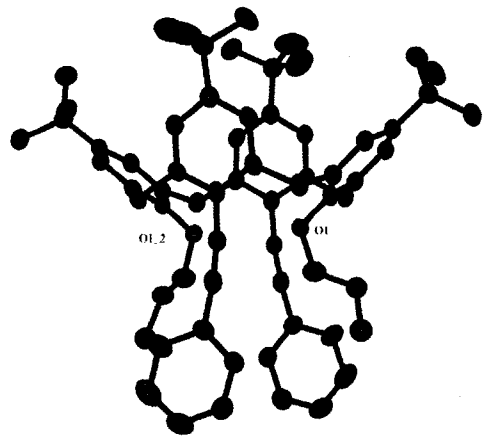
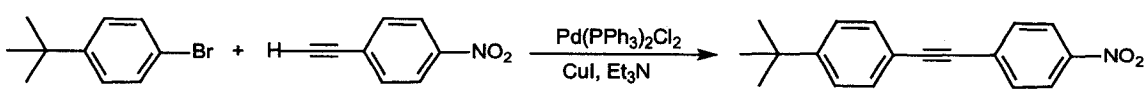


Figure 6.9 X-ray single-crystal ORTEP structural representation of **19** in a *pinched-cone* conformation (all of the H atoms have been removed for clarity).

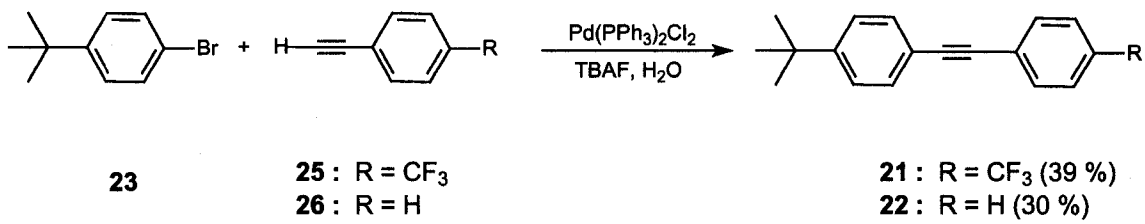
Finally, the Type-**C** tolanes **20-22** were synthesized to compare their spectroscopic properties with those of the corresponding calixarenes **17-19**, respectively. The 4-[(4-*tert*-butylphenyl-ethynyl] nitrobenzene (**20**) was prepared in 60 % yield via Sonogashira Pd-catalyzed coupling of 1-bromo-4-*tert*-butylbenzene (**23**) with 1-ethynyl-4-nitrobenzene (**24**), in Et_3N (Scheme 6. 4).



23 **24** **20** (60 %)

Scheme 6. 4 Synthesis of the nitro tolane **20**

The reaction conditions which were used for **20** however, were not suitable for the synthesis of tolanes **21** and **22**. After several different reaction conditions were tested, the best results were achieved by employing Pd-catalyzed coupling of **23** with 4-ethynyl-α,α,α-trifluorotoluene (**25**) and phenylacetylene (**26**) in the presence of TBAF and water. These modified Sonogashira conditions afforded the corresponding products **21** and **22**, in 39 and 30% yields, respectively (Scheme 6. 5).



23

25 : R = CF_3
26 : R = H

21 : R = CF_3 (39 %)
22 : R = H (30 %)

Scheme 6. 5 Synthesis of tolanes **21** and **22**

6.4- Spectroscopic properties

The spectroscopic and NLO properties are being investigated by the Leuven group and will be presented in a forthcoming manuscript.[18] The results obtained however, will bee too late for inclusion in this thesis.

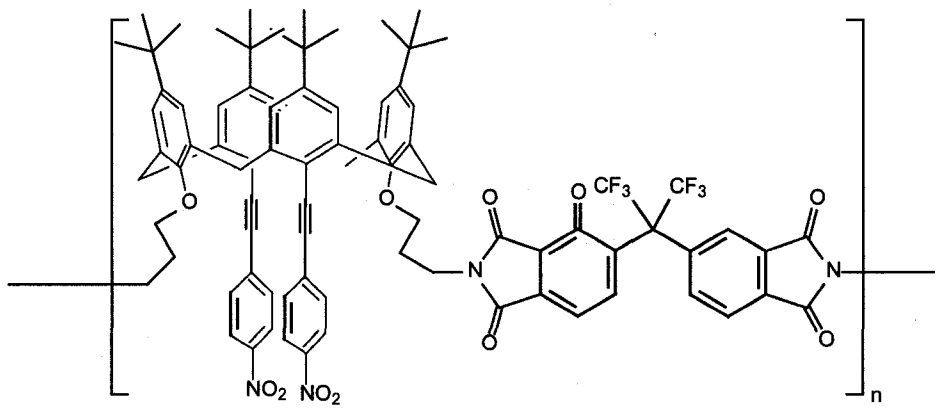
6.5- Conclusions

Several donor-acceptor narrow-rim functionalized alkynylcalix[4]arenes have been synthesized via Sonogashira coupling in reasonable yields. In order to

study their optical properties, i.e. their NLO properties, several donor-acceptor tolanes have been also synthesized. The NLO determinations are still in progress and it is anticipated that these results will be submitted in due course.

6.6- Suggestions for Future Work

Incorporating the calix[4]arenes, whose syntheses were described in this chapter, into a polymer chain could result in enhancing their photonic properties. For example, by analogy to the work of Reinhoudt et al.[12] the following calixarene-based polyimides could be targeted (Scheme 5.6).

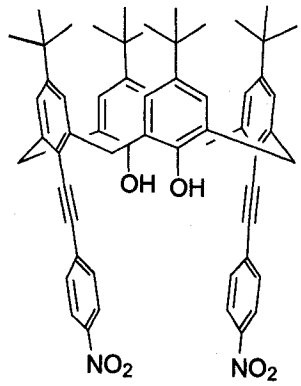


27

Scheme 6.6 The proposed synthesis for the calix[4]arene-based polyimides **27** as a targeted product for a future work.

6.7- Experimental

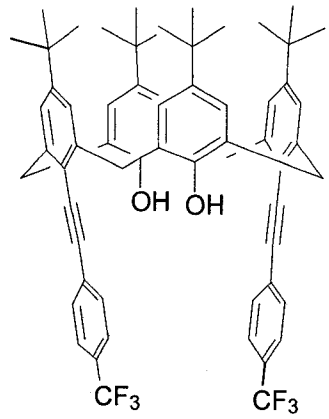
For general experimental information see Chapter 2, page 46.



10

5,11,17,23-Tetra(*tert*-butyl)-26,28-bis(*p*-nitrophenylethynyl)calix[4]arene (10): To a stirred mixture of *p-tert*-butylcalix[4]arene-1,3-bistriflate (**13**) (0.10 g, 0.11 mmol), $PdCl_2(PPh_3)_2$ (0.050 g, 0.007 mmol) and CuI (1.0 mg, 5.0 μmol) in dry toluene (10 mL), was added a solution of DBU (67 mg, 0.44 mmol) and 1-ethynyl-4-nitrobenzene (35 mg, 0.24 mmol) in dry toluene (3 mL) at reflux temperature. The resulting mixture was stirred for 24 h at the reflux temperature, cooled and poured into saturated aqueous ammonium chloride (20 mL) and then washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator. The residue was purified by PLC (1:99 ethyl acetate/hexanes) to give **10** (53 mg, 27%): mp 145-147 °C; ^{1}H NMR δ 0.91 (s, 18H), 1.33 (s, 18H), 3.65 (d, *J* = 14.0 Hz, 4H), 4.56 (d, *J* = 14.0 Hz, 4H), 5.29 (s, 2H, OH), 6.79 (s, 4H), 7.18(s, 4H), 7.54 (d, *J* = 8.0 Hz, 4H), 7.89 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR δ 30.8, 31.9, 34.2, 34.6, 37.1, 93.2, 95.6, 117.8,

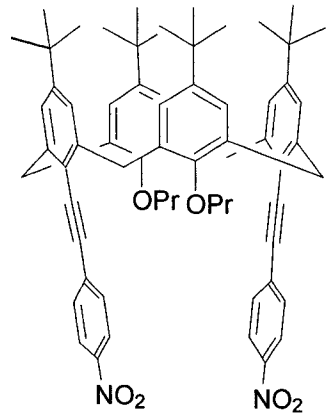
123.6, 124.7, 125.8, 128.5, 130.2, 132.0, 142.1, 143.1, 147.0, 151.3, 152.2, 152.4; MS (APCI+) *m/z* calculated for $C_{60}H_{62}N_2O_6$: 907.16, found 907.50 (M^+).



11

5,11,17,23-Tetra(*tert*-butyl)-26,28-bis[*p*-(triflouromethyl)-phenylethynyl] calix[4]arene (11): To a stirred mixture of (*p-tert*-butylcalix[4]arene-1,3-bistriflate (**13**) (0.10 g, 0.11 mmol), $PdCl_2(PPh_3)_2$ (5.0 mg, 7.0 µmol) and CuI (1.0 µg, 5.0 µmol) in dry toluene (10 mL), was added a solution of DBU (66.9 mg, 0.44 mmol) and 4-ethynyl-*α,α,α*-trifluorotoluene (40.8 mg, 0.24 mmol) in dry toluene (3 mL) at reflux temperature. The resulting mixture was stirred for 24 h at the reflux temperature, cooled and poured into saturated aqueous ammonium chloride (20 mL) and then washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator. The residue was purified by PLC (3:7 CH_2Cl_2 / petroleum ether) to give **11** (24.1 mg, 23%): mp 271-273 °C; ^{1}H NMR δ 0.91 (s, 18H), 1.31 (s, 18H), 3.63 (d, *J* = 14.0 Hz, 4H), 4.58 (d, *J* = 14.0 Hz, 4H), 5.33 (s, 2H, OH), 6.78 (s, 4H), 7.16 (s, 4H), 7.33 (d, *J* = 8.5 Hz, 4H), 7.53 (d, *J* = 8.5 Hz, 4H); ^{13}C NMR δ 30.9, 31.9, 34.2,

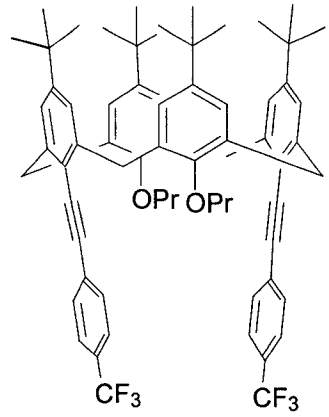
34.5, 37.1, 89.9, 95.9, 118.3, 122.9, 124.6, 125.4, 125.8, 127.2, 128.5, 130.4, 131.8, 142.0, 142.8, 151.2, 151.7; MS (APCI+) *m/z* calculated for $C_{62}H_{62}F_6O_2$ 953.16, found 953.50 (M^+).



17

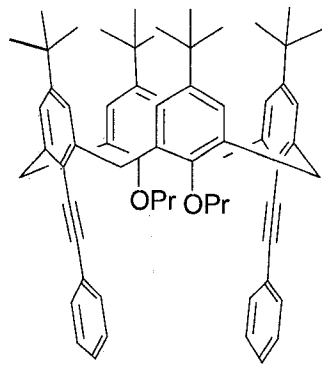
5,11,17,23-Tetra(*tert*-butyl)-25,27-dipropoxy-26,28-bis(*p*-nitrophenyl-ethynyl)calix[4]-arene (17). To a solution of **10** (0.060 g, 0.066 mmol) in anhydrous DMF (1 mL) and THF (10 mL) was added NaH (6.40 mg, 0.265 mmol), followed by the addition of *n*-propyliodide (45.1 mg, 0.265 mmol). The resulting mixture was heated at reflux temperature for 6 h, after cooling to rt the THF was evaporated on rotary evaporator and the residue was added to 10 mL of water to give a yellow precipitate which was purified by PLC (60% CH_2Cl_2 in petroleum ether) to give **17** (55.6 mg, 85%): mp > 330 °C; ^{1}H NMR δ 0.0.51-0.48 (m, 6H), 0.86 (s, 18H), 1.39 (s, 18H), 2.13-1.86 (m, 4H), 3.49 (d, *J* = 12.5 Hz, 4H), 4.08-4.05 (m, 4H), 4.680 (d, *J* = 12.5 Hz, 4H), 6.56 (s, 4H), 7.27(s, 4H), 7.61 (d, *J* = 8.0 Hz, 4H), 8.20 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR δ 9.9, 23.0, 31.0, 32.0, 34.4, 36.6, 75.5, 92.3, 97.5, 97.8, 118.3, 123.7, 123.9, 126.3, 131.6, 132.0,

135.6, 142.6, 146.0, 146.6, 150.8, 154.0; MS (APCI+) *m/z* calculated for $C_{66}H_{74}N_2O_6$: 991.3, found 991.5 (M^+).



18

5,11,17,23-Tetra(*tert*-butyl)-25,27-dipropoxy-26,28-bis(*p*-triflouromethyl-phenylethynyl)calix[4]arene (18). To a solution of **11** (0.05 g, 0.05 mmol) in anhydrous DMF (1mL) and THF (10 mL) was added NaH (4.8 mg, 0.20 mmol) followed by the addition of *n*-propyliodide (34 mg, 0.20 mmol). Then the reaction was conducted as with **17**, to give a pale white precipitate which was purified by PLC (30% CH_2Cl_2 in petroleum ether) to give **18** (48.2 mg, 93%): mp > 300 °C; ^{1}H NMR δ 0.48-0.44 (m, 6H), 0.85 (s, 18H), 1.37 (s, 18H), 2.01-1.93 (m, 4H), 3.45 (d, *J* = 12.5 Hz, 4H), 4.10-4.07 (m, 4H), 4.71 (d, *J* = 12.5 Hz, 4H), 6.54 (s, 4H), 7.19(s, 4H), 7.58-7.57 (m, 8H); ^{13}C NMR δ 9.7, 22.8, 31.0, 32.0, 34.3, 34.40, 36.7, 76.5, 92.1, 94.3, 99.8, 118.7, 123.1, 123.6, 125.4, 126.2, 131.4, 135.9, 142.3, 145.8, 150.1, 154.1 (one missing carbon in the aromatic region); MS (APCI+) *m/z* calculated for $C_{60}H_{62}N_2O_6$: 1037.3, found 1037.7 (M^+).

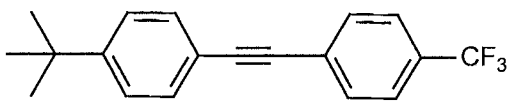


19

5,11,17,23-Tetra(*tert*-butyl)-25,27-dipropoxy-26,28-bis(phenyl-ethynyl)-calix[4]arene (19). To a solution of **12** (50.0 mg, 0.06 mmol) in anhydrous DMF (1mL) and THF (10 mL) was added NaH (5.8 mg, 0.24 mmol) followed by the addition of *n*-propyliodide (40.8 mg, 0.24 mmol). Then the reaction was conducted as for **17** above to give a pale yellow precipitate which was purified by PLC (10% ethyl acetate in hexanes) to give **19** (51.9 mg, 96%): mp > 300 °C; ^{1}H NMR δ 0.47-0.44 (m, 6H), 0.86 (s, 18H), 1.38 (s, 18H), 2.02-1.97 (m, 4H), 3.44 (d, *J* = 12.5 Hz, 4H), 4.16-4.13 (m, 4H), 4.77 (d, *J* = 12.5 Hz, 4H), 6.53 (s, 4H), 7.18(s, 4H), 7.32-7.28 (m, 6H), 7.53-7.51 (m, 4H); ^{13}C NMR δ 9.6, 22.7, 31.0, 32.0, 34.2, 34.4, 36.7, 76.5, 91.5, 93.3, 119.5, 123.4, 125.2, 126.0, 127.5, 128.2, 131.4, 136.3, 142.1, 145.6, 149.3, 154.2; MS (APCI+) *m/z* calculated for $C_{66}H_{76}O_2$: 901.3, found 901.5 (M+).

20

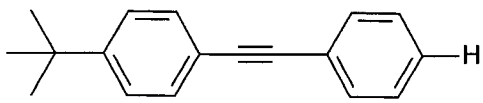
4-[(4-*tert*-butylphenyl)ethynyl]-nitrobenzene (20): A mixture of 1-bromo-4-*tert*-butylbenzene (**23**) (11 mg, 0.50 mmol), 1-ethynyl-4-nitrobenzene (**24**) (87 mg, 0.60 mmol) and $PdCl_2(PPh_3)_2$ (17.6 mg, 0.025 mmol) in dry degassed triethylamine (5 mL) was stirred at rt for 20 min, after which CuI (3.8 mg, 0.02 mmol) was added. The resulting mixture was stirred at reflux for 1h, and after cooling the solvent was evaporated on a rotary evaporator. The residue dissolved in ethyl acetate (2x10 mL) and then washed with water (15 mL). The organic layer extracted, dried over $MgSO_4$ and filtered. The solvent was removed on a rotary evaporator. The residue was purified by PLC (50% dichloromethane in petroleum ether) to give **20** (83 mg, 60 %): mp 145-146 °C. ^{1}H NMR δ 1.35 (s, 9H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 8.22 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 31.4, 35.2, 87.3, 95.3, 119.3, 123.9, 125.8, 130.9, 131.9, 132.4, 147.2, 153.0; GC-MS *m/z* calculated for $C_{18}H_{17}NO_2$: 279.3, found 279.0 (M^+).



21

4-[(4-*tert*-butylphenyl)ethynyl]-trifluoromethylbenzene (21): To a stirred mixture of 1-bromo-4-*tert*-butylbenzene (**23**) (11 mg, 0.50 mmol), 4-ethynyl-*α,α,α*-trifluorotoluene (**25**) (10 mg, 0.60 mmol) and $PdCl_2(PPh_3)_2$ (10.5 mg, 0.015

mmol) was added tetrabutylammonium fluoride (392 mg, 1.50 mmol) and water (27.5 mg, 1.50 mmol) under argon at room temperature. The resulting mixture was stirred for 3 h at 80 °C, then cooled, dissolved in water (10 mL) and extracted with ethyl ether (2x10 mL), The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure, the residue was purified by PLC (5% ethyl acetate in hexane) to give **21** (59 mg, 39%): mp 121-123 °C; ^1H NMR δ 1.33 (s, 9H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.63-7.58 (m, 4H); ^{13}C NMR δ 31.4, 35.1, 87.6, 92.2, 119.8, 123.1, 125.5, 125.7, 127.6, 130.1, 131.7, 132.0, 152.6; GC-MS *m/z* calculated for $C_{19}H_{17}F_3$: 302.33, found 302.0 (M^+).



22

4-[(4-*Tert*-butyl-phenyl)ethynyl]benzene (7): To a stirred mixture of **23** (21 mg, 1.0 mmol), phenylacetylene (**26**) (12 mg, 1.2 mmol) and $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol) was added tetrabutylammonium fluoride (78 mg, 3.0 mmol) and water (54 mg, 3.0 mmol) under argon at room temperature. The resulting mixture was stirred for 1.5 h at 80 °C, was then cooled, then water (10 mL) was added, and then extracted with diethyl ether (2x10 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated on a rotary evaporator. The

residue was purified by PLC (5% ethyl acetate in hexanes) to give **22** (70 mg, 30 %): mp 62-63 °C; ^{1}H NMR δ 1.33 (s, 9H), 7.38-7.31 (m, 4H), 7.53-7.46 (m, 5H); ^{13}C NMR δ 31.4, 35.0, 88.9, 89.8, 120.5, 123.8, 125.6, 128.3, 128.5, 131.6, 131.8, 151.8; GC-MS *m/z* calculated for $C_{18}H_{18}$: 234.1, 234.2 (M+).

6.8- References

1. Pal, T.; Kar, T.; Bocelli, G.; Rigi, L. *Crystal Growth & Design,* **2004**, *4,* 743. (and references in there).

2. Zyss, J., Ed. *Molecular Nonlinear Optics: Materials, Physics and Devices*; Academic Press: New York, **1994**.

3. Chemla, D. S., Zyss, J., Eds. *Nonlinear Optical Properties of Organic Molecules and Crystals*; Academic Press: Orlando, FL, **1987**.

4. Torre, G.; Vázquez, P.; López, F. A.; Torres, T. *Chem. Rev.* **2004,** *104,* 3723.

5. Diemer, V.; Chaumeil, H.; Defoin, A.; Fort, A.; Boeglin, A.; Carré, C. *Eur. J. Org. Chem.* **2006**, 272.

6. de la Torre, G.; Vazquez, P.; Agulló-López, F.; Torres, T. *J. Mater. Chem.* **1998**, *8*, 1671.

7. Gong, W.; Li, Q.; Li, Z.; Lu, C.; Zhu, J.; Li, S.; Yang, J.; Cui, Y.; Qin, J. *J. Phys. Chem. B,* **2006,** *110,* 10241.

8. Srinivasan, P.; Gunasekaran, M.; Kanagasekaran, T.; Gopalakrishanan, R.; Ramasamy, P. *Journal of Crystal Grouth,* **2006**, *289,* 639.

9. Kenis, P. A.; Noordman, O. J.; Houbrechts, S.; van Hummel, G. J.; Harkema, S.; Van Veggel, F. M.; Clays, K.; Engbersen, J. J.; Persoons, A.; Van Hulst, N. F.; Reinhoudt, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 7875.

10. a) Kelderman, E.; Derhaeg, L.; Heesik, G. J. T.; Verboom, W.; Engbersen, J. F. J.; Van Hulst, N. F.; Persoons, A.; Reinhoudt, D. N.; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1075. b) Kelderman, E.; Derhaeg, L.; Heesik, G. J. T.; Verboom, W.; Engbersen, J. F. J.; Van Hulst, N. F.; Persoons, A.; Reinhoudt, D. N.; *Angew. Chem.* **1992**, *104*, 1107. c) Kelderman, E.; Heesink, G. J. T.; Derhaeg,L.; Verbiest, T.; Klaase, P. T. A.; Verboom, W.; Engbersen, J. J.; van Hulst, N. F.; Clays, K.; Persoons, A.; Reinhoudt, D. N. *Advanced Materials* **1993**, *5*, 925.

11. a) Regayeg, M.; Vocanson, F.; Duport, A.; Blondeau, B.; Perrin, M.; Fort, A.; Lamartine, R. *Mater. Sci. Eng. C* **2002**, *21*, 131. b) Guo, X.; Zhang, L.; Lu, G.-Y. Zhang, C.Z.; Jin, C. M.; Liu, M. H. *Supramol. Chem.* **2005**, *17*, 271.

12. Kenis, P. A.; Noorman, O. J.; van Hulst, N. F.; Engbersen, J. J.; Reinhoudt, D. N.; Hams, B. M.; van der Vost, C. M. *Chem. Mater,* **1997**, *9*, 596.

13. Hennrich, G.; Murillo, M. T.; Prados, P.; Song, K.; Asselberghs, I.; Clays, K.; Persoons, A.; Benet-Buchholz, J.; de Mendoza, J. *Chem. Comun.* **2005**, 2747.

14. Hennrich, G.; Murillo, M.-T.; Prados, P. This group synthesized the wide-rim alkynyl calix[4]arene analogues at the Universidad Autonoma de Madrid, Madrid, Spain.

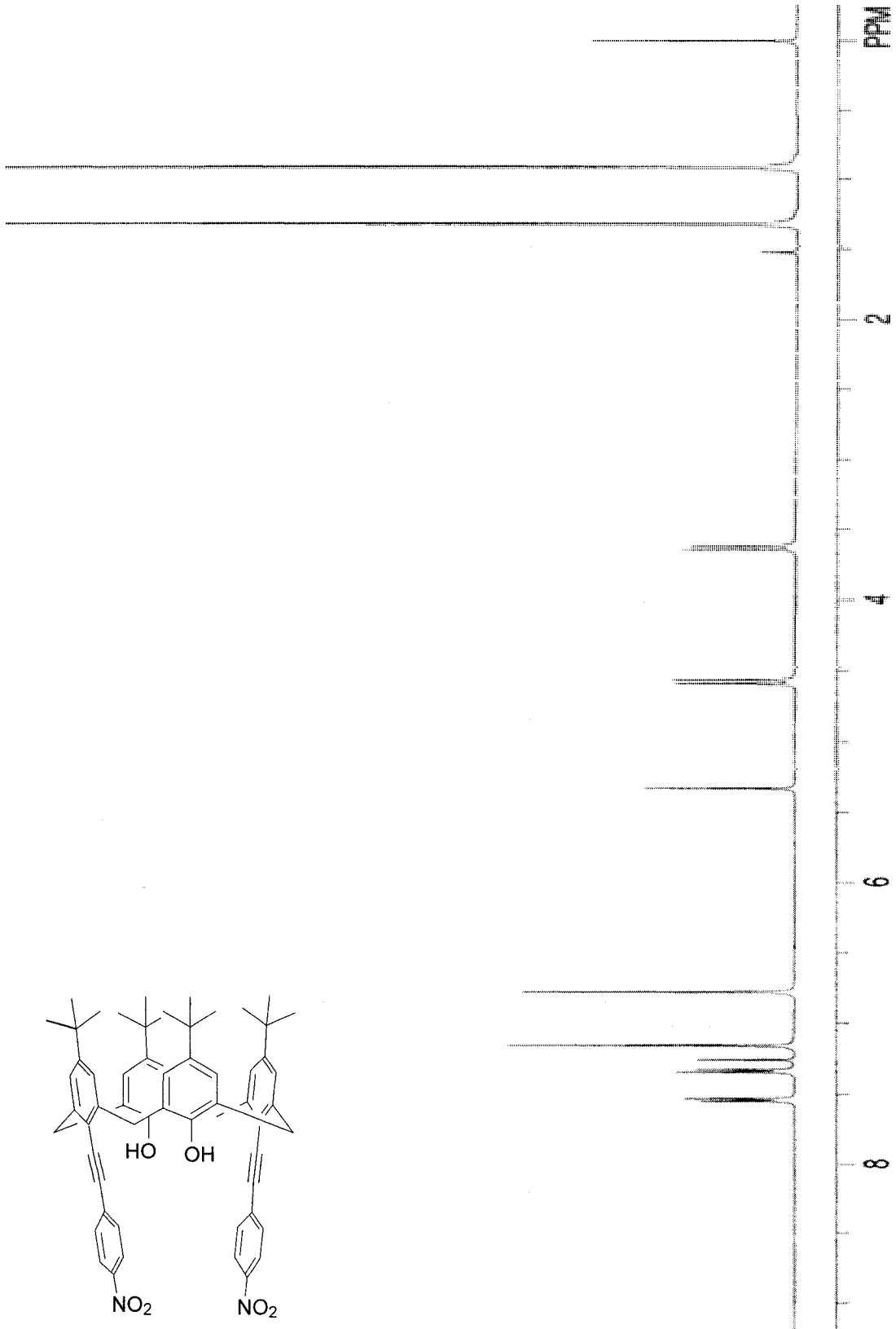
15. Teshome, A.; Asselberghs, I.; Clays, K. This group has been measuring the NLO properties of compounds described in this chapter, at the University of Leuven, Leuven, Belgium.

16. Hennrich, G; Murillo, M.-T.; Prados, P; Al-Saraierh, H.; El-Dali, A.; Thompson, D. W. Collins. J.; Georghiou, P.E.; Teshome, A.; Asselberghs, I; Clays, K. *Revision submitted on the 15th, June 2007.*

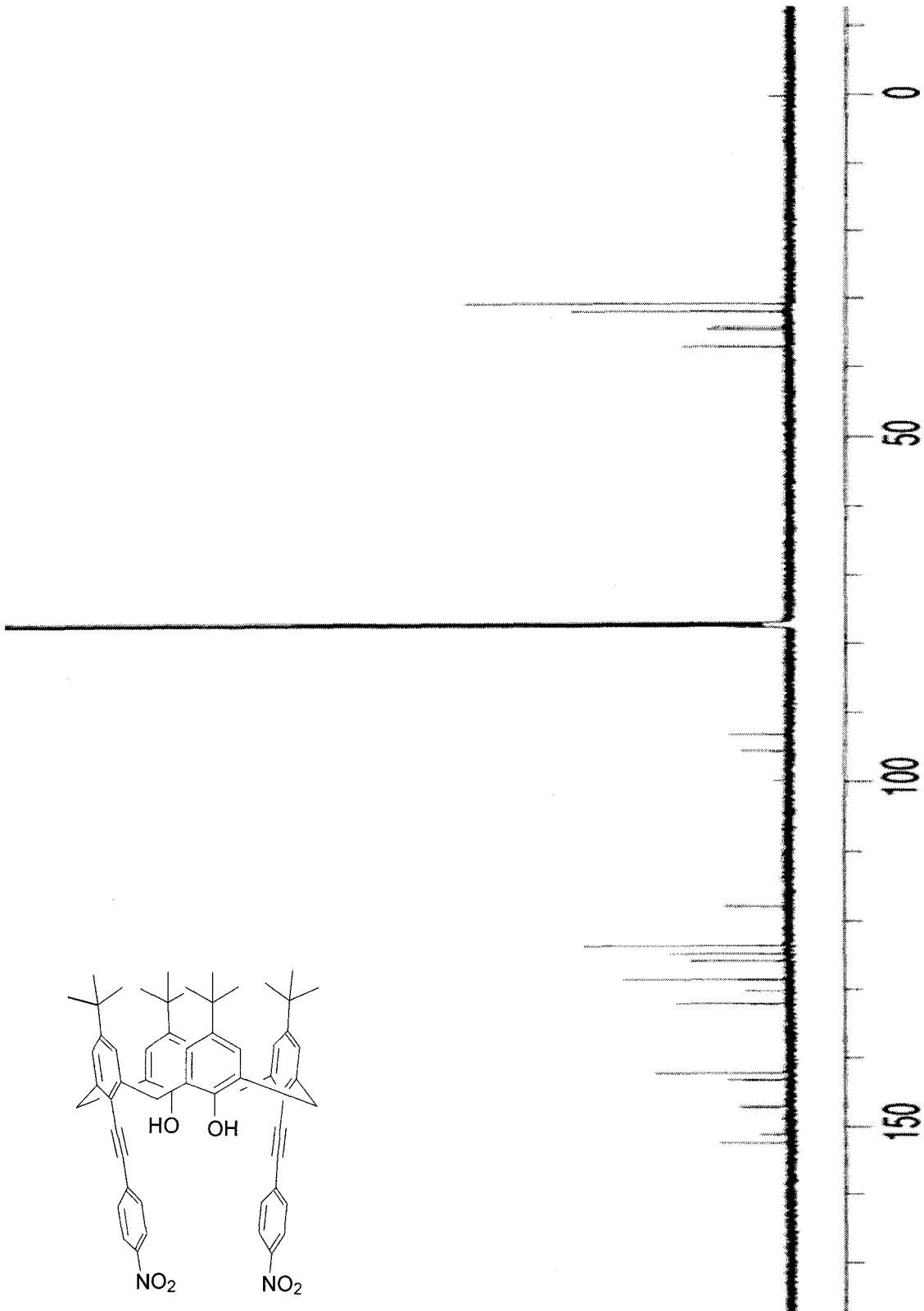
Appendix: Chapter 6

X-ray Crystal Data for 19: A colorless prism crystal (CH_3Cl/MeOH) of $C_{66}H_{76}O_2$ A colorless prism crystal of monoclinic, space group C2/c (#15) , Z = 4, a = 18.304(5) Å, b = 16.202(4) Å, c = 20.864(5) Å, β= 118.442(6)°, V = 5441(2) Å^3, $D_{Calcd.}$ = 1.100 g cm^{-3}, crystal size = 0.50 X 0.20 X 0.08 mm. Intensity data were measured -160 ± 1 °C on a Rigaku AFC8 diffractometer with graphite monochromated Mo-Kα (λ = 0.71070 Å) radiation $2\theta_{max}$ = 63.4°; 39303 reflections converged to a final R_{int} of 0. 081 for 4821 unique reflections and 317 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0. 1162 and 0. 2565, respectively, and GoF = 1. 294.

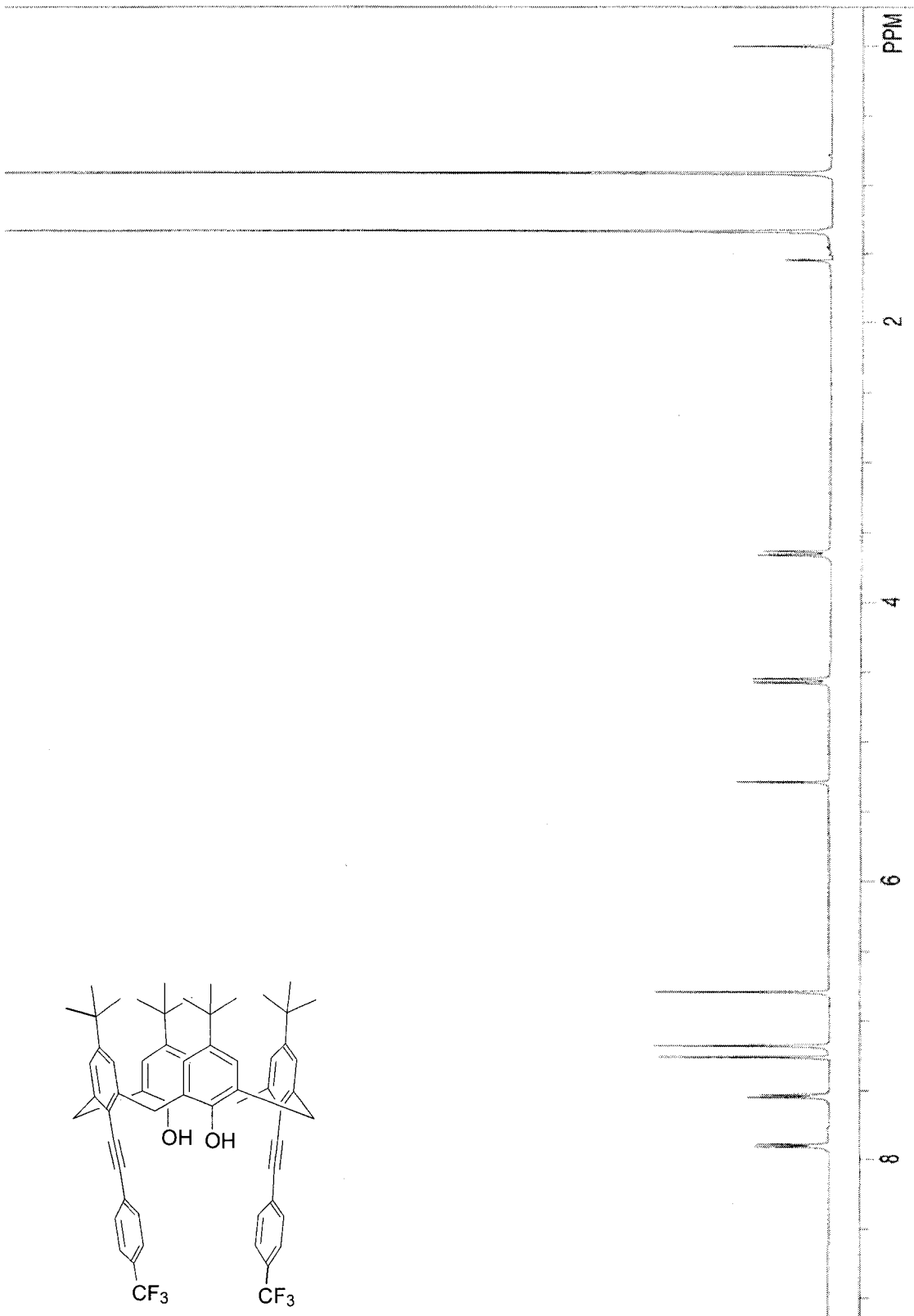
Prepared by: Julie L. Collins, Chemistry Department, Memorial University of Newfoundland January 17, 2007



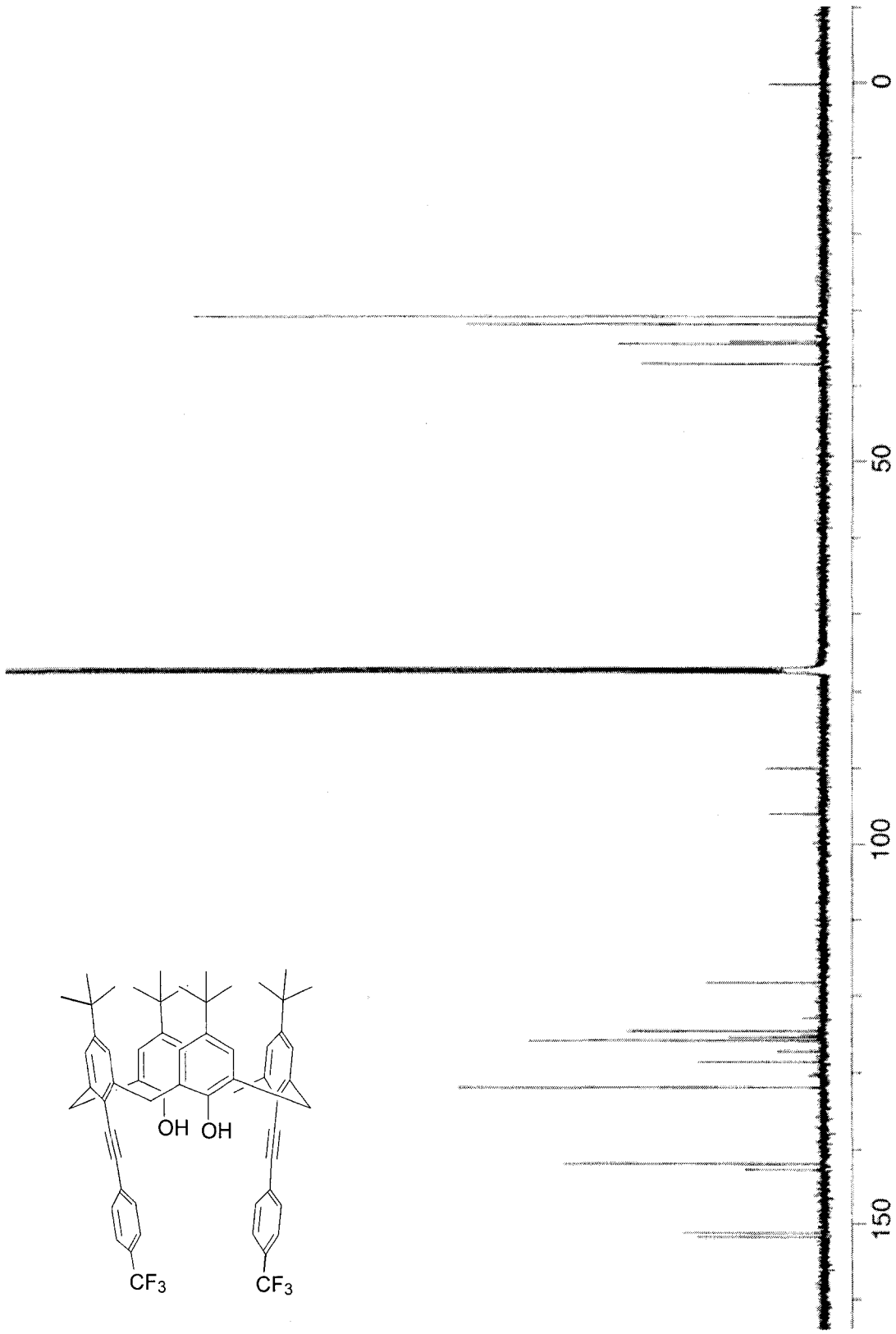
^{1}H NMR spectrum for compound **10**



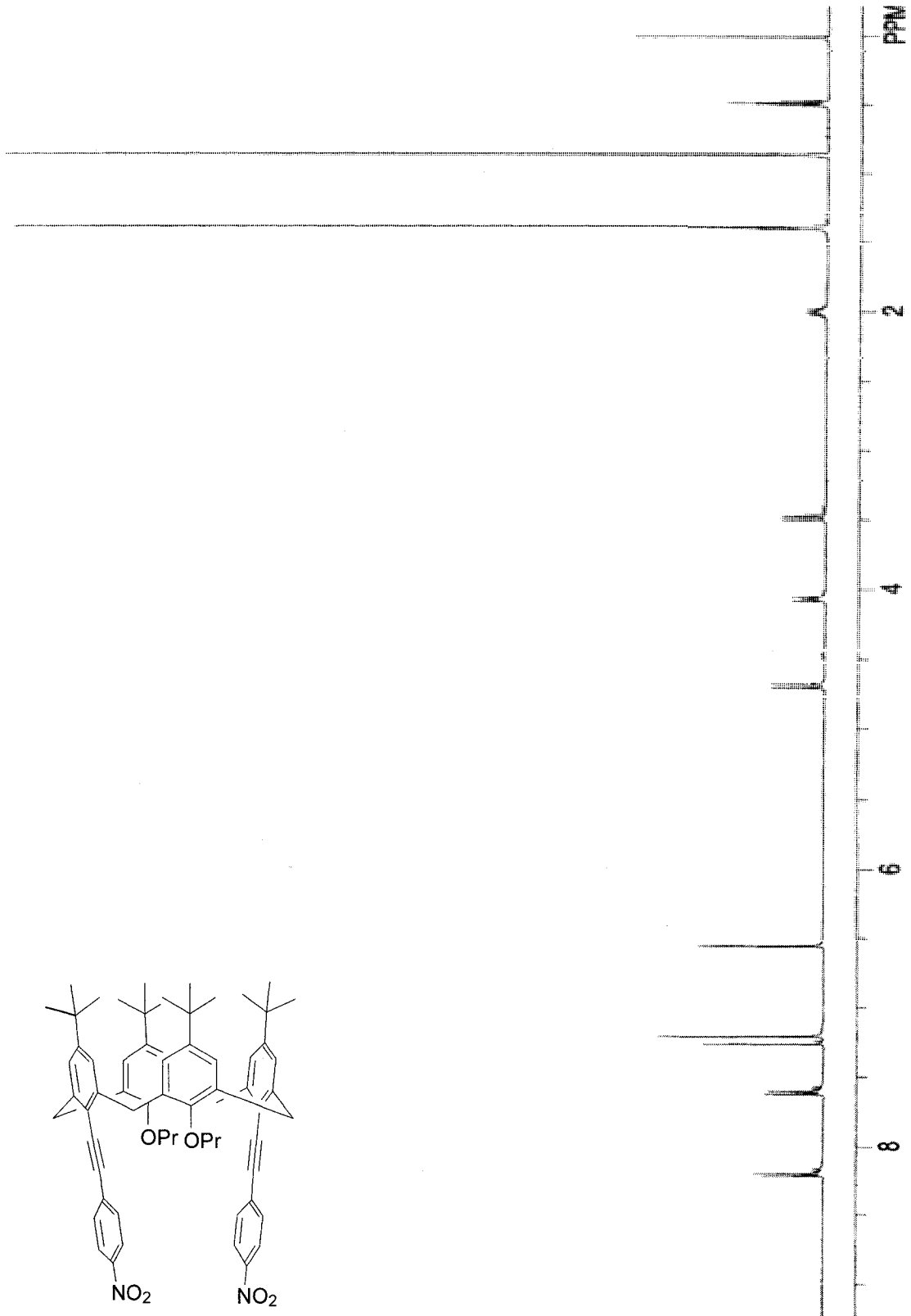
^{13}C NMR spectrum for compound **10**



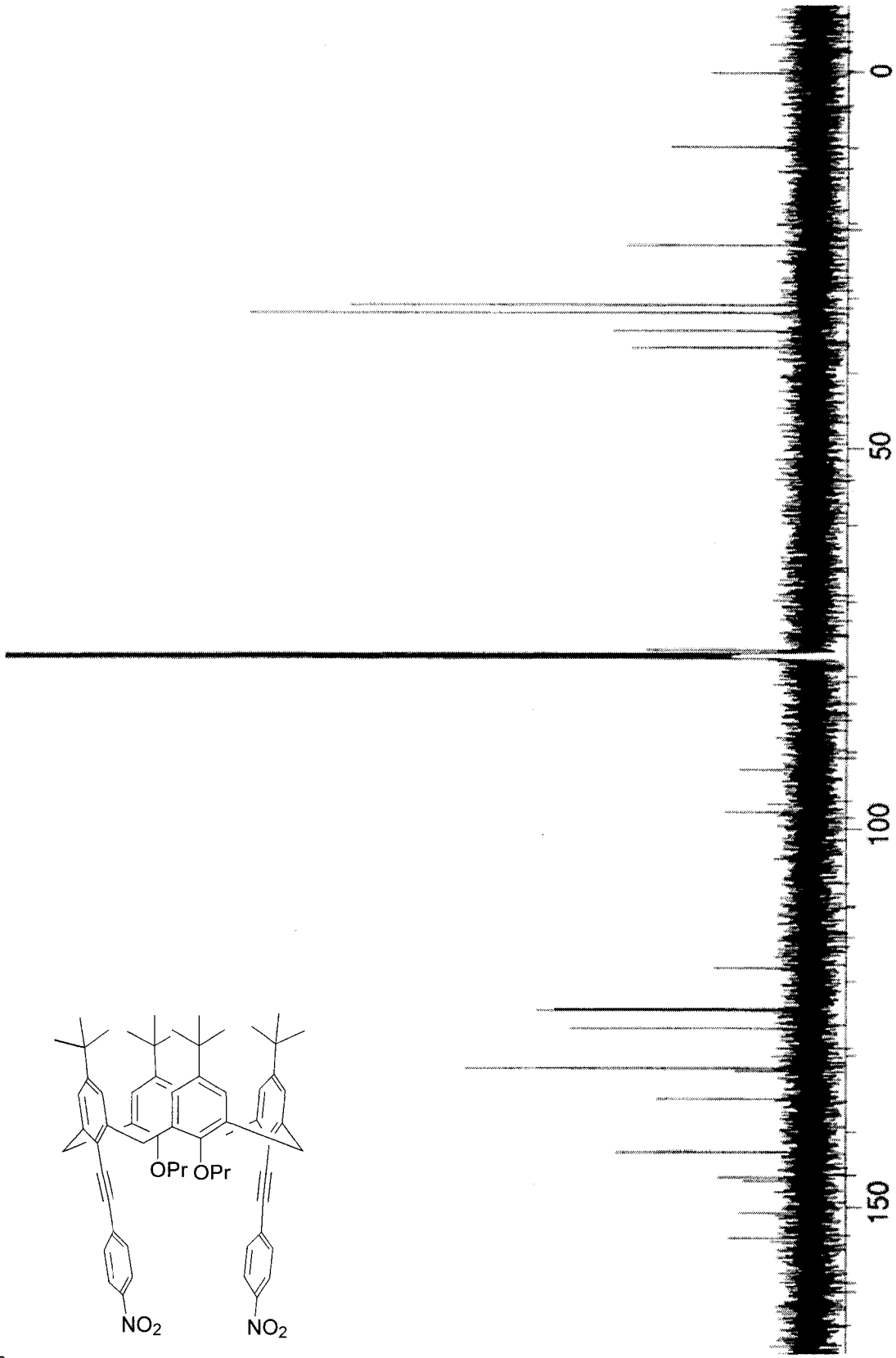
^{1}H NMR spectrum for compound **11**



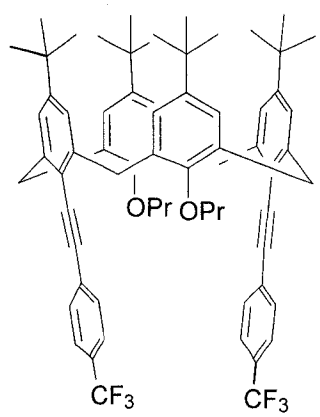
^{13}C NMR spectrum for compound **11**

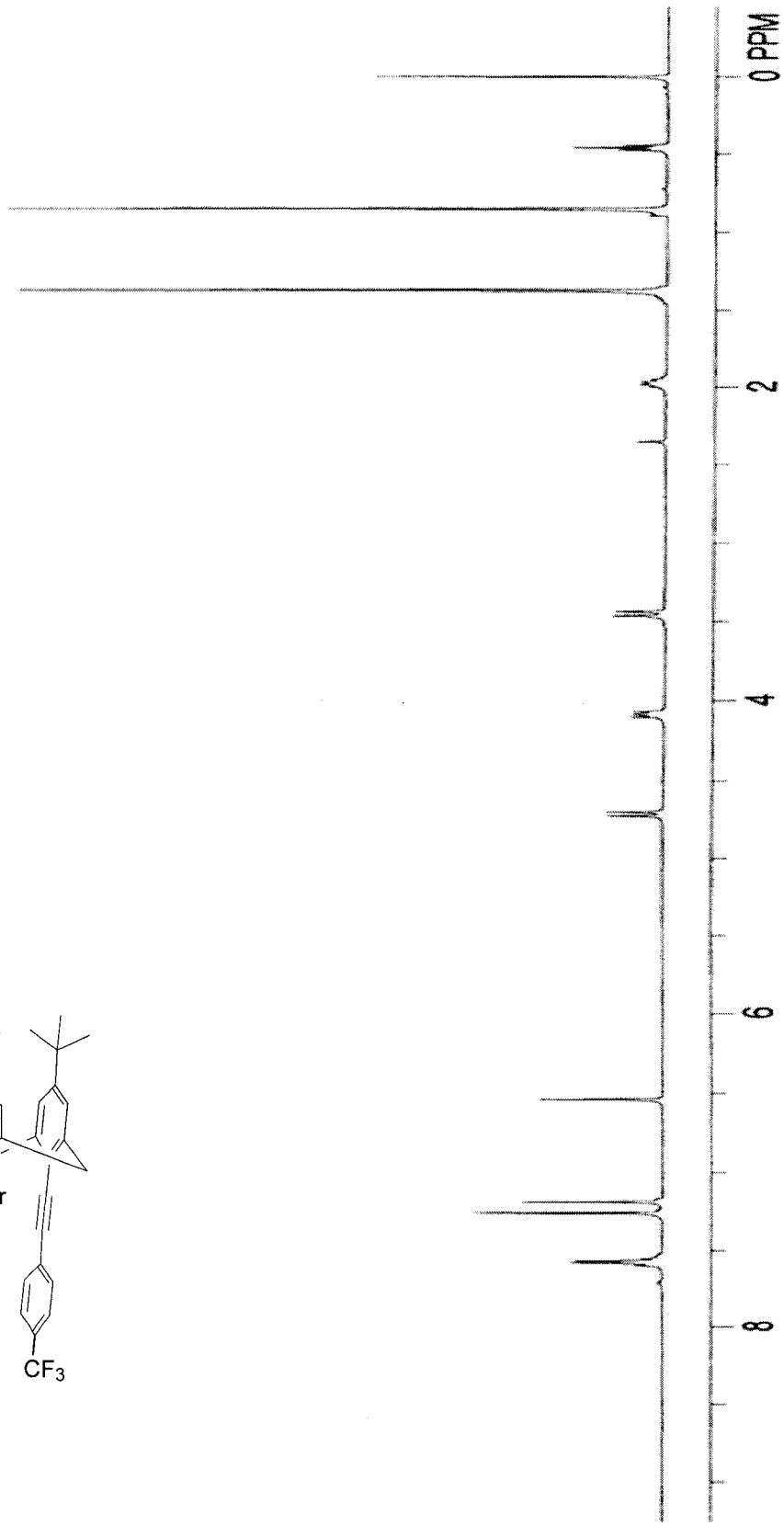


^{1}H NMR spectrum for compound **17**

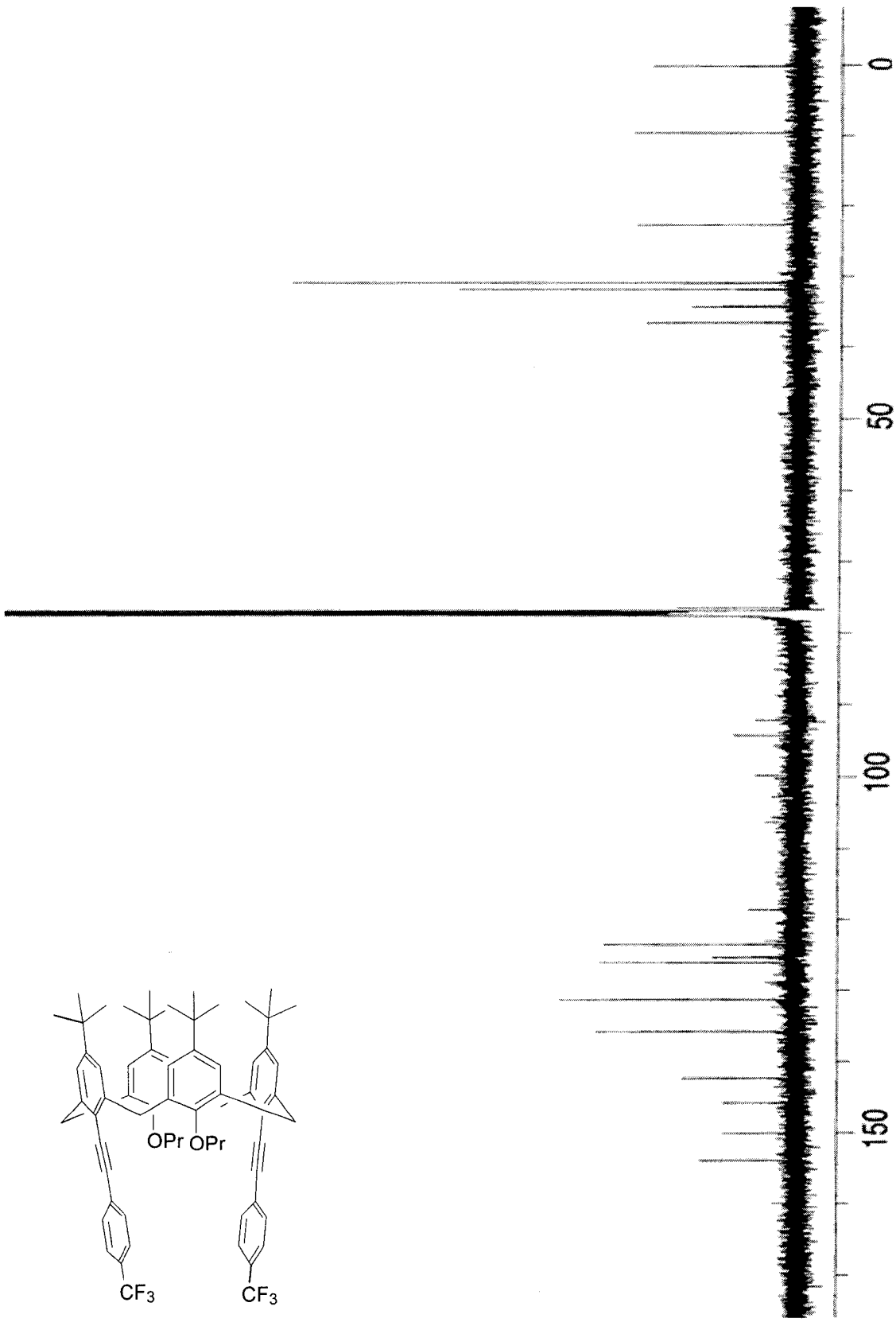


^{13}C NMR spectrum for compound **17**

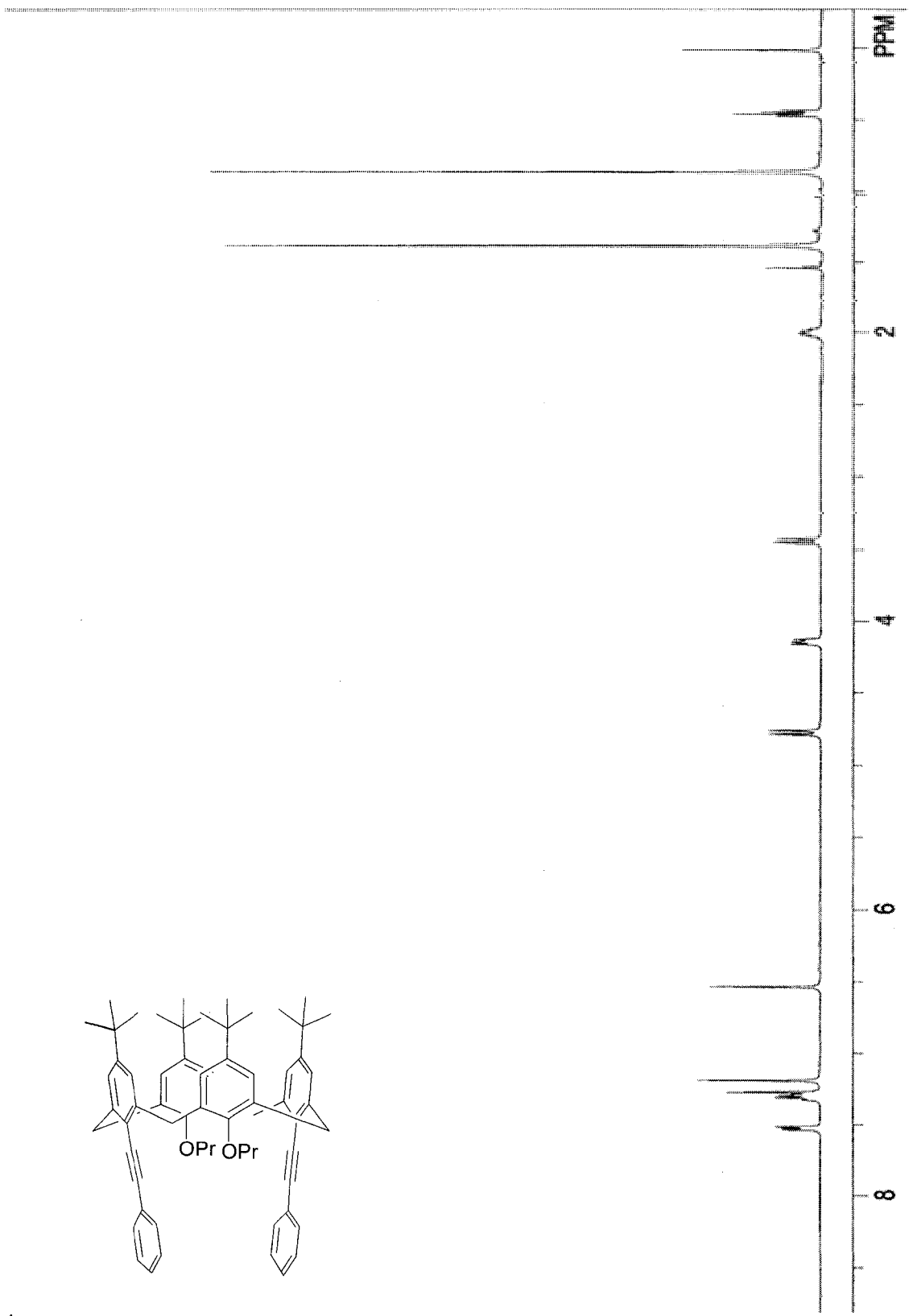




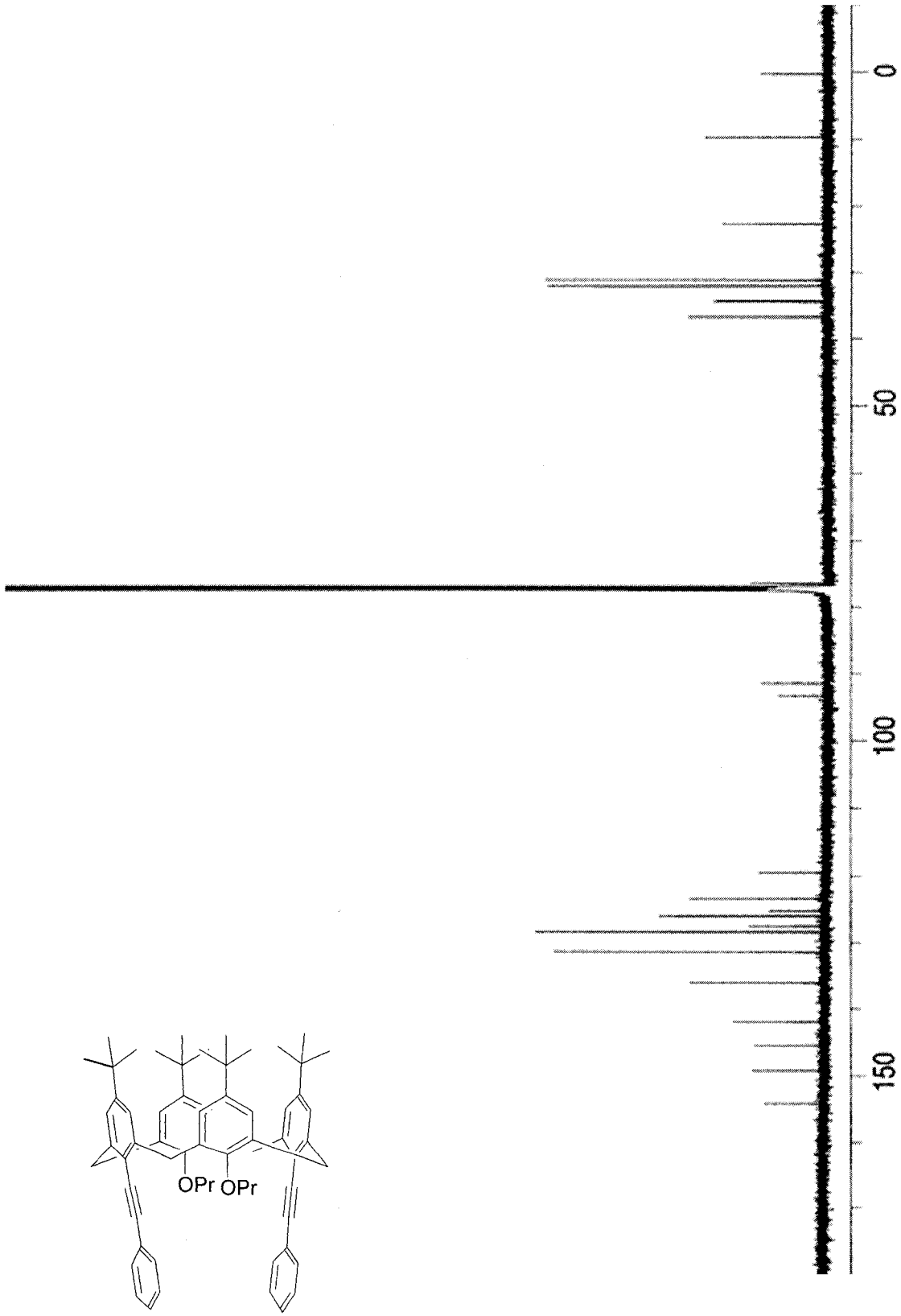
^{1}H NMR spectrum for compound **18**



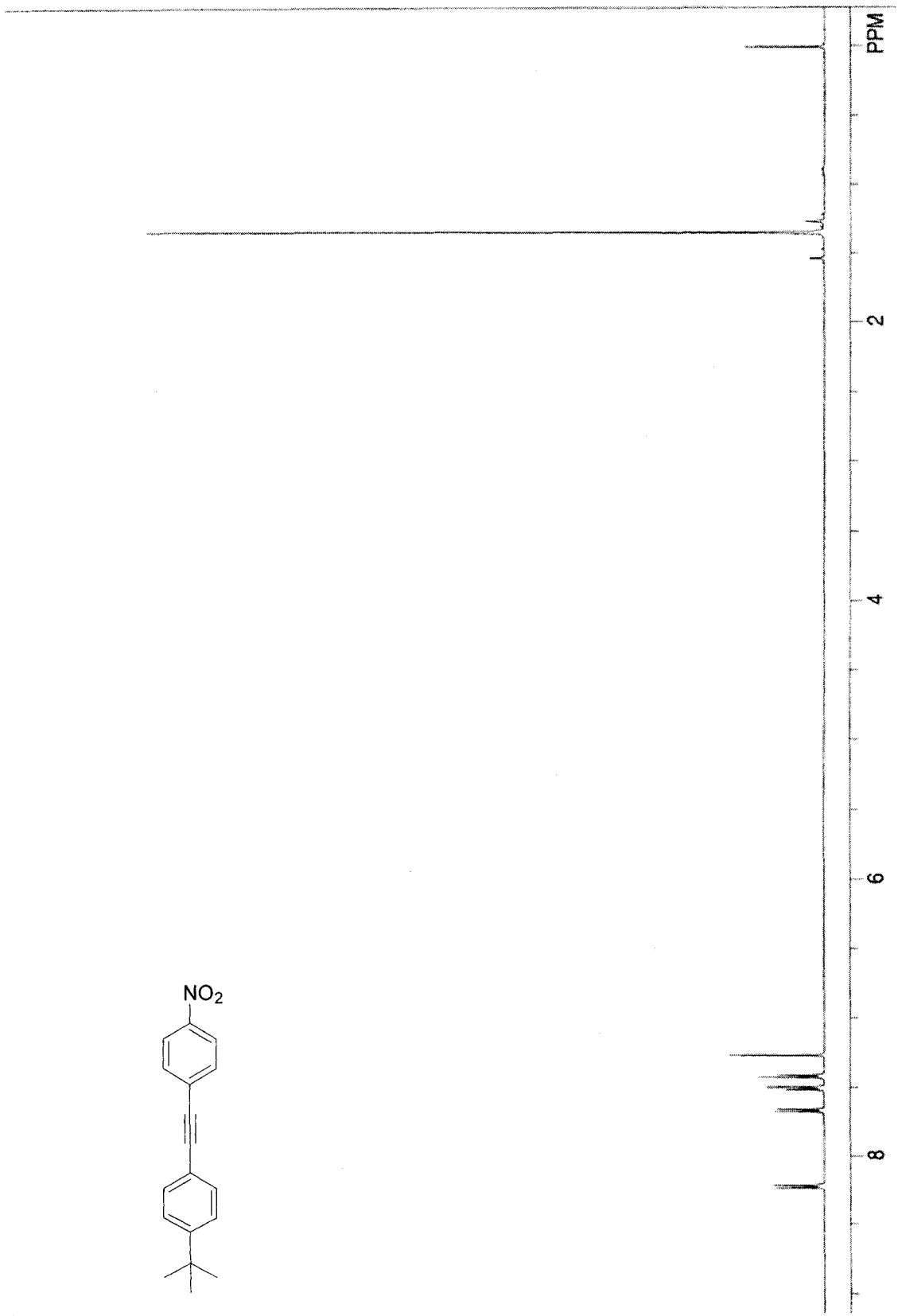
^{13}C NMR spectrum for compound **18**



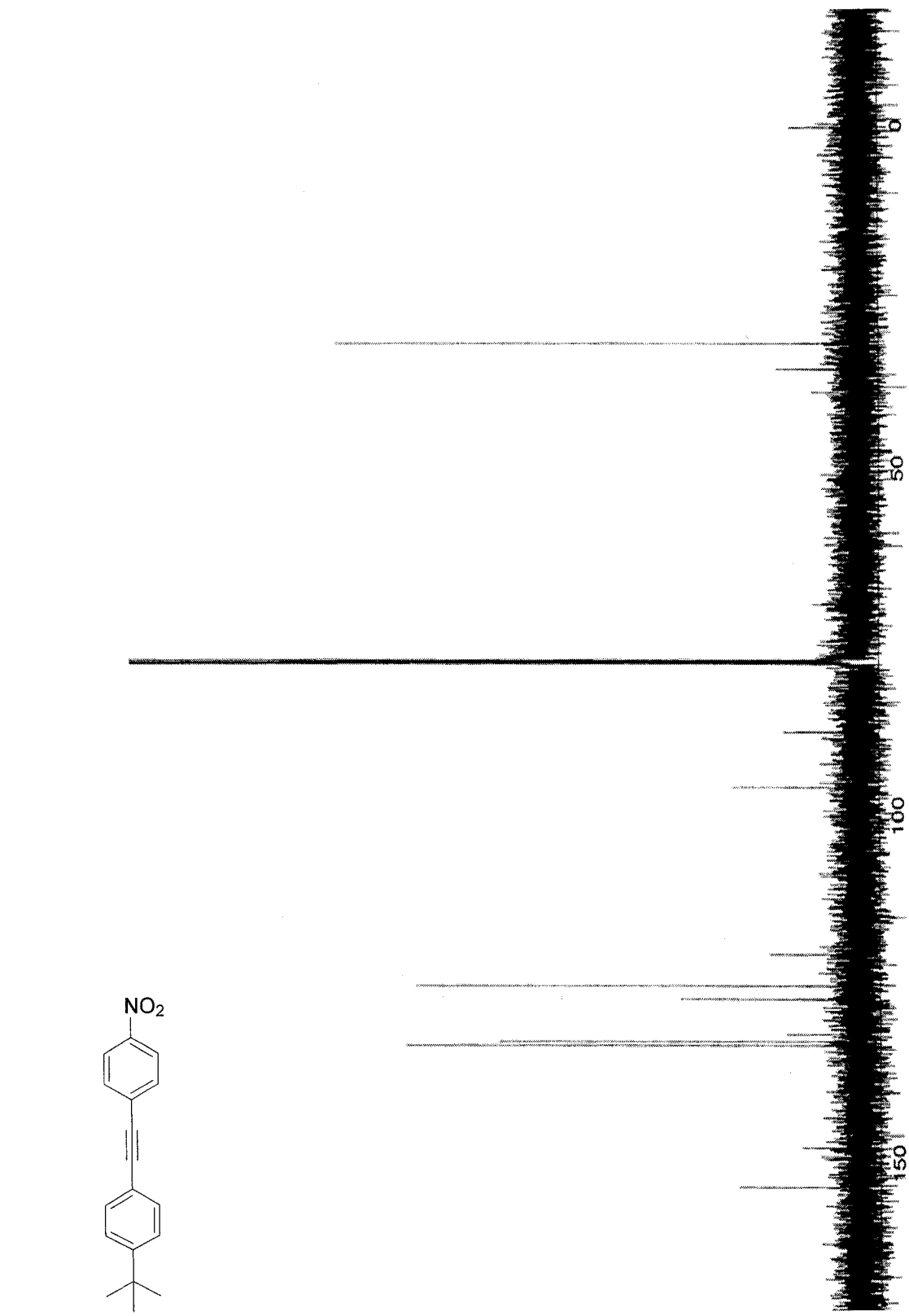
^{1}H NMR spectrum for compound **19**



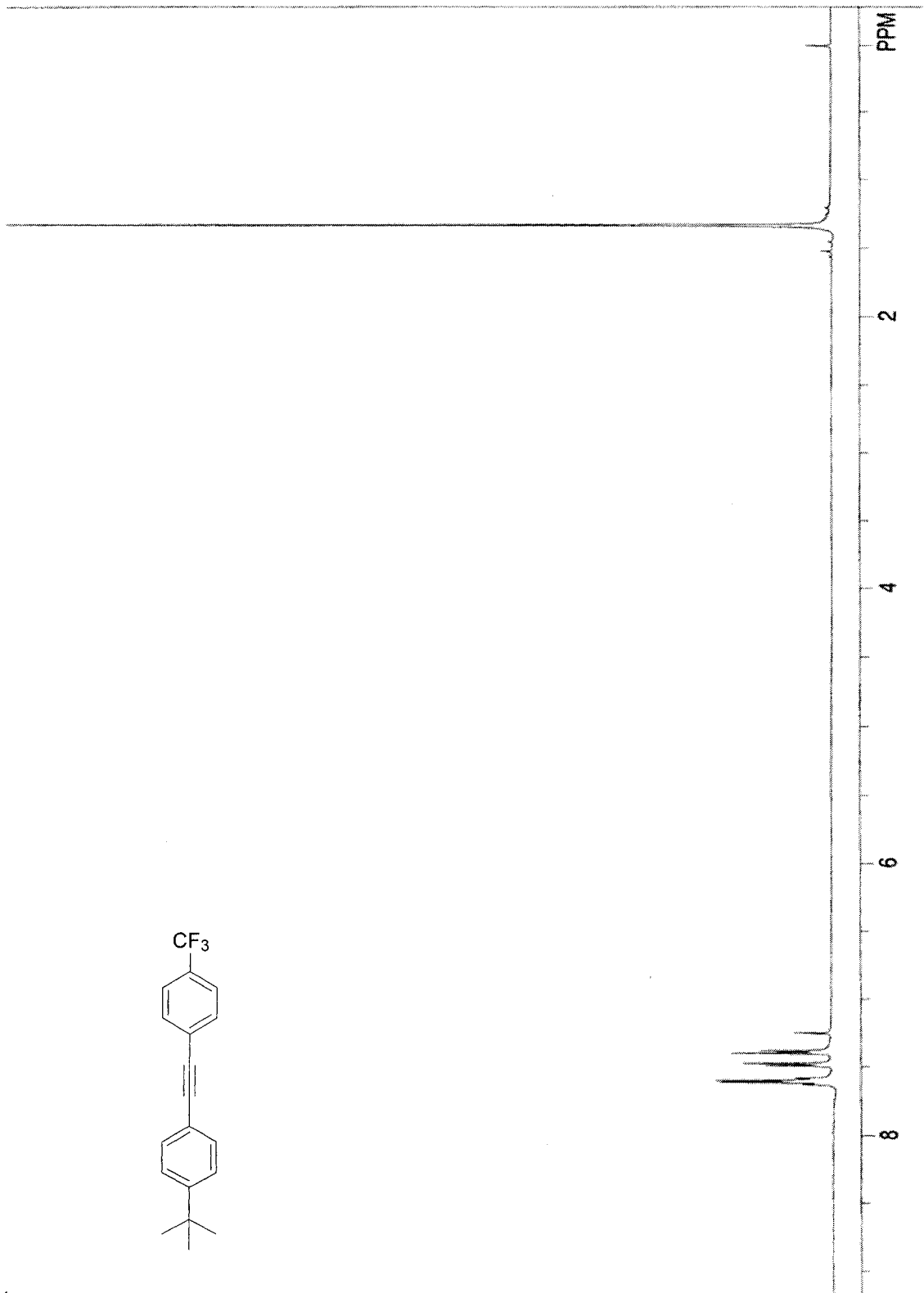
^{13}C NMR spectrum for compound **19**



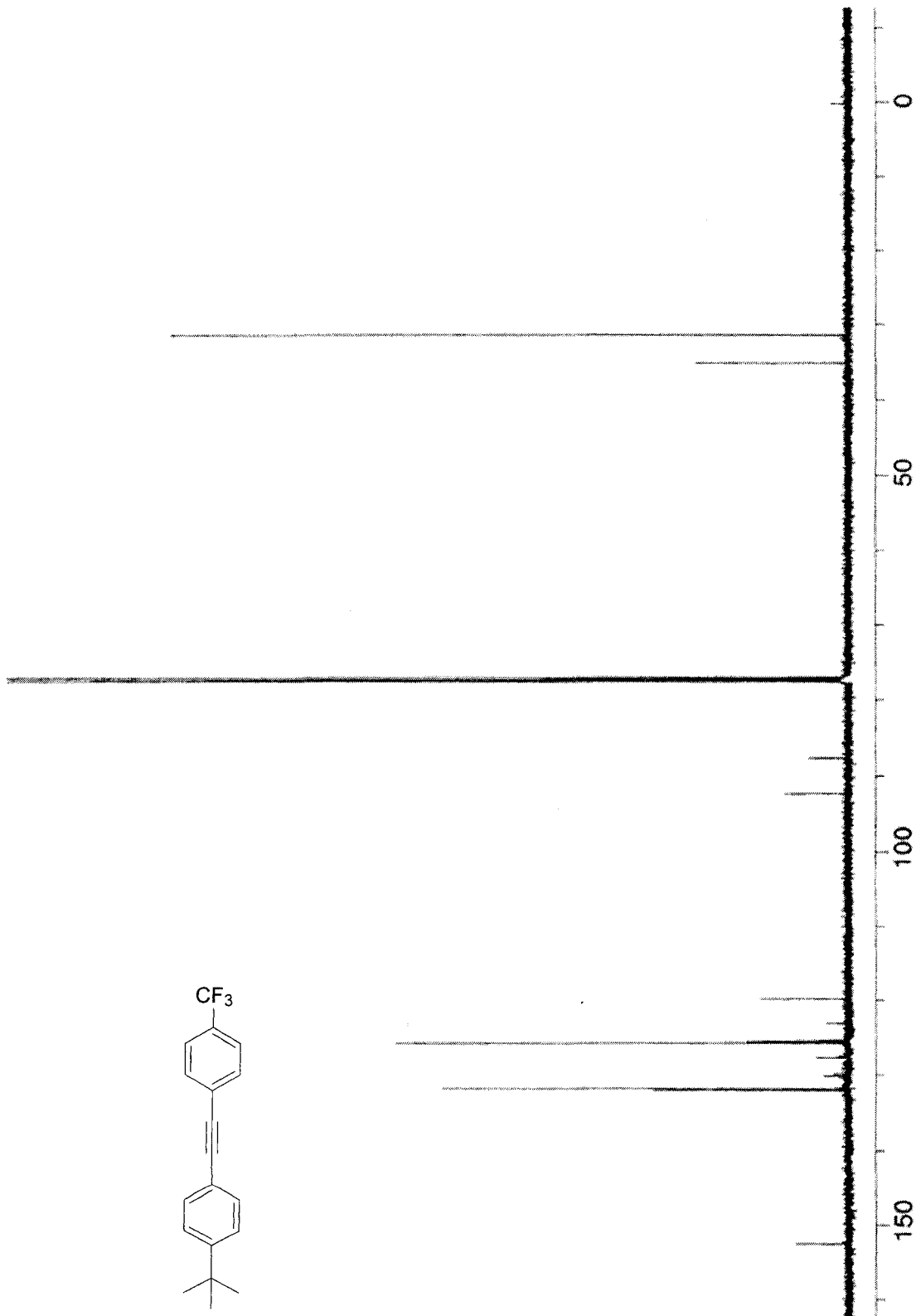
^{1}H NMR spectrum for compound **13**



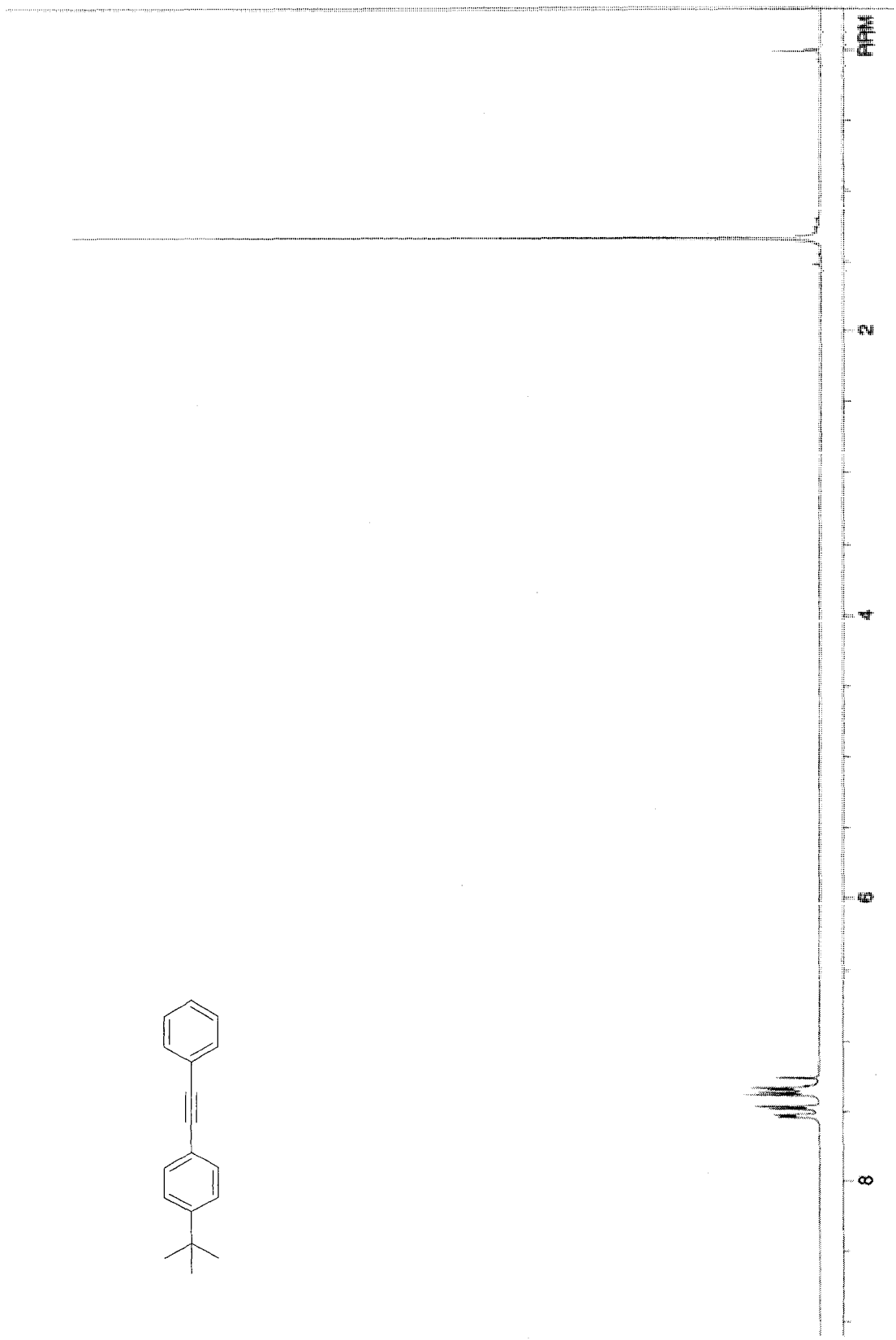
^{13}C NMR spectrum for compound **13**



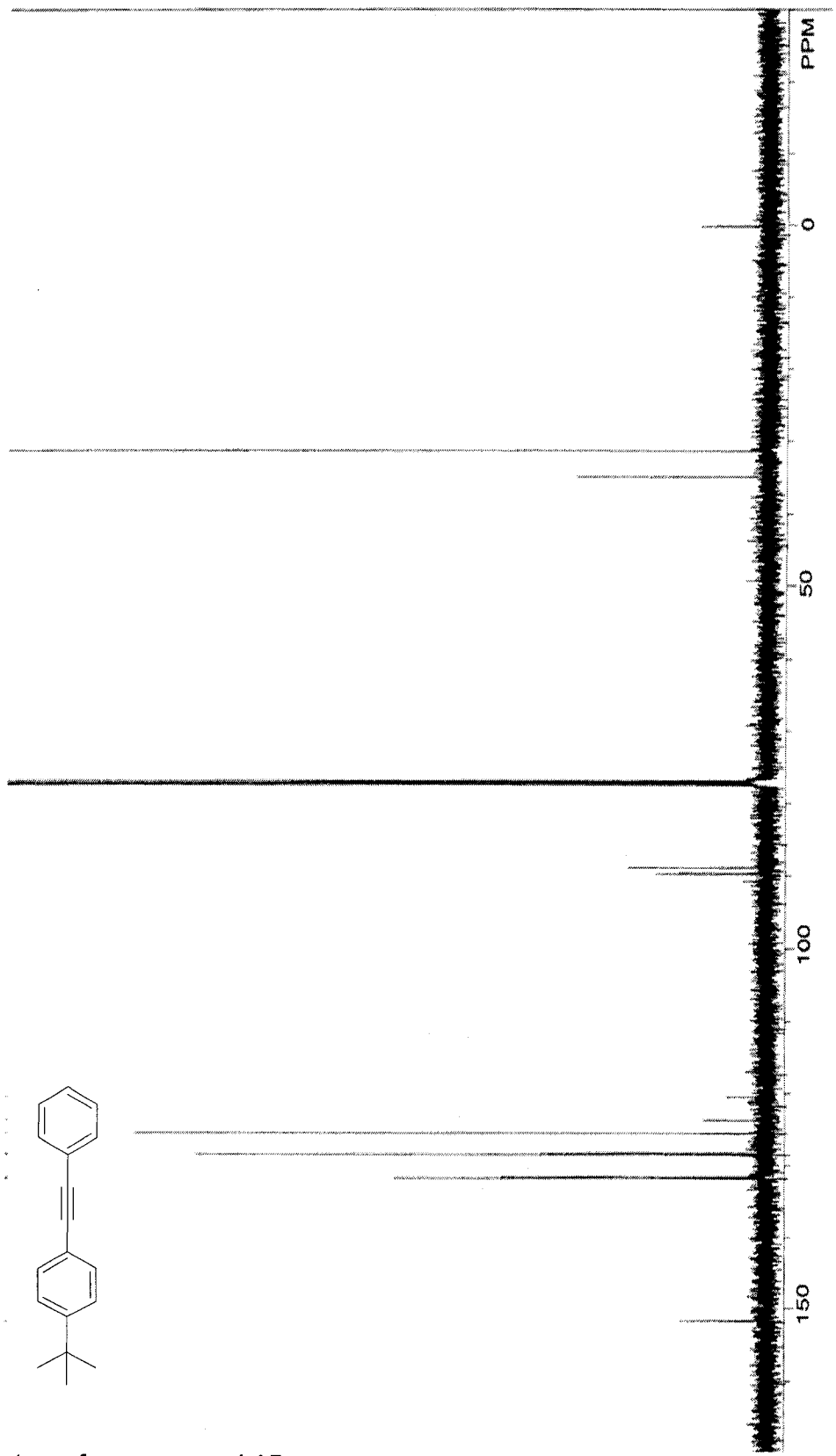
^{1}H NMR spectrum for compound **14**



^{13}C NMR spectrum for compound **14**



^{1}H NMR spectrum for compound **15**



^{13}C NMR spectrum for compound **15**

Chapter 7

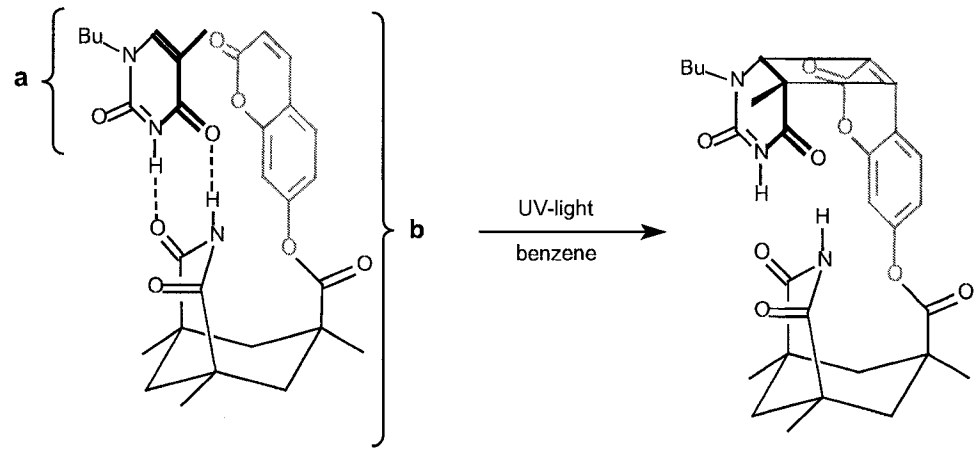
Photochemical Reactions of Calix[4]arenes and their Derivatives

7.1- Introduction

Photochemistry is "concerned with the chemical change that is brought about by the absorption of light".[1] Although it is difficult to control reaction selectivity with respect to regio- and stereochemistry in photochemical reactions, there are some transformations which can more easily be achieved photochemically than by thermal reactions. For example, [2+2]-cycloaddition reactions of alkenes do not readily occur under thermal conditions, whereas they can easily be obtained photochemically. Such reactions, and many others may be predicted in most cases, using the "Woodward-Hoffman Rules".[2]

Recent modifications of photochemical reaction methodology have been achieved in order to improve their selectivity. One such modification involves using a scaffold which serves as a controlling element in the photochemical reaction.[3] The scaffold could be a compound, such as a calixarene, a cyclodextrin, or DNA, and it could be bound to the substrate by either covalent or non-covalent ("supramolecular") bonding. Typically, the role of the scaffold is to make one of the substrate faces more accessible, relative to the other faces, in a given reaction. This facial selectivity is usually due to a steric effect generated by the scaffold itself and can lead to significant selectivity in the product formation in the photochemical reaction. For example, Mori et al.[4] reported the

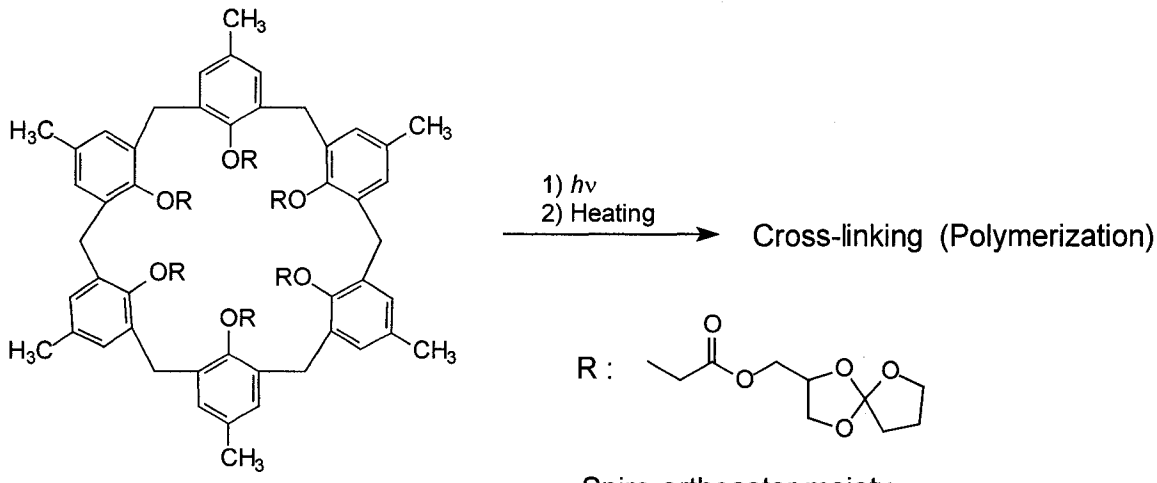
stereoselective photochemical reaction between the thymine (**a**) and the coumarin (**b**) substituent in the complex **1**, to give compound **2** (Scheme 7.1).



1(a:b) **2**

Scheme 7.1 Enhanced template-assisted photochemical reaction selectivity.

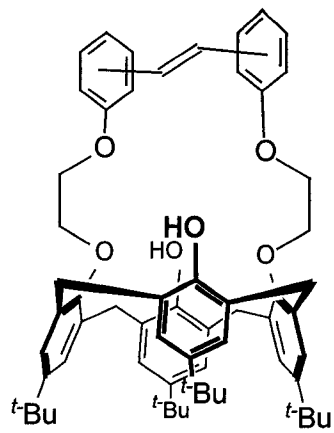
There are only a few examples which have been reported of photochemical reactions involving calixarenes. In 2002 Nishikubo *et al.*[5] investigated and reviewed the photochemistry of some calixarenes, in particular for their potential application to the field of photoresist technology and UV-curable coatings. More specifically, they reported the preparation of new lower-rim substituted and bridged calix[4]arenes and their photonic response. They also reported the polymerization of photoreactive narrow-rim *o*-functionalized *p-tert*-butylcalix[6]arene derivatives (Scheme 7.2).



3

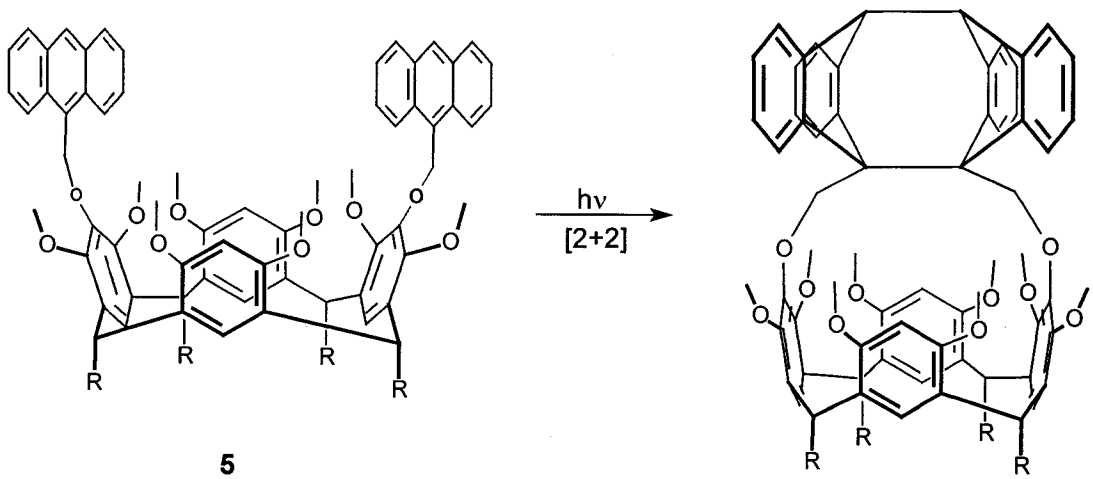
Scheme 7.2 Photo-polymerization of *p*-methylcalix[6]arene derivative **3**

Another example of a photochemical reaction using calixarenes was reported in 2005 by Sukwattanasinitt *et al.*[6] In this work, a narrow-rim stilbene-bridged *p-tert*-butylcalix[4]arene (**4**) (Figure 7.1) which could act as a "photoswitchable molecular receptor" for various small electron-deficient molecules was synthesized. Sukwattanasinitt *et al.* demonstrated that the complexation ability of compound **4** can be switched off when it is irradiated with UV-light. A similar photoswitchable molecular receptor involving a photochemical [4+4] cycloaddition with a related resorc[4]arene-anthracene **5** (Scheme 7.3) has been described by Schafer and Mattay.[7] More recently, Varma *et al.*[8] reported a novel photochemical reaction of the calixarene[4]arene-derived bis(spirodienones) **6** and **7** which produced the same rearrangement product, **8** (Scheme 7.4).



4

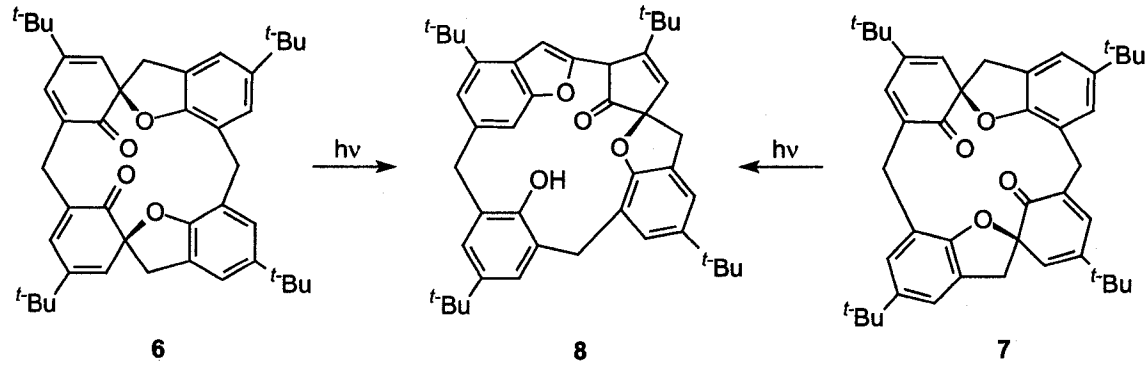
Figure 7.1 Stilbene-bridged *p-tert*-butyl calix[4]arenes (**4**).



5

Scheme 7.3 Photochemical [4+4] cycloaddition of resorc[4]arene-anthracene **5**.

During the course of our on-going research on narrow-rim substituted alkynyl calix[4]arenes[9] we observed some unprecedented photochemical reactions and these findings are described and discussed in this Chapter.



Scheme 7.4 Photochemical reaction of the calixarene[4]arene-derived bis(spirodienones) **6** and **7**

7.2- Results and Discussion

The respective emission intensities at (λ_{max} = 330 nm for **9a-b**, Figure 7.1a), and the corresponding absorbance intensities at (λ_{max} ~ 230 for **9a-b**; and at λ_{max} ~ 286 and 311 nm for **9a** and at λ_{max} ~ 295 and 329 nm for **9b**, Figure 7.1b) decreased between successive replicate measurements with the same samples (Scheme 7.5). These fluorescence measurements had been undertaken as part of the determination of the potential Non-linear Optical (NLO) properties of this new class of calix[4]arene derivatives, which were developed in our laboratory and are described in Chapter 6 of this dissertation.

Thin layer chromatographic analysis indicated that a new product was formed in each case, with **9a** and **9b**, and it became obvious that the changes in the observed absorbance intensities were due to photochemical reactions occurring.

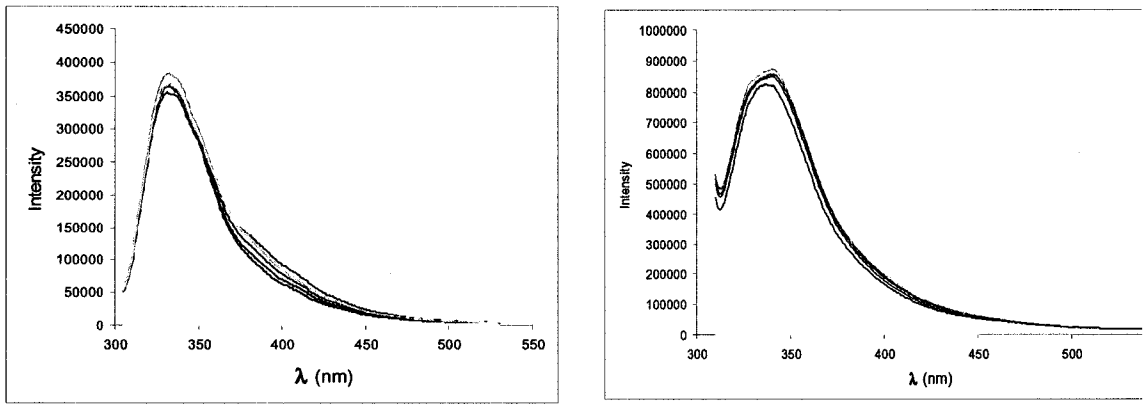


Figure 7.1a Fluorescence spectra of **9a** (*left*) and **9b** (*right*) (2.9 x 10^{-7} M) in CH_2Cl_2 showing decrease in emission intensity over 3 min intervals. Top spectrum (t=0 min).

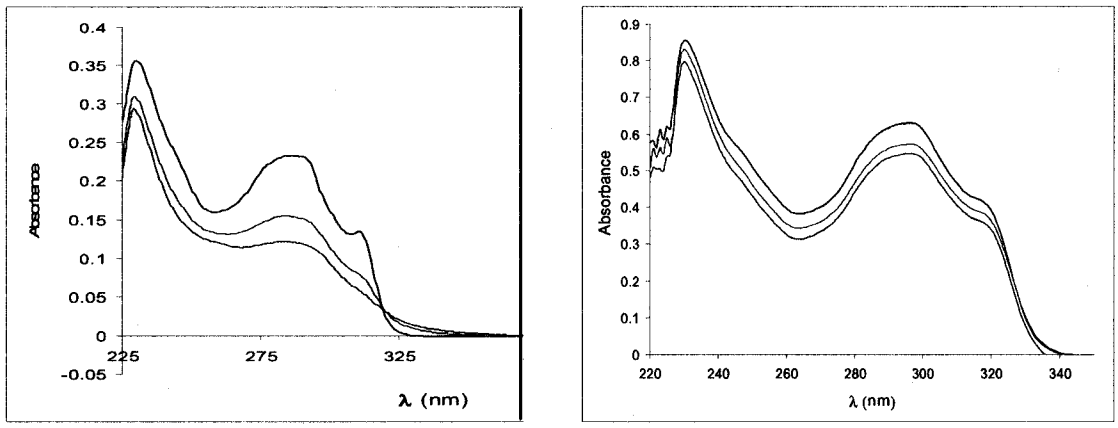


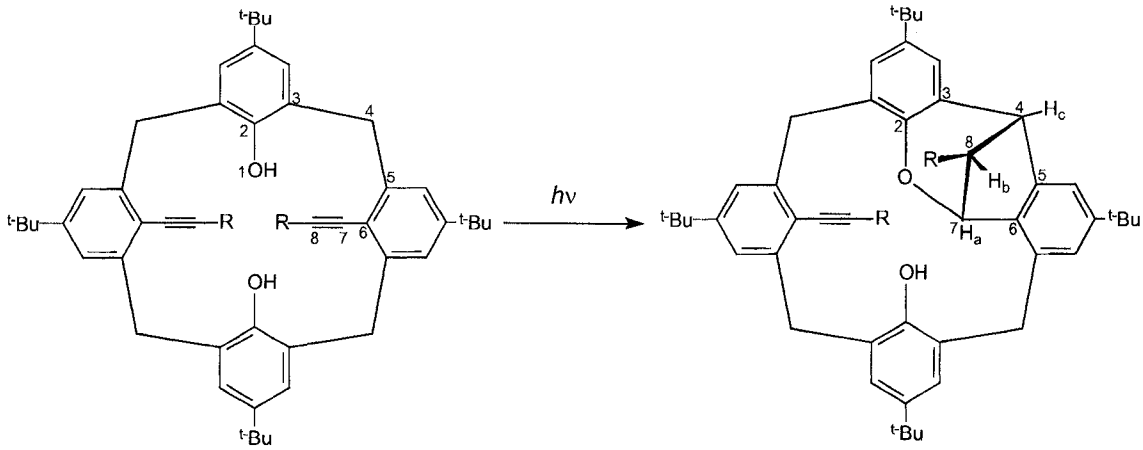
Figure 7.1b Uv-vis spectra of **9a** (*left*) and **9b** (*right*) (2.9 x 10^{-7} M) in CH_2Cl_2 showing decrease in absorption intensity over 3 min intervals. Top spectrum (t=0 min).

Detailed further investigations on these unexpected findings were then carried out with relatively larger-scale reactions than those which were used for

the UV-fluorescence spectroscopic determinations were conducted in a Rayonet® photochemical reactor using solutions of **9a** and **9b** in CH_2Cl_2. Since these calixarenes were both subsequently found to undergo the same types of photochemical reactions, the following discussion is focused on the photochemistry of **9a**, except for some significant differences between the two which need to be mentioned.

The first reactions were conducted by irradiating e.g. a solution of **9a (or 9b)** in CH_2Cl_2 at room temperature, for approximately 3 h, using only two 21 watt 3000 X lamps in the reactor so that the reaction could be easily monitored by both TLC and *in situ* ^{1}H NMR spectroscopy. According to the TLC analysis, only one new product which was less polar than the starting material had formed during this 3 h period. As well, it was clear that unreacted starting material **9a** still remained in the reaction mixture and that no other products appeared to be formed, as judged by TLC. This new compound was later determined to be a novel and unprecedented calixarene derivative, **10a** from **9a;** or **10b** from **9b** (Scheme 7.5).

Increasing the reaction times, for periods of longer than 3 h resulted in significantly diminished yields of both **10a** and unreacted **9a**. Subsequently, we found that this was due to the formation of at least two new photoproducts which were discussed later in this chapter. Calixarene **9b**, was found to react much faster than **9a**, and as monitored by ^{1}H NMR, the corresponding product **10b** was optimally obtained when the photoirradiation was conducted for only 0.5 h.



9a R = Ph
9b R = $C_6H_4CF_3$

10a R = Ph (33%)
10b: R = $C_6H_4CF_3$ (53%)

Scheme 7.5 Initial photochemically-induced cycloisomerization reactions of calixarenes **9a** and **9b**.

The ^{1}H NMR spectrum for calixarene **10a** (Figure 7.2) for example, revealed: (*a*) four non-equivalent *tert*-butyl groups, indicating that **10a** had no symmetry elements. By way of contrast, **9a** is C_{2v}-symmetrical and shows only two separate singlet signals in its ^{1}HMR spectrum for the two pairs of non-equivalent *tert*-butyl groups. (*b*) D_2O proton-exchange experiments with **10a** indicated that only one exchangeable hydroxyl proton, at δ ~ 7.28 ppm, remained in the product, suggesting that one of the two hydroxyl groups in **10a** had undergone a change during the photochemical reaction. (*c*) The appearance of a new one-proton doublet of doublet at ~ δ 6.26 ppm (J = 2.0 and = 1.5) was suggestive of a vinyl proton that could have resulted from the reaction of an alkynyl group with the hydroxyl group whose proton was no longer in evidence.

(*d*) three pairs of AB-type signals due to three methylene bridge protons having coupling constants of 13.5, 13.0 and 14.0 Hz, and two new, one-proton signals at δ ~ 3.73 (*J* = 4.0 and = 2.0) and at δ ~ 4.06 ppm (*J* = 4.0 and 1.5 Hz) which were clearly coupled with the proton at 6.26 ppm., thus indicating that one of the methylene bridges was involved in the same reactions suggested by observations *b*-*c*, above. Similar observations were made for **10b** (Figure 7.3).

Mass spectroscopic analysis of the product, **10a**, and the starting material **9a** showed that both had the same molecular mass, as was also the case for **10b** and **9b**. These results all supported our initial conclusions that a photochemically-induced cycloisomerization reaction had occurred upon the photoirradiation of **9a** (Scheme 7.5) involving a phenolic hydroxy group, an alkyne group, and one of the methylene bridges. The following analysis, which is summarized in Scheme 7.6, is based mainly upon insight gained later from the X-ray structure of another product, **11a** (Figure 7.4), which was obtained by subsequent photoirradiation of **10a** (Scheme 7.6).

There are two conceivable cycloisomerization routes involving a proximal hydroxyl group, an ethynyl group and a methylene group in calixarenes **9a** or **9b**. One route involves a "7-*exo*-dig" cyclization of **9a** (for example) to form, firstly, the seven-membered oxacycle **12a** as an intermediate.

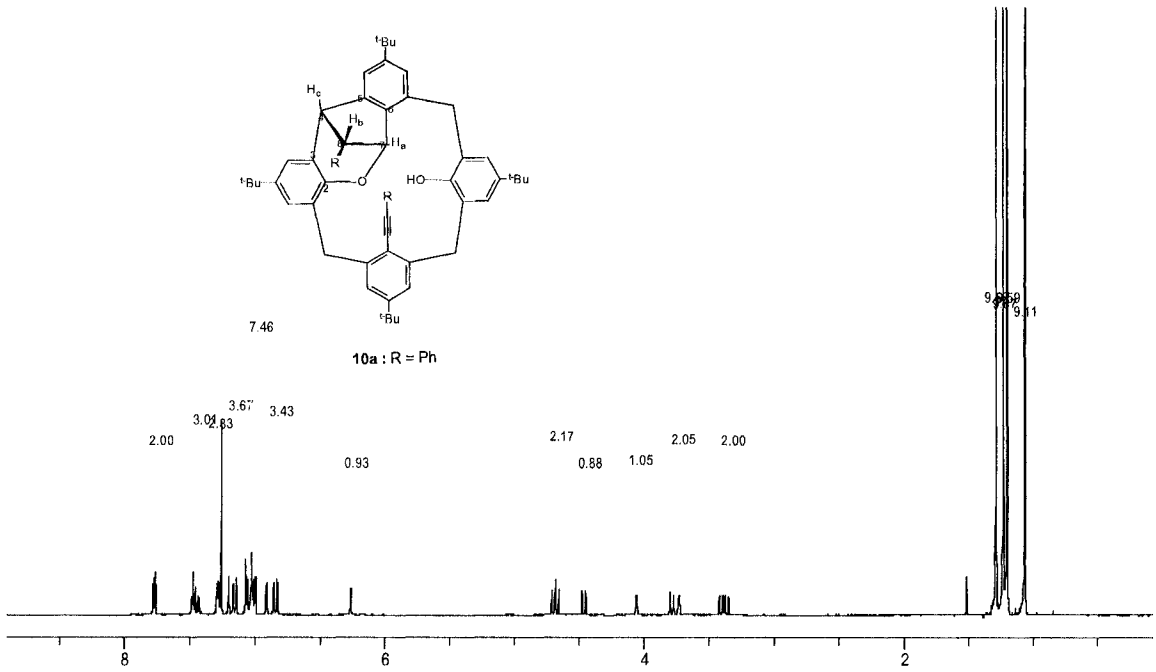


Figure 7.2 ^{1}H-NMR spectrum for compound **10a**

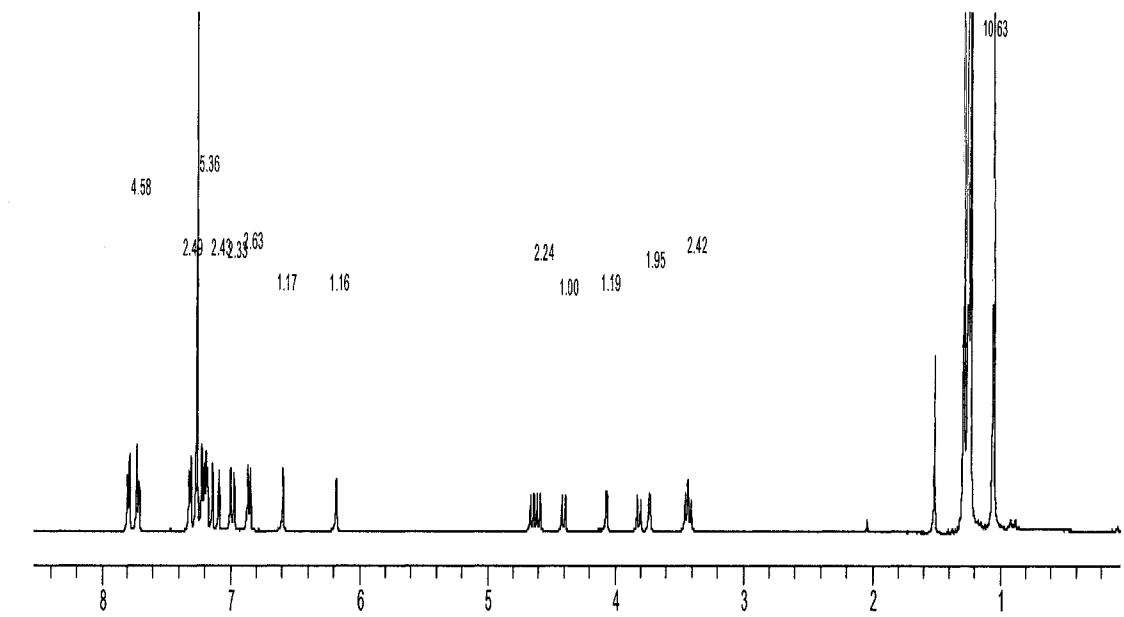


Figure 7.3 ^{1}H NMR spectrum for compound **10b**

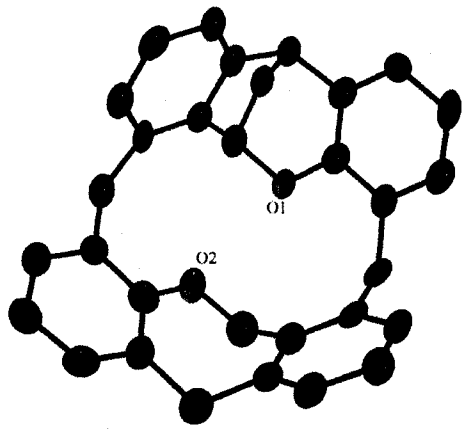


Figure 7.4a: X-ray ORTEP structural presentation of **13a** showing only the calixarene scaffold. All of the protons, the *tert*-butyl groups and the phenyl groups originating from the narrow-rim phenylethynyl substituents, have been removed for clarity. [12]

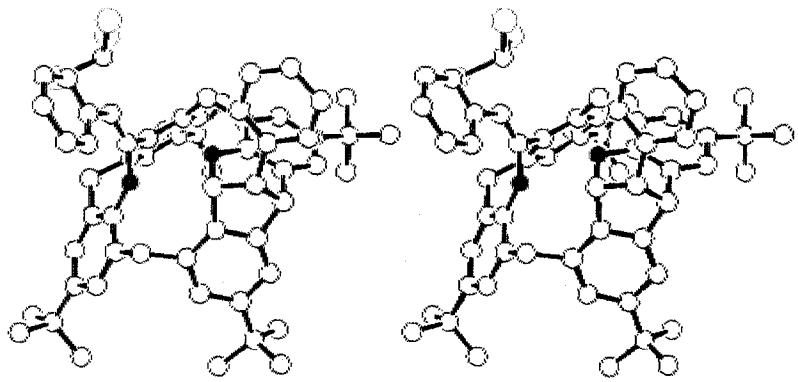
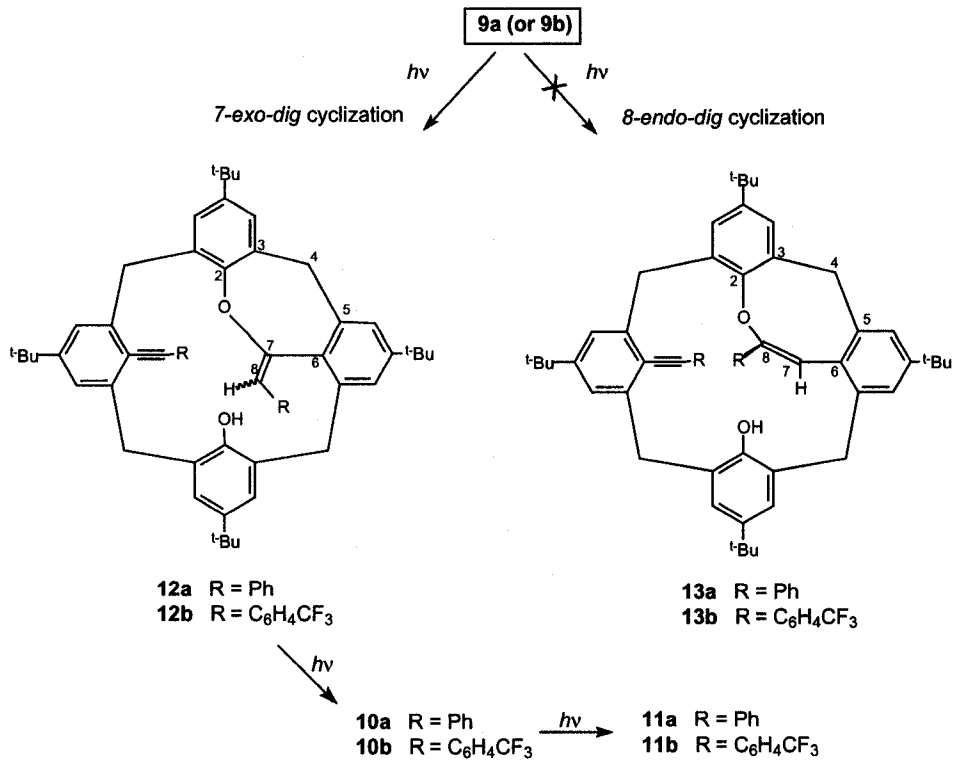


Figure 7.4b: X-ray PLUTO stereoview of **13a** in which all of the protons have been removed for clarity. A molecule of $CHCl_3$ can be seen at the top right. The oxygen atoms of the oxacycle are highlighted in red.

Intermediate **12a** then undergoes a second rapid reaction to produce the [3.2.1] oxabicyclic system which bridges a proximal pair of aromatic rings, as shown in structure **10a**.

The other conceivable route would involve an "8-*endo-dig*" cyclization to form, firstly, the eight-membered oxacycle **13a** as an intermediate which is analogous to **12a**. This could undergo a similar second reaction but would produce a much more highly-strained [4.0.0] oxabicyclic system, bond formation between C-4 and C-7 in **13a** by analogy with the presumed mechanism of formation of **10a** (Scheme 7.6).

According to Baldwin's rules[10] both of these initial cyclization routes are "favoured" processes. Extensive analysis of the 2D-NMR COSY, HMBC, and HMQC spectra of the first photochemically-formed product did not lead to an unambiguous assignment of the structure of **10a** at this stage. Furthermore, all attempts to obtain a suitable crystal for X-ray analysis for this product were also unsuccessful. Nevertheless, the structure was later concluded to be **10a**, on the basis of the single-crystal X-ray structure of **11a**, the product produced from the subsequent further photoirradiation of **10a** itself (see below). It is therefore postulated that the first step which occurs in the photochemical rearrangement to form **10a** is indeed most likely the *7-exo-dig* cyclization route via **12a** as depicted in Scheme 7.6. These results are elaborated upon and will be presented in the subsequent paragraphs, and with a more detailed mechanistic proposal.

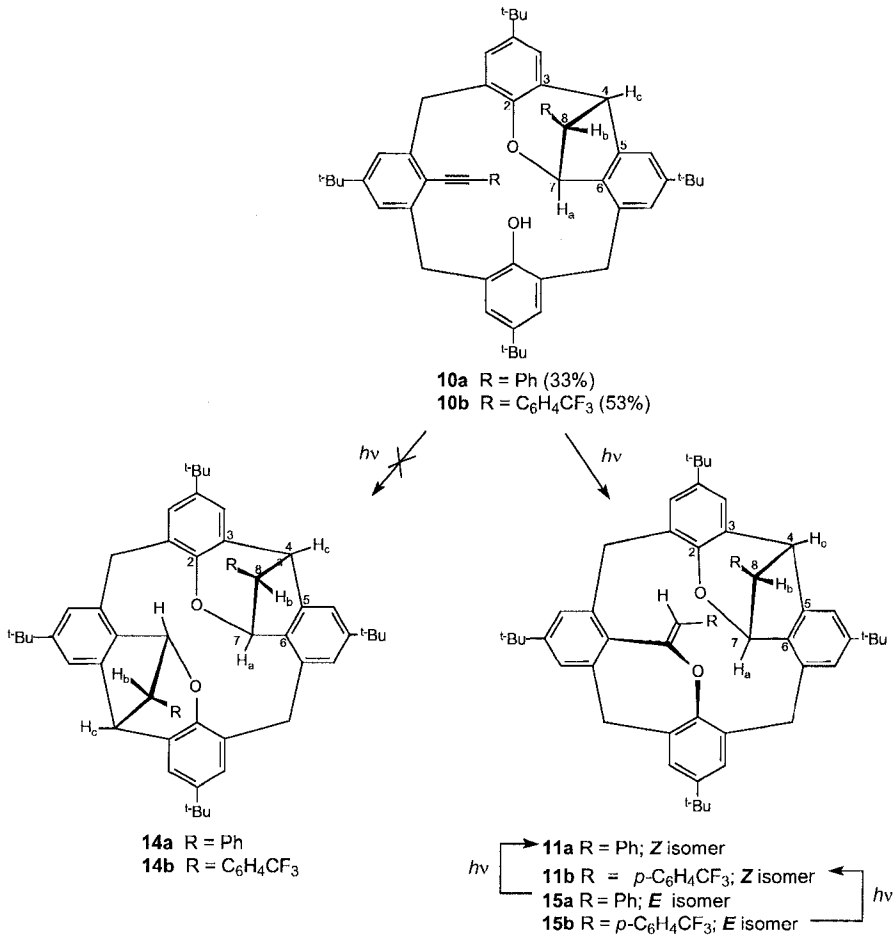


Scheme 7.6 Two possible routes for photochemically-induced cyclization of calixarene **9a** and **9b**.

With isolated and purified compounds **10a** and **10b** in hand, it was anticipated that a second photochemically-induced cyclization should be possible between the remaining hydroxyl and alkyne groups in these compounds. As well the initial cyclization could be followed by a similar second cyclization by analogy with that observed for **12a** (and also for **12b**) to generate a second [3.1.0] oxabicyclic system to bridge the remaining proximal pair of aromatic rings.

As was found with **9a** and **9b** a second cycloisomerization indeed occurred when solutions of either **10a** or **10b** in CH_2Cl_2 were photoirradiated in the same manner as before. The products obtained from these reactions, however,

according to the spectroscopic analysis, were not the expected calixarenes **14a** or **14b**, respectively (Scheme 7.7).



Scheme 7.7 The photochemically-induced cycloisomerization reactions of calixarenes **10a** and **10b**.

Structures **14a** and **14b** would be predicted to be C_2-symmetrical, and that their ^1H and ^{13}C NMR spectra should reflect this symmetry. For example, their ^1H NMR spectra should reveal only two different signals at high field for the *tert*-butyl groups and the corresponding ^{13}C NMR spectra should also reveal a total of only four different signals for these groups. However, the actual ^1H NMR and ^{13}C

NMR spectra indicated that this was not the case and that they were more complex. The ^{1}H NMR spectra of the photoproducts obtained from both **10a** and **10b** (Figures 7.5 and 7.6 respectively), both revealed four nonequivalent *tert*-butyl groups and four sets of nonequivalent methylene bridge protons. The mass spectra of these new products nevertheless indicated that they were isomeric with **10a** and **10b**, respectively.

However, despite this evidence and even with further spectroscopic evidence obtained from HMBC and HMQC 2-D NMR experiments, it was not possible to unambiguously assign a structure to these isomeric products. Fortunately, as mentioned previously, a suitable crystal for X-ray analysis for the product from the photoirradiation of **10a** was finally obtained, which revealed its structure to be **11a** (Figure 7.4). The structure confirmed that the photochemical reaction(s) most likely follows an initial 7-*exo*-dig and not the 8-*endo*-dig cyclization route.

Based on the X-ray structure evidence, it is proposed that the first ring closure generates the 7-membered oxacycle **12a** as an intermediate which bridges a pair of proximal aromatic rings in **12a** (and also in **12b** from **10b**; Scheme 7.6). This intermediate then undergoes covalent bond formation between C-4 and C-7 to produce the [3.1.0] oxabicyclic system which is clearly evident from the X-ray structure. In order to account for the formation of the unusual [3.1.0] oxabicyclic system it is further postulated that **12a** (and also similarly, in the case of **12b** from **10b**) undergoes a rapid 1,5 H-shift (via atoms

numbered 7-1-2-3-4 in the oxacycle) or a 1,4 H-shift (via atoms numbered 7-6-5-4 in the oxacycle) and that resulting diradical species at C-4 and C-7 then forms the covalent bond that results in the [3.2.1] oxabicycle.

The X-ray structure of **11a** also shows that it adopts a cone-like conformation which is consistent with its ^{1}H and ^{13}C NMR spectra. Its ^{1}H NMR spectrum (Figure 7.5) which is similar to that of **10a** (Figure 7.2) shows that two of the methylene protons do not show the geminal coupling of approximately 12 Hz. Instead; two protons, H_b and H_c, which appear at around δ 3.6 and 4.1 ppm, respectively have a relatively smaller apparent coupling constant value of ≤ 2.5 Hz. The observed coupling is small presumably because the dihedral angle between these two (vicinal) protons H_b-C-C-H_c as revealed by the X-ray structure is 54°. There are no exchangeable protons remaining in the molecule according to the D_2O proton-exchange experiments, and there are two signals which appear at low fields at δ = 5.82 and 5.85 ppm. These signals are assigned to the vinylic proton (H_d) and to the benzylic proton (H_a), respectively which is more deshielded than H_d, by the oxygen atom (O-1).

The stereoselectivity of the photochemical cyclization of **9a-b** and **10a-b**, is clearly established by the following facts: (a) The bicyclic ring formation, in **10a** or **10b** generates three stereogenic centers at C-4, C-7 and C-8 which have *S, R* and *R* configurations, respectively; (b) The products of the second ring closures gave only the *Z* isomers **11a** or **11b** with no evidence for any *E* isomer formation as concluded by the spectroscopic analysis (Figure 7.5 and 7.6), respectively.

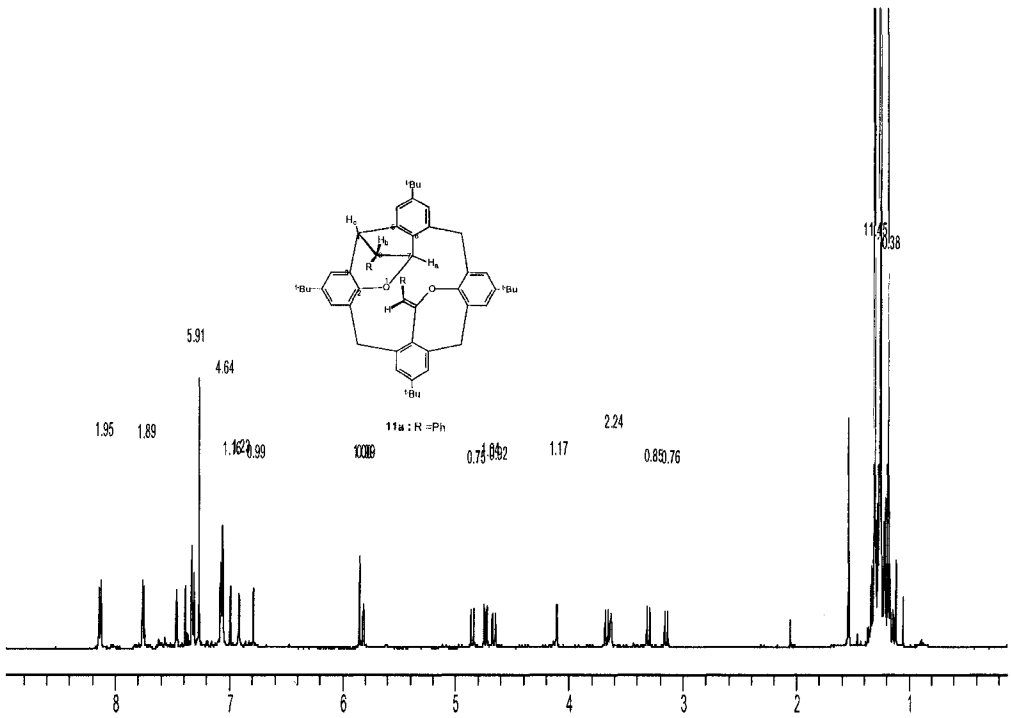


Figure 7.5 ^{1}H NMR of calixarene **11a**

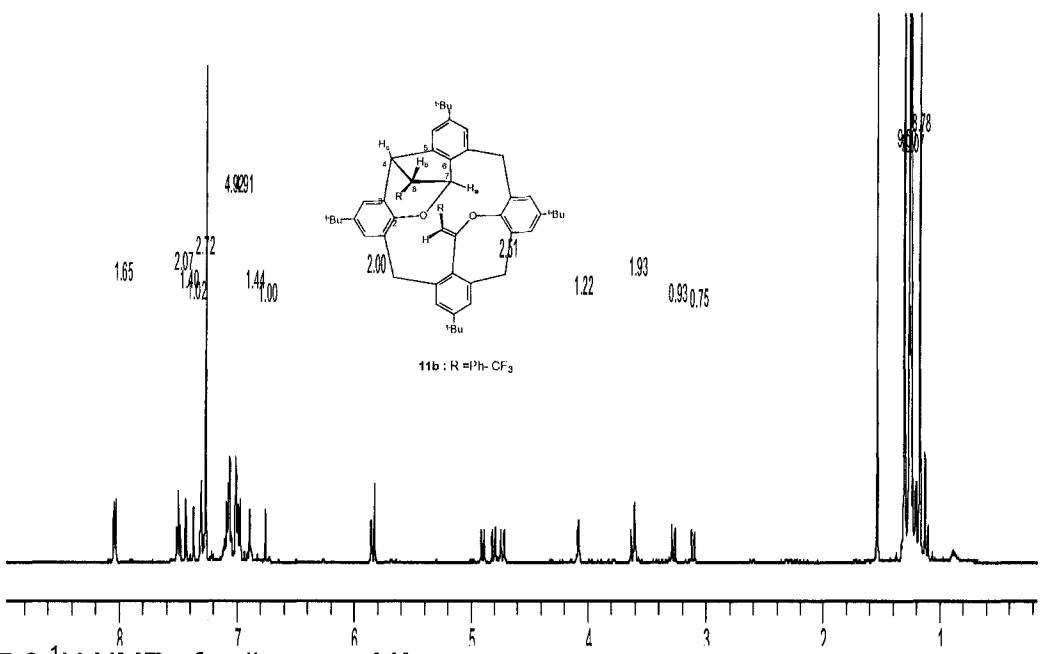
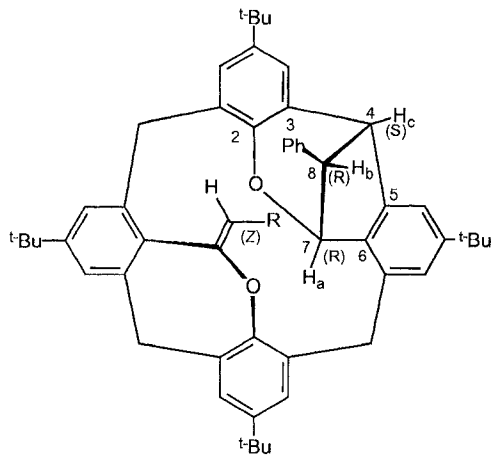


Figure 7.6 ^{1}H NMR of calixarene **11b**

The observed reaction selectivity can be attributed to the fact that both of the reactant sites, the hydroxyl group, and the alkynyl triple bonds in **9a-b** or **10a-b**, are arranged in such a way that only one diastereoisomer can be produced by the observed photochemical reactions. Therefore the reaction selectivity is most likely due to a templating effect afforded by the calixarene scaffolds in **9a-b** and **10a-b**.



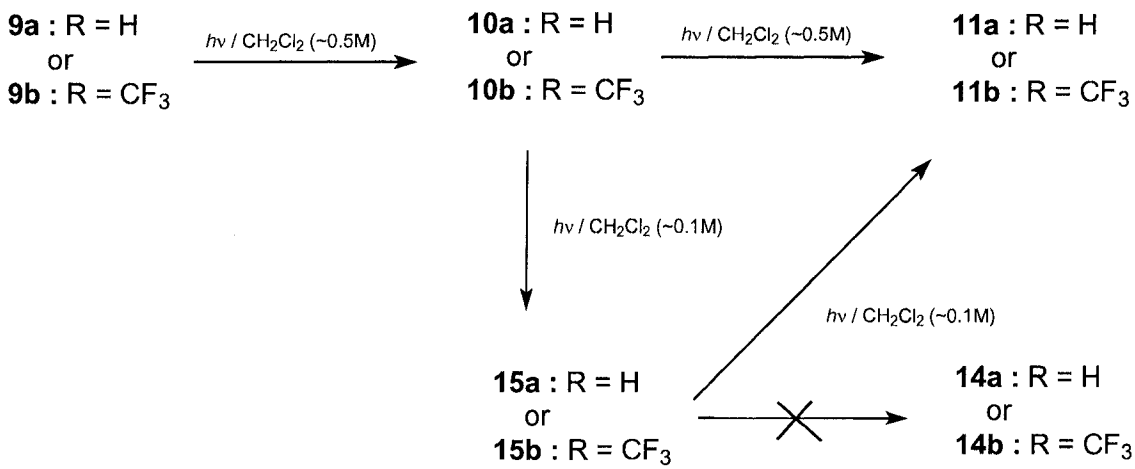
11a

Figure 7.7 Assignment of the stereochemistry of **11a**.

7.3- Photochemical reactions of (9a) and (9b) using different reaction conditions:

When more dilute (~ 0.1 M vs ~0.5 M) solutions of **9a** or **9b** were photoirradiated, permitted the observation of the formation of additional isomeric products, **15a** and **15b**, respectively (Scheme 7.8). Using these more dilute solutions the reactions were much slower than those described previously. For

9a the reaction needs ~12 h irradiation is required to give an optimum amount of **15a**, while **9b** needs only ~7 h to give optimum amounts of **15b**. Analysis of **15a** and **15b** by NMR and mass spectroscopy indicated that these intermediates were different isomers of **11a** and **11b**, respectively. D_2O proton-exchange experiments with the ^1H NMR spectra, for example, for calixarene **15b** (Figure 7.8) indicated that there are no exchangeable hydroxyl group protons remaining in the molecule. This implied that both of the hydroxyl groups are involved in the cyclization process(es). The absence of the two geminal protons implied also that the [3.1.0] oxabicyclic system seen in **11a** was also present in **15a** or **15b**.



Scheme 7.8 Summary of the overall photochemically-induced isomerization-rearrangement reactions of calixarenes **9a-b**, **11a-b**, and **15a-b**

The ^1H NMR spectra of **15a** and **15b** have similar patterns to those seen with **11a** and **11b**. The main differences between the two products are the

obvious changes in the chemical shifts of one of the geminal protons, and of the benzylic proton (which is equivalent to H_a in compound **11a**).

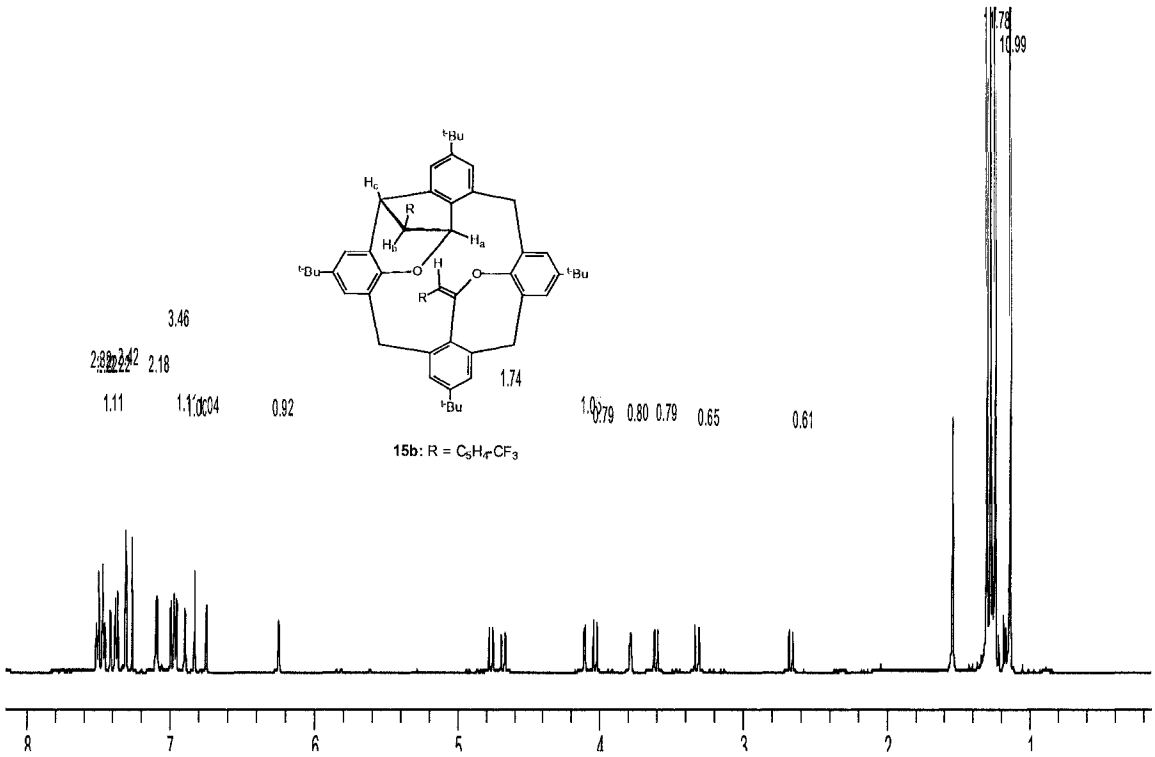


Figure 7.8: ^{1}H NMR spectrum of calixarene **15b**

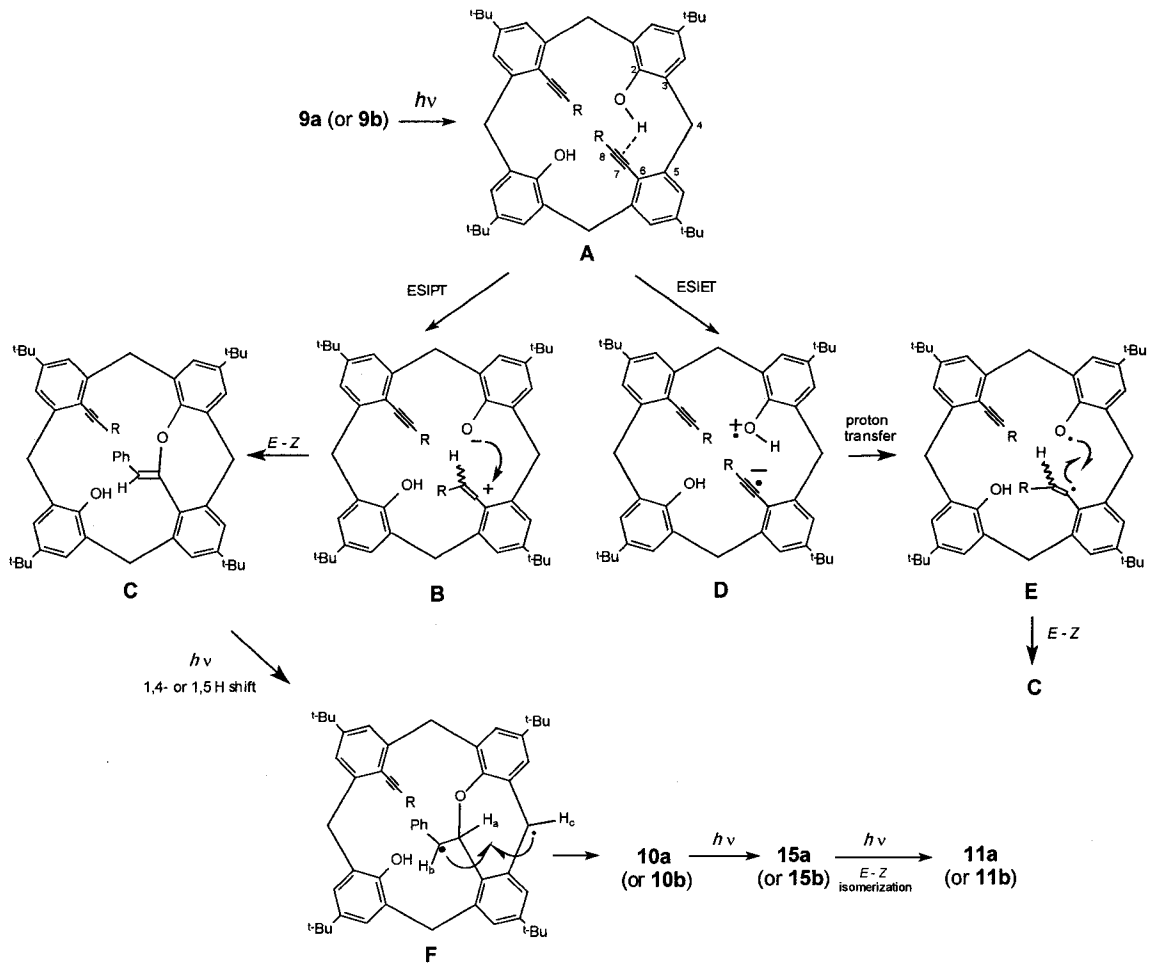
For example, in the ^{1}H NMR spectrum of compound **15b**, one of the geminal protons has became more shielded by a neighboring calixarene phenyl ring and has shifted to the high field region at δ 2.66 ppm, while the benzylic proton (H_a) has become more deshielded and has shifted to the low field region at $\delta \geq 6.7$ ppm. Based upon these observed chemical shift changes and on Drieding molecular models, we have concluded that **15a** and **15b** could be the less stable *E* geometrical isomers of **11a** and **11b** respectively, and we postulate that upon further photoirradiation they produce the corresponding *Z* geometrical isomers

11a and **11b**, respectively (Scheme 7.8). However, the product formation sequences which have been suggested in Scheme 7.8 were confirmed by taking ^{1}H NMR spectra after variable irradiation times (Figure 7.5, included in the appendix of this chapter). Molecular mechanics calculations with Spartan06 (MMFF94) using X-ray data from **11a** as the basis for generating the structure of **15a**, for example, supports this hypothesis since the difference in energy is approximately 10 kJ mol^{-1} in favor of **11a**.[11]

The actual mechanism can only be conjectured upon, but a mechanism which is consistent with the observed photochemically-induced cyclization reactions is depicted in Scheme 7.9 for **9a** (or **9b**). The first step could involve an intramolecular hydrogen bond interaction between one of the hydroxyl groups and one of the triple bonds, **9a** (or **9b**), as depicted in complex "**A**". By analogy with some intramolecular phenol-olefin reactions which have been reported by others,[12] there could be two possible mechanisms for the reactive excited state. The first is an "exited state intramolecular proton transfer" (ESIPT)[13] to form the zwitterionic-type intermediate "**B**". In this case, an intramolecular proton transfer has undergone a 1,8-hydrogen[14] shift. Covalent bond formation in **B** forms the intermediate "**C**" presumably formed via a rapid *E-Z* isomerization. A second possible mechanism leading to this same putative intermediate **C** involves an "excited state intramolecular electron transfer" (ESIET)[15] between a phenolic hydroxy group and the triple bond (as an electron acceptor) to produce the ionic diradicals as depicted in structure "**D**". Subsequent proton-transfer forms the 1,7-

diradical intermediate "**E**" which could then lead directly to the formation of **C**. The transformation from **C** to **10a** (or **10b**) could be achieved via a diradical species "**F**", formed by a 1,5-hydrogen shift[16] (or via a less common 1,4-hydrogen shift). The second 7-membered oxacycle is generated when **10a** (or **10b**) is photoirradiated to give **15a** (or **15b**) which undergoes a rapid *E* to *Z* isomerization to form **11a** (or **11b**).[17] Furthermore, the observation that the photoreactions which were observed to be faster in the more concentrated solutions suggests that *inter*molecular proton transfer may compete with intramolecular proton transfer in either the ESIPT or ESIET. This would not necessarily affect the final product outcomes.

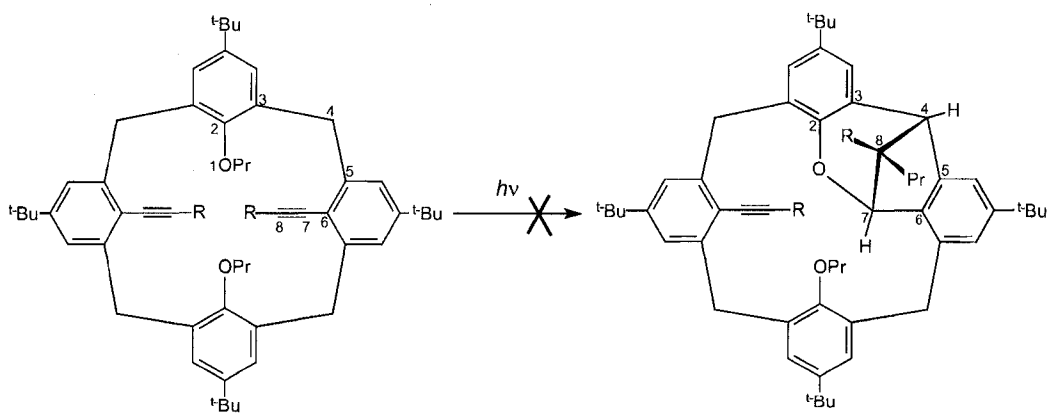
Experimentally, **C** was neither observed nor isolated, and it is likely a very short-lived intermediate, after which it directly photoisomerized to give **10a** (or **10b**). The transformation from **C** to **10a** (or **10b**) could be achieved through the diradical species "**F**", which could be produced by either a 1,5-hydrogen shift[18] or via a less common 1,4-hydrogen shift.[19] The second 7-membered ring is generated when **10a** (or **10b**) is photoirradiated to give **15a** which undergoes a further rapid *E* to *Z* isomerization to form intermediate **11a**. Molecular models[20] suggest that the structure of the predicted **14a** (or **14b**) from **11a** (or **11b**) would be much more strained. As a result, it may not be as stable as **11a** (or **11b**), since further photoirradiation resulted in degradation of the respective starting material, as determined by the ^{1}H NMR spectra of the reaction mixtures which showed no distinct or defined signals.



Scheme 7.9 Proposed mechanism for the photochemically-induced cyclization

Photoirradiation of **9c** and **9d**, the corresponding di-propoxy derivatives (whose syntheses are described in Chapter 5) of **9a** or **9b** respectively, were stable to the same conditions which were used with **9a** or **9b** and did not result in any new product formation (Scheme 7.10). While it was obvious that the presence of a hydroxyl group is essential for the observed photocyclization-rearrangement reactions, it was at first not unequivocal whether or not the calixarene skeleton provided any role as a scaffold in assisting the intramolecular

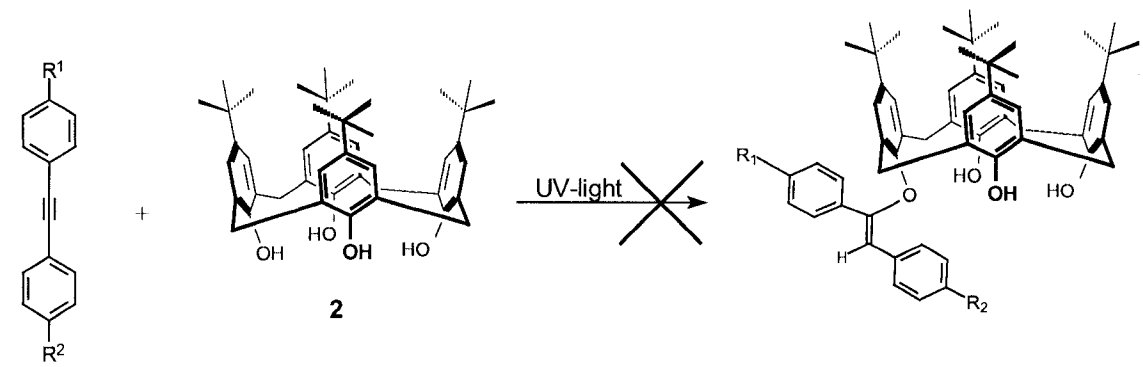
reactions. In order to ascertain this role, experiments were conducted to determine whether or not the same types of reactions would be seen *intermolecularly* between **2** and a tolane such as **16a-c**. Thus, solutions of *p-tert*-butylcalix[4]arene (**2**) itself with each of the tolanes **16a-c** were irradiated under the same reaction conditions which were used with **9a-d**. In all cases, none of the expected products **17a-c** were obtained and instead, only unreacted starting materials were recovered. Additional photoirradiation experiments were also conducted in which the mole ratios between **2** and, for example, the tolane **16b** were increased from 1:1 to 1:100, in order to simulate the putative scaffold effect, but again only unchanged starting compounds were recovered with no signs of any of the corresponding photo-addition product **17b**. These additional experiments lend support for the hypothesis that the observed photochemical rearrangement/cyclization reactions described in this Chapter are facilitated by a templating effect of the calixarene scaffold (Scheme 7.11).



9c R = Ph
9d R = $C_6H_4CF_3$

10c R = Ph
10d: R = $C_6H_4CF_3$

Scheme 7.10 Photochemical reaction of **9c-d** didn't give the expected products **10c-d**



16a : R^1 = H, R^2 = H
16b : R^1 = *tert*-butyl, R^2 = H
16c : R^1 = *tert*-butyl, R^2 = CF_3

17a : R^1 = H, R^2 = H
17b : R^1 = *tert*-butyl, R^2 = H
17c : R^1 = *tert*-butyl, R^2 = CF_3

Scheme 7.11 The photochemically-induced reactions of calixarenes **2** with the tolanes **16a-c**.

7.4- Conclusions

In conclusion, we have shown in this Chapter that the previously prepared narrow-rim 1,3-bis(arylethynyl)-*p*-*tert*-butylcalix[4]arenes which have free hydroxyl groups on the remaining two calixarene positions, are photo-labile. Upon photoirradiation, these compounds undergo facile cyclization-rearrangement reactions which are assisted by the templating effect provided by the calixarene scaffold. A mechanism is proposed to account for the observed results. These findings further expand the versatility of functionalized calixarenes, especially, with respect to their photochemical behavior. Furthermore, to the best of our knowledge the *7-exo-dig* photochemically-mediated cyclizations obtained

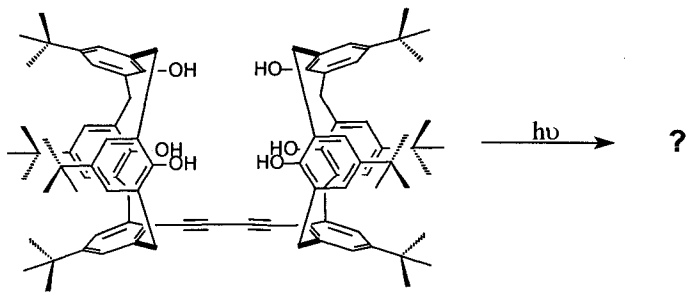
in this study are the first examples of intramolecular cyclizations of such alkynyl-substituted calixarenes to be reported.

7.5-Suggestions for Future Work

While unexpected and exceptional results have been obtained during the course of this work, further progress could be achievable by conducting the following experiments:

1- Examining the photochemical reactions - using the same photochemical reaction conditions which were used for **9a** and **9b** – on other derivative with different substituent on the phenylacetylenyl groups; such as the nitro derivative (calix[4]arene **18**, which described in Chapter 6), to verify the generality of these reactions and the effect of these derivatives on the reaction progress.

2- It is worth examining the photochemistry also on the previously obtained bis-calix[4]arene **18** (which was described Chapter 5) to see if this compound would follow the same photochemical behavior of **9a** and **9b**, leading to possibly several different new products.



18

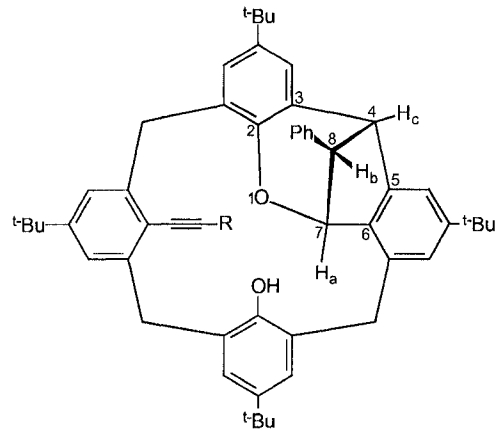
3- Photoirradiation of higher calixarene analogues (calix[n]arenes, where n = 5,6 and 8) to determine the templating parameters required for the observed photochemical cyclization reactions to occur.

4- During the course of this work it was noticed that if the photochemical reactions were conducted in a solvent which was not anhydrous, new products were formed. These new products appeared to be ones in which a molecule of H_2O had been added to **9a** (**9b**), as determined by mass spectrometry only. Further investigations into the nature of these new hydrated products should be conducted.

5- The work of Ferrer *et al.*[20] on the gold-catalyzed intramolecular cyclization reaction of indoles with alkynes indicates that using different oxidizing state of the catalyst can result in controlling the cyclization to afford either *7-exo-dig* versus *8-endo-dig* cyclization. Future work is suggested by using Ferrer's with our compounds (eg. **9a** or **9b**) in order to determine the possibility of controlling the regiochemistry.

7.6- Experimental

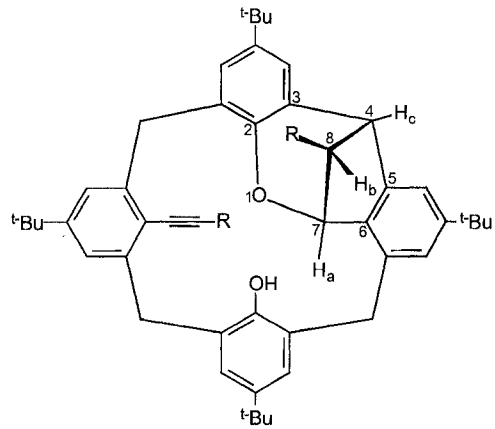
For general experimental information see Chapter 2, page 46



10a

Calixarene (10a): A solution of **9a** (18 mg) in anhydrous CH_2Cl_2 (35 ml) was irradiated for 3 h in a photoreactor using two 21 watt 3000 Å lamps. The solvent was evaporated in vacuo and the residue purified by PLC (20% CH_2Cl_2 in petroleum ether) to give (**10a**) (6 mg, 33%): mp 253- 255 °C; ^{1}H NMR δ 1.07 (s, 9H), 1.20 (s, 9H), 1.24 (s, 9H), 1.29 (s, 9H), 3.59 (d, J = 13.5 Hz, 1H), 3.40 (d, J = 13.0 Hz, 1H), 3.73 (dd, J_1 = 4.0, J_2 = 2.0 Hz, 1H), 3.87 (d, J = 14.0 Hz, 1H), 4.06 (dd, J_1 = 4.0 Hz, J_2 = 1.5 Hz, 1H), 4.46 (d, J = 13.5 Hz, 1H), 4.67 (d, J = 13.5 Hz, 1H), 4.70 (d, J = 14.0 Hz, 1H), 6.26 (dd, J_1 = 2.0, J_2 = 1.5 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 6.91 (m, 1H), 7.07-7.00 (m, 6H), 7.14 (d, J = 2.5 Hz, 1H), 7.16 (d, J = 2.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.27 (dd, J_1 = 8.0 Hz, J_2 = 2.5 Hz, 2H), 7.28 (s, D_2O exch, 1H), 7.49-7.42 (m, 3H), 7.77 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 2H); ^{13}C NMR δ 31.00, 31.67, 31.77, 31.84, 33.71, 33.93, 34.14, 34.71,

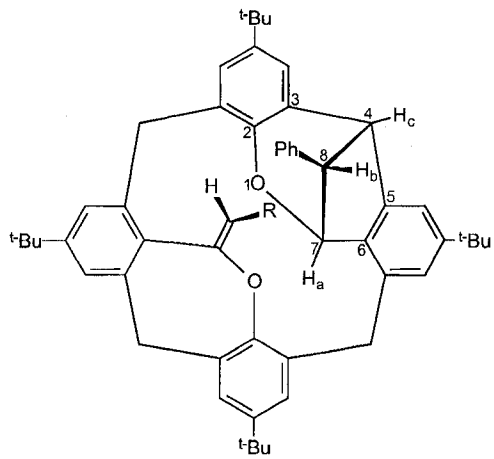
34.92, 36.99, 37.73, 49.35, 51.97, 77.43, 79.01, 88.40, 97.90, 116.56, 116.90, 122.41, 123.43, 123.99, 124.16, 124.64, 124.68, 124.79, 125.90, 126.00, 127.45, 127.59, 127.95, 128.08, 128.22, 128.75, 128.80, 128.86, 131.77, 137.57, 138.72, 141.78, 142.54, 142.99, 143.36, 149.47, 149.49, 151.41, 151.71, 151.84; MS (APCI+) *m/z* calcd for $C_{60}H_{64}O_2$ 817.16, found 817.30 (M^+).



10b: R = *p*-$C_6H_4CF_3$

Calixarene (10b): A solution of **9b** (10 mg) in anhydrous CH_2Cl_2 (20 ml) was irradiated for 30 min in a photoreactor using two 21 watt 3000 Å lamps.. The solvent was evaporated in vacuo and the residue purified by PLC (CH_2Cl_2/petroleum ether 3:7) afforded **10b** (5.3 mg, 53%): mp 147- 148 °C; ^{1}H-NMR δ 1.05 (s, 9H), 1.23 (s, 9H), 1.25 (s, 9H), 1.28 (s, 9H), 3.42 (d, J = 13.5 Hz, 1H), 3.44 (d, J = 13.0 Hz, 1H), 3.73 (m, 1H), 3.81 (d, J = 12.5 Hz, 1H), 4.07 (dd, J_1 = 4.0 Hz; J_2 = 1.5 Hz, 1H), 4.43 (d, J = 13.5 Hz, 1H), 4.60 (d, J = 13.0 Hz, 1H), 4.65 (d, J = 12.5 Hz, 1H), 6.18 (m, 1H), 6.59 (s, 1H, OH), 6.86 (d, J = 2.5 Hz, 1H), 6.87 (d, J = 2.5 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 7.00 (d, J = 2.5 Hz, 1H),

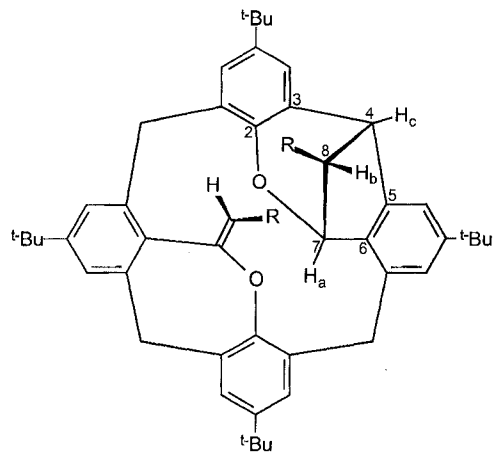
7.09 (d, J = 2.5 Hz, 1H), 7.14 (d, J = 2.5 Hz, 1H), 7.18 (m, 1H), 7.19 (brs, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H); ^{13}C NMR δ 29.93, 30.94, 31.63, 31.76, 31.81, 33.92, 33.99, 34.18, 34.76, 34.95, 37.05, 37.80, 49.00, 51.72, 79.19, 90.95, 96.49, 116.50, 116.58, 122.38, 124.30, 124.41, 124.85, 124.88, 124.96, 125.19, 125.83, 125.86, 126.06, 127.21, 127.41, 128.04, 128.31, 128.33, 128.79, 130.48, 130.74, 131.83, 136.95, 138.61, 142.42, 142.66, 142.88, 143.19, 143.74, 149.19, 149.42, 151.12, 152.08, 152.60; MS (APCI+) *m/z*, calcd for $C_{62}H_{62}F_6O_2$ 953.16, found 953.40 (M^+).



11a

Calixarene (11a): A solution of **9a** (16.0 mg) in anhydrous CH_2Cl_2 (130 ml) was irradiated for 10 h in a photoreactor using two 21 watt 3000 Å lamps. The solvent was evaporated in vacuo and the residue purified by PLC (20% CH_2Cl_2 in petroleum ether) to give **11a** (3.0 mg, 18.3 %): mp 260 - 263 °C; ^{1}H NMR δ 1.17

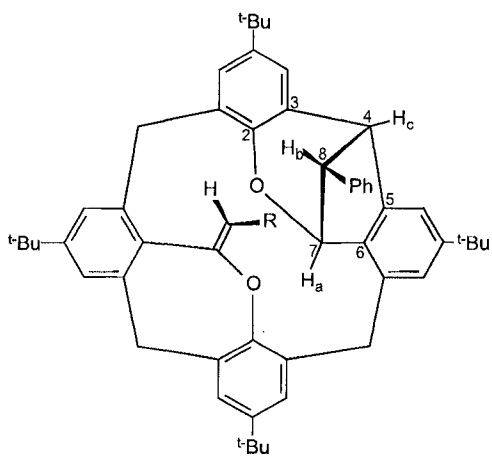
(s, 9H), 1.25 (s, 9H), 1.26 (s, 9H), 1.30 (s, 9H), 3.11 (d, J = 13.0 Hz, 1H), 3.28 (d, J = 14.0 Hz, 1H), 3.61 (m, 1H), 3.62 (d, J = 12.5 Hz, 1H), 4.08 (dd, J_1 = 4.0 Hz; J_2 = 1.5 Hz, 1H), 4.73 (d, J = 12.5 Hz, 1H), 4.81 (d, J = 12.5 Hz, 1H), 4.90 (d, J = 13.0 Hz, 1H), 5.83 (s, 1H), 5.86 (brs, 1H), 6.76 (d, J = 2.5 Hz, 1H), 6.80 (d, J = 12.5 Hz, 1H), 7.09-6.98 (m, 8H), 7.28-7.33 (m, 2H), 7.37 (d, J = 2.5 Hz, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 31.43, 31.65, 31.76, 31.82, 32.78, 34.00, 34.24, 35.01, 39.83, 48.34, 50.11, 77.14, 77.45, 114.38, 116.31, 120.75, 121.76, 124.75, 124.77, 124.82, 125.59, 125.92, 126.04, 126.43, 126.81, 127.71, 127.99, 128.14, 128.20, 128.26, 128.55, 128.77, 130.18, 134.98, 135.63, 136.74, 136.83, 138.49, 140.21, 141.85, 143.03, 144.44, 147.50, 150.51, 150.64, 151.44. MS (APCI+) *m/z* calcd for $C_{60}H_{64}O_2$ 817.16, found 817.50 (M^+).



11b : R = *p*-$C_6H_4CF_3$

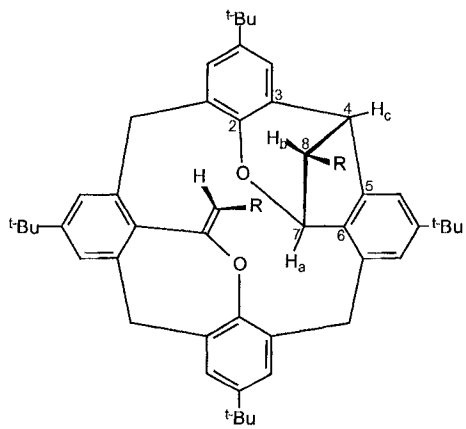
Calixarene (11b): A solution of **10b** (10.0 mg) in anhydrous CH_2Cl_2 (40 ml) was irradiated for 7 h in a photoreactor using two 21 watt 3000 Å lamps. The solvent

was evaporated in vacuo and the residue purified by PLC (25% CH_2Cl_2 in petroleum ether) to give **11b** (2.8 mg, 28%): mp 185 - 186 °C; ^{1}H NMR δ 1.19 (s, 9H), 1.25 (s, 9H), 1.27 (s, 9H), 1.31 (s, 9H), 3.15 (d, *J* = 12.5 Hz, 1H), 3.30 (d, *J* = 14.0 Hz, 1H), 3.63 (m, 1H), 3.67 (d, *J* = 13.0 Hz, 1H), 4.10 (m, 1H), 4.66 (d, *J* = 13.0 Hz, 1H), 4.74 (d, *J* = 13.0 Hz, 1H), 4.85 (d, *J* = 12.5 Hz, 1H), 5.82 (m, 1H), 5.85 (m, s, 1H), 6.79 (d, *J* = 2.5 Hz, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 7.07-7.06 (m, 4H), 7.31 (s, 1H, OH), 7.33 (m, 2H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 31.38, 31.60, 31.71, 31.76, 32.63, 32.66, 34.02, 34.29, 34.79, 35.05, 39.63, 48.07, 49.91, 77.43, 90.12, 94.27, 99.68, 101.84, 110.78, 112.59, 114.13, 116.46, 120.89, 121.78, 124.55, 124.83, 124.87, 124.96, 125.49, 125.52, 125.93, 126.13, 126.94, 127.73, 128.26, 128.60, 130.10, 130.43, 134.34, 136.65, 140.03, 142.49, 143.06, 145.12, 147.15, 148.57, 150.21, 151.94, 152.17, 153.12; MS (APCI+) *m/z* calcd for $C_{62}H_{62}F_6O_2$ 953.16, found 953.30 (M^+).



15a

Calixarene (15a): A solution of **9a** (18.4 mg) in anhydrous CH_2Cl_2 (40 ml) was irradiated for 4 h in a photoreactor using two 21 watt 3000 Å lamps. The solvent was evaporated in vacuo and the residue purified by PLC (30 % CH_2Cl_2 in petroleum ether) to give **15a** (5.9 mg, 32%): mp > 300 °C; ^{1}H NMR δ 1.18 (s, 9H), 1.24 (s, 9H), 1.26 (s, 9H), 1.30 (s, 9H), 2.60 (d, *J* = 13.0 Hz, 1H), 3.29 (d, *J* = 14.0 Hz, 1H), 3.58 (d, *J* = 13.0 Hz, 1H), 3.77 (m, 1H), 4.09-4.07 (d, *J* = 13.0 Hz, 1H; and m, 1H), 4.73 (d, *J* = 14.0 Hz, 1H), 4.78 (d, *J* = 13.0 Hz, 1H), 6.26 (m, 1H), 6.71 (d, *J* = 2.5 Hz, 1H), 6.93-6.82 (m, 12H), 7.23-7.20 (m, 2H), 7.28-7.43 (m, 4H); ^{13}C NMR δ 31.45, 31.63, 31.75, 31.77, 32.30, 32.82, 33.94, 34.80, 35.00, 40.04, 48.99, 50.18, 114.68, 116.28, 121.41, 121.60, 121.74, 124.58, 124.85, 125.12, 125.76, 126.00, 126.02, 126.04, 126.20, 126.83, 127.70, 128.08, 128.18, 128.25, 128.31, 128.55, 128.75, 129.22, 129.87, 135.30, 136.64, 136.76, 139.00, 139.83, 141.76, 142.13, 143.69, 147.36, 150.59, 151.57, 152.06, 152.17; MS (APCI+) *m/z* calcd for $C_{60}H_{64}O_2$ 817.16, found 817.50 (M^+).



15b : R = *p*-$C_6H_4CF_3$

Calixarene (15b): A solution of **9b** (18.3 mg) in anhydrous CH_2Cl_2 (40 ml) was irradiated for 5 h in a photoreactor using two 21 watt 3000 Å lamps. The solvent was evaporated in vacuo and the residue purified by PLC (20 % CH_2Cl_2 in petroleum ether) to give **15b** (8.2 mg, 45%): mp > 300 °C; ^{1}H NMR δ 1.14 (s, 9H), 1.25 (s, 9H), 1.28 (s, 9H), 1.30 (s, 9H), 2.67 (d, *J* = 12.5 Hz, 1H), 3.32 (d, *J* = 14.0 Hz, 1H), 3.61 (d, *J* = 13.0 Hz, 1H), 3.79 (m, 1H), 4.03 (d, *J* = 13.0 Hz, 1H), 4.10 (d, *J* = 1.5 Hz, 1H), 4.68 (d, *J* = 14.0 Hz, 1H), 4.76 (d, *J* = 12.5 Hz, 1H), 6.25 (m, 1H), 6.75 (d, *J* = 2.5 Hz, 1H), 6.83 (s, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 2.5 Hz, 1H), 7.10-7.89 (m, 2H), 7.30 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 31.43, 31.60, 31.71, 31.74, 32.05, 32.67, 34.00, 34.21, 34.88, 35.04, 39.88, 48.85, 50.05, 113.47, 116.32, 121.67, 121.73, 123.41, 124.30, 125.03, 125.17, 125.20, 125.27, 125.31, 126.13, 126.19, 126.23, 127.00, 127.63, 127.94, 128.48, 128.61, 129.87, 134.82, 136.72, 139.52, 140.40, 142.11, 142.39, 143.04, 144.19, 147.06, 149.78, 150.36, 151.92, 152.71, 154.39 (3 carbon signals not detected); MS (APCI+) *m/z* calcd for $C_{62}H_{62}F_6O_2$ 953.16, found 953.50 (M^+).

7.7- References

1. Wayne, R. P. *Principles and applications of Photochemistry,* Oxford Univ. Press. Oxford, **1988**, p 1.

2. Woodward, R. B.; Hoffman, R. *Angew. Chem. Int. Ed., Engl.*, **1969**, *8*, 781.

3. Svoboda, J.; König, B. *Chemical Review,* **2006**, *106*, 5413.

7.7- References

1. Wayne, R. P. *Principles and applications of Photochemistry,* Oxford Univ. Press. Oxford, **1988**, p 1.

2. Woodward, R. B.; Hoffman, R. *Angew. Chem. Int. Ed., Engl.*, **1969**, *8*, 781.

3. Svoboda, J.; König, B. *Chemical Review,* **2006**, *106*, 5413.

4. Mori, K.; Murai, O.; Hashimoto, S.; Nakamura, Y., *Tetrahedron Lett.* **1996**, *37*, 8523.

5. Nishikubo, T.; Kameyama, A.; Kudo. H.; Tsutsui, K. *J. Polymer Sc.(A),* **2002**, *40,* 1293.

6. Rojanathanes, R.; Tuntulani, T.; Bhanthumnavin, W.; Sukwattanasinitt, M., *Org. Lett.*, **2005**, *7* , 3401.

7. Schäfer, C; Mattay, J., J. *Photochem. Photobiol.Sci.* **2004**, *3*, 331.

8. Varma, R. L.; Ganga, V. B.; Sureshi, E., *J. Org. Chem.* **2007,** *72*,1017.

9. Al-Sarierh, H.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem.*, **2005**, *70*, 8273.

10. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

11. Molecular modeling was conducted using Spartan'06 Molecular Modeling Software from Wave-function Inc.: Irvine, CA.

12. Jiménez, M. C.; Miranda, M. A.; Tormos, R. *Chem. Soc. Rev.* **2005**, *34*, 783, and references cited therein.

13. Chow, Y. L.; Zhou, X. –M.; Gaitan, T. J.; Wu, Z. –Z. *J. Am. Chem. Soc.* **1989**, *111,* 3813.

14. McNab, H.; Reed, D.; Tipping, I. D.; Tyas, R. G. *ARKIVOC*, **2007**, *6,* 85.

15. Morrison, H. *Org. Photochem.*, **1979**, *4*, 143.

16. Cummins, J. M.; Dolling, U.-H.; Douglas, A. W.; Karady, S.; Leonard, W. R.; Marcune, B. F.; *Tetrahedron Lett.*, **1999**, *40*, 6153.

17. from **11a** as the basis for generating the structure of **15a**, for example, supports this hypothesis since the difference in energy is approximately 10 kJ mol^{-1} in favour of **11a**.

18. G. Bucher, *Eur. J. Org. Chem.* **2001**, 2447.

19. Molecular mechanics calculations with *Spartan'06* (MMFF94 using X-ray data from **11a** as the basis for generating the structure of **14a**) support this hypothesis. The difference in energy between **14a** and **11a** for example, is approximately 59 kJ mol^{-1} in favour of **11a**.

20. Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105.

Appendix: Chapter 7

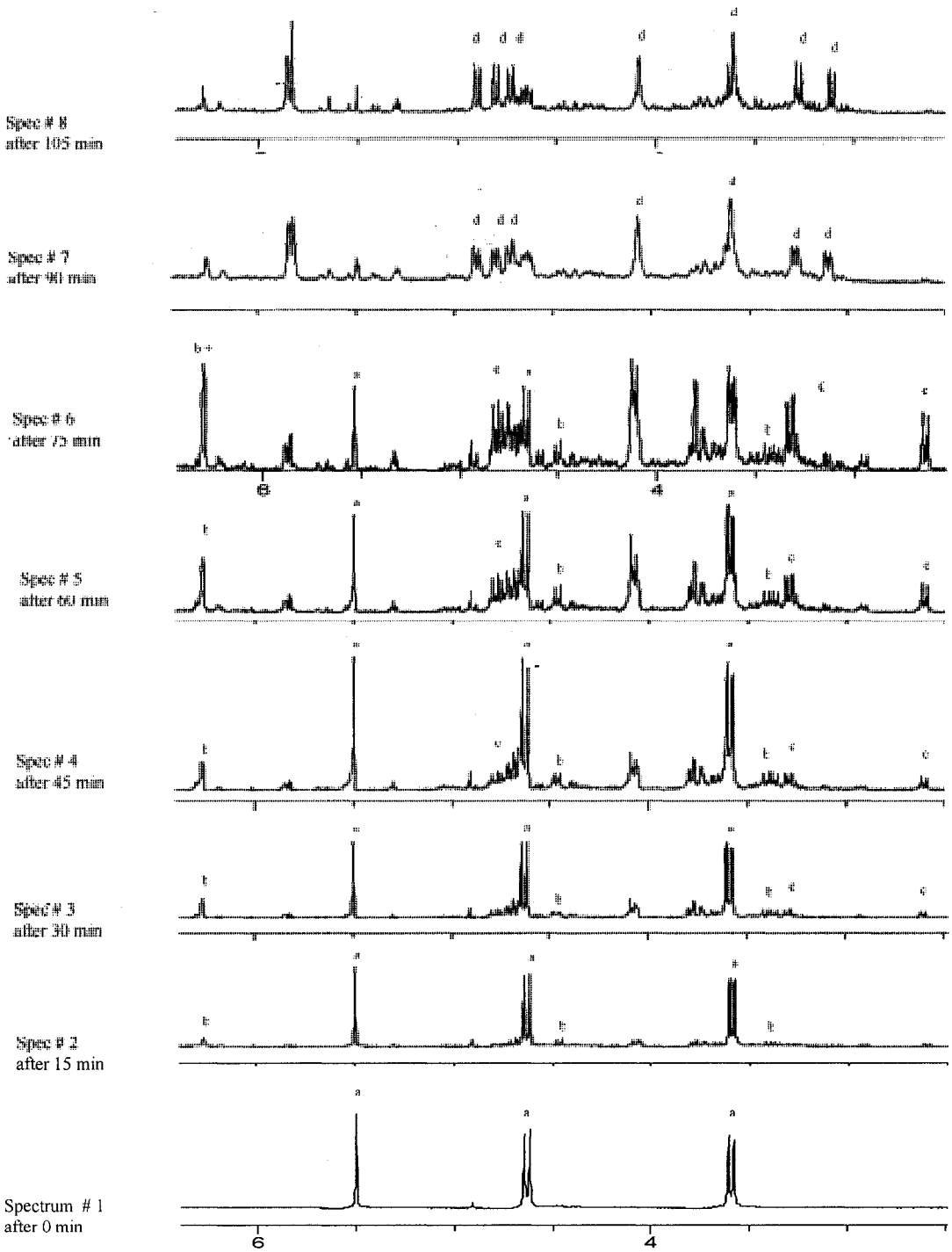
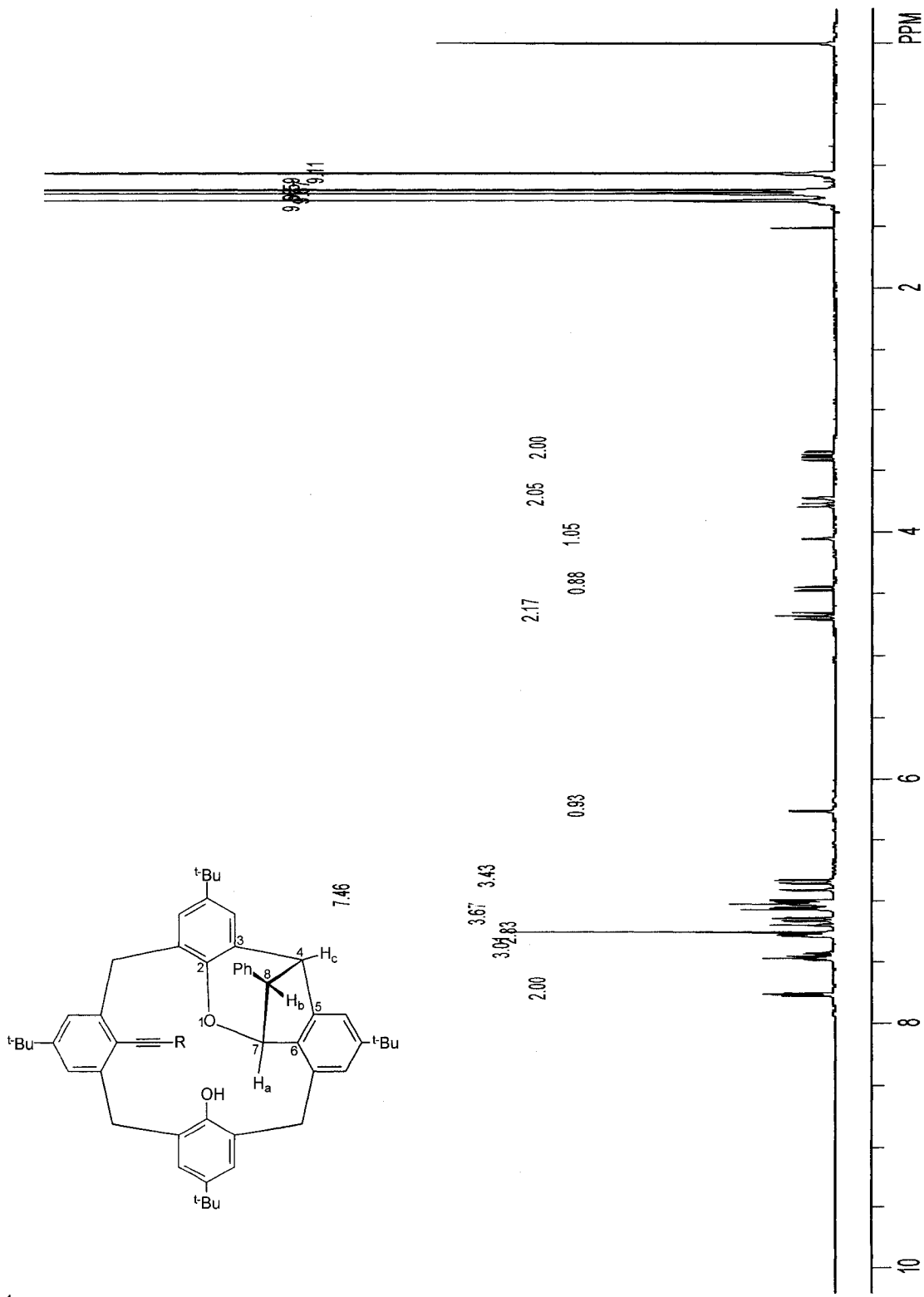


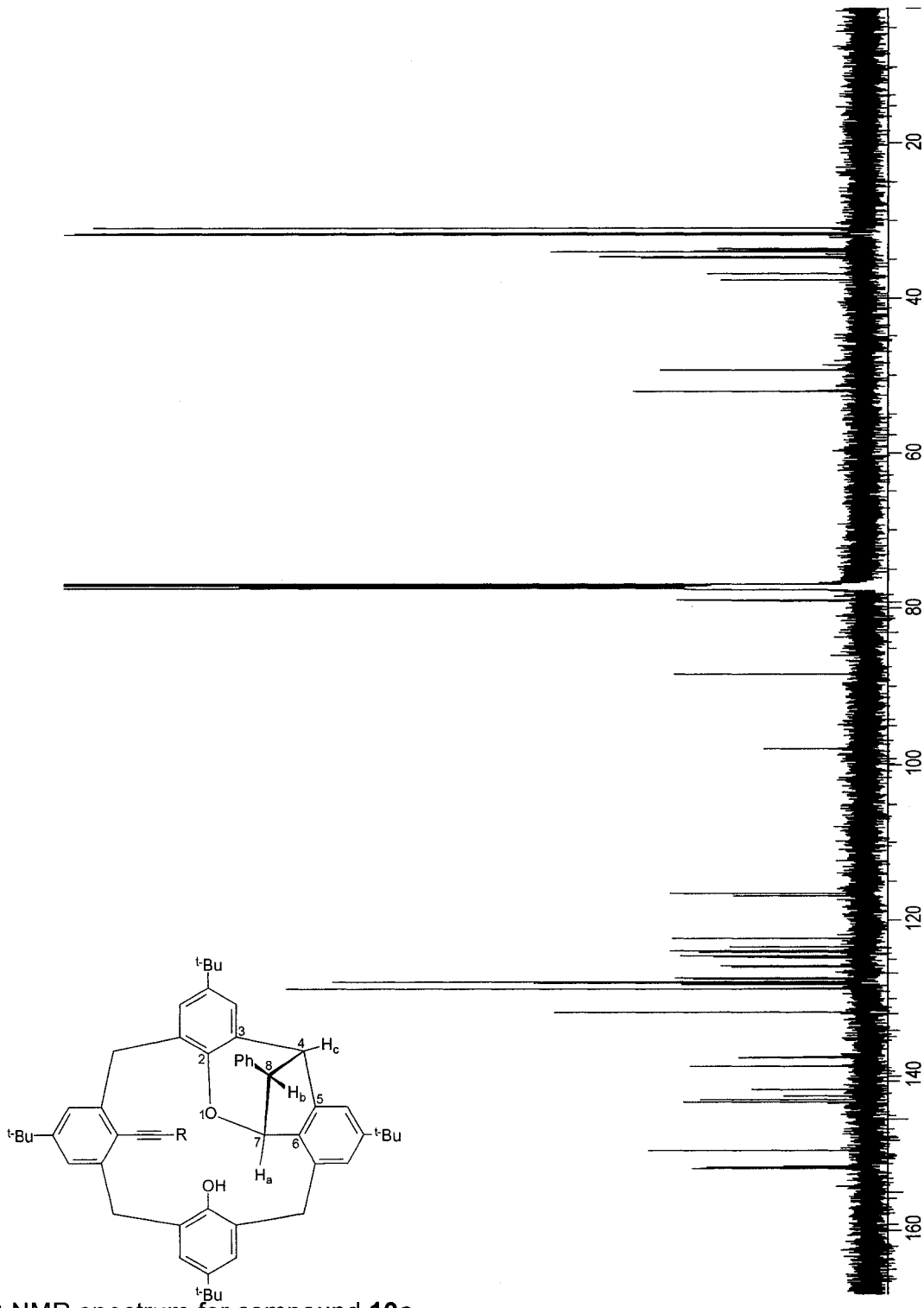
Figure 7.5 Combined partial ^{1}H NMR spectra from the photoirradiation of **9a** in CH_2Cl_2-d_2 solution (Spec **#**1: t_{irr} = 0 min to Spec **#**8: t_{irr} = 105 min. *Labels*: ***a***: Compound **9a**; ***b***: Compound **10a**; *c*: Compound **15a**; ***d***: Compound **11a**.

X-ray Crystal Data for 62: A c colorless platelet crystal of $C_{61}H_{65}Cl_3O_2$ (CH_3Cl/MeOH) of monoclinic, space group $P2_1/n$ (#14), Z = 4, a = 18.304(5) Å, b = 16.202(4) Å, c = 20.864(5) Å, β= 118.442(6)°, V = 5441(2) $Å^3$, $D_{Calcd.}$ = 1.100 g cm^{-3}, crystal size = 0.80 X 0.24 X 0.03 mm. Intensity data were measured -160 ± 1 °C on a Rigaku AFC8 diffractometer with graphite monochromated Mo-Kα (λ = 0.71070 Å) radiation $2\theta_{max}$ = 61.8 °; 24190 reflections converged to a final R_{int} of 0. 069 for 8999 unique reflections and 596 variable parameters and converged with unweighted and weighted factors of R1 and wR2. Final R1 and wR2 values were 0. 1301 and 0.3323, respectively, and GoF = 1. 117.

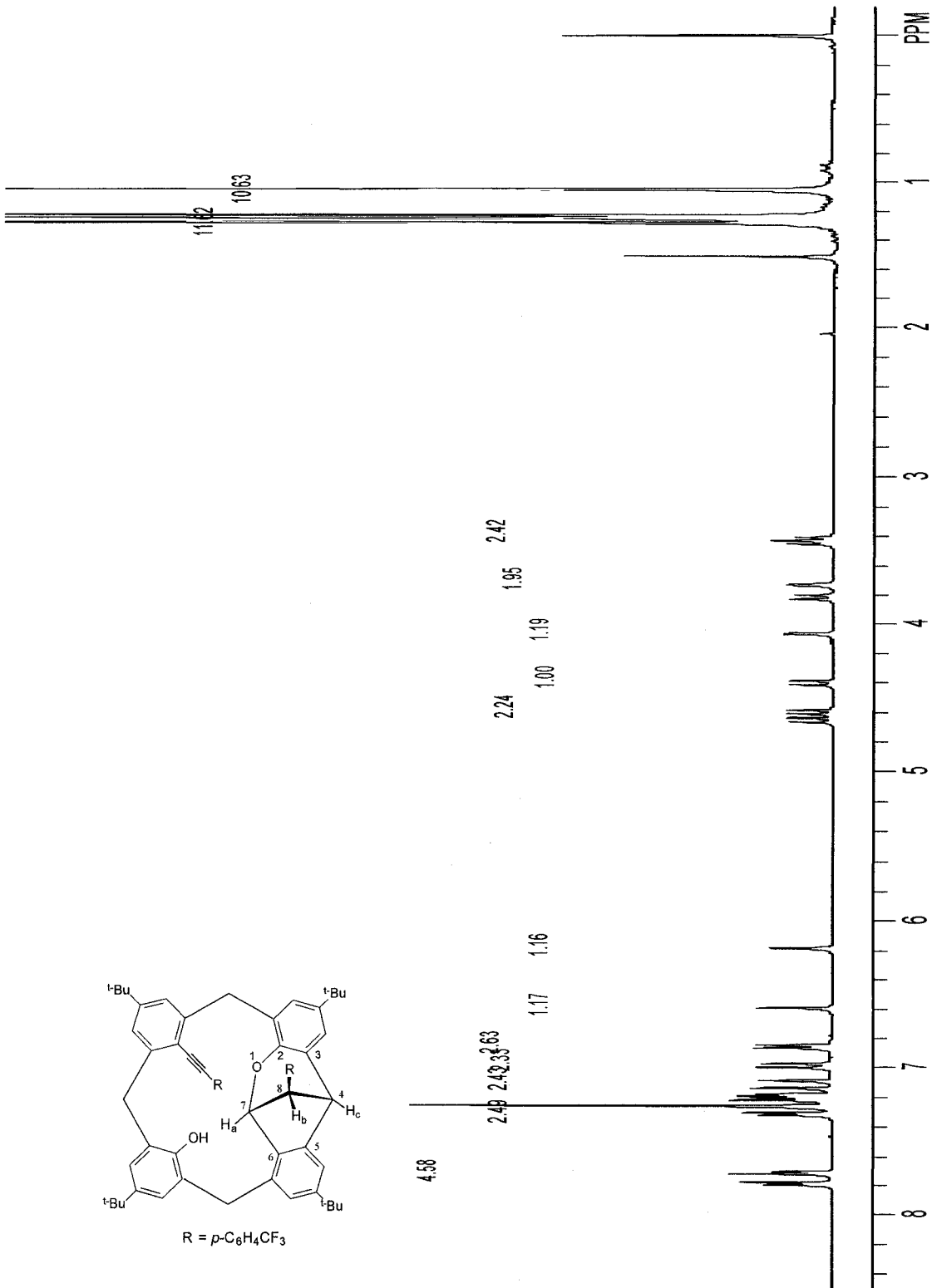
Prepared by: David O. Miller, Memorial University, Chemistry Department.



^{1}H NMR spectrum for compound **10a**

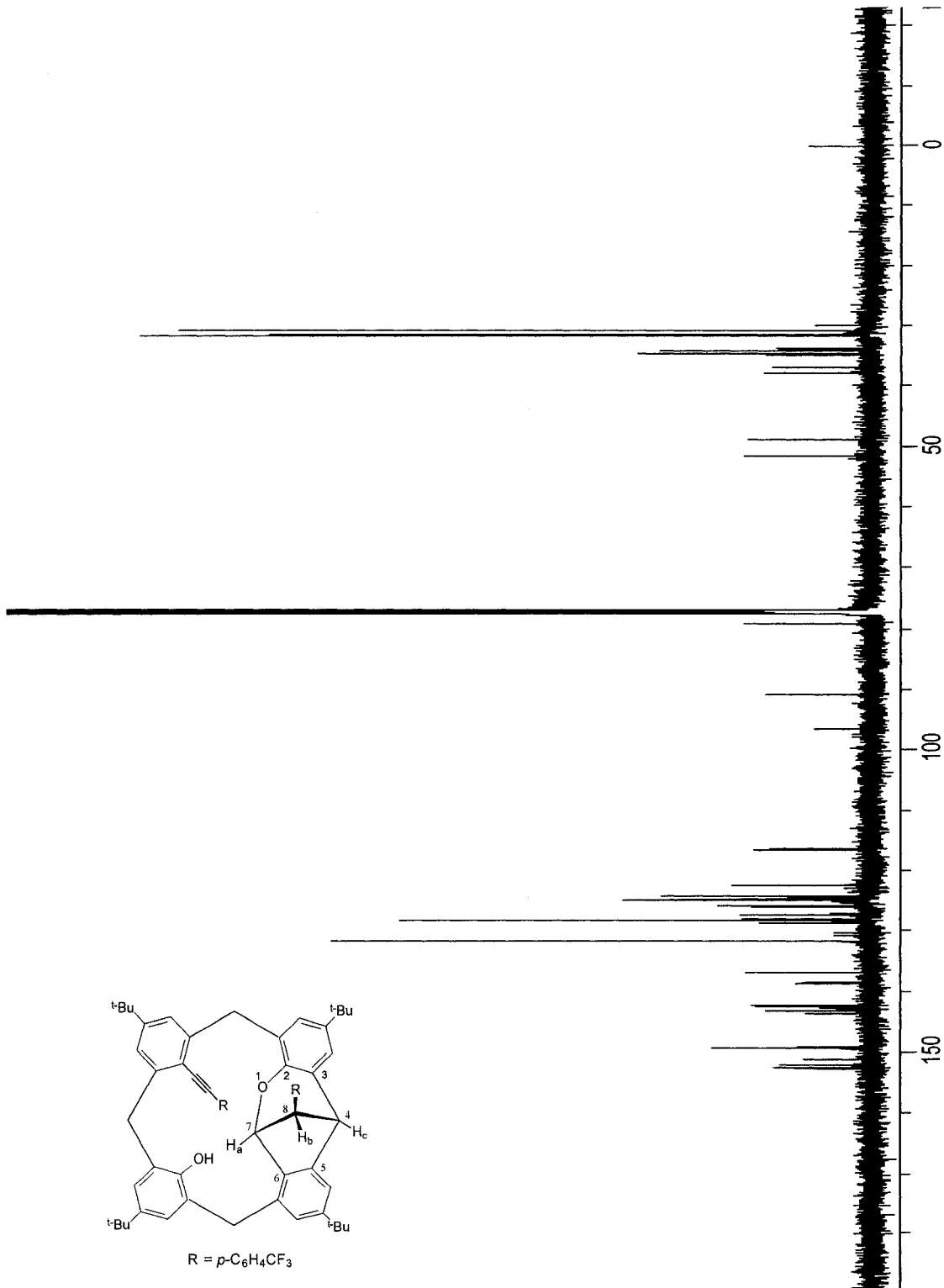


^{13}C NMR spectrum for compound **10a**



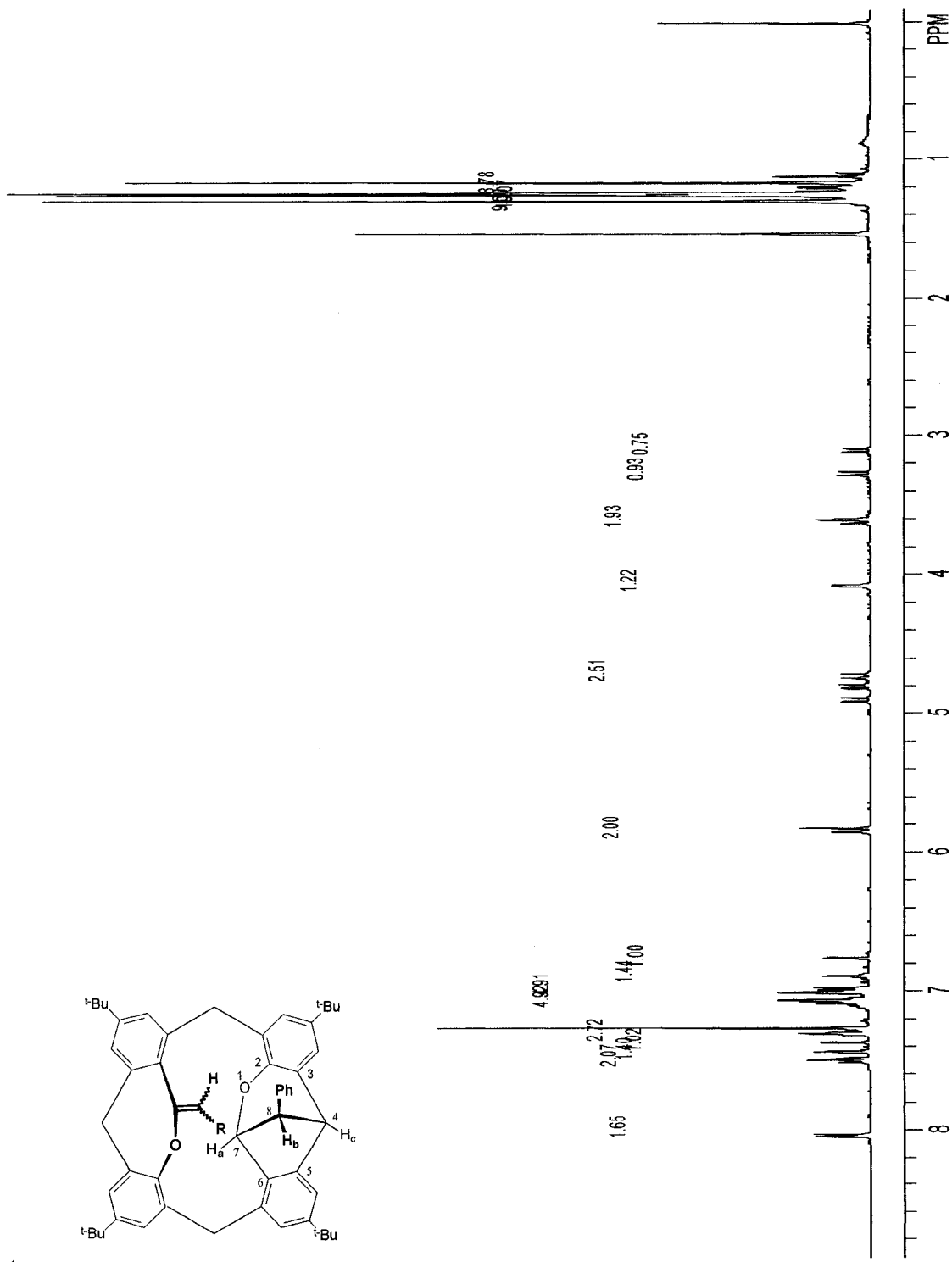
R = *p*-$C_6H_4CF_3$

^{1}H NMR spectrum for compound **10b**

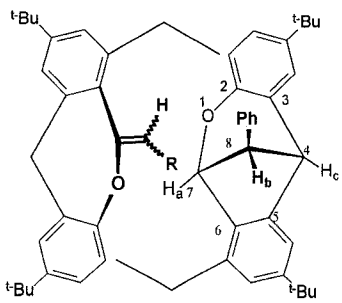


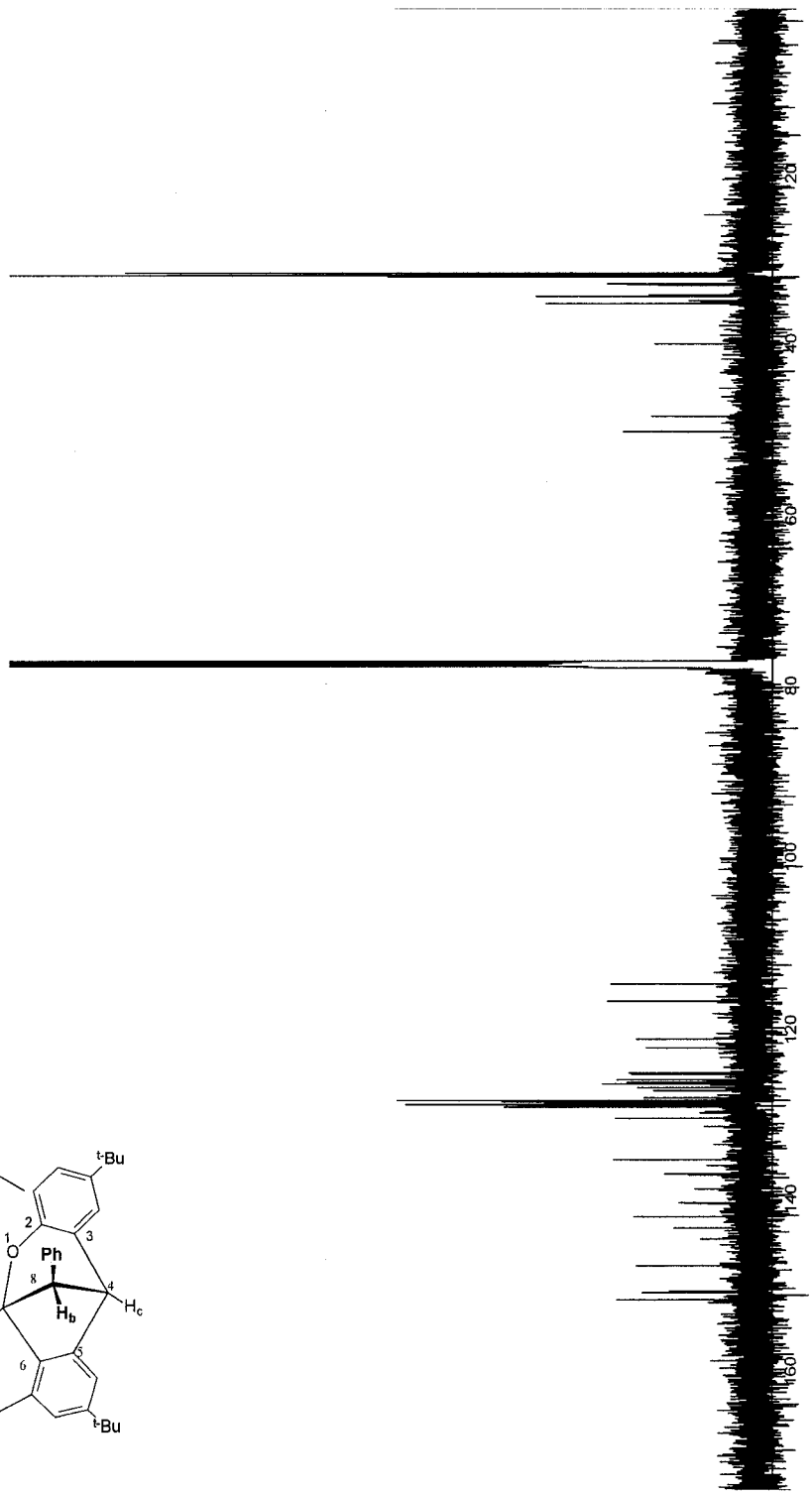
R = *p*-$C_6H_4CF_3$

^{13}C NMR spectrum for compound **10b**

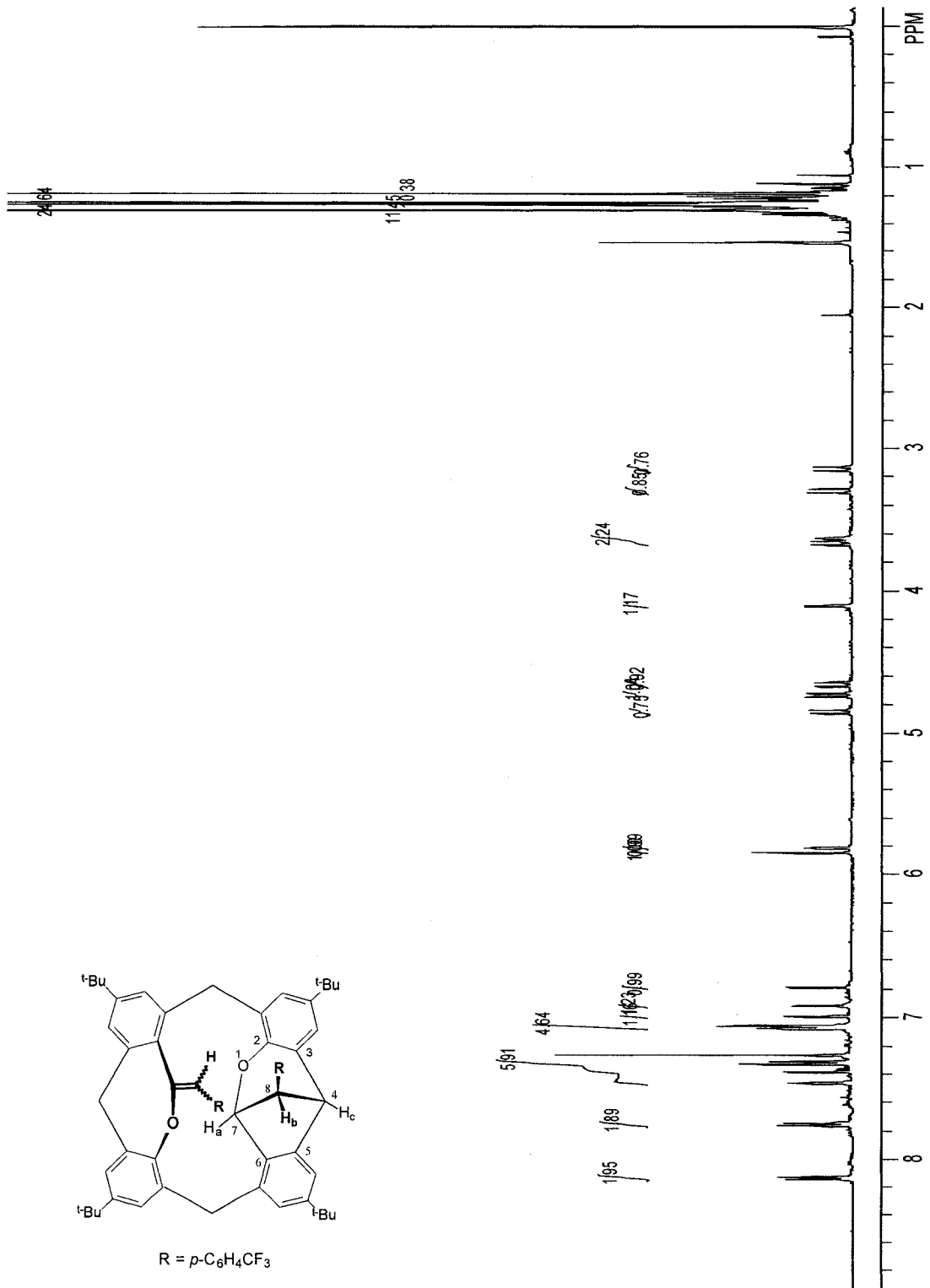


^{1}H NMR spectrum for compound **11a**



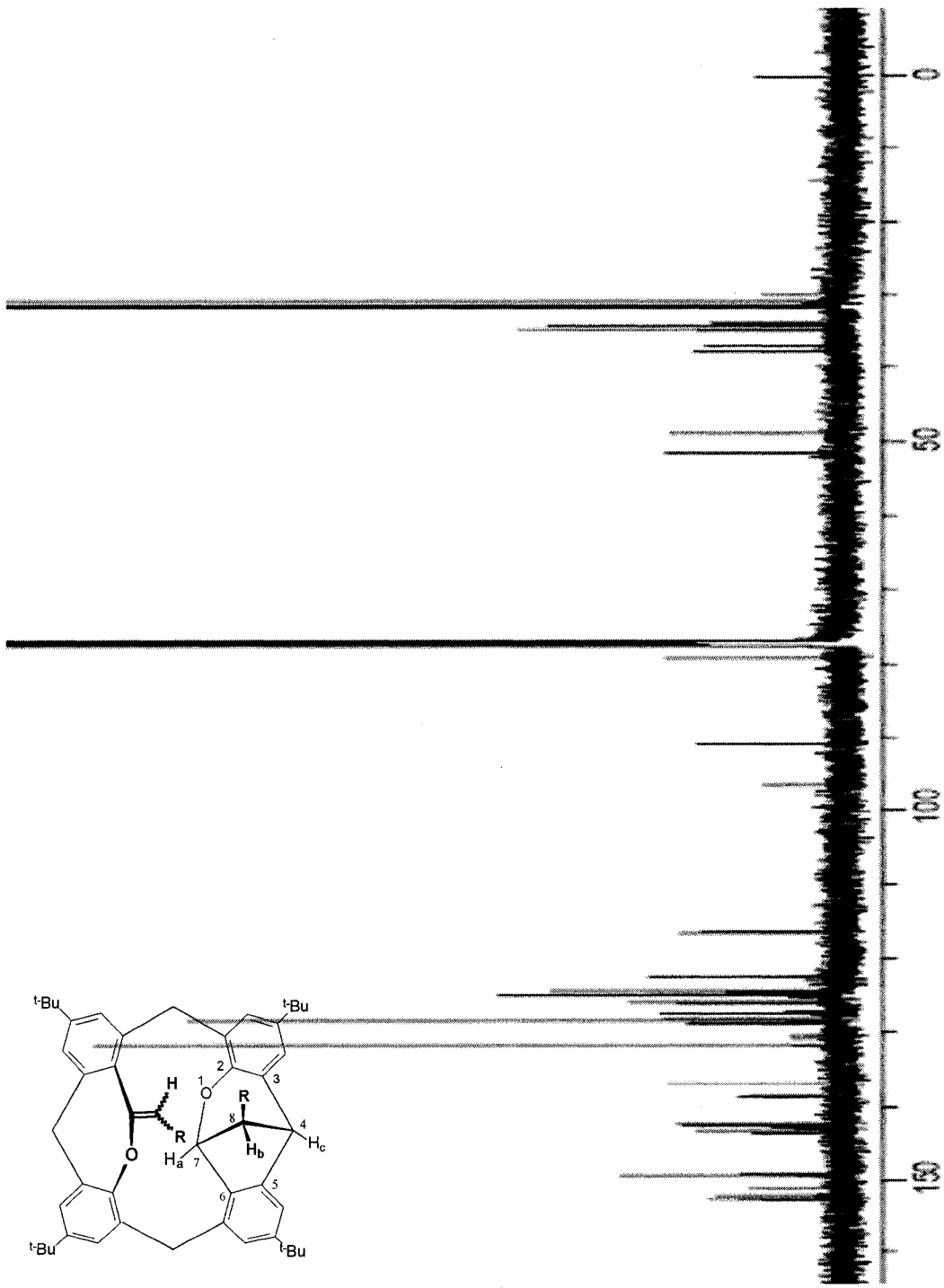


^{13}C NMR spectrum for compound **11a**



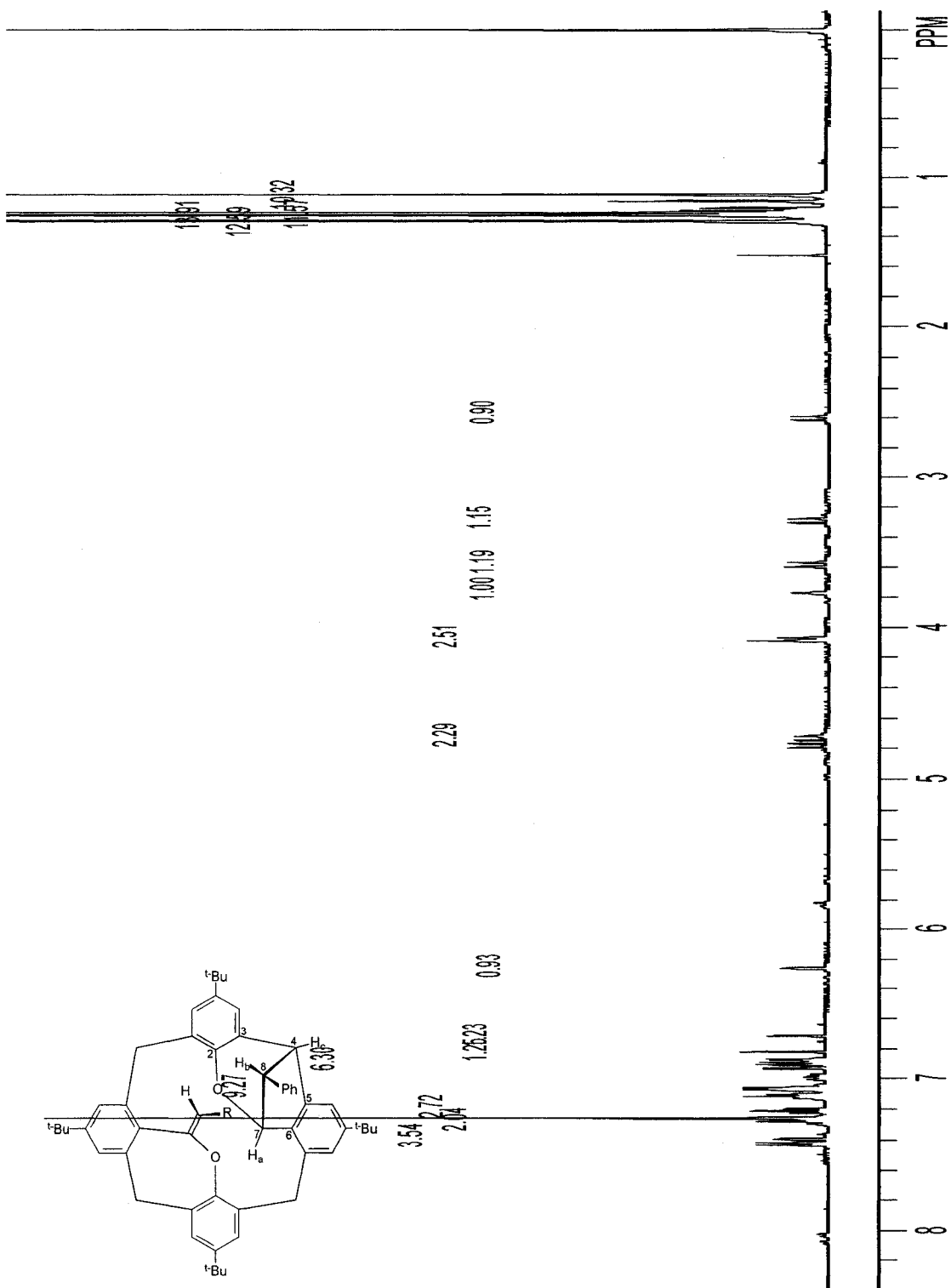
R = *p*-$C_6H_4CF_3$

^{1}H NMR spectrum for compound **11b**

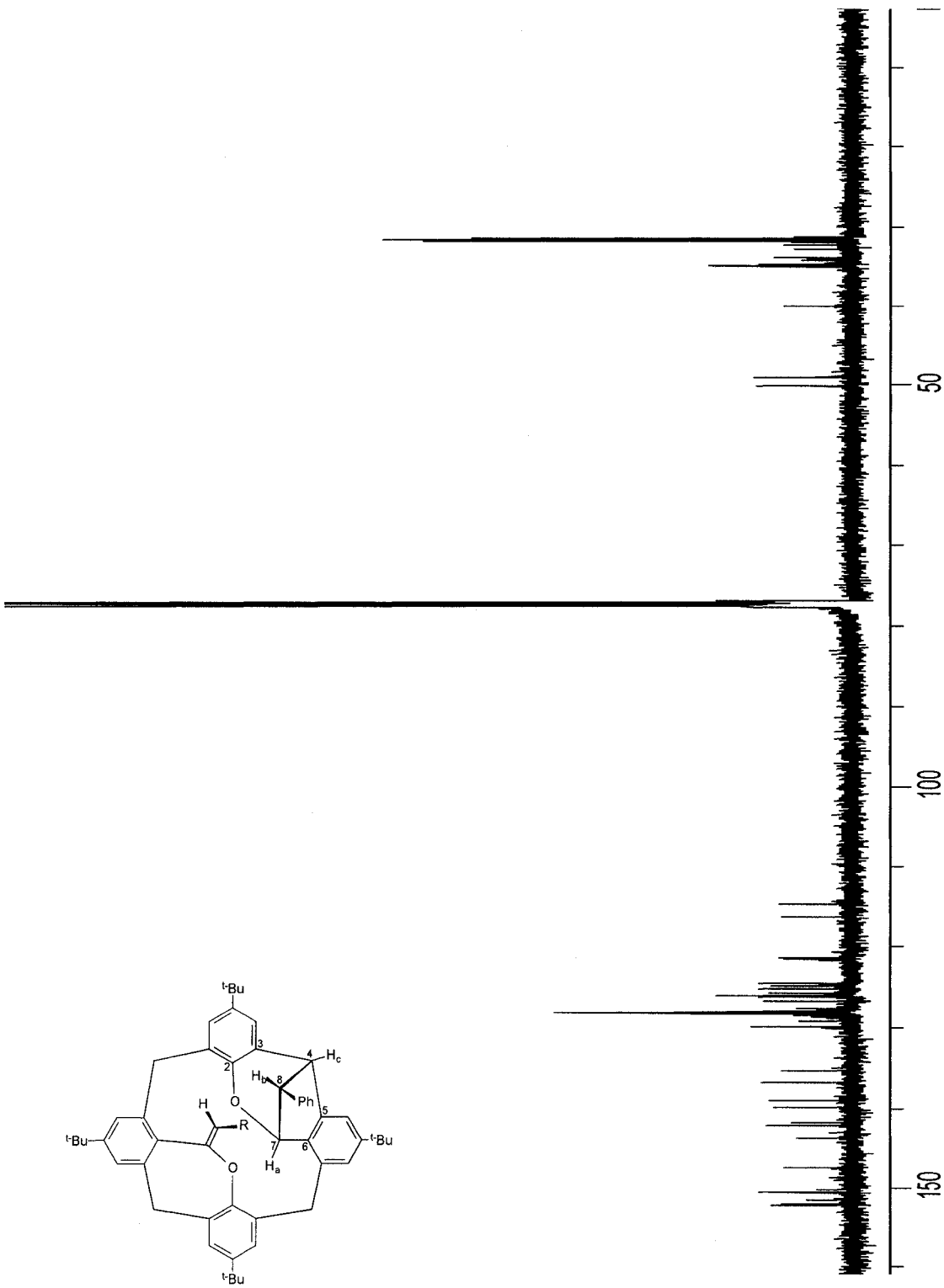


R = *p*-$C_6H_4CF_3$

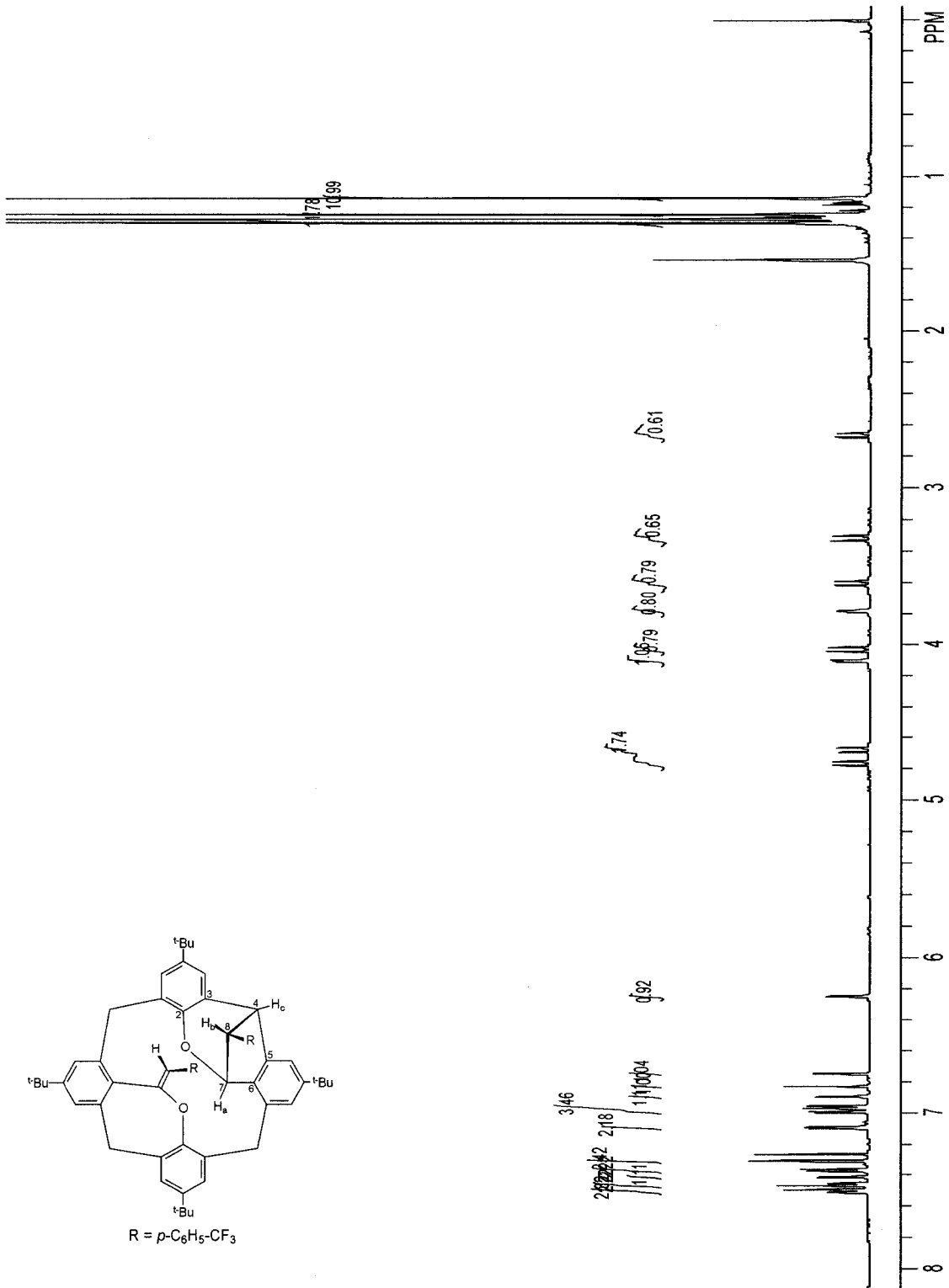
^{13}C NMR spectrum for compound **11b**



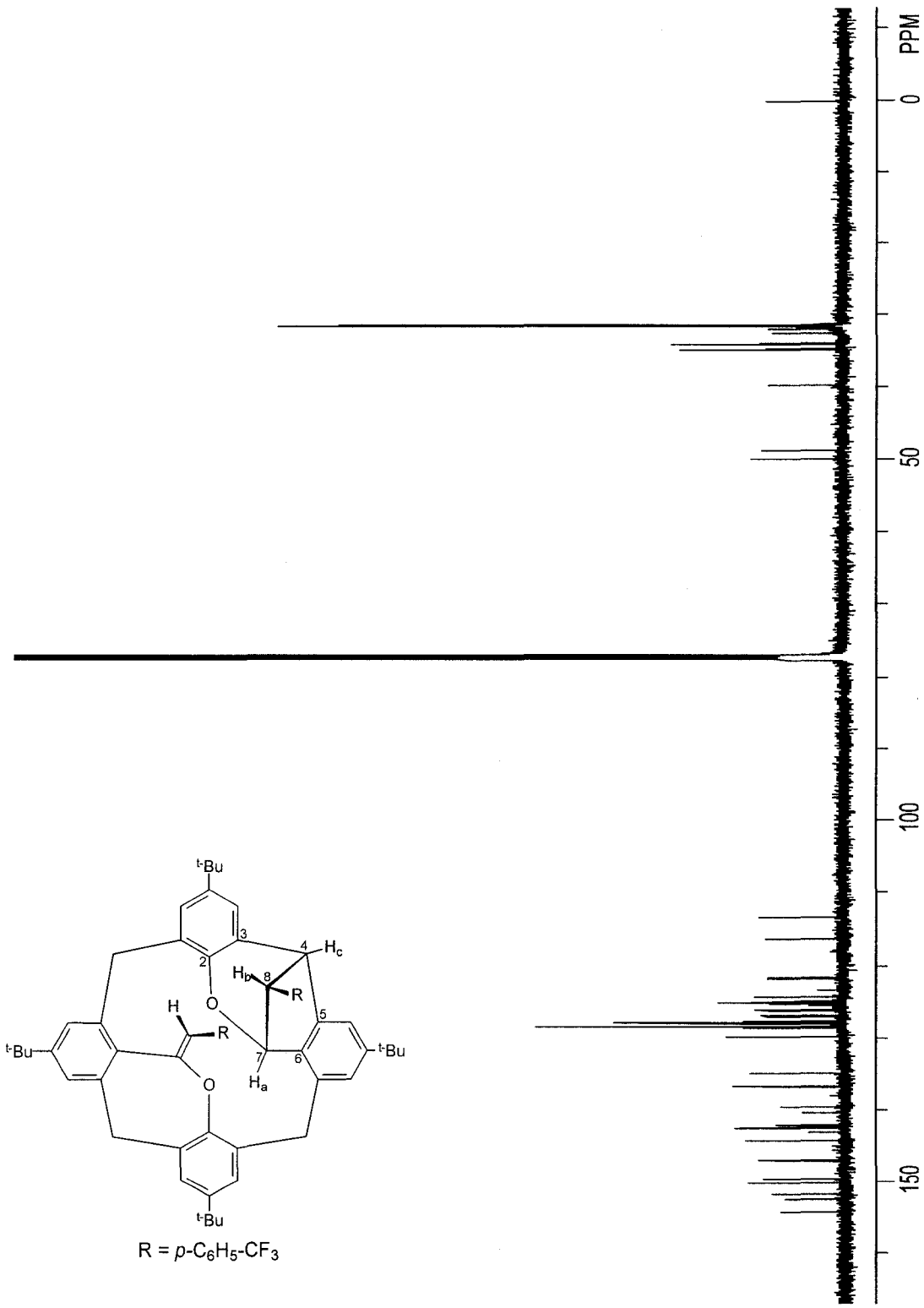
^{1}H NMR spectrum for compound **15a**



^{13}C NMR spectrum for compound **15a**



^{1}H NMR spectrum for compound **15b**



R = *p*-C_6H_5-CF_3

^{13}C NMR spectrum for compound **15b**