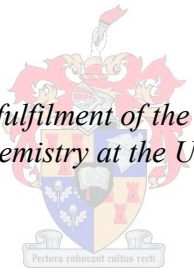
Selective distal functionalization of resorcinarenes via an ortholithiation approach

by
Lonwabo Ngodwana



Thesis presented in partial fulfilment of the requirements for the degree Master of Science in Chemistry at the University of Stellenbosch

Supervisor: Dr. Gareth Arnott
Co-supervisor: Prof. Willem van Otterlo
Department of Chemistry and Polymer Science

December 2012

Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining my qualifications.

December 2012

Acknowledgements

This thesis is a product of the support of a number of people without whom it would not have been possible. And these are the people I would like to honestly and faithfully thank:

My supervisors Dr. Gareth Arnott and Professor Willim van Otterlo for their undivided support and making this work a possibility.

My group mates in the Organic and Medicinal group for their team work, discussions and support towards my work. Arnott research lab people, you have made a great impact in my life and I will always be grateful. Also a name I must mention, Dewald a very special thank to you for all the time and effort you have spent showing me how to keep moving in the lab, chats and advices.

My parents (Vuyo Ngodwana and Nomsimelelo Ngodwana) who have always understood and supported my dreams and whose guidance have took me places and gave me a meaning of life. Also not forgetting my family as a whole (especially my aunt Thandiwe Orangia Mgidi), whose mentorship has always reminded me of the value of education.

To my brothers, sisters and friends who, in the most trying times of this world, remained with me, smiling, laughing and sometimes even crying with me.

Additional acknowledgements

I am grateful to the University of Stellenbosch for giving me the opportunity to be part of the university and to the NRF for supporting my studies at the university.

Abstract

Resorcinarenes are tetramers, belonging to a class of $[1]_4$metacyclophanes, easily formed by the acid- or base-catalysed condensation of resorcinol and aldehydes. Properties include, amongst others; bowl-like shape, adhesion to hydrophilic surfaces and formation of hexameric capsules. Their uses are, to mention some: components in liquid crystals, photoresistors, selective membranes, surface reforming agents, HPLC stationary phases, ion-channel mimics, metal-ion extraction, molecular switches and ligands for metal catalysts. Selective functionalization of resorcinarenes has been explored and achieved *via* relatively inefficient methodologies which limit studies, structural architecture and new applications. In this work, synthesis of C_{4v} symmetric resorcinarene ethers was performed which were used as templates in undertaking studies towards selective derivatisation of resorcinarenes *via* an ortholithiation approach.

Conditions for the efficient synthesis of distally substituted resorcinarenes using ortholithiation were optimized and tested with a range of electrophiles, lower rim lengths, scale, base equivalents, reaction times and solvent effects. Ortholithiation gave distally substituted resorcinarenes in reasonable yields (>80%).

Ortholithiation and its ability to form distal-resorcinarene esters could possibly be used as a way to synthesize distal-chloromethyl resorcinarene precursors whose further functionalization would furnish a range of distal-resorcinarene imidazolium salts, a class of distal bidentate carbene ligand staring materials for transition metal coordination.

Opsomming

Resorsinarene is sikliese tetramere, wat deel uitmaak van‘n klas van $[1]_4$metasiklofane, en kan maklik gevorm word deur die suur- of basis-gekataliseerde kondensasie van resorsinol en aldehiede. Eienskappe sluit onder andere in: bak-vormig, adhesie aan hidrofiliese oppervlakke en die vormasie van heksameriese kapsules. Tipiese voorbeelde van gebruike sluit die volgende in: komponente van vloeistof kristalle, fotoresistors, selektiewe membrane, oppervlak hervormings agente, HDVC stationêre fases, ioon-kanaal nabootsers, metaal-ioon ekstraksie, molekulêre skakelaars en ligande vir metaalkatalise. Selektiewe funksionalisering van resorsinarene was al voorheen bestudeer, maar die metodologieë was beperkend ten opsigte van die struktuele argitektuur en nuwe toepassings wat daaruit gekom het. In hierdie werk was C_{4v} simmetriese resorsinareen eters gesintetiseer wat gebruik was as uitgangstowwe om selektiewe funksionalisering deur orto-litiëring te bewerkstellig.

Kondisies vir die effektiewe sintese van distaal gesubstitueerde resorsinarene, deur gebruik te maak van orto-litiëring, was bepaal en ge-optimaliseer deur gebruik te maak van ‘n wye reeks elektrofiele, laer rand lengtes, reaksieskale, basis ekwivalente en reaksie tye. Deur dié proses was dit moontlik om distaal gesubstitueerde resorsinareen produkte te bekom in redelike opbrengste (>80%) met meeste funksionele goepe.

Daar word voorsien om orto-litiëring, en sy vermoë om distale-resorsinareen esters te vorm,van gebruik te maak as ‘n beginpunt in die sintese van distale-chlorometiel resorsinarene, wat op hulle beurt weer sal dien as uitgangstowwe vir die sintese van distale-resorsinareen imidasolium soute. Hierdie distale, bidentale soute kan gebruik word as karbeen ligande in oorgangsmetaal koordinasie.

Table of contents

Chapter II

Chapter III

List of abbreviations

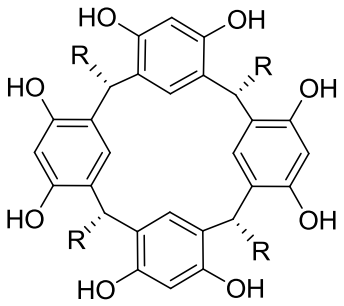
CIPE	Complex Induced Proximity Effect
DMG	Directing Metalation Group
DMS	Dimethyl disulfide
TEMEDA	Tetramethylethylenediamine
NHC	N-heterocyclic carbene
FLP	Frustrated Lewis pair
TLC	Thin layer chromatography
ESI	Electrospray ionization
IR	Infrared spectroscopy
MALDI-TOF	Matrix-Assisted Laser Desorption-Time of Flight
NMR	Nuclear Magnetic Resonance

Chapter I

Introduction

1.1. History and chemistry of resorcinarenes:

Resorcinarenes, the three-dimensional cyclic aromatic tetramers belonging to a class of $[1]_4$ metacyclophanes,[1-3] have been known since 1872 when Adolf von Bayer reported the condensation reaction of resorcinol and aldehydes.[4] About a decade later Micheal proposed that the compounds are formed by equimolar amounts of aldehyde and resorcinol.[5] Nearly a century later the structure **1** was proposed based on molecular weight determination methods. The structure was finally proved by Erdtman using crystallographic techniques.[6] Having known the structure of the compounds, NMR studies were performed on the conformational changes of resorcinarene esters in chloroform. This was accompanied by clarity on some of the acid catalysed rearrangement of stereoisomers which were later analysed by Mann.[7]

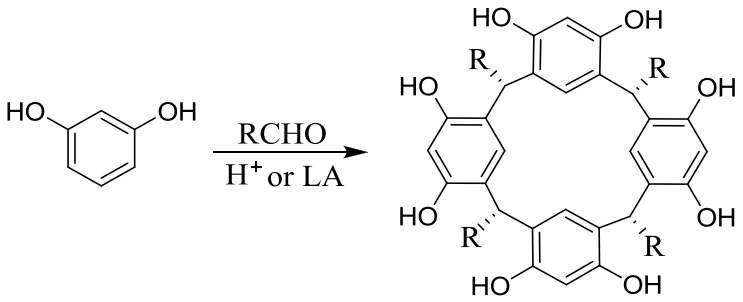


1 R = Alkyl, Aryl

Figure 1: Structure of resorcinarenes.

Various names, like Högberg compounds, calix[4]resorcinarenes, resorcinolarenes and octols, were given to the compounds until a widely accepted trivial name, resorcinarenes, was introduced in 1994.[8] Over the years resorcinarenes have gained access to a number of applications including use as solid support in gas chromatography,[9-11] HPLC stationary phases,[12-17] molecular receptors systems,[18-21] photo resists,[22-26] selective membranes,[27-30] ion channel mimics,[31-34] metal ion extraction agents,[35-38] ligands for organometallic catalysts,[39-42] starting materials for supramolecular compounds synthesis,[43-46] and molecular switches.[47-49] Research efforts performed on resorcinarenes so far are reflected in a number of reviews discussing their chemistry and applications.[46, 50-54]

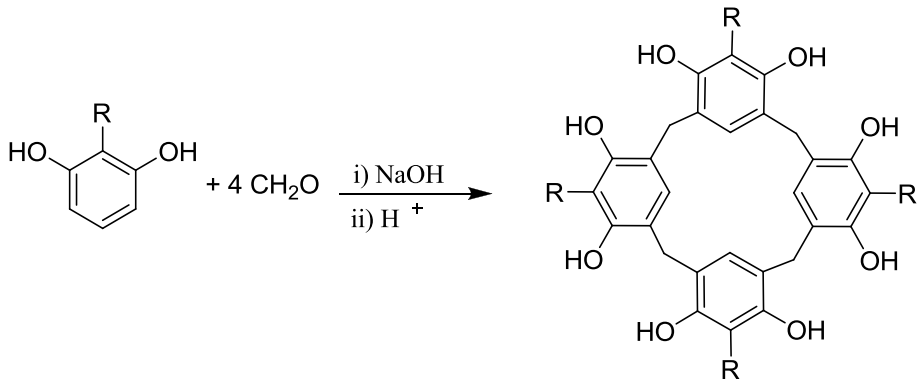
1.2. Synthesis of resorcinarenes:



Scheme 1: Acid-catalyzed preparation of resorcinarenes.

Resorcinarenes are synthesised *via* a one-pot reaction procedure using equimolar amounts of resorcinol and aldehyde under acidic conditions (Scheme 1). The reaction has been shown to tolerate a wide variety of aldehydes ranging from aliphatic (including saturated, unsaturated and derivatized) and aryl aldehydes.[55-57] The original preparation of these compounds was performed using a mixture of resorcinol and suitable aldehydes in ethanol under acidic conditions and stirring for twenty hours at mild temperatures (mostly between 0 °C and 70 °C). The product resorcinarene could be isolated in reasonable to excellent yields. The macrocyclic product, insoluble in solvents used in this reaction, precipitates out of the reaction once formed and is then easily collected by filtration.[55] Brønsted acid catalysis was used in the development stages of this technology, typically using hydrochloric acid. Over the years Lewis acid catalysts have been developed and proven to generate efficient yields. Some Lewis acid catalysts have been developed and designed to provide selectivity as to which stereoisomer is formed.[58] Green procedures using a solvent free system,[59-63] use of functionalized aldehydes, more than one aldehyde in ratios adding up to four equivalents in an effort to afford mixed alkyl chain (mixed feet) resorcinarenes,[64, 65] and use of 1,3,5-oxanes in place of aldehydes mark recent development in this synthesis.[66]

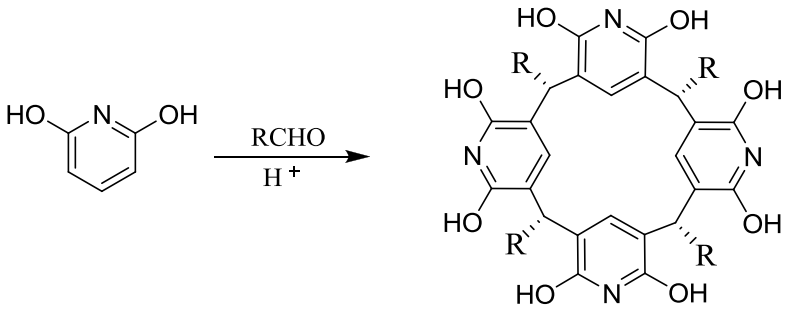
Functionalized resorcinols have also been used; these are used as starting materials in one-pot syntheses of functionalized resorcinarenes. However, it was found that though resorcinols with electron donating groups at their 2-positions preferred the usual acidic conditions to form any resorcinarenes, resorcinols with electron withdrawing groups at their 2-positions preferred rather basic conditions (Scheme 2).[67]



Entry	R	Yield (%)
1	NO_2	60
2	Ac	37
3	CO_2H	50
4	H	16

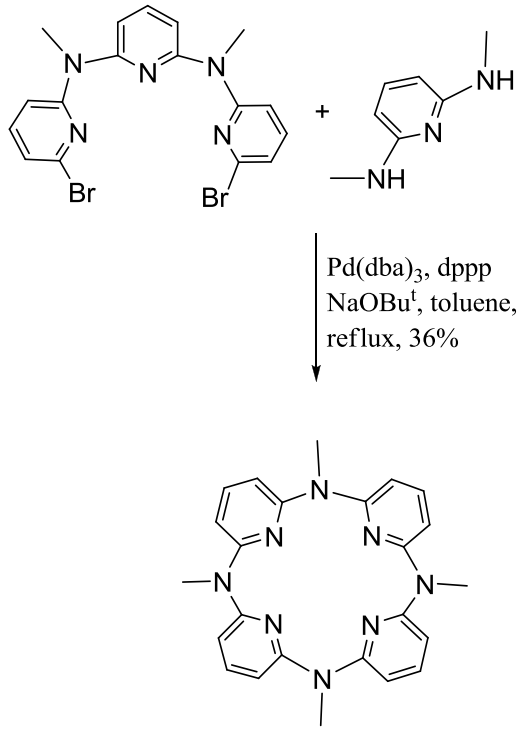
Scheme 2: Novel preparation of variant resorcinarenes.

Pyridine analogues of resorcinarenes, pyridine[4]arenes, have been derived from cyclocondensation of 2,6-functionalised pyridines and aldehydes following reaction procedures similar to those used when preparing resorcinarenes (Scheme 3).[68, 69]



Scheme 3: Preparation of pyridine derivatives of resorcinarenes.

The concept of introduction of heteroatom bridges at the benzylic positions of resorcinarenes instead of methylene bridges, e.g. NR in place of CH_2, is an exceptionally interesting modification giving rise to a class of resorcinarene derivatives called heterocalixaromatics (Scheme 4). Nitrogen, for instance, can adopt a sp^3 or sp^2 electronic configurations giving systems of different conjugation between the heteroatom and adjacent aromatic rings. Various C-N bond lengths and C_{Ar}-N-C_{Ar} bond angles are thus obtained. Simple control over macrocycle conformation and electronic properties through hetero atom choice are interesting features. Although these compounds are prepared using more complex procedures compared to resorcinarenes, they are an interesting variety.[70]



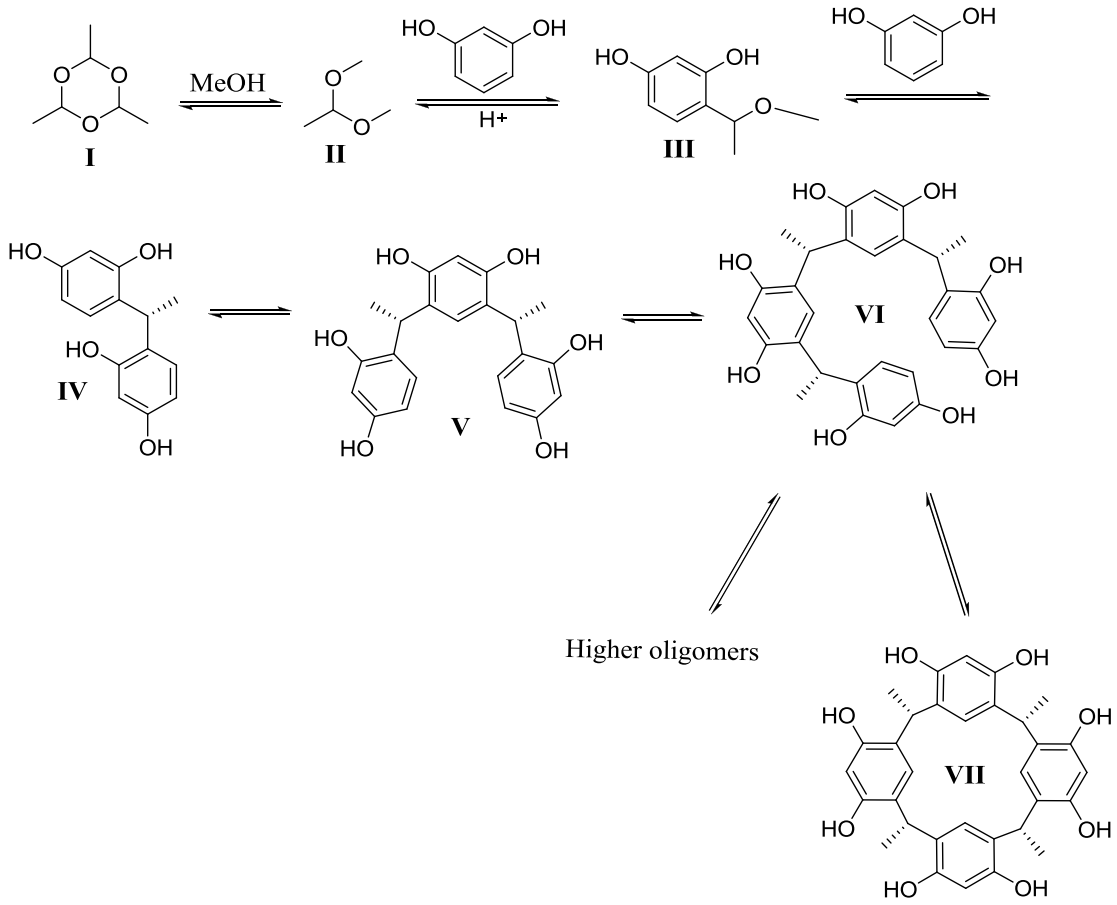
Scheme 4: Synthesis of heteroatom containing macrocyclic cyclophanes, hetero calixaromatics.

1.2.1. Mechanism of macrocyclic condensation:

It is of importance to understand the mechanistic aspects of resorcinarene formation as this allows the understanding as to why and how a macrocyclic tetramer forms favourably in such high yields without templates or dilution. The acid-catalyzed condensation has been studied in detail.[71]

According to the study the electrophilic species in the reaction is not the added aldehyde itself but rather its corresponding acetal **II**. The acid-mediated electrophilic addition of **II** to resorcinol leads to the formation of **III** accompanied by formation of a single molecule of methanol. The methoxy group of **III** is displaced and forms a second molecule of methanol upon addition of another resorcinol unit to **III** in order to form the dimer **IV**. A sequential addition of resorcinol units to **IV** leads to formation of **V** and eventually to the linear tetramereric intermediate **VI**. All intermediates did not exhibit any terminal methoxy groups, as observed in **III**, which is in accordance with known examples of acid-catalyzed condensations. Further sequential addition of more resorcinol units to form higher oligomers occurs during the reaction but mostly vanished towards the end of the reaction to form **VI**. Once formed, the linear tetramer **VI** rapidly cyclizes with another equivalent of the aldehyde derived acetal to form the cyclic tetramer **VII**. The rapid cyclisation in the last step is a result

of two main factors; namely lack of conformational strain and hydrogen bonding between adjacent hydroxyls of resorcinol units.



Scheme 5: Mechanism of resorcinarenes macrocycle formation.

1.2.2. Stereochemical aspects of resorcinarenes:

Resorcinarenes are non-planar, three-dimensional compounds and therefore have a number of strereoisomers are generated (Figure 2).[1,2,56] Three criteria are used to explain their stereochemistry: the first considers the flexibility of the benzylic positions between the resorcinol units. In one conformation resorcinol units can occupy a position where they are orientated upwards in a bowl-like shape, this forms the crown conformer. In another two opposite resorcinol rings can occupy an upward position with the other two rings lying in a perpendicular position to them, this sort of orientation forms the boat conformer. The molecule may contain one upward orientated ring with two adjacent rings perpendicular to it and the fourth in a downward position, in which case forms a chair isomer. The last two conformers have two rings orientated in an upward positions and the other orientated in a

downward position. The diamond isomer has two adjacent rings orientated upwards and the other adjacent two downwards whilst the saddle isomer had two opposite rings facing upwards and the other opposite two facing down.

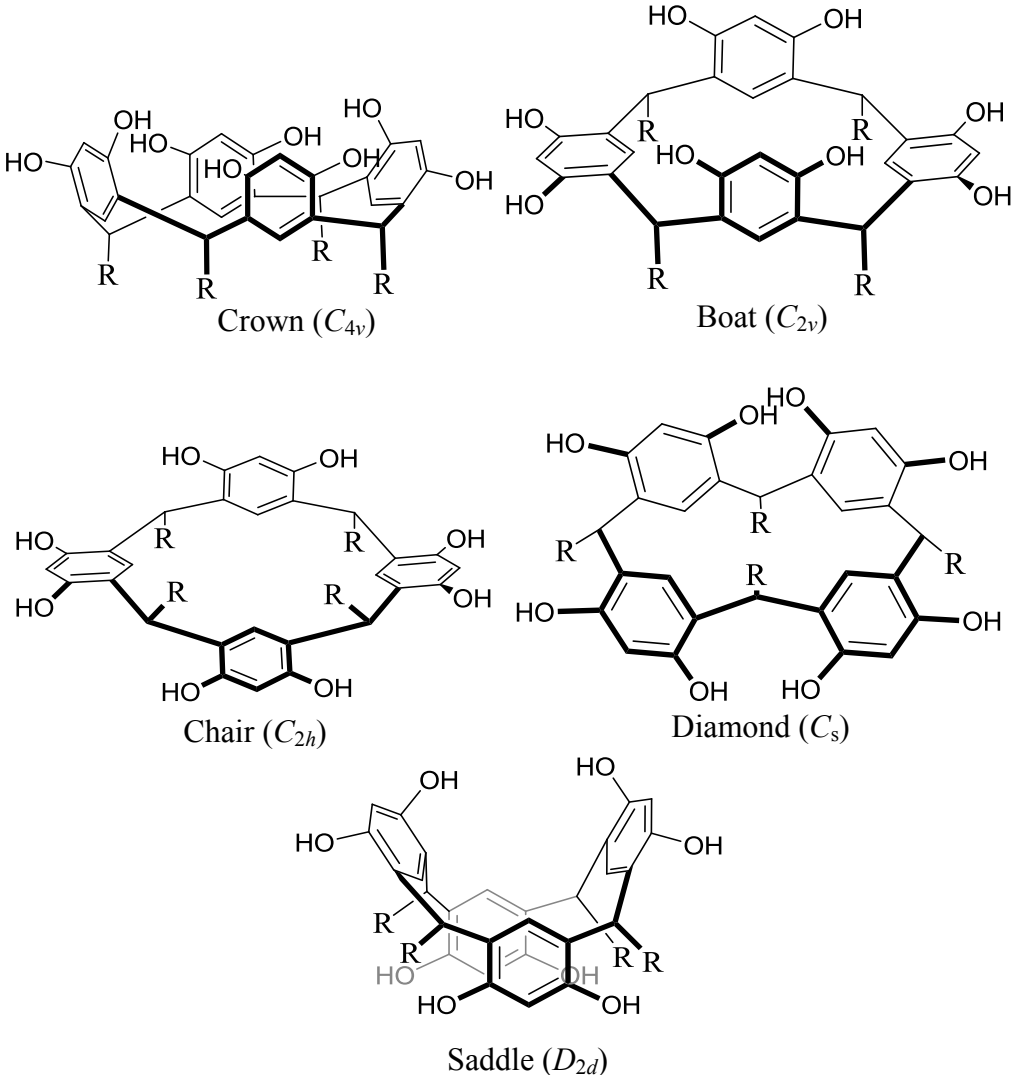


Figure 2: Macrocyclic ring conformation.

Another criterion defines the orientation of groups attached to carbon atoms at the benzylic positions of resorcinarenes (Ar-*C*-Ar). This results in four stereoisomers (Figure 3): one having all attached groups facing the same direction in a *cis*-relationship to a reference (r) group (rccc), one on opposite orientation (in a *trans*-relationship) to the other three (rcct), two groups opposite to a pair containing the reference group (rctt) and a scenario where the reference group is in a *cis*-relationship with the substituent opposite to it and in a trans relationship with those adjacent to it (rtct).

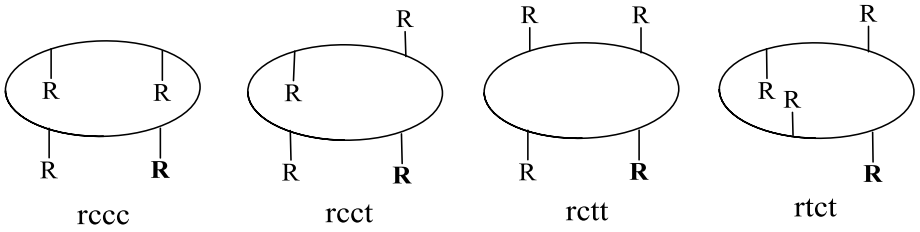


Figure 3: Relative configuration at methylene bridges.

The last criterion constitutes the individual stereochemistry of substituents on the carbon atoms at benzylic positions of the resorcinarene macrocycle which may be in an axial or equatorial position on the macrocycle *C* symmetry. The combination of all criteria provides a wide range of possible stereoisomers several of which have been observed experimentally.

1.3. Functionalisation of resorcinarenes:

Various methodologies to prepare functionalized resorcinarenes have been devised and developed over the years. Though these methodologies allow the preparation of various resorcinarenes, modification is mainly performed at the three functionalizable positions possessed by these compounds (Figure 4). The first, namely the lower rim, arises from the choice of aldehyde used in the synthesis of the resorcinarenes. Phenolic hydroxyl groups, which allow for O-alkylation or acylation reactions, and the third, the ortho position, refers to the 2-position on each resorcinol unit. Four of such positions are observed on resorcinarenes.

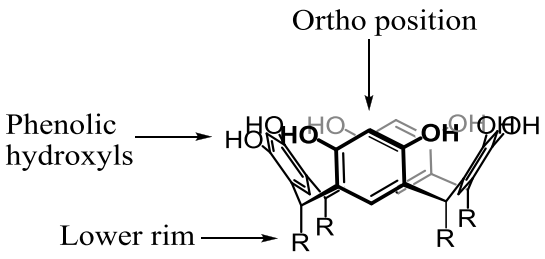
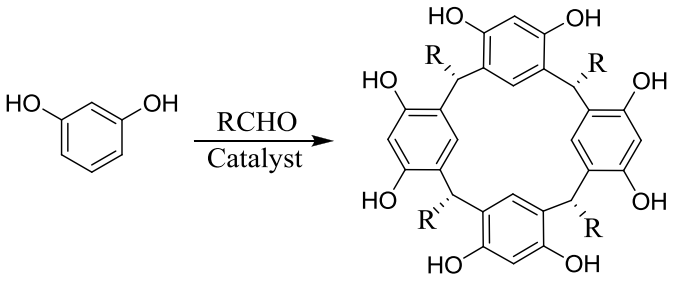


Figure 4: Functionalizable positions of resorcinarenes.

1.3.1. Lower rim functionalization:

Functionalization at this position is based on the choice of the aldehyde used in the reaction since the group attached to the aldehyde functionality ends up forming the lower rim. A wide variety of aldehydes has been used successfully in the synthesis, including saturated and

unsaturated alkyl aldehydes,[55,58,72] and phosphorus containing aldehydes.[73,74] Functionalized aldehydes can, therefore, provide access to lower rim functionalizable resorcinarenes. The tetrabutan-1-ol resorcinarene in Scheme 6 is a suitable example.[75,78] Also, use of a mixture of different aldehydes leads to formation resorcinarenes bearing various lower rim functionalities.

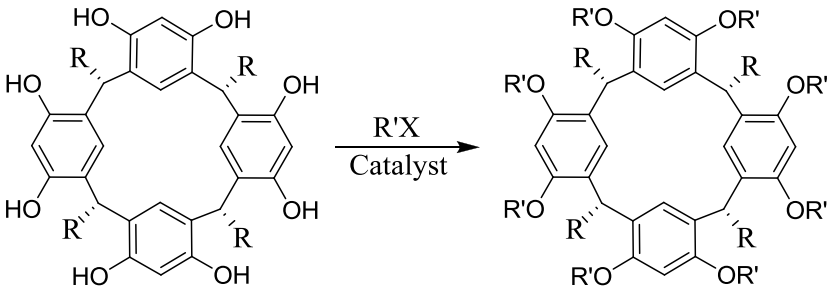


Entry	R	Yield (%)
1	CH_3	60
2	C_2H_5	88
3	C_5H_{11}	77
4	$C_{11}H_{23}$	68
5	C_6H_5	66
6	$HO(CH_2)_4$	88
7	Butoxy benzene	79
8	Benzo-15-crown-5	73

Scheme 6: Lower rim functionalization of resorcinarenes.

1.3.2. O-alkylation:

The phenolic alcohols of resorcinarenes undergo usual reactions known to other alcohols and phenols, e.g. esterification and etherification.

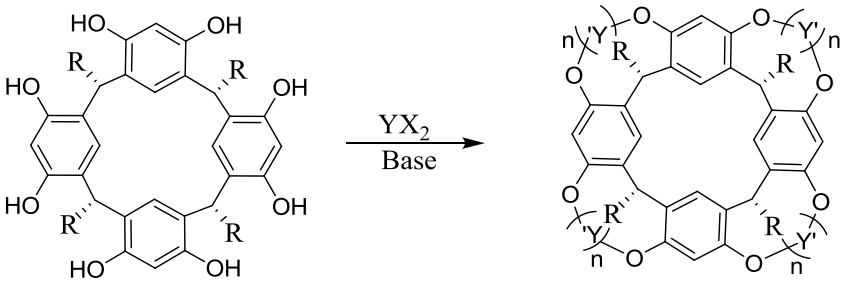


R'
p-$TolSO_2$
$PO(Oi\text{-}Pr)_2$
Bn
Ph_2P

Scheme 7: O-alkylation of resorcinarenes.

This functionalisation has been used to prepare octafunctionalised resorcinarenes by reacting alkyl groups, a review has been published on O-alkylation of the compounds.[79] For example, reacting the phenolic hydroxyls of resorcinarenes with 3-alkoxy-5-benzylbromidealkoxybenzyne in the presence of potassium carbonate managed to furnish resorcinarene dendrimers via this type of functionalisation. This approach, O-alkyl functionalisation, was extended by performing selective O-alkylation to induce chirality on resorcinarenes; a review on this topic has been published.[51, 80] Non-carbon atom containing compounds, e.g. sulphur and phosphorus, have been prepared.[81-84] O-functionalized resorcinarenes, including O-metal functionalized resorcinarenes, have also been prepared.[85]

Furthermore, the reaction of groups bearing two leaving groups with resorcinarenes under basic conditions allow for the formation of bridged (O-R-O) rigid resorcinarene derivatives, namely cavitands, where the linker group (R), if alkyl, can range in length and allow adjustment of the cavity.[86, 87] The linker group can be varied, for instance the use of 2,3-dichloroquinoxaline leads the formation of wall-possessing resorcinarenes, velcrands (vases and kites).[88-90]



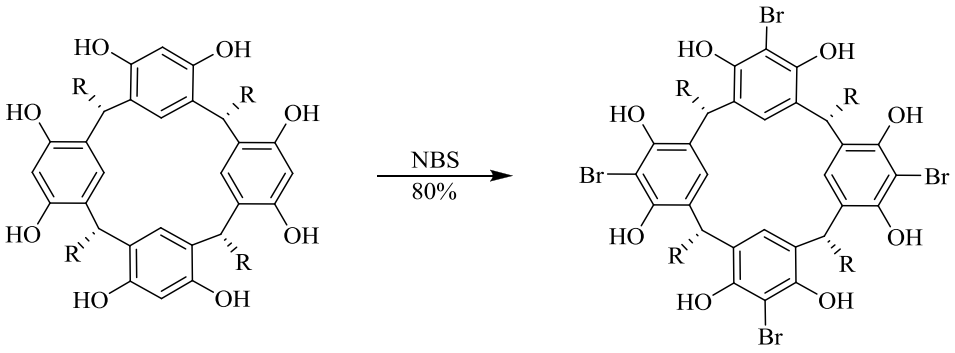
Y'	n	X
CH_2	1	LG
	2	
	3	
Si	1	
P	1	
Crown ether		
M = Zr, Fe	1	

*LG denotes a leaving group
*Y' is part of Y that encorporates to the reosrcinarene to form the product.

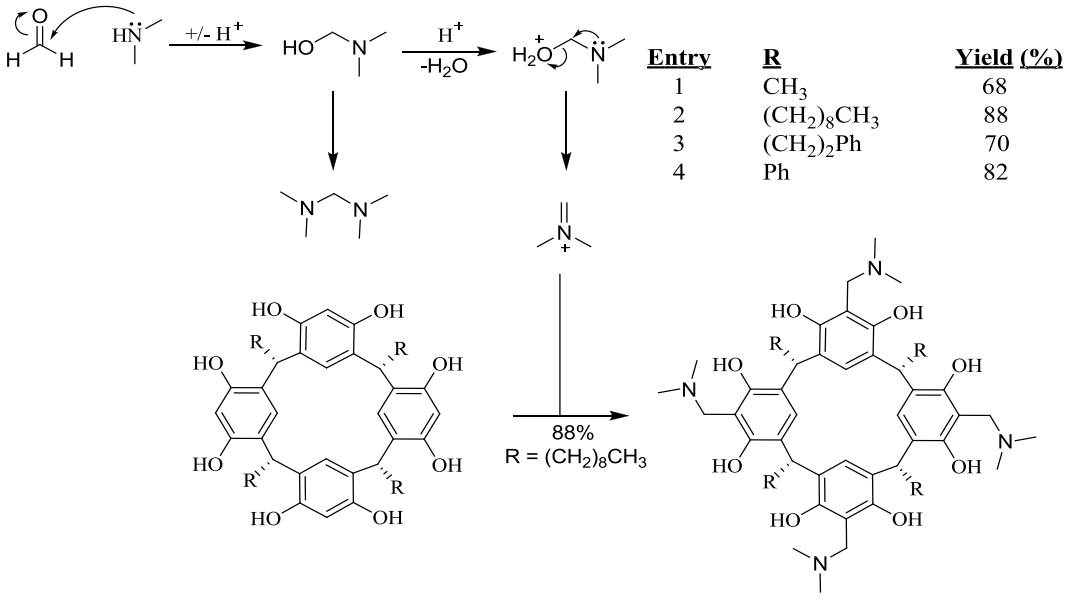
Scheme 8: Preparation of resorcinarene cavitands.

1.3.3. Upper rim functionalisation:

Like any other aromatic compound, resorcinarenes can undergo electrophilic substitution reactions, under suitable conditions, at their upper rims ortho positions to furnish tetrafunctionalized resorcinarenes. Since these positions are activated by the electron donating phenolic groups these compounds are suitable for aromatic electrophilic substitution. A simple demonstration of this is the reaction with *N*-bromosuccinamide to furnish tetrabrominated resorcinarenes in yields of up to 80%.[55, 77]



Scheme 9: NBS bromination of resorcinarenes.



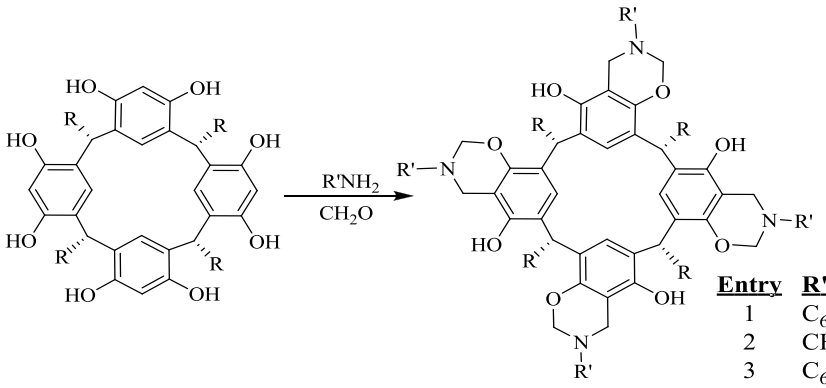
Entry	R	Yield (%)
1	CH_3	68
2	$(CH_2)_8CH_3$	88
3	$(CH_2)_2Ph$	70
4	Ph	82

Scheme 10: Mechanism of generation of Mannich iminium and its reaction with resorcinarenes.

Another well reported electrophilic substitution reaction on these compounds is the Mannich reaction. This approach has also been applied successfully on cavitands. The mechanism and an example of this reaction can be seen in Scheme 10. Here a reaction between formaldehyde

and an amine generates an electrophilic imine salt which reacts with resorcinarenes to return tetra-aminated resorcinarenes.[91-95]

The tetrabromo and tetraamino resorcinarenes can act as starting materials for performing further architectural constructions. To construct on the tetrabromo and tetraamino resorcinarenes, the resorcinarene 2-position substituents can be substituted for more complex moieties (*e.g.* on the tetrabromo compound using lithium-halogen exchange) or modified to more interesting groups (Scheme 11).

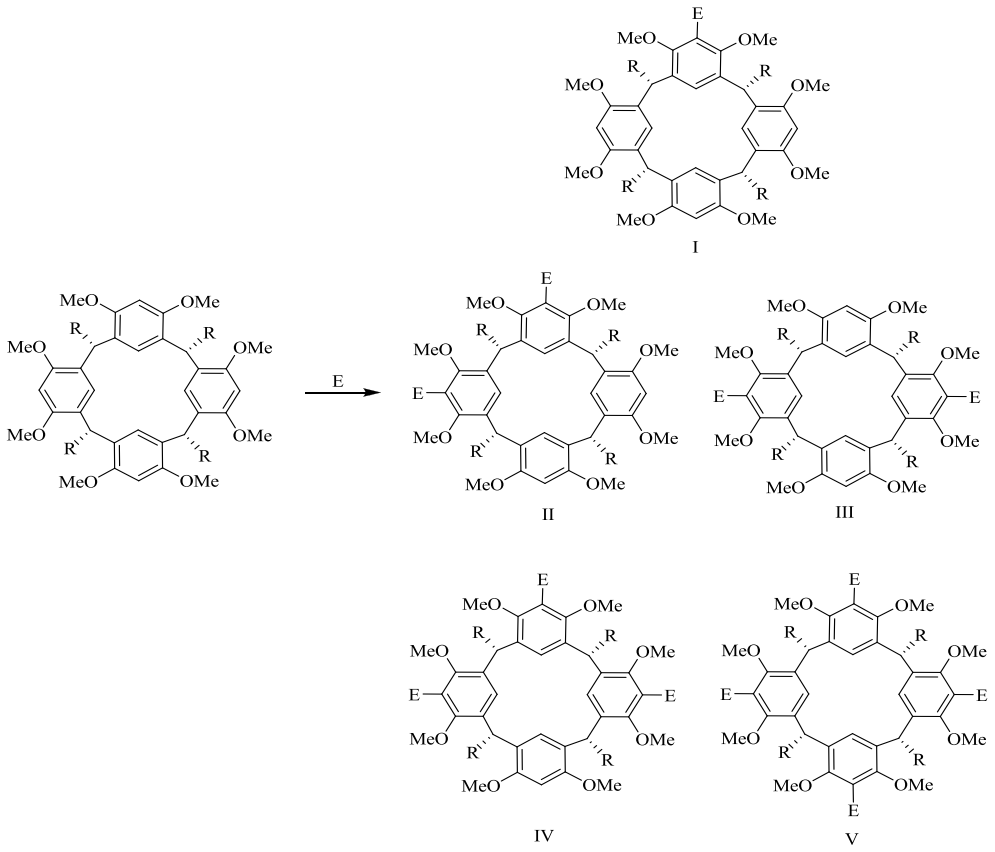


Entry	R'	Yield(%)
1	C_6H_{11}	72
2	CH_2CO_2Et	75
3	C_6H_5	84

Scheme 11: Aminomethylation of resorcinarenes.

1.4. Selective functionalization of resorcinarenes:

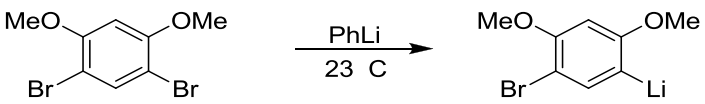
Apart from preparation of tetrafunctionalized resorcinarenes and their cavitands mentioned above, methodologies for selective functionalization of these compounds have been devised. Conceptually, since there are four electrophilic positions, incomplete functionalization would give rise to five differently substituted products (Scheme 12): a monofunctionalized product **I**, two bis-functionalized resorcinarenes (proximally **II** or distally **III** functionalized) and a tri- **IV** or a tetrafunctionalized **V** resorcinarenes. Two methodologies that can be used to obtain distal functionalized resorcinarenes are reported in literature. These are a lithium-halogen exchange reaction devised by Sherburn,[96,97] and the selective acylation approach devised by Shivanyuk.[98,99]



Scheme 12: Possible products formed by reactions of resorcinarenes with electrophiles.

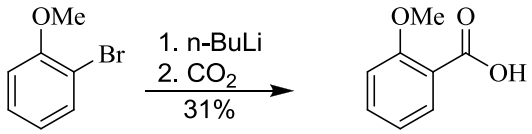
1.4.1. Lithium-halogen exchange:

Exchange of a halogen for a lithium atom, generating an organolithium compound, is one of the most useful applications of organolithium compounds. First reported by Wittig in 1938 while studying deprotonation of aromatic rings with phenyllithium,[100] lithium-halogen exchange generates nucleophilic organolithium intermediates from alkylhalides whose reactions with electrophiles leads to formation of functionalized organic compounds (Scheme 13).



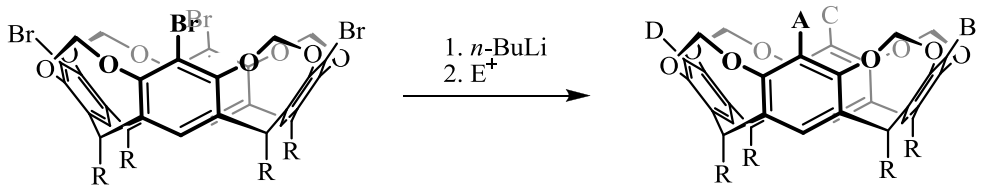
Scheme 13: Wittig's lithium-halogen exchange.

Shortly after Wittig's report, Gillman reported a demonstration of lithium-halogen exchange on *o*-bromo anisole using *n*-butyllithium in preparing *o*-methoxy benzoic acid in 31% yield by quenching the intermediate aryllithium species with CO_2 (Scheme 14).[101] In 2000 Sherburn performed lithium-halogen exchange on cavitands to achieve selective functionalisation.



Scheme 14: Gillman's lithiation of anisole.

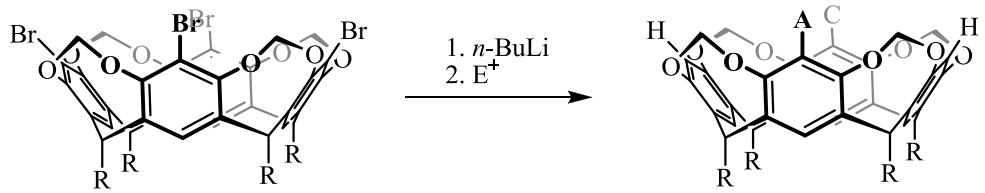
Using this approach he was able to achieve mono-, proximal-, distal-, *tri*- and *tetra*-functionalized cavitands in yields ranging between 46 and 69%.[96] Though the approach is not a one-pot process, it received a wide acceptance as it provides best achievable selectivities and yields and is a viable gateway to partial functionalization of the compounds (Scheme 15).



***n*-BuLi (equiv)**	**A**	**B**	**C**	**D**
1.1	E	H	H	H
2.2	E	E	H	H
	E	H	E	H
3.3	E	E	E	H
4.4	E	E	E	E

Scheme 15: Shurburn's lithium-halogen exchange on cavitands.

Shortly after this, in 2001, Sherburn and colleagues reported efficient conditions for distal-functionalisation of the rigid bowls demonstrating the application of the methodology to functionalizing cavitands with various functional groups other than hydroxyl groups.[102]

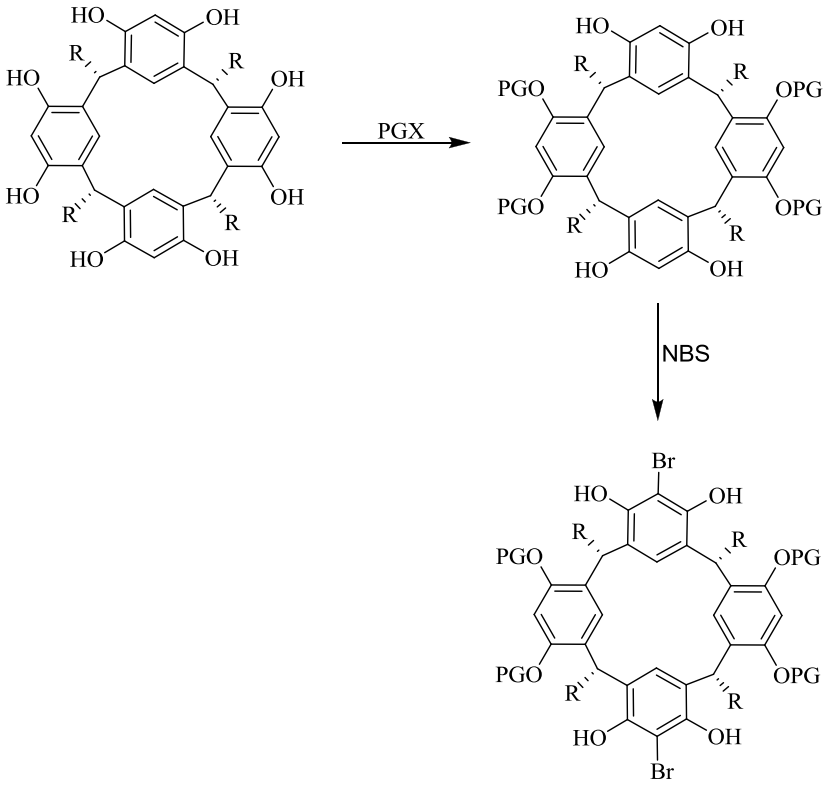


***n*-BuLi (equiv)**	**A & C**
2.2	I
	CHO
	CO_2Me
	COPh
	OH

Scheme 16: Selective distal functionalization of cavitands.

1.4.2. Selective acylation:

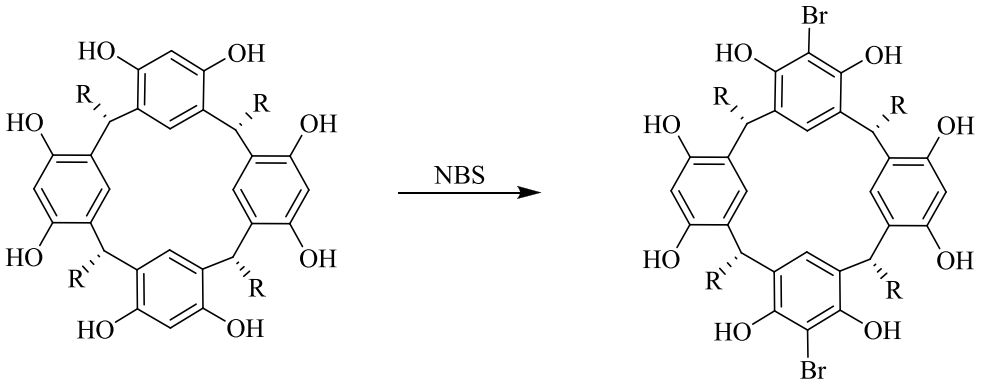
In 1994 Shivanyuk and co-workers found a procedure to selectively modify the phenolic hydroxyls of resorcinarenes to form tetraacylated products. By reacting resorcinarenes with phosphorylating agents they were able to obtain distal tetraphosphorylated resorcinarene. In an aim to extend the methodology, the group explored other protecting groups including sulfonyl, aroyl and heteroaroyl chlorides and benzylchloroformate. One conclusion from this work was that selective acylation depends mainly on the nature of both the solvent and the acylating agent.[103-105] Equipped with the methodology, selective distal functionalization of resorcinarenes was made possible and the group demonstrated a distal functionalization of the compounds via the Mannich technology. It was in 2004,[106] when they attempted the Mannich reaction on resorcinarenes using trishydroxymethylmethylamine, the group reported a rather unusual observation. Instead of isolating an aminated product they noticed that an alkoxy functionalization had occurred instead extending their methodological findings to alkoxy, acyloxy and bromomethylation.



Scheme 17: Shivanyuk's selective functionalisation.

Although the yields of the distal-protected products isolated via this technology were not obtained above 50%, without a comparable competitor it received considerable attention as a synthetic procedure for distally functionalized resorcinarenes.

Another selective methodology worth mentioning is Konishi's selective bromination. By reacting octahydroxy resorcinarenes with two equivalents of N-bromosuccinamide, Konishi and co-workers were able to isolate distally brominated resorcinarenes but only in low yields.[107]



Scheme 18: Konishi's selective bromination of resorcinarenes.

1.5. Ortholithiation:

Ortholithiation, the directed metalation of an aromatic compound at a position adjacent to a heteroatom containing functionality, has proved to be one of the most viable methodologies for functionalizing aromatic compounds.[108-113] As opposed to lithium-halogen exchange, the methodology requires no pre-halogenations for the metalation to occur and unlike electrophilic aromatic substitution it is more regiospecific. As the name suggests, lithium reagents (organolithiums), historically known to Ziegler in the 1930s,[114] are used to metalate aromatic compounds.

This aromatic substitution approach, whose initial attempts stem from Wittig and Gillman also in the 1930s,[100, 101] has received enormous attention from various authors over the decades whose efforts developed the understanding of the methodology in terms of conditions,[115-117] substrates,[111, 118] directing functional groups and organolithium reagents.[119-123]

1.5.1. Directing groups in Ortholithiation:

The ability of various functional groups containing heteroatoms to direct substituents in ortholithiation has been studied in detail by numerous authors and is governed by several principles. Firstly, the heteroatom acts as a Lewis basic point on the directing metalation group (DMG). This allows electron donation and enables coordination to the metal atom of the organolithium reagent. Most DMGs are also strongly electron withdrawing which acidifies the ortho proton in the aromatic ring. Lastly, they are useful transformable functional groups and can hence be modified. Most DMGs do suffer some drawbacks, however. These DMGs contain electrophilic points (e.g. carbonyl carbons) which may themselves be attacked by lithium reagents which then require steric encumbering. Though results from studies of the ability of DMGs to direct lithiation have disagreed at times it has been possible to elucidate tangible data to lay a basic understanding of their directing strength and sort them accordingly in their relative classes. This is indicated in the Figure 5 below. Ethers, in general, are relatively poor metalation directors but use of small ether groups (i.e. methoxy ethers) makes this DMG extremely good at directing metalation to a position next to them.[124]

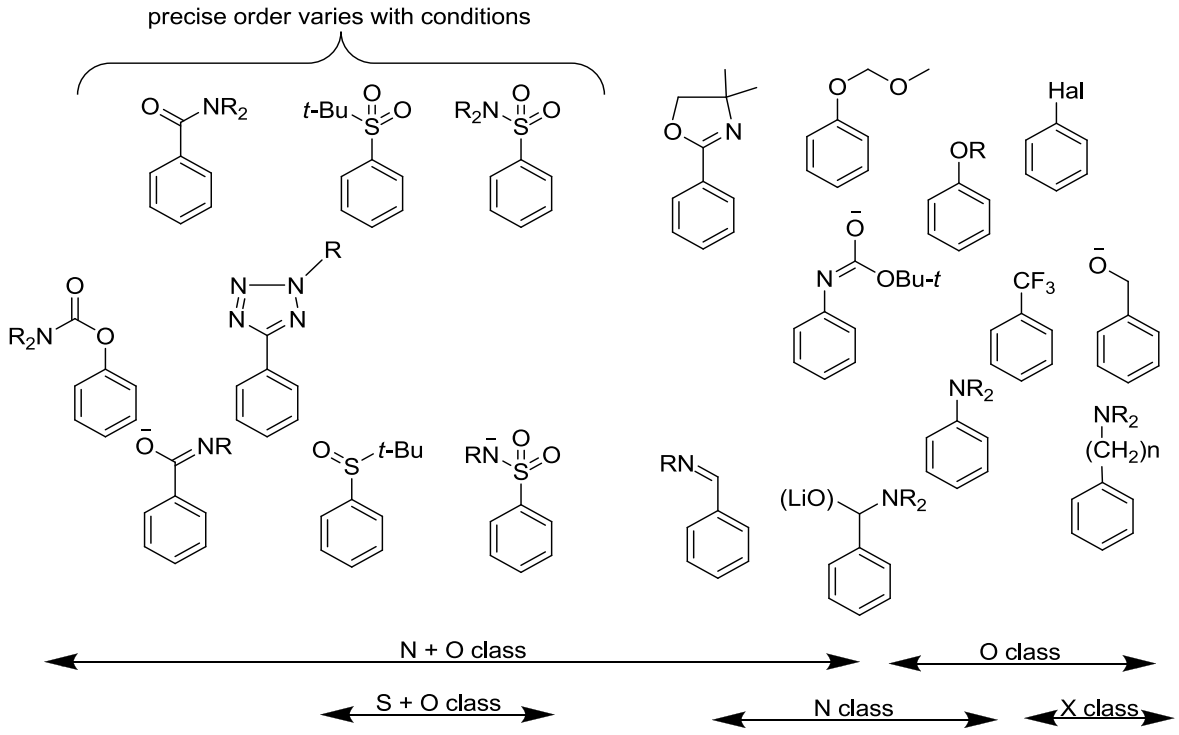
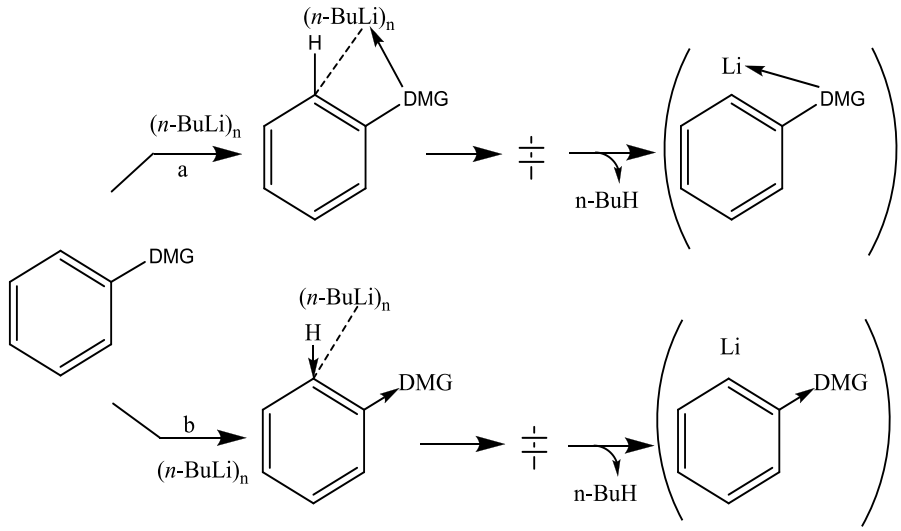


Figure 5: Directing metalation groups in relative classes.[124]

Octamethoxy resorcinarenes satisfy requirements for strong ether group metalation direction and each resorcinol unit possesses features possessed by anisole, e.g. joint directing effect, which are crucial for ortho-directed metalation.

1.5.2. Mechanism of Ortholithiation:

Up to the present time views on the mechanistic path of metalation (ortholithiation) holds that two limiting mechanisms occur: the complex induced proximity effect (CIPE) and the overriding base mechanisms. According to the CIPE mechanism the coordination complex formed between the alkyllihthium base (e.g. n-BuLi) and directing metalation group (DMG) on the substrate is important for the formation of the initial coordination complex. The complex induces lithiation by facilitating the proximity of the base to the ortho proton of the substrate (proximity effect). The overall effect is promotion of lithium-ortho-hydrogen exchange.[125-131]



Scheme 19: Limiting mechanisms for directed ortho metalation.[132]

The overriding base mechanism is driven by the acidity of ortho protons. As mentioned earlier although DMGs bear heteroatoms mainly for coordination to alkyllithiums, heteroatom-containing functionalities are mostly inductive withdrawers due to their high electronegetivity and, therefore, inductively acidify ortho protons. Bases are, therefore, highly likely to deprotonate substrates with DMGs bringing about facilitated ortho metalation. It does appear within existing views that most DMGs, including ethers, direct by

the combination of the two mechanisms which facilitates highly regiospecific metalation. Also, based on lithiation studies on anisole, most DMGs, including ethers, de-oligomerise alkyllithiums to lower aggregation states increasing their reactivity and bringing about substrate-controlled synthesis. A similar observation can be facilitated by solvents.

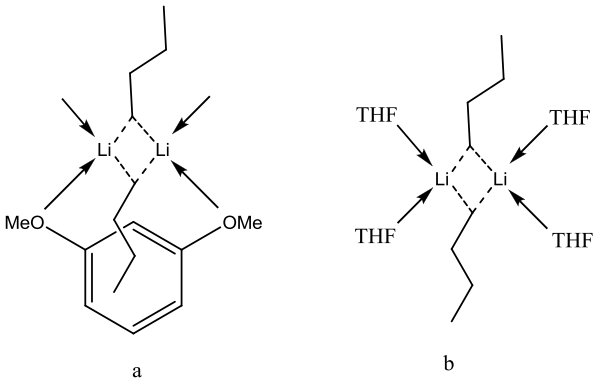


Figure 6: Substrate (anisole) and solvent (THF) facilitated deoligomerization of *n*-BuLi.[132]

1.6. Conclusion:

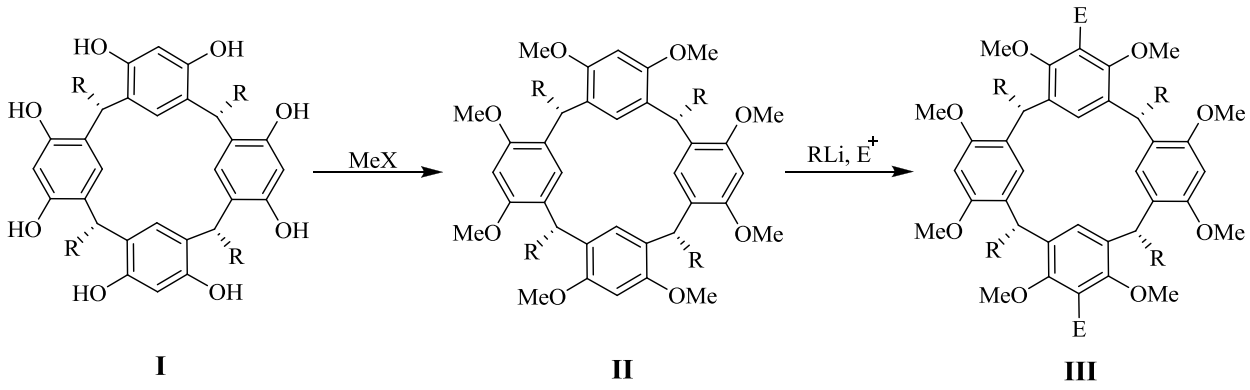
This literature survey mainly serves the purpose of introducing the reader to the synthesis, structure, chemistry, properties, potential applications and selective functionalization of resorcinarenes. Through research efforts methods to distally substituted resorcinarenes have been developed but their drawbacks still limit selective functionalization and hence applications of resorcinarenes. Overall, new methodologies for selective functionalization are still required.

1.7. Objectives:

Functionalization of resorcinarenes is a well performed task and has been carried out in many laboratories, documenting numerous findings in literature. Efficient and selective functionalization has also been attempted which offers distally functionalized resorcinarenes. Shivanyuk's methodology allows clean distal functionalization with a low yielding step. A more efficient methodology, offering various products selectively, applies to cavitands and does not hold when applied to resorcinarenes.[96]

For the current study, considering the structure of resorcinarenes, it was decided to develop conditions for selective distal functionalization of resorcinarenes using an ortholithiation approach. It was believed that functionalizing the hydroxyl units of octahydroxy resorcinarenes with methyl groups would offer a system which resembles a tetramer of

anisole and would be liable to ortholithiation as anisole. The methoxy groups would acidify the orho-hydrogen atoms and chelate alkyllithium reagents to facilitate lithiation at the ortho-positions. Through manipulation of conditions selective functionalization would be possible as performed by Sherburn on cavitands.



Scheme 20: Methylation and selective ortholithiation of resorcinarenes.

To prepare starting resorcinarene ethers, the resorcinarene hydroxyl groups would be methylated to form octamethoxy resorcinarenes. The materials would then be applied as study materials for the ortholithiaon methodology. The methodology would need to hold for various electrophiles and lower rim lengths in high yield to form a viable gateway to numerous differently functionalized resorcinarenes.

1.8. References

1. Högberg, A. G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6046.
2. Högberg, A. G. S. *J. Org. Chem.* **1980**, *45*, 4498.
3. Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663.
4. Baeyer A. *Tetrahedron* **1872**, *5*, 280.
5. Micheal, A. *Am. Chem. J.* **1883**, *5*, 338.
6. Erdtman, H.; Hogberg, S.; Abrahamsson, S.; Nilsson, B. *Tetrahedron Lett.,* **1968**, 1679.
7. Mann, G.; Weinelt, F.; Hauptmann, S. *J. Phys. Org. Chem.* **1989**, *45*, 4498.
8. Schneider, U.; Schneider, H. J. *Chem. Ber.* **1994**, *127*, 2455.
9. Zhang J.; Zhang T.; Lu G.; Fu R.; Zhao Z. *Fenxi Huaxue* **1999**, *27*, 85.

10. Zhang H.; Ling Y.; Dai R.; Wen Y.; Fu R.; Gu J. *Chem. lett.* **1997**, 225.

11. Zhang H.; Zhang T.; Lu G.; Fu R.; Zhao Z. *Fenxi Huaxue* **1997***, 840*, 145.

12. Sokoliess T.; Menyes U.; Roth U.; Jira T. *Chromatogr. , A* **2002***, 948*, 309.

13. Sokoliess T.; Opolka A.; Menyes U.; Roth U.; Jira T. *Pharmazie* **2002***, 57*, 589.

14. Sokoliess T.; Menyes U.; Roth U. Jira T. *laborPaxis* **2001***, 25*, 28.

15. Pietraszkiewics M.; Pietraszkiewics O.; Kozbial M. *Pol. J. Chem.* **1998***, 72*, 1963.

16. Pietraszkiewics M.; Pietraszkiewics O. *J. Inclusion Phenom.* **1999***, 35*, 261.

17. Ruderisch A.; Iwanek W.; Pfeiffer J.; Fischer G.; Albert K.; Schurig V. *J. Chromatogr. A* **2005***, 1095*, 40.

18. Hayashida, O.; Uchiyama, M. *Org. Biomol. Chem.* **2008***, 6*, 3166.

19. Botta B.; Caporuscio F.; D'Acquarica I.; Delle Monasche G.; Subissati D.; Taffi A.; Botta M.; Filippi A.; Speranza M. *Chem-Eur. J.* **2006***, 12*, 8096.

20. Maksimov A.; Sakharov D.A.; Filippova T.Y.; Zhuchkova A.Y.; Karakhanov E.A. *Ind. Eng. Chem. Res.* **2005***, 44*, 8644.

21. Demura M.; Yoshida T.; Hirokawa T.; Kumaki Y.; Aizawa T.; Nitta K.; Bitter I.; Toth K. *Bioorg. Med. Chem. Lett.* **2005***, 1415*, 1367.

22. Palmer, L. C.; Shivanyuk, A.; Yamanaka, M.; Rebek Jr, J. *Chem. Commun. (Camb)* **2005***, 7*, 857.

23. Cohen, Y.; Evan-Salem, T.; Avram, L. *Supramol. Chem.* **2008***, 20*, 71.

24. Avram, L.; Cohen, Y. *Org. Lett.* **2008***, 10*, 1505-1508.

25. Gottschalk, T.; Jarowski, P. D.; Diederich, F. *Tetrahedron* **2008***, 64*, 8307.

26. Shivanyuk, A. *J. Am. Chem. Soc.* **2007***, 129*, 14196-14199.

27. Benosmane, N.; Hamdi, S. M.; Hamdi, M.; Boutemeur, B. *Sep. Purif. Technol.* **2009***, 65*, 211.

28. Touaj, K.; Tbeur, N.; Hor, M.; Verchere, J.; Hlaibi, M. *J. Membr. Sci.* **2009***, 337*, 28.

29. Jain, V. K.; Pillai, S. G.; Gupte, H. S. *J. Iran. Chem. Soc.* **2008***, 5*, 646-656.

30. Kurzatkowska, K.; Radecka, H.; Dehaen, W.; Wasowicz, M.; Grzybowska, I.; Radecki, J. *Comb. Chem.* **2007***, 10*, 604.

31. Yoshino N.; Satake A.; Kobuke Y. *Angew. Chem. Int. Ed* **2001***, 40*, 457.

32. Kobuke Y.; Nagatani T. *Chem. Lett.* **2000**, 298.

33. Kobuke Y.; Ueda K.; Sokabe M. *Chem. Lett.* **1995**, 435.

34. Tanaka Y.; Kobuke Y.; Sokabe M. *Angew. Chem. Int. Ed* **1995**, *107*, 717.

35. Jain, V. K.; Pillai, S. G.; Mandalia, H. C. *J. Chil. Chem. Soc.* **2007**, *52*, 1177.

36. Mustafina, A. R.; Zagidullina, I. Y.; Maslennikova, V. I.; Serkova, O. S.; Guzeeva, T. V.; Konovalov, A. I. *Russ. Chem. Bull.* **2007**, *56*, 313.

37. Jain, V. K.; Pillai, S. G.; Kanaiya, P. H. *J. Braz. Chem. Soc.* **2006**, *17*, 1316.

38. Salorinne, K.; Nissinen, M. *Org. Lett.* **2006**, *8*, 5473.

39. El Moll, H.; Semeril, D.; Matt, D.; Toupet, L.; Harrowfield, J. *Org. Biomol. Chem.* **2012**, *10*, 372.

40. Lamb, J. D.; Morris, C. A.; West, J. N.; Morris, K. T.; Harrison, R. G. *J. Membr. Sci.* **2008**, *321*, 15.

41. Puddephatt, R. J. *Can. J. Chem.* **2006**, *84*, 1505.

42. Kleinhans D. J.; Arnott G. E. *Dalton Trans.* **2010**, *39*, 5780.

43. Lepakshaiah, M.; Guru Row, T. N. *J. Mol. Struct.* **2009**, *918*, 10.

44. Mel'nikova, N. B.; Kazakova, E. K.; Guljaev, I. V.; Volkov, A. A.; Gusikhina, M. S.; Zakharova, L. Y.; Voronin, M. A.; Makarova, N. A.; Muslinkina, L. A.; Konovalov, A. I. *Supramol. Chem.* **2009**, *21*, 532.

45. Mustafina, A. R.; Zakharova, L. Y.; Elistratova, J. G.; Voronin, M. A.; Syakaev, V. V.; Konovalov, A. I. *J. Colloid Interface Sci.* **2009**, *333*, 613.

46. Rebek, J. *Acc. Chem. Res.* **2009**, *42*, 1660.

47. Azov V.A.; Schlegel A.; Diederich F. *Chem. lett.* **2007**, *36*, 1926.

48. Lledo, A.; Hooley, R. J.; Rebek, J. *Org. Lett.* **2008**, *10*, 3669.

49. Barrett, E. S.; Dale, T. J.; Rebek, J. *J. Am. Chem. Soc.* **2007**, *129*, 3818.

50. McIldowie, M. J.; Mocerino, M.; Ogden, M. I. *Supramol. Chem.* **2010**, *22*, 13.

51. Iwanek, W.; Wzorek, A. *Rev. Org. Chem.* **2009**, *6*, 398.

52. Moore, D.; Matthews, S. E. *J. Inclusion Phenom. Macrocyclic Chem.* **2009**, *65*, 137.

53. Agrawal, Y. K.; Patadia, R. N. *Rev. Anal. Chem.* **2006**, *25*, 155.

54. Puddephatt, R. J. *Can. J. Chem.* **2006**, *84*, 1505.

55. Cram, D. J.; Karbach, S.; Kim, H. E.; Kobler, C. B.; Maverck, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229.

56. Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C. *J. Org. Chem.* **1989**, *54*, 1305.

57. Egberink, R. M. J.; Cobben, P. L. H. M.; Verboom, W.; Harkema, S.; Reinhoudt, D. N. *J. Inclusion Phenom. Macrocyclic Chem.* **1992**, *12*, 151.

58. Iwanek W.; Syzdo'l B. *Synthetic Commun.* **1999**, *29*, 1209.

59. Karami, B.; Khodabakhshi, S.; Safikhani, N.; Arami, A. *B. Kor. Chem. Soc.* **2012**, *33*, 123.

60. Liang Ya; Liu Xiu-Ming; Sun Guang-Yuan; Wei Rong-Bao *Chinese J. Org. Chem.* **2008**, *28*, 297.

61. Purse, B. W.; Butterfield, S. M.; Ballester, P.; Shivanyuk, A.; Rebek, J. Jr. *J. Org. Chem.* **2008**, *73*, 6480.

62. Wei Rong-Bao; Liang, Y. *Chem. J. Chinese U.* **2008**, *29*, 309-313.

63. Roberts, B. A.; Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Green Chem.* **2001**, *3*, 280-284.

64. Saito, S.; Rudkevich, D. M.; Rebek, J. *Org. Lett.* **1999**, *1*, 1241-1244.

65. Ihm H.; Ahn J.S.; Lah M.S.; KoY.H.; Peak K. *Org. Lett.* **2001**, *6*, 3893.

66. Morikawa, O.; Iyama, E.; Oikawa, T.; Kobayashi, K.; Konishi, H. *J. Phys. Org. Chem.* **2006**, *19*, 214-218.

67. Bourgeois, J. M.; Stoeckli-Evans, H. *Helv. Chim. Acta* **2005**, *88*, 2722-2730.

68. Gerkensmeier T.; Mattay J.; Nather C. *Chem. Eur. J.* **2001**, *7*, 465.

69. Burilov, A. R.; Gazizov, A. S.; Kharitonova, N. I.; Pudovik, M. A.; Habicher, W. D.; Baier, I.; Konovalov, A. I. *Russ. Chem. Bull.* **2007**, *56*, 330-335.

70. Wang, M. *Acc. Chem. Res.* **2012**, *45*, 182-195.

71. Weinelt, F.; Schneider, H. J. *J. Org. Chem.* **1991**, *56*, 5527-5535.

72. Vuano B.; Pieroni O.I. *Synthesis* **1999**, *27*.

73. Popova E.V.; Burylov A.P.; Pudovik M.A.; Habicher V.D.; Konovalov A.J. *Russ.J. Gen. Chem.* **2002**, *72*, 982.

74. Popova E.V.; Burylov A.P.; Pudovik M.A.; Habicher V.D.; Konovalov A.J. *Russ. Chem. Bull.* **2002**, *51*, 1968.

75. Han J.; Cai Y.H.; Liu L.; Yan G.C.; Li Q. *Tetrahedron* **2007**, *63*, 2275.

76. Falabu D.; Shivanyuk A.; Nissinen.; Rissanen *Org. Lett.* **2002**, *4*, 3019.

77. Konishi, H.; Yamaguchi, H.; Miyashiro, M.; Kobayashi, K.; Morikawa, O. *Tetrahedron Lett.* **1996**, *37*, 8547.

78. Agrawal, Y. K.; Patadia, R. N. *Synthetic Commun.* **2006**, *36*, 1083.

79. Moore, D.; Matthews, S. E. *J. Incl. Phenom. Macro.* **2009**, *65*, 137.

80. Wiegmann, S.; Mattay, J. *Org. Lett.* **2011**, *13*, 3226.

81. Morikawa, O.; Yamaguchi, H.; Katsube, Y.; Abe, K.; Kobayashi, K.; Konishi, H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 2877.

82. Faull, J. D.; Gupta, V. K. *Thin Solid Films* **2003**, *440*, 129.

83. Knyazeva, I. R.; Sadykova, Y. M.; Burilov, A. R.; Pudovik, M. A.; Konovalov, A. I. *Russ. J. Gen. Chem.* **2009**, *79*, 2456.

84. Zakharova, L. Y.; Valeeva, F. G.; Ibragimova, A. R.; Voronin, M. A.; Kudryavtseva, L. A.; Syakaev, V. V.; Kazakova, E. K.; Morozova, Y. E.; Makarova, N. A.; Mel'nikova, N. B.; Zemnyakova, O. E.; Konovalov, A. I. *Russ. Chem. B+* **2008**, *57*, 374-382.

85. Solari, E.; Lesueur, W.; Klose, A.; Schenk, K.; Floriani, C.; ChiesiVilla, A.; Rizzoli, C. *Chem. Comm.* **1996**, 807.

86. Cram, D. J.; Karbach, S.; Kim, H. E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229.

87. Cram, D. J. *Science* **1983**, *219*, 1177-1183.

88. Xiao, S.; Ajami, D.; Rebek, J. *Org. Lett.* **2009**, *11*, 3163.

89. Palmer, L. C.; Rebek, J. *Org. & Biomol. Chem.* **2004**, *2*, 3051.

90. Gissot, A.; Rebek, J. *J. Am. Chem. Soc.* **2004**, *126*, 7424.

91. Matsushita, Y.; Matsui, T. *Tetrahedron Lett.* **1993**, *34*, 7433.

92. Schneider U.; Schneider H. J. *Chem. Ber.* **1994**, *127*, 2455.

93. Buckley, B. R.; Page, P. C. B.; Heaney, H.; Sampler, E. P.; Carley, S.; Brocke, C.; Brimble, M. A. *Tetrahedron* **2005**, *61*, 5876.

94. Page, P. C. B.; Heaney, H.; McGrath, M. J.; Sampler, E. P.; Wilkins, R. F. *Tetrahedron Lett.* **2003**, *44*, 2965.

95. Arnott, G.; Hunter, R. *Tetrahedron* **2006**, *62*, 992.

96. Irwin, J. L.; Sherburn, M. S. *J. Org. Chem.* **2000**, *65*, 5846-5848.

97. Barrett, E. S.; Irwin, J. L.; Turner, P.; Sherburn, M. S. *J. Org. Chem.* **2001**, *66*, 8227-8229.

98. Lukin O.V.; Pirozhenko V.V.; Shivanyuk A.N. *Tetrahedron Lett.***1995**, *36*, 7725.

99. Shivanyuk A.; Paulus E.F.; Bohmer V.; Vogt W. *J. Org. Chem.* **1998**, *63*, 6448.

100. Wittig G.; Pockels U.; Droge H. *Ber.* **1938**, *71*, 1903.

101. Gilman H.; Langham W.; Jacoby A.L. *J. Am. Chem. Soc.* **1939**, *61*, 106.

102. Barrett, E. S.; Irwin, J. L.; Turner, P.; Sherburn, M. S. *J. Org. Chem.* **2001**, *66*, 8227-8229.

103. Kalchenko V.I.; Rudkevich D.M.; Shivanyuk A.N.; Pirozhenko V.V.; Tsymbal I.F.; Markovsky L.N. *Zhurn. Obsch. Khim.* **1994**, *64*, 731.

104. Kalchenko V.I.; Shivanyuk A.N.; Pirozhenko V.V.; Markovsky L.N. *Zhurn. Obsch.Khim.* **1994**, *64*, 1562.

105. Shivanyuk A.N.; Kalchenko V.I.; Pirozhenko V.V.; Markovsky L.N. *Zhurn.Obsch.Khim.***1994**, *64*, 1558.

106. Nummelin, S.; Falabu, D.; Shivanyuk, A.; Rissanen, K. *Org. Lett.* **2004**, *6*, 2869.

107. Konishi, H.; Nakamaru, H.; Nakatani, H.; Ueyama, T.; Kobayashi, K.; Morikawa, O. *Chem. Lett.* **1997**, 185.

108. Gachwend H.W.; Rodriguez H.R. *Org. React.* **1979**, *26*, 1.

109. Narasimhan N.S.; Mali R.S. *Top. Curr.Chem.* **1987**, *38*, 63.

110. Narasimhan N.S.; Mali R.S. *Synthesis* **1983**, 957.

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

112. Snieckus V. *Bull. Soc. Chim. Fr.* **1988**, *67*.

113. Beak P.; Snieckus V. *Acc. Chem. Res.* **1982**, *15*, 306.

114. Ziegler K.; Colonius H. *Annalen* **1930**, *476*, 135.

115. Kamienski C.W.; Esmay D.L. *J. Org. Chem.* **1960**, *25*, 1807.

116. Stanetty P.; Mihovilovic M.D. *J. Org. Chem.* **1997**, *62*, 1514.

117. Clayden J.; Yasin S.A. *New J. Chem.* **2002**, *26*, 191.

118. Stanetty P.; Koller H.; Mihovilovic M. *J. Org. Chem.* **1992**, *57*, 6833.

119. Wittig G.; Bebb R.L. *J. Am. Chem. Soc.* **1983**, *105*, 6350.

120. Lombardino J.G. *J. Org. Chem.* **1971**, *36*, 1843.

121. Meyers A.I.; Pansegrau P.D. *Tetrahedron Lett.* **1983**, *24*, 4935.

122. Fraser R.R.; Bresse M.; Mansour T.S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.

123. Beak P.; Brown R.A. *J. Org. Chem.* **1979**, *44*, 4463.

124. Clayden J. *Organolithiums: Selectivity for synthesis* **1st Ed.**, *Elsvier Science ltd*, UK-2002.

125. Beak P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

126. Hay, D.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145.

127. Warmus, J. S.; Rodkin, M. A.; Barkley, R.; Meyers, A. I. *J. Chem. Soc. , Chem. Commun.* **1993**, 1357.

128. van Eikema-Hommes, N. J. R.; Schleyer, P. v. R. *Tetrahedron* **1994**, *50*, 5903.

129. van Eikema-Hommes, N. J. R.; Schleyer, P. v. R. *Angew. Chem. , Int. Ed. Engl.* **1992**, *31*, 755.

130. Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **1946**, *68*, 1658.

131. Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191.

132. Slocum D.W.; Dumbris S.; Brown S.; Jackson G.; LaMastus R.; Mullins E. *Tetrahedron* **2003**, *59*, 8275.

Chapter II

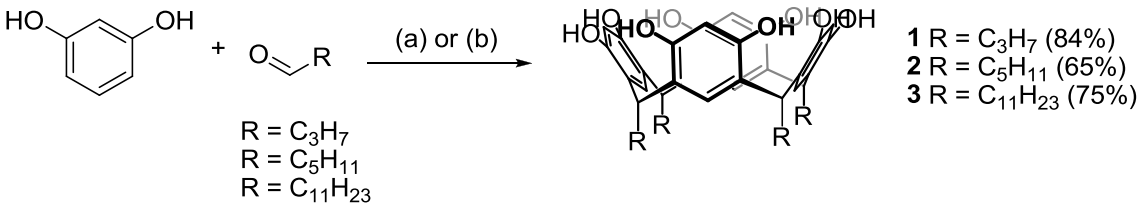
Synthesis of parent resorcinarene ethers

2.1. Introduction:

In this chapter the synthesis of resorcinarene ethers, carried out following a two-step methodology, will be described. The first step in this synthesis entails the synthesis of octahydroxy resorcinarenes as precursors of the ethers. It was decided to study resorcinarenes with three different alkyl chains. Efficient synthesis of resorcinarenes has been reported to be achieved *via* a wide range of methodologies,[1] of which two were explored in detail. The first method is the mineral acid catalyzed methodology developed in 1989 by Cram *et al.*[1a] The second route is a Lewis acid catalyzed synthesis of resorcinarenes using a modification of a $BF_3{\cdot}Et_2O$ catalyzed resorcinarene synthesis as reported by Yan *et. al.*[1b]

The second synthetic step involves etherification of C_{4v}-octahydroxy resorcinarenes to form C_{4v} parent resorcinarene ethers. These compounds are made by alkylation with dimethyl sulphate and have been synthesized previously in our group. In the current study these compounds are used in the directed metalation studies. A rigid resorcinarene ether, a cavitand,[2] was also synthesized from octahydroxy resorcinarenes for comparison.[3,4]

2.2. Synthesis of resorcinarene octols:



Scheme 1: Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, DCM, 26 h, 0 °C to rt;
(b) HCl (conc.), EtOH (95%), 21 h, rt to 57 °C.

Resorcinarenes with three different alkyl chain lengths (the description "feet" is used in an interchangeable manner with "lower rim"), **1** to **3** were synthesized using two different methodologies (Scheme 1).

2.2.1. Synthesis of the propyl-footed resorcinarene **1**:

The synthesis of the propyl-footed resorcinarene **1** was carried out using a Lewis acid, $BF_3{\cdot}Et_2O$, catalysed condensation reaction of resorcinol and butyraldehyde in equimolar ratio. The reaction, using dry DCM as a solvent, was initiated at 0 °C, allowed to warm to room temperature and left overnight under inert atmosphere. The product, was insoluble in DCM, and was, therefore, separated by filtration and washed repeatedly with portions of DCM. Drying of the compound under vacuum gave a yield of 84% of a reddish pink product **1** that had a melting point beyond 350 °C.[1a,5] A broad peak around 3200 cm^{-1} was observed in the IR spectrum and attributed to the eight resorcinarene phenolic hydroxyl groups; its presence confirmed the existence of intramolecular hydrogen bonding. This observation was also confirmed in the ^{1}H NMR spectrum of **1** in deuterated acetone as solvent, as phenolic protons appeared as a singlet downfield, at 8.45 ppm. Moreover, the compound exhibited two singlets in the aromatic region accounting for the four upper rim and four lower rim protons which suggested that **1** was not only hydrogen bonded but also exhibits C_{4v} symmetry. This observation was in accordance with literature.[6,7,8] Curiously, it was found that the reaction yield was often not reproducible.

The problem of reproducibility was dealt with by investigating the effect of the purity of all the starting materials, reagents and solvents. DCM which had previously been used freshly distilled from calcium hydride, was then dried using phosphorus pentoxide under strict inert conditions. A reaction performed using this DCM was found to give the same results. Therefore the situation was not a result of solvent purity. In addition, freshly distilled aldehyde was used, this did not result in formation of resorcinarenes. Purified resorcinol, recrystallized three times from toluene, was also tried; however, still no change in the sporadic results was observed. Use of distilled $BF_3{\cdot}Et_2O$ occasionally returned a better yield of resorcinarenes, especially when minute portions of diethyl ether were added during the distillation. The source of the problem is still unclear; however, observations thus far suggested that the problem was Lewis-acid based. Having had difficulties in the Lewis acid catalyzed synthesis of **1**, it was decided to synthesize the compound employing a different

methodology. Attempting use of a different Lewis acid was limited as literature precedent indicated that the use of other Lewis acids for the formation of resorcinarenes frequently led to the formation of a mixture of conformational isomers whose separation is difficult. Also, use of Cram's methodology using protic acid failed in all attempts when using butanal.[1a] Additions of larger amounts of HCl than described led to an immediate precipitation of an orange compound that did not dissolve in any of the standard laboratory solvents and in those that the target compound is known to dissolve in. Identification of the nature of the precipitate from this reaction was not carried out owing to its poor solubility.

An $AlCl_3$ catalyzed variant synthesis of **1** by Curtis was next performed.[9] According to the methodology, butanal was added to a mixture of dry Et_2O and THF (1:1 v/v) under argon. A solution of $AlCl_3$ (0.5 equivalent) in nitrobenzene was then added at room temperature and the mixture stirred for fifteen minutes before adding resorcinol (1 equivalent) and stirring for an additional 20 hours. The reaction gave a dark mixture. The mixture was subsequently added to diethyl ether as described in literature. No precipitate formed as expected. The solvent was removed after which crude NMR spectroscopy was performed. No formation of resorcinarene **1** was observed and the exact composition of the crude was inconclusive owing to the complexity of the NMR spectrum. The reason why preparation of resorcinarene **1** proved to be challenging is still of interest and is saved for later investigations.

2.2.2. Synthesis of the pentyl-footed resorcinarenes **2**:

Preparation of resorcinarene **2** was also attempted using the Lewis acid catalyzed synthesis described for resorcinarene **1**. Hexanal was, therefore, used as aldehyde which returned the pentyl-footed resorcinarene **2**. After work up, compound **2** was isolated as a reddish pink solid in 65% yield. The ^{1}H NMR spectrum of **2** was similar to that of **1**, exhibiting hydrogen bonding and C_{4v} symmetry, and had a downfield multiplet, at 1.3 ppm, that integrated for twenty four protons. Of importance was that Cram's literature procedure afforded the pentyl-footed resorcinarenes **2** in 60% and did not cause the same problems as in the synthesis of resorcinarene **1**.

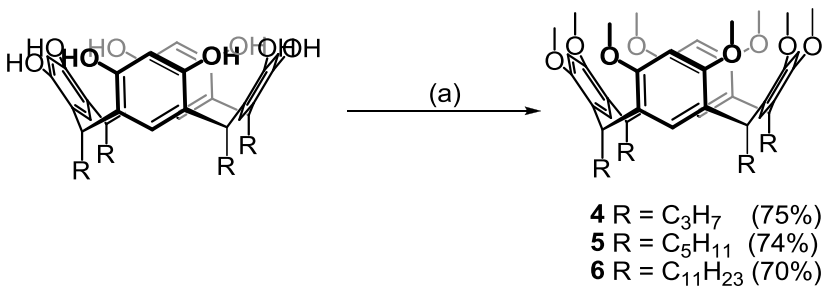
2.2.3. *Synthesis of the undecyl-footed resorcinarenes* **3**:

In preparing undecyl-footed resorcinarene ethers, compound **3** was synthesized as described for compound **1**. Multiple attempts to synthesize the target compound via this route, one of which involved high vacuum distillation of high boiling point dodecanal, were performed.

Unfortunately, synthesis of **3** using the $BF_3{\cdot}Et_2O$ catalysed procedure did not result in the formation of the compound and the optional route described by Cram and co-workers was followed. Resorcinol was, therefore, dissolved in a mixture of ethanol and concentrated HCl (3 : 1 v/v). A mixture of aldehyde in ethanol (equimolar to resorcinol) was then added dropwise to the solution. The resulting solution was stirred for two hours at 15 °C and heated to 75 °C for 21 hours. The dark reaction solution turned orange pink upon cooling. Several washes and recrystallizations from methanol subsequently afforded resorcinarene **3** in 75% yield, after vacuum drying.

2.3. Synthesis of parent resorcinarene ethers:

The functionalization of the phenolic groups was then attempted to synthesize four parent resorcinarene ethers, namely the propyl-, pentyl- and undecyl-footed resorcinarene methyl ethers (Scheme 2) and propyl-footed cavitand methyl ether (Scheme 3).



Scheme 2: Reagents and conditions: (a) Me_2SO_4, K_2CO_3, MeCN, 26 h, reflux.

2.3.1. Synthesis of resorcinarene ethers:

Synthesis of resorcinarene ethers **4**, **5** and **6** from **1**, **2** and **3**, resorcinarenes respectively, was carried out in acetonitrile using dimethyl sulphate (16 equiv.) as methylating agent and K_2CO_3 (22 equivalents) as base (Scheme 2). The choice of the methylating agent was based on the ease of handling of dimethyl sulphate compared to other methylating agents; for example, methyl trifluoromethansulfonate and diazomethane. A gentle overnight reflux resulted in a white-solution. After cooling, the flask contents were added to water and extracted three times with ethyl acetate. TLC analysis of the combined extracts revealed a major and minor product. The major and minor products were separated by silica gel column

chromatography eluted with a mixture of ethyl acetate and hexane to furnish **4**, **5** and **6**, after drying, as white solids in yields ranging from 70-75% along with an unknown minor product.

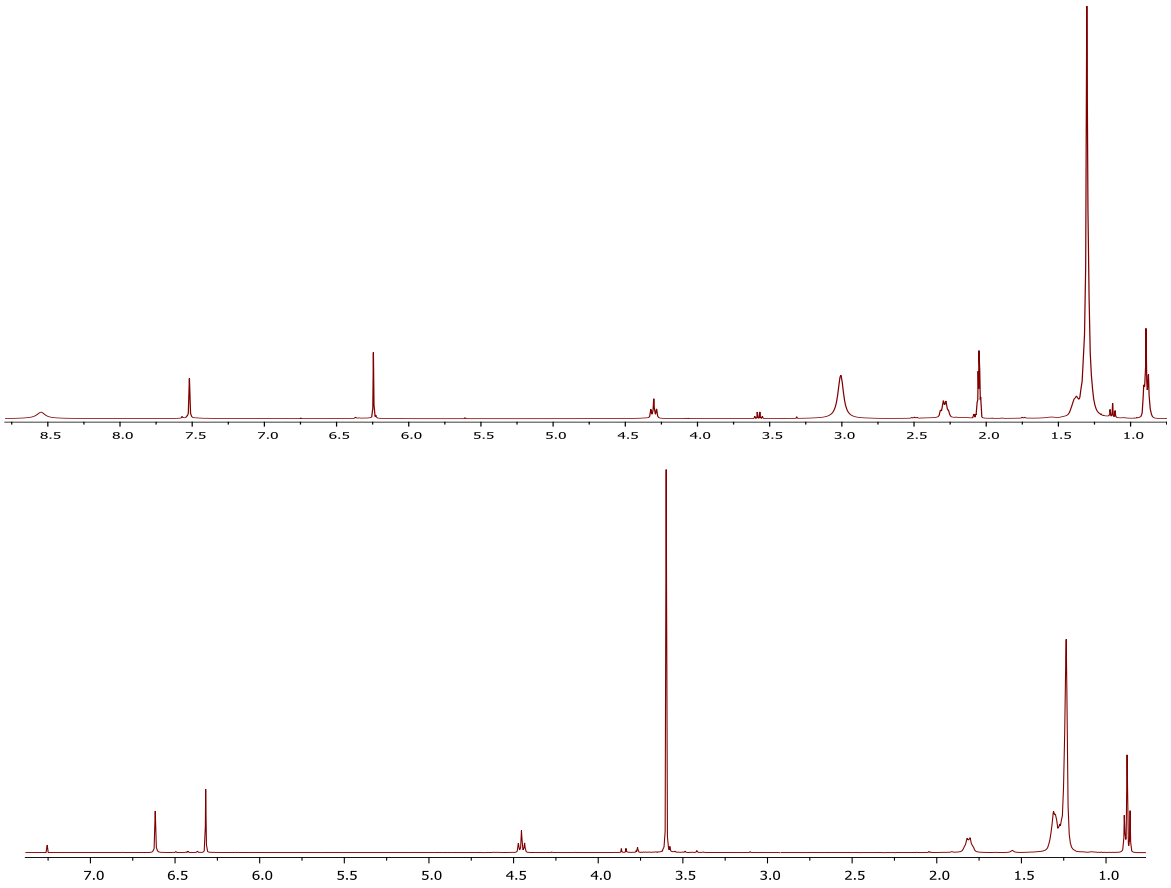
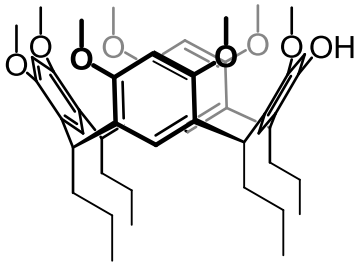


Figure 1: ^{1}H NMR of resorcinarene **3** (top) and resorcinarene **6** (bottom) depicting disappearance of –O*H* hydrogens at 8.6 ppm and emergence of –O*Me* signal at 3.7 ppm.

The ^{1}H NMR spectra of resorcinarene ethers **4**, **5**, and **6** revealed the disappearance of the phenolic hydroxyl signals above 8 ppm, and the emergence of a new signal at 3.6 ppm, (integrating to twenty four protons) was an indication of successful octa-methylation of octahydroxy resorcinarenes (Figure 1). In addition, pursuit of the unknown compound observed on TLC as a minor spot was decided upon. Addition of 4 equivalents of the methylating agent in excess, however, returned a mixture of the product and the unknown compound. On noting incomplete reaction with the gradual increase of base to 26 and 30 equivalents, it was decided to rather test the effect of solvent. Solvent purification did not change the ratio of product **6** and the minor unknown component either (by tlc). However, when freshly distilled methylating agent was used with shorter reaction times (6 hours), a single spot on TLC was observed and as such provided a simpler work up procedure. It was

noticed that the reagent efficiency slowly deteriorates with time. The fact that increments in methylating agent equivalents did not improve the results, whilst reagent purification lead to reaction completion, suggests that the reagent's decomposition products retard the final methylation step and result in the formation of side-products.

Indeed, combined fractions of the unknown compound revealed it to be a heptamethylated resorcinarene bearing a single unmethylated hydroxyl moiety **8**, Figure 3. As a potential substrate to asymmetric resorcinarene based ligands, efficient optimum conditions for the synthesis can thus be developed in the future. One way for pursuing development of the synthesis of **8** could be through addition of fewer equivalent of methylating agent. Another could be to forcibly contaminate the methylating agent.



8

Figure 2: Heptamethylated resorcinarene bearing a single unmethylated hydroxyl moiety.

Formation of **8** was confirmed by NMR spectroscopy and the loss of symmetry occurred on going from **4** to **8**. The emergence of several signals in the region where methoxy groups are observed in **4**, integrating to twenty one protons, indicated the missing of a single methyl group.

A hydroxyl moiety that was still intact was observed (at ~5.4 ppm) as a broad signal in the proton NMR spectrum. In addition, eight protons, usually observed as two signals for upper and lower rim protons on completely methylated resorcinarenes, now consisted of several peaks (two doublets and three singlets) within the aromatic region (Figure 3).

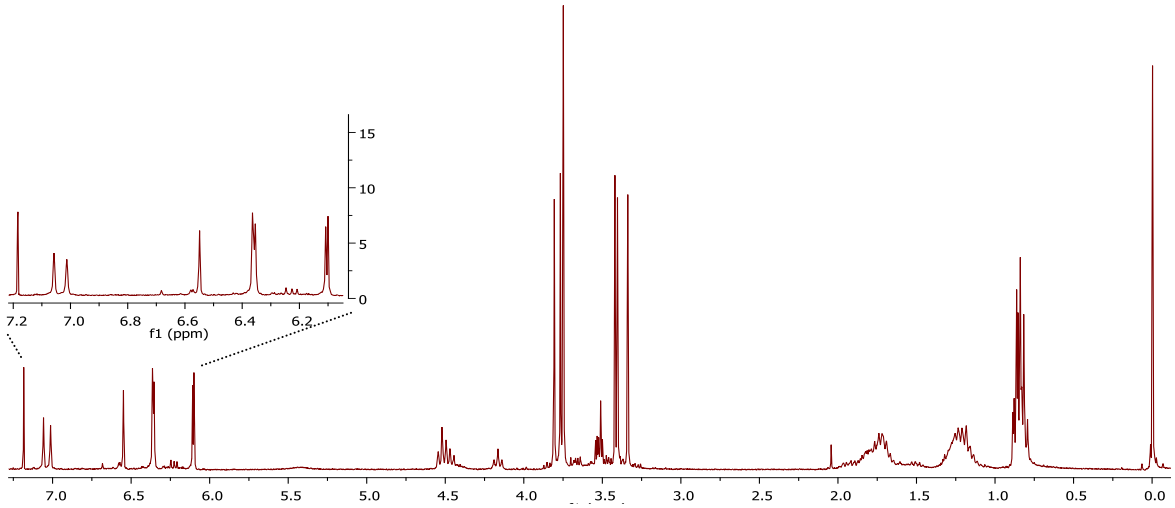
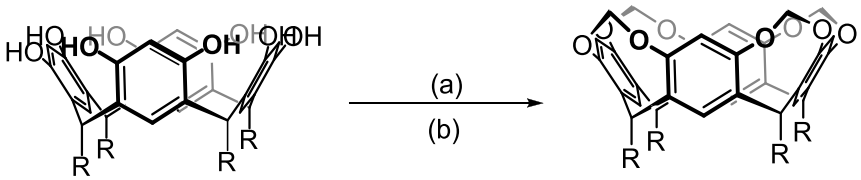


Figure 3: ^{1}H NMR spectrum of **8** and its aromatic region over area 7.2-6.0 ppm indicating upper and lower rim protons.

2.3.2. Synthesis of the resorcinarene based cavitand **7**:



7 R = C_3H_7 (65%)

Scheme 3: Reagents and conditions: (a) CH_2BrCl, K_2CO_3, DMF, 24 h, 70 °C; (b) CH_2BrCl, K_2CO_3, Me_2CO,24 h, 50 °C.

Finally, the cavitand **7** was synthesized as described in Scheme 3. A literature procedure used by Rheinhoudt and co-workers[3] in their synthesis of resorcinarene-cavitand based ligands was adopted for this purpose. Resorcinarene **1** was dissolved in DMF and to this was added CH_2BrCl (17 equivalents) and K_2CO_3 as base, before stirring at 70 °C overnight. The bridging reaction proceeds faster, in relatively high yields and in the presence of fewer equivalents of dihaloalkane compared to the bridging of tetrabrominated octols. The reaction progress was followed by TLC and revealed a number of faint spots, which could be due to incomplete bridging (trace formation of hermicarcirands) or even trace dimerization, as well as a major spot. Removal of large amounts of the high boiling point solvent, DMF, was

performed by high vacuum distillation leaving a dark brown residue. This residue was dissolved in DCM and passed through a short silica gel column eluted with DCM to afford crude material which was recrystallized from acetonitrile as described in the literature source. Initially, a brown precipitate crystallized out of solution and was separated using filtration. Analysis of this precipitate could was not performed owing to its low solubility. It was later discovered that the cavitand **7** remains in the acetonitrile mother liquor after precipitation of the brown residue, which is not as describe in the reference literature source. Complete purification of **7** was afterwards achieved using a silica gel chromatographic column eluted with a mixture of ethyl acetate and hexane to give cavitand **7** as a white solid in 60% yield. In addition, a procedure employing a lower boiling point solvent, an advantage that would simplify synthesis and work up procedures was attempted.[4] In this methodology lower boiling point solvent which is easier to remove and more environmentally acceptable, acetone, is used, instead of high boiling point solvents normally used (*i.e.* DMF and DMSO). Reaction conditions, nevertheless, remained the same in this procedure as conditions used when employing high boiling point solvents. The work-up was also much simpler but unfortunately the yield also dropped as only 40% of **7** was obtained. It appears that though high boiling point solvents lead to more complex work-up procedures than low boiling point solvents, high boiling point solvents return higher yield of the completely cyclised cavitand **7**. It was found that column chromatography of the crude material of **7** provided a more efficient work-up procedure than recrystallization followed by a short column as described in that in the literature.

Compound **7** possessed a similar NMR spectroscopic pattern of the aliphatic chain as resorcinarene **4** and did not lose the expected symmetry elements (Figure 2.4). The methylene bridges on top of the cavity appeared as a typical AX spin of two doublets at 4.36 ppm and 5.67 ppm. Of interest the spectroscopic data was in agreement with literature. One proton on each bridge is thus orientated into the deep cavity and hence more shielded, while the other proton is situated in a more equatorial position facing outside the macrocycle cavity and is hence relatively less shielded. Finally, the ^{1}H NMR spectroscopic data observed in the spectrum of **7** was in agreement with literature.[3,8] In addition, successful synthesis of the cavitand was also confirmed by mass spectrometry.

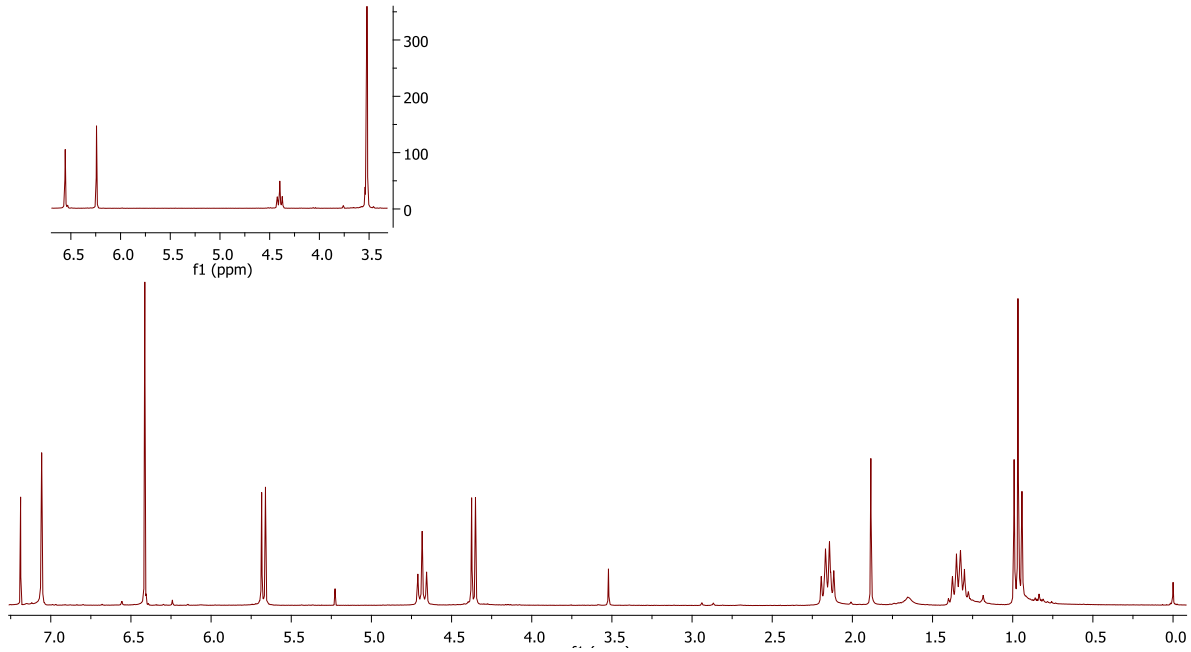


Figure 2.4: ^{1}H NMR of cavitand **7** (bottom) and the aromatic region of **4**.

In conclusion, three resorcinarenes were prepared, namely the propyl-, pentyl- and undecyl-footed resorcinarenes using both Lewis and Bronsted catalysed one pot procedures. Propyl-footed resorcinarene could be prepared *via* Lewis catalysis, undecyl could be prepared via Brønsted catalysis while pentyl could be prepared via both procedures. Etherification of the phenolic groups furnished propyl-, pentyl- and undecyl-footed resorcinarene ethers. In addition to these ethers a propyl-footed resorcinarene cavitand was prepared using ethylene groups as linkage bridges. With the four starting compounds in hand, a methoxy group directed ortholithiation procedure for selective functionalization of resorcinarenes was studied. Findings are discussed in chapter III.

2.4. References:

1. (a) Tunstad, L.M.; Tucker, J.A.; Dalcanale, E.; Weiser, J.; Bryant, J.A.; Sherman, J.C.; Helgeson, R.C.; Knobler, C.B.; Cram, D.J. *J. Org. Chem.* **1989**, *54*, 1305; (b) Ren, J.C.; Yan, C.G. *J. Incl. Phenom. Macro.* **2010**, *67*, 335; (c) Iwanek, W.; Syzdol, B. *Synth. Commun.* **1999**, *29*, 1209; (d) Iwanek, W. *Tetrahedron* **1998**, *54*, 14089; (e) Peterson, E.P.; Smith, R.C.; Mohan, R.S. *Tetrahedron Lett.* **2003**, *44*, 7723; (f) Bourgeois, J.; Stoeckli-Evans, H. *Helv. Chem. Acta* **2005**, *88*, 2723; (g) Barrett, A.G.M.; Braddock, D.C.; Henschke, J.P.; Walker, E.R.; *J. Chem. Soc.* **1999**, *1*, 873 (h) Botta, B.; Iacomacci, P.; Giovanni, C.D.; Monache, G.D.; Gacs-Baitz, E.; Botta, M.; Tafi, A.; Corelli, F.;

Misiti, D. *J. Org. Chem.* **1992**, *57*, 3259; (j) Deleersnyder, K.; Mehdi, H.; Horvath, I.T.; Binnemans, K.; Parac-Vogt, T.N. *Tetrahedron* **2007**, *63*, 9063; (k) Roberts, B.A.; Cave, W.V.; Raston, C.L.; Scott, J.L. *Green Chem.* **2001**, *3*, 280; (l) Sakhaii, P.; Verdier, L.; Ikegami, T.; Griesinger, C. *Helv. Chim. Acta,* **2002**, *85*, 3895;

2. Zhou, R.; Moran, J.R.; Karbach, S.; Cram, D.J. *J. Am. Chem. Soc.* **1982**, *21*, 5826.
3. Boerrigter, H.; Verboom, W.; Reinhoudt, D.N. *J. Org. Chem.* **1997**, *62*, 7148.
4. Pietraszkiewicz, M.; Prus, P.; Pietraszkiewicz, O. *Tetrahedron* **2004**, *60*, 10747.
5. Kleinhans, D.J.; Arnott, G.E. *Dalton Trans.* **2010**, *39*, 5780.
6. Hogberg, A.S.G. *J. Am. Chem. Soc.* **1980**, *102*, 6046.
7. Hauke, F.; Myles, A. J.; Rebek, J. *Chem. Comm.* **2005**, 4164.
8. Moran, R.J.; Karbach, S.; Cram, D.J. *J. Am. Chem. Soc.* **1982**, *104*, 5826.
9. Curtis, A.D.M. *Tetrahedron Lett.* **1997**, *38*, 4295.

Chapter III

Ortholithiation of resorcinarene ethers

3.1. Introduction:

Though synthesis of resorcinarenes usually involves a one-pot procedure, as shown in Chapter 2, their selective functionalization has proven to be challenging. Nevertheless, as described in Chapter 1, methods such as those developed by Shivanyuk *et al.*[1] (selective tetraacylation) and Sherburn *et. al.*[2] (lithium halogen exchange) have allowed for selective functionalization of these structures.

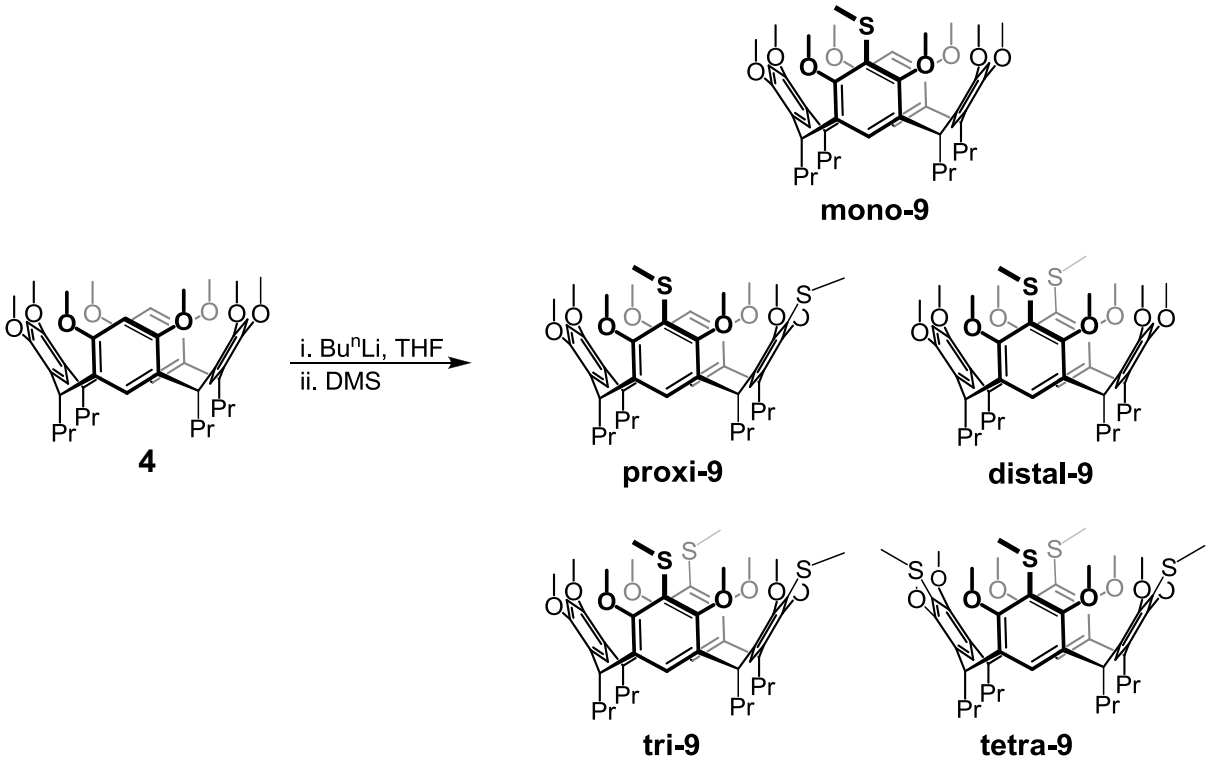
A new methodology to selectively functionalize resorcinarenes was envisaged to occur via an ortholithiation approach. It was hoped that this method would open a new and facile approach to C_{2v}-functionalized resorcinarenes.

3.2. General considerations:

For the ortholithiation study, starting materials were selected based on the lower rim length of resorcinarene, the functionality on the phenolic hydroxyls (i.e. directing metalation group), ease of handling and availability of alkyllithium base, electrophile and solvent. To allow sufficient solubility of the starting resorcinarene, a "propyl lower rim" resorcinarene was chosen since shorter alkyl chains are less soluble in ethereal solvents. The directing metalation group was chosen based on the fact that methyl ethers are known directing groups and are sufficiently small not to sterically encumber the four ortho-positions. Ortholithiation on anisoles have been reported in the literature and provided a preliminary study of the methodology. As the study was envisaged to give a simple and efficient procedure, a readily available alkyllithium base was chosen, namely *n*-butyllithium (*n*-BuLi). Next an electrophile showing "high" reactivity such that it does not limit the reaction (especially its rate) was needed. A number of electrophiles have been used in our laboratory and dimethyl disulfide (DMS) has, in many cases, returned satisfying yields. For this reason, DMS was chosen as an electrophile. Solvent choice was important, but due to solubility issues tetrahydrofuran (THF) was chosen since this solvent is also known to coordinate to and deoligomerize alkyllithiums. In addition, it was deemed a suitable solvent for this reaction since it is a good solvent for resorcinarene ethers.

A general procedure involved dissolving resorcinarene ether **4** in THF and stirring the mixture at a given temperature until complete dissolution. Butyllithium (*n*-BuLi) was then added and the reaction was incubated at a given temperature to allow lithiation. Finally, the electrophile (DMS) was added to quench the intermediate lithio-resorcinarenes and further incubation was carried out overnight before work-up. A general work-up procedure involved protonation of unreacted base and remaining reaction intermediates with water. The aqueous crude was then extracted with ethyl acetate. Products observed by thin layer chromatography were then separated using column chromatography eluted with a mixture of ethyl acetate and hexane.

During the course of this study five products were obtained; namely **mono-9**, **proxi-9**, **distal-9**, **tri-9** and **tetra-9** (Scheme 1) and were fully characterized.



Scheme 1: Obtained ortholithiation products.

The characterization of each of these compounds will be discussed first, followed by a description of the method used to determine their relative ratios after a reaction. After this, the complete study and results will be reported.

*3.2.1. Mono-substituted resorcinarene (***mono-9***)*:

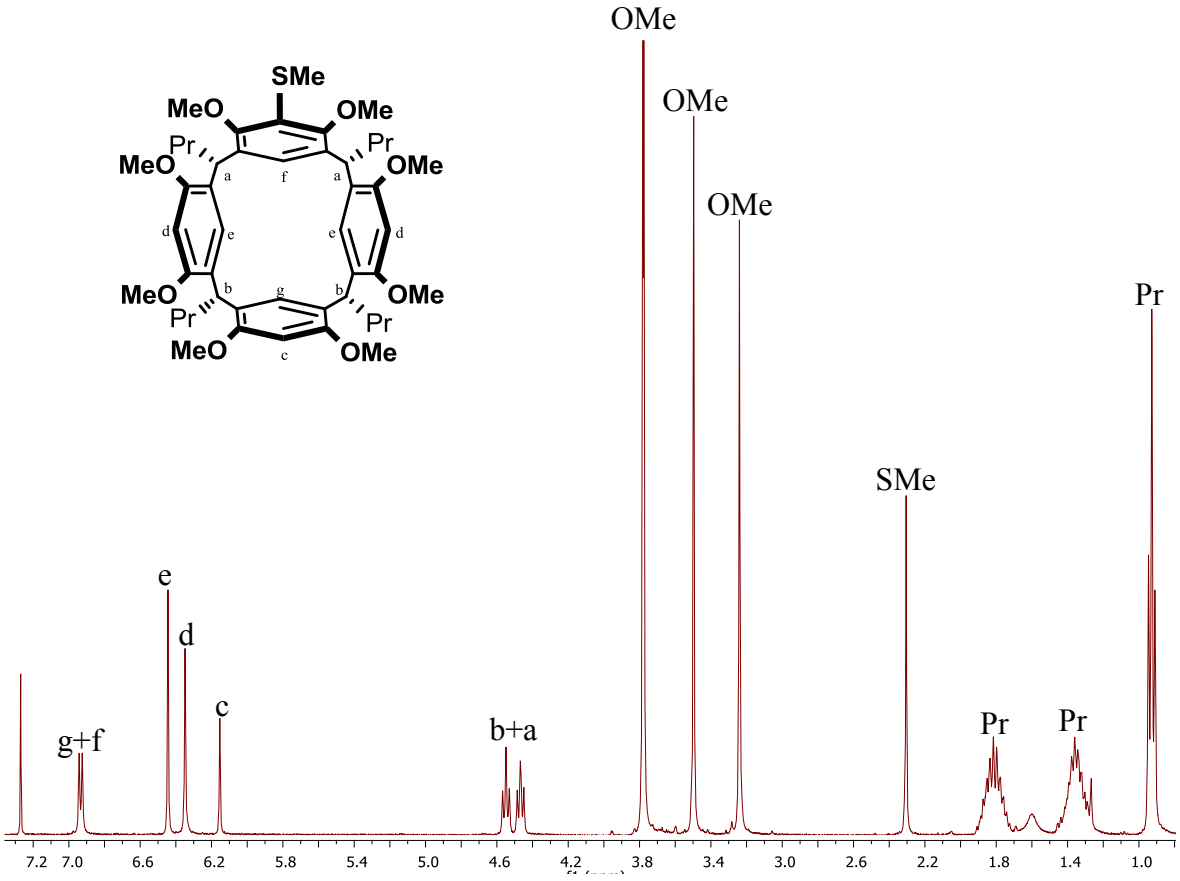


Figure 1: ^{1}H NMR spectrum of **mono-9**.

The proton NMR spectra of the resorcinarene products had comparable aliphatic regions (Figure 1). These included a triplet and two multiplets upfield of 2.0 ppm, which were assigned to the lower rim alkyl chains. The methyl group protons of the alkyl chains were split into a triplet by the two neighbouring methylene protons. These methyl groups are also the most shielded and hence appear furthest upfield. The two methylene groups of the lower rim chains were observed slightly downfield at 1.30 ppm and 1.80 ppm. These two groups had five and three neighbouring protons, respectively, which meant that they should have appeared as a sextet and a quartet. However, because of the breaking of symmetry, due to the difference in chemical environments and resulting diastereotopic relationship of the methylene protons, they appeared as complex multiplets. The single group thiomethyl appeared as a singlet at 2.30 ppm. The methoxy groups of the compound appeared as four singlets (at 3.60 ppm, 3.5 ppm, 3.76 ppm and 3.78 ppm), two of which were overlapping (3.76 ppm and 3.78 ppm). Two chemical environments of the benzylic protons could be

observed. These benzylic protons, neighboured by two protons of the propyl chain, appeared as two triplets (at 4.45 ppm and 4.55 ppm).

The aromatic region of the ^{1}H NMR spectrum of **mono-9** (Figure 1) had five singlets. A close inspection of this region also offered some insight into the structural properties of the compound in solution. The remaining three protons of the upper rim at 6.15 ppm and 6.35 ppm (labelled c and d) are not equivalent as the proton opposite the thiomethyl group appeared at a higher shift (6.35 ppm). Above the shielding of the protons by the methoxy groups, this observation suggested the shielding of the proton opposite the thiomethyl group (labelled c) by the aromatic ring bearing the thiomethyl group. The other two protons (labelled d, at 6.35 ppm) are equivalent and appeared to be less shielded which suggested that these are at an angle, almost perpendicular, to the macrocyclic ring. The lower rim protons (labelled e) of the rings bearing protons labelled d (appearing at 6.45 ppm) are equivalent and hence appeared as a singlet. Also, these were more shielded than the other lower rim protons which suggested that these protons are orientated inside the bowl of the macrocycle. The other two protons, labelled f and g appearing as overlapping singlets at 6.95 ppm, are orientated outside the bowl and hence less shielded.

*3.2.2. Proximally-substituted resorcinarene (***proxy-9***)*:

The aliphatic region of the spectrum of **proxy-9** was not very different from that of **mono-9** (Figure 2). It possessed a triplet (at 0.82 ppm, Pr) and two multiplets (at 1.30 ppm and 1.95 ppm, Pr). The two proximal thiomethyl groups appear as a singlet accounting for six protons (2.32 ppm, SMe). These also appeared at a higher field than the methoxy groups because sulphur is not as electron-withdrawing as oxygen. They are, therefore, more shielded. The methoxy groups were separated into three chemical environments (at 3.40 ppm and 3.60 ppm). The methoxy groups at 3.40 ppm are more shielded by donation of electrons by the sulphur atoms and hence appear more upfield than the methoxy groups on the unfunctionalized rings (at 3.60 ppm). These methoxy groups appear as two closely overlapping singlets at a shift slightly below the signal at 3.40 ppm. The benzylic protons are split into triplet signals by the neighbouring methylene groups of the propyl alkyl chains (signal a). These three triplets are close to each other and hence overlap.

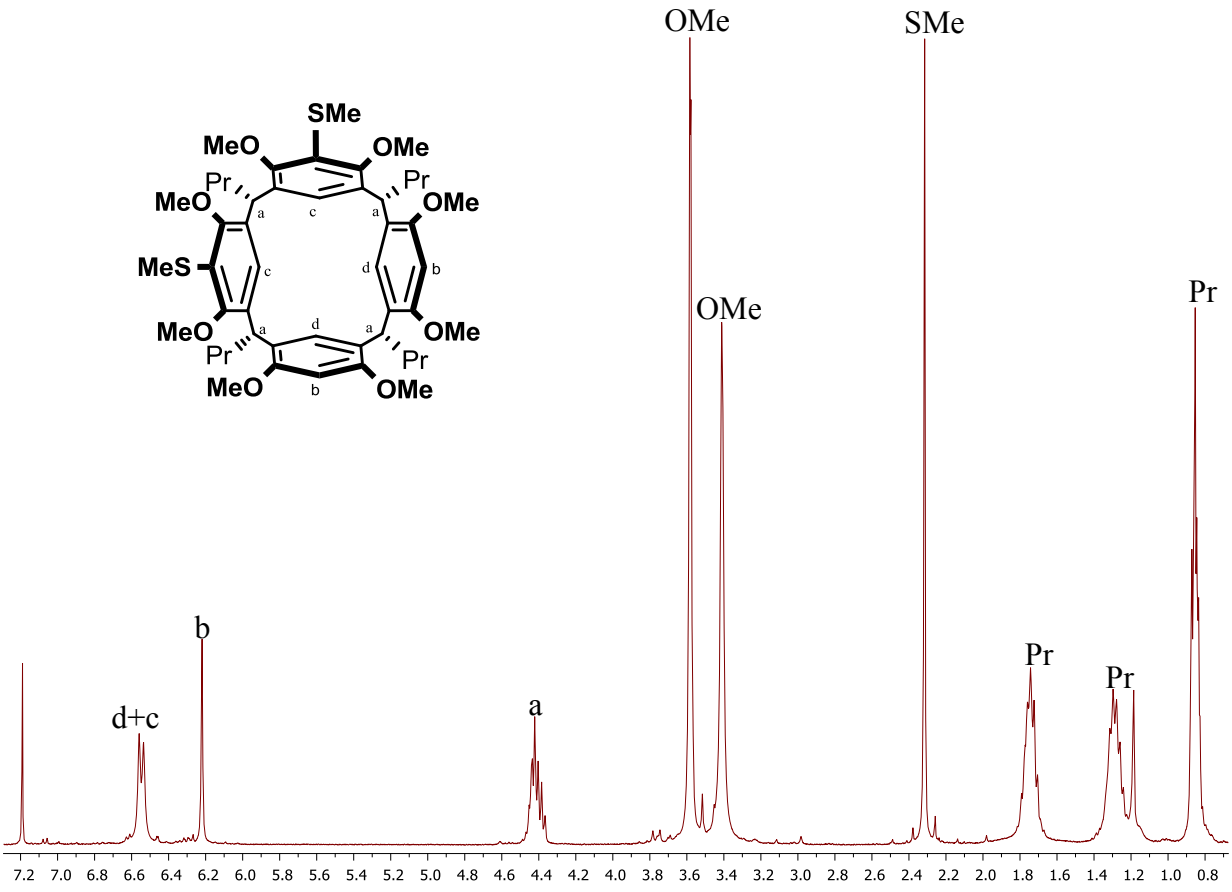


Figure 2: ^{1}H NMR spectrum of **proxy-9**.

The aromatic region of **proxy-9** had three singlets, two of which were slightly overlapping. The remaining two upper rim protons at 6.22 ppm (labelled b) are equivalent and hence, give a single singlet. These are more shielded than the lower rim protons because of resonance donation of electrons by the oxygen atoms of the methoxy groups. However, lower rim protons appear as two slightly overlapping singlets (signals d and c). Functionalized rings' lower rim protons are slightly different and shielded. They, therefore, appear slightly upfield than protons on the lower rims of the unfunctionalized rings.

*3.2.3. Distal-substituted resorcinarene (***distal-9***)*:

The propyl groups of **distal-9** are also equivalent and similar to those of **proxi-9** (Figure 3). They also appear as a triplet (0.90 ppm) and two multiplets (1.35 ppm and 1.80 ppm) in the aliphatic region. The two distal thiomethyl groups occupy the same magnetic position and hence show as a singlet integrating for six protons. The methoxy groups reveal the high symmetry of the compound and are divided into two groups. Four methoxy groups in a distal relationship and on the functionalized rings are equivalent. These also experience more

shielding compared to the methoxy groups on the unfunctionalized rings, which also form a singlet. Shielding is a result of resonance donation of electrons by sulphur. This shielding is also influenced by conformation of the compound which appears to be more crown-like in solution.

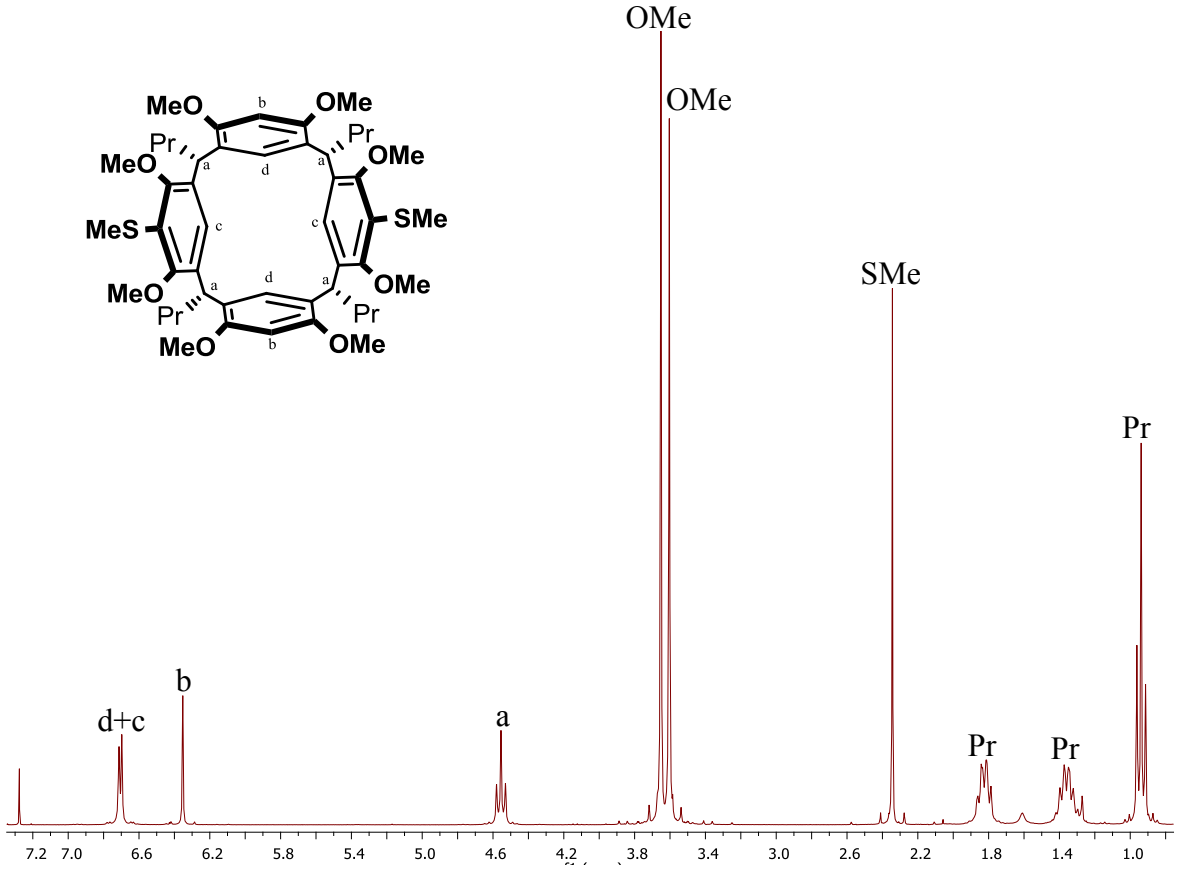


Figure 3: ^{1}H NMR spectrum of **distal-9**.

All four benzylic protons (signal a) are identical and neighboured by methylene groups (1.80 ppm) which splits these into a triplet. Finally, three singlets were visible in the aromatic region. The two protons ortho to the methoxy groups were the most shielded and appeared as a singlet (at 6.35 ppm, labelled b). The presence of the thiomethyl moieties made the lower rim protons on the functionalized rings to appear slightly upfield than the lower rim protons on the unfunctionalized rings. Also, the likely crown conformation would place these protons (labelled c and d) in similar positions and hence appear at similar shifts.

*3.2.4. Tri-substituted resorcinarene (***tri-9***)*:

The aliphatic region of **tri-9** was slightly different from other compounds (Figure 4). The multiplet below 2.0 ppm appeared as pairs (signals at 1.30 ppm and 1.75 ppm, Pr). The

signal, assigned to the lower rim ethylene groups of the compound, can appear as a pair as a result of various results. These are adjacent to a chiral centre and hence their protons and the benzylic proton are diastereotopic. Also, the lower rim chains adjacent to the unfunctionalized ring are not in an equivalent position as the other two lower rim chain and as a result could differ in chemical shifts causing these multiplets to appear in this way.

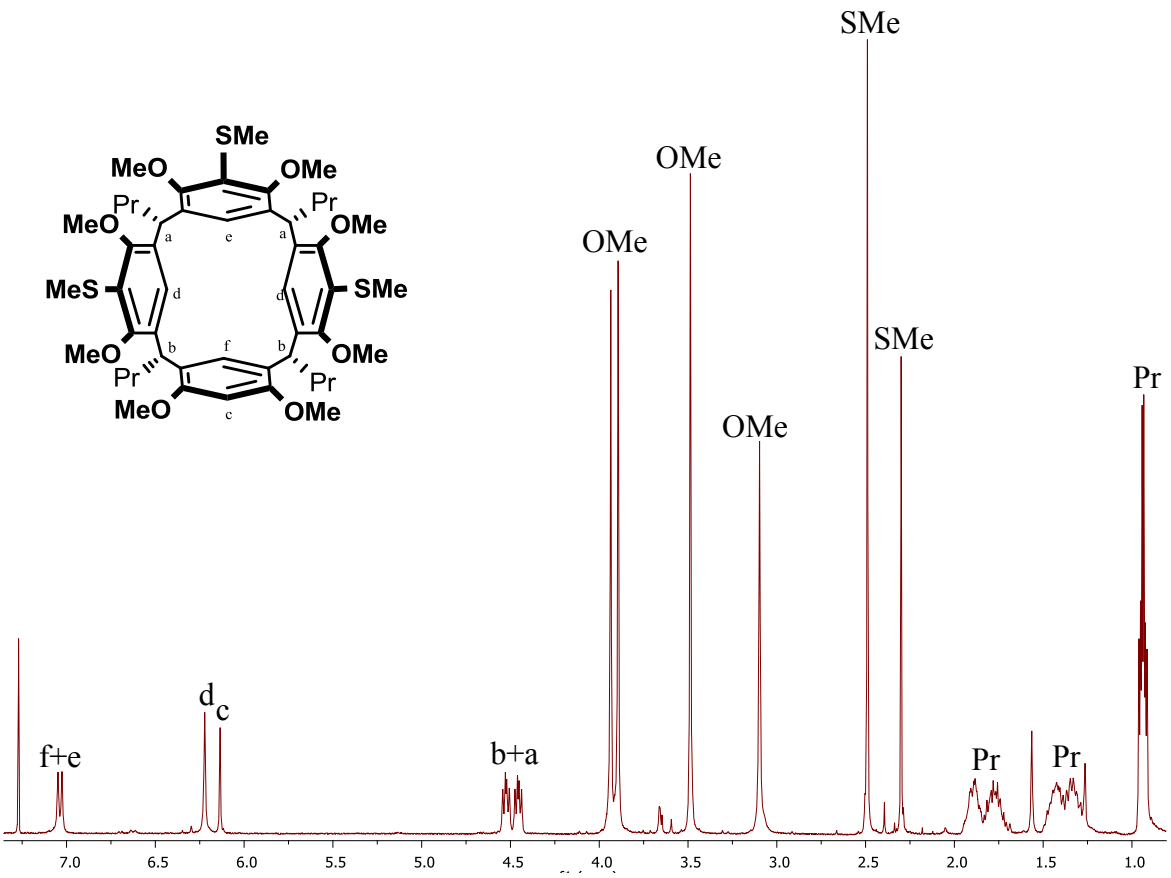


Figure 4: ^{1}H NMR spectrum of **tri-9**.

The ^{1}H NMR of **tri-9** gave an insight into the structural properties of the compound in solution. Firstly, the thiomethyl groups appear as two singlets at 2.30 ppm and 2.50 ppm integrating for three and six protons, respectively. These shifts suggest that the two thiomethyl-functionalized rings in distal relationship to each other are possibly occupying a position more perpendicular to the bowl of **tri-9**. Since they face away from the bowl they are less shielded compared to the thiomethyl moiety opposite the unfunctionalized ring. For this to be the case the functionalized aromatic ring opposite the unfunctionalized ring and the unfunctionalized ring itself are facing more upright and hence are more shielded.

The methoxy groups appear as four singlets at 3.10 ppm, 3.50 ppm, 3.85 ppm and 3.90 ppm. This is in correspondence with the number of chemical environments observed for the

methoxy groups. These possible chemical environments are labelled OMe. The two chemical environments of the benzylic protons caused these protons, split into triplets by the adjacent ethylene groups of the lower rim chains, to appear as two triplets at 4.0 ppm and 5.0 ppm. Four singlets are observed in the aromatic region of **tri-9**. These are observed at 6.15 ppm (labelled c), 6.25 ppm (Labelled d), 7.04 ppm (labelled e) and 7.09 ppm (labelled f). The signal at 6.15 ppm integrated for one proton, for the remaining single upper rim proton. The following signal, at 6.25 ppm, integrated for two protons possibly the lower rim protons on the thiomethyl-functionalized rings that are distal to each other. This observation confirms the structural information observed form the chemical shifts of the thiomethyl groups of the compound. This also suggests that these two protons occupy similar positions which may be inside or outside the bowl. However, these protons are more shielded compared to the other lower rim protons and hence are possibly orientated inside the bowl. This then means that the rings bearing the protons lie more perpendicular to the macrocyclic bowl. The other two aromatic protons (7.04 ppm and 7.09 ppm, labelled e and f) are not equivalent as one is on a functionalized ring and the other on an unfunctionalized ring. However, since the two rings bearing these protons are orientated more upright, the two protons are more outside the macrocyclic bowl and hence less, shielded when compared to the other pair of protons (labelled d)

*3.2.5. Tetra-substituted resorcinarenes (***tetra-9***)*:

The proton NMR spectrum of **tetra-9** was simple to interpret because of the high symmetry possessed by the molecule (Figure 5). The propyl groups appeared as a triplet and two multiplets at the aliphatic region. All four thiomethyl groups are equivalent and hence appear as a singlet accounting for 12 protons. This is clearly upfield to the methoxy signal. Also, all methoxy groups are equivalent and give a single singlet signal. The signal integrated to 24 protons. The benzylic protons are equivalent as well and are split into a triplet signal by the adjacent methylene proton (labelled Pr, at 1.80 ppm). No upper rim protons are present in the molecule and hence only one singlet is observed in the aromatic region (labelled b). However, it was noted that a slight contamination of the sample by **tri-9** occurred, which was difficult to remove. The high symmetry and similar chemical shifts observed suggest that this compound is in a crown conformation in solution.

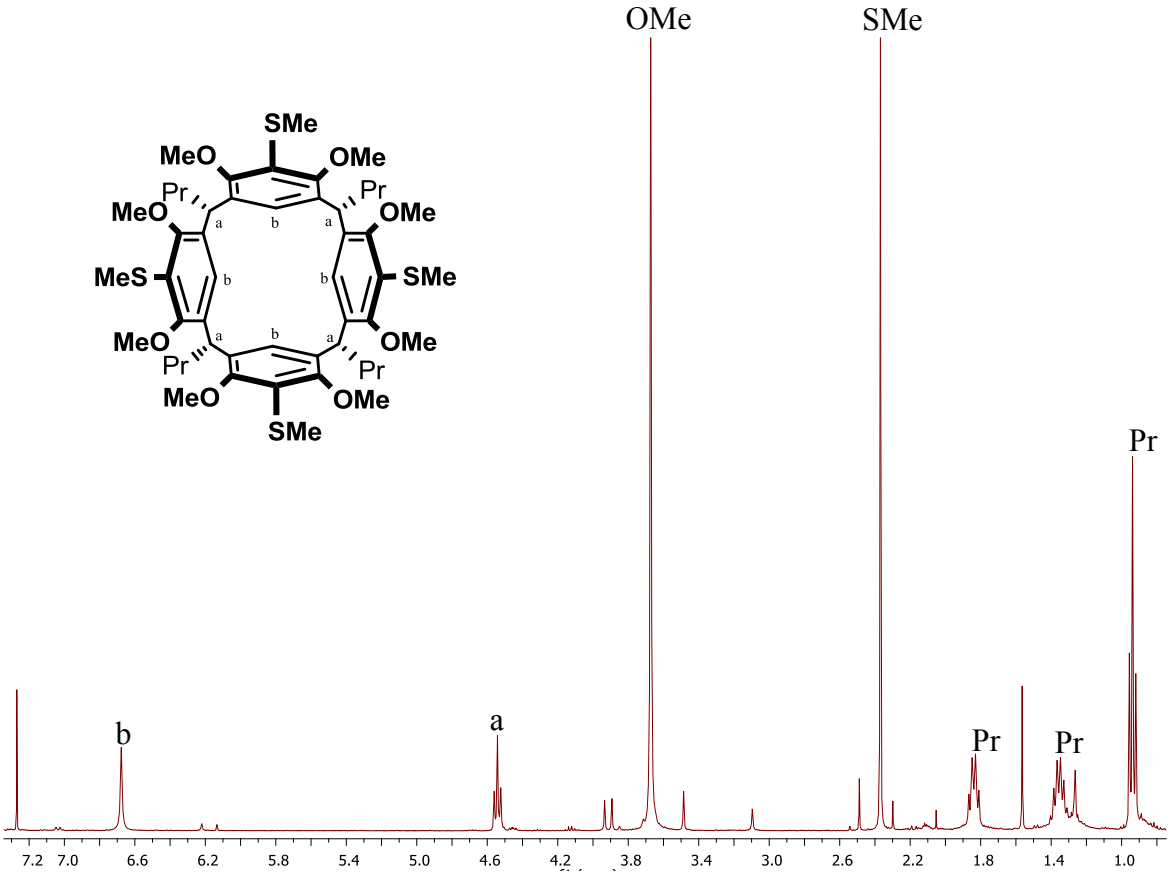


Figure 5: ^{1}H NMR spectrum of **tetra-9**.

3.2.6. Analysis method:

It was decided to use an NMR spectroscopic method to analyse data and calculate yields. A chromatographic method using HPLC could have been used instead but due to poor HPLC availability within the research group an NMR spectroscopic method favourable. Crude mixtures that typically contained four expected resorcinarene products (without **tetra-9**) and starting material would be expected to show seventeen signals in the aromatic region on the ^{1}H NMR spectrum. However, because of overlap, only fifteen signals were observed (Figure 6). In general, one signal of **proxi-9** was overlapping with one starting material singlet and one signal of **mono-9** was strongly overlapping with a **distal-9** signal; hence only fifteen signals could be used.

The Spin Works 3 NMR data interpretation program was used for deconvolution of overlapping signals (Figure 7) since these signals were used for yield calculation and hence an efficient integration method was necessary to ensure accuracy. Signals for aromatic protons were integrated on each deconvoluted spectrum and the integral under each signal was divided by the number of protons represented by the signal to account for a single

proton. Single proton values from different signals of the same compound were averaged together to gain precision. The averaged single proton values from signals of different compounds were summed and used as the total resorcinarene percentage content of the crude material. By dividing the averaged value of each compound by the summed value and multiplying by 100%, a relative proportion of each compound in the mixture was obtain.

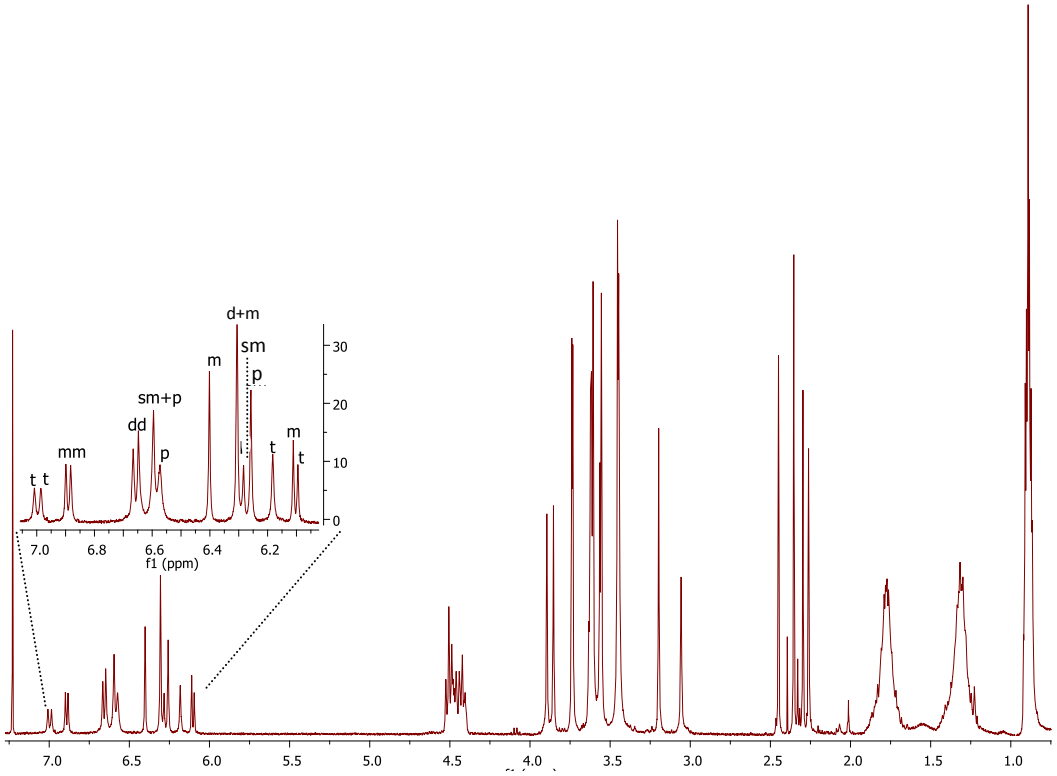


Figure 6: ^{1}H NMR spectrum of crude material (sm = **4**, m = **mono-9**, p = **proxy-9**, d = **distal-9**, t = **tri-9**).

This yield calculation concept was applied in programming of an in-house Microsoft Exel spreadsheet created for Spin Works 3 deconvoluted peak integrals.* This spreadsheet was used to automate and simplify the yield calculation method. This is shown in Figure 8 below. The spreadsheet was equipped with a percentage error function. This function served to detect values that deviated from average values so that consistency and accuracy could be kept. Percentage error values were made to appear as highlighted values using a small range of colours.

*Microsoft Excel spread sheet used for ortholithiation yield calculation was designed and written by Dr. Gareth Arnott.

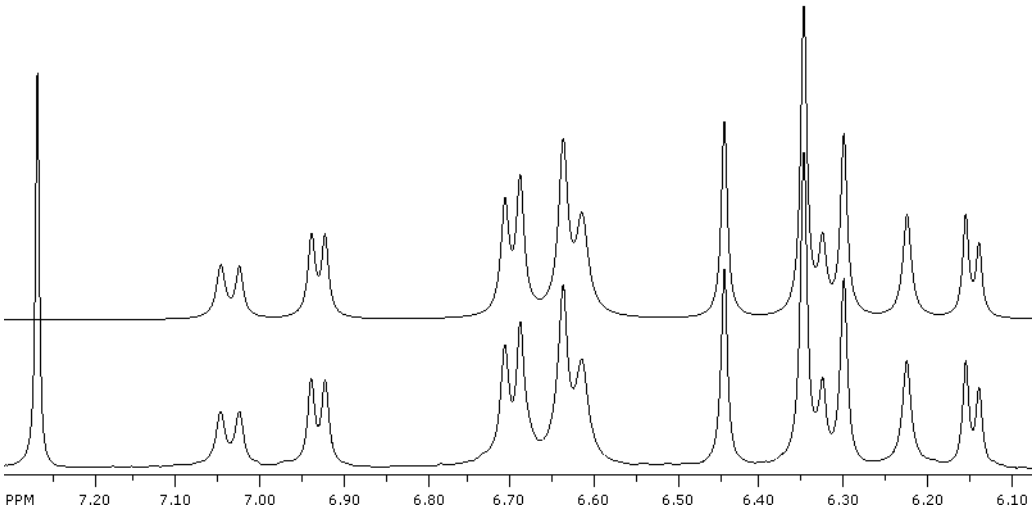


Figure 7: Crude ^{1}H NMR spectrum (bottom) and deconvoluted spectrum (top).

Experiment Name:LN27

Number	Freq.Hz	Freq.ppm	Gauss area		
1	2819.3	7.0493	0.157	17%	t
2	2810.34	7.0269	0.145		t
3	2775.68	6.9402	0.183		m
4	2769.03	6.9236	0.181		m
5	2682.47	6.7072	0.304		d
6	2675.07	6.6887	0.337		d
7	2654.61	6.6375	0.474		sm + p
8	2645.41	6.6145	0.357		p
9	2577.02	6.4435	0.359		m
10	2538.57	6.3474	0.638		d+m
11	2529.5	6.3247	0.147	11%	sm
12	2519.29	6.2992	0.354		p
13	2489.01	6.2235	0.242		t
14	2460.53	6.1522	0.17		m
15	2454.25	6.1365	0.126		t

	total area	protons	area/H	%
Starting Material	0.266	8	0.033	**5%**
Mono	0.893	5	0.179	**26%**
Distal	0.922	6	0.154	**23%**
Proximal	0.711	4	0.178	**26%**
Tri	0.670	5	0.134	**20%**

% error	
	10-15%
	15-20%
	>20%

Figure 8: A typical calculation using a Microsoft Excel spread sheet.

3.3. Preliminary studies:

The first reactions were performed using two equivalents of *n*-BuLi at −78 °C and incubated for 2 and 24 hours, respectively, before quenching with DMS. An excess amount of the electrophile was used to ensure complete quenching. Thin layer chromatography showed a single spot for both reactions, corresponding with the starting material **4**. ^{1}H NMR spectroscopy of crude reaction mixture only served to confirm this observation. Since it was known in our laboratory that ortholithiation occurs on resorcinarenes at −40 °C to return complex crude mixture in low yields,* changing the temperature was looked into. However, on increasing the temperature to −20 °C and allowing the reaction to occur for 2 hours returned the same result as observed at −78 °C (Table 1, entry 3). For this reason other reaction aspects were also investigated. Firstly, the initial inert atmosphere used in the reaction, nitrogen, was changed to the higher purity and heavier argon. Caution was also taken when adding reagents so as to minimize exposure of the reaction to the atmosphere. In this way, repetition of the reaction at −20 °C and incubating for two hours returned mono-functionalized product **mono-9** in 16% yield, along with starting material **4**. Increasing the reaction time to four hours, however, returned **mono-9** in trace amounts (Table 1, entry 5).

Table 1: Low temperature ortholithiation studies.

Entry	Time (hrs)	Temperature (°C)	Yield of **Mono-9** (%)	Yield of **Proxi-9** (%)	Yield of **Distal-9** (%)	Yield of **Tri-9** (%)	Yield of **Tetra-9** (%)
1	2	−78	0	0	0	0	0
2	24	−78	0	0	0	0	0
3	2	−20	0	0	0	0	0
4	2	−20	0	0	0	0	0
5	4	−20	0	0	0	0	0
6	4	−20	48	14	0	0	0

Based on the observations made thus far it was clear that temperature had an effect, but that other factors were causing the intermediate aryllithium to be quenched. Therefore, certain measures were taken in attempts to improve yields. An initial attempt involved performing the reaction with a sealed solvent flask. Four hour incubation at −20 °C gave 48% of **mono-9**, along with the proximally-functionalized product **proxi-9** formed in 14% yield.

* Dr. Gareth Arnott unpublished results 2007.

However, when the reaction was allowed to occur for longer reaction times loss of these products to starting material **4** was observed.

Even though the distal resorcinarene had not formed, and considerable amounts of starting material were isolated, it was evident that an external proton source, adventitious water for example, was affecting the reaction by protonating intermediates before the electrophile was added. In support of this a reaction incubated for a shorter time and higher temperature (30 minutes at 0 °C) provided a 14% drop in the yield of **mono-9** and a 34% increment in that of **proxi-9** (Table 2, entry 1).

A second attempt at drying the starting material for yield improvement was a method used by Sherburn.[2] Two small scale (50 mg) and large scale (400 mg) reactions were dried three times by evaporating THF under vacuum. After addition of the solvent, and drying, one small scale and one large scale reaction was incubated for 2 hours, while the remaining reactions were incubated for fifteen hours. These reactions were carried out at 0 °C. Analysis of the reaction revealed insignificant differences between small and large scale experiments. A rather pleasing observation made in this data set was the emergence of the distally substituted resorcinarene **distal-9**, as well as the tri-substituted resorcinarene **tri-9** (Table 2, entry 2).

Table 2: Ortholithiation at 0 °C to room temperature, after rigorous drying.

Entry	Time (hrs)	Temperature (°C)	Yield of **Mono-9** (%)	Yield of **Proxi-9** (%)	Yield of **Distal-9** (%)	Yield of **Tri-9** (%)
1	0.5	0	34	48	0	0
2	2	0	23	29	20	20
3	15	0	49	17	29	29
4	17	0	15	3	59	59
5	24	0	4	2	74	74
6	17	25	6	0	80	80

Since the results of table 2, entry 3 suggested the presence of adventitious water or a proton source, a third attempt involved the addition of sodium hydride (NaH) as a drying measure. It was hoped that any proton source would react with NaH and therefore, no longer negatively affect the reaction. In confirmation of this, a repetition of the reaction at 0 °C and allowing the reaction to occur for 17 hours returned 59% of **distal-9**, along with some **proxi-9** and **tri-9**. **Mono-9** was still present in 15% yield (Table 2, entry 4). Allowing a few more hours to 24

hours returned 74% of **distal-9**, along with minor amounts of other products. A slight increase of the temperature to room temperature (Table 2, entry 6) not only managed to provide **distal-9** in 80% yield, but also led to complete loss of **proxi-9** and **tri-9**. This crude mixture of products provided **mono-9** in only 6% yield.

During these studies it was mentioned that the silica tubing on the argon lines could be the source of the problem of adventitious water. Repeating the experiment of entry 4 Table 2 without NaH, but using thick vacuum tubing instead of the silica-based tubing, gave a similar yield distribution. Thus, most of the proton source accessed in this reaction arose from the silica-based tubing. The use of vacuum tubing, however, was able to minimize this diffusion. This also confirmed that NaH had a sole purpose of drying, instead of mechanistically intervening with the reaction. Having observed this, a further investigation into the temperature effect was carried out.

An analysis of the results in Table 2 revealed an interesting picture of what may be occurring in the reaction. **Proxi-9** was observed in larger quantities within shorter reaction time (Table 2, entries 1 and 2). Given time, however, **distal-9** is formed in larger quantities (Table 2, entry 3, and entries 4 and 5). This clearly indicated that **proxi-9** was indeed the kinetically favoured product. The fact that **distal-9** forms over time and is favoured at higher temperatures (Table 2, entries 4 and 6) suggested that this is a thermodynamic product. Beyond considerable doubt, this suggests that, in some order, reaction intermediates equilibrate to yield the most favourable product. It appeared that **tri-9** persists to exist for longer times than **proxi-9**, suggesting that **proxi-9** may possibly equilibrate to **distal-9** via **tri-9**. Mechanistic aspects of the reaction are discussed later (section 3.3.6).

An observation generally made at this point was the fact that **tetra-9** has not been observed. This made sense because its quantitative formation would require four equivalent of base and only two were used. Also, its formation and dissociation would be faster than that of **proxi-9** and **tri-9** and hence, based on the previous results and observations, low temperatures, excess base and extended reaction times would be required (see section 3.3.6).

3.3.1. Temperature and time effects:

At this point it was known that the increase in temperature favoured selective formation of **distal-9** at the cost of **proxi-9** and **tri-9**. Also, that increased reaction times were needed. To improve yields of the distal product it was decided to increase the temperature to 40 °C. A

reaction performed at this temperature and allowed to run for two hours returned 60% of **distal-9**. Formation of the distal product was still maintained as **proxi-9** and **tri-9** did not form at all. **Mono-9** on the other hand was found in low yields, thus about 35% starting material remained. Gradually increasing the reaction time to 24 hours returned a similar yield distribution (60 - 66%) of **distal-9**. It was interesting to note that the longer reaction times did not result in **distal-9** being destroyed and thus suggested that it was relatively stable under the reaction conditions. An attempt to increase the yield by increasing equivalents of Bu^nLi used to 2.5 equivalents and incubating for 24 hours (Table 3, entry 4) returned a similar yield distribution.

Table 3: Ortholithiation at high temperatures

Entry	Time (hrs)	Temperature (°C)	Yield of **Mono-9** (%)	Yield of **Proxi-9** (%)	Yield of **Distal-9** (%)	Yield of **Tri-9** (%)
1	5	40	5	0	60	0
2	14	40	5	0	62	0
3	24	40	4	0	62	0
4	24[a]	40	7	0	66	0

[a]2.5 equivalents of n-BuLi was used.

Once again, this suggested that n-BuLi was being destroyed in the reaction. This could likely still be due to a proton source accessing the reaction, which would be more effective at elevated temperatures. Another option was that something else was consuming the base and hence limiting ortholithiation at high temperatures. This second possibility will be addressed later. A set of reactions performed under an inert atmosphere passed over 4Å molecular sieves at this temperature gave 82% of **distal-9**. This indicated that some proton source was still accessing the reaction through the inert gas.

With the knowledge that reaction times above two hours are not necessary and two hours may be more than enough, it was decided to investigate the shortest reaction time required to achieve good yields. A series of reactions were set up and incubated at time intervals between 30 and 120 minutes and the results are tabulated in Table 4.

Table 4: Optimization of reaction time.

Entry	Time (min)	Temperature (°C)	Yield of **Mono-9** (%)	Yield of **Proxi-9** (%)	Yield of **Distal-9** (%)	Yield of **Tri-9** (%)
1	30	40	5	1	71	15
2	50	40	6	0	76	2
3	75	40	14	0	83	0
4	100	40	5	0	85	0
5	120	40	4	0	85	0

Analysis of these results revealed favoured formation of **distal-9** within 30 minutes. Another observation shown by this data set was the slow disappearance of **tri-9** compared to **proxi-9**. This observation may suggest that the mechanism of equilibration of **proxi-9** to **distal-9** might be via **tri-9**. Nevertheless, the reaction reaches quantitative yields within 75 minutes and no change is observed between 100 and 120 minutes. Therefore, a reaction time between 75 and 100 minutes is sufficient.

3.3.2. Base equivalents effect:

Table 5: Optimization of base equivalents.

Entry[a]	Time (hrs)	*n*-BuLi (equivalents)	Yield of **Mono-9** (%)	Yield of **Proxi-9** (%)	Yield of **Distal-9** (%)	Yield of **Tri-9** (%)
1	2	2	4	0	85	0
2	2	2.5	7	0	77	0
3	2	3	6	0	83	0
4	2	4	6	0	82	0
5	2	5	6	0	82	0

[a]reaction performed at 40 °C.

With all the attempts carried out thus far, at least 10% to 15% of the starting resorcinarene **4** remained unreacted. Moreover, at least 4% to 7% of the singly functionalized resorcinarene product, **mono-9**, persisted (Table 5, entries 1 to 5). To achieve complete di-lithiation of these remaining materials, a gradual increase in base equivalents was performed. As observed in table 5, excess amounts of the base did not in any way improve the results. This could be attributed to the fact that the reaction may have reached maximum capacity and adding

excess base could no longer shift the equilibrium towards products. It was unlikely that the base remained in solution since no **tri-9** or **tetra-9** was detected. Therefore, something must be reacting with the base and **tri-9** and **tetra-9** aryllithium intermediates. This will possibly be addressed later.

3.3.3. Effect of increasing the reaction scale:

Having a feasible methodology in hand it was a necessity to investigate whether the **distal-9** product could be formed on larger scales, since up until now reactions were performed at 50 mg scale. This new investigation began at 300 mg scale and was performed under optimized conditions, i.e. two equivalents of *n*-BuLi at 40 °C and maintaining the same concentration as before. The findings are as tabulated in table 6. Disappointingly, a 300 mg scale reaction under these conditions furnished only 22% of **distal-9**. However, complete loss of **proxy-9** and **tri-9** were also noted and **mono-9** was only recovered in trace amounts. In general, should the drop of yield be due to up-scaling then a further increase in scale should lead to even lower yields. This was indeed the case. When the reaction was performed on a 400 mg scale under the same conditions, the yield of **distal-9** dropped further to 15% (Table 6, entry 2).

Table 6: Results of scale-up reaction.

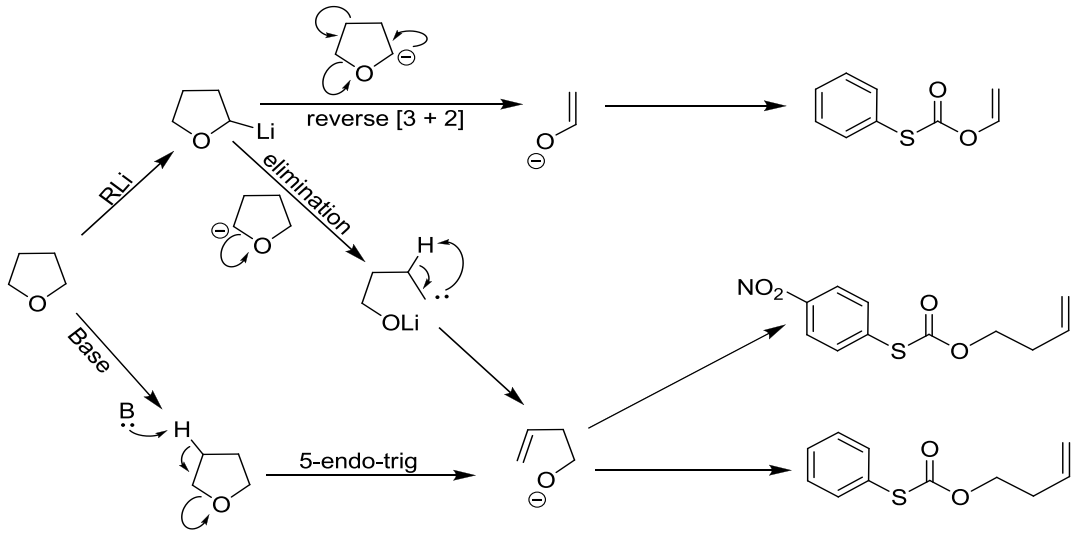
Entry	Time (hrs)	Temperature (°C)	Yield of **Mono-9** (%)	Yield of **Proxi-9** (%)	Yield of **Distal-9** (%)	Yield of **Tri-9** (%)
1	2	40	3	0	22	0
2	2	40	3	0	15	0
3	2	40	3	0	30	0
4	4	40	2	0	24	0
5	8	40	2	0	6	0
6	2	40	4	0	86	0

[a]reaction performed at 300 mg scale.
[b]reaction performed at 400 mg scale.
[c]5 equivalents of *n*-BuLi used.

Attempts to increase yields were next explored. Firstly, the reaction time was increased to 4 hours (Table 6, entry 4) but was found not to be effective as it returned a similar result. A further reaction time increase to eight hours furnished only 6% of **distal-9** (Table 6, entry 5). The effect of product degradation at larger scale was certainly increasing with an increase in

reaction time. Since it seemed unreasonable that such low yields were being obtained, it was decided to use an excess of *n*-BuLi since it was already known that this did not change the product distribution. In this way adding five equivalents of *n*-BuLi returned 86% of **distal-9** after two hours of incubation (Table 6, entry 6).

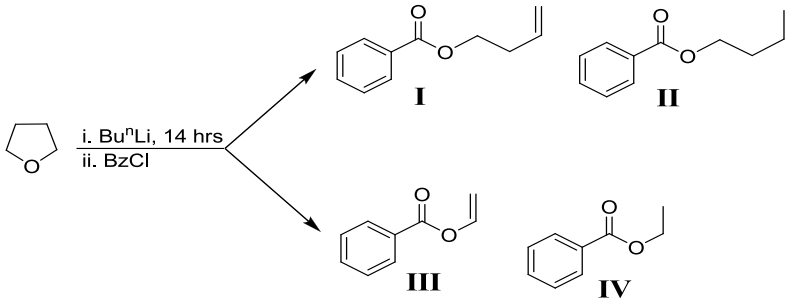
It was decided to investigate this discrepancy in result. Based on facts discussed above the intermediates were quenched *in situ*. This meant that the proton source was itself deprotonated and these intermediates could be trapped, isolated and analysed. A literature survey revealed that indeed some solvents react with and are decomposed by strong bases, including alkyllithium reagents.[3] This occurs particularly with solvents having slightly acidic protons like ethers. This phenomenon has been reported for THF and occurs significantly at high temperatures and long reaction times. THF decomposition can occur via three distinct pathways. These include the reverse [2 + 3] cycloaddition,[4] α–elimination or 5–endo–trig mechanisms (Scheme 2).[5] The small decomposition intermediates of THF have been trapped with large and UV active electrophiles. This makes these intermediates less volatile and easy to detect. Phenyl thiochlorocarbonate and *p*-nitrobenzoylchloride are two such electrophiles that have been used in literature.



Scheme 2: Pathways for degradation of THF.

In an attempt to trap and isolate any THF decomposition intermediate formed in the reaction upon scale-up, a similar concept was employed. A 300 mg scale reaction was allowed to occur at 40 °C for fourteen hours. The long reaction time was chosen to allow sufficient formation of the degradation intermediates. Quenching the reaction with benzoyl chloride

allowed the trapping and UV detection of the decomposition intermediates. A schematic representation of the findings (Scheme 3) appears below.



Scheme 3: Products of THF degradation (**I** and **III** expected; **II** and **IV** found).

According to literature data, compound **I** and **III** should form upon the reaction of THF with alkyllithium. Although unsaturated products **I** and **III** were expected, only saturated products **II** and **IV** were detected, as was evident from the ^{1}H NMR spectrum (Figure 9).

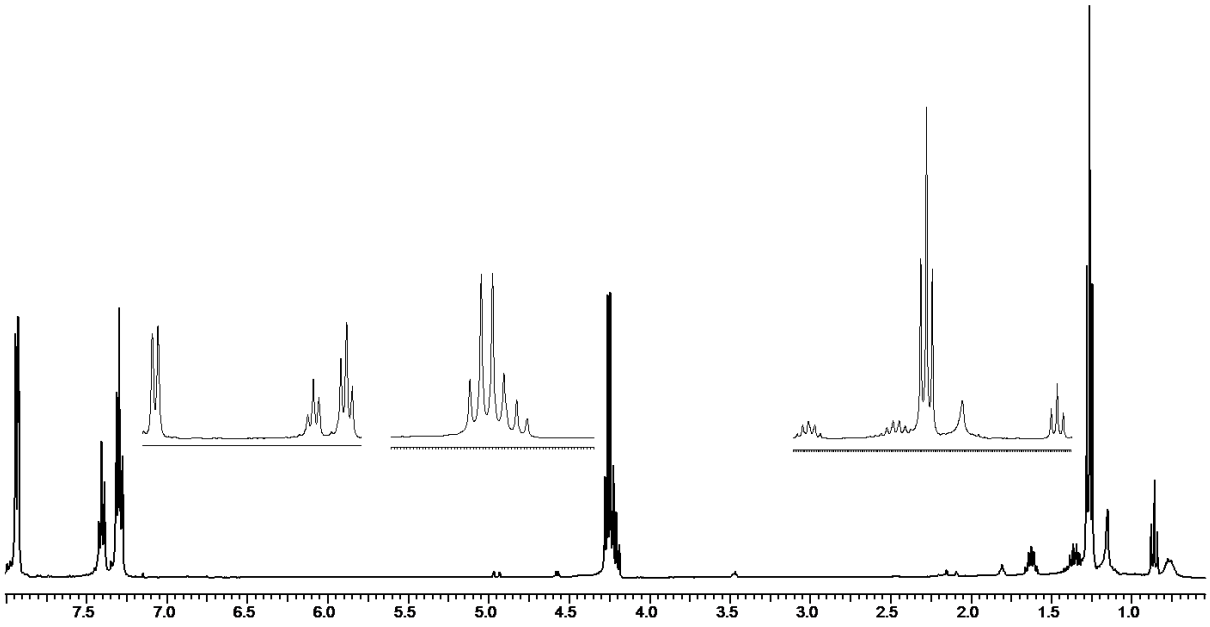
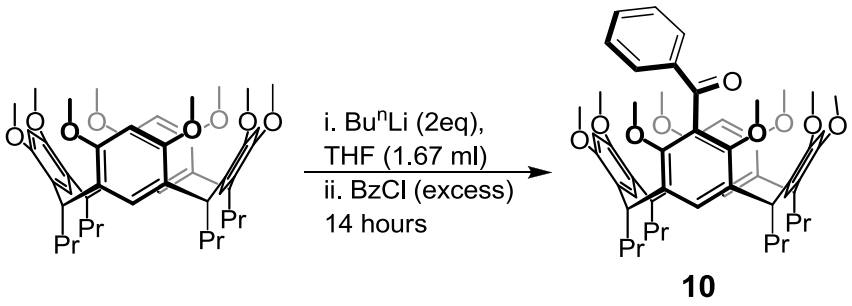


Figure 9: ^{1}H NMR of THF degradation products **II** and **IV**.

^{1}H NMR spectroscopy revealed a major product that had a triplet at 1.25 ppm and a quartet at 4.25 ppm. These signals correspond to the ethyl chain of **IV** (scheme 3). The aromatic region had two triplets (7.30 ppm and 7.40 ppm) and a single doublet (7.8 ppm) showing a singly substituted aryl ring. This corresponded to the aromatic rings of the products. Also observed in lower intensities was a triplet at 0.7 ppm, two multiplets at 1.40 ppm and 1.70 ppm and a triplet that slightly overlapped with the quartet of **IV** at 4.25ppm. These signals suggested

compound **II**. Aromatic signals of **II** would appear at comparatively similar shifts as those of **IV** and hence overlap with each other. Seemingly, the [3 + 2] reverse cycloaddition path was more favoured by our reaction conditions than the α-elimination and 5-endo-trig paths. Therefore, the [3 + 2] cycloaddition product, **II**, formed in higher yields. The reduction step from **I** and **III** to **II** and **IV** has not been explained, something which should be pursued in the future. Along with these decomposition products, resorcinarene mono-ester **10** was isolated. This result gave away the fact that after fourteen hours of incubation on larger scale, only small amounts of the singly lithiated resorcinarene intermediate exist. To generalize, resorcinarene lithio-intermediates do form but can act as alkyllithium reagent to decompose THF.



Scheme 4: Resorcinarene ketone formed along with THF decomposition products.

A single crystal of **10** was isolated and characterized by single crystal X-ray crystallography, and is shown in Figure 10 below. A single molecule of acetonitrile was included in the unit cell and is not shown for clarity.

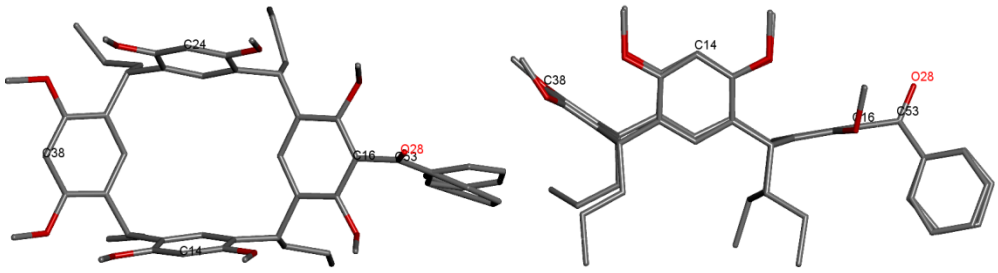


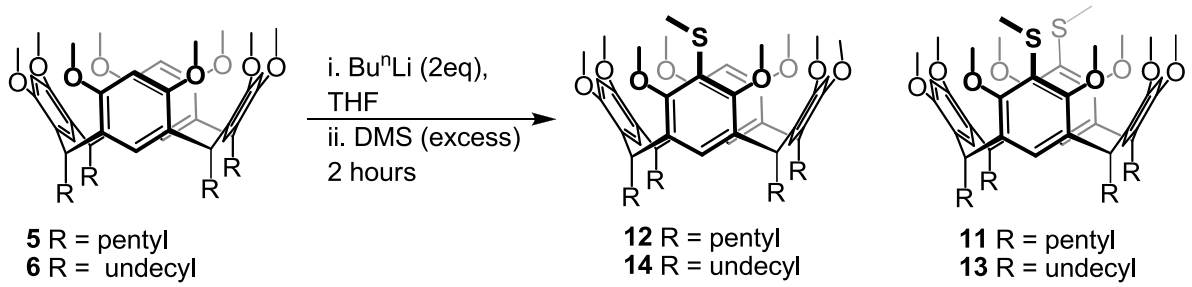
Figure 10: X-ray crystal structure of **10** with atoms labelled in gray (carbons) and red (oxygens). The crystal structure also shows the distorted phenyl ring.

The crystal structure of **10** had the phenyl ring of the benzoyl group distorted over two positions and orientated outside the cavity. In addition, the macrocycle rings adjacent to the ortho-substituted ring (C14 and C24) are orientated slightly away from the vertical plane.

Ring bearing C38 lies in a slight up-right position compared to the ring bearing the functional group, giving a distorted boat.

3.3.4. Lower rim length:

The effect of the variation of lower rim alkyl chains on the methodology was also investigated. Two longer lower rim length resorcinarene ethers, **5** and **6**, were subjected to ortholithiation conditions (Scheme 5). The reactions were performed on a 300 mg scale so as to also allow chromatographic quantification of products. Results are documented in Table 7 below. Ortholithiation of **5**, the pentyl-footed resorcinarene returned the distally-functionalized product **11** in 87% yield by ^{1}H NMR spectroscopy. This compound was accompanied by 5% of a mono-functionalized product **12** (Table 7, entry 1). Ortholithiation of **6** returned a similar result; 85% of distally-functionalized resorcinarene **13** was formed along with 3% of mono compound **14** (Table 7, entry 2). Slightly lower yields were achieved by chromatography (75% and 70%, relatively).



Scheme 5: Effect of lower rim length variation.

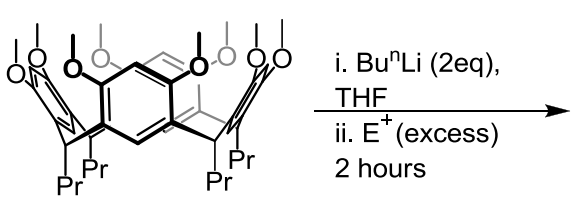
The yields were comparable with those of template starting material **4**. Of note, proximally and tri- functionalized products were not formed. These results are tabulated below.

Table 7: Yields of ortholithiation products of resorcinarenes **5** and **6**.

Entry	Material	Time (hrs)	Temperature (°C)	Yield of **Mono-9** (%)	Yield of **Distal-9** (%)
1		5	40	5	87
2		6	40	3	84

The ^{1}H NMR spectra of **11** and **13** were similar to that of **distal-9**, likewise, spectra of **12** and **14** were similar to that of **mono-9**. The main difference between these spectra was the number of protons in the region around 1.2 ppm due to the alkyl chains. In the case of **distal-9** this accounted for 8 protons, but now increases to 24 and 72 for **11** and **13**, respectively. However the ^{13}C NMR spectrum did show that this multiplet, 1.2 ppm on ^{1}H NMR, was due to overlapping proton signals rather than equivalent protons, as these carbons peaks appeared as multiple signals in the carbon NMR spectrum.

3.3.5. Effect of electrophile variation:



Entry	E	Compound
1	CO_2CH_3	**15**
2	Me	**16**
3	CO_2H	**17**

Scheme 6: Ortholithiation using a small range of electrophiles.

Flexibility with regards to the nature of electrophiles used allows for the further development of new compounds. It also serves as access to starting materials suitable for architectural construction of robust supramolecular compounds. Introduction of other functional groups to **4** was thus attempted (Scheme 6). A small range of electrophiles were selected for the investigation. They included methyl chloroformate, methyl iodide, carbon dioxide. Yields were as documented in table 8 below.

Table 8: Yields of distal products with other functionalities.

Entry	Time (hrs)	Temperature (°C)	Electrophile (E)	Product	Yield (%)
1	2	40	$ClCO_2CH_3$	**15**	75
2	2	40	MeI	**16**	70
3	2	40	CO_2 (s)	**17**	40

An ortholithiation reaction incubated for two hours at 40 °C and quenched with methyl chloroformate as an electrophile managed to furnish the distal-ester **15**. This compound was isolated in 75% yield via flash chromatography. Incorporation of ester groups was confirmed by emergence of a singlet at 3.86 ppm in the ^{1}H NMR spectrum, integrating for six protons (Figure 11). In the molar mass spectrum peaks for [M^{+}] and [M+Na] of the ester were observed at 884.5 m/z and 907.5 m/z, respectively, confirming the molecular weight of the compound.

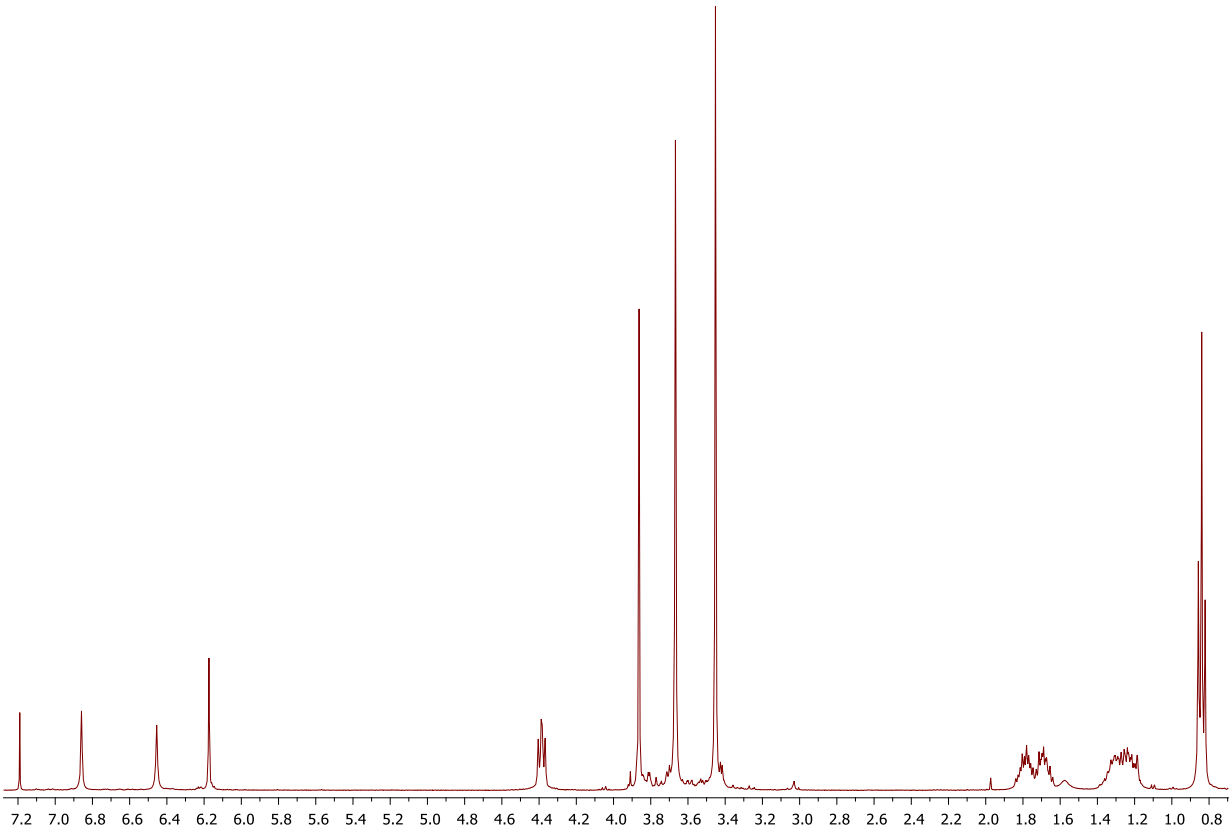


Figure 11: ^{1}H NMR spectrum of di-ester **15**.

The X-ray crystal structure of **15**, grown from acetonitrile, shows the two distal-methyl ester functionalised rings lying more in the plane of the cavity (Figure 12). The ring bearing carbonyl-carbon C53 lies in a more up-right position, giving a distorted boat structure. Finally, the two unsubstituted rings lie in an up-right position, slightly distorted from the vertical plane.

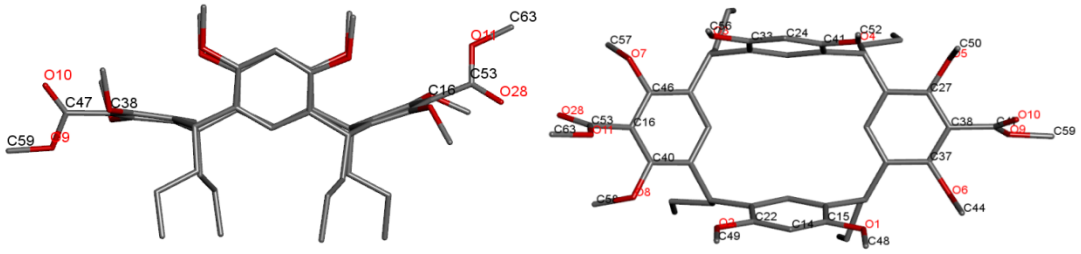


Figure 12: Side (Left) and Top (Right) views of crystal structure of **15** with atoms labelled in gray (carbons) and red (oxygens).

Quenching the reaction with methyl iodide as an electrophile furnished 70% of distally methylated product **16** (Scheme 6) after chromatography.

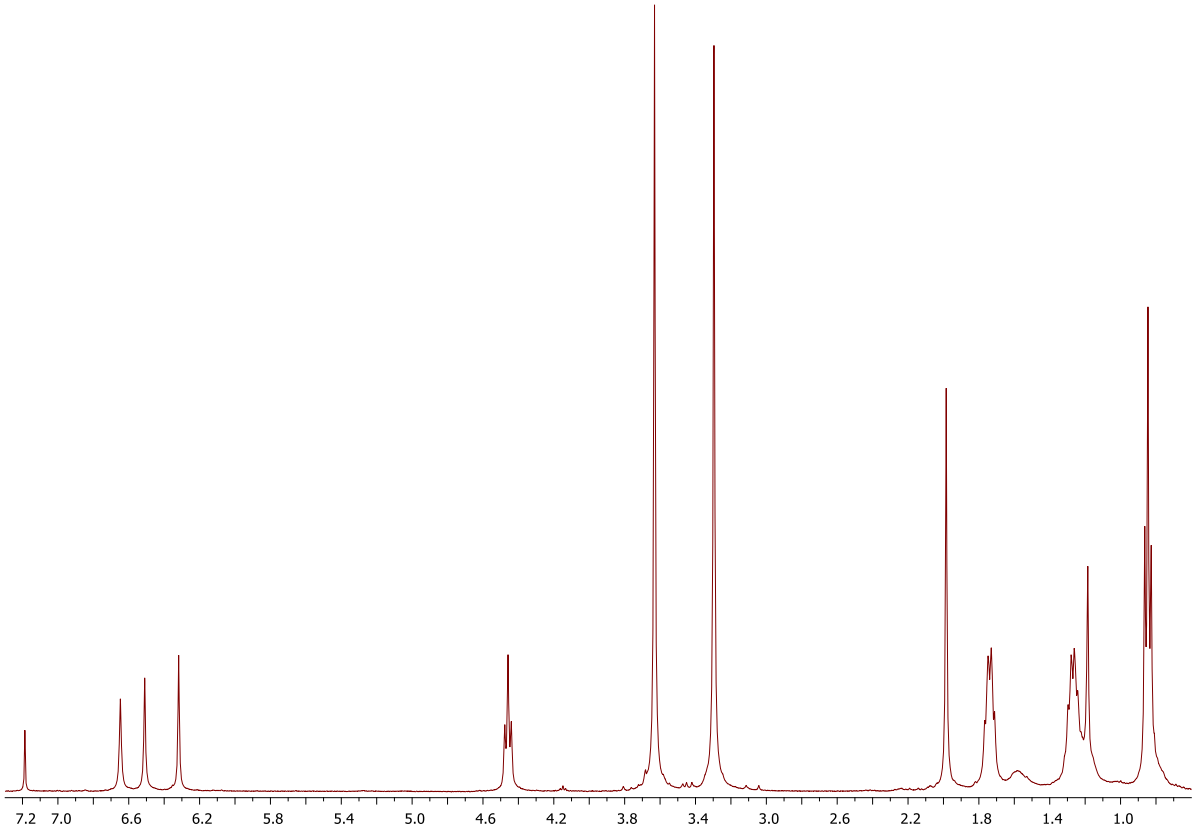


Figure 13: ^{1}H NMR spectrum of **16**.

Successful incorporation of two methyl groups was evident on the emergence of a singlet at 1.90 ppm integrating for six protons (Figure 13). Symmetry on ^{1}H NMR spectrum was shown to be similar to that for **15**. The mass spectrum for compound **16** had peaks for [M^{+}] and [M+Na] at 797.5 *m/z* and 820.5 *m/z*, respectively. Introduction of carboxylic groups was attempted using solid CO_2 as an electrophile. To this end, quenching with solid CO_2 at 40 °C

after a 2 hour incubation managed to furnish the distally functionalized di-acid **17**. Because of its difficulty and tediousness to purify this mixture using flash chromatography, its isolation was more efficient performed via liquid-liquid extraction. The crude of **17** was thus dissolved in DCM and washed three times with dilute sodium hydroxide solution. The combined extracts were neutralised by addition of HCl which precipitated **17**. The precipitate was recovered by filtration and dried to give 40% of **17**. Lower yields are possibly due to the fact that the reaction temperature was too high for CO_2 to remain in solution. It therefore volatilizes before sufficiently quenching the reaction.

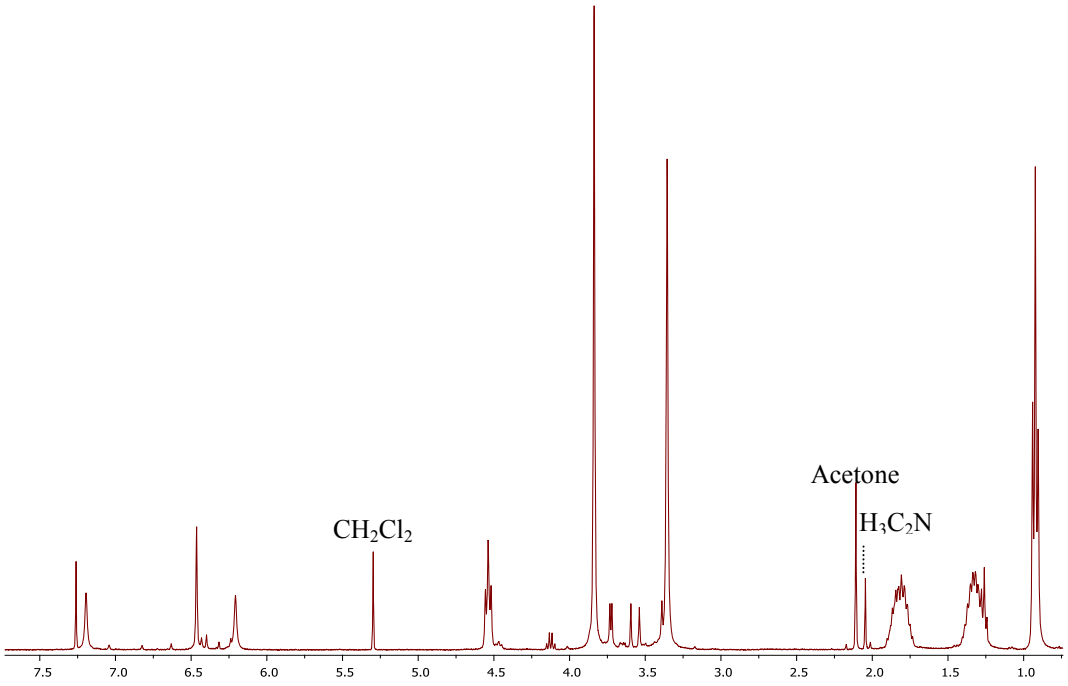


Figure 14: ^{1}H NMR spectrum of di-acid **17**.

Unfortunately the product was difficult to purify under conventional conditions, but the ^{1}H NMR spectrum suggested that the diacid was obtained. Observed was a broad flattened peak at 10.90 ppm accounting for the two carboxylic acid protons. In addition, the methoxy groups appeared as two singlets at 3.36 and 3.84 ppm. The remaining ortho-position protons appeared as a singlet at 6.21 ppm (Figure 14). However, this material was clearly contaminated with some other minor products frustrating absolute characterisation. MALDI-TOF mass spectrometry provided a molecular ion peak [M^+] at 856 *m/z* corresponding to calculated molar mass of **17**. A peak at 879 *m/z*, accounting for [M+Na], was also observed. Attempts to improve yields by quenching with gaseous CO_2 led to rapid solvent evapouration when the gas was bubbled through the solution. Though the gas managed to give **17,** yields

were comparatively lower. This is because the reaction could not be given enough time to quench as the solvent was being lost.

*3.3.6. Synthesis of resorcinarene **tetra-9**:*

The tetra-functionalized resorcinarene **tetra-9** was not formed in earlier reactions. However, it was decided to target this compound. Since it was known that at higher temperatures the compound was not observed, it was decided to attempt these reactions at 0 °C with 5 equivalents of Bu^nLi and using DMS as an electrophile. Results from three reactions performed under these conditions are shown in Table 8 below. Only three resorcinarene products were observed, namely **mono-9**, **tri-9** and **tetra-9**. At least 89% of **tetra-9** could be achieved within ninety minutes at 0 °C. Raising the temperature to 25 °C revealed lower conversion of **tetra-9**. The molecular mass of compound **tetra-9** was confirmed by mass spectroscopy which gave a peak at 955.4 *m/z* corresponding to the expected molecular ion, $[M^+]$.

Table 9: Selective tetra-functionalization or resorcinarenes.

Entry	Time (hrs)	Temperature (°C)	Yield of **Mono-9** (%)	Yield of **Tri-9** (%)	Yield of **Tetra-9** (%)
1	30	0	3	25	73
2	60	0	0	28	72
3	90	0	0	11	89
4	30	25	4	35	66

The crystal structure of **tetra-9** (Figure 15) showed that the compound had distal thiomethyl-functionalised rings lying on a horizontal plane, in the plane of the cavity. Methyl groups of both thiomethyls, C46 and C50, face outside the ring. The other two rings, bearing S47 and S51, are orientated directly on the vertical axis. Finally, the thiomethyl functionality S47 faces into the macrocycle cavity while the other, S51, faces outside the cavity.

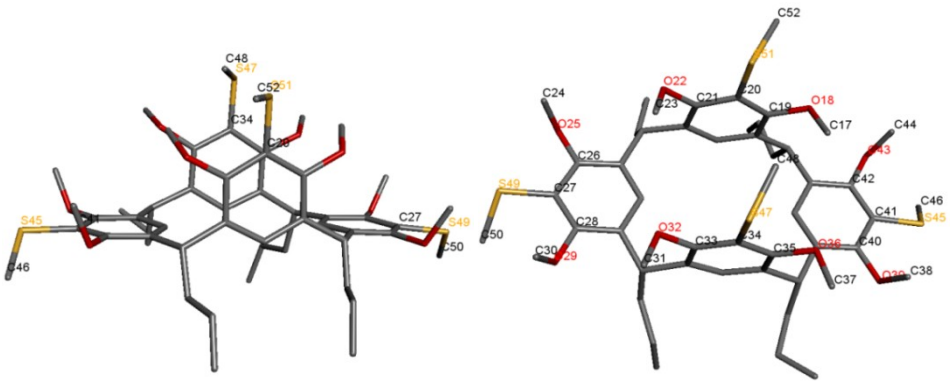
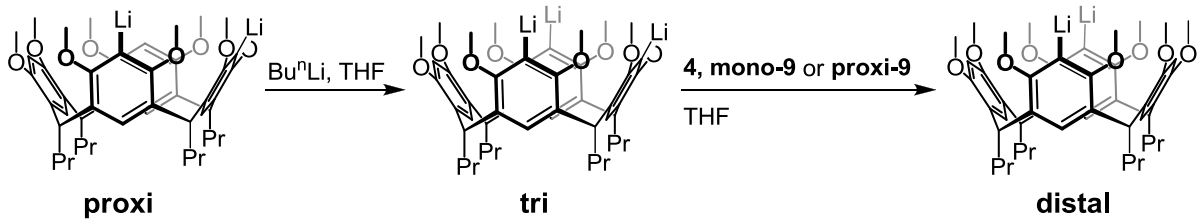


Figure 15: Side (Left) and Top (Right) views of crystal structure of **tetra-9** with atoms labelled in grey (carbons), red (oxygens) and yellow (sulphur).

3.3.7. Mechanistic aspects:

Though methods for mechanistic studies were not devised or performed, observations made thus far do provide an insight into the mechanism of the reaction. In all temperature ranges where the reaction actually occurs, product distribution is greatly affected by time; the reaction equilibrated to the more favoured product as reaction time increased. Disappearance of unfavoured intermediates was also observed over time. For instance, a 17 to 24 hour reaction at 0 °C allows for high returns of **distal-9** as compared to a two hour reaction where complex mixtures are achieved. A similar case is observed in the synthesis of **tetra-9**, where **tri-9** is observed in higher yield after 30 minutes and **mono-9** is still present at 0 °C and diminished to 11% and 0%, respectively, after 90 minutes (table 8, entry 3), as well as in the complete loss of **proxi-9** and **tri-9** after two hours at 40 °C (e.g. table 4, entry 5). This observation suggests a more random lithiation of resorcinarenes to form intermediates of all expected products. With time, the intermediates equilibrate, although the mechanism is not known. Presumably these could be through organo-lithio-resorcinarene intermolecular interactions or via intramolecular lithium atom migration. Intramolecular migration is thought to be highly unlikely. The reason for this is that the distance between two neighbouring ortho positions is considerably large and there are two methoxy groups between them. Compound **tetra-9** is probably not observed in most reactions because it rapidly lithiates intermediates of lower lithiation degree, e.g. lithiation of **4** to form **mono-9** or of **mono-9** to form **proxi-9** or **dista-9**. Lithio-intermediate of **tetra-9** may also lithiate intermediates of **proxi-9** or **distal-9** to form **tri-9**. **Tetra-9** may also degrade by rapidly lithiating the solvent.

It is highly possible that the equilibration to the distal intermediate goes via certain intermediate lithio-resorcinarenes. This stems from the observation that though both **proxi-9** and **tri-9** are completely lost upon equilibration, **proxi-9** disappears faster. This suggests that the unstable kinetic proximal lithio-intermediated is lithiated to form the tri intermediate. The tri intermediate then loses the most basic lithio-functionality, the middle one, to lithiation of other intermediates or starting material to form the distal lithio-intermediate (Scheme 7).



Scheme 7: Possible equilibration path of lithio-resorcinarene intermediated to the distal intermediate.

The stability of the distal intermediate is possibly a result of electronic properties of the compound (Figure 16).

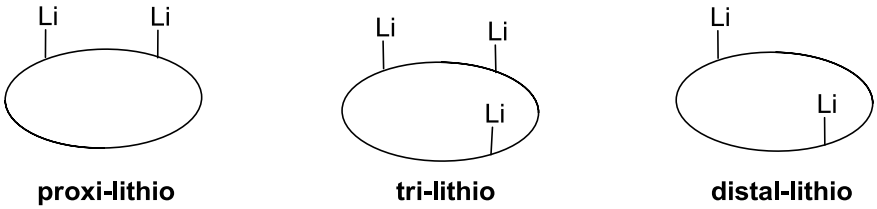


Figure 16: Relative stability of resorcinarene lithio intermediates.

The proximal intermediate gives rise to a compound that is more crown-like in conformation (section 3.2.2) and hence the two lithio groups are most likely to repel. However, the tri intermediate results in a compound that is in a boat conformation (section 3.2.4) and therefore has the distal lithio groups almost perpendicular to the bowl, relieving repulsion. The lithio group of the tri intermediate adjacent to the other two is more basic and is readily lost to form the more stable distal intermediate (see section 3.2.3 for possible conformation).

3.4. Conclusion:

To conclude, resorcinarene ethers with various lower rim lengths were synthesized and applied as templates to study selective functionalisation of resorcinarenes. Any means to

prepare propyl-footed resorcinarenes using Cram's procedure were not successful. Distally substituted resorcinarenes modified with a small variety of functional groups were synthesized using an ortholithiation approach. Also, conditions for selective tetra-functionalisation of the compounds were optimized. Higher temperatures (40 °C) are required to achieve good yields of the distal product over short reaction times. Though the methodology accepts lower rim variation, it still needs excess amount of base on larger scales.

3.5. Future work:

3.5.1. Further condition optimization:

Conditions for the preparation of resorcinarenes **mono-9**, **proxi-9** and **tri-9** were not optimized in this thesis. Optimization of these conditions is one aspect that falls within the future work of the project. Also, there are other parameters that still need to be considered to fine-tune the methodology; i.e. solvent change, additives like TMEDA as performed in calixarenes,[6] base variation and base concentration. Alternative routes to bis-phosphine, analogues of cavitand and calixarene bis-phosphines,[7] and bis-boronic acid resorcinarene compounds can be developed as well. Another future aspect is the optimization of conditions for the selective synthesis of heptamethoxy resorcinarene **8** made as a by-product in this thesis. This compound can then, as mentioned earlier, be applied in the preparation of asymmetric resorcinarene ligand and hence in catalysis.

3.5.2. Synthesis of carbene complexes (NHC's) and catalysis:

With a reasonably yielding methodology for preparation of distally functionalized resorcinarenes, resorcinarene bis-imidazolium salts will be prepared from the distal di-ester **15**. Resorcinarene-palladium complexes and their catalytic study, as seen on calixarenes,[8] will be pursued using these imidazolium salts as ligands. This can then be transferred to resorcinarene bis-benzimidazolium ligands and ultimately to resorcinarene bis-caffeine ligands. These complexes, which will be mainly prepared for application in carbon-carbon formation reactions, can also be tested in other reactions like Buchwald-Hartwig amination and carbene transfer,[9,10] in the case of rhodium complexes, reactions. Extending literature on resorcinarene NHC's could involve preparation and study of tin and silicon analogues of these 2-ylidines.[11,12]

3.5.3. Frustrated Lewis pairs (FLPs):

Sterically separated Lewis acid and Lewis base pairs incorporated into the same molecule are hindered from quenching.[13] The Lewis acid and Lewis base points are close enough to trap small molecules between them, like dihydrogen,[14] but are far enough not to react with each other. Such compounds are referred to as Frustrated Lewis pairs (FLPs). Resorcinarene analogues of such compounds can be designed using the developed methodology, namely ortholithiation, as a pathway. Also within this concept and with studies on resorcinarene NHC precursors reported in chapter 4, preparation of NHC carbene and Lewis acid FLPs fall within reach.[15]

3.6. References:

1. (a) Lukin V.O.; Pirozhenko V.V.; Shivanyuk N.A. *Tetrahedron Lett.* **1995**, *36*, 7725; (b) Shivanyuk A.; Paulus E.F.; Böhmer V.; Vogt W. *J. Org. Chem.* **1998**, *63*, 6448; (c) Luostarinen M.; Nissinen M.; Nieger M.; Shivanyuk A.; Rissanen K. *Tetrahedron* **2007**, *63*, 1254.
2. (a) Irwin L.J.; Sherburn M.S. *J. Org. Chem.* **2000**, *65*, 5846; (b) Barrett E.S.; Irwin J.L.; Turner P.; Sherburn M.S. *J. Org. Chem.* **2001**, *66*, 8227.
3. (a) Clayden J.; Yasin A.S. *New J. Chem.***2 002**, *26*, 191; (b) Maercker A.; Demuth W. *Angew. Chem. Int. Ed.* **1973**, *12*, 75; (c) Lewis H.L.; Brown T.L. *J. Am. Chem. Soc.* **1970**, *92*, 4664; (d) Bailey W.F.; (d) Zarcone L. M.J. *Chirality* **2002**, *14*, 163.
4. Bates R.E.; Kroposki H.; Potter D.E. *J. Org. Chem.* **1972**, *37*, 560.
5. Fleming I.; Mack S.R.; Clark B.P. *Chem. Commun.* **1998**, *6*, 713.
6. Herbert H.A.; Arnott G.E. *Org. Lett.* **2009**, *11*, 4986.
7. (a) Moll E.H.; Sémeril D.; Matt D.; Toupet L. *Eur. J. Org. Chem.* **2010**, 1158; (b) Fang X.; Scott B.L.; Watkin J.G.; Carter C.A.G.; Kubas G.J. *Inorg. Chimica Acta* **2001**, *317*, 276.
8. (a) Brendgen T.; Frank M.; Schatz J. *Eur. J. Org. Chem.* **2006**, 2378; (b) Fahlbusch T,; Frank M.; Maas G.; Schatz J. *Organometallics* **2009**, *28*, 6183.
9. Gurum A.; Rennels R.; Buchwald S. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348; Louie J.; Hartwig J. *Tetrahedron Lett.* **1995**, *36*,3609.

10. Seitz J.; Mass G. *Chem. Comm.* **2002**, 338.

11. Mansell S.M.; Russell C.A.; Wass D.F. *Inorg. Chem.* **2008**, *47*, 11367.

12. Heinemann C.; Müller T.; Apeloig Y.; Schwarz H. *J. Am. Chem. Soc.* **1996**, *118*, 2023.

13. Wittig G.; Benz E. *Chem. Ber.* **1959**, *92*, 1999.

14. Kronig S.; Theuergarten E.; Holschumacher D.; Bannenberg T.; Daniliuc C.G.; Jones P.G. Tamm M. *Inorg. Chem.* **2011**, *50*, 7344.

15. Chase P.A.; Gille A.L.; Gilbert T.M.; Stephan D.W. *Dalton Trans.* **2009**, 7179.

Chapter IV

Experimental

4.1. General experimental:

Chemicals were purchased from Merk or Aldrich. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone, under argon. Dichloromethane and acetone were distilled from calcium chloride or phosphorus pentoxide, under argon. Other chemicals were either purified using known methods or used as analytical reagents.[1] The concentration of Bu^{n}Li was measured using 2,5-dimethoxy benzyl alcohol as a self indicating acid, following a described procedure.[2]

All reactions were carried out under inert atmosphere, nitrogen or argon, unless otherwise stated. Reaction temperature was either achieved by use of a mixture of acetone and dry ice in a Dewar (−78 °C), thermostatic controller, ice water or an oil bath.

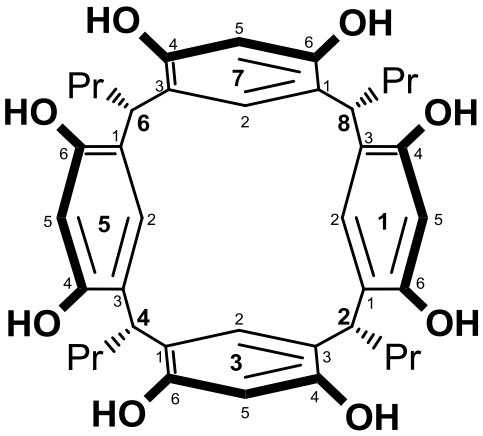
^{1}H and ^{13}C nuclear magnetic resonance spectroscopy was performed either using a 300 MHz Varian VNMS (75 MHz for ^{13}C), or 400 MHz Varian Unity Inova (100 MHz for ^{13}C). Chloroform-d was used as a standard unless stated otherwise. Chemical shifts (δ) were calculated using chloroform-d (δ 7.26 for ^{1}H NMR and δ 77 for ^{13}C NMR), acetone-d_6 (δ 205.05 for ^{1}H NMR and δ 207.85 for ^{13}C NMR), or dimethylsuphoxide-d_6 (δ 2.50 for ^{1}H NMR and δ 39.50 for ^{13}C NMR) residual peaks, unless otherwise stated. All NMR spectroscopy was performed at 25 °C.

Mixtures of hexane, ethyl acetate and acetone were used as elution solvents for thin layer chromatograph (TLC), performed using aluminum supported silica gel F_{254} plates. Visualization of TLCs was through UV/ Vis lamp, Cerium sulfate solution or Cerium ammonium molybdate solution with heating. Mixtures of the above solvents and Merk silica gel 60 (size 0.040-0.063) were used in flash column chromatography.

Melting Points were obtained with a Gallenkamp Melting Point apparatus and are uncorrected. Infra red spectroscopy was performed on a Nexus Thermo-Nicolet FT-IR instrument using a diamond tip, all samples were in a solid state. Mass spectrometry was performed by the Central Analytical Facility (CAF) at the University of Stellenbosch, using a waters API Q-TOF Ultimer spectrometer. ESI+ was used as an ionization method.

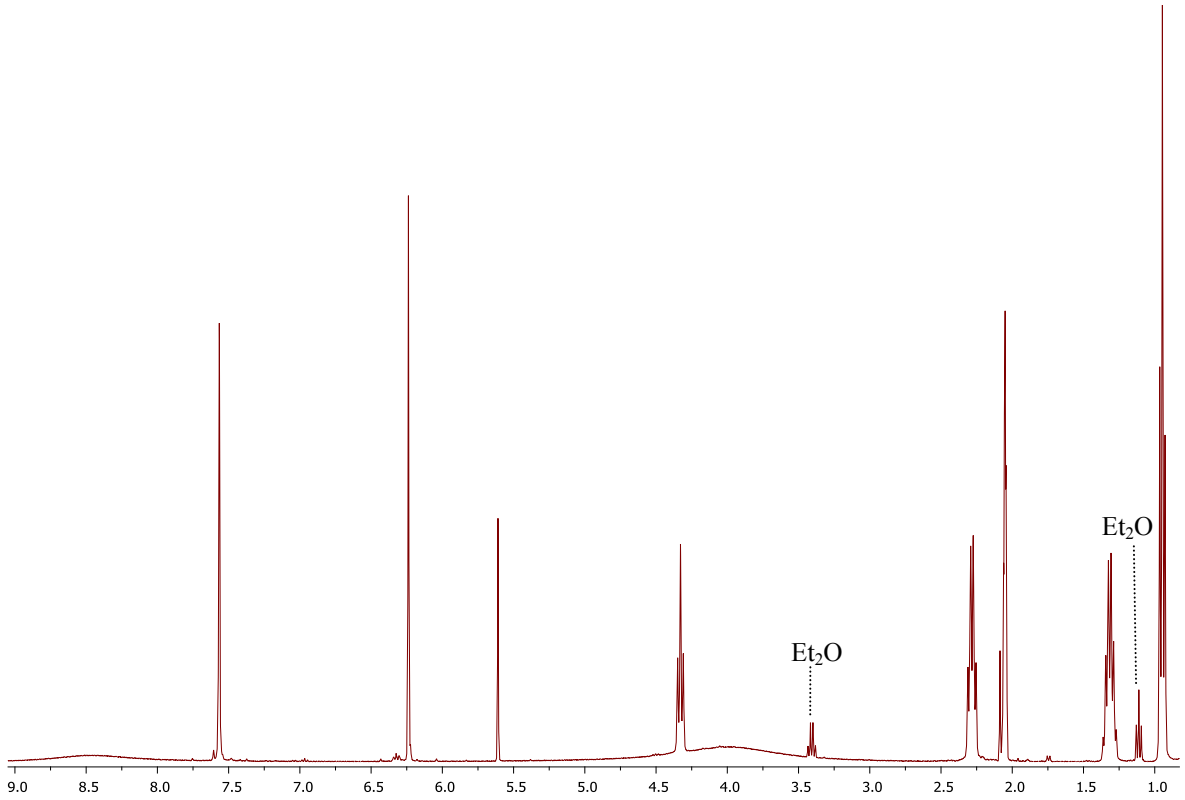
4.2. Compound characterization:

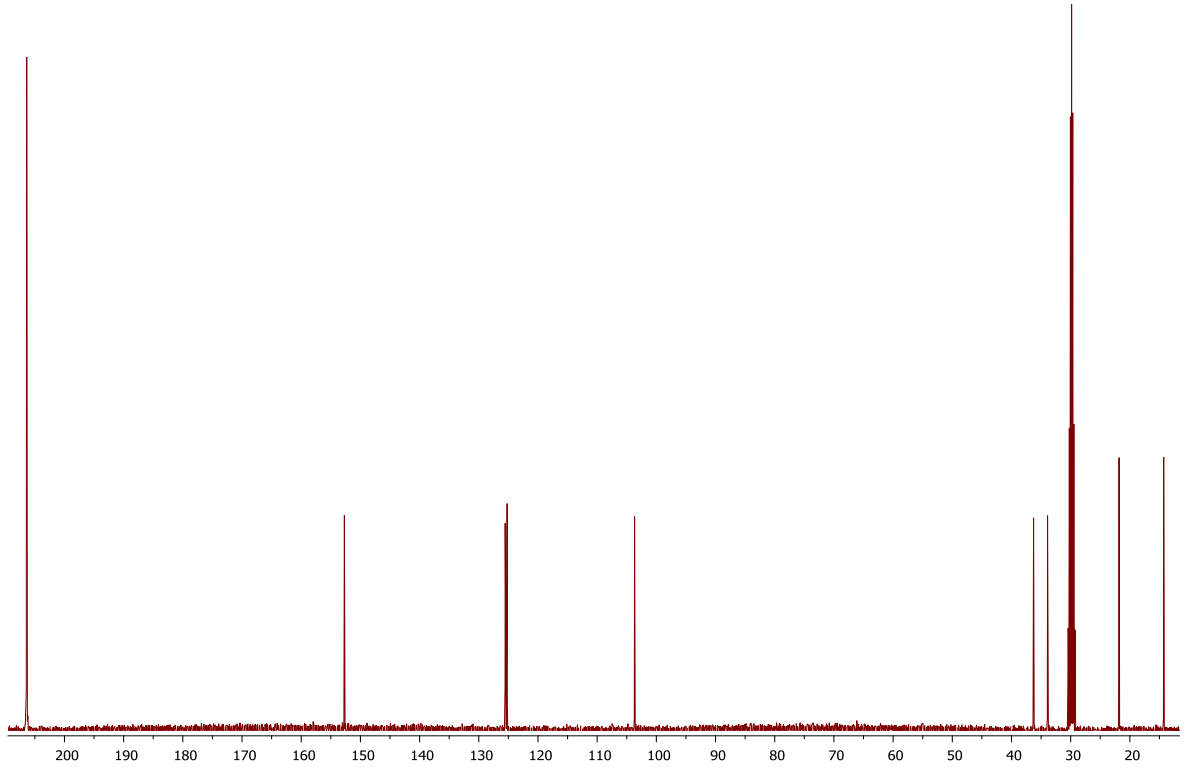
1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6-octahydroxy-2, 4, 6, 8-tetrapropyl-1, 3, 5, 7 (1, 3)-tetrabenzenacyclooctaphane (1)



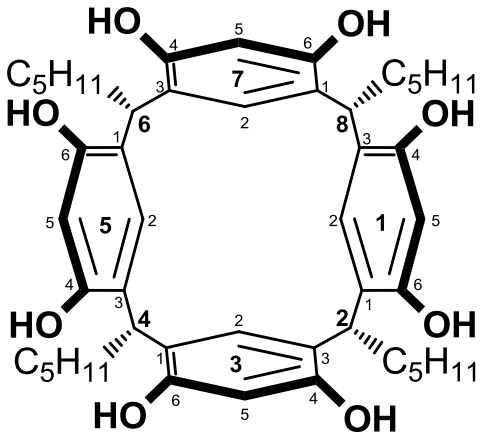
Procedure I. Resorcinol (5.5 g, 49.9 mmol) was dissolved in dichloromethane (90 ml). The solution was cooled to 0 °C and butanal (4.5 ml, 49.9 mmol) was added. Boron trifluorodietherate (13.3 ml, 103.9 mmol) was added over 30 minutes through a dropping funnel. The solution was warmed to room temperature and left to stir for 26 hours. The pink precipitate was filtered, washed with dichloromethane and dried under high vacuum to give the octahydroxy resorcinarene **1** (84%). The spectroscopic data were in agreement with reported data.[3]

Mp 331 °C; $\mathbf{R_f}$ = 0.486 (Hexane/Acetone 1:1); **^{1}H NMR** (400 MHz, acetone-d_6) δ 8.46 (s, 8H, Ar – *OH*), 7.57 (s, 4H, H – 1^2, 3^2, 5^2, 7^2), 6.24 (s, 4H, H – 1^5, 3^5, 5^5, 7^5), 4.33 (t, J = 7.9 Hz, 4H, H – 2, 4, 6, 8), 2.28 (m, 8H, – CH_2CH$_2$CH$_3$), 1.39 – 1.25 (m, 8H, – CH$_2$CH_2CH$_3$), 0.95 (t, J = 7.4 Hz, 12H, – CH$_2$CH$_2$CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6) δ 152.7 (C – 1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6), 125.5 (C– 1^1, 1^3, 3^1, 3^3, 5^1, 5^3, 7^1, 7^3), 125.2 (C – 1^2, 3^2, 5^2, 7^2), 103.7 (C – 1^5, 3^5, 5^5, 7^5), 36.3 (C – 2, 4, 6, 8), 33.91 (– *C*H$_2$CH$_2$CH$_3$), 21.8 (– CH$_2$*C*H$_2$CH$_3$), 14.3 (– CH$_2$CH$_2$*C*H$_3$); ***m/z* (%)**: 365 (100), 656 [M], 679 [M+ Na]; **IR (cm^{-1})**: 3220 (O-H), 2950 (C-H), 1620 (Ar), 1500 (Ar).



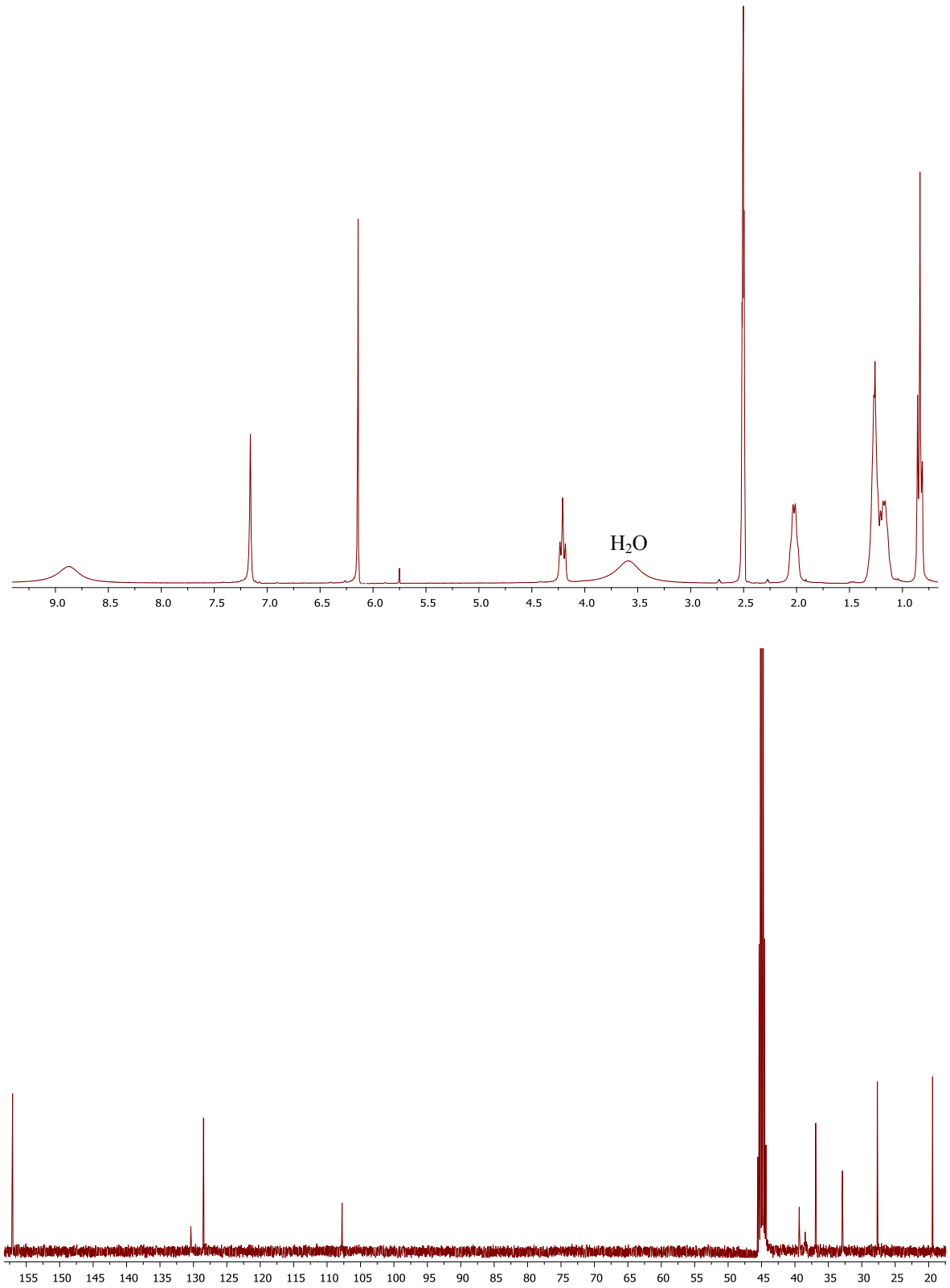


1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6-octahydroxy-2, 4, 6, 8-tetrapentyl-1, 3, 5, 7 (1, 3)-tetrabenzenacyclooctaphane (2)

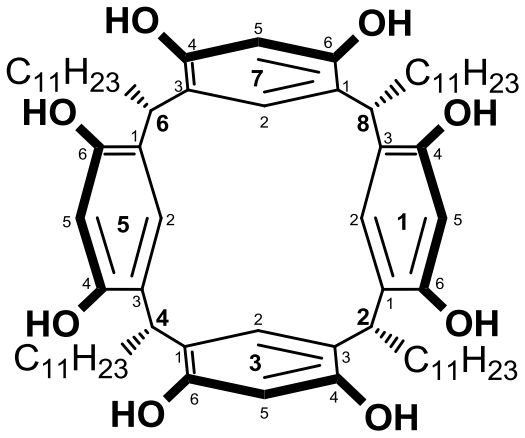


Procedure I was adopted using hexanal as an aldehyde. Octahydroxy resorcinarene **2** was isolated in 65% yield after work up. The spectroscopic data were in agreement with reported data.[3]

Mp>300 °C ; **^{1}H NMR** (400 MHz, dmso-d_6) δ 8.8 (s, 8H, Ar – *OH*), 7.2(s, 4H, H – 1^2, 3^2, 5^2, 7^2), 6.2(s, 4H, H – 1^5, 3^5, 5^5, 7^5), 4.22 (t, *J* = 7.9 Hz, 4H, H – 2, 4, 6, 8), 2.0 (m, 8H, – $CH_2CH_2CH_3$), 1.5 (m, 24H, – $CH_2CH_2CH_3$), 0.8 (t, *J* = 7.4 Hz, 12H, – $CH_2CH_2CH_3$); **^{13}C NMR** (400 MHz, DMSO-d_6) δ 159.4 (C – 1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6), 131.0 (C– 1^1, 1^3, 3^1, 3^3, 5^1, 5^3, 7^1, 7^3), 128.5 (C – 1^2, 3^2, 5^2, 7^2), 107.9 (C – 1^5, 3^5, 5^5, 7^5), 39.5 (C – 2, 4, 6, 8), 38.0 (–$CH_2CH_2CH_2CH_2CH_3$), 37.0 (–$CH_2CH_2CH_2CH_2CH_3$), 32.7 (–$CH_2CH_2CH_2CH_2CH_3$), 27.5 (–$CH_2CH_2CH_2CH_2CH_3$), 19.5 (– $CH_2CH_2CH_2CH_2CH_3$); **IR (cm^{-1})**: 3300 (O-H), 2950 (C-H), 1600 (Ar), 1500 (Ar).

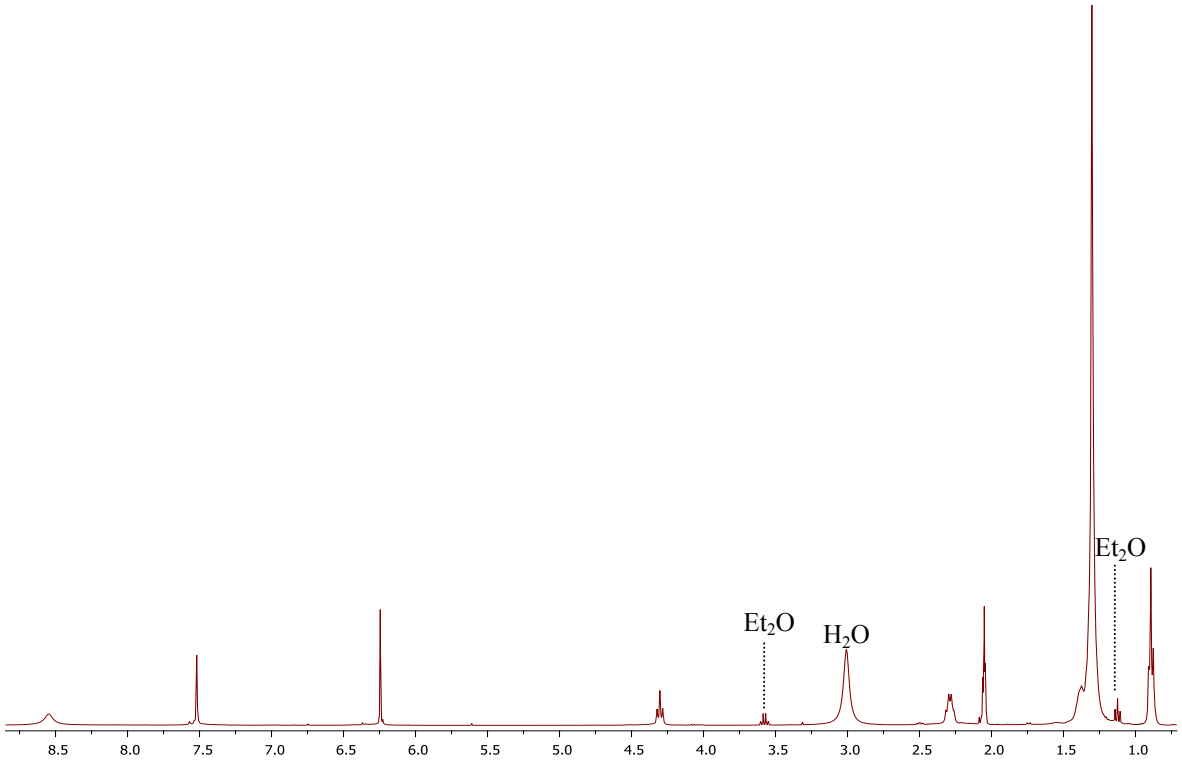


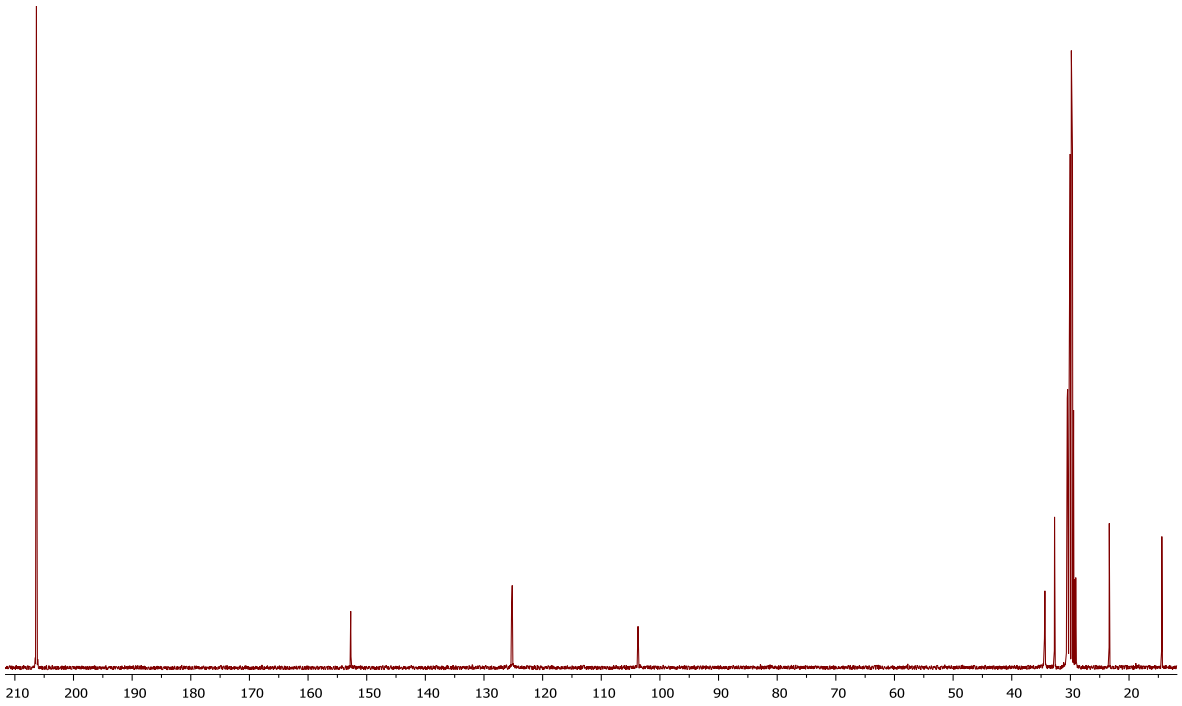
1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6-octahydroxy-2, 4, 6, 8-tetraundecyl-1, 3, 5, 7 (1, 3)-tetrabenzenacyclooctaphane (3)



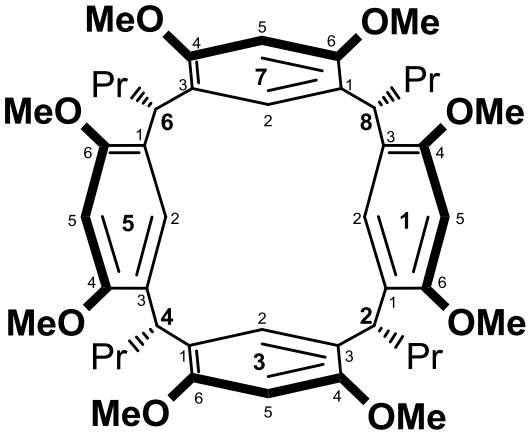
To a solution of resorcinol (19.8 g, 0.18 mol) in ethanol (75 ml, 95 %) was added concentrated hydrochloric acid (25 ml) and the resulting solution cooled to 2 °C. A solution of lauric aldehyde (33.2 g, 0.18 mol) in ethanol (50 ml of 95%) was added dropwise to the solution over 2 hours. The solution was then allowed to warm up to room temperature and then heated to 75 °C for 21 hr. The reaction was allowed to cool to room temperature and was washed with a mixture of methanol/water (2x100 ml, 6:4). The filtrate was recrystallized twice from methanol to obtain the octol **3** in 75% yield. The spectroscopic data were in agreement with reported data.[3]

Mp 297 °C; $\mathbf{R_f}$ = 0.686 (Hexane/ Acetone, 1:1); **^{1}H NMR** (400 MHz, Acetone-d_6) δ 8.47 (s, 8H, Ar – O*H*), 7.53 (s, 4H, H – 1^2, 3^2, 5^2, 7^2), 6.24 (s, 4H, H – 1^5, 3^5, 5^5, 7^5), 4.31 (t, *J* = 7.8 Hz, 4H, H – 2, 4, 6, 8), 2.43 – 2.18 (m, 8H, –CH_2(CH$_2$)$_9$CH$_3$), 1.31 (m, 72H, –CH$_2$(CH_2)$_9$CH$_3$), 0.90 (t, *J* = 6.7 Hz, 12H, –CH$_2$(CH$_2$)$_9$CH_3); **^{13}C NMR** (101 MHz, Acetone-d_6) δ 152.7 (C – 1^4, 1^6, 3^4 , 3^6, 5^4, 5^6, 7^4, 7^6), 125.2 (C – 1^1, 1^3, 3^1, 3^3, 5^1, 5^3, 7^1, 7^3), 103.7 (C – 1^2, 3^2, 5^2, 7^2), 34.38 (C – 1^5, 3^5, 5^5, 7^5), 32.71 (C – 2, 4, 6, 8),35.39 (–*C*H$_2$(CH$_3$)$_9$CH$_3$), 34.72 (–CH$_2$*C*H$_2$(CH$_2$)$_8$CH$_3$), 32.0 (–(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_7$CH$_3$), 30.0 ((CH$_2$)$_3$*C*H$_2$(CH$_2$)$_6$CH3), 29.9 (–(CH$_2$)$_4$*C*H$_2$(CH$_2$)$_5$CH$_3$), 29.9 ((CH$_2$)$_5$*C*H$_2$(CH$_2$)$_4$CH$_3$), 29.7 ((CH$_2$)$_6$*C*H$_2$(CH$_2$)$_3$CH$_3$), 29.40((CH$_2$)$_7$*C*H$_2$(CH$_2$)$_2$CH$_3$), 28.2 (–(CH$_2$)$_8$*C*H$_2$CH$_2$CH$_3$), 22.7 (–CH$_2$(CH$_3$)$_8$*C*H$_2$CH$_3$), 14.1 (–CH$_2$(CH$_2$)$_9$*C*H$_3$); ***m/z* (%)**: 575 (100), 1128 [M$^+$ + Na]; **IR (cm^{-1})**: 3220 (O-H), 2930 (C-H), 1620 (Ar), 1510 (Ar).



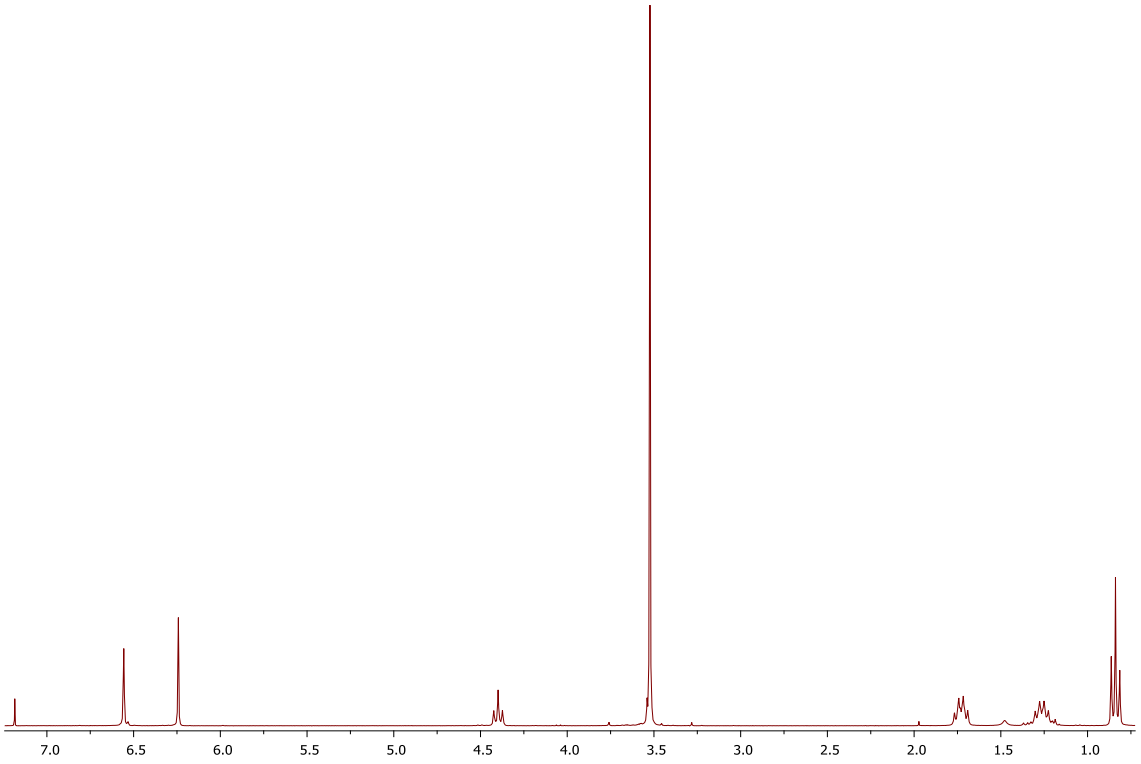


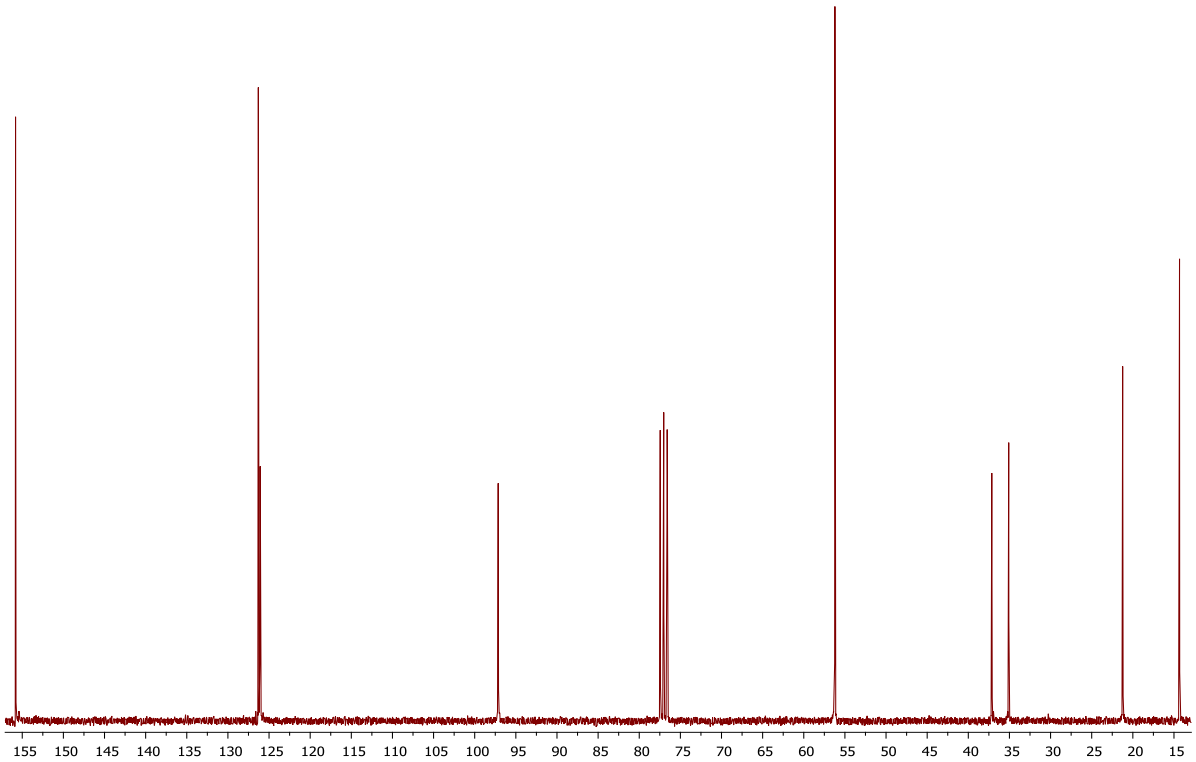
1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6-octamethoxy-2, 4, 6, 8-tetrapropyl-1, 3, 5, 7 (1, 3)-tetrabenzenacyclooctaphane (4)



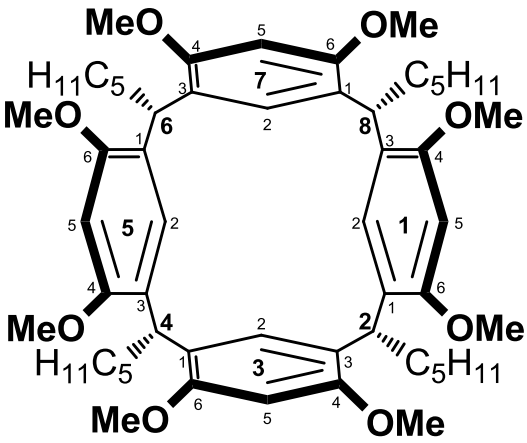
Procedure II. Octahydroxy resorcinarene **1** (5 g, 8.9 mmol) was dissolved in acetonitrile (50 ml). Potassium carbonate (19.6 g, 142.4 mmol) was added followed by dimethyl sulphate (13.6 ml, 142 mmol). The resulting solution was refluxed for 26 hours. The reaction was stopped and cooled to room temperature. Water (100 ml) was added to the crude reaction material and extracted with ethyl acetate (3x100 ml). The organic extracts were combined, dried with anhydrous magnesium sulphate and filtered. Removal of the solvent was achieved under vacuum and the resulting solid was recrystallized from acetone (3x), dissolved in ethyl acetate (100 ml) and washed with water (3x50 ml) to yield octamethoxy resorcinarene **4** (75%).

Mp 279 °C ; $\mathbf{R_f}$ = 0.54 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.63 (s, 4H, H – 1^2, 3^2, 5^2, 7^2), 6.31 (s, 4H, H – 1^5, 3^5, 5^5, 7^5), 4.47 (t, J = 7.5 Hz, 4H, H – 2, 4, 6, 8), 3.59 (s, 24H, Ar – OCH_3), 1.80 (m, 8H, – CH_2CH$_2$CH$_3$), 1.39 – 1.28 (m, 8H, – CH$_2$CH_2CH$_3$), 0.91 (t, J = 7.3 Hz, 12H, – CH$_2$CH$_2$CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.8 (C – 1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6), 126.4 (C – 1^1, 1^3, 3^1, 3^3, 5^1, 5^3, 7^1, 7^3), 126.1 (1^2, 3^2, 5^2, 7^2), 97.2 (1^5, 3^5, 5^5, 7^5), 56.3 (Ar – OCH$_3$) , 37.15 (C – 2, 4, 6, 8), 35.1 (– CH$_2$CH$_2$CH$_3$), 21.2 (– CH$_2$$CH_2CH_3$), 14.3 (– CH$_2CH_2$$CH_3$); ***m/z* (%)**: 299 (100), 792 [M+ Na]; **IR (cm^{-1})**: 2920 (C-H), 1600 (Ar), 1500 (Ar).



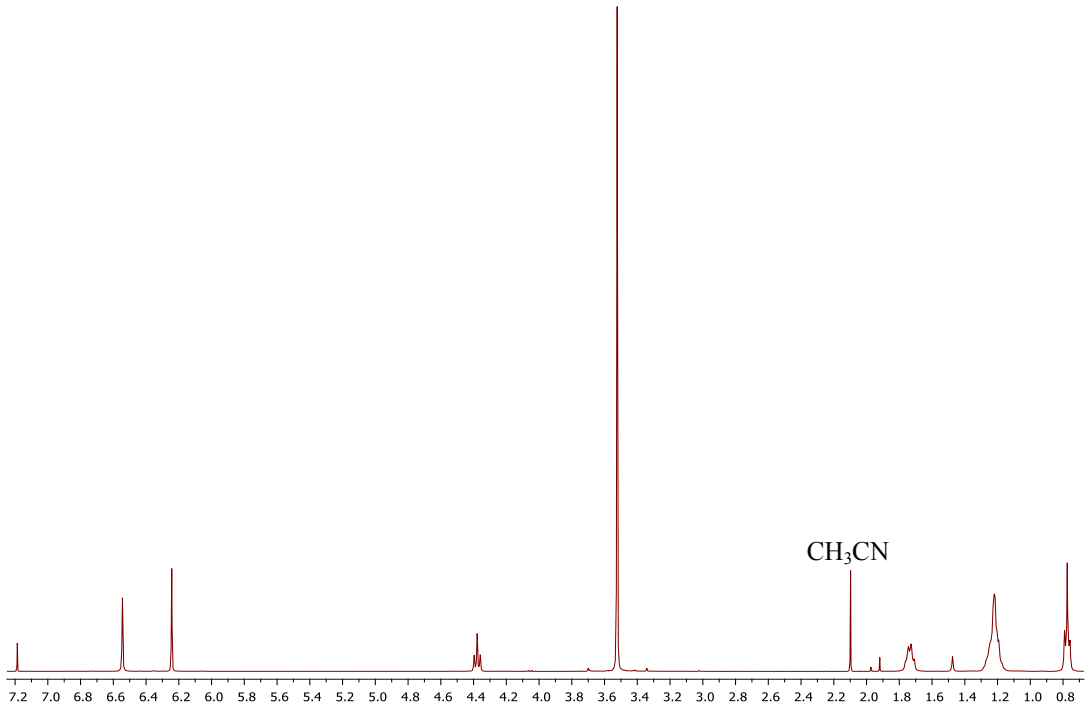


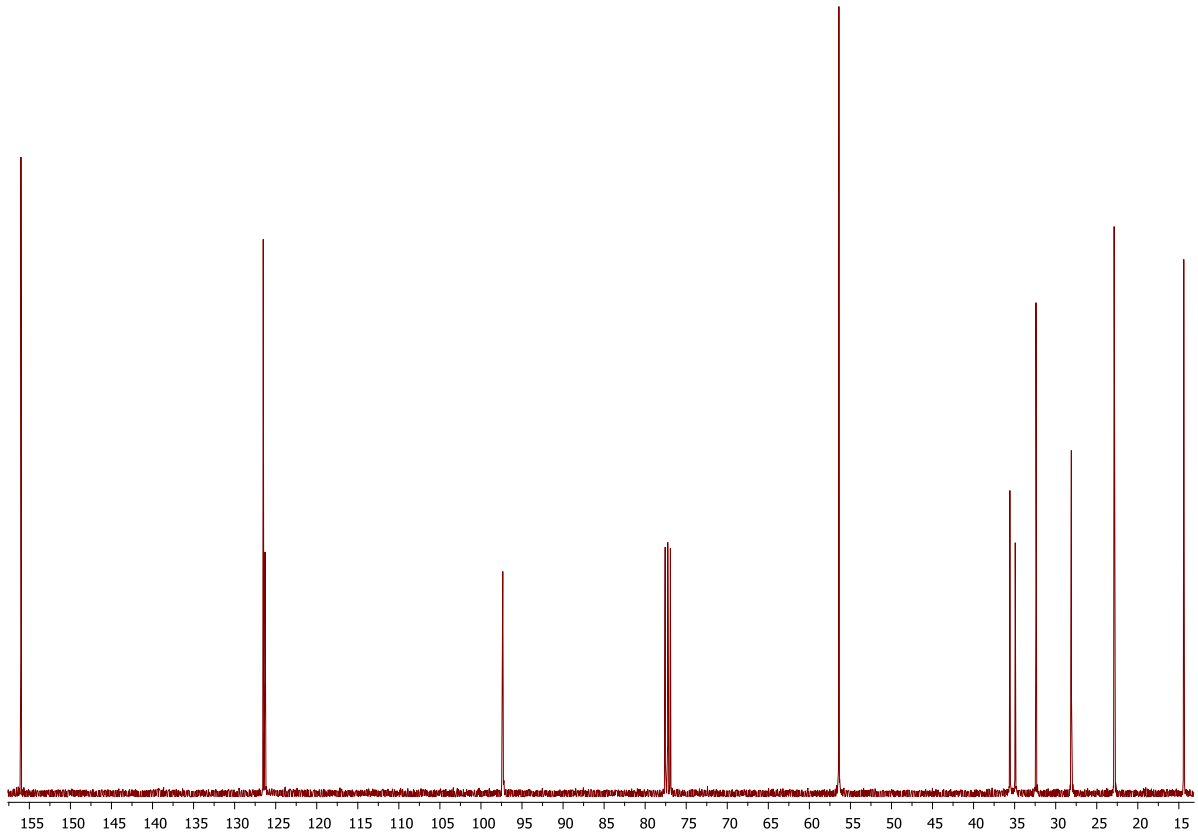
1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6-octamethoxy-2, 4, 6, 8-tetrapentyl-1, 3, 5, 7 (1, 3)-tetrabenzenacyclooctaphane (5)



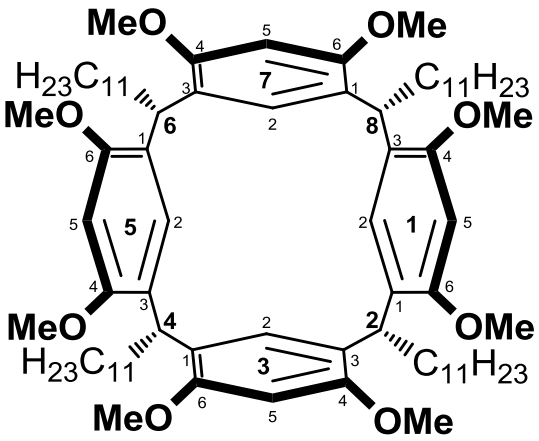
Procedure II was adopted and applied to octahydroxy resorcinarene **2**. Octamethoxy resorcinarene **5** was isolated in 74% yield after work up.

Mp 204 °C ; $\mathbf{R_f}$ = 0.63 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.54 (s, 4H, H – 1^2, 3^2, 5^2, 7^2), 6.24 (s, 4H, H – 1^5, 3^5, 5^5, 7^5), 4.38 (t, *J* = 7.4 Hz, 4H, H – 2, 4, 6, 8), 3.52 (s, 24H, Ar – OC*H*$_3$), 1.91 – 1.52 (m, 8H, – C*H*$_2$CH$_2$CH$_3$), 1.42 – 0.90 (m, 24H, – CH$_2$C*H*$_2$CH$_3$), 0.77 (t, *J* = 6.9 Hz, 12H, – CH$_2$CH$_2$C*H*$_3$); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 155.9 (*C* – 1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6), 126.0 (*C* – 1^1, 1^3, 3^1, 3^3, 5^1, 5^3, 7^1, 7^3), 126.5 (1^2, 3^2, 5^2, 7^2), 97.5 (1^5, 3^5, 5^5, 7^5), 56.5 (Ar – O*C*H$_3$) , 35.6 (*C* – 2, 4, 6, 8), 35.0 (– *C*H$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 32.5 (–CH$_2$*C*H$_2$CH$_2$CH$_2$CH$_3$), 28.0 (–CH$_2$CH$_2$*C*H$_2$CH$_2$CH$_3$), 23.0 (–CH$_2$CH$_2$CH$_2$*C*H$_2$CH$_3$), 14.9 (–CH$_2$CH$_2$CH$_2$CH$_2$*C*H$_3$); **IR (cm^{-1})**: 2920 (C-H), 1590 (Ar), 1460 (Ar), 1045 (C-O).



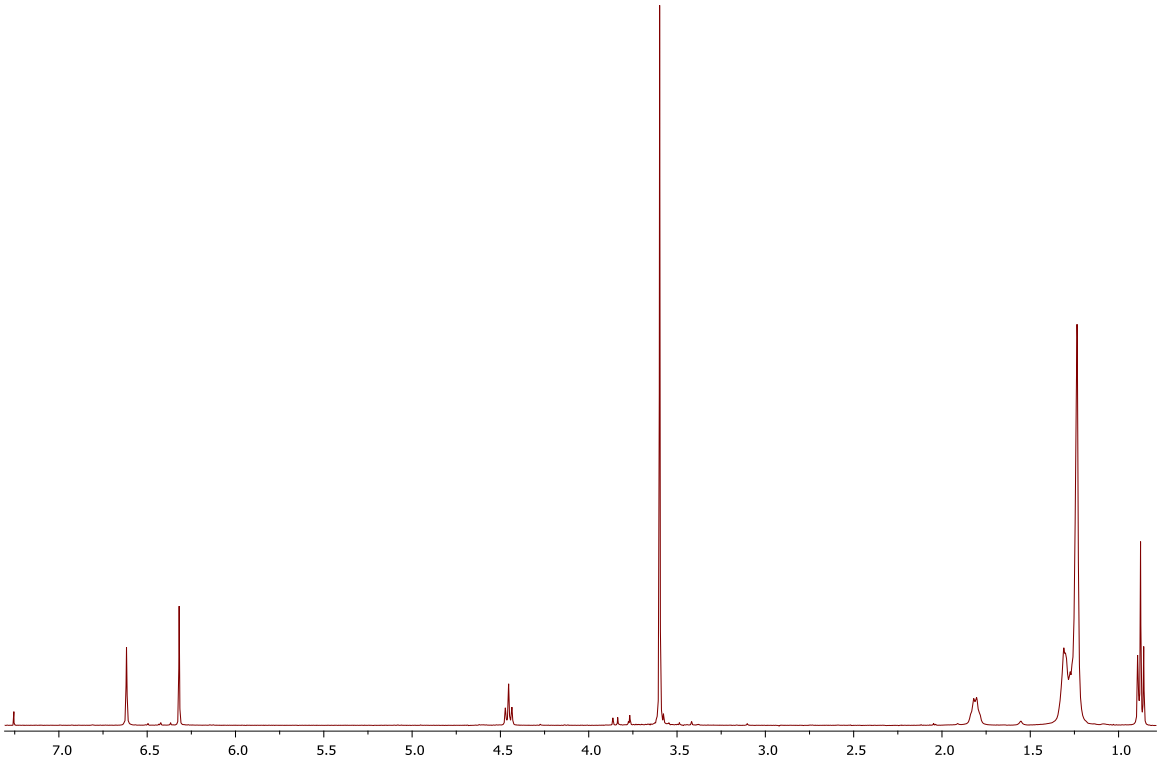


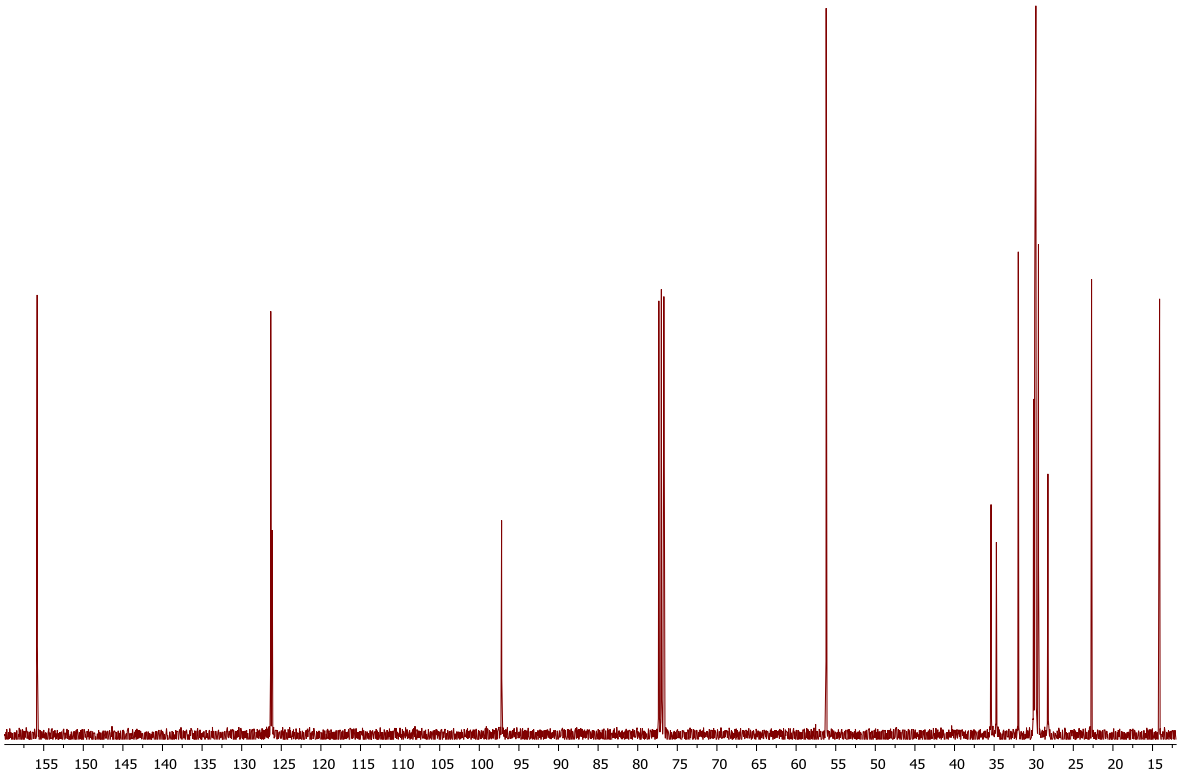
1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6-octamethoxy-2, 4, 6, 8-tetraundecyl-1, 3, 5, 7 (1, 3)-tetrabenzenacyclooctaphane (6)



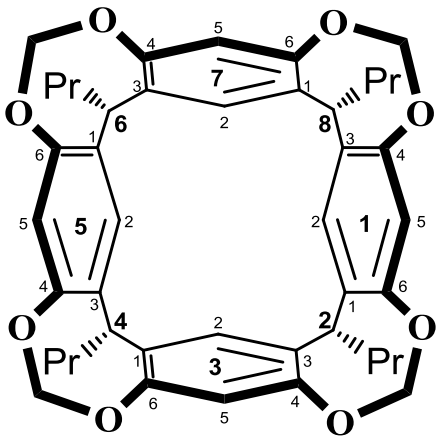
Procedure II was adopted and applied to octahydroxy resorcinarene **3**. Octamethoxy resorcinarene **6** was isolated in 70% yield after work up.

Mp 130 °C; $\mathbf{R_f}$ = 0.68 (Hexane/ EtOAc, 7:3); **^{1}H NMR**(400 MHz, $CDCl_3$) δ 6.62 (s, 4H, H – 1^2, 3^2,5^2,7^2), 6.32 (s, 4H, H – 1^5, 3^5, 5^5, 7^5), 4.45 (t, J = 7.4 Hz, 4H, H – 2, 4, 6, 8), 3.60 (s, 24H, Ar – OCH_3), 1.81 (m, 8H, –$CH_2$$(CH_2)_9CH_3$), 1.34 – 1.20 (m, 72H, –$CH_2$$(CH_2)_9CH_3$), 0.88 (t, J = 6.9 Hz, 12H, –$CH_2$$(CH_2)_9CH_3$). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.8 (C – 1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6), 126.4 (C – 1^1, 1^3, 3^1, 3^3, 5^1, 5^3, 7^1, 7^3), 126.1 (C – 1^2, 3^2, 5^2, 7^2), 97.2 (C – 1^5, 3^5, 5^5, 7^5), 56.2 (C – 2, 4, 6, 8), 35.4 (Ar – OCH_3), 35.4 (–$CH_2$$(CH_3)_9CH_3$), 34.7 (–$CH_2CH_2(CH_2)_8CH_3$), 32.0 (–$(CH_2)_2CH_2(CH_2)_7CH_3$), 30.0 (($(CH_2)_3CH_2(CH_2)_6$CH3), 29.9 (–$(CH_2)_4CH_2(CH_2)_5CH_3$), 29.9 (($(CH_2)_5CH_2(CH_2)_4CH_3$), 29.7 (($(CH_2)_6CH_2(CH_2)_3CH_3$), 29.4 (–$(CH_2)_7CH_2(CH_2)_2CH_3$), 28.2 (–$(CH_2)_8CH_2CH_2CH_3$), 22.7 (–$CH_2$$(CH_3)_8CH_2CH_3$), 14.1 (–$CH_2$$(CH_2)_9CH_3$); ***m/z* (%)**: 365 (100), 656 [M^+], 679 [M+ Na]; **IR (cm^{-1})**: 2969 (C-H), 1640 (Ar), 1460 (Ar), 1045 (C-O).



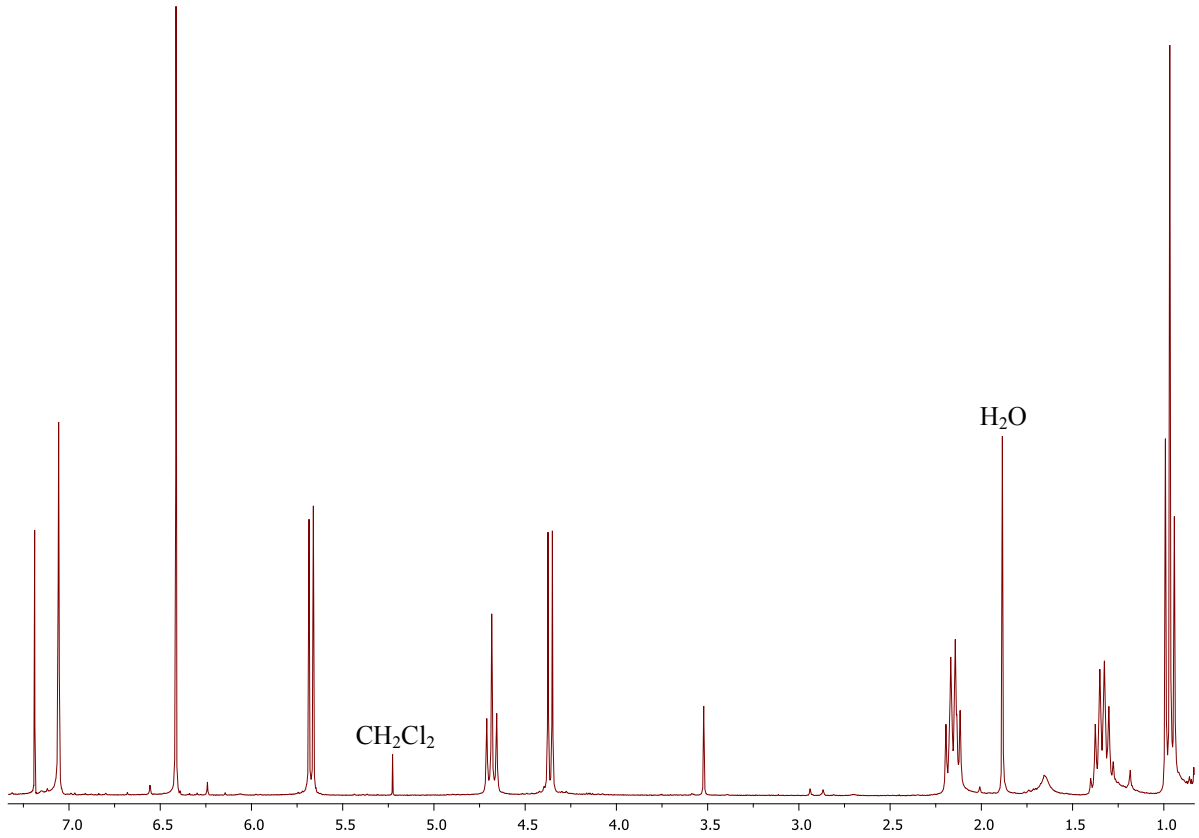


Tetramethylene bridged cavitand (7)



A solution of resorcinarene **1** (2 g, 3.05 mmol), CH_2BrCl (3.30 mL, 4.13 mmol), and K_2CO_3 (8.95 g, 11.2 mol) in DMF (152 mL) was stirred at 70 °C overnight. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (50 ml) and washed with 2 M HCl (3 x 50 mL), H_2O (30mL), and dried over $MgSO_4$. After solvent removal, the organic layer was passed through a silica gel column eluted with a mixture of ethyl acetate and hexane (0.5 : 9.5) and then the solvent was removed to afford **7** as a white powder in 65% yield. The spectroscopic data were in agreement with reported data.[4]

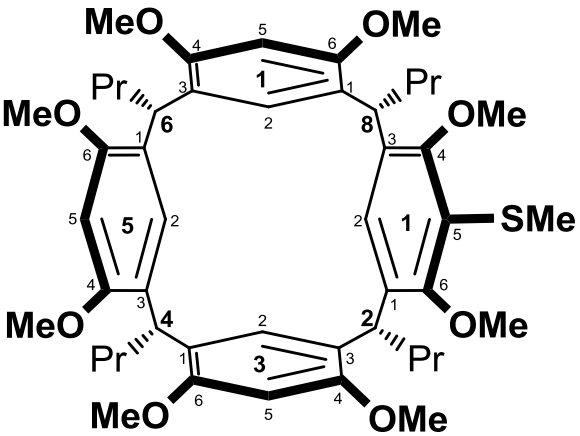
R_f = 0.83; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.06 (s, 4H – Aromatic), 6.41 (s, 4H – Aromatic), 5.67 (d, *J* = 7.2 Hz, 4H – Methylene), 4.68 (t, *J* = 8.2 Hz, 4H – Benzylic), 4.36 (d, *J* = 7.24 Hz, H – Methylene), 2.27 – 2.03 (m, 8H – $CH_2CH_2CH_3$), 1.44 – 1.17 (m, 8H – $CH_2CH_2CH_3$), 0.97 (t, *J* = 7.4 Hz, 12H – $CH_2CH_2CH_3$); ***m/z* (%):** 802.19 [M^+]



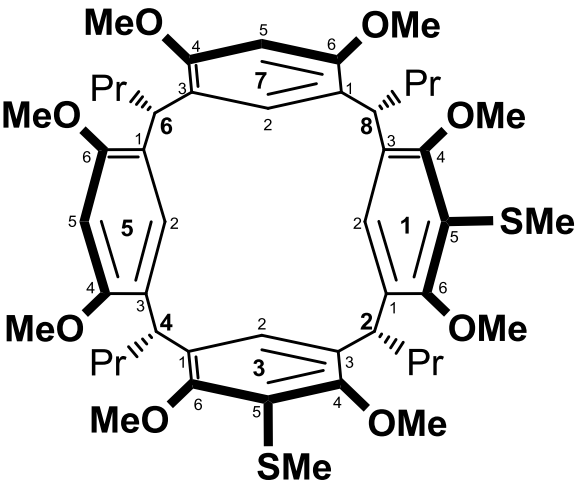
1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5-methylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (Mono-9);

1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,3^5-dimethylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (Proxi-9);

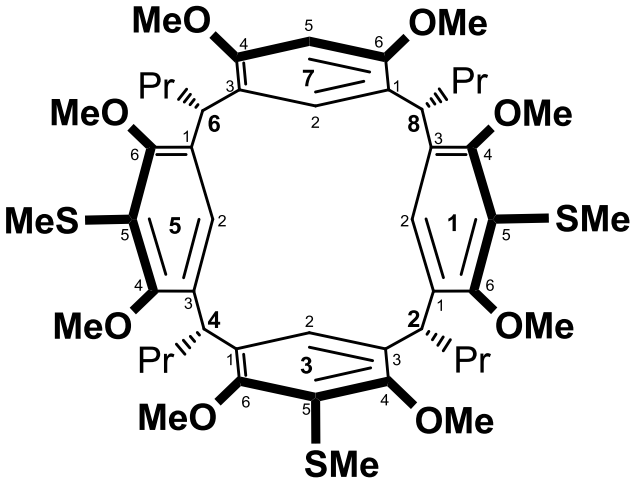
1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,3^5,5^5-trimethylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (Tri-9);



Mono-9



Proxi-9

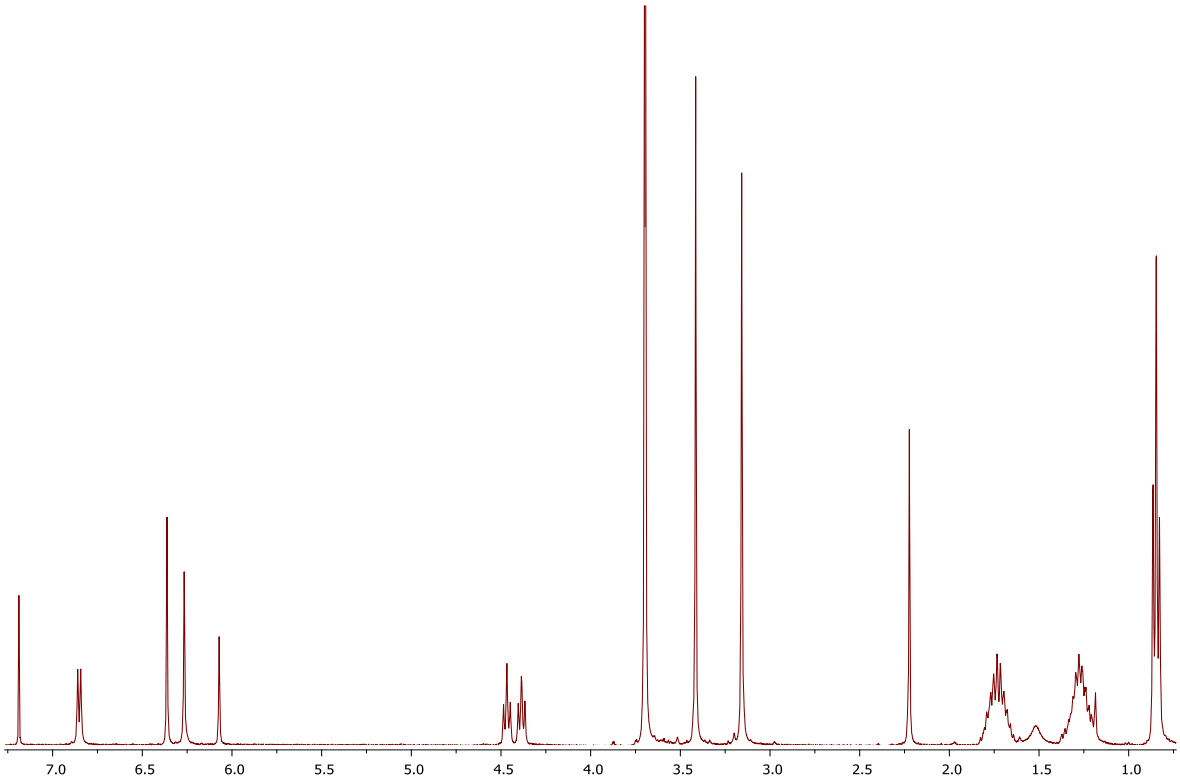


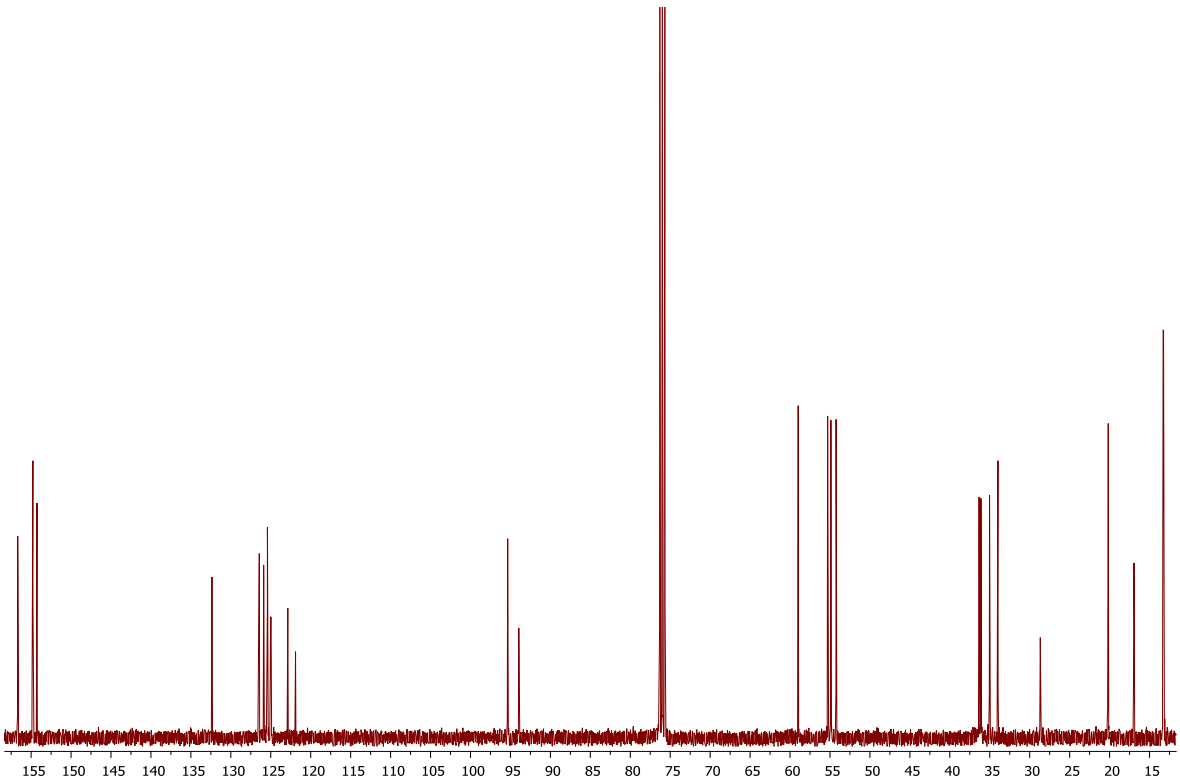
Tri-9

Octamethoxy resorcinarene **2** (50 mg, 0.065 mmol) was dissolved in tetrahydrofuran (1.65 ml) and the solution was cooled to 0 °C. Bu^nLi (0.093 ml, 0.13 mmol) was added. The solution was stirred for 2 hours. Dimethyl disulfide (0.48 ml, 0.52 mmol) was added and stirring was continued overnight. Water was added (10 ml) to the crude reaction material and extracted with ethyl acetate (3x15 ml). The organic extracts were collected, dried with anhydrous magnesium sulphate and filtered. The solvent was evaporated under reduced pressure and the remaining solid was dried under high vacuum to leave a mixture of methylthiyls **mono-9**, **proxy-9**, **distal-9**, **tri-9** and **tetra-9** which over the course of this study were isolated as solids and characterized.

Compound **Mono-9**:

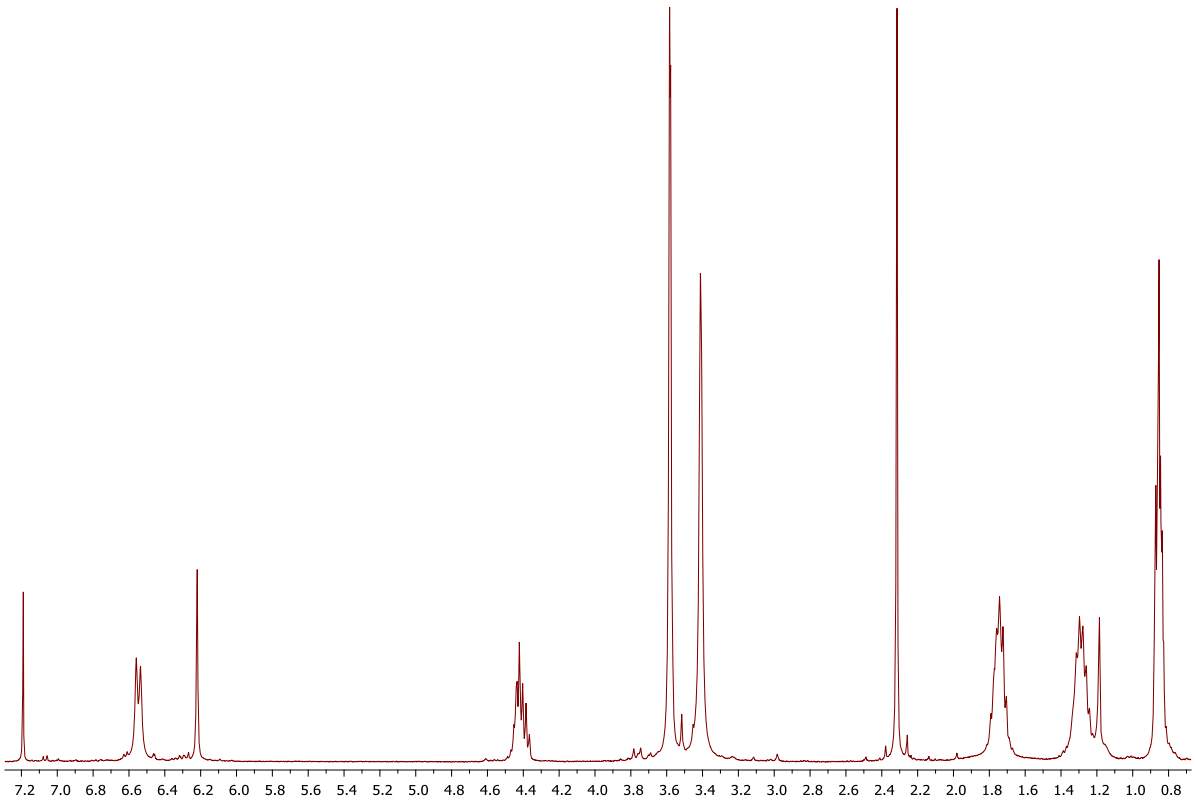
R_f = 0.77 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.94 (s, 1H, H – 1^2), 6.93 (s, 1H, H –5^2), 6.36 (s, 2H, H – 7^2, 3^2), 6.27 (s, 2H, H – 3^5, 7^5), 6.07 (s, 1H, H – 5^5), 4.47 (t, *J* = 7.5 Hz, 2H, ArCH_2Ar), 4.39 (t, *J* = 7.5 Hz, 2H, ArCH_2Ar), 3.69 (s, 12H, Ar – OCH_3), 3.41 (s, 6H, Ar – OCH_3), 3.16 (s, 6H, Ar – OCH_3), 2.22 (s, 3H, Ar – SCH_3), 1.85 – 1.62 (m, 8H, – CH_2CH$_2$CH$_3$), 1.38 – 1.20 (m, 8H, – CH$_2$CH_2CH$_3$), 0.85 (t, *J* = 7.1 Hz, 12H, – CH$_2$CH$_2$CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.7 (Aromatic), 154.8 (Aromatic), 154.3 (Aromatic), 132.4 (Aromatic), 126.4 (Aromatic), 126.0 (Aromatic), 125.4 (Aromatic), 125.0 (Aromatic), 122.9 (Aromatic), 121.9 (Aromatic), 95.3 (Aromatic),93.8 (Aromatic), 55.2 (Ar – OCH$_3$), 54.9 (Ar – OCH$_3$), 54.2 (Ar – OCH$_3$), 36.1 (Ar – OCH$_3$), 35.1 (Benzylic), 34.0 (Benzylic), 28.7 (– SCH$_3$), 20.2 (– CH$_2$CH$_2$CH$_3$), 17.0 (– CH$_2$CH$_2$CH$_3$), 13.3 (– CH$_2$CH$_2$CH$_3$); ***m/z* (%)**: 836.9 [M^+ + Na]; **IR (cm^{-1})**: 2980 (C-H), 1650 (Ar), 1450 (Ar), 1050 (C-O).

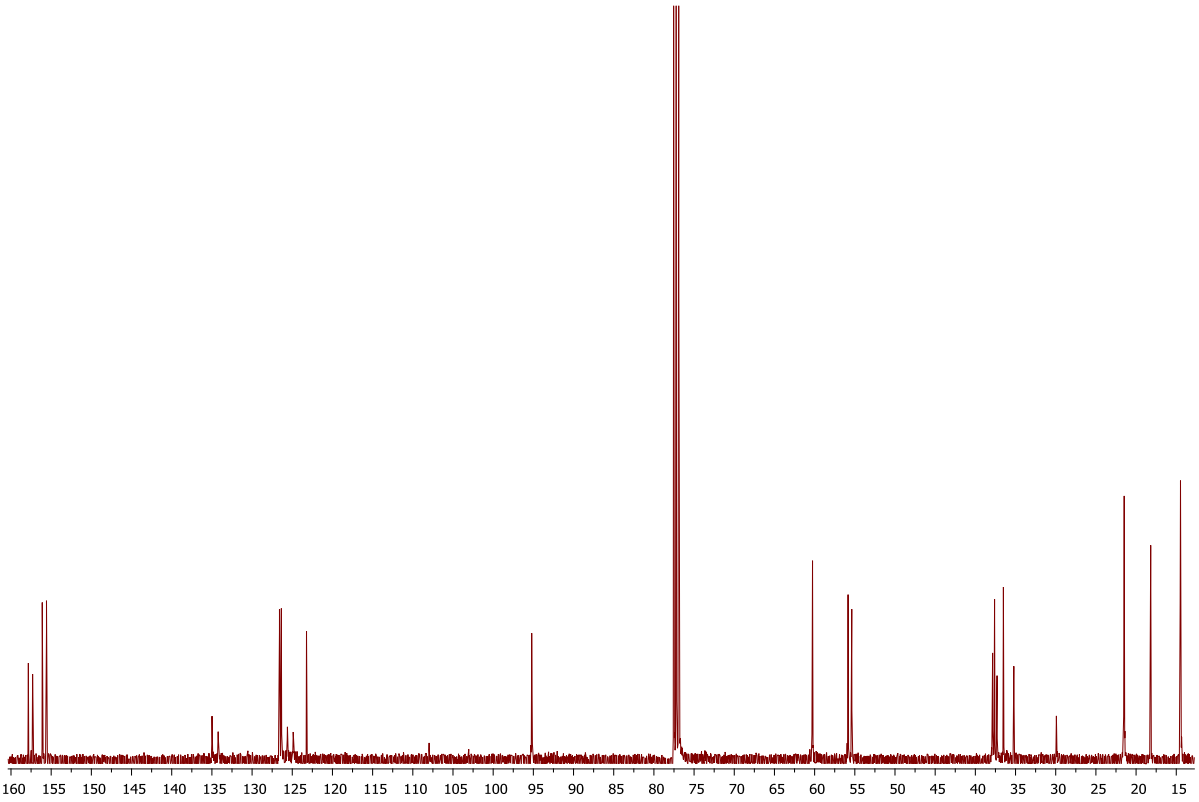




Compound **Proxi-9**:

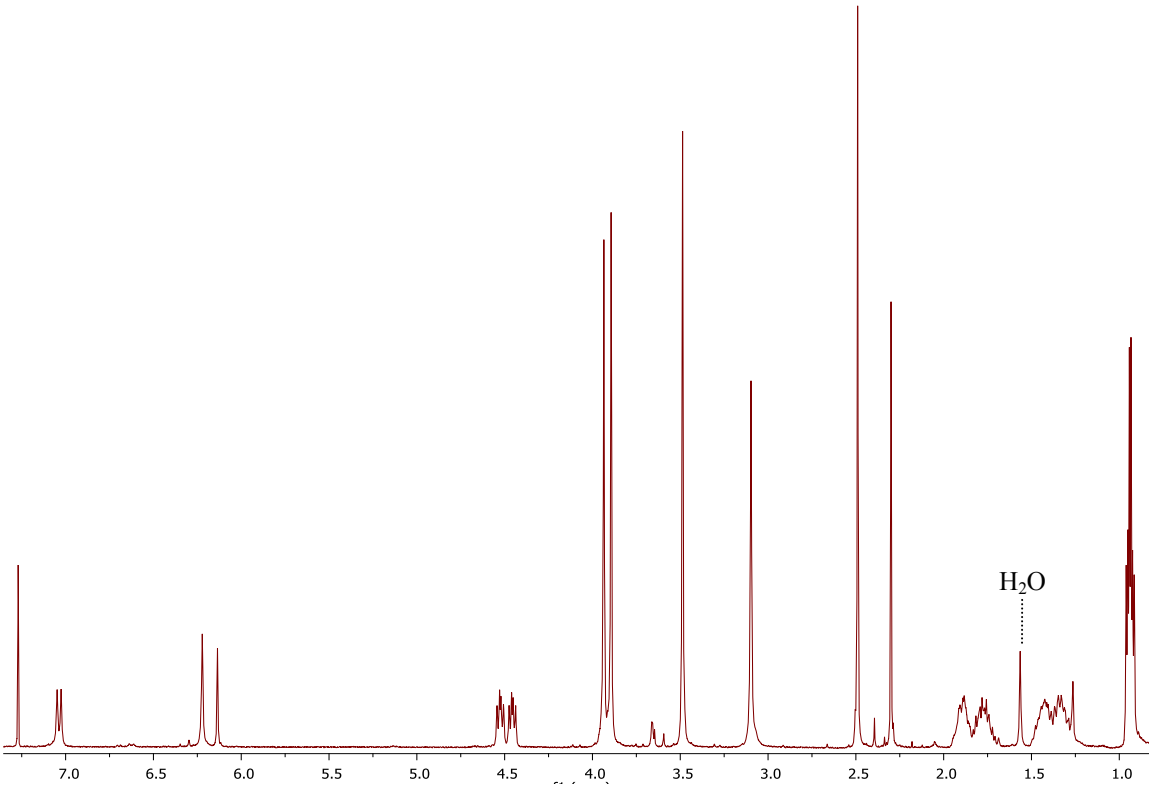
Mp145 °C; $\mathbf{R_f}$ = 0.829 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.59 (s, 1H, H – 1^2, 3^2), 6.52 (s, 2H, H –5^2, 7^2), 6.22 (s, 2H, H – 5^5, 7^5), 4.51 – 4.34 (m, 4H, H – 2,4,6,8), 3.59 (m, 12H, Ar – OCH_3), 3.41 (s, 12H, Ar – OCH_3), 2.32 (s, 6H, Ar – SCH_3), 1.83 – 1.67 (m, 8H, – CH_2CH$_2$CH$_3$), 1.28 (m, 8H, – CH$_2$CH_2CH$_3$), 0.85 (t, J = 7.3 Hz, 12H, – CH$_2$CH$_2$CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.8 (Aromatic), 157.3 (Aromatic), 156.1 (Aromatic), 155.6 (Aromatic), 135.0 (Aromatic), 134.2 (Aromatic), 126.6 (Aromatic), 126.4 (Aromatic), 125.6 (Aromatic), 124.9 (Aromatic), 123.2 (Aromatic), 95.2 (Aromatic), 60.3 (Benzylic), 55.8 (Benzylic), 55.4 (Benzylic), 37.9 (Ar – OCH_3), 37.6 (Ar – OCH_3), 37.3 (Ar – OCH_3), 36.5 (Ar – OCH_3), 35.2 (Ar – SCH_3), 18.2 (– CH_2CH$_2$CH$_3$), 14.5 (– CH$_2$CH_2CH$_3$), 1.2 (– CH$_2$CH$_2$CH_3); ***m/z* (%)**: 861 [M^+]; **IR (cm^{-1})**: 2990 (C-H), 1640 (Ar), 1450 (Ar), 1050 (C-O).

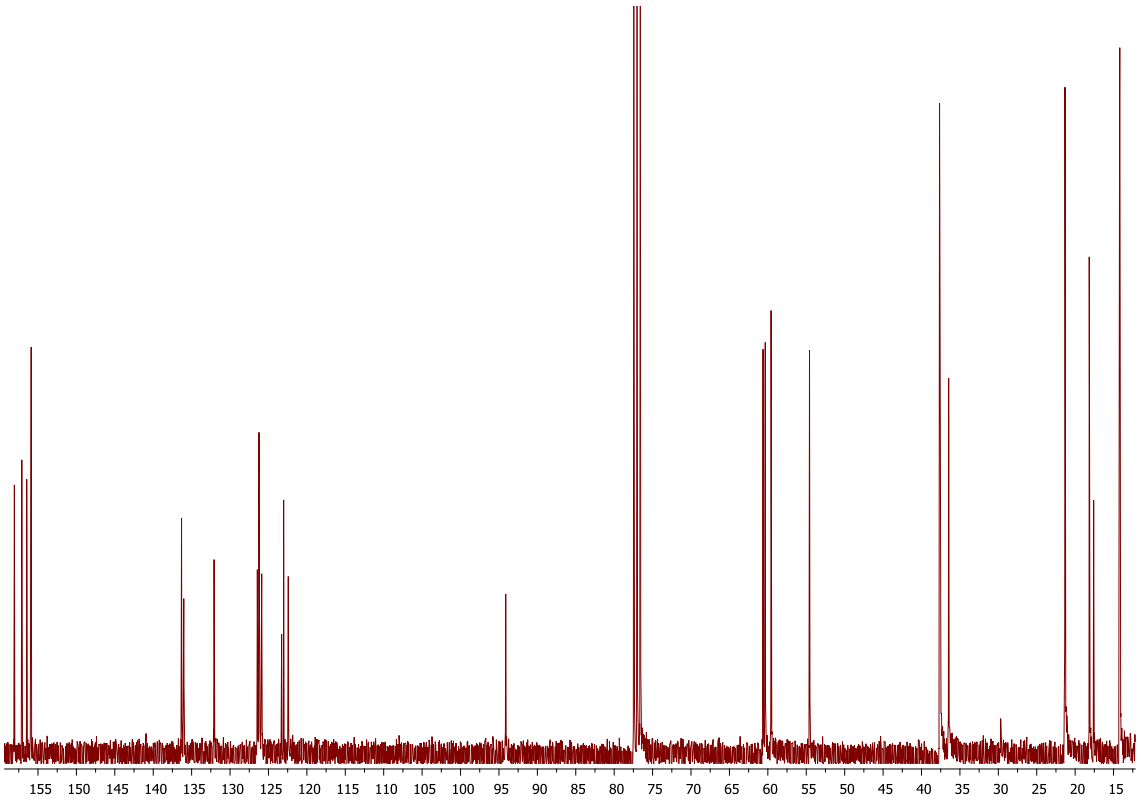




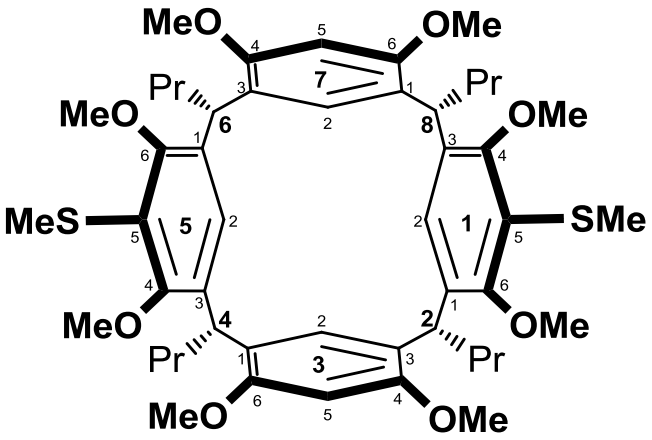
Compound **Tri-9**:

Mp187 °C; $\mathbf{R_f}$ = 0.886 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (s, 1H, H – 3^2), 7.03 (s, 1H, H – 7^2), 6.22 (s, 2H, H – 1^2, 5^2), 6.13 (s, 1H, H – 7^5), 4.53 (t, *J* = 7.5 Hz, 2H, H – 2,4), 4.46 (t, *J* = 7.5 Hz, 2H, H – 6,8), 3.93 (s, 6H, Ar – O*C*H_3), 3.89 (s, 6H, Ar – O*C*H_3), 3.49 (s, 6H, Ar – O*C*H_3), 3.10 (s, 6H, Ar – O*C*H_3), 1.74 (m, 8H, – *C*$H_2$$CH_2CH_3$), 1.28 (m, 8H, , – CH_2*C*H_2CH_3), 0.85 (t, *J* = 7.3, 12H, – CH_2CH_2*C*H_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.1 (Aromatic), 157.1 (Aromatic), 156.5 (Aromatic), 155.9 (Aromatic), 136.3 (Aromatic), 136.0 (Aromatic), 132.1 (Aromatic), 126.5 (Aromatic), 126.2 (Aromatic), 125.9 (Aromatic), 123.9 (Aromatic), 123.0 (Aromatic), 122.4 (Aromatic), 94.1 (Aromatic), 60.6 (Benzylic), 60.3 (Benzylic), 59.6 (Ar – O*C*H_3), 54.6 (Ar – O*C*H_3), 37.7 (Ar – O*C*H_3), 36.5 (Ar – O*C*H_3), 21.3 (Ar – S*C*H_3), 18.2 (Ar – S*C*H_3), 17.6 (– *C*$H_2CH_2CH_3$), 14.2 (– CH_2*C*H_2CH_3), 1.0 (– CH_2CH_2*C*H_3); ***m/z*(%)**: 908.1 [M^+]; **IR (cm^{-1})**: 2980 (C-H), 1450 (Ar), 1050 (C-O).



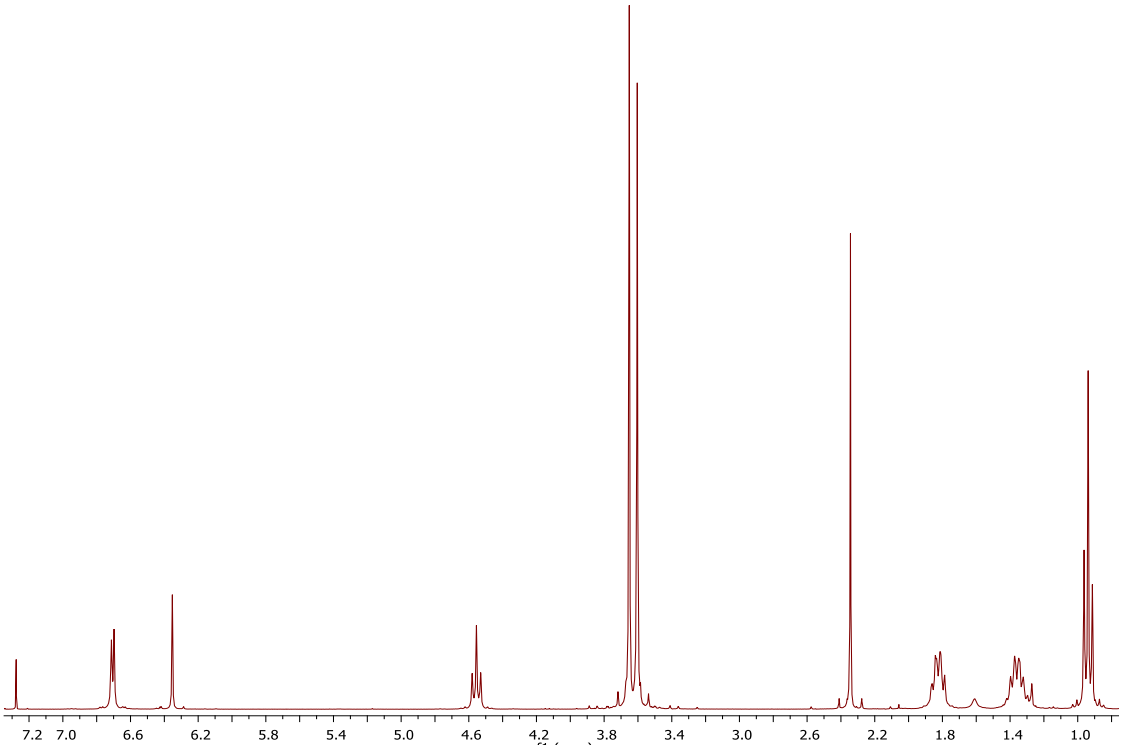


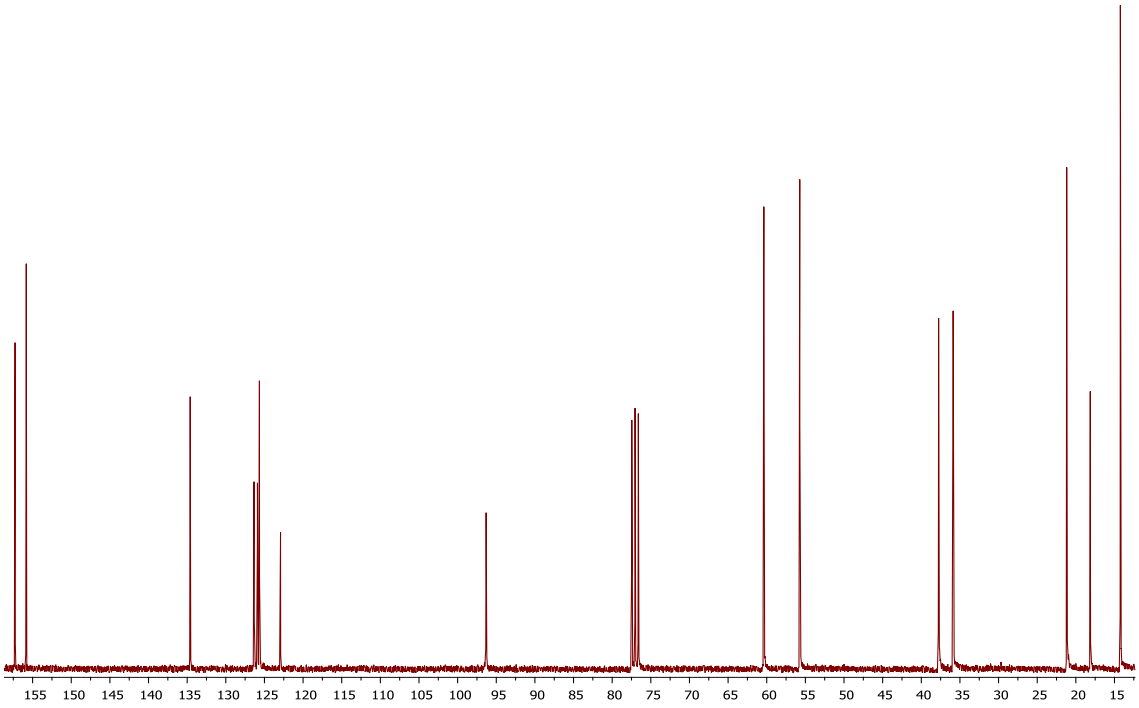
1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,5^5-dimethylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (Distal-9);



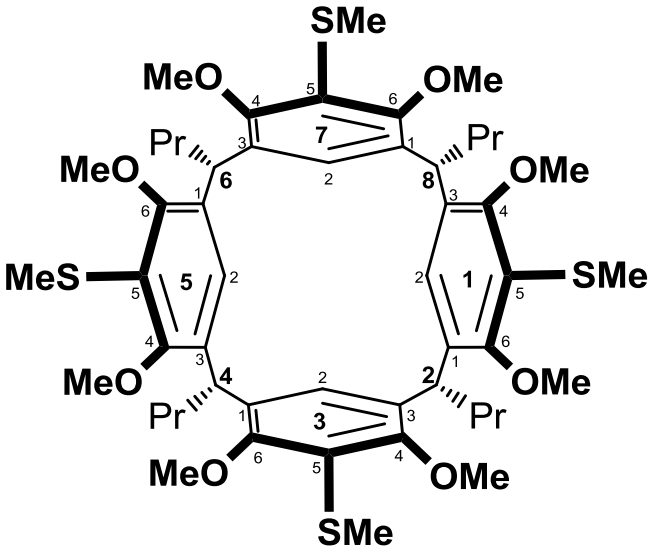
Procedure III. Octamethoxy resorcinarene **4** (50 mg, 0.065 mmol) was dissolved in tetrahydrofuran (1.65 ml). The solution was warmed to 40 °C, *n*-butyllithium (3.7 ml, 6.5 mmol) was added and the solution was stirred for 2 hours. Dimethyl disulfide (0.48 ml, 0.52 mmol) was added and the reaction was allowed to stir overnight. Water was added (10 ml) to the reaction crude material and extracted with ethyl acetate (3x15 ml). The organic extracts were collected, dried with anhydrous magnesium sulphate and filtered. The solvent was evaporated under reduced vacuum and the remaining solid was dried under high vacuum to leave dimethylthiyl **distal-9** (86 %). Reproduction of a similar result in 300 mg scale required use of 5 equivalent of Bu^nLi. From this reaction **distal-9** was isolated chromatographically in 73% yield. The spectral data were in agreement with reported data.[5]

Mp 199 °C; $\mathbf{R_f}$ = 0.8 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.70 (s, 2H, H – 3^2, 7^2), 6.68 (s, 2H, H – 1^2, 5^2), 6.34 (s, 2H, H – 3^5, 7^5), 4.54 (t, *J* = 7.5 Hz, 4H, 2, 4, 6, 8), 3.63 (s, 12H, Ar – O*C*H_3), 3.58 (s, 12H, Ar – O*C*H_3), 2.32 (s, 6H, Ar – S*C*H_3), 1.81 (m, 8H, – *C*$H_2$$CH_2CH_3$), 1.43 – 1.27 (m, 8H, – CH_2*C*H_2CH_3), 0.92 (t, *J* = 7.3 Hz, 12H, – CH_2CH_2*C*H_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.3 (C – 3^4, 3^6, 7^4, 7^6), 155.8 (C – 1^4, 1^6, 5^4, 5^6), 134.6 (C – 1^1, 1^3, 5^1, 5^3), 126.4 (C – 3^2, 7^2), 125.9 (C – 1^2, 5^2), 125.7 (C – 3^1, 3^3, 7^1, 7^3), 122.9 (C – 1^5, 5^5), 96.4 (C – 3^5, 7^5), 60.4 (Ar – OCH_3), 55.7 (Ar – OCH_3), 37.8 (C – 2, 4, 6, 8), 35.9 (Ar – SCH_3), 21.2 (– *C*$H_2CH_2CH_3$), 18.1 (– CH_2*C*H_2CH_3), 14.2 (– CH_2CH_2*C*H_3); ***m/z* (%)**: 427 (100), 884 [M^+ + Na]; **IR (cm^{-1})**: 2960 (C-H), 1600 (Ar), 1450 (Ar), 1040 (C-O).



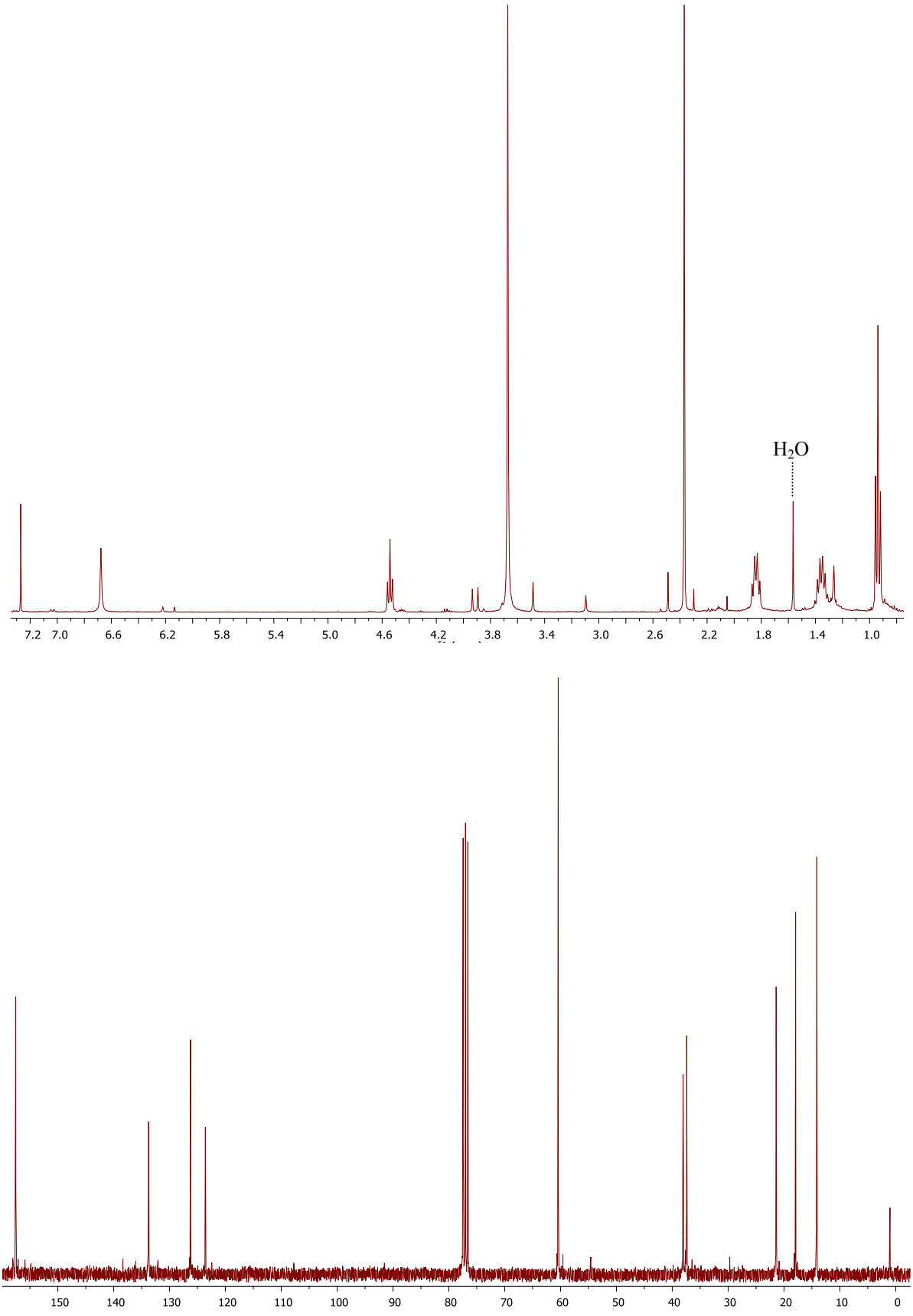


1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,3^5,5^5,7^5-trimethylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (Tetra-9);

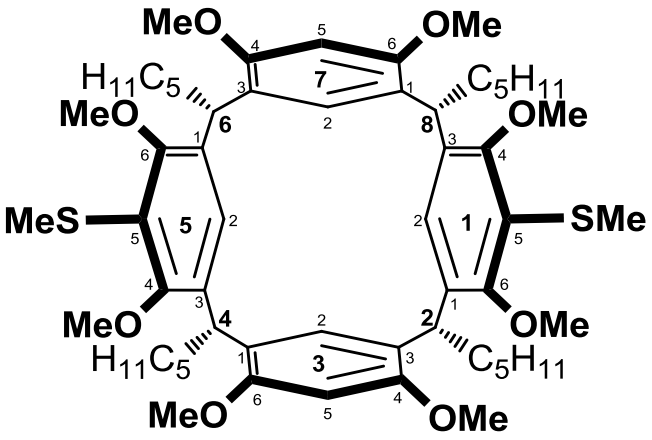


Octamethoxy resorcinarene **2** (50 mg, 0.065 mmol) was dissolved in tetrahydrofuran (1.65 ml). The solution was cooled to 0 °C and *n*-butyllithium (0.233 ml, 0.325 mmol) was added. The solution was stirred for 90 minutes at this temperature before adding dimethyl disulfide (0.48 ml, 0.52 mmol) and continuing stirring overnight. Water was added (10 ml) to the reaction crude material and extracted with ethyl acetate (3x15 ml). The organic extracts were collected, dried with anhydrous magnesium sulphate and filtered. The solvent was evaporated under reduced vacuum and the remaining solid was dried under high vacuum to leave methylthiyl **tetra-9** (56 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 4H, H – 1^5, 3^5, 5^5, 7^5), 4.46 (t, J = 7.5 Hz, 4H, H – 2, 4, 6, 8), 3.59 (s, 24H, Ar – OCH_3), 2.29 (s, 12H, Ar – SCH_3), 1.76 (m, 8H, – $CH_2CH_2CH_3$), 1.28 (m, 8H, – $CH_2CH_2CH_3$), 0.86 (t, J = 7.3 Hz, 12H, – $CH_2CH_2CH_3$); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 155.9 (C – 1^4, 1^6, 3^4, 3^6, 5^4, 5^6, 7^4, 7^6), 126.4 (C – 1^1, 1^3, 3^1, 3^3, 5^1, 5^3, 7^1, 7^3), 126.1 (1^2, 3^2, 5^2, 7^2), 97.2 (1^5, 3^5, 5^5, 7^5), 56.3 (Ar – OCH_3) , 37.2 (C – 2, 4, 6, 8), 35.9 (Ar – SCH_3), 35.1 (– $CH_2CH_2CH_3$), 21.2 (– $CH_2CH_2CH_3$), 14.3 (– $CH_2CH_2CH_3$); **IR (cm^{-1})**: 2980 (C-H), 1600 (Ar), 1450 (Ar), 1050 (C-O).

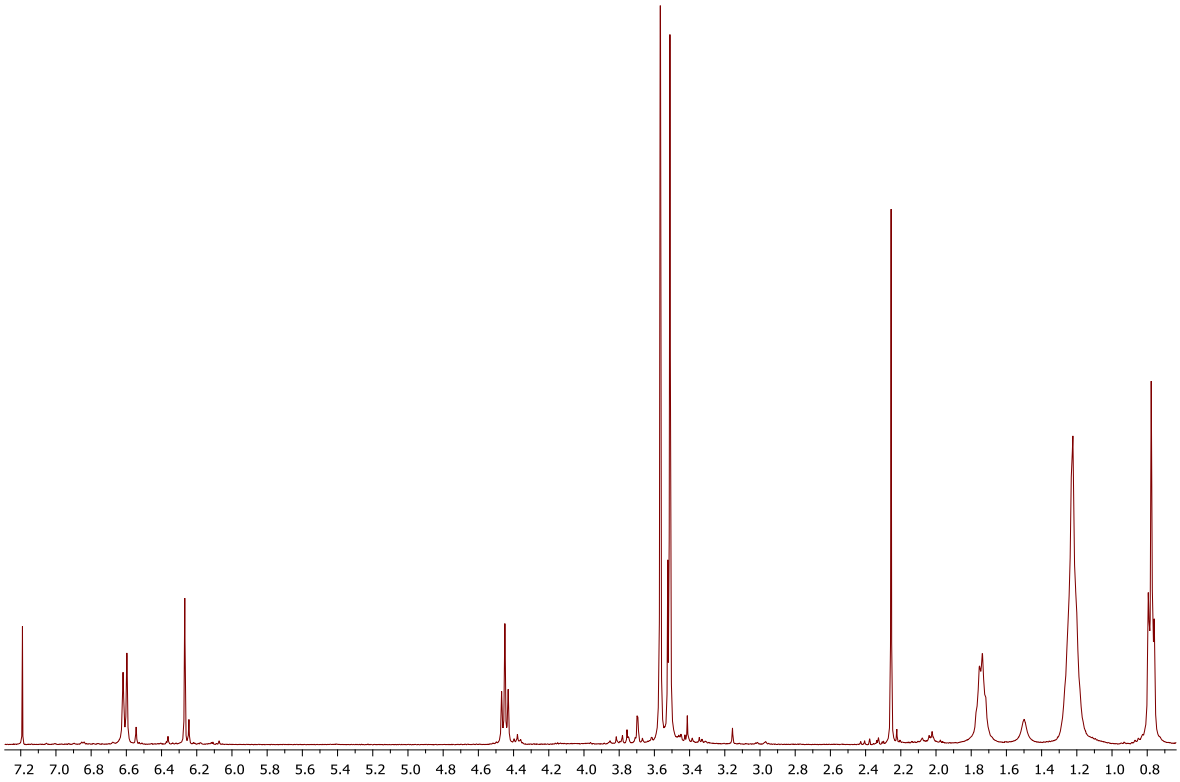


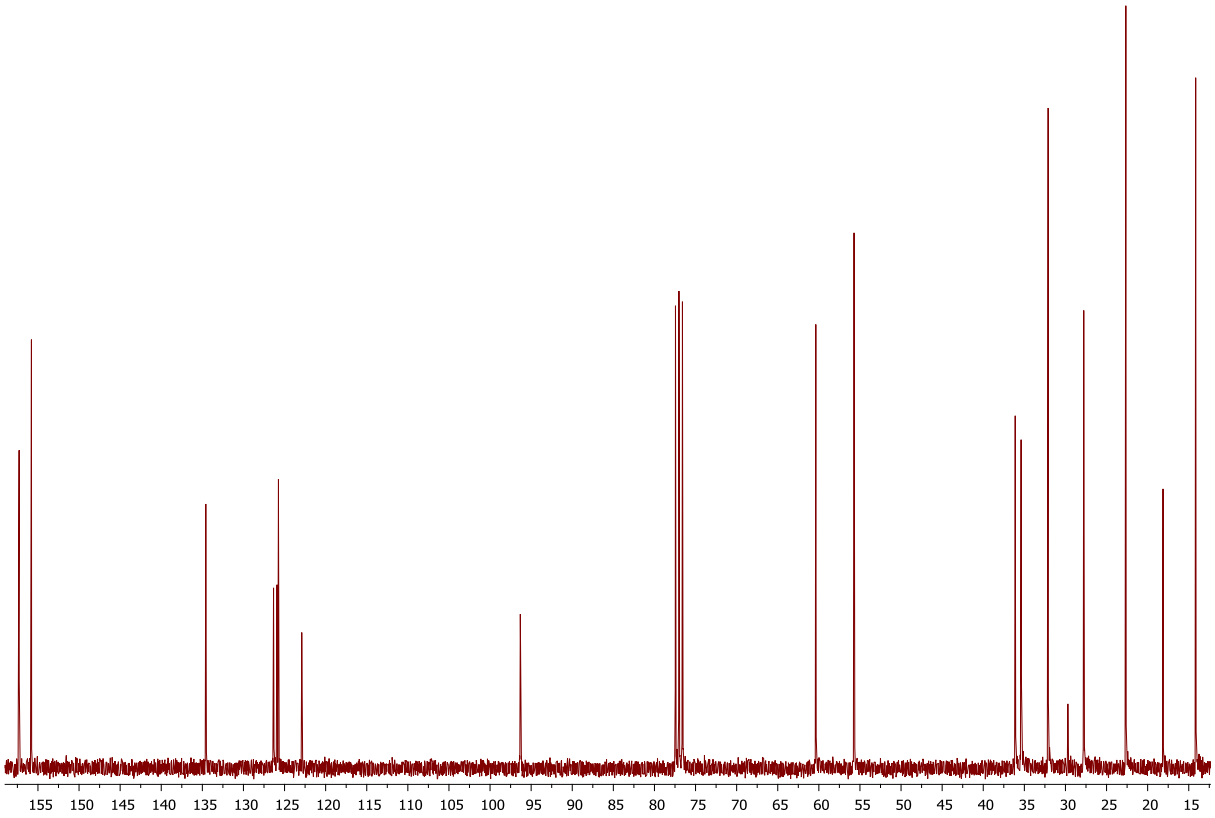
1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,5^5-dimethylthiyl-2,4,6,8-tetrapentyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (11);



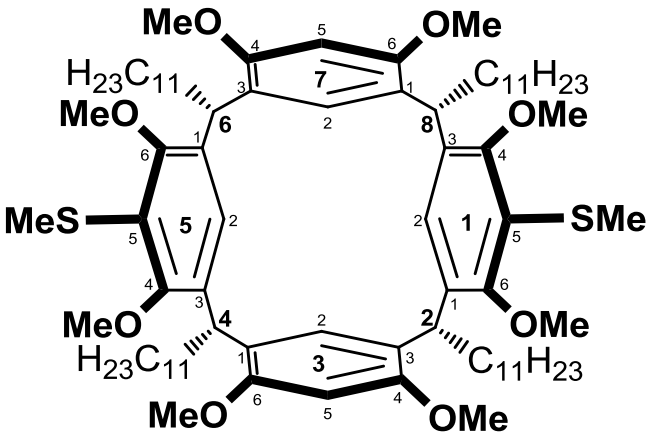
Procedure III was adopted and applied to octamethoxy resorcinarene **5**. Dithiomethyl resorcinarene **11** was isolated in 75% yield after work up.

Mp 152.50 °C; $\mathbf{R_f}$ = 0.80 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.62 (s, 2H, H – 3^2, 7^2), 6.6 (s, 2H, H – 1^2, 5^2), 6.24 (s, 2H, H – 3^5, 7^5), 4.43 (t, *J* = 7.5 Hz, 4H, 2, 4, 6, 8), 3.58 (s, 12H, Ar – OC*H*$_3$), 3.5 (s, 12H, Ar – OC*H*$_3$), 2.23 (s, 6H, Ar – SC*H*$_3$), 1.73 (m, 8H, – C*H*$_2$CH$_2$CH$_3$), 1.2 (m, 24H, – CH$_2$C*H*$_2$CH$_3$), 0.79 (t, *J* = 7.3 Hz, 12H, – CH$_2$CH$_2$C*H*$_3$); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 157.3 (C – 3^4, 3^6, 7^4, 7^6), 155.8 (C – 1^4, 1^6, 5^4, 5^6), 134.61 (C – 1^1, 1^3, 5^1, 5^3), 126.4 (C – 3^2, 7^2), 125.9 (C – 1^2, 5^2), 125.7 (C – 3^1, 3^3, 7^1, 7^3), 122.9 (C – 1^5, 5^5), 96.36 (C – 3^5, 7^5), 60.4 (Ar – O*C*H$_3$), 55.7 (Ar – OCH$_3$), 37.8 (C – 2, 4, 6, 8), 35.9 (Ar – S*C*H$_3$),35.0(–*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_3$),32.5(–CH$_2$*C*H$_2$CH$_2$CH$_2$CH$_3$),28.0(CH$_2$CH$_2$*C*H$_2$CH$_2$CH$_3$), 23.0(–CH$_2$CH$_2$CH$_2$*C*H$_2$CH$_3$), 14.9 (– CH$_2$CH$_2$CH$_2$CH$_2$*C*H$_3$); **IR (cm^{-1})**: 2920 (C-H), 1620 (Ar), 1480 (Ar), 1045 (C-O).



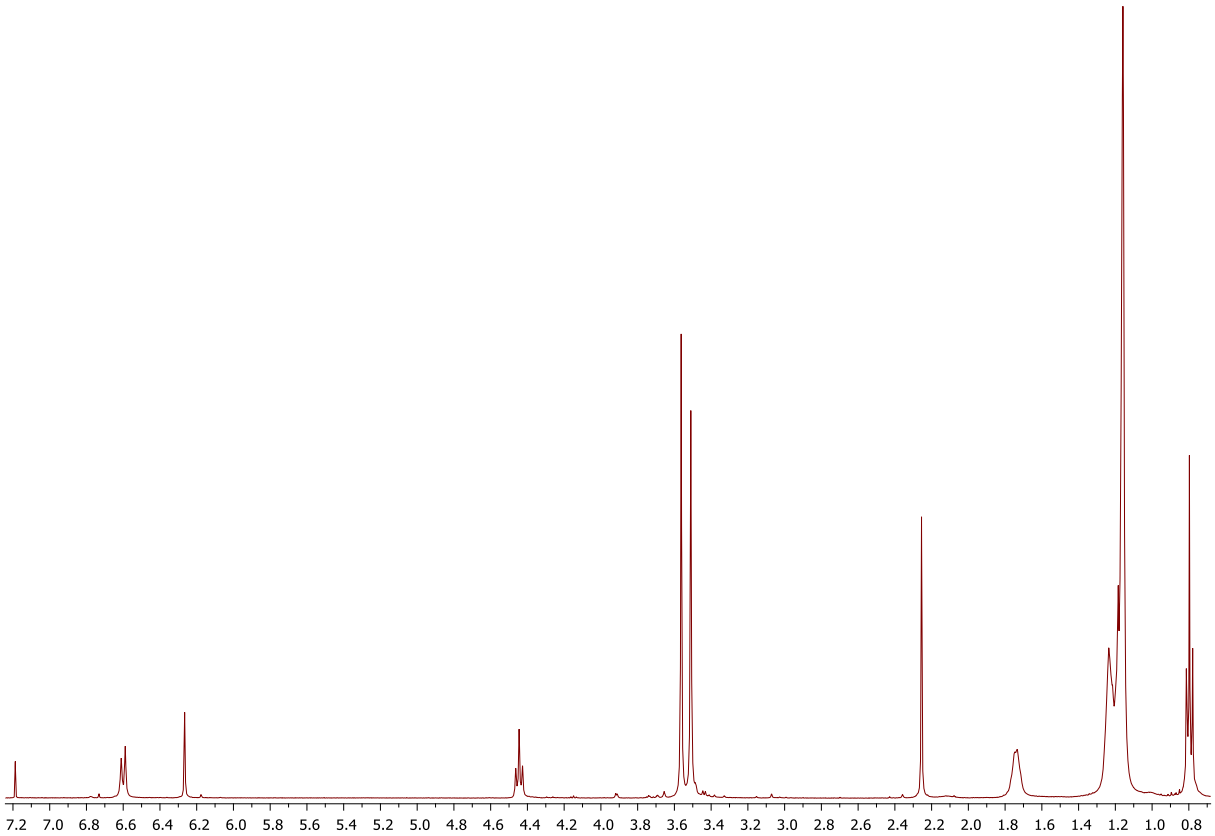


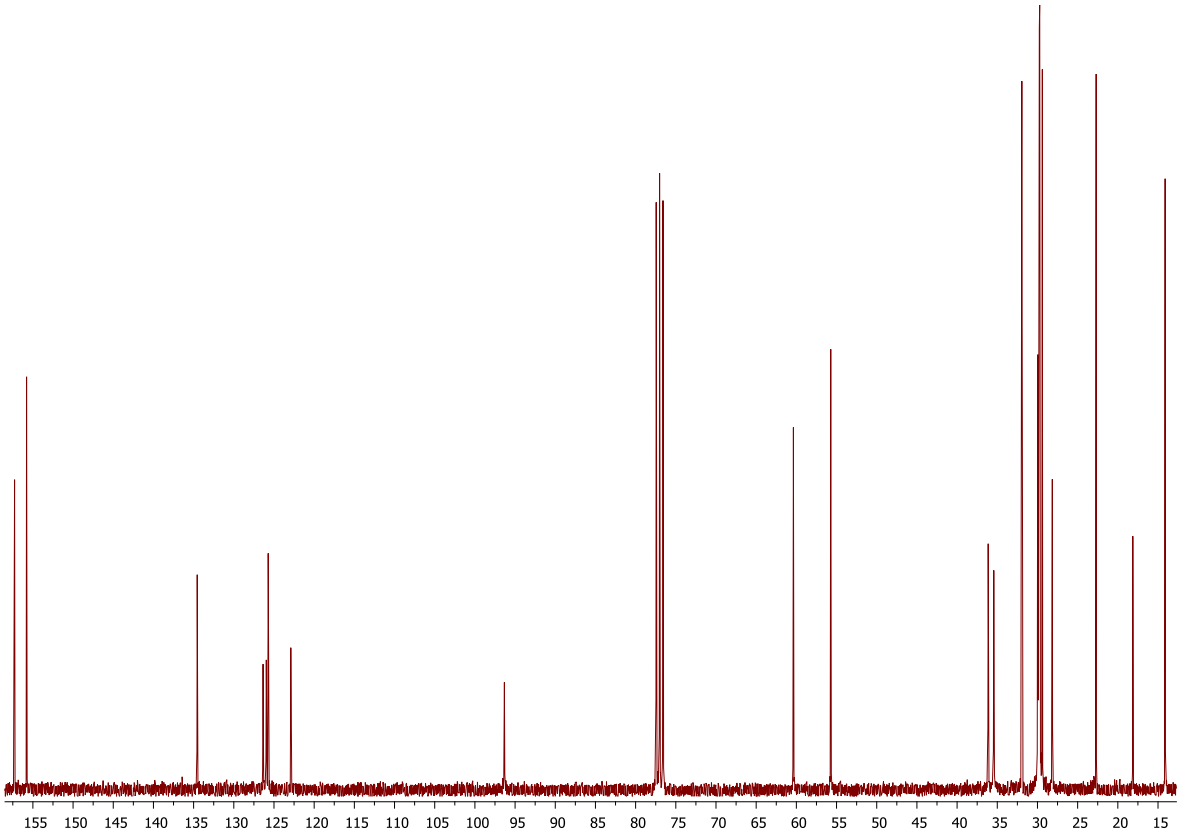
1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,5^5-dimethylthiyl-2,4,6,8-tetraundecyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (13);



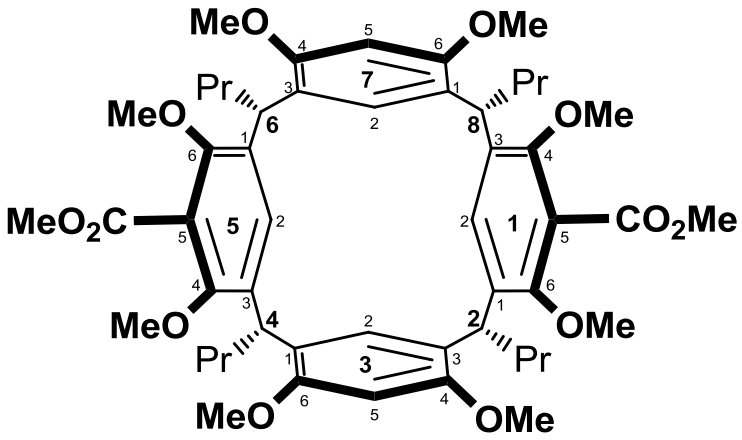
Procedure III was adopted and applied to octamethoxy resorcinarene **6**. Dimethylthiyl resorcinarene **13** was isolated in 70% yield after work up.

Mp 78 °C; $\mathbf{R_f}$ = 0.83 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.62 (s, 2H, H – 3^2, 7^2), 6.6 (s, 2H, H – 1^2, 5^2), 6.24 (s, 2H, H – 3^5, 7^5), 4.43 (t, J = 7.5 Hz, 4H, 2, 4, 6, 8), 3.58 (s, 12H, Ar – OCH_3), 3.5 (s, 12H, Ar – OCH_3), 2.23 (s, 6H, Ar – SCH_3), 1.73 (m, 8H, – CH_2CH$_2$CH$_3$), 1.2 (m, 72H, – CH$_2$CH_2CH$_3$), 0.79 (t, J = 7.3 Hz, 12H, – CH$_2$CH$_2$CH_3); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 157.3 (C – 3^4, 3^6, 7^4, 7^6), 155.8 (C – 1^4, 1^6, 5^4, 5^6), 134.6 (C – 1^1, 1^3, 5^1, 5^3), 126.4 (C – 3^2, 7^2), 125.9 (C – 1^2, 5^2), 125.7 (C – 3^1, 3^3, 7^1, 7^3), 122.9 (C – 1^5, 5^5), 96.4 (C – 3^5, 7^5), 60.4 (Ar – OCH$_3$), 55.7 (Ar – OCH$_3$), 37.8 (C – 2, 4, 6, 8), 35.9 (Ar – SCH$_3$),), 35.4 (–CH$_2$(CH$_3$)$_9$CH$_3$), 34.7 (–CH$_2$$CH_2$(CH$_2$)$_8CH_3$), 32.0 ((CH$_2$)$_2$$CH_2$(CH$_2$)$_7CH_3$), 30.0 (–(CH$_2$)$_3$$CH_2$(CH$_2$)$_6$CH3), 29.9 ((CH$_2$)$_4$$CH_2$(CH$_2$)$_5CH_3$), 29.9 (–(CH$_2$)$_5$$CH_2$(CH$_2$)$_4CH_3$), 29.73 (–(CH$_2$)$_6$$CH_2$(CH$_2$)$_3CH_3$), 29.4 ((CH$_2$)$_7$$CH_2$(CH$_2$)$_2CH_3$), 28.2 (–(CH$_2$)$_8$$CH_2CH_2CH_3$), 22.7 (–CH$_2$(CH$_3$)$_8$$CH_2CH_3$), 14.1 (–CH$_2$(CH$_2$)$_9$$CH_3$); **IR (cm^{-1})**: 2920 (C-H), 1620 (Ar), 1480 (Ar), 1045 (C-O).



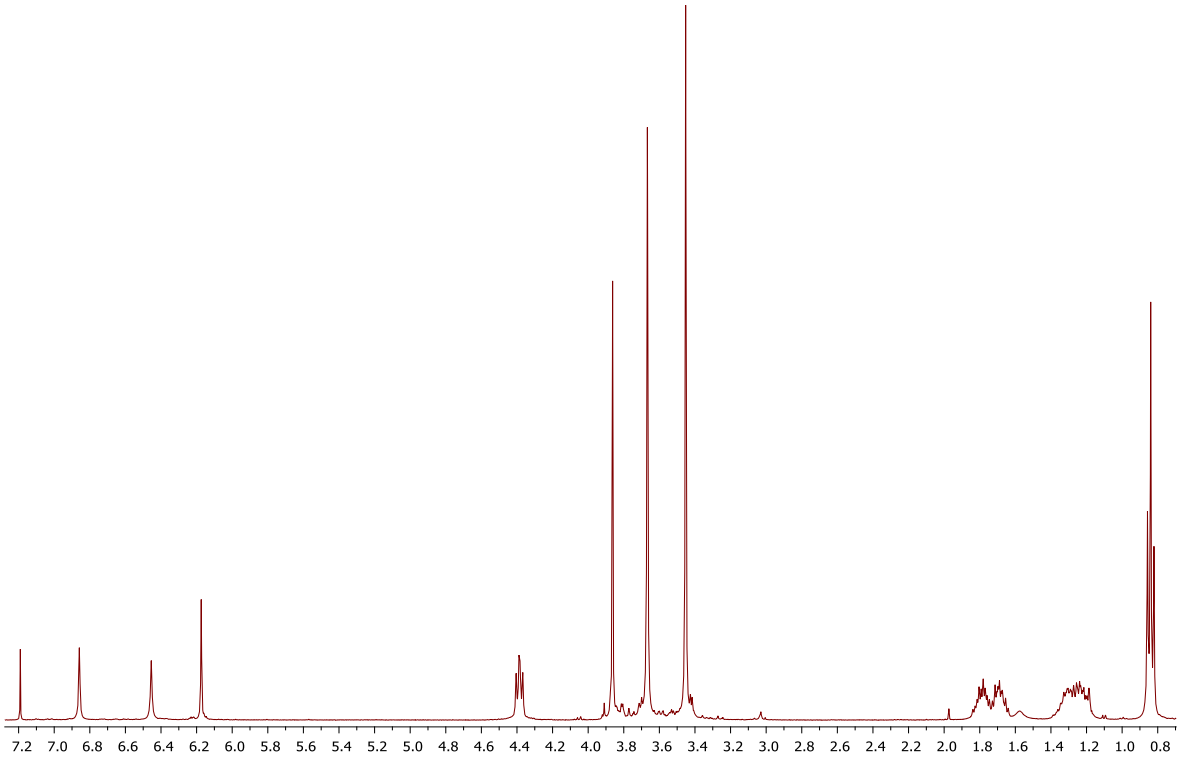


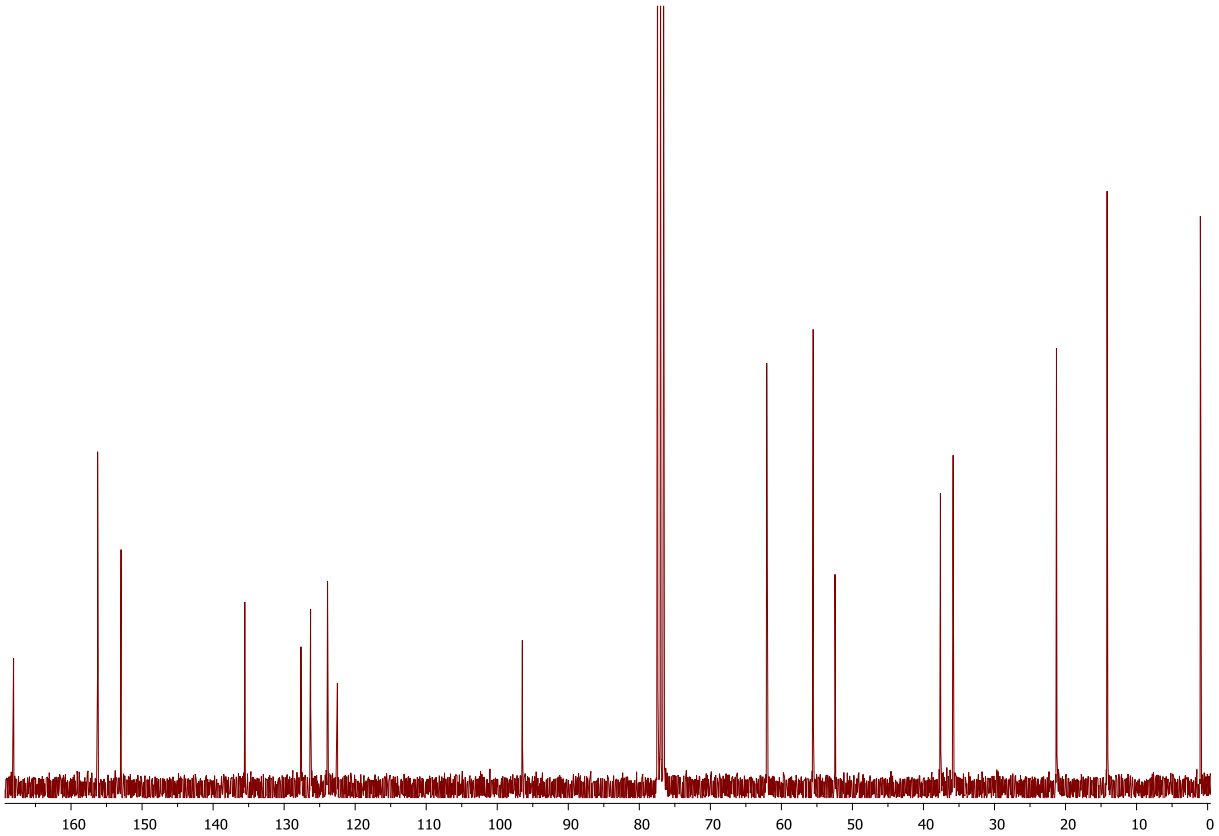
1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,5^5-dimethyformate-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (15);



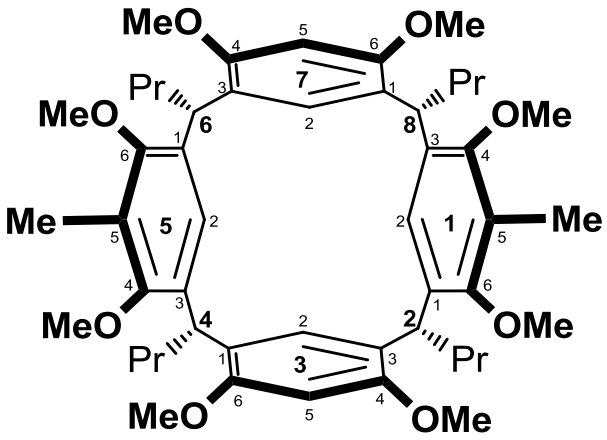
Procedure III was adopted and applied to octamethoxy resorcinarene **4** using methyl chloroformate as an electrophile. The diester resorcinarene **15** was isolated in 75% yield after work up.

Mp 263 °C ; $\mathbf{R_f}$ = 0.45 (Hexane/ EtOAc, 6:4); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.86 (s, 3H), 6.45 (s, 3H), 6.17 (s, 3H), 4.38 (t, 6H), 3.86 (s, 8H), 3.67 (s, 14H), 3.45 (s, 14H), 1.89 – 1.58 (m, 12H), 1.41 – 1.09 (m, 14H), 0.84 (t, *J* = 7.3 Hz, 16H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1 (C - CO_2CH_3), 156.3 (C – 3^4, 3^6, 7^4, 7^6), 153.0 (C – 1^4, 1^6, 5^4, 5^6), 135.5 (C – 1^1, 1^3, 5^1, 5^3), 127.6 (C – 3^2, 7^2), 126.3 (C – 1^2, 5^2), 123.9 (C – 3^1, 3^3, 7^1, 7^3), 122.5 (C – 1^5, 5^5), 96.5 (C – 3^5, 7^5), 62.1 (C - CO_2CH_3), 55.5 (Ar – OCH_3), 52.5 (C – 2, 4, 6, 8), 37.6 (Ar – OCH_3), 35.8 (– $CH_2CH_2CH_3$), 21.3 (– $CH_2CH_2CH_3$), 14.2 (– $CH_2CH_2CH_3$); ***m/z* (%)**: 884.1 [M^+]; **IR (cm^{-1})**: 2900 (C-H), 1720 (C=O), 1640 (Ar), 1470 (Ar), 1045 (C-O).



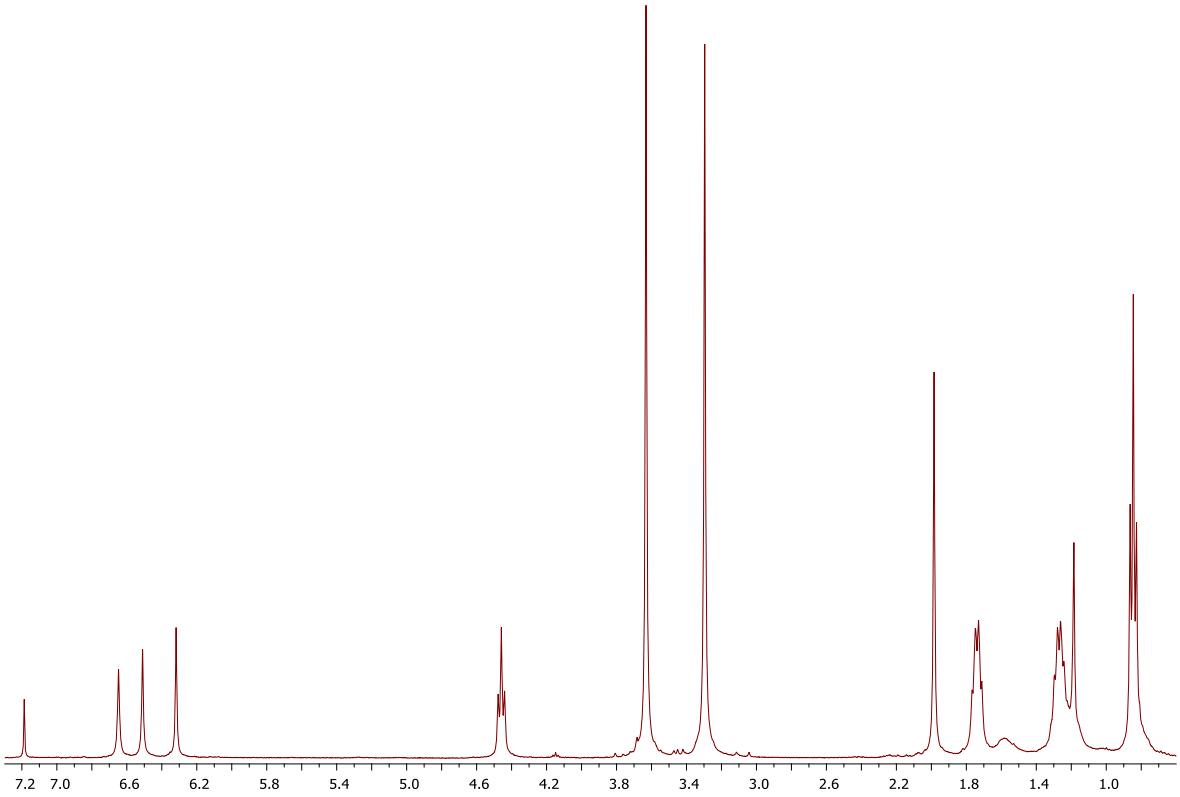


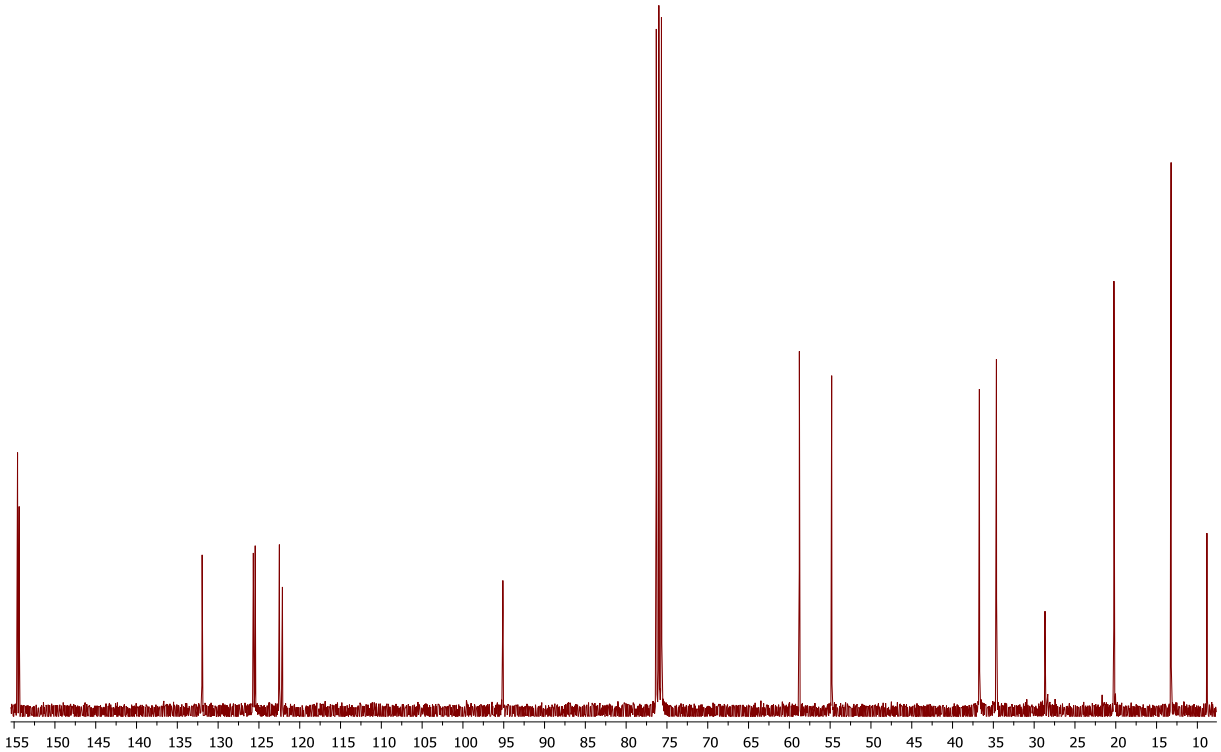
1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,5^5-dimethyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (16);



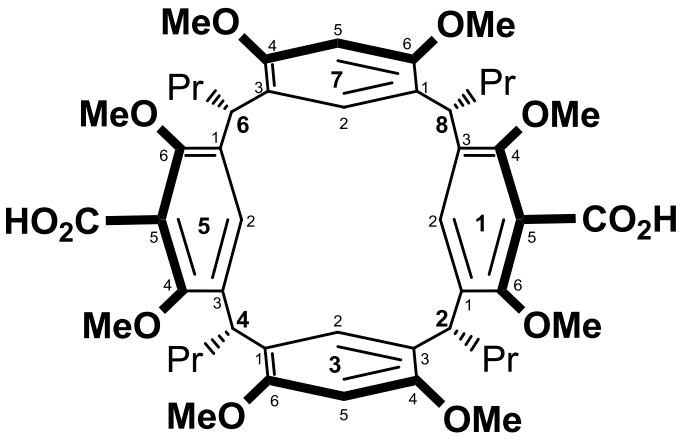
Procedure III was adopted and applied to octahydroxy resorcinarene **4** using methyl iodide as an electrophile. Octamethoxy dimethylthiyl resorcinarene was isolated in 70% yield after work up.

Mp 180 °C; **R_f** = (Hexane/ EtOAc, 6:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.70 (s, 2H, H – 3^2, 7^2), 6.68 (s, 2H, H – 1^2, 5^2), 6.34 (s, 2H, H – 3^5, 7^5), 4.54 (t, *J* = 7.5 Hz, 4H, 2, 4, 6, 8), 3.63 (s, 12H, Ar – OC*H*$_3$), 3.58 (s, 12H, Ar – OC*H*$_3$), 2.32 (s, 6H, Ar – SC*H*$_3$), 1.81 (m, 8H, – C*H*$_2$CH$_2$CH$_3$), 1.43 – 1.27 (m, 8H, – CH$_2$C*H*$_2$CH$_3$), 0.92 (t, *J* = 7.3 Hz, 12H, – CH$_2$CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.3 (C – 3^4, 3^6, 7^4, 7^6), 155.8 (C – 1^4, 1^6, 5^4, 5^6), 134.6 (C – 1^1, 1^3, 5^1, 5^3), 126.36 (C – 3^2, 7^2), 125.92 (C – 1^2, 5^2), 125.70 (C – 3^1, 3^3, 7^1, 7^3), 122.94 (C – 1^5, 5^5), 96.4 (C – 3^5, 7^5), 60.4 (Ar – O*C*H$_3$), 55.7 (Ar – O*C*H$_3$), 37.8 (C – 2, 4, 6, 8), 35.9 (Ar – *C*H$_3$), 21.2(– *C*H$_2$CH$_2$CH$_3$), 18.1 (– CH$_2$*C*H$_2$CH$_3$), 14.2 (– CH$_2$CH$_2$*C*H$_3$); ***m/z* (%):** 796.1[M^+]; **IR (cm^{-1})**: 2940 (C-H), 1650 (Ar), 1450 (Ar), 1050 (C-O).





1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5,5^5-dibenzoyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (17);



Procedure III was adopted and applied to octahydroxy resorcinarene **4** using solid carbon dioxide as an electrophile. Octamethoxy dimethyl resorcinarene was isolated in 40% yield after work up.

Mp 255 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.90 (s, 2H), 7.19 (s, 2H), 6.46 (s, 2H), 6.21 (s, 2H), 4.54 (t, *J* = 7.4 Hz, 4H), 3.84 (s, 12H), 3.36 (s, 12H), 1.82 (m, 8.1 Hz, 8H), 1.33 (m, 7.1 Hz, 8H), 0.92 (t, *J* = 7.3 Hz, 12H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 172.43 (Aromatic), 155.5 (Aromatic), 154.3 (Aromatic), 132.8 (Aromatic), 128.1 (Aromatic), 126.7 (Aromatic), 126.4 (Aromatic), 122.2 (Aromatic), 96.4 (Aromatic), 62.1 (Ar – O*C*H$_3$), 55.9(Ar – O*C*H$_3$), 37.2 (C – 2, 4, 6, 8), 35.4 (– *C*H$_2$CH$_2$CH$_3$), 21.1 (– CH$_2$*C*H$_2$CH$_3$), 14.2 (– CH$_2$CH$_2$*C*H$_3$); ***m/z*(%)**: 856 [M^+], 879 [M^+ + Na] (100).

4.3. Crystal structures:

4.3.1. 1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octamethoxy-1^5-benzoyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (10);

Empirical formula	$C_{55}H_{72}O_9$
Formula weight	876.52
Temperature (K)	104(2)
Wavelength (Å)	0.71073

Crystal system	triclinic
Space group	*P*-1
Unit cell dimension (Å, °)	$a = 10.4159(7)$ $\alpha = 97.3380(10)$
	$b = 15.0191(11)$ $\beta = 102.3220(10)$
	$c = 17.3106(12)$ $\gamma = 103.7800(10)$
Volume (Å^3)	$V = 2523.6(3)$
Z	2
Calculated density (g cm^{-3})	1.203
Absorption coefficient (mm^{-1})	0.080
F_{00}	984
θ range for data collection (°)	2.04 to 28.63
Miller index ranges	$-13 \leq h \leq 13$, $-20 \leq k \leq 19$, $-23 \leq l \leq 23$
Reflections collected	28187
Independent reflections	11761 ($R_{int} = 0.0259$)
Completeness to θ_{max} (%)	57.3
Max. and min. transmission	0.907 and 0.988
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9590/ 0/ 578
Goodness of fit F^2	0.974
Final R indices [$I>2\sigma(I)$]	$R1 = 0.0591$, $wR2 = 0.1586$
R indices (all data)	$R1 = 0.072$, $wR2 = 0.176$

Largest diff. peak and hole (e $Å^{-3}$)	0.966 and −0.748

4.3.2. $1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5,5^5$-dimethyformate-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (15);

Empirical formula	$C_{52}H_{68}O_{12}$
Formula weight	884.47
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	triclinic
Space group	*P*-1
Unit cell dimension (Å, °)	a = 10.9142(8) α = 68.9630(10)
	b = 14.4914(11) β = 85.5390(10)
	c = 16.5792(12) γ = 79.5740(10)
Volume ($Å^3$)	2406.8(3)
Z	2
Calculated density (g cm^{-3})	1.221
Absorption coefficient (mm^{-1})	0.086
F_{00}	952
Crystal size (mm^3)	0.34 × 0.25 × 0.17
θ range for data collection (°)	1.63 and 28.29
Miller index ranges	$-14 \leq h \leq 14$, $-19 \leq k \leq 18$, $-21 \leq l \leq 21$

Reflections collected	27093
Independent reflections	11231 (R_{int} = 0.0216)
Completeness to θ_{max}(%)	56.6
Max. and min. transmission	0.938 and 0.991
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	9456/ 0/ 591
Goodness of fit F^2	1.021
Final R indices [$I>2\sigma(I)$]	$R1$ = 0.0443, $wR2$ = 0.1111
R indices (all data)	$R1$ = 0.0531, $wR2$ = 0.1169
Largest diff. peak and hole (e Å^{-3})	0.442 and −2.33

4.3.3. $1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6$-Octamethoxy-$1^5,3^5,5^5,7^5$-trimethylthiyl-2,4,6,8-tetrapropyl-1,3,5,7(1,3)-tetrabenzenenacyclooctaphane (Tetra-9);

Empirical formula	$C_{52}H_{72}O_8S_4$
Formula weight	952.41
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	triclinic
Space group	*P*-1
Unit cell dimension (Å, °)	a = 12.1528(16) α = 70.5870(10)
	b = 14.6643(19) β = 81.489(2)

	c = 15.401(2) γ = 78.4710(10)
Volume (Å^3)	V = 2526.6(6)
Z	2
Calculated density (g cm^{-3})	1.253
Absorption coefficient (mm^{-1})	0.240
F_{00}	1024
Crystal size (mm^3)	0.57 × 0.38 × 0.27
θ range for data collection (°)	2.08 and 28.30
Miller index ranges	$-16 \leq h \leq 16$, $-19 \leq k \leq 19$, $-19 \leq l \leq 20$
Reflections collected	30467
Independent reflections	11942 (R_{int} = 0.0178)
Completeness to θ_{max}(%)	56.6
Max. and min. transmission	0.8745 and 0.9374
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10510/ 0/ 593
Goodness of fit F^2	1.040
Final R indices [I>2σ(I)]	$R1$ = 0.0340, $wR2$ = 0.0903
R indices (all data)	$R1$ = 0.0393, $wR2$ = 0.939
Largest diff. peak and hole (e Å^{-3})	.419 and −0.286

4.4. References:

1. Perrin D.D.; Armarego W.L.F. *Purification of laboratory chemicals.* 3rd Ed. **1989**.

2. Winkle M.R.; Lansinger J.M.; Ronald R.C. *J.Chem. Soc., Chem. Commun.***1980** , *3*, 87.

3. Tunstad L.M.; Tucker J.A.; Dalcanale E.; Weiser J.; Bryant J.A.; Sherman J.C.; Helgeson R.C.; Knobler C.B.; Cram D.J. *J. Org. Chem.* **1989**, *54*, 1305.

4. Pietraszkiewicz M.; Prus P.; Pietraszkiewicz O. *Tetrahedron* **2004**, *60*, 10747.

5. Kleinhans D.J.; Arnott G.E. *Dalton Trans.* **2010**, *39*, 5780.