NOVEL SYNTHETIC STRATEGIES TOWARDS UPPER RIM MODIFIED CALIX[4]ARENES VIA BIS(SPIRODIENONE) AND RELATED CHEMISTRY

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BY
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UNDER THE SUPERVISION OF
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2010

.....To My Amma

DECLARATION

I hereby declare that Ph. D. thesis entitled "**NOVEL SYNTHETIC STRATEGIES TOWARDS UPPER RIM MODIFIED CALIX[4]ARENES VIA BIS(SPIRODIENONE) AND RELATED CHEMISTRY**" is an independent work carried out by me and it has not been submitted anywhere else for any other degree, diploma or title.

Sreeja T.

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CERTIFICATE

This is to certify that the work embodied in the thesis entitled "**NOVEL SYNTHETIC STRATEGIES TOWARDS UPPER RIM MODIFIED CALIX[4]ARENES VIA BIS(SPIRODIENONE) AND RELATED CHEMSITRY**" has been carried out by **Ms. Sreeja T.** under my supervision and guidance at the Organic Chemistry Section of National Institute for Interdisciplinary Science and Technology (CSIR), Thiruvanathapuram and the same has not been submitted elsewhere for any other degree.

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Sreeja T.

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ABBREVIATIONS

Ac	: acetyl
Ar	: argon
bs	: broad singlet
Bu^t	: *tert*-butyl
COSY	: correlation spectroscopy
d	: doublet
dd	: double doublet
Et	: ethyl
FAB	: fast atom bombardment
FT	: Fourier transform
h	: hours
HMTA	: hexamethylenetetramine
Hz	: hertz
IR	: infrared
J	: coupling constant
LAH	: lithium aluminium hydride
LDA	: lithium diisopropylamide
m	: multiplet
Me	: methyl
mg	: milligram
mL	: millilitre
mp	: melting point

NMR	: nuclear magnetic resonance
Ph	: phenyl
^{i}Pr	: isopropyl
rt	: room temperature
s	: singlet
t	: triplet
TFA	: trifluoroacetic acid
TFE	: trifluoro ethanol
TLC	: thin layer chromatography
TMS	: tetramethylsilane
TS	: transition state
UV	: ultraviolet

PREFACE

Calixarenes are a widely recognized and researched topic in supramolecular chemistry. Their particular charm is the easy availability by the base induced condensation of phenols with formaldehyde providing high yields of calixarenes in a variety of cavity sizes. The crater or basket-like shape of calix coupled with the unlimited possibilities for modifications of calixarenes have played a very important role in shaping the entire architecture of calixarene for its application in host-guest chemistry.

Considerable synthetic efforts have been invested in the last few years in the modification of calixarene skeleton. To alter their preferred conformation, chemical properties and binding capabilities, the calixarenes have been modified at the intraannular (lower rim) and extraannular (upper rim) positions. Among them, selective introduction of functional groups on specific the upper rim of calixarene is an essential prerequisite for the application of calixarenes as versatile building blocks in molecular recognition. By exploiting the results of the selective functionalization of the lower rim of calix[4]arenes, regiocontrolled introduction of the substituents at the upper rim of the calix has been accomplished. These methods take advantage of the different reactivity between phenol and phenol ethers; in aromatic transformations and in oxidation processes. In this way it has been possible to introduce selectively a variety of substituents on the phenol rings by electrophilic aromatic and *ipso* substitution.

Biali *et al*. have developed a novel approach for the modification of calixarenes, in which the phenolic groups were oxidized into carbonyl and five-membered cyclic ether functionalities. These appealing molecules are conferred with two cyclohexadienone rings attached to a five-membered cyclic ether ring through a

spirocentre. These molecules have proved to be valuable intermediates for functionalization of the calixarene framework and design of new macrostructures. The chemical transformations are generally achieved by the electrophilic substitution reactions on the dienone moieties. The Diels-Alder cycloaddition strategies have also been utilized to a great extent for the synthesis of calixarene based novel macrocyclic compounds. However, there has been only little attempt to introduce a nucleophilic group directly or indirectly onto the upper rim of calix moiety. The fact that the introduction of a nucleophile onto the upper rim of the calix[4]arenes *via* spirodienone intermediate would open new vistas in calixarene chemistry prompted us to take up this research problem. Against this background, we have carried out a systematic study of the nucleophilic substitution of calix[4]bis(spirodienones) with a wide range of nucleophiles, with an objective to devise novel calixarenes. The results of our efforts are embodied in the thesis titled "**NOVEL SYNTHETIC STRATEGIES TOWARDS UPPER RIM MODIFIED CALIX[4]ARENES VIA BIS(SPIRODIENONE) AND RELATED CHEMISTRY"**.

The thesis is divided into four chapters which are presented as independent units and therefore the structural formulae, schemes and figures are numbered chapter wise. References are given separately towards the end of the thesis.

A comprehensive review of the chemistry of calixarenes and calix[4]spirodienones is presented in the first chapter. The definition of the research problem is provided at the end of the chapter.

The second chapter details our efforts towards a novel and seemingly *ipso* like nucleophilic substitution of the upper rim of *p*-*tert*-butylcalix[4]arene *via* calix[4]bis(spirodienone) route using *p*-toluenesulphonic acid (*p*-TSA). The new

methodology furnished upper rim mono- and dialkoxy/aryloxy substituted calix[4]arenes.

The efficacy of the above developed methodology is manifested by further chemical modification of the new products obtained. The first part of the third chapter gives an account of the usefulness of this strategy towards the synthesis of calixquinones and biscalixarenes. During the investigation of methodology described above, we have also come across a serendipitous finding where both *p-tert*-butylcalix[4]arene and *p-tert*-butylthiacalix[4]arene can be fully de-*tert*-butylated, which forms the focus of the second part.

The final chapter comprises of the details our investigations toward the synthesis of upper rim isocyanide functionalized calix[4]arenes for its potential applications towards multifunctionalized calix[4]arenes *via* multicomponent reactions.

Chapter 1

Calixarenes to Calix[4]bis(spirodienones): A Prelude

1.1 Calixarenes

The world of organic chemistry is populated by several million compounds distributed among hundreds of families. Some of these families have commanded the attention of chemists for many decades and have reached a venerable patrician status. Many others are more recently discovered and are yet to establish their place in the hierarchy of chemical importance. Among the latter, is a family of compounds called calixarenes which, although more than 100 years old, has gained widespread attention from the chemical community only during the last four decades.

Calixarenes [Asfari 2001] **1** are broadly defined as a class of cyclophane-like macrocycles consisting of a series of aromatic rings *meta*-linked by methylene bridging groups. Calixarenes have a long history dating back to 1872, when Adolph von Baeyer reported reactions between phenols and aldehydes [Baeyer 1872]. Many of the products could not be identified at that time and it took almost 70 years before the Austrian chemists Zinke and Ziegler assigned the cyclic tetrameric structure to the product resulting from the base catalyzed condensation of *p*-substituted phenols with formaldehyde [Zinke and Ziegler 1941]. Experiments carried out by Cornforth and coworkers in the 1950s indicated that the Zinke products were actually mixtures [Kappe 1994; Conforth *et al.* 1973]. It wasn't until the mid-1970s that the identity of three of the components of the mixture was established by Gutsche and coworkers as the cyclic tetramer, cyclic hexamer and cyclic octamer [Gutsche *et al.* 1981]. Further

work conducted by Gutsche revealed reliable and reproducible synthetic procedures for a series of oligomers from *p*-alkyl phenols and formaldehyde. The most accessible among them are the tetramers, hexamers and octamers, although all members of the series from n = 4-20 are known (Figure 1.1) [Gutsche 1989].

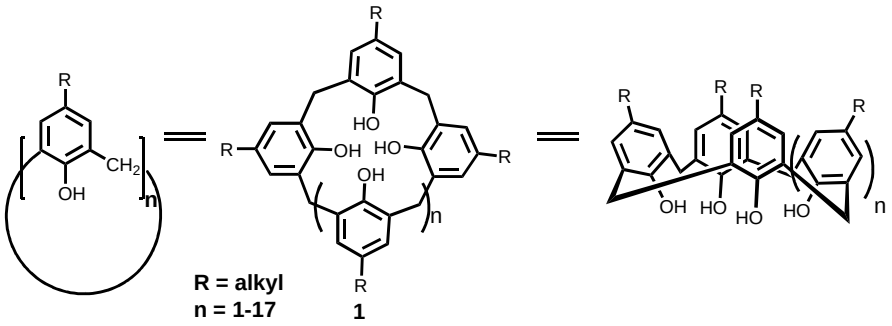


Figure 1.1: *General representations of calixarene*

1.2 Nomenclature and representation of calixarenes

The name “calixarene” was given by Gutsche [Gutsche and Muthukrishnan 1978] in 1978, as he noticed the analogy between an ancient vase shape (calix in Greek) and the space filling models of the tetramer (Figure 1.2). Arene refers to the presence of aromatic rings in the structure. Although the name has not yet been embodied as the official IUPAC nomenclature, it appears to have been generally accepted by chemists working in this field. The name was initially given to the tetramer in the conformation which had all four aryl groups oriented in the same direction.

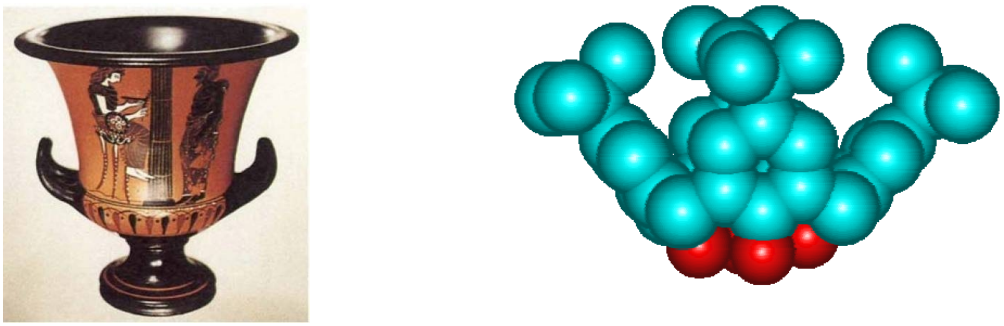


Figure 1.2: *Calix crater and space filling model of calixarene*

Thus the trivial names of calixarenes are constructed by placing a bracketed number in between calix and arene to identify the number of phenol units incorporated into the cyclic ligand, such as calix[4]arene. The hydroxyl groups and other substituents (e.g., *tert*-butyl) are designated as appendages. Thus, the cyclic tetramer derived from *p-tert*-butylphenol is called *p-tert*-butylcalix[4]arene. For systematic nomenclature, the basic name "calix[n]arene" is retained, while the identities of all substituents are designated and their positions specified by numbers as shown in figure 1.3. So the systematic name of *p-tert*-butylcalix[4]arene is 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene.

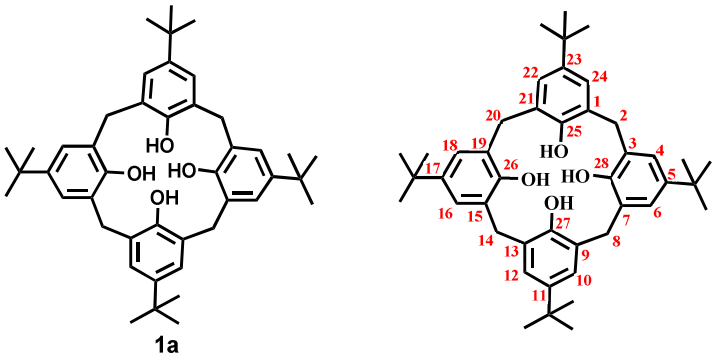


Figure 1.3: *Structure and numbering of calix[4]arene*

In the structure of the calixarenes (Figure 1.4), two different zones can be distinguished *viz*. the intraannular phenolic hydroxyl group termed as the 'lower rim' and the extraannular *para* position of the phenol termed as the 'upper rim' [Gutsche and Muthukrishnan 1978].

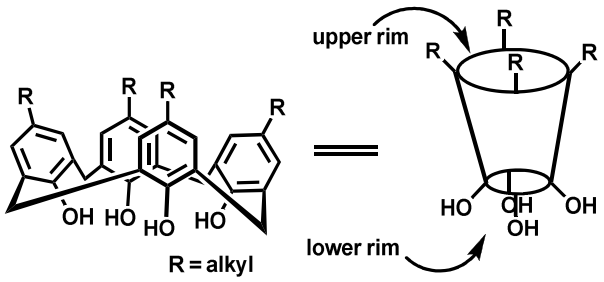


Figure 1.4: *Designation of the two rims of calixarene*

1.3 Conformations of calixarenes

One of the most fascinating aspects of calixarenes lies in the variety of conformations which they can assume; these result from the (more or less) free rotation of phenolic rings about the σ bonds of the Ar-CH_2-Ar groups. In the case of calix[4]arene, the orientation of phenol units, relative to a plane defined by the carbon atom of the methylene bridges, presents four different conformations. These conformations were later named by Gutsche [Gutsche *et al.* 1983] as 'cone', 'partial cone', '1,2-alternate' and '1,3-alternate', as illustrated in figure 1.5.

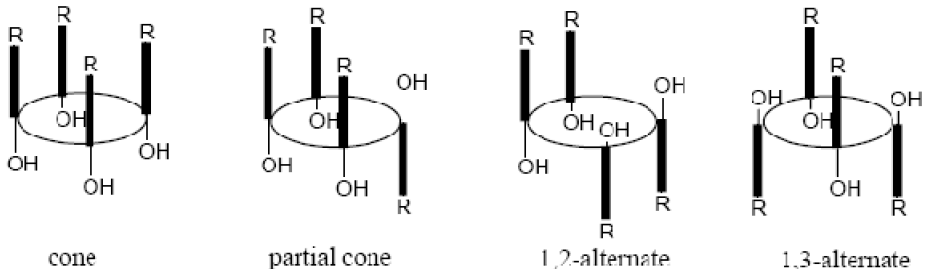


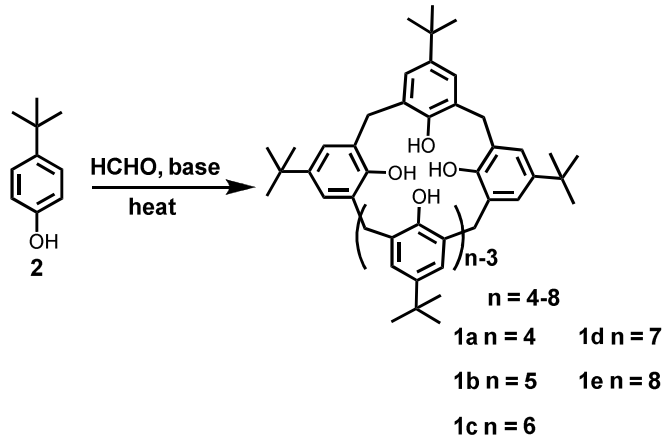
Figure 1.5: *Conformations of calix[4]arenes*

As the number of aryl groups in the cyclic array increases, the number of conformations also increases. While calix[5]arene exhibits four true conformations like calix[4]arene, calix[6]- and calix[8]arenes show eight and sixteen conformations respectively.

1.4 Synthesis of calixarenes

The main reason for the growing interest in calixarene chemistry in the last two decades is their ready availability. Large amounts of calixarenes can be obtained on a laboratory scale in a relatively simple manner using cheap starting materials. In this respect, calixarenes differ from other synthetic macrocycles like crown ethers, cyclodextrins etc. Although several methods for the synthesis of calixarenes have been developed over the years, still the most general and useful method is the one-step base catalyzed condensation of *p*-substituted phenols and formaldehyde. Condensation of *p*-

tert-butylphenol **2** with formaldehyde under alkaline conditions (NaOH, KOH) leads in one step to calix[n]arenes **1a-1e** (Scheme 1.1); depending on the reaction conditions, the yields of tetramer, hexamer and the octamer are 50, 80 and 63% respectively [Bohmer 1995].



Scheme 1.1: *Synthesis of calixarenes*

Calixarenes with odd number of building blocks (pentamer [Knop et al. 1989], heptamer [Afsari and Vicens 1989]) are also obtained by this method but the yields are considerably lower. The amount of base and reaction conditions are the main factors which determine the number of phenol rings involved in the cyclization. The optimum amount of base for the formation of the tetramer and octamer appears to be about 0.03 mole NaOH per mole of *p-tert*-butylphenol; the tetramer requires a higher temperature (boiling diphenyl ether) than the octamer (boiling xylene). A large amount of base (0.4 mole KOH per mole of *p-tert*-butyl phenol) favours the formation of hexamer.

Treatment of *p-tert*-butylphenol with s-trioxane and *p*-toluenesulfonic acid in $CHCl_3$ gave an almost quantitative yield of calixarenes [Gutsche *et al.* 1990]. In contrast to the base-induced reaction, conditions have not been found that lead to high yields of individual cyclic oligomers. Instead, the reaction product is a mixture of all of the calixarenes ranging from the cyclic tetramer to the cyclic eicosomer. Typically, the larger calixarenes are present in greater amounts than in the base-induced reaction.

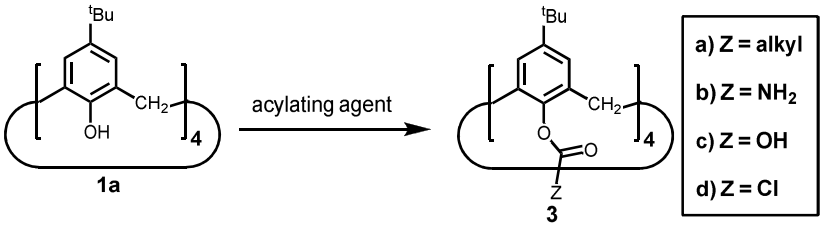
1.5 Modifications of calixarenes

Much of the interest in calixarenes is derived from their potential for use in a wide variety of applications. In most cases, this depends not only on the basket-like shape of the molecules but also on the presence of appropriate functional groups. In this context, chemical modification of calixarenes assumes great importance. Calixarenes can undergo modifications in two main ways: 1) by the introduction of functional groups at the phenolic hydroxyl groups; 2) by (electrophilic) substitution at the *p*-position with respect to the phenolic hydroxyl group.

1.5.1 Functionalization involving the OH groups

The phenol-derived calixarenes are already functionalized with OH groups in the lower rim, and these provide excellent handles for further functionalization by making use of the 'phenol chemistry'.

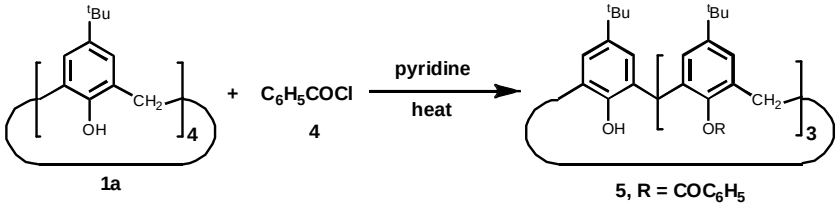
The esters of calixarenes were the earliest derivatives to be prepared (Scheme 1.2) [Bohmer 1995]. With acid halides and NaH, acid halides and $AlCl_3$, or acid anhydrides and H_2SO_4, the acylation or aroylation generally involves all of the OH groups, if the derivatizing agent is used in excess. A study of the esterification of calix[4]arenes showed that acetylation, propionylation, butyrylation, and isobutyrylation yield the tetraacylates **3**, although with varied and somewhat unpredictable conformational outcomes.



Scheme 1.2: *Esterification of calixarenes*

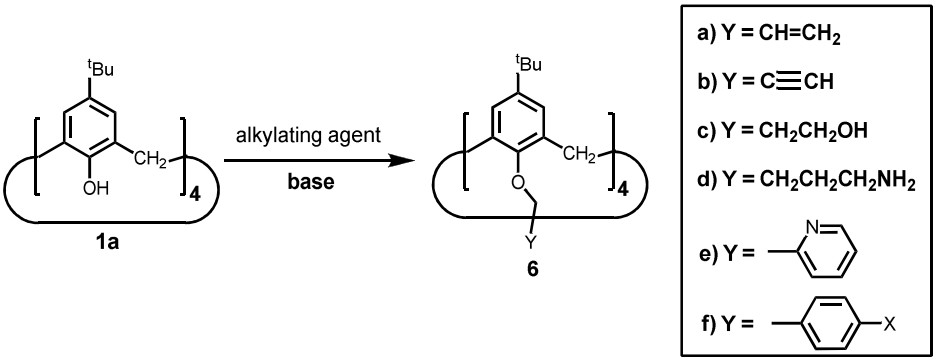
Regioselective esterification in calixarenes is important for many purposes, in particular for the construction of larger molecules starting from several calixarene

building units. By using limiting amounts of the esterifying reagent and/or by using bulky esterifying reagents, it is often possible to obtain partially substituted calixarenes in a selective fashion, in the presence of bases weaker than NaH. An early example for selective functionalization is *p-tert*-butylcalix[4]arene **1a** reacting with 3.2 equivalents of benzoyl chloride **4** in the presence of pyridine to give the tribenzoate **5** (Scheme 1.3) [Gutsche and Lin 1986].



Scheme 1.3: *Partial esterification of calix[4]arene*

Alkylation has been studied in considerable detail in the calix[4]arene (Scheme 1.4), and methods have been devised for preparing the mono-, di- (both distal and proximal), tri- and tetra-ethers [Gutsche *et al.* 1983; Dykstra *et al.* 1989; No *et al.* 1990; van Loon *et al.* 1990; Iwamoto *et al.* 1991; Veravong *et al.* 2000].

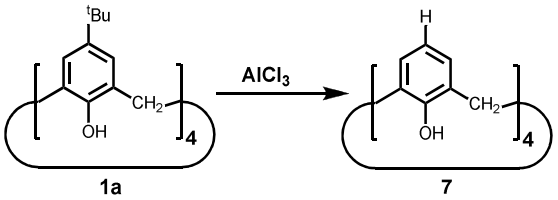


Scheme 1.4: *Etherification of calixarenes*

1.5.2 Functionalization of upper rim of calixarenes

It is a fortunate circumstance that the few phenols that provide calixarenes in good yields in the one-step procedure, *viz. p-tert*-butylphenol, *p-tert*-pentylphenol, are those from which the *para*-substituent can be easily removed by $AlCl_3$-catalyzed

transalkylation in the presence of a suitable acceptor such as toluene or phenol (Scheme 1.5) [Gutsche *et al.* 1985]. This reaction which furnishes *p*-H-calixarenes **7** plays a key role in calixarene chemistry, as a large variety of calixarenes with different substitutions in the *p*-position can be obtained by subsequent electrophilic substitution.



Scheme 1.5: *De-tert-butylation of calixarenes*

Virtually all the common reactions which are possible for phenols (or phenol ethers) have been carried out on calixarenes or their alkyl ether derivatives: halogenations [Gutsche and Pagoria 1985], nitration [Verboom et *al.* 1992], sulfonation [Shinkai *et al.* (a) 1987; Casnati et al. 1993], sulfochlorination [Morzherin et al. 1993], aminomethylation [Gutsche and Nam 1988; Gutsche and Alam 1988], acylation [Shinkai *et al.* 1991] and coupling with diazonium salts [Shinkai *et al.* 1989; Yeh *et al.* 1994]. Sulfonation [Vicens and Bohmer 1991] and nitration [Verboom *et al.* 1992] products have also been obtained directly by *ipso*-substitution of the *tert*-butyl groups. Selective functionalization of the *para* positions such as partial nitration [Verboom *et al.* 1992], formylation [Arduini *et al.* 1991], iodination [Arduini *et al.* 1990] are also possible.

Additionally, modifications of calixarenes may be carried out at the methylene bridges [Middel *et al.* 2000; Scully *et al.* 2001; Kumar *et al.* (a) 2002; Kuno *et al.* 2007; Columbus and Biali 2008], at the aromatic system of the phenolic units as a whole, *viz*. oxidation [Morita *et al.* 1992], hydrogenation [Grynspan and Biali 1996] *etc*. or by the replacement of the OH function by other groups [Goren and Biali 1990;

Ting *et al*. 1990; Grynspan *et al.* (a) 1991; Grynspan *et al.* (b) 1991; Grynspan and Biali 1991; Grynspan *et al.* 1994; Ohesto *et al.* 1992].

1.6 Applications of calixarenes

The spurt in the increase of literature regarding calixarenes in the last 25 years can be ascribed to the growing interest in introducing different functional groups *via* different synthetic procedures. But also the major factor that has contributed is the tailor-made structure of calixarenes for its use as complexing agents, for it is this possibility and its potential that has brought calixarenes the recognition that they enjoy today. The use of these modified calixarenes as sensors for metal ions, organic/neutral molecules, and drug recognition has brought calixarenes to limelight. On the other hand, the conformational properties of calixarenes have been largely exploited to create new shapes and architectures for molecular receptors. They have become a wonder molecule at the hands of a chemist. This wonder molecule has its roots in host-guest chemistry. Due to the very rapid expansion of the subject it was not possible to cover all fields in which calixarenes are in *action*. A concise account of the relevant examples illustrating the spectacular role of calixarenes in supramolecular field is given below.

1.6.1 Calixarenes as host molecules

Due to the presence of their preformed cavities, the calixarenes are able to act as host molecules. This “crater” or “basket” plays a very important role in shaping the entire architecture of calixarene for its function in host-guest chemistry, since this theory is highly interdependent on two terms: “shape” and “functionality”.

1.6.1.1 Recognition of neutral molecules

Using the cavity as binding site for a substrate (guest), a calixarene receptor (host) can perform structural recognition in the complexation process on the basis of

the structural complementarity of the two molecular species. Calixarenes most studied for neutral molecule complexation are usually in cone conformation, the cavity of which can accept neutral guest molecules of similar size. A large number of inclusion complexes of neutral organic molecules and *p*-alkylcalix[4]arenes have been isolated and structures determined by X-ray crystallography. Among them, the most well known example is the complex of the *p-tert*-butylcalix[4]arene and toluene [Andreetti *et al.* 1979].

The study of the two upper rim bridged calixarenes **8** and **9** (Figure 1.6) by Pochini and Arduini indicated that the existence of a rigid cavity is an essential requirement to observe strong gas-phase supramolecular interactions, and the complexation efficiency strongly depended on the structure and length of the bridge present at the upper rim [Andreetti *et al.* 1995]. Nitromethane, malononitrile and acetonitrile were chosen as guests. The strength of complexation was determined by multiple interactions between the acidic methyl hydrogens of the guest and the π-electrons of both the phenolic cavity and the bridge.

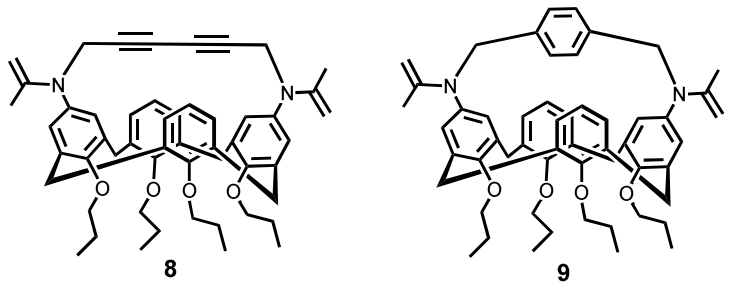


Figure 1.6: *Calix[4]arenes for recognition of neutral guests in the gas phase*

1.6.1.2 Recognition of anions

Anions, such as nitrates and phosphates etc., are significant agricultural and industrial pollutants, and are also causative agents for many diseases such as cystic fibrosis, triggered by the misregulation of chloride channels [Quinton 1990]. Calixarenes have played an ever increasing role in the development of anion

coordination chemistry. Several strategies have been developed for the binding of anions, including hydrogen bonds, electrostatic and Lewis acid attractions. According to the different strategies adopted in the design process, the calixarene receptors can be classified into two categories: charged calixarene and neutral calixarene anion receptors.

The cobaltocenium calix[4]arene anion receptor **10** showed strong binding of halide anions in DMSO and formed a strong 1:1 complex with the dicarboxylate dianion $^{-}O_2C(CH_2)_4CO_2^{-}$ in acetone (Figure 1.7) [Beer *et al.* 1993].

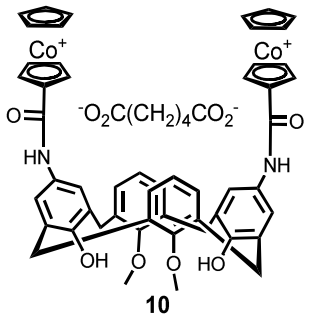


Figure 1.7: *A cobaltocenium calix[4]arene anion receptor*

In the design of neutral calixarene anion receptors, several hydrogen bonding motifs, such as urea and thiourea, have been incorporated in upper and lower rim calixarene frameworks for the purpose of anion coordination (Figure1.8). Receptor **11** showed high binding capacity for Cl^- and Br^- anions in $CDCl_3$ with 1:1 stoichiometry [Scheerder *et al.* 1994].

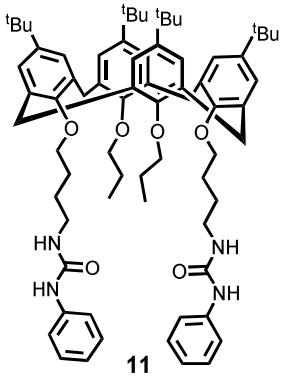


Figure 1.8: *A neutral calixarene anion receptor*

1.6.1.3 Recognition of metal cations

During the last decade, calixarenes have received the attention of many researchers mainly due to their unique complexing abilities toward various metal cations. The broad spectrum of selectivities exhibited by these ligands led to applications in metal ion recognition and separation. Typically, these recognitions are mainly focused on the complexation behaviours of alkali, alkaline-earth, lanthanide and transition/heavy metal ions.

Arduini and coworkers synthesized tetradiethylamidecalix[4]arene **12** which exhibited excellent efficiency for complexation of alkaline earth metal ions [Sato *et al.* 1997]. System such as the one shown in figure 1.9 is an excellent Na^+ binder and has been widely used in a variety of sensory schemes [Arnaud-Neu *et al.* 1999; Casnati *et al.* 1993; van der Veen *et al.* 1999].

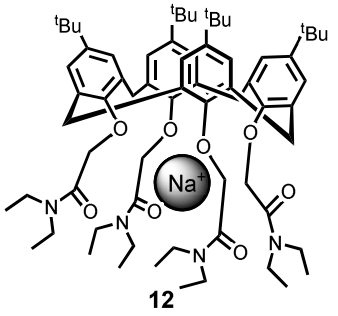


Figure 1.9: *Calixarene tetramides as Na^+ binders*

The incorporation of ionophoric crown ether groups into calixarenes was pioneered by the group of Ungaro [Arduini *et al.* 1986]. In contrast to the system described above, the 'calixcrowns' show a preference for larger alkali metal ions, like Cs^+ and even Fr^+ (Figure 1.10) [Haverlock *et al.* 2003]. Much of the interest in this area has been motivated by the need for ligands that selectively extract heavier alkali metal cations from solutions containing Na^+. This application is of special importance

in the treatment of aqueous nuclear waste containing mixtures of radioactive ^{137}Cs and non-radioactive Na isotopes.

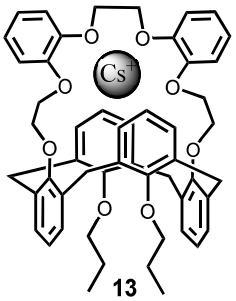


Figure 1.10: *A Cs^+ selective calixcrown*

1.6.2 Calixarenes in self-assembly

Design and investigation of molecules capable to form well defined, functional supramolecular structures by self-assembly has attracted considerable interest during the last decade. The development of artificial molecules, bearing in their chemical structure all the informations to build up assemblies of increasing complexity, is a challenge in itself [Prins *et al.* 1998]. Calixarenes endowed with accolades such as ready availability, easy chemical modifications and above all, a concave shape forms an attractive molecular platform for the construction of supramolecular structures. A few significant results in the calixarene field which reflects the self assembling properties are discussed below.

Timmerman *et al*. created box like assemblies by the noncovalent organization of melamine substituted calixarenes **14** with barbiturates **15** or cyanurates **16** (Figure 1.11) *via* hydrogen bonds [Timmerman *et al.* 1997].

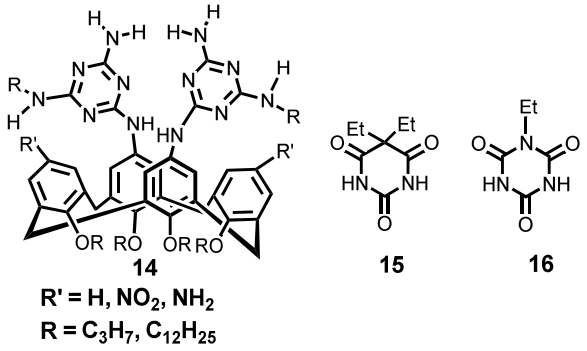


Figure 1.11: *Melamine substituted calixarene*

Long-chain *p*-acylcalixarenes form stable gels [Kumar et al. (a) 2002] in a variety of organic solvents including some alcohols probably through hydrogen bonds between the alcoholic hydroxyl and carbonyl groups (Figure 1.12).

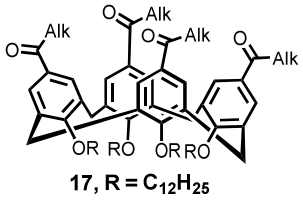


Figure 1.12: *A gelating p-acylcalix[4]arene*

Calix[n]arenes have been used to form Langmuir-Blodgett (LB) mono- and multilayers, as well as self-assembled mono- and multilayers. Amphiphilic calix[n]arene **18** bearing both hydrophobic (long alkyl chains) and hydrophilic groups (Figure 1.13) are generally suitable for the formation of LB films [Markowitz *et al.* 1989].

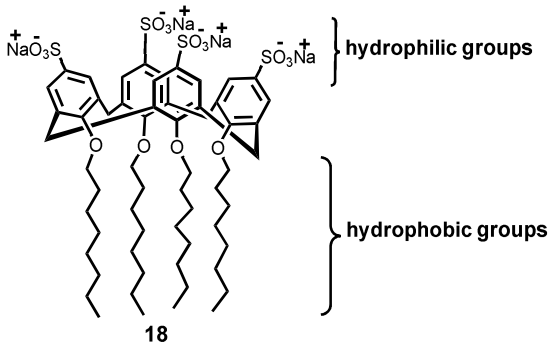


Figure 1.13: *Example of an amphiphilic calixarene*

1.6.3 Calixarene based catalytic systems

Several features possessed by the calixarenes, notably their ability to form host-guest complexes and the possibility of introducing a large variety of functions by means of selective derivatization, qualify them as good candidates to act as enzyme mimics or, in general, as synthetic catalysts [Shinaki *et al.* 1993; Nomura *et al.* (a) 1994; Nomura *et al.* (b) 1994; Shinkai *et al.* 1986].

A highly efficient Rh(I) catalyst reported by Paciello *et al.* [Paciello *et al.* 1999] provides an elegant example of catalyst design by lower rim modification of calix[4]arene. Ligand **19** (Figure 1.14) catalyzes the hydroformylation of 1-octene with $[Rh(CO)_2(acac)]$ resulting in the selective formation of the linear nonanal rather than the branched isomer.

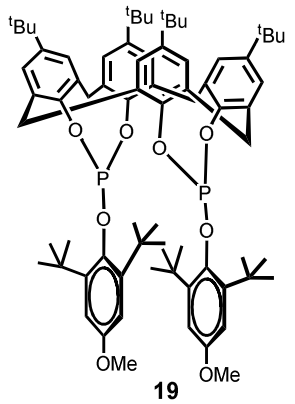


Figure 1.14: *A calix[4]arene based phosphite chelator*

Calix[4]arene based di- and trinuclear Zn(II) and Cu(II) complexes developed by the group of Reinhoudt [Molenveld *et al.* 1997; Molenveld *et al.* 1998] showed excellent phosphodiesterase activity towards RNA and DNA model compounds (Figure 1.15).

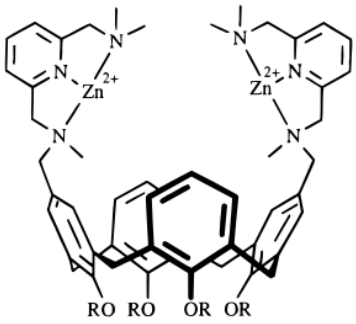


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Figure 1.15: *A phosphodiesterase mimic*

1.7 Other members of the family

Resorcinol-derived calixarenes, termed as, resorcarenes **21** [Bohmer 1995], the sulfur analogues of calixarenes, termed as, thiacalixarenes **22** [Ohba *et al.* 1991], homocalixarenes **23** [Tashiro and Yamato 1981], azacalixarenes **24** and oxacalixarenes **25** are some of the closely related macrocycles (Figure 1.16) known in literature. Recent examples include macrocycles derived from furans [Musau and Whiting 1993; Musau and Whiting 1994], thiophenes [Black *et al.* 1993] and pyrroles [Georghiou and Li 1993]

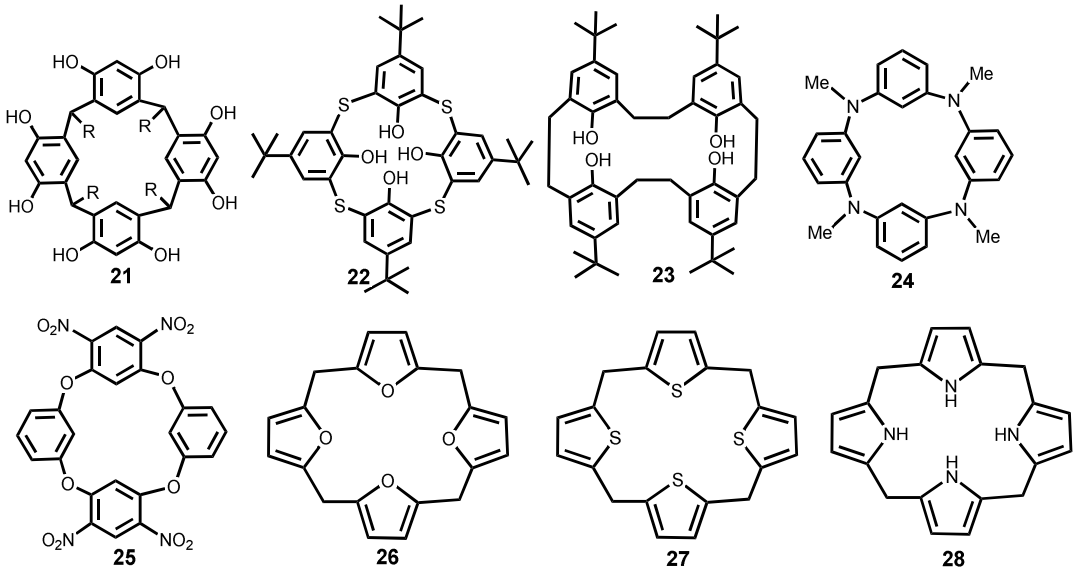


Figure 1.16: *Other members of calixarene family*

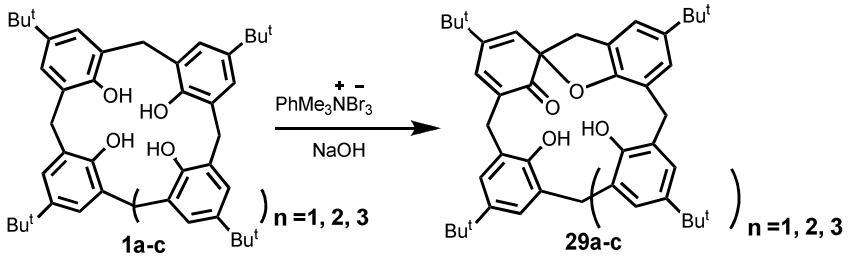
A concise sketch of the fundamental features, synthesis, chemical transformations and applications of calixarenes has been portrayed in the preceding pages. Spirodienones are an interesting class of molecules obtained by a mild oxidative cyclization of calixarenes. They have emerged as versatile synthetic intermediates for the preparation of selectively functionalized and a few chemically modified calixarenes that are otherwise difficult to obtain by conventional methods. In continuation of our interest in the chemistry of spirodienone derivatives, we have selected calix[4]bis(spirodienones) as the synthon for most of the work reported in this thesis. In this context, it is most befitting to undertake a survey of literature relating to the chemistry of this class of compounds as prelude to the present work.

1.8 Spirodienones: Versatile synthons for calixarene modification

1.8.1 Aromatic ring oxidation to spirodienones

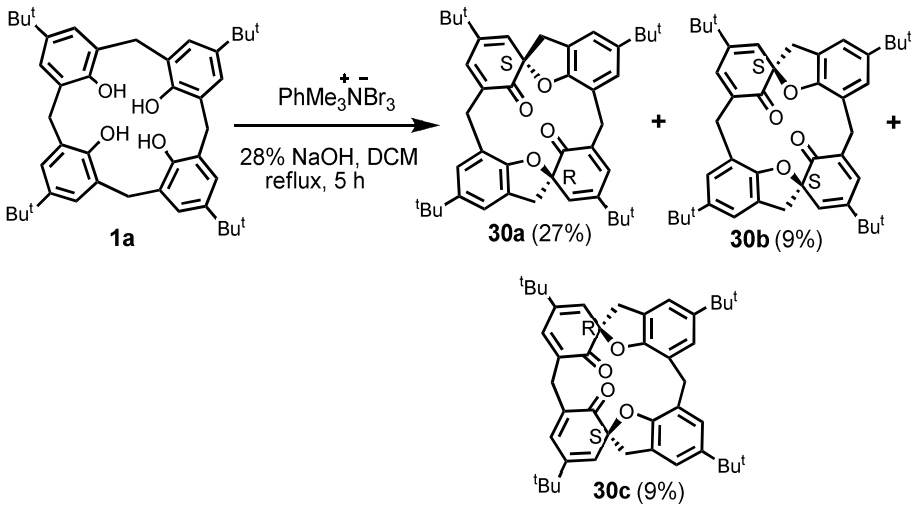
Biali and coworkers serendipitously discovered that mild oxidizing agents convert phenolic rings of calixarenes to spirodienone moieties. This discovery was

made during the alkylation of **1a** using a bifunctional alkylating agent, 1,4-dibromobutane in the presence of an aqueous base under phase transfer catalysis conditions. Using trimethylphenyl ammonium tribromide instead of the intended monobromide as the phase transfer catalyst, *p-tert*-butylcalix[4]arene **1a** was transformed to monospirodienone **29a** (Scheme 1.6) [Biali 2001; Aleksiuk *et al.* (b) 1993].



Scheme 1.6: *Serendipitous formation of spirodienones*

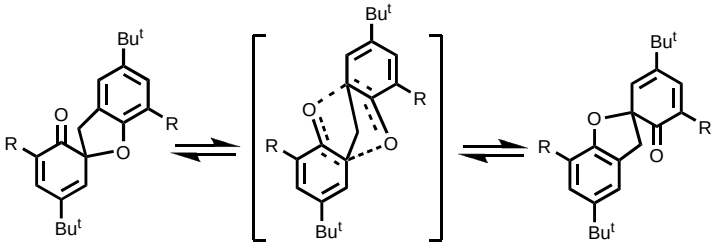
Further investigations showed that more strenuous oxidation in a two-phase basic system (dichloromethane, aqueous NaOH) resulted in the smooth conversion of **1a** to a new series of isomers **30(a-c)**, the major product being **30a** (Scheme 1.7) [Litwak and Biali 1992; Litwak and Biali 1993]. The major product of the reaction was found to be isomer **30a**.



Scheme 1.7: *Oxidative cyclization of calix[4]arene to calix[4]bis(spirodienones)*

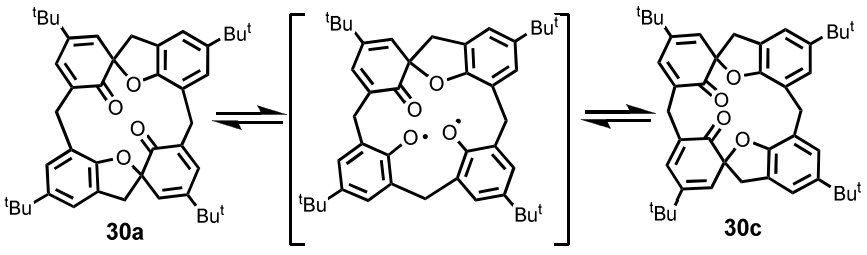
The isomers were found to exist as an equilibrium mixture consisting of approximately 27% **30a**, 9% **30b** and 9% **30c** [Litwak *et al.* 1993]. The isolation of the major bis(spirodienone) isomer **30a** in superior yield (> 95%) is possible by heating a mixture of bis(spirodienone) isomers at 170 °C (below the melting point) [Agbaria and Biali (a) 2001].

Two simple mechanisms have been suggested for the isomerization of **30**. The mechanism suggested on the basis of Cope rearrangement involves the concerted cleavage and formation of spiro bonds (Scheme 1.8). This rearrangement should be stereospecific and the new stereocenter created should have a configuration identical to the one destroyed.



Scheme 1.8: *Mechanism via Cope rearrangement*

The most probable mechanism involves the cleavage of C(sp^3)-O bond of the spirodienone moiety leading to two phenoxy radicals. Regeneration of the C-O bond could occur with inversion or retention of the configuration of the spiro carbon and with retention or reversal of the directionality of the spirodienone moiety (Scheme 1.9) [Litwak *et al.* 1993].



Scheme 1.9: *Mechanism via radical route*

The larger calixarenes behave in a similar manner. Calix[5]- and [6]arenes give mono-, bis- and tris-(spirodienone) derivatives. The major product obtained in the oxidation of calix[6]arene with excess of oxidizing reagent is the tris(spirodienone) **31** (Figure 1.17) with an alternating arrangement of carbonyl and ether groups and three spiro stereocenters with different configurations [Agbaria and Biali (b) 2001; Grynszpan and Biali (b) 1996].

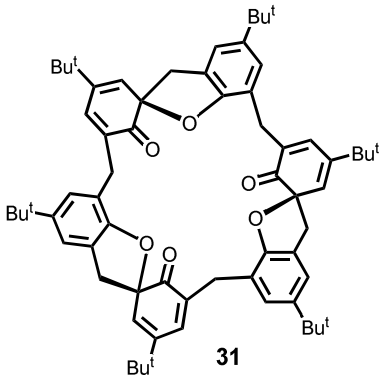


Figure 1.17: *Calix[6]tris(spirodienone)*

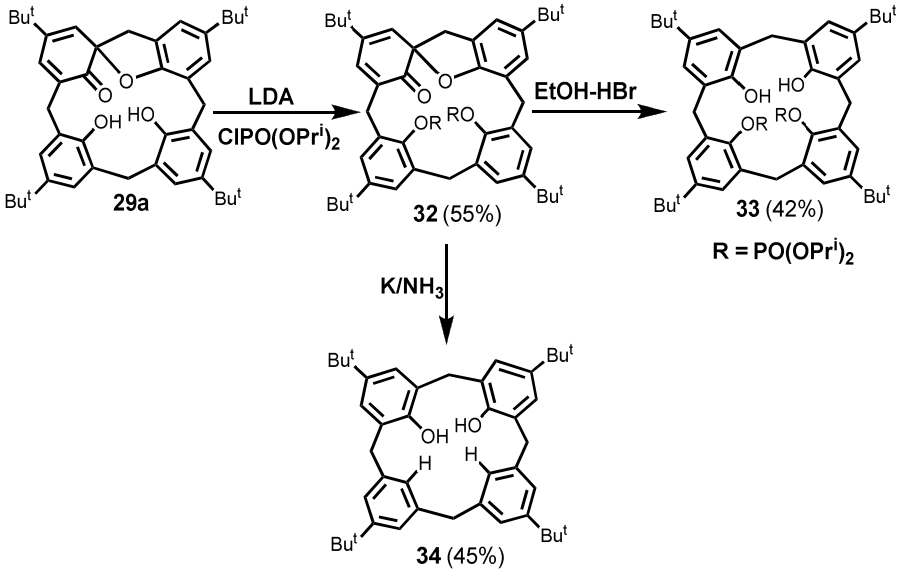
1.8.2 Chemistry of spirodienone calixarene derivatives

The oxidation of calixarene to the bis(spirodienone) derivatives is remarkable since in a single step, the -OH groups are transformed into carbonyl and ether functionalities, two phenolic rings are transformed to dienone moieties and at the same time two spiro stereo-centers are also created. Biali has ingeniously exploited his discovery by demonstrating that spirodienone derivatives can engage in reactions that lead to a variety of altered calixarenes. The succeeding section would deliberate on the use of spirodienones for the functionalization of calixarene at the intraannular, extraannular positions and also for the modification of the methylene groups.

1.8.2.1 At the intraannular positions

1.8.2.1.1 Spirodienones as protecting groups

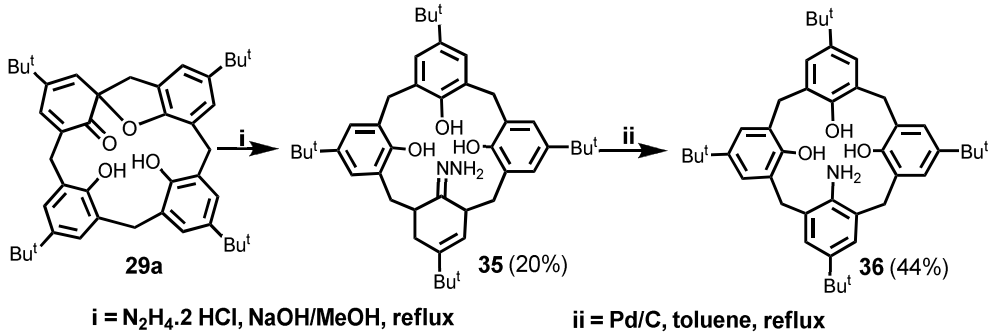
A spirodienone group can be used as a protecting group for the preparation of calixarenes substituted at proximal rings.[75] Calix[4]mono(spirodienone) **29a** on reaction with diisopropylchlorophosphate in the presence of LDA yielded a disubstituted spiro derivative **32** (Scheme 1.10). **32** on treatment with HBr in ethanol led to the formation of proximally disubstituted calixarene **33** and a didehydroxylated calixarene **34** on reaction with K/NH_3. In this example the K/NH_3 played a dual role, cleaving both the spiro bond and the dialkylphophate ester groups of the derivatized spirodienone **32**.



Scheme 1.10: *Synthesis of proximally disubstituted calixarene*

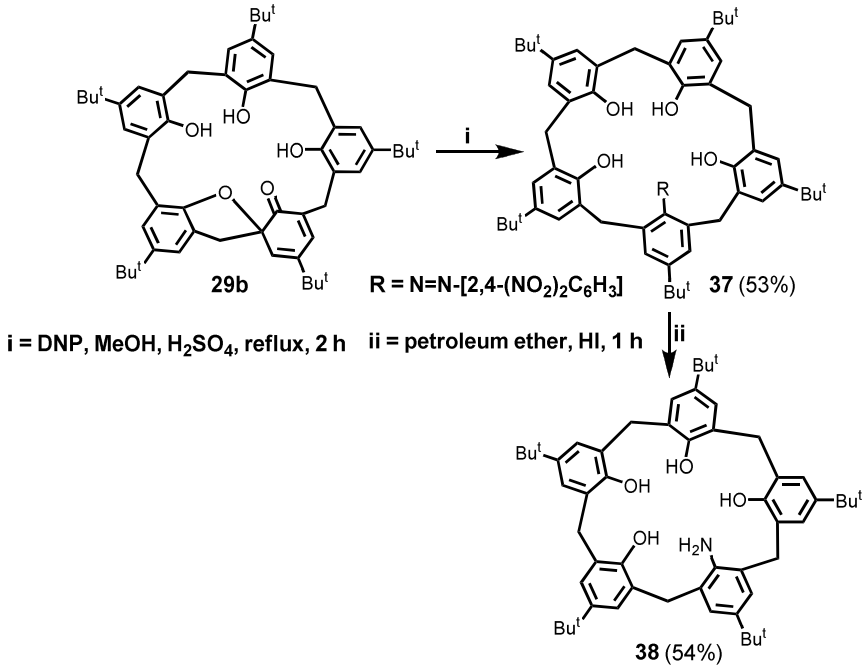
1.8.2.1.2 Selective aminodehydroxylation of calixarenes

The spirodienone route has also been employed for the replacement of hydroxyl group by an amino group, which is considered the most difficult synthetic task in calixarene chemistry. Biali's approach involved the treatment of monospirodienone **29a** with hydrazine hydrochloride in the presence of NaOH under methanol reflux conditions. The reaction afforded the hydrazine derivative **35**, which on refluxing in toluene with Pd/C fetched the monoaminocalixarene **36** in 44% yield (scheme 1.11) [Aleksiuk *et al.* (b) 1993].



Scheme 1.11: *Preparation of monoaminotrihydroxy calix[4]arene*

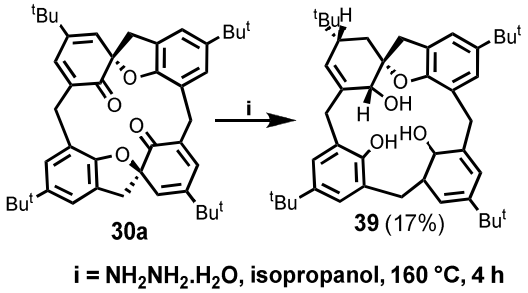
When the same reaction was conducted on monospirodienone of calix[5]arene **29b** using 2,4-dinitrophenyl hydrazine as the amino nucleophile, monoaminated calix[5]arene **38** was obtained in 54% yield (Scheme 1.12) [Aleksiuk *et al.* 1995].



Scheme 1.12: *Reaction of calix[5]mono(spirodienone) with 2,4-dinitrophenyl hydrazine*

In principle the reaction of the bis(spirodienone) systems with hydrazine could facilitate the preparation of both hydrazo and aminocalixarene derivatives. However, the reaction of calix[4]bis(spirodienone) **30a** with hydrazine hydrate did not yield the

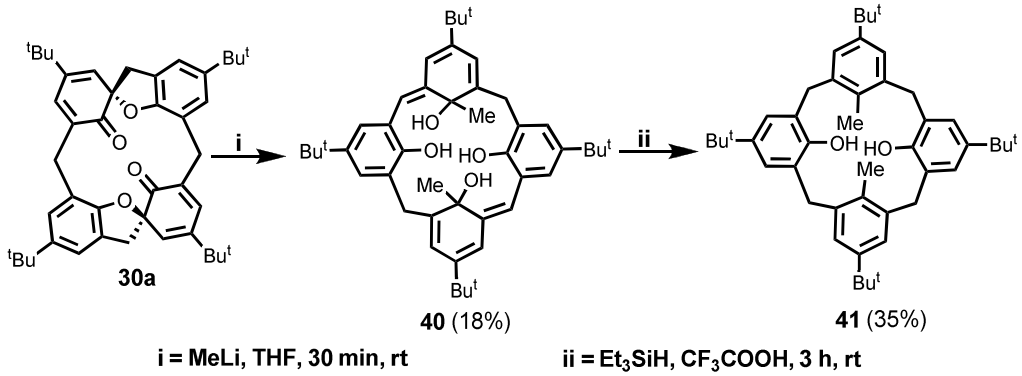
expected dihydrazo derivative but afforded a reduced product **39** (Scheme 1.13) [Grynspan and Biali 2003]



Scheme 1.13: *Reaction of calix[4]bis(spirodienone) with hydrazine hydrate*

1.8.2.1.3 Selective replacement of OH groups by methyls

A calixarene derivative, in which two distal OH groups were replaced by methyls was prepared from calix[4]bis(spirodienone) by the reaction sequence depicted in scheme 1.14. Reaction of calix[4]bis(spirodienone) **30a** with excess MeLi afforded **40**, derived from the addition of the organometallic reagent to the carbonyl groups of the bis(spirodienone) derivative followed by elimination. The diol **40** on reaction with CF_3COOH/Et_3SiH produced the calixarene **41** [van Gelder *et al.* 1997].



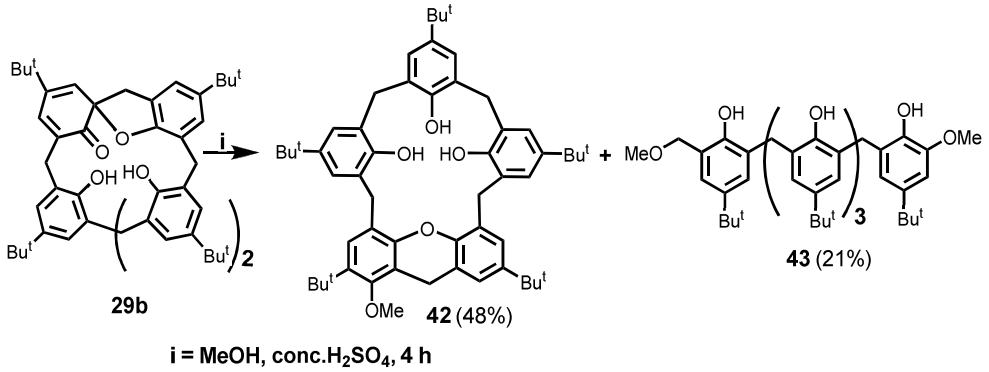
Scheme 1.14: *Preparation of 4**1** from calix[4]bis(spirodienone)*

1.8.2.1.4 Dehydration of two proximal phenol groups

Attempts made to dehydrate calixarenes to prepare xantheno derivatives often culminated in either fragmentation of the calix skeleton or reaction with solvent

molecules yielding undesired products [Yamato *et al.* 1991; Aleksiuk and Biali (a) 1993].

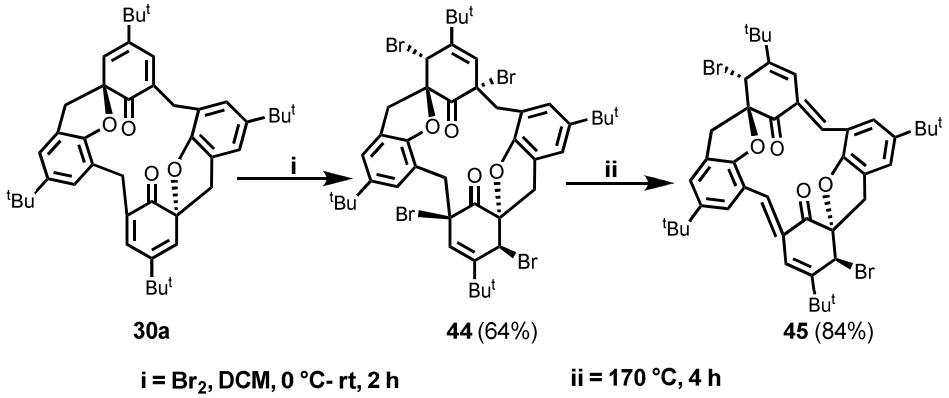
Biali's group succeeded in dehydrating calixarenes *via* spirodienone route. Treatment of monospirodienone **29b** with methanol and H_2SO_4 yielded the xanthenocalixarene derivative **42** with a methoxy group (originating from the solvent) incorporated into one of the rings of the xanthene unit (Scheme 1.15) [Aleksiuk *et al.* 1995]. Along with the xanthene derivative a fragmented product **43** was also observed (Scheme 1.15). Analogous reactivity was shown by the monospirodienone derivative of calix[6]arene [Shinkai *et al.* 1986].



Scheme 1.15: *Synthesis of xanthenocalixarene*

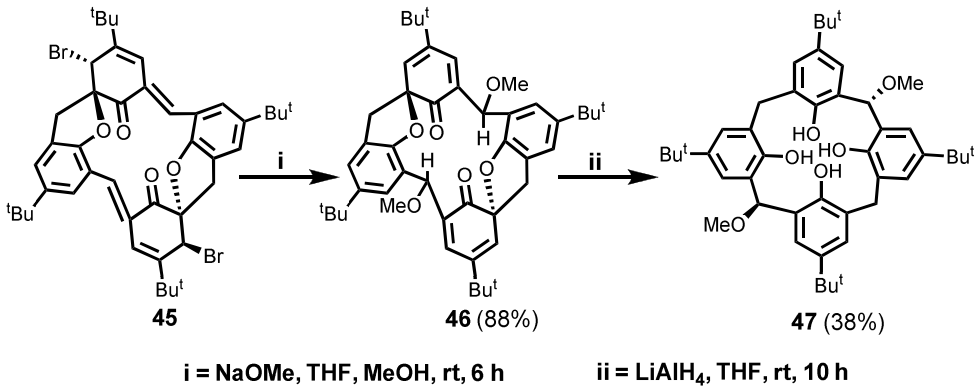
1.8.2.2 The spirodienone route for methylene functionalization

Direct functionalization of the methylene groups of a calixarene have been achieved in only a few cases [Columbus and Biali 2008; Kumar et al. (a) 2002; Middel et al. 2000; Scully et al. 2001; Kuno et al. 2007]. Among them, the synthetic route enabling the functionalization of two distal (i.e., non-vicinal) methylene groups through spirodienone calixarenes is the most prominent. The method is based on the sequence of reactions shown in scheme 1.16 [Agbaria and Biali (a) 2001]. Addition of two equivalents of bromine to **30a** led to the formation of the tetrabromo derivative **44**, followed by dehydrobromination furnished the alkenyl spiro derivative **45**.



Scheme 1.16: *Preparation of alkenyl spiro derivative*

The alkenyl spiroderivative thus synthesized presented the prospect for the attack of nucleophiles. When reacted with NaOMe, **45** afforded the corresponding methoxide functionalized derivative **46** which on LAH reduction resulted in the formation of a calixarene derivative **47** with two substituents on the bridging methylenes in a mutual *trans* relationship (Scheme 1.17) [Agbaria and Biali (a) 2001; Simaan *et al.* 2002].

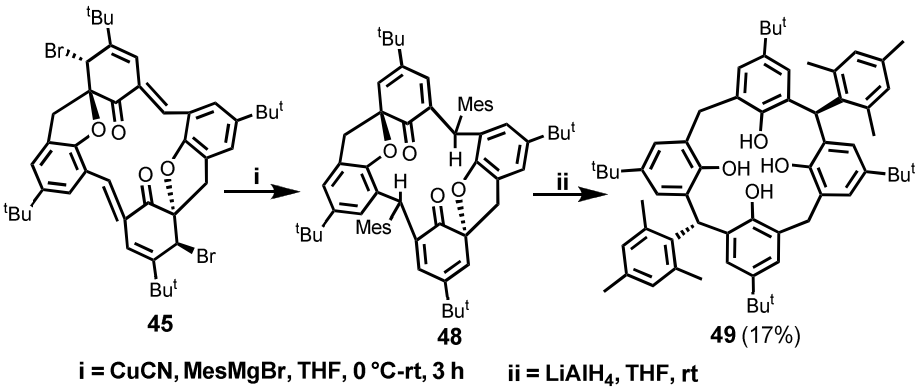


Scheme 1.17: *An example for the synthesis of methylene functionalized calixarene*

These displacement reactions at the methylene groups were generalized using a wide range of S-, N-, O-, and C-containing nucleophiles, fetching differently functionalized calixarenes at the distal methylene junctions [Simaan *et al.* 2002].

Recently Biali and coworkers utilized the same synthetic sequence for the introduction of aryl substituents at distal methylene bridges of calix[4]arene. The

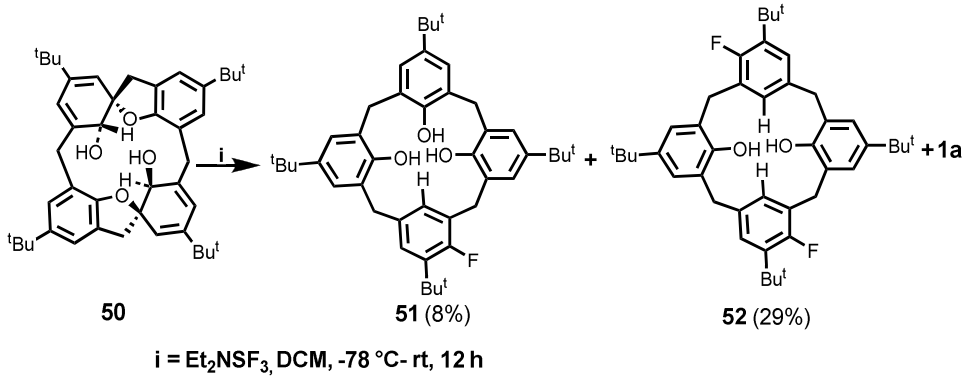
reaction of the alkenyl derivative of spirodienoene **45** with mesitylmagnesium bromide (MesMgBr)/CuCN followed by LAH reduction resulted in the formation of the corresponding calixarene derivative **49** (Scheme 1.18) [Simaan and Biali 2004]. It forms the first example of a classical tetrahydroxycalixarene that adopts a 1,2-alternate conformation in solution.



Scheme 1.18: *Synthesis of calixarenes having aryl substituents at the methylene bridges*

1.8.2.3 Extraannular modification of the calix scaffold

Biali introduced the spirodienone path for the synthetic transformation of calixarenes at the extraannular position. The bis(spirodienones) on reduction with $NaBH_4$ afforded a mixture of three isomers of bis(spirodienols) [Agbaria *et al.* 2001; Agbaria and Biali (b) 2001]. Treatment of the bis(spirodienol) **50** with diethylaminosulfur trifluoride (DAST) at -78 °C furnished a mixture of mono and difluorinated derivatives **51** and **52** together with *p-tert*-butylcalix[4]arene **1a** (Scheme 1.19).

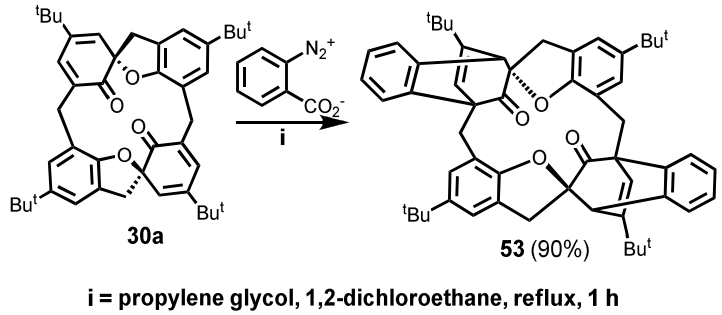


Scheme 1.19: *Extraannular modification of calixarene*

Details of extraannular modifications of calixarenes based on spirodienones will be furnished in chapter 2.

1.8.2.4 Diels-Alder reaction of bis(spirodienones)

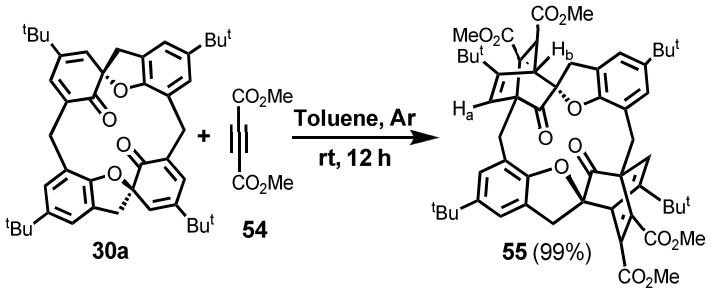
The dienone moieties of the cyclohexadienone rings in compounds **30a**, **30b** and **30c** are in principle proficient of acting as 4π components in cycloaddition reactions. It was verified by Biali *et al*. by a single reaction of bis(spirodienone) with benzyne [Grynspan and Biali 2003] (generated from benzenediazonium-2-carboxylate hydrochloride). The bis(spirodienones) **30a** on cycloaddition reaction with benzyne in the presence of propylene glycol afforded the (4+2) adduct **53** (Scheme 1.20).



Scheme 1.20: *Diels-Alder reaction of 1,3-isomer with benzyne*

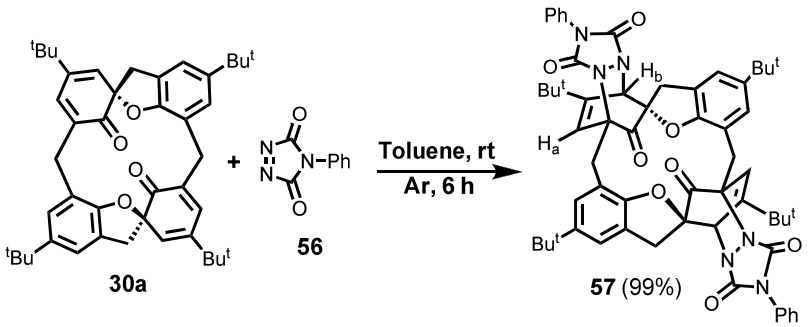
Except for the above isolated reaction, its Diels-Alder reactivity remained largely dormant. Later on, our group initiated work in this area and the results revealed the role of bis(spirodienone) as an efficient diene in its cycloaddition reaction with a

number of carbo and heterodienophiles [Varma *et al.* 2005; Varma *et al.* 2006; Ganga *et al.* 2007]. The reaction of the most stable isomer of the calix[4]bis(spirodienone), **30a** with two equivalents of DMAD **54** in anhydrous toluene at ambient conditions afforded the (4+2) adduct bis(bicyclo[2.2.2]octadienone) derivative **55** in quantitative yield (Scheme 1.21).



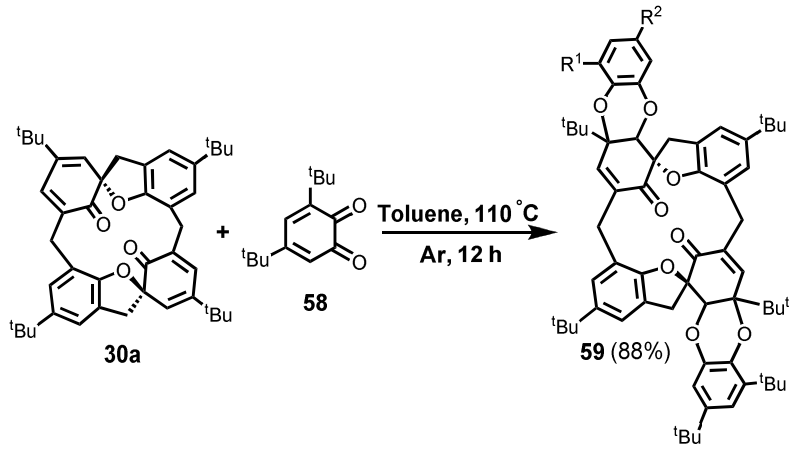
Scheme 1.21: *(4+2) Cycloaddition reaction of bis(spirodienone)* ***30a*** *with DMAD*

1,2,4-Triazoline-3,5-diones are very reactive cyclic azadienophiles and they have an intrinsic capability to introduce an N-N moiety into the structure of the cycloadduct. A facile reaction occurred with N-phenyl 1,2,4-triazoline-3,5-dione **56** at ambient conditions leading to the formation of the cycloadduct **57** in quantitative yield (Scheme 1.22) [Ganga *et al.* 2007].



Scheme 1.22: *Reaction of bis(spirodienone) with N-phenyl-1,2,4-triazoline-3,5-dione*

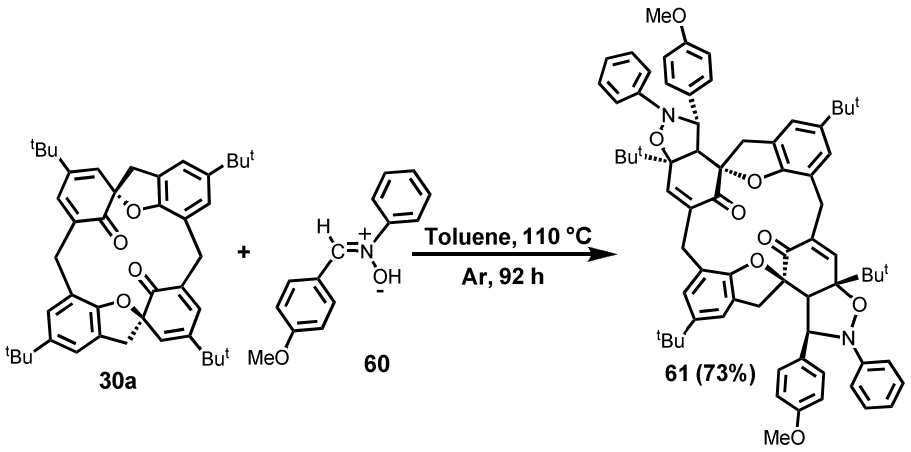
The reaction of calix[4]bis(spirodienone) **30a** with 1,2-benzoquinone **58** revealed an unexpected reactivity pattern *viz.* it acted as a 2π component yielding benzodioxin derived macrocycle **59** (Scheme 1.23) [Varma *et al.* 2006].



Scheme 1.23: *Reaction of bis(spirodienone) with 1,2-benzoquinone*

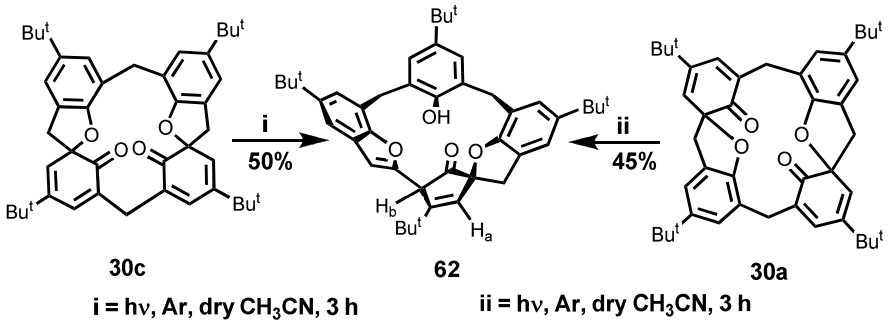
However, with 1,4-quinones the bis(spirodienone) acted as a diene and the reaction was found to be highly selective yielding a single adduct.

The dipolarophilic behaviour of calix[4]bis(spirodienone) **30a** was also investigated using a variety of C,N-diarylnitrones. **30a** on reaction with two equivalents of *C*-(4-methoxyphenyl)-*N*-phenylnitrone **60** in dry toluene under reflux led to the formation of the [3+2] cycloadduct, 5-substituted isoxazolidine derivative **61** in good yield (Scheme 1.24) [Ganga *et al.* 2008].



Scheme 1.24: *[3+2] Dipolar cycloaddition of bis(spirodienone) with C-(4-methoxyphenyl)-N-phenylnitrone*

A novel photochemical rearrangement of the calix[4]bis(spirodienone) skeleton was recently reported from our group. When degassed solutions of **30a** and **30c** in acetonitrile were irradiated at 300 nm separately in a photochemical reactor (Scheme 1.25), a highly functionalized macrocycle containing a spirocyclic cyclopentenone-THF unit, a trisubstituted phenol and a benzofuran moiety **62** resulted in good yield. The macrocyclic ring system was endowed with a 14 member irregular cavity and resembled a partial bowl in the solid state [Varma *et al.* 2007].



Scheme 1.25: *Photochemical rearrangement of calix[4]bis(spirodienones)*

1.9 Conclusion and present work

The importance of calixarenes and the envious position it now occupies in the annals of supramolecular chemistry stems from many factors. Their unique three dimensional structures with almost unlimited derivatization abilities and tunable shapes make calixarenes ideal candidates in the design of new and more sophisticated molecules. The initial part of this chapter provided an updated and reasonably detailed account of various aspects of calixarene chemistry.

The chapter also accounts for the chemistry of calix[4]bis(spirodienones), versatile synthons obtained by the oxidative cyclization of *p-tert*-butylcalix[4]arene. The presence of several functionalities such as carbonyl, ether and diene within the calix scaffold assists them to endure a large number of synthetic transformations. The

modification of calixarene skeleton facilitated through spirodienone route unravels the synthetic utility of spirodienone derived calixarenes. The modifications are mostly effected by nucleophilic or electrophilic substitution reactions on the dienone moieties. The spirodienone calixarene derivatives have been utilized for the selective derivatization of two vicinal OH groups, the rearrangement of one or two OH groups, the formation of Ar-O-Ar bonds between neighbouring aryl groups, the functionalization of the calix scaffold at the extraannular positions (*via* spirodienol derivatives) and the modification of the methylene groups.

Selective introduction of functional groups on specific phenol rings of the calixarene is an essential prerequisite for the application of calixarenes as versatile building blocks in molecular recognition. By exploiting the results of the selective functionalization of the lower rim of calix[4]arenes, regiocontrolled introduction of the substituents at the upper rim of the calix has been accomplished. These methods take advantage of the different reactivity between phenol and phenol ethers; in aromatic transformations and in oxidation processes. In this way it has been possible to introduce selectively a variety of substituents on the phenol rings by electrophilic aromatic and *ipso* substitutions.

A careful investigation of the literature shows that very little attempt has been made to introduce an ether linkage either directly or indirectly onto the upper rim of calix moiety. The fact that the introduction of ether linkage on the upper rim of the calix[4]arenes *via* spirodienone intermediate would open new vistas in calixarene chemistry prompted us to take up this research problem. The second chapter details our efforts towards a novel and seemingly *ipso* like nucleophilic substitution of the upper rim of *p-tert*-butylcalix[4]arene *via* calix[4]bis(spirodienone) route using p-

toluenesulphonic acid (*p*-TSA). The new methodology furnished upper rim mono- and dialkoxy/aryloxy substituted calix[4]arenes.

The efficacy of the above developed methodology is manifested by further chemical modification of the new products obtained. The first part of the third chapter gives an account of usefulness of this strategy towards the synthesis of calixquinones and biscalixarenes. During the investigation of methodology described above, we have also come across a serendipitous finding where both *p*-*tert*-butylcalix[4]arene and *p*-*tert*-butylthiacalix[4]arene can be fully de-*tert*-butylated, which forms the focus of the second part.

The last chapter focuses on our investigation towards the synthesis of upper rim isocyanide functionalized calix[4]arenes and its application towards multicomponent reactions.

Chapter 2

Bis(spirodienone) Route to Nucleophilic Functionalization of Calixarene: Accessing Upper Rim Substituted Mono- and Dialkoxy/aryloxy Calix[4]arenes

2.1 Introduction

Calixarenes have been most befittingly described as 'hosts with (almost) unlimited possibility' by Bohmer *et al.* due to their easy availability and amenability for chemical transformations to 3-dimensional functional molecules [Bohmer 1995]. Functionalized calixarenes can perform a myriad of functions as host components in sensors [Kremer *et al.* 1994; Yainamoto and Shinkai 1994; Maldolini and Ungaro 2000], as pseudo-stationary phases in capillary electrophoresis [Gomez-Kaifer *et al.* 1994], as phase transfer catalysts [Shohat and Grushka 1994], as enzyme mimics [Maldolini and Ungaro 2000], as non-linear optics [Maldolini and Ungaro 2000] etc. to mention a few. Hence development of newer techniques for easy functionalization of calixarenes assumes great significance. The focus of modifying the calixarenes was much concentrated on the lower rim, due to the easy manipulation of OH groups that are already present at the lower rim, with many applications [Iwamoto *et al.* 1991; Konig *et al.* 1999]. Although a great number of derivatization procedures have been used, methods which permit modification at the upper rim are highly limited. Probably

this is connected with the difficulty of functionalization of the upper rim either selectively or exhaustively, due to the involvement of multiple steps *viz*. protection of the lower rim hydroxyls and de-tertiarybutylation followed by electrophilic substitution at the reactive *para*-position. There is no doubt that development of effective approaches for the selective functionalization of the upper rim of calixarenes, unsubstituted at the lower rim offers the greatest promise, because in that case very useful building blocks for supramolecular design can be created. This chapter deals with *para*-toluene sulfonic acid mediated nucleophilic functionalization of the upper rim of calix[4]arene *via* calix[4]bis(spirodienone) route. Before going into the details of the work, the various modifications effected at the upper rim, starting from *p-tert*-butylcalixarene and calix[4]bis(spirodienone) are discussed in the following sections.

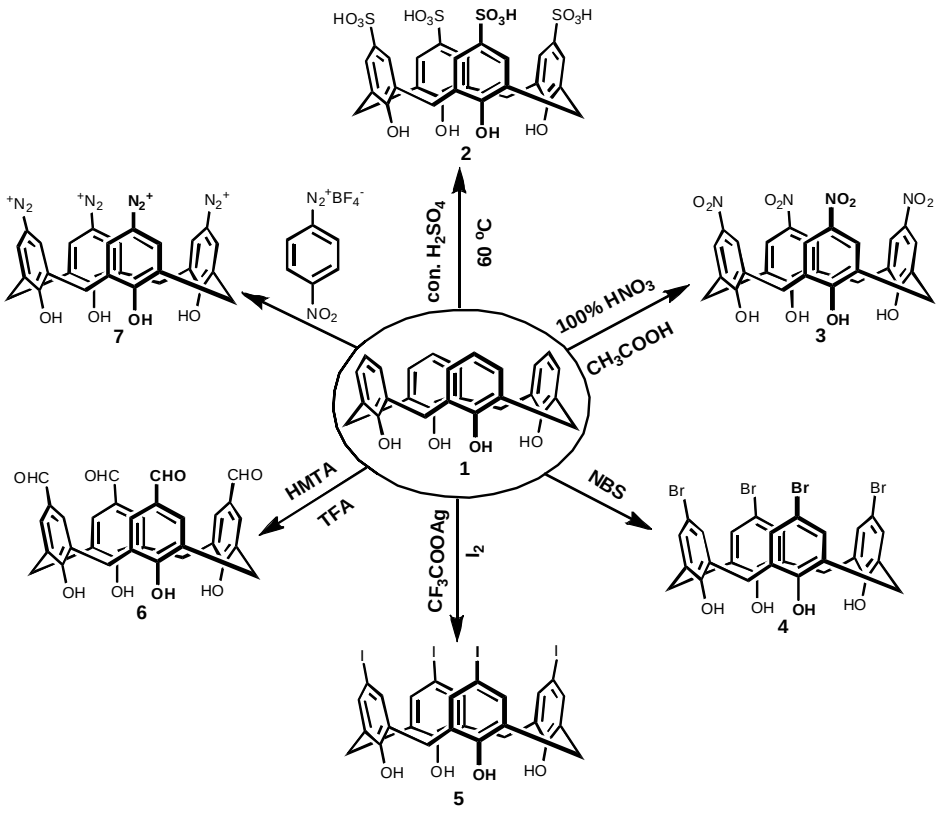
2.1.1 Upper rim modifications

Over the past two decades, the chemical modification of calixarenes has been largely investigated to change the chemical and supramolecular properties of the parent macrocycles. Among the possible approaches, the functionalization at the *para* position of the aromatic rings (the upper or wide or exo rim) assumes significance, as it is considered the best way to exploit the preformed calix cavity in recognition processes. The common pathways to introduce new functionalities at the calixarene upper rim includes a range of electrophilic aromatic substitution reactions, the classical "Claisen rearrangement route", "*p*-quinonemethide route", and "*p*-chloromethylation route" devised by Gutsche and Ungaro.

2.1.1.1 Electrophilic substitution reactions

One of the earliest of the water soluble calixarenes was made by direct sulfonation of de-*tert*-butylated calixarene **1** using con. H_2SO_4 [Shinkai *et al.* (a) 1987; Shinkai *et al.* (b) 1987]. The sulfonato calixarenes **2** are important in their own right as

water soluble compounds but can also serve as intermediates for additional functionalization, generally by conversion to sulfonamide or chlorosulfonyl compounds [Casnati *et al.* 1993]. Direct nitration using KNO_3 and $AlCl_3$ in CH_3CN at 0 ^oC has been shown to afford high yields of the nitrocalixarenes **3** [Zhang *et al.* 1997], although a comparative study of nitration procedures [Kumar *et al.* 2004] concludes that 100% nitric acid in acetic acid is the preferred reagent. The nitrocalixarenes are extremely useful intermediates for the introduction of other functional groups, *via* the amino calixarenes obtained by reduction with H_2 and Raney Ni, NH_2NH_2 and Raney Ni [Verboom *et al.* 1995], NH_2NH_2 and $FeCl_3$ or $SnCl_2$ [Rudkevich *et al.* 1994; Mislin *et al.* 1996]. Tetrabromination of the calix[4]arene to give **4** can be effected in high yield with N-bromosuccinimide [Gutsche and Pagoria 1985]. Iodination to give **5** has been accomplished in quantitative yield through the use of silver trifluoroacetate and I_2 in $CHCl_3$ [Timmerman *et al.* 1994]. Halocalixarenes are useful intermediates for the introduction of other moieties like carboxylic acid [Gutsche and Pagoria 1985] and formyl group [Lhotak and Shinkai 1996] into the *p*-positions. The first reported calixarene diazo coupling involved the reaction of *p*-nitrophenyldiazonium tetrafluoroborate with calix[4]arene and since that time, it has found occasional use [Shinaki *et al.* 1986]. One of the most useful methods of functionalization of the upper rim, which allows the synthesis of a large variety of host molecules is (selective) formylation. The reaction is usually carried out using hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA) if exhaustive functionalization is required [Komori and Shinaki 1992] or through Gross formylation ($TiCl_4$ or $SnCl_4/Cl_2CHCOCH_3$) which allows a certain degree of regioselective control [Arduini *et al.* 1991]. All these reactions are depicted in scheme 2.1.



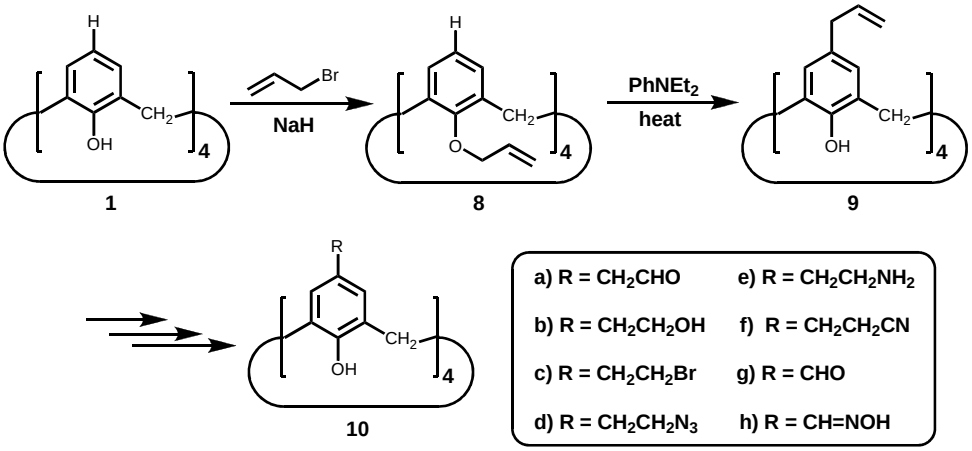
Scheme 2.1: *Upper rim modifications via electrophilic substitutions*

To enrich the chemical repertoire and to avoid the troublesome detertiarybutylation of calixarenes, various scientists have also devised *ipso*-alternatives for most of the above mentioned electrophilic substitutions. *Ipso*-substitution involves the direct displacement of *tert*-butyl groups and it has the obvious advantage of not having to remove the *tert*-butyl groups in a separate step. It also makes possible a variety of selective replacements based on the difference in the reactivity of phenols and phenolic ethers. *Ipso*-sulfonation was first employed by Shinkai and co-workers using hot conc. H_2SO_4 [Shinkai *et al.* 1988]. *Ipso*-substitution for nitro groups was implemented by using a mixture of HNO_3 (63%) and $(CH_3CO)_2O$ [Ranjbar and Ganjali 2000]. HMTA and TFA under reflux conditions resulted in the *ipso*-formylation of calixarene methyl ethers [Chawla *et al.* 2006]. A regioselective

and highly efficient *ipso*-chlorosulfonation has been carried out on O-alkylated phenolic units of calixarene using chlorosulfonic acid [Coquiere *et al.* 2006].

2.1.1.2 *p*-Claisen rearrangement route

The initial difficulties encountered with the electrophilic substitution reactions of calix[4]arene prompted Gutsche and co-workers to explore alternative routes. One of the most productive of these employed the *para*-Claisen rearrangement, as illustrated in scheme 2.2 [Gutsche and Levine 1982]. Calix[4]arene **1** is readily converted into the tetraallyl ether **8**, which on refluxing in N,N-diethylaniline underwent a *para*-Claisen rearrangement to produce *p*-allylcalix[4]arene **9** in *ca.* 75% yield. The *p*-toluenesulfonate of this product could be converted into a variety of functionalized calix[4]arenes, including the *p*-(2-oxoethyl) compound **10a**, the *p*-(2-hydroxyethyl) compound **10b**, the *p*-(2-bromoethyl) compound **10c**, the *p*-(2-azidoethyl) compound **10d**, the *p*-(2-aminoethyl) compound **10e**, the *p*-(2-cyanoethyl) compound **10f**, the *p*-formyl compound **10h** and oxime **10g**.

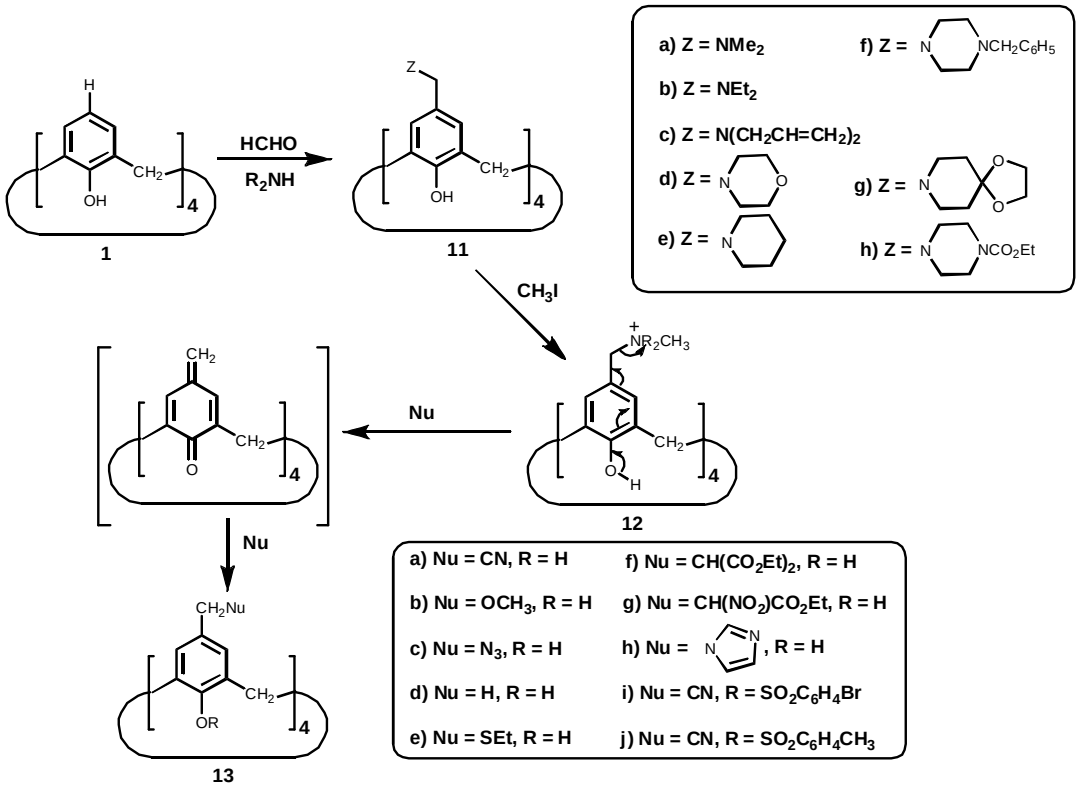


Scheme 2.2: *Functionalization of calix[4]arene via the p-Claisen rearrangement route*

2.1.1.3 *p*-Quinonemethide route

Another alternate route to the direct electrophilic substitution takes advantage of the nucleophilic character of the *para*-position of phenolates [Gutsche and Nam

1988]. When calix[4]arene **1** was mixed with formaldehyde along with any number of secondary amines, a Mannich-type reaction occurs to produce *p*-[dialkylamino]methylcalixarenes (**11a-h**), as illustrated in scheme 2.3. The aminomethylcalixarenes **11** served as intermediates for a functionalization pathway in which the quaternary ammonium compounds **12** on treatment with two equivalents of a nucleophile afforded calixarenes of the general structure **13**.



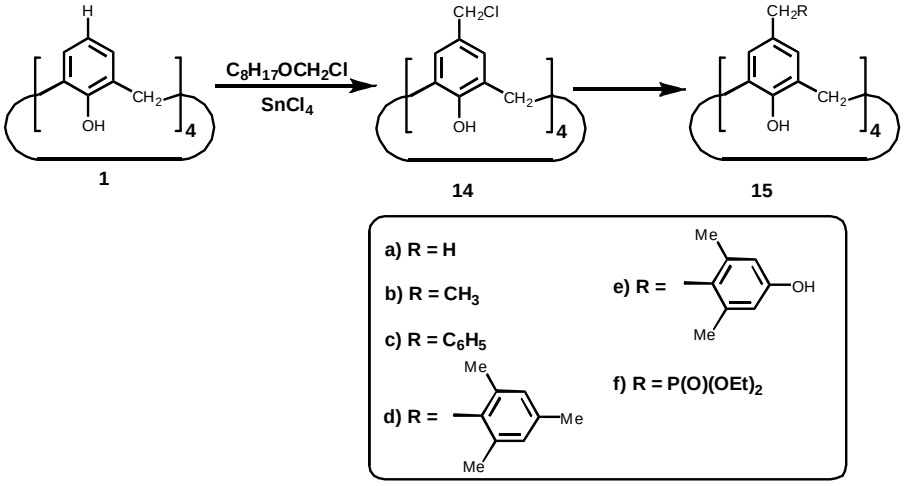
1 **11** **12** **13**

Scheme 2.3: *Functionalization of calix[4]arenes via the p-quinonemethide route*

2.1.1.4 *p*-Chloromethylation route

The embroidering of calixarenes *via* functionalization has been further expanded by *p*-chloromethylation route introduced by the Parma group [Almi *et al.* 1989], as illustrated in the scheme 2.4. Treatment of **1** with octyl chloromethyl ether and $SnCl_4$ afforded 80% yield of *p*-chloromethylcalix[4]arene **14**. From **14** a variety of compounds have been obtained, including *p*-methylcalix[4]arene (**15a**) *via* $LiAlH_4$ reduction (83%), *p*-ethylcalixarene (**15b**) *via* MeLi (35%), *p*-benzylcalix[4]arene (**15c**)

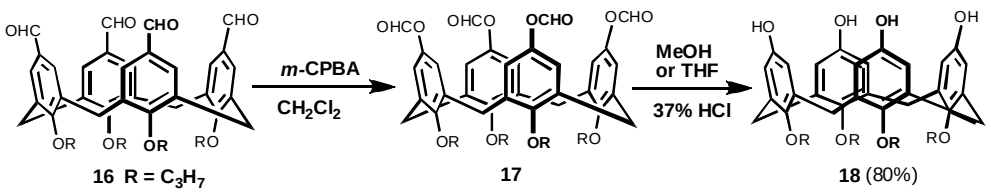
via benzene in the presence of BF_3 (40%), *p*-mesitylcalixarene (**15d**) *via* mesitylene in the presence of BF_3 (42%), *p*-(3,5-dimethyl-4-hydroxybenzyl)calix[4]arene (**15e**) *via* 2,6-dimethylphenol and BF_3 (37%) and *p*-diethylphosphorylmethylcalix[4]arene (**15f**) *via* triethylphosphite (>90%).



Scheme 2.4: *Functionalization of calix[4]arenes via the p-chloromethylation route*

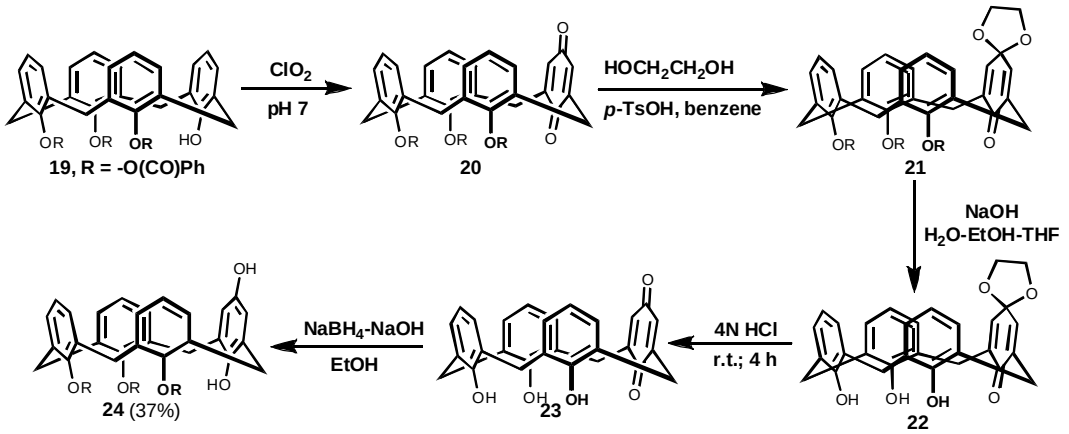
2.1.1.5 Nucleophilic substitution reactions on the upper rim

A literature survey reveals that efficient and direct methodologies to introduce nucleophilic groups (eg. -OH, -OR, -SR, -NHR etc) to the upper rim of calixarenes are limited due to the inherent nucleophilicity of the aromatic rings. However, a few indirect methods to introduce such groups to the upper rim of calixarenes involving multi-step conversions have been reported. Arduini *et al.* have carried out exhaustive hydroxylation of the lower rim protected formyl calixarene **16** *via* Baeyer-Villiger oxidation followed by hydrolysis of the formate derivative **17** (Scheme 2.5) [Arduini *et al.* 1996].



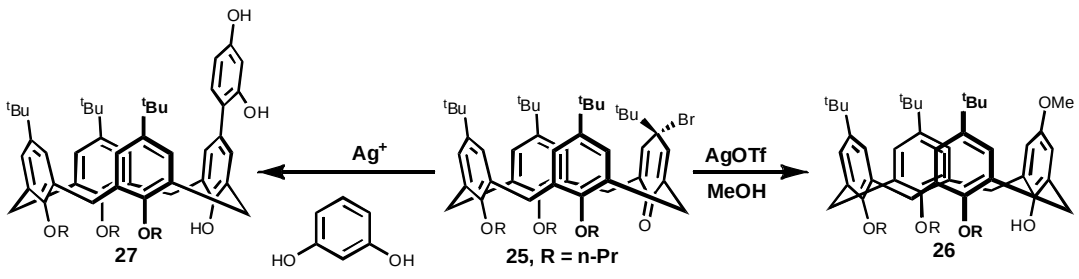
Scheme 2.5: *Hydroxylation via Baeyer-Villiger oxidation followed by hydrolysis*

Selective hydroxylation at one of the upper rim of calix[4]arene has also been achieved by a six-step synthetic strategy by Lee and co-workers [Lee *et al.* 2001]. The oxidation of calix[4]arene tribenzoate **19** with chlorine dioxide yielded the corresponding calix[4]monoquinone tribenzoate **20**. Reaction of monoquinone **20** with ethylene glycol under acidic conditions produced the protected monoketal derivative **21**. The basic hydrolysis of the benzoate followed by an acidic cleavage of ketal moieties and a metal hydride reduction of the quinones or *vice versa*, converted **21** to 5-hydroxycalixarene **24** (Scheme 2.6).



Scheme 2.6: *A six-step synthetic strategy for 5-hydroxycalixarene*

Troisi *et al.* have recently reported a novel "*p*-bromodienone route" to functionalize the calixarene *exo* rim with O- and C-nucleophiles [Troisi *et al.* (a) 2009; Troisi *et al.* (b) 2009]. They have demonstrated that calixarene *p*-bromodienone derivative **25** underwent a silver triflate mediated nucleophilic substitution and a subsequent rearomatisation with a range of different O- and C-nulceophiles to give *p*-alkoxy/*p*-acyloxy and *p*-aryl calixarenes in workable yields (Scheme 2.7).



Scheme 2.7: *p-Bromodienone route for the nucleophilic substitution of calix[4]arene upper rim*

2.1.1.6 Spirodienones as versatile synthetic intermediates for upper rim functionalization

Taking a detour from upper rim modifications starting from *p-tert*-butylcalix[4]arene, in the coming section we will consider the modifications based on calix[4]bis(spirodienone). Among various modifications of calix[4]arenes, the calixarene derived bis(spirodienones) (Figure 2.1) are an interesting class of molecules discovered by Biali *et al.* [Litwak and Biali 1992; Biali 2003]a and are obtained by the oxidative cyclization of the four phenolic hydroxyl groups of *p-tert*-butylcalix[4]arene **28**. The molecules are bestowed with two carbonyl and two ether functionalities in an alternant or non-alternant fashion as part of a 14-membered irregular cavity, making them potential candidates as ionophores or as precursors for designing modified calixarenes. They have been successfully utilized by the parent group (Biali's group) as synthetic intermediates for modifying calixarenes at the intraannular, extraannular and bridging methylene positions, a detailed account of which was presented in the introductory chapter.

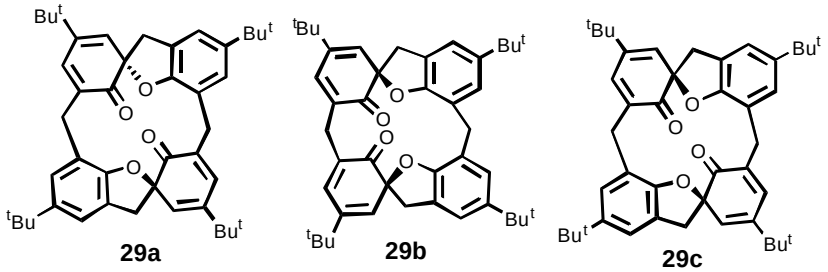
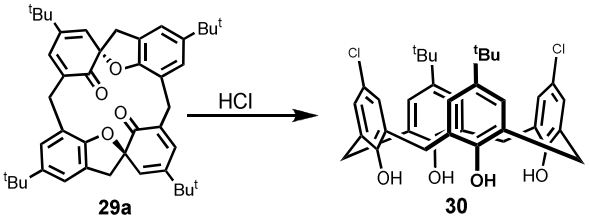


Figure 2.1: *Isomers of calix[4]bis(spirodienones)*

A selective extraannular reaction which was omitted in the first chapter and worth mentioning here is the selective upper rim chlorination of calix[4]arene *via*

calix[4]bis(spirodienone) route [Litwak *et al.* 1993]. During their attempts to react the carbonyl group of **29** with amine nucleophiles, they treated a solution of **29a** in MeCN with hydrazine and added concentrated HC1 as catalyst. The only product isolated from the reaction in addition to a large amount of an insoluble compound formed by self-condensation of the MeCN was the 11,23-di-*tert*-butyl-5,17-dichlorocalix[4]arene **30**; i.e., the reaction resulted in aromatization of two cyclohexadienones and chloro-de-*tert*-butylation of two distal rings. The same product was obtained in the absence of hydrazine (Scheme 2.8).



Scheme 2.8: *Selective chloro-de-tert-butylation of calix[4]arene*

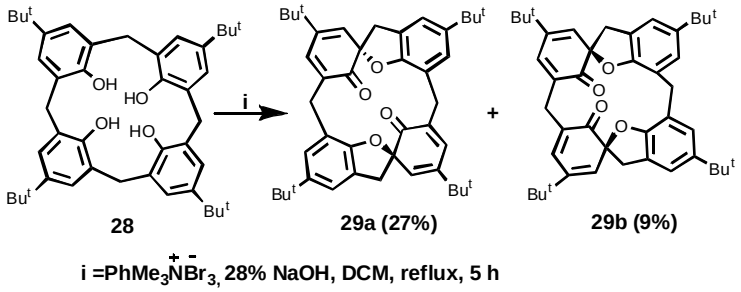
2.2 Statement of the problem

To develop the chemistry of bis(spirodienones) further, we were looking into the reactivity of the dienone carbonyls towards acetal formation. Accordingly when the most stable bis(spirodienone) isomer **29a** was reacted with 1,2-ethylene glycol in the presence of *p*-TSA, a calix[4]arene with alkoxy-substitution at the upper rim was obtained along with the expected cyclic acetal. This serendipitous discovery prompted us to investigate further this reaction with other nucleophilic reagents. If successful a new methodology can be developed for the upper rim functionalization of calixarene with nucleophilic groups using spirodienone route. The results of our investigations which culminated in the synthesis of a variety of alkoxy and aryloxy substituted calixarenes are presented in this chapter.

2.3 Results and discussion

2.3.1 Synthesis of calix[4]bis(spirodienones)

The calix[4]bis(spirodienones) **29a** and **29b** used as starting materials throughout our investigation were synthesized following Biali's procedure (Scheme 2.9) [Litwak and Biali 1992].

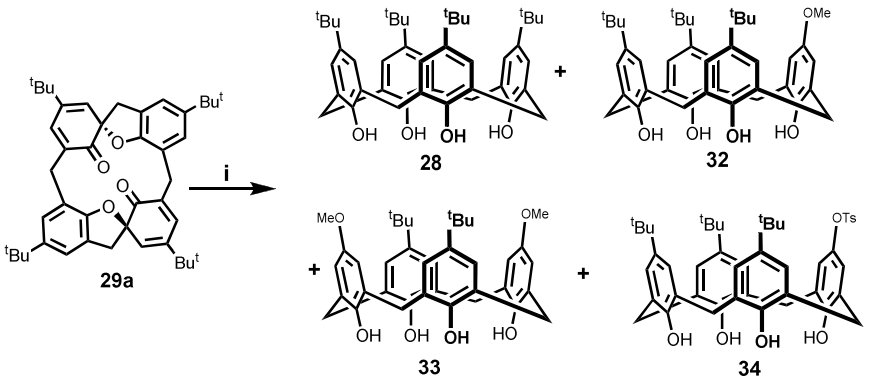


Scheme 2.9: *Preparation of bis(spirodienones) from p-tert-butylcalix[4]arene*

2.3.2 Reaction of bis(spirodienones) with nucleophiles

2.3.2.1 Reaction with aliphatic alcohols: Synthesis of upper rim mono- and dialkoxy substituted calix[4]arene

Our experiments started by reacting the most stable isomer of the calix[4]bis(spirodienone) **29a** with dry methanol in anhydrous toluene under reflux in the presence of *p*-TSA (0.6 equiv.) for 6 h. The reaction mixture after work up followed by column chromatography afforded a mixture of four products **28** and **32-34** (Scheme 2.10) [Thulasi *et al.* 2009].



Scheme 2.10: *p-TSA mediated reaction of calix[4]bis(spirodienone)* ***29a*** *with methanol.*

All the products obtained were analyzed using various spectral techniques. The ^{1}H NMR spectrum of **28** revealed it to be *p-tert*-butylcalix[4]arene. The IR spectrum of **32** showed characteristic absorption at 3173 cm^{-1}, which corresponded to -OH group and at 1259 cm^{-1}, which indicated the O-C stretching of the ether moiety. In the ^{1}H NMR spectrum (Figure 2.2), the exclusively hydrogen bonded lower rim hydroxyl protons were displayed as a singlet at δ 10.20. The aromatic protons were discernible as a singlet and a multiplet at δ 7.02 and 6.55 respectively. The methylene protons resonated as two broad peaks at δ 4.24 and 3.45. A sharp singlet at δ 3.64 was observed for -OCH_3 protons. The *tert*-butyl group appeared as two singlets at δ 1.22 and 1.19 integrating for eighteen and nine protons respectively, indicating the absence of one *tert*-butyl group.

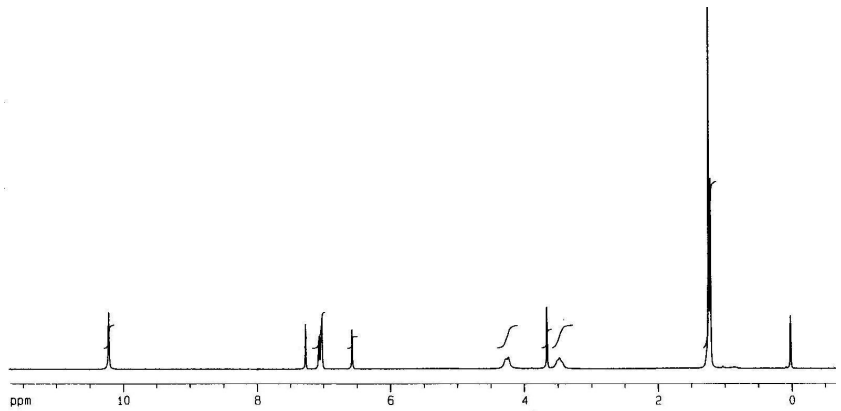


Figure 2.2: *^{1}H NMR spectrum of* ***32***

The proposed structure was supported by ^{13}C NMR spectrum showing the aromatic carbon to which -OH was attached at δ 153.9 (Figure 2.3). A methoxy carbon resonated at δ 55.2. The aliphatic signals were observed in the δ 34.0 - 29.8 region. This was further supported by mass spectral analysis showing the M^{+} ion peak at 622.85. The assigned structure was confirmed by satisfactory elemental analysis.

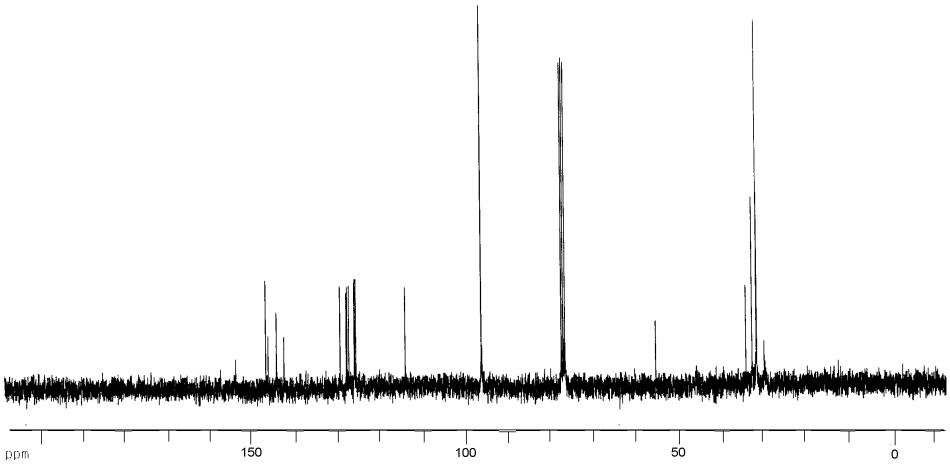


Figure 2.3: *^{13}C NMR spectrum of* ***32***

The structure **33** was assigned to the product on the basis of spectroscopic and analytical data. In the IR spectrum, a peak at 3172 cm^{-1} corresponding to the -OH absorption and another one at 1259 cm^{-1} corresponding to the ether group were observed. In the ^{1}H NMR spectrum, the product displayed (Figure 2.4) a singlet at δ 10.04 corresponding to the phenolic OH. Aromatic protons appeared as two singlets at δ 7.04 and 6.52. A pair of doublets were observed for the methylene protons at δ 4.23 (J = 13.2 Hz) and 3.43 (J = 13.5 Hz). The singlet obtained at δ 3.62 was attributed to the methoxy group. The *tert*-butyl protons gave a singlet at δ 1.24.

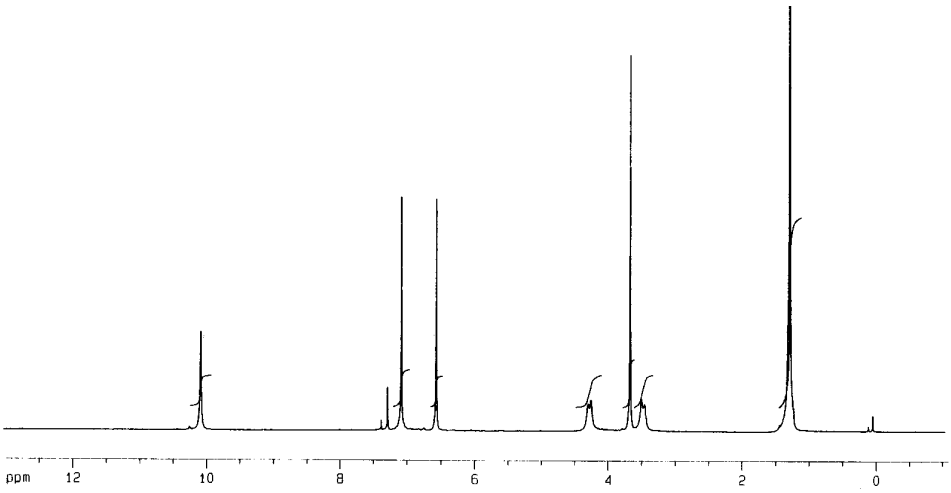


Figure 2.4: *^{1}H NMR spectrum of* ***33***

The ^{13}C NMR spectrum (Figure 2.5) positioned the two methoxy carbons at δ 55.9 and 55.2. The signal at δ 153.9 was ascribed to the carbon to which -OH was attached. The spectrum displayed aliphatic carbons in the region δ 34.0 - 29.7. This was further supported by mass spectral analysis showing the M^{+} ion peak at 596.82.

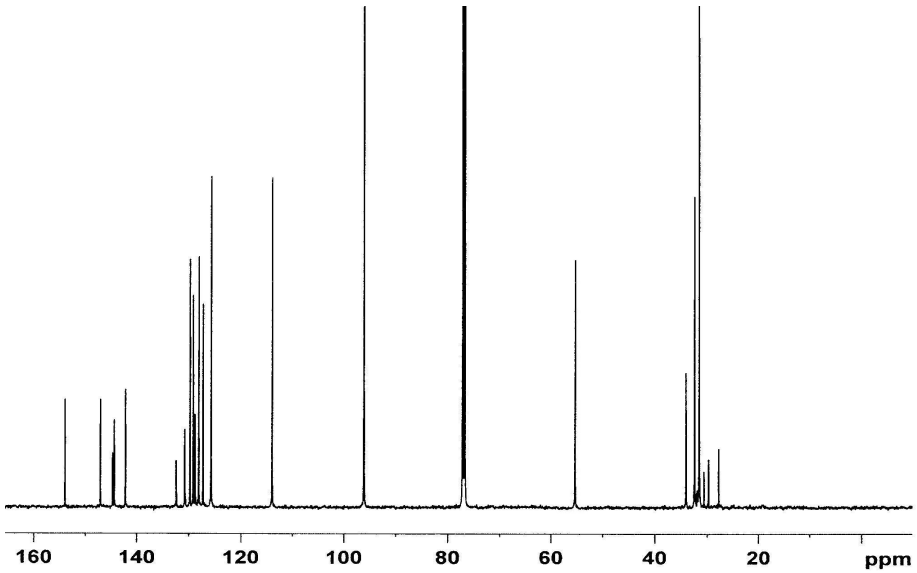


Figure 2.5: *^{13}C NMR spectrum of* ***33***

The structure of the fourth product was deduced from the spectral data as **34**. The ^{1}H NMR spectrum (Figure 2.6) displayed a singlet at δ 10.25 integrating for four hydroxyl protons, two multiplets for the six aromatic protons at δ 7.05 and 6.68

respectively. The four aromatic protons of the tosyl group resonated as a doublet at δ 7.70 (J = 8.3 Hz) and a multiplet at δ 7.32. The pair of broad peaks at δ 4.20 and 3.44 were assigned to the bridging methylene protons and the singlet at δ 2.46 integrating for three protons to the tosyl methyl group. The *tert*-butyl protons resonated as two singlets at δ 1.20 and 1.19.

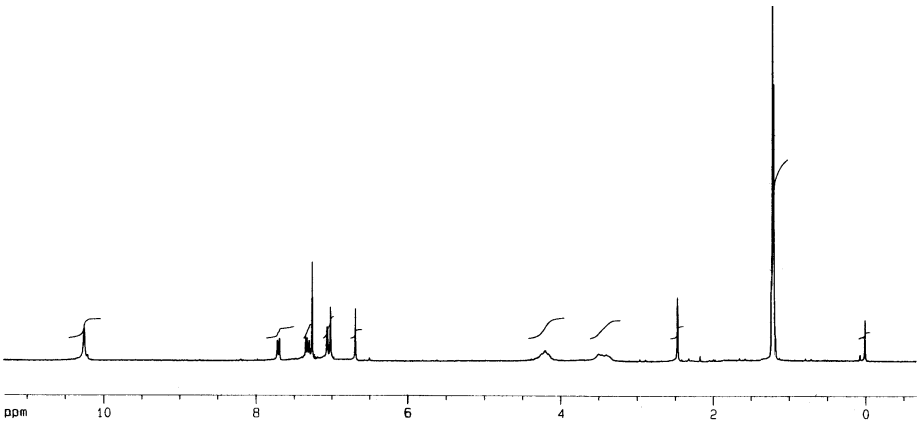


Figure 2.6: *^{1}H NMR spectrum of* ***34***

The salient features of the ^{13}C NMR spectrum (Figure 2.7) include the peaks at: (a) δ 152.2 ppm due to hydroxyl attached carbons; (b) δ 20.2 ppm due to tosyl CH_3. The proposed structure was further verified by the MALDI-TOF spectrum which showed the $[M+Na]^+$ ion peak at 785.64.

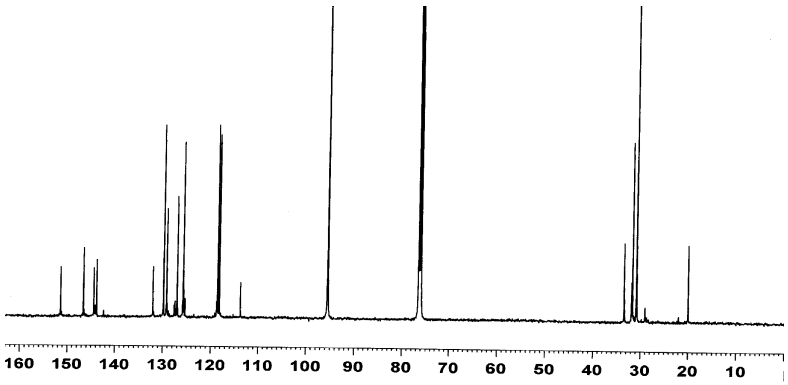
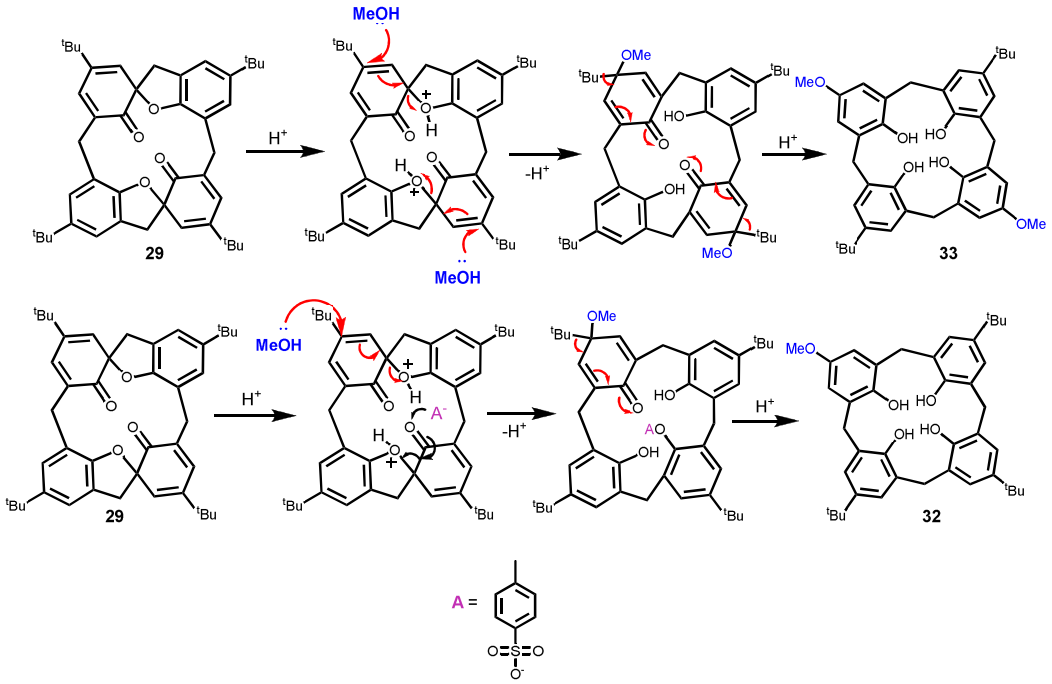


Figure 2.7: *^{13}C NMR spectrum of* ***34***

The conformations of the products **32**-**34** were established as 'cone' by NMR analysis - as all the four lower rim phenolic hydroxyls, stabilized by the circular array

of hydrogen bonding, of each product appeared as a singlet. The cone conformation was further confirmed from ^{13}C values obtained for the methylene bridges of the three products and on comparison to literature precedents [Jaime *et al.* 1991].

The mechanism outlined in scheme 2.11 has been suggested to rationalise the formation of the products **32** and **33**. Protonation of the spiro oxygen followed by the nucleophilic attack of methanol at the carbon atom bearing the *tert*-butyl group results in the cleavage of the spiro bonds and formation of a protonated cross-dienone. The aromaticity of cross-dienone can be regained by the removal of the *tert*-butyl group resulting in the formation of the disubstituted product **33**. The formation of monosubstituted product **32** can be rationalized on the basis of acid assisted reductive cleavage of the remaining spiro bond [Litwak *et al.* 1993].

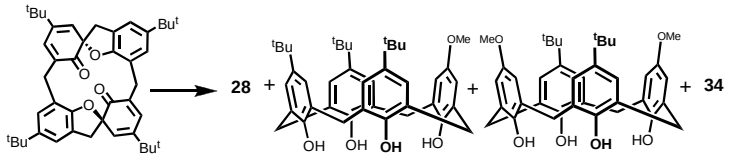


Scheme 2.11: *Proposed mechanistic pathways for the reaction between bis(spirodienone)* ***29a*** *and methanol in the presence of p-TSA.*

A wider applicability to this reaction can be foreseen since it provides direct access to calix[4]arenes substituted with one or two methoxy groups which can be

further manipulated to bring specific functionalities selectively to the upper rim. Hence a detailed optimization study was conducted to maximize the yields of the products and the results are summarized in table 2.1. The use of 5.0 equiv. of *p*-TSA was found to give both mono- and dimethoxy calixarenes in 32% and 45% yields respectively. Since the mechanism postulated [Thulasi *et al.* 2009] involved the initial formation of an oxonium ion at the spiro oxygen by protonation, we also explored the effect of different Lewis acids on the reaction. The reactions in the presence of anhydrous $ZnCl_2$, Montmorillonite K10, $La(OTf)_3$, $Yb(OTf)_3$ and camphor sulfonic acid failed to yield the anticipated products (entries 10-14). When $BF_3.OEt_2$ or AgOTf were used as the catalysts, a noticeable improvement in the yield of both the mono- and dimethoxy substituted products were observed. However while using $BF_3.OEt_2$ (entry 5), mild etching of glassware was observed due to release of hydrogen fluoride vapors at the reflux temperature of toluene. Finally, considering the cost effectiveness, ease of handling and the yields of the desired products, 5.0 equiv. of *p*-TSA (entry 4) in toluene was selected as the optimal acid concentration.

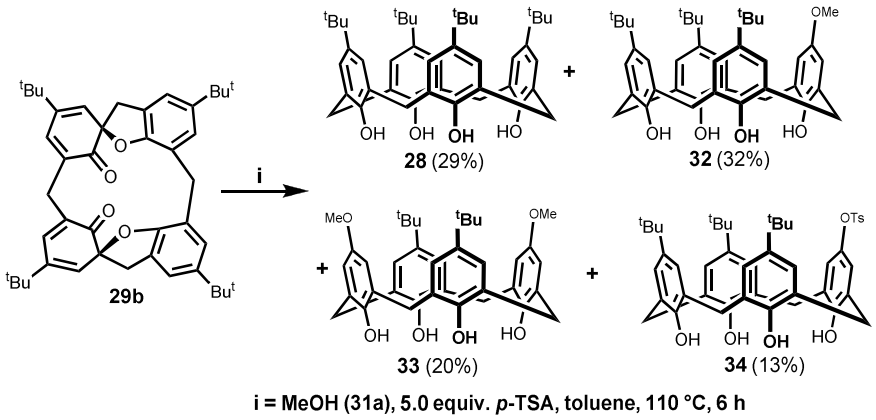
Table 2.1: *Optimization of the title reaction with various Lewis acids.*



entry	substrate	Lewis acid[a]	solvent	yield (%)			
				28	**32**	**33**	**34**
1	**29a**	*p*-TSA (0.6 equiv.)	toluene	16	51	5	10
2		*p*-TSA (0.6 equiv.)	xylene	10	14	3	15
3		*p*-TSA (0.6 equiv.)	benzene	12	20	10	13
4		*p*-TSA (5.0 equiv.)	toluene	11	32	45	13
5		$BF_3.OEt_2$	toluene	6	56	22	-
6		$Sc(OTf)_3$	toluene	17	50	-	-
7		$Cu(OTf)_2$	toluene	58	2	-	-
8		AgOTf	toluene	8	54	11	-
9		$Sn(OTf)_2$	toluene	26	(50:50)[b]	-	-
10		Anhydrous $ZnCl_2$	toluene		No reaction		
11		Montmorillonite K-10	toluene		No reaction		
12		$La(OTf)_3$	toluene		No reaction		
13		$Yb(OTf)_3$	toluene		No reaction		
14		CSA	toluene		No reaction		

Reaction conditions: MeOH, solvent, reflux, 6 h.
a. unless otherwise stated, 0.6 equiv. of Lewis acid was used.
b. obtained as an inseparable mixture of **29a** and **32**

Subsequent to the optimization studies with the 1,3-isomer **29a** of the bis(spirodienone), we turned our attention to the reaction of the 1,2-isomer **29b** with methanol. The reaction under the optimized conditions also yielded the same products, though in slightly lower yields (Scheme 2.12). The formation of the same products from both the isomers can be easily explained as the stereoisomers **29a** and **29b** exist in equilibrium in solution [Aleksiuk *et al.* (a) 1993].



Scheme 2.12: *Reaction of bis(spirodienone)* ***29b*** *with methanol*

On the basis of this result and to make the entire procedure more expeditious and to see if the isolation step can be avoided, we decided to test the reaction directly on a mixture of 1,3- and 1,2-isomers of **29**. Thus the mixture of stereoisomers **29a** and **29b** was directly treated with methanol under optimized conditions. Column chromatography on silica gel of the reaction mixture afforded the products in much lower yields and hence we decided to use the most stable isomer **29a** for carrying out further reactions.

Upon obtaining the upper rim mono- and dimethoxy substituted calix[4]arenes in acceptable yields, we proceeded further by reacting bis(spirodienone) with various alcohols to check the generality of the process. Accordingly the reaction between **29a** and ethanol **31b** was investigated. The reaction proceeded to completion within 6 h but unlike in the case of methanol, only monoethoxy product **35** was isolated in 49% yield along with *p-tert*-butylcalix[4]arene **28** and upper rim monotosylated product **34**. The product **35** was fully characterized on the basis of spectral analysis. Reactions of **29a** with other aliphatic primary alcohols like *n*-propanol **31c**, *n*-butanol **31d** and *n*-pentanol **31e** were also investigated. The reactions afforded the monoalkoxy substituted products, the structures of which were confirmed by spectroscopic methods.

We further extended the reaction to unsaturated primary alcohols such as propargyl alcohol **31f**, allyl alcohol **31g** and *n*-pentenyl alcohol **31h** under similar conditions. When bis(spirodienone) **29a** was reacted with propargyl alcohol **31f** in anhydrous toluene at 110 ^{o}C, the yellow colour of the original reaction mixture changed to dark brown within 10 min. Thin layer chromatography of the reaction mixture showed the absence of the starting materials and on column chromatography afforded the upper rim monopropargylated calix[4]arene **39** and dipropargylated calix[4]arene **40** in 33% and 38% yield. Structures of the compounds were established by spectral data.

The IR spectrum of **39** showed characteristic absorptions at 3175 cm^{-1}, which corresponded to the OH group and at 1259 cm^{-1}, which showed the presence of the ether moiety. In the ^{1}H NMR spectrum (Figure 2.8), the hydrogen bonded lower rim hydroxyl protons appeared as a singlet at δ 10.23. The aromatic protons were discernible as a multiplet and a singlet at δ 7.03 and 6.65. The -OCH_2 protons appeared as a singlet at δ 4.51. The methylene bridge protons appeared as two peaks: a doublet at δ 4.23 and a broad singlet at δ 3.46. The acetylenic proton resonated at a higher δ value of 2.42 as a singlet. The two singlets at δ 1.22 and 1.19 in a 2:1 ratio were assigned to *tert*-butyl protons.

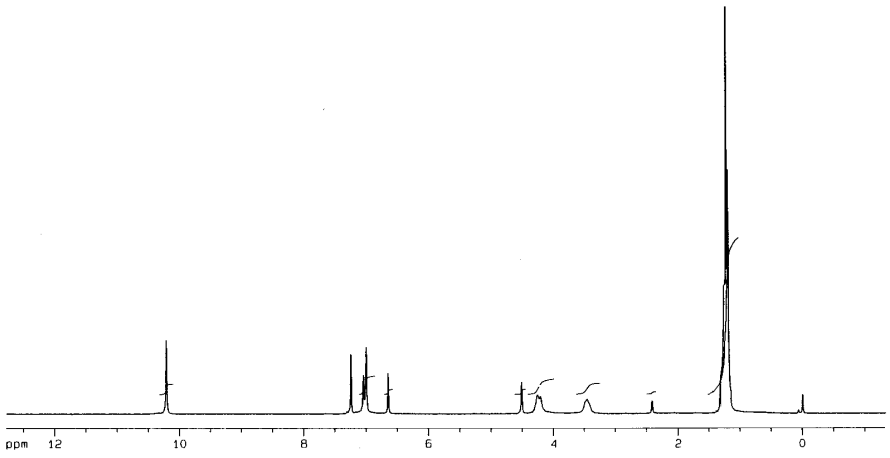


Figure 2.8: *^{1}H NMR spectrum of **39***

In the ^{13}C NMR spectrum (Figure 2.9), the acetylenic carbons appeared at δ 78.9 and 75.4. The characteristic peak due to -OCH_2 carbon was discernible at δ 56.1.

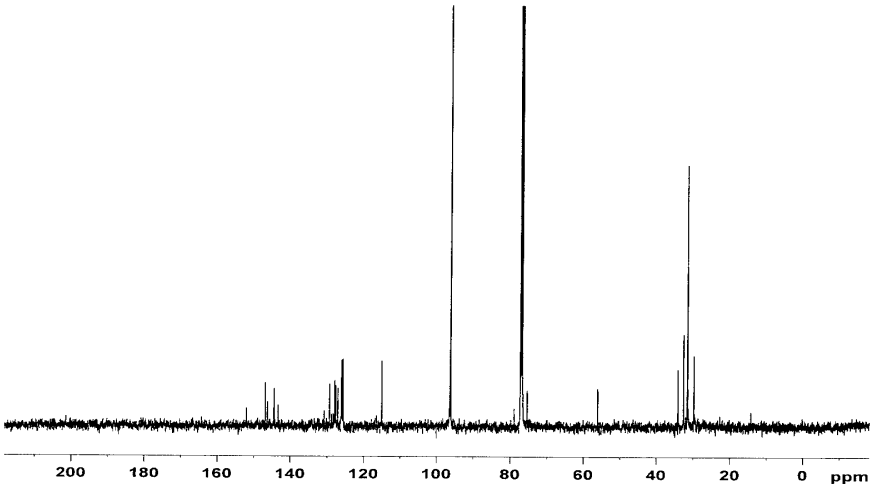


Figure 2.9: *^{13}C NMR spectrum of **39***

The ^{1}H NMR spectrum (Figure 2.10) of **40** provided clear indications of the formation of a symmetrically substituted calix[4]arene. The salient features of the spectrum pointing towards this conclusion were the appearance of: (a) four singlets at the low field region, i.e.; at δ 10.11 (OH protons), at δ 7.07 and 6.66 (aromatic protons) and at δ 4.51 (-OCH_2 protons); (b) two well-defined doublets at δ 4.24 (J = 13.2 Hz) and 3.46 (J = 13.3 Hz) which were assigned for the bridging methylenes; (c) two singlets at δ 2.45 and 1.24 for the acetylenic and *tert*-butyl protons respectively.

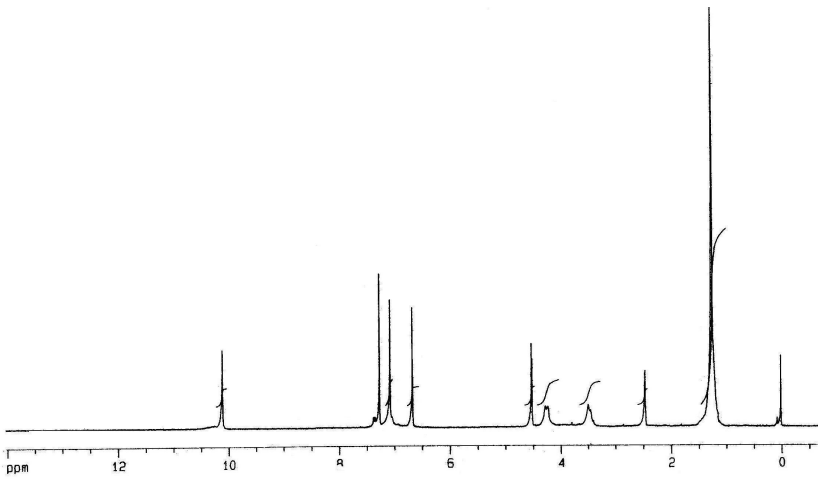


Figure 2.10: *^{1}H NMR spectrum of* ***40***

The significant features of the ^{13}C NMR spectrum (Figure 2.11) include peaks at: (a) δ 152.3 due to carbons bearing hydroxyl groups; (b) δ 79.1 and 75.3 due to acetylenic carbons; (c) δ 56.1 due to the -OCH_2 carbon. The proposed structure was further supported by FAB mass spectrum which showed the $[M+1]^+$ ion peak at 645.62 and satisfactory elemental analysis.

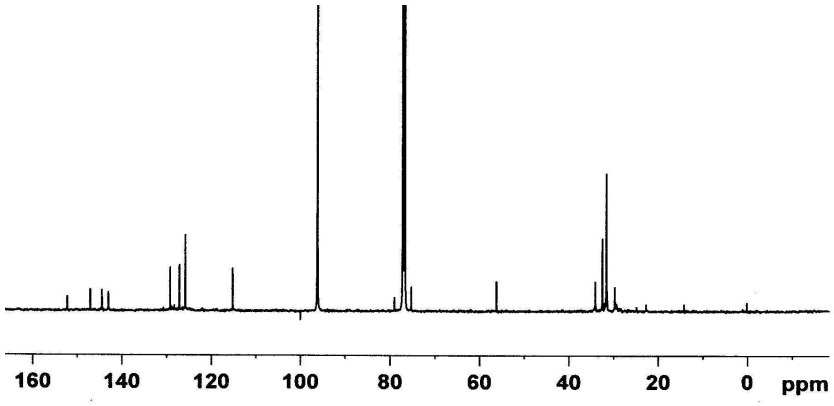


Figure 2.11: *^{13}C NMR spectrum of* ***39***

To check whether an increase in the reaction time would enhance the yield of the two upper rim propargylated products, we subjected the reaction to longer reaction times. However charring of the reaction mixture was observed with considerable decrease in the yield of both the products.

Analogous reactivity was observed in the reaction of **29a** with **31h** and **31g**, however the reactions afforded only the monosubstituted products in workable yields. The structure of both products **41** and **42** were established on the basis of spectral data.

As an extension, we allowed the bis(spirodienone) to react with representative examples of secondary and tertiary alcohols under optimized conditions. Accordingly when **29a** was reacted with *iso*-propyl alcohol **31i**, the monosubstituted product was obtained in moderate yield. The structure of the product **43** was confirmed on the basis of spectral data. On the other hand, by using *tert*-butyl alcohol under various

conditions, no *tert*-butoxy derivative could be traced. This difficulty could be explained either by the steric crowding of the intermediate *p-tert*-butoxydienone as well as by the lability of the final *tert*-butyl ether linkage. Table 2.2 summarizes the results obtained in the selective nucleophilic substitution of bis(spirodienone) **29a** with various aliphatic alcohols.

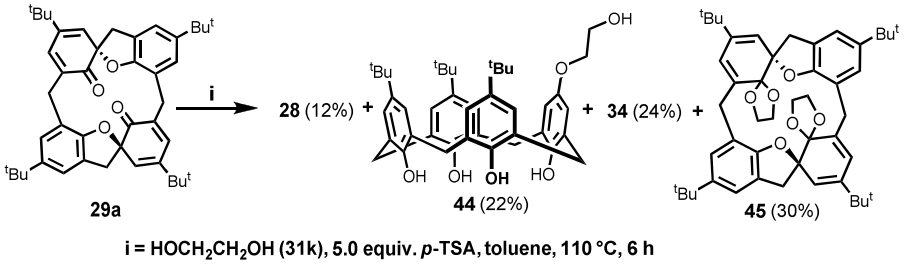
Table 2.2: *Generalization of the reaction of* ***29a*** *with various alcohols.*

Entry	Alcohols	Products (yield)		
1	CH_3OH **(31a)**	**28** (11%)	**32** (32%)	**34** (15%) **33** (45%)
2	OH **(31b)**	**28** (17%)	**35** (49%)	**34** (20%)
3	OH **(31c)**	**28** (20%)	**36** (37%)	**34** (26%)
4	OH **(31d)**	**28** (22%)	**37** (35%)	**34** (28%)
5	OH **(31e)**	**28** (18%)	**38** (30%)	**34** (31%)
6	OH **(31f)**	**28** (12%)	**39** (33%) **40** (38%)	**34** (17%)
7	OH **(31g)**	**28** (16%)	**41** (28%)	**34** (18%)
8	OH **(31h)**	**28** (20%)	**42** (22%)	**34** (34%)
9	OH **(31i)**	**28** (15%)	**43** (41%)	**34** (23%)
10	OH **(31j)**	No Reaction		

Reaction conditions: 31, 5.0 equiv. *p*-TSA, toluene, 110 °C, 6 h.
For entries 6-8, the reaction time is 10 min.

2.3.2.2 Reaction with diols

As mentioned earlier we had come across the nucleophilic substitution reaction of bis(spirodienones) quite unexpectedly during the investigation of the protection of enone carbonyls by ethylene glycol. To investigate further, we reacted **29a** with ethylene glycol **31k** in the presence of *p*-TSA (5.0 equiv.). Besides *p-tert*-buytlcalix[4]arene **28**, upper rim tosylated product **34** and cyclic acetal **45**, the reaction also afforded upper rim monoalkoxylated calix[4]arene **44** in 22% yield (Scheme 2.13).



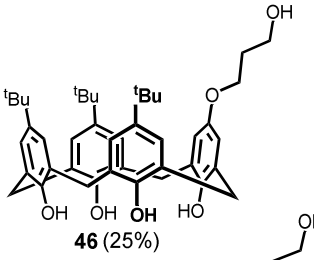
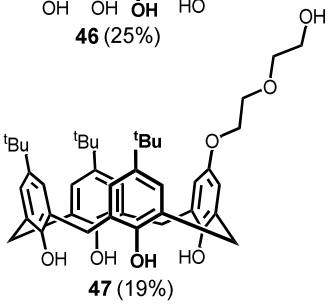
Scheme 2.13: *Reaction of bis(spirodienone)* ***29a*** *with ethylene glycol*

The product **44** was identified on the basis of spectroscopic data. The IR spectrum of **44** showed broad absorption at 3175 cm^{-1} corresponding to the hydrogen bonded hydroxyl groups. The salient features of the ^{1}H NMR spectrum are the following: (a) OH protons appeared as a singlet at δ 10.21; (b) the aromatic protons resonated as a multiplet and a singlet at δ 7.02 and 6.54 respectively; (c) the bridge protons appeared as a doublet at δ 4.24 (J = 12.0 Hz) and as a multiplet at δ 3.46; (d) the -OCH_2 protons resonated as a triplet at δ 3.86 (J = 6.0 Hz). All other signals were in good agreement with the assigned structure. The ^{13}C NMR spectrum positioned the hydroxyl bonded carbons at δ 155.2. The signals at δ 63.4 and 56.9 were ascribed to the -OCH_2 carbons. The sp^3 carbons were discernable in the region δ 34.1-15.1. In addition, compound **44** dispalyed 12 signals in the δ 148.8-116.3 region corresponding

to the carbons of sp^2 hybridization. Further the structure was confirmed by MALDI-TOF analysis showing $[M+Na]^+$ peak at 675.80.

We also investigated the title reaction with other diols like propane-1,3-diol **31l** and diethylene glycol **31m** and the results are summarized in table 2.3.

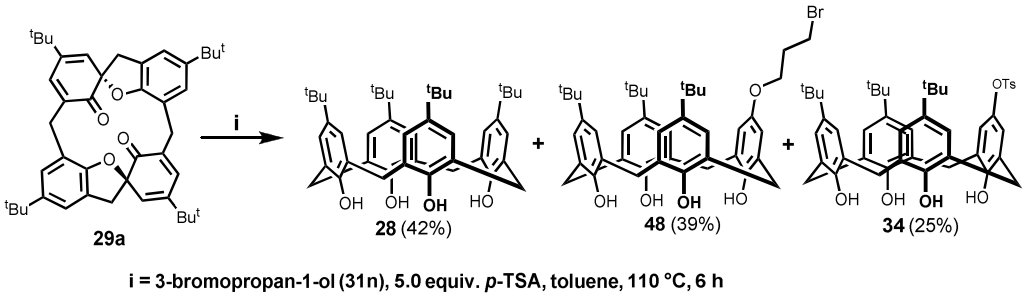
Table 2.3: *Generalization of the reaction with glycols.*

Entry	Alcohols	Products (yield)		
1	HO OH **(31l)**	**28** (23%)	 **46** (25%)	**34** (22%)
2	HO O OH **(31m)**	**28** (27%)	 **47** (19%)	**34** (25%)

Reaction conditions: 31, 5.0 equiv. *p*-TSA, toluene, 110 °C, 6 h.

2.3.2.3 Reaction with bromoalcohols

Encouraged by the motivating results obtained with simple aliphatic alcohols, we further extended our study to bifunctional alcohols with the aim of introducing additional functional groups at the upper rim of calix[4]arene. Initially we reacted bis(spirodienone) **29a** with 3-bromopropan-1-ol **31n** under optimized conditions. Besides *p-tert*-butylcalix[4]arene **28** and the upper rim monotosylated product **34**, the reaction furnished the upper rim monofunctionalized calix[4]arene **48** in 39% yield (Scheme 2.14).



Scheme 2.14: *Reaction of bis(spirodienone)* ***29a*** *with bromopropanol*

The structure of **48** was assigned by IR, NMR, mass and elemental analysis. The IR spectrum indicated the characteristic absorption of the hydrogen bonded hydroxyl group at 3172 cm^{-1}. In the ^{1}H NMR spectrum (Figure 2.12), the OH protons resonated as a singlet at δ 10.21. The aromatic protons appeared as a multiplet and a singlet at δ 7.03 and 6.55 respectively. One of the methylene bridges were seen as a broad peak at δ 4.23 whereas the other seemingly appeared as a multiplet merged with the triplet of one of the methylene groups of the propyl chain at δ 3.49. Other protons were in agreement with the assigned structure.

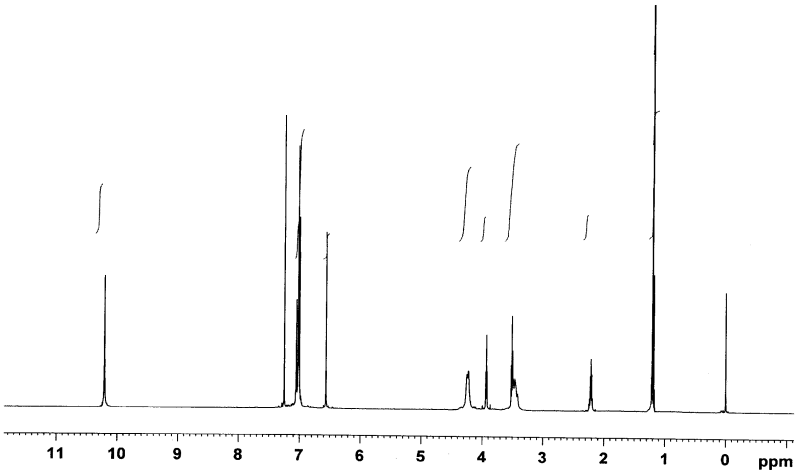


Figure 2.12: *^{1}H NMR spectrum of* ***48***

The signals at δ 65.5 and 56.9 in the ^{13}C NMR spectrum (Figure 2.13) were assigned to $-OCH_2$ and $-CH_2Br$ carbons respectively. The compound obtained was

further supported by satisfactory elemental analysis (Anal. calcd for $C_{43}H_{53}BrO_5$: C, 70.77; H, 7.32. Found: C, 70.73; H, 7.35).

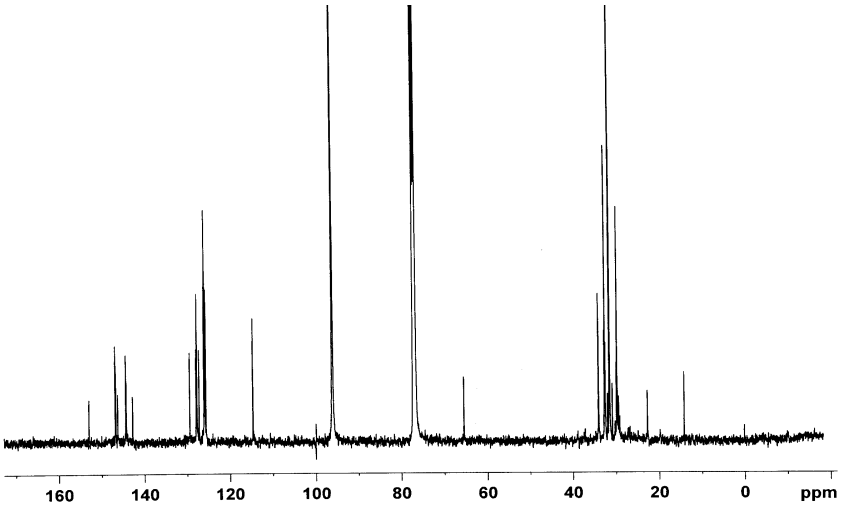
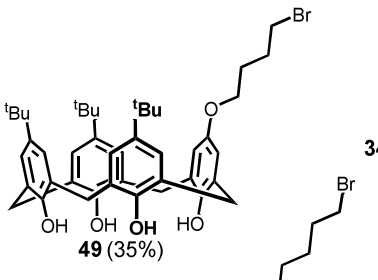


Figure 2.13: *^{13}C NMR spectrum of **48***

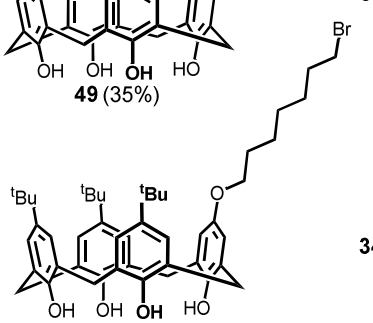
To establish the general nature of the reaction, we reacted the substrate **29a** with two other bromoalcohols under the optimized conditions. The reaction of bis(spirodienone) **29a** with 4-bromobutan-1-ol **31o** and 7-bromoheptan-1-ol **31p** proceeded smoothly affording monosubstituted products in acceptable yields. The results are summarized in table 2.4.

Table 2.4: *Generalization of the reaction with bromoalcohols.*

Entry	Alcohols	Products (yield)	
1	Br–(CH$_2$)$_4$–OH **(31o)**	**28** (20%)	**34** (23%)
2	Br–(CH$_2$)$_7$–OH **(31p)**	**28** (20%)	**34** (27%)



49 (35%)



50 (28%)

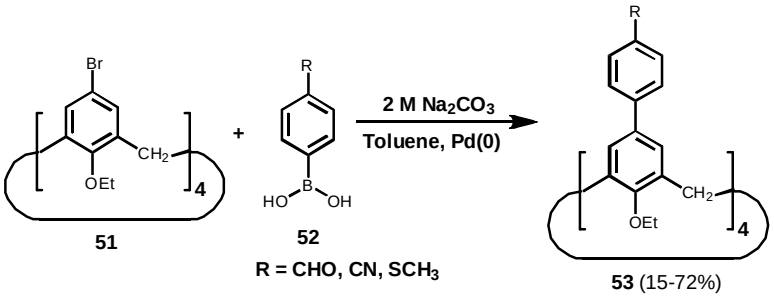
Reaction conditions: 31, 5.0 equiv. *p*-TSA, toluene, 110 °C, 6 h.

2.3.2.4 Reaction with amines

When the substrate **29a** was subjected to the reaction with diethyl amine in the presence of *p*-TSA (5.0 equiv.) in toluene at reflux conditions, reaction failed to give any products. Action of other Lewis acids like AgOTf, $Sc(OTf)_3$, $BF_3.OEt_2$ etc. as alternate acidic source on the reaction was also investigated but no products were obtained. Hence it is inferred that the non-reactivity of amines towards the nucleophilic substitution is due to its basicity. Due to protonation or co-ordination with Lewis acids under the reaction conditions employed, the lone-pair of electrons on the amino group becomes unavailable obliterating its nucleophilic character.

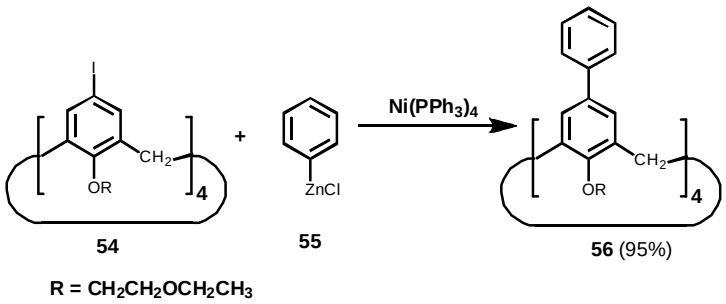
2.3.2.5 Reaction with phenols

In continuation of our interest to broaden the versatility of calix[4]bis(spirodienones), we also initiated a study to probe into the reactions of bis(spirodienones) with phenols. If feasible, this reactions would result in calix[4]arenes having aryloxy groups at the upper rim with possible chromophoric and fluorophoric properties. A literature survey indicated that several groups have synthesized deep cavity calix[4]arenes by substituting the upper rim with phenyl groups [Troisi *et al.* (a) 2009; Troisi *et al.* (b) 2009]. Wong *et al.* [Wong and Nicoud 1993] synthesized different tetraarylcalix[4]arenes **53** from lower rim ethyl protected tetrabromocalix[4]arene **51** and arylboronic acids **52** by a Suzuki type [Miyaura *et al.* 1981] coupling reaction in 15-72% yields (Scheme 2.15).



Scheme 2.15: *Suzuki reaction to synthesize arylated calix[4]arene*

Arduini *et al.* [Arduini *et al.* 1990] prepared tetraphenylcalix[4]arene **56** by a Negishi [Negishi 1977] type cross-coupling reaction of phenylzinc chloride **55** and the corresponding tetraiodocalix[4]arene **54** in the presence of $Ni(PPh_3)_4$ as catalyst in 95% yield (Scheme 2.16).

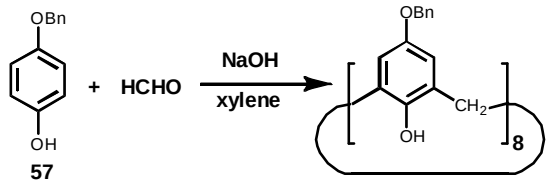


54 **55** **56** (95%)

R = $CH_2CH_2OCH_2CH_3$

Scheme 2.16: *Negishi reaction to synthesize arylated calix[4]arene*

There also has been a report in the literature of the synthesis of upper rim benzyloxy substituted calixarene. Ungaro's group has carried out a one-pot synthesis of *p*-(benzyloxy)calix[8]arene **58** in 48% yield from a 45:82:1 molar mixture of *p*-benzyloxyphenol, paraformaldehyde and NaOH in refluxing xylene (Scheme 2.17) [Casnati et al. 1997].

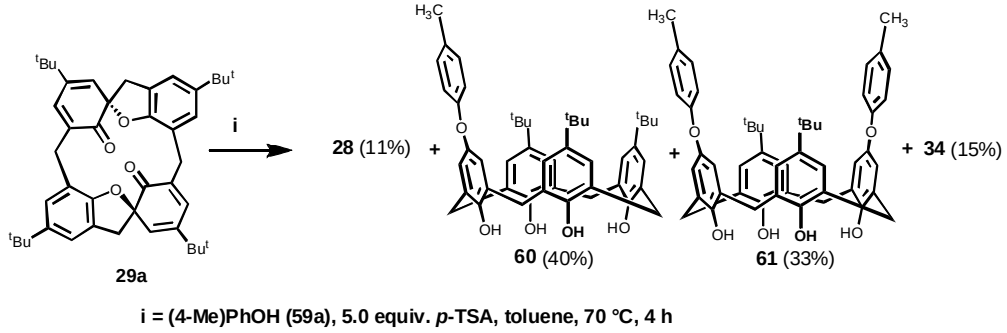


57 **58** (48%)

Scheme 2.17: *One-pot synthesis of benzyalted calix[8]arene*

Against this background, we initiated our studies by reacting *p*-cresol **59a**, an activated phenol, with bis(spirodienone) **29a** in the presence of 5.0 equiv. of *p*-TSA under toluene reflux conditions for 6 hours. Despite noticeable charring of the reaction mixture, four products were isolated, by column chromatography over silica gel in low yields. Subsequently the reaction was repeated at less drastic conditions and at an

optimum temperature of 70 ^{o}C after 4 h; the reaction yielded four products in acceptable yields (Scheme 2.18).



Scheme 2.18: *Reaction of bis(spirodienone)* ***29a*** *with p-cresol*

The structures of **60** and **61** were fully characterized by various spectroscopic techniques. The hydroxyl group showed a broad absorption band at 3173 cm^{-1} in the IR spectrum of **60**. In the ^{1}H NMR spectrum (Figure 2.14), the exclusively hydrogen bonded lower rim phenolic hydroxyls appeared as a singlet at δ 10.19, indicating cone conformation and the methyl group of the cresol part appeared at δ 2.33 as a sharp singlet. The *tert*-butyl protons resonated as two singlets at δ 1.22 and 1.19 in a 2:1 ratio.

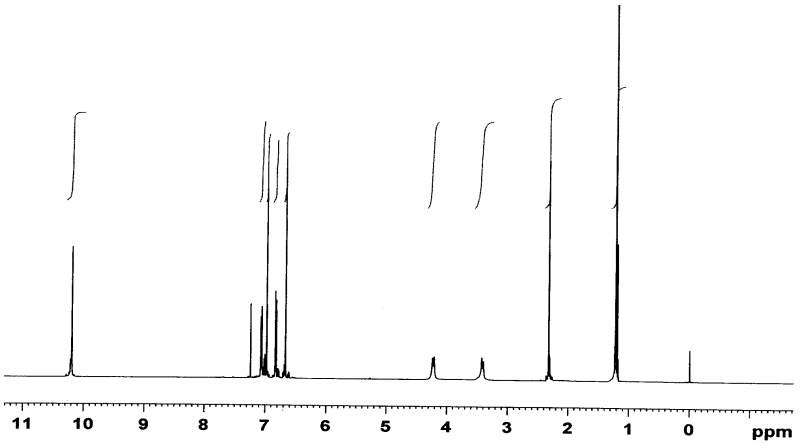


Figure 2.14: *^{1}H NMR spectrum of* ***60***

In the ^{13}C NMR spectrum (Figure 2.15), the signal due to the methyl group of the *p*-cresol part appeared at δ 20.0. The chemical shift values of the bridging

methylenes in ^{13}C NMR and the ^{1}H and ^{13}C NMR spectral pattern further confirm that **60** is present in the cone conformation [Jaime *et al.* 1991]. The structure was further confirmed by CHN analysis (Anal. Calcd. for $C_{47}H_{54}O_5$: C, 80.77; H, 7.79. Found: C, 80. 74; H, 7.75).

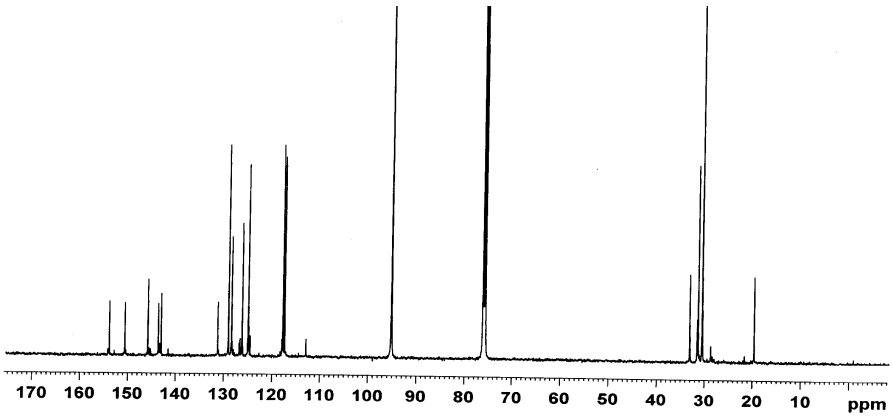


Figure 2.15: *^{13}C NMR spectrum of **60***

The ^{1}H NMR spectrum (Figure 2.16) of **61** showed one singlet for OH (δ 10.07), two singlets for the aromatic protons of the calixarene moiety (δ 6.81 and 6.64), one pair of doublets for the methylene bridges (δ 4.20 and 3.39, J = 13.5 Hz) and one singlet for the *tert*-butyl protons (δ 1.23), in agreement with the C_{2v} symmetrical structure.

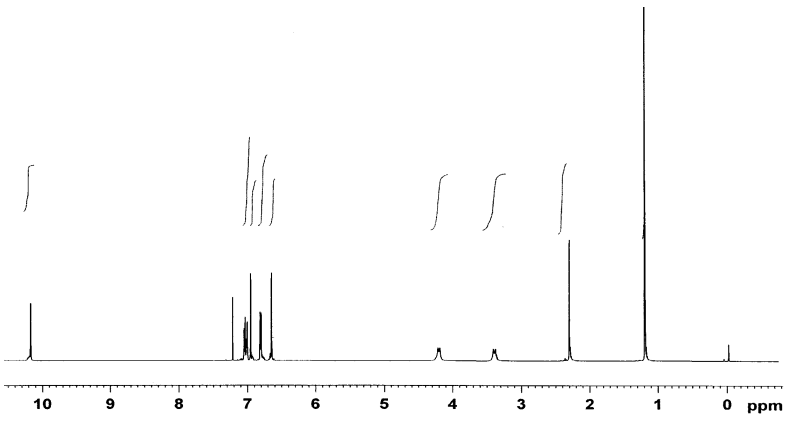


Figure 2.16: *^{1}H NMR spectrum of **61***

The ^{13}C NMR spectrum (Figure 2.17) positioned the hydroxyl group attached carbons at δ 151.2. The spectrum displayed five signals in the δ 34.0-20.1 region

corresponding to carbons of sp^3 hybridization. Further the structure was proved by mass spectral analysis showing M^+ ion peak at 748.54.

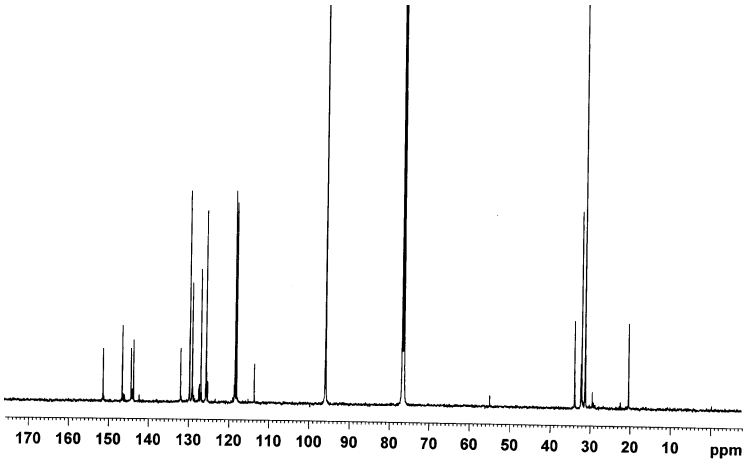


Figure 2.17: *^{13}C NMR spectrum of **61***

Subsequent to the inspiring results obtained with *p*-cresol, we examined the reaction of bis(spirodienone) with other substituted phenols (both activated and deactivated). When **29a** was reacted with 4-methoxyphenol **59b** under the above mentioned conditions, the reaction fetched both upper rim mono- and diphenoxy substituted products in good yields. The structure of **62** and **63** were established by spectral analyses. Similar reactivity was observed with 4-bromophenol **59c** and 4-iodophenol **59d**.

We then turned our attention to sterically hindered phenols, with substituents at the 2nd position of the phenolic ring. As an initial reaction, the spirodienone was treated with 2-iodophenol **59e** and the two products **68** and **69** were obtained in slightly lower yields than the corresponding *para*-substituted phenol. Analogous reaction was observed with 2,4-diiodophenol **59f** which lead to the formation of two products **70** and **71** in 17% and 6% yields respectively.

We further allowed the bis(spirodienone) to react with phenols having electron withdrawing substitutents at various positions. Among the phenols used, only 4-

phenylphenol **59g** reacted with **29a** to afford the monosubstituted calix[4]arene **72** in 30% yield, besides *p-tert*-butylcalix[4]arene **28** and tosylated calix[4]arene **34**. Formation of the disubstituted product was not observed during the reaction. With 4-nitro, 2-nitro and 4-formylphenols, reactions were unsuccessful and the unreacted bis(spirodienone) was recovered quantitatively in each case. All the reactions are summarized in table 2.5.

Table 2.5: *Generalization of the reaction with various phenols.*

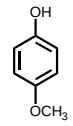
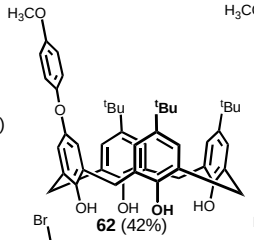
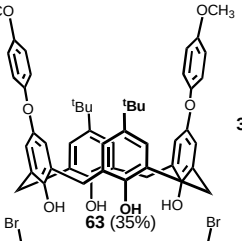
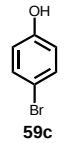
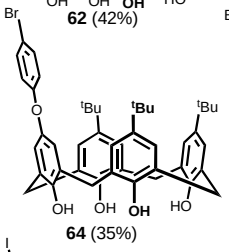
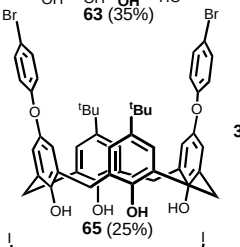
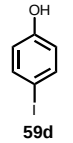
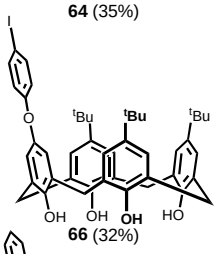
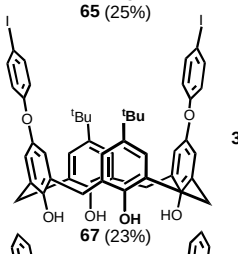
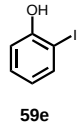
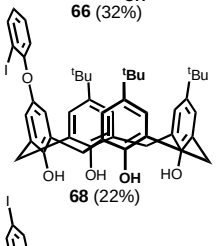
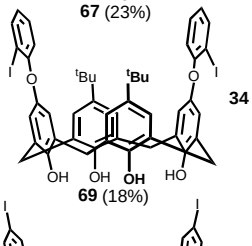
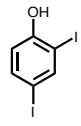
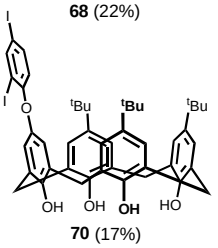
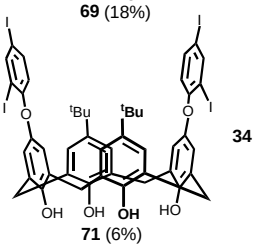
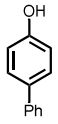
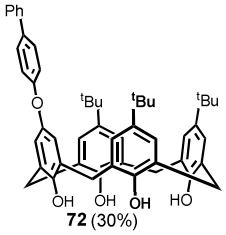
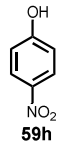
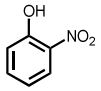
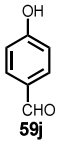
Entry	Phenols	Products (yield)		
1	 **59b**	**28** (17%)	 **62** (42%)	 **63** (35%) **34** (20%)
2	 **59c**	**28** (20%)	 **64** (35%)	 **65** (25%) **34** (26%)
3	 **59d**	**28** (22%)	 **66** (32%)	 **67** (23%) **34** (28%)
4	 **59e**	**28** (25%)	 **68** (22%)	 **69** (18%) **34** (23%)
5	 **59f**	**28** (30%)	 **70** (17%)	 **71** (6%) **34** (20%)

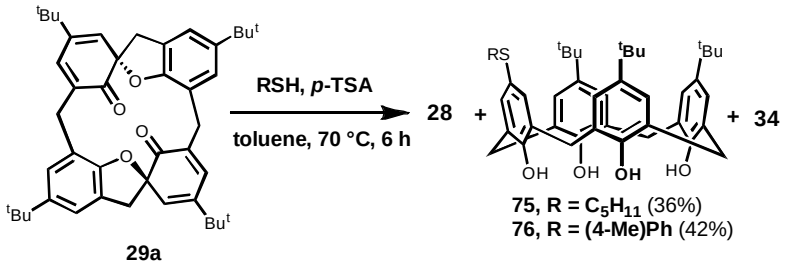
Table 2.5 Continued

Entry	Phenols	Products (yield)		
6	 **59g**	**28** (20%)	 **72** (30%)	-	**34** (17%)
7	 **59h**	No reaction			
8	 **59i**	No reaction			
9	 **59j**	No reaction			

From the above discussion it is obvious that phenols with electron donating substituents react satisfactorily with bis(spirodienone) to give both mono- and di-phenoxy substituted calixarenes in acceptable yields (table 2.5, entries 1-5). In the case of sterically hindered phenols (entries 4 & 5), the yields of the mono- and disubstituted products obtained were comparatively low, with calix[4]arene **28** being the major product. Phenols with electron withdrawing substituent (entries 7-9) failed to react and the substrate **29a** was recovered unchanged in all the cases.

2.3.2.6 Reaction with thiols

To examine the versatility of this process, we also looked into the reactivity of bis(spirodienone) with thiols, which turned out to be excellent nucleophiles for the above reaction. When bis(spirodienone) **29a** was reacted with *n*-pentanethiol **73** under the optimized conditions, monothio ether derivative **75** was obtained in good yield (Scheme 2.19). The reaction under the stipulated conditions failed to fetch the dithiosubstituted product.



Scheme 2.19: *Reaction of bis(spirodienone)* ***29a*** *with thiols*

The structure of **75** was established on the basis of various spectroscopic techniques. In the ^{1}H NMR spectrum (Figure 2.18) of **75**, the OH protons resonated as a singlet at δ 10.21 and the -SCH_2 protons occurred at 3.77 as a triplet. The *tert*-butyl groups appeared as two singlets at δ 1.23 and δ 1.19 integrating in 2:1 ratio.

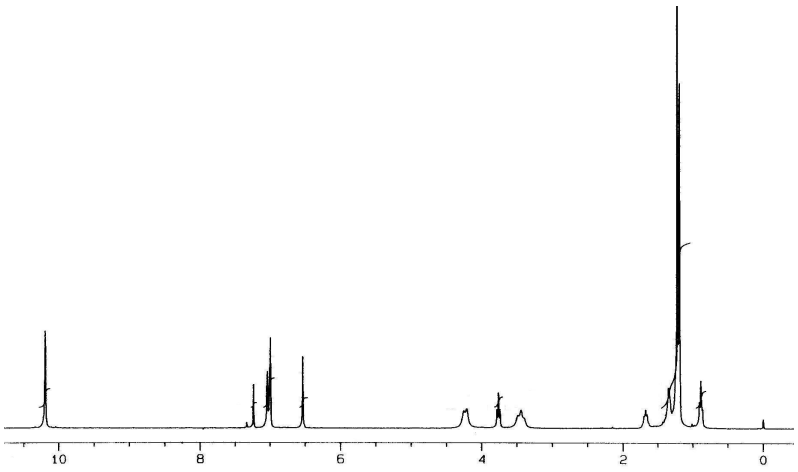


Figure 2.18: *^{1}H NMR spectrum of* ***75***

The peak corresponding to -SCH_2 carbon was observed at δ 43.5 in the ^{13}C NMR spectrum (Figure 2.19). The cone conformation was confirmed by the ^{13}C NMR spectrum which showed the methylene bridge carbons at δ 34.0 and δ 32.6.

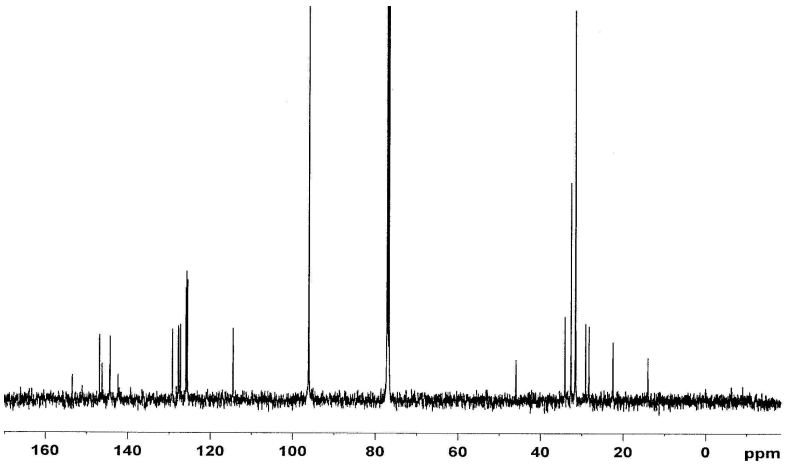


Figure 2.19: *^{13}C NMR spectrum of **75***

As representative examples for aromatic thiols, we chose *p*-thiocresol and *p*-trifluoromethylthiophenol for the above reaction. Under the above reaction conditions, *p*-thiocresol reacted smoothly with bis(spirodienone) to fetch the corresponding monothio ether derivative **76** in moderate yields (Scheme 2.19), but the *p*-trifluoromethylthiophenol failed to react with the substrate. This reaction is noteworthy as it is the first synthesis of calix[4]arene with a thioether moiety attached directly at the upper rim.

2.4 Conclusion

In summary, a direct and efficient acid-mediated protocol for the nucleophilic functionalization of calix[4]arene upper rim *via* bis(spirodienone) chemistry has been opened up. In the first part, the reactivity of alcohols towards bis(spirodienones) leading to the formation of upper rim mono- and dialkoxy substituted calix[4]arenes is being discussed. The transformation is distinguished by mild reaction conditions, experimental simplicity and considerable generality. Moreover, this *ipso*-like nucleophilic substitution reaction of bis(spirodienone) furnishes upper rim modification of calix[4]arene without resorting to any protection/deprotection strategy

involving the lower rim of calixarenes. All the compounds were thoroughly characterized on the basis of spectral data.

The latter part dealt with the reaction of bis(spriodienones) with various phenols. The reaction was found to occur under mild conditions and afforded the mono- and diaryloxy calix[4]arenes in good yields. Our methodology offers a simple and metal free route for the synthesis of mono- and diphenoxy calix[4]arene, within a very short reaction time in 'one-pot', in contrast to the coupling reactions that has been earlier reported for the synthesis of deep-cavity calixarenes.

The present chapter also unravelled a straightforward methodology for the selective introduction of thioether moiety at the upper rim of calix[4]arene. To the best of our knowledge this is the first reported procedure for the synthesis of calix[4]arene with a thioether moiety attached directly at the upper rim.

The products obtained by various nucleophilic substitution reactions can be potential candidates for further functionalization and it is conceivable that the present strategy may open up possibilities for the construction of new macrocycles from the calix[4]arene skeleton.

2.5 Experimental details

All reactions were conducted in oven-dried glassware under an atmosphere of argon with magnetic stirring unless otherwise stated. Solvents used for experiments were distilled and dried according to procedures given in standard manuals. Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 & 500 (^{1}H) and 125 & 75 (^{13}C) MHz respectively on a Bruker Avance DPX-300 MHz and Bruker AV-500 NMR spectrometers. Chemical shifts are reported in δ (ppm) relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constants (*J*) are reported in Hertz (Hz). IR spectra were recorded

on Shimadzu FT-IR spectrometer; absorbances are reported in cm^{-1}. Mass spectra were recorded under FAB/LRMS at 5000 resolution using JEOL JMS 600H mass spectrometer. MALDI-TOF mass spectra were recorded using Shimadzu Axima CFR Plus Mass Spectrometer. Elemental analyses were carried out using Perkin Elmer-2400 CHNS analyzer. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate as the binder; visualization was effected with a UV lamp and/or by developing in iodine. Gravity column was performed using 100-200 mesh silica gel and mixtures of hexane-ethyl acetate were used for elution. The reagents used were purchased from Aldrich Chemical Co. and were used without further purification.

2.5.1 Procedure for the preparation of calix[4]bis(spirodienones) 29a and 29b

To a solution of *p-tert*-butylcalix[4]arene (2.0 g, 3.08 mmol) in 80 mL of CH_2Cl_2, phenyltrimethylammonium tribromide (2.3 g, 6.14 mmol) dissolved in 27 mL of CH_2Cl_2 was added drop wise with stirring during 1 h, and then 100 mL of a 28% aqueous NaOH solution was added slowly during 30 min. The resulting solution was refluxed under stirring for 4 h. The solution was cooled to rt, 10 mL of CH_2Cl_2 and 10 mL of water were added, and after phase separation the organic phase was washed with brine, water and then dried over anhydrous Na_2SO_4. After the organic solvent was evaporated, the residue was chromatographed (100-200 silica, eluent: chloroform) and the compounds isolated were recrystallized from CH_2Cl_2-CH_3CN mixture yielding 500 mg of **29a** (27%) and 150 mg of **29b** (9%).

2.5.2 General procedure for the reaction of calix[4]bis(spirodienone) with alcohols

A mixture of calix[4]bis(spirodienone) **29a** (50.0 mg, 0.08 mmol), alcohol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was taken in a 50 mL R.B. flask and was stirred under reflux temperature (110 °C). The refluxing was continued till the reaction was complete as shown by TLC (~ 6 h). The solvent was removed under reduced pressure. The reaction mixture was diluted with dichloromethane (50 mL) and washed with water (2x25 mL) and saturated brine (25 mL) solution. The organic layer was then dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo* and the solid mass obtained was purified by column chromatography.

2.5.2.1 Procedure for the reaction of calix[4]bis(spirodienone) with methanol

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), methanol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first compound (16%) isolated from the column was identified as *p-tert*-butylcalix[4]arene from its ^{1}H NMR spectral data. The details of the other three compounds are listed below.

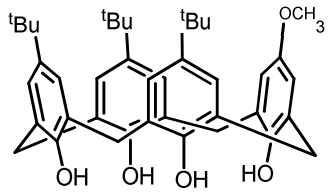
5-Methoxy-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (32)

Yield: 32% as white solid.

R_f: 0.90 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.



32

^{1}H NMR: δ 10.20 (s, OH, 4H), 7.02 (m, ArH, 6H), 6.55 (s, ArH, 2H), 4.24 (broad peak, $ArCH_2Ar$, 4H,), 3.64 (s, $-OCH_3$, 3H), 3.46 (broad s, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 153.9 (C-OH), 146.9, 146.3, 144.4, 144.3, 142.6, 129.4, 127.9, 127.7, 127.3, 126.0, 125.9, 125.6, 113.9 (Ar-C), 55.3 ($-OCH_3$), 34.1, 32.6, 31.6, 31.5, 29.8 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{41}H_{50}O_5$, M^+: 622.37; Found: 622.85.

Elemental Analysis calculated for $C_{41}H_{50}O_5$: C, 79.06; H, 8.09. Found: C, 79.03; H, 8.12.

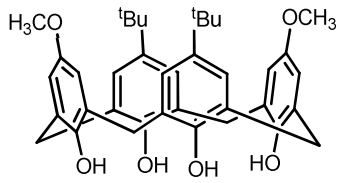
5,17-Dimethoxy-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (33)

Yield: 45% as white solid.

R_f: 0.83 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3172, 2963, 1259, 1051 cm^{-1}. **^{1}H NMR**: δ 10.04 (s, OH, 4H), 7.04 (s, ArH, 4H),



33

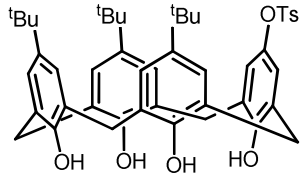
6.52 (s, ArH, 4H), 4.23 (d, J = 13.2 Hz, $ArCH_2Ar$, 4H,), 3.62 (s, $-OCH_3$, 6H), 3.43 (d, J = 13.5 Hz, $ArCH_2Ar$, 4H,), 1.24 (s, *t*-Bu, 18H).

^{13}C NMR: δ 154.0 (C-OH), 147.1, 144.7, 144.4, 142.2, 132.4, 130.8, 129.8, 129.2, 128.8, 128.3, 128.1, 127.3, 125.7, 113.9 (Ar-C), 55.9 ($-OCH_3$), 34.0, 32.4, 31.5, 30.6, 29.7, 27.7 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{38}H_{44}O_6$, M^+: 596.31; Found: 596.82.

Elemental Analysis calculated for $C_{38}H_{44}O_6$: C, 76.48; H, 7.43. Found: C, 76.44; H, 7.40.

5-Tosyloxy-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (34)



34

Yield: 15% as a brown pasty mass.

R_f: 0.30 (90:10 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3165, 2954, 1309, 1233 cm^{-1}.

^{1}H NMR: δ 10.25 (s, OH, 4H), 7.70 (d, J = 8.3 Hz, ArH tosyl, 2H), 7.32 (m, ArH tosyl, 2H), 7.05 (m, ArH, 6H), 6.68 (s, ArH, 2H), 4.20 (broad s, $ArCH_2Ar$, 4H), 3.44 (broad s, $ArCH_2Ar$, 4H), 2.46 (s, $-CH_3$, 3H), 1.20 (s, *t*-Bu, 18H,), 1.19 (s, *t*-Bu, 9H).

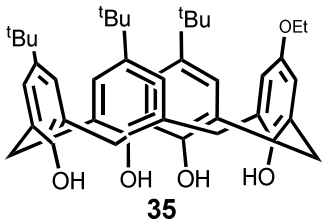
^{13}C NMR: δ 152.2 (C-OH), 147.4, 145.7, 144.4, 132.5, 130.3, 129.8, 127.7, 126.6, 126.3, 119.2, 118.7, 114.3 (Ar-C), 34.0, 31.7, 31.6, 30.7, 30.5, 20.2

($ArCH_2Ar$, *t*-Bu, $-CH_3$).

MS (MALDI-TOF): Calcd for $C_{47}H_{54}O_7S$, $(M+Na)^+$: 785.36; Found: 785.64.

5-Ethoxy-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (35)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), ethanol **31b** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**



35

Yield: 49% as a white solid.

R_f: 0.90 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1052 cm^{-1}.

^{1}H NMR: δ 10.20 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.54 (s, ArH, 2H), 4.21 (broad s, $ArCH_2Ar$, 4H), 3.84 (m, $-OCH_2$, 2H), 3.44 (broad s, $ArCH_2Ar$, 4H), 1.29, 1.22 & 1.19 (broad peak, *t*-Bu and $-CH_3$, 30 H).

^{13}C NMR: δ 153.3 (C-OH), 146.9, 146.3, 144.4, 144.3, 142.5, 129.3, 127.9, 127.7, 127.3, 126.0, 125.9, 125.6, 114.5 (Ar-C), 63.4 ($-OCH_2$), 34.1,

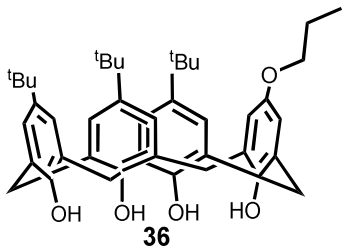
32.6, 31.6, 31.5, 14.9 ($ArCH_2Ar$, $-CH_3$, *t*-Bu).

MS (FAB): Calcd for $C_{42}H_{52}O_5$, M^+: 636.38; Found: 636.63.

Elemental Analysis calculated for $C_{42}H_{52}O_5$: C, 79.21; H, 8.23. Found: C, 79.25; H, 8.20.

5-Propyloxy-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (36)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), *n*-propanol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**



36

Yield: 37% as a white solid.

R_f: 0.89 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.20 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.55 (s, ArH, 2H), 4.24 (d, *J* = 13.3 Hz, $ArCH_2Ar$, 4H,), 3.73 (t, *J* = 6.0 Hz, OCH_2, 2H,), 3.45 (broad s, $ArCH_2Ar$, 4H), 1.70 (m, $-CH_2$, 2H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H), 0.96 (t, *J* = 7.4 Hz, $-CH_3$, 3H).

^{13}C NMR: δ 153.9 (C-OH), 146.9, 144.4, 129.3, 127.9, 127.8, 127.4, 126.1, 125.9, 125.7, 114.6 (Ar-C), 69.6 (-OCH_2), 34.1, 32.6, 31.6, 22.7 ($ArCH_2Ar$, -CH_3, *t*-Bu).

MS (FAB): Calcd for $C_{43}H_{54}O_5$, M^+: 650.40; Found: 650.52.

Elemental Analysis calculated for $C_{43}H_{54}O_5$: C, 79.35; H, 8.36. Found: C, 79.32; H, 8.30.

5-Butyloxy-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (37)

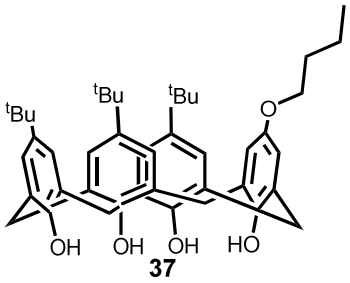
Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), *n*-butanol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**

Yield: 35% as a pasty mass.

R_f: 0.89 (90:10 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.20 (s, OH, 4H), 7.02 (m, ArH, 6H), 6.54 (s, ArH, 2H), 4.24 (d, *J* = 13.8 Hz, $ArCH_2Ar$, 4H), 3.77 (t, *J* = 6.5 Hz, -OCH_2, 2H), 3.45 (broad s, $ArCH_2Ar$, 4H), 1.66 (t, *J* = 7.3 Hz,



37

-CH_2, 2H), 1.41(m, -CH_2, 2H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H), 0.96 (t, *J* = 7.4 Hz, -CH_3, 3H).

^{13}C NMR: δ 153.5 (C-OH), 146.9, 146.7, 146.3, 144.3, 142.3, 142.0, 129.7, 129.2, 128.9, 128.6, 127.9, 127.7, 127.3, 126.0, 125.7, 125.6, 114.5 (Ar-C), 67.7 (OCH_2), 34.0, 32.5, 32.2, 31.5, 30.8, 29.7, 21.6, 19.6, 13.9, 13.4 ($ArCH_2Ar$, -CH_2, -CH_3, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{44}H_{56}O_5$, $(M+Na)^+$: 687.41; Found: 687.62.

5-Pentyloxy-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (38)

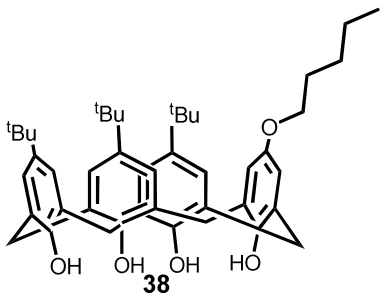
Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), *n*-pentanol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:2 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**

Yield: 30% as a pasty mass.

R_f: 0.90 (90:10 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.20 (s, OH, 4H), 7.02 (m, ArH,



38

6H), 6.54 (s, ArH, 2H), 4.23 (d, *J* = 12.6 Hz, $ArCH_2Ar$, 4H), 3.76 (t, *J* = 6.4 Hz, $-OCH_2$, 2H), 3.45 (broad s, $ArCH_2Ar$, 4H), 1.67 (m, $-CH_2$, 2H), 1.34 (m, $-CH_2$'s, 4H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H), 0.89 (uneven t, J_1 = 6.7, J_2 = 6.9 Hz, $-CH_3$, 3H).

^{13}C NMR: δ 153.4 (C-OH), 146.9, 146.3, 144.4, 144.3, 137.7, 129.2, 129.1, 127.9, 127.7, 127.3, 126.0, 125.8, 125.6, 115.2, 114.5 (Ar-C), 67.2 ($-OCH_2$), 34.1, 32.6, 32.0, 31.4, 30.1, 29.7, 28.5 ($ArCH_2Ar$, $-CH_2$, $-CH_3$, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{45}H_{58}O_5$, $(M+Na)^+$: 701.42; Found: 701.58.

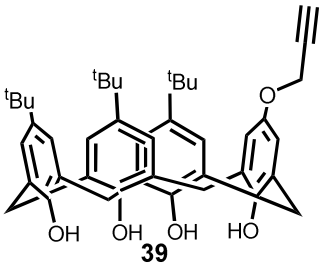
5-(Prop-3-yn-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (39)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), propargyl alcohol **31f** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 10 min. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first and the fourth products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**

Yield: 33% as a white powder.

R_f: 0.88 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.



39

IR (KBr) υ_{max}: 3175, 2960, 2858, 2135, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.23 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.65 (s, ArH, 2H), 4.51 (s, $-OCH_2$, 2H), 4.23 (d, J = 14.3 Hz, $ArCH_2Ar$, 4H), 3.46 (broad s, $ArCH_2Ar$, 4H), 2.42 (s, acetylenic H, 1H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 152.0 (C-OH), 146.9, 146.3, 144.5, 144.4, 143.4, 130.9, 129.4, 128.9, 128.4, 127.9, 127.6, 127.1, 125.9, 125.7, 115.1 (Ar-C), 78.9, 75.4 (acetylenic carbons), 56.1 ($-OCH_2$), 34.1, 34.0, 32.6, 31.6, 29.8, 14.2 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{43}H_{50}O_5$, $[M+1]^+$: 647.36; Found: 647.37.

Elemental Analysis calculated for $C_{43}H_{50}O_5$: C, 79.84; H, 7.79. Found: C, 79.80; H, 7.76.

5,17-Di(prop-3-yn-1-oxy)-11,17,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (40)

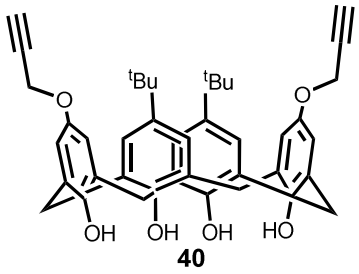
Yield: 20% as a off-white powder.

R_f: 0.74 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3170, 2960, 2858, 2140, 2135, 1263, 1050 cm^{-1}.

^{1}H NMR: δ 10.11 (s, OH, 4H), 7.07 (s, ArH, 4H),



40

6.66 (s, ArH, 4H), 4.51 (s, -OCH_2, 4H), 4.24 (d, *J* = 13.2 Hz, $ArCH_2Ar$, 4H), 3.46 (d, *J* = 13.3 Hz, $ArCH_2Ar$, 4H), 2.45 (s, acetylenic H, 2H), 1.24 (s, *t*-Bu, 18 H).

^{13}C NMR: δ 152.3 (C-OH), 147.1, 144.5, 143.1, 129.3, 128.4, 127.2, 125.9, 115.3, 115.2 (Ar-C), 79.1, 75.3 (acetylenic carbons), 56.1 (-OCH_2), 34.1, 32.5, 31.6, 29.8 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{42}H_{44}O_6$, $[M+1]^+$: 645.31; Found: 645.62.

Elemental Analysis calculated for $C_{42}H_{44}O_6$: C, 78.23; H, 6.88. Found: C, 78.19; H, 6.90.

5-(Prop-3-en-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (41)

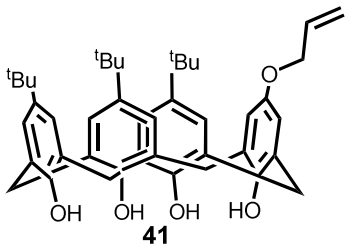
Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), allyl alcohol **31g** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 10 min. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**

Yield: 28% as a white powder.

R_f: 0.84 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3175, 2959, 2858, 1645, 1259, 1053



41

cm^{-1}.

^{1}H NMR: δ 10.22 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.58 (s, ArH, 2H), 5.97 (m, CH, 1H), 5.34 (dd, J_1 = 1.5 Hz, J_2 = 17.5 Hz, allylic H, 1H), 5.22 (dd, J_1 = 1.5 Hz, J_2 = 10.5 Hz, allylic H, 1H), 4.36 (m, -OCH_2, 2H), 4.23 (d, J = 13.5 Hz, $ArCH_2Ar$, 4H), 3.45 (m, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 153.4 (C-OH), 146.9, 146.4, 144.5, 144.4, 142.8, 136.1, 133.8, 129.3, 127.9, 126.1, 125.9, 125.7, 117.5, 114.9 (Ar-C, double bonded C's), 69.2 (-OCH_2), 38.3, 34.1, 32.6, 32.0, 31.4, 29.7, 22.7, 22.0, 14.2 ($ArCH_2Ar$, *t*-Bu).

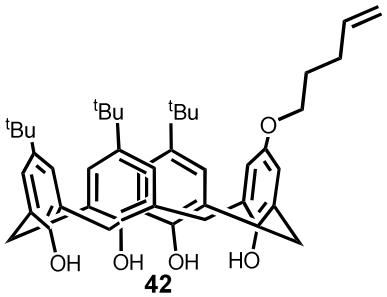
MS (FAB): Calcd for $C_{43}H_{52}O_5$, $[M+1]^+$: 649.38; Found: 649.56.

Elemental Analysis calculated for $C_{43}H_{52}O_5$: C, 79.59; H, 8.08. Found: C, 79.55; H, 8.03.

5-(Pent-4-en-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (42)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), *n*-pentenyl alcohol **31h** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 10 min. The reaction mixture on silica gel column chromatography using 97:3 hexane-

ethyl acetate solvent mixture afforded four products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**



42

Yield: 22% as a white solid.

R_f: 0.72 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3175, 2965, 2858, 1650, 1261, 1048 cm^{-1}.

^{1}H NMR: δ 10.20 (s, OH, 4H), 7.02 (m, ArH, 6H), 7.00 (s, ArH, 2H), 5.78 (m, CH, 1H), 4.98 (m, CH_2, 2H), 4.23 (d, *J* = 11.1 Hz, $ArCH_2Ar$, 4H), 3.78 (t, *J* = 6.0 Hz, -OCH_2, 2H), 3.44 (broad s, $ArCH_2Ar$, 4H), 2.14 (m, -CH_2, 2H), 1.78 (m, -CH_2, 2H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H).

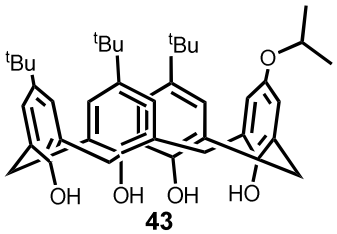
^{13}C NMR: δ 153.4 (C-OH), 146.9, 146.3, 144.4, 144.3, 142.4, 137.7, 129.2, 129.1, 127.9, 127.7, 127.3, 126.0, 125.8, 125.7, 125.6, 115.2, 114.5 (Ar-C, double bonded C's), 67.2 (-OCH_2), 34.1, 34.0, 32.6, 32.0, 31.5, 31.4, 30.1, 29.7, 28.4 ($ArCH_2Ar$, -CH_2's, *t*-Bu).

MS (FAB): Calcd for $C_{45}H_{56}O_5$, $[M+1]^+$: 677.41; Found: 677.62.

Elemental Analysis calculated for $C_{45}H_{56}O_5$: C, 79.84; H, 8.34. Found: C, 79.81; H, 8.30.

5-(1-Methyleth-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (43)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), iso-propanol **31i** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**



43

Yield: 41% as a white pasty mass.

R_f: 0.62 (90:10 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

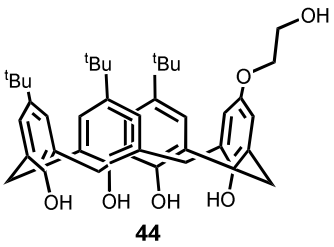
^{1}H NMR: δ 10.20 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.54 (s, ArH, 2H), 4.64 (m, CH, 1H), 4.21 (bs, $ArCH_2Ar$, 4H), 3.44 (bs, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H), 0.86 (d, *J* = 6.7 Hz, CH_3, 6H).

^{13}C NMR: δ 155.4 (C-OH), 148.9, 148.3, 146.3, 144.3, 131.2, 129.8, 129.7, 129.3, 127.9, 127.8, 127.6, 116.5, 67.7(Ar-C, CH), 34.3, 32.7, 31.7, 31.6, 29.2, 28.4, 22.5 ($ArCH_2Ar$, CH_3, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{43}H_{54}O_5$, $(M+Na)^+$: 673.40; Found: 673.65.

5-(2-Hydroxyeth-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (44)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), ethylene glycol **31k** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**



44

Yield: 22% as a white pasty mass.

R_f: 0.56 (90:10 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3175, 2958, 2860, 1810, 1261, 1048 cm^{-1}.

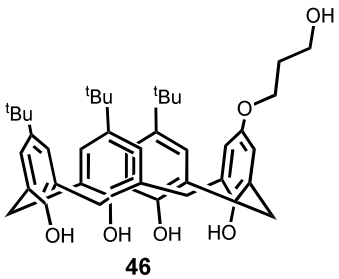
^{1}H NMR: δ 10.21 (s, OH, 4H), 7.02 (m, ArH, 6H), 6.54 (s, ArH, 2H), 4.24 (d, *J* = 12.0 Hz, $ArCH_2Ar$, 4H), 3.86 (t, *J* = 6.0 Hz, $-OCH_2$, 2H), 3.46 (m, $ArCH_2Ar$, 4H), 3.09 (m, $-CH_2$, 2H), 1.21 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H), one of the OH protons could not be detected.

^{13}C NMR: δ 155.2 (C-OH), 148.8, 148.1, 146.2, 144.3, 131.1, 129.7, 129.5, 129.1, 128.8, 127.7, 127.4, 116.3 (Ar-C), 63.4, 56.9 ($-OCH_2$), 34.1, 32.6, 31.6, 15.1 ($ArCH_2Ar$, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{42}H_{52}O_6$, $[M+Na]^+$: 675.38; Found: 675.80.

5-(3-Hydroxyprop-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (46)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), propylene glycol **31l** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be p-tert-butylcalixarene **28** and tosyl substituted product **34**.



46

Yield: 25% as a white pasty mass.

R_f: 0.52 (90:10 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3173, 2964, 2869, 1823, 1250, 1032 cm^{-1}.

^{1}H NMR: δ 10.24 (s, OH, 4H), 7.04 (m, ArH, 6H), 6.56 (s, ArH, 2H), 4.24 (d, *J* = 12.0 Hz, $ArCH_2Ar$, 4H), 3.82 (t, *J* = 6.0 Hz, $-OCH_2$, 2H), 3.46 (broad s, $ArCH_2Ar$, 4H), 3.04 (m, $-CH_2$, 2H), 1.85 (m, $-CH_2$, 2H), 1.21 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H), one of the OH protons could not be detected.

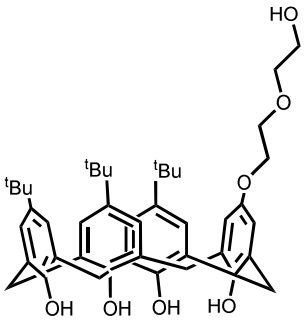
^{13}C NMR: δ 155.6 (C-OH), 148.9, 146.3, 144.3, 131.2, 129.7, 129.1, 127.7, 127.4, 114.2 (Ar-C), 62.3, 57.5 ($-OCH_2$), 34.2, 34.1, 33.8, 32.6, 31.6, 31.5, 15.1 ($ArCH_2Ar$, $-CH_2$, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{43}H_{54}O_6$,

$[M+Na]^+$: 689.38; Found: 689.45.

Calix[4]bis(spirodienone) 29a with diethylene glycol (31m) to yield (47)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), diethylene glycol **31m** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34**.



47

Yield: 19% as a white pasty mass.

R_f: 0.49 (90:10 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3173, 2955, 2874, 1832, 1257, 1066 cm^{-1}.

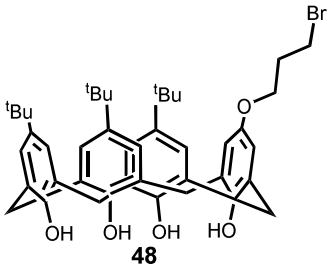
^{1}H NMR: δ 10.23 (s, OH, 4H), 7.05 (m, ArH, 6H), 6.60 (s, ArH, 2H), 4.23 (d, *J* = 13.2 Hz, $ArCH_2Ar$, 4H), 3.88 (t, *J* = 6.0 Hz, $-OCH_2$, 2H), 3.62 (m, $-OCH_2$, 4H), 3.51 (broad s, $ArCH_2Ar$, 4H), 3.13 (m, $-CH_2$, 2H), 1.21 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H), one of the OH protons could not be detected.

^{13}C NMR: δ 156.1 (C-OH), 149.7, 148.2, 147.7, 142.3, 141.1, 130.7, 129.3, 129.0, 127.6, 127.1, 113.4 (Ar-C), 62.5, 58.1, 55.3 ($-OCH_2$), 34.2, 32.7, 31.5, 22.0, 15.1 ($ArCH_2Ar$, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{44}H_{56}O_7$, $[M+Na]^+$: 719.40; Found: 719.56.

5-(3-Bromoprop-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (48)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), bromopropanol **31n** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34**.



48

Yield: 39% as a white solid.

R_f: 0.86 (90:10 hexane-ethyl acetate).

Mp: Decomposed >230 °C.

IR (KBr) υ_{max}: 3172, 2960, 2862, 1814, 1258, 1050 cm^{-1}.

^{1}H NMR: δ 10.21 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.55 (s, ArH, 2H), 4.23 (broad s, $ArCH_2Ar$, 4H), 3.93 (uneven t, $-OCH_2$, 2H), 3.49 (m, $ArCH_2Ar$, $-CH_2$, 6H), 2.16 (m, $-CH_2$, 2H), 1.21 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 152.9 (C-OH), 146.8, 146.7, 146.3, 144.4, 144.2, 142.8, 129.4, 127.9, 127.7, 127.2, 126.0, 125.9, 125.6, 114.6 (Ar-C), 65.5 ($-OCH_2$), 56.9 ($-CH_2Br$), 34.1, 31.5, 30.8, 29.9, 29.4, 22.7,

14.1 ($ArCH_2Ar$, $-CH_2$, *t*-Bu).

MS (FAB): Calcd for $C_{43}H_{53}BrO_5$, $[M+1]^+$: 729.31; Found: 729.64, 730.58.

Elemental Analysis calculated for $C_{43}H_{53}BrO_5$: C, 70.77; H, 7.32. Found: C, 70.73; H, 7.35.

5-(4-Bromobut-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (49)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), bromobutanol **31o** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34**.

Yield: 35% as a white solid.

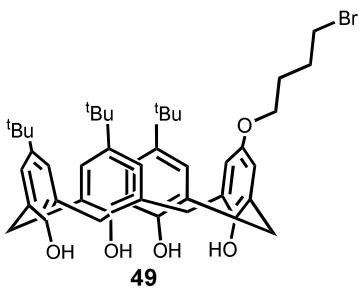
R_f: 0.83 (90:10 hexane-ethyl acetate).

Mp: Decomposed >230 °C.

IR (KBr) υ_{max}: 3171, 2957, 2860, 1810, 1258, 1050 cm^{-1}.

^{1}H NMR: δ 10.21 (s, OH, 4H), 7.02 (m, ArH, 6H), 6.54 (s, ArH, 2H), 4.24 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 3.81 (t, *J* = 6.0 Hz, $-OCH_2$, 2H), 3.44 (m, $ArCH_2Ar$, $-CH_2$, 6H), 1.98 (m, $-CH_2$, 2H), 1.84 (s, $-CH_2$, 2H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 157.6 (C-OH), 146.8, 144.3, 129.3,



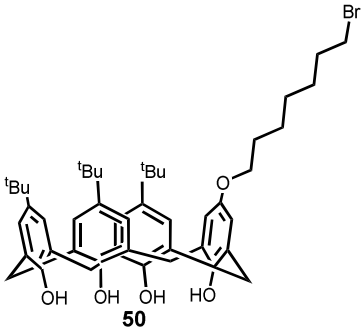
49

127.9, 127.7, 127.2, 126.0, 125.8, 125.6, 114.5 (Ar-C), 66.8 (-OCH_2), 52.4 (-CH_2Br), 34.0, 33.2, 32.5, 31.5, 31.4, 29.4, 27.9 ($ArCH_2Ar$, -CH_2, *t*-Bu). **MS** (FAB): Calcd for $C_{44}H_{55}BrO_5$, $[M+1]^+$: 743.81; Found: 743.95, 744.84.

Elemental Analysis calculated for $C_{44}H_{55}BrO_5$: C, 71.05; H, 7.45. Found: C, 71.08; H, 7.48.

5-(7-bromohept-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (50)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), 4-bromoheptanol **31p** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred under reflux temperature (110 °C) for 6 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded three products. The first and the third products were found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.**



50

Yield: 28% as a white pasty mass.

R_f: 0.82 (90:10 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3171, 2957, 2860, 1810, 1258, 1050 cm^{-1}.

^{1}H NMR: δ 10.20 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.54 (s, ArH, 2H), 4.22 (broad s, $ArCH_2Ar$, 4H), 3.77 (t, *J* = 6.5 Hz, $-OCH_2$, 2H), 3.38 (m, $ArCH_2Ar$, $-CH_2$, 6H), 1.85 (m, $-CH_2$, 2H), 1.22 (m, *t*-Bu, $-CH_2$, 33H), 0.88 (m, $-CH_2$, 2H).

^{13}C NMR: δ 157.9 (C-OH), 146.2, 144.2, 129.2, 125.9, 125.8, 125.6, 114.4 (Ar-C), 60.8 ($-OCH_2$), 44.3 ($-CH_2Br$), 34.0, 33.6, 32.7, 31.5, 29.7, 29.2, 28.6, 28.1 ($ArCH_2Ar$, $-CH_2$, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{47}H_{61}BrO_5$, $[M+Na]^+$: 807.37; Found: 807.45.

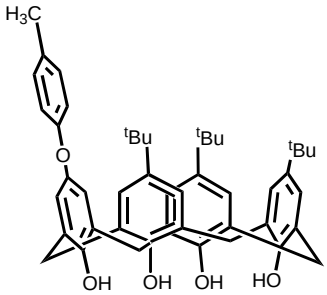
2.5.3 General procedure for the reaction of calix[4]bis(spirodienone) with phenols

A mixture of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), phenol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was taken in a 50 ml R.B. flask and was stirred at a temperature of 70 ^oC. The stirring was continued till the reaction was complete as shown by TLC (~ 4 h). The solvent was removed under reduced pressure. The reaction mixture was diluted with dichloromethane (25 mL) and washed with water (2x25 mL) and saturated brine (25 mL) solution. The organic layer was then dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo* and the solid mass obtained was purified by column chromatography.

2.5.3.1 Procedure for the reaction of calix[4]bis(spirodienone) with *p*-cresol

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), *p*-cresol **59a** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred at 70 ^{o}C for 4 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first and the fourth products were identified to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.** The details of the other two compounds are listed below.

5-(4-Methylphenyloxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (60)



60

Yield: 40% as white solid.

R_f: 0.90 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.19 (s, OH, 4H), 7.07 (s, ArH, 4H), 6.98 (s, ArH, 2H), 6.83 (m, ArH, 4H), 6.67 (s, ArH, 2H), 4.22 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 3.41 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 2.33 (s, -CH_3, 3H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H).

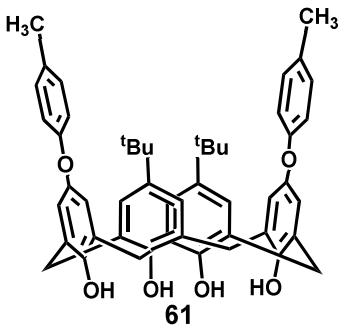
^{13}C NMR: δ 154.3 (C-OH), 150.9, 146.2, 144.0, 143.4, 131.6, 129.4, 128.8, 126.6, 125.3, 125.2, 118.1, 117.8, 113.3 (Ar-C), 33.4, 31.9, 31.7, 30.9,

30.8, 20.0 ($ArCH_2Ar$, $-CH_3$, *t*-Bu).

MS (FAB): Calcd for $C_{47}H_{54}O_5$, $[M]^+$: 698.40; Found: 698.57.

Elemental Analysis calculated for $C_{47}H_{54}O_5$: C, 80.77; H, 7.79. Found: C, 80. 74; H, 7.75.

5,17-Di(4-methylphenyloxy)-11, 23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (61)



61

Yield: 33% as white solid.

R_f: 0.84 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.07 (s, OH, 4H), 7.02 (m, ArH, 4H), 6.96 (s, ArH, 4H), 6.81 (s, ArH, 4H), 6.64 (s, ArH, 4H), 4.20 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 3.39 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 2.30 (s, $-CH_3$, 6H), 1.23 (s, *t*-Bu, 18H).

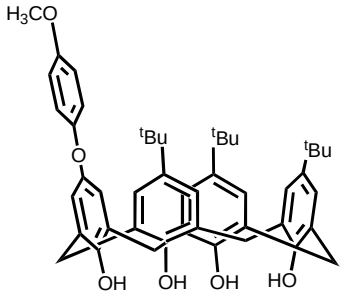
^{13}C NMR: δ 151.2 (C-OH), 146.4, 144.7, 143.5, 131.3, 129.3, 128.9, 126.8, 125.6, 125.3, 118.2, 117.7, 113.3 (Ar-C), 34.0, 31.7, 31.6, 30.8, 30.5, 20.1 ($ArCH_2Ar$, $-CH_3$, *t*-Bu).

MS (FAB): Calcd for $C_{50}H_{52}O_6$, $[M]^+$: 748.38; Found: 748.54.

Elemental Analysis calculated for $C_{50}H_{52}O_6$: C, 80.18; H, 7.00. Found: C, 80.15; H, 6.96.

5-(4-Methoxyphenyloxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (62)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), 4-methoxy phenol **59b** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred at 70 ^{o}C for 4 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first and the fourth products were identified to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.** The details of the other two compounds are listed below.



62

Yield: 42% as white solid.

R_f: 0.91 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.14 (s, OH, 4H), 6.96 (m, ArH, 8H), 6.74 (s, ArH, 2H), 6.49 (s, ArH, 2H), 4.17 (d, *J* = 11.2 Hz, $ArCH_2Ar$, 4H), 3.58 (s, $-OCH_3$, 3H), 3.39 (bs, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H).

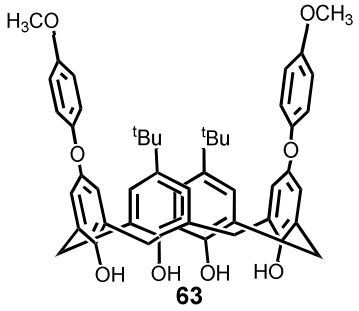
^{13}C NMR: δ 154.4 (C-OH), 146.9, 146.3, 144.2, 142.5, 137.5, 129.2, 129.1, 127.9, 127.7, 125.8, 125.7, 125.6, 119.2, 118.5 (Ar-C), 57.2 ($-OCH_3$),

34.1, 34.0, 32.6, 31.9, 31.5, 31.4, 30.1, 29.7, 28.5, 23.6, 15.1 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{47}H_{54}O_6$, $[M]^+$: 714.39; Found: 714.62.

Elemental Analysis calculated for $C_{47}H_{54}O_6$: C, 78.96; H, 7.61. Found: C, 79.02; H, 7.57.

5,17-Di(4-methoxyphenyloxy)-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (63)



63

Yield: 35% as white solid.

R_f: 0.84 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3172, 2957, 2859, 1802, 1260, 1055 cm^{-1}.

^{1}H NMR: δ 10.05 (s, OH, 4H), 7.30 (m, ArH, 4H), 7.04 (s, ArH, 4H), 6.55 (s, ArH, 4H), 6.52 (s, ArH, 4H), 4.23 (d, *J* = 13.2 Hz, $ArCH_2Ar$, 4H), 3.64 (s, OCH_3, 6H), 3.43 (d, *J* = 14.7 Hz, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H).

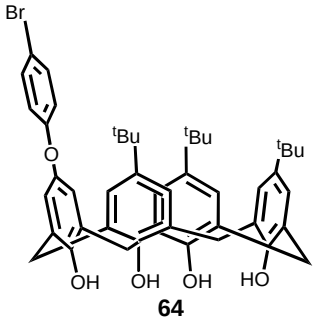
^{13}C NMR: δ 156.2 (C-OH), 152.2, 147.4, 145.7, 144.5, 132.3, 130.3, 129.9, 127.8, 126.6, 126.3, 119.2, 118.7, 114.3 (Ar-C), 59.6 (-OCH_3), 34.0, 31.7, 30.8, 20.2, 16.3 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{50}H_{52}O_8$, $[M]^+$: 780.37; Found: 780.65.

Elemental Analysis calculated for $C_{50}H_{52}O_8$: C, 76.90; H, 6.71. Found: C, 76.86; H, 6.69.

5-(4-Bromophenyloxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (64)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), 4-bromo phenol **59c** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred at 70 ^{o}C for 4 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first and the fourth products were identified to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.** The details of the other two compounds are listed below.



64

Yield: 35% as white solid.

R_f: 0.89 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.30 (s, OH, 4H), 7.34 (d, *J* = 9.0 Hz, ArH, 2H), 7.05 (m, ArH, 6H), 6.95 (s, ArH, 2H), 6.69 (s, ArH, 2H), 4.24 (d, *J* = 10.5 Hz, $ArCH_2Ar$, 4H), 3.50 (m, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.21 (s, *t*-Bu, 9H).

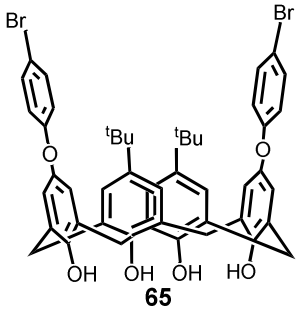
^{13}C NMR: δ 156.9 (C-OH), 150.3, 146.7, 146.5, 145.1, 144.6, 144.4, 132.5, 129.8, 127.8, 127.7, 126.9, 126.2, 125.9, 125.8, 119.9, 119.2, 115.1,

114.7 (Ar-C), 34.0, 32.7, 31.5, 30.8, 29.7, 22.7 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{46}H_{51}BrO_5$, $[M+1]^+$: 763.29; Found: 763.57, 764.62.

Elemental Analysis calculated for $C_{46}H_{51}BrO_5$: C, 72.33; H, 6.73. Found: C, 72.29; H, 6.75.

5,17-Di(4-bromophenyloxy)-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (65)



65

Yield: 25% as white solid.

R_f: 0.81 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3172, 2957, 2859, 1802, 1260, 1055 cm^{-1}.

^{1}H NMR: δ 10.15 (s, OH, 4H), 7.18 (m, ArH, 4H), 6.92 (s, ArH, 4H), 6.44 (s, ArH, 4H), 6.40 (s, ArH, 4H), 4.24 (d, *J* = 12.9 Hz, $ArCH_2Ar$, 4H), 3.43 (d, *J* = 11.74 Hz, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H).

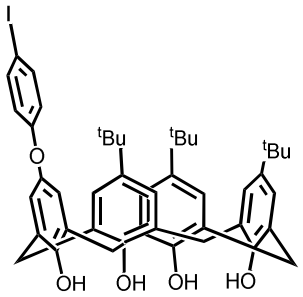
^{13}C NMR: δ 154.1 (C-OH), 147.8, 145.1, 144.7, 142.6, 132.5, 130.7, 129.8, 129.2, 128.8, 128.3, 127.3, 125.7, 113.9 (Ar-C), 34.0, 32.4, 31.5, 30.6, 27.7 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{48}H_{46}Br_2O_6$, $[M+1]^+$: 877.17; Found: 877.32, 878.43.

Elemental Analysis calculated for $C_{48}H_{46}Br_2O_6$: C, 65.61; H, 5.28. Found: C, 65.66; H, 5.25.

5-(4-Iodophenyloxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (66)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), 4-iodophenol **59d** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred at 70 ^{o}C for 4 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first and the fourth products were identified to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.** The details of the other two products are listed below.



66

Yield: 32% as white solid.

R_f: 0.91 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.21 (s, OH, 4H), 7.05 (s, ArH, 4H), 6.96 (m, ArH, 2H), 6.81 (m, ArH, 4H), 6.65 (s, ArH, 2H), 4.23 (d, *J* = 12.5 Hz, $ArCH_2Ar$, 4H), 3.42 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H).

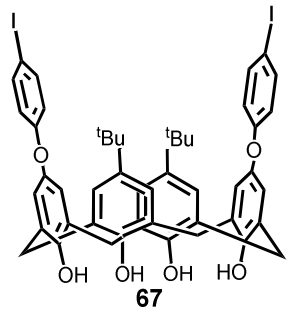
^{13}C NMR: δ 154.3 (C-OH), 150.9, 146.2, 144.0, 143.4, 131.6, 129.4, 128.8, 126.6, 125.3, 125.2, 118.1, 117.8, 113.3 (Ar-C), 34.0, 32.4, 31.9, 31.2,

30.9 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{46}H_{51}IO_5$, $[M+1]^+$: 811.28; Found: 811.52.

Elemental Analysis calculated for $C_{46}H_{51}IO_5$: C, 68.14; H, 6.34. Found: C, 68.10; H, 6.29.

5,17-Di(4-iodophenyloxy)-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (67)



67

Yield: 23% as white solid.

R_f: 0.80 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3172, 2957, 2859, 1802, 1260, 1055 cm^{-1}.

^{1}H NMR: δ 10.11 (s, OH, 4H), 7.13 (m, ArH, 8H), 7.07 (s, ArH, 6H), 6.66 (s, ArH, 2H), 4.24 (d, *J* = 13.2 Hz, $ArCH_2Ar$, 4H), 3.46 (d, *J* = 12.3 Hz, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H).

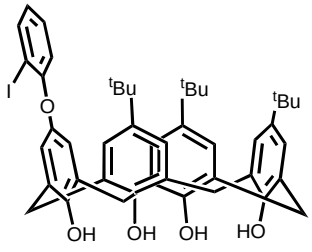
^{13}C NMR: δ 153.4 (C-OH), 146.9, 146.3, 144.4, 144.3, 137.7, 129.2, 129.1, 127.9, 127.7, 127.3, 126.0, 125.8, 125.6, 115.2, 114.5 (Ar-C), 34.1, 32.6, 31.4, 30.1, 29.7 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{48}H_{46}I_2O_6$, $[M+1]^+$: 973.14; Found: 973.37.

Elemental Analysis calculated for $C_{48}H_{46}I_2O_6$: C, 59.27; H, 4.77. Found: C, 59.24; H, 4.75.

5-(2-Iodophenyloxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (68)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), 2-iodophenol **59e** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred at 70 ^{o}C for 4 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first and the fourth products were identified to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.** The details of the other two products are listed below.



68

Yield: 22% as white solid.

R_f: 0.88 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3176, 2957, 2868, 1770, 1269, 1066 cm^{-1}.

^{1}H NMR: δ 10.21 (s, OH, 4H), 7.08 (m, ArH, 4H), 7.02 (m, ArH, 2H), 6.86 (m, ArH, 4H), 6.67 (s, ArH, 2H), 4.23 (d, *J* = 12.5 Hz, $ArCH_2Ar$, 4H), 3.42 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H).

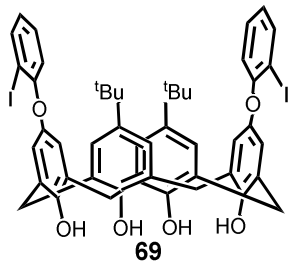
^{13}C NMR: δ 155.5 (C-OH), 147.9, 147.2, 146.0, 144.4, 132.6, 130.4, 129.8, 126.4, 125.2, 117.1, 116.8, 114.6 (Ar-C), 34.0, 32.4, 31.9, 31.2, 30.9 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{46}H_{51}IO_5$, $[M+1]^+$: 811.28;

Found: 811.43.

Elemental Analysis calculated for $C_{46}H_{51}IO_5$: C, 68.14; H, 6.34. Found: C, 68.21; H, 6.25.

5,17-Di(2-iodophenyloxy)-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (69)



69

Yield: 18% as white solid.

R_f: 0.78 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3172, 2957, 2859, 1802, 1260, 1055 cm^{-1}.

^{1}H NMR: δ 10.19 (s, OH, 4H), 7.12 (m, ArH, 4H), 6.96 (m, ArH, 8H), 6.62 (m, ArH, 4H), 4.24 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 3.44 (d, *J* = 12.6 Hz, $ArCH_2Ar$, 4H), 1.23 (s, *t*-Bu, 18H).

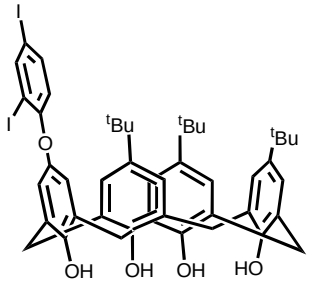
^{13}C NMR: δ 154.9 (C-OH), 146.2, 145.4, 144.8, 133.6, 130.7, 129.7, 128.8, 128.5, 127.3, 125.4, 113.9 (Ar-C), 33.9, 32.4, 31.5, 30.6, 29.7 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{48}H_{46}I_2O_6$, $[M+1]^+$: 973.14; Found: 973.52.

Elemental Analysis calculated for $C_{48}H_{46}I_2O_6$: C, 59.27; H, 4.77. Found: C, 59.16; H, 4.81.

5-(2,4-Diiodophenyloxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (70)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), 2,4-diiodophenol **59f** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred at 70 ^{o}C for 4 h. The reaction mixture on silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first and the fourth products were identified found to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.** The details of the other two products are listed below.



70

Yield: 17% as white solid.

R_f: 0.91 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

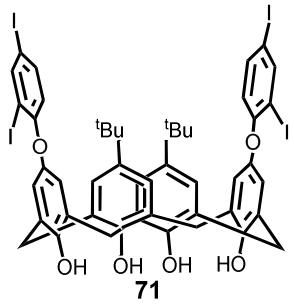
IR (KBr) υ_{max}: 3172, 2960, 2862, 1814, 1258, 1050 cm^{-1}.

^{1}H NMR: δ 10.21 (s, OH, 4H), 7.06 (m, ArH, 4H), 6.93 (m, ArH, 5H), 6.63 (s, ArH, 2H), 4.23 (d, *J* = 13.3 Hz, $ArCH_2Ar$, 4H), 3.43 (d, *J* = 14.4 Hz, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 154.6 (C-OH), 146.7, 145.1, 144.6, 144.4, 132.6, 129.7, 128.1, 127.6, 125.9, 125.3, 119.9, 119.1, 114.7 (Ar-C), 34.0, 32.6, 32.5, 31.4, 29.3 ($ArCH_2Ar$, *t*-Bu). **MS** (FAB): Calcd for $C_{46}H_{50}I_2O_5$, $[M+1]^+$: 937.17; Found: 937.23.

Elemental Analysis calculated for $C_{46}H_{50}I_2O_5$: C, 58.98; H, 5.38. Found: C, 59.12; H, 5.47.

5,17-Di(2,4-diiodophenyloxy)-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (71)



71

Yield: 6% as white solid.

R_f: 0.83 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3172, 2958, 2860, 1813, 1256, 1044 cm^{-1}.

^{1}H NMR: δ 10.07 (s, OH, 4H), 7.26 (m, ArH, 4H), 7.12 (m, ArH, 6H), 6.76 (s, ArH, 4H), 4.23 (d, *J* = 13.2 Hz, $ArCH_2Ar$, 4H), 3.46 (d, *J* = 12.7 Hz, $ArCH_2Ar$, 4H), 1.25 (s, *t*-Bu, 18H).

^{13}C NMR: δ 152.5 (C-OH), 149.6, 146.5, 144.6, 143.3, 131.6, 129.7, 128.8, 126.8, 125.6, 118.2, 117.4, 114.3 (Ar-C), 34.1, 32.0, 31.4, 30.8, 29.4, ($ArCH_2Ar$, *t*-Bu).

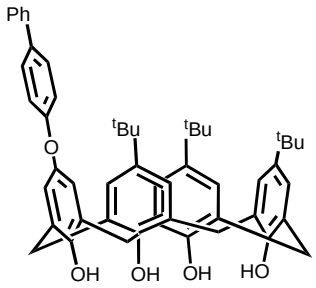
MS (FAB): Calcd for $C_{48}H_{44}I_4O_6$, $[M+1]^+$: 1224.93; Found: 1225.18.

Elemental Analysis calculated for $C_{48}H_{44}I_4O_6$: C, 47.08; H, 3.62. Found: C, 47.14; H, 3.71.

5-(4-Phenylphenyloxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (72)

Following the general experimental procedure, a solution of calix[4]bis(spirodienone) **29a** (50 mg, 0.08 mmol), 4-phenylphenol **59g** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was stirred at 70 ^oC for 4 h. The reaction mixture on

silica gel column chromatography using 97:3 hexane-ethyl acetate solvent mixture afforded four products. The first and the fourth products were identified to be *p-tert*-butylcalixarene **28** and tosyl substituted product **34.** The details of the other two products are listed below.



72

Yield: 30% as white solid.

R_f: 0.89 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}.

^{1}H NMR: δ 10.29 (s, OH, 4H), 7.83 (m, ArH, 2H), 7.53 (m, ArH, 5H), 7.05 (m, ArH, 8H), 6.75 (s, ArH, 2H), 4.25 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 3.48 (d, *J* = 14.0 Hz, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.20 (s, *t*-Bu, 9H).

^{13}C NMR: δ 156.4 (C-OH), 146.6, 146.4, 145.0, 144.4, 144.1, 138.0, 129.7, 128.8, 127.9, 127.7, 127.6, 127.5, 127.3, 126.9, 126.7, 126.6, 126.0, 125.8, 125.7, 119.0, 118.2 (Ar-C), 34.0, 33.9, 32.5, 32.3, 31.4, 31.3, 29.6 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{52}H_{56}O_5$, $[M+1]^+$: 761.41; Found: 761.55.

Elemental Analysis calculated for $C_{52}H_{56}O_5$: C, 82.07; H, 7.42. Found: C, 82.02; H, 7.39.

2.5.4 General procedure for the reaction of calix[4]bis(spirodienone) with thiols

A mixture of bis(spirodienone) **29a** (50 mg, 0.08 mmol), thiol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was taken in a 50 ml R.B. flask and was stirred at 70 °C. The reaction was continued till it was complete as shown by TLC (~ 6 h). The solvent was removed under reduced pressure. The reaction mixture was worked up using dichloromethane-water mixture and the solid mass obtained was purified by column chromatography.

2.5.4.1 Calix[4]bis(spirodienone) 29a with *n*-pentanethiol 73 to yield 75

In accordance with the general procedure, a mixture of bis(spirodienone) **29a** (50 mg, 0.08 mmol), *n*-pentanethiol **73** (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was taken in a 50 ml R.B. flask and was stirred at 70 °C. The reaction was continued till it was complete as shown by TLC (~ 6 h). The solvent was removed under reduced pressure. The reaction mixture was worked up using dichloromethane-water mixture and the solid mass obtained was purified by column chromatography. Out of the three products obtained, *p-tert*-butylcalixarene **28** and tosylated compound **34** were identified from their spectroscopic values obtained. The analytical details of the third product is given below.

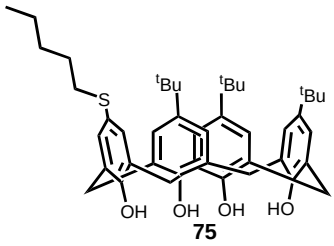
Yield: 36% as a pasty mass.

R_f: 0.78 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3170, 2956, 2860, 1784, 1058 cm^{-1}.

^{1}H NMR: δ 10.21 (s, OH, 4H), 7.02 (m, ArH, 6H), 6.55 (s, ArH, 2H), 4.23 (d, J = 12.3 Hz, $ArCH_2Ar$, 4H), 3.77 (t, J = 6.0 Hz, CH_2, 2H), 3.46 (d, J = 13.5 Hz, $ArCH_2Ar$, 4H), 1.68 (m, CH_2, 2H), 1.34,



75

1.23, 1.19 (m, CH_2, *t*-Bu, 31H), 0.89 (m, CH_3, 3H).

^{13}C NMR: δ 154.4 (C-OH), 146.9, 146.3, 144.4, 144.2, 142.3, 129.2, 127.8, 127.6, 127.2, 125.9, 125.8, 125.7, 115.5 (Ar-C), 43.5 (-SCH_2), 34.0, 32.6, 31.5, 31.4, 29.2, 28.1, 22.6, 14.9 ($ArCH_2Ar$, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{45}H_{58}O_4S$, $(M+Na)^+$: 717.40; Found: 717.86.

2.5.4.2 Calix[4]bis(spirodienone) 29a with *p*-thiocresol 74 to yield 76

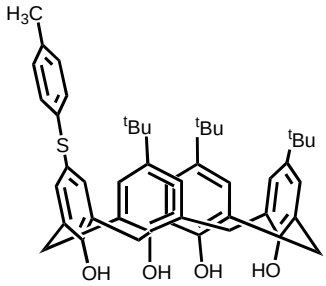
In accordance with the general procedure, a mixture of bis(spirodienone) **29a** (50 mg, 0.08 mmol), *p*-thiocresol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was taken in a 50 ml R.B. flask and was stirred at 70 °C. The reaction was continued till it was complete as shown by TLC (~ 6 h). The solvent was removed under reduced pressure. The reaction mixture was worked up using dichloromethane-water mixture and the solid mass obtained was purified by column chromatography. Out of the three products obtained, *p-tert*-butylcalixarene **28** and tosylated compound **34** were identified from their spectroscopic values obtained. The analytical details of the third product is given below.

Yield: 42% as white solid.

R_f: 0.75 (90:10 hexane-ethyl acetate).

Mp: Decomposed >240 °C.

IR (KBr) υ_{max}: 3172, 2958, 2860, 1790, 1259, 1053 cm^{-1}.



76

^{1}H NMR: δ 10.19 (s, OH, 4H), 7.06 (s, ArH, 4H), 6.98 (s, ArH, 2H), 6.83 (m, ArH, 4H), 6.67 (s, ArH, 2H), 4.23 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 3.42 (s, $ArCH_2Ar$, 4H), 2.13 (s, CH_3, 3H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 156.9 (C-OH), 150.3, 146.7, 145.1, 144.6, 144.4, 144.2, 132.5, 129.8, 127.7, 127.6, 126.9, 126.2, 125.9, 125.8, 119.9, 119.3, 115.1, 114.7 (Ar-C), 34.0, 32.7, 32.5, 34.4, 31.5, 30.8, 29.7, 22.6 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{47}H_{54}O_4S$, $[M+1]^+$: 715.37; Found: 715.64.

Elemental Analysis calculated for $C_{47}H_{54}O_4S$: C, 78.95; H, 7.61; S, 4.48. Found: C, 78.92; H, 7.59; S, 4.50.

Chapter 3

Part A:

Applications of Spirodienone Route for *ipso*-Nucleophilic Substitution of Calix[4]arene towards the Synthesis of Calixquinones and Biscalixarenes

Part B:

p-TSA Mediated de-*tert*-Butylation of *p*-*tert*-Butylcalix[4]arene and *p*-*tert*-Butylthiacalix[4]arene

The design and practice of new synthetic methodologies is an extremely important aspect of modern synthetic organic chemistry. New methodologies have facilitated to enrich the chemical repertoire of many families of organic compounds, especially calixarenes. The spectacular development of calix[4]arenes as molecular receptors is primarily related to many possible structural and functional modifications of their core molecular architecture [Hwang and Kim 2002; Lhotak *et al.* 2003; Dondoni *et al.* 2002], which constitutes a hollow cavity flanked by a hydrophobic upper rim and a hydrophilic lower rim. The most commonly employed approach for the modification of the calix scaffold uses a calixarene as starting material. Necessarily this approach rests on the chemistry of the phenol group, which rather unfortunately is

not very rich. In this context, calix[4]bis(spirodienones) have emerged as useful synthetic intermediates for the selective functionalization of calixarenes. The spirodienone calixarene derivatives have been utilized for the selective derivatization of calixarenes in extraannular, intraannular and methylene bridge positions [Litwak and Biali 1992; Grynspan *et al.* 1991; Grynspan *et al.* 1994]. Using bis(spirodienones) as starting compounds, we have demonstrated in the last chapter, a novel *ipso*-like selective nucleophilic substitution reaction of the upper rim of calix[4]arenes to furnish mono- and dialkoxy/aryloxy calixarenes. In continuation, we have undertaken efforts towards exploitation of the synthetic potential of the new products obtained from the above reactions and the major observations will be described in part A. The part B of this chapter will be focusing on an alternate method, which we came across during our investigation of the *ipso*-nucleophilic substitution reactions, for the de-*tert*-butylation of *p*-*tert*-butylcalix[4]arene and *p*-*tert*-butylthiacalix[4]arene using *p*-TSA.

Part A

Applications of Spirodienone Route for *ipso*-Nucleophilic Substitution of Calix[4]arene towards the Synthesis of Calixquinones and Biscalixarenes

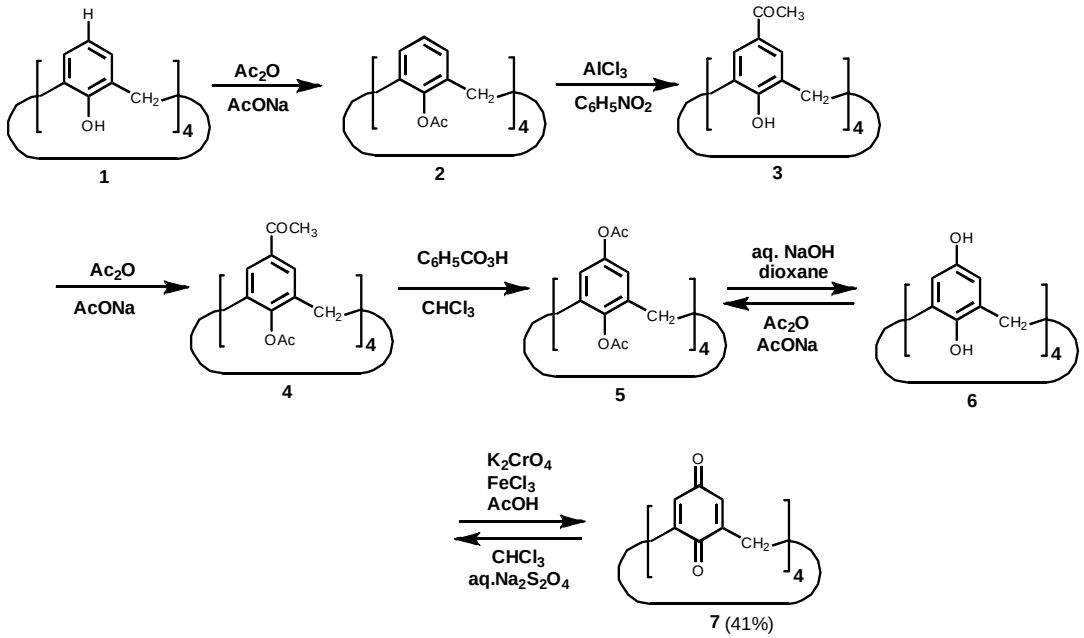
3.1 Introduction

Among functionalized calixarenes, calixhydroquinones and calixquinones are of particular interest because of their potential use as redox systems, as participants in charge-transfer complexes [Aviram and Sieden 1982] and as synthetic intermediates. One current application of calixquinones is their use as sensors for the detection of various metal cations; the efficiency of the metal recognition process relying on several factors, notably the ability of the oxygen atom(s) of the quinone to bind the metal ion in combination with other donors linked to the calixarene skeleton as well as on the ligand's flexibility [Bethell *et al.* 1995]. Novel synthetic methodologies towards both calixhydroquinones and quinones are highly desirable in view of the tremendous applications of these calixarene derivatives. We have utilized two products obtained by the nucleophilic substitution reaction of calix[4]bis(spirodienones) using methanol; i.e., upper rim monomethoxy and dimethoxy calixarenes as starting materials for synthesizing calixhydroquinone and calixquinone. Our efforts in this direction are discussed in the beginning of this chapter. The different procedures for the synthesis of calixhydroquinones and calixquinones are briefly discussed in the introductory sections. Along with calixquinones and hydroquinones, this chapter also describes the

synthesis of triazole appended calixarene derivatives using ‘click’ chemistry’. The subsequent section also gives a brief introduction on ‘clicked’ calixarenes.

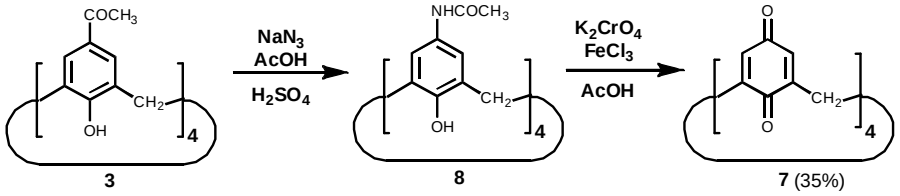
3.1.1 Indirect routes for the synthesis of calixhydroquinones and calixquinones

The first publication detailing the synthesis of calix[4]hydroquinone and calix[4]quinone described three different pathways [Nomura and Taniguchi 1992]. The first pathway to quinone from calix[4]arene **1** consists of six steps: acetylation of **1** using acetic anhydride and sodium acetate afforded 25,26,27,28-tetraacetoxycalix[4]arene **2** in 84% yield. The conversion of **2** to 5,11,17,23-tetraacetyl-25,26,27,28-tetrahydroxycalix[4]arene **3** was achieved successfully by the Fries rearrangement. The calixarene **3** was allowed to react with acetic anhydride in the presence of sodium acetate to give **4** in 76% yield. The Baeyer-Villiger oxidation of **4** to 5,11,17,23,25,26,27,28-octaacetoxycalix[4]arene **5** using perbenzoic acid required prolonged time in the dark, with occasional shaking at room temperature for completion. The hydrolysis of **5** under basic conditions proceeded smoothly to produce **6** in 95% yield. The recrystallization of **6** from methanol-water followed by oxidation using $FeCl_3$ gave the desired tetraquinone **7** in 89% yield. The overall yield of **7** based on calixarene **1** was 41% (Scheme 3.1).



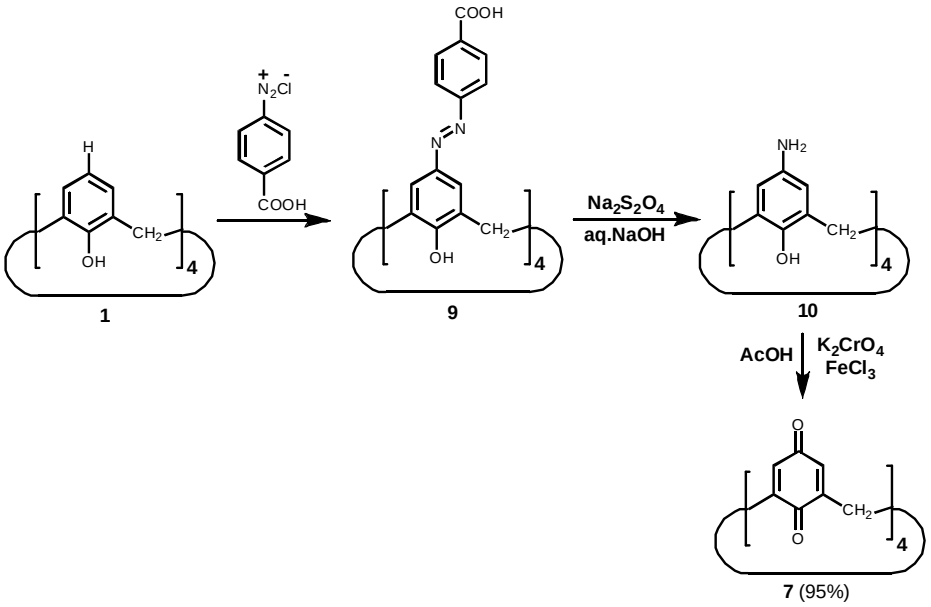
Scheme 3.1: *Synthesis of calix[4]quinone via a six-step synthetic strategy*

The second pathway to **7** from **1** consists of four steps: acetylation, Fries rearrangement, reaction of the product obtained by Fries rearrangement with sodium azide followed by oxidation (Scheme 3.2).



Scheme 3.2: *Synthesis of calix[4]quinone via Fries rearrangement followed by oxidation*

The third pathway to **7** from **1** is the most convenient and consists of three steps: diazo coupling reaction, reduction and oxidation (Scheme 3.3).



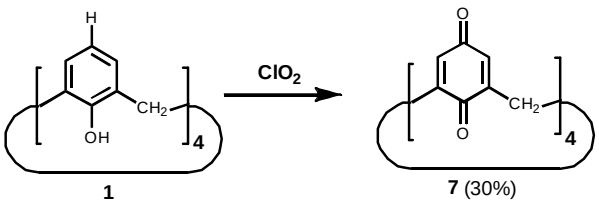
Scheme 3.3: *Synthesis of* ***7*** *starting from diazotization*

Apart from the reactions reported above, Arduini *et al.* have reported a three step strategy for the synthesis of upper rim tetrahydroxylated calix[4]arene [Arduini et al. 1996] and Lee *et al.* have reported a six step synthetic procedure for the synthesis of upper rim monohydroxylated calix[4]arene [Lee *et al.* 2001]. Both these methods have been discussed in detail in the introductory portion of chapter 2.

With regard to calixquinones, several synthetic protocols have been reported concerning its direct synthesis.

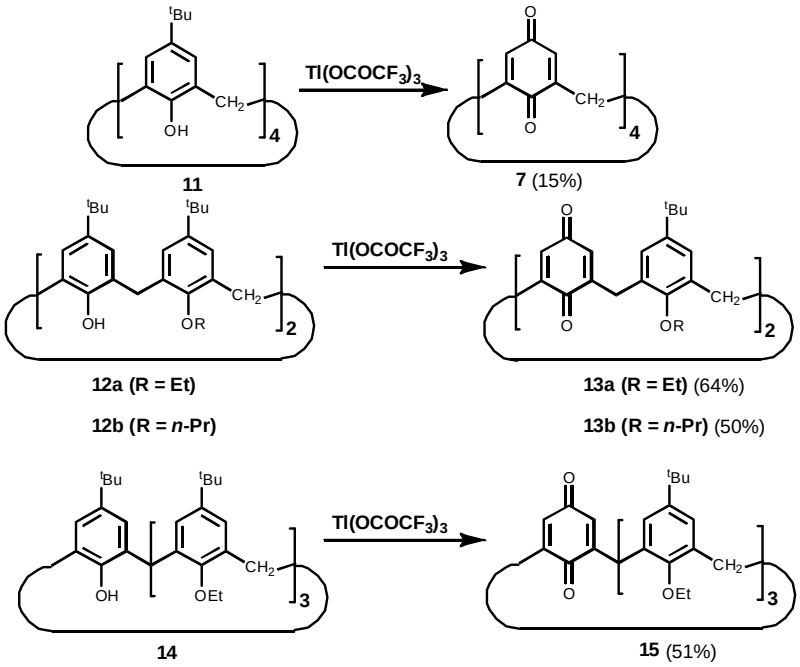
3.1.2 Direct routes for the synthesis of calixquinones

A one step synthetic strategy for generating calixquinone was introduced in 1980s but the details did not appear until 1992 showing that chlorine dioxide converts **1** to calix[4]quinone in 30% yield (Scheme 3.4) [Reddy *et al.* 1992].



Scheme 3.4: *Single step synthesis of calix[4]quinone using ClO_2*

During the course of this study, Gutsche and coworkers found that $Tl(OCOCF_3)_3$, which was introduced a number of years ago by Mckillop and coworkers [Mckillop *et al.* 1970] for the oxidation of 2,6-disubstituted-4-*tert*-butylphenols to 2,6-disubstituted-1,4-benzoquinones, could also serve as a useful reagent for calixquinone formation. The advantage of this reagent is that it can be used directly on *p-tert*-butylcalixarenes, obviating the necessity for removing the *tert*-butyl groups in a separate step. Although the yield of **7** from *p-tert*-butylcalixarene **11** is only *ca.* 15%, much better yields of calixquinones are obtained from partially etherified or esterified *p-tert*-butylcalixarenes (Scheme 3.5). For example 1,3-diquinone **13a** is obtained in 64% yield from the diether **12a**; 1,3-diquinone **13b** is obtained in 50% yield from diether **12b** [Reddy and Gutsche 1993].



Scheme 3.5: *Thallium triflate mediated synthesis of calixquinones*

The monoquinone **15** is obtained in 51% yield from the triether **14** (Scheme 3.5). Because of greater accessibility and solubility of the monoquinone **15** and

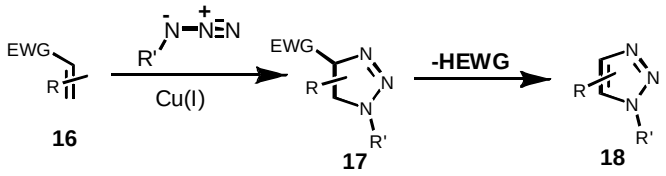
diquinones **13a** and **13b**, as compared with polyquinones, they have gained widespread acceptance as synthetic intermediates and sensing agents [Aviram and Seiden 1982].

3.1.3 Copper assisted Azide Alkyne Cycloaddition (CuAAC) (click reaction)

Click chemistry is a chemical philosophy introduced by K. Barry Sharpless in 2001 and describes chemistry tailored to generate substances quickly and reliably by joining small units together [Kolb *et al.* 2001]. This is inspired by the fact that nature also generates substances by joining small modular units. Click chemistry in combination with combinatorial chemistry, high-throughput screening and building chemical libraries speeds up new drug discoveries by making each reaction in a multistep synthesis fast, efficient and predictable. For a reaction to be termed ‘click’, the reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be easily removed by nonchromatographic methods and be stereospecific. The required process characteristics include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (such as water) or easily removed and simple product isolation. Purification - if required - must be by nonchromatographic methods, such as crystallization or distillation and the product must be stable under physiological conditions.

One of the most popular reactions within the click chemistry philosophy is the azide-alkyne Huisgen cycloaddition using a Cu catalyst at room temperature discovered concurrently and independently by the groups of K. Barry Sharpless and Morten Meldal [Kolb *et al.* 2001; Meldal and Tornoe 2008] (Scheme 3.6). This was an improvement over the same reaction first popularized by Rolf Huisgen in the 1970s, albeit at elevated temperatures in the absence of water and without a Cu catalyst.

Besides the advantage of efficiency, regioselectivity and compatibility with reaction conditions, the unique properties of the 1,4-disubstituted 1,2,3-triazole ring, in terms of participation in hydrogen bonding and dipole-dipole interactions has made click chemistry even more attractive [Ryu *et al.* 2005; Ornelas *et al.* 2007; David *et al.* 2007].

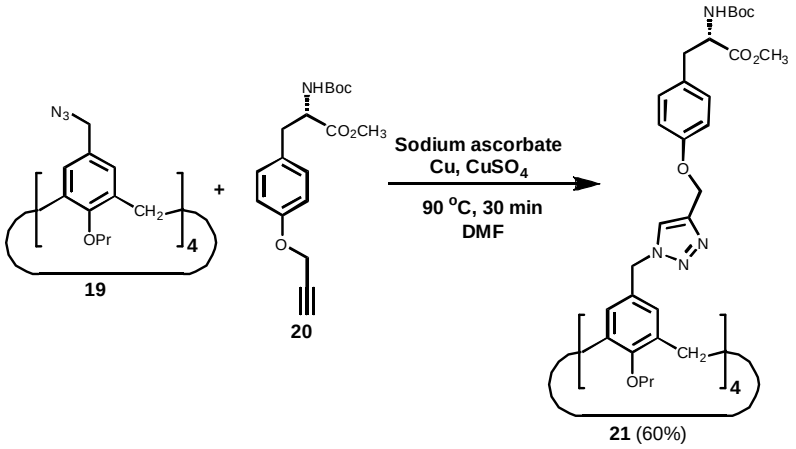


Scheme 3.6: *Cu(I) mediated Huisgen's 1,3-dipolar cycloaddition*

3.1.4 Clicked calixarenes

The efficiency and user-friendliness of CuAAC has established this reaction as a universal synthetic tool that has been rapidly adopted by almost all areas of chemistry, enabling applications in drug discovery [Tron *et al.* 2008], bioconjugation [Angell and Burgess 2007], polymer and science materials [Fournier *et al.* 2007] and related areas [Moses and Moorhouse 2007], and also in supramolecular chemistry [Aprahamian *et al.* 2007]. However, in the particular case of calixarenes, click chemistry has been applied up to the present in limited cases to decorate both the upper and the lower rim of such macrocycles. Some examples validating the use of CuAAC in the synthesis of calixarene derivatives are given below.

Click concept has been ingeniously utilized by Bew *et al.* for making upper rim triazole appended calixarenes bearing α-aminoacids for performing chemo-enzymatic procedures [Bew *et al.* 2007]. When an aqueous DMF solution of **19** and **20** was stirred at 90 ^{o}C under microwave conditions with Cu, $CuSO_4$ and sodium ascorbate, triazole containing calix[4]arene-aminoacid hybrid **21** was afforded as a single regioisomer (Scheme 3.7).



Scheme 3.7: *'Click' chemistry derived upper rim calix[4]arene-aminoacid hybrid*

The same group has also appended carbohydrates to the upper rim of a calix[4]arene using 'click' methodology. 1,4-Disubstituted-[1,2,3]-triazole disaccharide **22** and bis(disaccharide) **23** were afforded in 74% and 88% yields (Figure 3.1), respectively using O-*n*-propoxy-1,3-diazidomethylenecalix[4]arene and readily synthesized O-propargyl-3,4,5,6-tetra-O-acetyl-β-D-glucopyranoside or O-propargyl-2,3,4,6-tetra-O-β-D-galactopyranosyl-(1,4)-O-2,3,6-tri-O-acetyl-β-D-glucopyranoside.

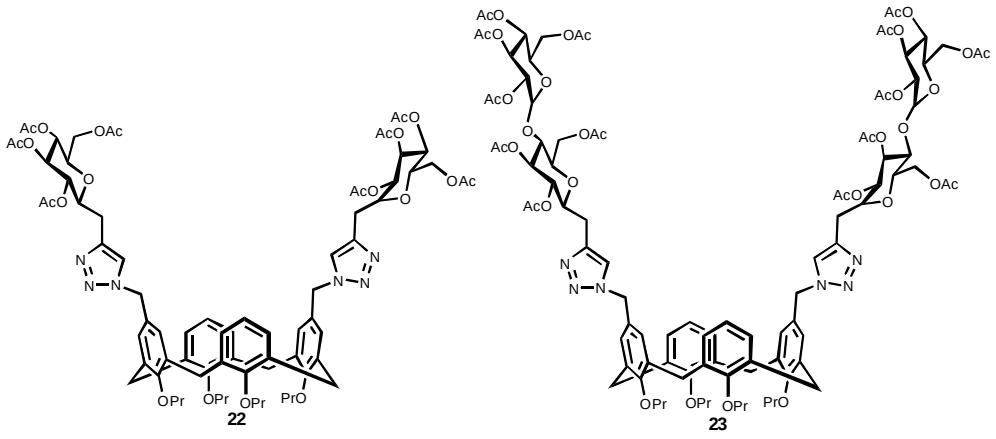
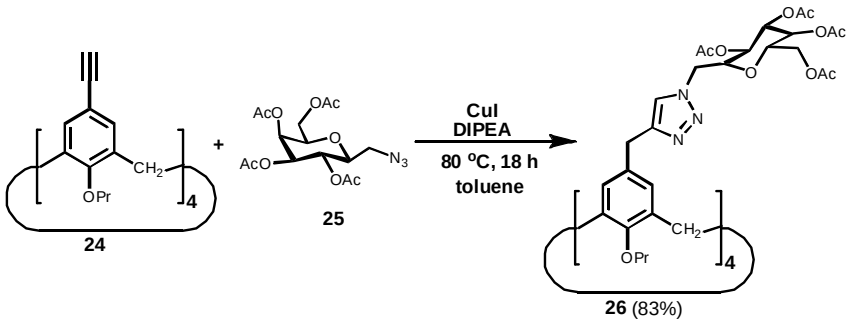


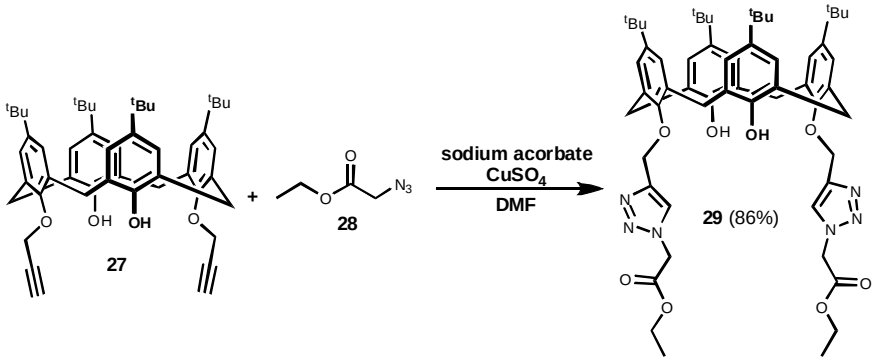
Figure 3.1: *Sugar appended hybrid calixarenes*

The azide-alkyne cycloaddition approach to regioisomeric triazole linked C-glycoclusters appended on calix[4]arene was employed by Dondoni *et al.* by reacting azidomethyl C-glycoside **25** with upper rim tetraethynylcalix[4]arene **24** (Scheme 3.8) [Dondoni *et al.* 2006].



Scheme 3.8: *Upper rim triazole appended glycocalixarene via 'click' chemistry*

A lower rim triazole modified calix[4]arene diester was synthesized *via* Huisgen 1,3-dipolar cycloaddition between azide ester **28** and alkynylcalixarene **27** in the presence of $CuSO_4$ and sodium ascorbate in DMF (Scheme 3.9). Two-phase extraction experiments indicated that triazole modified calix[4]arene diethylester **29** exhibited high Cs^+ selectivity through the cooperative complexation of the triazole and ester groups [Li *et al.* 2009].



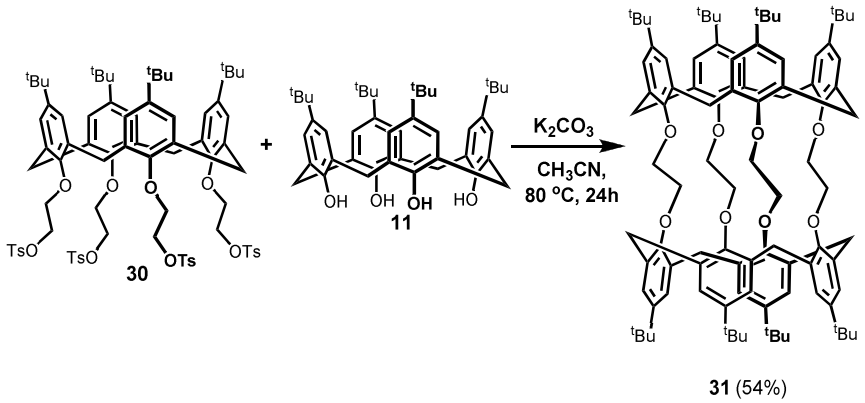
Scheme 3.9: *Synthesis of triazole-modified calix[4]arene ester*

3.1.5 Biscalixarenes

The versatility of calix[4]arenes as host molecules suggested that they might serve as potential building blocks for designing more elaborate structures. Of particular interest in this regard is the construction of double- and multi-calixarenes, for their peculiar multi-cavity structures and molecular recognition properties [Ikeda and Shinkai 1997; Higler *et al.* 1998]. Depending on the connecting site, there are

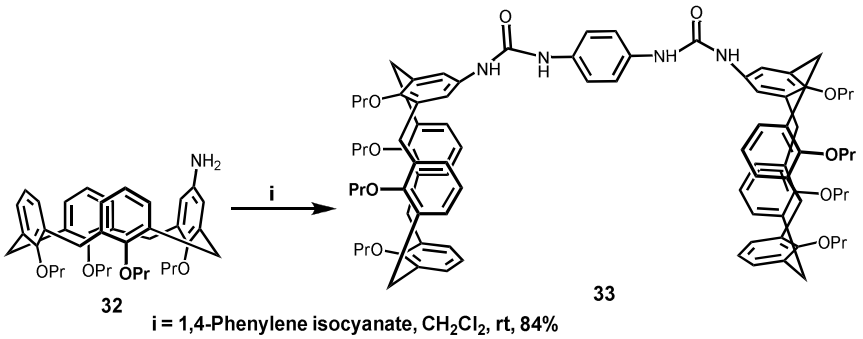
three possible modes of assembly for biscalix[4]arenes: head-to-head, tail-to-tail, or head-to-tail. Or, put another way, by both upper rims, by both lower rims, or by the upper rim of one and the lower rim of another, respectively. Molecules of this type are expected to organise themselves taking advantage of the presence of several proximate cavities, to nano-scale architectures. Notably, these may interact synergistically when disposed properly relative to each other, thereby amplifying the receptor or physico-chemical properties of the individual components.

Beer *et al.* reported the synthesis of a novel biomimetic tail-to-tail linked biscalixarene **31** by the template driven condensation of *p-tert*-butylcalix[4]arene **11** with pertosylated derivative **30** in acetonitrile (Scheme 3.10) [Schmitt *et al.* 1997].



Scheme 3.10: *Template-driven synthesis of tail-to-tail linked biscalixarenes*

A head-to-head linked biscalixarene **33** possessing pre-organized urea moiety in the structure was synthesized by Stibor *et al.* These compounds represent well preorganised cavities with interesting complexation abilities towards anions (Scheme 3.11) [Stastny *et al.* 2002].

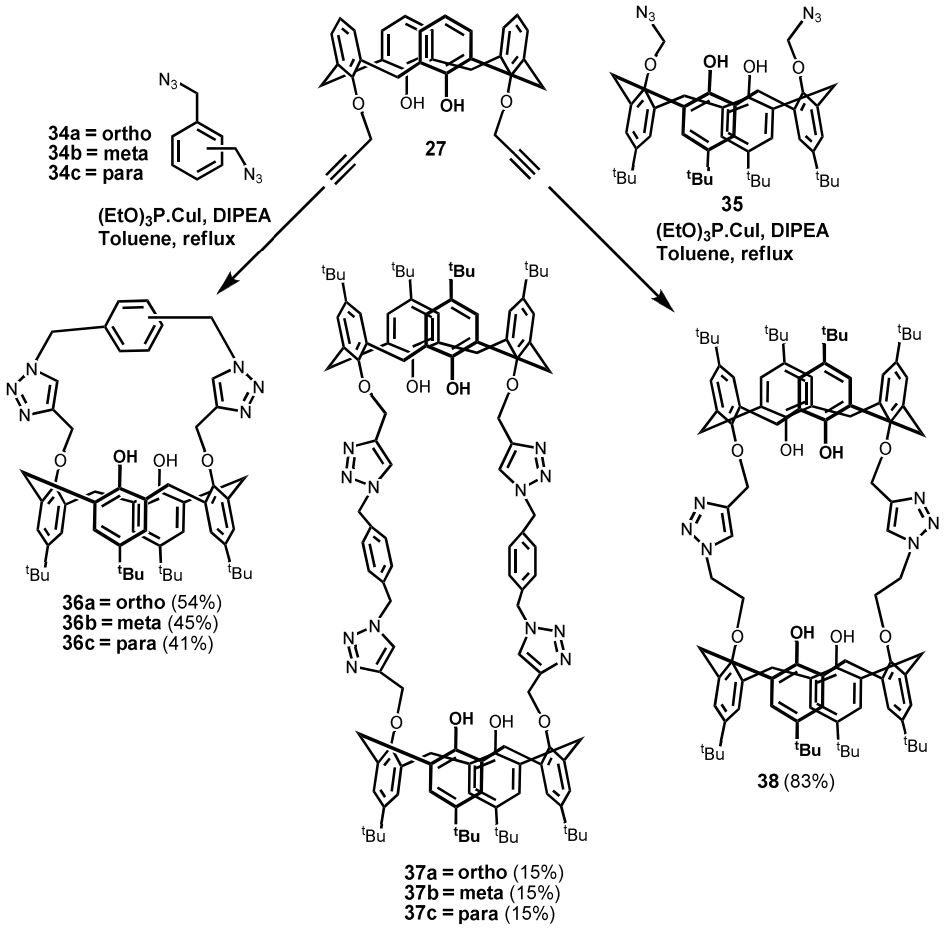


Scheme 3.11: *Synthesis of a head-to-head linked biscalixarene*

Besides these two representative examples, there are a number of reports for the construction of biscalixarenes by other groups working in this field [Pitarch *et al.* 1998; Brody *et al.* 1999; Santoyo-Gonzalez *et al.* 2000]. However in most of the above mentioned reports, there is one limitation or the other like the poor availability of starting materials, drastic reaction conditions, longer reaction times and poor yield of the products.

3.1.6 Biscalixarenes by click chemistry

The validity of click chemistry for the synthesis of biscalixarenes have been limited to one report in which Sanfrutos *et al.* synthesized a variety of lower rim calixarene based supramolecular structures [Sanfrutos *et al.* 2008]. Their strategy was based on the use of the dipropargylated calix[4]arene derivative **27** as a clickable pivotal compound that allowed capping at its lower rim when reacted with diazide reagents, fixing the calix[4]arenes in a rigid cone conformation by means of 1,2,3-triazole rings acting as heterocyclic bridges. When 1,2-, 1,3- and 1,4-bis-azidomethyl benzene **34a-c** were reacted with **27** using $(EtO)_3P{\cdot}CuI$ as catalyst in refluxing toluene, the capped calixarenes **36a-c** and tube-like doubly interbridged bis(calix[4]arenes) **37a-c** were obtained. A tail-to-tail linked double calixarene **38** is easily formed by reacting **27** with the diazide **35** (Scheme 3.12).



Scheme 3.12: *Synthesis of capped calixarenes and biscalixarenes*

3.2 Statement of the problem

A clear picture of the various methods for the synthesis of calixhydroquinones and calixquinones is evident from the foregoing section. It also contained a brief overview of the justification of the use of CuAAC chemistry in the synthesis of calixarene frameworks, especially biscalixarenes. The preceding chapter had uncovered a novel *ipso*-nucleophilic substitution of calix[4]bis(spirodienones) by nucleophiles like alcohols, phenols, thiols etc. The reaction fetched upper rim monosubstituted calix[4]arenes in all cases and also disubstituted calix[4]arene, in some cases.

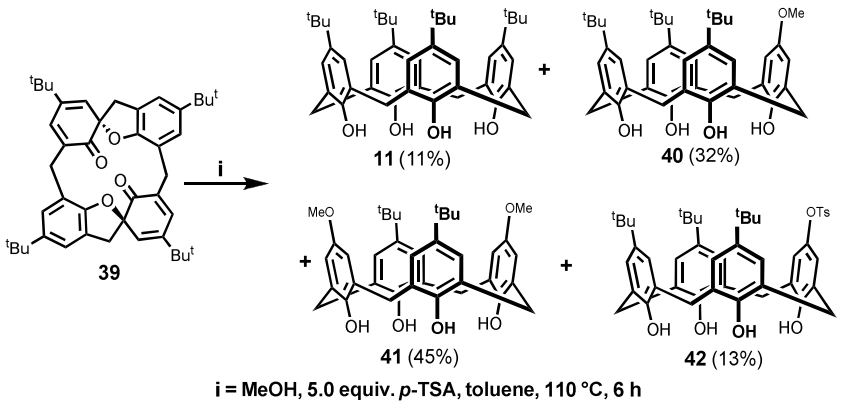
In the perspective of our general interest in designing novel calixarene based frameworks and to bring out the usefulness of the synthetic protocol developed by us,

we decided to study the synthetic utility of some of the products obtained using the above methodology. Accordingly, we looked into the possibility of cleavage of methyl group from the mono- and dimethoxy calix[4]arenes and subsequent oxidation of the hydroxyl compounds obtained thereby. Furthermore we validated the use of click chemistry (CuAAC) in the synthesis of a library of triazole appended calixarene based frameworks. A detailed account of our investigations is provided in the oncoming sections.

3.3 Results and discussion

3.3.1 Synthesis of 5-hydroxy and 5,17-dihydroxycalix[4]arene

The starting materials, the upper rim mono- and dimethoxy substituted calix[4]arenes **40** and **41** were prepared by the reaction shown below (Scheme 3.13) [Thulasi *et al.* 2009].

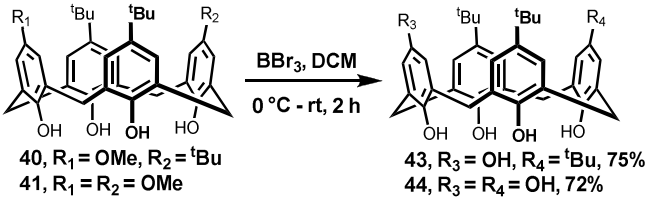


Scheme 3.13: *p-TSA mediated reaction of calix[4]bis(spirodienone)* ***39*** *with methanol.*

Since the products **40** and **41** contained easily cleavable methoxy groups at the upper rim, we explored the possibility of selectively cleaving methoxy groups in 5-methoxycalix[4]arene **40** and 5,23-dimethoxycalix[4]arene **41**. Boron-based reagents are particularly versatile for cleaving C–O bonds, giving an alkyl bromide and an alkoxyborane, which then is hydrolyzed to the corresponding alcohol. Alkyl aryl ethers

are cleaved at the alkyl–oxygen bond, yielding the corresponding phenol and the alkyl bromide. Among the various boron halides used, boron tribromide is an excellent demethylating or dealkylating agent for phenolic ethers [Hwang and Wang 1993].

Accordingly the monomethoxy compound **40** was treated with boron tribromide in dichloromethane at 0 °C for 2 h. Removal of the solvent followed by column chromatography of the residue on silica gel furnished 5-hydroxycalix[4]arene **43** in 75% yield (Scheme 3.14).



Scheme 3.14: *Synthesis of calix[4]hydroquinones*

The structure **43** was assigned to the product on the basis of spectral and analytical data. In the ^{1}H NMR spectrum (Figure 3.2), the hydroxyl protons resonated at δ 10.20 as a singlet. The aromatic protons appeared as a multiplet at δ 7.04 and as a singlet at δ 6.53. The methylene protons resonated as two broad singlets at δ 4.10 and 3.32. The *tert*-butyl signals appeared as two singlets at δ 1.22 and 1.19 in a 2:1 ratio. The absence of the -OCH_3 peak which was so conspicuous in the parent compound gave further proof for the formation of the product.

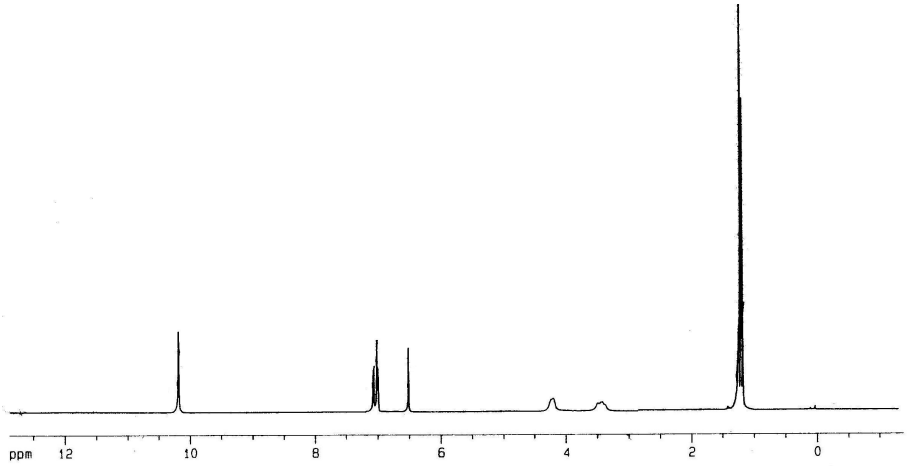


Figure 3.2: *^{1}H NMR spectrum of* ***43***

The ^{13}C resonance signal for the carbons to which OH was attached was observed at δ 153.9. The aliphatic signals were found in δ 34.1- 29.8 region (Figure 3.3). The proposed structure was further verified by the MALDI-TOF mass spectrum which showed the $[M+Na]^{+}$ ion peak at 632.06.

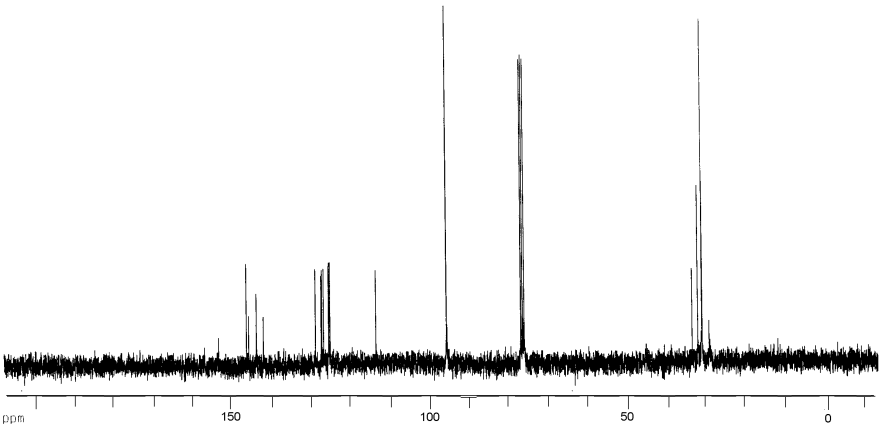


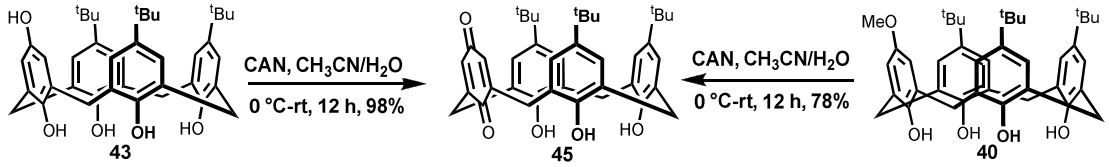
Figure 3.3: *^{13}C NMR spectrum of* ***43***

The structure of the product **44** was also ascertained using various NMR and MALDI-TOF mass spectroscopic techniques. It is noteworthy that the upper rim hydroxyl groups however could not be detected in the ^{1}H NMR spectra of **43** and **44**, probably due to fast flipping of the hydroquinone moiety. In an attempt to arrest the flipping of aryl rings through the annulus and to distinguish the peak due to upper rim hydroxyl groups, low temperature ^{1}H NMR spectra of both the compounds were recorded using CD_2Cl_2 as solvent. However no change in the nature or splitting pattern of any of the peaks was noticed. This observation indicated the dynamic nature of **43** and **44** even at as low a temperature as -60 ^{o}C.

3.3.2 Synthesis of calixmonoquinone and diquinone

Compounds **43** and **44** were unique since they contained one and two hydroquinone moiety respectively in the calix structure and the other aryl rings

contained unprotected phenolic groups. The oxidation of hydroquinone(s) to quinone(s) could be carried out easily using any of the oxidizing agents. The oxidizing agent of our choice was cerium (IV) ammonium nitrate (CAN) [Walker 1991]. CAN is a one-electron oxidizing agent that is used for oxidative addition reactions of electrophilic radicals to alkenes, enabling intermolecular and intramolecular carbon-carbon and carbon-heteroatom bond formation. CAN is also useful as an oxidant for many functional groups (alcohols, phenols and ethers) as well as C-H bonds, especially those that are benzylic. In the redox process Ce(IV) is converted to Ce(III), a one-electron change, signalled by the fading of the solution color from orange to pale yellow (provided that the substrate and product are not strongly colored). Accordingly, a reaction was carried out using **43** with CAN in CH_3CN:H_2O (8:2) mixture at 0 °C. The reaction on work up followed by column chromatography yielded calix[4]monoquinone **45** as a red solid in quantitative yield. The oxidation of **40** using CAN also afforded **45** in 78% yield (Scheme 3.15).



Scheme 3.15: *Synthesis of calix[4]monoquinone **45***

The product **45** was characterized on the basis of spectroscopic data. In the IR spectrum of **45**, a peak at 3259 cm^{-1} corresponding to the –OH absorption and another one at 1647 cm^{-1} corresponding to the carbonyl were observed. In the ^1H NMR spectrum (Figure 3.4), the OH protons were discernible as two singlets at δ 9.13 and 8.88. The aromatic protons appeared as singlets at δ 7.10, 7.03 and 6.89. The signal due to the protons of the quinone was observed at δ 6.68. Two singlets at δ 3.86 and

3.76 were assigned to the bridging methylene protons. The *tert*-butyl protons appeared as two singlets at δ 1.21 and 1.20.

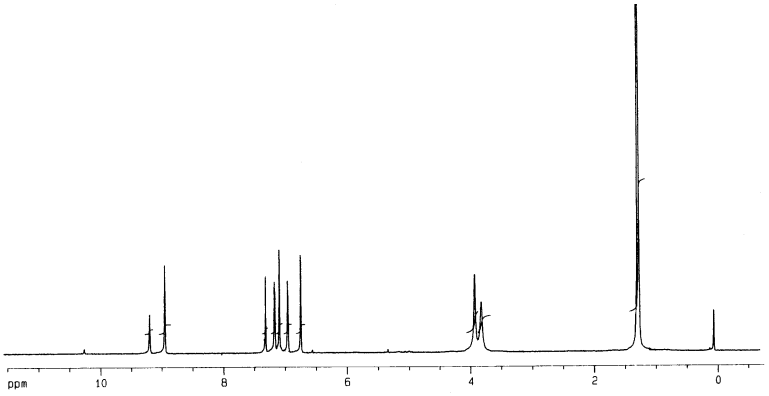


Figure 3.4: *^{1}H NMR spectrum of **45***

The structure was further supported by ^{13}C NMR spectrum (Figure 3.5) showing two carbonyl peaks positioned at δ 190.5 and 187.4. The OH attached carbons resonated at δ 148.2. The structure was further confirmed by satisfactory elemental analysis (Anal. Calcd for $C_{40}H_{46}O_5$: C, 78.19; H, 7.64. Found: C, 78.34; H, 7.91).

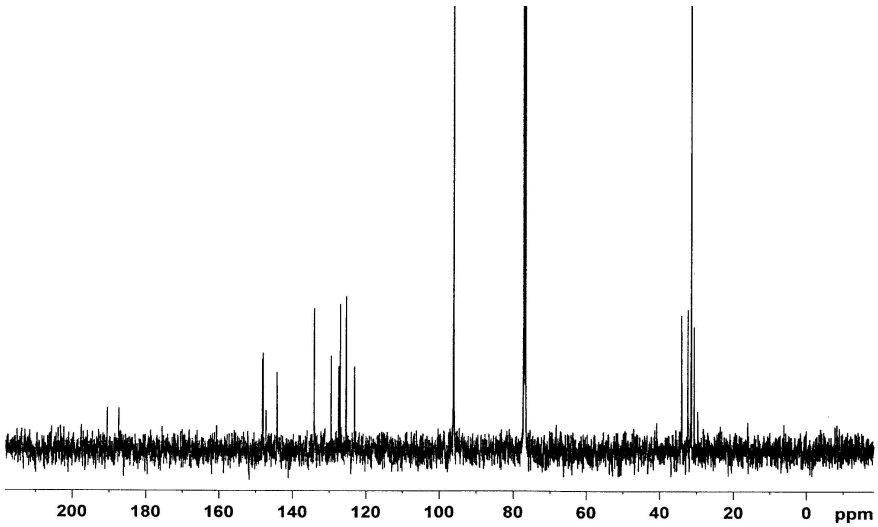
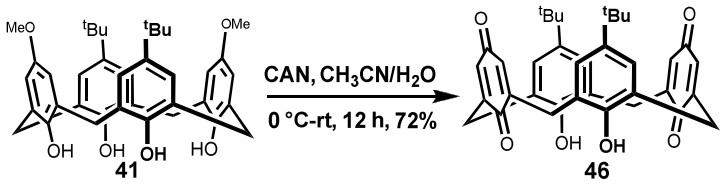


Figure 3.5: *^{13}C NMR spectrum of **45***

Similarly, **41** on oxidation with CAN offered the 1,3-calix[4]diquinone **46** in 72% yield (Scheme 3.16).



Scheme 3.16: *Synthesis of calix[4]diquinone* ***46****.*

The ^{1}H NMR spectrum of **46** showed singlets for all the protons in the compound (Figure 3.6). The OH proton appeared at δ 7.31, the aromatic region showed two peaks at δ 6.89 and 6.68, corresponding to aryl and quinone protons respectively and the *tert*-butyl groups resonated at δ 1.14. Interestingly, the ^{1}H NMR spectrum displayed a broad singlet at δ 3.72 for the methylene protons which suggested fast flipping of the quinone as well as the aromatic rings.

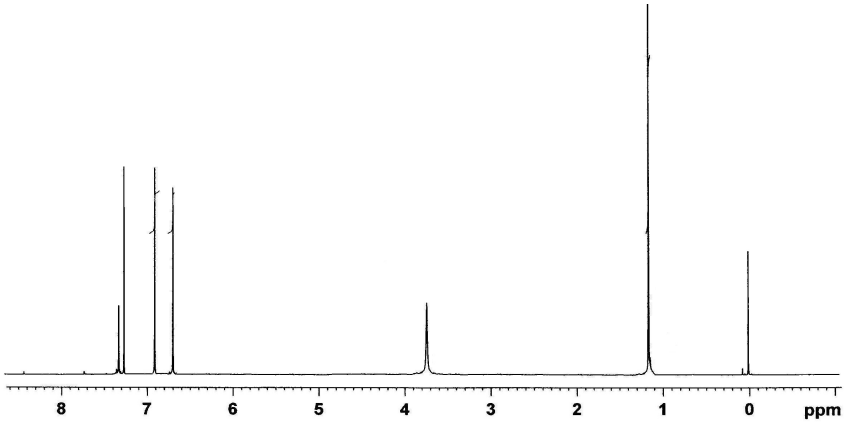


Figure 3.6: *^{1}H NMR spectrum of* ***46***

To understand the conformational preference of **46**, a variable temperature ^{1}H NMR study was conducted and it presented two significant changes as the temperature was lowered from 298 to 223 K (Figure 3.7). A marginal high field shift of 0.33 ppm was observed for the OH protons, which suggested a slight increase in the intramolecular hydrogen bonding. The singlet due to the methylene bridge gradually broadens on cooling before collapsing near 223 K. This observation is a clear indication that **46** is dynamic in solution. Furthermore, the lowering of temperature

could not freeze out the flipping of the quinone and aromatic rings. Thus, calix[4]diquinone possesses a highly mobile structure in solution.

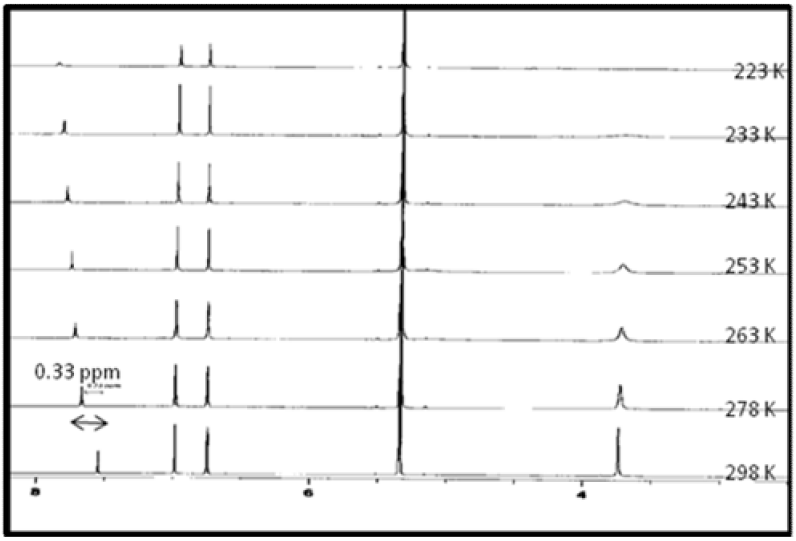


Figure 3.7: *Temperature varied ^{1}H NMR spectra of **46** in CD_2Cl_2, 500 MHz.*

The proposed structure was further supported by ^{13}C NMR spectrum (Figure 3.8) showing two carbonyl peaks positioned at δ 189.0 and 187.5. The sp^2 hybridized carbons resonated in the δ 149.4-125.4 region. The aliphatic signals were observed in the δ 34.1-30.9 region. In the mass spectrum, the $[M+1]^+$ ion peak appeared at 564.86. Satisfactory elemental analysis data also supported the formation of the diquinone.

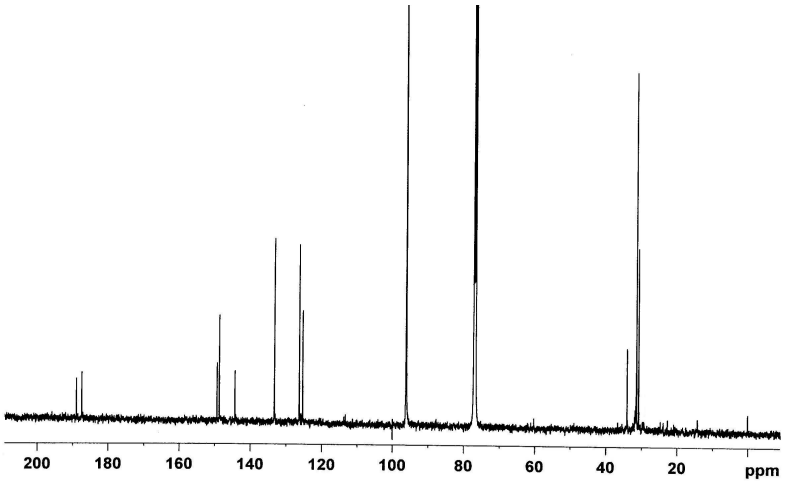


Figure 3.8: *^{13}C NMR spectrum of **46***

Anticipating complexation behaviour of calixquinones towards alkali metal ions [Kaifer *et al.* 1997], ^{1}H NMR titrations with various alkali metal ions were conducted. However, addition of Li^+, Na^+ and K^+ to solution of **45** and **46** (in 4:1 $CDCl_3$:CD_3CN) did not cause any change in their ^{1}H NMR spectra, indicating absence of any complexation between the ligands and the metal ions. The figure 3.9 shows the ^{1}H NMR spectrum of **46** on addition of Na^+, K^+ and Li^+ ions as their perchlorate solutions in CD_3CN.

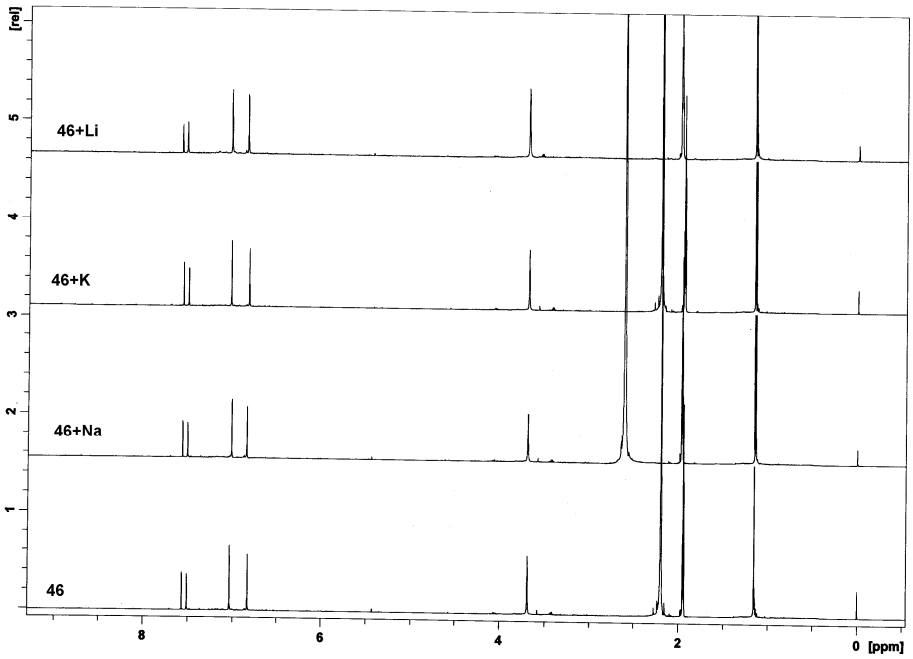


Figure 3.9: *^{1}H NMR spectrum of **46** on addition of alkali metal ions*

The electrochemical properties of **45** and **46** were investigated in dichloromethane:acetonitrile (1:9) using cyclic voltametry with $(^nBu)_4NPF_6$ as the supporting electrolyte. The compound **45** did not give any characteristic peaks of quinone moieties present, as it was highly insoluble in the medium employed. The calixdiquinone **46** (Figure 3.10) showed three redox waves in its voltamogram, two of which were close together and reversible, 2/2' and 3/3', and the other wave, 1, occurring at a less negative potential, being irreversible. In simple calixdiquinones, the redox waves 1 and 2 are considered to be two one-electron process and wave 3 is

considered to be a two-electron process [Beer *et al.* 1997]. The irreversibility of wave 1 may be due to the formation of insoluble hydroquinone species [Bethell *et al.* 1995].

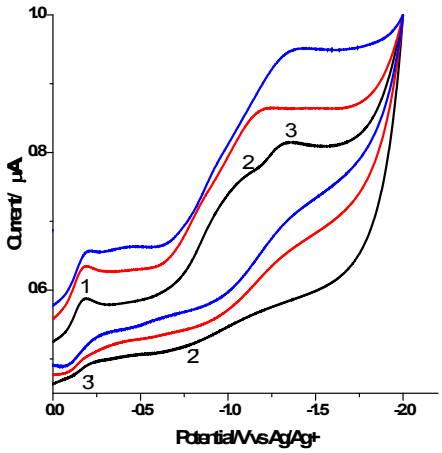
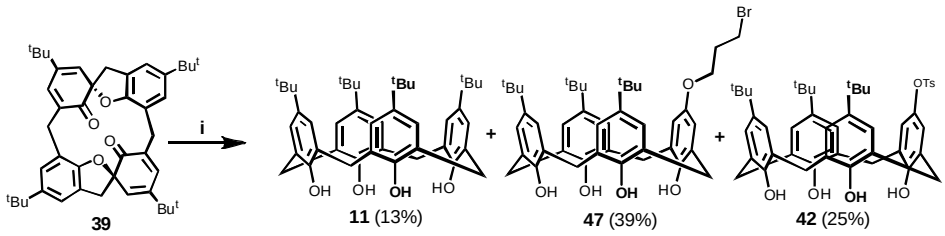


Figure 3.10: *CVs at various scan rates (in the order of increasing amplitude of current: 50, 100, 200 mV s^{-1}) of* ***46*** *(1.4x10^{-3} M) in 1:9 CH_2Cl_2:CH_3CN.*

3.3.3 Click reaction of azidocalixarene with phenyl acetylenes

The upper rim monosubstituted bromopropylcalix[4]arene **47** used as starting material in our investigations was synthesized as follows (Scheme 3.17) [Thulasi *et al.* 2009].

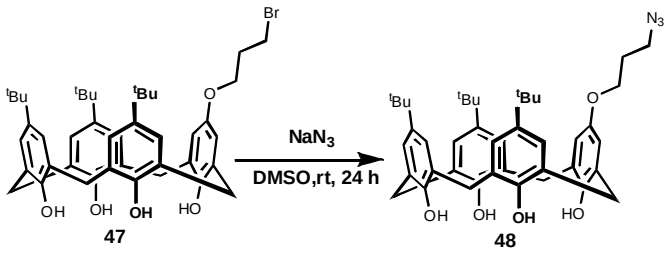


i = 3-bromopropan-1-ol, 5.0 equiv. *p*-TSA, toluene, 110 °C, 6 h.

Scheme 3.17: *Synthesis of bromopropyl substituted calix[4]arene*

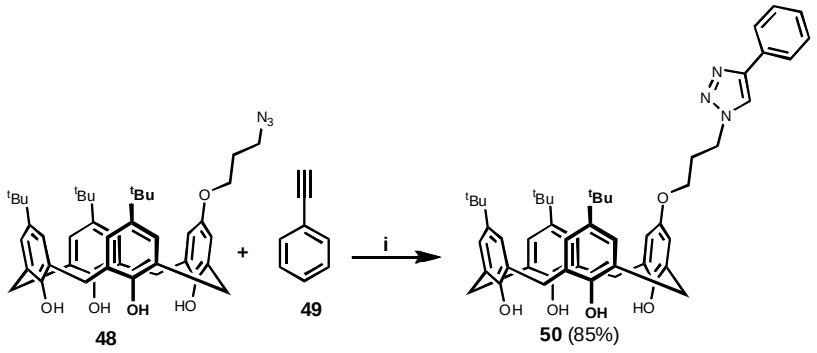
Various phenylacetylenes, the alkyne partners selected for clicking with azidocalixarene were prepared by the Sonogashira reaction of respective bromobenzenes and TMS acetylene using literature procedures [Sonogashira *et al.* 1975]

Preliminary endeavours towards clicking focused on utilizing one-pot *in situ* azide synthesis/'click' protocol reported by van der Eycken *et al.* [Appukuttan and van der Eycken 2002]. Treating bromofunctionalized calixarene **47**, sodium azide and phenyl acetylene **49** in DMSO at 80 ^{o}C for 12 h did not yield the desired click calixarene adducts. All of the starting materials were recovered in good mass balances. Switching to a stepwise protocol, the synthesis of the core starting material **48** was readily undertaken via S_N2 displacement on bromofunctionalized calixarene (Scheme 3.18).



Scheme 3.18: *Reaction of **47** with NaN_3*

With both partners in hand, we next attempted the copper(I) catalyzed [3+2]-dipolar cycloaddition reaction between **48** and **49** utilizing a procedure reported by Rostovtev *et al.* [Rostovtsev et al. 2002] Accordingly, an aqueous *tert*-butyl alcohol (1:1 v/v) solution of **48** and **49** was stirred (96 h) at ambient temperature with copper(II) sulfate and sodium ascorbate. The reaction failed to fetch any product due to solubility problems and the starting materials were recovered unchanged. Even though the solubility problem was alleviated by changing the solvent to aqueous DMF, no reaction ensued, both at ambient and reflux temperature. Solvents like THF, CH_3CN etc. were also used in the presence of CuI and $CuSO_4$/sodium ascorbate combination but without much success. Interestingly, employing $CuSO_4$/sodium ascorbate in *aqueous* ethanol at ambient temperature gave solely the triazole linked calixarene **50** in 85% yield (Scheme 3.19).



i = $CuSO_4$/Na ascorbate, DIPEA, EtOH/H_2O (2:1), rt, 2h.

Scheme 3.19: *Reaction of azidocalixarene with phenylacetylene under 'click' protocol*

The structure **50** was established by IR, ^1H and ^{13}C NMR and mass spectral analyses. The IR spectrum showed strong absorption at 3454 cm^{-1} due to N=N stretching of triazole ring. The significant features of the ^1H NMR spectrum (Figure 3.11) consist of: (a) the appearance of CH proton of the triazole ring at δ 7.41; (b) the presence of signals due to the three -CH_2's at δ 3.90, 3.49, 2.39; (c) the presence of aromatic protons as a multiplet centered at δ 7.04 and as a singlet at δ 6.54.

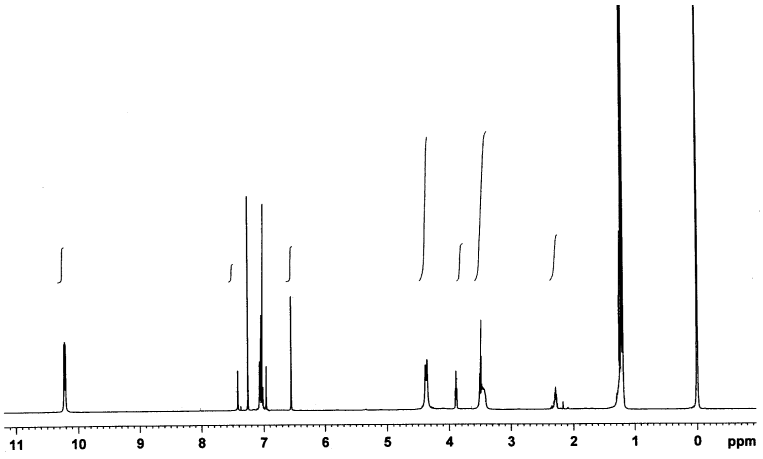


Figure 3.11: *^1H NMR spectrum of the **50***

The ^{13}C NMR spectrum (Figure 3.12) of **50** showed the characteristic peaks as follows: (a) the -OCH_2 and -NCH_2 carbons were visible at δ 65.5 and 46.7; (b) the characteristic signal due to hydroxyl attached carbons of the aromatic moieties appeared at δ 152.9.

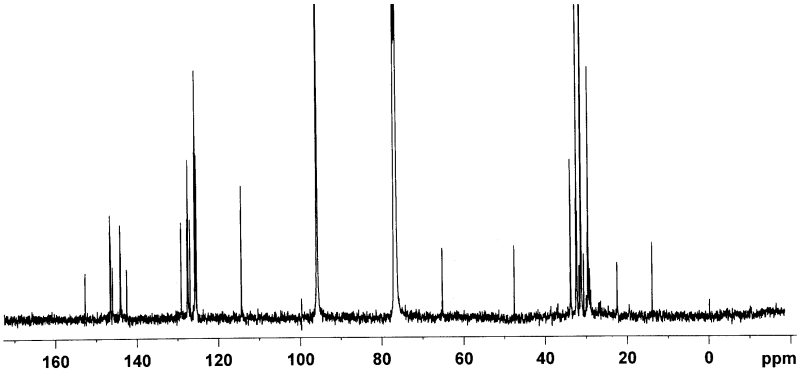
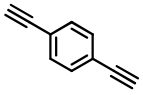
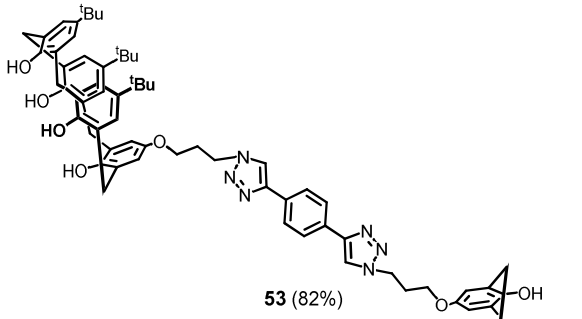
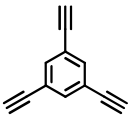
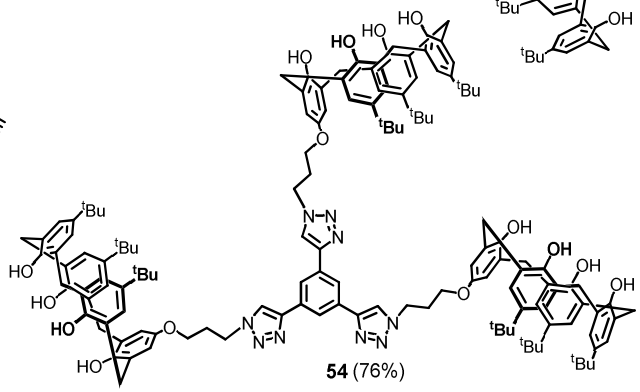


Figure 3.12: *^{13}C NMR spectrum of the cycloadduct **50***

The interesting result obtained with phenylacetylene encouraged us to extend the Cu(I) catalyzed cycloaddition reaction of azidocalixarene **48** to diacetylene and triacetylene benzenes. Accordingly, we attempted the reaction of azidocalixarene with diacetylene benzene **51** and triacetylene benzene **52** under similar conditions. Results revealed that in the above cases the respective triazole appended calixarenes **53** and **54** were obtained as the sole products in excellent yields. The gross structures of both the products were determined by their IR, ^{1}H NMR, ^{13}C NMR and MALDI-TOF analyses.

The details of the above discussed reactions are summarized in table 3.1.

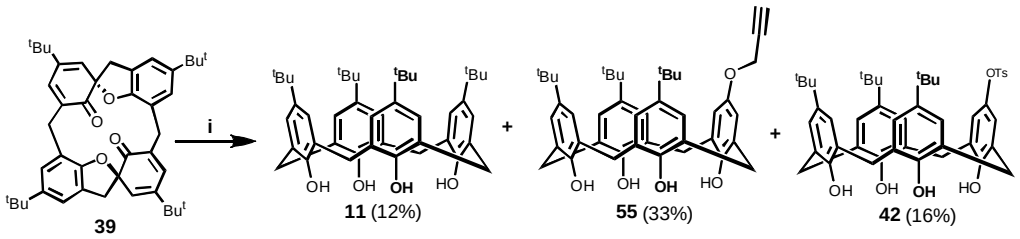
Table 3.1: *Triazole linked calix[4]arene frameworks from* ***48***

Entry	Acetylenes	Products (yield)
1	 **51**	 **53** (82%)
2	 **52**	 **54** (76%)

Reaction conditions: **48**, $CuSO_4$/Na ascorbate, DIPEA, EtOH/H_2O (2:1), rt, 2h

3.3.4 Clicking azidocalixarene and propargylated calixarene

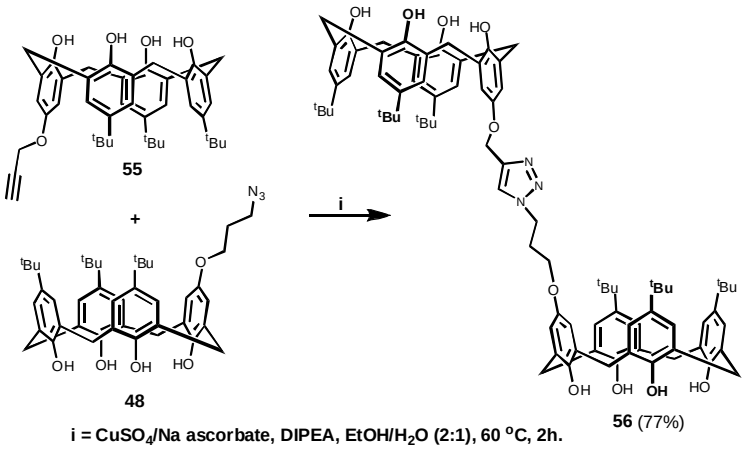
As a follow-up of the investigations described above, it was of interest to study the [2+3]-cycloaddition of azidocalixarene **48** with propargylated calixarene **55** obtained using the same reaction as that of bromopropylated calixarene (Scheme 3.20).



i = propargyl alcohol, 5.0 equiv. *p*-TSA, toluene, 70 °C, 10 min

Scheme 3.20: *Synthesis of propargylated calixarene*

In a prototype experiment, the azidocalixarene **48** was treated with propargylated calixarene **55** in ethanol-water system at room temperature. However the expected reaction did not take place and the starting materials were recovered unchanged. When the same reaction was carried out at 60 ^{o}C, the reaction yielded the expected triazole linked biscalixarene **56** as a single product in 77% yield (Scheme 3.21).



Scheme 3.21: *Cycloaddition reaction between **48** and **55***

The product **56** was identified as a triazole linked biscalixarene on the basis of spectroscopic data. The IR spectrum of the bisadduct **56** showed strong N=N absorption at 3467 cm^{-1} corresponding to the triazole ring. The ^{1}H NMR spectrum of **56** (Figure 3.13) exhibited the triazole proton at δ 7.51 as a singlet. Moreover, the fixed cone conformation of the two calix[4]arene scaffolds was substantiated by the presence of signals for the equatorial and axial protons of the methylene bridges as a broad doublet and a multiplet at δ 4.24 and 3.47, respectively. The OH protons of the two calixarene units appeared as two singlets close to each other at δ 10.23 and 10.21. The signals due to various CH_2 protons appeared at δ 5.03 (singlet), 4.45 (triplet), 3.81 (triplet), 2.29 (multiplet).

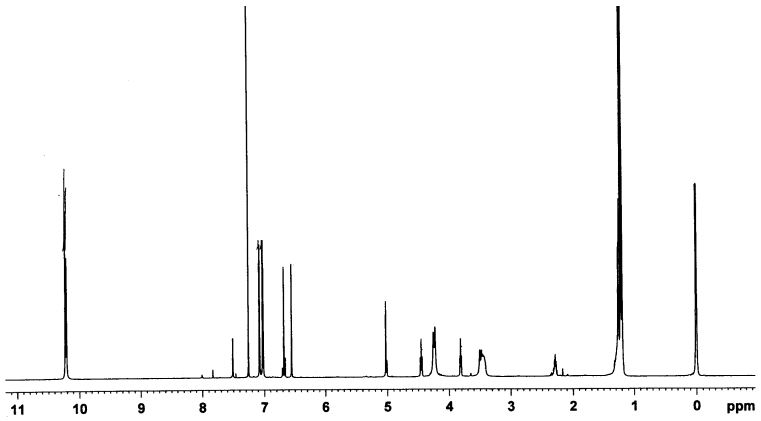


Figure 3.13: *^{1}H NMR spectrum of the compound **56***

The ^{13}C NMR of **56** exhibited a peak at δ 152.7 attributable to carbon to which OH is attached. The aliphatic carbon cluster representing *t*-Bu and bridging methylenes appeared within δ 34.1-22.7 range (Figure 3.14).

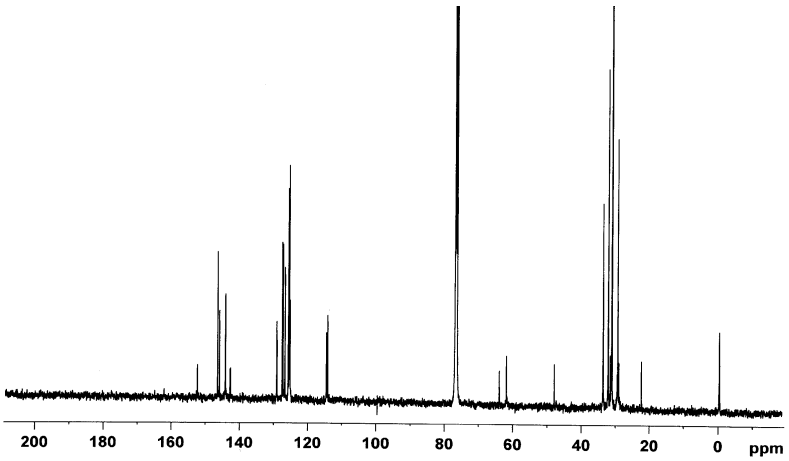


Figure 3.14: *^{13}C NMR spectrum of **56***

The other carbons were assigned with the help of HMQC experiment. Accordingly the two -OCH_2 carbons were assigned to peaks at δ 64.3 and 62.1 and the -NCH_2 carbon to the peak at δ 49.9. The triazole CH appeared immersed in a cluster of aromatic carbons around δ 127.0 (Figure 3.15).

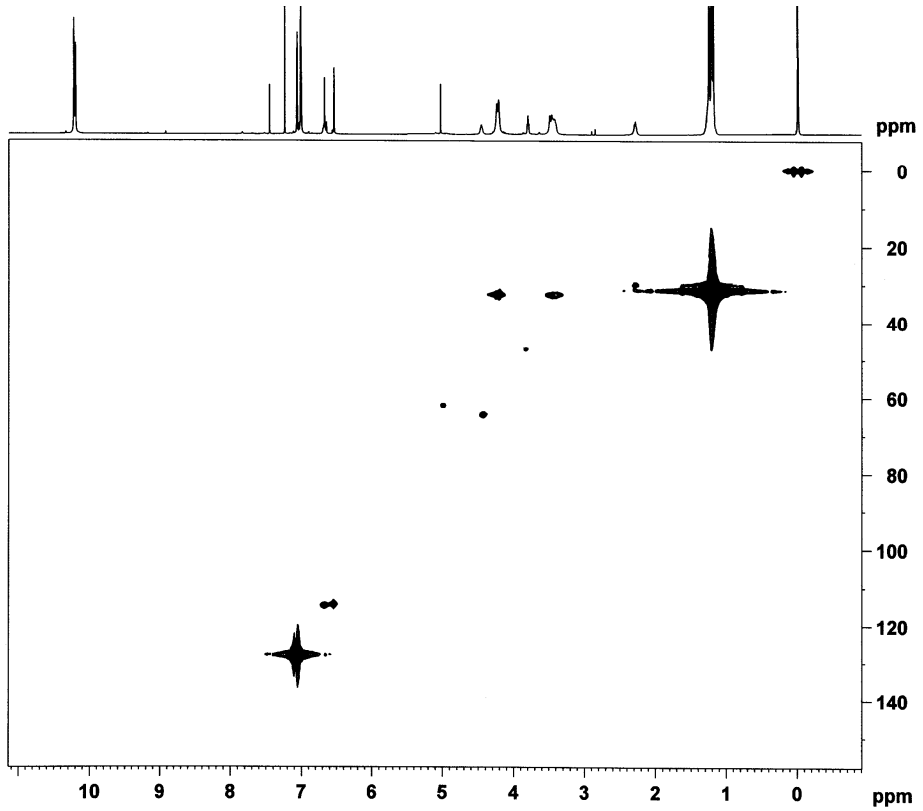


Figure 3.15: *HMQC spectrum of the compound **56***

3.4 Conclusion

This chapter deals with our sincere efforts to explore the synthetic utility of the products obtained by *ipso*-nucleophilic substitution of calix[4]bis(spirodienone) described in chapter 2. Our investigations have unraveled a relatively simple and efficient strategy, starting from monomethoxy- and dimethoxycalix[4]arene, for the synthesis of calix[4]arenes selectively functionalized at the upper rim by hydroxyl groups. A methodology for the highly selective synthesis of calix[4]mono- and diquinones have also been developed.

Our explorations have also led to a relatively simple strategy for the synthesis of head-to-head linked biscalixarenes and triple calixarene from upper rim bromopropyl and propargylated calix[4]arenes using CuAAC chemistry.

Part B

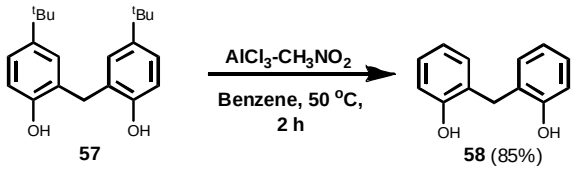
p-TSA Mediated de-*tert*-Butylation of *p*-*tert*-Butylcalix[4]arene and *p*-*tert*-Butylthiacalix[4]arene

3.5 Introduction

Removal of *tert*-butyl groups from the upper rim of calixarenes plays an important role in calixarene chemistry as a large variety of calixarenes with different substitutions in the *p*-positions can be obtained by the subsequent electrophilic reactions. It is fortuitous that *tert*-butyl groups from *p*-*tert*-buytlcalixarenes can be easily removed by a reverse Friedel-Crafts reaction, thereby making the *para*-positions available for subsequent reactions. Besides this method, a super acid catalyzed method has also been described for the purpose of removing the *tert*-butyl groups. The next section outlines a detailed description of both these methods.

3.5.1 $AlCl_3$ catalyzed de-*tert*-butylation

The Lewis acid catalyzed transalkylation was applied to phenols in 1975 by Tashiro and coworkers (Scheme 3.22) [Tashiro *et al.* 1975].

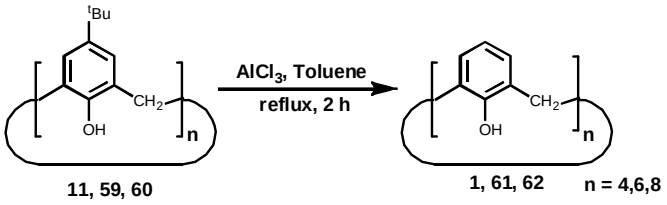


57 **58** (85%)

Scheme 3.22: *Lewis acid mediated transalkylation of dihydroxydiphenylmethanes*

In 1978, the Mainz group [Bohmer *et al.* 1978] adapted the above procedure to calixarenes, thus setting the stage for its subsequent widespread use in calixarene

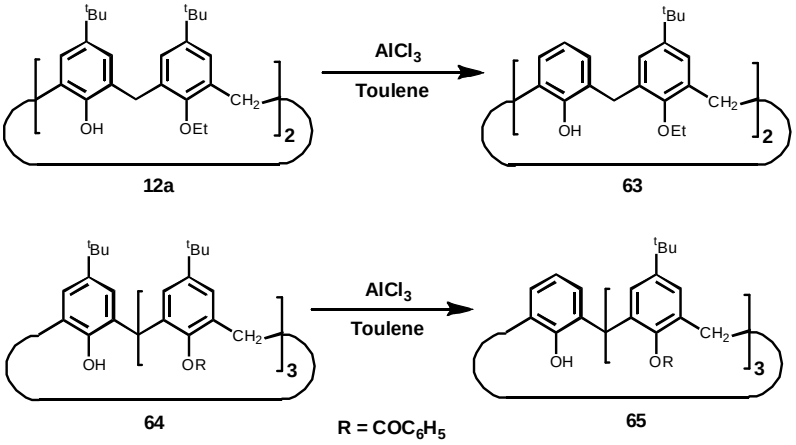
chemistry. Bohmer *et al.* treated *p-tert*-butylcalixarenes **11**, **59** and **60** with $AlCl_3$ in toluene reflux conditions to afford the de-*tert*-butylated calixarenes in good yield (Scheme 3.23).



Scheme 3.23: *De-tert-butylation of calix[n]arenes using $AlCl_3$*

Small amounts of phenol are often added to the de-*tert*-butylating mixture to increase the rate of the reaction, possibly because phenol is a good acceptor molecule and also because, for steric reasons, it may be more effective than calixarenes in generating the H^+ necessary to initiate the reaction.

Besides the standard 4-fold de-*tert*-butylation of *p-tert*-butylcalix[4]arene by $AlCl_3$, Reinhoudt *et al.* were able to remove selectively two *tert*-butyl groups from dialkoxy *p-tert*-butylcalix[4]arene **12a** by making use of the difference in the reactivity between phenols and alkylated phenols (Scheme 3.24) [Gutsche *et al.* 1985].



Scheme 3.24: *Selective de-tert-butylation of p-tert-butylcalix[4]arene*

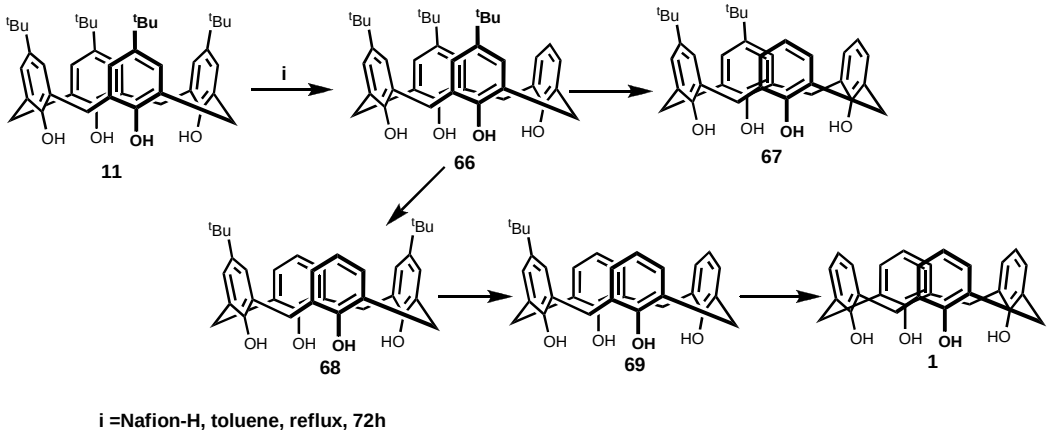
They also demonstrated the dependence of the rate of de-*tert*-butylation on substituents on the phenolic oxygen. For example, the proximate A,B-dimethyl ether

of *p-tert*-butylcalix[4]arene undergoes selective de-*tert*-butylation at C,D rings and tribenzoate **64** loses a single *tert*-butyl group, illustrative of the general phenomenon that *p-tert*-butylphenols are usually more easily dealkylated than their corresponding ethers or esters (Scheme 3.24).

The great disadvantage of Friedel–Crafts dealkylation is the contamination of the alkyl aromatic products with chlorinated compounds. Moreover, the use of $AlCl_3$ is not friendly to the environment from two points of view, namely operation of the unit and deposition of the spent catalyst.

3.5.2 Nafoin-H catalyzed de-*tert*-butylation

In 1998, Chang *et al.* has reported the use of Nafion-H, a superacidic resin for the complete as well as the sequential removal of *tert*-butyl groups from *p-tert*-butylcalix[4]arene (Scheme 3.25) [Rha and Chang 1998].



Scheme 3.25: *Sequential removal of tert-butyl groups using Nafion-H*

3.6 Statement of the problem

It is evident from the above discussion that the synthetic strategies towards de-*tert*-butylation of calixarenes are limited to mainly two procedures: i) the $AlCl_3$ catalyzed transalkylation; ii) Nafion-H catalyzed de-*tert*-butylation. Though $AlCl_3$ catalyzed reaction is widely employed, it offers only 4-fold de-

tert-butylation; synthesis of partially de-*tert*-butylated compounds, often requires the troublesome protection/deprotection procedures employing the lower rim. De-*tert*-butylation procedure with Nafion-H affords fully and partially de-*tert*-butylated calixarenes in 'one-pot'; however it is often marred by strenuous reaction conditions and very lengthy reaction time. In this context, novel synthetic strategies are highly desirable in view of the molecular design of novel supramolecular systems with specific functions by utilizing the characteristics of *p*-*tert*-butyl groups.

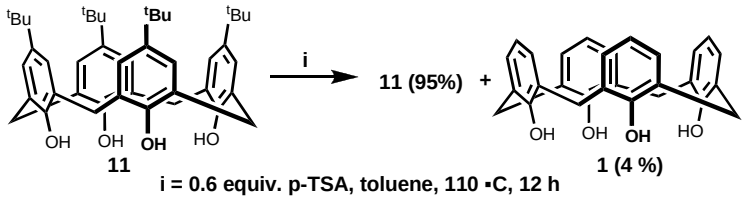
In the initial phase of our study, we presented a detailed account of the reactivity of bis(spirodienone) towards various nucleophiles resulting in the formation of selective upper rim substituted calixarenes. Preceding section (part A) of this chapter had captured the synthetic utilities of the above developed methodology. During our investigation of the nucleophilic substitution of calix[4]bis(spirodienones), we came across an unanticipated finding where both *p*-*tert*-butylcalix[4]arene and *p*-*tert*-butylthiacalix[4]arene can be fully de-*tert*-butylated in excellent yield using *p*-TSA. The results of our findings form the subject matter of the present section.

3.7 Results and discussion

3.7.1 De-*tert*-butylation of *p*-*tert*-butylcalix[4]arene using *p*-TSA

In an initial reaction, *p*-*tert*-butylcalix[4]arene **11** was treated with 0.6 equiv. of *p*-TSA in anhydrous toluene at reflux temperature. After 12 h, the reaction yielded a product along with large excess of unreacted *p*-*tert*-butylcalix[4]arene. After column chromatographic separation, the product obtained in 4% yield was characterized as *p*-

H-calix[4]arene **1** by spectral techniques and comparison with literature data (Scheme 3.26) [Gutsche *et al.* 1985; Rha and Chang 1998].



Scheme 3.26: *Reaction of p-tert-butylcalix[4]arene with 0.6 equiv. of p-TSA.*

The diagnostic spectral features of **1** are as follows. In the IR spectrum, the hydrogen bonded hydroxyl group appeared at 3180 cm^{-1}. In the ^{1}H NMR spectrum (Figure 3.16), the hydroxyl protons appeared at δ 10.19. The aromatic protons appeared as a doublet at δ 7.02 (J = 7.5 Hz) and as a triplet at δ 6.70 (J = 7.5 Hz). Two broad singlets at δ 4.25 and 3.53 were assigned to the methylene bridge protons. The spectrum was conspicuous by the absence of *tert*-butyl protons.

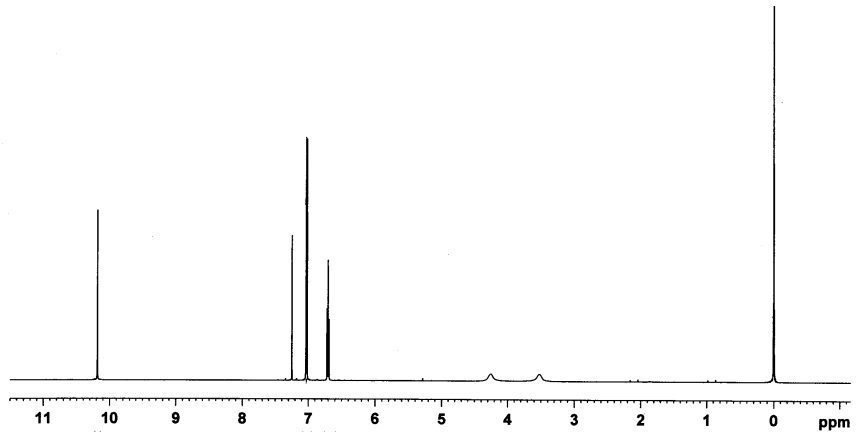


Figure 3.16: *^{1}H NMR spectrum of the compound **1***

In the ^{13}C NMR spectrum (Figure 3.17), the carbons attached to the hydroxyl group resonated at δ 148.8. It displayed 3 signals at δ 128.9, 128.2 and 122.2 corresponding to the carbons of sp^2 hybridization. The signal at δ 31.8 was assigned to the bridging methylenes. The product obtained was further confirmed by mass spectral analysis showing the M^+ ion peak at 424.72 and satisfactory elemental analysis.

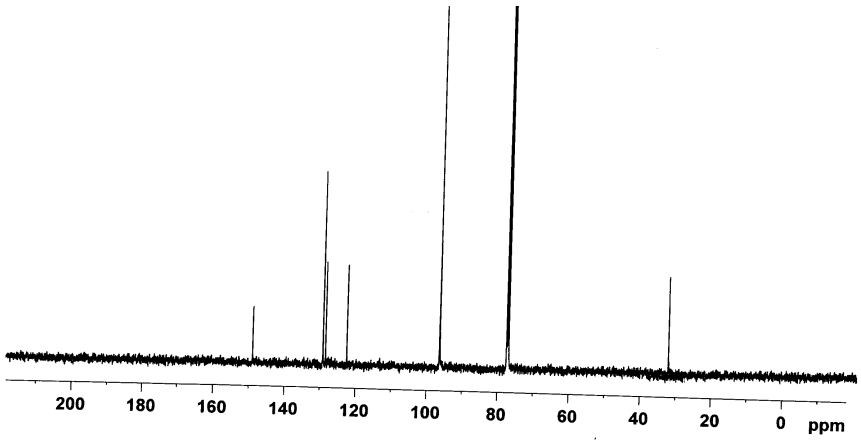
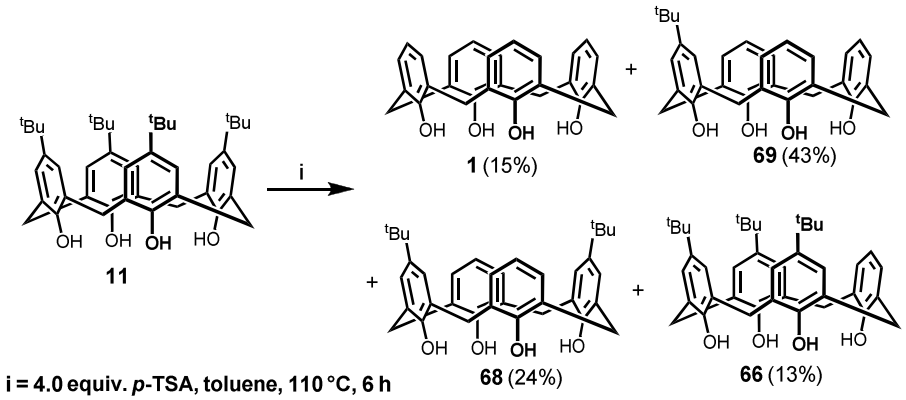


Figure 3.17: *^{13}C NMR spectrum of **1***

Increasing the reaction time to 24 h or increasing the *p*-TSA concentration to 3.0 equiv. did not fetch any significant improvement in yield. When 4.0 equiv. of *p*-TSA was employed under the above reaction conditions, after 6 h, the TLC showed the absence of the starting material (Scheme 3.27). After work up, the ^{1}H NMR analysis of the crude reaction mixture revealed it to be a mixture of four different calix[4]arenes as evidenced by the appearance of four different peaks in the range δ 10.10 - 10.30. These peaks are attributed to the lower rim hydrogen bonded hydroxyls of four different calix[4]arenes.



Scheme 3.27: *Reaction of p-tert-butylcalix[4]arene with 4.0 equiv. of p-TSA*

The four products were separated by recycling HPLC and characterized by spectroscopic methods, as calix[4]arenes having varying numbers of *p-tert*-butyl

groups at the upper rims with tri-de-*tert*-butylated product **69** as the major one in 43 % yield. Varying structures of debutylated calix[4]arenes exhibited characteristic ^{1}H and ^{13}C NMR spectra in their *tert*-butyl, bridging methylene, and aromatic resonances. The compound **1** was identified as *p*-H-calix[4]arene from NMR data. The IR spectrum of **69** showed characteristic absorption at 3174 cm^{-1}, indicating the presence of OH groups. In the ^{1}H NMR spectrum (Figure 3.18), the hydroxyl protons resonated as a singlet at δ 10.27. The aromatic protons were displayed as two multiplets around δ 7.07 and 6.73. The methylene protons appeared as two broad singlets at δ 4.29 and 3.55. The *tert*-butyl group appeared as singlet at δ 1.26.

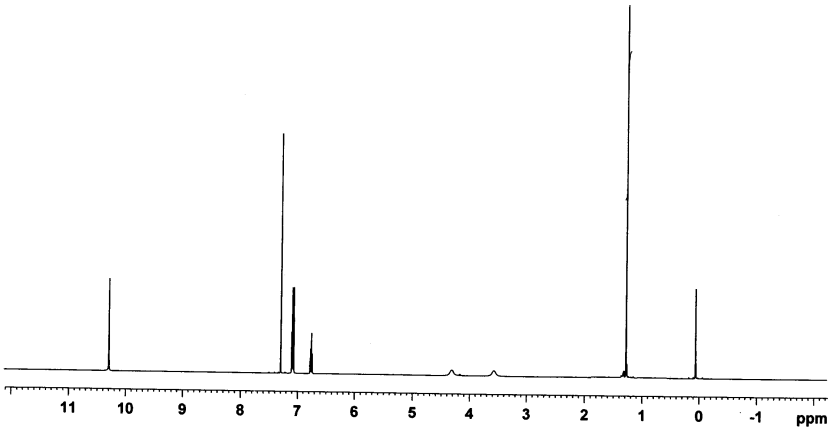


Figure 3.18: *^{1}H NMR of the compound **69***

The ^{13}C NMR spectrum (Figure 3.19) of **69** displayed four peaks at δ 148.9, 148.7, 146.6 and 144.6 which are diagnostic of the aromatic carbon bearing oxygen or *tert*-butyl groups. The spectrum displayed methylene and *tert*-butyl carbons in the region δ 34.1- 31.5.

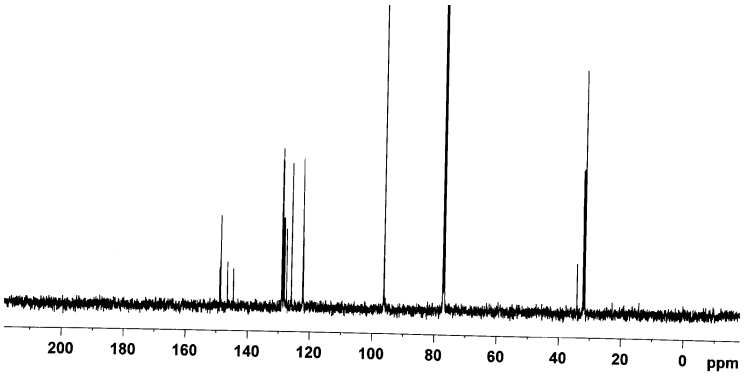


Figure 3.19: *^{13}C NMR spectrum of the compound **69***

The third product obtained in 24% yield was identified to be di-de-*tert*-butylcalix[4]arene **68**. The IR spectrum showed characteristic absorption at 3172 cm^{-1}, indicating the presence of OH groups. In the ^{1}H NMR spectrum (Figure 3.20), the hydroxyl protons were displayed as a singlet at δ 10.26. The aromatic protons appeared as two multiplets at δ 7.03 and 6.70. The methylene protons resonated as two broad doublets at δ 4.26 and 3.50. *tert*-Butyl groups appeared as a singlets at δ 1.22 integrating for 18 protons.

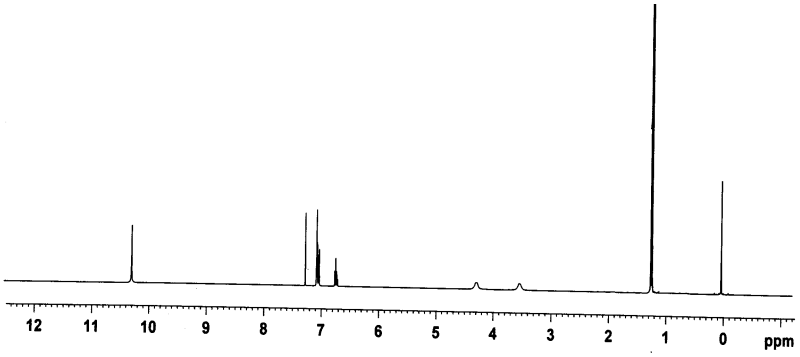


Figure 3.20: *^{1}H NMR spectrum of the compound **68***

The ^{13}C NMR spectrum (Figure 3.21) positioned the carbon to which OH was attached at δ 148.9. The spectrum displayed methylene and *tert*-butyl carbons in the region δ 34.0-31.4. This was supported by mass spectral analysis showing the M^{+} ion peak at 536.88.

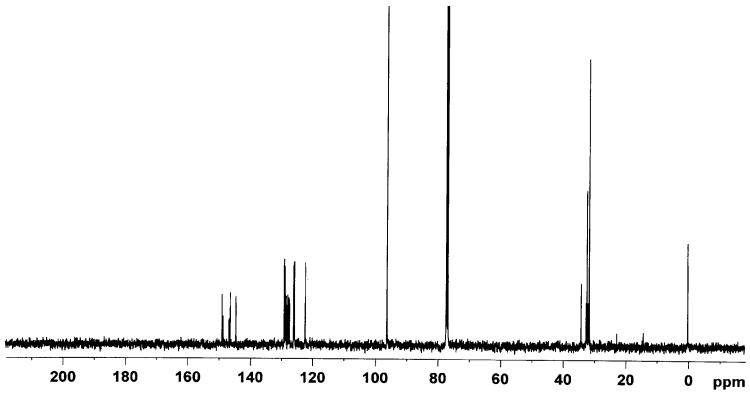


Figure 3.21: *^{13}C NMR spectrum of the compound **68***

The IR spectrum of mono-de-*tert*-butylated calix[4]arene **66** showed characteristic absorption at 3167 cm^{-1}, indicating the presence of OH groups. In the ^{1}H NMR spectrum (Figure 3.22), the hydroxyl protons were displayed as a singlet at δ 10.29. The aromatic protons appeared as a triplet at δ 6.70 and a multiplet at δ 7.02. The methylene protons resonated as a broad singlet at δ 4.25 and a multiplet at δ 3.48. The *tert*-butyl groups appeared as two singlets at δ 1.22 and 1.19 integrating for eighteen and nine protons respectively.

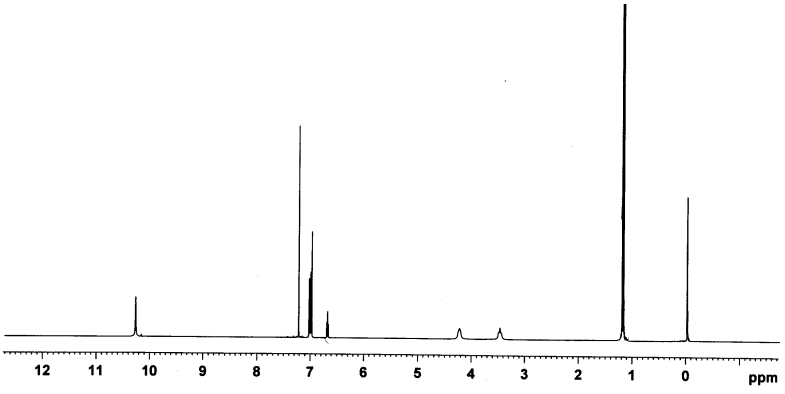


Figure 3.22: *^{1}H NMR spectrum of the compound **66***

The ^{13}C NMR spectrum (Figure 3.23) positioned the carbon to which OH was attached at δ 148.9. The spectrum displayed methylene and *tert*-butyl carbons in the region δ 33.9-31.3. This was supported by mass spectral analysis showing the M^{+} ion peak at 592.92 and satisfactory elemental analysis.

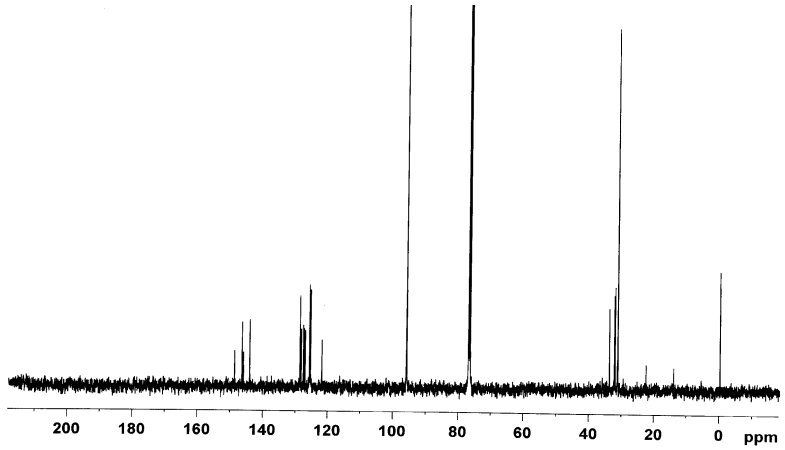


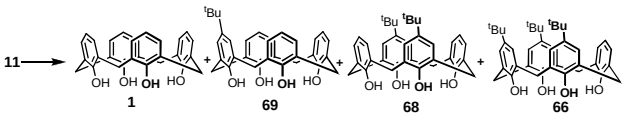
Figure 3.23: *^{13}C NMR spectrum of the compound **66***

It is noteworthy to mention that the reaction affords the highly elusive tri-de-*tert*-butylated calix[4]arene **69** in substantial amount under the optimized condition. In contrast to the Nafion-H catalyzed method, formation of the 1,2-di-*tert*-butylated calix[4]arene was not observed at any point of time in the reaction mixture. To study the effect of other closely related solvents like benzene and xylene, the de-*tert*-butylation reaction were carried out in the respective solvents at their reflux temperatures. While the former reaction fetched no products, the later underwent considerable charring resulting in an intractable mixture. Since attempts at increasing the yield of the products by altering the parameters such as temperature, solvent and reaction time were not successful, we decided to repeat the reaction by increasing the molar equivalence of *p*-TSA used. This was also triggered from our earlier observations, which evidenced that equivalents of *p*-TSA play some role in modulating the outcome of the reaction. The results of the reactions using varying equivalents of *p*-TSA are summarized in table 3.2.

The reaction mixture obtained from the reaction of *p-tert*-butylcalix [4]arene with 5.0 equiv. of *p*-TSA, on subjecting to HPLC yielded two products. The spectroscopic values confirmed the products as tri-de-*tert*-butylated calix[4]arene **69** (23%) and tetra-de-*tert*-butylated calix[4]arene **1** (48%) respectively. Surprisingly, the

formation of **66** and **68** was not observed during the reaction. A similar result was obtained when the reaction was carried out with 6.0 equiv. of *p*-TSA. Thus as the concentration of H^+ ions in the reaction mixture was increased, the tendency of formation of tridealkylated and tetradealkylated product was found to increase indicating the crucial role played by the concentration of protons. When the reaction was performed in the presence of 7.0 equiv. of *p*-TSA, interestingly only the 4-fold debutylated product was formed in 88% yield. On further increasing the concentration of *p*-TSA, no appreciable increase in the yield of the product was observed.

Table 3.2: *Optimization with varying equivalents of p-TSA.*



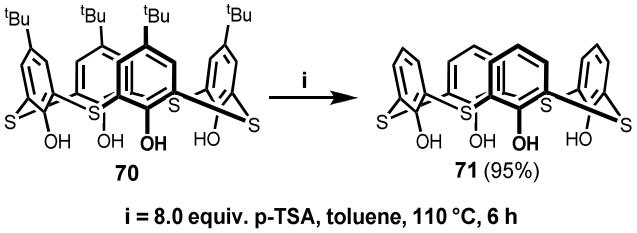
Entry	Equiv.	Yield (%)			
		1	**69**	**68**	**66**
1	0.6	4	-	-	-
2	1.0	5	-	-	-
3	2.0	8	-	-	-
4	3.0	9	-	-	-
5	4.0	15	43	24	13
6	5.0	48	23	-	-
7	6.0	57	28	-	-
8	7.0	87	-	-	-
9	8.0	88	-	-	-

Reaction Conditions: toluene, 110 ▪C, 6 h.

The crucial role played by protons encouraged us to use other acids to achieve detertiarybutylation reactions in p-*tert*-butylcalix[4]arene. Towards this end a number of acids like con. HCl, con. H_2SO_4, CH_3COOH, CF_3COOH were used but none of them gave promising results indicating the role of counter anions in the title reaction.

3.7.2 De-*tert*-butylation of *p-tert*-butylthiacalix[4]arene using *p*-TSA

The interesting results obtained in the reactions concerning de-*tert*- butylation of *p-tert*-butylcalix[4]arene prompted us to employ similar reactions to another important member of calixarene family viz, thiacalix[4]arene. When *p-tert*-butylthiacalix[4]arene **70** was reacted with 8.0 equiv. of *p*-TSA in anhydrous toluene at reflux temperature for 6 h, *p*-H-thiacalix[4]arene **71** was obtained in almost quantitative yield (Scheme 3.28). Treatment of *p-tert*-butylthiacalix[4]arene with lower concentrations of *p*-TSA under similar reaction conditions resulted in the formation of complicated reaction mixtures. This might be due to the attack of protons from the acid at the sulphur bridges.



Scheme 3.28: *Reaction of p-tert-butylthiacalix[4]arene with 8.0 equiv. of p-TSA*

The IR spectrum of **71** showed broad absorption at 3175 cm^{-1} corresponding to the hydroxyl group. The salient features of the ^1H NMR spectrum (Figure 3.24) include: (a) the signal due to the hydroxyl protons at δ 9.45; (b) the aromatic protons appearing as a doublet at δ 7.59 (J = 7.5 Hz) and as an uneven triplet at δ 6.74 (J_1 = 7.8 Hz, J_2 = 7.5 Hz).

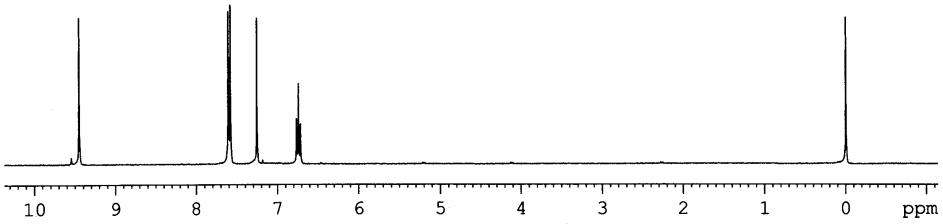


Figure 3.24: *^{1}H NMR spectrum of the compound **71***

The ^{13}C NMR spectrum (Figure 3.25) positioned the hydroxyl bonded carbons at δ 165.7. The other sp^2 hybridized carbons were seen as three signals at δ 125.3, 124.9 and 116.9. The structure was further confirmed by mass spectral analysis showing the $[M]^+$ peak at 496.35 and satisfactory elemental analysis.

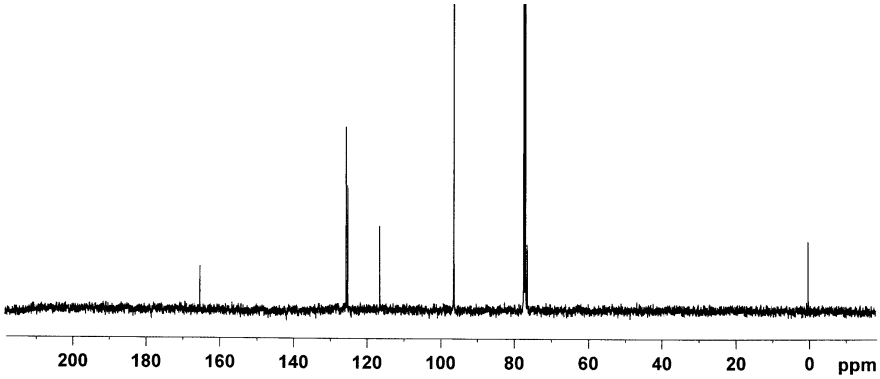


Figure 3.25: *^{13}C NMR spectrum of the compound **71***

On comparison with the $AlCl_3$ [Hamada *et al.* 2000] mediated de-*tert*-butylation of *p*-*tert*-butylthiacalix[4]arene, this method offers better yield of the 4-fold de-*tert*-butylated thiacalix[4]arene at milder reaction conditions.

3.8 Conclusion

To conclude, the present work describes an alternate route to synthesize fully and partially de-*tert*-butylated calix[4]arenes using *p*-TSA. At an optimum condition, it is also possible to obtain tri-de-*tert*-butylated calix[4]arene in acceptable yield without employing lower rim protection-deprotection strategies as used in the $AlCl_3$ catalyzed method. On comparison with the Nafion-H procedure which requires 72 h for the completion of the reaction, the present methodology is noteworthy in terms of shorter reaction time (6 h). The methodology also offers a very efficient and simple route for the synthesis of *p*-H-thiacalix[4]arene in almost quantitative yield.

3.9 Experimental Details

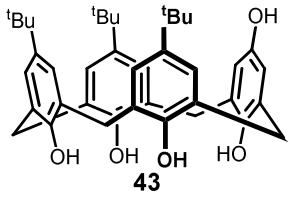
General information about the experiments is given in section 2.5 (Chapter 2).

3.9.1 Procedure for the preparation of 5-methoxy- and 5,17-dimethoxycalix[4]arene

The procedure for the preparation of 5-methoxycalix[4]arene **40** and 5,17-dimethoxycalix[4]arene **41** is given in section 2.5.2.1 (Chapter 2).

3.9.2 Procedure for the preparation of 5-hydroxy-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene

5-Methoxy-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene, **40** (50 mg, 0.08 mmol) dissolved in 10 ml dry dichloromethane was taken in a two necked R.B. flask, cooled in ice-salt mixture (-10 ^{o}C), BBr_3 (30 mg, 0.12 mmol) was added to it over a period of 30 min and the reaction mixture was allowed to stir under argon atmosphere for 3 h (0 $^{\circ}$C). The completion of the reaction was tested by TLC. The product was obtained after purification by column chromatography [hexane-ethyl acetate (95: 5)] as a colorless mass **43** (36 mg, 75%).



43

R_f: 0.65 (70:30 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3173, 2960, 2858, 1786, 1060 cm^{-1}.

^{1}H NMR: δ 10.20 (s, OH, 4H), 7.04 (m, ArH, 6H), 6.53 (s, ArH, 2H), 4.10 (broad s, $ArCH_2Ar$, 4H), 3.32 (broad s, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H), one of the OH protons could not be detected.

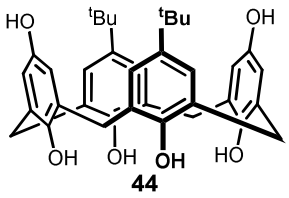
^{13}C NMR: δ 153.9 (C-OH), 146.9, 146.3, 144.4, 144.3, 142.6, 129.4, 127.9, 127.7, 127.3, 126.0,

125.9, 125.6, 113.9 (Ar-C), 34.1, 32.6, 31.6, 31.5, 29.8 ($ArCH_2Ar$, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{40}H_{48}O_5$, $(M+Na)^+$: 631.81; Found: 632.06.

3.9.3 Procedure for the preparation of 5,17-dihydroxy-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene

5,17-Dimethoxy-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene, **41** (50 mg, 0.09 mmol) dissolved in 10 ml dry dichloromethane was taken in a two necked R.B. flask, cooled in ice-salt mixture (-10 ^oC), BBr_3 (87 mg, 0.35 mmol) was added to it over a period of 30 min and the reaction mixture was allowed to stir under argon atmosphere for 3 h (0 ^oC). The completion of the reaction was tested by TLC. The product was obtained after purification by column chromatography [hexane-ethyl acetate (93:7)] as a colorless mass **44** (34 mg, 72%).



44

R_f: 0.60 (70:30 hexane-ethyl acetate).

IR (KBr) υ_{max}: 3172, 2960, 2860, 1786, 1060 cm^{-1}.

^{1}H NMR: δ 10.14 (s, OH, 4H), 7.06 (s, ArH, 4H), 6.52 (s, ArH, 4H), 4.22 (d, *J* = 13.8 Hz, $ArCH_2Ar$, 4H), 3.45 (broad s, $ArCH_2Ar$, 4H), 1.24 (s, *t*-Bu, 18H), two of the OH protons could not be detected.

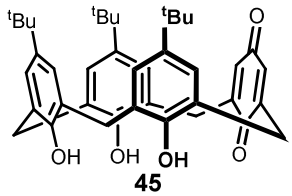
^{13}C NMR: δ 154.7 (C-OH), 147.2, 144.0, 143.4, 142.6, 132.4, 130.8, 129.8, 129.2, 128.8, 128.3, 128.1, 127.3, 125.7, 114.1 (Ar-C), 34.1, 32.3, 30.6, 27.7, 19.2 ($ArCH_2Ar$, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{36}H_{40}O_6$,

$(M+Na)^+$: 591.28; Found: 591.77.

3.9.4 Procedure for the synthesis of calix[4]monoquinone 45

To 5-hydroxycalix[4]arene **43** (25 mg, 0.04 mmol) dissolved in minimum amount of dichloromethane, CH_3CN (8 mL)-H_2O (2 mL) mixture was added and cooled to 0 °C. CAN (45 mg, 0.08 mmol) dissolved in CH_3CN (6 mL)-H_2O(4 mL) mixture was added over a period of one hour, stirred at 0 °C for 12 h. The completion of the reaction was checked using TLC. The color of the reaction mixture turned from light yellow to dark red. Solvent was removed under reduced pressure. The solid mass obtained was extracted with dichloromethane and dried over anhydrous sodium sulfate. The residue obtained after removal of the solvent was purified by column chromatography [hexane-ethyl acetate (80:20)] to afford **45** as a red crystalline solid (24 mg, 98%).



45

R_f: 0.69 (70:30 hexane-ethyl acetate).

Mp: 330-334 °C.

IR (KBr) υ_{max}: 3259, 2956, 1647, 1485 cm^{-1}.

^{1}H NMR: δ 9.13 (s, OH, 1H), 8.88 (s, OH, 2H), 7.10 (d, *J* = 2.0 Hz, ArH, 2H), 7.03 (s, ArH, 2H), 6.89 (d, *J* = 2.0 Hz, ArH, 2H), 6.68 (s, quinoneH, 2H), 3.86 (s, $ArCH_2Ar$, 4H), 3.76 (s, $ArCH_2Ar$, 4H), 1.21 (s, *t*-Bu, 18 H), 1.20 (s, *t*-Bu, 9H).

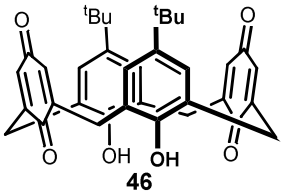
^{13}C NMR: δ 190.5, 187.4 (C=O), 148.2, 148.0 (C-OH), 147.2, 144.3, 144.1, 134.2, 129.6, 127.5, 127.1, 125.5, 123.2 (Ar-C), 34.1, 34.0, 32.4, 31.5, 31.4, 30.7 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{40}H_{46}O_5$, $[M+1]^+$: 607.33; Found: 607.34.

Elemental Analysis calculated for $C_{40}H_{46}O_5$: C, 78.19; H, 7.64. Found: C, 78.34; H, 7.91.

3.9.5 Procedure for the synthesis of calix[4]diquinone 46

To 5,17-dimethoxycalix[4]arene **41** (25 mg, 0.04 mmol) dissolved in minimum amount of dichloromethane, CH_3CN (8 mL)-H_2O (2 mL) mixture was added and cooled to 0 °C. CAN (45 mg, 0.08 mmol) dissolved in CH_3CN (6 mL)-H_2O(4 mL) mixture was added over a period of 1 h, stirred at 0 °C for 12 h. The completion of the reaction was checked using TLC. The color of the reaction mixture turned from light yellow to dark red. Solvent was removed under reduced pressure. The solid mass obtained was extracted with dichloromethane and dried over anhydrous sodium sulfate. The residue obtained after removal of the solvent was purified by column chromatography [hexane-ethyl acetate (60:40)] to afford **46** as a red crystalline solid (17 mg, 72%).



46

R_f: 0.71 (70:30 hexane-ethyl acetate).

Mp: 330-334 °C

IR (KBr) υ_{max}: 3266, 2978, 1650, 1470 cm^{-1}.

^{1}H NMR: δ 7.31 (s, OH, 2H), 6.89 (s, ArH, 4H), 6.68 (s, quinone H, 4H), 3.72 (s, $ArCH_2Ar$, 8H), 1.14 (s, t-Bu, 18H).

^{13}C NMR: δ 189.0, 187.5 (C=O), 149.4 (C-OH), 148.8, 144.4, 133.3, 126.4, 125.4 (Ar-C), 34.1, 31.9, 31.5, 30.9 ($ArCH_2Ar$, *t*-Bu).

MS (FAB): Calcd for $C_{36}H_{36}O_6$, $[M+1]^+$: 564.25; Found: 564.86.

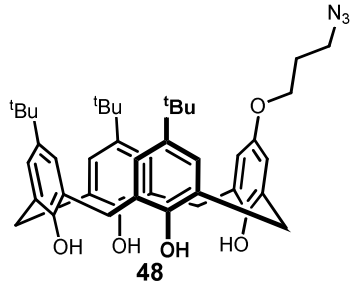
Elemental Analysis calculated for $C_{36}H_{36}O_6$: C, 76.57; H, 6.48. Found: C, 76.53; H, 6.45.

3.9.6 Procedure for the reaction of calix[4]bis(spirodienone) with 3-bromopropan-1-ol

The procedure for the reaction is given in section 2.5.2.1 (Chapter 2).

3.9.7 Procedure for the synthesis of azidocalixarene 48

To a solution of **47** (50 mg, 0.07 mmol) in 2 mL dichloromethane was added a 0.5 M solution of NaN_3 in DMSO (20 mL) and stirred at 25 ^oC for 2 days. The reaction was quenched with water (10 mL) and stirred until it cooled to room temperature. The reaction mixture was washed with water (2x20 mL) and once with brine (10 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and the solvent removed under vacuum to alkyl azide **48** in almost quantitative yield (93 mg, 99%).



48

R_f: 0.86 (80:20 hexane-ethyl acetate).

Mp: Decomposed >230 °C.

IR (KBr) υ_{max}: 2960, 2102, 1814, 1358, 1060 cm^{-1}.

^{1}H NMR: δ 10.22 (s, OH, 4H), 7.06 (m, ArH, 6H), 6.43 (s, ArH, 2H), 4.23 (broad s, $ArCH_2Ar$, 4H), 3.86 (uneven t, $-OCH_2$, 2H), 3.50 (m, $ArCH_2Ar$, CH_2, 6H), 2.13 (m, $-CH_2$, 2H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 156.2 (C-OH), 149.8, 149.1, 146.2, 144.3, 131.1, 129.7, 129.5, 129.1, 128.8, 127.7, 127.4, 116.3 (Ar-C), 63.4, 56.9, 34.1, 32.6, 31.6, 31.5, 15.1 ($ArCH_2Ar$, $-CH_2$'s, t-Bu).

MS (FAB): Calcd for $C_{43}H_{53}N_3O_5$, $[M+1]^+$: 692.89; Found: 692.96

Elemental Analysis calculated for $C_{43}H_{53}N_3O_5$: C, 74.64; H, 7.72; N, 6.07. Found: C, 74.83; H, 7.35; N, 5.98.

3.9.8 Typical procedure for the preparation of phenylacetylenes

To a mixture of bromobenzene, $PdCl_2(PPh_3)_2$ (10 mol %), CuI (20 mol %), and PPh_3 (20 mol %) under an argon atmosphere were added Et_3N (30 mL) and then a solution of TMS acetylene in Et_3N (10 mL). The resulting mixture was stirred at refluxing temperature for 24 h. After evaporation of Et_3N, the residue was triturated with $CHCl_3$ and filtered. The filtrate was partitioned between $CHCl_3$ and H_2O, where the aqueous layer was neutralized with diluted HCl. The organic layer was washed with H_2O and brine and dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was subjected to column chromatography on silica gel eluted with hexane-$CHCl_3$ (1.7:1) to give slightly crude phenylacetylenes substituted by TMS. The TMS group was deprotected using tetrabutylammonium fluoride to afford phenylacetylenes in excellent yield.

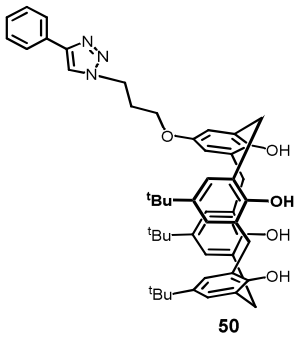
3.9.9 General Procedure for the click reaction between azidocalixarene and phenylacetylenes

Phenylacetylene, $CuSO_4.5H_2O$, sodium ascorbate and DIPEA were added to a solution of azidocalixarene **48** in 2:1 EtOH/H_2O (20 ml) mixtures. The mixture was stirred at ambient temperature for 2 h, when the TLC indicated the absence of

azidocalixarene. Evaporation of solvent followed by work up using $CHCl_3/H_2O$ yielded a crude mixture. The solid mass obtained was purified by column chromatography in hexane-ethyl acetate solvent system.

3.9.9.1 Reaction of azidocalixarene 48 with phenylacetylene 49

Following the general procedure, phenylacetylene **49** (15.0 mg, 0.14 mmol), $CuSO_4.5H_2O$ (0.2 mg, 1 mol%), sodium ascorbate (2.0 mg, 5 mol%) and DIPEA (44.0 mg, 0.43 mmol) were added to a solution of azidocalixaene **48** (100.0 mg, 0.14 mmol) in 20 ml $EtOH/H_2O$ (2:1) and stirred at room temperature for 2 h. The reaction afforded the product **50** as a yellow solid (97 mg, 85%).



50

R_f: 0.64 (70:30 hexane-ethyl acetate).

Mp: >250 °C.

IR (KBr) υ_{max}: 3428, 3255, 1635, 1392, 1284, 1144, 984cm^{-1}.

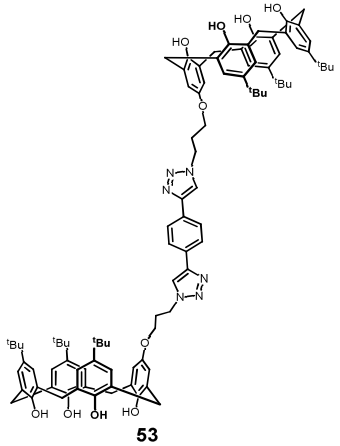
^{1}H NMR: δ 10.21 (s, OH, 4H), 7.41 (s, triazole CH, 1H), 7.04 (m, ArH, 11H), 6.54 (s, ArH, 2H), 4.25 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 3.90 (t, *J* = 6.0 Hz, $-OCH_2$, 2H), 3.49 (m, $ArCH_2Ar$, $-CH_2$, 6H), 2.39 (m, $-CH_2$, 2H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 152.9 (C-OH), 146.8, 146.7, 146.3, 144.4, 144.2, 129.4, 127.9, 127.7, 126.0, 125.8, 125.6, 114.6 (Ar-C), 65.5, 46.7, 34.1, 34.0, 32.8, 32.7, 32.5, 31.9, 31.5, 30.8, 29.8, 29.7, 29.4, 22.7, 14.2 ($ArCH_2Ar$, $-CH_2$'s, t-Bu).

MS (MALDI-TOF): Calcd for $C_{51}H_{59}N_3O_5$, $[M+23]^+$: 817.03; Found: 817.27.

3.9.9.2 Reaction of azidocalixarene 48 with 1,4-diphenylacetylene 51 to yield 53

Following the general procedure, 1,4-diphenylacetylene **51** (15.0 mg, 0.14 mmol), $CuSO_4.5H_2O$ (0.2 mg, 1 mol%), sodium ascorbate (2.0 mg, 5 mol%) and DIPEA (44.0 mg, 0.43 mmol) were added to a solution of azidocalixaene **48** (100.0 mg, 0.14 mmol) in 20 ml EtOH/H_2O (2:1) and stirred at room temperature for 2 h. The reaction afforded the product **53** as a yellow solid (174 mg, 82%).



53

R_f: 0.57 (70:30 hexane-ethyl acetate).

Mp: Decomposed >230 °C.

IR (KBr) υ_{max}: 3456, 2954, 1640, 1484, 1210, 1123, 909 cm^{-1}.

^{1}H NMR: δ 10.21 (s, OH, 8H), 7.85 (s, ArH, 4H), 7.76 (s, triazole CH, 2H), 7.03 (m, ArH, 12H), 6.58 (s, ArH, 4H), 4.56 (t, *J* = 7.0 Hz, -OCH_2, 4H), 4.25 (broad s, $ArCH_2Ar$, 8H), 3.86 (t, *J* = 6.0 Hz, -NCH_2, 4H), 3.46 (m, $ArCH_2Ar$, 8H), 2.29 (m, -CH_2, 4H), 1.23 (s, *t*-Bu, 36H), 1.19 (s, *t*-Bu, 18H).

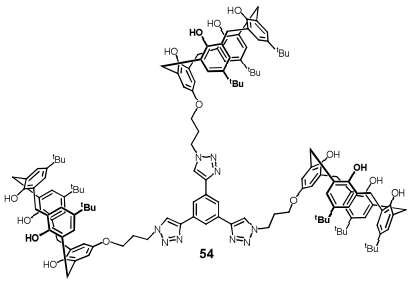
^{13}C NMR: δ 152.8 (C-OH), 146.8, 146.2, 144.5, 129.5, 127.9, 127.7, 126.1, 125.9, 125.6, 120.2, 114.6 (Ar-C), 64.5, 62.1, 34.1, 32.5, 31.5, 31.4, 29.7, 23.7, 15.1 ($ArCH_2Ar$, -CH_2's, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{96}H_{112}N_6O_{10}$,

$[M]^+$: 1531.84; Found: 1532.29.

3.9.9.3 Reaction of azidocalixarene 48 with 1,3,5-triphenylacetylene 52

Following the general procedure, 1,3,5-triacetylenebenzene **52** (4.0 mg, 0.01 mmol), $CuSO_4.5H_2O$ (0.4 mg, 2 mol%), sodium ascorbate (2.0 mg, 10 mol%) and DIPEA (56.0 mg, 0.43 mmol) were added to a solution of azidocalixaene **48** (50.0 mg, 0.14 mmol) in 30 ml $EtOH/H_2O$ (2:1) and stirred at 60 ^oC for 6 h. The reaction afforded the product **54** as a yellow solid (60 mg, 76%).



R_f: 0.48 (70:30 hexane-ethyl acetate).

Mp: Decomposed >230 °C.

IR (KBr) υ_{max}: 3354, 1667, 1440, 1225, 1113, 1038, 788 cm^{-1}.

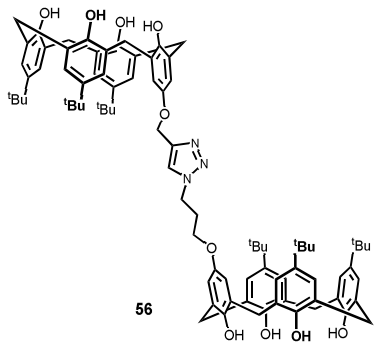
^1H NMR: δ 10.22 (s, OH, 12H), 7.91 (s, ArH, 3H), 7.79 (s, triazole CH, 3H), 7.14 (m, ArH, 18H), 6.62 (s, ArH, 6H), 4.58 (t, *J* = 7.2 Hz, -OCH_2, 6H), 4.26 (broad s, $ArCH_2Ar$, 12H), 3.92 (t, *J* = 6.1 Hz, -NCH_2, 2H), 3.50 (m, $ArCH_2Ar$, 12H), 2.35 (m, -CH_2, 6H), 1.25 (s, *t*-Bu, 54 H), 1.19 (s, *t*-Bu, 27H).

^{13}C NMR: δ 153.2 (C-OH), 147.3, 146.8, 145.3, 129.6, 128.1, 127.5, 126.5, 126.1, 125.1, 122.4, 116.3 (Ar-C), 65.3, 62.4, 34.0, 32.1, 31.2, 29.5, 22.1, 15.3 ($ArCH_2Ar$, -CH_2's, *t*-Bu).

MS (MALDI-TOF): Calcd for $C_{141}H_{165}N_9O_{15}$, $[M+1]^+$: 2225.26; Found: 2225.54.

3.9.9.4 Reaction of azidocalixarene 48 with upper rim monopropargylcalix[4]arene 55 to yield 56

Following the general procedure, monopropargylated calix[4]arene **55** (23.0 mg, 0.04 mmol), $CuSO_4.5H_2O$ (0.1 mg, 1 mol%), sodium ascorbate (0.4 mg, 5 mol%) and DIPEA (14.0 mg, 0.12 mmol) were added to a solution of azidocalixaene **48** (25.0 mg, 0.14 mmol) in 20 ml $EtOH/H_2O$ (2:1) and stirred at 60 ^oC 2 h. The reaction afforded the product **56** as an off-white powder (35 mg, 77%).



56

R_f: 0.54 (70:30 hexane-ethyl acetate).

Mp: Decomposed >230 °C.

IR (KBr) υ_{max}: 3467, 1640, 1484, 1296, 1203, 1123, 1064 cm^{-1}.

^{1}H NMR: δ 10.23 (s, OH, 4H), 10.21 (s, OH, 4H), 7.51 (s, triazole CH, 1H), 7.03 (m, ArH, 12H), 6.68 (s, ArH, 2H), 6.55 (s, ArH, 2H), 5.03 (s, $-OCH_2$, 2H), 4.45 (t, J = 7.5 Hz, $-OCH_2$, 2H), 4.24 (d, J = 13.5 Hz, $ArCH_2Ar$, 8H), 3.81 (t, J = 5.0 Hz, $-NCH_2$, 2H), 3.47 (m, $ArCH_2Ar$, 8H), 2.29 (m, $-CH_2$, 2H), 1.22 & 1.19 (s, *t*-Bu, 54 H).

^{13}C NMR: δ 152.7 (C-OH), 146.8, 146.3, 144.5, 143.2, 143.0, 129.4, 127.9, 127.7, 127.1, 126.1, 125.9, 125.8, 114.9, 114.6 (Ar-C), 64.3, 62.1, 49.9 ($-CH_2$), 34.1, 34.0, 32.5, 31.5, 31.4, 29.7, 22.7 ($ArCH_2Ar$, $-CH_2$, *t*-Bu).

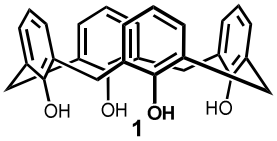
MS (MALDI-TOF): Calcd for $C_{86}H_{103}N_3O_{10}$,

$[M]^+$: 1337.76; Found: 1337.26.

3.9.10 Procedure for the reaction of *p-tert*-butylcalix[4]arene 11 in the presence of 4.0 equiv. of *p*-TSA.

A mixture of *p-tert*-butylcalix[4]arene **11** (100.0 mg, 0.15 mmol) and *p*-TSA (106.0 mg, 0.62 mmol) in toluene was taken in a 50 ml R.B. flask and stirred at reflux temperature (110 °C). The refluxing was continued till the reaction was complete as shown by TLC (~ 6 h). The solvent was removed under reduced pressure. The reaction mixture was worked up using dichloromethane-water mixture and the solid mass obtained was purified by column chromatography. Since column chromatography afforded a mixture of products, the resultant mixture was subjected to High Performance Liquid Chromatography using chloroform as the solvent.

***p*-H-calix[4]arene 1**



1

Yield: 15% as white solid.

R_f: 0.65 (90:10 hexane-ethyl acetate).

Mp: 249 °C

IR (KBr) υ_{max}: 3180, 2931, 2860, 1460, 1249, 908, 840, 694, 648, 563 cm^{-1}.

^{1}H NMR: δ 10.19 (s, OH, 4H), 7.02 (d, *J* = 7.5 Hz, ArH, 8H), 6.70 (t, *J* = 7.5 Hz, ArH, 4H), 4.25 (broad s, $ArCH_2Ar$, 4H), 3.53 (broad s, $ArCH_2Ar$, 4H).

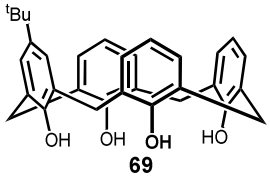
^{13}C NMR: δ 148.8 (C-OH), 128.9, 128.2, 122.2 (Ar-C), 31.8 ($ArCH_2Ar$).

MS (FAB): Calcd for $C_{28}H_{24}O_4$, $[M^+]$: 424.16;

Found: 424.72.

Elemental Analysis Found: C, 79.34; H, 5.88. $C_{28}H_{24}O_4$ requires C, 79.22; H, 5.70.

5,11,17-H-23-(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene 69



69

Yield: 43% as white solid.

R_f: 0.68 (90:10 hexane-ethyl acetate).

Mp: 285-287 ^oC.

IR (KBr) υ_{max} : 3174, 2960, 1598, 1456, 1253, 1244, 908, 839 cm^{-1}.

^{1}H NMR: δ 10.27 (s, OH, 4H), 7.07 (m, ArH, 8H), 6.73 (m, ArH, 3H), 4.29 (broad s, $ArCH_2Ar$, 4H), 3.55 (broad s, $ArCH_2Ar$, 4H), 1.26 (s, *t*-Bu, 9H).

^{13}C NMR: δ 148.9, 148.7, 146.6, 144.6 (C-OH), 129.1, 128.9, 128.5, 128.3, 128.2, 127.5, 125.9, 122.3, 122.1 (Ar-C), 34.1, 32.2, 31.8, 31.5 (*t*-Bu, $ArCH_2$ Ar).

MS (FAB): Calcd for $C_{32}H_{32}O_4$, $[M^+]$: 480.23; Found: 480.63.

Elemental Analysis Found: C, 80.11; H, 6.86. $C_{32}H_{32}O_4$ requires C, 79.97; H, 6.71.

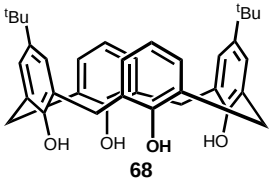
5,17-H-11,23-bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene 68

Yield: 24% as white solid.

R_f: 0.70 (90:10 hexane-ethyl acetate).

Mp: 351-354 ^{o}C.

IR (KBr) υ_{max}: 3172, 2962, 2872, 1481, 1460, 1384, 1255, 908, 837 cm^{-1}.



68

^{1}H NMR: δ 10.26 (s, OH, 4H), 7.03 (m, ArH, 8H), 6.70 (m, ArH, 2H), 4.25 (d, *J* = 9.0 Hz, $ArCH_2Ar$, 4H), 3.49 (d, *J* = 9.5 Hz, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu,18H).

^{13}C NMR: δ 148.9, 148.5, 146.7, 146.3, 144.4 (C-OH); 128.9, 128.6, 128.5, 128.3, 127.8, 127.4, 127.2, 125.9, 125.7, 125.6, 122.2, 122.1 (Ar-C); 34.0, 33.9, 32.4, 32.1, 31.8, 31.4 (*t*-Bu, $ArCH_2Ar$).

MS (FAB): Calcd for $C_{36}H_{40}O_4$, [M^+]: 536.29; Found: 536.88.

Elemental Analysis found: C, 80.71; H, 7.84. $C_{36}H_{40}O_4$ requires C, 80.56; H, 7.51.

5-H-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene 66

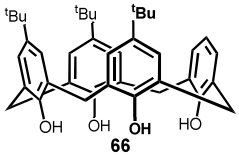
Yield: 13% as white solid.

R_f: 0.73 (90:10 hexane-ethyl acetate).

Mp: 360-364 ^{o}C.

IR (KBr) υ_{max}: 3167, 2960, 2870, 1481, 1460, 1386, 1290, 1244, 908, 875, 827 cm^{-1}.

^{1}H NMR: δ 10.29 (s, OH, 4H), 7.02 (m, ArH, 8H), 6.70 (t, *J* = 7.5 Hz, ArH, 1H), 4.25 (bs, $ArCH_2Ar$,



66

4H), 3.48 (m, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H).

^{13}C NMR: δ 148.9, 146.6, 146.2, 144.3 (C-OH), 128.8, 128.5, 127.8, 127.2, 125.9, 125.8, 125.6, 122.1 (Ar-C), 33.9, 32.5, 32.2, 31.5, 31.4, 31.3 (*t*-Bu, $ArCH_2Ar$).

MS (FAB,): Calcd for $C_{40}H_{48}O_4$, $[M^+]$: 592.35; Found: 592.54.

Elemental Analysis found: C, 81.11; H, 8.45. $C_{40}H_{48}O_4$ requires C, 81.04; H, 8.16.

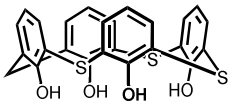
3.9.11 Procedure for the reaction of *p-tert*-butylcalix[4]arene 11 in the presence of 8.0 Equiv. of *p*-TSA.

A mixture of *p-tert*-butylcalix[4]arene **11** (100.0 mg, 0.15 mmol) and *p*-TSA (212.0 mg, 1.23 mmol) in toluene was taken in a 50 ml R.B flask and was stirred at reflux temperature (110 °C). The refluxing was continued till the reaction was complete as shown by TLC (~ 6 h). Then, the solvent was removed under reduced pressure and the residue was subjected to purification by column chromatography on silica gel using 98:2 hexane-ethyl acetate mixture to obtain the de-*tert*-butylated calix[4]arene **1** (57.0 mg, 88%) as a white crystalline solid. m.p.: 249 °C. The spectroscopic details of the compound **1** are given in the above section.

3.9.12 Procedure for the reaction of *p-tert*-butylthiacalix[4]arene 70 in the presence of 8.0 Equiv. of *p*-TSA.

A mixture of *p-tert*-butylthiacalix[4]arene **70** (100.0 mg, 0.14 mmol) and *p*-TSA (191.0 mg, 1.11 mmol) in toluene was taken in a 50 ml R.B flask and stirred at reflux temperature (110 °C). The refluxing was continued till the reaction was

complete as shown by TLC (~ 6 h). Then, the solvent was removed under reduced pressure and the residue was subjected to purification by column chromatography on silica gel using 98:2 hexane-ethyl acetate mixture to obtain the de-*tert*-butylated thiacalix[4]arene **71** (65.0 mg, 95%) as a white crystalline solid. Mp. decomposed > 350 °C.



71

R_f: 0.54 (90:10 hexane-ethyl acetate).

Mp: Decomposed >350 °C.

IR (KBr) υ_{max}: 3175, 2920, 2869, 1472, 1329, 1128, 975, 764, 648 cm^{-1}.

^{1}H NMR: δ 9.45 (s, OH, 4H), 7.59 (d, ArH, J = 7.8 Hz, 8H), 6.74 (uneven t, ArH, J_1 = 7.8 Hz, J_2 = 7.5 Hz, 4H).

^{13}C NMR: δ 165.7 (C-OH), 125.3, 124.9, 116.9 (Ar-C).

MS (FAB,): Calcd for $C_{24}H_{16}O_4S_4$, [M^+]: 495.99; Found: 496.35.

Elemental Analysis found: C, 58.23; H, 3.67, S, 26.34, $C_{24}H_{16}O_4S_4$ requires C, 58.04; H, 3.25; S, 25.83.

3.9.13 Procedure for measuring cyclic voltamogram of 46.

Cyclic voltammetry (CV) measurements were carried out with the model 1100A electrochemical analyzer (CH Instruments). This instrument is a conventional three electrode cell that uses a Pt button working electrode of 2 mm in diameter, Pt wire as the counter electrode, and Ag/AgCl as the reference electrode. The experiment was carried out using 0.1 M Bu_4NPF_6 as the supporting electrolyte under nitrogen gas protection. All electrochemical solutions were degassed with argon and maintained

under an argon atmosphere for the duration of the experiment. A solution of **46** in 9:1 acetonitrile:dichloromethane ($1.4x10^{-3}$ M) was used for the investigation of electrochemistry.

Chapter 4

Synthesis of Novel Upper Rim Isocyanide Functionalized Calix[4]arene and Its Application in Multicomponent Reactions

4.1 Introduction

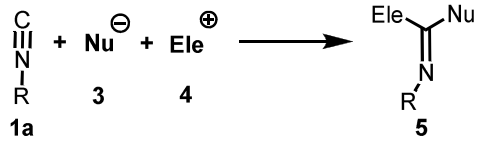
Isocyanides [Ugi 1971] belong to a rare class of organic compounds with a formally divalent carbon. For a long time isocyanides were considered as an unnatural molecule with a vile odour but last century saw a number of natural products containing isocyanide functionality being isolated. Isocyanide chemistry underwent a facelift with the discovery of the monumental Ugi and Passerini reactions. These reactions provided a new approach towards efficient synthesis of highly functionalized compounds and compound libraries. As the focal theme of this chapter is the synthesis of novel calix[4]arenes derivatized at the upper rim with the isocyanide moiety and its application in multicomponent reactions, a brief discussion of the synthesis and chemistry of isocyanide is warranted. Hence the following section outlines a brief account of the same followed by a concise introduction to multicomponent reactions.

4.1.1 Isocyanides

Isocyanides are isoelectronic with carbon monoxide and is shown to be of a linear geometry by electron diffraction and microwave studies [Brockway 1936].

Figure 4.1: *Resonating structures of isocyanide and carbon monoxide*

As opposed to most functional groups in Organic Chemistry, isocyanides react with both nucleophiles and electrophiles at the same atom, the isocyanide carbon, to form a reactive α-adduct intermediate (Scheme 4.1). This dual character is imparted to the isocyanide carbon by the presence of both non-bonding electrons and electron-deficient π-orbitals. The above mentioned α-adduct forms the basis for all of the subsequent rearrangements and product forming steps.

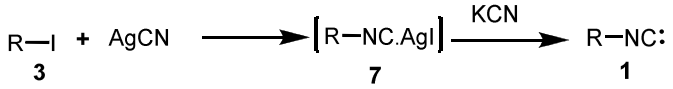


Scheme 4.1: *Dual nature of isocyanides*

4.1.2 Synthesis of isocyanides

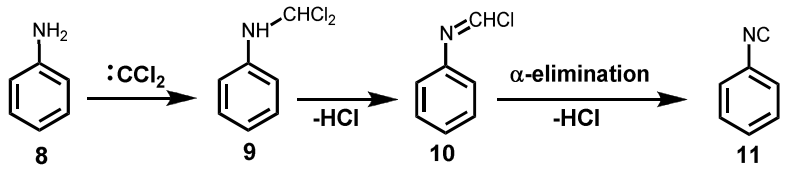
The reason why isocyanides were not used for a long time was neither suspected toxicity nor their vile odour, but rather the lack of accessibility to pure isocyanides. There are various methods available for the synthesis of isocyanides and these are given below.

Although many workers have noticed the formation of a foul smelling product [Lieke 1859] in the reactions of alkyl iodides with silver cyanide, Gautier was the first to recognize the reaction as the formation of an isocyanide. The isocyanide-silver complex formed in the reaction is fragmented to isocyanide by treating with KCN (Scheme 4.2) [Gautier 1867].



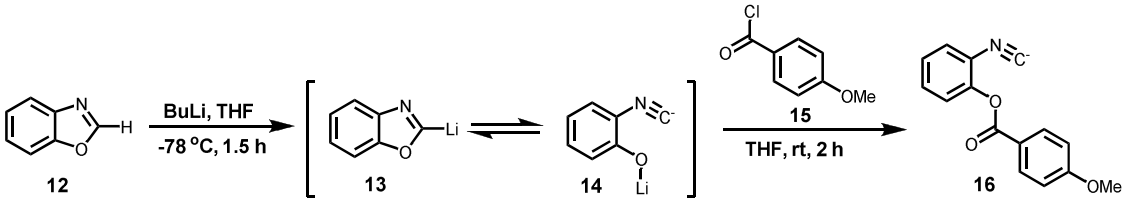
Scheme 4.2: *AgCN mediated synthesis of isocyanide*

Another early method for the synthesis of isocyanide is the carbylamine reaction by Hofmann [Hofmann 1867]. The reaction of primary amines with chloroform in highly basic conditions has been recommended for the quantitative detection of primary amines (Scheme 4.3).



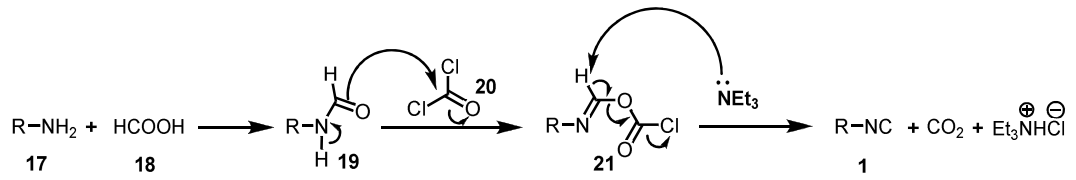
Scheme 4.3: *Hofmann carbylamine reaction*

Isocyanides can also be synthesized by the reaction of organolithium compounds with oxazoles and benzoxazoles (Scheme 4.4) [Michael and Subir 2006]. The benzoxazole **12** gets deprotonated at the second position by *n*-butyllithium. The lithium compound **13** is in chemical equilibrium with isocyanophenolate **14**, which can be captured by an electrophile such as an acid chloride **15**.



SScheme 4.4: *Synthesis of isocyanide from benzoxazoles*

Another synthetic route towards an isocyanide is: 1) condensation of an amine with formic acid, yielding a formamide, and 2) dehydrating this formamide [Skorna and Ugi 1977]. Excellent results were obtained with phosgene/diphosgene in the presence of triethyl amine or phosphorus oxychloride in the presence of diisopropyl amine as illustrated in scheme 4.5.



Scheme 4.5: *Dehydration of N-formamides*

To circumvent the use of phosgene, a variety of dehydrating agents have been introduced in isocyanide synthesis. Thionyl chloride [Ugi and Meyr 1960; Hertler and Corey 1958], *p*-toluenesulfonyl chloride, phosphorus tribromide, triphenylphosphine tribromide and chlorodimethylformiminium chloride (vilsmeier reagent) are some of them used in combination with bases like trialkylamines, pyridine, quinoline, potassium carbonate and potassium *tert*-butoxide.

4.1.3 Multicomponent reactions

Multicomponent reactions (MCRs) [Domling and Ugi 2000] are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. The reactants (also called educts) can be different molecules or different functionalities in a simple compound. In general multicomponent reactions are characterized by their speed, efficiency, convergence, high yields and environmental amiability. By their nature MCRs are by no means restricted to a particular application, but rather they can be used advantageously in any area of modern chemistry based technology. Recent applications of MCRs unrelated to drugs include EPR-spin labelling, bio-compatible materials, e.g. for artificial eye lenses, polymers with novel properties, chiral phases for HPLC, natural products, synthesis of peptides, nucleic acids and agrochemicals.

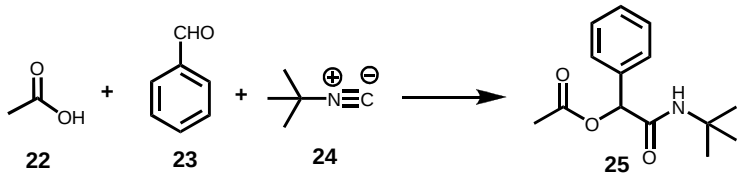
4.1.4 Isocyanide based multicomponent reactions (IMCR)

There are many different types of MCRs, according to different classifications, but among the most useful are isocyanide-based MCRs (IMCR) [Domling 2006]. IMCRs allow for the synthesis of the largest number of different scaffolds. Moreover many of these scaffolds are assembled from commercially available starting materials

thus enabling access to potentially large libraries of compounds through one type of reactions.

4.1.4.1 Passerini reaction

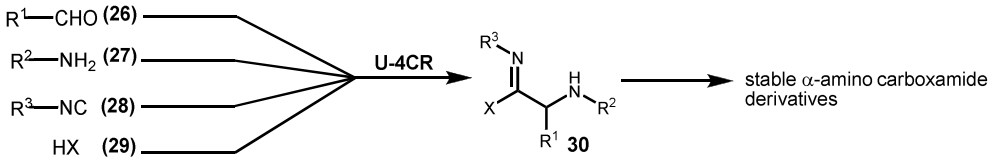
In his seminal work in 1921, Passerini discovered the three component reaction (P-3CR) of electrophilic ketones or aldehydes with isocyanides and carboxylic acids leading to α-acyloxy amides. An illustrative example is given below (Scheme 4.6) [Passerini 1921].



Scheme 4.6: *Three component Passerini reaction*

4.1.4.2 Ugi reaction

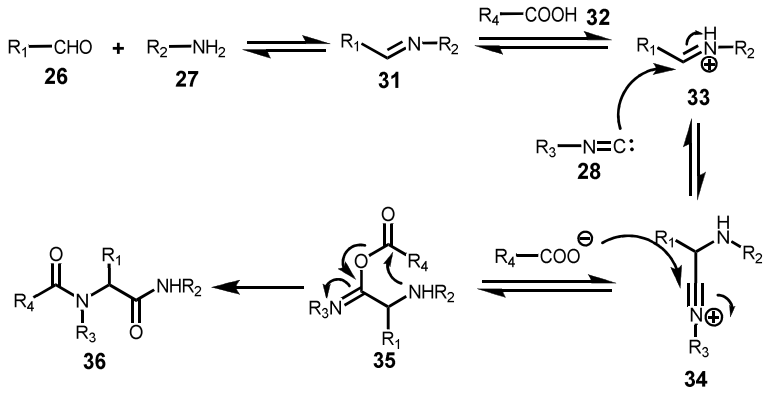
In 1959 Ugi showed that by exposing amines to carbonyl compounds, isocyanides and acids, high yields of α-aminocarboxamide derivatives were obtained (Scheme 4.7) [Ugi *et al.* 1959].



Scheme 4.7: *Ugi four component reaction*

Mechanistic rationale for the formation of the products can be outlined as in scheme 4.8. The acid component protonates the nitrogen atom of the Schiff base, formed from the aldehyde and amine. This electrophilic iminium ion and the nucleophilic acid anion add to the isocyanide carbon atom, to form the α-adduct **35**. The latter can be seen as a heteroanalogue of an acid anhydride. Anhydrides are strong

acylating agents and so are their heteroanalogues. After the intramolecular acylation [Mumm 1910; Mumm *et al.* 1915] of the amine, the stable Ugi product **36** is obtained.



Scheme 4.8: *Mechanism of Ugi reaction*

All the elementary steps of the Ugi reaction sequence are in equilibria, with the exception of the last step. When examined carefully, Ugi reaction is formally a combination of Mannich and Passerini reactions. Its versatility is attributed to the wide variations possible in the reactants and the possibility of different rearrangements. Any known type of C-isocyanide [Zinner *et al.* 1969] can be used as the isocyanide component and the only restriction for the acid component is that it must be able to rearrange irreversibly from the intermediate α-adduct of the isocyanide to deliver a stable product. Except for sterically hindered ketones, most aldehydes and ketones can generally be used as the carbonyl component. Primary and secondary amines, hydrazines and hydroxyl amines can act as the amine component. The U-4CR and related reactions are used extensively in the synthesis of peptides and β-lactum derivatives [Ugi and Marquarding 1982; Ugi *et al.* 1991].

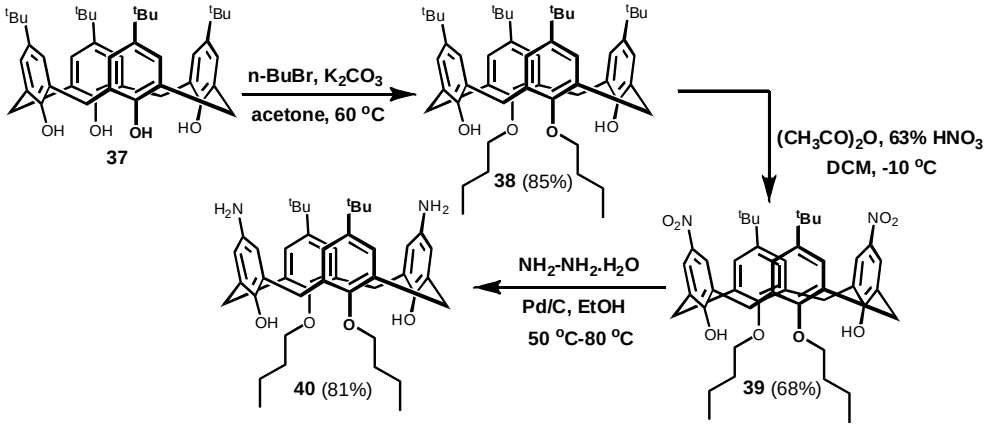
4.2 Statement of the problem

Calixarenes have seen many modifications being carried out at the upper rim, all of which have paved way for the manifold applications for which they are known. However there has not been any attempt to mount an isocyanide moiety onto the

calixarene upper rim. The upper rim modification by introducing an isocyanide group could be an innovative way of embroidering the calixarene. The introduction of isocyanide group makes calixarene a highly functionalized moiety with innumerable possibilities. As already discussed in the previous section, multicomponent reactions provide access to synthesis of "large collections of compounds" referred to as libraries, while requiring only a minimum of effort. The labor efficiency and the access to such enormous chemical structure space is a major driving force behind the recent flurry of activity in MCR research and patent applications. Calixarene chemistry has been relatively untouched by the concept of multicomponent reactions. A large number of multicomponent reactions are possible on the newly introduced isocyanide group which ensures further intricate functionalization of calixarenes in a single step. Sensing an opportunity in this relatively unattended area, we embarked upon a series of investigations for synthesizing isocyanide functionalized calixarenes and to conduct multicomponent reactions with it. In this chapter we describe our preliminary results in this direction.

4.3 Results and discussion

The route towards the synthesis of isocyanide functionalized calix[4]arene starts with selective protection of the lower rim hydroxyl group of *p-tert*-butylcalix[4]arene **37** (Scheme 4.9). Treatment of **37** with *n*-butyl bromide in refluxing acetone in the presence of K_2CO_3 afforded selectively diprotected calix[4]arene **38** in 85% yield. The nitration of diprotected calixarene **38** with 63% HNO_3 and $(CH_3CO)_2O$ in dichloromethane yielded 68% dinitrocalix[4]arene **39**. The reduction of **39** with NH_2-NH_2.H_2O in the presence of Pd/C furnished diaminocalix[4]arene **40** in 81% yield [Gutsche *et al.* 1983; Suzuki *et al.* 1997].

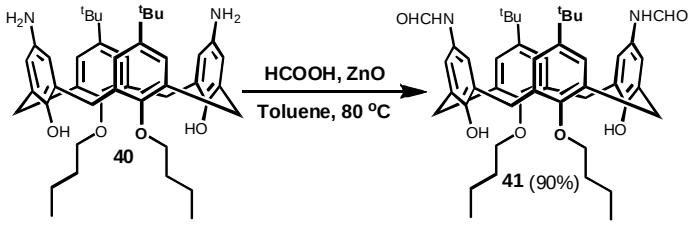


Scheme 4.9: *Conversion of p-tert-butylcalix[4]arene to diaminocalix[4]arene*

The next step required the conversion of aminocalix[4]arene to N-formamide. N-formyl compounds have been widely used in organic synthesis as protecting group of amines [Green and Wuts 1999], precursor for isocyanide preparation [Waki and Meienhofer 1977], an intermediate for monomethylated amines from primary amines [Effenberger and Eichhorn 1997] and catalyst for allylation or reduction [Iseki *et al.* 1999; Kobayashi and Nishi 1994]. A number of methods have been reported in recent years for the formylation of amines. Acetic formic anhydride [Strazzolini *et al.* 1990] continues to be the most widely used formylating agent, but it is sensitive to atmospheric moisture and cannot be stored due to decomposition to acetic acid and carbon monoxide. Many other useful reagents have been reported such as chloral [Blicke and Lu 1952], activated formic acid using DCC [Waki and Meienhofer 1977] or EDCI [Chen and Benoiton 1979], and activated formic acid esters [Yale 1971; Kisfaludy *et al.* 1987; Duczek *et al.* 1996]. However, there are several factors limiting their applications, for example, thermal instability, formation of byproducts and difficult accessibility to the preparation of the formylating agents.

Feiser [Feiser and Jones 1955] and then later on Jung and coworkers [Jung *et al.* 2002] developed a practical and convenient procedure for the N-formylation using 85% aqueous formic acid. Initially we adopted this procedure for the conversion of

diamine calix[4]arene to N-formyl derivatives. When diaminocalixarene **40** was treated with 85% aqueous formic acid using toluene as a solvent, N-formylated calixarene was obtained in 7% yield after 2 days of reaction. This prompted us to search for more efficient procedure and found out that Shargi and coworkers [Sarvari and Shargi 2006] have recently developed an efficient protocol for N-formylation with formic acid using non-toxic, inexpensive and bio-compatible ZnO as the catalyst. Based on this procedure, we reacted diaminocalix[4]arene with formic acid in toluene at 80 ^{o}C in the presence of ZnO powder as the solid catalyst. Filtering off ZnO after 24 h and removal of solvent furnished N-formamide as a 1:1 mixture of *cis/trans* isomers in 90% yield (Scheme 4.10).



Scheme 4.10: *Conversion of amine to N-formamide*

The structure of **41** was assigned to the product on the basis of spectroscopic and analytical data. The compound showed characteristic -NH and -OH stretching at 3279 cm^{-1} and carbonyl stretching at 1688 cm^{-1} in the IR spectrum. In the ^{1}H NMR spectrum of **41** (Figure 4.2), the aldehydic protons of the *trans* isomer appeared as a singlet at δ 8.56 and that of the *cis* appeared as a doublet at δ 8.36. The -NH protons were found as singlet at δ 8.40 (*trans*) and as a doublet at δ 8.25 (*cis*). The aromatic protons appeared in the range δ 7.21-6.77 integrating for 16 protons. The methylene bridge protons were discernible as two multiplets centered at δ 4.32 and δ 3.33. All the other signals were in agreement with the proposed structure.

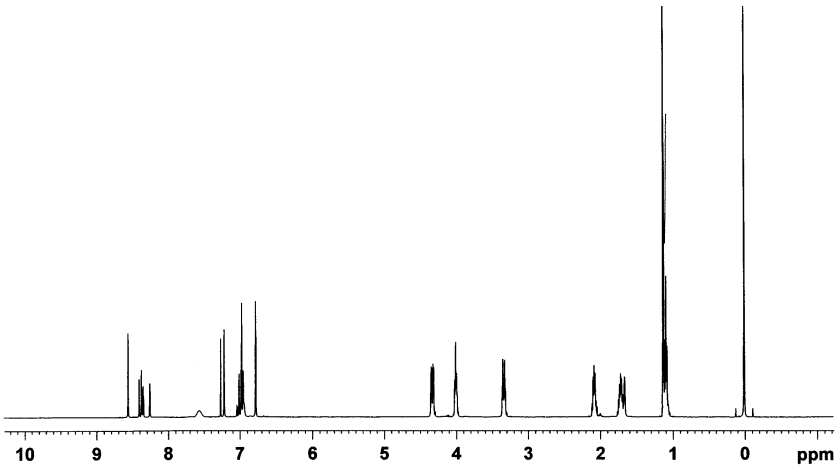


Figure 4.2: *^{1}H NMR spectrum of **41***

An HMQC experiment (Figure 4.3) was run to establish the position of various proton attached carbons in the compound. From this, we were able to assign the aldehydic carbons to be at δ 168.2 and δ 158.5 (Figure 4.4). The -OCH_2 carbons resonated at δ 76.3.

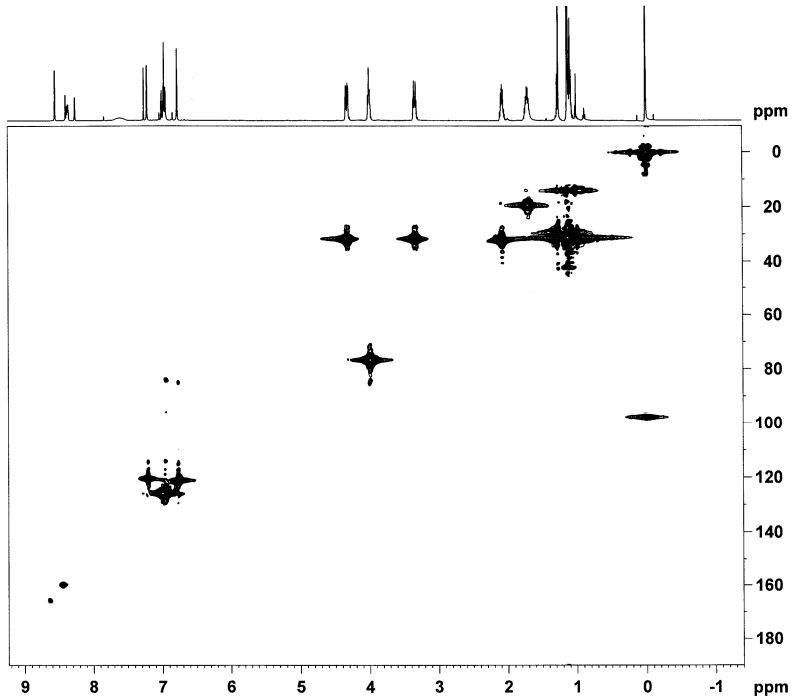


Figure 4.3: HMQC Spectrum of ***41***

The product obtained was further supported by mass spectral analysis showing the $[M+23]^+$ peak at 756.97.

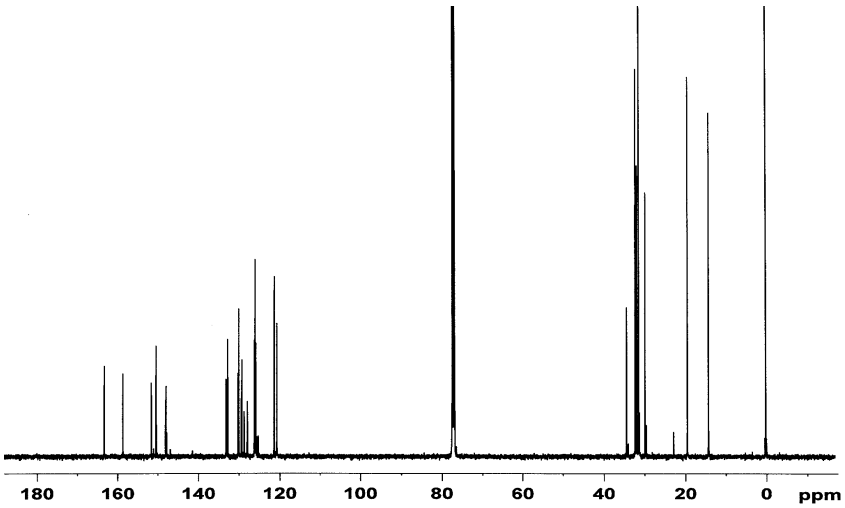
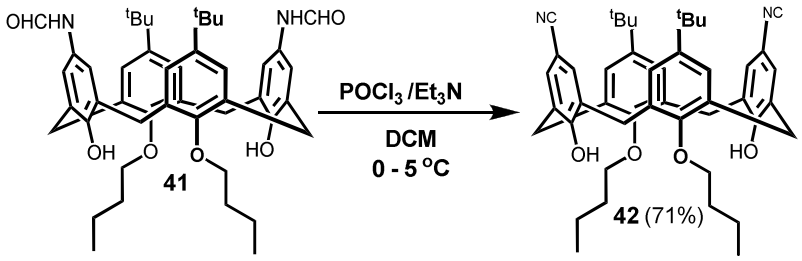


Figure 4.4: *^{13}C NMR spectrum of **41***

The formamide obtained can be easily converted to isocyanide *via* its dehydration. There are several methods reported for isocyanide synthesis by dehydration of formamides with various reagents [Obrecht *et al.* 1985] like chlorodimethylformiminium chloride[Walborsky and Niznik 1972] phosgene [Ugi *et al.* 1965] or diphosgene [Skorna and Ugi 1977], DABCO [Barton *et al.* 1988], aryl chlorothionoformate [Bose and Goud 1999], 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride, TCT) [De Luca *et al.* 2001; De Luca *et al.* 2002], and supported sulfonyl chlorides under microwave irradiation [Launay *et al.* 2002]. Unfortunately, most of these methods have limited utility and applicability due to the extreme toxicity, cumbersome handling and high costs of the reagents. Sometimes the reagents employed require tedious preparation procedures or workup, and purification of the reaction product can be problematic due to the reactivity of the isocyanides.

Taking into account our interest in the adaptation of multicomponent reactions to calixarene scaffolds, especially isocyanide based multicomponent reactions, we decided to investigate the possibility to synthesize isocyanide using a very cheap reagent, phosphorus oxychloride ($POCl_3$). The reaction was checked using a CH_2Cl_2 solution of $POCl_3$ (4.0 equiv.) and the formamide **41**, which was charged with Et_3N

(5.0 equiv.), at 0-5 ^{o}C for half-an-hour (Scheme 4.11). The reaction afforded the required isocyanide **42** in 71% yield.



Scheme 4.11: *Dehydration of formamide to isocyanide*

The product **42** obtained was analyzed using various spectral techniques. The IR spectrum of **42** showed characteristic absorption at 2119 cm^{-1}, which corresponded to -NC stretching of isocyanide group and at 3277 cm^{-1} corresponding to the -OH group. In the ^{1}H NMR spectrum (Figure 4.5), the lower rim hydroxyl protons were seen as a singlet at δ 8.73. The aromatic protons were discernible as two singlets at δ 7.09 and 6.91 respectively. The methylene protons resonated as two doublets at δ 4.24 (J = 13.0 Hz) and 3.33 (J = 13.0 Hz). A triplet at δ 3.98 was observed for -OCH_2 proton. The *tert*-butyl group appeared as a singlet at δ 1.09 integrating for eighteen protons. All other signals were in agreement with the proposed structure.

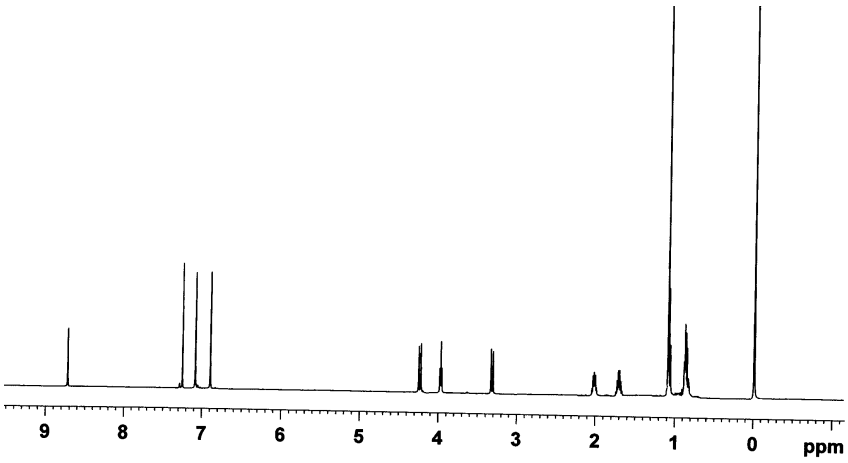


Figure 4.5: *^{1}H NMR spectrum of* **42**

The proposed structure was supported by ^{13}C NMR spectrum showing the isocyanide carbon at δ 161.1 (Figure 4.6). The -OCH_2 carbon resonated at δ 64.9. The aliphatic signals were observed in δ 34.2-19.4 region. This was further supported by mass spectral analysis showing the $[M+Na]^+$ peak at 721.44.

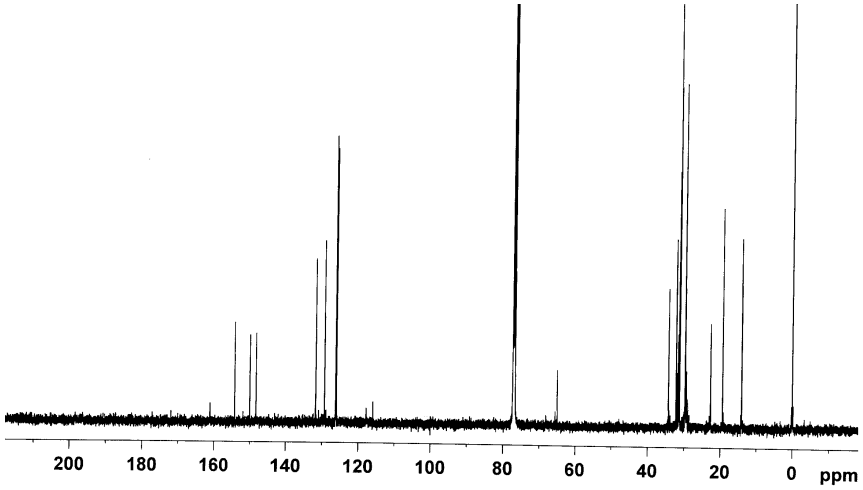
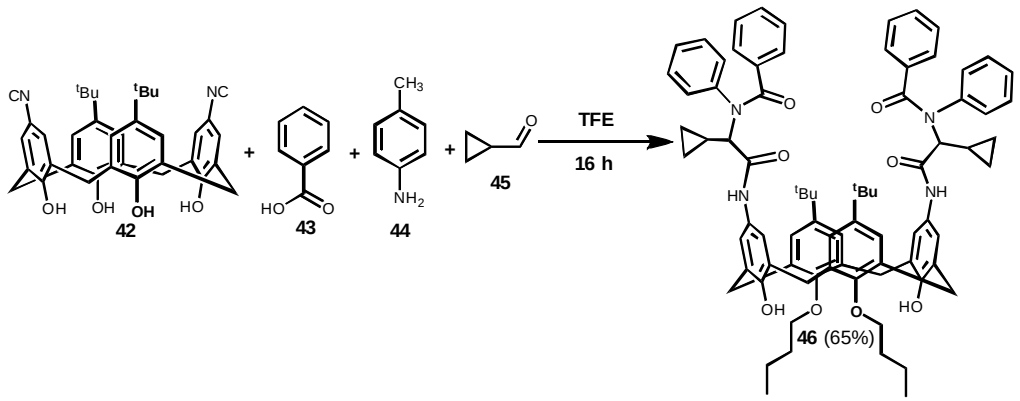


Figure 4.6: *^{13}C NMR spectrum of **42***

With the novel isocyanide derivatized calixarene in hand, we attempted a Ugi four component reaction in the hope of preparing highly functionalized calixarene based macrocycles. Accordingly, we reacted the diisocyanide **42** with benzoic acid **43**, toluidine **44** and cyclopropane carboxaldehyde **45** in trifluoro ethanol (TFE) at room temperature (Scheme 4.12) and stirring was continued until the consumption of the starting material as indicated by TLC. After 16h, removal of the solvent followed by column chromatography of the residue on alumina afforded the highly functionalized α-acyl aminocarboxamide **46** in 65% yield.



Scheme 4.12: *Ugi reaction of diisocyanocalix[4]arene*

The structure **46** was assigned to the product on the basis of spectroscopic data. The IR spectrum of **46** showed absorptions at 1690 and 1635 cm^{-1} indicating the presence of amide group while hydroxyl group was discernible at 3006 cm^{-1}. In the ^{1}H NMR spectrum (Figure 4.7), the -OH and -NH protons resonated a singlets at δ 8.56 and 8.39 respectively. Adequate number of aromatic protons appeared in δ 7.43-6.94 region. A doublet at δ 4.44 was assigned to the -CH proton of the cyclopropyl aldehyde part and the sharp singlet at δ 2.23 to the toluidine $-CH_3$ group. The $-CH_2$ groups of the cyclopropyl group appeared as multiplet at δ 0.78 and 0.53. All other signals were in agreement with the proposed structure.

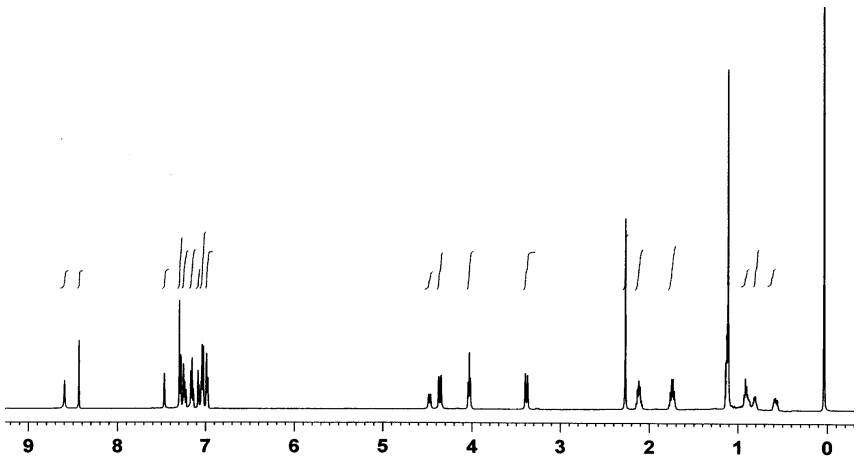


Figure 4.7: *^{1}H NMR spectrum of* ***46***

The ^{13}C NMR spectrum (Figure 4.8) showed the amide carbonyls at δ 172.1 and 167.2. The cyclopropyl -CH_2's appeared at δ 5.9 and 4.2. The structure was further supported by MALDI-TOF analysis which gave the $[M+23]^+$ peak at 1223.72.

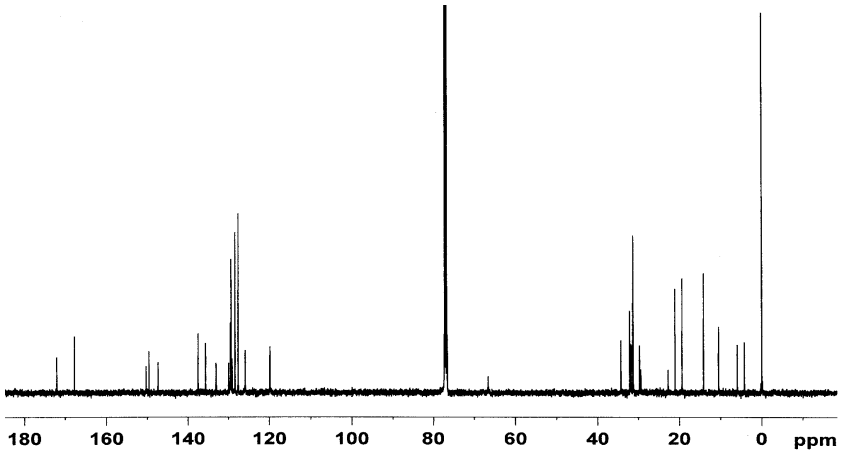


Figure 4.8: *^{13}C NMR spectrum of **46***

Thus we have developed a versatile approach toward peptoid containing calixarene based macrocycles in one-pot process. The fascinating scope of this strategy lies in the straightforward assembly of extremely complex molecular entities from simpler and available building blocks as well as in the high level of diversity that can be obtained by varying the nature of the Ugi components taking part in the process.

4.4 Conclusion

In conclusion, we have synthesized N-formamide functionalized calix[4]arene, for the first time, from diaminocalixarene in excellent yields using formic acid and non-toxic, inexpensive and biocompatible ZnO powder. These compounds are important calixarene intermediates since they can act as Lewis bases, which are known to catalyze reactions such as allylation and hydrosilylation of carbonyl compounds. Further, we have utilized N-formamidocalixarene for the synthesis of novel upper rim isocyanide functionalized calix[4]arene. In addition we have demonstrated that the isocyanide derivatized calix[4]arene could be used as a starting source for performing

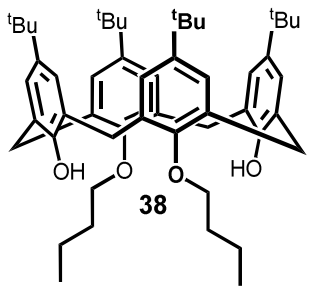
Ugi reaction to afford multiply functionalized calixarenes in a single step. The multicomponent approach on calixarene would provide collections of structurally diverse macrocycles that may be suitable for molecular recognition processes, pharmaceutical applications etc.

4.5 Experimental Details

General information about the experiments is given in section 2.5 (Chapter 2).

4.5.1 Synthesis of distally dialkylated calix[4]arene from *p-tert*-butylcalix[4]arene.

p-Tert-butylcalix[4]arene **37** (200.0 mg, 3.08 mmol), K_2CO_3 (4.26 g, 30.81 mmol) and dry acetone (60 ml) were taken in a 250 ml R. B. flask and stirred for 1 h at 60 ^oC. *n*-Butyl bromide (0.5 mL) was added after 1 h and stirred well for 3 days. Acetone was removed under reduced pressure, and the residue worked up with $CHCl_3$-H_2O mixture. The organic layer was subsequently separated, dried over anhydrous Na_2SO_4 and evaporated to dryness. The product was recrystallised from $CHCl_3$-MeOH.



38

Yield: 85% as white solid.

IR (KBr) υ_{max}: 3389, 2957, 2872, 1485, 1198, 999 cm^{-1}.

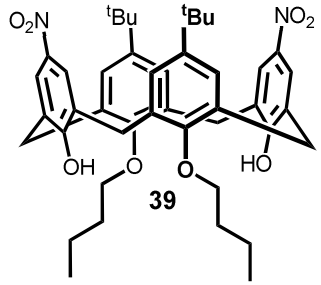
^{1}H NMR: δ 7.84 (s, OH, 2H), 7.03 (s, ArH, 4H), 6.84 (s, ArH, 4H), 4.30 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 3.97 (t, *J* = 6.5 Hz, $-OCH_2$, 4H), 3.30 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 1.99 (m, $-CH_2$, 4H), 1.75 (m, $-CH_2$, 4H), 1.27 (s, *t*-Bu, 18H), 1.06 (t, *J* = 7.5 Hz, $-CH_3$, 6H), 1.00 (s, *t*-Bu, 18H)

^{13}C NMR: δ 150.8, 150.0 (C-OH), 146.7, 141.2, 132.9, 127.8, 125.5, 125.0, (Ar-C), 76.3 (-OCH_2), 33.9, 33.8, 32.2, 31.9, 31.7, 31.4, 31.0, 19.4, 14.0 (Ar-CH_2-Ar, *t*-Bu, -CH_2, -CH_3)

MS (FAB): Calcd for $C_{52}H_{72}O_4$, $[M+Na]^+$: 783.54; Found: 783.25.

4.5.2 Synthesis of dinitrocalix[4]arene

To a solution of lower rim diprotected calix[4]arene **38** (500.0 mg, 0.68 mmol) in dichloromethane (25 mL) and $(CH_3CO)_2O$ (4 mL) at -10 ^oC, 63% HNO_3 (0.5 mL) was added in 2 min. and was then stirred at room temperature for 5 min. The reaction mixture was poured into water (250 mL). The organic layer was extracted by dichloromethane (2x100 mL). The organic layer was removed and the solid residue was dissolved in MeOH (100 mL); concentration of solution to ca., 50 mL led to a white precipitate. The precipitate is recrystallized from a mixture of dichloromethane-MeOH in 65% yield.



39

Yield: 65% as white solid.

IR (KBr) υ_{max}: 3275, 2961, 2872, 1514, 1335, 1107 cm^{-1}.

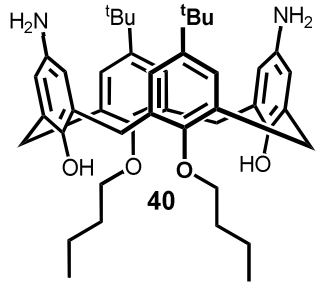
^{1}H NMR: δ 9.44 (s, -OH, 2H), 8.04 (s, ArH, 4H), 6.97 (s, ArH, 4H), 4.23 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 4.03 (t, *J* = 6.5 Hz, $-OCH_2$, 4H) 3.48 (d, *J* = 13.5 Hz, 4H, $ArCH_2Ar$), 2.04 (m, $-CH_2$, 4H), 1.75 (m, $-CH_2$, 4H), 1.11 (t, *J* = 7.5 Hz, $-CH_3$, 6H), 1.07 (s, *t*-Bu, 18H).

^{13}C NMR: δ 159.7 (C-NO_2), 149.7, 148.6, (C-OH), 139.8, 131.1, 128.7, 126.3, 124.4 (Ar-C), 76.8 ($-OCH_2$), 34.2, 32.2, 31.6, 31.2, 19.4, 14.1 (*t*-Bu, Ar-CH_2-Ar, $-CH_2$, $-CH_3$)

MS (FAB): Calcd for $C_{44}H_{54}N_2O_8$, $[M+Na]^+$: 761.38; Found: 761.53.

4.5.3 Synthesis of diaminocalix[4]arene

Diprotected nitrocalix[4]arene **39** (100.0 mg, 0.14 mmol) was refluxed with 10 mL absolute ethanol in argon atmosphere, Pd/C catalyst added followed by hydrazine, NH_2-$NH_2.2H_2O$. Temperature was raised to 80º C and stirred overnight. The reaction mixture was worked up by passing through celite column, washing down with hot ethanol. The solvent was evaporated under reduced pressure till a precipitate appears. Then the R.B. was kept in ice and about 50 ml of water added to the reaction mixture. Kept it for half an hour, and the product was filtered out using buchner funnel.



40

Yield: 81% as white solid.

IR (KBr) υ_{max}: 3172, 2902, 2872, 2733, 1734, 1451, 1450, 1384, 1288, 1255 cm^{-1}.

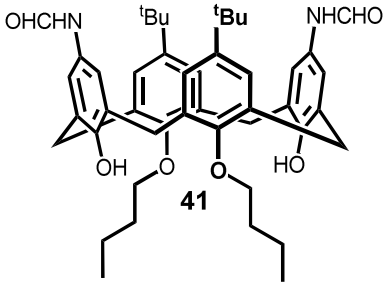
^{1}H NMR: δ 7.68 (s, OH, 2H), 6.93 (s, ArH, 4H), 6.42 (s, ArH, 4H), 4.31 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 3.97 (t , *J* = 6.5 Hz, $-OCH_2$, 4H), 3.22 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 2.06 (m, $-CH_2$, 4H), 1.73 (m, $-CH_2$, 4H) 1.12 (s, *t*-Bu, 18H), 1.05 (m, $-CH_3$, 6H), $-NH_2$ protons appeared as a hump in the δ 3-2 range.

^{13}C NMR: δ 158.6 (C-NH_2), 151.2, 150.2, (C-OH), 150.1, 147.8, 133.0, 132.7, 132.5, 129.9, 129.2, 128.6, 127.6, 125.8, 125.1, 120.9, 120.5, (Ar-C), 76.8 ($-OCH_2$), 34.2, 32.1, 31.7, 31.3, 31.1, 29.7, 19.3, 14.1 (*t*-Bu, $ArCH_2Ar$, $-CH_2$, $-CH_3$)

MS (FAB): Calcd for $C_{44}H_{58}N_2O_4$, $[M+Na]^+$: 701.44; Found: 701.49.

4.5.4 Synthesis of upper rim formamido calix[4]arene

To a mixture of HCO_2H (0.22 mL, 6 mmol) and ZnO (160.0 mg, 2 mmol) in toluene (2 ml) was added the aminocalixarene **40** (100.0 mg, 0.15 mmol) and the reaction mixture was heated in an oil bath at 70 ^oC. The progress of the reaction was monitored by TLC. After the reaction was complete, EtOAc was added to the reaction mixture and ZnO was filtered off. The organic solvent was washed with H_2O (2x20 mL) and saturated solution of $NaHCO_3$. After the removal of the solvent, the pure product was obtained as a mixture of *cis* and *trans* isomers.



41

Yield: 90% as white solid.

IR (KBr) υ_{max}: 3279, 3011, 2961, 1688, 1483, 1252, 1215, 1101, 756, 665 cm^{-1}.

^{1}H NMR: δ 8.56 (s, CHO, 2H), 8.40 (s, NH, 2H), 8.36 (dd, *J* = 3.5 Hz, *J* = 11.5 Hz, CHO, 2H), 8.25 (d, *J* =1.5 Hz, NH, 2H), 7.56 (broad s, OH, 4H), 7.21 (s, ArH, 2H), 7.00 (d, *J* = 2.0 Hz, ArH, 2H), 6.98 (s, ArH, 2H), 6.97 (s, ArH, 2H), 6.95 (d, *J* = 2.0 Hz, ArH, 4H), 6.77 (d, *J* = 2.5 Hz, ArH, 4H), 4.32 (m, $ArCH_2Ar$, 8H), 3.99 (m, $-OCH_2$, 8H), 3.33 (m, $ArCH_2Ar$, 8H), 2.08 (m, $-CH_2$, 8H), 1.71 (m, $-CH_2$, 8H), 1.13 (s, t-Bu, 36H), 1.09 (m, $-CH_3$, 12H).

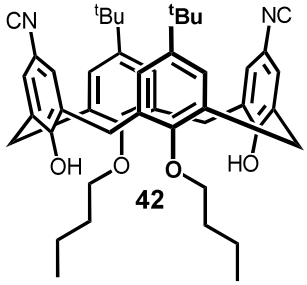
^{13}C NMR: δ 168.2 (-CHO), 158.5 (-CHO), 151.4, 150.2, 147.7, 133.3, 132.8, 132.6, 130.0, 129.8, 129.1, 128.5, 127.7, 126.0, 125.7, 121.1, 120.5, 76.3 ($-OCH_2$), 32.1, 31.9, 31.7, 31.3, 29.7, 29.4, 19.3, 14.1, (*t*-Bu, Ar-CH_2-Ar, $-CH_2$, $-CH_3$)

MS (MALDI-TOF): Calcd for $C_{46}H_{58}N_2O_6$, $[M+Na]^+$: 757.43; Found: 756.97.

4.5.5 Synthesis of calix[4]arene isocyanide

To a solution of formamidocalix[4]arene **41** (136.0 mg, 0.19 mmol) in dichloromethane (5 mL), was added triethyl amine (5.0 equiv.) and $POCl_3$ (4.0 equiv.) at 0 ^oC under nitrogen. After being stirred for 0.5 h, the reaction mixture was poured into 10% aqueous Na_2CO_3 solution. The reaction mixture was worked up with

dichloromethane-water mixture. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexanes-ethyl acetate in 85:15).



42

Yield: 71% as white solid.

IR (KBr) υ_{max}: 3277, 2961, 2932, 2119, 1476, 1362, 96, 995 cm^{-1}.

^{1}H NMR: δ 8.73 (s, OH, 2H), 7.09 (s, ArH, 4H), 6.91 (s, ArH, 4H), 4.24 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 3.98 (t , *J* = 5.0 Hz, -OCH_2, 4H), 3.33 (d, *J* = 13.5 Hz, $ArCH_2Ar$, 4H), 2.03 (m, -CH_2, 4H), 1.72 (m, -CH_2, 4H), 1.09 (s, *t*-Bu, 18H), 0.87 (m, -CH_3, 6H)

^{13}C NMR: δ 161.1, (NC) 154.2, 149.9, 148.2, 131.7, 130.8, 129.3, 128.8, 126.2, 117.8, 115.9 (Ar-C) , 64.9 (-OCH_2), 34.2, 32.2, 31.9, 31.6, 29.7, 22.7, 19.4 (t-Bu, Ar-CH_2-Ar, CH_2, CH_3)

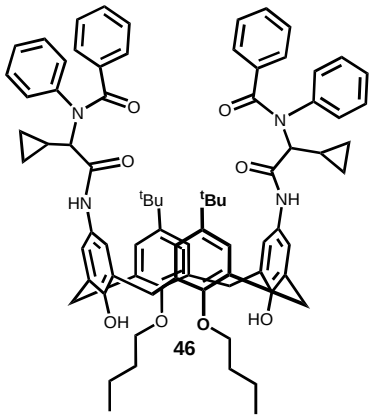
MS (FAB): Calcd for $C_{46}H_{54}N_2O_4$, $[M+Na]^+$: 721.41; Found: 721.44.

Elemental Analysis calculated for $C_{46}H_{54}N_2O_4$: C, 76.05; H, 7.79; N, 4.01 Found: C, 76.11; H, 7.73; N, 4.05.

4.5.6 Synthesis of α-diamidocalixarene by the U-4CR of calix[4]arene isocyanide

A solution of toludine (9 mg, 0.09 mmol) and cyclopropyl carboxaldehyde (0.01 mL, 0.09 mmol) in 1 mL TFE as the solvent was stirred at room temperature for 2 h. To this solution was added benzoic acid (10 mg, 0.09 mmol) followed by

calixarene isocyanide (20.0 mg, 0.03 mmol). After completion of the reaction as indicated by TLC (16 h), the solvent was removed on a rotavapour and the residue was subjected to column chromatography on neutral alumina using hexane-ethyl acetate solvent mixture (70:30) to afford the pure product.



46

Yield: 65% as white solid.

IR (KBr) υ_{max}: 3006, 1690, 1635, 1512, 1482, 1252, 1216, 1181, 763.

^{1}H NMR: δ 8.56 (s, OH, 2H), 8.39 (s, NH, 2H), 7.43 (s, ArH, 2H), 7.24 (s, ArH, 4H), 7.20 (m, ArH, 4H), 7.12 (m, ArH, 4H), 7.04 (m, ArH, 2H), 7.00 (m, ArH, 4H), 4.44 (d, *J* = 10.5 Hz, CH, 2H), 4.32 (d, *J* = 12.5 Hz, $ArCH_2Ar$, 4H), 3.99 (t , *J* = 6.5 Hz, -OCH_2, 4H), 3.35 (d, *J* = 13.0 Hz, $ArCH_2Ar$, 4H), 2.23 (s, -CH_3, 6H), 2.08 (m, -CH_2, 4H), 1.71 (m, -CH_2, 4H), 1.21 (s, *t*-Bu, 18H), 0.87 (m, -CH_3, 6H), 0.78 (m, -CH_2, 4H), 0.53 (m, -CH_2, 4H)

^{13}C NMR: δ 172.1, 167.8 (CONH), 150.3, 149.6, 147.4, 137.5, 135.7, 133.1, 133.0, 129.9,129.6, 129.4, 129.1, 128.4, 127.6, 125.9, 125.8, 119.9, 119.8 (Ar-C), 77.2, 66.7, 34.3, 32.1, 31.8, 31.4, 31.3, 29.7, 22.7, 21.0, 19.3, 14.1, 10.5, 5.9, 4.1 (t-Bu, Ar-CH2-Ar, CH_2, CH_3)

MS (MALDI-TOF): Calcd for $C_{80}H_{88}N_4O_6$, $[M+Na]^+$: 1223.67; Found: 1223.72.

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SUMMARY

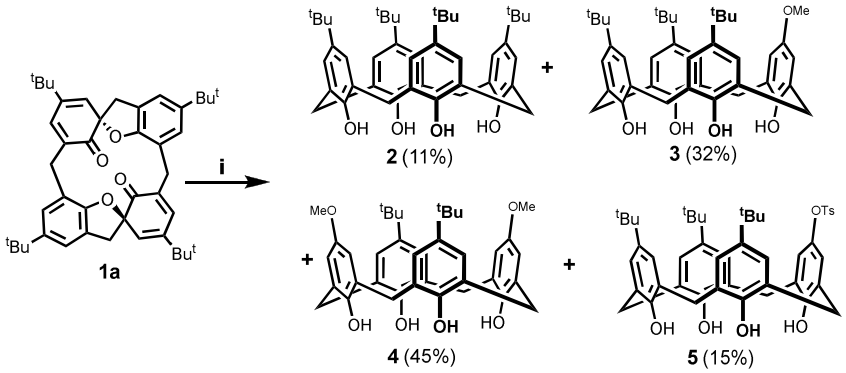
The thesis titled "**Novel Synthetic Strategies towards Upper Rim Modified Calix[4]arenes via bis(spirodienone) and Related Chemistry**" presents the results of our investigation on the various synthetic transformation of calixarenes and calix[4]bis(spirodienones) leading to multifunctional macrocycles.

The thesis work consists of three main parts: (i) Accessing selective upper rim alkoxy/aryloxy substitution of calix[4]arene *via* calix[4]bis(spirodienone) route. (ii) Tapping the synthetic potential of compounds synthesized from the above said *ipso*-substitution reaction of bis(spirodienone). (iii) Investigations on synthesis of a novel upper rim isocyanide functionalized calix[4]arene.

The calix[n]arenes are synthetic macrocycles consisting of a cyclic array of phenols connected by methylene bridges. To alter the properties of the macrocycle, the calixarene scaffold usually has been modified by introduction of substituents at the intraannular (lower rim) and/or extraannular (upper rim) positions. Biali *et al*. developed a detour route for the functionalization of calixarene. That is, on mild oxidation of calixarene in the presence of base affords spirodienone derivatives. The transformation of calixarene to calix[4]bis(spirodienone) is of interest since carbonyl and ether functionalities as well as spiro stereocenters are introduced in the macrocycle in a single synthetic step. They have been successfully utilized by the Biali's group as synthetic intermediates for modifying calixarenes at the intraannular, extraannular and bridging methylene positions.

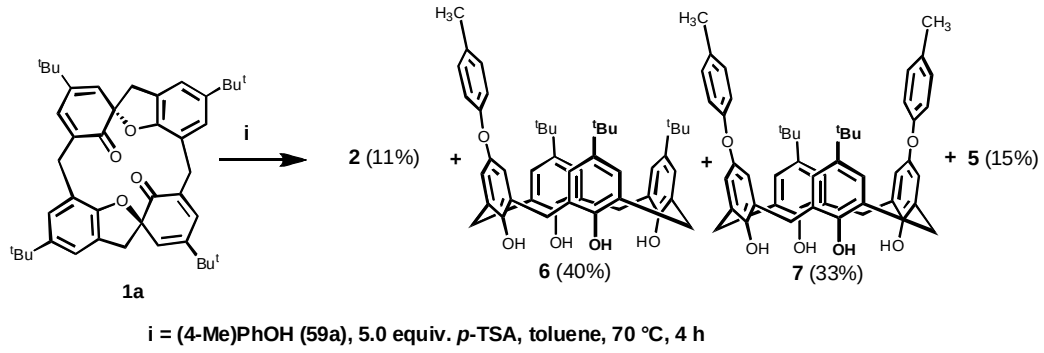
Intrigued by the unexploited synthetic potential of this class of synthons, we have embarked on a research program on "chemistry of calix[4]bis(spirodienones)" with the

main aim of evolving new synthetic methodologies, especially based on the nucleophilic substitution of spirodienones. With this perception we initiated our work by reacting the most stable bis(spirodienone) isomer with methanol in toluene in the presence of *p*-toluene sulphonic acid (*p*-TSA) under reflux for 6 h. The reaction resulted in the synthesis of upper rim monomethoxy and dimethoxy substituted calix[4]arene in acceptable yields (Scheme 1). This has been published in *Tetrahedron Lett*. **2009**, *50*, 770-772.



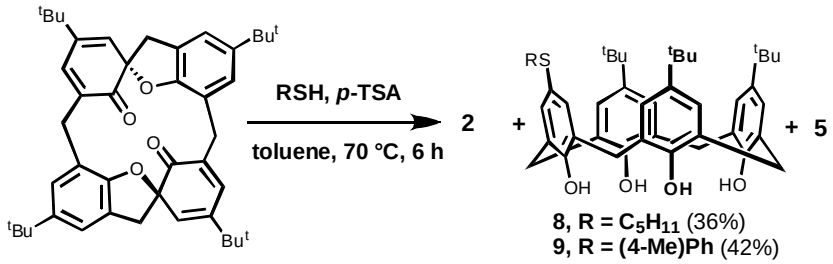
Scheme 1

With the interesting results obtained with alochols we extended our study to phenols. The reaction of bis(spirodienone) with *p*-cresol furnished the upper rim mono- and diaryloxy substituted calix[4]arene in good yields (Scheme 2).



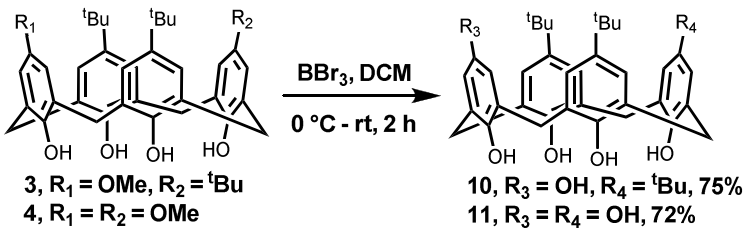
Scheme 2

To examine the versatility of this process, we also looked into the reactivity of bis(spirodienone) with thiols, which turned out to be excellent nucleophiles for the above reaction. When bis(spirodienone) was reacted with *n*-pentanethiol under the optimized conditions, monothio ether derivative was obtained in good yield (Scheme 3).



Scheme 3

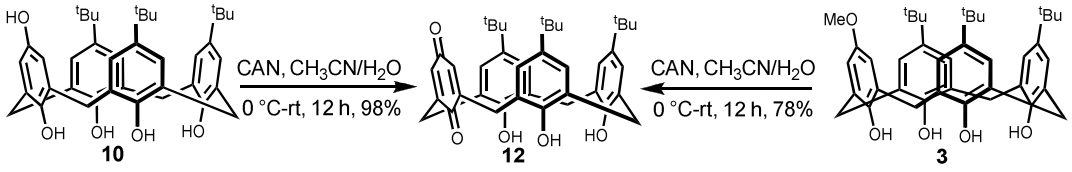
In the perspective of our general interest in designing novel calixarene based frameworks and to bring out the usefulness of the synthetic protocol developed by us, we decided to study the synthetic utility of some of the products obtained using the above methodology. Accordingly, we looked into the possibility of cleavage of methyl group from the mono- and dimethoxy calix[4]arenes and subsequent oxidation of the hydroxyl compounds obtained thereby. This resulted in the selective synthesis of mono- and diquinone calixarenes which are otherwise difficult to synthesize. In an initial experiment we treated monomethoxy compound **3** with boron tribromide in dichloromethane at 0 °C for 2 h. Removal of the solvent followed by column chromatography of the residue on silica gel furnished 5-hydroxycalix[4]arene **10** in 75% yield (Scheme 4). To the best of our knowledge, this is the first synthesis of 7,11,23-tri-*p*-*tert*-butylcalix[4]arene with a hydroxyl group on the upper rim.



Scheme 4

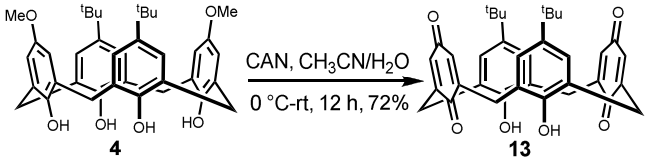
The dimethoxy compound **4** was also subjected to the above reaction which afforded the dihydroxylated product in 72% yield.

Since compounds **10** and **11** contained one and two hydroquinone units, they can be readily oxidised to the respective mono- and diquinones. Oxidation of **10** with cerium(IV)ammonium nitrate (CAN) in CH_3CN:H_2O mixture at 0 °C, calix[4]monoquinone **12** was obtained in quantitative yield. The oxidation of **3** using CAN also afforded **12** in 78% yield (Scheme 5)



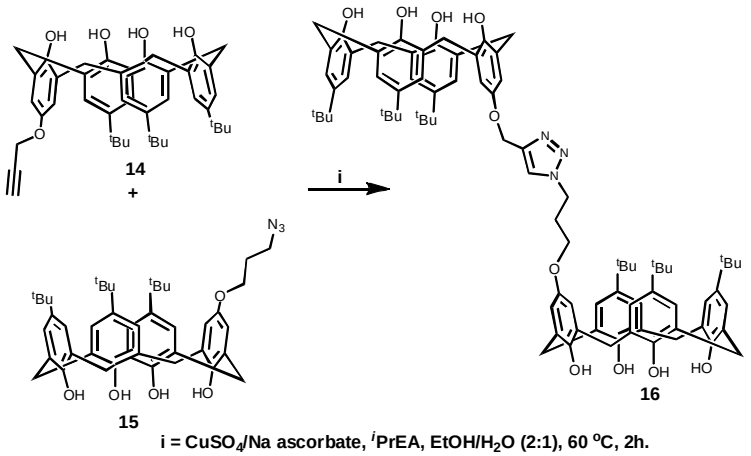
Scheme 5

Similarly, **4** on oxidation with CAN offered the 1,3-calix[4]diquinone **13** in 72% yield (Scheme 6). This work along with the results obtained for aryloxy substitutions of calix[4]arene was published as a full paper in *Tetrahedron* **2010** (Accepted)



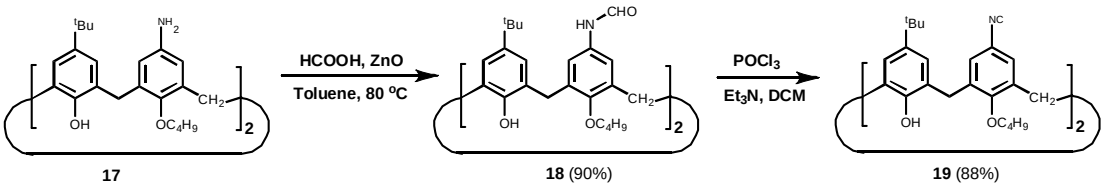
Scheme 6

Furthermore we validated the use of click chemistry (CuAAC) in the synthesis of a library of triazole appended calixarene based frameworks, starting from a compound obtained *via* the *ipso*-nucleophilic substitution of bis(spirodienone) with bromoalcohols and propargyl alcohol (Scheme 7). This work has been submitted to *Pure Appl. Chem.*



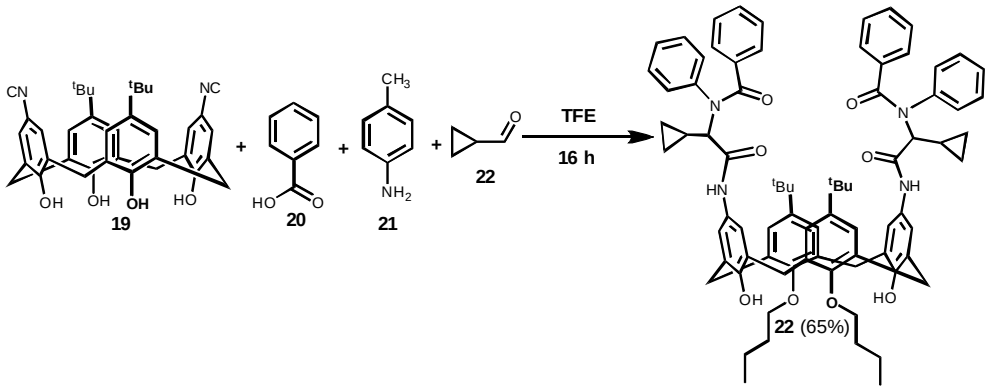
Scheme 7

The last part of the thesis discusses the synthesis of a novel upper rim isocyanide appended calixarene from selectively diaminated calixarene **17** *via* a two step process and its application in Ugi reaction. Initially the amine was treated with formic acid in the presence of ZnO to yield a 1:1 *cis-trans* isomeric mixture of N-formamide functionalized calixarene. The N-formamido calixarene on dehydration with $POCl_3$ in the presence of Et_3N yielded the isocyanide fumctionalized calixarene in 88% yield.



Scheme 8

We have utilized the newly synthesized isocyanide derivatized calix[4]arene towards the synthesis of multifunctionalized calixarene scaffold via an Ugi reaction (Scheme 9).



Scheme 9

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1. Direct Access to Upper Rim Substituted Mono- and Diaryloxy Calix[4]arenes via Bis(spirodienone) route. **Sreeja T.**; Jisha, B.; Adarsh, B.; Viji, S.; Varma, L. R. *Tetrahedron* **2010**, *66*, 5270-5276.
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2. Hybrid Macrocyclic Receptors Based on Lower Rim Functionalised Thiacalix[4]arene and Amino acids: Synthesis, Structure and Binding Properties Towards Metal Ions. **Sreeja T.**; Ganga, V. B.; Praveen, L.; Varma, L. R. *Ind. J. Chem.* (Submitted, Ms. Ref. No.: Pub:3/4(OC-1275)/2009)
3. Calix[4]bis(spirodienone) as a versatile Synthon for Upper Rim Alkoxylation of Calixarenes : Synthesis of Novel Triazole based Biscalixarene by 'CuAAC' Chemistry. **Sreeja T.**; Anupriya, S.; Varma, L. R. *Pure Appl. Chem.* (Submitted)
4. *p*-TSA Mediated de-*tert*-Butylation of *p*-*tert*-Butylcalix[4]arene and *p*-*tert*-Butylthiacalix[4]arene. **Sreeja T.**; Anupriya, S.; Nabeela, U.; Varma, L. R. *Synth. Commun.* (Submitted).
5. Expeditious synthesis of N-bridged heterocycles via dipolar cycloaddition of pentafulvenes with 3-oxidopyridinium betianes. Kuthanapillil, J. M.; **Sreeja T**.; Rajan, R.; Krishnan, K. S.; Radhakrishnan, K. V. (Under preparation)

ORAL / POSTERS PRESENTED IN NATIONAL AND INTERNATIONAL CONFERENCES

Oral presentations:

1. A Novel Methodology for the Wider Rim Alkoxy Substitution of Calix[4]arene through Bis(spirodienone) route: Application Towards Selective Synthesis of Mono- and 1,3-Diquinone Calix[4]arenes. **Sreeja T.** *National Seminar on Recent Trends in Organic Chemistry (RETROC-2009)* (student lecture), Christian College, Chengannur, Kerala, January, **2009**.

Posters presented:

2. Calix[4]bis(spirodienone) as a Versatile Synthon for Upper Rim Alkoxylation of Calixarenes : Synthesis of Novel Triazole based Biscalixarene by 'CuAAC'

Chemistry. **Sreeja T.**; Anupriya, S.; Varma, L. R. *International Conference on Materials for the Millennium (MATCON 2010),* CUSAT, Kochi, January 11-13, **2010**.

3. A Novel Method for the Upper Rim Alkoxy Substitution of Calix[4]arene via a Bis(spirodienone) route. **Sreeja T.**; Varma, L. R. 4th *Junior National Organic Symposium Trust* (J-NOST) conference, Madurai Kamraj University, Madurai, December, **2008**.
4. Synthesis, Structure and Binding Properties of Hybrid Macrocyclic Receptors Based on Lower Rim Functionalised Thiacalix[4]arene and Amino acids. **Sreeja T.**; Anupriya, S.; Varma, L. R. 12th International Conference on "*Interface of Chemistry-Biology in Biomedical Research" (ISCB-2008),* BITS, Pilani, Rajasthan, February, **2008**.