Investigations into the Synthesis of Inherently Chiral Calix[4]arenes

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This thesis is submitted in partial fulfilment for the requirements for the award of Master of Science.

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School of Chemistry

Declaration

The research presented in this thesis is, to the best of my knowledge, original, except where due reference is made.

Deeptee Horil Roy

Acknowledgments

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Abbreviations

AIBN	Azobisisobutyronitrile
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
DMF	*N,N*-Dimethylformamide
HPLC	High Performance Liquid Chromatography
HRMS	High-resolution Mass Spectrometry
IR	Infra-red
ISE	ion-selective electrode
IUPAC	International Union of Pure and Applied Chemistry
m.p	Melting point
MALDI	Matrix-assisted laser desorption/ionisation
MeCN	Acetonitrile
n-BuLi	*n*-Butyllithium
n-PrI	*n*-Propyl iodide
$Pd(PPh_3)_4$	*Tetrakis*(triphenylphosphine) palladium(0)
rt	Room temperature
TMS	Trimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Abstract

The design and synthesis of highly functionalised calix[4]arenes are of great interest for research. The modification of the upper-rim of calix[4]arene allows the lower-rim to act as a potential molecular binding site. Our objective is to develop methodologies and synthetic routes that allow us to generate a range of *tetra*-substituted, upper-rim functionalised calix[4]arenes in an AABC and ABCD pattern. We started by the selective functionalisation of calix[4]arenes by iodination at the upper-rim in the presence of aldehyde moieties. The Cannizzaro method has been developed within the *Bew* group, utilising a simple pestle and mortar, which has proved to be an extremely efficient method of grinding both the base and the calix[4]arene with a few drops of solvent. Protection of the Cannizzaro compound made the next step easier as acid compounds tend to streak during purification *via* column chromatography. We were able to obtain AABC compounds *via* Sonogashira cross-coupling. For the ABCD compounds, the first step of the synthesis begins *via* a Suzuki-Miyuara coupling of the *bis-1,3*-aldehyde-*bis-2,4*-iodo calix[4]arene with a variety of boronic acids affording *mono*-aryl and *di*-aryl compounds, followed by the Cannizzaro and alkylation to the benzyl esters. This procedure is an amenable tool for the synthesis of 'inherently chiral' calix[4]arenes in an AABC and ABCD pattern.

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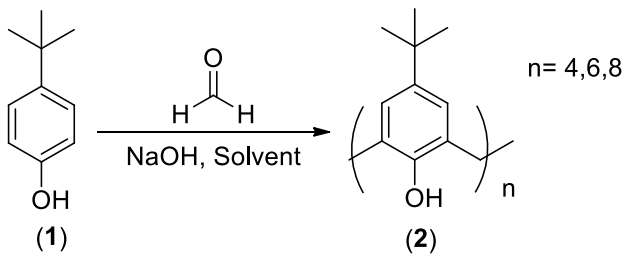
Chapter 1

Introduction

1. History of Calixarene

Calixarenes are macrocyclic molecules formed from the condensation of phenols and aldehydes.[1] This type of reaction was first performed by Nobel Prize winner, Adolph von Baeyer. He described the product obtained by mixing formaldehyde and phenols in the presence of a strong acid as 'resinous tars'.[2] However, Leo Baekeland was able to find appropriate conditions that would generate a material with useful properties, which he named Bakelite and in doing so gave birth to the age of the synthetic plastics.[3] Inspired by this early work, Zinke and Ziegler investigated the resins obtained from the phenol-formaldehyde condensation, and found they were obtained due to the cross linked polymerization which occurs in the reaction.[4] To give more tractable products, Zinke investigated the base catalysed reaction with substituted phenols. *Para*-alkyl phenols were found to give more tractable products since they are unable to react in both the *ortho* and *para* positions giving rise to cross linked polymers. When *p-tert*-butylphenol was reacted with formaldehyde under basic conditions (**Scheme 1**), the Austrian workers were able to isolate a crystalline solid with a melting point of 314 °C, and had a high molecular weight of 1725. This suggested a cyclic structure which comprised of 8 phenolic moieties. They formulated their products as cyclic tetramers, despite the difficulty in obtaining what Zinke considered an 'acceptable' molecular weight.[5]



Scheme 1: Based-catalysed synthesis of calixarenes.

In 1944, Zinke suggested that cyclic products could be formed from phenol and formaldehyde with sodium hydroxide, but the high molecular weight was dismissed due to mixed crystals.[6] The work was based on Niederl and Vogel in 1940, who had assigned cyclic tetrameric structures to acid catalysed reactions of aldehydes and *p*-alkyl phenols.[7, 8] In 1955, John Cornford repeated the Zinke's procedure using *p-tert*-butylphenol, where they made a surprising discovery. They found two products rather than a single one. Both of the structures

were crystalline, sparingly soluble with high but non-identical melting points.[9] Cornforth concluded that these two products must be the diastereomers due to the hindered rotation about the methylene bridges which he proposed with the help of x-ray data and molecular models. In the 1970's, with the aid of ^{1}H NMR spectroscopy Gutsche and co-workers were able to reinvestigate these mixtures and identify three major products the cyclic tetramer, hexamer and octamer. Gutsche and co-workers were also able to identify procedures that would produce pure samples of the 'major calix[4], [6] and [8]arenes'.[10]

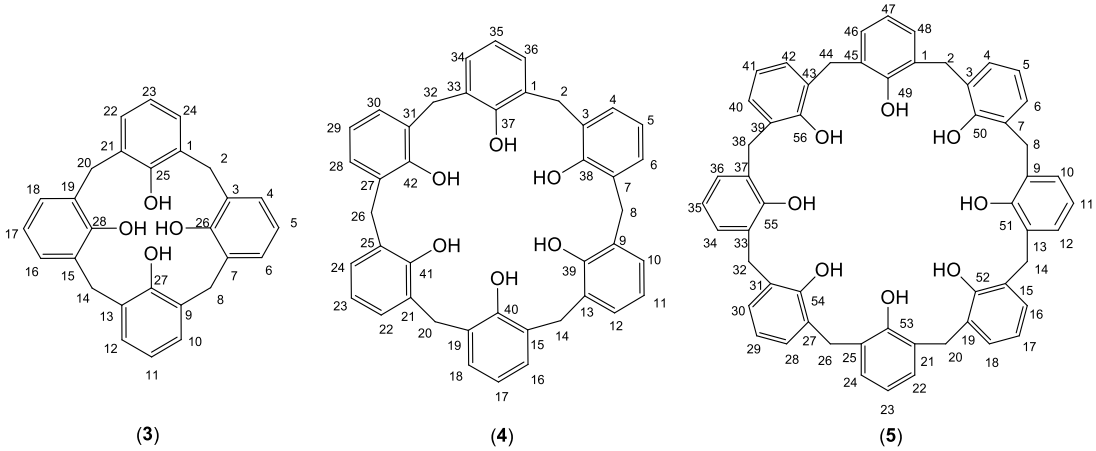


Figure 1: Structure and numbering calix[4], [6] and [8]arene.

Gutsche suggested the name 'calixarene' in 1975– the prefix 'calix' referring to the resemblance of *p-tert*-butylcalix[4]arene to a Greek vase known as a calix crater. The name is derived from the Greek *calix*, meaning 'vase' or 'chalice' while *arene* indicates the presence of aryl residues in the macrocyclic array.[11] Although initially considered unacceptable by IUPAC and *Chemical Abstracts*, it eventually gained official status in 1978.[12]

1.2 Structural Characteristics of Calixarenes

Calixarenes are macrocyclic molecules, which consist of repeating phenolic units linked by methylene bridges to form a distinct bowl cavity. The wider side of the cavity is defined as the upper rim, and the narrower hydroxyl side as the lower rim (**Figure 2**).

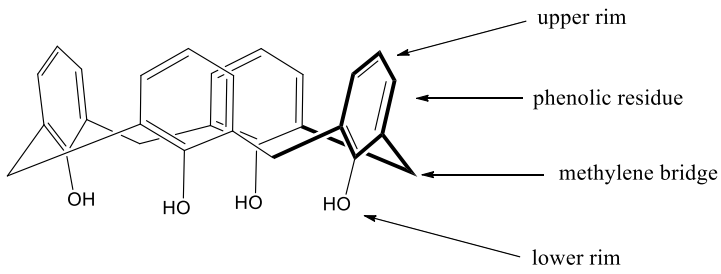


Figure 2: calix[4]arene framework showing the upper and lower rim with phenol groups linked by methylene bridges.

As proposed by Cornforth, calix[4]arenes can exist in a number of different conformations. The aryl groups can be considered to point upward ("u") or downward ("d") relative to the average plane defined by the bridging methylene groups. In the absence of bulky substituents (larger than ethyl) on the phenolic OH, the benzene rings can rotate around the methylene bridges, resulting in four different conformations- the cone, partial cone, 1,3 alternate and 1,2 alternate, named by Gutsche (**Figure 3**).[13]

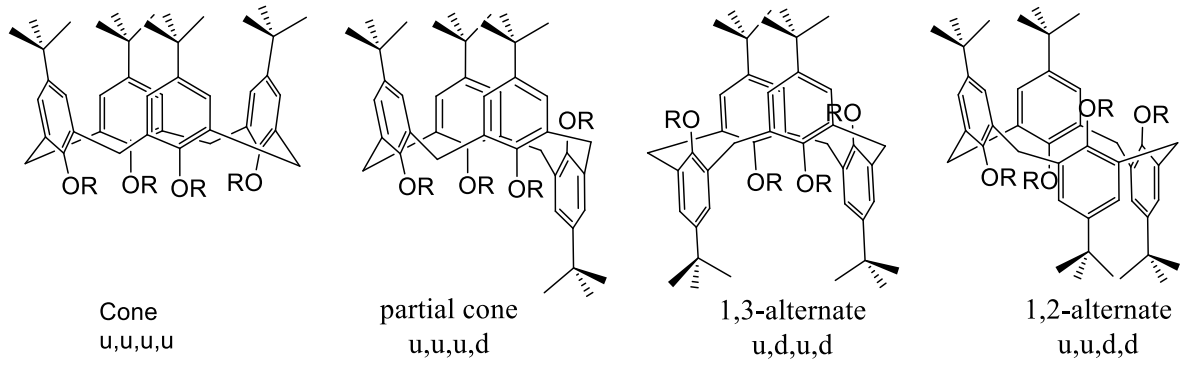


Figure 3: Calix[4]arene possible conformations.

In 1970, temperature-dependent ^{1}H-NMR studies were carried out on cyclic tetramers. These had revealed that the barrier to inversion was not as great as Conforth and co-workers proposed. The *p-tert*-butylcalix[4]arene underwent conformational inversion at approximately 150 s^{-1} in deuterated chloroform at room temperature but rapidly to higher temperature. [14] The 'cone' is the most favoured conformation due to the strong intramolecular hydrogen bonding between the hydroxyl functions at the lower rim, which is significant in non-polar solvents such as chloroform or benzene.

When a conformational transformation takes place, an aromatic group is rotated round the C_2/C_6 axis that brings the OH groups through the centre of the macrocyclic ring. The OH groups experience some steric interference, whereas larger groups would be expected to experience a greater steric constraint. Further control of conformation can be achieved by alkylating the phenolic OH of lower rim functionalities with ester or ether groups, which lock selectively the conformation of the calixarene. Using the right conditions allows the selective synthesis of mono-, di-, tri- and tetra substituted derivatives at the *endo* rim with three or more carbon atoms in length. [15]

Analysing the ^{1}H NMR spectra show that the methylene bridges give distinguished splitting patterns used to differentiate between conformers. In the cone conformation, a calix[4]arene with C_{4v} symmetry will give rise to a pair of doublets for its methylene protons, with a $\Delta\delta$

value of approximately 0.9 ± 0.2. In the 1,3-alternate conformation, a calix[4]arene with D_{2d} symmetry will give rise to a sharp singlet for its methylene protons. [16]

Mendoza *et al.* have shown that the resonance of the bridge methylene carbon in ^{13}C NMR spectra is near δ 31 when the aryl groups are in the *syn* conformation (the cone conformation) and δ 37 in the *anti* conformation (1,3-alternate conformation). This observation provides a useful method of characterisation for calix[4]arenes with substitution patterns which give rise to ^{1}H NMR signals that are identical in both the 1,3-alternate and cone conformations.[17]

1.3 Properties of Calixarenes

For the purification of the calixarenes, for example the one-step synthesis of *p-tert*-butylcalix[4], [6] and [8]arenes can be separated *via* recrystallisation. Gutsche *et al*. found an array of mixtures from the trace of the product from *p-tert*-butylphenol/formaldehyde reaction *via* HPLC. Other techniques that can be used are a combination of trituration, chromatography and crystallisation.[18]

One of the physical properties of calixarenes that played an important role in their chemistry is the melting point. Calixarenes are typically characterised by high melting point of over 250 ℃, particularly those with hydroxyl groups. The melting point can be useful evidence for the purity of a given calixarene. It was found that *p-tert*-butylcalix[4]arene melts at 342-344 ℃, *p-tert*-butylcalix[6]arene melts at 372-374 ℃ and finally *p-tert*-butylcalix[8]arene melts between a range of 411-412 ℃ to 418-420 ℃. Modification in the calixarene structure can affect the melting point, where esters and ethers derivatives of calixarenes tend to have a lower melting point than the original compound due to their inability to form intermolecular hydrogen bonding with one another. For example, tetramethyl and tetrabenzyl ethers of *p-tert*-butylcalix[4]arene melt at 226-228 ℃ and 230-231 ℃. Other exceptions, tetra-trimethylsilyl ether of *p-tert*-butylcalix[4]arene melts at 411-412 ℃ and tetraacetate melts at 383-386 ℃.

Another property that Zinke studied was the solubility of calixarenes. He found that calixarene is insoluble in water, aqueous base, and has a low solubility in organic solvents. Due to these drawbacks, Zinke found it difficult to get an exact molecular weight of some calixarenes as it was hard to isolate, purify and characterise. Most calixarenes were found to be sufficiently soluble in chloroform, pyridine, tetrahydrofuran and *N,N*–dimethylformamide. By converting calixarenes to esters or ethers usually increases the solubility in organic solvents. Ungaro *et al.* was able to increase the solubility of calixarene in water by preparing

tetracarboxymethyl ether of *p-tert*-butylcalix[4]arene. The compounds were soluble to the extent of 5×10^{-3} to 5×10^{-4} M, depending on the cation.[19]

1.4. Synthesis of Calixarene

1.4.1 The base catalysed synthesis of calixarenes

The first report of the calixarene synthesis as described by Zinke and later Cornforth, involved the base catalysed condensation of *p*-alkyl phenols with formaldehyde. However these procedures have been described as somewhat unreliable, with good yields obtained in some instances and poor yields in others – the reasons for which were generally unclear. A study into the reaction conditions was carried out by Gutsche, specially in regard to the amount of base present in each stage of the reaction, synthetic procedures were developed to give access to pure samples of the 'major calix[n]arenes' (n=4,6,8). One method, reported by Zinke, is the reaction of *para*-substituted phenols with formaldehyde in the presence of a base at temperatures of 140-220 °C (**Scheme 1**). In his procedure, the product distribution has been shown to contain cyclic oligomers, which depends strongly on the reaction conditions. A range of yields could be obtained with suitable manipulation, 35% of *p-tert*-butylcalix[4]arene, 75% of *p-tert*-butylcalix[6]arene, and 65% or higher of *p-tert*-butylcalix[8]arene.[20]

The *modified Zinke-Cornford procedure* for the preparation of the cyclic tetramer involves multiple steps. The first of which is where a solution of *p-tert*-butyl-phenol in the presence of 37% formaldehyde and 0.045 equivalents of NaOH per phenol unit are heated for two hours at 110-120°C.[21] The "precursor" is then refluxed for a further two hours in diphenyl ether and the product collected by filtration and recrystallised from toluene.

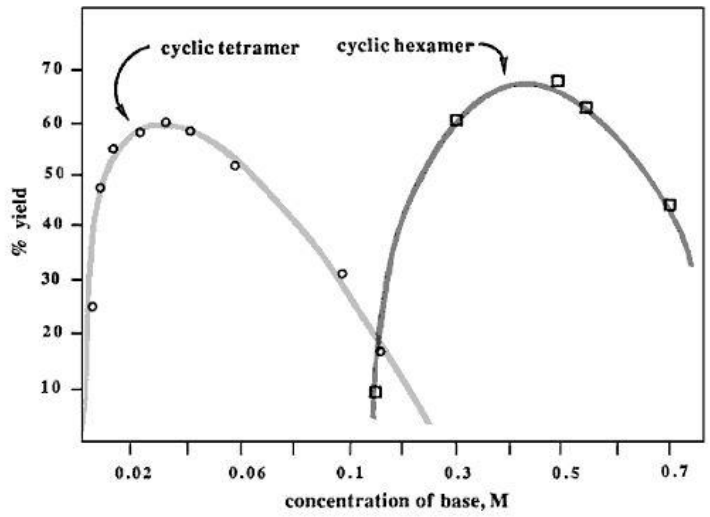
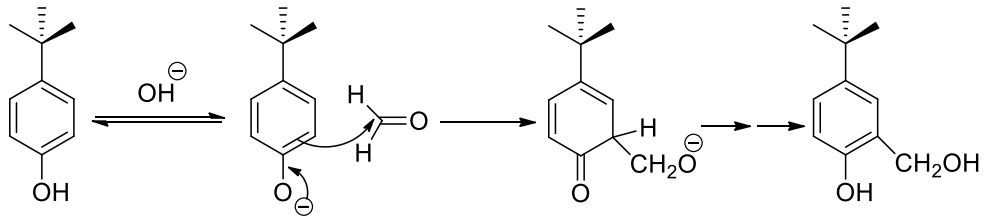


Figure 4: The effect of NaOH concentration on the formation of p-*tert*-butylcalix[4]arene.

If the reaction is conducted with greater than 0.30 equivalents of base, it is the cyclic hexamer which is isolated as the major product. This strong dependence on the concentration of base is illustrated in **Figure 4**. Studies carried out on the base used in the reaction showed that the amount of base affects the outcome of the reaction significantly, but also revealed smaller but significant effects; (a) lithium hydroxide is generally inferior in all calixarene cyclooligomerisation reactions, (b) potassium hydroxide, rubidium hydroxide and caesium hydroxide were found to give higher yields of calix[6]arene in the *Modified Petrolite Procedure* and (c) sodium hydroxide gave higher yields of calix[8]arene in the *Petrolite Procedure*.[22]

The *Modified Petrolite Procedure*, the hexamer can be prepared with a mixture of *p-tert*-butylphenol and formaldehyde. They were heated for two hours with 0.3 equivalence of potassium hydroxide. The precursor is then dissolved in xylene and refluxed for a further three hours. The crude product can then be collected by filtration which is neutralised then finally recrystallised from chloroform/methanol to afford calix[6]arene.[23]

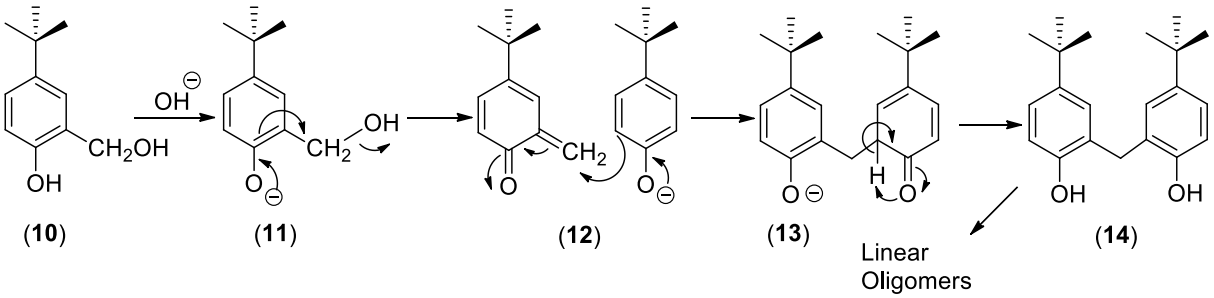
The *Standard Petrolite Procedure* is used to prepare calix[8]arene where *p*-formaldehyde and *p-tert*-butylphenol are heated for four hours in xylene with 0.03 equivalent of NaOH. The crude product is then collected *via* filtration and finally crystallised from chloroform.[24]
Under mild conditions, the phenoxide formed acts as a nucleophile (**Scheme 3**). Studies into the mechanism of calixarenes formation have revealed that under mild conditions, the compound can be isolated in high yield.[25]



(**6**) (**7**) (**8**) (**9**)

Scheme 3: Mechanism of the base catalysed formaldehyde and *p-tert*-butylphenol condensation.

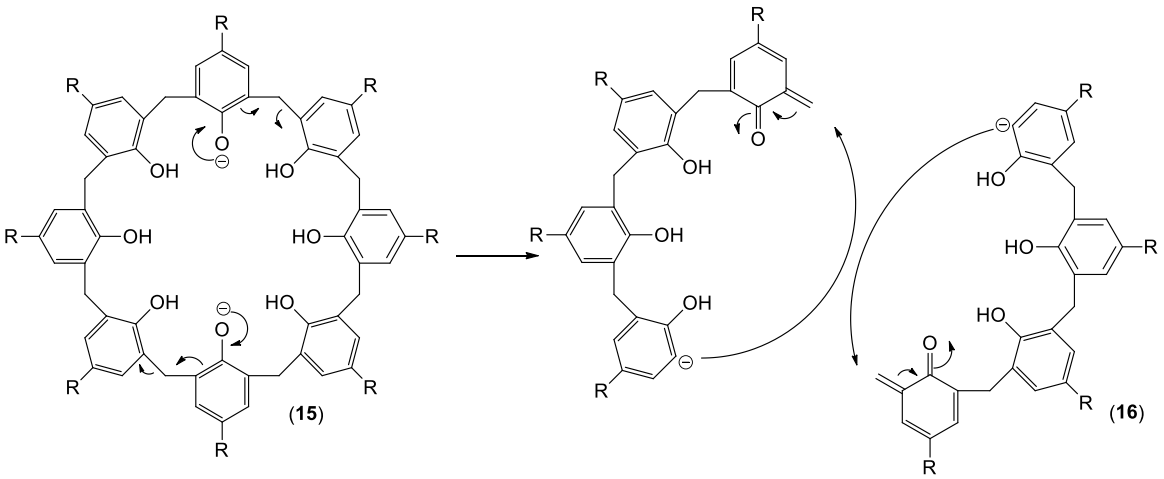
Under more strenuous conditions, the reaction continues to give diarylmethyl compounds *via* a pathway that involves *o*-quinone-methide intermediates which react with the phenoxide in a Michael-like process (**Scheme 4**) and finally linear oligomers which can cyclise.[26]



Scheme 4: Mechanism of the linear oligomer formation.

The linear oligomers can cyclise to give calix[4]arene, calix[6]arene or calix[8]arene depending on the reaction conditions.[27] These reactions have also been performed under acid catalysis. However, due to lower yields obtained, this method is not used for the synthesis of calixarenes.

Since it has been observed that the cyclic octamers are formed under milder conditions than the tetramers, it was suggested that *p-tert*-butylcalix[8]arene is the kinetic product of the reaction, whilst *p-tert*-butylcalix[4]arene is the thermodynamic product. The conversion from the octamer to the tetramer can be affected under high temperature, and this process has been suggested to be a result of 'molecular mitosis' or of a fragment-recombination process (**Scheme 5**).[21]



Scheme 5: The conversion of cyclic octamer to tetramer *via* 'molecular mitosis'.

Gutsche and co-workers tested the 'molecular mitosis' pathway, they designed a deuterium labelling study, where a 1:1 mixture of deuterated and protonated calix[8]arenes were converted to a mixture of deuterated and protonated calix[4]arenes. If the reaction proceeded by the intramolecular pathway, a 1:1 mixture of protonated and deuterated tetramers would be formed. If a fragmentation-recombination pathway would occur, mixed calixarenes of both protonated and deuterated residues would be expected. The product distribution was analysed

by FAB mass spectrometry revealed the presence of mixed calixarenes in an unexpected ratio for a complete fragmentation-recombination pathway.

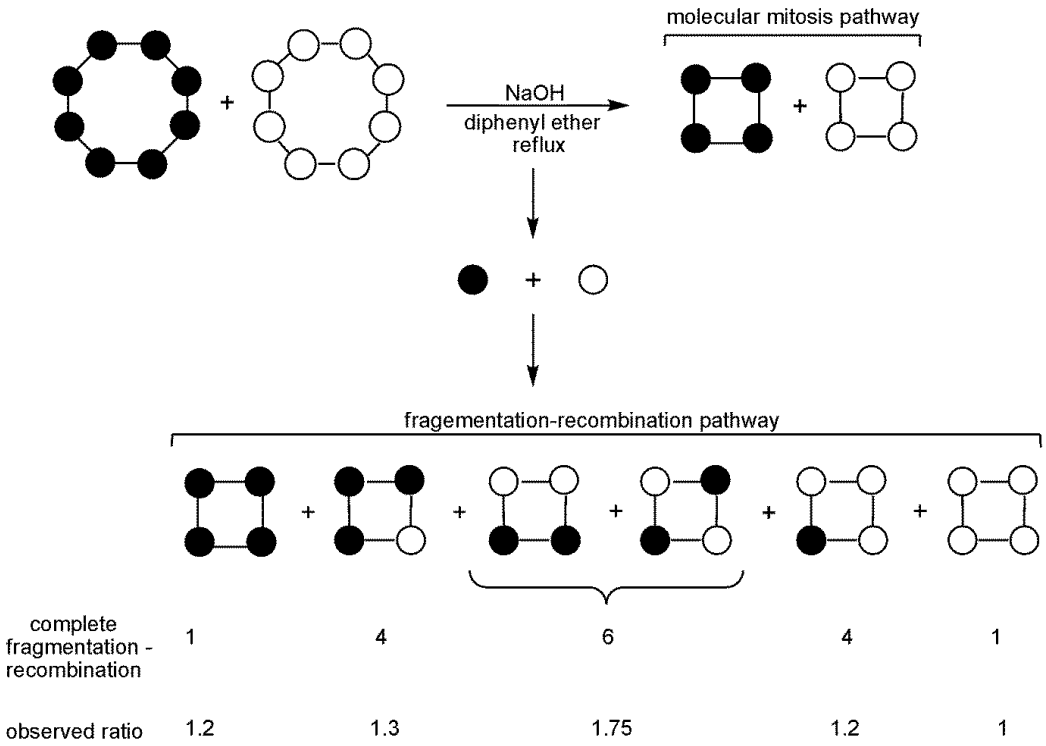


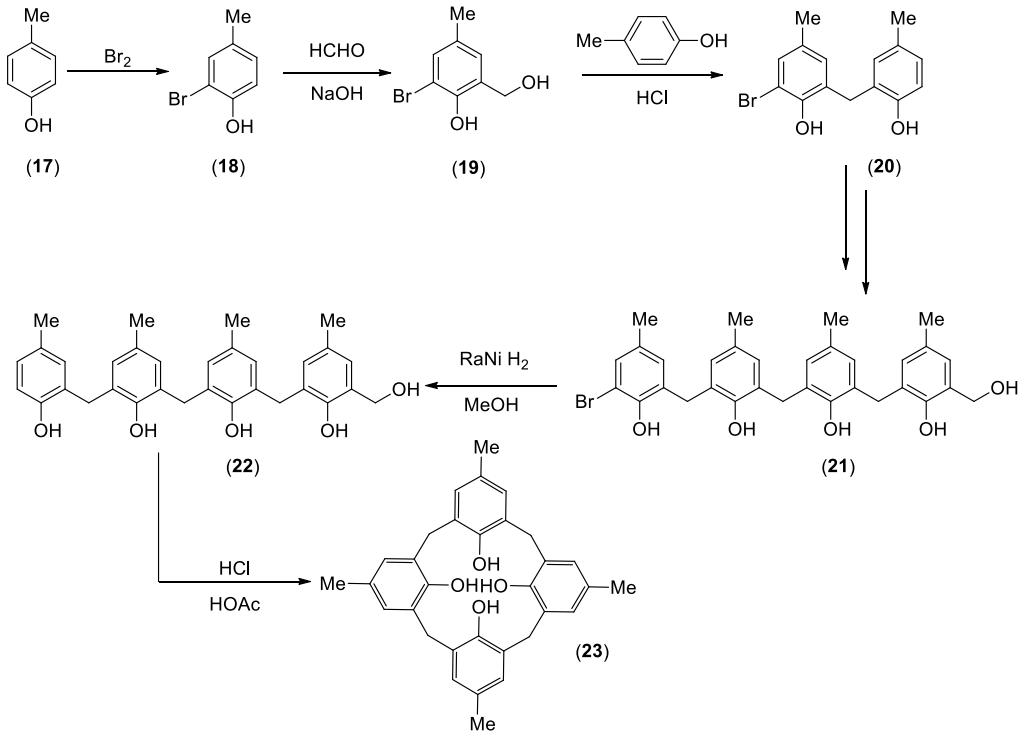
Figure 5: Test for molecular mitosis pathway.

The results suggested that the fragmentation-recombination pathway is very important in the formation of the smaller calixarene where the molecular mitosis pathway doesn't play a key role. If one calixarene undergoes molecular mitosis for every three which undergo fragmentation-recombination, the expected ratio can be shown to be 1.0 : 1.1 : 1.64 : 1.1 : 1.0, and this is quite close to the product distribution that Gutsche observed. As noted in the original report, these results do not rule out the possibility that fragmentation-recombination occurs after the molecular mitosis pathway has produced the fully protonated and fully deuterated calix[4]arenes (**Figure 5**).

1.4.2 Multi-Step Synthesis of Calixarenes

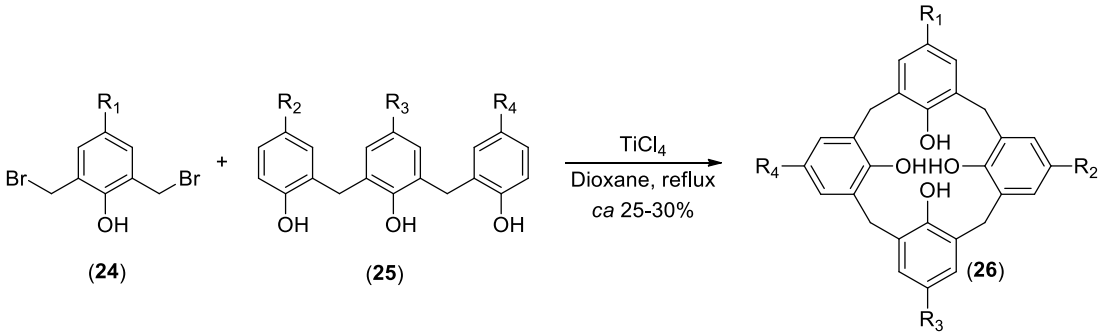
Alternative routes for the synthesis of calixarene have been studied. The 10- step synthesis of *p*-methyl[4]calixarene procedure was first reported by Hayes and Hunter in 1950's. Their synthesis made use of a protecting group.[28] A bromine atom is introduced at the *ortho*-position at the first step of the synthesis, followed by a base-induced hydroxymethylation. The product was then treated with concentrated hydrochloric acid and a large excess of the starting material, then heated at 70 ℃ for 18 hours. The halogen was then removed by hydrogenolysis

and followed by the cyclisation under high dilution to afford the tetramer (**Scheme 6**). It showed the same products as the one-pot synthesis were produced. Their synthesis showed that the cyclic structures can be produced under suitable conditions in the harsh process of phenol-formaldehyde resins.[29]



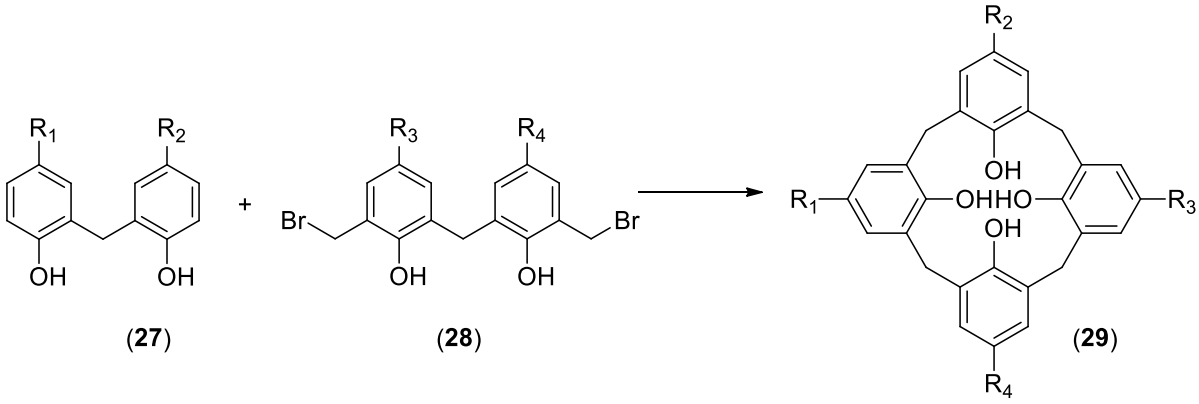
Scheme 6: Hayes and Hunter stepwise synthesis of a calix[4]arene.

The Hunter and Hayes stepwise synthesis is however quite tedious, giving an overall yield of 0.5-11% for a range of *p*-alkyl phenols. Due to these difficulties, Böhmer and his group have developed convergent pathways that reduce the number of synthetic steps.[30] A "3 + 1" approach was developed, where the condensation of a linear trimer and a 2,6-*bis*-halomethyl phenol leads to **26** (**Scheme 7**).



Scheme 7: The synthesis of a calix[4]arene *via* a 3 + 1 convergent protocol.

Böhmer and his group found that using excess $TiCl_4$ as a catalyst and carrying out the cyclisation in dioxane improves the yield.[31] Other approach, the "2+2" procedure was studied by Böhmer and coworkers (**Scheme 8**).

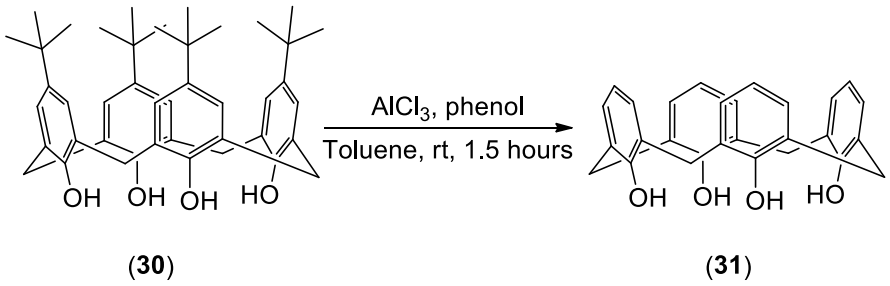


Scheme 8: "2+2" convergent stepwise synthesis of calix[4]arene.

The choice between "3 +1" and "2 + 2" depends on the ease of synthesis of the corresponding fragments.[32]

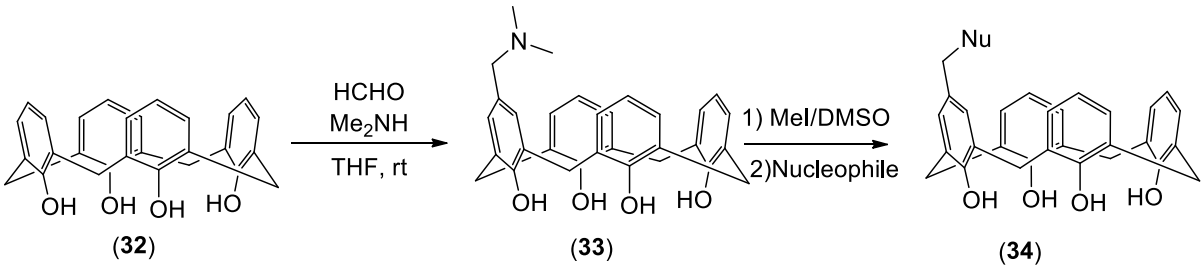
1.5. Modification of the Calix[4]arene

Calix[4]arenes can be easily functionalised at either the upper rim or lower rim. Functionalising the upper rim provides the means to incorporate larger structures while maintaining the properties of the lower rim. Shinkai *et al.* succeeded in sulfonation and nitration on the cavity of the upper rim.[33] Friedel-Crafts reverse alkylation is a common strategy frequently used to replace the tert-butyl group with a proton. The *tert*-butyl groups (**31**) can be easily removed by the treatment with aluminium (III) chloride and phenol (**Scheme 9**).



Scheme 9: Removal of *tert*-butyl groups.

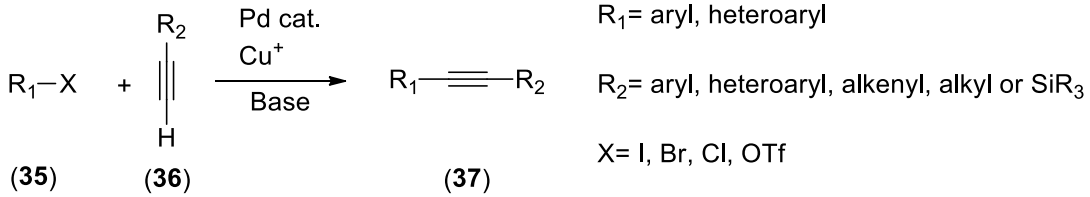
Gutsche *et al.* have described modification *via* an intermediate *p*-quinone methide.[34] The *p*-quinonemethide route was introduced in 1980s; the protocol starts with the formation of a Mannich base, followed by a methylation to give a quaternary salt and further conversion allowed the subsequent substitution by other nucleophiles such as CN^-, N_3^-, H^- and imidazole (**Scheme 10**).



Scheme 10: Modification *via* an intermediate *p*-quinone methide.

The chloromethylation route is a particularly useful Friedel-Crafts alkylation procedure, which was introduced by Ungaro *et al.* in the late 1980s. They used chloromethyl alkyl ether (i.e. propyl groups) in the presence of a Lewis acid to give the *p*-chloromethylcalixarenes.[35] With de-*tert*-butylation, the free *para* position of the calixarene can be easily functionalised using a wide variety of procedures such as alkylation and acylation.

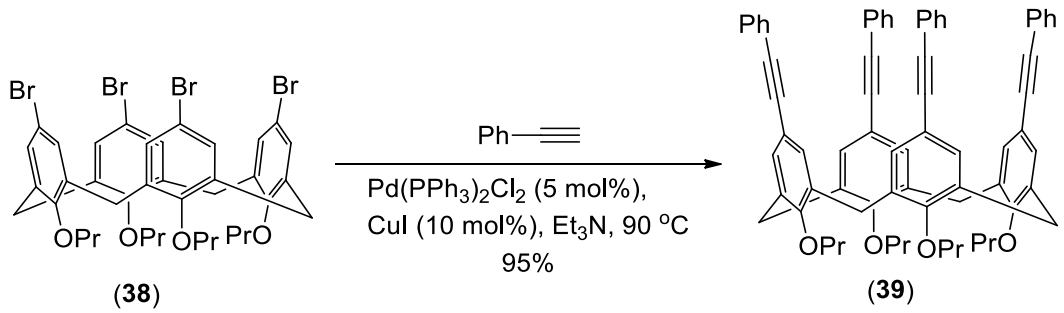
Other methods, transition-metal-catalysed cross-coupling reactions, can be used to modify either the upper or lower rim of the calixarene. These cross-coupling reactions can be considered as a great importance in the organic synthetic field. [36] The palladium-catalysed sp^2-sp coupling reaction between aryl, alkenyl halides or triflates and terminal alkynes, with or without a copper(I) salt as co-catalyst, this synthetic route has become a very important method to generate aryl alkynes (**Scheme 11**).[37] These molecules are useful precursors for natural products, pharmaceutical and organic synthesis.[38]



Scheme 11: General procedure for palladium catalysed coupling reaction to afford aryl alkynes.

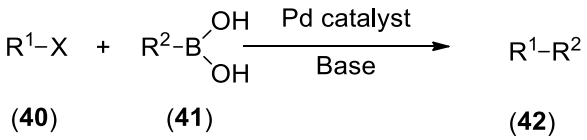
Previous studies were reported by Heck[39] and Cassar.[40] Heck's procedure consisted of the palladium-catalysed arylation/alkenation of alkenes; his method developed the coupling reactions, where he employed a phosphane-palladium complex as catalyst and triethylamine or piperidine as a base. Cassar used phosphane-palladium as a catalyst in the presence of sodium methoxide as a base and DMF as solvent. In 1975, Sonogashira and Higihara reported the catalytic addition of copper(I) iodide, increasing the rate of the reaction while displaying good conversion at room temperature, under mild conditions. This Sonogashira-Higihara

procedure became more popular for the alkynylation of arylation and alkenyl halides. Dyker *et al.* were able to prepare calixarenes with electron rich cavities *via* Sonogashira cross-coupling. Due to fixed cone conformation of the calix[4]arenes, they are able to bind cations in their bowl shaped cavity.



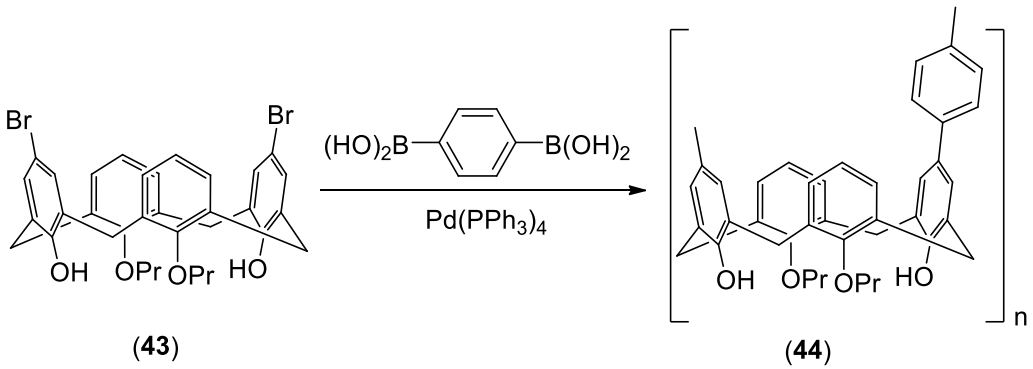
Scheme 12: Sonogashira cross-coupling reaction on a tetra-bromocalix[4]arene

They developed two synthetic pathways, one shown in **scheme 12**. They performed a Sonogashira cross-coupling reaction between tetrabromominated calixarene (**38**) and phenylacetylene. The product, tetraalkynylated calixarene (**39**), was obtained in good yield. The calixarenes obtained were used in the synthesis of tetrakis(pyridylethynyl) compounds, and were tested as hosts for binding of pyridinium salts.[41] Another example is modifying the lower rim of the calixarene *via* Suzuki-Miyaura reaction. It is a palladium-catalysed cross-coupling of organic halides with organoboron compounds (**Scheme 13**), it is one of the most important and powerful tools for the formation of carbon-carbon bonds.[42]



Scheme 13: General procedure for palladium catalysed Suzuki cross-coupling reaction.

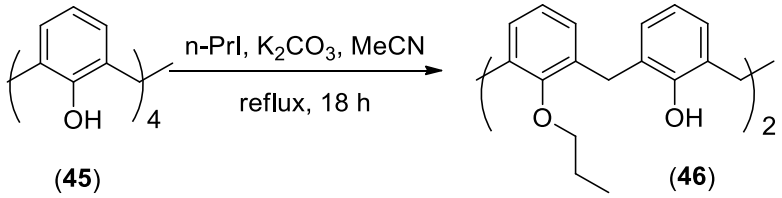
The advantages of Suzuki cross coupling are that it employs easily handled and usually air- and moisture-stable organoboron starting materials, proceeds under mild and convenient reaction conditions and finally the easy removal of the less-toxic inorganic by-products. These aspects make the Suzuki–Miyaura coupling reaction especially useful for industrial applications.[43]



Scheme 14: Suzuki cross-coupling reaction carried out by Dondoni *et al.*

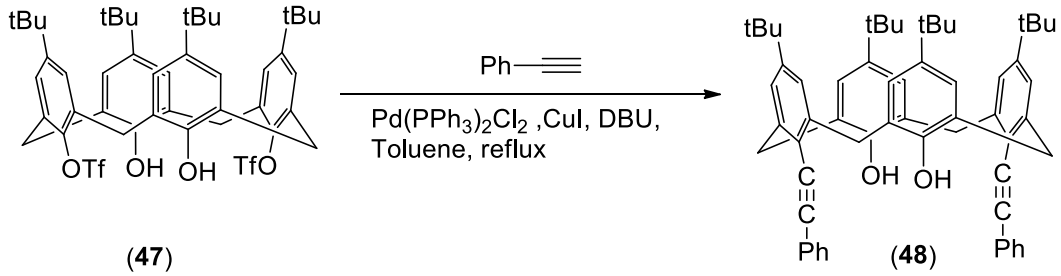
Dondoni *et al.* were able to synthesise polymers by having the calixarene unit linked through a phenylene moiety *via* Suzuki cross-coupling. The reaction of the 1,3-dibromocalix[4]arene derivative with the 1,4-phenylene-*bis*-boronic acid was carried out in the presence of $Pd(PPh_3)_4$ as the catalyst, to afford the product in reasonably good yield (**Scheme 14**).[44]

Modifying the *endo* rim helps in the conformational flexibility of the calixarene. The free hydroxyl groups allow phenol rings to rotate around the methylene bridges.



Scheme 15: Alkylation of the lower rim of the calix[4]arene.

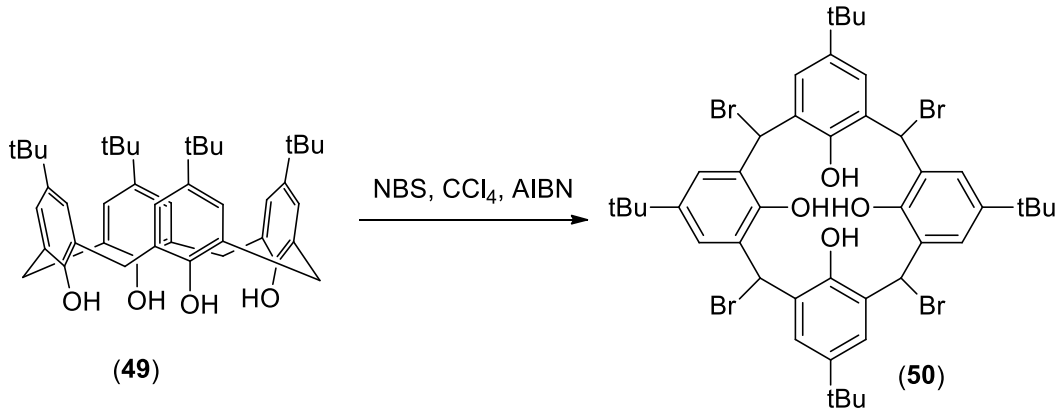
There are 4 different types of conformations the cone, partial cone, 1,3 alternate and 1,2 alternate. It is possible to selectively lock the conformation of the calix[4]arenes by alkylating the phenolic OH using a suitable base and solvent (**Scheme 15**). Georghiou *et al.* were able to functionalise the lower rim of the calix[4]arene *via* Sonogashira cross coupling.



Scheme 16: Sonogashira cross-coupling at the lower rim of the calix[4]arene.

The bistriflate was used as the starting material, after trying different bases and solvents; they found that DBU and toluene were the best combination. The Sonogashira reaction afforded the narrow-rim substituted compound in acceptable yield (**Scheme 16**).[45]

In addition to the functionalising sites at the *endo* and *exo* rims of the calixarenes, the methylene group can be a potential site for functionalisation, although it is less common. The methylene bridges join the phenolic units together in the cyclic structure. By treating the acetates of the *p-tert*-calixarenes with chromium trioxide one or more of the $ArCH_2Ar$ methylene groups is converted to a carbonyl group. The monosubstitution at these positions opens the scope of functionalising calixarenes, as the methylene protons are not equivalent, being the equatorial position the preferred one.[46] Other methods such as esterification and etherification have been used to functionalise the lower rim of the calix[4]arenes. Klenke *et al.* was able to brominate the methylene bridges in the presence of *N*-bromosuccinimide and tetrachloromethane and AIBN to afford the brominated compounds in 48% yield (**Scheme 17**).[47]



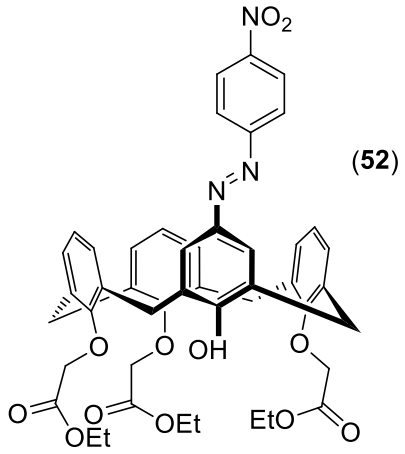
Scheme 17: Modification of the methylene bridges.

1.6. Applications of Calixarenes

The chemistry of calixarene has progressed steadily over the past few decades. [48] Their rigid conformation enables calixarenes to act as host molecules. By modifying either the upper or lower rims, various derivatives can be prepared. [49] These calixarenes have been used as a list of applications, such as sensors, some calixarene-based sensors for example, were found to be helpful in measuring sodium in blood.[50]

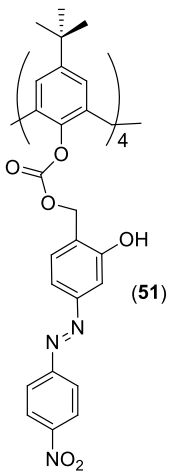
1.6.1. Calixarenes as Sensors

Chemical sensors can be used to monitor the activity of chemical and biochemical species in different environments. Calixarene derivatives have been employed as chemical sensors in a number of diverse applications. The first major study in this area was reported by McKervey and co-workers who developed calixarene for use as ion-complexing agents. Many of the calixarene derivatives prepared by the group are being used in environmental and biomedical monitoring for example they are employed for the *in vivo* monitoring of blood electrolytes. ISE is an ion-selective electrode, it is a sensor that converts the activity of an ion in solution into an electrical potential. This can be measured by either a voltmeter or pH meter.[51] Calixarenes with cation-complexing groups at the lower rim would be ideal for ionophores used in ISEs.[52] Tetramers in a cone conformation have been used for ionophores especially calixarenes with oxygen donor atoms. These macromolecules are suitable for selectively binding alkali ions, where nitrophenol or azophenol moieties (**Figure 7**) equipped with additional ester groups exhibit selectivity for lithium ions against sodium and potassium ions. The tetraazophenol calix[4]arene can be used in the detection of amines (**Figure 6**).[53] Anthracene and pyrene, common fluorescent complexes, are attached to the *endo* rim of calix[4]arenes, these can be used as ion sensitive detectors (**Figure 8**). These groups are efficient fluorophores,



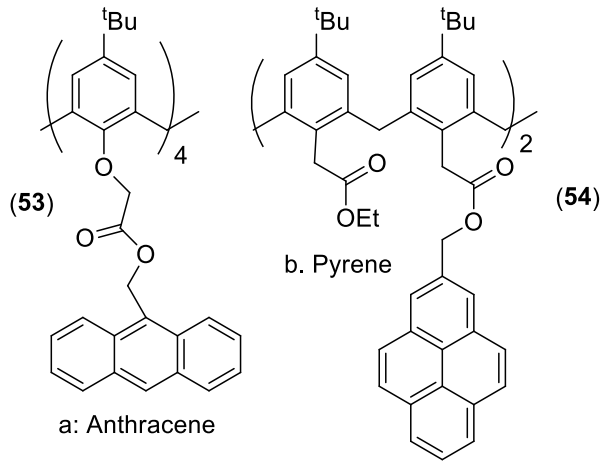
(**52**)

Figure 7: Compound suitable for binding with alkali ions.



(**51**)

Figure 6: Tetraazophenol calix[4]arene



(**53**) (**54**)

Figure 8: Examples of calix[4]arenes affixed with different moieties a) anthracene b) pyrene

as they are suited to reflect intramolecular interactions.[54]

The anthracene compound was synthesised by Diamond *et al.* in which four anthracene units were introduced at the lower rim. The new metal sensing compound demonstrated that the intensity of its fluorescence spectrum was greatly affected by alkali metal ion complexation.[55] Compound **54** is a calix[4]arene sodium sensor containing two pyrene elements at the lower rim. Upon complexation with Na^+, the calix[4]arene complex induces large shifts in fluorescence emission spectra.[56]

1.6.2. Biomimetic and Non-biomimetic Catalysts

Calixarenes are molecular baskets suitable for designing enzyme mimics. Enzyme mimic building is used to construct a receptor for a substrate molecule, equipping the receptor with functional groups that are appropriate for interacting with the substrate molecule (**Figure 9**).[57]

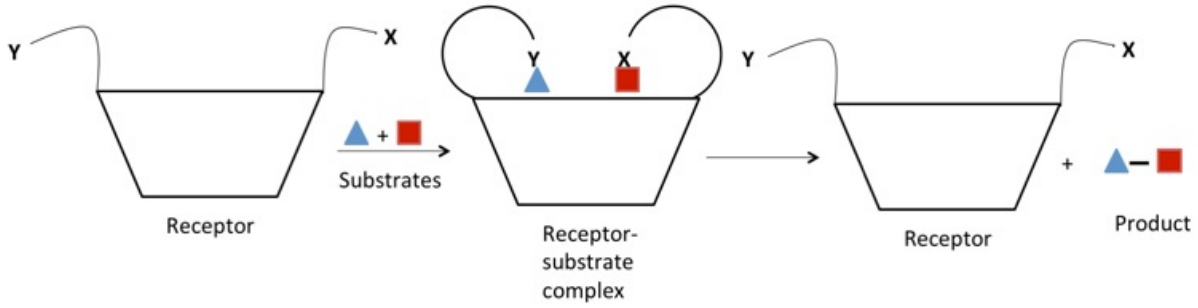


Figure 9: Enzyme mimic.

Calixarenes are architecturally similar to cyclodextrins; they are malleable to both variation and control. Attempts have been made on these molecules to construct *in vitro* systems that mimic *in vivo* catalytic activity of the enzymes.[58] Numerous examples of calixarene-based enzyme mimics have been published. Mono-, di- and trinuclear Zinc (II)-calixarene complexes have been reported as biomimetic catalysts. The mono-nuclear calix[4]arene complex (**Figure 10a**) is a factor 6 more active than the reference complex (**Figure 10b**), as there is no calixarene backbone, which plays an important role.[59]The conversion of the substrate in the di-nuclear complex (**Figure 10c**) proved to be more efficient than the mono-nuclear (**Figure 10a**) one due to the binding of both the substrates.

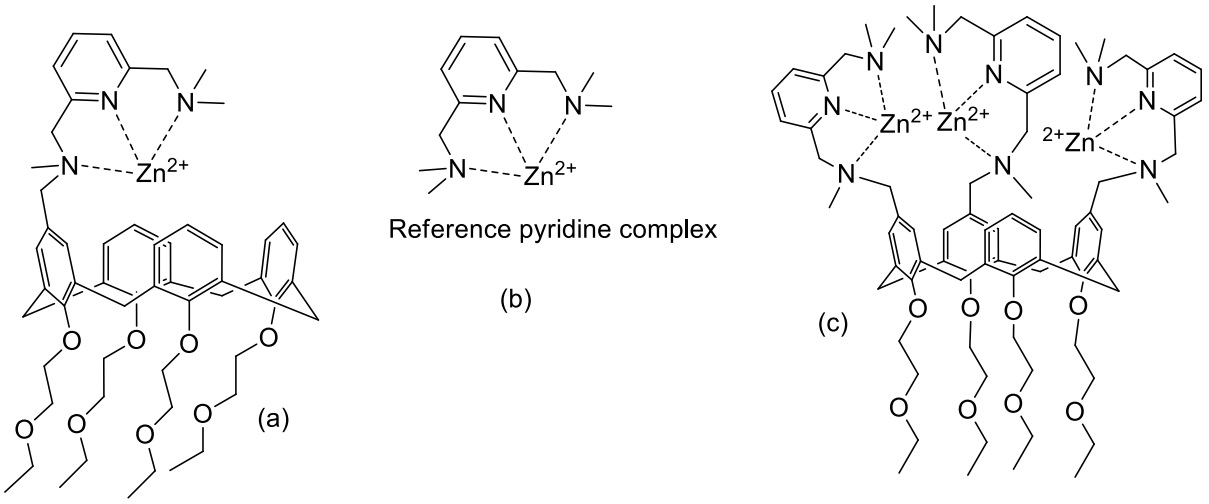


Figure 10: **a)** Mono-nuclear Zn(II) model calix[4]arene **b)** Reference pyridine complex **c)** Tri-nuclear complex

The catalytic activity of mono-nuclear complex was found to have factor of 50 lower, compared to the di-nuclear complex. A proposed mechanism was suggested for the di-nuclear Zn(II) model (**Figure 10c**).[60] The model binds to the HPNP by two point coordination. One zinc (II) centre activated the phosphoryl group and the other activated the ß-hydroxyl, later followed by a base promoted cyclisation.[61] As seen from the structure, the tri-nuclear Zn(II) complex (**Figure 11**) mimics the active site of tri-nuclear metallohydrolases. This model was an effective catalyst for cleaving RNA dinucleotides, the cooperative effect of the Zn(II) centres give high rate enhancement and important nucleobase specificity.[62] Another example of biomimetic catalyst is copper(II) complexes. There are examples where *cis*-diaqua Cu(II) complexes either mono-nuclear[63] or di-nuclear [64] act as active artificial catalysts for the cleavage of phosphate diesters.

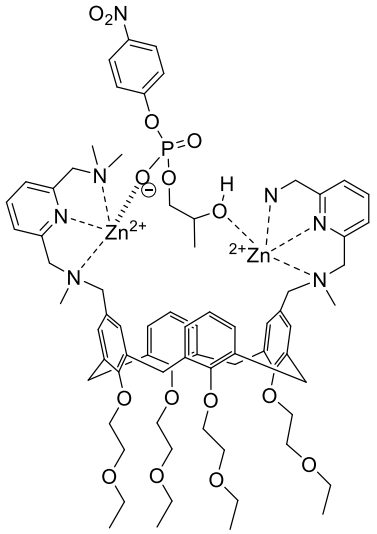


Figure 11: Proposed mechanism for HPNP cleavage by calix[4]arene based di-nuclear Zn(II) models

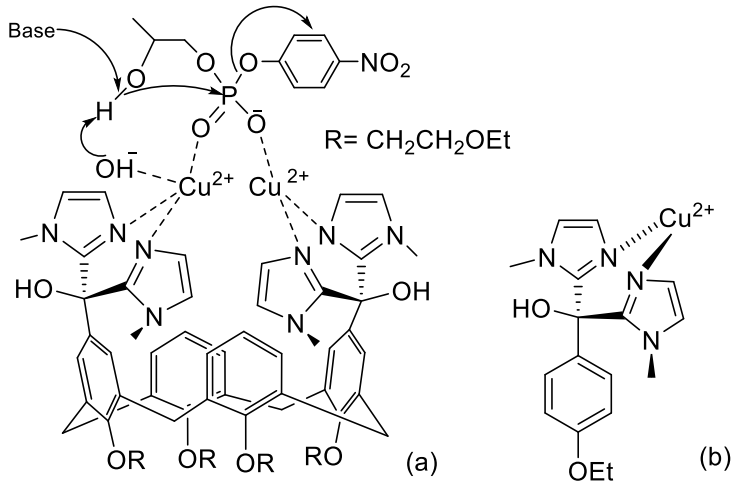
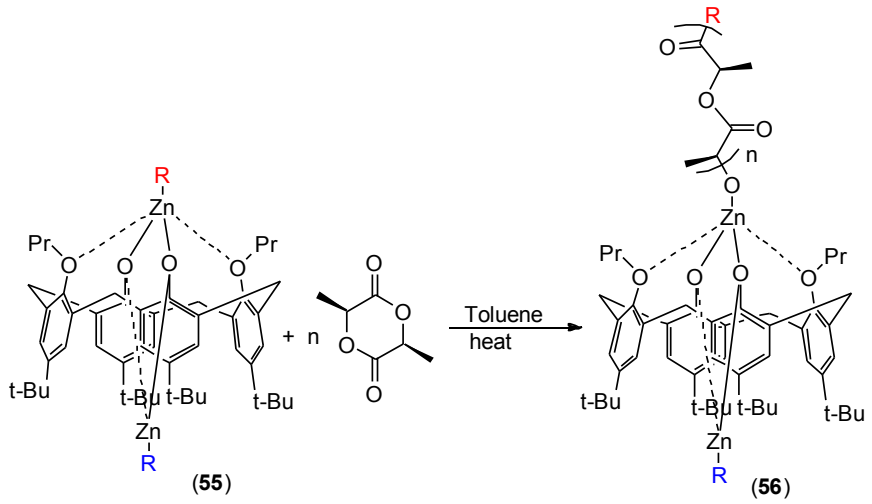


Figure 12: a) Proposed mechanism for HPNP cleavage by di-nuclear calix[4]arene-Cu(II) complex b) Mono-nuclear reference complex.

The di-nuclear calix[4]arene-Cu(II) complex [65] (**Figure 12a**) binds and cleaves the phosphate diesters HPNP and EPNP more effectively, compared to the mono-nuclear reference complex [66] (**Figure 12b**). The collaborative action of both the Cu(II) centres are preorganised on the calix[4]arene scaffold. These based artificial metalloenzymes have low pK_a of the metal(II) bound water molecules, making the artificial enzymes active under the slightly acidic to neutral conditions.[67.,68,69] More complex bifunctional calixarenes containing copper (II) chelators and hydroxymethyl groups have also been tested in transesterification reactions of HPNP. Other bi-functional calix[4]arene complexes bearing extra amino groups showed a high activity in the catalysis of intramolecular transesterification of HPNP.



Scheme 17: Ring-opening polymerisation of L- lactide.

An example of non-biomimetic was described by Vigalok and co-workers. They studied the use zinc-calix[4]arene complex in the catalysis of the ring-opening polymerisation of L-lactide (**Scheme 17**). The two zinc centres can be determined whether they participate in the catalysis. This can be done by developing a system which consists of two zinc atoms close to each other and kinetically stable.[70 ,71, 72, 73] The catalytic reaction can indicate whether a single-site mechanism can operate in a bimetallic zinc system, if one the zinc centres is sterically inaccessible.[74]

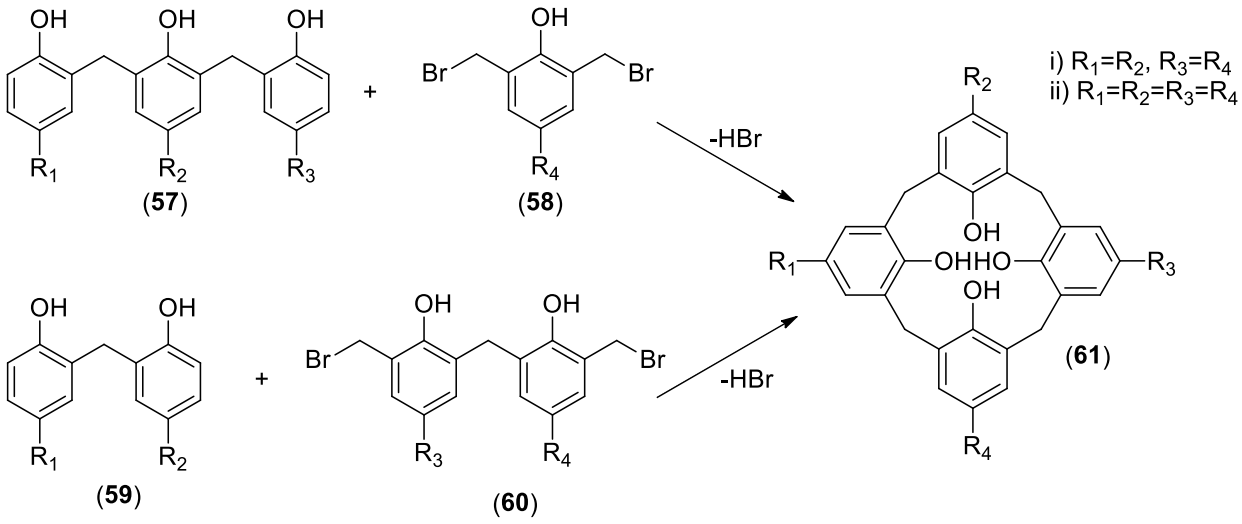
1.7. Chiral Calixarenes

The chemistry of chiral calixarenes has received great interest in recent years, as it is important to develop new chiral receptors for asymmetric recognition and gives potent tools for understanding the stereochemistry of biochemical systems. A variety of calixarenes containing chiral residues at either the *exo* or *endo* rim have been prepared as chiral receptors and catalysts.[75, 76] Achieving chirality in a calixarene has been accomplished by attaching a chiral group to the framework and by establishing a dissymmetric or asymmetric set of aryl moieties in the cyclic array of the scaffold. Attaching a chiral moiety at the *endo* rim can usually be accomplished *via* esterification and etherification. Synthesising inherently chiral calixarenes is more challenging compared to simply attaching a chiral moiety. This can be done by substituting on either *endo* or *exo* rim, to establish ABCD, AABC and ABAC pattern of aryl groups.[77] Certain AABC calixarene with groups at the *endo* rim have been resolved into enantiomers by chromatography in chiral stationary phase.[78]

Inherently chirality was originally discovered by Gutsche during a chemical modification. It involved the asymmetric arrangement of achiral groups on the bowl-shaped calix[4]arene scaffold, which resulted in an interesting product with holistic chirality.[79] Böhmer described the different types of 'inherently chiral' calixarene.[80] .

a) **Asymmetric Calix[4]arenes with Different Phenolic Units**

They attempted to prepare calix[4]arene with three (AABC) or four different *p*-substituted phenolic units.



Scheme 18: Preparation of calix[4]arene *via* [3+1] and [2+2] method.

These molecules can be obtained by fragment condensation of the appropriate trimers with *bis*-bromomethylated phenols [3+1] or dimers with *bis*-bromomethylated compounds [2+2]. By preventing racemisation, stable enantiomers can be obtained. This can be done by introducing large residues on the phenolic oxygen atoms. The OH groups must be converted to a *cone*-derivative to prevent any problems (**Scheme 18**).

b) **Calix[4]arenes with a Single *m*-Substituted Phenolic Unit**

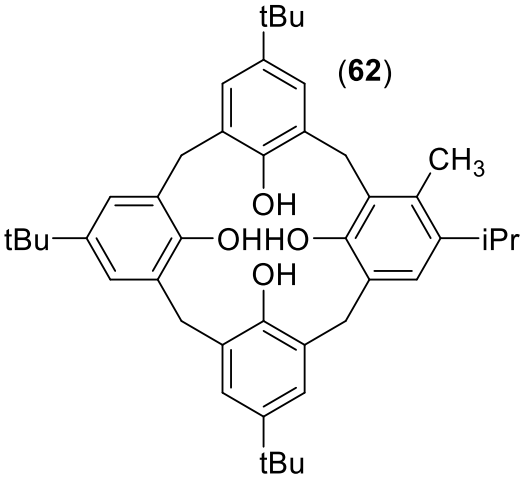


Figure 13:Calix[4]arenes with a single *m*-substituted phenolic unit.

By introducing a single *meta*-substituted phenolic units, they can form asymmetric calix[4]arenes. The compounds have been synthesized by [3+1] fragment condensation. From compound **62** in **figure 13** the tetrapropyl ether can be prepared in the *cone* conformation. It can be resolved *via* chromatography on chiral stationary phases, which gave the enantiomers of an inherently chiral calixarene.[81]

Böhmer proposed the term "inherently chiral" to describe asymmetric calix[4]arenes.[82] The term was defined by Szumna as "inherent chirality arises from the introduction of a curvature in an ideal planar structure that is devoid of perpendicular symmetry planes in its bidimensional representation".[83, 84]

c) **Asymmetric Calix[4]arenes by *O*-Alkylation with Achiral Residues**

Two different residues are needed for a syn arrangement of the *O*-alkyl groups, however at an anti position, more possibilities will be available. Compounds **64** and **65** with unique *O*-alkyl groups are asymmetric or dissymmetric.

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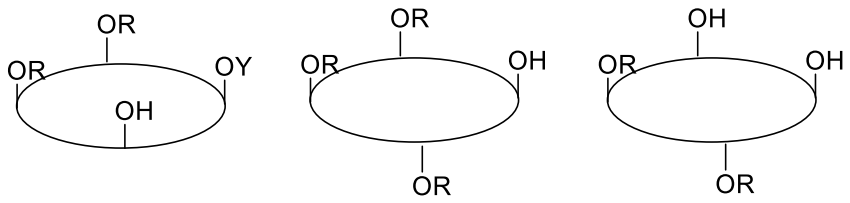


(**63**) (**64**) (**65**)

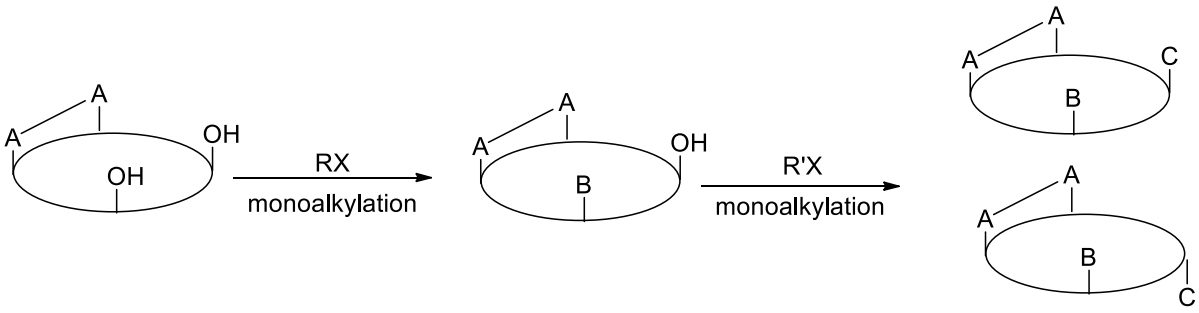
Figure 14: Asymmetric calix[4]arenes by *O*-alkylation with achiral residues.

Some of the multiple *O*-alkylation products can be described as cone, partial cone, 1,2- and 1,3-alternate; they can only be used for the tetraethers.[85] The mutual arrangement of the *O*-alkyl groups can describe the essential conformations. For compound **63**, cone and partial cone conformations are possible, for **64** partial cone and 1,2-alternate and for **65** all conformations are possible except for the cone conformation. Configurational isomerism, including cis/trans and optical isomerism may occur in calixarenes. The conformations can be locked by adding bulkier groups at the *endo* rim of the calixarene.

A review by Zheng *et al.* described the advances in syntheses, structures and applications of inherently chiral calixarenes.[86] Two types of chirality was described, the "acquired chirality" and "inherent chirality". Acquired chirality occurs due to a chiral group. It is an enantiomerically pure chiral calixarene that can be obtained *via* direct introduction of chiral compounds such as BINOL, chiral epoxides, amino alcohols etc. onto either the upper or lower rim of the calixarene.[87] Inherently chiral was previously described by Böhmer; the definition is now described as "a range of chiral molecules whose chirality comes from the introduction of a curvature in an ideal planar structure that is free of perpendicular symmetry planes in its bidimensional representation".[88,89] They also discussed about non-stereoselective synthesis, which can be done by using achiral reactants and conditions to afford the racemic products. To obtain enantiopure products, optical resolution will be necessary. It is usually realised by HPLC method with chiral or nonchiral columns. It is preferable to achieve

chemical resolution using a simple column chromatography, thereby allowing manageable scale-ups.

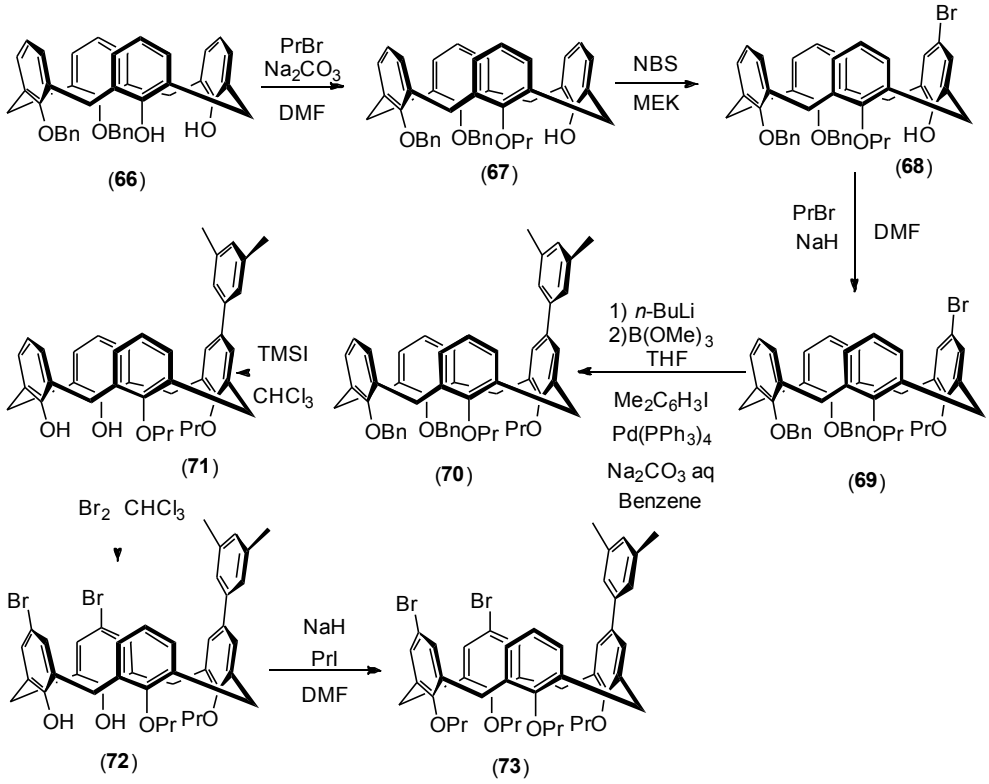
Huang *et al*. reported the synthesis of a range of tri-*O*-alkylated and tetra-*O*-alkylated inherently chiral calix[4]crown derivatives in a cone and partial cone conformations *via* sequential alkylation (**Scheme 19**). (*S*)-BINOL was used as the chiral auxiliary to form diasteroisomers, which could be separated by simple column chromatography. The enantiomers were obtained by hydrolysis of the separated diastereoisomers.



Scheme 19: Inherently chiral calix[4]arene *via* sequential alkylation.

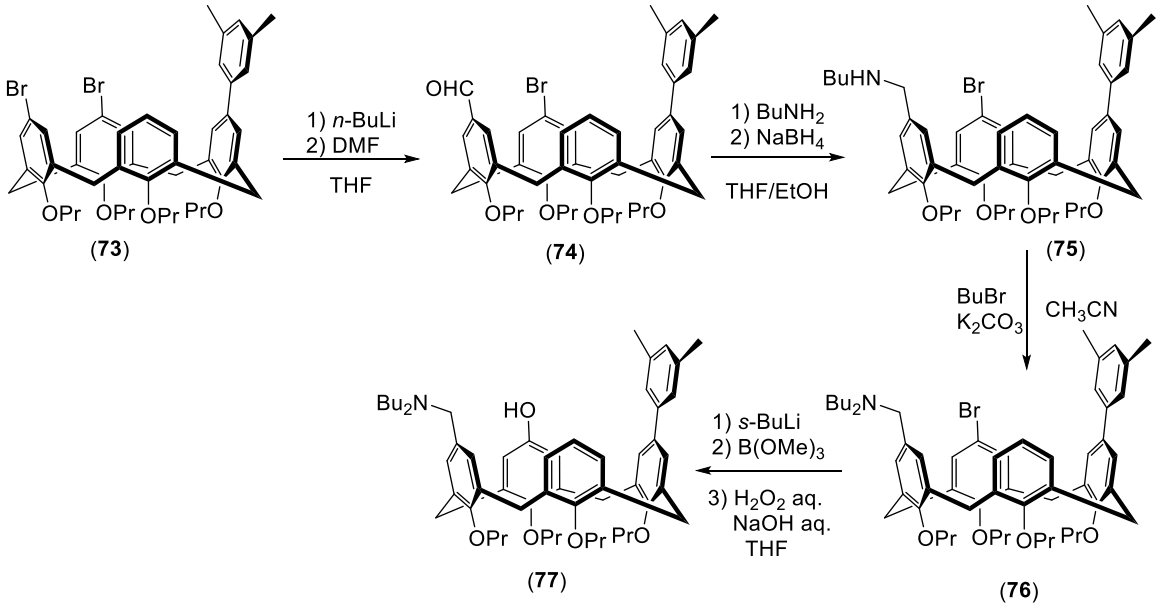
They discussed the relationship between the structure and optical resolution. To obtain better resolution, both the carboxylic and 1,2-crown ether group must be convergent, by having bigger crown ether groups reduces optical resolution of the tri-*O*-alkylated cone conformers and lastly complete alkylation makes the narrow rim bulkier, which is an advantage on optical resolution.[90,91]

One of the successful synthetic route among the others to prepare inherently chiral calix[4]arenes with an ABCD substitution pattern at the *exo* rim was developed by Shimizu *et al*.[92] The synthesis begins with the preparation the intermediate 5,11-dibromo-17-(3,5-dimethylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene in an 8 step reaction. The starting material **66** was readily made using Shimizu *et al.'s* procedure. Compound **67** was readily prepared using propyl bromide in the presence of Na_2CO_3 as the base for a selective mono-*O*-alkylation, followed by the selective bromination at the para position to afford compound **69**. After *O*-propylation, compound **69** was treated with n-BuLi where the lithiated compound was converted into the corresponding boronate by treating it with $B(OMe)_3$. This was followed by a Suzuki- Miyaura coupling reaction with 1-iodo-3,5-dimethylbenzene to afford compound **70**. The following step was the selective dealkylation of the benzyl groups at the *endo* rim by treatment with trimethylsilyl iodide to afford compound **71**.



Scheme 20: Preparation of inherently chiral calix[4]arene by Shimizu *et al.*

After the selective dibromination at the para positions to afford compound **72**, which was followed by the *O*-alkylation with propyl iodide with NaH to produce compound **73**.



Scheme 21: Preparation of inherently chiral calix[4]arene by Shimizu *et al.*

Compound **73** was treated with *n*-BuLi followed by *N,N*-dimethylformamide to obtain **74**, which was treated with aqueous hydrochloric acid after lithiation. A reductive amination of the formyl group with *n*-butylamine gave the secondary amine, followed by formation of a tertiary amine **75**, when treated with *n*-butyl bromide **75**. **76** was lithiated and treated with $B(OMe)_3$ to afford the boronate. The boronate was then oxidised by H_2O_2 in a one-pot synthesis to produce the target calix[4]arene as racemates. Shimizu and co-workers were successful in producing multifunctionalised inherently chiral ABDC-type calix[4]arenes, they used compound **77** as an organocatalyst in asymmetric Michael addition reactions of thiophenols and resolved into optically pure enantiomers

1.8. Aim Of The Project

The aim of the project is to functionalise the upper rim of the calix[4]arene by establishing an ABCD (**78**) and AABC (**79**) patterns (**figure 15**). We developed a plan where we can achieve chirality *via* cross-coupling reactions such as Sonogashira and Suzuki cross-coupling reactions as shown on **Scheme 22**.

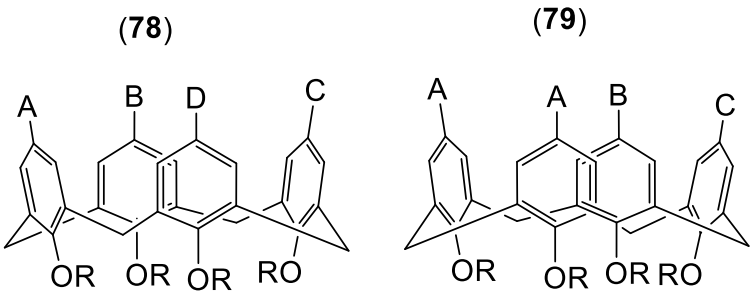
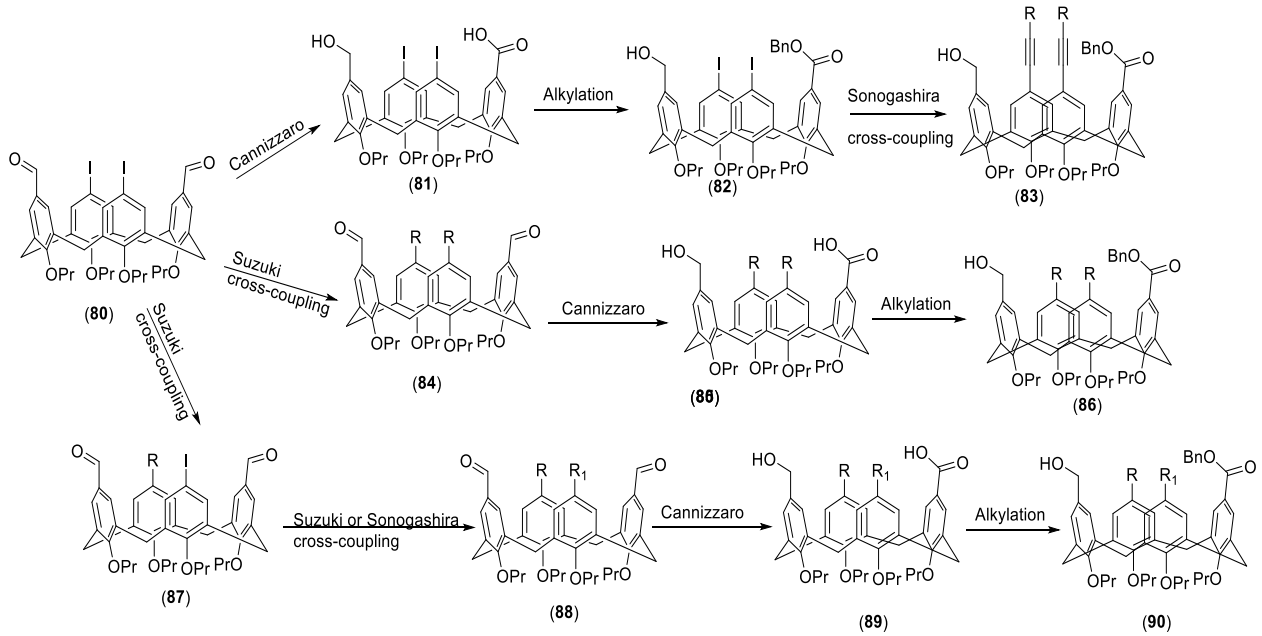


Figure 15: Inherently chiral calix[4]arene in the cone conformation.



Scheme 22: Plan of the synthesis route.

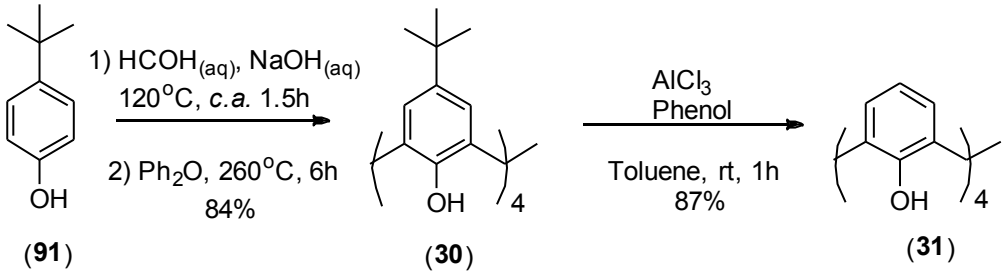
As **scheme 22** shows, we devised a route on how to achieve and obtain our desired compounds. Compound **80** will be prepared using Ungaro *et al.'s* method of halogenation and then following the steps to afford the final compounds.

Chapter 2

Results and Discussion

2. The synthesis of the tetra-hydroxycalix[4]arene

To begin the project, we required a reproducible protocol for the synthesis of the tetra-hydroxycalix[4]arene (**31**). Following the literature procedure of Gutsche *et al*, para-tert-butylcalix[4]arene (**30**) was synthesised on a 100 g scale *via* the base catalysed condensation of para-*tert*-butylphenol (**91**) and formaldehyde in aqueous sodium hydroxide. The pure compound (**30**) was isolated as an off-white solid in 84% yield. The removal of the *tert*-butyl groups to produce the desired calixarene (**31**) was affected by treatment with aluminium chloride and phenol in a retro Friedel Crafts reaction, where phenol acts as an acceptor molecule. The reaction was carried out on a 100 g scale to afford our desired compound (**31**) in 87% yield.



Scheme 23: Synthesis of the tetra-hydroxycalix[4]arene.

The ^{1}H-NMR spectrum (**figure 16**) of **31** confirmed the loss of the *tert*-butyl groups, and showed the aromatic protons at 7.05 ppm and 6.73 ppm as a doublet and triplet. Residual solvents dichloromethane, methanol and acetone were present.

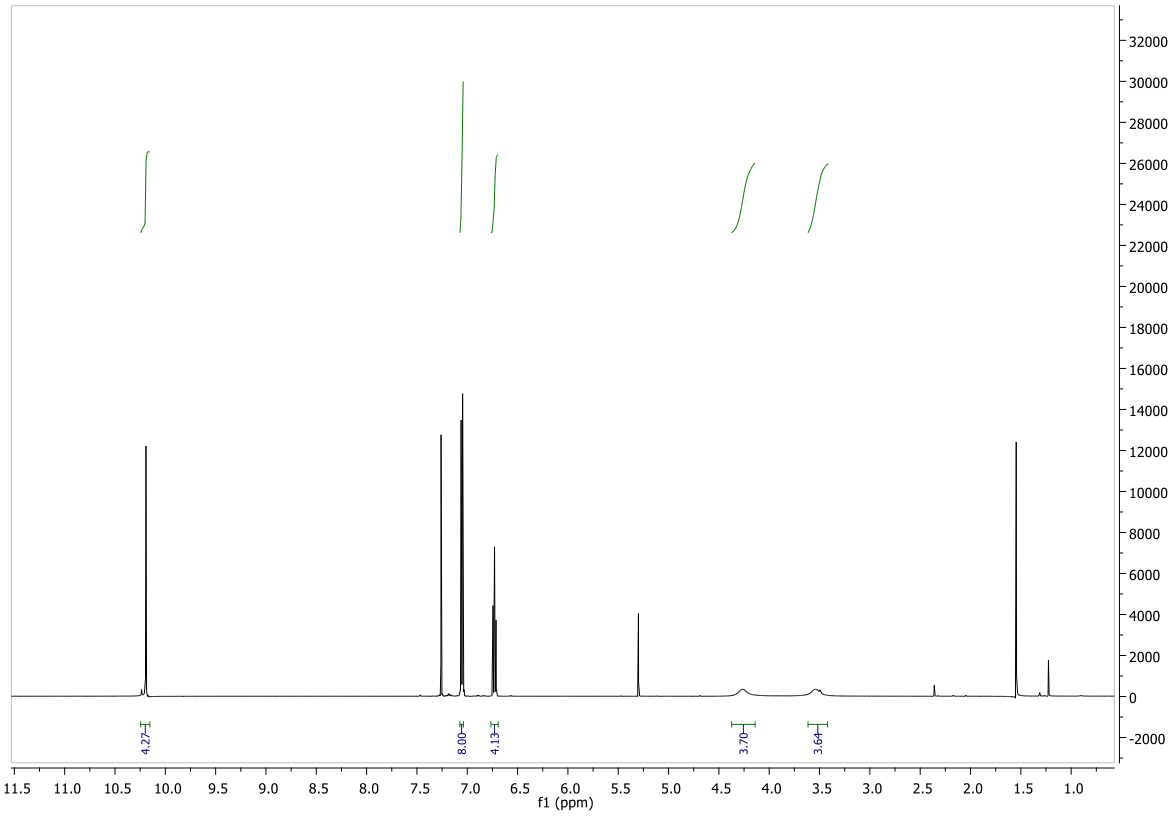
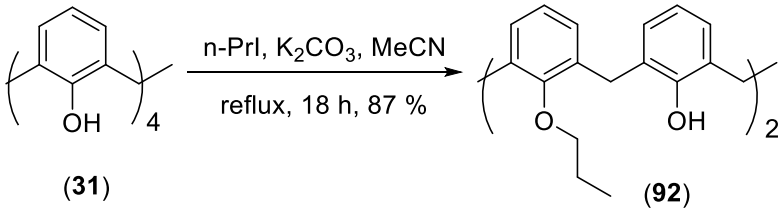


Figure 16: ^{1}H-NMR of compound **93**.

2.1. The synthesis of 1,3-diformylcalix[4]arene

Using the tetra-hydroxycalix[4]arene, the phenolic residues were selectively substituted at the 1,3 positions of the calix[4]arene. This was readily achieved with *n*-propyl iodide and potassium carbonate as the base in refluxing acetonitrile. The reaction was carried out on 14g scale to afford the product in 87% yield after recrystallisation from $CHCl_3$/MeOH (**92**). The ^{1}H-NMR spectrum matched the data in the literature procedure. It also indicated that the product is held in the cone conformation by hydrogen bonding at the lower-rim as shown by the doublets for the methylene bridges at 4.31 and 3.37 ppm.

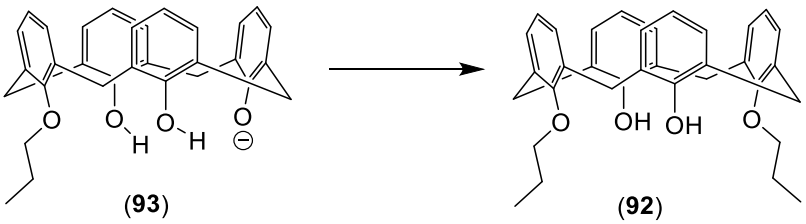


(**31**) (**92**)

Scheme 24: Alkylation of the OH groups

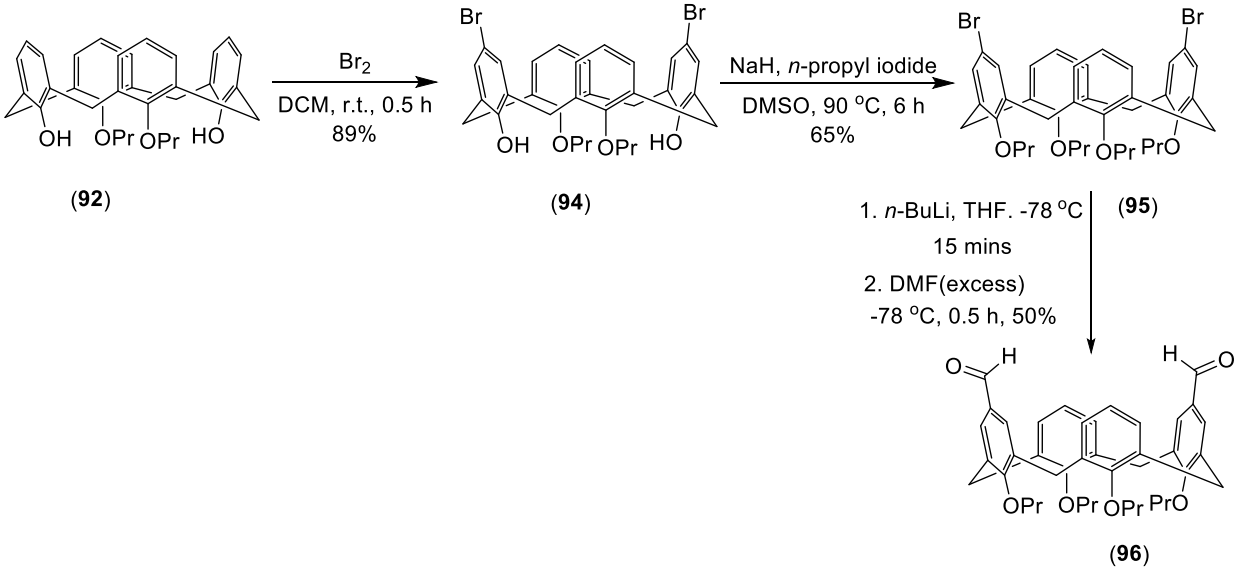
A consideration of the mechanism allows for some rationalisation of this selectivity. After the monoalkylation of the tetra-hydroxycalix[4]arene, proton abstraction from the hydroxyl

function group opposite the alkoxy group produces an oxyanion (**93**), stabilised by two hydrogen bonds. This interaction holds the calixarene in the cone conformation and directs the second electrophile. [93]



Scheme 25: Mechanism of the alkylation.

Larsen *et al.* reported the synthesis of the di-formyl calix[4]arene **96** *via* a halogen lithium exchange of the 1,3-dibromo-tetra-propoxycalix[4]arene followed by reaction with *N,N*-dimethylformamide in 75% yield.[94] As this compound represents a key intermediate in our synthesis of inherently chiral calix[4]arenes, we were encouraged by the apparent simplicity of this procedure and the potential for obtaining this material in a high yield. Thus we opted to employ their synthetic route for the synthesis of **96**. Following the literature procedure, **93** was treated with bromine in dichloromethane solution for 0.5 hours to afford the 5,17-dibromo-26,28-dihydroxy-25,27-bis(propyloxy)calix[4]arene **94** in 89% yield.[95] Subsequent propylation with sodium hydride and *n*-propyl iodide in DMSO afforded our desired dibromo precursor **95** in 65% yield. The ^{1}H-NMR spectrum of **95** indicated that the product was fixed in the cone conformation, as shown by the doublets at 4.37 and 3.08 ppm for the protons of the methylene bridges.



Scheme 26: Synthesis of the 1,3-diformylcalix[4]arene.

We were now in a position to attempt the formylation reaction as described by Larsen *et al.* Performing the reaction on a 1 g scale, we were delighted to find that **96** could be obtained in a 50% yield after recrystallisation from *n*-hexane. The ^{1}H-NMR spectrum (**Figure 17**) clearly shows the formyl resonance at 9.44 ppm, indicating that the reaction had proceeded as expected.

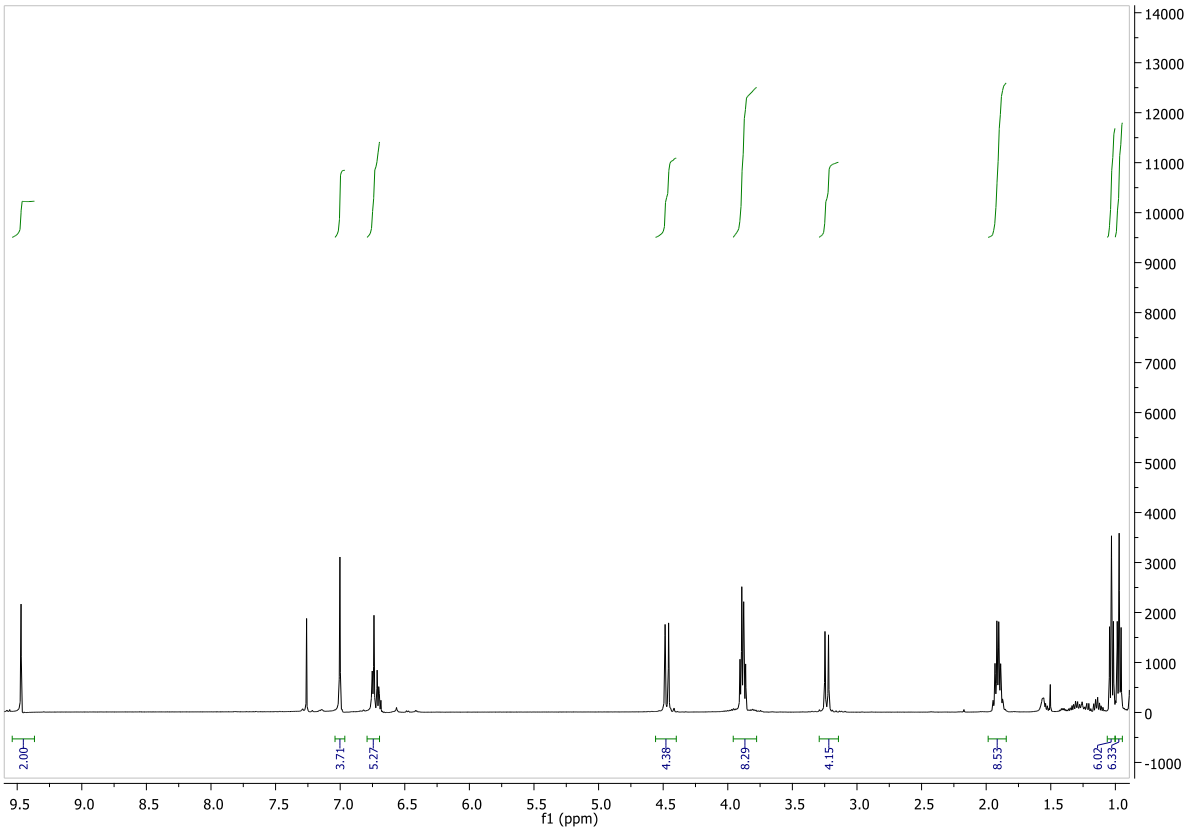
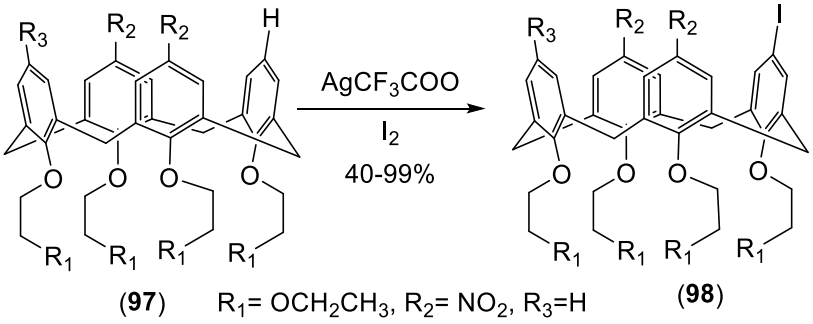


Figure 17: ^{1}H-NMR of compound **96**.

2.2. The synthesis of *bis-1,3*-aldehyde-*bis-2,4*-iodo calix[4]arene

With a suitable route to the 1,3-diformylcalix[4]arene (**96**) identified, we next required a suitable procedure for the halogenation (*i.e.* iodination or bromination) of the two remaining aromatic rings - since with such a functionalised calix[4]arene, palladium catalysed cross-coupling chemistry could be performed. To date, only a handful of protocols for the halogenation of calix[4]arenes have been reported. However in one notable example, Ungaro and co-workers were able to selectively iodinate the upper rim in the presence of a range of other functionalities (**Scheme 25**).



Scheme 27: iodination by Ungaro *et al.*

They found that treating their substrates with 1-1.5 equivalents of silver trifluoroacetate and 1-1.5 equivalents of iodine in chloroform afforded the desired compounds in good yields (*i.e.* 40-99%) after heating in refluxing chloroform overnight. Thus we decided to see if these conditions were amenable to our system, although we opted to employ dichloromethane instead of chloroform for its lower toxicity. Heating the diformyl calix[4]arene with 2.2 equivalents of silver trifluoroacetate and 2 equivalents of iodine in dichloromethane under microwave irradiation (90 °C, 1.5 hours) afforded our desired product **102** in excellent yield (*i.e.* 97 %) and purity (**Figure 18**).

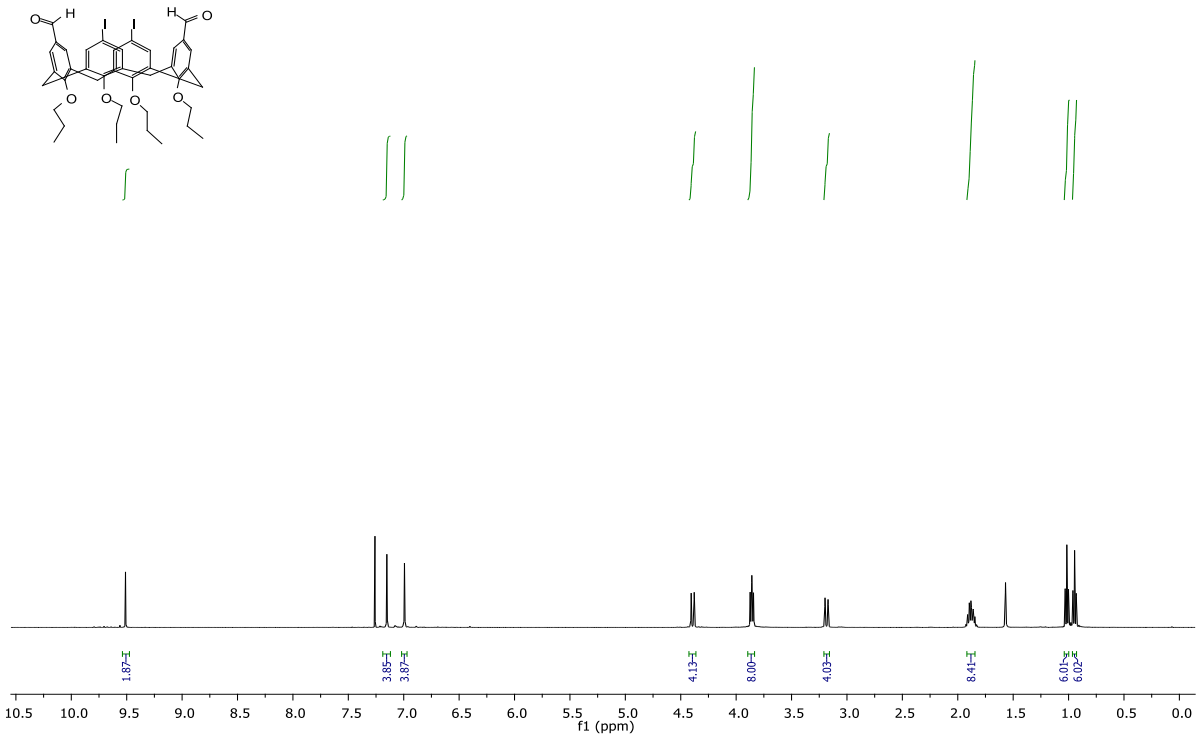
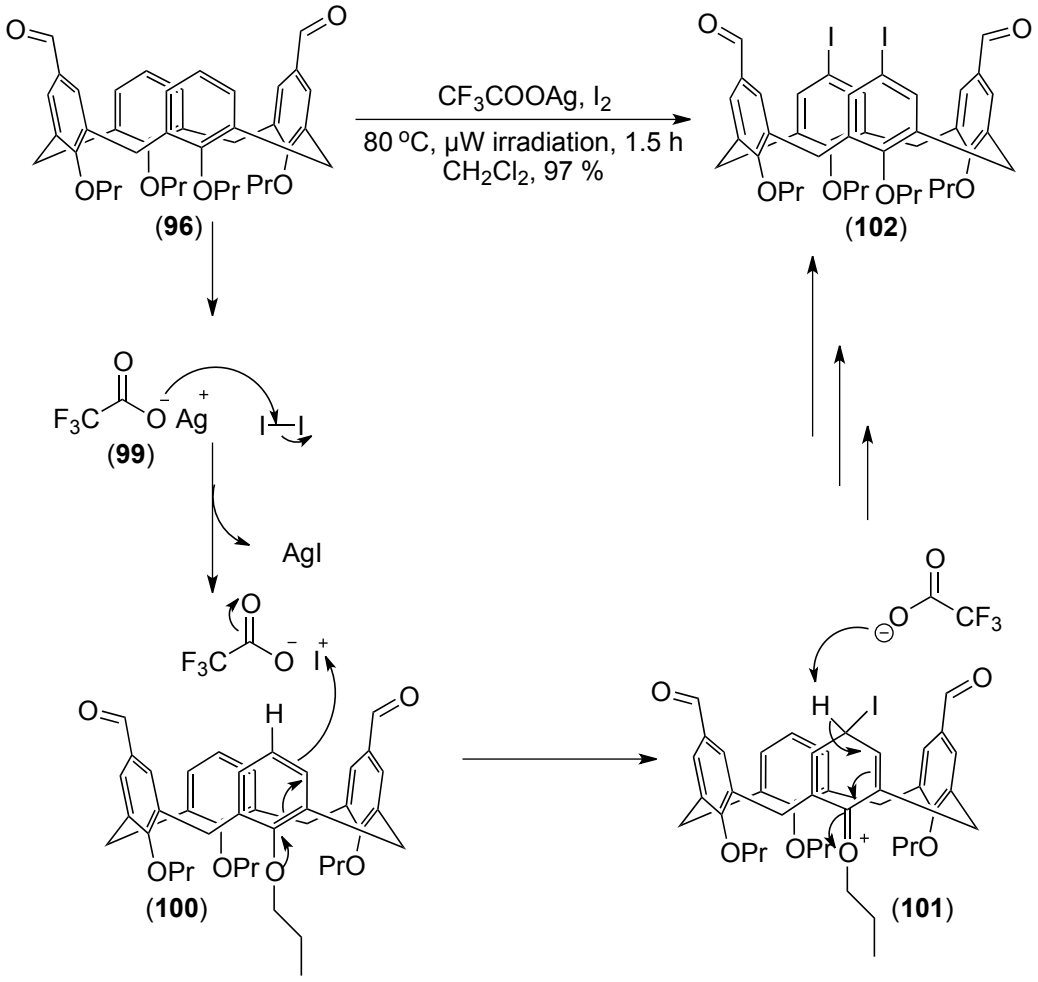


Figure 18: ^{1}H-NMR of compound **102**.



Scheme 28: Conditions and mechanism for the halogenation of compound **96**.

The proposed mechanism (**Scheme 26**) involves the initial reaction of silver trifluoroacetate with iodine to form silver iodide and a highly electrophilic iodine species (**99a**). Electrophilic aromatic substitution then follows on both free para positions to afford the doubly substituted iodinated calixarene **102**.

2.3. Cannizzaro reaction on the *bis-1,3*-aldehyde-*bis-2,4*-iodo calix[4]arene

In 1853, Stanislao Cannizzaro discovered the base-induced disproportionation reaction of benzaldehyde to afford benzoic acid and benzyl alcohol as part of his studies into the reactivity of benzaldehydes. This Cannizzaro reaction, as it became known, was considered an important synthetic procedure for the reduction of aldehydes to alcohols until the development of more sophisticated reagents such as $LiAlH_4$ in 1946. It still finds synthetic utility however, with one particularly interesting example reported by the group of Casnati in

2012. In their publication, Casnati *et al.* disclosed the highly efficient and selective intramolecular reaction between the formyl groups of the *cone*-calix[4]arene to afford the corresponding product of, what was proposed to be, an intramolecular disproportionation.[96]

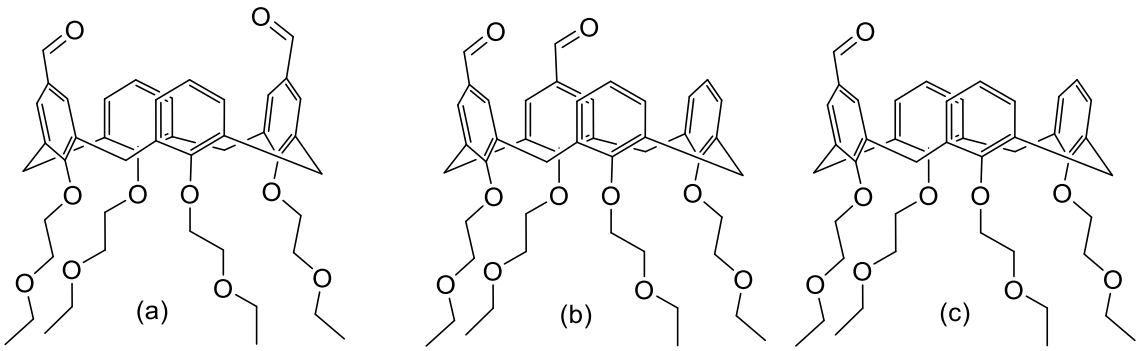
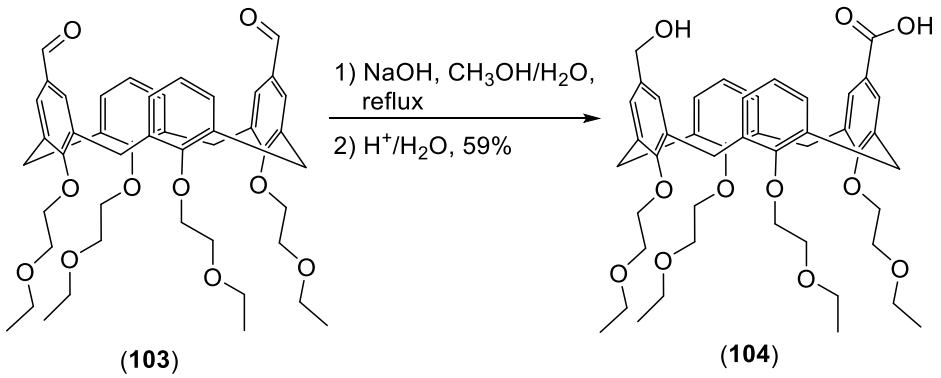


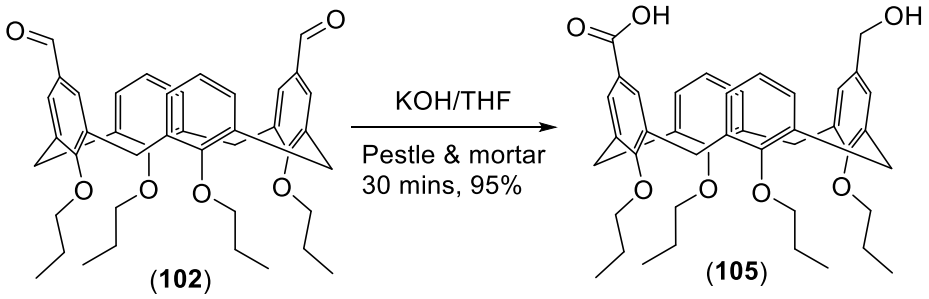
Figure 19: **a)** 1,3-distal *cone*-calix[4]arene **b)** 1,2-vicinal regioisomer **c)** monoaldehyde.

Performing the reaction on 1,3-distal *cone*-calix[4]arene **a**, 1,2-vicinal aldehyde **b** and the monoaldehyde **c** gave further evidence in support of this conclusion, since when the vicinal di-aldehyde or mono-aldehydes were subjected to the reaction conditions, only starting materials were recovered (**Figure 19**).



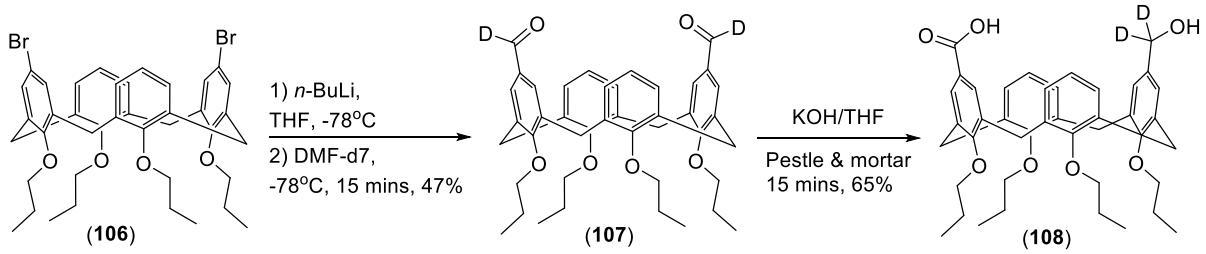
Scheme 29: Intramolecular Cannizzaro in aqueous methanol.

The failure of the 1,2-vicinal dialdehyde to react under these conditions also illustrates the importance of the correct geometry between the two formyl groups. When the reaction is performed on the 1,3-distal calix[4]arene, the desired product could be isolated in a 59% yield (**104**).[97] Intrigued by the possibility of employing this method in our preparation of inherently chiral calix[4]arenes, we began investigating this reaction in our group. Luis Martinez was able to show that this reaction could be performed under solvent free conditions by simply grinding 1,3-diformyl calix[4]arene **102** with potassium hydroxide in a pestle and mortar (**Scheme 28**).[98] This resulted in the formation of **108** in high yield (*i.e.* 95 %), and much reduced reaction time (*i.e.* 30 minutes).



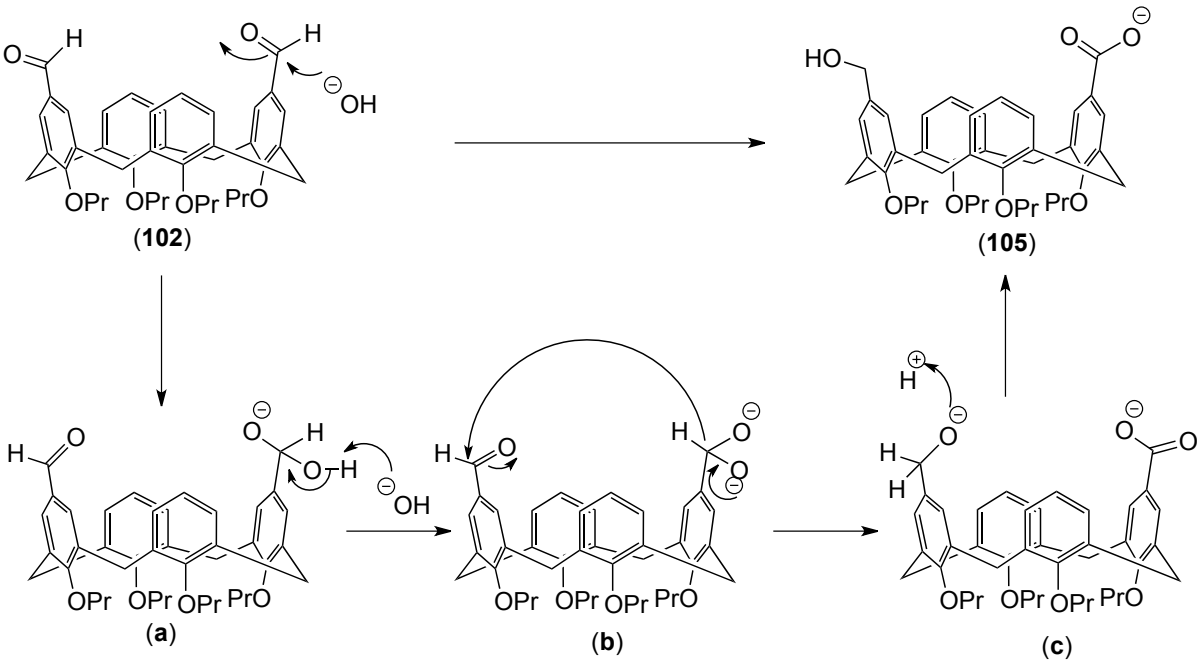
Scheme 30: Solvent free Cannizzaro performed by Luis Martinez

Keen to establish whether the intramolecular nature of this reaction was retained under the solvent-free regime, a deuteration experiment was performed in which an equimolar mixture of deuterated and proteated calixarenes were reacted together. Analysing the product distribution by ^{2}H-NMR spectroscopy, it was found that the single peak corresponding to the deuterium labelled formyl groups was replaced by a single peak consistent with the chemical shift of deuterium attached to a benzylic carbon. These results are consistent with an intramolecular process, since if an intermolecular process were operational, a mixture of mono and bis deuterated calix[4]arenes would be expected (**Scheme 29**)



Scheme 31: Synthesis and intramolecular Cannizzaro reaction of deuterated *bis*-formyl calix[4]arene (**108**).

With these improved conditions established within our group, we were able to carry out this reaction on our newly-synthesised *bis*-1,3-aldehyde-*bis*-2,4-iodo calix[4]arene **102** (**Scheme 28**). We were apprehensive given the large size of the two iodine atoms, and were concerned they may slow or even inhibit our reaction entirely. However, we were delighted to find that only a slightly extended reaction time (*i.e.* 0.5-1 h) was required to furnish our desired Cannizzaro product in high yield (*i.e.* 95%) and purity **105**(**Scheme 30**).



Scheme 32: Mechanism of Cannizzaro reaction.

The reaction begins with the attack of the hydroxide anion onto the carbonyl group of **102**, followed by a second deprotonation and intramolecular hydride transfer (**b**). Protonation upon work-up with aqueous 1M HCl forms the alcohol/carboxylic acid **105**, the structure of which was confirmed *via* ^{1}H-NMR, ^{13}C-NMR, FTIR and mass spectrometery (**Figure 19**).

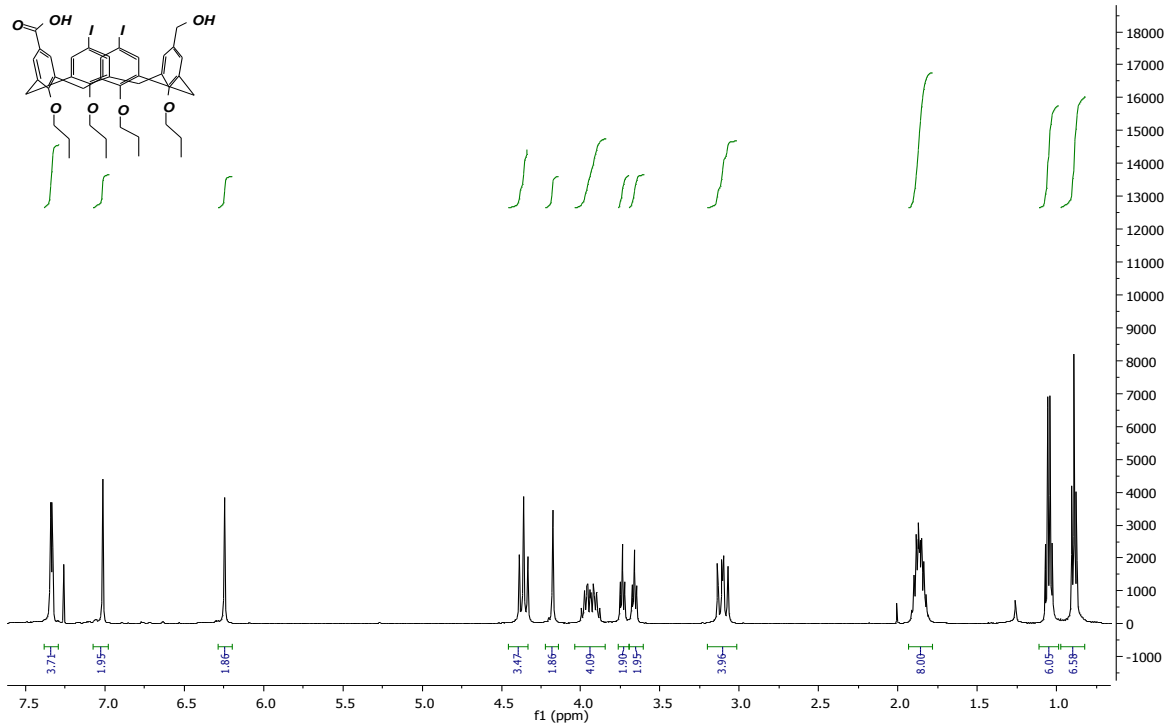


Figure 19: ^{1}H-NMR of pure Cannizzaro compound **105**.

Although we were confident in our structural assignment, we sought further confirmation *via* x-ray crystallography. After several attempts utilising different solvents and crystallisation methods, X-ray quality crystals of **105** were finally obtained from pentane/DCM. The X-ray crystal structure of our Cannizzaro compound **105** is illustrated below (**Figure 20**).

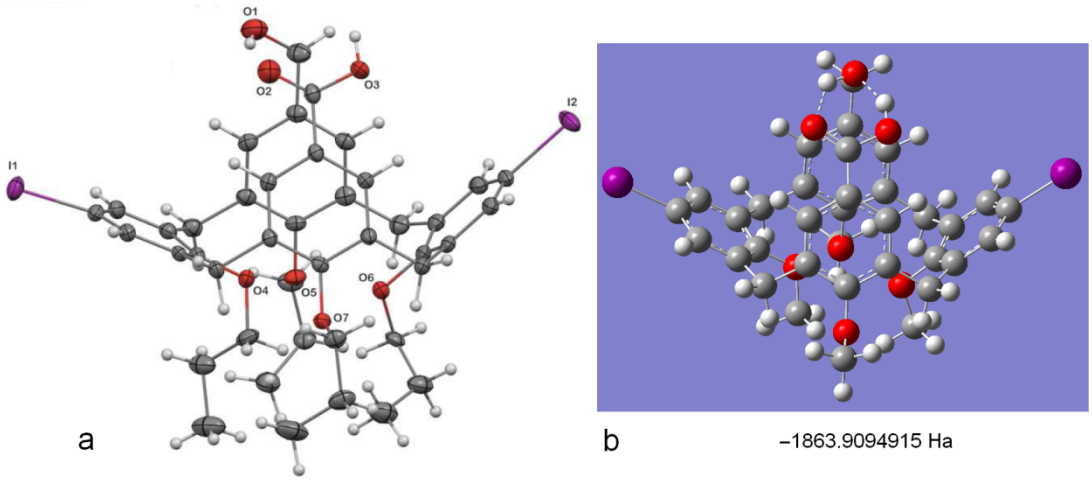
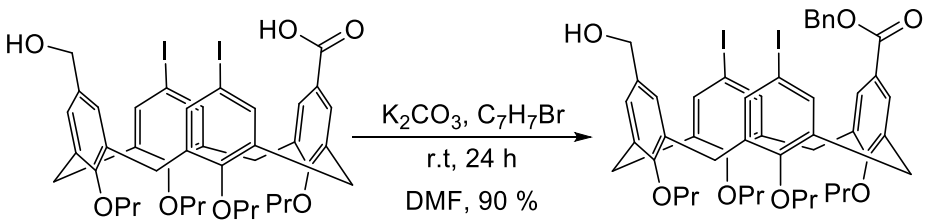


Figure 20: The X-Ray structure of compound **105**.

The iodine atoms are coloured in purple and oxygen atoms in red. In addition, the crystallographer (Dr Mateusz B. Pitak – UK National Crystallography Service) was able to identify a fascinating intramolecular hydrogen bonding arrangement (**Figure 20b**). The hydrogen bonding can be seen between the primary alcohol and the carboxylic acid, with a bond length of 2Å. Due to this intramolecular interaction, the calixarene takes on the so-called pinched cone conformation.

2.4. Alkylation of the carboxylic Acid

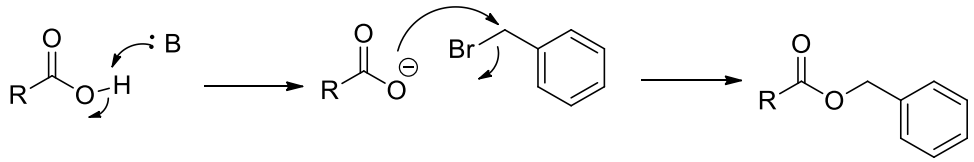
Allyl and benzyl groups are commonly used for the protection of carboxylic acid moieties for ease of synthesis and convenient deprotection. As the aim of our project was to develop a high yielding, operationally simple synthetic route towards ABCD functionalised calix[4]arenes, we opted to protect the carboxylic acid functionality as a benzyl ester at this stage. Since molecules containing this functionality typically produce broad bands on silica gel chromatography, benzyl protection would allow for a more straightforward purification. We searched the literature for an appropriate procedure, and identified a combination of benzyl bromide and potassium carbonate in DMF as common reagents to affect this transformation. Thus, stirring a mixture of our calix[4]arene derivative **105** with 3 equivalents of potassium carbonate and 1.2 equivalents of benzyl bromide in DMF overnight afforded a 90% yield of the corresponding benzyl ester **109** (**Scheme 30**).



(**105**) (**109**)

Scheme 33: Alkylation of the carboxylic acid to produce the benzyl ester.

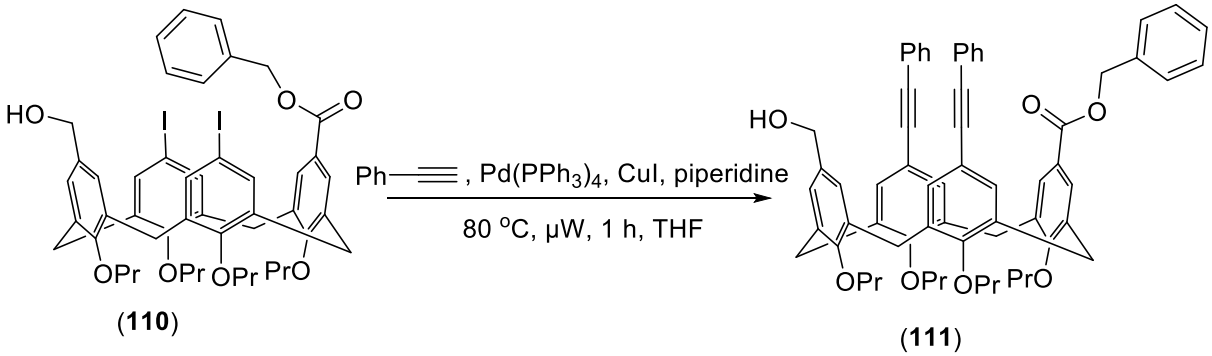
The reaction proceeds *via* nucleophilic attack of the carboxylate anion onto benzyl bromide in an S_N1 process (**Scheme 31**).



Scheme 34: Mechanism of the benzylation reaction.

We were pleased that this protection proceeded in a high yield, and also that the product could be readily purified *via* column chromatography, as these properties would be important for the next stage of our synthesis – the investigations into cross-coupling reactions at the upper-rim.

2.5. Sonogashira cross-coupling reaction

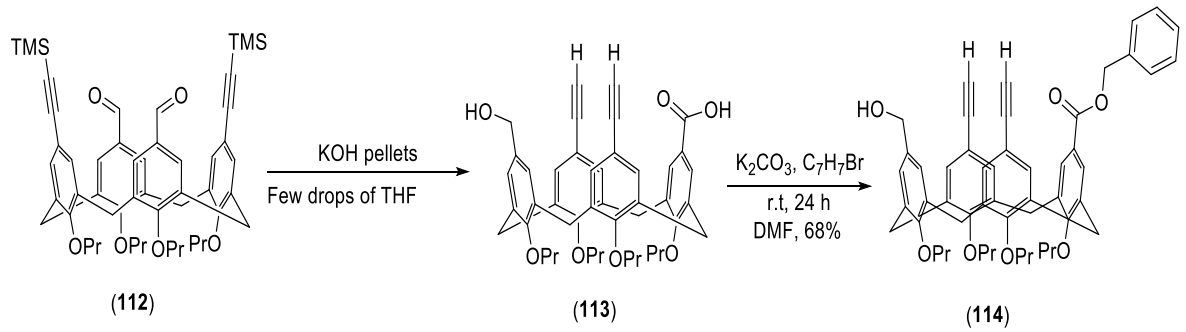


(**110**) (**111**)

Scheme 35: Sonogashira cross-coupling reaction.

Following our synthesis plan outlined in **Scheme 20** to achieve an AABC pattern *via* cross-coupling reactions, the next stage was to investigate conditions for the Sonogashira coupling of a range of aryl alkynes which would furnish our desired AABC calix[4]arenes in high yields. Employing standard conditions for this reaction commonly used in our group, the calix[4]arene ester **110** was dissolved in anhydrous THF followed by the addition of the catalyst, *tetrakis*(triphenylphosphine) palladium(0), piperidine, copper(I) iodide and

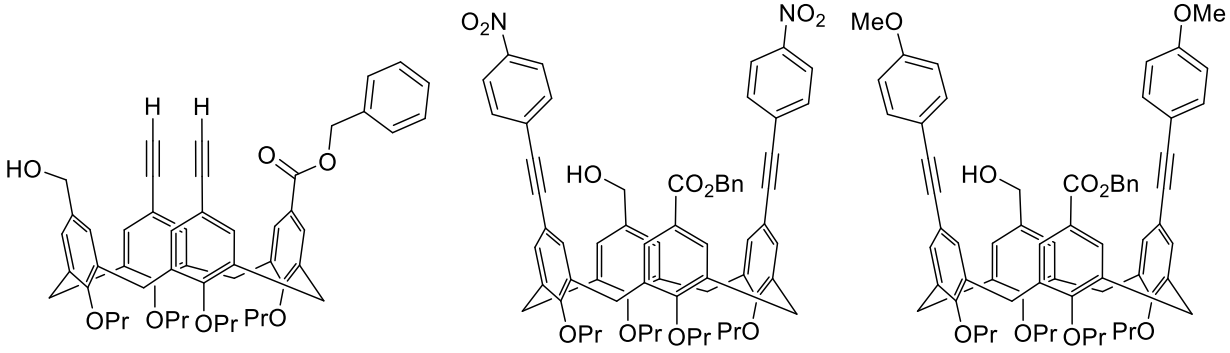
appropriate alkyne, and then heated under microwave irradiation for 1 hour. The reaction proceeded smoothly, and after purification *via* silica gel chromatography, the pure products were obtained in yields between 50-78%. The bis substituted phenyl alkyne **111** for example, was obtained in an excellent 78% isolated yield. ^{1}H-NMR and ^{13}C-NMR analysis indicated that both iodine atoms had reacted, and HRMS analysis found 974.4990 for $[M + NH_4]^+$, further confirming the formation of **111**. Interested to examine how the alkyne functionalities might tolerate the conditions of the Cannizzaro reaction, we sought to prepare the bis-ethynyl calix[4]arene **114** *via* an alternative route (**Scheme 33**).



(**112**) (**113**) (**114**)

Scheme 36: Different route for the synthesis of compound **114**.

The initial Sonogashira cross-coupling was carried out on our *bis*-iodo calix[4]arene **102** using identical conditions to those already described, and TMS acetylene and the alkyne coupling partner. Interestingly, when carrying out the Cannizzaro reaction as before, the base (potassium hydroxide) was able to cleave the TMS protecting groups in addition to promoting the disproportionation reaction. A subsequent benzyl protection afforded the ether **114** in a 68% overall yield after purification *via* silica gel column chromatography.



(**114**)-68% (**115**)-64% (**116**)-50%

Figure 21: A representative scope of the compounds prepared for this study.

The Sonogashira cross-coupling reaction involves two independent catalytic cycles – one with palladium and the other with copper. The mechanism begins with oxidative addition of an organohalide to the Pd(0) species to form a Pd(II) complex (**Figure 22**).

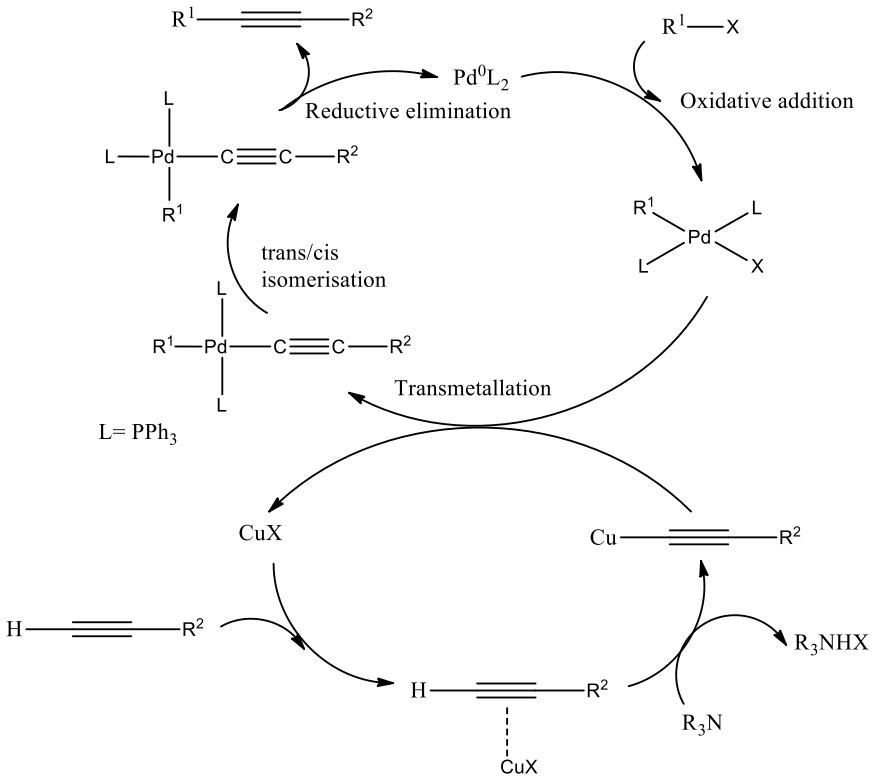


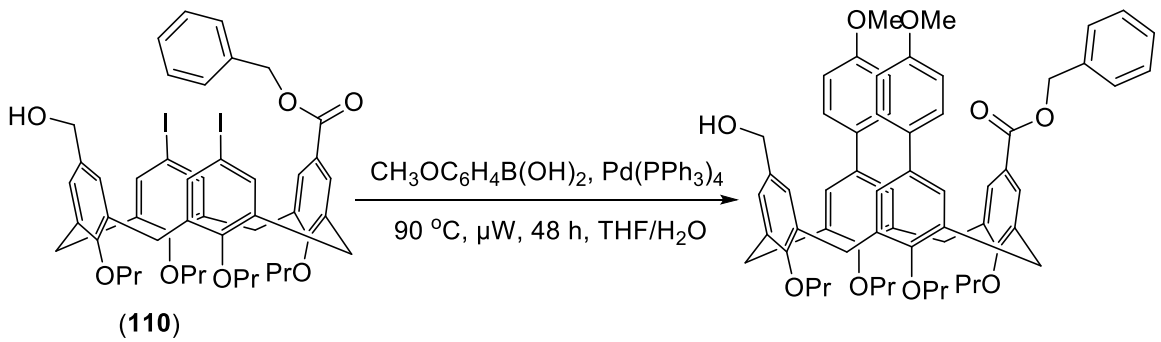
Figure 22: Mechanism of Sonogashira cross-coupling.

This is followed by transmetalation of the Pd(II) complex with the copper acetylide formed by base promoted reaction of CuI with the alkyne, and furnishes the final internal alkyne after trans/cis isomerisation and reductive elimination accompanied by the regeneration of the Pd(0) catalyst.

2.6. Suzuki cross-coupling reaction

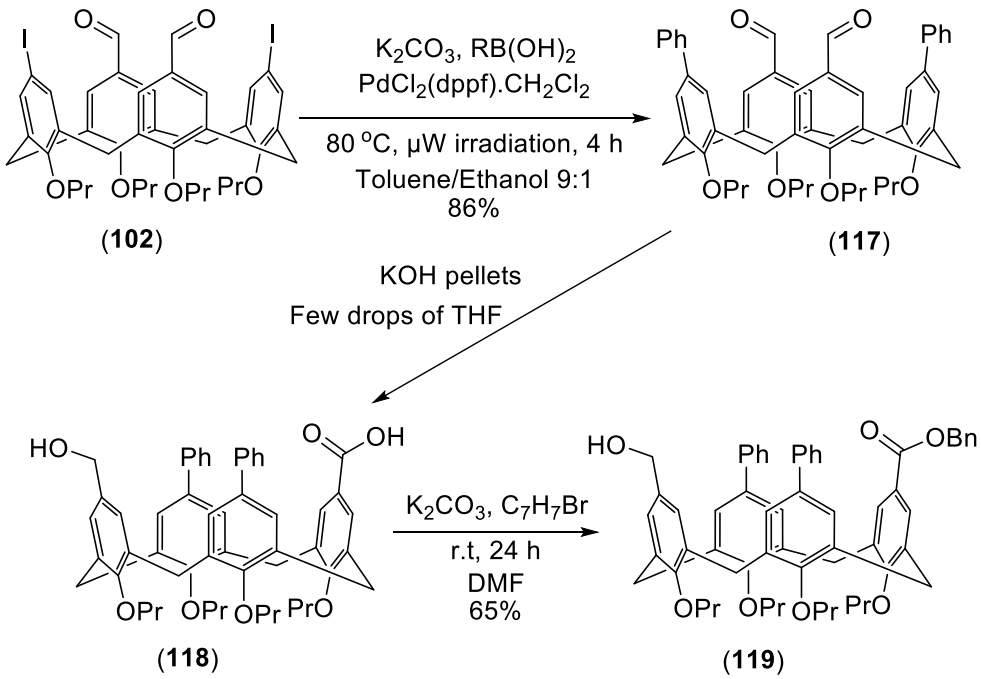
After the success of our Sonogashira coupling reactions in our system, we were keen to explore other cross-coupling reactions which might work. This would allow us easy access to a range of structures, and would also afford more options in terms of future asymmetric versions of this chemistry. A particularly well known and well studied cross-coupling reaction is the Suzuki reaction, in which an alkyl halide is coupled to an aryl boronic acid under Palladium catalysis. In addition, some precedent was available for the application of such chemistry on the upper-rim of calix[4]arenes, so we decided to explore this in our system.[99] After studying a number of literature procedures, we were able to identify a range of suitable conditions to couple boronic acids with our AABC benzyl protected calix[4]arene **110**. We opted to start by attempting to couple **110** with the reactive *p*-methoxyphenyl boronic acid, using *tetrakis*(triphenylphosphine) palladium(0) as our catalyst, potassium carbonate as our

base, and a mixture of THF and water as the solvent. However, even after heating to 90 °C under microwave irradiation for 48 hours, no reaction had occurred (**Scheme 34**).



Scheme 37: The failed Suzuki coupling between **110** and *p*-methoxyphenyl boronic acid

Disappointed by this lack of reactivity we screened a large number of boronic acid, catalyst, base and solvent combinations (*i.e.* toluene/ethanol, tetrahydrofuran/water, tetrahydrofuran) but we were unable to identify any conditions which would promote this reaction, with starting materials recovered in all cases. We surmised that this lack of reactivity might be arising from electronic and steric effects due to the benzyl ester on **110**, so we decided to investigate the same conditions employing the *bis-1,3*-aldehyde-*bis-2,4*-iodo calix[4]arene instead. After some work, we were able to find that performing the reaction in a mixture of 9:1 toluene/ethanol, with potassium carbonate, boronic acid and [1,1′-*Bis*(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane afforded our desired *di*-substituted Suzuki compounds in good yields (*i.e.* 38 to 86 %). Following the reactions by TLC, we were able to see that all were complete after heating to 80°C *via* microwave irradiation for 4 hours. The formation of Suzuki coupled derivative **118** in a 65% isolated yield for example, was confirmed by physiochemical analysis and indicated that the coupling had occurred on both positions.



Scheme 38: The synthesis for the Suzuki cross-coupling.

Some derivatives proved more problematic than others. For example, the *di*-nitro derivative illustrated in **Figure 23** while formed in high yield - as indicated by ^{1}H-NMR analysis - presented a considerable purification challenge. The compound 'crashed out' on the column as a yellow solid and was remained insoluble in a range of different eluents used to wash the column (*i.e.*5% methanol in dichloromethane, 50% ethyl acetate in hexane); interestingly however, the mono-substituted nitro compound could be purified readily by chromatography. This was presumably because of its reduced polarity compared to the *di*-nitro derivative, and ability to remain solvated in the eluent we employed for its purification. We were however able to isolate a small quantity of *di*-nitro material for characterisation, but it wasn't sufficient for any further chemistry. In addition to these two derivatives, we were able to prepare three more employing the electron-rich 4-methoxyphenyl boronic acid, the weakly deactivated 4-bromophenylboronic acid and the unsubstituted phenylboronic acid (**Figure 24**).

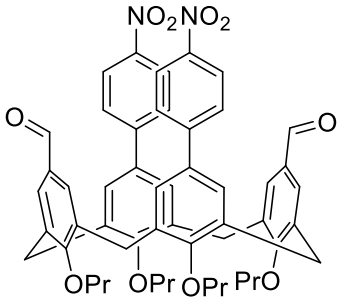
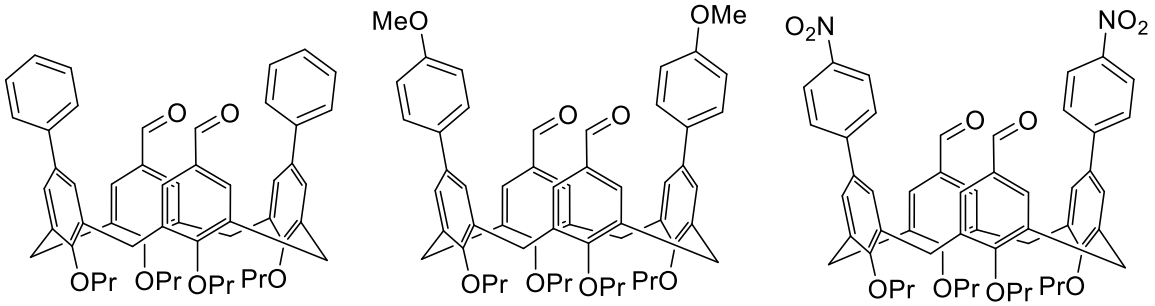


Figure 23: The di-nitro Suzuki compound.

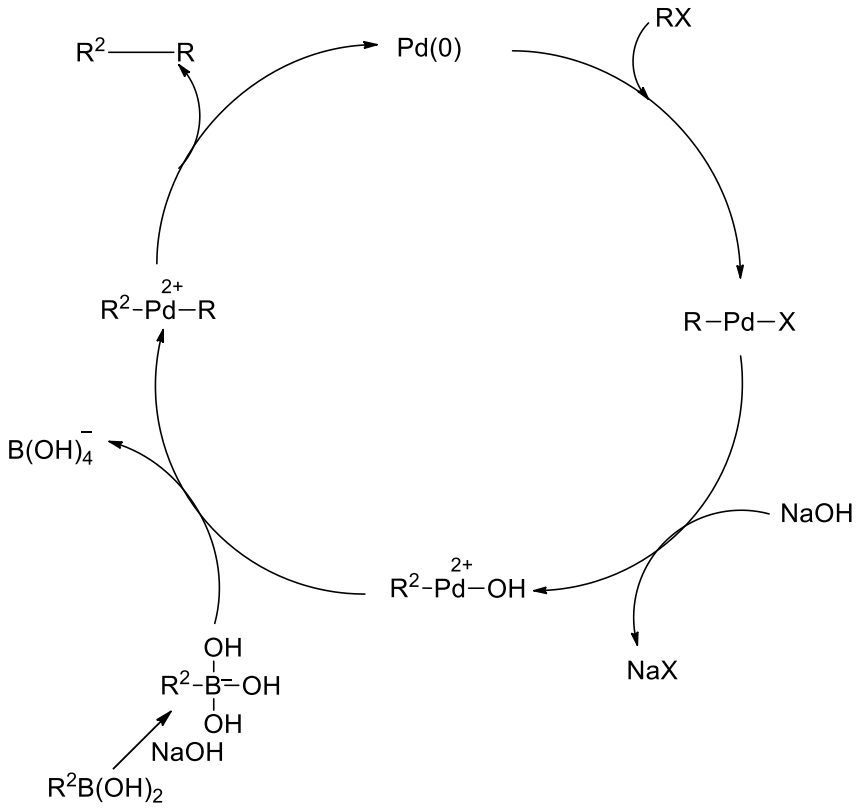
The electron-rich, and therefore highly reactive 4-methoxyphenyl boronic acid, afforded the corresponding coupled product in an excellent yield (*i.e.* 80%). Presumably in this case the coupling reaction proceeded at a faster rate than that of protodeboronation or homodimerisation of the starting boronic acid.



117-86% **120**-80% **121**-38%

Figure 24: Suzuki compounds.

The catalytic cycle is similar to that for the Sonogashira coupling, and begins with oxidative addition of the organohalide to the Pd(0) species to form a Pd(II) complex (**Scheme 39**).



Scheme 39: Catalytic cycle for the Suzuki cross-coupling.

The rate determining step in the catalytic cycle is generally thought to be this oxidative addition. Subsequent transmetalation occurs after the base activates the boron compound to facilitate the formation of the R^2-Pd^{2+}-OH complex. Without the addition of base, the reaction does not occur. The final step is reductive elimination, which in addition to furnishing the

desired product also regenerates the palladium catalyst so that it can participate again in the catalytic cycle.[100]

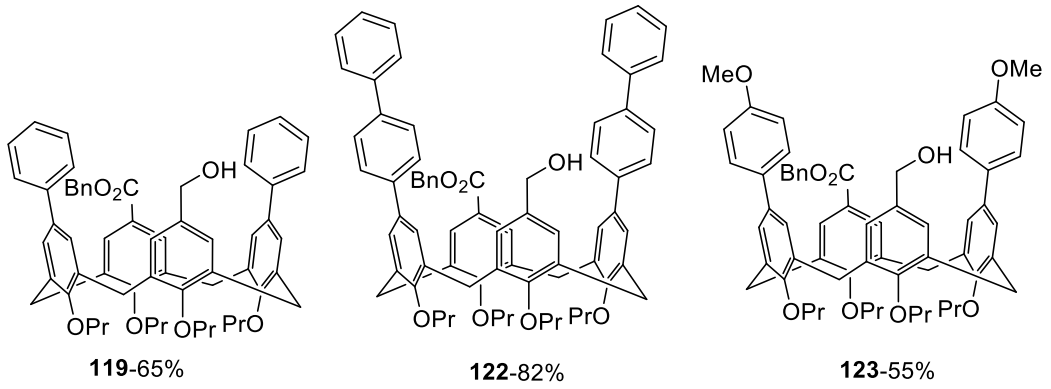


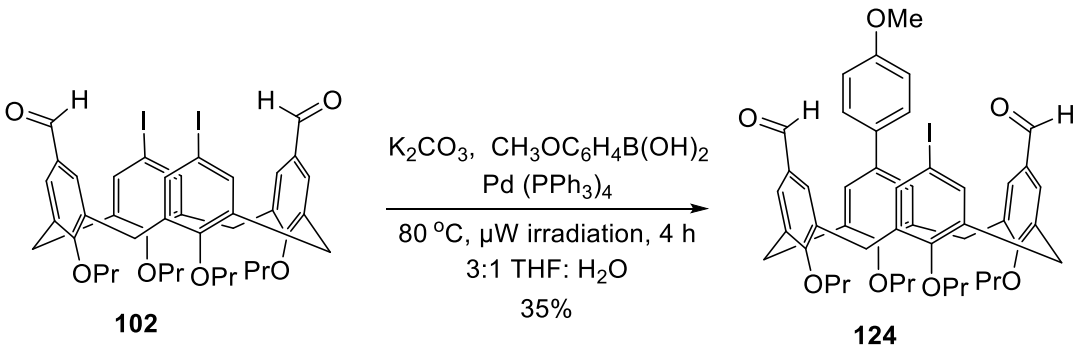
Figure 25: The final Suzuki compounds containing the benzyl ester groups.

As the route for the synthesis of AABC *di*-substituted Suzuki was proving successful, we moved on to test the same conditions to make the corresponding mono-substituted products. However, when we employed just 1 equivalent of boronic acid, we could only obtain starting material and *di*-substituted Suzuki compounds. Somewhat puzzled by this result, we decided to conduct a base and solvent study to find the appropriate conditions for making mono-substituted Suzuki compounds starting with the *bis-1,3*-aldehyde-*bis-2,4*-iodo calix[4]arene **102**. Testing a range of solvent/water combinations and bases - summarised in the table below - we were able to identify conditions which would allow our desired mono-substituted derivatives to be formed in acceptable yields (**Scheme 37**).

Entry	**Solvent**	**Base**	**Product (% yield)**
1	Tetrahydrofuran: Water (3:1)	Potassium carbonate	20% starting material 50 % mono-substituted 30 % *di*-substituted
2	Tetrahydrofuran: Water (3:1)	Caesium carbonate	18% starting material 50 % mono-substituted

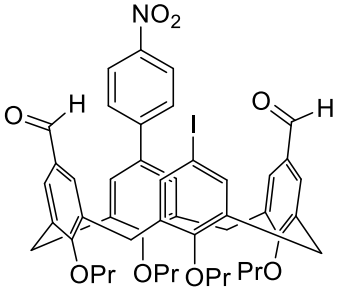
			32 % *di*-substituted
3	Tetrahydrofuran: Water (3:1)	Barium hydroxide	50 % starting material The rest was a complex mixture
4	Dioxane: Water (3:1)	Potassium carbonate	A complex mixture was obtained.
5	Dioxane: Water (3:1)	Caesium carbonate	A complex mixture was obtained.
6	Dioxane: Water (3:1)	Barium hydroxide	A complex mixture was obtained.

Scheme 40: Optimization towards Suzuki cross-coupling reaction.



Scheme 41: Conditions for the mono-Suzuki compounds.

After purification *via* column chromatography, the pure compound **124** could be isolated as clear oil in 35% yield. The corresponding mono-nitro derivative **125** was formed in a 26% yield. This lower yield is consistent with the lower yields obtained for the more



(**125**)

Figure 25: Mono-nitro compound obtained in 26% yield.

deactivated boronic acids described previously. In any case, we were pleased to have enough of our prochiral starting materials **124** and **125** to attempt the Cannizzaro reactions. We opted not to isolate these carboxylic acids, and instead isolate them as their benzyl esters for ease of purification. After these two steps, (±)-**126** and (±)-**127** were obtained in 70 and 48% overall yields respectively.

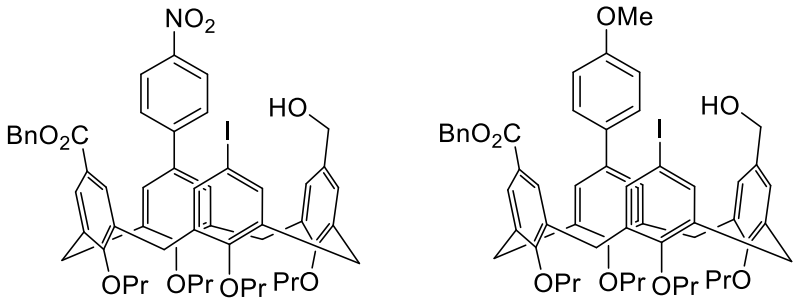
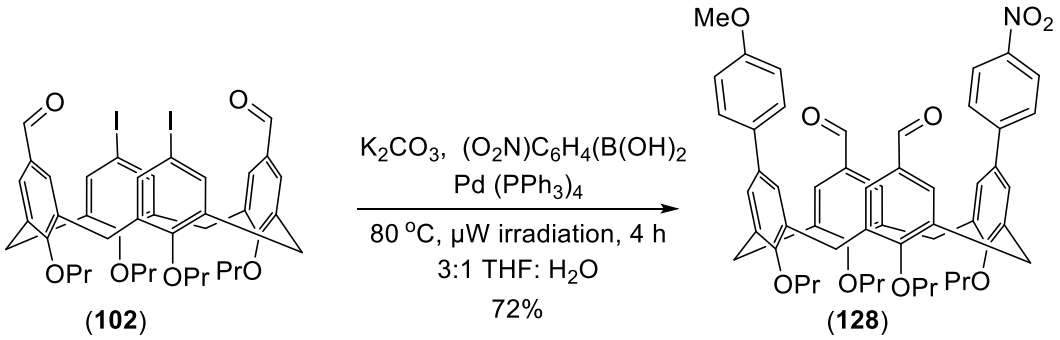


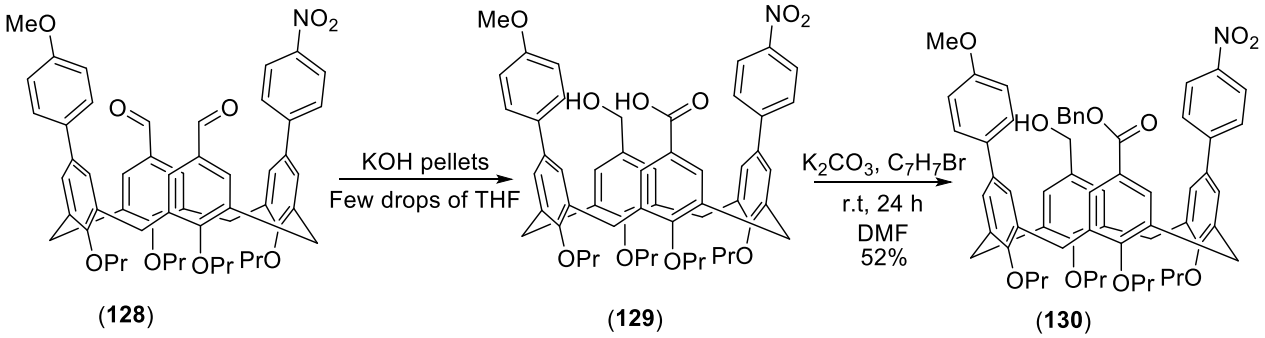
Figure 26: Inherently chiral calix[4]arenes (±)-**126** and (±)-**127**.

Extending our approach, we were interested in producing 'deep-walled' inherently chiral calix[4]arenes by substituting both iodine atoms with different boronic acids. Aware from our previous experience that Suzuki coupling was likely to fail on esters (±)-**126** and (±)-**127**, we opted to react the prochiral aldehyde **124** with 4-nitrophenylboronic acid to afford **128** in a 72% isolate yield after purification by column chromatography (**Scheme 42).**



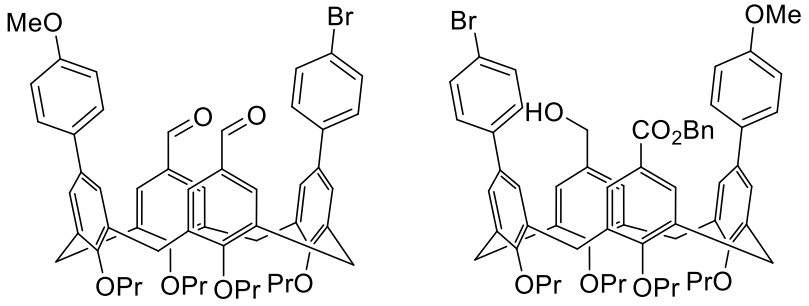
Scheme 42: Synthesis of the prochiral AABC substituted calix[4]arene **128**.

Following our previous approach, we opted to perform the Cannizzaro reaction and form the benzyl ester before attempting to isolate (±)-**130**. Purification *via* column chromatography then afforded (±)-**130** in a 52% overall yield from **128** (**Scheme 40).**



(**128**) (**129**) (**130**)

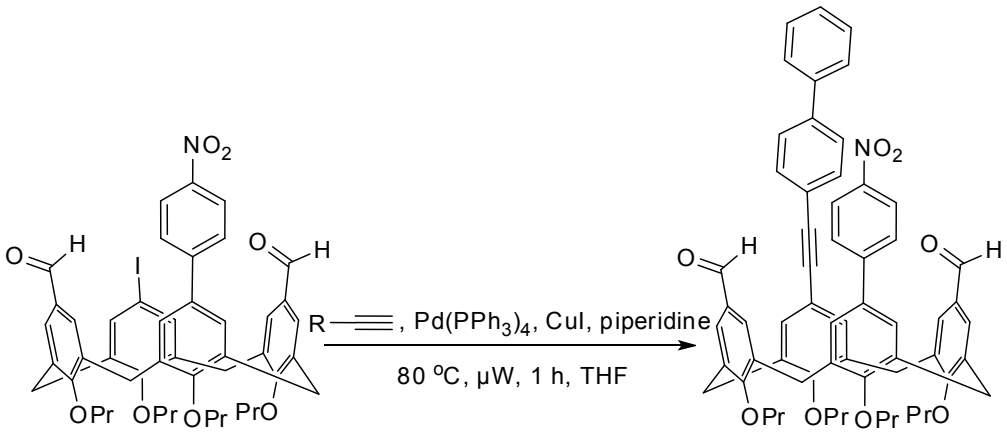
Scheme 43: ABCD calix[4]arene (±)-**130** derived from two sequential Suzuki coupling reactions.



(**131**)-42% (**132**)-55%

Figure 27: AABC and ABCD calix[4]arenes.

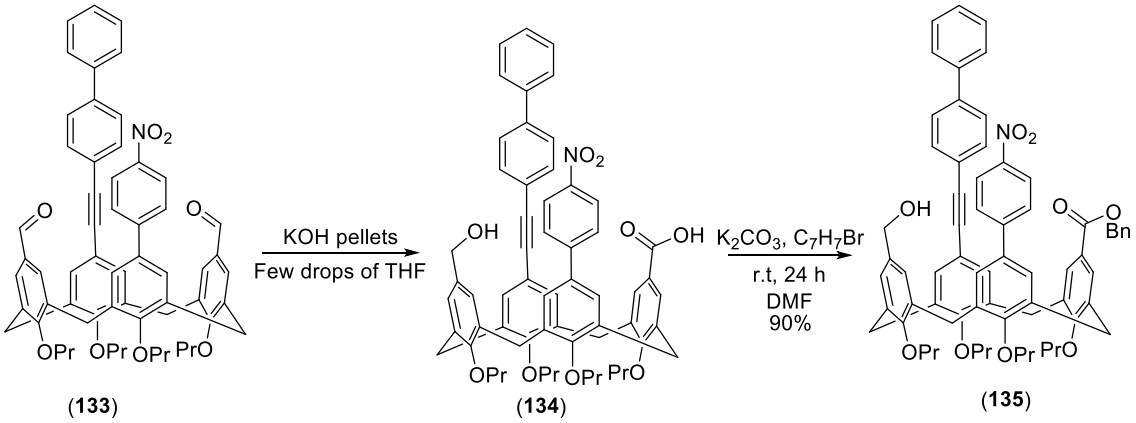
Encouraged by these results, we were interested to see if we could combine both types of coupling reaction in one substrate. Thus we decided to react prochiral **125** with 4-phenylethynyl benzene under the conditions we had optimised for Sonogashira coupling in our system. To our delight, the reaction proceeded smoothly affording the AABC substituted calix[4]arene **133** in a 74% isolated yield.



(**125**) (**133**)

Scheme 44: Double palladium catalysed cross-coupling

The solvent-free Cannizzaro reaction, followed by benzyl esterification, afforded the inherently chiral 'deep-walled' ABCD functionalised calix[4]arene in an excellent 90% overall yield from **133**. Physiochemical analysis confirmed the formation of (±)-**135**, with HRMS analysis finding 1071.5154 for $[M + NH_4]^+$ further confirming its identity.



(**133**) (**134**) (**135**)

2.7. Summary and future work

Employing a solvent-free Cannizzaro reaction developed in our group, and subsequent cross-coupling chemistry, we have developed an operationally simple protocol for the synthesis of 'inherently chiral' calix[4]arenes substituted at the upper-rim in an ABCD pattern. We were able to synthesise a wide array of structurally diverse 'deep-walled' calix[4]arenes, and demonstrate the use of different coupling reactions on a single calix[4]arene scaffold.

To proceed with this project, we propose that the use of chiral-HPLC or chiral derivitisation might allow us to separate the two enantiomers that we produce. We could then initiate studies into the use of these compounds to accommodate chiral guests, and also towards their asymmetric synthesis using homochiral palladium complexes of the sort pioneered by Cammidge *et. al.* for the asymmetric Suzuki reaction.[101]

Chapter 3

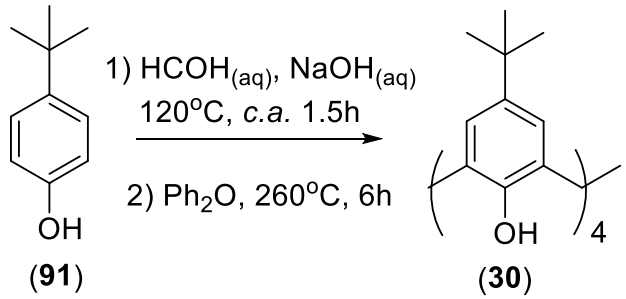
Experimental

General Information

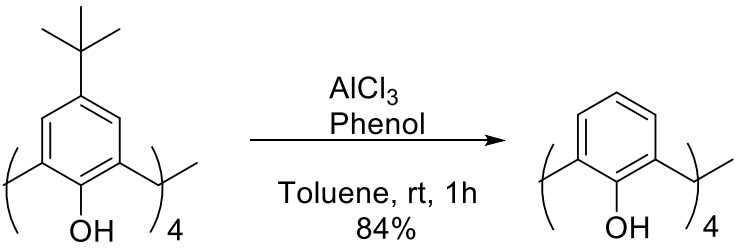
Reactions were conducted in flame-dried glass apparatus under an atmosphere of nitrogen or argon. Water refers to distilled water, all commercially available chemicals and reagents were used as supplied. Melting points were recorded using open capillary tubes on melting point apparatus and are uncorrected. Infrared spectra were recorded either as a thin film or neat sample. ^{1}H- and ^{13}C-NMR spectra were recorded in Fourier transform mode at the field strength indicated and unless otherwise stated deuterated chloroform was used as solvent. The ^{1}H-spectra were recorded in ppm and referenced to the residual $CHCl_3$ signal located at δ 7.26 ppm. ^{13}C-NMR spectra were recorded in ppm and referenced to the residual $CHCl_3$ signal found at δ 77.00. Multiplicities in the NMR spectra are described as: s = singlet, d = doublet, t = triplet, q= quartet, m = multiplet, br = broad; coupling constants are reported in Hz. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units. Microwave reactions refer to a closed vessel microwave reactor 300W.

Characterisation

Flash column chromatography was carried out on silica gel (Fluka Silica gel 60, 70-230 mesh). Analytical thin-layer chromatography (TLC) was performed on Merck plates (aluminium coated with 0.2 mm silica gel 60 F_{254}), with visualization by UV light and/or potassium permanganate stain followed by heating. Melting points were recorded using open capillary tubes on melting point a Stuart Scientific SMP1 apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded in Fourier transform mode on a Bruker Ascend 500 MHz spectrometer at the field strength indicated and unless otherwise stated deuterated chloroform was used as solvent. The ^{1}H-spectra were recorded in ppm and referenced to the residual $CHCl_3$ signal located at δ 7.26 ppm. ^{13}C-NMR spectra were recorded in ppm and referenced to the residual $CHCl_3$ signal found at δ 77.16 ppm. Multiplicities in the NMR spectra are described as: s = singlet, d = doublet, t = triplet, q= quartet, m = multiplet, br = broad; coupling constants are reported in Hz. Ion mass/charge (m/z) ratios are reported as values in atomic mass units and carried out on a Shimadzu Kratos MALDI-TOF. FT-IR spectra were recorded on a 123 Perkin-Elmer 298 spectrometer either as a thin film or neat sample and are reported in wavenumbers (cm^{-1}). HRMS was carried out by the EPSRC at the National Mass Spectrometry Service, University of Wales, Swansea.

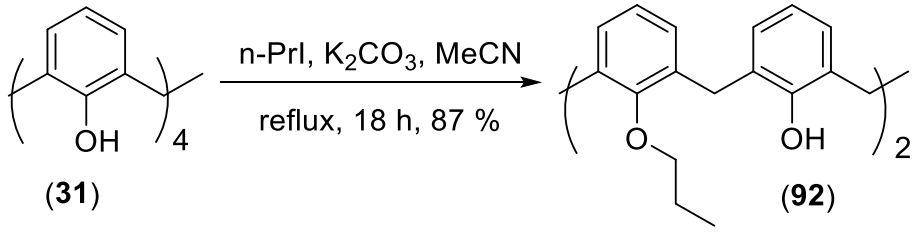


Synthesis of 92: A three-necked 3 L RBF was charged with a solution of (**30**) (100 g, 154 mmol) in toluene (900 mL) under an atmosphere of nitrogen. Phenol (69.6 g, 740 mmol) was added in one portion, and the mixture stirred at room temperature for 10 minutes, before the addition of anhydrous aluminium chloride (108 g, 809 mmol) in one portion with vigorous stirring. The mixture was then stirred for 1 h at room temperature, before being poured onto crushed ice (ca. 800 g). The mixture was extracted with dichloromethane (1 L), and the solvent reduced (ca. 400 mL). The product was precipitated by the addition of MeOH (500 mL), and collected by suction filtration to afford a white solid (54.9 g, 129 mmol, 84%). Analysis revealed the solid to be the title compound. Spectral data was in accordance with literature values. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 10.18 (s, 4H, OH), 7.0 (d, 8H, ArH, *J* 7.7 Hz), 6.7 (t, 4H, ArH, *J* 7.7 Hz), 4.2 (brs, 4H, $ArCH_2Ar$), 3.5 (brs, 4H, $ArCH_2Ar$).



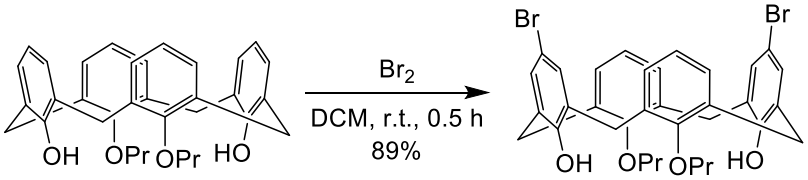
(**30**) (**31**)

Synthesis of 31: A three-necked 3 L RBF was charged with a solution of (**30**) (100 g, 154 mmol) in toluene (900 mL) under an atmosphere of nitrogen. Phenol (69.6 g, 740 mmol) was added in one portion, and the mixture stirred at room temperature for 10 minutes, before the addition of anhydrous aluminium chloride (108 g, 809 mmol) in one portion with vigorous stirring. The mixture was then stirred for 1 h at room temperature, before being poured onto crushed ice (ca. 800 g). The mixture was extracted with dichloromethane (1 L), and the solvent reduced 52 ca. 400 mL). The product was precipitated by the addition of MeOH (500 mL), and collected by suction filtration to afford a white solid (54.9 g, 129 mmol, 84%). Analysis revealed the solid to be the title compound. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 10.18 (s, 4H, OH), 7.0 (d, 8H, ArH, *J* 7.7 Hz), 6.7 (t, 4H, ArH, *J* 7.7 Hz), 4.2 (brs, 4H, $ArCH_2Ar$), 3.5 (brs, 4H, $ArCH_2Ar$).



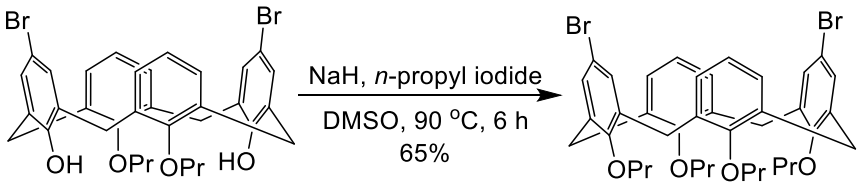
(**31**) (**92**)

Synthesis of 92: A 500 mL RBF was charged with a solution of (**31**) (14.727 g, 34.7 mmol) in dry MeCN (150 mL) under an atmosphere of nitrogen. Potassium carbonate (5.37 g, 38.9 mmol) and n-propyl iodide (7.6 mL, 78 mmol) were added, and the mixture heated at reflux for 18 hours. The reaction mixture was allowed to cool to room temperature, and the solvent removed *in vacuo*. The residue was taken up in dichloromethane (100 mL), washed with 1 M HCl (2 x 50 mL) and water (50 mL), dried ($MgSO_4$), filtered, and the organics concentrated *in vacuo* to afford a yellow solid. Recrystallisation from $CHCl_3$/MeOH afforded a white solid (15.395 g, 30.3 mmol, 87%). Analysis revealed the solid to be the title compound. Spectral data was in accordance with literature values. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.32 (s, 2H, OH), 7.04 (d, 4H, ArH, *J* 7.5 Hz), 6.91 (d, 4H, ArH, *J* 7.5 Hz), 6.74 (t, 2H, ArH, *J* 7.5 Hz), 6.63 (t, 2H, ArH, *J* 7.5 Hz), 4.31 (d, 4H, $ArCH_2Ar$, *J* 12.8 Hz), 3.97 (t, 4H, OCH_2, *J* 6.9 Hz), 3.37 (d, 4H, $ArCH_2Ar$, *J* 12.8 Hz), 2.06 (sextet, 4H, CH_2, *J* 6.9 Hz), 1.30 (t, 6H, CH_3, *J* 6.9 Hz).



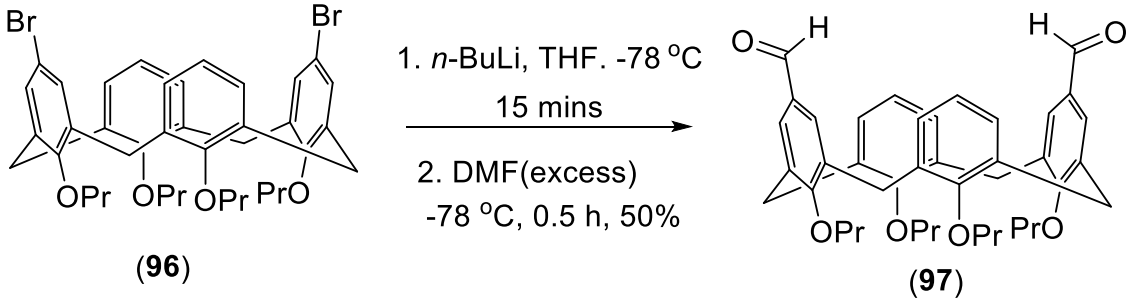
(**94**) (**95**)

Synthesis of 95: A solution of bromine (750 µL, 14.75 mmol) in dry dichloromethane (40 mL) was added dropwise *via* syringe to a solution of (**94**) (3 g, 5.9 mmol) in dry DCM (140 mL) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 30 minutes, after which time the precipitate formed was collected by suction filtration and washed with dichloromethane. The precipitate was dried to constant weight to afford a white solid (3.54 g, 5.3 mmol, 89%). Analysis revealed the solid to be the title compound. Spectral data was in accordance with literature values. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.36 (s, 2H, OH), 7.14 (s, 4H, ArH), 6.91 (d, 4H, ArH, *J* 7.0 Hz), 6.78 (t, 2H, ArH, *J* 7.0 Hz), 4.22 (d, 4H, $ArCH_2Ar$, *J* = 12 Hz), 3.92 (t, 4H, OCH_2, *J* 6.0 Hz), 3.29 (d, 4H, $ArCH_2Ar$, *J* 12 Hz), 2.03 (m, 4H, CH_2), 1.26 (t, 6H, CH_3, *J* 8Hz).



(**95**) (**96**)

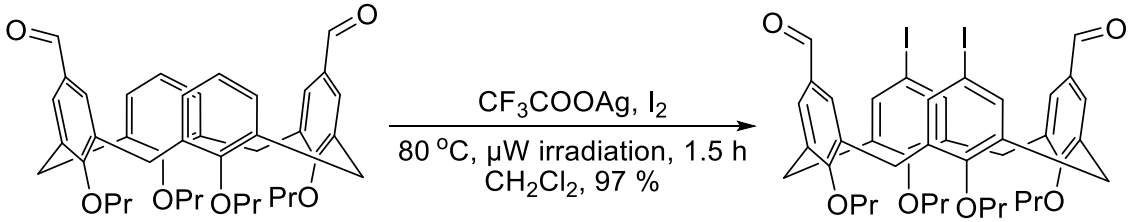
Synthesis of 96: A 50 mL RBF was charged with a suspension of (**95**) (1.5 g, 2.25 mmol) in anhydrous DMSO (20 mL) under an atmosphere of nitrogen. Sodium hydride (60% in oil, 517 mg, 22.5 mmol) was added, and the mixture stirred for 30 minutes before the addition of n-propyl iodide (1.75 mL, 18 mmol). The reaction mixture was then heated to 90 °C for 6 hours. After cooling to room temperature, 1 M HCl (30 mL) was added, and the pale yellow precipitate collected by suction filtration. Recrystallisation from $CHCl_3$/MeOH afforded a white solid (1.203 g, 1.6 mmol, 71%). Analysis revealed the solid to be the title compound. Spectral data was in accordance with literature values. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.74 (s, 4H, ArH), 6.61 (s, 6H, ArH), 4.37 (d, 4H, $ArCH_2Ar$, *J* 13.3 Hz), 3.79 (m, 8H, OCH_2), 3.08 (d, 4H, $ArCH_2Ar$, *J* 13.3 Hz), 1.87 (m, 8H, CH_2), 0.95 (m, 12 H, CH_3).



(**96**) (**97**)

Synthesis of 97: To a stirred solution of (**96**) (1 g, 1.33 mmol) in anhydrous THF (20 mL) at -78°C under an atmosphere of nitrogen was added *n*-BuLi (2.5 M in hexanes, 740 µL, 8 mmol) *via* syringe. The reaction mixture was stirred for 15 minutes before the addition of anhydrous DMF (10 mL, 129 mmol) *via* syringe in one portion. After stirring for a further 30 minutes at -78°C, the reaction mixture was poured onto ice cold 4 M HCl (100 mL), and extracted with chloroform (2 x 40 mL). The organics were washed with a saturated solution of sodium hydrogen carbonate (80 mL) and water (4 x 80 mL), then dried (MgSO4), filtered, and concentrated to afford an off white solid. Purification by column chromatography (15% EtOAc in Petrol) afforded a white solid (457 mg, 0.704 mmol, 50%). Analysis revealed the solid to be the title compound. Spectral data was in accordance with literature values. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 9.44 (s, 2H, C*H*O), 6.97 (s, 4H, ArH), 6.69 (m, 6H, ArH), 4.44 (d, 4H, $ArCH_2Ar$, *J* 13.6 Hz), 3.85 (m, 8H, OCH_2), 3.20 (d, 4H, $ArCH_2Ar$, *J* 13.6 Hz), 1.88 (m, 8H, CH_2), 1.00 (t, 6H, CH_3, *J* 7.4 Hz), 0.94 (t, 6H, CH_3, *J* 7.4 Hz).

Synthesis of 102

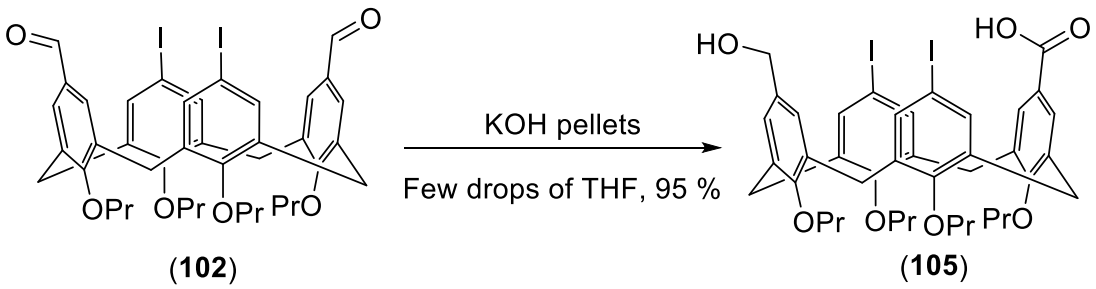


(**96**) (**102**)

A 20 mL capacity microwave vial was charged with a mixture of **96** (1 g, 1.541 mmol), silver trifluoroacetate (0.75 g, 3.39 mmol) and iodine (0.78 g, 3.08 mmol) in dichloromethane (8 mL). The vial was sealed with a PTFE lined crimp cap, and mixture was heated and stirred at 80°C for 1.5 hours under microwave irradiation. The precipitate was removed by filtration, and the mixture partitioned between dichloromethane (25 mL) and saturated sodium

thiosulfate (25 mL). The organics were separated, then dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford **102** as a pale yellow solid (1.3 g, 1.433 mmol, 97%). R_f 0.59 (20% EtOAc in petrol); M.p. 230-244°C (dec.); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.51 (s, CHO, 2H), 7.15 (s, ArH, 4H,), 6.99 (s, ArI, 4H), 4.39 (d, $ArCH_2Ar$, 4H, *J* 13.6 Hz), 3.86 (m, OCH_2, 8H), 3.19 (d, $ArCH_2Ar$, 4H, *J* 13.6 Hz), 1.94-1.82 (m, CH_2, 8H), 1.02 (t, CH_3, 6H, *J* 7.4 Hz), 0.95 (t, CH_3, 6H, *J* 7.4 Hz) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 161.7, 156.9, 137.6, 137.5, 135.3, 131.5, 130.0, 86.3, 77.3, 30.8, 29.8, 23.4, 23.2, 22.8, 14.3, 10.5, 10.2 ppm; FTIR (thin film) 2923, 2855 (C-H stretch), 1784, 1694 (C=O stretch) 1463, 1455 (C=C stretch) cm^{-1}; MS (MALDI) *m/z* 939.29 $[M+K]^+$; HRMS $[M+NH_4]^+$ Calculated for $C_{42}H_{50}I_2NO_6$: 918.1722; Found: 918.1728.

General procedure for Cannizzaro 1

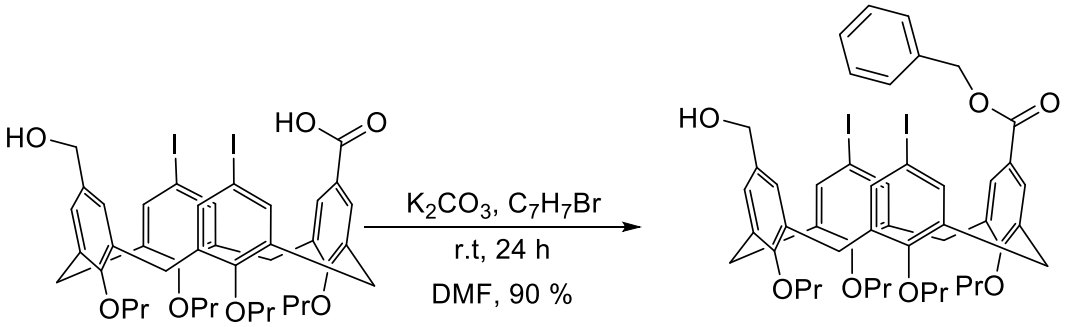


(**102**) (**105**)

A mortar was charged with **102** (500 mg, 0.56 mmol) and potassium hydroxide (3.11 g, 55.5 mmol). The mixture was ground using the pestle with the occasional addition of tetrahydrofuran (a few drops) to aid mixing until the starting material had been consumed (*ca*. 1 h) as indicated by TLC analysis (40% ethyl acetate in petrol). The reaction mixture was partitioned between 1M HCl $_{(aq.)}$ (50 mL) and diethyl ether (50 mL), and the ethereal phase separated. The organics were dried over magnesium sulfate, filtered and concentrated to afford the crude carboxylic acid. Purification *via* flash column chromatography on silica gel (1% MeOH in CH_2Cl_2) afforded compound **105** as an off white solid (490 mg, 0.53 mmol, 96%). Crystallisation from dichloromethane/pentane afforded crystals suitable for X-ray diffraction. R_f 0.25 (1% MeOH in CH_2Cl_2); M.p. > 250°C (dec.); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, ArI, 4H, *J* 4.6 Hz), 7.01 (s, ArCOOH, 2H), 6.25 (s, $ArCH_2OH$, 2H), 4.36 (t, $ArCH_2Ar$, 4H, *J* 13.2 Hz), 4.18 (s, $ArCH_2$-alcohol, 2H), 3.94 (m, OCH_2, 4H, *J* 18.2, 10.9, 8.1 Hz), 3.74 (t, OCH_2, 2H, *J* 6.9 Hz,), 3.66 (t, OCH_2, 2H, *J* 6.9 Hz 3.05 (d, $ArCH_2Ar$, 2H, *J* 13.8 Hz), 3.01 (d, $ArCH_2Ar$, 2H, *J* 13.8 Hz), 1.92 – 1.80 (m, CH_2, 8H), 1.05 (m, CH_3, 6H), 0.89 (t, CH_3, 6H, *J* 7.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.5, 160.6, 157.5, 155.2, 139.0, 138.3, 137.8, 137.4, 134.7, 133.9, 133.2, 130.2, 126.3, 123.3, 85.9, 77.2, 77.1, 76.8, 64.2, 30.9, 30.7, 23.49, 23.0, 10.8, 10.7, 10.0 ppm; FTIR (thin film) 2963, 2924, 2876, 2850 (C-H

Stretch), 1683 (C=O stretch), 1462 (C=C stretch), 1265, 1201 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 957 $[M+K]^+$; HRMS [M-H] Calculated for $C_{42}H_{47}I_2O_7$: 917.1417; Found: 917.1389.

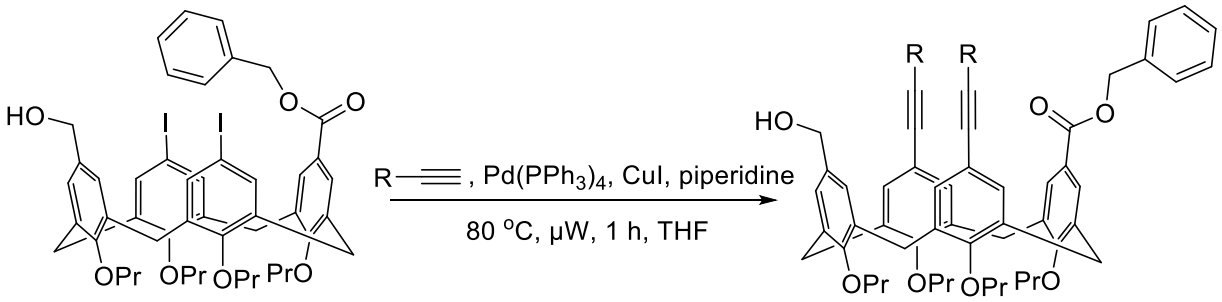
General procedure for esterification 2



(**105**) (**109**)

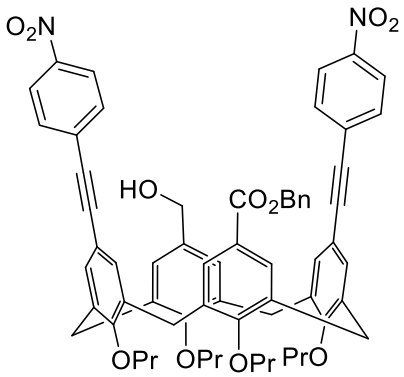
The cannizzaro precursor (500 mg, 0.54 mmol) was taken up in *N,N*-dimethylformamide (5 mL) and potassium carbonate (150 mg, 1.09 mmol) and benzyl bromide (78 μL, 0.65 mmol) were added. The mixture was stirred at room temperature overnight, after which time TLC analysis (15% EtOAc in petrol) indicated the starting material had been consumed. The mixture was diluted with diethyl ether (25 mL) and washed with water (4 x 20 mL) and brine (20 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated to afford a clear oil. Purification *via* flash column chromatography on silica gel (15% EtOAc in petrol) afforded XX as an off-white solid (0.494 g, 0.49 mmol, 90%). R_f 0.38 (15% EtOAc in petrol); M.p. > 250°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 – 7.44 (m, ArOBn, 2H), 7.41 – 7.28 (m, ArOBn, 3H), 7.21 (d, ArI, 4H, *J* 1.1 Hz), 7.16 (s, ArO, 2H), 6.34 (s, ArOH, 2H), 5.27 (s, OCH_2Bn, 2H), 4.50 (s, OH, 1H), 4.37 (t, $ArCH_2Ar$, 4H, *J* 13.4 Hz), 3.97 (s, CH_2OH, 2H), 3.95 – 3.82 (m, OCH_2 4H), 3.79 (t, OCH_2, 2H, *J* 7.2 Hz), 3.72 (t, OCH_2, 2H, *J* 7.2 Hz), 3.13 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 3.08 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 1.92 – 1.81 (m, CH_2, 8H), 1.02 (m, CH_3, 6H), 0.93 (t, CH_3, 6H, *J* 7.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.7, 160.5, 157.2, 155.4, 138.5, 137.9, 137.6, 137.2, 136.4, 135.3, 134.3, 133.6, 129.9, 128.9, 128.2, 127.8, 126.3, 123.9, 85.8, 77.1, 77.0, 66.3, 64.3, 30.8, 30.7, 23.4, 23.1, 10.6, 10.5, 10.1 ppm; FTIR (thin film) 2960, 2928, 2873 (C-H Stretch), 1715 (C=O stretch) 1456 (C=C stretch), 1186 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 1031 $[M+Na]^+$; HRMS $[M+NH_4]^+$ Calculated for $C_{49}H_{58}I_2O_7N_1$: 1026.2293; Found: 1026.2297.

General procedure for Sonogashira 3



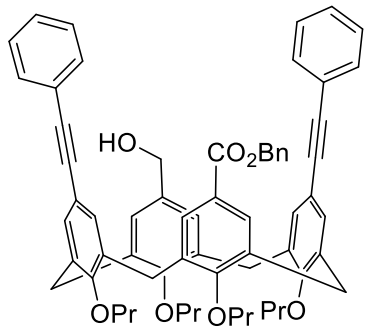
(**109**) (**a**)

A 5 mL microwave vial was charged with a solution of (**109**) (1 eq.), *tetrakis*(triphenylphosphine) palladium(0) (0.1 eq.) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen. Piperidine (3 eq.) was added *via* syringe, followed by a solution of the appropriate alkyne (4 eq.) in tetrahydrofuran (0.5 mL) and finally copper (I) iodide (0.2 eq.). The vial was sealed with a PTFE lined crimp cap; the mixture was degassed and finally heated to 80°C for 1 hour under microwave irradiation. The reaction mixture was transferred to a 25 mL separating funnel. It was washed with water (2 × 20 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and solvents were removed *in vacuo*.

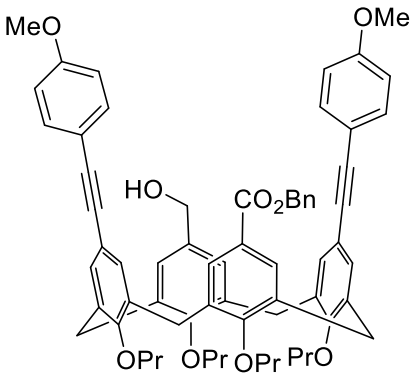


Synthesis of 115: The crude compound was purified *via* column chromatography on silica gel (30% Et_2O in petrol) to afford an orange solid (13 mg, 0.013 mmol, 64%). R_f 0.05 (30% Et_2O in petrol); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.14 (d, $ArNO_2$, 4H, *J* 8.9 Hz), 7.59 (d, $ArNO_2$, 4H, *J* 8.9 Hz), 7.38 (t, ArOBn, 2H, *J* 7.6 Hz), 7.32 (d, ArOBn, 3H, *J* 7.0 Hz), 7.20 (s, ArCC, 4H, *J* 5.9 Hz), 7.14 (s, ArCOO, 2H), 6.32 (s, $ArCH_2$, 2H), 5.24 (s, $COOCH_2$, 2H), 4.45 (m, $ArCH_2Ar$, 4H), 4.08 – 3.96 (m, OCH_2, 4H), 3.95 (s, $ArCH_2OH$, 2H), 3.81 (t, OCH_2, 2H, *J* 7.1 Hz), 3.74 (t, OCH_2, 2H, *J* 3.3 Hz), 3.15 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 3.11 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz)1.99 – 1.82 (m, CH_2, 8H), 1.06 (dd, CH_3, 6H, *J* 13.7, 7.4 Hz), 0.95 (t, CH_3, 6H, *J* 7.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.9, 160.4, 158.7, 155.3, 146.7, 136.8, 136.4, 136.1, 135.2, 134.2, 133.4, 132.8, 132.5, 132.1, 130.9, 129.8, 128.8, 128.1, 127.6, 126.1, 123.6, 115.8, 95.8, 87.0, 77.3, 77.1, 66.2, 64.3, 31.1, 30.9, 29.8, 23.5, 23.3, 10.7, 10.6, 10.1

ppm; FTIR (thin film) 2967, 2921, 2853 (C-H stretch), 1341 (C-O) cm^{-1} ; MS (MALDI) *m/z* 1070 $[M+Na]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{65}H_{66}N_3O_{11}$: 1064.4665; Found: 1064.4692.



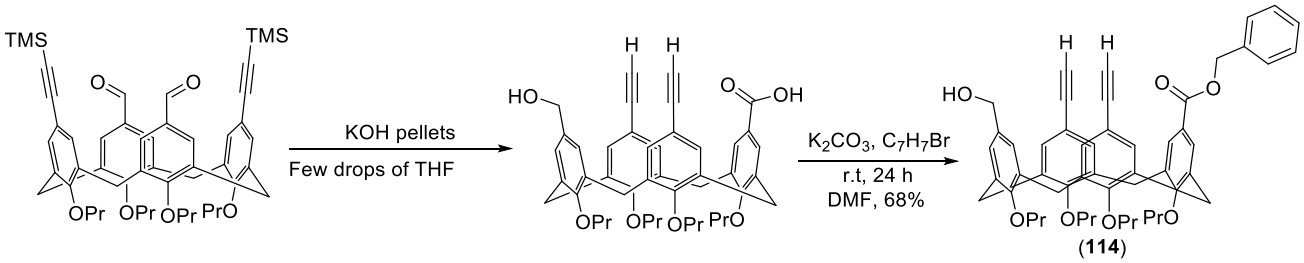
Synthesis of 110: The crude compound was purified by flash chromatography (30% Et_2O in petrol) to afford a clear oil (38 mg, 0.039 mmol, 78%). R_f 0.14 (30% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, ArH, 3H), 7.42 – 7.37 (m, ArH, 3H), 7.36 – 7.29 (m, ArH, 12H), 7.02 (s, ArH, 2H), 5.21 (s, CH_2OBn, 2H), 4.44 (t, $ArCH_2Ar$, 4H, *J* 13.7 Hz), 4.12 – 3.95 (m, OCH_2, 4H), 3.81 (s, CH_2OH, 2H), 3.75 (t, OCH_2, 2H, *J* 6.9 Hz), 3.68 (t, OCH_2, 2H, *J* 6.9 Hz), 3.12 (d, $ArCH_2Ar$, 4H, *J* 13.7 Hz), 3.09 (d, $ArCH_2Ar$, 4H, *J* 13.7 Hz), 2.00 – 1.82 (m, CH_2, 8H), 1.09 (m, CH_3, 6H), 0.92 (t, CH_3, 6H, *J* 7.5 Hz) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 160.0, 158.2, 154.9, 137.0, 136.4, 136.3, 135.3, 133.9, 133.0, 132.7, 132.3, 131.7, 129.6, 128.8, 128.4, 128.0, 128.0, 127.5, 125.8, 123.9, 116.9, 90.1, 88.5, 66.0, 64.1, 31.1, 31.0, 23.6, 23.6, 23.2, 10.9, 10.8, 10.0 ppm; FTIR (thin film) 3546 (O-H stretch), 2961, 2930, 2875 (C-H stretch), 1715 (C=O stretch), 1185 (C-O) cm^{-1}; MS (MALDI) *m/z* 980 $[M+Na]^+$; MS (MALDI) *m/z* 980 $[M+Na]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{65}H_{68}NO_7$: 974.4973; Found: 974.4990.



Synthesis of 116: The crude was purified by flash chromatography (30% Et_2O in petrol) to afford an orange solid (31 mg, 0.030 mmol, 50%). R_f 0.06 (30% Et_2O in petrol); ^1H NMR (500 MHz, CDCl3) δ 7.47 (d, ArHOMe, 2H, *J* 8.9 Hz), 7.39 (m, 3H), 7.33 – 7.26 (m, 6H), 7.02 (s, 2H), 6.87 (d, ArH, 2H, *J* 8.9 Hz), 6.18 (s, 1H), 5.21 (s, 1H), 4.42 (t, 2H, *J* 13.6 Hz), 4.12 – 3.91 (m, 4H), 3.84 (s, 6H), 3.81 (s, 2H), 3.74 (t, 2H, *J* 6.9 Hz), 3.68 (t, 2H, *J* 6.9 Hz), 3.19 (d, 2H, *J* 13.7 Hz), 3.15 (d, 2H, *J* 13.6 Hz), 1.96 – 1.83 (m, 8H), 1.10 – 1.06 (m, 12H), 0.90 (t, *J* 7.5 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.8, 160.0, 159.5, 157.9, 154.9, 136.8, 136.4, 136.2, 135.3, 133.9, 133.1, 133.1, 132.5, 132.1, 129.6, 128.8, 128.0, 127.5, 125.8, 123.8, 117.2, 116.0, 114.1, 88.7, 88.3, 77.2, 76.8, 66.0, 64.1, 55.4, 31.0, 30.9, 23.6, 23.5, 23.1, 10.8, 10.8, 10.0 ppm; FTIR (thin film) 3530 (O-H stretch), 2960, 2931, 2874 (C-H stretch), 1715 (C=O stretch), 1606, 1510 (C=C stretch), 1248

(C-O stretch) cm^{-1}; MS (MALDI) *m/z* 1040 $[M+Na]^+$; MS (MALDI) *m/z* 1040 $[M+Na]^+$; HRMS $[M + H]^+$ Calculated for $C_{67}H_{69}O_9$: 1017.4937; Found: 1017.4936.

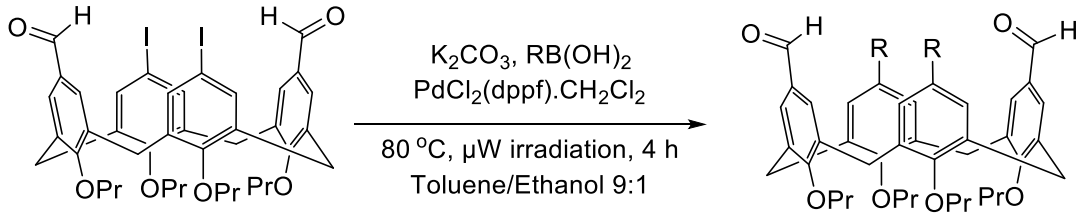
Synthesis of 114



(**114**)

The crude mixture was purified by flash column chromatography (40% Et_2O in petrol) to afford an off-white solid (27 mg, 0.033 mmol, 68%). R_f 0.28 (40% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, OBn ,2H), 7.37 – 7.30 (m, OBn, 3H), 7.16 – 7.06 (m, ArH, 6H), 6.27 (s, ArH ,2H), 5.24 (s, CH_2OBn, 2H), 4.40 (t, $ArCH_2Ar$, 4H, *J* 13.7 Hz), 4.02 – 3.90 (m, OCH_2, 4H), 3.90 (s, CH_2OH, 2H), 3.78 (t, OCH_2, 2H, *J* 7.1 Hz), 3.71 (t, OCH_2, 2H, *J* 7.1 Hz), 3.17 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 3.12 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 2.99 (s, Alkyne-H, 2H), 1.94 – 1.83 (m, CH_2, 8H), 1.04 (m, CH_3, 6H), 0.92 (t, CH_3, 6H, *J* 7.5 Hz) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 160.3, 158.1, 155.3, 136.5, 136.4, 135.8, 135.3, 134.2, 133.5, 13.0, 132.6, 129.80, 128.8, 128.1, 127.7, 126.1, 123.9, 115.8, 84.3, 77.7, 76.1, 66.1, 64.3, 31.0, 30.9, 23.5, 23.2, 10.7, 10.6, 10.1 ppm; FTIR (thin film) 3300 (O-H stretch), 2963, 2933, 2875 (C-H stretch), 1713 (C=O) cm^{-1}; MS (MALDI) *m/z* 844 $[M+K]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{53}H_{60}NO_7$: 822.4352; Found 822.4364.

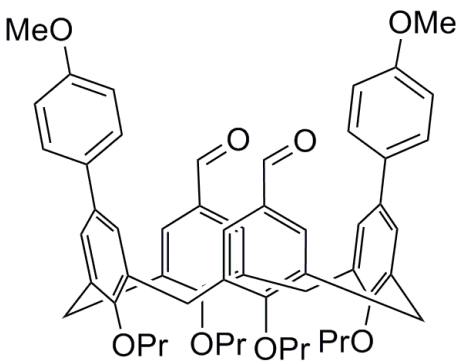
General procedure for di-Suzuki 4



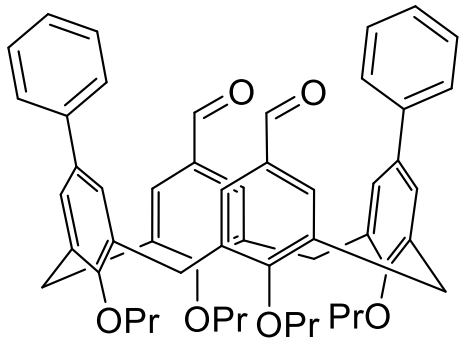
(**102**) (**b**)

A 5 mL microwave vial was charged with a solution of **102** (1 eq.) in 9:1 toluene/ethanol, with potassium carbonate (3 eq.), boronic acid (3 eq.) and [1,1′-

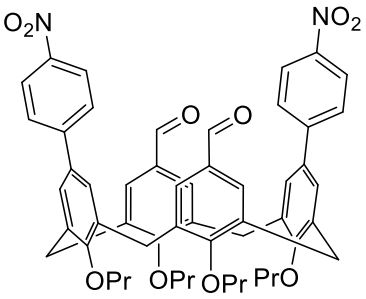
Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.1 eq.). The vial was sealed with a Teflon cap and heated *via* microwave irradiation for 4 hours at 80°C. The mixture was diluted with ethyl acetate (2 × 10 mL), transferred to a 25 mL separating funnel and washed with water (2 × 20 mL). The organic phase was dried over magnesium sulfate, filtered, and solvents were removed *in vacuo*.



Synthesis of 120: The crude mixture was purified by flash column chromatography (15% EtOAc in petrol) to afford a yellow solid (23 mg, 0.027 mmol, 80%). R_f 0.29 (15% EtOAc in petrol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, CHO, 2H), 7.15 (s, ArH, 4H), 7.07 (d, ArOMe, 4H, *J* 8.6 Hz), 6.87 (s, ArH, 4H), 6.70 (d, ArOMe, 4H, *J* 8.8 Hz), 4.52 (d, $ArCH_2Ar$, 4H, *J* 13.5 Hz), 3.98 (t, OCH_2, 4H, *J* 7.4 Hz), 3.91 – 3.87 (m, OCH_2, 4H), 3.78 (s, OMe,3H), 3.30 (d, $ArCH_2Ar$, 4H, *J* 13.5 Hz), 2.00 – 1.88 (m, CH_2, 8H), 1.08 – 0.97 (m, CH_3, 12H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.9, 162.3, 158.6, 155.7, 136.2, 135.3, 134.7, 133.2, 131.2, 130.1, 127.7, 127.0, 113.9, 55.2, 31.3, 23.5, 23.4, 10.5, 10.4 ppm; FTIR (thin film) 2964, 2932, 2871 (C-H stretch), 1698 (C=O stretch), 1520, 1467 (C=C stretch), 1273, 1123 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 884 $[M+Na]^+$; HRMS $[M + H]^+$ Calculated for $C_{56}H_{61}O_8$: 861.4367; Found 861.4361.

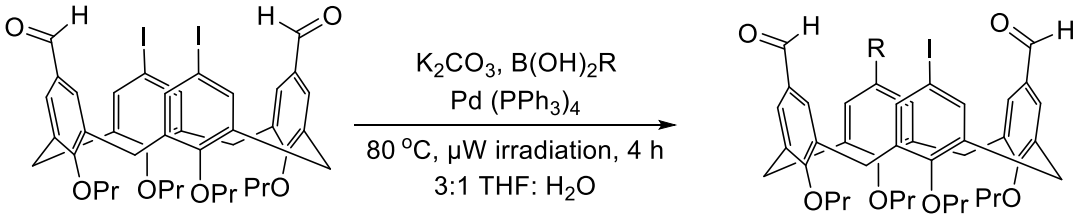


Synthesis of 117: The impure material was purified by flash chromatography (15% EtOAc in petrol) to afford an off-white solid (23 mg, 0.029 mmol, 86%). R_f 0.48 (15% EtOAc in petrol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, CHO, 2H), 7.34 (d, ArH, 4H, *J* 7.1 Hz,), 7.29 – 7.26 (m, H, 3H), 7.25 – 7.20 (m, ArH, 3H), 7.10 (s, ArH, 4H), 7.00 (s, ArH, 4H), 4.52 (d, $ArCH_2Ar$, 4H, *J* 15.2 Hz), 3.99 – 3.87 (m, OCH_2, 8H), 3.30 (d, 4H, *J* 13.6 Hz), 2.01 – 1.89 (m, CH_2, 8H), 1.08 (t, 6H, *J* 7.3 Hz), 0.98 (t, 6H, *J* 7.4 Hz) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.78, 161.77, 156.58, 140.6, 135.7, 135.7, 135.4, 131.36, 129.9, 129.8, 128.7, 127.6, 126.9, 126.8, 31.3, 23.5, 23.3, 10.6, 10.2 ppm; FTIR (thin film) 2963, 2933, 2875 (C-H stretch), 1692 (C=O stretch), 1596, 1466 (C=C stretch), 1122 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 840 $[M+K]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{56}H_{60}NO_6$: 801.4150; Found 801.4152.

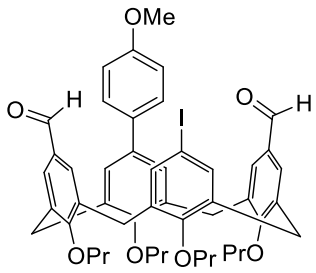


Synthesis of 121: The crude was purified by flash chromatography (15% EtOAc in petrol) to afford an off-white solid (15 mg, 0.017 mmol, 38%). R_f 0.15 (15% EtOAc in petrol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, CHO, 2H), 7.92 (d, $ArNO_2$,4H, *J* 8.8 Hz), 7.29 (s, ArH, 4H, *J* 6.3 Hz), 7.14 (d, $ArNO_2$, 4H, *J* 8.6 Hz), 6.84 (s, ArH, 4H), 4.56 (d, $ArCH_2Ar$, 4H, *J* 13.6 Hz), 4.06 – 4.02 (m ,OCH_2, 4H), 3.92 – 3.87 (m, OCH_2 ,4H), 3.36 (d, $ArCH_2Ar$, 4H, *J* 13.7 Hz), 1.96 (m, CH_2, 8H), 1.04 (m, CH_3, 12H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 162.5, 157.5, 146.6, 146.5, 136.3, 135.2, 133.0, 131.3, 130.3, 127.4, 126.9, 123.8, 31.3, 23.4, 23.4, 10.5, 10.3 ppm; FTIR (thin film) 2961, 2927, 2874 (C-H stretch), 1690 (C=O stretch), 1510 (C=C stretch), 1343 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 930 $[M+K]^+$; HRMS $[M + H]^+$ Calculated for $C_{54}H_{55}N_2O_{10}$; 891.3872; Found: 891.3851.

General procedure for the mono-Suzuki 5

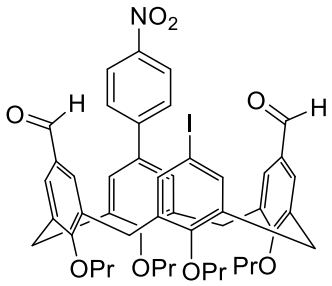


A 5 mL biotage type microwave vial was charged with a solution of **102** (1 eq.) in 3:1 tetrahydrofuran in water, with potassium carbonate (3 eq.), boronic acid (1 eq.) and tetrakis(triphenylphosphine) palladium(0) (0.1 eq.). The vial was sealed with a Teflon cap and heated *via* microwave irradiation for 4 hours at 80°C. The mixture was dissolved in ethyl acetate (2 × 10 mL), transferred to a 25 mL separating funnel, washed with water (2 × 20 mL). The organic mixture was dried over magnesium sulfate, filtered, and solvents were removed *in vacuo*.

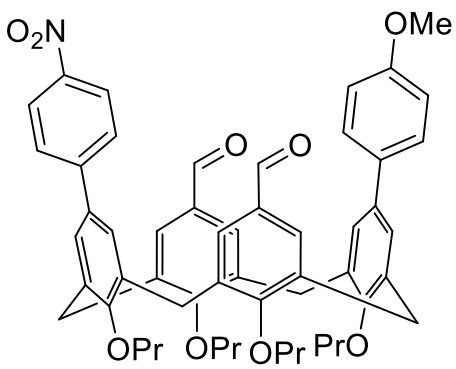


Synthesis of 124: The crude was purified by flash chromatography (30% Et_2O in petrol) to afford a clear oil (21 mg, 0.023 mmol, 35%). R_f 0.34 (15% EtOAc in petrol); ^{1}H NMR (500

MHz, $CDCl_3$) δ 9.45 (s, OCH_2,2H), 7.41 (d, ArOMe, 2H, *J* 8.7 Hz), 7.17 (s, ArHI, 2H), 7.07 (s, ArHArOMe, 2H), 7.02 (d, ArOMe, 2H, *J* 1.8 Hz), 6.95 – 6.92 (m, ArH, 4H), 4.51 (d, $ArCH_2Ar$, 2H, *J* 13.5 Hz), 4.42 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 3.95 – 3.85 (m, OCH_3, 8H), 3.83 (s, OMe, 3H), δ 3.30 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 3.18 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 1.97 – 1.85 (m, CH_2, 8H), 1.05 (t, CH_3, 6H, *J* 7.4 Hz,), 0.96 (m, CH_3, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.7, 161.6, 158.9, 156.9, 156.0, 137.7, 137.6, 135.8, 135.4, 135.2, 135.1, 133.4, 131.4, 130.2, 129.6, 128.2, 127.2, 114.2, 86.0, 55.5, 31.3, 30.7, 23.5, 23.2, 23.1, 10.5, 10.4, 10.2, 10.1 ppm; FTIR (thin film) 2962, 2939, 2881 (C-H stretch), 1693 (C=O stretch), 1463 (C=C stretch), 1278, 1123 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 920 $[M+K]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{49}H_{57}NIO_7$: 898.3180; Found 898.3174.

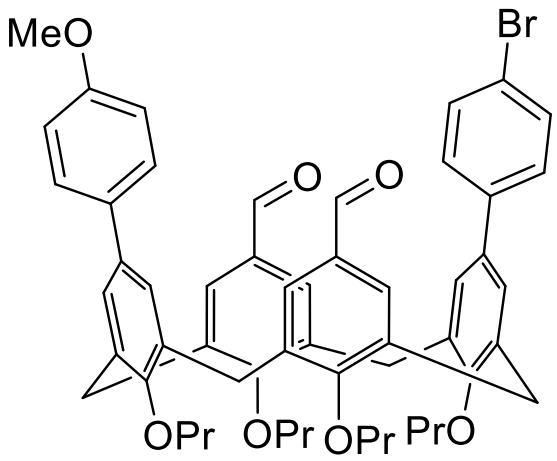


Synthesis of 125: The crude was purified by flash chromatography (30% Et_2O in petrol) to afford an off-white solid (25 mg, 0.017 mmol, 26%). R_f 0.32 (30% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 2H), 8.21 (d, $ArNO_2$, 2H, *J* 8.9 Hz), 7.50 (d, $ArNO_2$, 2H, *J* 8.8 Hz), 7.18 (d, ArH, 2H, *J* 1.5 Hz), 7.12 (d, ArH, 2H, *J* 1.6 Hz), 7.00 (d, ArH, 4H, *J* 6.1 Hz), 4.54 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 4.41 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 3.99 – 3.89 (m, OCH_3, 6H), 3.86 – 3.80 (m, OCH_3, 2H), 3.34 (d, $ArCH_2Ar$, 2H, *J* 13.7 Hz), 3.20 (d, $ArCH_2Ar$, 2H, *J* 13.6 Hz), 1.99 – 1.86 (m, CH_2, 8H), 1.05 – 0.97 (m, CH_3, 12H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 162.1, 157.6, 156.6, 147.0, 146.7, 137.4, 137.1, 135.9, 135.7, 135.4, 133.2, 131.5, 130.4, 130.0, 127.7, 127.7, 124.2, 86.1, 77.4, 77.3, 31.3, 30.8, 23.4, 23.4, 23.2, 10.4, 10.4, 10.3 ppm; FTIR (thin film) 2964, 2933, 2876 (C-H stretch), 1693 (C=O stretch), 1595, 1515, 1463 (C=C stretch), 1342 (C-O) cm^{-1}; MS (MALDI) *m/z* 918 $[M+Na]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{48}H_{54}IN_2O_8$: 913.2921; Found: 913.2919.



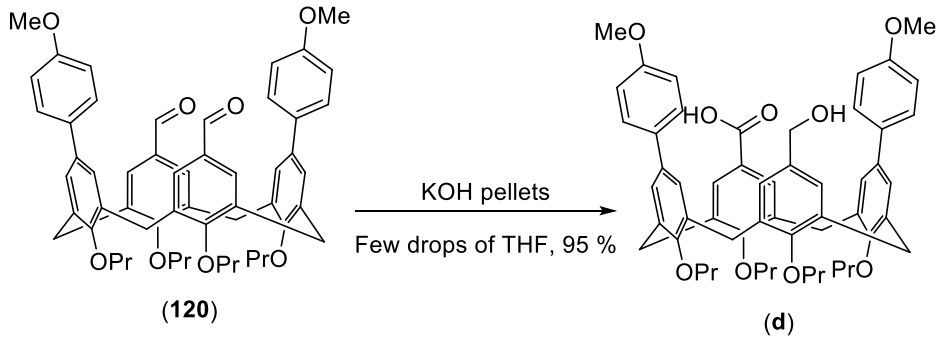
Synthesis of 126: The crude was purified by flash chromatography (15% EtOAc in petrol) to afford an off-white solid (21 mg, 0.024 mmol, 72%). R_f 0.40 (15% EtOAc in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 2H), 7.82 (d, $ArNO_2$, 2H, *J* 8.7 Hz), 7.44 (d, ArH, 4H, *J* 3.4 Hz), 6.93 (d, $ArNO_2$, 2H, *J* 8.5 Hz), 6.76 (d, ArOMe, 2H *J* 8.5 Hz), 6.66 (s, ArH, 2H), 6.59 (s, ArH, 4H), 6.48

(d, ArOMe, 2H, *J* 8.7 Hz), 4.55 (t, $ArCH_2Ar$, 4H, *J* 13.8 Hz), 4.10 (m, OCH_3, 4H), 3.82 (m, OCH_3, 4H), 3.68 (s, OMe, 3H), 3.36 – 3.29 (m, CH_2, 4H), 2.03 – 1.89 (m, CH_2, 8H), 1.07 (m, CH_3, 6H), 1.00 (m, CH_3, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.1, 163.1, 161.9, 158.7, 157.1, 155.3, 146.8, 146.3, 137.1, 136.6, 135.0, 134.7, 133.9, 133.2, 132.6, 131.1, 131.0, 130.1, 127.4, 127.2, 126.9, 126.4, 126.3, 123.7, 115.8, 113.7, 55.2, 31.3, 23.5, 23.4, 10.6, 10.6, 10.3 ppm; FTIR (thin film) 2962 (C-H stretch), 1692 (C=O stretch), 1595, 1515, 1463 (C=C stretch), 1342 (C-O) cm^{-1}; MS (MALDI) *m/z* 915 $[M+K]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{55}H_{61}N2O_9$: 894.4410; Found: 894.4406.



Synthesis of 131: The crude was purified by column chromatography (15% EtOAc in petrol) to afford a clear oil (14 mg, 0.015 mmol, 42%). R_f 0.34 (15% EtOAc in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 2H), 7.24 – 7.21 (m, 5H), 7.01 (d, 2H, *J* 8.6 Hz), 6.92 (d, 2H, *J* 8.3 Hz), 6.80 (d, 4H, *J* 5.7 Hz), 6.68 (d, 2H, *J* 8.8 Hz), δ 4.54 (d, 2H, *J* 4.4 Hz), 4.51 (d, 2H, *J* 4.4 Hz), 4.04 – 3.98 (m, 4H), 3.90 – 3.84 (m, 4H), 3.81 (s, 3H), 3.32 (s, 2H), 3.29 (s, 2H), 1.95 (m, 8H), 1.06 – 0.98 (m, 12H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.8, 162.5, 158.8, 155.6, 139.5, 136.5, 136.3, 135.3, 134.8, 134.5, 134.4, 132.9, 132.6, 131.5, 131.2, 130.5, 130.0, 128.4, 127.6, 127.1, 126.8, 120.7, 117.4, 113.9, 55.4, 31.3, 23.5, 23.4, 10.5, 10.4, 10.4 ppm; FTIR (thin film) 2961, 2931, 2873 (C-H stretch), 1690 (C=O stretch), 1464 (C=C stretch), 1276 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 948 $[M+K]^+$; HRMS $[M + H]^+$ Calculated for $C_{55}H_{58}Br_1O_7$: 909.3372; Found: 909.3360.

General Procedure 6 for the Mechanochemical Cannizzaro Reaction



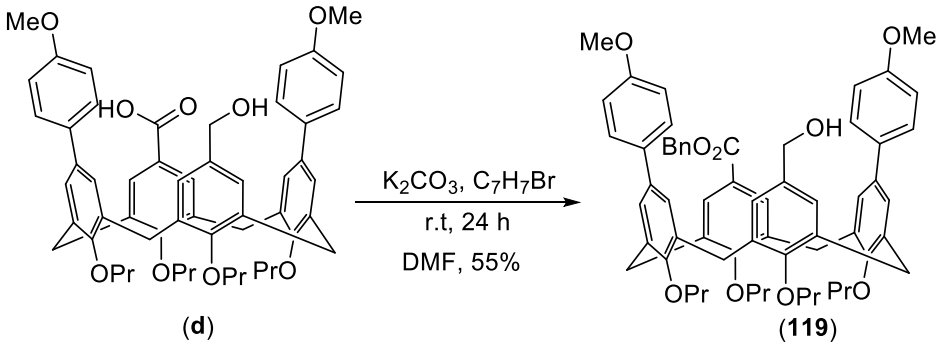
(**120**) (**d**)

A mortar was charged with the appropriate diformyl calix[4]arene (1 eq.) and potassium hydroxide (100 eq.). The mixture was ground using the pestle with the occasional addition of tetrahydrofuran (a few drops) to aid mixing until the starting material had been consumed as indicated by TLC analysis (15% EtOAc in petrol). The reaction mixture was partitioned between 1M HCl (10 mL) and diethyl ether (10 mL), and the ethereal phase separated. The organics were dried over magnesium sulfate, filtered and concentrated to afford the crude Cannizzaro product.

General Procedure 7 for the Formation of Benzyl Esters

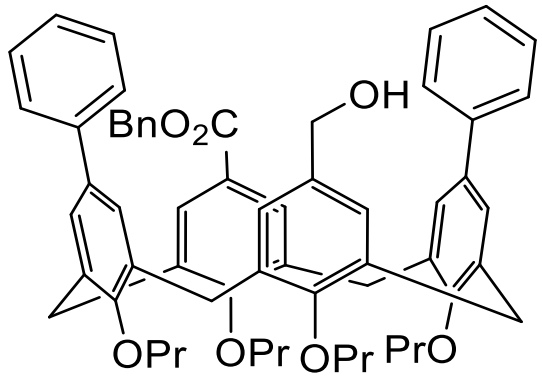
The crude Cannizzaro derived calix[4]arenes (1 eq.) were taken up in *N,N*-dimethylformamide (5 mL) and potassium carbonate (2 eq.) and benzyl bromide (1.2 eq.) were added. The mixture was stirred overnight at room temperature, after which time TLC analysis indicated the starting material had been consumed. The mixture was diluted with diethyl ether (10 mL) and washed with water (4 x 5 mL) and brine (5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to afford the crude AABC and ABCD calix[4]arenes.

<u>Synthesis of 119</u>

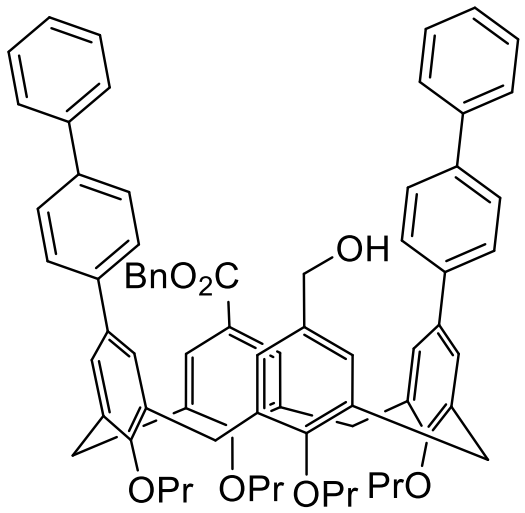


(**d**) (**119**)

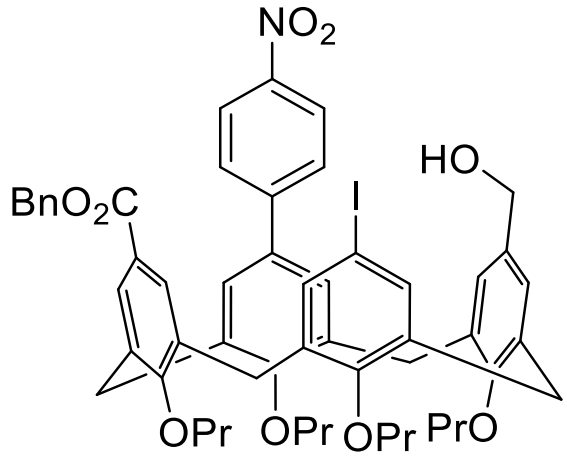
The crude was purified by flash column chromatography (30% Et_2O in petrol) to afford an oil (21 mg, 0.021 mmol, 55%). R_f 0.03 (30% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.37 (m, ArOBn, ArPhOMe, 11H), 7.01 (d, ArPhOMe, 4H, *J* 8.7 Hz), 6.59 (s, ArH, 2H), 5.38 (s, OBn, 2H), 4.51 (d, $ArCH_2Ar$, 4H, *J* 11.6 Hz), 4.48 (d, $ArCH_2Ar$, 4H, *J* 11.6 Hz)4.23 – 4.09 (m, OCH_2, 4H), 4.05 (t, OCH_3, 2H, *J* 7.1 Hz), 4.02 (s, OCH_3, 6H), 3.99 (t, OCH_2, 2H, *J* 7.1 Hz), δ 3.17 (d , $ArCH_2Ar$, 2H, *J* 3.5 Hz), 3.13 (d, $ArCH_2Ar$, 2H, *J* 13.4 Hz), 2.21 – 2.08 (m, CH_2, 8H), 1.26 (m, CH_3, 6H), 1.16 (t, CH_3, 6H, *J* 7.5 Hz) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 160.7, 158.6, 156.4, 155.6, 136.4, 136.2 135.5, 134.9, 134.9, 134.9, 134.2, 133.8, 129.8, 128.6, 128.0, 127.9, 127.7, 127.3, 126.8, 126.1, 123.5, 114.0, 66.2, 64.5, 55.4, 31.3, 31.3, 23.5, 23.5, 23.3, 10.7, 10.6, 10.2 ppm; FTIR (thin film) 3512 (O-H stretch), 2960, 2931, 2874 (C-H stretch), 1715 (C=O stretch), 1464 (C=C stretch), 1184 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 1007 $[M+K]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{63}H_{68}NO_9$: 986.5192; Found: 986.5202.



Synthesis of 117: The crude was purified by column chromatography (30% Et_2O in petrol) to afford a clear oil (35 mg, 0.038 mmol, 65%). R_f 0.37 (30% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, ArH, 4H, *J* 7.2 Hz), 7.35 (m, OBn, 5H), 7.28 (t, ArH, 2H, *J* 6.2 Hz), 7.25 – 7.14 (m, ArH, 8H), 7.12 (s, ArH, 2H), 6.28 (s, Ar*H*, 2H), 5.15 (s, CH_2Bn, 2H), 4.55 – 4.47 (m, ArCH_2Ar, 4H), 4.03 (m, OCH_2, 4H), 3.87 (s, CH_2OH, 2H), 3.82 (t, OCH_2, 2H, *J* 7.0 Hz), 3.76 (t, OCH_2, 2H, *J* 7.0 Hz), 3.18 (d, ArCH_2Ar, 2H, *J* 13.6 Hz), 3.15 (d, ArCH_2Ar, 2H, *J* 13.5 Hz), 2.03 – 1.89 (m, CH_2, 8H), 1.10 (m, CH_3, 6H), 0.95 (t, CH_3, 6H, *J* 7.5 Hz) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 160.2, 157.0, 155.1, 141.0, 136.5, 136.2, 135.9, 135.1, 134.9, 134.4, 133.6, 129.6, 128.6, 128.5, 127.9, 127.8, 127.5, 127.3, 126.9, 126.6, 125.8, 123.5, 66.0, 64.2, 31.2, 31.2, 23.5, 23.4, 23.1, 10.7, 10.6, 10.0 ppm; FTIR (thin film) 2961,2930, 2874 (C-H stretch), 1715 (C=O stretch), 1465 (C=C stretch), 1185 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 947 $[M+K]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{61}H_{64}NO_7$: 926.4995; Found: 926.4990.

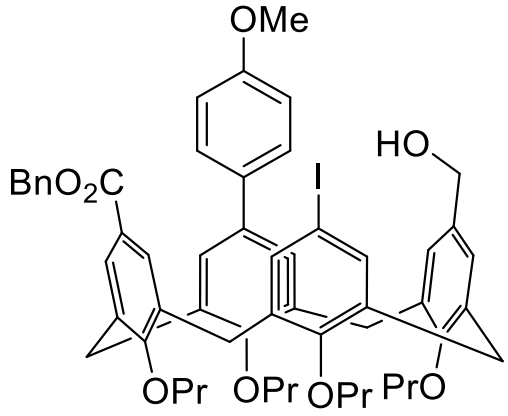


Synthesis of 122: The crude was purified by column chromatography (30% Et_2O in petrol) to afford a clear oil (27 mg, 0.025 mmol, 82%). R_f 0.16 (30% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, ArH, ArPhPh, 6H), 7.50 (m, ArH, ArPhPh, 3H), 7.42 – 7.26 (m, ArH, ArPhPh, OBn, 11H), 7.25 – 7.17 (m, ArH, ArPhPh, 9H), 6.33 (s, ArH, 2H), 5.11 (s, CH_2Bn, 2H), 4.54 (d, $ArCH_2Ar$, 2H, *J* 11.5 Hz), 4.51 (d, $ArCH_2Ar$, 2H, *J* 11.4 Hz), 4.00 – 3.86 (m, CH_2OH, OCH_3, 6H), 3.80 (t, OCH_3, 2H, *J* 7.1 Hz), 3.74 (t, OCH_3, 2H, *J* 7.1 Hz), 3.29 (d, $ArCH_2Ar$, 2H, *J* 13.5 Hz), 3.25 (d, $ArCH_2Ar$, 2H, *J* 13.4 Hz), 1.96 – 1.84 (m, CH_2 8H), 1.00 (m, CH_3, 6H), 0.90 (t, CH_3, 6H, *J* 7.5 Hz) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 160.6, 157.0, 155.5, 141.0, 140.1, 139.4, 136.4, 135.7, 134.8, 134.1, 129.8, 128.9, 128.6, 128.0, 127.7, 127.4, 127.4, 127.2, 127.1, 126.1, 123.7, 77.0, 66.2, 64.5, 31.4, 31.3, 29.8, 23.5, 23.3, 10.7, 10.7, 10.2 ppm; FTIR (thin film) 2960, 2926, 2874 (C-H stretch), 1714 (C=O stretch), 1465 (C=C stretch), 1184 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 1100 $[M+K]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{73}H_{76}NO_7$: 1078.5585; Found: 1078.5616.

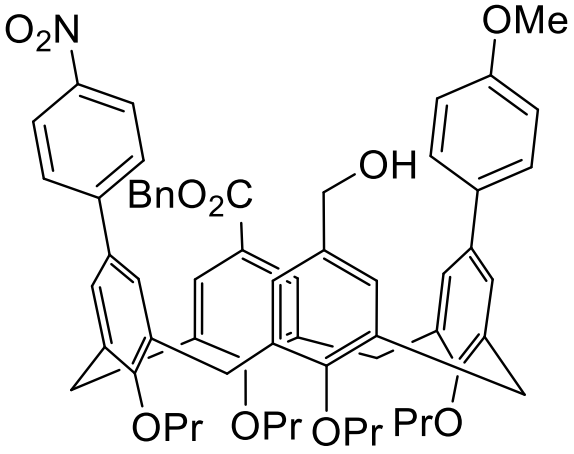


Synthesis of 126: The crude was purified by column chromatography (30% Et_2O in petrol) to afford a clear oil (21 mg, 0.021 mmol, 70%). R_f 0.07 (30% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 – 8.20 (m, $ArNO_2$, 2H), 7.56 – 7.52 (m, $ArNO_2$, 2H), 7.40 – 7.32 (m, OBn, 5H), 7.31 (d, ArH, 1H, *J* 1.8 Hz), 7.27 (d, ArH, 1H, *J* 2.0 Hz), 7.11 – 7.06 (m, ArH, 4H), 6.53 (d, ArH, 1H, *J* 1.7 Hz), 6.43 (d, ArH, 1H, *J* 1.7 Hz), 5.25 (q, CH_2Bn, 2H, *J* 12.7 Hz), 4.51 (t, $ArCH_2Ar$, 2H, *J* 12.9 Hz), 4.41 – 4.34 (m, $ArCH_2Ar$, 2H), 4.09 (q, CH_2OH , 2H, *J* 12.8 Hz), 4.01 – 3.78 (m, OCH_3, 8H), 3.28 (d, $ArCH_2Ar$, 1H, *J* 13.6 Hz), 3.24 (d, $ArCH_2Ar$, 1H, *J* 13.5 Hz), 3.15 (d, $ArCH_2Ar$, 1H, *J* 13.5 Hz), 3.10 (d, $ArCH_2Ar$, 1H, *J* 13.5 Hz), 2.00 – 1.86 (m, CH_2, 8H), 1.07 – 0.94 (m, CH_2, 12H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 160.8, 158.0, 156.9, 155.7, 147.5, 146.6, 138.2, 137.6, 137.4, 137.1, 136.4, 136.3, 135.7, 135.2, 134.9, 134.6, 134.3, 134.0, 132.8, 130.1,

131.0, 128.8, 128.2, 127.9, 127.9, 127.7, 127.4, 126.6, 126.4, 124.2, 123.9, 85.7, 66.4, 64.5, 31.3, 31.2, 30.8, 30.8, 23.4, 23.4, 23.2, 10.5, 10.5, 10.3, 10.3 ppm; FTIR (thin film) 2962, 2932, 2875 (C-H stretch), 1714 (C=O stretch), 1459 (C=C stretch), 1342, 1186 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 1026 $[M+Na]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{55}H_{62}IN_2O_9$: 1021.3477; Found: 1021.3495.

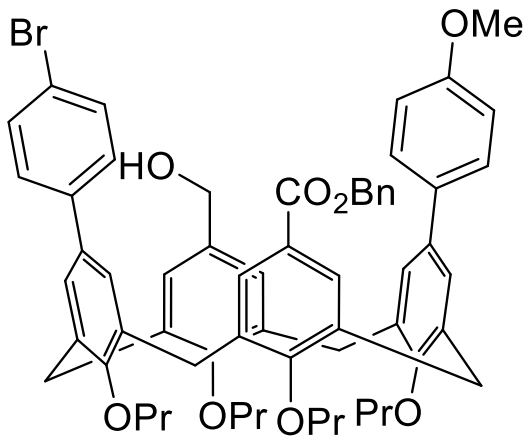


Synthesis of 127: The crude was purified by column chromatography (30% Et_2O in petrol) to afford a clear oil (20 mg, 0.020 mmol, 48%). R_f 0.13 (30% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, ArOMe, 2H), 7.35 – 7.26 (m, OBn, 5H), 7.18 (d, ArH, 1H, *J* 2.1 Hz), 7.14 (s, ArH, 2H), 7.10 (d, ArH, 1H, *J* 2.0 Hz), 6.97 – 6.93 (m, ArOMe, 2H), 6.35 (d, ArH, 1H, *J* 1.8 Hz), 6.26 (d, ArH, 1H, *J* 1.8 Hz), 5.22 (q, CH_2Bn, 2H, *J* 12.8 Hz), 4.47 (t, ArC*H*$_2$Ar, 2H, *J* 13.2 Hz), 4.39 (t, ArC*H*$_2$Ar, 2H, *J* 13.2 Hz), 4.05 – 3.69 (m, $ArOCH_3$, OCH_3, CH_2OH, 13H), 3.24 (d, ArC*H*$_2$Ar, 1H, *J* 13.5 Hz), 3.21 (d, ArC*H*$_2$Ar, 1H, *J* 13.4 Hz), 3.13 (d, ArC*H*$_2$Ar, 1H, *J* 13.5 Hz), 3.09 (d, ArC*H*$_2$Ar, 1H, *J* 13.5 Hz), 1.99 – 1.84 (m, C*H*$_2$, 8H), 1.06 (m, CH_3, 6H), 0.96 – 0.91 (m, C*H*$_3$, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 160.4, 158.8, 157.4, 156.5, 155.3, 138.9, 138.2, 137.7, 137.3, 136.4, 136.3, 135.6, 135.2, 135.0, 134.7, 134.1, 134.0, 133.9, 133.3, 130.0, 129.5, 128.8, 128.2, 128.1, 127.7, 127.5, 127.0, 126.3, 125.8, 123.7, 114.2, 85.6, 66.2, 64.3, 55.5, 31.3, 31.2, 30.9, 30.7, 23.5, 23.2, 23.1, 10.7, 10.6, 10.2, 10.1 ppm; FTIR (thin film) 2961, 2933, 2875 (C-H stretch), 1713 (C=O stretch), 1463 (C=C stretch), 1184 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 1011 $[M+Na]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{56}H_{64}INO_8$: 1006.3741; Found: 1006.3749.

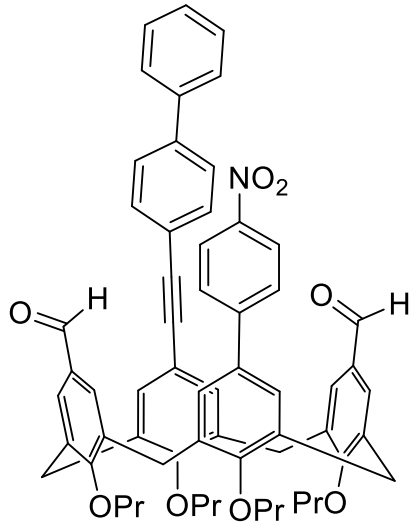


Synthesis of 130: The crude was purified by column chromatography (30% Et_2O in petrol) to afford a clear oil (20 mg, 0.02 mmol, 52%). R_f 0.06 (30% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, $ArNO_2$, 2H, *J* 8.8 Hz), 7.52 (dd, ArH, 2H, *J* 17.5, 1.8 Hz), 7.36 (dd, OBn, 2H, *J* 6.6, 3.0 Hz), 7.31 – 7.28 (m, OBn, 3H), 7.10 (d, ArOMe, 2H, *J* 8.7 Hz),

6.92 (d, ArOMe, 2H, *J* 8.6 Hz), 6.80 (d, ArH, 2H, *J* 6.2 Hz), 6.73 (d, ArH, 4H, *J* 7.0 Hz), 6.57 (d, $ArNO_2$, 2H, *J* 8.7 Hz), 5.28 (s, CH_2Bn, 2H), 4.51 (m, $ArCH_2Ar$, 4H), 4.30 (d, CH_2OH, 2H, *J* 1.8 Hz), 4.06 – 3.79 (m, OCH_3, 8H), 3.72 (s, $ArOCH_3$, 3H), 3.29 (d, $ArCH_2Ar$, 1H, *J* 7.1 Hz), 3.27 (d, $ArCH_2Ar$, 1H, *J* 7.0 Hz), 3.24 (d, $ArCH_2Ar$, 1H, *J* 11.1 Hz), 3.21 (d, $ArCH_2Ar$, 1H, *J* 11.0 Hz), 1.99 – 1.91 (m, CH_2, 8H), 1.08 – 0.92 (m, CH_3, 12H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 161.5, 158.6, 157.5, 156.4, 155.6, 147.3, 146.3, 136.4, 136.0, 135.8, 135.63, 135.5, 135.1, 135.0, 134.9, 134.7, 134.3, 133.2, 132.8, 130.4, 130.1, 128.7, 128.2, 128.0, 127.6, 127.4, 127.2, 127.0, 126.8, 126.7, 126.2, 123.7, 123.6, 113.7, 66.5, 64.9, 55.2, 31.3, 31.2, 29.8, 23.5, 23.4, 23.3, 10.5, 10.5, 10.4, 10.3 ppm; FTIR (thin film) 3500 (O-H stretch), 2960, 2926, 2874 (C-H stretch), 1714 (C=O stretch), 1463 , 1342 (C=C stretch), 1186 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 1007 $[M+Na]^+$; HRMS $[M + H]^+$ Calculated for $C_{62}H_{66}NO_{10}$: 982.4536; Found: 982.4525.

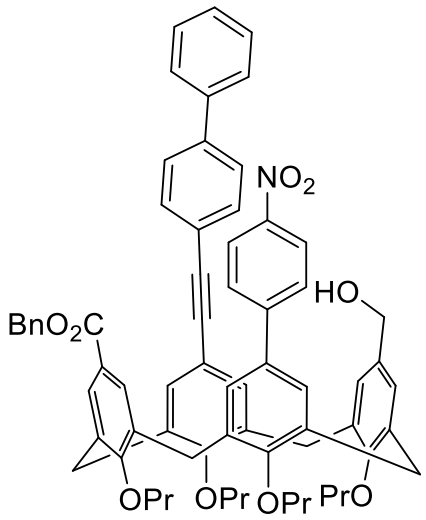


Synthesis of 132: The crude was purified by column chromatography (15% EtOAc in petrol) to afford a clear oil (13 mg, 0.013 mmol, 55%). R_f 0.24 (15% EtOAc in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, ArBr, 2H), 7.31 – 7.26 (m, OAr, 5H), 7.25 – 7.19 (m, ArOMe, 2H), 7.12 (m, ArBr, ArH, 4H), 6.98 (d, ArH, 4H, *J* 3.9 Hz), 6.80 – 6.77 (m, ArOMe, 2H), 6.46 (d, ArH, 2H, *J* 2.6 Hz), 5.20 (s, CH_2OAr, 2H), 4.49 (m, $ArCH_2Ar$, 4H), 4.05 (s, CH_2OH, 2H), 3.98 – 3.86 (m, OCH_2, 6H), 3.84 (s, OCH_3, 3H), 3.83 – 3.80 (m, OCH_2, 2H), 3.26 (s, $ArCH_2Ar$, 1H), 3.24 (s, $ArCH_2Ar$, 1H), 3.22 (s, $ArCH_2Ar$, 1H), 3.19 (s, $ArCH_2Ar$, 1H), 2.00 – 1.89 (m, CH_2, 8H), 1.04 (m, CH_3, 6H), 0.98 (m, CH_3, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) 166.9, 160.9, 158.7, 157.0, 156.2, 155.8, 140.0, 136.4, 136.2, 135.9, 135.5, 135.2, 134.9, 134.6, 134.4, 134.1, 133.6, 131.6, 130.0, 129.9, 128.7, 128.5, 128.1, 127.8, 127.8, 127.4, 127.2, 127.0, 126.7, 126.4, 126.3, 123.6, 120.6, 114.0, 66.3, 64.6, 55.5, 31.3, 23.5, 23.3, 10.6, 10.6, 10.3 ppm; FTIR (thin film) 2963, 2930, 2877 (C-H stretch), 1719 (C=O stretch), 1464 (C=C stretch), 1184, 1006 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 1057 $[M+K]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{62}H_{69}Br_1O_8N_1$: 1034.4210; Found: 1034.4201.



Synthesis of 133: Synthesis employing general procedure **3** from Mono-nitro **125**. Purification by column chromatography (30% diethyl ether in petrol) afforded **133** as an orange oil (32.4 mg, 0.034 mmol, 74%). R_f 0.13 (30% Et_2O in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 9.63 (s, CHO, 2H), 8.04 (d, $ArNO_2$, 2H, *J* 8.8 Hz), 7.62 (m, ArH-ArH, 2H), 7.52 – 7.49 (m, $ArNO_2$, 2H), 7.47 – 7.33 (m, ArH-ArH, 8H), 7.23 (s, ArH, 4H), 6.93 (s, ArH, 2H), 6.86 (s, ArH, 2H), 4.57 (s, $ArCH_2Ar$, 1H), 4.54 (s, $ArCH_2Ar$, 1H), 4.50 (s, $ArCH_2Ar$, 1H), 4.48 (s, $ArCH_2Ar$, 1H), 4.00 (t, OCH_3, 4H, *J* 7.5 Hz), 3.94 – 3.85 (m, OCH_3, 4H), 3.36 (s, $ArCH_2Ar$, 1H), 3.34 (s, $ArCH_2Ar$, 1H), 3.29 (s, $ArCH_2Ar$, 1H), 3.26 (s, $ArCH_2Ar$, 1H), 2.01 – 1.89 (m, CH_2, 8H), 1.07 – 0.98 (m, CH_3, 12H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) 191.8, 162.3, 157.5, 156.9, 147.0, 146.6, 141.0, 140.7, 136.1, 135.3, 134.7, 133.4, 132.0, 131.8, 131.4, 130.6, 130.1, 128.9, 127.7, 127.6, 127.5, 127.3, 127.1, 124.0, 122.2, 117.5, 90.0, 88.5, 77.3, 77.3, 31.3, 31.0, 23.5, 23.4, 23.4, 10.4, 10.4, 10.3 ppm; FTIR (thin film) 2962, 2931, 2875 (C-H stretch), 1692 (C=O stretch),1595, 1342 (C=C stretch) cm^{-1}; MS (MALDI) *m/z* 969 $[M+Na]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{62}H_{63}N_2O_8$: 963.4591 Found: 963.4579.

.



Synthesis of 135: Purification by column chromatography (15% EtOAc in petrol) afforded **135** as a yellow oil (24.2 mg, 0.023 mmol, 90%). R_f 0.1 (15% EtOAc in petrol); ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 – 8.06 (m, 2H), 7.64 – 7.60 (m, 2H), 7.56 – 7.52 (m, 2H), 7.51 – 7.43 (m, 6H), 7.39 – 7.31 (m, 8H), 7.04 (d, 2H, *J* 2.4 Hz), 7.00 (s, 2H), 6.54 (s, 1H), 6.51 (s, 1H), 5.26 (q, 2H, *J* 12.7 Hz,), 4.48 (m, 4H), 4.13 (q, 2H, *J* 12.8 Hz), 4.01 – 3.80 (m, 8H), 3.29 (d, 1H, *J* 13.6 Hz), 3.25 (d, 1H, *J* 9.7 Hz), 3.22 (d, 1H, *J* 9.7 Hz), 3.17 (d, 1H, *J* 13.5 Hz), 1.99 – 1.89 (m, 8H), 1.06 – 0.95 (m, 8H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) 166.9, 160.9, 158.0, 157.4, 155.8, 140.9, 140.7, 136.4, 136.3, 135.9, 135.8, 135.3, 135.1, 135.0, 134.9, 134.4, 133.0, 132.2, 131.9,

130.1, 130.0, 129.0, 128.8, 128.2, 127.9, 127.9, 127.7, 127.5, 127.5, 127.3, 127.1, 126.6, 126.5, 124.1, 123.8, 122.5, 121.7, 117.0, 90.5, 88.2, 77.7, 77.4, 77.2, 76.9, 66.4, 64.6, 29.9, 23.4, 23.4, 23.3, 10.6, 10.5, 10.3 ppm; FTIR (thin film) 3488 (O-H stretch), 2963, 2925, 2853 (C-H stretch), 1714 (C=O stretch), 1595, 1345 (C=C stretch), 1186 (C-O stretch) cm^{-1}; MS (MALDI) *m/z* 1077 $[M+Na]^+$; HRMS $[M + NH_4]^+$ Calculated for $C_{69}H_{71}N_2O_9$: 1071.5127; Found:1071.5154.

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