The Synthesis and Derivation of Tetra-substituted Methylene Bridge Calix[4]arenes

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Abstract

Chapter 1 discusses the history of calix[n]arenes dating back to the initial investigation of the phenol-formaldehyde procedure up to the seminal work by Gutsche that developed the synthesis of these macrocycles allowing ease of access. Modification of these macrocycles is discussed on the upper- and lower-rim followed by a detailed look into different methods utilised to build functionalisation at the methylene bridge. Finally, methods of introducing multiple functionalities to the methylene bridge is considered.

Chapter 2 presents the synthesis of a previously reported calix[4]arene which has been mono-substituted at the methylene bridge containing a saturated 1,4 diketone. This compound is then used as an intermediate to the synthesis of pyrrole appended C[4]s through the Paal-Knorr synthesis with a range of different anilines. A library of these C[4]s is presented with observations and discussions.

Chapter 3 contains a further look into the Paal-Knorr synthesis using the saturated 1,4 diketone intermediate with a set of long chain alkyl-amines. The exploration into other heterocycles is then discussed including a synthesis of a thiophene using the 1,4 saturated intermediate and a 1,4 unsaturated diketone with subsequent pyridazine ring closure. The deprotection of the pyridazine, Thiophene and a long chain alkyl pyrrole is discussed along with issues encountered, how they are overcome and decomposition of these compounds.

Chapter 4 discusses introducing pyridyl functionality at the methylene bridge using the Paal-Knorr synthesis. The different methods considered and trialled followed by synthesis of two extended anilines and the reaction of 2-,3- and 4-(pyridyl)aniline with the 1,4 saturated diketone forming the respective pyrroles, the products synthesised and how these could be used to form asymmetrical calix[4]arenes.

Chapter 5 is a summary and overview of the work presented in this thesis with a small section on the possible future work in this area.

Acknowledgements

Firstly, I would like to thank my supervisor, Dr Scott J. Dalgarno, for offering me the opportunity to undertake research within his group on a difficult but exciting area of chemistry. His encouragement and constant reassurance during what has been a difficult and uncertain period of time will always be remembered. I am honoured to be continuing under his supervision as I progress into academia.

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Symbols and Abbreviations

°C	Degrees Celsius
Å	Angstrom (0.1 nm)
AcOH	Acetic Acid
Ar	Aryl
ASU	Asymmetric unit
Br. s	Broad Singlet
$CDCl_3$	Deuterated Chloroform
$CHCl_3$	Chloroform
C[4]	Calix[4]arene
CH_3CN	Acetonitrile
d	Doublet
DCM	Dichloromethane
d_6-DMSO	Deuterated Dimethyl sulfoxide
d_3-ACN	Deuterated Acetonitrile
DMF	Dimethylformamide
ESI-MS	Electronspray Ionisation Mass spectrometry
Et_2O	Diethyl ether
EtOAc	Ethyl Acetate
H_2SO_4	Sulfuric acid
$H_4TBC[4]$	p-tert-Butylcalix[4]arene
HCl	Hydrochloric acid
HFIP	Hour
Hr	Heteronuclear Single Quantum
HSQC	Coherence
Hz	Hertz

IR	Infrared
K	Kelvin
KOH	Potassium Hydroxide
m	Multiplet
M^+	Molecular ion peak
mCPBA	Meta-chloroperbenzoic acid
MeOH	Methanol
Mins	Minutes
mmol	Millimoles
MS	Mass Spectrometry
MW	Molecular Weight
m/z	Mass/electric charge ratio
NaH	Sodium Hydride
NaOH	Sodium Hydroxide
NBS	N-bromosuccinimide
NMR	Nuclear Magnetic Resonance
OH	Hydroxy
OMe	Methoxy
PET	Petroleum Ether (40-60 °C)
Ph	Phenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
p-TsOH·H_2O	*p*-Toluenesulfonic acid monohydrate
py	Pyridine
R_f	Retention Factor
s	Singlet
t	Triplet

t-Bu	*tert*-Butyl
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
VT	Variable Temperature

Chapter 1
Introduction

1.1. History of Calix[n]arenes.

The origins of calix[*n*]arenes (C[*n*]s) can be traced back to 1872, where Adolf Von Baeyer discovered the synthesis of phenolphthalein, a phthalein dye made through the condensation of phenol and phthalic anhydride under acidic conditions.[1] Moving forward, Baeyer decided to continue experimenting with condensation reactions shifting to phenol with formaldehyde. This yielded a thick resinous cement like substance that is known today to be an amorphous rigid cross-linked polymeric material.[1,2] Due to a lack of analytical techniques at the time, Baeyer was unable to fully characterise this material and instead moved on in his search for organic dyes.[3,4] In 1882 his synthesis of Indigo was first published and later in 1905 he was awarded the Nobel prize for his contribution to organic chemistry, dyes, and hydroaromatic compounds. It wasn't until Baekeland, in his search for a profitable synthetic resin, was the phenol-formaldehyde procedure investigated further. After refining the process, he found that by using only a small amount of base he could produce an appealing resin-like material and so in 1907 he filed a patent for Bakelite, known now as the first commercially available synthetic polymer.[5] These polymers consisted of phenol units bound together at the *ortho* and *para* positions by a methylene bridge.

Moving forward, Zinke and Ziegler adapted this phenol-formaldehyde procedure by using phenols with alkyl functional groups in the *para* position. By doing so they were able to block substitution at this position and, therefore, due to the *ortho/para* directing electron donating OH groups, reaction would primarily occur at the two ortho positions, thus reducing crosslinking possibilities. Zinke *et al.* reacted a variety of *p*-substituted phenols (*p*-methyl, *p*-*tert*-butyl and *p*-cyclohexyl) with formaldehyde in a one pot base catalysed condensation using NaOH. An insoluble high melting point (>300 °C) crystalline solid was isolated, and from this Zinke and Ziegler predicted an intuitively appealing cyclic tetramer through mass spectroscopy and elemental analysis.[6] However, full structural determination was restricted due to lack of analytical techniques available at the time. By the time Zinke published a detailed account of his findings in 1952, the

cyclic tetramer had become well known to chemists studying the formaldehyde phenol reaction, and in 1956 Hayes and Hunter published a stepwise procedure to the species using *p*-cresol and concluded similar results, a crystalline material with a high melting point (>300 °C). However, when Cornforth repeated Zinke's procedure he found that not one, but two crystalline products could be isolated with only a small difference in melting point. This was attributed to different diastereomers being unable to rotate around the methylene bridge but was later disproved by the work of Gutsche and co-workers that revealed the Zinke procedure actually yielded a mixture of cyclic oligomers, majorly the tetramer, hexamer, and octamer but small quantities of the pentamer and heptamer were found.[7] Based on these findings it was thought that the two compounds Zinke and Cornforth isolated were the cyclic tetramer and octamer.

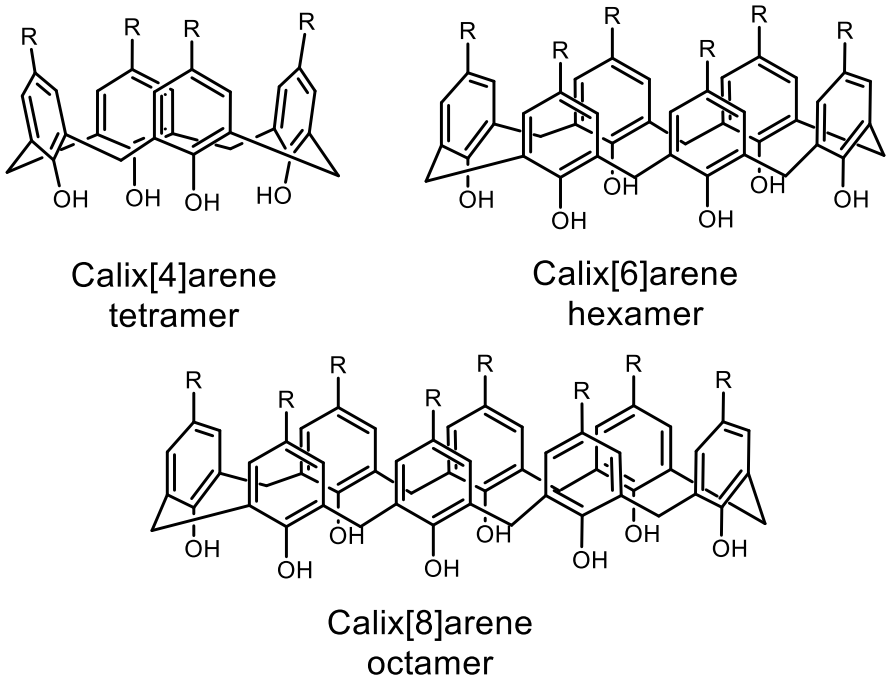


Figure 1.1. Representation of the major cyclic products obtained from the Zinke-Cornforth procedure under different conditions.

Later work by Gutsche focused on the synthesis of these molecules and the nomenclature he coined as calix[*n*]arenes.[8] Gutsche found a resemblance between the cone cyclic structure and a Greek vase known as the Calyx-krater. This, coupled with the arene units in the backbone make up the name calix[*n*]arene where *n* donates the number of arene units in the macrocycle. Following acceptance by IUPAC, officially recognising

calixarene as the established nomenclature a systematic naming system was required. The systematic name for the cyclic tetramer formed from *p-tert*-butylphenol and formaldehyde is 5,11,17,23-tetra(*tert*-butyl)-25,26,27,28-tetrahydroxycalix[4]arene, however, this can lead to very complex and hard to understand names so for ease of use, it is more commonly shortened to *p-tert*-butylcalix[4]arene (H_4TBC[4]). The work in this thesis is exclusively based on the derivation of *p-tert*-butylcalix[4]arene and therefore it is important to know the numbering convention used to understand the full naming of these compounds for substituents at different positions. For calix[4]arene, 5, 11, 17 and 23 relate to the para position substituent on the phenyl ring, 25, 26, 27 and 28 to the lower-rim substitution, and finally positions 2, 8, 14, and 20 to the substituents at the methylene bridges. The full numbering system can be seen in the figure below. (Figure 1.2).

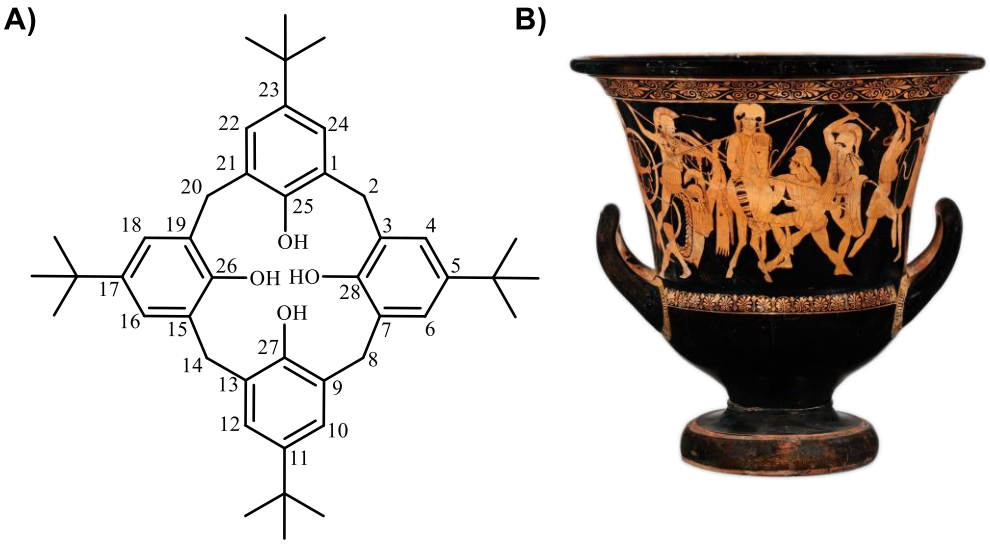
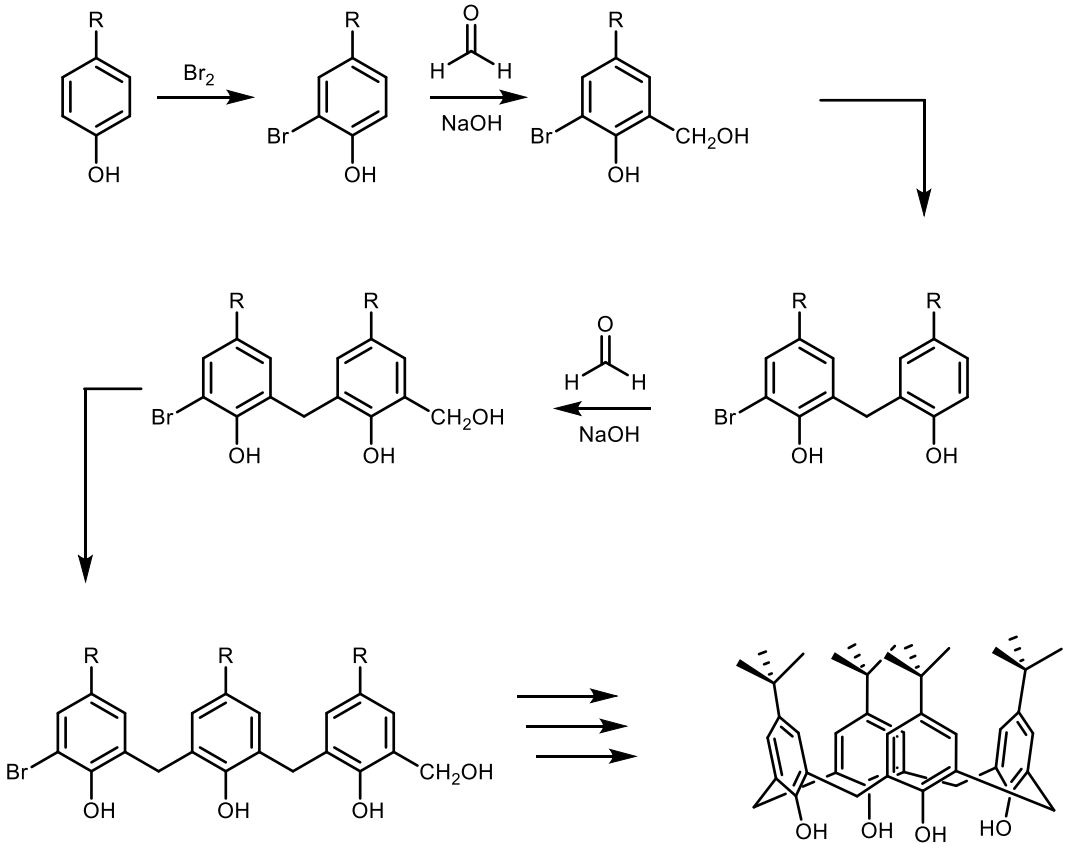


Figure 1.2. (A) Number convention for 5,11,17,23-tetra(*tert*-butyl)-25,26,27,28-tetrahydroxycalix[4]arene (H_4TBC[4]). (B) Greek vase known as the calyx-crater from which Gutsche coined the calix[*n*]arene name.

Key findings in this study were that the Zinke-Cornforth procedure was especially sensitive to both base and temperature which allowed calix[n]arenes, n = 4 - 9 of different size to be synthesised with the major products being n = 4, 6 and 8. It was seen that seemingly insignificant deviations had a significant impact on yield. If too little or too much base was added the yield of the tetramer would tend towards 0 %, with even larger quantities leading to increased formation of the hexamer. Gutsche also showed that not

only does concentration of base play a role, but also the base used, whereby NaOH tends to favour the cyclic tetramer and octamer, but when KOH is employed the hexamer is favoured. This would indicate that the nature of cation plays a role in the reaction and it is postulated that this may be due to a templating effect. It was also noted that by using an elevated temperature, the cyclic tetramer would be created over the cyclic octamer, indicating that these calix[n]arenes were under thermodynamic and kinetic control. The boiling point of the solvent employed therefore played a significant role in the synthesis. Overall, recapping the findings it was shown that the major C[*n*]s could all be synthesised reliably by controlling the reaction conditions. It was using these findings that Gutsche produced a series of papers detailing efficient, highly scaleable and well yielding processes for the synthesis of C[4], C[6] and C[8] in 60%, 88% and 65%, respectively.[9–11] This propelled their use into many areas of molecular chemistry and materials as supramolecular building blocks. This work was a major improvement over the alternate method which utilised a step-wise convergent synthesis and was first achieved by Hunter and Hayes in 1950s for the synthesis of *p*-methyl-calix[4]arene, later expanded by Kämmerer in the 1970s to include calix[5], [6] and [7]arenes. The reaction by Hunter and Hayes was a 10-step procedure consisting of alternative hydroxymethylation and subsequent condensation which in turn built a linear oligomer which was then cyclised forming the desired calix[4]arene (Scheme 1.1). Due to the number of long and tedious steps, along with inefficient overall reaction yields which rarely achieved higher than 10%, modification of these products was limited and rarely undertaken. A stepwise procedure does, however, pose advantages as one can select multiple different substituted phenols to react together before cyclisation. An improvement of this stepwise procedure was introduced by Böhmer who utilised a convergent 3+1 synthesis in which a trimer would be first synthesised and then cyclised with a 2,6-bishalomethyl-phenol under high dilution, with later advancements using excess $TiCl_4$ avoiding the need for high dilution.[12,13] A similar procedure also undertaken by Böhmer was that of the [2+2] convergent synthesis which as the name suggests utilised two dimers which were cyclised together using $TiCl_4$.[14] Both procedures had one main common denominator, the yields were usually quite low ranging (9-21%) and the limiting factor was the ease of synthesis of respective trimers or dimers. This has, however, been used to great effect when synthesising asymmetrical calix[4]arenes in which different groups are appended to the methylene bridge or upper-rim positions. Further discussion on this is presented later in this chapter.



Scheme 1.1. Synthetic scheme for synthesis of calix[4]arene utilising Hunter and Hayes stepwise synthesis.[15]

1.1.2. Conformations of Calix[n]arenes.

The vase like shape that C[*n*]s adopt is usually referenced as the cone conformation, with all *para*-substituents pointing up (*exo*) and hydroxyl groups pointing down (*endo*). The *exo* and *endo* faces are more commonly referred to as the upper- and lower-rim, respectively (Figure 1.3). The other conformers C[4] can adopt are known as; partial cone, 1,3-alternate and 1,2 alternate as proposed by Cornforth *et al.*[16] and later adopted by Gutsche.[17] The cone conformation is favoured in H_4TBC[4] due to strong intramolecular bonding between the hydroxyl groups at the lower-rim.[18,19]

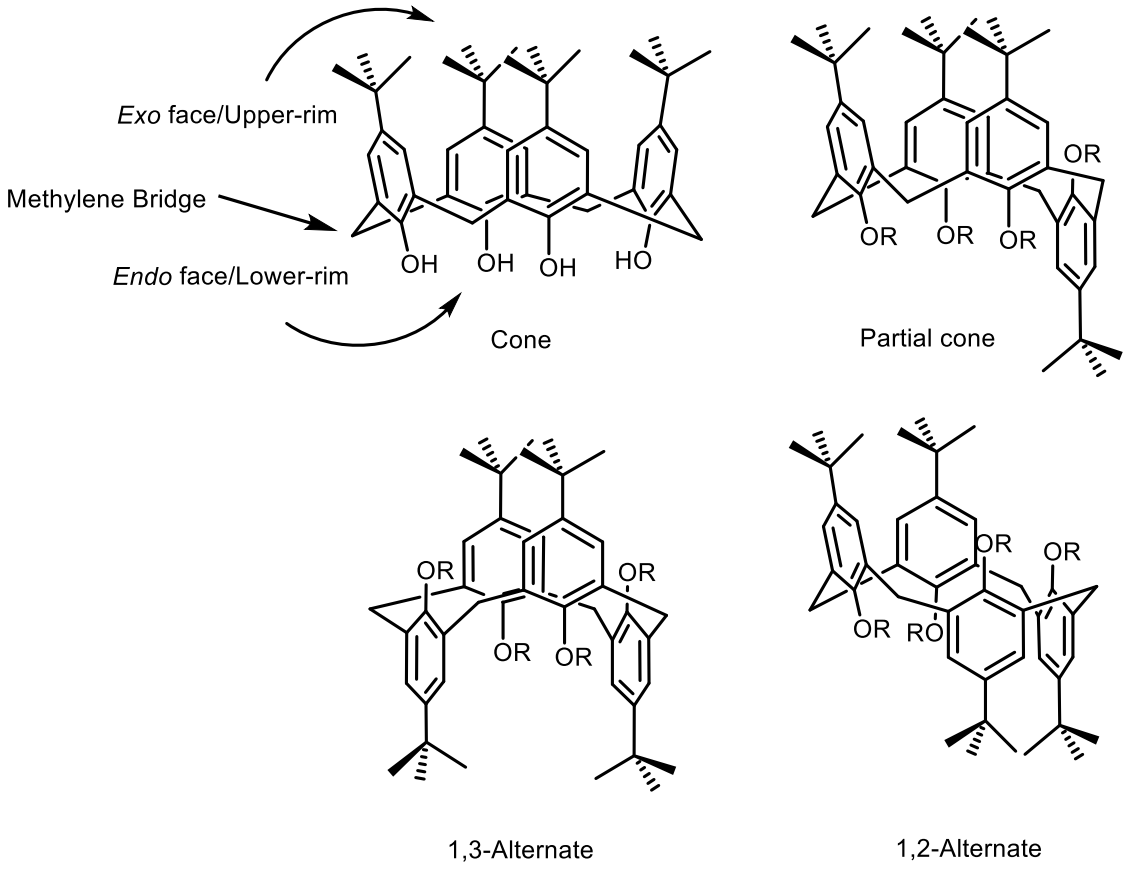


Figure 1.3. The four different conformations C[4]s can adopt with the *exo* face/upper-rim, *endo* face/lower-rim and methylene bridge being labelled.

However, C[*n*]s are conformationally labile as the phenolic units can ring flip through the anulus by rotating around the methylene bridge. This can be seen in solution at different temperatures depending on the *para*-substituent or solvent present. The barrier for interconversion *of* calix[4]arene compared to that of *p-tert*-butylcalix[4]arene in

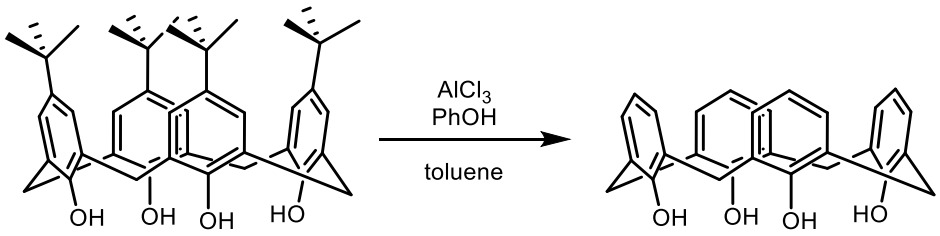
chloroform (a non-polar solvent) differs by 0.8 kcal/mol from 14.9 kcal/mol to 15.7 kcal/mol respectively, showing that the *para*-substituent plays a minor role in stabilisation of the conformations.[20] Interestingly, when performed in polar solvents such as acetonitrile, the barrier of rotation decreases which is attributed to the disruption of the hydrogen bonding interactions by the solvent. Further evidence can been seen when using a strongly hydrogen bonding solvent such as pyridine which shows a further decrease to 13.2 kcal/mol.[20,21]

1.2. Upper- and Lower-rim Modification of Calix[n]arenes.

The widespread use of C[*n*]s throughout supramolecular chemistry comes from the variety and complexity of modifications possible to the macrocyclic framework.[22] There are three main positions for functionalisation on a calixarene and they are known as the upper-rim, lower-rim and methylene bridge (Figure 1.3). This thesis will mainly focus on methylene bridge functionalisation; however, it is worth mentioning the others in order to give a conclusive overview. Due to the extent of research / modification performed on upper- or lower-rims, and in the interests of brevity, only a few examples will be provided for each region. Due to reasons spoke about previously most modifications focus on reactions which reemploy the Zinke-Cornforth procedure as a basis and it is of use to researchers to reduce the number of steps and improve atom economy of the overall process.

1.2.1. Upper-rim Modification.

A generally accepted starting point for upper-rim modification is calix[4]arene. This is obtained by removal of the *tert*-Butyl group from *p*-*tert*-butylcalix[4]arene, previously used to avoid crosslinking in the Zinke-Cornforth procedure. This allows the *para* positions to become available for functionalisation and is achieved by use of a reverse Friedel-Craft type reaction using aluminium chloride as a Lewis acid (Scheme 1.2).[23] An alternative route for de-*tert*-butylation was carried out by Suk-Kyu Chang where Nafion^{TM} was utilised, a known superacid and interestingly they were able to isolate all partially de-*tert*-butylated derivatives.[24]



Scheme 1.2. Synthetic Scheme for the synthesis of calix[4]arene from *p-tert*-butylcalix[4]arene using $AlCl_3$.

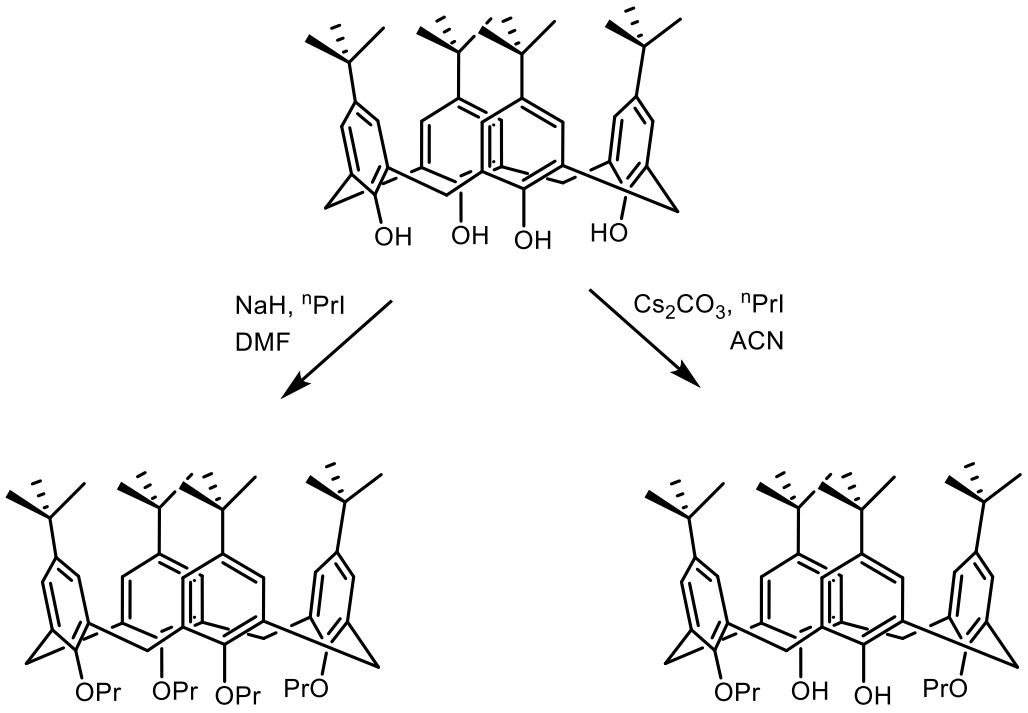
Once the *para*-positions become available for further functionalisation a search of the literature shows a wide range of possibilities. These are including, but not limited to, bromination[25], nitration,[26,] formylation[27] and sulfonation,[28] with many even being able to selectively functionalise forming mono, di or tri substituted products.[29] Halogenation of the upper-rim is an interesting synthetic intermediate as it allows the introduction of a range of groups through cross coupling reactions with in the presence of a Pd catalyst.[30,31]

1.2.2. Lower-rim Modification.

Hydroxyl groups residing at the bottom of the calix[*n*]arene can be functionalised through a variety of organic reactions. The two most common and easiest of which are the esterification and etherification using an alkylating agent and base. This area has had an exhaustive amount of research so only a few relevant procedures will be mentioned.[32]

It has been shown that due to the pKa of the lower-rim hydroxyl groups, *mono*, *di*, *tri* and *tetra* alkylated species can all be synthesised using slightly different conditions.[33,17] Shinkai and co-workers synthesised a range of water soluble calix[4]arenes through upper-rim modification, adding NO_2, SO_3Na and, $SO_2N(CH_2CH_2OH)_2$ groups in the *para* position to investigate pKa values of the hydroxyl groups. They found that the initial deprotonation occurs at a very low pH (pK_{a1} 1 – 3) and subsequent deprotonations increase to around $pK_{a2\text{-}4}$ 10 – 14. [33, 34] This shows that calix[4]arenes have a very acidic proton that can easily be removed due to the mono-anion produced being stabilised through hydrogen bonding to other lower-rim hydroxyl

groups. Because of this, the base employed in these reactions is of particular interest. For example, strong bases such as NaH are mainly used for tetra-alkylation whereas weaker bases such as sodium or caesium carbonate can facilitate di-alkylation. Barium hydroxide has also found use synthesising trimethyl ethers (Scheme 1.3).[17]



Scheme 1.3. Scheme for the synthesis of tetra and distal alkylated calix[4]arenes.

Substitution of the lower-rim remove the hydrogens of the phenol groups, which in-turn disrupts the strong hydrogen bonding and facilitates interconversion between the four conformers. This can be seen for small groups such as methyl in the tetra methyl ether, even at room temperature. However, when moving to larger groups such as *n*-propyl rotation around the methylene bridge is blocked and the molecule remains conformationally frozen even at high temperatures.[35] This can be very useful as it allows for easier analysis through NMR spectroscopy facilitating retention of symmetry. This results in sharp signals which are symmetry equivalent, especially when locked in the cone conformation. If using conformationally labile groups on the lower-rim such as methoxy or ethoxy chains the ^{1}H NMR spectrum can be simplified using sodium ions where, complexation to the Na^{+} occurs, resulting in the calix[4]arene adopting the cone conformation and sharper signals are subsequently observed.

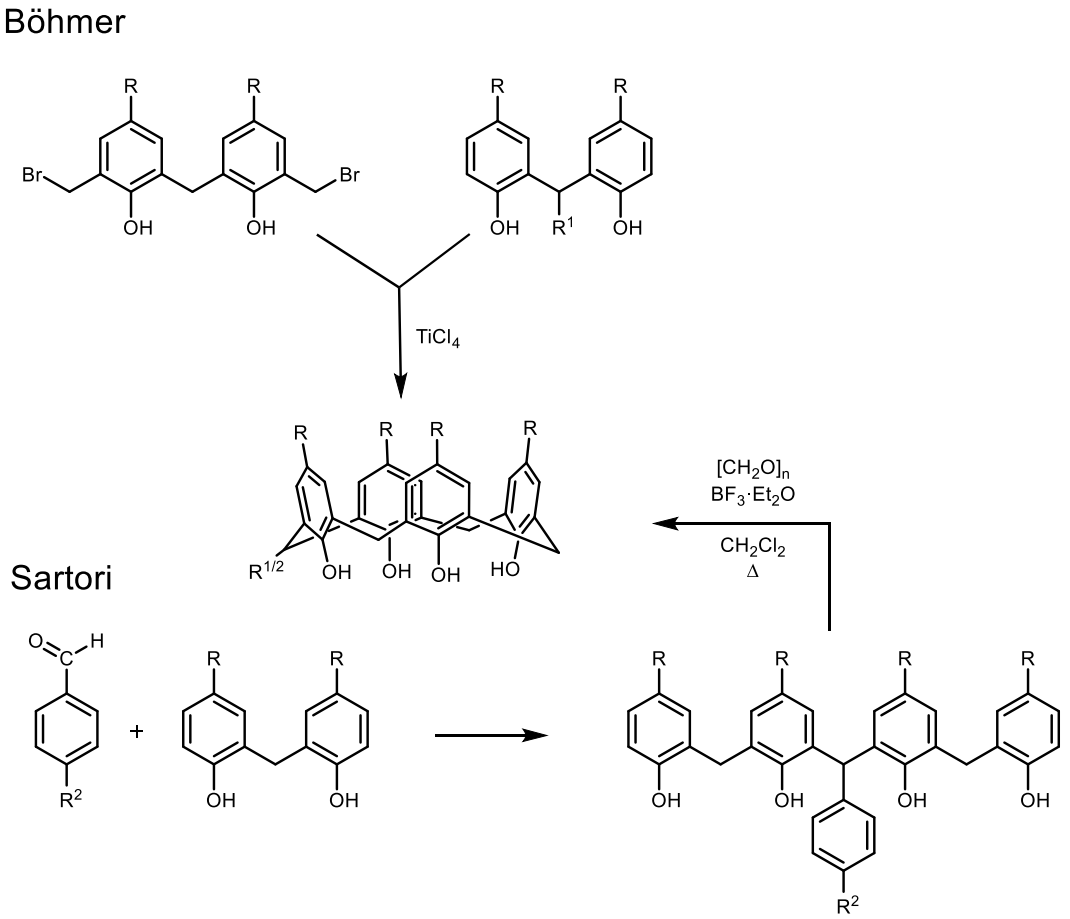
1.3. Methylene Bridge Functionalisation.

As this thesis focuses on the synthesis of methylene bridge substituted calix[4]arenes, it is worth devoting a section to explore the advancements in this area. In contrast, the study of methylene bridge substituted calixarenes has trailed well behind that of the upper/lower-rim, owing partly to a lack of synthetic procedures / accessibility. There are four methylene bridge positions available for substitution in calix[4]arenes, each possessing two C-H bonds. It can be seen at room temperature in the ^{1}H NMR spectra of H_4TBC[4] that these methylene bridge protons exist as a pair of doublets due to geminal coupling between axial and equatorial positions.[21] Arduini *et al.* were able to assign each of these NMR shifts through the Nuclear Overhauser Effect (NOE) and pyridine shift experiments with the proton in the axial position (closest to hydroxyl group) being assigned the lower field doublet, and the equatorial proton assigned the higher field doublet.[36] It was also shown by Kämmerer *et al.* that these doublets coalesced upon heating, demonstrating conformational flexibility of calix[4]arenes.[7] These methylene bridge positions can be functionalised at a varying number of positions. Most notably, mono, di or tetra-substitution and are of a keen interest to supramolecular researchers as functionalisation at the bridge could incorporate additional binding sites / functionality close to the molecular cavity. Substitution at one position is dominated by such procedures as the fragment condensation method,[37] spirodienone routes,[38] anionic ortho-Fries rearrangement,[39] and mono lithiation.[40]

1.3.1. Convergent Synthesis.

The fragment condensation route has been used to great effect in producing mono- and di-substituted methylene bridge calix[4]arenes. The Sartori and Böhmer groups synthesised a range of monosubstituted calix[4]arenes with different functionality through a [2+2] fragment condensation, however the cyclisation differs slightly from one another.[41,42] Bohmer used an alkyldene diphenol and a bisbromomethyl diphenol and cyclisation using a Lewis acid such as $TiCl_4$ (Scheme 1.4).[41] Interestingly, they were also able to add alkyl and aryl groups to the bridge such as *p*-nitro and 2-pyridyl. Sartori approached the synthesis slightly differently, using a [2+2] fragment condensation utilising a substituted benzaldehyde to combine the fragments whilst adding additional aryl functionality at one methylene bridge. This was then cyclised using a different Lewis

acid (boron trifluroetherate) with paraformaldehyde to combine fragments to afford a similar product. Typical yields for the cyclisation were between 35 – 20% and therefore the products are available in reasonable quantities.

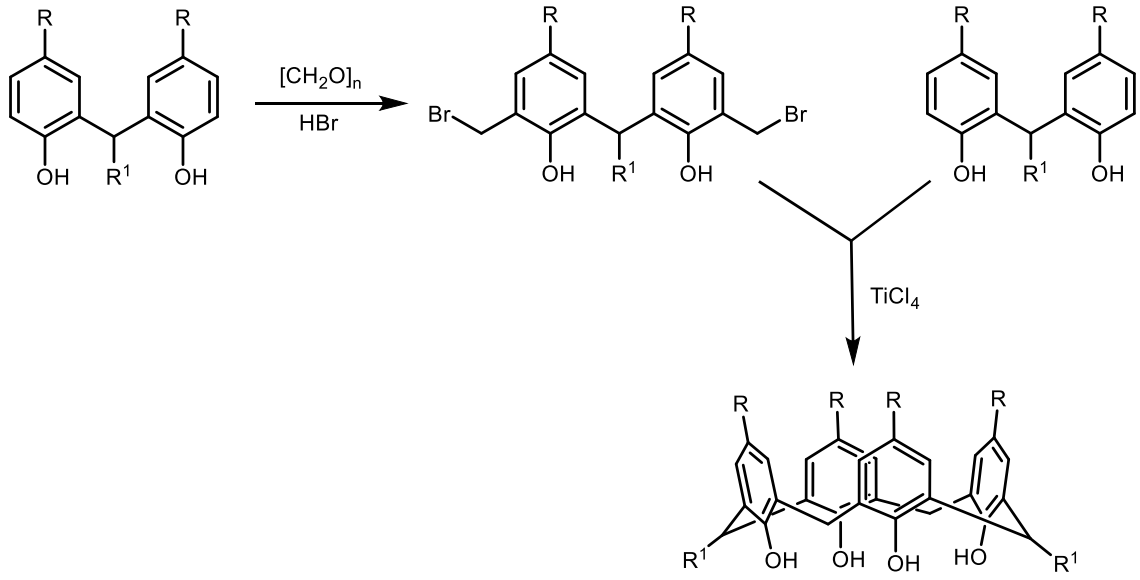


Scheme 1.4. Scheme for the synthesis of monosubstituted methylene bridge calix[4]-arenes by the groups of Böhmer and Sartori using different [2+2] fragment condensation methods. Böhmer R^1 = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, *p*-Ph-NO_2, 2-pyridyl.[41,42]

The Böhmer group further modified their method to include the synthesis of di-substituted methylene bridge calix[4]arenes.[37,41] They achieved this by reacting a substituted bis-phenol with paraformaldehyde and HBr to afford a substituted bis(bromomethyl phenol) which could then be cyclised with an additional equivalent of the substituted diphenol affording a distal di-substituted methylene bridge calix[4]arene (Scheme 1.5). Interestingly, it should also be possible to combine both methods to react the substituted diphenol with benzaldehyde to form a trisubstituted tetra phenol and then cyclise. This

would allow the synthesis of a tris-substituted calix[4]arene. However, no work around this topic was discovered in the literature.

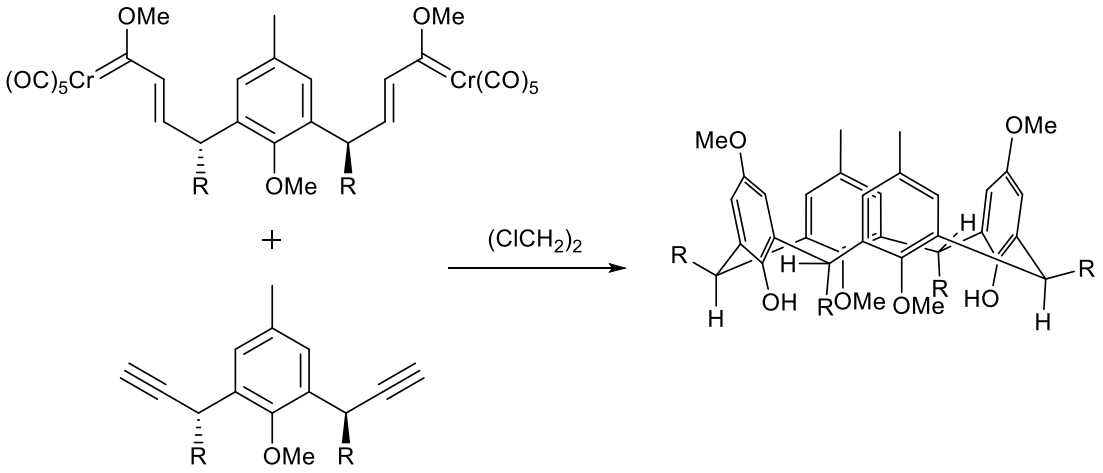
Later studies by Böhmer investigated the orientation in which the substituents. It was noted that hydrogen bonding at the lower-rim allowed retention of the cone conformation however due to there being two hydrogen atoms, one axial and the other equatorial, the substituents could also be substituted axial or equatorial and thus exist as diastereomers. It was concluded in the study that aliphatic functionality has a strong preference for the equatorial position, whilst aromatic groups show no definitive preference but may be controlled by the use of aliphatic functionality in di-substituted derivatives.



Scheme 1.5. Scheme for the synthesis of di-substituted methylene bridge calix[4]arene by Böhmer and co-workers.[41]

It is worth mentioning the work done by Wulff and co-workers who utilised a stepwise procedure to synthesise calix[4]arenes using a different approach. They utilised the reaction of a bis-carbene complex with that of a diyne which is able to produce two benzene rings and close the macrocyclic ring all in the same step.[43] They then developed this further by functionalising the diyne and / or bis-carbene before cyclisation to synthesise methylene bridge substituted calix[4]arene in which one, two, three or four positions had been substituted (scheme 1.6).[44,45] The authors also used this method to introduce chirality at the methylene bridge as, during the cyclisation step, the methylene

positions are not cleaved and so the chirality introduced beforehand will be retained in the product. However, as with other stepwise procedures, multiple steps are required to synthesise the precursors and cyclisation is low yielding (13-41%).



Scheme 1.6. Scheme for the synthesis of optically active methylene bridge substituted calix[4]arene by Wulff and co-workers utilising a stepwise procedure.[44,45]

1.3.2. Direct Substitution of the Framework.

Performing substitution directly onto the calix[4]arene framework can reduce the number of steps needed and thus time taken. Importantly, it also avoids the cyclisation step which (as mentioned previously) is typically low yielding. Lithiation of TBC[4] has been used to great effect for introducing a range of different functional groups at one methylene bridge position. The reaction involves lithiation of the methylene bridge position and subsequently react with an electrophile. This method was first introduced by Scully *et al.*[40] and later popularised by Fantini and co-workers, adding chloroalkyl groups which could be further functionalised or tethered to one another to afford a bis-calix[4]arene.[46] Interestingly this route cannot be applied for the functionalisation of additional bridge positions on a calix[4]arene; substitution still only occurs at one position on the framework even in the presence of excess lithiating reagent. The Dalgarno group have investigated mono-substituted methylene bridge calix[4]arenes using this mono lithiation route adapted from the work of Fantini[46] to synthesise a library of alkyl[47] and xylyl[48] tethered bis-calixarenes linked through the methylene bridge. The lower-rim was protected by methoxy etherification prior to lithiation at the bridge position and reaction

with an bis alkyl/ xylyl bromide resulting in a tethered bis-calix[4]arene. The final step was to reopen the lower-rim binding sites which was performed by reacting with iodocyclohexane, converting the methoxy ether back to hydroxyl groups; the products were investigated in cluster formation with 3d, 4f or a mixture of 3d/4f metal ions.[47,48]

1.3.3. Tetra-Substitution Directly onto the Methylene-Bridge.

Moving to tetra-substitution, that is introducing mono functionality at all positions, there is considerably less literature and fewer synthetic procedures available, however pioneering work by Biali and co-workers has seen two diverse starting points emerge; ketocalixarenes and bromocalixarenes,[49] both of which can be attacked by nucleophiles for further modification of the framework. Fischer *et al.* have even shown bromocalixarenes to act as intermediates to ketocalixarenes in a one-step procedure from the methyl ether of TBC[4].[50] When synthesising a calix[4]arene with methylene bridge substituents it is important to understand the orientation of the methylene bridge substituent. Considering a calix[4]arene in which all bridge positions are monofunctionalised, that being containing one substituent and one hydrogen at each position, four configurational stereoisomers can occur (Figure 1.5).

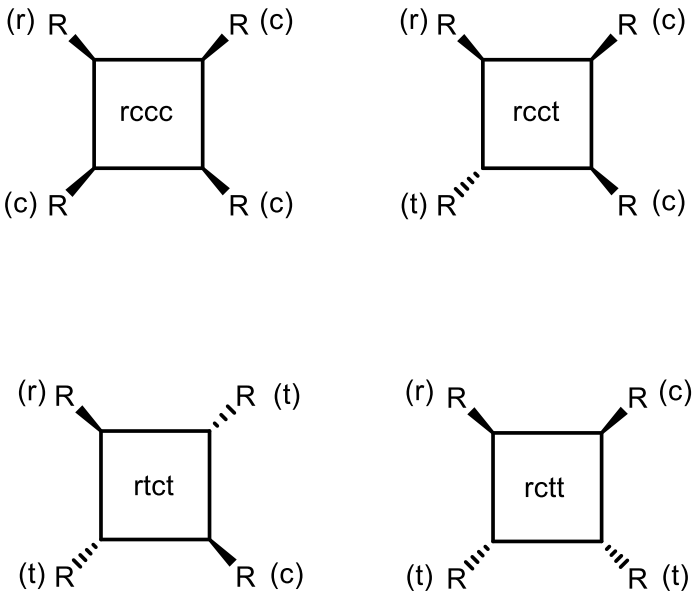
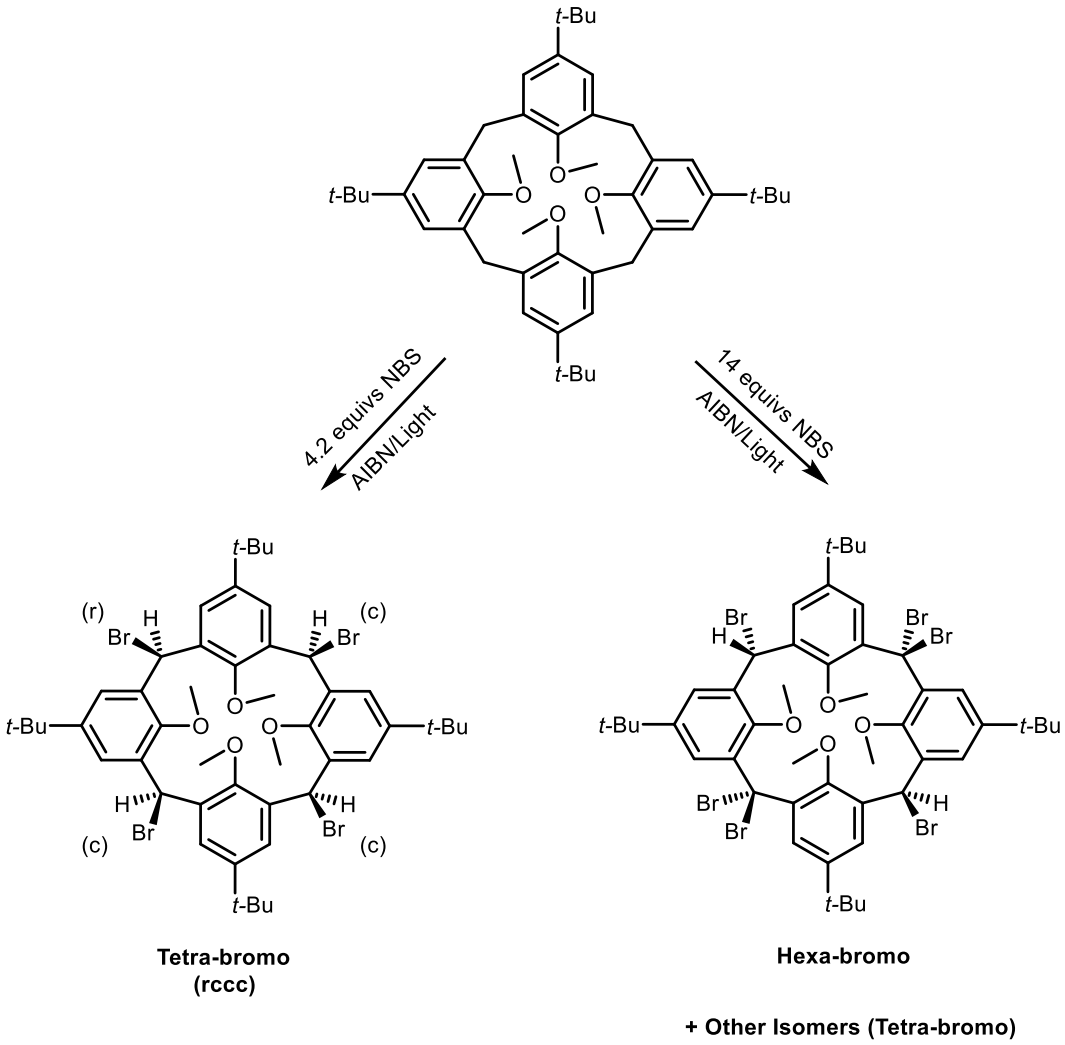


Figure 1.5. Isomers of calix[4]arenes monosubstituted at each methylene bridge labelling clockwise from the reference (r) and the substituents are labelled as either cis (c) or trans (t) to the point of reference.

Figure 1.5 shows a 2D representation of the different possibilities for calix[4]arene if all the groups at the bridge are identical. These are named by taking one substituent as a reference (r) and labelling clockwise either cis (c) or trans (t) to the reference. Note that if calix[4]arene adopts the cone conformation the configurational isomer least affected by steric hinderance is the rccc isomer, whereby all substituents are positioned equatorial. As expected, moving to larger C[*n*]s increases the number of configurational isomers to 8 and 18 for calix[6]- or calix[8]arene, respectively. Therefore, it is important to know which diastereomer(s) are present in the reaction.

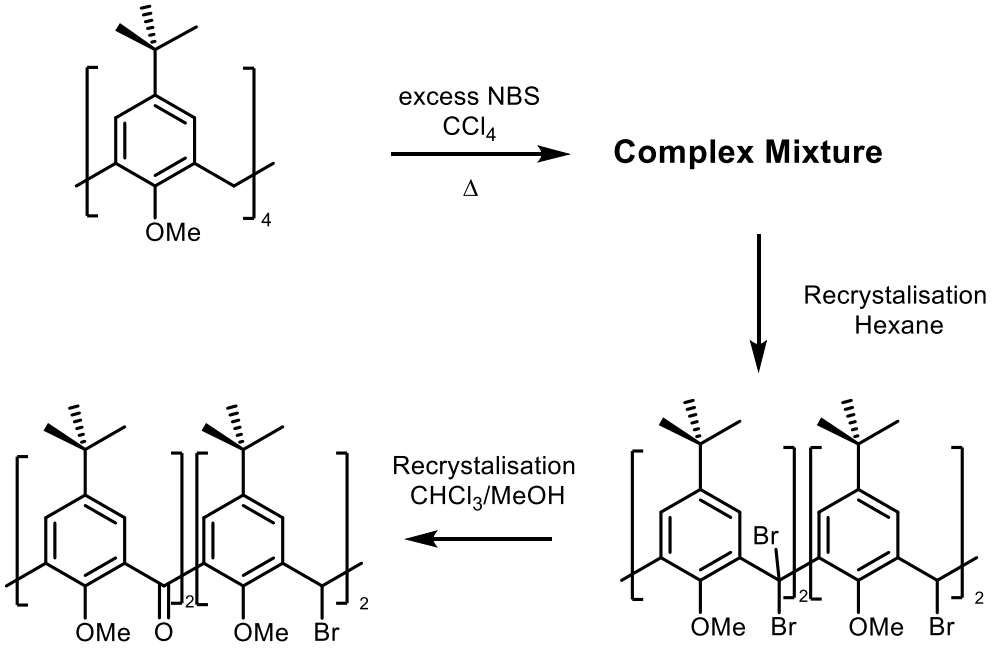


Scheme 1.7. Formation of brominated products using different equivalents of NBS.[51–53]

The tetra-substituted bromocalix[4]arene is known to adopt the rccc isomer, as reported by Biali and co-workers when they repeated the work of Klenke[51] and Kumar.[52] Klenke *et al.* first reported the tetrabrominated species, reacting *tetra*-methoxy calix[4]arene with

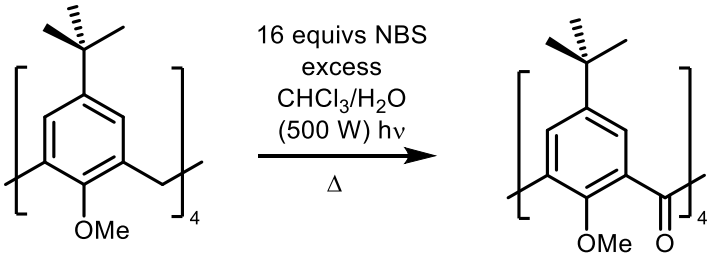
an excess of *N*-bromosuccinimide (NBS) using azobisisobutyronitrile (AIBN) as an initiator. This was later adapted by Kumar *et al.*, replacing AIBN for light as the initiator. Biali and co-workers repeated this to find that upon recrystallisation of the product from hexane they had in-fact isolated the hexabromo derivative. Knowing this, they decided to use near stoichiometric amounts of NBS (4.2 equivalents) to help avoid formation of the hexabromo product and this afforded them the tetrabrominated species from which they obtained a structure through single crystal X-ray diffraction (Scheme 1.7).[53]

A ^{1}H NMR spectrum of the tetrabrominated species isolated by Biali and co-workers differed from that found in the literature, therefore it was suggested the spectrum and product reported by Kumar *et al.* and Klenke *et al. was* in fact a mixture of substituted derivatives. Biali investigated this further and found that recrystallisation of the complex mixture from hexane afforded a pure hexa-substituted product and further recrystallisation using $CHCl_3$/MeOH produced a dibromo dioxycalix[4]arene due to the dibromo positions being very labile (Scheme 1.8).[53] Further studies on this reaction pathway were investigated and found that both the distal and proximal hexabromo isomers could be obtained and subsequent hydrolysis afforded the desired dioxycalix[4]arene derivaties.[54]



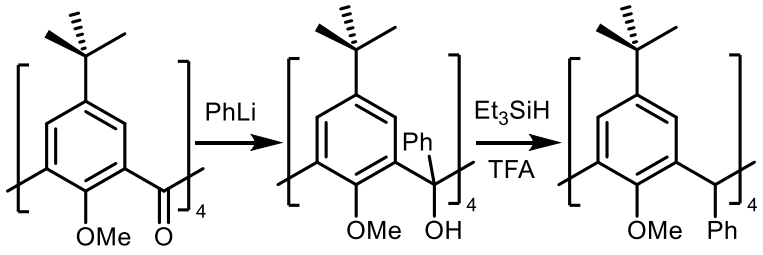
Scheme 1.8. Synthetic scheme for the products obtained by Biali *et al.* when repeating the work of Klenke and Kumar.[53,54]

This led the group of Fischer *et al.* to explore this route further, finding that the tetraoxycalix[4]arene or tetraketocalix[4]arene, that is a calix[4]arene in which carbonyl groups replace the methylene bridge hydrogens, can be synthesised in one step from the methylated ether using a similar procedure. Reaction of methylated TBC[4] (OMeTBC[4]) with an excess (14 equivs) of NBS irradiating using a 500W UV light in a mixture of $CHCl_3/H_2O$ results in tetra substituted ketocalix[4]arene (Scheme 1.9).[50] Ketocalix[4]arenes can be further reacted with nucleophiles. Görmar *et al.* reported the reduction of ketocalix[4]arene with $NaBH_4$ in propan-2-ol and subsequent reflux in $MeOH/H_2SO_4$ to afford the octa-hydroxyl calix[4]arene.[55] That is a calix[4]arene containing four of the hydroxyl (OH) groups located on the methylene bridge and four on the lower-rim. However, when repeated by Biali and co-workers, it was proven that the reaction actually afforded a mixture of isomeric tetrahydroxy calix[4]arene where the methylene bridge positions had been substituted with methoxy groups.[56]



Scheme 1.9. Scheme for the preparation of a tetrasubstituted ketocalix[4]arene by Fischer *et al.* starting from OMe TBC[4].[50]

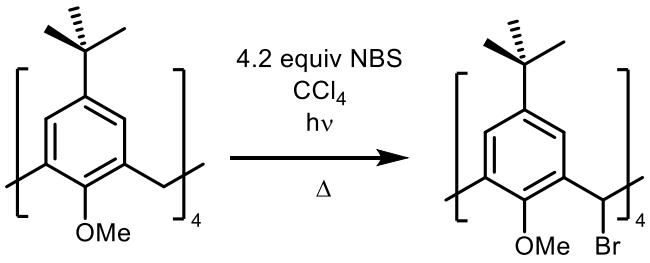
The first example of a tetra substituted aryl group substituted at the methylene bridge was achieved by Biali and co-workers when they reacted the tetrasubstituted ketocalix[4]arene with phenyl lithium, reducing the carbonyls to hydroxyls in combination with addition of a phenyl substituent.[57] It was shown that this was in fact a mixture of stereoisomers (rccc, rcct, rctt, rtct). Recrystallisation from $CHCl_3$/Acetone afforded pure rccc isomer which was reacted further to reduce the OH groups. This was achieved using Et_3SiH/TFA affording a calix[4]arene tetrasubstituted with phenyl groups at the methylene bridge with unchanged stereochemistry, in this case displaying the rccc configuration with all groups equatorial (Scheme 1.10).



Scheme 1.10. Scheme for the reaction of ketocalix[4]arene with phenyl lithium and further reduction using Et_3SiH/TFA.[57]

The same reaction was applied to synthesising a radialene group at the bridge, replacing PhLi with MeLi and heating at reflux in *p*-TsOH/$CHCl_3$ to afford the calix[4]radialene.[58]

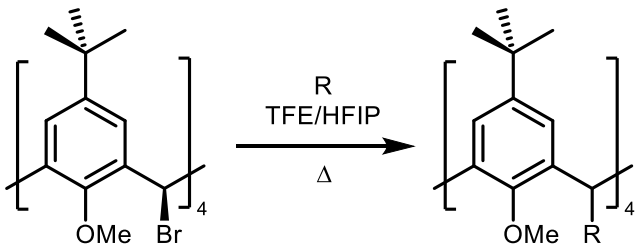
Another starting point for forming substituted methylene bridge calix[4]arenes is to utilise the tetra-substituted methylene bridge bromocalix[4]arene. As mentioned earlier, this is formed through reaction with near stoichiometric amounts of NBS to avoid formation of the higher brominated products (Scheme 1.11).



Scheme 1.11. Synthetic scheme for photochemical bromination of TBC[4]OMe.[59]

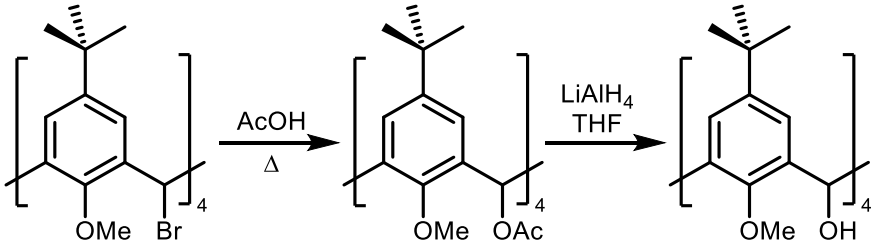
The tetra-bromo species can also be used as an intermediate to further modification by undergoing nucleophilic attack, this was trialled by Biali and co-workers first by lithiation and subsequent reaction with a nucleophile. However, this seemed to lead to decomposition of the product. They have however now adapted the procedure and so the reaction of tetrabrominated methoxy species with MeLi which is a very strong nucleophile can be used to afforded the desired tetramethyl methxoxycalix[4]arene.[60] Another idea was to replace the bromine under solvolytic S_N1 conditions. This was achieved by using a solvent which was high ionising potential and low nucleophilicity. TFE (Trifluoroethanol)/ HFIP (Hexafluoroisopropanol) and in some cases TFA

(Trifluoracetic acid) was utilised for this and used to form a range of compounds with C-O, C-C, C-S and C-N bonds at all four methylene bridge positions (Scheme 1.12).[53,59]



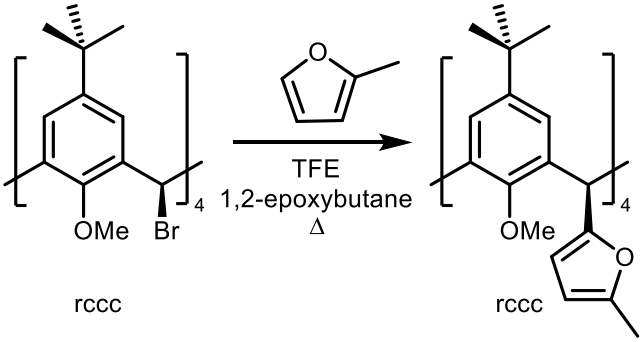
Scheme 1.12. Solvolysis of tetra-bromo TBC[4] (where R = OCH_2CF_3, OMe, OEt, O-*n*-Pr, O-*i*-Pr, O-*t*-Bu and N_3).

To begin, the tetrabrominated calix[4]arene was reacted in TFE with no additional nucleophile and obtained the desired tetra-substituted product (R = OCH_2CF_3). The next set of reactions replaced the ionising solvent with a nucleophile of choice. Due to the solvent being present in excess, the nucleophilicity of the substrate must be higher than that of the solvent. A range of tetra-alkoxy derivatives were synthesised and the major product for every reaction was the rccc isomer which was assigned through ^{1}H-NMR spectroscopy. It was also demonstrated that forming an alkoxy group at the bridge was possible without the presence of TFE or HFIP. This was employed to form a calix[4]arene bearing hydroxyl groups at the bridge which had been previously attempted using Görmar's reported synthesis and proved unsuccessful. The tetrabrominated methoxy calix[4]arene was heated at reflux in acetic acid to afford the tetra acetoxy species which could then be reduced in the presence of $LiAlH_4$ to form the tetrahydroxy methylated calix[4]arene (Scheme 1.13). Interestingly, there were two functional group that when reacted in fluorinated alcohols displayed poor selectivity and reportedly did not yield exclusively the rccc isomer. The tetra-azide derivative formed through reaction with sodium azide yielded a mixture of isomers (rcct, rctt, rccc) with rcct being the major and unable to be separated from one another. A thiocyanate group was also able to be added by trapping with potassium thiocyanate displaying a mixture of products with rccc being the major product. Finally, C-C bond forming reactions could also be achieved using a similar procedure and adapted from the work of Mayr and co-



Scheme 1.13. Reaction scheme for the conversion of the tetrabrominated methoxycalix[4]arene to the tetrahydroxy methoxycalix[4]arene in two steps.[53]

workers.[61] The tetra-bromo methylated calix[4]arene was reacted with 2-methyl furan in TFE using 2-epoxybutane as a HBr scavenger to afford the tetra-substituted 2-methyl furanyl C[4] derivative in which the rccc conformer was the major product (Scheme 1.14).[59]



Scheme 1.14. Reaction scheme for the synthesis of tetrakis(2-methylfuranyl) TBC[4] using 2-methyl furan in trifluoroethanol.[59]

A single crystal of the tetrakis(2-methylfuranyl) C[4] was grown and analysed to confirm that the equatorial position of the substituents remained unchanged and the calix[4]arene had adopted the pinched cone conformation (Figure 1.6). The pinched cone conformation is when two opposite phenyl substituents are splayed outwards and two are 'pinched' inwards such that they are near-parallel. This is very common in tetra-substituted methylene bridge calix[4]arenes with both the bromo and 2-methylfuran calix[4]arenes displaying the pinched cone in the crystal structure. No evidence for this is however seen

at room temperature in the ^{1}H NMR spectra so it is thought that at this temperature the structure is interconverting fast enough on the NMR timescale and is therefore averaged.

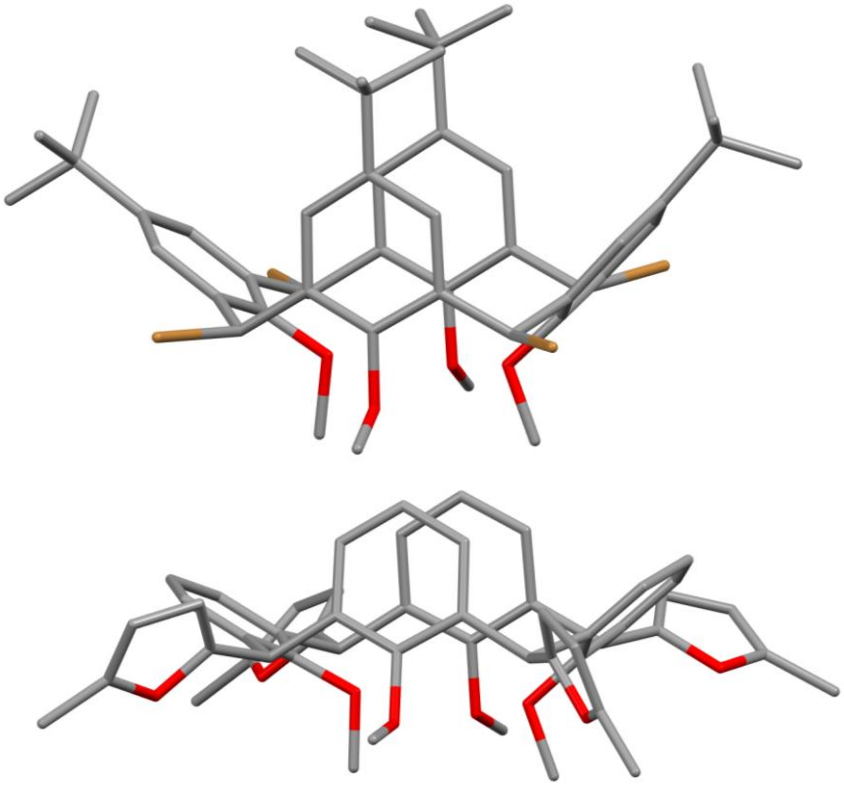
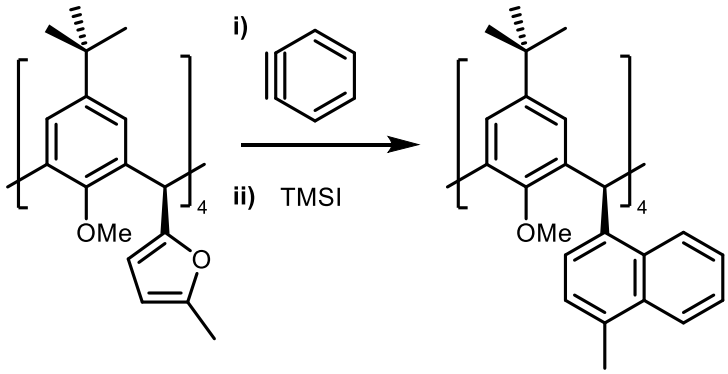


Figure 1.6. Crystal structures of tetra-brominated calix[4]arene (top) and tetrakis(2-methylfuranyl)calix[4]arene (bottom) both displaying the pinched cone conformation.[59]

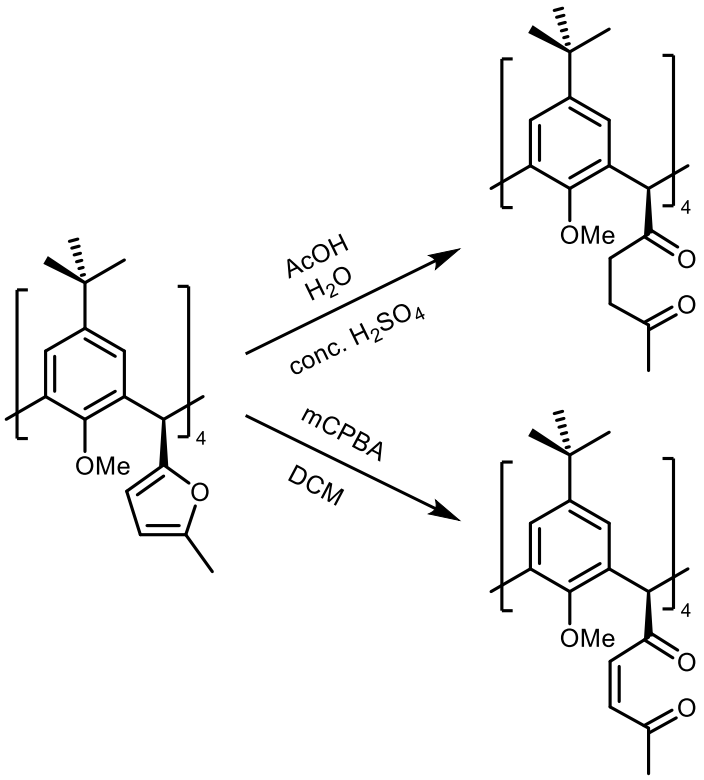
The 2-methylfuranyl product was of interest to the authors as it has the ability to be further functionalised. They report performing a Diels-Alder reaction on the tetrakis(2-methylfuranyl) TBC[4]arene and is the only example outside of the Dalgarno group in which the product has been reacted further. This was achieved by reaction with benzyne and deoxygenated using trimethylsilyl iodide (TMSI) (Scheme 1.15).[53]



Scheme 1.15. Further functionalisation of 2-methyl furanyl TBC[4].[53]

It is interesting to note that TMSI has been used as a demethylating agent for the conversion of OMe groups back to the hydroxyl OH on a calix[4]arene framework[62] however no demethylation was observed in this instance.

Work by Fong further functionalised the 2-methylfuranyl TBC[4] by employing oxidative ring opening reactions to form saturated and unsaturated 1,4-diketones (Scheme 1.14).[63,64] These could then be ring closed to form new heterocycles at every bridge position. This work is used as a basis for the research undertaken within this thesis and so is discussed in more detail throughout. One important detail to note is that all reactions from the tetra-bromo to new diketones and new heterocycles all remain rccc where the methylene bridge functionalities are equatorial and the conformation of the calix[4]arene remains in the cone.



Scheme 1.14. Further functionalisation of 2-methylfuranyl calix[4]arene by Fong, employing oxidative ring opening reactions using either strongly acidic conditions or a peroxyacid (mCPBA) to form saturated or unsaturated 1,4-diketones, respectively.[63]

1.4. Bridged Calix[4]arenes with Multiple Functionalities.

The possibility of building multiple different functionalities onto the same framework was also investigated by Biali and co-workers. As discussed previously, and as seen in scheme 1.7, an excess of phenyl lithium could be reacted with the ketocalixarene to form a tetraphenyl, tetrahydroxyl bridge substituted calix[4]arene which was then reduced to the tetraphenyl derivative. However, by restricting the equivalents and instead using 2.2 equivs of PhLi, they were able to reduce only two of the carbonyl groups to hydroxyls whilst adding phenyl groups at the same position, thus leaving two carbonyl groups unreacted. The authors only mention synthesising a distal product in *cis* orientation which was obtained after recrystallisation and therefore it is not understood if other products are formed. They also seem to neglect any further reduction of the alcohol groups which is

most likely due to the presence of the carbonyl which can also be reduced by triethyl silane.[65] This procedure was also performed using excess *tert*-butyl lithium (*t*-butyl) with the tetrasubstituted ketocalix[4]arene, affording two products after column chromatography identified as the di and tri substituted products both of which can be seen in Figure 1.7.[66] Unlike the product formed when using PhLi the substituents were proximal to one another, an excess could not force synthesis of the tetra-substituted product.

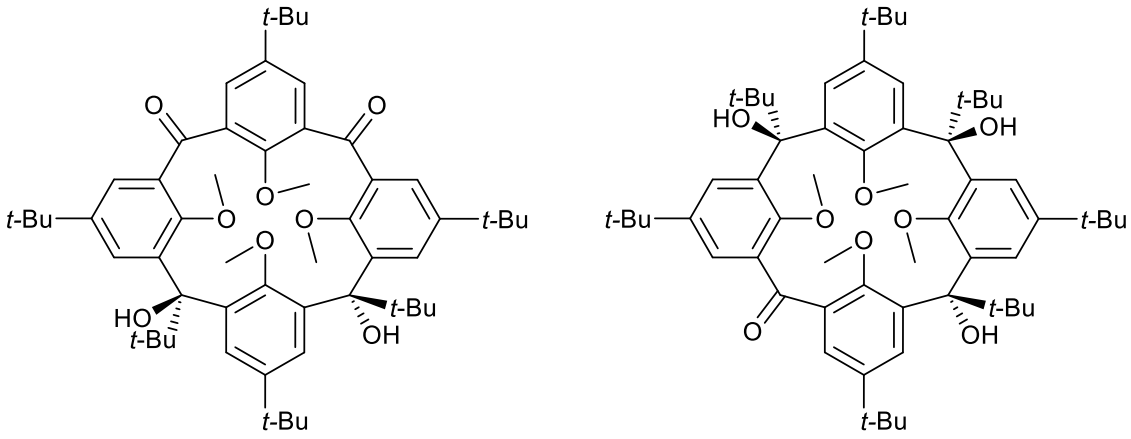
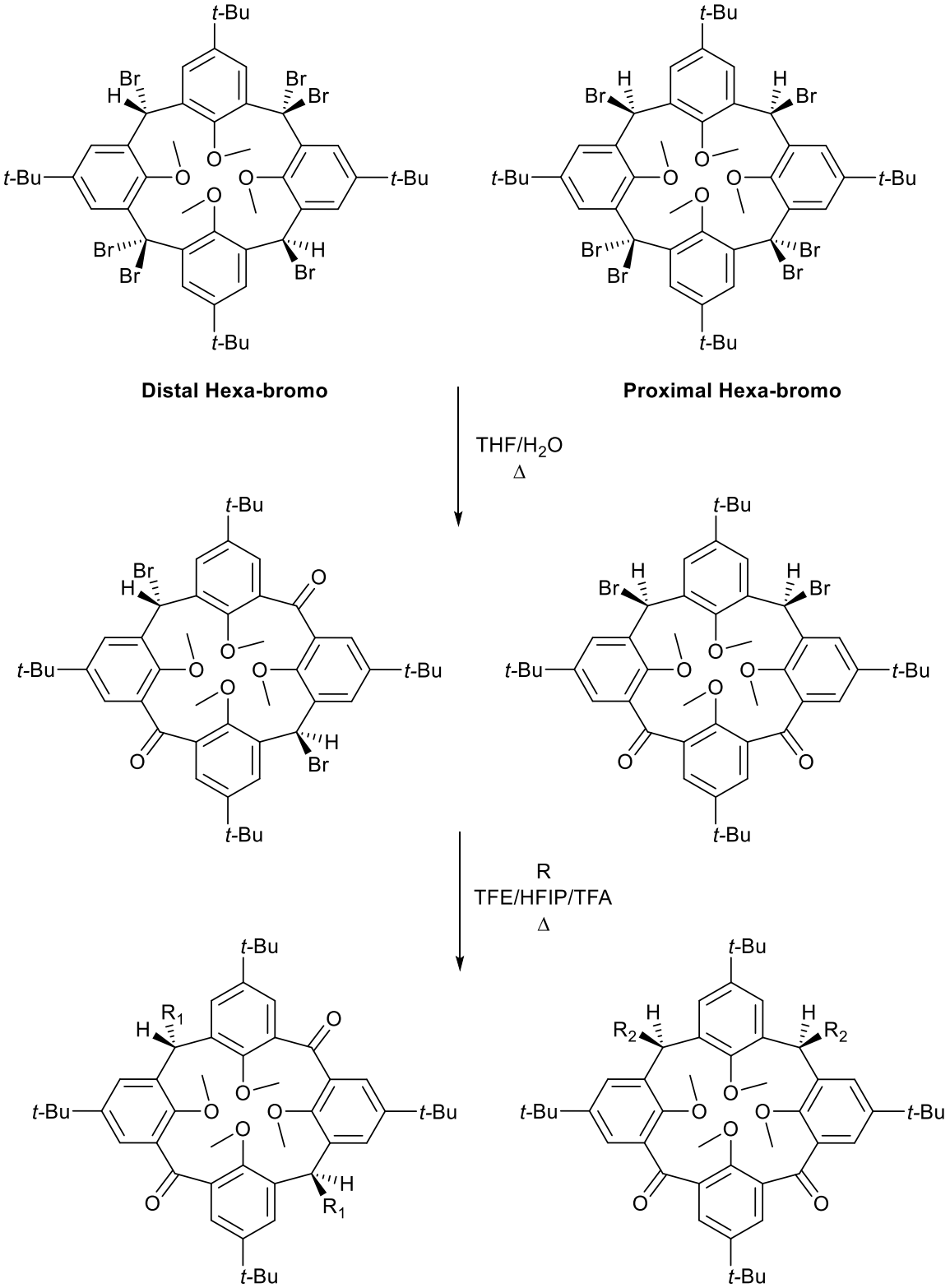


Figure 1.7. Structures of both products isolated from the reaction of the tetra-ketocalix[4]arene with *t*-BuLi.[66]

Another pathway for the synthesis of calix[4]arenes with multiple functionalities was performed by utilising the synthesis discussed previously for bromo calixarenes. It was shown that when attempting to synthesise the tetra-brominated calix[4]arene, the hexabromo was isolated after recrystallisation from hexane when using an excess of NBS. The dibromomethylene groups were also identified as being distal to one another. These groups were shown to be incredibly labile and recrystallisation from $CHCl_3$/MeOH could replace these with carbonyl substituents (Scheme 1.8).[53] This is an example of introducing multiple functionalities to the same framework, however in a follow-up study the synthesis and further modification of this process was undertaken. Knowing that the hexa-bromo product was formed when using a large excess (14 equivalents) of NBS, the use of near stoichiometric (6.3 equivs) was trailed. Upon work-up it was found that both the distal and proximal hexa-bromo derivatives were formed along with some of the tetra-bromo discussed earlier.[54] However despite best efforts the authors could not isolate the pure proximal product so instead was converted to the hydrolysis product by refluxing in

THF/H_2O whereby the dibromo positions are converted to a carbonyl. Interestingly any attempt to further brominate the *cis* tetra-bromo (rccc) product resulted in only the recovery of starting material, indicating the hexa-bromo products do not proceed through this pathway. It was theorised that instead other stereoisomeric forms act as intermediates in the formation of the hexa-bromo derivatives.

The distal hexa-bromo derivative was further reacted using solvolytic Friedel-Crafts conditions previously mentioned when reacting the tetra-bromo species with various nucleophiles. It was shown that when reacting under these conditions of nucleophile in an ionising solvent TFE or TFA (most reactions were performed in TFA for this study), the dibromethylene groups were converted to the carbonyl whilst the mono bromo groups were substituted with the desired nucleophile. It was also demonstrated that the hydrolysed product possessing two carbonyls could be reacted with the desired nucleophile under the same conditions and proceeded more smoothly and so therefore was employed as the main starting material for substitution (Scheme 1.15) The same authors were able to use these conditions to form a wide variety of multiply substituted calix[4]arenes where R was an alcohol, carboxylic acid, azide, alkyl and aryl, displaying a wide scope of functionality that can be added through this method. One major development was introducing the carbonyls as it also allowed functionality to the bridge that was unsuccessful before on a calix[4]arene, such as a 1,3 pentanedione affording the bis-acetylacetonate. This is thought to be due to the carbonyl groups which are electron



Scheme 1.15. Synthetic scheme for the preparation of tetrasubstituted calix[4]arenes with multiple different functionalities where R_1 = OMe, OEt, O-*i*-Pr, OCH_2CF_3 OCH_2CH_2OH, OAc, $OCOF_3$, N_3, 4-*t*-Bu-C_6H_4, 4-Me-C_6H_4, 2,4-$Me_2C_6H_3$, 2,4,6-$Me_3C_6H_2$ (Mes), 2-Methylfuranyl, $CH(COMe)_2$ R_2 = OMe, OEt, O-*i*-Pr, OCH_2CF_3, OAc, $OCOF_3$, (2,4-$Me_2C_6H_3$, 4-*t*-Bu-C_6H_4, Mes.[54]

withdrawing and therefore increasing the electrophilicity of the carbocation intermediate formed through cleavage of the C-Br bond.[54]

As discussed previously, carbonyl groups can also be further modified by reaction with a alkyl lithium reagent and this route was also briefly investigated reacting PhLi with a methylene bridged distal bis-carbonyl, bis-mesityl to form the hydroxyl product displaying that more modification to the framework is possible. These reactions demonstrate a relatively simple synthetic pathway for the preparation of calix[4]arenes with multiple functionality at the bridge positions. The electron withdrawing character associated with the carbonyl functionality was also exploited to substitute groups which were not previously possible using the tetra-bromoinated product. However, due to the carbonyl groups present this allows different isomers to form (*cis* and *trans* for distal along with a meso *cis* isomer and d/l *trans* isomers for proximal). In addition, the calixarene can also adopt different conformations which can cause difficult and long purification. A key advantage of utilising the tetra-brominated derivative is that the cone conformation is retained, and almost all the functionality is substituted equatorially.

1.5 Aims

Further functionalisation of the tetrakis(2-methyfuranyl) TBC[4] has been achieved within the Dalgarno group and is used as a basis for the work conducted in this study and is discussed in detail herein. The aim of this work was to utilise previous results obtained by Fong[64] to build a library of methylene bridge substituted calix[4]arenes. As this introduction displays, there is very limited literature regarding tetra-substitution in which every methylene bridge position is mono substituted. Therefore the first aim of the project was to develop a library of novel calix[4]arenes which possess different functionality near the lower-rim binding pocket. For adding additional functionality near the lower-rim, maintaining the cone conformation and having functional groups that retain the rccc configuration is of importance. This would allow the pseudo-cavity at the lower-rim to be exploited whilst also placing functionality within close proximity. This is of interest to the group as it could have wide applications in metal cluster formation (amongst other uses). One unique starting point emerged and that was the saturated and unsaturated 1,4-diketones formed through the oxidative ring opening of the 2-methylfuranyl TBC[4]. These methylene bridge modified calix[4]arenes show retention of this desired configuration during heterocycle formation and so are perfect to investigate. The second aim of this project was to deprotect the lower-rim methoxy groups and reinstate the hydroxyl functionality which could be utilised in multiple areas of supramolecular chemistry such as metal cluster formation,[67] host guest binding,[68] sensing.[69]

1.6 References.

1 A. Baeyer, *Berichte der Dtsch. Chem. Gesellschaft*, 1871, **4**, 658–665.

2 A. Baeyer, *Ber*, 1872, **5**, 1094–1100.

3 A. Baeyer, *Ber*, 1872, **5**, 280–282.

4 A. Baeyer and V. Drewsen, *Berichte der Dtsch. Chem. Gesellschaft*, 1882, **15**, 2856–2864.

5 *Am. Chem. Soc. Natl. Hist. Chem. Landmarks. Bakelite World's First Synth. Plast.*

6 A. Zinke and E. Ziegler, *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.*, 1944, **77**, 264–272.

7 C. D. Gutsche, *Acc. Chem. Res.*, 1983, **16**, 161–170.

8 C. D. Gutsche and R. Muthukrishnan, *J. Org. Chem.*, 1978, **43**, 4905–4906.

9 *Org. Synth*, 1990, **68**, 234.

10 *Org. Synth*, 1990, **68**, 238.

11 *Org. Synth*, 1990, **68**, 243.

12 V. Böhmer, P. Chhim and H. Kämmerer, *Die Makromol. Chemie*, 1979, **180**, 2503–2506.

13 V. Boehmer, F. Marschollek and L. Zetta, *J. Org. Chem.*, 1987, **52**, 3200–3205.

14 V. Böhmer, L. Merkel and U. Kunz, *J. Chem. Soc. Chem. Commun.*, 1987, 896–897.

15 B. T. Hayes and R. F. Hunter, *J. Appl. Chem.*, 1958, **8**, 743–748.

16 J. W. CORNFORTH, P. D. HART, G. A. NICHOLLS, R. J. W. REES and J. A. STOCK, *Br. J. Pharmacol. Chemother.*, 1955, **10**, 73–86.

17 C. D. Gutsche, B. Dhawan, J. A. Levine, K. Hyun No and L. J. Bauer, *Tetrahedron*, 1983, **39**, 409–426.

18 G. D. Andreetti, R. Ungaro and A. Pochini, *J. Chem. Soc. Chem. Commun.*, 1979, 1005–1007.

19 G. D. Andreetti, A. Pochini and R. Ungaro, *J. Chem. Soc. Perkin Trans. 2*, 1983, 1773–1779.

20 C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.*, 1985, **107**, 6052–6059.

21 C. D. Gutsche and L. J. Bauer, *Tetrahedron Lett.*, 1981, **22**, 4763–4766.

22 Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens and M. Saadioui, *Calixarenes 2001*, 2001.

23 C. D. Gutsche and L.-G. Lin, *Tetrahedron*, 1986, **42**, 1633–1640.

24 S. G. Rha and S.-K. Chang, *J. Org. Chem.*, 1998, **63**, 2357–2359.

25 S. Shimizu, S. Shirakawa, Y. Sasaki and C. Hirai, *Angew. Chemie Int. Ed.*, 2000, **39**, 1256–1259.

26 S. Kumar, N. D. Kurur, H. M. Chawla and R. Varadarajan, *Synth. Commun.*, 2001, **31**, 775–779.

27 H. M. Chawla and A. Santra, *Synth. Commun.*, 2001, **31**, 2605–2611.

28 S. Shinkai, K. Araki, T. Tsubaki, T. Arimura and O. Manabe, *J. Chem. Soc. Perkin Trans. 1*, 1987, 2297–2299.

29 V. Arora, H. M. Chawla and A. Santra, *Tetrahedron*, 2002, **58**, 5591–5597.

30 M. Larsen and M. Jørgensen, *J. Org. Chem.*, 1997, **62**, 4171–4173.

31 D. Shetty, I. Jahovic, J. Raya, F. Ravaux, M. Jouiad, J.-C. Olsen and A. Trabolsi, *J. Mater. Chem. A*, 2017, **5**, 62–66.

32 In *Calixarenes: An Introduction (2)*, The Royal Society of Chemistry, 2008, pp. 116–146.

33 S. Shinkai, K. Araki, P. D. J. Grootenhuis and D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans. 2*, 1991, 1883–1886.

34 S. Shinkai, K. Araki, H. Koreishi, T. Tsubaki and O. Manabe, *Chem. Lett.*, 1986, **15**, 1351–1354.

35 K. Iwamoto, K. Araki and S. Shinkai, *Tetrahedron*, 1991, **47**, 4325–4342.

36 A. Arduini, A. Pochini, S. Raverberi and R. Ungaro, *J. Chem. Soc. Chem. Commun.*, 1984, 981–982.

37 S. E. Biali, V. Böhmer, S. Cohen, G. Ferguson, C. Grüttner, F. Grynszpan, E. F. Paulus, I. Thondorf and W. Vogt, *J. Am. Chem. Soc.*, 1996, **118**, 12938–12949.

38 S.E. Biali, *Synlett*, 2003, **1**, 1–11.

39 O. Middel, Z. Greff, N. J. Taylor, W. Verboom, D. N. Reinhoudt and V. Snieckus, *J. Org. Chem.*, 2000, **65**, 667–675.

40 P. A. Scully, T. M. Hamilton and J. L. Bennett, *Org. Lett.*, 2001, **3**, 2741–2744.

41 C. Grüttner, V. Böhmer, W. Vogt, I. Thondorf, S. E. Biali and F. Grynszpan, *Tetrahedron Lett.*, 1994, **35**, 6267–6270.

42 G. Sartori, R. Maggi, F. Bigi, A. Arduini, A. Pastorio and C. Porta, *J. Chem. Soc. Perkin Trans. 1*, 1994, 1657–1658.

43 V. Gopalsamuthiram and W. D. Wulff, *J. Am. Chem. Soc.*, 2004, **126**, 13936–13937.

44 V. Gopalsamuthiram, A. V Predeus, R. H. Huang and W. D. Wulff, *J. Am. Chem. Soc.*, 2009, **131**, 18018–18019.

45 V. Gopalsamuthiram, R. Huang and W. D. Wulff, *Chem. Commun.*, 2010, **46**, 8213–8215.

46 L. T. Carroll, P. A. Hill, C. Q. Ngo, K. P. Klatt and J. L. Fantini, *Tetrahedron*, 2013, **69**, 5002–5007.

47 M. Coletta, R. McLellan, J.-M. Cols, K. J. Gagnon, S. J. Teat, E. K. Brechin and S. J. Dalgarno, *Supramol. Chem.*, 2016, **28**, 557–566.

48 M. Coletta, R. McLellan, P. Murphy, B. T. Leube, S. Sanz, R. Clowes, K. J. Gagnon, S. J. Teat, A. I. Cooper, M. J. Paterson, E. K. Brechin and S. J. Dalgarno, *Chem. – A Eur. J.*, 2016, **22**, 8791–8795.

49 S. E. Biali, eds. P. Neri, J. L. Sessler and M.-X. Wang, Springer International Publishing, Cham, 2016, pp. 75–93.

50 C. Fischer, G. Lin, W. Seichter and E. Weber, *Tetrahedron Lett.*, 2013, **54**, 2187–2189.

51 B. Klenke, C. Näther and W. Friedrichsen, *Tetrahedron Lett.*, 1998, **39**, 8967–8968.

52 S. Kumar, H. M. Chawla and R. Varadarajan, *Tetrahedron Lett.*, 2002, **43**, 7073–7075.

53 I. Columbus, *J. Org. Chem.*, 2008, **73**, 2598–2606.

54 L. Kuno and S. E. Biali, *J. Org. Chem.*, 2011, **76**, 3664–3675.

55 G. Görmar, K. Seiffarth, M. Schulz, J. Zimmermann and G. Flämig, *Die Makromol. Chemie*, 1990, **191**, 81–87.

56 N. B. Itzhak Silvio E., *Synthesis (Stuttg).*, 2015, **47**, 1678–1682.

57 L. Kuno, N. Seri and S. E. Biali, *Org. Lett.*, 2007, **9**, 1577–1580.

58 D. Poms, N. Itzhak, L. Kuno and S. E. Biali, *J. Org. Chem.*, 2014, **79**, 538–545.

59 I. Columbus and S. E. Biali, *Org. Lett.*, 2007, **9**, 2927–2929.

60 O. Shalev and S. E. Biali, *Org. Lett.*, 2018, **20**, 3390–3393.

61 M. Hofmann, N. Hampel, T. Kanzian and H. Mayr, *Angew. Chemie Int. Ed.*, 2004, **43**, 5402–5405.

62 A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M.-J. Schwing, R. J. M. Egberink, F. de Jong and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1995, **117**, 2767–2777.

63 A. Fong, C. L. Campbell, S. Huynh, L. J. McCormick McPherson, S. J. Teat, M. W. P. Bebbington and S. J. Dalgarno, *Chem. Commun.*, 2022, **58**, 3302–3305.

64 A. Fong, Heriot-Watt, 2019.

65 G. L. Larson and J. L. Fry, in *Organic Reactions*, 2008, pp. 1–737.

66 L. Kuno and S. E. Biali, *Org. Lett.*, 2009, **11**, 3662–3665.

67 P. Murphy, R. G. McKinlay, S. J. Dalgarno and M. J. Paterson, *J. Phys. Chem. A*, 2015, **119**, 5804–5815.

68 J. Rebek Julius, *Chem. Commun.*, 2000, 637–643.

69 D. Maity, A. Chakraborty, R. Gunupuru and P. Paul, *Inorganica Chim. Acta*, 2011, **372**, 126–135.

Chapter 2

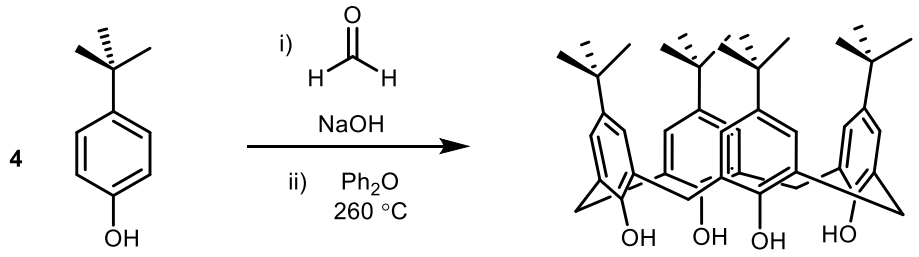
Synthesis of a C[4] Methylene Bridged 1,4 Saturated Diketone and Investigation of the Paal-Knorr Synthesis.

2.1. Introduction.

The work discussed in this chapter involves the synthesis and modification of a previously utilised 2-methylfuranyl group mono-substituted at every bridge position of a *p-tert*-butylcalix[4]arene. Ring opening of the furan group is achieved under acidic conditions, forming a saturated 1,4 diketone as a result which can be utilised to form a variety of heterocycles. In this chapter Paal-Knorr pyrrole condensation is investigated with a selection of primary anilines, developing a library of C[4]s that are methylene bridge-substituted with pyrroles. This method for introducing new functional groups at the C[4] methylene bridge position has wide scope, e.g. there are a vast number of commercially available anilines to exploit.

2.2. Synthesis of 2-Methylfuranylcalix[4]arene, 4.

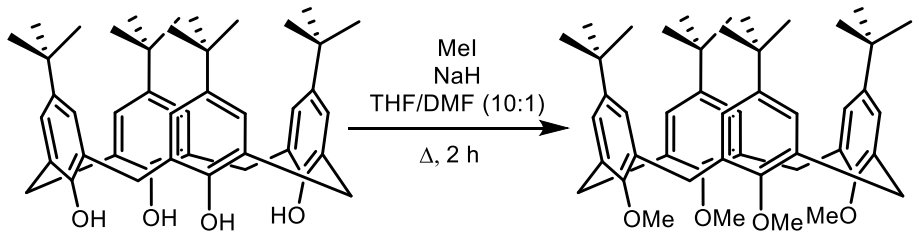
The synthesis of a C[4] in which all methylene bridge positions have been mono-substituted by a 2-methyl furan group was carried out according to literature procedures.[1,2] The first step in this work was the synthesis of *p-tert*-butylcalix[4]arene (H_4TBC[4]), **1**. This is carried out in a one pot synthesis involving the base-induced condensation between *p-tert*-butylphenol and formaldehyde (Scheme 2.1).[1] The reaction is usually thought about in two steps, first whereby *p-tert*-butylphenol and formaldehyde are heated at reflux in the presence of sodium hydroxide using a Dean-Stark apparatus to remove the water. Once this water has been removed the mixture polymerises and a large thick yellow mass is formed. This polymerised intermediate is then dissolved in toluene and diphenyl ether before heating at reflux (at 260 °C) for 4 hours. Upon cooling a solid is formed which is filtered and washed with ethyl acetate to afford **1** as a crystalline white solid.



1

Scheme 2.1. Scheme for the synthesis of *p-tert*-butylcalix[4]arene, H_4TBC[4], **1**.

Compound **1** is relatively insoluble in most organic solvents and contains four acidic phenolic hydrogens.[3] Therefore, to inhibit reactivity and increase solubility, the lower-rim was protected by conversion to the tetra-ether derivative. Various lengths of alkyl can be introduced at the lower-rim by reaction with alkyl halides in the presence of a suitable base. These hydroxyl groups are, however, vital for utilisation of the lower-rim in metal binding,[4,5,6] so the simplest ether (methoxy) was chosen as this is a common protecting group employed in organic synthesis.[7] The subsequent removal of this group is discussed in Chapter 3. To synthesise 5,11,17,23-tetra-*tert*-butyl-25,26,27,28 tetramethoxycalix[4]arene, **2** (Scheme 2.2), compound **1** was reacted with iodomethane using sodium hydride to deprotonate the lower-rim hydroxyl groups, forming the phenoxide ion. This general procedure is most famously known as the Williamson ether synthesis, and recrystallisation from $CHCl_3$/MeOH afforded the pure product **2** in 80 % yield.



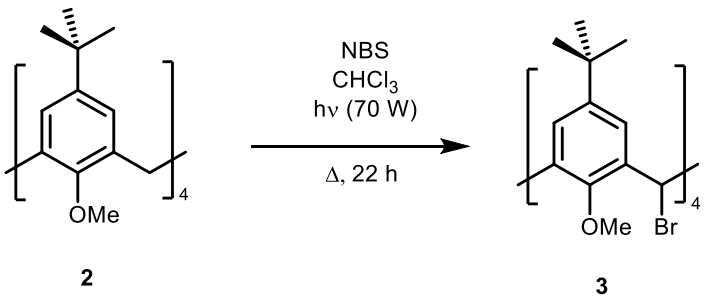
1 2

Scheme 2.2. Synthetic scheme for the synthesis 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene, **2**.

Installation of methoxy groups at the lower-rim disrupts the hydrogen bonding found in **1** allowing -OMe though the anulus rotation to occur readily at room temperature. This is demonstrated on an NMR timescale as the ^{1}H NMR spectrum shows peak broadening,

implying that the C[4] is no longer adopting the cone conformation. The cone conformation can be restored to allow full analysis of the ^{1}H NMR spectrum by complexation with an Na^+ ion. This is achieved by dissolving **2** in a saturated $CDCl_3/d_3$-ACN (3:1 v/v) solution of sodium iodide. Analysis of the spectrum shows loss of the hydroxyl signal at 10.35 ppm and introduction of a new signal at 4.01 ppm relating to the methoxy protons, thus confirming synthesis.

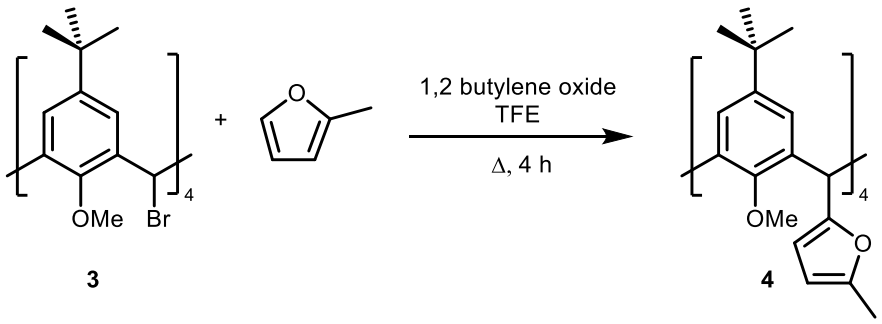
Following protection of the lower-rim, the next step involves mono-substitution of the methylene bridge positions with bromine atoms. This was carried out following a slightly modified literature procedure.[2] Photochemical bromination was performed by reacting **2** with stoichiometric amounts of *N*-bromosuccinimide (NBS) in chloroform using a spot lamp (70 W) as a source of light and as an initiator. After work-up and recrystallisation from hot $CHCl_3$/MeOH, 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrabromo-25,26,27,28-tetramethoxycalix[4]arene, **3**, was obtained in 65 % yield. Interestingly, all bromine atoms substitute equatorially at the methylene bridge positions, and the cone conformation adopted as previously determined by single crystal X-ray diffraction. The ^{1}H NMR spectrum has also returned to a symmetrical nature with sharp signals as the calixarene once again adopts the cone conformation. This is known by cross referencing to the previous work done by Biali and co-workers who proved the cone conformation by single crystal x-ray diffraction.[2] Comparison of the ^{1}H NMR spectrum to that of **3** showed concordant sharp signals in the correct region.



2 **3**

Scheme 2.3. Synthetic scheme for the photochemical radical bromination of **2** using NBS to afford 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrabromo-25,26,27,28 tetramethoxycalix[4]arene, **3**.

Replacement of the bromine atoms was achieved by following the literature procedure reported by Biali and co-workers.[2] They used a highly ionizing solvent, either trifluoroethanol (TFE) or hexafluoro-2-propanol (HFIP), to conduct a solvolysis reaction replacing the bromine atoms at the bridge with different functional groups. Utilising their method, compound **3** was heated at reflux in TFE and 2-methylfuran added as the nucleophile, with 1,2 epoxybutane acting as an HBr scavenger. This reaction proceeds through an Sn1 pathway and all methyl furan groups retain the equatorial position at the methylene bridge, with retention of the cone conformation. Due to this it is the ideal starting point for building additional functionality at the C[4] methylene bridge positions.



Scheme 2.4. Schematic for the Friedel-craft solvolysis reaction using TFE in the presence of 2-methylfuran to afford 11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(2-methylfuranyl)-25,26,27,28-tetramethoxycalix[4]arene, **4**.

In Biali and co-worker's previous report the authors did not include a crystal structure of **4**, and only reported data for a de-*tert* butyl analogue. Therefore, a single crystal suitable for X-ray diffraction studies was grown from the slow evaporation of dichloromethane (DCM). These were found to be in a triclinic unit cell and structure solution was carried out in the space group $P2_1/n$ (Figure 2.1). Figure 2.1 shows the structure of **4**, clearly highlighting tetra-substitution at the equatorial bridge positions with a 2-methylfuran substituent, whilst the molecule adopts a pinched cone conformation. From the ^{1}H NMR spectrum of **4** it can be seen there is no splitting in the *t*-butyl or OMe signals and therefore the pinched cone is most likely an effect of crystallisation, i.e. the molecule is fluxional in solution.

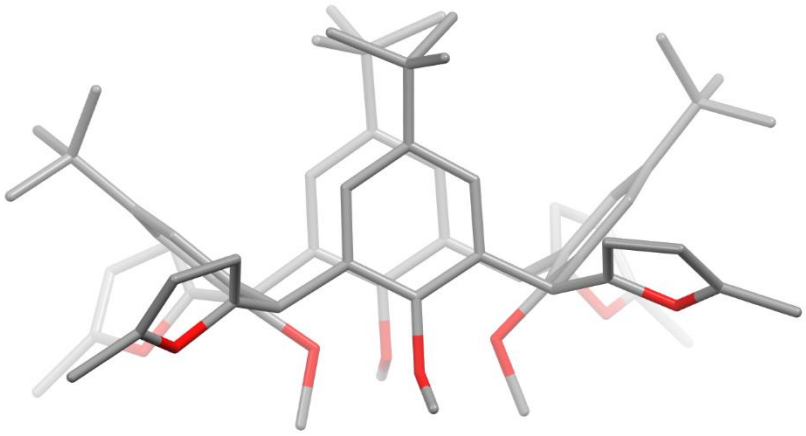


Figure 2.1. Sticks representation of the partial single crystal X-ray structure of **4** showing 2-methyl furan groups monosubstituted at all equatorial bridge positions of a tert-butylcalix[4]arene in the pinched cone conformation. H atoms and solvent of crystallisation (DCM) are omitted for clarity. Colour code C - Grey; O - Red.

Interestingly, a side product isolated from this reaction was believed at first to be partially substituted at the methylene bridge positions as the ^{1}H NMR was very broad and indecipherable. All attempts to lock the conformation through the use of a saturated sodium iodide solution as outlined above proved unsuccessful. A single crystal of compound **4a** that was suitable for X-ray diffraction studies was grown from a saturated solution of acetone. The single crystal solution was found in a triclinic unit cell and the structure solution carried out in space group $P\bar{1}$ (Figure 2.2).

Analysis of Figure 2.2 shows compound **4a** in a partial cone conformation in which one of the phenyl groups has flipped and is pointing down with respect to the others. Interestingly the configuration is observed as the rcct whereby 3 subsituents are bound equatorially and one is bound axial which could be account for the unusual features in solution. The molecule appears to be very strained and therefore it possesses no symmetry elements. Due to the methoxy groups on the lower-rim it was quite surprising to see an alternate configuration being formed, especially in the rcct configuration and therefore it was theorised that the equatorial groups must have some impact on how fluxional the molecule is. The next step was to see if, by deprotecting the lower-rim methoxy groups, compound **4a** would remain as an alternate conformation or rotate / revert to a cone synthesising different configuration (rcct) derivative of the demethylated version of **4**.

Following a previously employed method, compound **4a** was reacted at reflux in DMF for 48 hours under N_2 in the presence of cyclohexyl iodide as the demethylating agent.[6,8] Upon workup, analysis of the ^{1}H NMR spectrum demonstrated that the cone was re-established as all the signals had sharpened and interestingly spectrum was matched to that of the previously synthesised rccc demethylated derivative.[6] As expected, this conformation is preferred due to the hydrogen bonding interactions present on the lower-rim reforming. However unexpectedly the configuration has also changed back to the rccc. This would indicate that the cone conformation favours the rccc configuration.

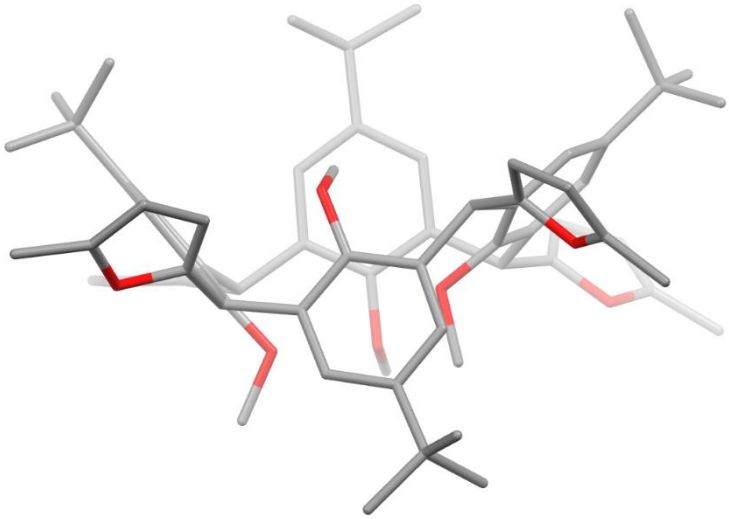


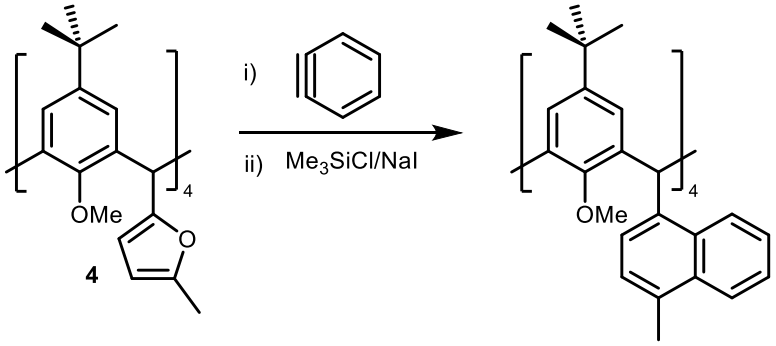
Figure 2.2. Sticks representation of the single crystal X-ray structure of **4a** showing 2-methyl furan groups monosubstituted on all equatorial bridge positions of a tert-butylcalix[4]arene in a strained partial cone conformation in the rcct configuration. Solvent (Acetone) has been masked. H atoms are omitted for clarity. Colour code C - Grey; O - Red.

2.3. The Acidic Ring Opening of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(2-methylfuranyl) 25,26,27,28-tetramethoxycalix[4]arene, 4.

The introduction of a 2-methyl furnayl group to the methylene bridge position offers a wide range of further potential modification due to the synthetic diversity of the furan moiety. However, outside of the Dalgarno group, this compound has only been further modified once. Biali and co-workers reacted **4** with benzyne in a Diels-Alder reaction

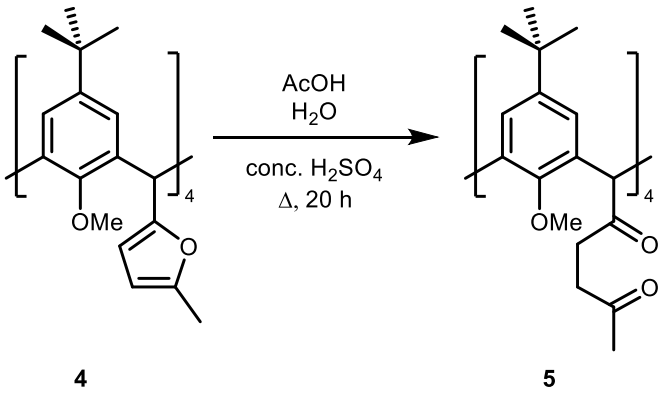
followed by subsequent deoxygenation using Me_3SiCl/NaI to afford the desired arene derivative (Scheme 2.5).[9]

There are many different routes for the formation of new heterocyclic compounds. Ring opening of the furan moiety was previously explored in the group. This was of interest as it provides the opportunity to isolate other equatorial heterocycles at each methylene bridge position. Both saturated and unsaturated diketones have been isolated, however the work in this chapter will focus on the reactions of the saturated diketone species with anilines, whilst discussion involving the unsaturated species can be found in Chapter 3.



Scheme 2.5. Synthetic scheme for the preparation of 5,11,17,23-Tetra-tert-butyl-2,8,14,20-tetra(4-methylnaphthyl)-25,26,27,28-tetramethoxycalix[4]arene reported by Biali and Columbus utilising the furanyl derivative, **4**.

Acid catalysed hydrolysis of compound **4** using a combination of acetic acid, water and concentrated sulfuric acid heated to reflux (Scheme 2.6) afforded 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(pentane-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, **5**, in 51 % yield using a modified literature procedure developed by Fong *et al.*[10] From comparison of the ^1H NMR spectra it can be seen that the set of doublet of doublets for the backbone of the furan at 5.98 and 5.91 ppm (J = 3.0, 1.2 Hz) had disappeared and a new set of doublet of triplets indicative of a $-CH_2-CH_2-$ backbone at 2.95 and 2.83 ppm (J = 7.2, 5.1 Hz) had evolved. These triplets are very useful for monitoring future reactions as the distinctive signals can be utilised as convenient NMR handle to quickly assess if onward reactions have occurred (Figure 2.3).



4 **5**

Scheme 2.6. Synthetic scheme for the acidic ring opening reaction of tetrafuranyl TBC[4]OMe using a mixture of acetic acid, sulfuric acid and water.

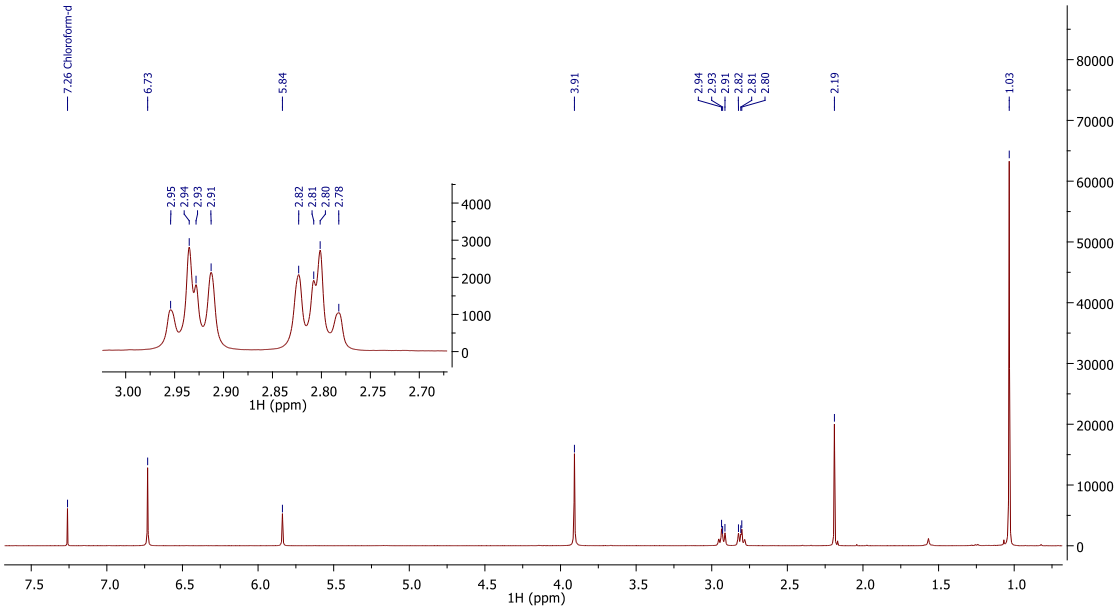


Figure 2.3. ^{1}H NMR spectrum of **5** in chloroform-d showing the indicative triplets of -CH_2-CH_2- backbone at 2.93 and 2.81 ppm which can be used as an NMR handle for future reactions.

The previously reported crystal structure of **5** shows that the molecule adopts a pinched cone conformation. Interestingly, no splitting of the OMe or *t*-Bu groups is observed in the ^{1}H NMR spectrum suggesting, again that this is likely a crystallisation effect and the molecule remains fluxional in solution. Once **5** had been successfully synthesised, the Paal-Knorr pyrrole synthesis could be further explored. Previous work in the group

demonstrated the synthesis of a small library of pyrrole-appended C[4]s (Figure 2.4). For all reactants which the reaction had taken place in Figure 2.4, the desired product was obtained and fully characterised.

It is interesting to note that 3-aminopyridine was successful, however the 2- and 4-aminopyridine analogues were not. It was postulated that the reaction conditions were too acidic and consequently the 2- and 4-aminopyridines were being protonated and therefore not acting as nucleophiles.[11] This relates to the electronics of the pyridine. 2- ,3- and 4-aminopyridine all possess different resonance forms in which the exocyclic nitrogen possesses a positive charge, and a negative charge resides in the ring. 2- and 4-aminopyridine can stabilise this negative charge through the nitrogen whereas 3-aminopyridine does not. These mesomeric forms, which are more stable in 2- and 4-aminopyridine result in increased nucleophilicity at the ring nitrogen and decreased nucleophilicity at the exocyclic nitrogen.[12] This decrease in nucleophilicity could account for the failed reaction as the Paal-Knorr pyrrole synthesis mechanism resolves around the exocyclic nitrogen attacking the carbonyl forming an enamine.[13]

Due to the potential that 2- and 4-aminopyridines have for cage formation with metal salts such as Pd. For instance Zhong *et al* used an upper-rim tetra substituted 4-pyridylcalix[4]arene with Pd to form a self-assembling molecular capsule.[14] These compound are seen as targets of high interest and discussions involving the work undertaken to achieve compounds where a 2- or 4-pyridyl group is substituted off the methylene bridge can be found in chapter 4.

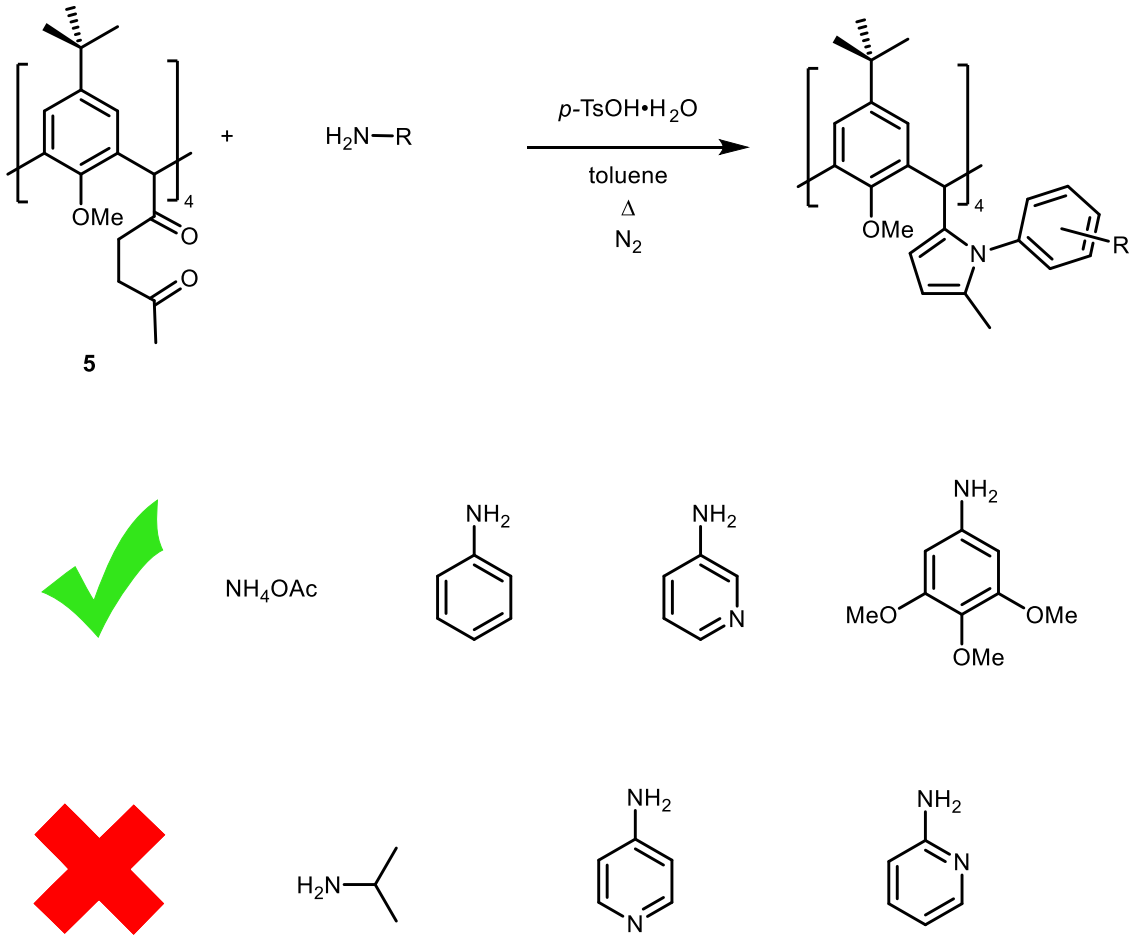


Figure 2.4. General scheme for the Paal-Knorr reaction of **5** with a substituted Amine. Amine reactants previously investigated are seen besides the green tick whilst those unsuccessful and starting material recovered are seen next to the red cross.

2.4. Synthesis of *N*-substituted Pyrrole Derivatives on a Calix[4]arene through the Paal-Knorr Synthesis.

As discussed previously, a proof of concept was established within the group whereby several different secondary amines could be successfully reacted with **5** to form the respective pyrrole derivative. The aim for this chapter is to further investigate the scope of this reaction by using a variety of secondary anilines to synthesise a library of methylene bridge pyrrole-appended calix[4]arenes. The scope of anilines trialled is shown in Figure 2.5.

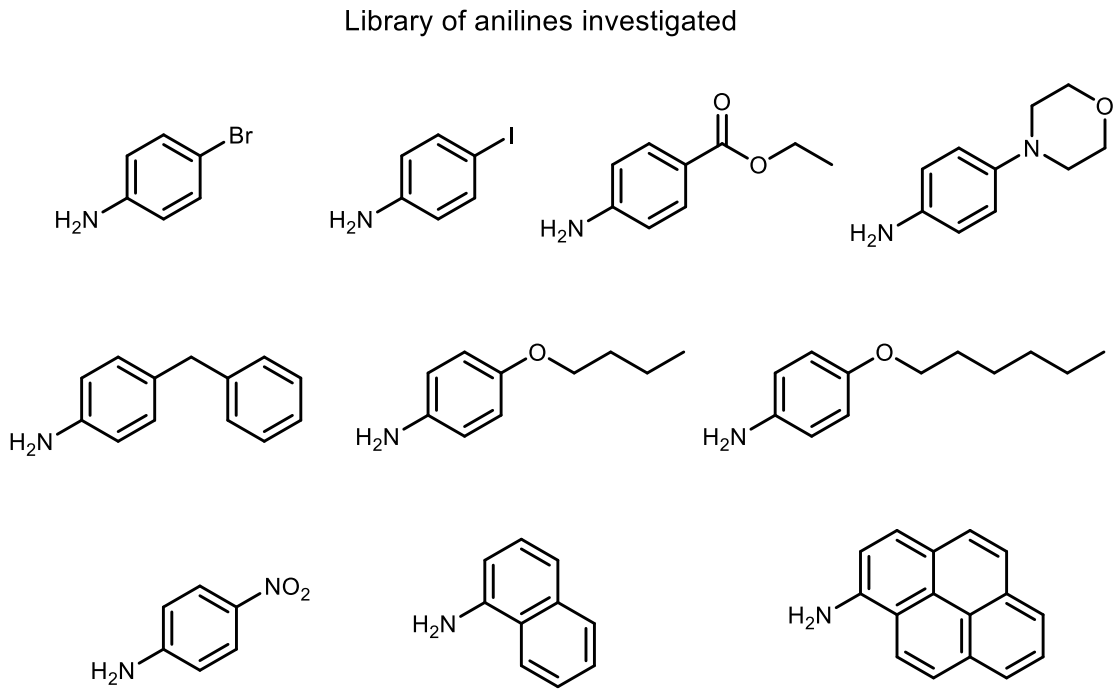
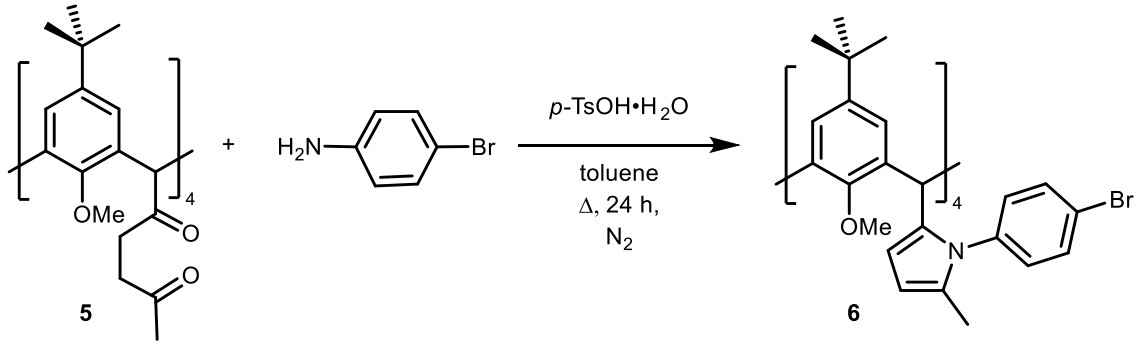


Figure 2.5. Anilines chosen to test scope and develop a new library of methylene bridged pyrrole *p-tert*-butylcalix[4]arenes.

The project began by investigating halogenated anilines, 4-bromoaniline and 4-iodoaniline as aryl halides are known for being very important / versatile building blocks within organic chemistry. They are most notably used for a range of metal-mediated cross coupling reactions such as Suzuki-Miyaura , Heck, and Negishi which are now fundamental reactions in organic chemistry and earned Suzuki and Miyaura the Nobel prize in 2010.[15] Therefore, being able to synthesise aryl halide substituted calix[4]arenes could allow further, facile modification to the framework.

2.4.1. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-bromophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 6.

4-Bromoaniline was reacted with compound **5** using standard Paal-Knorr conditions employed by Fong *et al.*,[16] although one change made in that all reactions were performed under an inert atmosphere of N_2 to minimise oxidation products forming during the reaction. It should be noted here that, during the course of the doctoral study, degradation of the pyrrole was observed in the presence of light and therefore some reactions were also subsequently wrapped with aluminium foil to avoid light ingress. It will be written throughout which reactions were performed with or without this measure, however if sufficient time had been available, every reaction would have been repeated in the absence of light. The present reaction was carried out in toluene in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH· H_2O) under N_2 (Scheme 2.7). Heating to reflux overnight afforded a brown crude product which was recrystallised from $CHCl_3$/MeOH to afford **6** in 71 % yield as a tan solid. When discussing yields for these pyrrole-substituted calix[4]arenes it is important to highlight that the reaction is taking place at four positions, therefore a 71% yield would equate to roughly a 92% yield at each methylene bridge position. The reaction between 2,5-hexadione and 4-bromoaniline can be found throughout the literature. A paper using a similar procedure report yields of up to 90%,[17] indicating that this method for substitution onto the calixarene can achieve comparable yields to its individual components if four reaction positions are being considered.



Scheme 2.7. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-bromophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxy-calix[4]arene, **6**.

Analysis of the ^{1}H NMR spectrum showed complete loss of the signals for the 1,4-diketone NMR handle and introduction of a new set of doublets at 5.93 and 5.99 ppm corresponding to the CH protons of the pyrrole moiety. Four broad signals can also be seen in the aromatic region of the spectrum and correspond to the C-H protons on the aryl halide thought to arise from free rotation around the N-C bond. This is a feature commonly observed with phenyl substituted pyrroles and would be interesting to see if these signals would sharpen upon heating using variable temperature (VT) NMR studies. Colourless single crystals of **6** suitable for X-ray diffraction studies grew from a saturated $CHCl_3$ solution. The crystals were found to be in a triclinic unit cell and the structure solution was carried out in the space group $P\bar{1}$. The ASU was found to contain one full molecule of **6** in the pinched-cone conformation with all phenyl bromo groups at the pyrroles pointing down as shown in Figure 2.6.

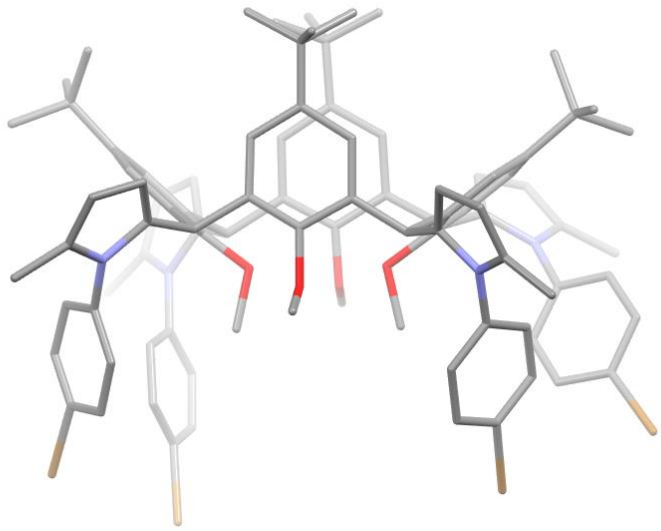


Figure 2.6. Sticks representation of the single crystal X-ray structure of **6** showing a 4-bromophenyl substituent appended to the N atom of the pyrrole in sticks representation. Solvent has been masked ($CHCl_3$). Colour code C - Grey; O - Red; N - Blue; Br - Brown. H atoms omitted for clarity.

Inspection of Figure 2.6. clearly shows that the 1,4 diketone has ring closed to form the desired pyrrole derivative. Solvent of crystallisation (chloroform) was unable to be modelled and so a solvent mask was applied. It is also interesting to see that the calix[4]arene has been de-symmetrised and adopts a pinched cone conformation, whereby two distal phenyl rings are almost parallel whilst the remaining two are splayed outwards.

Further evidence that this also occurs in solution and isn't just a crystallisation effect comes from the ^{1}H NMR spectrum (Figure 2.7.) whereby the *t*-butyl (two singlets at 0.87 and 1.19 ppm), OMe (two singlets at 2.72 and 3.23 ppm) and Ar-H (phenyl, two singlets 6.41 and 6.82 ppm) are all split into two signals. This indicates that there are two distinct environments for each of these positions and something that the pinched cone would support.

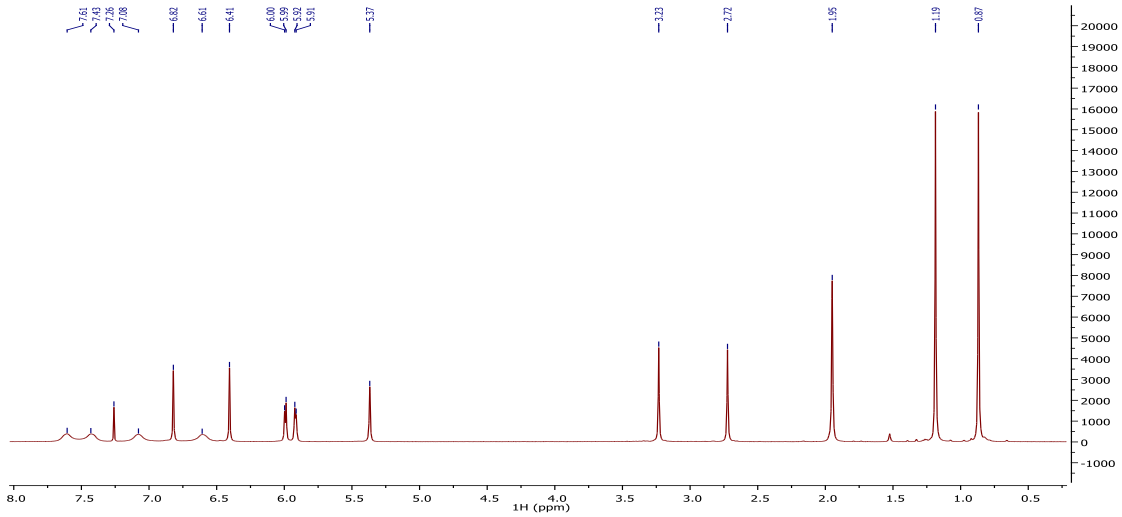
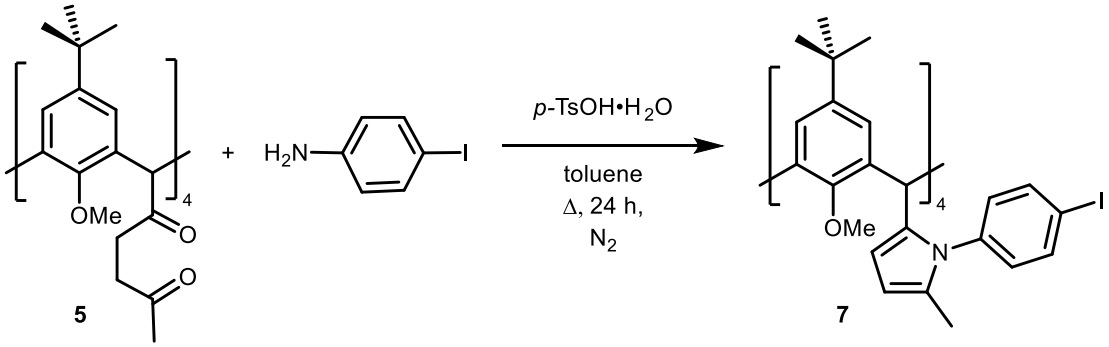


Figure 2.7. ^{1}H NMR spectrum of compound **6** in chloroform-d at 25 °C.

2.4.2. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-iodophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 7.

The next reaction investigated employed the iodo aniline analogue relative to the previous reaction. Compound **5** and 4-iodoaniline were heated to reflux in toluene using *p*-TsOH·H_2O as a catalyst under N_2 whilst wrapped in aluminium foil for 24 hrs (Scheme 2.8). Inspection of the ^{1}H NMR spectrum showed that the reaction had proceeded as the indicative triplets located in the starting material had disappeared and a new set of doublets appeared at 6.02 ppm, relating to reaction formation of the desired product as the backbone becomes conjugated and therefore the signals are observed more downfield. Splitting of the *t*-butyl, OMe and Ar-H enviroments would also suggest that the desired product has been formed as this splitting is commonly observed upon pyrrole formation at the methylene bridges as the calixarene adopts a pinched cone conformation. As found for the bromo analogue, the phenyl Hs directly bonded to the pyrrole were broad, thus indicating free rotation. The crude product was purified via column chromatography to afford **7** in 31% yield, corresponding to a 75% per methylene bridge position. However

the literature reports yields upwards of 95% for the reaction of 2,5 hexadione and 4-iodooaniline in toluene using *p*-TsOH·H_2O.[18] It is therefore interesting that the yield in this case is so much lower, particularly in comparison to the bromo analogue. A crystal grown from a saturated $CHCl_3$ solution was grown, however it was found that the crystals were degrading so quickly in the mounting oil that only poor quality data could be obtained. It was ultimately not possible to structurally characterise **7**. Atmospheric solid analysis probe mass spectroscopy (ASAP-MS) was used to further confirm the successful synthesis of **7** as a clear peak at 1831.15 m/z could be seen.

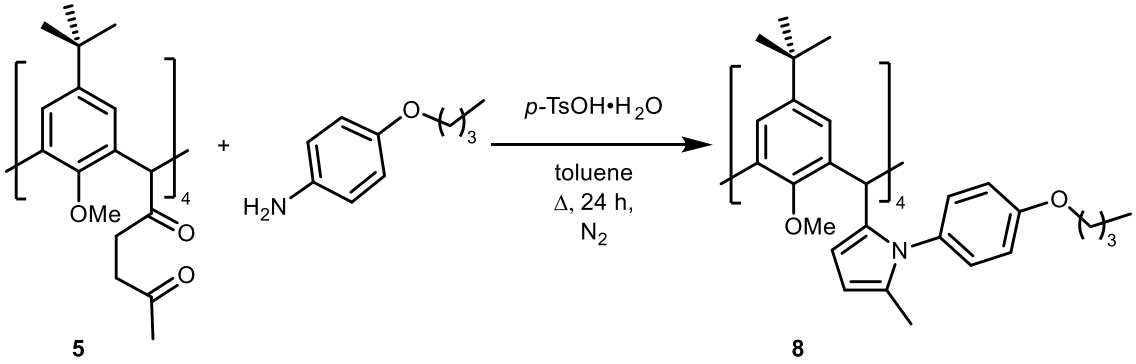


Scheme 2.8. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-iodophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, **7**.

2.4.3. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-butoxyphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 8.

The next reactions investigated involved anilines with long chain ether chains attached. It was postulated that this would increase solubility, something that had previously been an issue when investigating the reaction of compound **5** with aniline.[16] Compound **5** was reacted with 4-butoxyaniline under the standard Paal-Knorr conditions used previously, affording a brown solid crude upon workup. Following purification via column chromatography, **8** was isolated in 74% yield, equating to a 93% yield per methylene bridge position. Analysis of the ^{1}H NMR spectra showed complete loss of the diketone backbone signals and the formation of a new set of doublets downfield. This is indicative of pyrrole formation as aromaticity is reintroduced. The *t*-butyl, OMe and Ar-Hs on the calixarene ring are all seen to split from what a singlet in the starting material, to two different signals in the product, suggesting that the calixarene has adopted the pinched

cone formation. The long chain ether signals can also be seen in the ^{1}H NMR spectra at 3.95, 1.76, 1.47 and 0.94 ppm, and the hydrogens furthest downfield correspond to those closest to the oxygen due to the electronegativity de-shielding the protons. It was also observed that the substituted phenyl protons present as two pairs of doublets rather than broad singlets as seen previously. This would indicate that there is hindered rotation around the bond, possibly due to steric effects arising from the long chain ethers.



Scheme 2.9. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-butoxyphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxy-calix[4]arene**, 8**.

Colourless single crystals, suitable for analysis via single crystal X-ray diffraction, were grown through a solvent diffusion of hexane into dichloromethane. The crystals were found to be in a monoclinic cell and the structure solution carried out in the space group $P2_1/c$. The ASU contains two molecules of **8**, both of which are in the pinched cone conformation, however only one is shown in Figure 2.8 for simplicity. The crystal structure shows disorder in two of the butoxy chains whereby they are distributed over two positions assigned with 0.6 and 0.4 occupancy. This is not uncommon for alkyl chains in the solid state and some example of long chain lower-rim substituted ether chains are referenced.[19,20] Hexane can also be seen in the crystal structure whereby it sits in a pseudo cavity generated by the methylene bridge substituents. It is thought that due to the pinched cone conformation solvent will preferentially crystalise between the methylene bridge substituents at the lower-rim over the upper-rim, as the pocket has become harder to access / is sterically blocked for occupation by reasonably large guests.

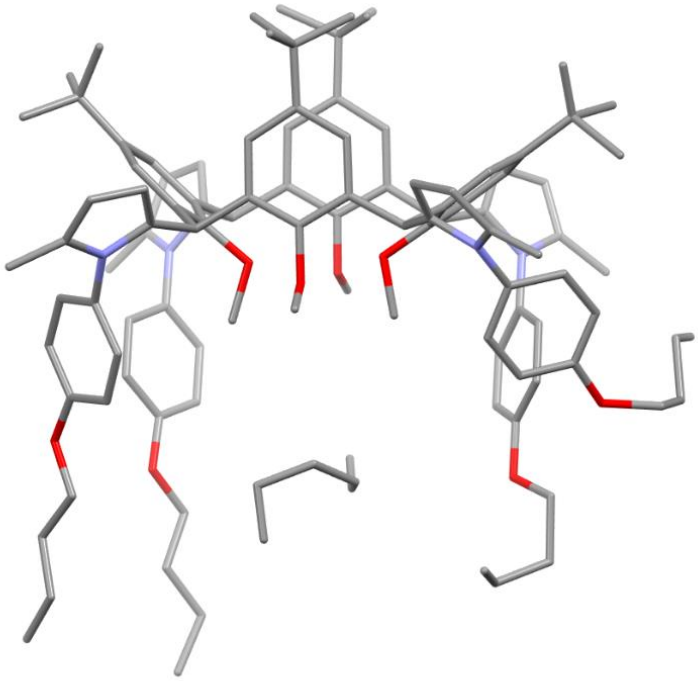
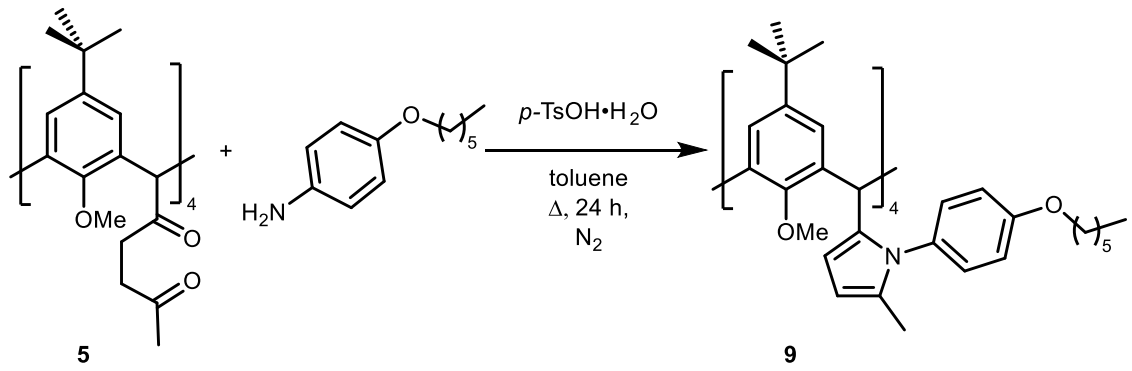


Figure 2.8. Sticks representation of the partial single crystal X-ray structure of **8** showing a 4-butoxyphenyl substituent appended to the N atom of the pyrrole, and one molecule of hexane sitting in a pseudo cavity generated at the lower-rim by the methylene bridge substituents. Only one calixarene of **8** is shown in the figure although two exist in the unit cell. Some solvent of crystallisation has been masked. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

2.4.4. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-hexoxyphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 9.

The reaction of 4-hexyloxyaniline with compound **5** was investigated using analogous reaction conditions, heating at reflux in toluene in the presence of *p*-TsOH·H_2O under N_2 (Scheme 2.10). Following purification via column chromatography, compound **9** was obtained in 43% yield, equating to an 81% yield for each position. Interestingly this is significantly lower than the butoxy analogue, compound **8**.



Scheme 2.10. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-hexoxyphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetra-methoxycalix[4]arene, **9**.

Analysis of the ^{1}H NMR spectrum indicates that the desired compound has been formed as the distinctive triplets disappeared and introduction of new signals in both the aromatic and alkyl regions observed. Splitting of the *t*-butyl, OMe and Ar-H signals was also observed, indicating that that the methylene bridge has been further substituted. Interestingly the aromatic signals assigned to the pyrrole Ar-H groups are again seen as pairs of doublets. This suggests that the environments can be resolved on the NMR timescale, which could arise from the hindered rotation due to the long chain groups. Colourless single crystals that were suitable for diffraction studies were grown from a saturated acetone solution. The crystals were found to be in a triclinic unit cell and the structure solution carried out in space group $P\bar{1}$. The ASU was found to contain one full calixarene unit as shown in Figure 2.9.

Inspection of Figure 2.9 indicates that the 1,4-diketone groups at the methylene bridge have been ring-closed to form pyrrole groups with substituted 4-hexyloxyphenyl groups and the calixarene has adopted the expected pinched cone conformation. These newly appended groups are seen to point down and towards one another other, facing the phenyl groups that are splayed due to the pinched cone conformation. This is thought to arise from sterics, as when the pinched conformer is adopted, the OMe groups on the lower-rim are orientated further into the lower cavity, allowing more space for the bridged substituents to occupy. The pyrrole substituents are seen facing one another, and therefore distal hexyl ether chains are oriented in different directions, either into the lower cavity or away.

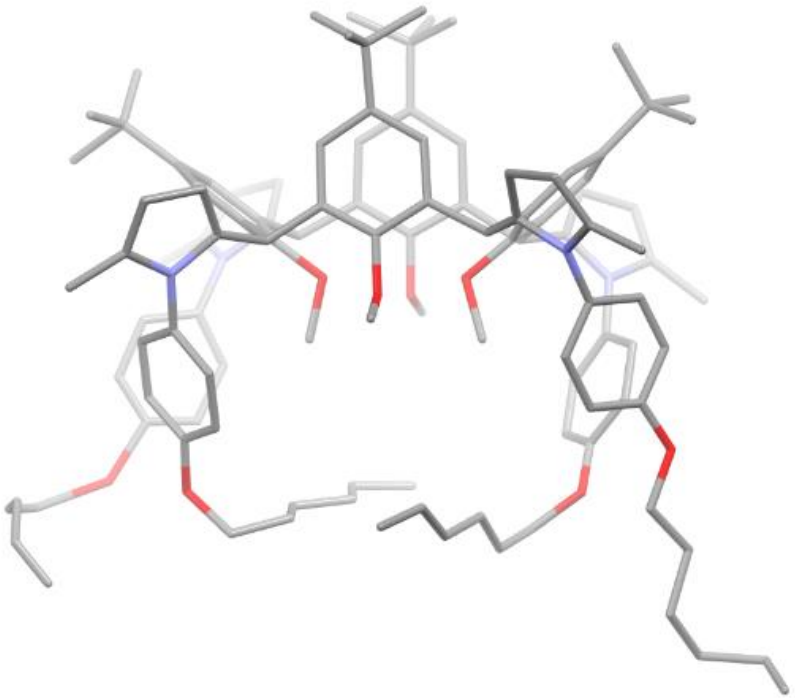


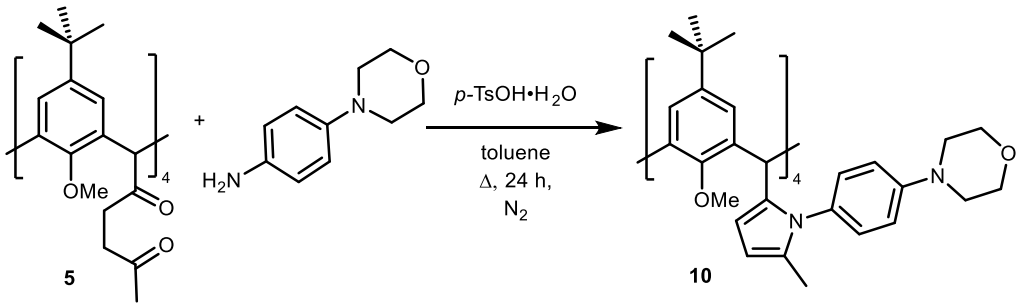
Figure 2.9. Sticks representation of the single crystal X-ray structure of **9** showing a 4-hexyloxyphenyl substituent appended to the N atom of the pyrrole. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

In comparison to the butoxy derivative no solvent is seen to occupy the lower-rim pseudo cavity, but it is anticipated that crystallising using a different solvent could achieve this by increasing intramolecular interactions between the appended groups and the solvent of crystallisation.

The addition of long chain alkyl ethers to the methylene bridge did deliver significant improvements in solubility in a range of organic solvents compared to the *N*-phenyl substituted pyrrole previously synthesised by Fong *et al.*[16] The ether chains below the lower-rim cavity is an attractive property as, upon deprotection of the methoxy groups re-opening, the pseudo cavity these long chains present could potentially act as hydrophobic tails and allow for ion transport or recognition.

2.4.5. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-morpholino phenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 10.

The next reactions trialled employed larger, bulkier groups appended to the phenyl ring, starting with a morpholine group substituted to the phenyl of the N atom of the pyrrole. This was achieved following the same procedure as outlined above (Scheme 2.11).



Scheme 2.11. Synthetic scheme for the preparation of 5,11,17,23--tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-morpholinophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetra-methoxycalix[4]arene, **10**.

Following a 24 hour reflux a brown crude was obtained which was washed with petroleum ether (40-60°) to afford the desired product in 28% yield equating to a 70% yield for each bridge position. Interestingly this is significantly higher than the reported 37% in literature for the simple reaction of hexane-2,5-dione with 4-morphoaniline.[21] Analysis by ^{1}H NMR showed all the key characteristics of product formation. The distinct triplets had disappeared and were replaced with a set of downfield doublets. Four sharp roofing doublets could also be seen in the aromatic region, along with additional signals in the alkyl region that are indicative of a morpholine group. Splitting of the *t*-butyl, OMe and Ar-H signals was also observed, disrupting the symmetry, suggesting that the reaction was successful and the calix[4]arene had adopted the pinched cone conformation. Single crystals suitable for analysis by X-ray diffraction studies were grown from a saturated solution of ethyl acetate. The crystals were a monoclinic unit cell and the structure solution carried out in $P2_1/n$. The ASU contains two molecules of **10** and six molecules of ethyl acetate of crystallisation. The ethyl acetate was unable to be fully modelled and so a solvent mask was used to correct the electron density around the molecule.

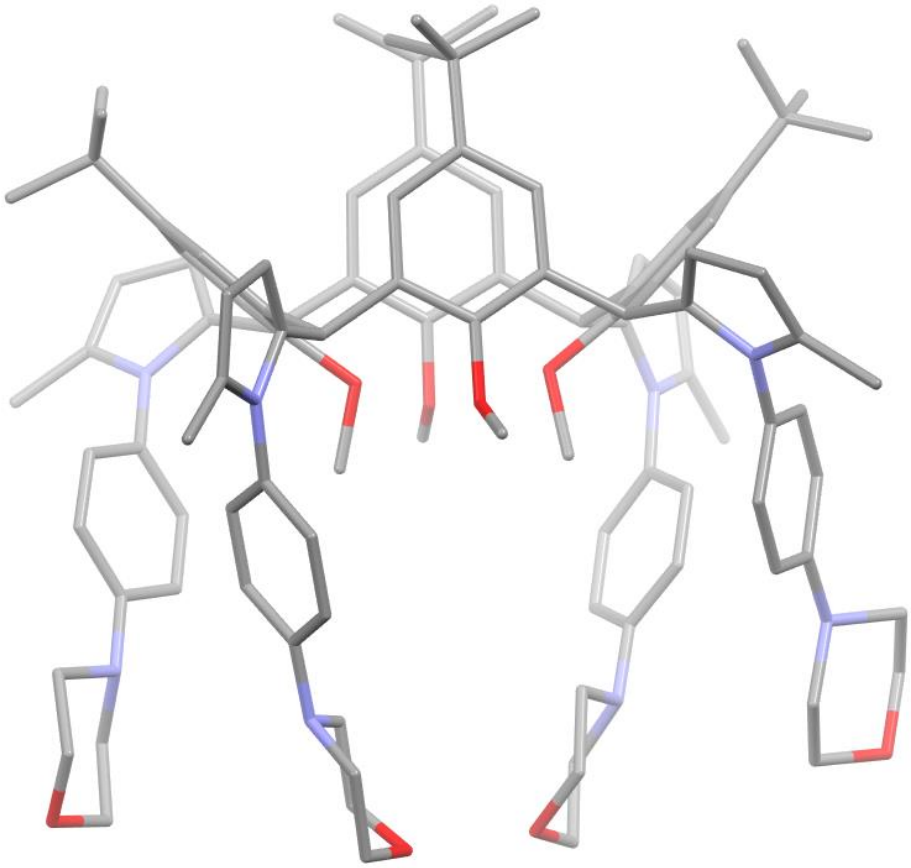
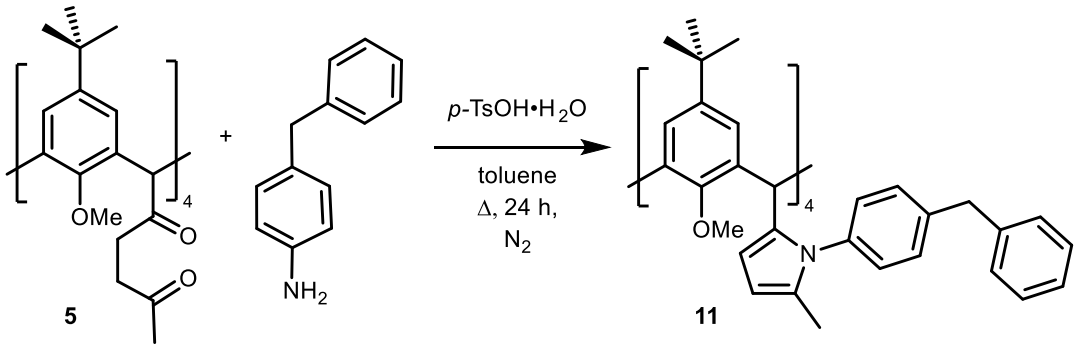


Figure 2.10. Sticks representation of the partial single crystal X-ray structure of **10** showing a 4-phenylmorpholine substituent appended to the N atom of the pyrrole. Only one calixarene of **10** is shown in the figure although two exist in the unit cell. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

2.4.6. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-benzylphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 11.

The next reaction involved refluxing 4-benzylaniline with compound **5** in toluene using *p*-TsOH·H_2O as a catalyst under N_2 (Scheme 2.12). The ^{1}H NMR spectra of the crude shows complete disappearance of the distinctive triplets and introduction of a set of doublets relating to that of pyrrole backbone. Following purification via column chromatography the ^{1}H NMR spectrum was fully investigated. Additional signals had appeared in the aromatic region which can be related to the appended phenyl substituents. A doublet of doublets was also observed at 3.97 ppm, relating to the CH_2 methylene group

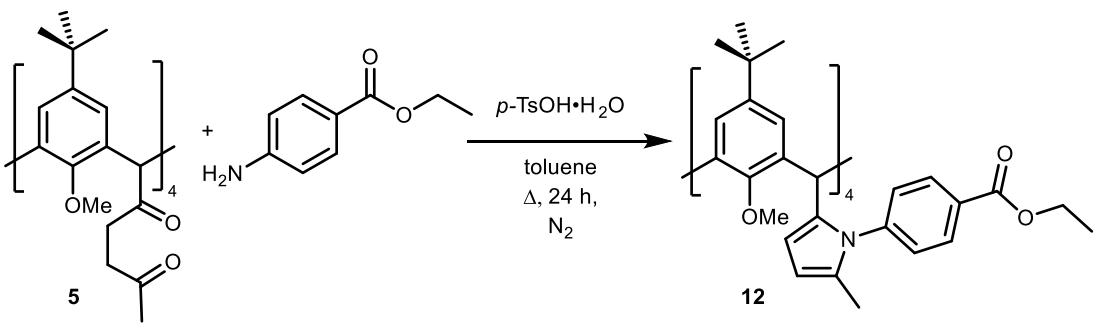
between the two appended phenyl rings. This splitting pattern arises due to the diastereotopic nature of the methylene bridge protons. However, full analysis of this compound wasn't achieved due to degradation of the product. Being one of the first reactions investigated during the doctoral study, the compound was left in solution for a prolonged period whilst attempting to grow single crystals, this had been sufficient enough to decompose the product. This degradation process will be discussed in greater detail in Chapter 3, however from the initial ^{1}H NMR spectrum of the product it was clear a reaction had taken place and the desired product had formed. If this reaction was to be repeated, necessary steps should be taken to avoid degradation by light in solution, e.g. wrapping in foil or not leaving the product in solution for extended periods of time. Compound **11** could then be isolated, and full analysis completed to confirm synthesis.



Scheme 2.12. Synthetic scheme for the preparation of 5,11,17,23--tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-benzylphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetra-methoxycalix[4]arene, **11**.

2.4.7. Synthesis of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(ethyl 4-(2-methyl-1H-pyrrol-1-yl)benzoate)-25,26,27,28-tetramethoxycalix[4]arene, 12.

Another reaction investigated was that between compound **5** and benzocaine (4-aminobenzoate). The reaction was carried out using the same reaction conditions as above, heating to reflux in toluene in the presence of *p*-TsOH·H_2O for 24 hours under N_2 (Scheme 2.13). During this time the reaction mixture darkened in colour and removal of solvent afforded a black crude solid. It is believed that the darkening which is observed was due to degradation by light of the product, as future reactions which were wrapped in foil showed much less darkening of the reaction mixture. Following aqueous workup of the



Scheme 2.13. Synthetic scheme for the preparation of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(ethyl-4-(2-methyl-1H-pyrrol-1-yl)benzoate)-25,26,27,28-tetra-methoxycalix[4]arene, **12**.

crude and recrystallisation from $CHCl_3$/MeOH, the desired product, **12**, was isolated in 69% yield or 91% per methylene bridge position. Analysis of the ^{1}H NMR spectrum showed that the distinctive 1,4-diketone -HC-CH- backbone signals had disappeared with new set of doublets appearing downfield, again being indicative of pyrrole formation. Both the *t*-butyl, OMe and phenyl-H peaks on the framework of the calixarene had been split into two different singlets as a result of the peripheral groups causing the calixarene to adopt a pinched cone conformation. Single crystals suitable for X-ray diffraction were grown from slow evaporation of a saturated ethyl acetate solution. The crystals were in a monoclinic cell, and the structure solution carried out in the $P2_1/c$ space group (Figure 2.11).

It is clear from Figure 2.11 that the saturated diketone has successfully ring closed to form the respective pyrrole with benzoate substituents added. The crystal structure confirms substitution at all methylene bridge positions. The structure contained disordered benzoate groups along with disordered ethyl acetate. The benzoate substituents were successfully modelled at partial occupancies, but the disorder associated with the ethyl acetate of crystallisation was severe and as such this was handled using a solvent mask. Both approaches markedly improved the agreement indices accordingly.

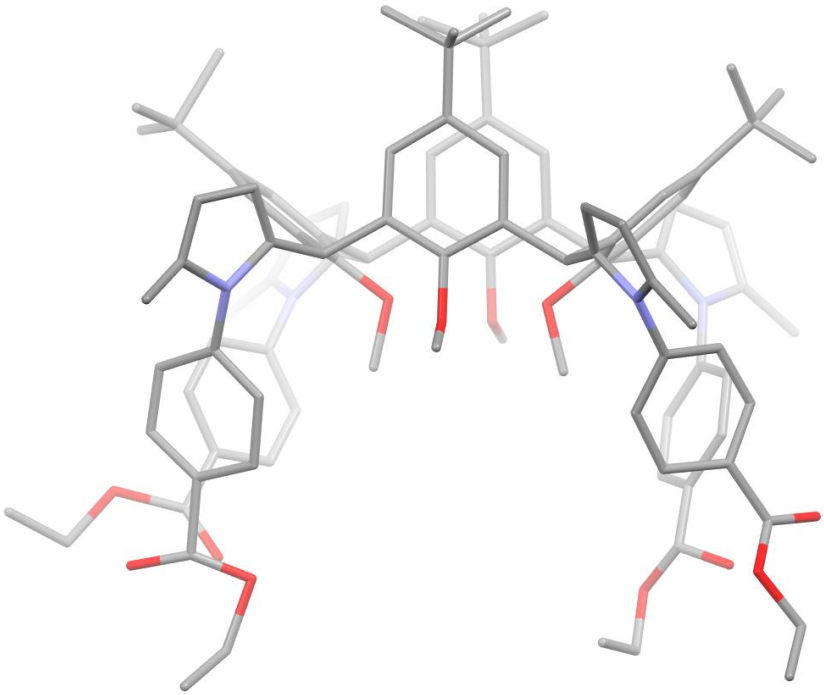
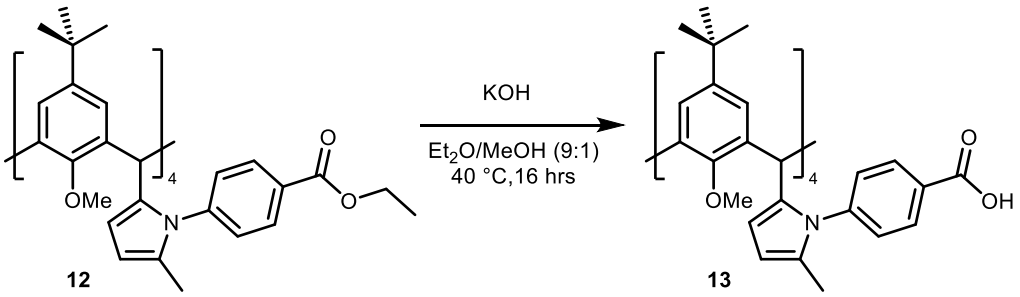


Figure 2.11. Sticks representation of the single crystal X-ray structure of **12** showing a benzoate substituent appended to the N atom of the pyrrole. Solvent of crystallisation (ethyl acetate) was masked. Colour code C - Grey; O - Red; N - Blue. H atoms were omitted for clarity.

2.4.8. Synthesis of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(4-(2-methyl-1H-pyrrol-1-yl)benzoic)-25,26,27,28-tetramethoxycalix[4]arene, 13.

Further modification of **12** was investigated given that the benzoate moiety has been widely exploited in MOF synthesis, for example.[22] Hydrolysis of esters to carboxylic acids can be readily undertaken through reaction with a base such as NaOH or KOH. Previous work in the group concerning C[4] upper-rim modification has shown hydrolysis of *p*-carboxyethylcalix[4]arene to the corresponding acid.[23] Therefore compound **12** was stirred overnight at 40°C in a mixture of Et_2O/MeOH and KOH, with MeOH added to aid solubility. The solvent was then removed, water added, acidified to pH~3 using 1M HCl and left to cool to 0 ^oC before filtering as a light brown solid. The solid was then dissolved in EtOAc and washed with water before drying over $MgSO_4$ and

removal of solvent to afford **13** in in 48 % yield (Scheme 2.14). This was found to be much higher than the example performed on the upper-rim.



Scheme 2.14. Synthetic scheme for the preparation of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(ethyl 4-(2-methyl-1H-pyrrol-1-yl)benzoic acid)-25,26,27,28-tetramethoxycalix[4]arene, **13**.

Inspection of the ^{1}H NMR spectrum showed the distinguishable ethyl peaks to have disappeared, however it was noted that the product was relatively insoluble in chloroform-d and therefore spectra were also recorded in DMSO-d^{6} or methanol-d. Comparison of these ^{1}H NMR spectra showed interesting differences. It was seen that the ^{1}H NMR spectrum taken in chloroform-d did not correspond to a typical pinched cone conformation. The peaks relating to the *t*-butyl had split into 3 different signals, each having a 1:1:2 ratio of integrations. However, inspection of the same sample in a solution of DMSO-d_6 or methanol-d displayed 2 signals for the same environment. This is thought to arise from the polarity of the solvent. It has been shown that polar solvents greatly affect the conformational inversion in calix[4]arene by disrupting the lower-rim hydrogen bonding.[24,25] Although no lower-rim hydrogen bonding is occurring in this compound due to the methoxy groups, a similar phenomena is thought to be happening with polar solvents disrupting the hydrogen bonding on the benzoate groups. This is postulated to lead to the calix[4]arene occupying the pinched cone conformation in d^{6}-DMSO and methanol-d^{1}, but adopt a slightly different conformation in chloroform-d. A single crystal grown from $CHCl_3$ was analysed using X-ray diffraction. The unit cell was found to be monoclinic and the structure solution carried out in space group $P2_1/c$. The ASU was found to contain one molecule of **12** in the pinched cone conformation as shown in Figure 2.12. Seeing as the crystal was grown from chloroform it was postulated that a different conformation might be observed. However, the pinched cone is exclusively seen. This is thought to be a crystallisation effect and solution is displaying a slightly different

conformation. Although we don't believe any ring flipping to be occurring and instead hydrogen bonding between adjacent molecules could exist.

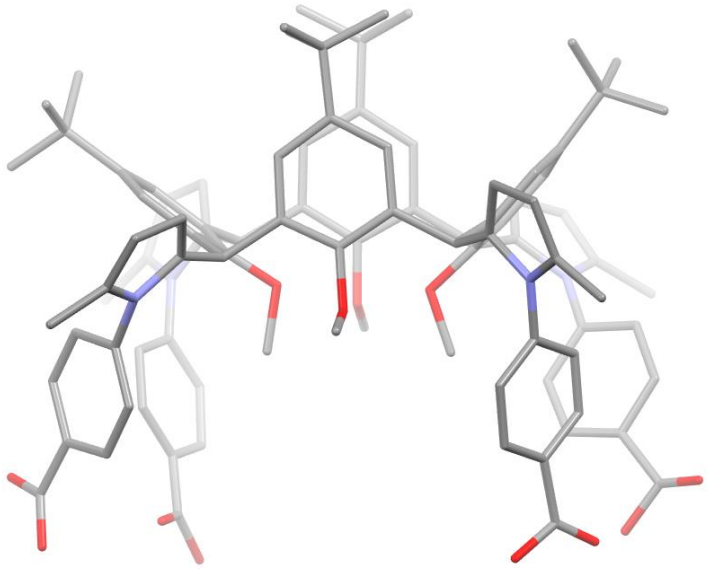


Figure 2.12. Sticks representation of the single crystal X-ray structure of **13** showing a benzoic acid substituent appended to the N atom of the pyrrole. Solvent of crystallisation ($CHCl_3$) has been masked. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

Figure 2.12 shows that all four ethyl benzoate groups have been reduced to the corresponding carboxylic acids. It would be expected to see hydrogen bonding interactions through these carboxylate groups however symmetry expansion shows no evidence for this. Disorder can be seen throughout the compound which has been modelled. The solvent disorder was severe and has been masked improving the agreement indices. Pyridine templated formation has been investigated in the group previously when synthesising carboxylate groups on the upper rim utilising the Py···CO_2H synthon.[26] It was thought that crystalising from pyridine would display interactions between the solvent and substituents on the C[4]. A single crystal grown from a saturated pyridine solution was analysed via single crystal X-ray diffraction. They were found to occupy a triclinic unit cell and structure solution carried out in space group $P\bar{1}$. The ASU contained two full molecules of **13** with pyridine displaying hydrogen bonding to the carboxylate groups (Figure 2.13). The pyridine able to be modelled sufficiently has been included, those with severe disorder were masked. The O-H···N hydrogen bond lengths range from

1.989(7) to 1.799(6) Å with an average length of 1.874(4) Å. Typical for pyridyl - carboxylate interactions previously reported.[26]

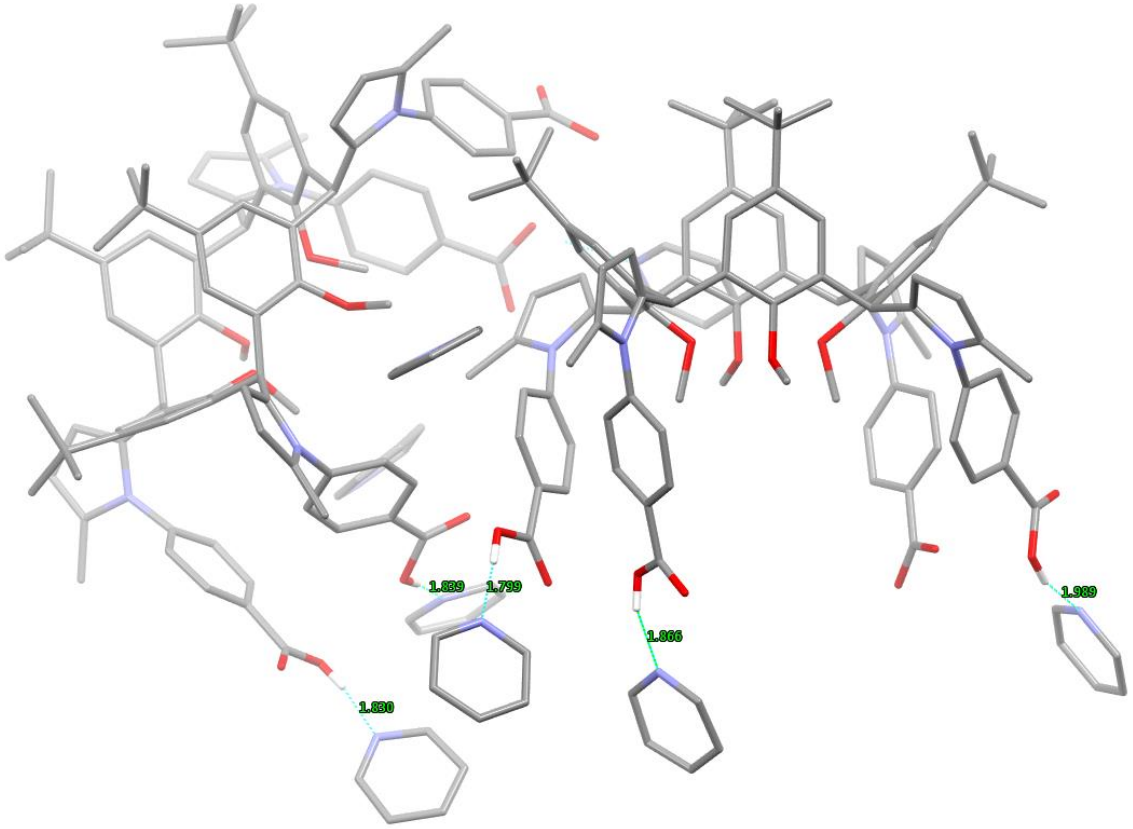
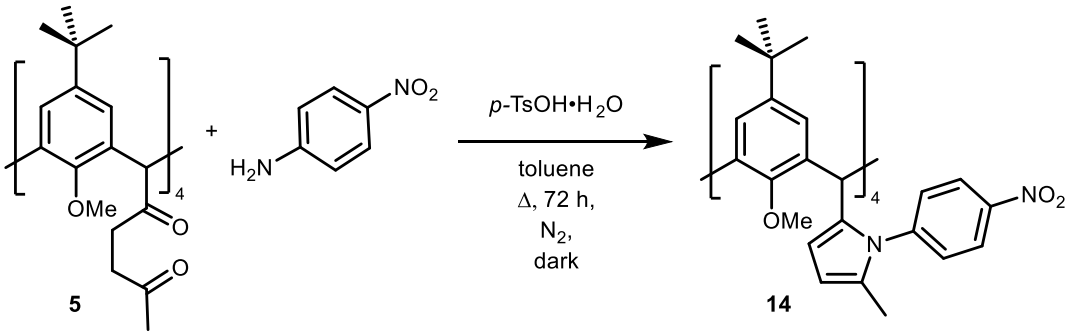


Figure 2.13. Sticks representation of the single crystal X-ray structure of **13** crystalised from pyridine showing the benzoate substituent hydrogen bonding to the solvent. O-H···N hydrogen bond lengths are included in the figure. Pyridine unable to be modelled has been masked. Colour code C - Grey; O - Red; N - Blue. H atoms (except from those H bonding) are omitted for clarity. O-H···N bond lengths from left to right in the figure read, 1.830, 1.839, 1.799, 1.866, 1.989 Å.

2.4.9. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-nitrophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 14.

The reaction of 4-nitroaniline and compound **5** was then investigated. Nitro groups are known to be very strongly electron withdrawing and are thus useful for testing functional group tolerance. Nitro-groups are also open to further modification, as reduction of an NO_2 group using Raney nickel[27] or Pd/C[28] with hydrazine can afford an amine derivative. This could then allow for further modification such as using Schiff base chemistry which has been previously applied to the upper-rim of a calix[4]arene,[27] or potential cage formation by reacting with **5**. Although *p*-phenyldiamine was never tested, both *o*- and *m*-phenyl diamine were trialled and indicated that a reaction had taken place. However, a large product mixture was forming which was unable to be separated. Having a large mixture of products, even if one could separate them, would result in a low yield of the desired product and therefore it was decided that if further modification was to be looked at in the future this would be the more desirable route. Standard reactions conditions were employed, and the mixture was heated at reflux in toluene in the presence of *p*-TsOH.H_2O as a catalyst under N_2 for 72 hours whilst also being wrapped in aluminium foil (Scheme 2.15). This afforded a brown crude that was analysed via ^{1}H NMR spectroscopy to confirm synthesis. The distinctive diketone triplets had fully disappeared indicating a complete reaction had taken place, however it was also noted that there appeared to be multiple products due to the number of peaks seen in key regions of the spectrum. Two distinct products were isolated following purification via column chromatography. The first was determined to be the desired product in the pinched cone conformation, representing the major product and isolated in 26% yield.



Scheme 2.15. Synthetic scheme for the preparation of 5,11,17,23--tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-nitrophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetra-methoxycalix[4]arene, **14**.

The ^{1}H NMR spectrum shows the *t*-butyl, OMe and Ph-H signals have split and new signals in the aromatic region relating to the backbone of the pyrrole and nitrophenyl have appeared. The Ar-H peaks on the nitrophenyl substituent are shown as four broad singlets, indicating hindered rotation of the appended groups, possibly due to nitro interactions with the solvent or another equivalent of **14**. VT NMR experiments could be performed to investigate whether this broadness would sharpen upon heating. An ASAP-MS experiment was performed and m/z peaks at 1505.60 and 1506.65 corresponding to [M] and $[M+H]^{+}$ found. Single crystals suitable for X-ray analysis were grown from a saturated $CHCl_3$ solution. These were found to be in a triclinic unit cell and the structure solution carried out in space group $P\bar{1}$. The ASU contained two full molecules of **14**, both displaying the pinched cone conformation (Figure 2.14).

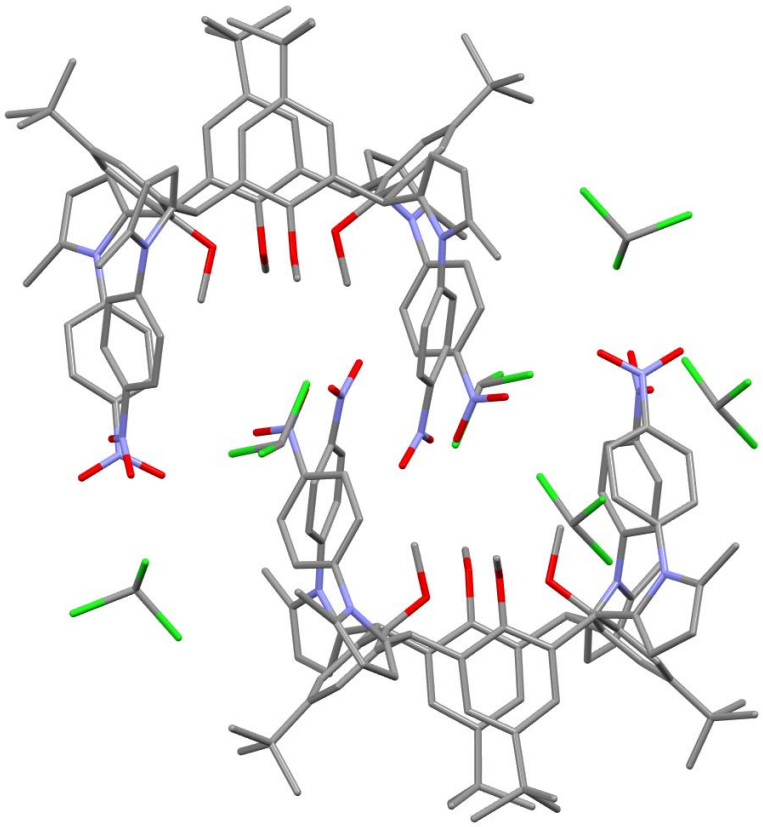


Figure 2.14. Sticks representation of the single crystal X-ray structure of **14** displaying two calix[4]arenes in the ASU both showing a 4-nitrophenyl substituent appended to each N atom of the pyrroles. Some solvent has been masked due to inability to model sufficiently. Colour code C - Grey; O - Red; N - Blue; Cl - Green. H atoms were omitted for clarity.

Inspection of Figure 2.14 clearly shows that all diketone groups have been ring closed and pyrrole groups are facing into the splayed area of the structure. Generating a centroid between the plane encompassing the lower rim oxygens and between each individual phenyl rings allows the measurement of an angle which describes the extent to which each C[4] is pinched. The splayed angle from opposite phenyl centroids and the oxygen plane for both molecules of **14** was found to be 118.52(10) and 118.39(10)º whilst the pinched angle was measured as 66.08(12) and 66.04(12). Due to the almost perpendicular geometry of the pinched angle this is thought to close off the upper-rim cavity, but in-turn create more space at the lower-rim and open space for binding.

The second product from the column was isolated in 23% yield. Inspection of the ^{1}H NMR spectrum showed splitting in almost every region, indicating that this species had been de-symmetrised. The only region which could not be identified as split was the Ar-H peaks on the nitrophenyl substituent due to their broadness. It was first theorised that this could be fully substituted at the bridge positions, but in a different conformation as no carbonyl peaks could be seen in the ^{13}C NMR spectrum. It is known that nitro groups have stretching vibrations that can conveniently be analysed through IR spectroscopy. Both displayed very similar stretching bands of 1524, 1342 cm^{-1} and 1525, 1340 cm^{-1} which are common values for aromatic nitro and so this adds further evidence for the formation of two different nitro derivatives although unable to give anymore detail into the product. An ASAP-MS experiment was run and no peak at 1505 was observed but instead peaks at 1384.70 and 1385.65 m/z. Crystallization attempts using different methods and solvent systems were trialled, eventually affording suitable single crystals from a saturated acetone solution. Analysis using X-ray diffraction studies found these to be in a triclinic unit cell and the structure solution was carried out in the space group $P\bar{1}$ (Figure 2.15). The crystal data obtained was of limited quality as it was observed that the single crystals were cracking and degrading under light on the microscope when in mounting oil. A suitable crystal was eventually mounted, and during data collection the light on the diffractometer was fully dimmed to help avoid any further degradation (and light into the room extinguished as much as possible). Surprisingly, the crystal structure revealed an asymmetric methylene bridge substituted C[4], having 3 bridge positions containing a substituted 1-(4-Nitrophenyl)pyrrole and one displaying a 2-methylfuran group. Disorder was present in the nitrophenyl groups and was modelled over two positions, potentially originating from sample degradation due to light / compromised data quality.

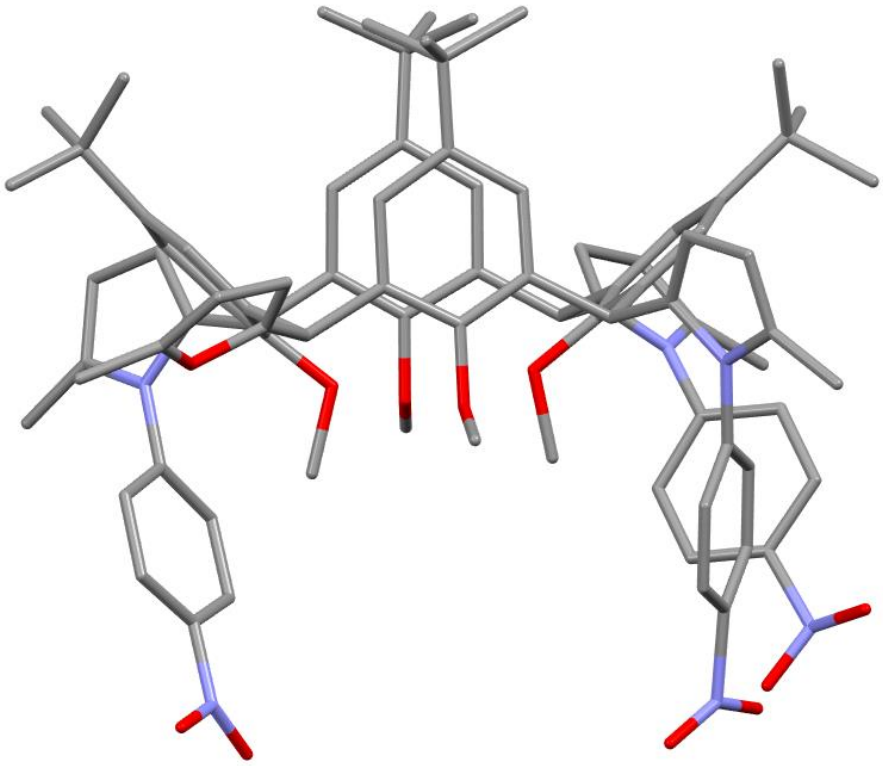
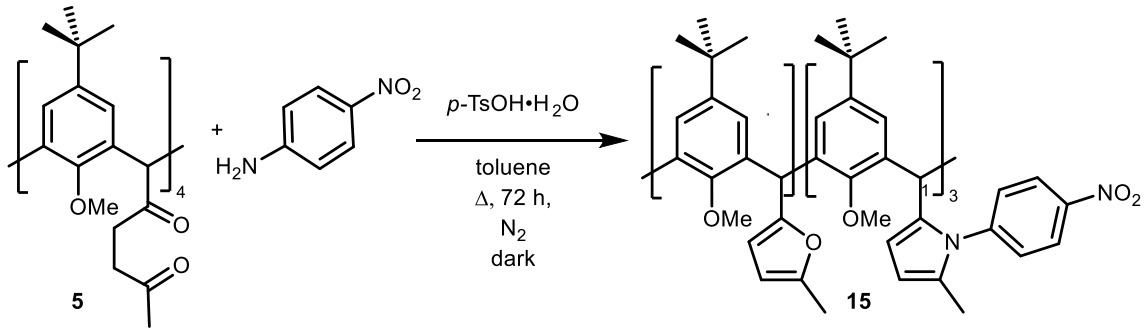


Figure 2.15. Sticks representation of the partial single crystal X-ray structure of **15** showing three nitrophenyl and one furan substituent appended to the N atom of the pyrrole. Colour code C - Grey; O - Red; N - Blue. H atoms and solvent of crystallisation were omitted for clarity.

It is notable that this is the only example encountered where performing the Paal-Knorr pyrrole synthesis on a saturated diketone C[4] has resulted in the formation of a furan. It is discussed later in the thesis that bridge substituted asymmetrical C[4]s can be formed through partial substitution whereby some positions remain as the starting saturated diketone. However, in this case the diketone has ring closed to afford a furan as shown in Scheme 2.16). It is known in the literature that furans can be formed from saturated 1,4 diketones under similar reaction conditions, e.g. refluxing in toluene using catalytic amounts of *para*-toluene sulfonic acid monohydrate, so it is not wholly surprising.[29,30] What was surprising, however, was that catalytic amounts of *p*-TsOH·H_2O have been used in every other example to date, and no evidence of furan formation had been identified at any point with these systems. The yield of this product was reported at 23% for **15** vs 26% for tetra-substituted **14**, producing a near 1:1 ratio of tris vs tetra-substituted nitrophenyl pyrrole C[4]s.

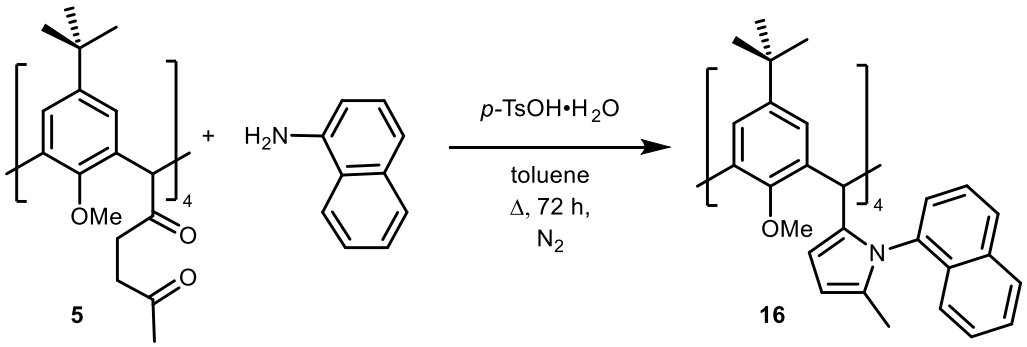
The reason for this occurring is still unknown, but we postulate that the acidity of the reaction mixture is the main contributing factor. Catalytic amounts of *p*-TsOH·H_2O (pK_a -2.8) along with 4-nitroaniline could be producing a sufficiently acidic solution to form furan. It would therefore be interesting to investigate this reaction further and understand the reason that this is forming in more depth (though this was not possible due to time constraints). It would be interesting to investigate whether altering the acidity of the solution by using more *p*-TsOH·H_2O or a lower *p*Ka acid (HCl or H_2SO_4) which have pK_a of -5.9 or -10, respectively. Alternatively, if a higher pK_a acid such as pyridinium *p*-toluenesulfonate (PTSS) was used, with a pK_a of 5.2, this may affect the yields of both **14** and **15**. That leads to the question of whether it would then be possible to form other asymmetrical C[4]s by simply changing the acidity of the solution, forming mono-, di- and tris-substituted nitrophenyl substituents accompanied by furans at the remaining positions.



Scheme 2.16. Synthetic scheme for the preparation of 5,11,17,23--tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-nitrophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetra-methoxycalix[4]arene, **15**.

2.4.10. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-napthalphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 16.

All the groups substituted so far have been either flexible or quite linear, and therefore face down and outwards in the crystal structures obtained. It was therefore decided to explore larger polycyclic systems for comparison with those outlined. The next reaction investigated was between compound **5** and 1-aminonapthanlene. After a 72-hour reflux in toluene, in the presence of *p*-toluenesulfonic acid monohydrate as a catalyst under a N_2 atmosphere, a deep red crude solid was obtained (Scheme 2.17).



Scheme 2.17. Synthetic scheme for the preparation of 5,11,17,23--tetra-tert-butyl-2,8,14,20-tetrakis(1-(napthalen-1-yl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetra-methoxycalix[4]arene, **16**.

An aliquot of the refluxing sample was taken at 20 and 40 hours, worked up and a ^{1}H-NMR spectra recorded in each case. This was used to monitor the progression of the reaction, utilising the diketone backbone NMR handle. At 20 hours the ^{1}H NMR spectrum shows small multiplets in the diketone region indicating that the reaction was still progressing. At 40 hours these had disappeared, and no diketone was observed. However, there were multiple signals in the *t*-butyl, OMe and methylene bridge regions. This is something quite common when a reaction of this type hasn't fully completed and a product mixture of mono-, di-, tris- and tetra-substituted pyrroles has formed. It was therefore decided to leave the reaction for a further 24 hours. After 72 hours the reaction was fully worked up and the ^{1}H NMR spectrum recorded. Comparison to the 40 hour ^{1}H NMR spectrum showed no further change and so therefore it is believed that the reaction was complete by this time, though the spectrum still indicated the presence of multiple products. Three products were isolated via column chromatography, all of which are believed to conformers of one another and due to the sterics of the substituted naphthalene group locking different orientations. One isomer was obtained pure following column chromatography whilst the other two were observed as a combined mixture, therefore the separated isomer will be discussed first with full characterisation before moving onto the mixture. This will include analysis of the conformers that could be formed, and identification of what conformers were present in the mixture with full justification.

The first conformer to be discussed, **16-1**, was isolated in 10 % yield. Analysis via ^{1}H NMR showed that the calixarene had been de-symmetrised with respect to the normal splitting patterns seen upon formation of the pyrrole. Due to the de-symmetrisation and nature of substituent, the aromatic region of these spectra are hard to

interpret and therefore three key signals are used to help identify the conformation of the calixarene, namely the *t*-butyl (a), OMe (b) and 2-methyl pyrrole (c) in Figure 2.16. The *t*-butyl groups had been split into a 3 different signals of ratio 2:1:1 integrating to 18 H, 9 H and 9 H, whilst the 2-methyl pyrrole group is displayed as a singlet at 1.72 ppm which integrates to 12 H. The OMe peaks are found at 1.74, 2.39 and 3.59 ppm and are split into the same ratio as the *t*-butyl 2:1:1 integrating to 6 H, 3H and 3H. A section of the ^{1}H NMR spectrum can be seen in Figure 2.16 displaying the integration and assignments.

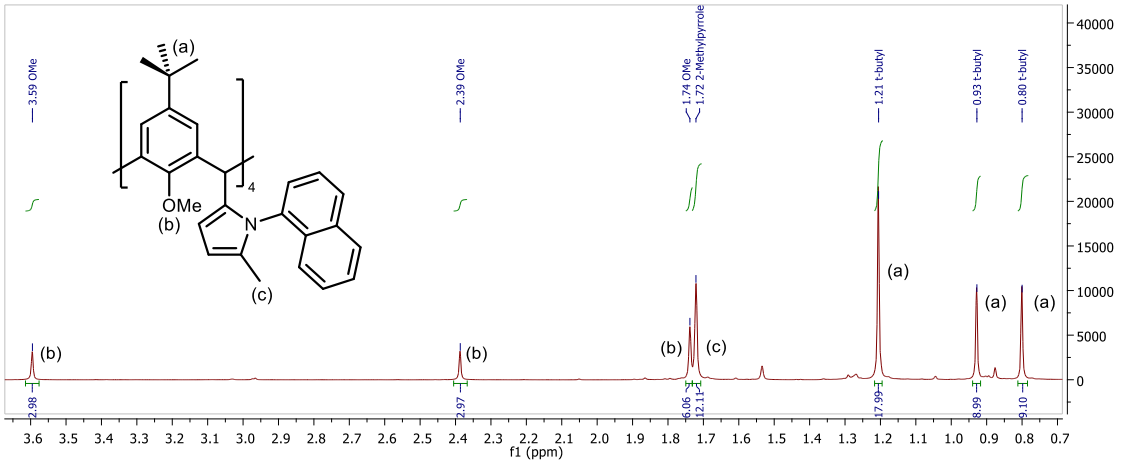


Figure 2.16. Overlay of the schematic of **16** with labelled *t*-butyl (a), OMe (b) and 2-methylpyrole (c). ^{1}H-NMR spectrum of **16-1** in chloroform-d showing the splitting patterns in the *t*-butyl, OMe and 2-methylpyrrole regions.

It is interesting that the OMe signals in the ^{1}H NMR spectrum have been shifted to different extents with large differences in ppm. The peak at 1.74 ppm integrating to 6 H has been shifted heavily up-field into the same region as the alkyl CH_3 of the 2 position of the pyrrole (c). This would imply that two of the OMe signals at the lower-rim of the calix[4]arene are being heavily shielded whilst the remaining two are being shielded to a lesser extent. These phenomena can be attributed to the naphthalene groups appended at the methylene bridge positions. Single crystals suitable for X-ray diffraction were grown from slow evaporation of a saturated chloroform solution. The crystals were found to be in a monoclinic cell, and the structure solution (Figure 2.17) was carried out in the space group $P2_1/n$.

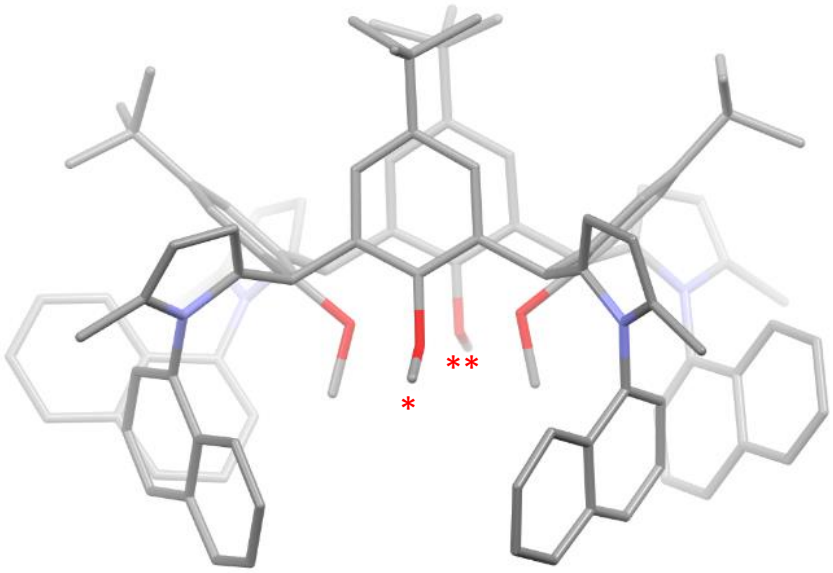


Figure 2.17. Single crystal X-ray structure of **16-1** showing a naphthalene substituent appended to the N atom of the pyrrole in sticks representation. Colour code C - Grey; O - Red; N - Blue. H atoms and solvent of crystallisation were omitted for clarity. OMe's labelled * and ** are referenced in the text as front and back environments.

From inspection of the crystal structure of **16-1** it was clear that all the diketones had been ring closed, forming a tetrasubstituted pyrrole with naphthalene groups appended whilst the C[4] had adopted the pinched cone conformation as expected. The pyrrole groups are orientated in the expected manner whereby they are angled towards the pinched section of the C[4] framework. However, it is noteworthy that the naphthalene groups are positioned in two distinct fashions. One set is facing towards one another and inwards, whilst the other set face away and outwards. This allows the C[4] to retain a plane of symmetry, but introduces three different environments for the OMe and *t*-butyl groups. Two environments lie on the plane of symmetry through the centre and the other either side of the plane at the 'splayed' position of the C[4]. This explains the splitting pattern seen in the ^{1}H NMR spectrum, and also helps explain the shielding effect seen for the OMe groups due to the large naphthalene systems. The OMe groups either side of the plane of symmetry are almost encased by the phenyl rings, thus causing a shielding effect from the magnetic field during the NMR experiment. This is also experienced to a lesser extent by the OMe groups lying in the plane of symmetry at the front and back of the C[4]

(with respect to Figure 2.17). The two naphthalene groups at the front are facing towards the OMe and therefore shielding the magnetic field to a greater extent that the two facing outwards at the back of the calixarene. This would allow one to confidently predict that the signal at 2.39 ppm is the OMe at the front of Figure 2.16 (the OMe identified as OMe*) and the signal at 3.59 ppm which is more commonly seen for the OMe groups in the previous examples discussed in this chapter, is the group at the back of Figure 2.17 (identified as OMe**). This can be attributed to the lack of shielding as the naphthalene's are facing out and away from the methoxy group. The ^{1}H NMR spectrum and single crystal X-ray structure display agreement with one another, confirming that the C[4] retains this conformation in solution. These different conformations are thought to arise due to the size of the naphthalene groups hindering rotation around the pyrrole, thus locking it in a given conformation. Knowing that the naphthalene group can lock the C[4] conformation, all possible conformations can be worked out and are shown in Figure 2.18.

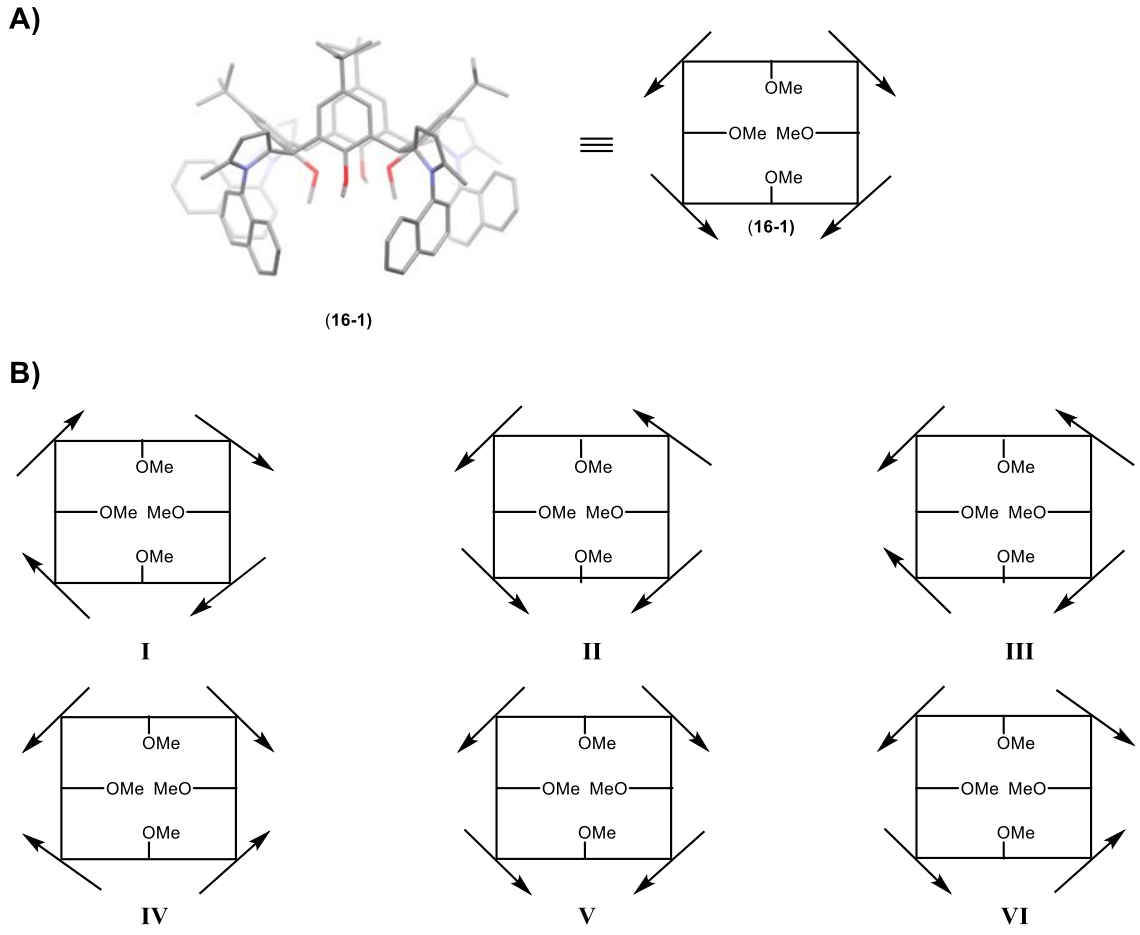


Figure 2.18. Crystal structure of **16** and a 2D representation using a rectangle to display the pinched cone conformation with arrows depicting the direction of the naphthalene substituent. Rectangular representations of all 6 possible tetrasubstituted conformers that could form from the reaction of 1-aminonapthalene with compound **5** are drawn below.

The next two compounds were found to exhibit the exact same rf value and therefore eluted simultaneously during column chromatography. Despite best efforts they were unable to be completely separated and therefore full characterisation was hindered. A ^{1}H NMR was run of all the combined fractions containing both conformers. As before, the most important peaks to help decipher which conformers are present are those relating to *t*-butyl, OMe and 2-methylpyrrole groups. Attempts were made to separate these conformers via recrystallisation, however this was only partially successful. The filtered crystals were shown to exhibit more of one conformer, whilst the filtrate showed the opposite. This indicates that these can be separated by recrystallisation to some extent, however due to the small scale of the experiment it proved very difficult to obtain pure samples of each in this way. This did allow for comparison of ^{1}H NMR spectra of both the crystals and the filtrate to determine which peaks belonged to each conformer, integrate them, and assign as either *t*-butyl (a), OMe (b) or 2-methylpyrrole (c) signals. The NMR spectra will be discussed briefly below, starting with **16-2** (Figure 2.19).

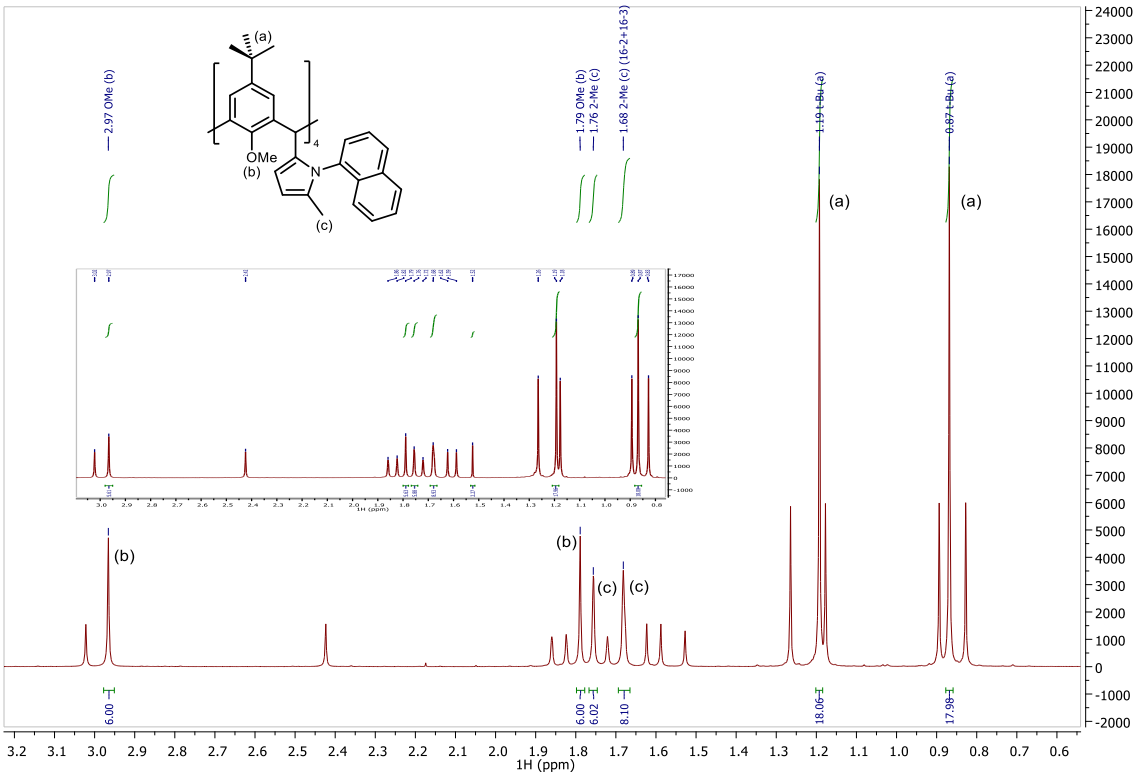


Figure 2.19. Overlay of **16** with labelled *t*-butyl (a), OMe (b) and 2-methylpyrrole (c). ^{1}H NMR spectrum of **(16-2)** after recrystallisation with an insert of the mixed fraction from the column displayed over the top to indicate differences. The spectra are recorded in chloroform-d showing the splitting patterns in the *t*-butyl, OMe and 2-methylpyrrole regions.

From the ^{1}H NMR spectra shown in Figure 2.19 after recrystallisation it can clearly be seen that the *t*-butyl environments have been split as there are signals at 0.87 and 1.19 ppm each integrating to 18 H. This is very common upon substituted pyrrole formation as the C[4] adopts the pinched cone conformation. There are now four other signals observed in the spectrum that relates to this conformer, each integrating to 6 H. The peak at 1.68 ppm integrates higher at ~ 8 H, which is due to overlapping with a signal from the other conformer, **16-3**, and therefore would otherwise integrate to 6 H. These are assigned to both the OMe (b) and 2-methylpyrrole (c) groups, whereby the more downfield peaks 1.79 and 2.97 ppm are OMe and the more upfield, 1.68 and 1.76 are 2-methylpyrrole (c). The ^{1}H NMR spectrum of the mixed fraction after column chromatography has been placed in the figure for comparison. The peak at 1.79 ppm is quite unusual for an ether, but this is attributed to a shielding effect from the naphthalene groups that is similar to that found in the spectrum of **16-1**. The splitting pattern for the *t*-butyl, OMe and 2-methylpyrrole groups indicates that there is 2-fold symmetry within the molecule and, if so, therefore the only two possible arrangements are **I** and **IV** from Figure 2.18. A single crystal suitable for X-ray diffraction analysis was grown from a saturated chloroform solution. This was found to be in a monoclinic unit cell and structure solution carried out in the space group *C*2/*c*. The ASU contained one half of **16-2** which, upon symmetry expansion, afforded the full molecule displaying the pinched cone conformation (Figure 2.20). From the crystal structure it is clear to see all four diketone positions have been ring closed to afford the tetra-pyrrole naphthyl derivative. The naphthalene groups are orientated in a clockwise direction around the lower rim of the calix[4]arene, aligning with the ^{1}H NMR spectrum and confirming the synthesis of conformer **I** seen in Figure 2.18. Disorder was observed in two of the *t*-butyl groups and was modelled over two positions at partial occupancies of 0.6 and 0.4. Disordered chloroform was also modelled over two positions at occupancies of 0.5. Another disordered chloroform of crystallisation was observed in the difference map but it was not possible to model this, so it was handled using a solvent mask. Examination of the extended structure shows that chloroforms of crystallisation occupy the interstitial spaces between the C[4] units, creating solvent channels as a result. It would be interesting if **16-2** could be crystallised from a solvent able to undergo pi-pi stacking, or a strong hydrogen bond donor to investigate whether this would cause a similar effect or occupy the space in between the lower-rim naphthalene units that present a pseudo cavity.

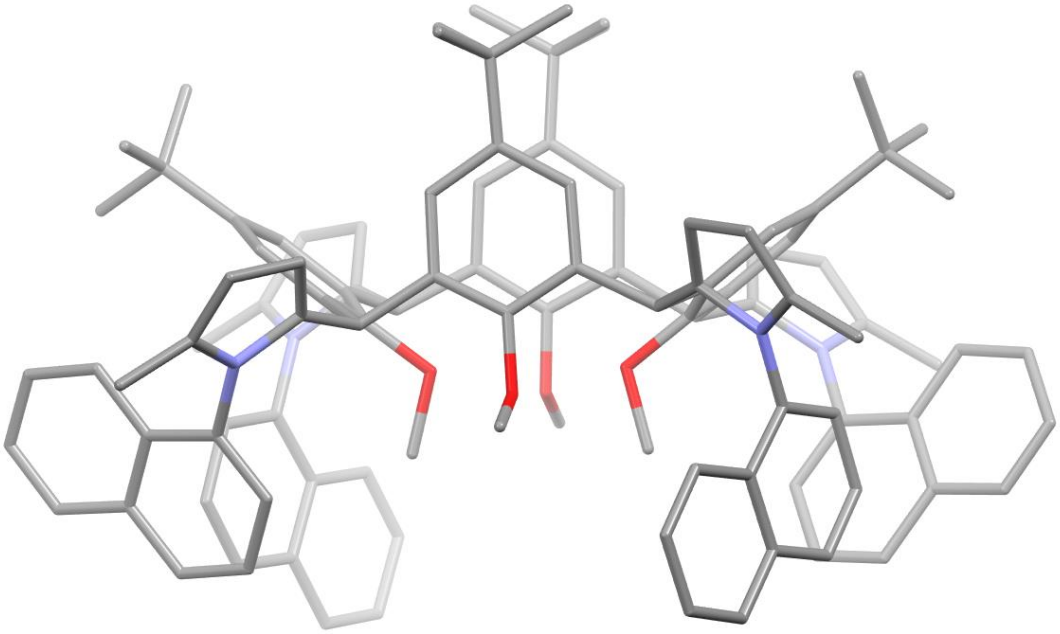


Figure 2.20. Sticks representation of the partial single crystal X-ray structure of **16-2** showing four naphthalene substituents appended to the N atom of the pyrrole orientated in a clockwise direction. Colour code C - Grey; O - Red; N - Blue. H atoms and solvent of crystallisation were omitted for clarity.

Despite best efforts it was not possible to isolate the final conformer formed in this reaction for analysis with single crystal X-ray crystallography. The confirmation of the naphthalene groups could therefore note be quantitatively confirmed. However, a discussion based on the data obtained is presented below with a prediction of which conformer was formed. The ^{1}H NMR spectrum of the product mixture was obtained and the signals assigned to the second conformer are presented in Figure 2.21.

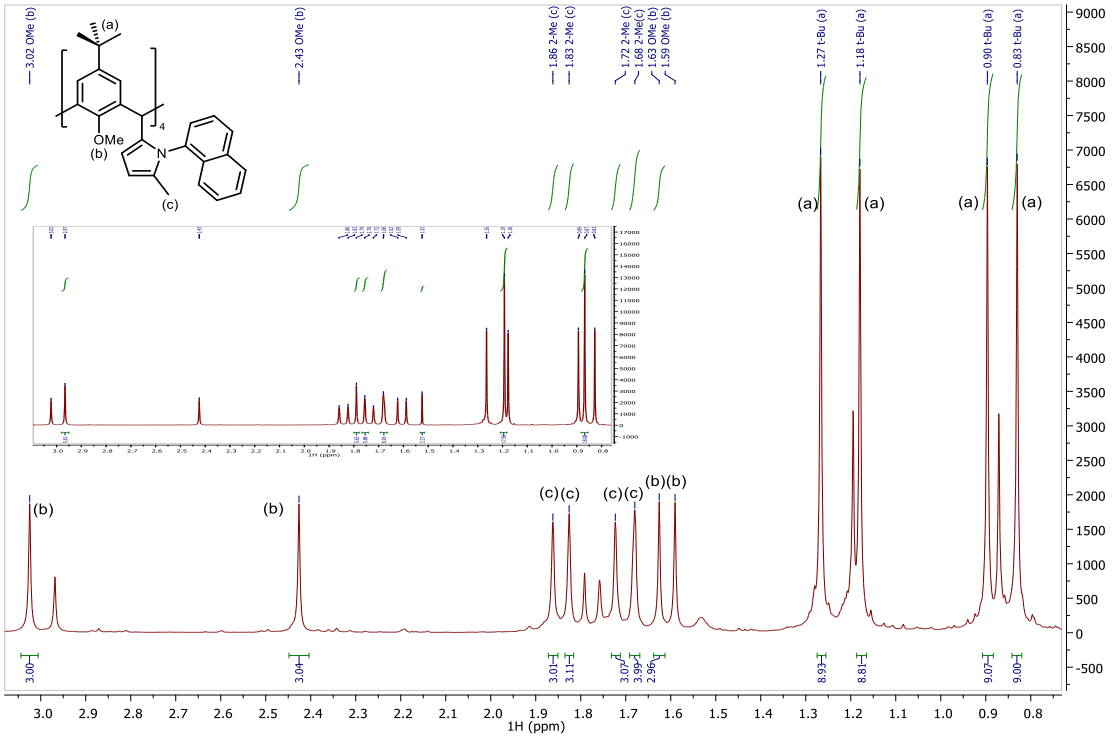


Figure 2.21. Overlay of **16** with labelled *t*-butyl (a), OMe (b) and 2-methylpyrrole (c). ^{1}H NMR spectrum of **16-3** filtrate after recrystallisation with an insert of the mixed fraction from the column displayed over the top to indicate differences. chloroform-d showing the splitting patterns in the *t*-butyl, OMe and 2-methylpyrrole regions.

From the ^{1}H NMR spectrum it can be seen that the *t*-butyl, OMe and 2-methylpyrrole regions have each been split into 4 different environments integrating to 9 H, 3 H and 3 H respectively, excluding the signal at 1.68 ppm which integrates to 4 H as this overlaps with a peak from **16-2**. This indicates that the conformer has been completely de-symmetrised as each position around the calix[4]arene exists in a different environment and therefore there is no mirror plane present within the molecule. Based on this evidence only conformers **II** and **VI** from Figure 2.18 contain no mirror plane. Using the OMe shifts in the ^{1}H NMR spectrum, identified as 3.02, 2.43, 1.63 and 1.59 ppm using a HSQC (Heteronuclear Single Quantum Coherence) experiment, it is theorised that conformer **II** is the most probable product. Predictions can be made from the two conformers already isolated and then relate that to the unknown conformer (Figure 2.22).

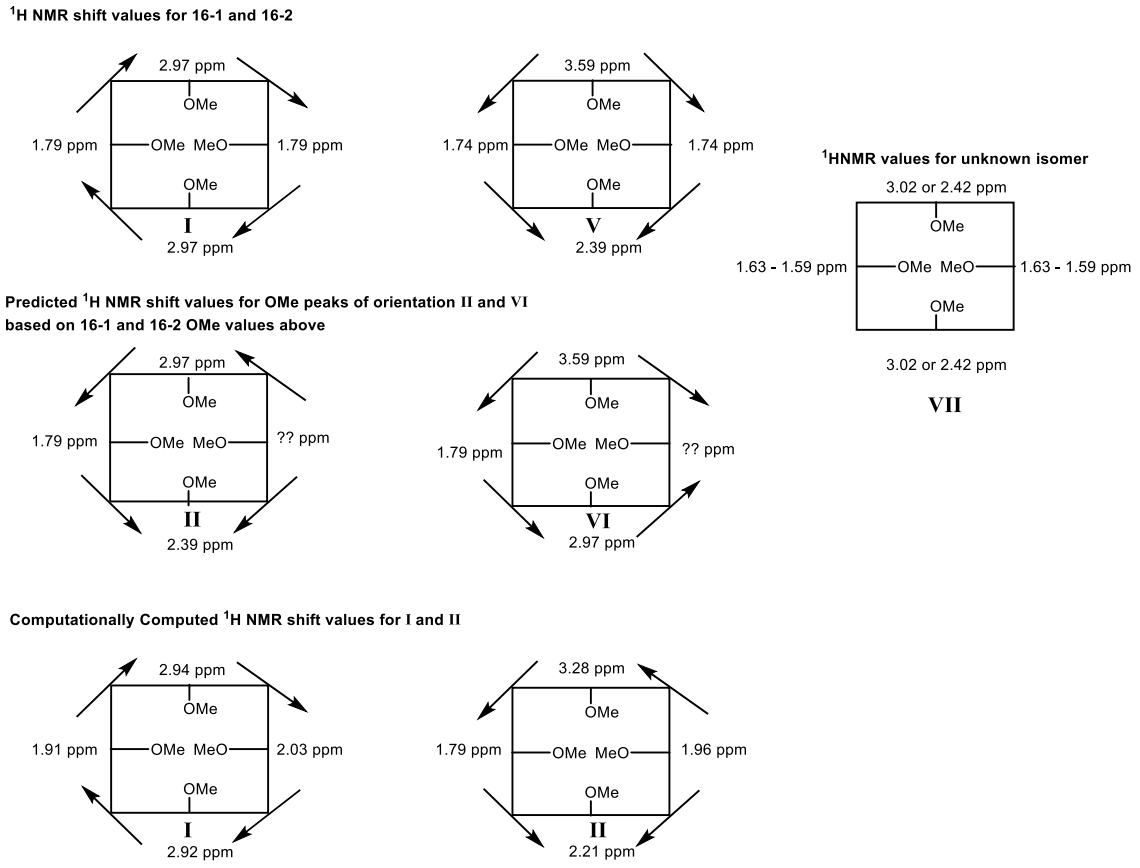


Figure 2.22. Rectangular representations of methylene bridge substituted C[4]s substituted with naphthalene groups. Arrows are used to symbolise the orientation of the naphthalene rings. ^{1}H-NMR signal values are attached for the OMe environments for **16-1** and **16-2** and predicted values for conformers **II** and **VI** using these data. Finally, the observed data for unknown conformer labelled **VII** are also shown.

From Figure 2.22 the values are consistent with conformer **II** as there are no heavily de-shielded OMe environments (3.02 ppm being the most downfield environment) which would occur if conformer VI was present. The orientation of the groups is more probable based on 16-1 as two naphthalene groups are found to be facing one another on the 'pinched' face of the calixarene, whereas conformer **VI** would imply they are facing one another on the 'splayed' face of the calixarene which would be a more sterically hindered situation. Nearing the end of this study computational moddeling preformed by Professor Paterson was done to predict the ^{1}H NMR values for comformers **I** and **II** to compare to those obtained experimentally. The computational values for values compound **I** and **II** are shown in Figure 2.22 and relate to those given for isomer **II**.

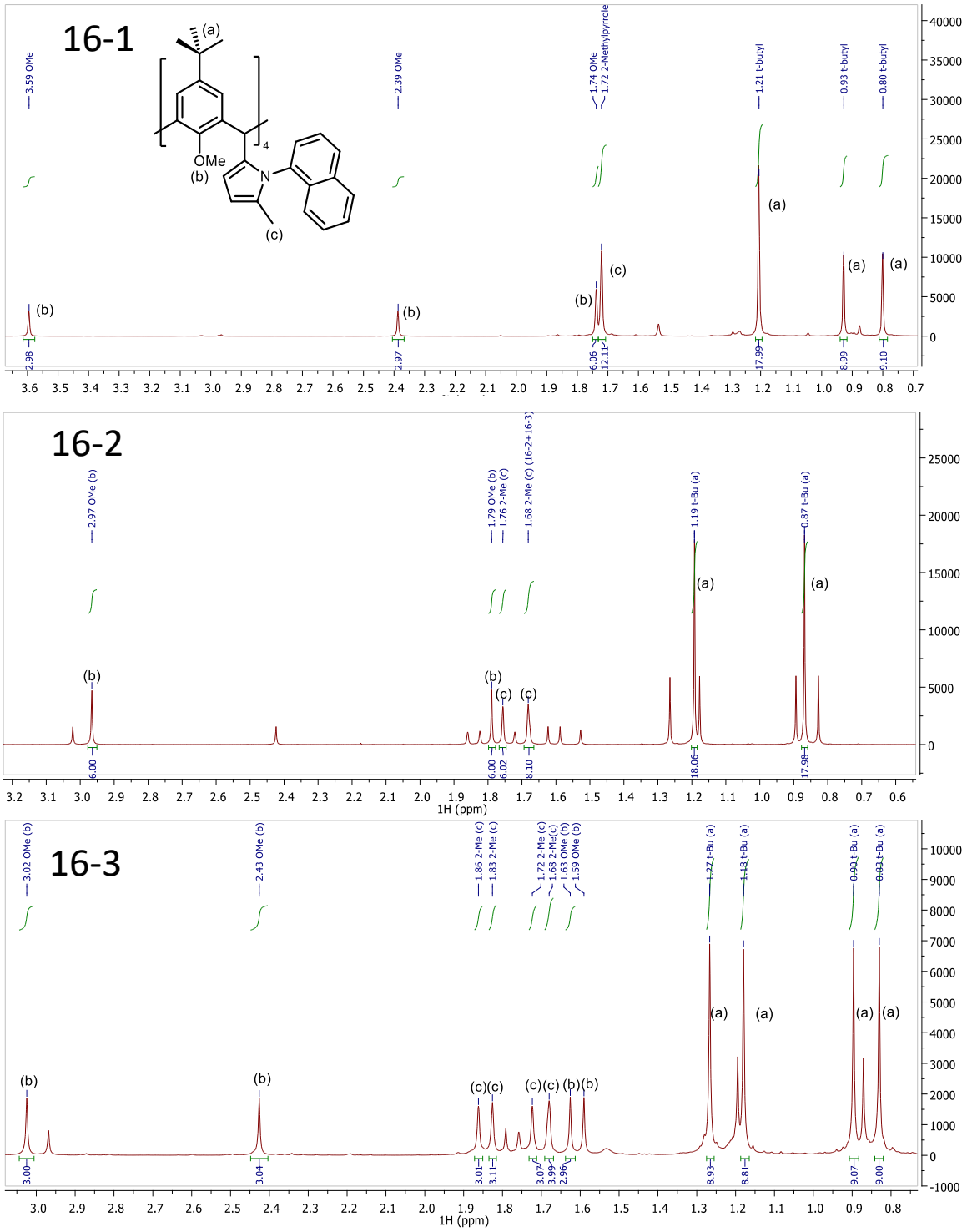
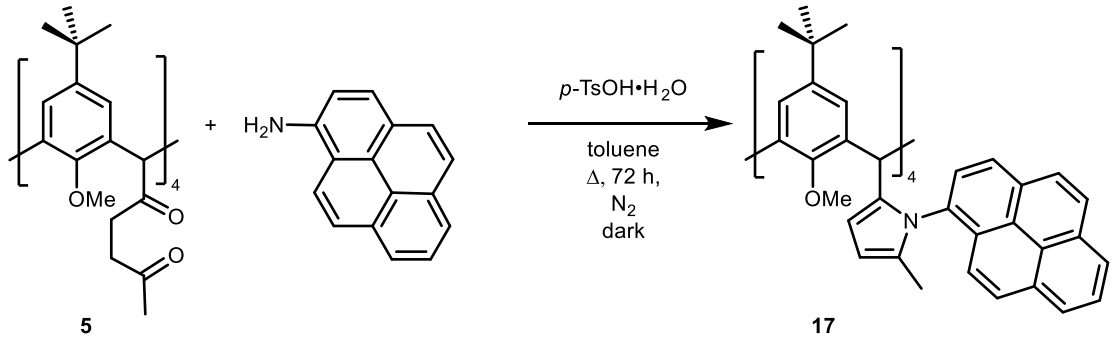


Figure 2.23. Overlay of the ^{1}H NMR spectrum of all conformers from the reaction of 2-aminonapthalene with **5**. **16-1** is the pure product and **16-2** and **16-3** are mixtures with labelled *t*-butyl (a), -OMe (b) and 2-methylpyrrole (c) signals.

2.4.11. Synthesis of 5,11,17,23--tetra-tert-butyl-2,8,14,20-tetrakis(1-(pyren-1-yl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 17.

The final reaction investigated in this chapter was that of 1-aminopyrene with compound **5** under the standard reaction conditions, heating at reflux in toluene using *p*-TsOH·H_2O as a catalyst avoiding light (Scheme 2.18).



Scheme 2.18. Synthetic Scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(pyren-1-yl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetra-methoxycalix[4]arene, **17**.

Following a 72-hour reflux and subsequent work-up, a ^{1}H NMR spectrum was obtained and showed that a complete reaction had taken place as no distinctive diketone signals were observed. However, just as in the previous reaction involving 1-aminonaphthalene, there appeared to be multiple products with six clear peaks in the *t*-butyl region of the spectrum. This was attributed to the C[4] locking in different conformations. Following column chromatography, only one fraction was isolated. Analysis of the ^{1}H NMR spectrum showed that two conformations were present. Washing with cold toluene allowed the isolation (with tiny impurities of other conformer) of one conformer in small yield due to slight differences in solubility, through which full characterisation was achieved. The aromatic region of the ^{1}H NMR spectrum for molecule **17** was very complex due to the pyrene functional groups. As the previous reaction, the peaks of interest are the *t*-butyl, OMe and 2-methyl pyrrole CH_3. Analysis of the ^{1}H NMR spectrum showed two different environments for all three group types. The *t*-butyl peaks are found at 1.33 and 0.92 ppm and integrate to 18 H, providing evidence that this is in the pinched cone conformation and the pyrene groups are orientated in a circle whilst retaining the C_2v plane of symmetry through the molecule.

Methoxy ether CH_3 and 2-methylpyrrole signals were assigned using a HSQC (Heteronuclear Single Quantum Coherence) experiment. This allowed for the determination of proton-carbon single bond correlation. This was used to identify which signals in the ^1H NMR spectrum correlate to the methoxy or 2-methylpyrrole groups as the methoxy carbons will be observed in a higher ppm region of the ^{13}C NMR due to the electronegativity of the bonded oxygen (Figure 2.24).

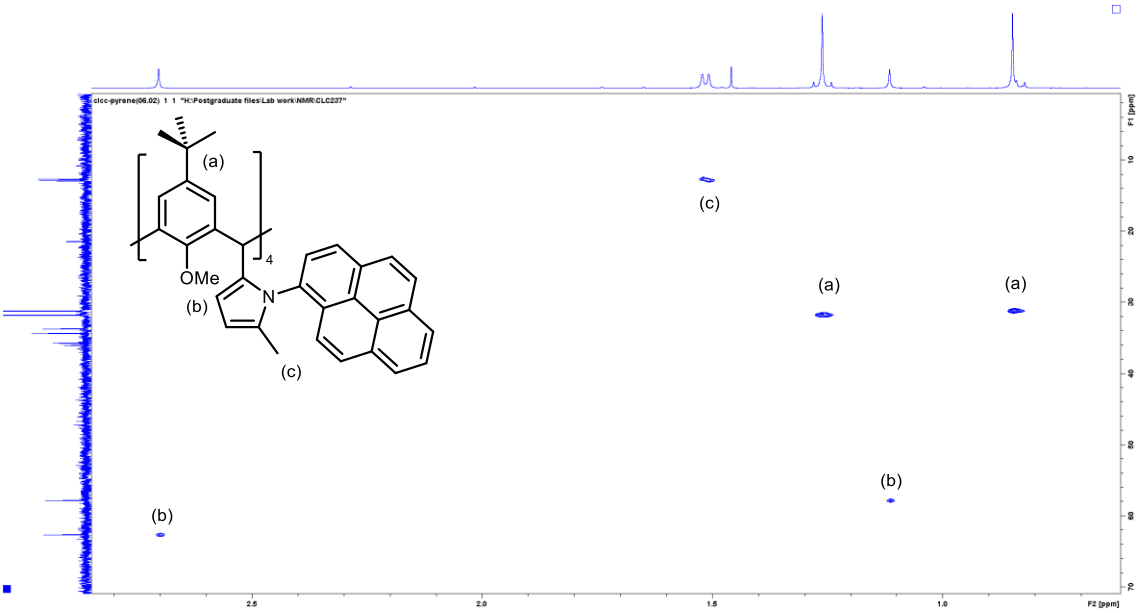


Figure 2.24. HSQC spectrum of compound **17-1** with F1 axis showing the ^{13}C NMR spectrum and F2 axis showing the ^1H NMR spectrum. A 2D representation of compound **17** is overlayed with letters (a), (b) and (c) indicating which cross peaks are assigned to each position.

From Figure 2.24 the 2-methylpyrrole CH_3 singlets at 1.59 and 1.58 ppm which are similar to the values found for the naphthalene derivative (1.76 and 1.68 ppm) and the two OMe signals at 2.78 and 1.19 ppm were assigned corresponding to the downfield signals in the ^{13}C NMR spectrum. The value of 2.78 ppm corresponds well to those observed previously for the naphthalene derivative **16-2** of 2.97 ppm for the pinched environment of the calix[4]arene. The other signal at 1.19 ppm is heavily shifted up-field for a methoxy ether. This large shift can be attributed to the pyrene groups shielding the hydrogens from the magnetic field. All attempts to crystallise this compound were unsuccessful, but by comparison to the previous example with the naphthalene derivative it can be inferred that the conformer obtained is that of the pinched cone conformation in

which all pyrene substituents are orientated in the same direction around the C[4] framework, conformer **I** from Figure 2.18.

Unfortunately, the other conformer **17-2** was unable to be fully characterised as the toluene wash still contained considerable amounts of both conformer and therefore could not be isolated. However, knowing which peaks are assigned to the first conformer, **17-1**, it was possible to predict which other conformer was present. The *t*-btuyl, OMe and 2-methylpyrrole signals are all spilt into 4 different environments which is the same as for **16-3**, the naphthalene equivalent. Therefore, using the same analysis method used to predict **16-3** the other conformer present in this case should be in orientation **II** (Figure 2.17). It is noted that in this reaction only conformers with orientation **I** and **II** are formed, whilst **I**, **II** and **V** are formed in the naphthyl analogue. It is therefore theorised that pyrene groups are too large for this to occur, and the formation of another conformer is disfavoured.

2.5. Summary and Conclusions.

A search using Sigma Aldrich chemical catalogue returns over 250 different aniline derived organic building blocks whilst another popular chemical vendor Doug Discovery returns over 1000 results in a search of secondary anilines. Therefore, given the number of commercially available anilines available, it would be of enormous benefit to develop a facile method for the fourfold synthesis of methylene bridged calix[4]arenes in which functionalisation is added via reaction with a secondary aniline. This would allow specific functionality to be chosen based on the desired use of the product. This chapter has begun work on this idea, proving that the scope of using a Paal-Knorr pyrrole condensation to add functionality is viable and functional group tolerant. However more work on this area is required to fully understand the full potential of this route. Interesting findings such as using large functional groups (aminonaphthalene / aminopyrene) have been shown to lock the methylene bridge substituents in different conformations. These conformers could lead to the synthesis of chiral calixarenes and if time permitted on this project, it would be worth pursuing this possibility. Naphthalene and pyrene groups appended to the C[4] at either the lower- or upper-rim have been utilised as fluorophores for developing efficient monitoring of cellular events, drug delivery, ion or explosive sensors and much more.[31] Fluorophore groups bound to the periphery of the calix[4]arene framework via the methylene bridge have now been synthesised and so It would therefore be of interest to investigate their use as molecular sensors.

The reaction of **5** with 4-nitroaniline to afforded two different products which was theorised to arise from the inherent acidity of 4-nitroaniline allowing one position on the C[4] to re-form a furan whilst the others formed the desired pyrrole. Although not the target product, asymmetric calixarenes are desirable due to being able to contain various functionality, allowing for unique coordination chemistry in the formation of metal organic assemblies or clusters. Having the potential to include multiple different functionalities at the bridge should allow for specific host guest interactions.

In summary, now that a procedure has been established for the synthesis of mono-functionalised calix[4]arenes at the methylene bridge the next step is to deprotect the lower-rim methoxy groups reintroducing hydroxyl functionality. This functionality will allow these molecules to be applied in areas such as coordination chemistry / cluster formation or catalysis. Deprotection work has been undertaken in this study and discussion based on this topic can be found in chapter 3.

2.6 Experimental

All experiments were carried out under ambient conditions unless otherwise stated. Analytical thin layer chromatography was performed on precoated silica gel plates (Merck, 60, F_{254}) and column chromatography was performed using 60Å silica (Fisher Scientific, 35 – 70 micro particle size). All reagents and starting materials employed in this work were commercially available and used without further purification unless otherwise stated. ^{1}H, ^{13}C, COSY, ROSEY and HSQC NMR spectroscopy were recorded on either a 300 MHz Bruker AVIII 300 NMR or 400 MHz Bruker AVIII 400 NMR spectrometer at room temperature. All chemical shifts are reported in ppm. ESI mass spectra were recorded on a Bruker ESI MicroTOF Focus II spectrometer. ASAP-MS were recorded using a Shimadzu LCMS-2040 using an ASAP-MS probe. IR experiments were performed on a Thermo Scientific Nicolet iS5/iD5 ATR spectrometer. All the single crystals were analysed on a Bruker D8 diffractometer equipped with a PHOTON 100 detector with a synchrotron radiation source, a Rigaku Oxford Diffraction SuperNova diffractometer with a MoKα radiation source or a Kappa Rigaku Saturn724+ diffractometer with a Cu α radiation source.

5,11,17,23-tetra(*tert*-butyl)-25,26,27,28-tetrahydroxycalix[4]arene, 1.

Compound 1 was synthesised following a literature procedure first reported by Gutsche *et al.*,[1] A mixture of p-tert-butylphenol (250 g), 37% formaldehyde solution (150 mL) and NaOH (1.25 g) in water (6 mL) was heated at reflux, under a high flow of N_2, until a yellow-green mass had formed. The water generated from the condensation reaction was removed by means of a Dean-Stark apparatus. The reaction was allowed to cool to room temperature before toluene (1 L) and diphenyl ether (2 L) was added. The reaction mixture was heated to remove toluene via a dean stark and then heated at 260 °C for 4 h. The mixture was then left to cool to room temp. before ethyl acetate (1.5 L) was added and the solution stirred for 2 h. The solution was then filtered and the solid washed with ethyl acetate to afford 136.68 g (51 %) of 1 as glistening crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.34 (s, 4H), 7.05 (s, 8H), 4.26 (d, J = 13.7 Hz, 4H), 3.49 (d, J = 14.0 Hz, 4H), 1.21 (s, 36H).

^{1}H NMR spectrum in chloroform-d was recorded and compared against literature to confirm purity and product used in subsequent reactions.

5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene, 2.

Compound 1 (20.0 g, 30.84 mmol) was suspended in a 10:1 THF:DMF mixture (100:10 mL). NaH (5.0 g) was slowly added to the reaction flask with stirring and then MeI (20 mL) was added using a disposable syringe. The reaction mixture was then heated at reflux for 2 h, after which it was cooled to room temperature before MeOH was added to remove any unreacted NaH. The solvents were then removed under reduced pressure and the resulting solid was collected, washed with water, and filtered. The solid was dissolved in $CHCl_3$ and then the solution was dried using $MgSO_4$. After filtering off the $MgSO_4$ the solvent was removed under reduced pressure. The crude product was recrystallised using hot $CHCl_3$/MeOH to yield 17.45 g (80%) of 2. The compound was dissolved in a 3:1 mixture of $CDCl_3$/CD_3CN which had been saturated with NaI in order to lock the calix[4]arene in the cone conformation to obtain a ^{1}H NMR spectrum with sharp proton signals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 8H), 3.92 (d, *J* = 12.4 Hz, 4H), 3.78 (s, 12H), 3.13 (d, *J* = 12.4 Hz, 4H), 0.85 (s, 36H).

^{1}H NMR spectrum in a saturated NaI solution of chloroform-d/acetonitrile-d^3 (3:1 w/v) was recorded and compared against literature to confirm purity and product used in subsequent reactions.

5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrabromo-25,26,27,28-tetramethoxycalix[4]arene, 3.

A mixture of compound (2) (15.2 g, 21.56 mmol) and NBS (15.34 g, 86.24 mmol) was heated at reflux in chloroform (750 mL) for 22 h whilst irradiated with a spotlight (~70 W). After this time the orange/red solution was cooled to room temp and then washed once with Na_2SO_3(aq) (150 mL) and twice with water (2 x 100 mL). The organic phase was collected, dried with $MgSO_4$ and then filtered. The solvent was removed under reduced pressure and the crude was recrystallised from $CHCl_3$/MeOH to yield 14.40 g (65 %) of 3 as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 8H), 6.71 (s, 4H), 3.99 (s, 12H), 1.12 (s, 36H).

^{1}H NMR spectrum in chloroform-d was recorded and compared against literature to confirm purity and product used in subsequent reactions.

5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(2-methylfuranyl)-25,26,27,28-tetramethoxycalix[4]arene, 4.

A mixture of compound **3** (5.00 g, 4.90 mmol), 2-methylfuran (8 mL, 18.44 mmol) and 1,2-butylene oxide (8 mL) in TFE (500 mL) was heated at reflux for 4 h. During this time, the solution goes from pink to peach and continues to lighten in colour as product is seen forming. The solution was cooled to room temperature at which point a whiter solid forms. The white solid was filtered and then recrystallised from $CHCl_3$/MeOH to yield 1.603 g (32 %) of **4** as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 8H), 6.02 (s, 4H), 5.98 (dd, *J* = 3.0, 1.2 Hz, 4H), 5.92 (dd, *J* = 3.0, 1.1 Hz, 4H), 3.91 (s, 12H), 2.30 (s, 12H), 1.05 (s, 36H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ ppm: 155.3, 154.3, 151.1, 144.6, 134.3, 123.7, 109.1, 105.5, 61.9, 37.8, 34.0, 31.3, 13.6.

^{1}H NMR spectrum in chloroform-d was recorded and compared against literature to confirm purity and product used in subsequent reactions.

Crystal Data for $C_{70}H_{83}Cl_4O_8$ (*M* =1194.16 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 10.8355(2) Å, *b* = 32.7430(6) Å, *c* = 19.2590(4) Å, *β* = 101.5670(10)°, *V* = 6694.1(2) Å^3, *Z* = 4, *T* = 100(2) K, μ(CuKα) = 2.016 mm^{-1}, *Dcalc* = 1.185 g/cm^3, 112937 reflections measured (5.398° ≤ 2Θ ≤ 140.298°), 12606 unique (R_{int} = 0.1195, R_{sigma} = 0.0564) which were used in all calculations. The final R_1 was 0.0612 (I > 2σ(I)) and wR_2 was 0.1681 (all data).

5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(2-methylfuranyl)-25,26,27,28-tetramethoxycalix[4]arene, 4a, Partial Cone (Rcct)

This conformer was recovered as a side product in the reaction. The solid was obtained through recrystallisation of the filtrate obtained when filtering **4**. **4a** was attained as a slightly off white solid in 0.613 g (12 %) yield.

Crystal Data for Partial cone, 4a:

Crystal Data for $C_{71}H_{86}O_9$ (*M* =1083.39 g/mol): triclinic, space group P-1 (no. 2), *a* = 12.9781(2) Å, *b* = 13.7129(2) Å, *c* = 19.7621(3) Å, *α* = 72.2080(10)°, *β* = 81.2640(10)°, *γ* = 70.4500(10)°, *V* = 3150.91(9) Å^3, *Z* = 2, *T* = 100(2) K, μ(CuKα) = 0.582 mm^{-1}, *Dcalc* = 1.142 g/cm^3, 97141 reflections measured (4.704° ≤ 2Θ ≤ 140.478°), 11968 unique (R_{int} = 0.0562, R_{sigma} = 0.0325) which were used in all calculations. The final R_1 was 0.0914 (I > 2σ(I)) and wR_2 was 0.2913 (all data).

5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(pentane-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, 5.

Compound 4 (1.00 g, 0.975 mmol) in acetic acid (300 mL), water (120 mL) and conc. sulfuric acid (20 mL) was heated at reflux for 20 hours. Over time the solution became lime green. The lime green solution was cooled to room temperature and diluted with water (150 mL) before extraction with $CHCl_3$ (3 ×100 mL). The combined organic phase was washed with water (5 × 200 mL), then dried over $MgSO_4$ before the solvent was removed under reduced pressure. The crude solid was purified by column chromatography (7:3 $CHCl_3$/EtOAc) to yield 0.508 g (48 %) of **5** as an off-white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 8H), 5.84 (s, 4H), 3.91 (s, 12H), 2.93 (dd, J = 7.2, 5.1 Hz, 4H), 2.80 (dd, J = 7.2, 5.1 Hz, 4H), 2.19 (s, 12H), 1.03 (s, 36H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ ppm 208.8, 207.4, 155.2, 145.9, 131.6, 125.0, 62.5, 51.6, 37.9, 36.7, 34.5, 31.7,30.3. ESI-MS: 1119.6, $[M+Na]^+$.

Synthesis of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(1-(4-bromophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 6.

Compound **5** (1.00 g, 0.729 mmol), 4-Bromoaniline (0.800 g, 0.729 mmol), and *p*-TsOH·H_2O (0.136 g) were dissolved in toluene (120 mL). The mixture was refluxed for 24 h before cooling to room temp. The solvent was removed under reduced pressure to afford a crude. The crude was then dissolved in chloroform (100 mL) before being washed with 1M HCl (1 × 50 mL), H_2O (2 × 50 mL), and brine (1 × 50 mL). The Organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum to afford a golden brown crude. Crude was recrystalised from hot $CHCl_3$/MeOH and washed with ice cold methanol to afford (0.852, 71.2 %) of **6** as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 4H), 7.42 (s, 4H), 7.08 (s, 4H), 6.82 (s, 4H), 6.60 (s, 4H), 6.41 (s, 4H), 5.99 (d, *J* = 3.4 Hz, 4H), 5.92 (d, *J* = 3.4 Hz, 4H), 5.37 (s, 4H), 3.23 (s, 6H), 2.72 (s, 6H), 1.95 (s, 12H), 1.19 (s, 18H), 0.87 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.58, 152.95, 144.62, 143.49, 138.51, 137.47, 133.78, 132.62, 129.19, 124.45, 122.49, 121.48, 109.67, 106.20, 62.13, 58.74, 36.08, 34.31, 33.73, 31.66, 31.15, 13.13. ESI-MS: 1637.4 $[M+Na]^+$

Crystal Data for $C_{112}H_{106}Br_4N_4O_4$ (*M* =1891.64 g/mol): triclinic, space group P-1 (no. 2), *a* = 14.7325(10) Å, *b* = 14.8640(11) Å, *c* = 25.577(2) Å, *α* = 78.984(6)°, *β* = 88.908(4)°, *γ* = 70.967(4)°, *V* = 5191.5(7) Å^3, *Z* = 2, *T* = 100(2) K, μ(CuKα) = 2.282 mm$^-$

[1], *Dcalc* = 1.210 g/cm^3, 188248 reflections measured (6.354° ≤ 2Θ ≤ 150.694°), 21295 unique (R_{int} = 0.1017, R_{sigma} = 0.0479) which were used in all calculations. The final R_1 was 0.1174 (I > 2σ(I)) and wR_2 was 0.4028 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-iodophenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 7.

Compound **5** (0.100 g, 0.0911 mmol), 4-iodoaniline (0.0816 g, 0.382 mmol), and *p*-TsOH·H_2O (0.005 g) were dissolved in toluene (25 mL). The mixture was refluxed for 24 h, before cooling to room temp. The solvent was then removed under reduced pressure before being dissolved in chloroform (100 mL) and then washed with 1M HCl (1 × 50 mL), H_2O (2 × 50 mL), and brine (1 × 50 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum to afford a crude. The crude was then purified via column chromatography (DCM:Hex 1:1) to afford 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-iodophenyl)-2-methyl-1H-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene (0.052 g, 31%).

1H NMR (400 MHz, $CDCl_3$) δ 7.82 (br. s, 4H), 7.64 (br. s, 4H), 6.95 (br. s, 4H), 6.84 (s, 4H), 6.48 (br. s, 4H), 6.40 (s, 4H), 5.99 (d, *J* = 3.3 Hz, 4H), 5.92 (d, *J* = 3.3 Hz, 4H), 5.38 (s, 4H), 3.20 (s, 6H), 2.79 (s, 6H), 1.95 (s, 12H), 1.18 (s, 18H), 0.87 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.77, 153.12, 144.72, 143.61, 139.42, 138.17, 137.63, 133.95, 132.86, 131.28, 131.03, 129.31, 124.62, 122.69, 109.93, 106.46, 93.10, 62.27, 58.97, 36.26, 34.46, 33.87, 31.80, 31.30, 22.80, 14.26, 13.32.

ASAP-MS 1831.15 $[M+H]^+$

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-butoxyphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 8.

Compound **5** (0.250 g, 0.228 mmol), 4-butoxyaniline (0.158 g, 0.956 mmol) and *p*-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 24 hours, under N_2. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed once with 1M $HCl_{(aq)}$ (1 × 50 mL), H_2O (2 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by column chromatography (DCM:Pet, 1:1) to afford (0.274 g, 74%) of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-butoxyphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-

tetramethoxycalix[4]arene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 8.5, 1.8 Hz, 4H), 6.91 (dd, *J* = 8.4, 2.3 Hz, 4H), 6.83 (s, 4H), 6.71 (dd, *J* = 8.5, 2.2 Hz, 4H), 6.57 (dd, *J* = 8.5, 1.7 Hz, 4H), 6.43 (s, 4H), 5.97 (d, *J* = 3.3 Hz, 4H), 5.89 (dd, *J* = 3.3, 0.7 Hz, 4H), 5.39 (s, 4H), 4.09 – 3.95 (m, 8H), 3.23 (s, 6H), 2.71 (s, 6H), 1.94 (s, 12H), 1.83 (dt, *J* = 14.6, 6.7 Hz, 8H), 1.59 – 1.48 (m, 8H), 1.19 (s, 18H), 1.02 (t, *J* = 7.4 Hz, 12H), 0.86 (s, 18H).^{13}C NMR (101 MHz, $CDCl_3$) δ 158.40, 153.79, 153.29, 144.16, 143.36, 137.67, 134.49, 132.94, 132.16, 130.68, 129.70, 129.43, 124.64, 122.55, 114.48, 114.21, 108.93, 105.43, 68.20, 62.29, 58.88, 36.22, 34.42, 33.84, 31.84, 31.74, 31.60, 31.31, 22.80, 19.43, 14.27, 14.10, 13.31. ASAP-MS 1615.35 $[M+H]^+$. **Crystal Data** for $C_{228}H_{292}N_8O_{16}$ (*M* =3400.68 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 41.4523(7) Å, *b* = 16.4591(3) Å, *c* = 32.4222(6) Å, *β* = 111.6240(10)°, *V* = 20563.8(7) Å^3, *Z* = 4, *T* = 100(2) K, μ(CuKα) = 0.524 mm^{-1}, *Dcalc* = 1.098 g/cm^3, 363464 reflections measured (4.586° ≤ 2Θ ≤ 145.434°), 40739 unique (R_{int} = 0.1203, R_{sigma} = 0.0782) which were used in all calculations. The final R_1 was 0.1102 (I > 2σ(I)) and wR_2 was 0.3621 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-hexoxyphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 9.

Compound **5** (0.250 g, 0.228 mmol), 4-hexyloxyaniline (0.185 g, 0.956 mmol) and *p*-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 36 hours, under N_2. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed once with 1M $HCl_{(aq)}$ (1 × 50 mL), H_2O (2 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by column chromatography (DCM:Pet, 1:1) to afford (0.1702 g, 43 %) of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-hexoxyphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 8.3, 1.8 Hz, 4H), 6.91 (dd, *J* = 8.6, 2.2 Hz, 4H), 6.83 (s, 4H), 6.71 (dd, *J* = 8.6, 2.3 Hz, 4H), 6.57 (dd, *J* = 8.4, 1.9 Hz, 4H), 6.43 (s, 4H), 5.97 (d, *J* = 3.3 Hz, 4H), 5.89 (dd, *J* = 3.3, 0.8 Hz, 4H), 5.39 (s, 4H), 4.01 (dtd, *J* = 15.9, 9.1, 6.7 Hz, 8H), 3.24 (s, 6H), 2.72 (s, 6H), 1.94 (s, 12H), 1.88 – 1.80 (m, 8H), 1.49 (m, *J* = 16.1, 8.1 Hz, 8H), 1.37 (td, *J* = 7.2, 3.7 Hz, 16H), 1.19 (d, *J* = 4.2 Hz, 18H), 0.94 (t, *J* = 7.0 Hz, 12H), 0.86 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.43, 153.84, 153.33, 144.19, 143.37, 137.74, 134.53, 132.97, 132.23, 130.70, 129.72 (s), 129.47 (s), 124.69,

122.60, 114.42, 109.02, 105.48, 68.53, 62.27, 58.87, 36.30, 34.44, 33.86, 31.87, 31.34, 29.53, 25.94, 22.81, 14.19, 13.28. ASAP-MS 1727.45 $[M+H]^+$. **Crystal Data** for $C_{116}H_{148}N_4O_8$ (*M* =1726.38 g/mol): triclinic, space group P-1 (no. 2), *a* = 15.3047(4) Å, *b* = 16.5632(5) Å, *c* = 21.8253(6) Å, *α* = 103.4490(10)°, *β* = 99.6520(10)°, *γ* = 101.741(2)°, *V* = 5132.3(3) $Å^3$, *Z* = 2, *T* = 100(2) K, μ(CuKα) = 0.532 mm^{-1}, *Dcalc* = 1.117 g/cm^3, 96845 reflections measured ($4.272° \leq 2\Theta \leq 133.366°$), 18113 unique ($R_{int}$ = 0.0485, R_{sigma} = 0.0392) which were used in all calculations. The final R_1 was 0.1241 ($I > 2\sigma(I)$) and wR_2 was 0.4395 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-morpholino phenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 10.

Compound **5** (0.250 g, 0.228 mmol), 4-morpholinoaniline (0.170 g, 0.956 mmol), and *p*-TsOH·H_2O (0.010 g) were dissolved in toluene (50 mL). The mixture was refluxed under N_2 for 24 h before cooling to room temp. The solution was washed with 1 M HCl (1 × 50 mL), H_2O (1 × 50 mL), and brine (1 x 50 mL). The crude was then washed with cold pet ether (40-60 °C) to afford (0.088 g, 28.1 %) of **10.** Crystals were grown from a saturated EtOAc solution. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 8.5, 1.8 Hz, 4H), 6.95 (dd, *J* = 8.4, *J* = 2.0 Hz, 4H), 6.92 (s, 4H), 6.68 (dd, *J* = 8.6, 2.1 Hz, 4H), 6.58 (dd, *J* = 8.5, 1.7 Hz, 4H), 5.98 (d, *J* = 3.3 Hz, 4H), 5.89 (dd, *J* = 3.3, 0.7 Hz, 4H), 5.36 (s, 4H), 3.97 – 3.85 (m, 16H), 3.28 – 3.20 (m, 8H), 3.16 (s, 6H), 3.14 – 3.07 (m, 8H), 2.79 (s, 6H), 1.94 (s, 12H), 1.22 (s, 18H), 0.86 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.68, 153.15, 150.64, 144.00, 143.26, 137.62, 134.45, 132.85, 132.01, 130.41, 129.51, 129.35, 124.60, 122.65, 116.00, 115.44, 108.99, 105.46, 66.71, 62.24, 58.90, 49.98, 41.36, 36.12, 34.3, 33.70, 31.69, 31.17, 29.05, 27.66, 22.59, 20.42, 19.41, 14.28, 13.19, 11.39. ASAP MS 1668.00 $[M+H]^+$.

Crystal Data for $C_{254}H_{332}N_{16}O_{35}$ (*M* =4169.34 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 29.8134(8) Å, *b* = 22.2200(6) Å, *c* = 35.9386(10) Å, *β* = 94.5397(17)°, *V* = 23733.0(11) $Å^3$, *Z* = 4, *T* = 100(2) K, μ(CuKα) = 0.615 mm^{-1}, *Dcalc* = 1.167 g/cm^3, 276654 reflections measured ($3.71° \leq 2\Theta \leq 122.548°$), 36499 unique ($R_{int}$ = 0.1151, R_{sigma} = 0.0659) which were used in all calculations. The final R_1 was 0.1299 ($I > 2\sigma(I)$) and wR_2 was 0.4033 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-benzylphenyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 11.

Compound **5** (0.250 g, 0.228 mmol), 4-Benzylaniline (0.158 g, 0.956 mmol) and p-TsOH·H2O (0.010 g) in toluene (50 mL) was heated at reflux for 72 hours. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed with 1M HCl (1 × 50 mL), and water (2 × 50 mL) The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. Despite best efforts the crude could not be fully purified and therefore full characterisation is limited.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 4H), 7.23 – 7.20 (m, 4H), 7.12 (br. s, 16H), 7.06 (s, 4H), 7.04 (s, 4H), 6.86 (s, 4H), 6.67 (br. s, 4H), 6.44 (s, 4H), 6.00 (d, *J* = 3.3 Hz, 4H), 5.91 (d, *J* = 2.7 Hz, 4H), 5.41 (s, 4H), 3.97 (dd, *J* = 15.4 Hz, 8H), 3.21 (s, 6H), 2.76 (s, 6H), 1.94 (s, 12H), 1.19 (s, 18H), 0.88 (s, 18H).

5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(ethyl 4-(2-methyl-1H-pyrrol-1-yl)benzoate)-25,26,27,28-tetramethoxycalix[4]arene, 12.

Compound **5** (0.700 g, 0.638 mmol), benzocaine (0.550 g, 3.03 mmol) and *p*-toluenesulfonic acid monohydrate (0.020 g) in toluene (100 mL) were heated at reflux for 24 h under N_2. During this time, the reaction mixture darkened. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure to yield a crude. The crude was dissolved in chloroform (100 mL) which was then washed with 1M HCl (1 × 100 mL), H_2O (2 × 100 mL) and brine (1 × 100 mL) The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was then purified either by column chromatography (8.5:1.5 PET/Ethyl acetate) or recrystallised from $CHCl_3$/MeOH to yield 0.711 g (69 %) of **6** as a light brown powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 4H), 7.81 (s, 4H), 7.22 (s, 3H), 6.88 (s, 4H), 6.77 (s, 4H), 6.43 (s, 4H), 6.02 (d, J = 3.4 Hz, 4H), 5.94 (dd, J = 3.4, 1.0 Hz, 4H), 5.35 (s, 4H), 4.45 (qd, J = 7.1, 2.5 Hz, 8H), 3.16 (s, 6H), 2.64 (s, 6H), 1.94 (s, 12H), 1.42 (t, J = 7.1 Hz, 12H), 1.21 (s, 18H), 0.86 (s, 18H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.79, 143.47, 137.37, 133.91, 132.67, 129.87, 129.12, 109.82, 106.51 (Ar-C), 61.25 (Methylene-CH_2), 34.34 (Ar-C), 31.66 (OMe-CH_3), 31.15

(Pyrrole-CH_3), 30.93 (Ethyl ether-CH_3), 14.33 (^{t}Bu-CH_3), 13.16 (^{t}Bu-CH_3) ASAP MS 1615.00 $[M+H]^+$.

Crystal Data for $C_{105}H_{120}N_4O_{20}$ (*M* =1758.04 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 15.7901(3) Å, *b* = 15.8418(3) Å, *c* = 40.1062(7) Å, *β* = 94.1260(10)°, *V* = 10006.3(3) Å^3, *Z* = 4, *T* = 100(2) K, μ(CuKα) = 0.651 mm^{-1}, *Dcalc* = 1.167 g/cm^3, 202042 reflections measured (4.418° ≤ 2Θ ≤ 149.866°), 20504 unique (R_{int} = 0.0656, R_{sigma} = 0.0346) which were used in all calculations. The final R_1 was 0.1040 (I > 2σ(I)) and wR_2 was 0.3108 (all data).

5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(4-(2-methyl-1H-pyrrol-1-yl)benzoic)-25,26,27,28-tetramethoxycalix[4]arene, 13.

Compound 12 (0.30 g, 0.186 mmol) was dissolved in Et_2O (18 mL) before KOH (0.125 g, 2.23 mmol) dissolved in MeOH (2 mL) was added. The reaction was stirred at 40 ° C for 20 hours. The solvent was removed, diluted with H_2O (5 mL) and 1 M HCl was added until pH ~ 4. The solution was left covered in a fridge before solid was filtered to afford 0.112 g (48.2 %) of **13**. ^{1}H NMR (300 MHz, DMSO) δ 8.09 (s, 4H), 7.81 (s, 4H), 7.37 (s, 4H), 6.81 (s, 4H), 6.65 (s, 4H), 6.37 (s, 4H), 5.93 (s, *J* = 2.7Hz, 4H), 5.89 (s, *J* = 2.5Hz, 4H) 5.34 (s, 4H), 3.13 (s, 6H), 2.71 (s, 6H), 1.91 (s, 12H), 1.14 (s, 18H), 0.80 (s, 18H). ^{13}C NMR (101 MHz, DMSO) δ 166.63 (s), 153.05 (s), 152.90 (s), 143.55 (s), 142.69 (s), 142.16 (s), 136.71 (s), 133.07 (s), 132.50 (s), 130.48 (s), 128.53 (s), 123.99 (s), 121.97 (s), 109.01 (s), 106.59 (s), 79.18 (s), 62.20 (s), 58.36 (s), 35.51 (s), 33.87 (s), 33.27 (s), 31.31 (s), 30.78 (s), 12.89 (s). ESI-MS: 1523.72 $[M+Na]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.68 (br. s, 4H), 8.32 (br. s, 2H), 8.24 (br. s, 2H), 8.03 (br. s, 4H), 7.33 (br. s, 2H), 7.24 (br. s, 2H) 6.92 (d, J = 2.1 Hz, 2H), 6.89 (br. s, 2H), 6.80 (br. s, 2H), 6.77 (d, J = 2.2 Hz, 2H), 6.46 (s, 2H), 6.40 (s, 2H), 6.12 (d, J = 3.3 Hz, 2H), 5.96 (d, J = 3.2 Hz, 4H), 5.92 (d, J = 2.9 Hz, 2H), 5.44 (s, 2H), 5.25 (s, 2H), 3.40 (s, 3H), 3.14 (s, 3H), 2.46 (s, 6H), 1.96 (s, 6H), 1.84 (s, 6H), 1.23 (s, 18H), 0.90 (s, 9H), 0.89 (s, 9H).

^{1}H NMR (400 MHz, MeOD) δ 8.17 (br. s, 4H), 7.90 (br. s, 4H), 7.31 (br. s, 4H), 6.89 (s, 4H), 6.78 (br. s, 4H), 6.47 (s, 4H), 6.00 (d, J = 3.3 Hz, 4H), 5.96 (d, J = 3.4 Hz, 4H), 5.42 (s, 4H), 3.25 (s, 6H), 2.63 (s, 6H), 1.95 (s, 12H), 1.21 (s, 18H), 0.89 (s, 18H).

Crystal Data for $C_{101}H_{102}Cl_{15}N_4O_{12}$ (*M* =2095.61 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 18.8893(3) Å, *b* = 16.4272(3) Å, *c* = 34.5946(5) Å, *β* = 90.5610(10)°, *V* =

10734.1(3) Å^3, Z = 4, T = 100(2) K, μ(CuKα) = 3.991 mm^{-1}, *Dcalc* = 1.297 g/cm^3, 120362 reflections measured (4.678° ≤ 2Θ ≤ 117.86°), 15405 unique (R_{int} = 0.1209, R_{sigma} = 0.1073) which were used in all calculations. The final R_1 was 0.1105 (>2sigma(I)) and wR_2 was 0.3588 (all data).

Acid-Pyridine, Crystal Data for $C_{272}H_{280}N_{24}O_{24}$ (M =4269.18 g/mol): triclinic, space group P-1 (no. 2), a = 18.8712(3) Å, b = 24.5002(5) Å, c = 27.6142(5) Å, α = 89.2230(10)°, β = 70.7350(10)°, γ = 79.9990(10)°, V = 11856.2(4) Å^3, Z = 2, T = 100(2) K, μ(CuKα) = 0.609 mm^{-1}, *Dcalc* = 1.196 g/cm^3, 231874 reflections measured (3.394° ≤ 2Θ ≤ 118.296°), 33774 unique (R_{int} = 0.0972, R_{sigma} = 0.0750) which were used in all calculations. The final R_1 was 0.0894 (I > 2σ(I)) and wR_2 was 0.3135 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(4-nitrophenyl)2-methyl-1H pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 14.

Compound **5** (0.200 g, 0.1882 mmol), 4-Nitroaniline (0.110 g, 0.790 mmol) and *p*-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 24 hours. The reaction apparatus was wrapped in foil to avoid light ingress. The black reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and washed with 1M HCl (2 × 50 mL) and water (1 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude which was purified via column chromatography 4:1 $CHCl_3$:DCM → 1:1 $CHCl_3$/DCM to yield (0.073 g, 26%) of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(1-hexyl-2-methyl-1H-pyrrole)-25,26,27,28 tetramethoxycalix[4]arene as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br. s, 4H), 7.92 (br. s, 4H), 7.27 (br. s, 4H), 6.83 (br. s, 4H), 6.77 (s, 4H), 6.33 (s, 4H), 5.96 (d, J = 3.3 Hz, 4H), 5.91 (dd, J = 3.4, 0.7 Hz, 4H), 5.29 (s, 4H), 3.18 (s, 6H), 2.60 (s, 6H), 1.90 (s, 12H), 1.14 (s, 18H), 0.80 (s, 18H).^{13}C NMR (101 MHz, $CDCl_3$) δ 153.60, 153.03, 147.10, 145.41, 145.31, 144.05, 137.32, 133.64, 132.43, 129.94, 129.56, 124.74, 122.86, 111.00, 107.53, 62.38, 59.02, 36.25, 34.51, 33.90, 31.78, 31.25, 13.31. ASAP-MS: 1505.70 $[M+H]^+$

Crystal Data for $C_{196}H_{204}Cl_{36}N_{16}O_{24}$ (M =4443.94 g/mol): triclinic, space group P-1 (no. 2), a = 16.8895(7) Å, b = 23.5130(8) Å, c = 28.9693(11) Å, α = 99.360(3)°, β = 106.443(2)°, γ = 91.745(3)°, V = 10851.3(7) Å^3, Z = 2, T = 100(2) K, μ(CuKα) = 4.653

mm^{-1}, *Dcalc* = 1.360 g/cm^3, 368411 reflections measured (4.542° ≤ 2Θ ≤ 144.806°), 42701 unique (R_{int} = 0.0574, R_{sigma} = 0.0374) which were used in all calculations. The final R_1 was 0.0785 (I > 2σ(I)) and wR_2 was 0.3066 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,-tris(1-(4-nitrophenyl)2-methyl-1H-pyrrole)-20-(2-methylfuranyl)-25,26,27,28-tetramethoxycalix[4]arene, 15.

Compound **5** (0.200 g, 0.1882 mmol), 4-Nitroaniline (0.110 g, 0.790 mmol) and *p*-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 24 hours. The reaction apparatus was wrapped in foil to avoid light ingress. The black reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and washed with 1M HCl (2 × 50 mL) and water (1 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude which was purified via column chromatography 4:1 $CHCl_3$:DCM → 1:1 $CHCl_3$/DCM to yield (0.064 g, 23%) of 5,11,17,23-tetra-tert-butyl-2,8,14,-tris(tert-butyl(1-hexyl-2-methyl-1H-pyrrole)-20-(2-methylfuranyl)-25,26,27,28-tetramethoxycalix[4]arene as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br. s, 6H), 7.38 (br. s, 3H), 6.95 (br. s, 3H), 6.87 (dd, *J* = 9.1, 2.3 Hz, 2H), 6.80 (s, 2H), 6.47 (dd, *J* = 8.8, 2.4 Hz, 2H), 6.43 (dd, *J* = 9.9, 2.4 Hz, 2H), 6.11 (d, *J* = 3.3 Hz, 1H), 6.05 – 6.02 (m, 3H), 5.97 (d, *J* = 2.8 Hz, 2H), 5.87 (dd, *J* = 8.2, 2.8 Hz, 2H), 5.56 (s, 1H), 5.50 (s, 1H), 5.45 (s, 1H), 5.44 (s, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.17 (s, 3H), 2.80 (s, 3H), 2.29 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.22 (s, 9H), 1.18 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.87, 153.89, 153.67, 153.48, 153.14, 151.20, 147.09, 147.06, 147.00, 145.50, 145.45, 145.43, 145.23, 145.16, 137.38, 137.32, 137.27, 136.78, 133.98, 133.88, 133.70, 132.58, 132.49, 132.28, 131.87, 130.04, 129.92, 129.51, 129.45, 129.42, 125.12, 124.86, 124.66, 124.52, 124.34, 122.92, 122.79, 122.38, 110.99, 110.95, 110.52, 109.26, 107.64, 107.45, 107.10, 105.82, 62.53, 62.43, 59.86, 59.03, 37.80, 36.37, 36.21, 36.19, 34.51, 34.40, 33.91, 33.86, 31.78, 31.68, 31.28, 31.20, 13.87, 13.35, 13.29, 13.21. ASAP-MS: 1384.70 $[M-H]^+$.

Crystal Data for $C_{87.5}H_{93.5}Cl_{4.5}N_6O_{11}$ (*M* =1564.70 g/mol): triclinic, space group P-1 (no. 2), *a* = 14.4771(6) Å, *b* = 17.5117(8) Å, *c* = 19.0306(8) Å, *α* = 93.094(3)°, *β* = 111.983(3)°, *γ* = 98.511(3)°, *V* = 4393.0(3) $Å^3$, *Z* = 2, *T* = 100(2) K, μ(CuKα) = 1.839 mm^{-1}, *Dcalc* = 1.183 g/cm^3, 62535 reflections measured (5.044° ≤ 2Θ ≤ 122.462°), 13277 unique (R_{int} = 0.1732, R_{sigma} = 0.1203) which were used in all calculations. The final R_1 was 0.1230 (I > 2σ(I)) and wR_2 was 0.4083 (all data).

5,11,17,23--tetra-tert-butyl-2,8,14,20-tetrakis(1-(napthalen-1-yl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 16.

Compound **5** (0.250 g, 0.228 mmol), 1-napthylamine (0.142 g, 0.991 mmol) and *p*-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 72 hours. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed once with 1M HCl (1 × 50 mL, twice with H_2O (2 × 50 mL) and once with $NaHCO_3$ (1 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified via column chromatography DCM:Hex (2:1) to yield 0.150 g of (**16-2)** and (**16-3**) combined along with (0.040 g, 10 %) of (**16-1**).

16-1

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.07 (s, 1H), 8.03 (s, 1H), 8.01 (s, 1H), 7.74 (s, 1H), 7.71 (s, 1H), 7.60 – 7.49 (m, 8H), 7.42 – 7.36 (m, 5H), 7.35 (s, 1H), 7.16 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 2H), 6.91 (d, *J* = 2.4 Hz, 2H), 6.82 (s, 1H), 6.80 (s, 1H), 6.65 (d, *J* = 2.4 Hz, 2H), 6.48 (s, 2H), 6.26 (s, 2H), 6.09 (d, *J* = 3.3 Hz, 2H), 6.01 (dd, *J* = 3.3, 0.8 Hz, 2H), 5.99 – 5.95 (m, 4H), 5.92 (dd, *J* = 3.3, 0.8 Hz, 2H), 5.77 – 5.71 (m, 4H), 4.56 (s, 2H), 3.59 (s, 3H), 2.38 (s, 3H), 1.74 (s, 6H), 1.72 (s, 12H), 1.20 (s, 18H), 0.93 (s, 9H), 0.80 (s, 9H). ASAP MS 1526.05 $[M+H]^+$,^{13}C NMR (101 MHz, $CDCl_3$) δ 153.42, 152.92, 152.77, 143.75, 143.38, 142.69, 137.91, 136.82, 136.34, 135.38, 134.88, 134.31, 134.24, 133.46, 133.05, 132.14, 131.92, 131.71, 130.86, 130.20, 127.83, 127.68, 127.58, 127.41, 127.15, 126.52, 126.30, 126.20, 125.81, 125.48, 125.22, 124.71, 124.56, 124.41, 123.73, 122.35, 122.15, 110.44, 108.87, 105.97, 104.99, 62.61, 62.37, 58.20, 35.97, 35.68, 34.22, 33.81, 33.59, 31.68, 31.28, 31.07, 13.00, 12.41.

Crystal Data for $C_{110.5}H_{110.5}Cl_{7.5}N_4O_4$ (*M* =1824.40 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 18.874(3) Å, *b* = 26.177(4) Å, *c* = 21.770(3) Å, *β* = 111.543(8)°, *V* = 10004(3) Å^3, *Z* = 4, *T* = 160(2) K, μ(CuKα) = 2.348 mm^{-1}, *Dcalc* = 1.211 g/cm^3, 93309 reflections measured (5.316° ≤ 2Θ ≤ 146.09°), 18497 unique (R_{int} = 0.0711, R_{sigma} = 0.0565) which were used in all calculations. The final R_1 was 0.1164 (I > 2σ(I)) and wR_2 was 0.3742 (all data).

16-2

ASAP-MS 1526.05 $[M+H]^+$.

Crystal Data for $C_{110.5}H_{110.5}Cl_{7.5}N_4O_4$ (M =1824.40 g/mol): monoclinic, space group C2/c (no. 15), a = 34.7747(8) Å, b = 11.0706(3) Å, c = 26.0198(6) Å, β = 96.3290(10)°, V = 9956.0(4) $Å^3$, Z = 4, T = 100(2) K, μ(CuKα) = 2.359 mm^{-1}, *Dcalc* = 1.217 g/cm^3, 147946 reflections measured (8.076° ≤ 2Θ ≤ 144.832°), 9824 unique (R_{int} = 0.0653, R_{sigma} = 0.0380) which were used in all calculations. The final R_1 was 0.0686 (I > 2σ(I)) and wR_2 was 0.2053 (all data).

5,11,17,23--tetra-tert-butyl-2,8,14,20-tetrakis(1-(pyren-1-yl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 17.

Compound **5** (0.230 g, 0.210 mmol), 1-Aminopyrene (0.191 g, 0.879 mmol) and *p*-TsOH·H2O (0.010 g) in toluene (50 mL) was heated at reflux for 72 hours, under N_2 wrapped in foil to avoid light ingress. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed once with 1M HCl (1 × 50 mL, twice with H_2O (2 × 50 mL) and once with brine (1 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by column chromatography (1:1 $CHCl_3$/Hex) to afford (0.110 mg, 32 %) of a mixture of two conformers. The mixture can be washed with cold toluene to afford 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(pyren-1-yl)-2-methyl-1H-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene (0.23 mg, 6.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 8.20 (s, 2H), 8.19 (s, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 8.10 – 7.97 (m, 8H), 7.92 (s, 1H), 7.90 (s, 1H), 7.89 (s, 1H), 7.87 (s, 1H), 7.75 (s, 1H), 7.72 (d, J = 1.1 Hz, 2H), 7.70 (s, 1H), 7.64 (s, 1H), 7.62 (s, 1H), 7.06 (d, J = 2.4 Hz, 2H), 6.94 (s, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 6.85 (s, 1H), 6.75 (d, J = 2.4 Hz, 2H), 6.42 (s, 4H), 6.18 (d, J = 3.4 Hz, 2H), 6.14 (d, J = 3.4 Hz, 2H), 6.01 (t, J = 3.4 Hz, 4H), 5.98 (s, 1H), 5.96 (s, 1H), 5.48 (s, 2H), 4.76 (s, 1H), 4.74 (s, 1H), 4.50 (s, 2H), 2.77 (s, 6H), 1.59 (s, 6H), 1.58 (s, 6H), 1.33 (s, 18H), 1.19 (s, 6H), 0.92 (s, 18H). ASAP MS 1822.20 $[M]^+$, 1823.05 $[M+H]^+$,^{13}C NMR (101 MHz, $CDCl_3$) δ 153.27, 152.97, 144.26, 143.18, 138.23, 138.03, 137.10, 135.58, 134.97, 133.79, 132.78, 132.62, 132.51, 131.58, 131.44, 131.18, 131.10, 131.00, 130.95, 130.72, 130.23, 129.31, 129.19,

128.82, 128.38, 128.08, 127.96, 127.90, 127.56, 127.32, 127.08, 126.83, 126.29, 126.14, 125.86, 125.74, 125.45, 125.32, 125.29, 125.10, 124.72, 124.67, 124.51, 124.28, 124.23, 123.31, 122.94, 122.42, 77.16, 62.83, 58.03, 36.20, 35.89, 34.52, 33.89, 31.94, 31.39, 21.61, 13.05, 12.83.

2.7. References

1 C. D. Gutsche, M. Iqbal and D. Stewart, *J. Org. Chem.*, 1986, **51**, 742–745.

2 I. Columbus and S. E. Biali, *Org. Lett.*, 2007, **9**, 2927–2929.

3 S. Shinkai, K. Araki, H. Koreishi, T. Tsubaki and O. Manabe, *Chem. Lett.*, 1986, **15**, 1351–1354.

4 G. Karotsis, S. Kennedy, S. J. Teat, C. M. Beavers, D. A. Fowler, J. J. Morales, M. Evangelisti, S. J. Dalgarno and E. K. Brechin, *J. Am. Chem. Soc.*, 2010, **132**, 12983–12990.

5 G. Karotsis, M. Evangelisti, S. J. Dalgarno and E. K. Brechin, *Angew. Chemie Int. Ed.*, 2009, **48**, 9928–9931.

6 A. Fong, L. McCormick, S. J. Teat, E. K. Brechin and S. J. Dalgarno, *Supramol. Chem.*, 2018, **30**, 504–509.

7 In *Greene's Protective Groups in Organic Synthesis*, 2006, pp. 16–366.

8 M. Coletta, R. McLellan, J.-M. Cols, K. J. Gagnon, S. J. Teat, E. K. Brechin and S. J. Dalgarno, *Supramol. Chem.*, 2016, **28**, 557–566.

9 I. Columbus, *J. Org. Chem.*, 2008, **73**, 2598–2606.

10 A. Fong, C. L. Campbell, S. Huynh, L. J. McCormick McPherson, S. J. Teat, M. W. P. Bebbington and S. J. Dalgarno, *Chem. Commun.*, 2022, **58**, 3302–3305.

11 N. A. Caballero, F. J. Melendez, C. Muñoz-Caro and A. Niño, *Biophys. Chem.*, 2006, **124**, 155–160.

12 A. J. Boulton and A. McKillop, eds. A. R. Katritzky and C. W. B. T.-C. H. C. Rees, Pergamon, Oxford, 1984, pp. 29–65.

13 R. J. Sundberg, eds. A. R. Katritzky and C. W. B. T.-C. H. C. Rees, Pergamon, Oxford, 1984, pp. 313–376.

14 Z. Zhong, A. Ikeda, M. Ayabe, S. Shinkai, S. Sakamoto and K. Yamaguchi, *J. Org. Chem.*, 2001, **66**, 1002–1008.

15 A. Suzuki, *Angew. Chemie Int. Ed.*, 2011, **50**, 6722–6737.

16 A. Fong, PhD Thesis, Heriot-Watt, 2019.

17 M. S. Albrecht Yun, *Synthesis (Stuttg).*, 2006, **2006**, 3037–3042.

18 Wallmann, *Synthesis.*, 2008, 2008, 2446–2450.

19 C. R. Patel, M. Samipillai, H. B. Friedrich, H. G. Kruger, T. Govender and G. E. M. Maguire, 2017, **232**, 397–402.

20 S. Shinkai and A. Ikeda, *Gazz. Chim. Ital.*, **127**, 657–662.

21 M. Helmstädter, J. Vietor, J. Sommer, S. Schierle, S. Willems, A. Kaiser, J. Schmidt and D. Merk, *ACS Med. Chem. Lett.*, 2021, **12**, 267–274.

22 J. Lincke, D. Lässig, K. Stein, J. Moellmer, A. Viswanath Kuttatheyil, C. Reichenbach, A. Moeller, R. Staudt, G. Kalies, M. Bertmer and H. Krautscheid, *Dalt. Trans.*, 2012, **41**, 817–824.

23 R. E. Fairbairn, S. J. Teat, K. J. Gagnon and S. J. Dalgarno, *Chim. Int. J. Chem.*, 2015, **69**, 516–519.

24 C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.*, 1985, **107**, 6052–6059.

25 C. D. Gutsche and L. J. Bauer, *Tetrahedron Lett.*, 1981, **22**, 4763–4766.

26 S. Kennedy and S. J. Dalgarno, *Chem. Commun.*, 2009, 5275–5277.

27 J. Klimentová and P. Vojtíšek, *J. Mol. Struct.*, 2007, **826**, 48–63.

28 F. Sansone, M. Dudič, G. Donofrio, C. Rivetti, L. Baldini, A. Casnati, S. Cellai and R. Ungaro, *J. Am. Chem. Soc.*, 2006, **128**, 14528–14536.

29 D. S. Mortensen, A. L. Rodriguez, K. E. Carlson, J. Sun, B. S. Katzenellenbogen and J. A. Katzenellenbogen, *J. Med. Chem.*, 2001, **44**, 3838–3848.

30 C. Liu, Y. Deng, J. Wang, Y. Yang, S. Tang and A. Lei, *Angew. Chemie Int. Ed.*, 2011, **50**, 7337–7341.

31 R. Kumar, A. Sharma, H. Singh, P. Suating, H. S. Kim, K. Sunwoo, I. Shim, B. C. Gibb and J. S. Kim, *Chem. Rev.*, 2019, **119**, 9657–9721.

Chapter 3

Further Exploration of the Paal-Knorr Synthesis, Additional Derivation Pathways and Deprotection of Methyl Ethers.

3.1. Introduction.

This chapter primarily focuses on the combination of the diketone examined in chapter 2 with primary amines in which the amine resides at the end of a chain (rather than phenyl ring as an aniline). This was achieved by using the same procedure to afford a small library of C[4]s with *n*-alkyl-pyrroles substituted at all methylene bridges. These are presented in detail before discussion moves to the modification of alternative substituents at the methylene bridge. Thiophene synthesis using the same saturated diketone analogue has been investigated, whilst the unsaturated analogue has been accessed via the tetrafuranyl C[4], **4**, and subsequently been employed in the synthesis of a tetrapyridazinyl C[4]. The deprotection of the latter along with one *n*-alkyl-pyrrole C[4] has been probed and a discussion on the different methods explored is presented, covering synthetic hurdles that arose and how these were tackled. Finally, a discussion on the stability of these compounds can be found at the end of the chapter which highlights observations made elsewhere in this thesis.

3.2. Paal-Knorr Pyrrole Condensation of 5 with Primary-Amines.

Earlier work in the group synthesised a C[4] with simplest pyrrole present at the methylene bridge positions, i.e. containing just a hydrogen substituted on the nitrogen-atom. This was achieved using a modified literature procedure by Orito *et al*,[1] whereby the saturated diketone was reacted with ammonium acetate in acetic acid.[2] The reaction of saturated diketone and isopropyl amine was also investigated, however it was noted here that the reaction was unsuccessful as only starting material was recovered and therefore focus was placed on the reaction with anilines as these seemed most promising (Chapter 2). Synthesis with isopropyl amine was shown to be unsuccessful, it was theorised that this was hindered due to electronics with the NH_2 being in the iso position.

This led to the investigation of substituting amines in which the amino functionality resides at the end of the chain. These could pose advantages over the anilines synthesised in Chapter 2 in that they should pose less steric bulk around the methoxy groups at the lower-rim and increase solubility in organic solvents due to the hydrophobic chains. Both were hypothesised to affect the deprotection step and therefore introducing these groups should increase the ability to probe the deprotection of the methoxy groups under a range of conditions. Firstly, a small selection of straight chain amines was chosen as shown in Figure 3.1. Syntheses using these amines were performed using the same Paal-Knorr procedure as in Chapter 2; a *p*-toluene sulfonic acid catalysed reaction in toluene at reflux under N_2, wrapped in aluminium foil to eliminate light as much as possible.

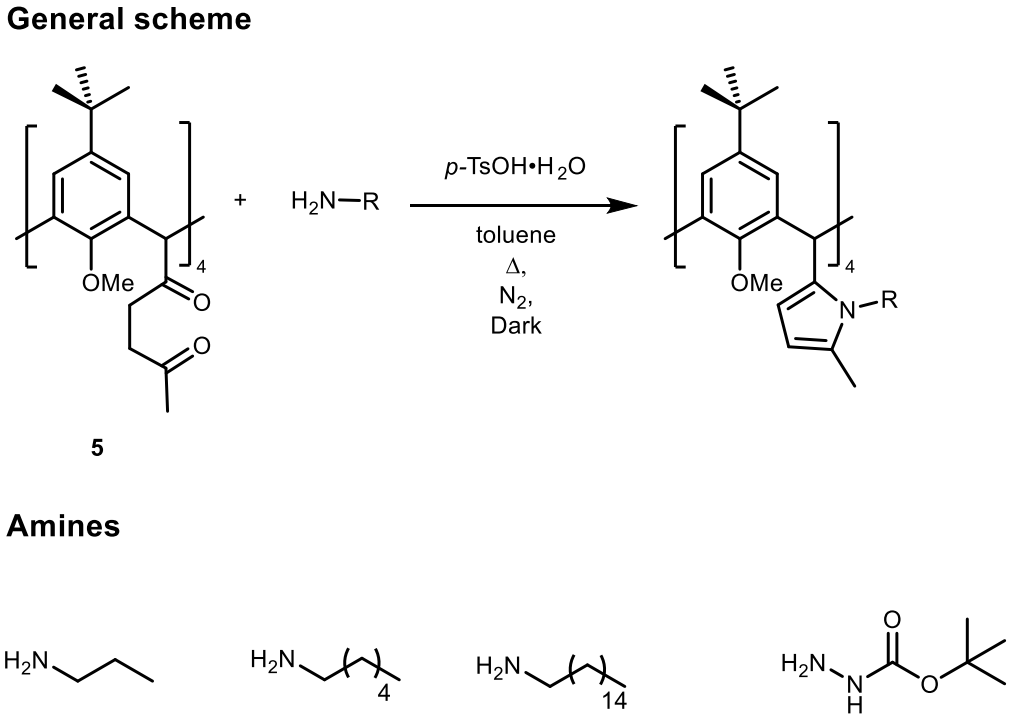
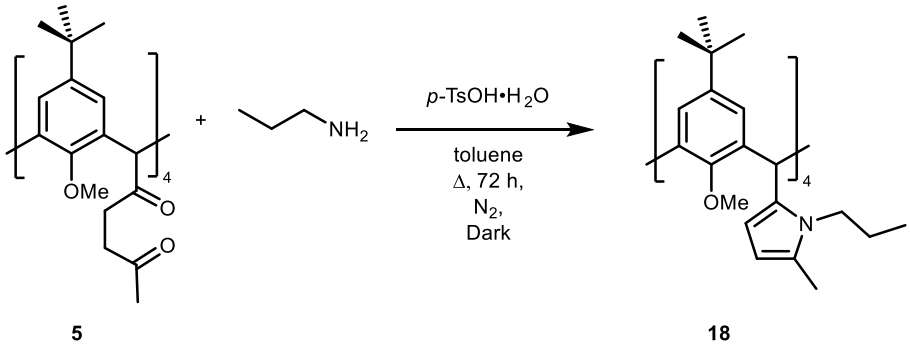


Figure 3.1. General scheme for the Paal-Knorr synthesis using **5** and a series of primary amines. Amine reactants to be trialled are seen below the scheme where, R = $-(CH_2)_2CH_3$, $-(CH_2)_5CH_3$, $-(CH_2)_{15}CH_3$, $-NHCOOC(CH_3)_3$.

3.2.1. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(1-propyl-2-methyl-1H-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 18.

Propyl amine was the first amine to be investigated. The reaction of diketone **5** and propyl amine was heated at reflux in toluene for 3 days using *p*-TsOH·H_2O as a catalyst.

Following workup, a light brown crude was obtained and purified via column chromatography affording the desired product **17** in 31% yield, which translates to a 75% yield per position (Scheme 3.1).



Scheme 3.1. Synthetic scheme for the preparation of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(tert-butyl(1-propyl-2-methyl-1H-pyrrole)-25,26,27,28-tetramethoxy-calix[4]arene, **18**.

Inspection of the ^{1}H NMR spectrum shows the distinctive diketone backbone handles mentioned in Chapter 2 had disappeared, with appearance of a new set of doublets at 5.82 and 5.79 ppm, ($^{3}J_{H\text{-}H}$ = 3.3 Hz). This is indicative of successful pyrrole formation. Suitable single crystals for X-ray diffraction analysis were grown from slow evaporation of a saturated chloroform solution containing **18**. The colourless crystals were found to be in a monoclinic unit cell and structure solution was carried out in the space group *P*2/*c*. The ASU was found to contain half of a molecule of **18** which, upon symmetry expansion, afforded a full molecule in the pinched cone conformation as shown in Figure 3.2. The conformation in solution is most likely also the pinched cone, evidence for which comes from the splitting of signals in the ^{1}H NMR spectrum, displaying two different *t*-Bu, O-Me and Ar-H environments. All pyrrole groups were found to be in the equatorial position with the *N*-substituent pointing towards the lower-rim (Figure 3.2). Two pyrrole groups on each side of the C[4] can be seen facing one another in the region at which the C[4] rings splay outwards. This is seen to occur in all the previous examples when the pyrrole ring is substituted apart from the N-H pyrrole MeOH structure previously synthesised by Fong *et al.*. In this example the crystal structure still displays the pinched cone conformation however the pyrroles are facing each other towards the 'pinched' region of the C[4], hydrogen bonding to methanol of crystallisation (Figure 3.3). The ^{1}H NMR

spectrum of the NH-pyrrole derivative only shows one distinct signal for each environment and is therefore believed to be fluxional in solution compared to substituted pyrroles (which are theorised to be less fluxional due to the extended groups substituted at the pyrrole nitrogen atom). This would suggest that the extra steric bulk possessed by the substituents forces the C[4] to adopt a pinched cone conformation.

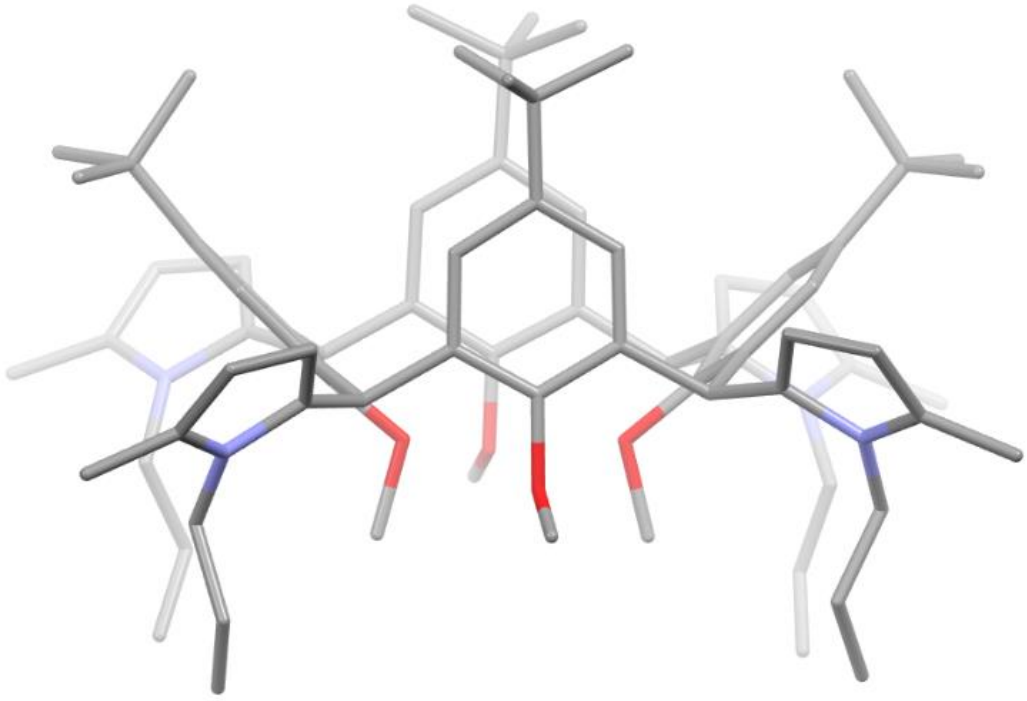


Figure 3.2. Stick representation of the single crystal X-ray structure of **18** showing a propyl substituent appended to the N atom of the pyrrole. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

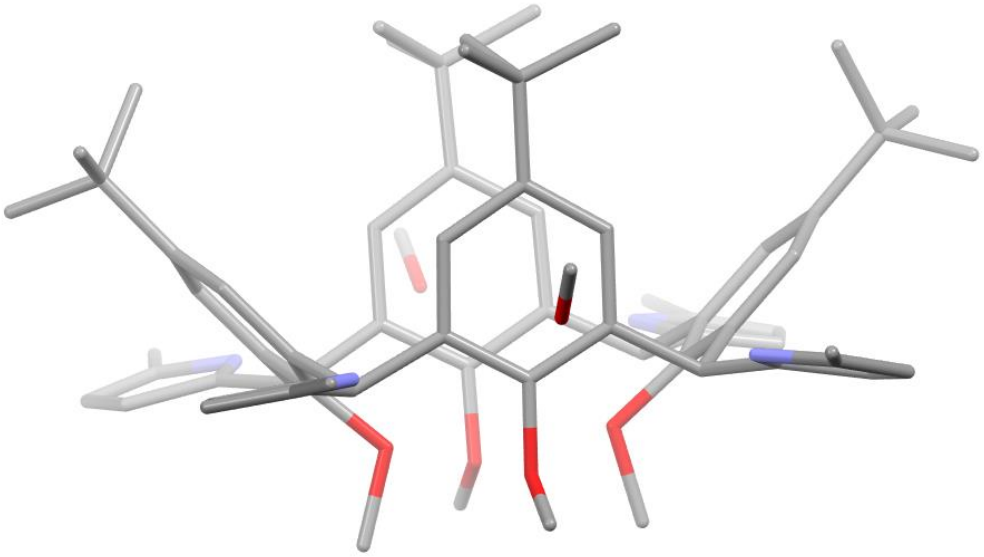


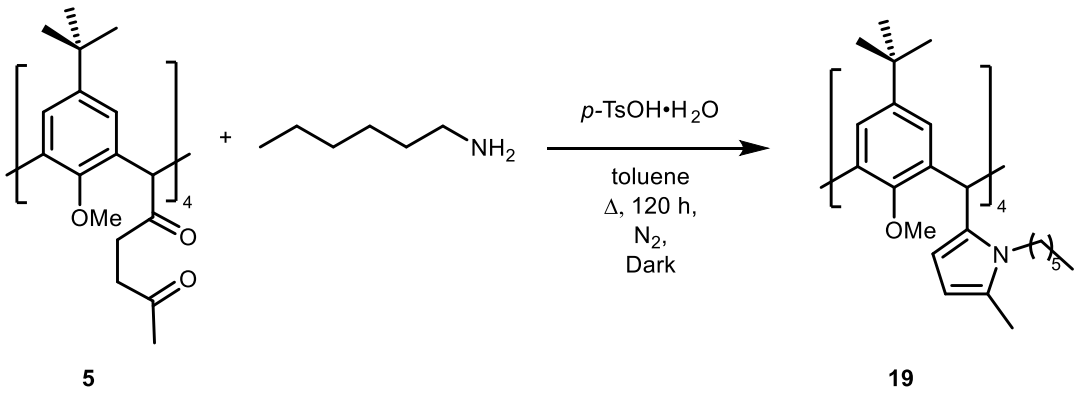
Figure 3.3. Stick representation of the single crystal X-ray structure of a methylene bridged substituted N-H pyrrole with two bonding methanol's previous synthesised by Fong.[3] Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity

3.2.2. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(1-hexyl-2-methyl-1H-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 19.

The next reaction to be investigated was Paal-Knorr pyrrole synthesis using hexylamine. It was anticipated that this would afford a C[4] with increased solubility that can be exploited in the future when investigating the deprotection of these compounds, particularly as it is known that overall solubility generally decreases upon moving from lower-rim methoxy to hydroxyl groups. The standard reaction conditions used previously were employed, with hexylamine and **5** being reacted in the presence of *p*-TsOH·H_2O under N_2 whilst being wrapped in aluminium foil (Scheme 3.2).

This formed a light brown crude which afforded **19** upon purification via column chromatography. It was noted that wrapping the apparatus and solution in aluminium foil to help prevent light degradation actually increased the yield from 26% to 59% in this case, a greater than two-fold increase. Inspection of the ^{1}H NMR spectrum shows that the diketone signals had fully disappeared and a new set of doublets had emerged more

downfield at 5.78 and 5.82 ppm. This is indicative of pyrrole formation and the ^{3}J coupling provides further evidence at 3.4 and 3.2 Hz respectively, these being values typical of those found in previous examples involving anilines in the previous chapter.



5 **19**

Scheme 3.2. Synthetic scheme for the preparation of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(tert-butyl(1-hexyl-2-methyl-1H-pyrrole)-25,26,27,28 tetramethoxycalix[4]arene, **19**.

Multiple other alkyl signals were also observed, the most downfield of which was an expected triplet located at 3.66 ppm corresponding to the CH_2 directly bonded to the nitrogen of the pyrrole (-N-$\underline{CH_2}$-CH_2-). Due to the electronegativity of the nitrogen atom, electron density is being pulled away from the methyl group and de-shielding the nuclei which in turn results in a downfield shift in the ^{1}H NMR spectrum. A single crystal suitable for X-ray diffraction analysis was obtained from slow evaporation of acetone and the structure is shown in Figure 3.3. The crystals were found to be in triclinic unit cell and the structure solution was carried out in the space group $P\bar{1}$. The ASU was found to contain one full molecule of **19** in the pinched cone conformation. From the crystal structure it is clear to see that all four positions of the diketone have been ring closed, forming four hexyl substituted pyrroles as expected. These pyrroles are again all equatorial and oriented towards the splayed region of the C[4]with its substituents facing towards the lower-rim.

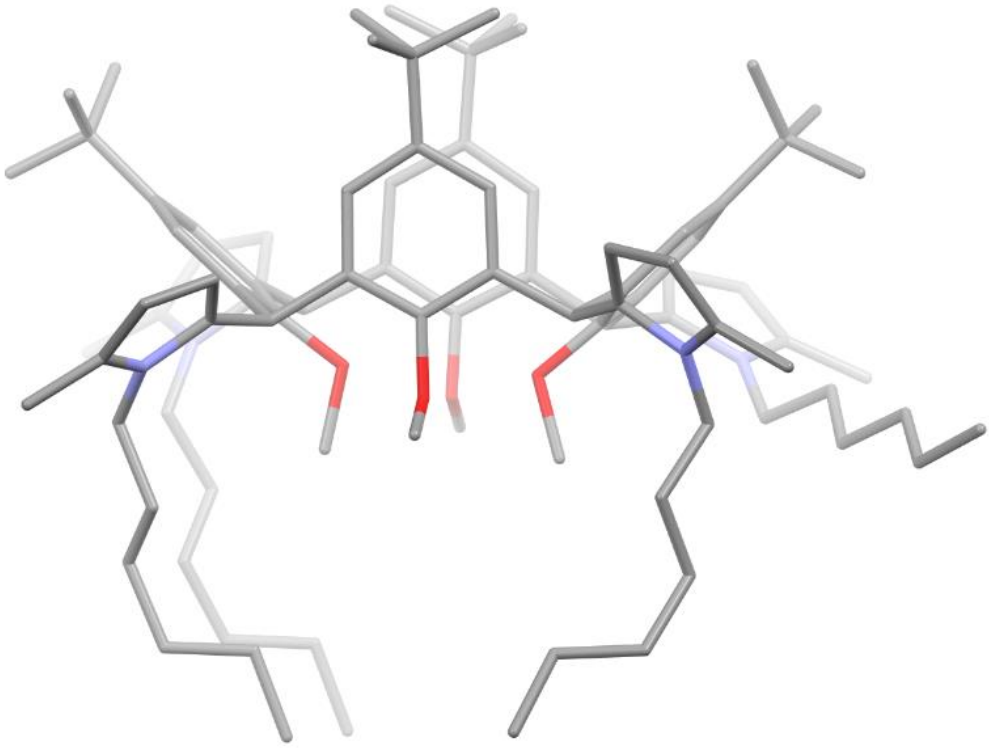
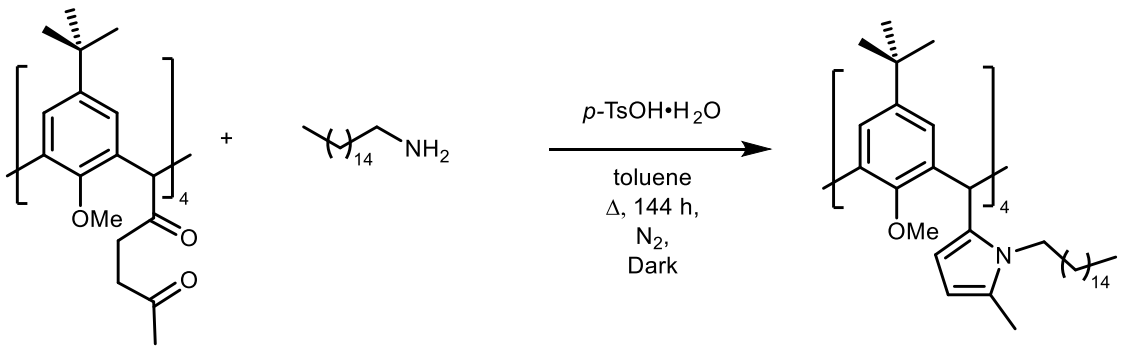


Figure 3.3. Single crystal X-ray structure of **19** showing a hexyl substituent appended to the N atom of the pyrrole. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

3.2.3. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(1-hexadecan-2-methyl-1H-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 20.

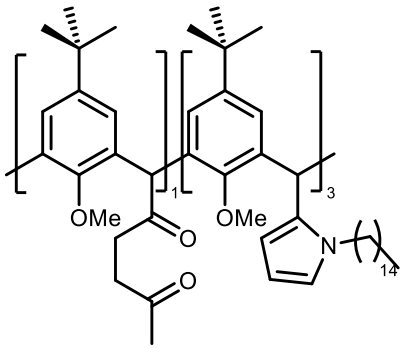
The next amine to be tested was hexadecylamine, which was chosen to investigate whether there was a limit to the length of amine chain that could be substituted, but also how this might affect the properties of the C[4]. Although longer amine chains exist, hexadecylamine is commercially available and relatively cheap, so was a good candidate for this study. The reaction of **5** with hexadecylamine under the standard reaction conditions laid out previously afforded an oily brown crude (Scheme 3.3).



5 **20**

Scheme 3.3. Synthetic scheme for the preparation of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(tert-butyl(1-hexadecyl-2-methyl-1H-pyrrole)-25,26,27,28-tetra-methoxycalix[4]arene, **20**.

Inspection of the ^{1}H NMR spectrum showed loss of the diketone signals and concomitant emergence of signals in both the alkyl and aryl regions, indicating that synthesis had been successful. A set of doublets was observed in the aryl region at 5.80 and 5.84 ppm with ^{3}J coupling constants of 3.1 and 3.3 Hz respectively, all of which is consistent with what that seen previously for the propyl and hexyl analogues. Mass spectrometry (ESI-MS) was also used to confirm synthesis and clearly indicated a m/z $[M+H]^{+}$ peak at 1919.66. Two products were isolated both as brown oils following purification via column chromatography. The first was that of the desired tetra-substituted product and was confirmed through ^{1}H, ^{13}C and IR spectroscopies, and mass spectrometry. As this compound remained as an oil it was thought the long chain length had lowered the melting point below room temperature and therefore that it could be solidified by cooling down. Placing in a -20 °C freezer had no effect and therefore to reach lower temperatures liquid nitrogen (-90 °C) was used. Upon cooling the liquid solidified and could be manipulated as a solid, however upon warming the compound returned to it's original state. This indicates that the melting point is in the region of -20 to -90 °C. Further work is needed here to determine the exact melting point of the compound but it was not possible to explore this further due to time constraints.



21

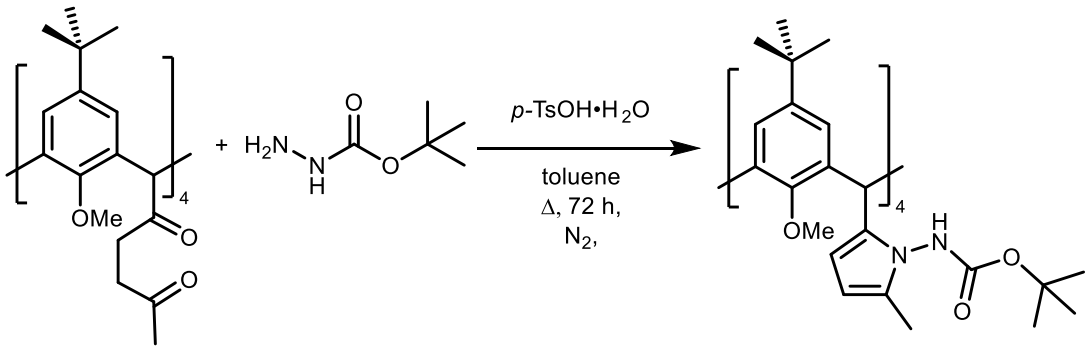
Figure 3.4. Chemical representation of **21** the alternate product isolated from the reaction in in Scheme 3.3.

The second compound isolated from column chromatography was thought to be the tris substituted product **21** (Figure 3.4). Analysis using ^{1}H NMR spectroscopy showed multiple signals in all regions of the NMR spectrum indicating that the compound had been desymmetrised. The upper-rim *t*-butyl, and lower-rim OMe environments which are commonly used to quickly determine the symmetry of the molecule were investigated. The *t*-butyl and OMe signals are both split into four different environments. Examination of the indicative diketone signals showed that a small set of multiplets remained visible in that region of the spectrum. Further evidence for a tris substituted product came from the IR spectrum which clearly showed a carbonyl stretch at 1716.98 cm^{-1}. The ^{13}C NMR spectrum showed two signals at 207.36 and 209.20 ppm, further indicating that carbonyls are still present and ESI-MS found an m/z peak at 1752.40 m/z corresponding to $[M+K]^{+}$. This compound was also found to exist as an oil at room temperature and so therefore no crystal was obtained. No further investigation was performed on this compound due to the small amounts obtained.

3.2.4. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(2-methyl-1H-pyrrole)carbamate)-25,26,27,28-tetramethoxycalix[4]arene, 22.

Previous work in this group investigated the reaction between *tert*-butylcarbazate and the saturated diketone **5** as a way of introducing a protected NH_2 group to the bridge which, in turn, could be deprotected and would afford NH_2 groups and allow for further synthetic

transofrmation.[4] Reaction of **5** with *tert*-butyl carbamate in the presence of *p*-TSOH•H_2O as a catalyst at reflux in toluene for 72 hours afforded a yellow crude which was purified by column chromatography to afford **22** as an off white powder in 42.5 % yield equating to an 80 % yield per position. (Scheme 3.4).



5 **22**

Scheme 3.4. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(2-methyl-1H-pyrrole)carbamate)-25,26,27,28-tetra-methoxycalix[4]arene **22**.

Analysis of the ^{1}H NMR spectrum in chloroform-d showed complete loss of the diketone signals at 2.93 and 2.81 ppm with multiple contaminants growing in, as well as splitting in the *t*-butyl region. This is commonly observed in product formation as the conformation changes from a cone with C4v symmetry to a pinched cone with C2v symmetry. Additional signals in this region are noted as having double the integration which can be attributed to the tert-butyl group off the pyrrole. All the signals through the NMR were however still quite broad. This was ascribed to free rotation around multiple bonds and attempts to lock with NaI at the lower-rim were unsuccessful. An IR spectrum of the product was recorded and a band at 3230 cm^{-1} could be seen which was attributed to the N-H stretch. A single crystal suitable for X-ray diffraction analysis was grown from a saturated ethyl acetate solution. Crystals were observed to be contained in an orthorhombic unit cell and the structure solution carried out in space group *Pbcn*. The ASU contained one half of molecule of **22** and upon symmetry generation afforded the full calix[4]arene in the pinched cone conformation (Figure 3.5).

Inspection of the crystal structure displayed in Figure 3.5 shows that the ring has closed, forming the desired product. Bond lengths for the N-NH were 1.379(7) and 1.378(8) Å which is in a typical range for other similar N-N single bonds found in the CSD.[5] Solvent

of crystallisation has been removed using a solvent mask as these were heavily disordered and could not be modelled effectively. Examination of the packing in the crystal lattice shows hydrogen bonding interactions between the N-H and carbonyl groups of two carbamate groups, whilst the remaining carbamate groups point towards the lower-rim of the calixarene as shown in Figure 3.6. The N-H···O bond distances were calculated to be 2.001(2) Å, this is again comparable to structures already reported in the literature.[6]

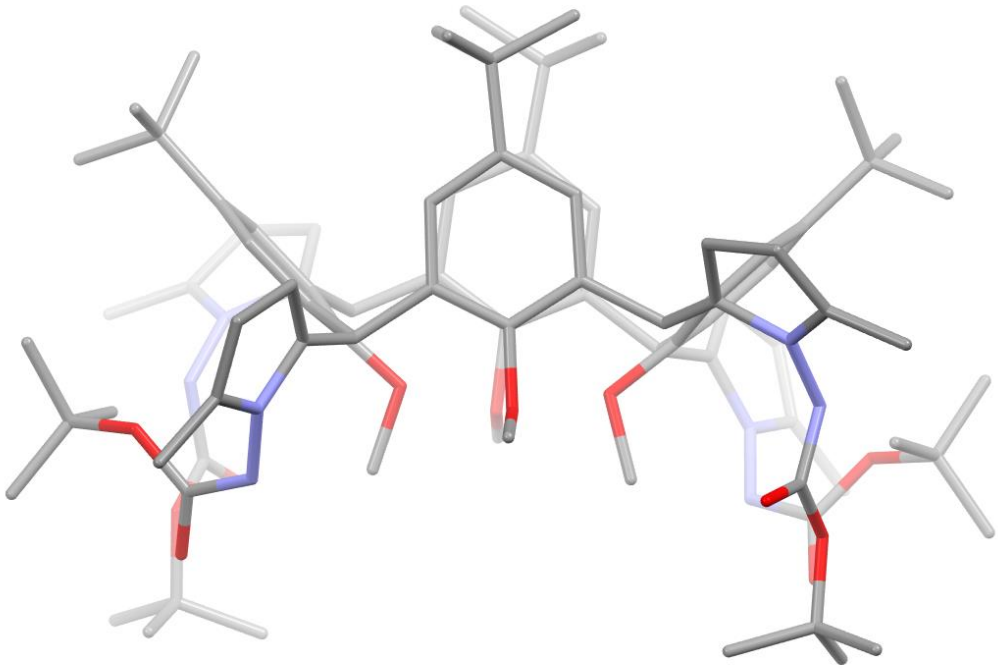


Figure 3.5. Sticks representation of the single crystal X-ray structure of **22** showing a tert-butyl carbamate substituent appended to the N atom of the pyrrole. Solvent of crystallisation (ethyl acetate) was unable to be modelled and so a mask was applied. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

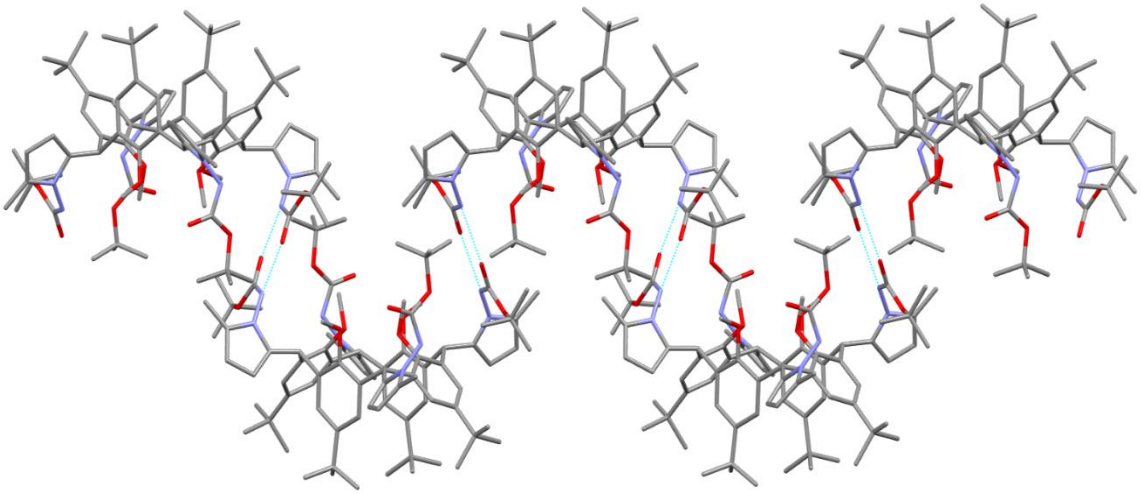
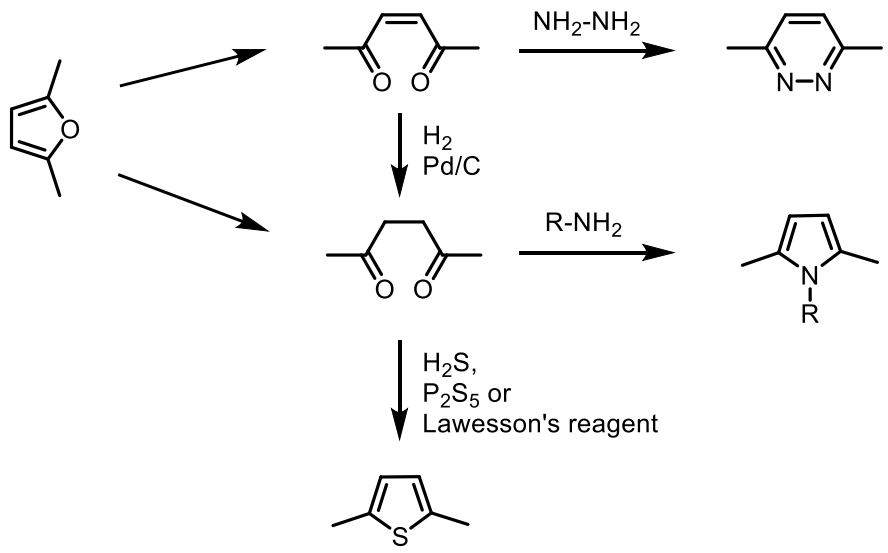


Figure 3.6. Sticks representation of the partial single crystal X-ray structure of **22** showing the packing arrangement dominated by intermolecular interactions between the N-H and carbonyl. Colour code C - Grey; O - Red; N - Blue. H-Bonding interactions are shown as light blue dotted lines. H atoms omitted for clarity.

3.3. Alternative Derivation of Methylene Bridge Substituted Calix[4]arenes using the Tetrafuranyl Derivative.

Furans are known as synthetically diverse molecules[7] and so far in this thesis only one derivation has been discussed, that being the acidic ring opening wherein the furan is hydrolysed to afford a saturated diketone that is subsequently ring-closed through the Paal-Knorr pyrrole synthesis by reacting with a primary amine and acid catalyst. The Paal-Knorr synthesis can also be used to form thiophenes from saturated 1,4 diketones, which is typically achieved using hydrogen sulfide,[8] di-phosphorus pentasulfide (P_2S_5)[9] or Lawesson's reagent (LR).[10]

Another possible synthetic route involves reacting a furan with a peroxy acid (such as *meta*-chloroperbenzoic acid, *m*CPBA) to undergo an oxidative ring opening to afford an unsaturated diketone.[11] This can then be reacted with hydrazine, forming a 6-membered heterocycle known as a pyridazine. This is summarised in the scheme below. (Scheme 3.5)

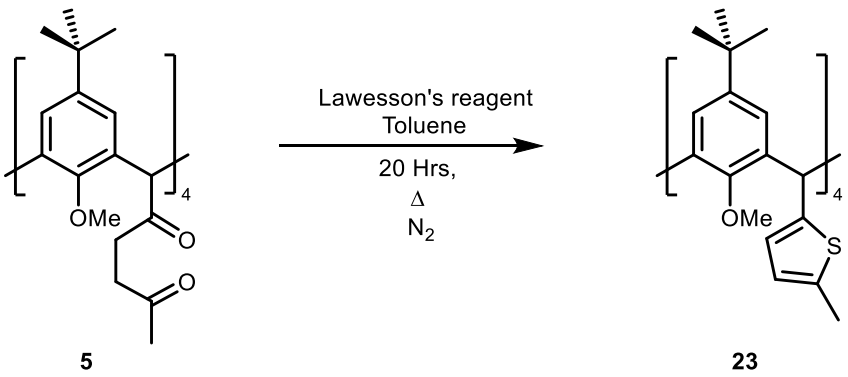


Scheme 3.5. Synthetic scheme displaying different derivation of a furan moiety and the subsequent reactions forming various heterocycles.[7]

Work by Fong previously attempted the synthesis of the tetra thiophene derivative using H_2S, however all attempts proved unsuccessful and time constraints prevented further investigation.[2] Therefore, in this project it was decided to explore different methods for forming the thiophene, as it is a target of interest for coordination clusters and catalysis and is structurally relatable in some respects to thiacalix[4]arenes.[12,13]

3.3.1. Synthesis of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(2-methylthiophene)-25,26,27,28-tetramethoxycalix[4]arene, 23.

The reaction of **5** with di-phosphorus pentasulfide was investigated using a modified procedure from Orito *et al*.[14] The reaction was worked up and crude analysed via ^{1}H NMR spectroscopy, returning just starting material. Compound **5** was then reacted with Lawesson's reagent using a modified literature procedure from Lichtenthaler and co-workers.[11] Saturated diketone **5** was heated in toluene at reflux with Lawesson's reagent under N_2 for 20 hours (Scheme 3.6).



5 23

Scheme 3.6. Synthetic scheme for the preparation of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(2-methylthiophene)-25,26,27,28-tetramethoxycalix[4]arene, **23**.

Analysis of the ^{1}H NMR spectrum shows the distinctive diketone signals to have disappeared whilst new signals further downfield in the aromatic region had grown in, which is expected given the composition of thiophene. Purification via column chromatography afforded an off-white powder, the ^{1}H NMR spectrum of which showed the desired product along with slight impurities. Interestingly, these other signals also appeared in similar regions to the desired product and therefore were assumed to be that a different substituted C[4]. Recrystallisation from $CHCl_3$/MeOH or EtOAc/MeOH afforded an off white crystalline product, but analysis by ^{1}H NMR showed that slight impurities remained. ASAP-MS confirmed that the desired product had formed as peaks at 1089.50 and 1090.50 corresponded to $[M^+]$ and $[M+H]^+$. Continual recrystallisation using EtOAc afforded pure **23** and therefore full characterisation was achieved. A single crystal suitable for X-ray diffraction was grown from a saturated solution of ethyl acetate. The single crystals were observed to be contained in a monoclinic unit cell and structure solution carried out in the space group $P2_1/m$. The ASU contained one half of **23** which, upon symmetry generation, afforded the full molecule as shown in Figure 3.7.

Inspection of Figure 3.7 shows that the diketones have ring closed, forming thiophenes at every equatorial bridge position. The crystal structure shows the calixarene to display the pinched cone conformation, however, as was the case for the furanyl and N-H pyrrole analogues, no evidence for the pinched cone is found in the ^{1}H NMR spectrum as only 1 signal corresponding to the *t*-butyl and OMe signals are seen. This would indicate that the thiophene is not bulky enough to lock the conformation in solution and is therefore

fluxional. The average bond lengths for the C=C range between 1.332(4) - 1.369(3), C-C between 1.411(3) - 1.423(3) and C-S between 1.699(3) – 1.731(2) Å which are typical bond lengths for a thiophene when compared to similar compounds found in the CSD.[15,16]

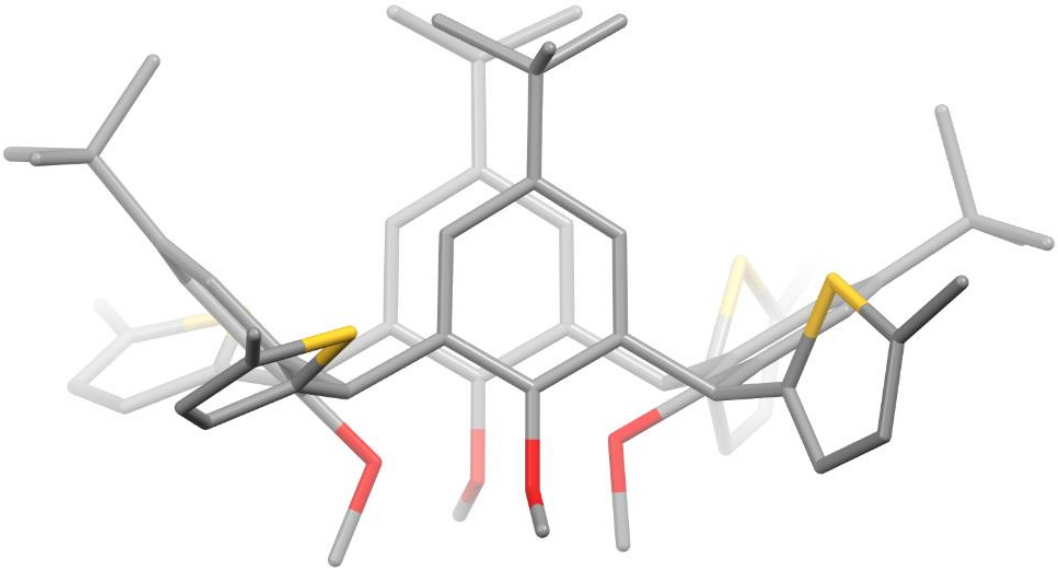


Figure 3.7. Single crystal X-ray structure of **23** showing a 2-methyl thiophene substituent appended off the equatorial bridge position of a calix[4]arene. Colour code C - Grey; O - Red; S - Yellow. H atoms omitted for clarity.

The impurity found in the sample was believed to be another substituted C[4] due to the overlapping nature of signals in the ^{1}H NMR spectrum. One distinctive set of signals attributed to the impurity was that of two doublet of doublets and a singlet, something very commonly seen in the NMR of the **4**, the furanyl analogue. A review of the literature indicates that furans can be formed when using Lawessons reagent[10] and therefore it was theorised that a furan was being formed at the bridge simultaneously with thiophenes.

Due to the overlapping nature of the signals in the ^{1}H NMR spectrum it wasn't possible to assign the different environments of this second product. Analysis using ASAP-mass spectroscopy identified two other peaks of interest, 1073.50 and 1057.55 m/z, which correspond to a tris-thiophene-monofuran and dithiophene-difuran substituted calix[4]arene. Having discovered this possibility, a search of the literature found a study by Taddei and co-workers showing that when reacting substituted 1,4-hexanediones with

Lawesson's reagent the major product was the thiophene derivative but also isolating between 10-25 % of the corresponding furan.[17] They go on to mention how using a large excess of LR can prevent furan formation. Therefore, a reaction involving a large excess (20 equivs) of LR was trialled. Analysis of the crude ^{1}H NMR integrals of impurity to product were the same as seen previously when using 4 equivalents, however this was much harder to purify due to the large amounts of unreacted LR present.

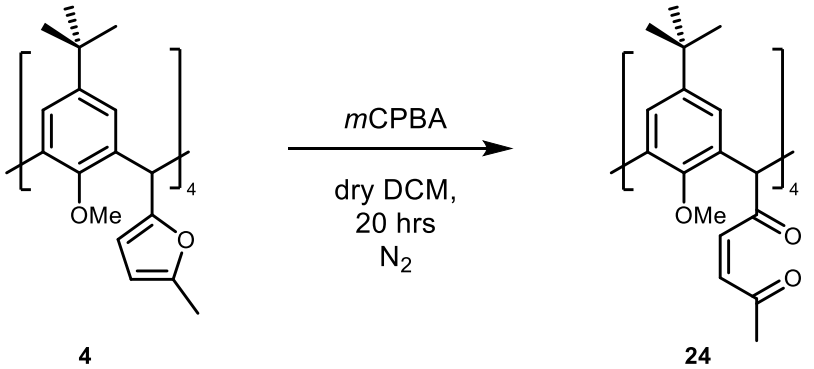
Another method trialled was that using a nucleophilic substitution route previously employed in the synthesis of **4**. Biali *et al* synthesised a variety of methylene bridge-substituted calix[4]arenes[18] by applying the work of Mayr and co-workers who reported that Friedel-Craft alkylations could be conducted with the absence of a Lewis acid in alcoholic solutions.[19] Compound **3** was heated at reflux with 2-methylthiophene in tri-fluroethanol (TFE) however no product was observed upon workup. It is thought that due to the lower nucleophilicity parameter for 2-methyl thiophene being roughly equal to that of the solvent that it could not displace the alcohol.[19] Biali and Columbus managed to substitute *m*-xylene which exhibits a much lower nucleophilicity parameter than 2-methyl thiophene onto the bridge of a calix[4]arene using a lower nucleophilic solvent, hexafluoroisopropanol (HFIP).[18] If time permitted it would have been interesting to try using this method as it would reduce the number of steps needed to synthesise **23** and also avoid the formation of furan substituents which are difficult to separate.

3.3.2. Unsaturated Diketone and Tetra-Pyridazine TBC[4] Synthesis, 24, 25.

Previous work in this group involved the synthesis of a tetra-substituted C[4] displaying pyridazine functionality off each methylene bridge and preliminary investigation into the deprotection of the lower-rim OMe groups was undertaken.[2] These results proved to be promising and so therefore in order to further probe the deprotection, the pyridazine compound was resynthesised in this study and a brief description of the synthesis is described.

3.3.3. Synthesis of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(pent-2-ene-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, 24.

As seen in Scheme 3.5, many different derivations of the furan can be achieved. In order to introduce pyridazine functionality an unsaturated 1,4 diketone must first be synthesised. This oxidative ring opening reaction is carried out by stirring **4** with mCPBA in DCM at room temperature under N_2 (scheme 3.7) It was found that when performing this reaction unwanted by products were forming resulting in lower yields and longer purification processes. This could be reduced by using dry solvents and Schlenk line techniques, leading us to conclude that other oxidation products must have been forming.



4 24

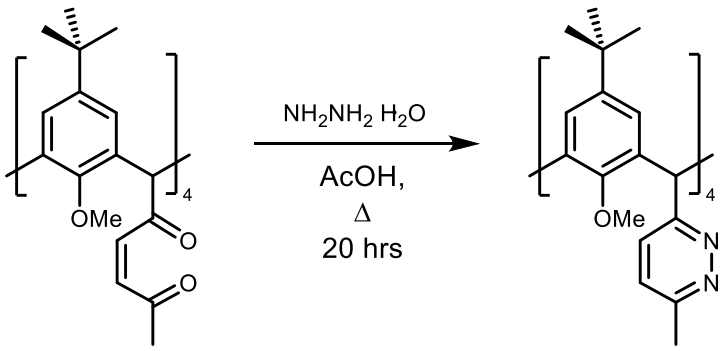
Scheme 3.7. Synthetic scheme for the preparation 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(pent-2-ene-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, **24**.

Compound **24** was purified via column chromatography and purity was determined by comparison of the ^{1}H NMR spectrum with that previously synthesised by Fong. This was deemed to be pure enough to progress to the next reaction in the sequence.

3.3.4. Synthesis of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(3-methylpyridazine-25,26,27,28-tetramethoxycalix[4]arene, 25.

The next step was to ring close the unsaturated diketone to afford the pyridazine analogue. This was achieved by heating **24** in acetic acid at reflux with hydrazine monohydrate. The

crude product was purified using column chromatography to afford **25** in 60% yield (scheme 3.8). As was the case for **24**, the purity of **25** was determined through comparison with the ^{1}H NMR spectrum of a previously synthesised pure sample.



24 **25**

Scheme 3.8. Synthetic scheme for the preparation 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(3-methylpyridazine-25,26,27,28-tetramethoxycalix[4]arene, **25**.

3.4. Deprotection of Methylene Bridge Functionalised Calix[4]arenes.

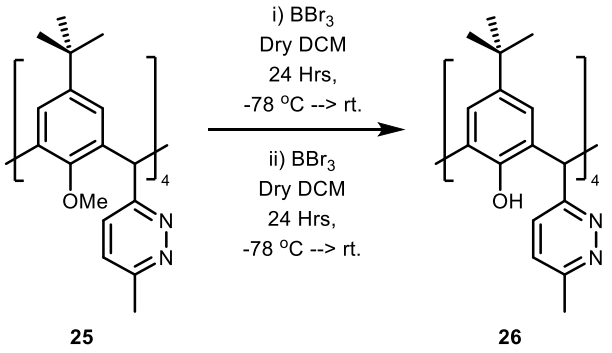
Deprotection of the lower-rim methoxy groups facilitates reintroduction of the hydroxyl groups and allows access to the lower-rim binding pocket. This in conjunction with the newly formed peripheral groups should allow novel and interesting metal coordination and cluster formation. Previously, demethylating agents such as iodocyclohexane have been used to great effect. Zuo *et al* showed that iodocyclohexane provided the best yields in the shortest reaction times even compared to the more conventional reagents such as boron tribromide (BBr_3).[20] Iodocyclohexane has been used on the C[4] framework as seen in the previous chapter with **4a** and the previously reported deprotection of **4** which was isolated in 21% yield.[21]

3.4.1 Deprotection of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(3-methylpyridazine-25,26,27,28-tetramethoxycalix[4]arene, 25.

Previous work in the group showed iodocyclohexane to be unsuitable for this reaction and only returned starting material. This was postulated to be due to the steric bulk of the pyridazine groups hindering the demethylation step. Boron tribromide (40 equivalents) was therefore trialled and reaction with **25** over 24 hours afforded a mixture of products determined to be the mono-, di- and tri- hydroxycalix[4]arene products, as confirmed using mass spectrometry and ^{1}H NMR spectroscopy. This indicated that the reaction was progressing, but not going to completion. Hardman *et al* previously reported fully demethylating a C[4] substituted with a chloroalkyl chain at the methylene bridge using 6.5 equivs of BBr_3 over 14-20 hours,[22] possibly supporting the hypothesis that bulky groups at the bridge hinder demethylation at the lower-rim. Increasing the time of the present reaction to 48 hours, following progress using TLC, mass spectroscopy and NMR spectroscopy, it was clear that a mixture was still forming but evidence for a fully demethylated species was observed. Using this information, and knowing that extending the reaction time resulted in further demethylation, the reaction was left for 7 days to stir at room temperature. Following aqueous workup, analysis of the ^{1}H NMR spectrum again showed a large mixture of products that was near identical to the 48 hour reaction mixture. Fantini and co-workers found that a mixture of partially demethylated products was also observed when demethylating a methylene bridge linked bis-C[4] using BBr_3. Therefore they employed a two-step protocol whereby the reaction was fully worked up before using a second equivalent of BBr_3.[23] This was thought to avoid the build-up of borate esters formed in the reaction and stop them interfering with the demethylation process. Hence a modification of this process was used as shown in Scheme 3.9.

Compound **25** was dissolved in dry DCM, cooled to -78 ºC before 20 equivalents of BBr_3 was added dropwise over 15 minutes, this was then kept at -78 ºC for 1 hour before leaving to heat to room temperature and stirred for 24 hours. Analysis of the ^{1}H NMR spectrum displayed mostly mono- and di- methoxy products. After a second addition of BBr_3 following the same method as above the ^{1}H NMR spectrum displayed one methoxy signal corresponding to the tri-hydroxy product. The reaction mixture was purified via column chromatography to afford a fully demethylated species in 5% yield. During the reaction of **25** with BBr_3 a brown solid could be seen crashing out immediately upon

addition and it was thought that if this could be reduced would help the reaction go towards completion.



25 **26**

Scheme 3.9. Synthetic scheme for the demethylation of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(3-methylpyridazine-25,26,27,28-tetramethoxycalix[4]arene, **25** using a two stage protocol to afford 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(3-methylpyridazine-25,26,27,28-tetrahydroxycalix[4]arene, **26**.

A crystal grown from chloroform confirmed the formation of the fully demethylated species (Figure 3.9). The crystal was found to be in a tetragonal unit cell and the structure solution carried out in space group $I\bar{4}$. The ASU contains one quarter of a calix[4]arene which upon symmetry generation affords the whole molecule as shown in Figure 3.9. From the crystal structure it can be seen that all four of the hydroxyl groups have been reformed and the calix[4]arene has adopted the 1,3 alternate conformation due to the hydrogen bonding interactions with the pyridazine ring. The pyridazine is facing towards the lower-rim hydroxyls adjacent to it whereby the nitrogen in the 2-position of the ring hydrogen bonds to lower-rim hydroxyl groups. The O-H···N hydrogen bond distance here was calculated to be 1.944(2) Å. Due to the four fold symmetry generated structure the values for each positions are equal. It is expected that upon deprotonation of this compound, and subsequent interruption of the hydrogen bonding, the C[4] would revert to the cone conformation and maintain the rccc conformation. However, due to the low yield of this compound it was decided to move forward with the project and attempt the deprotection of other methylene bridge-functionalised C[4]s.

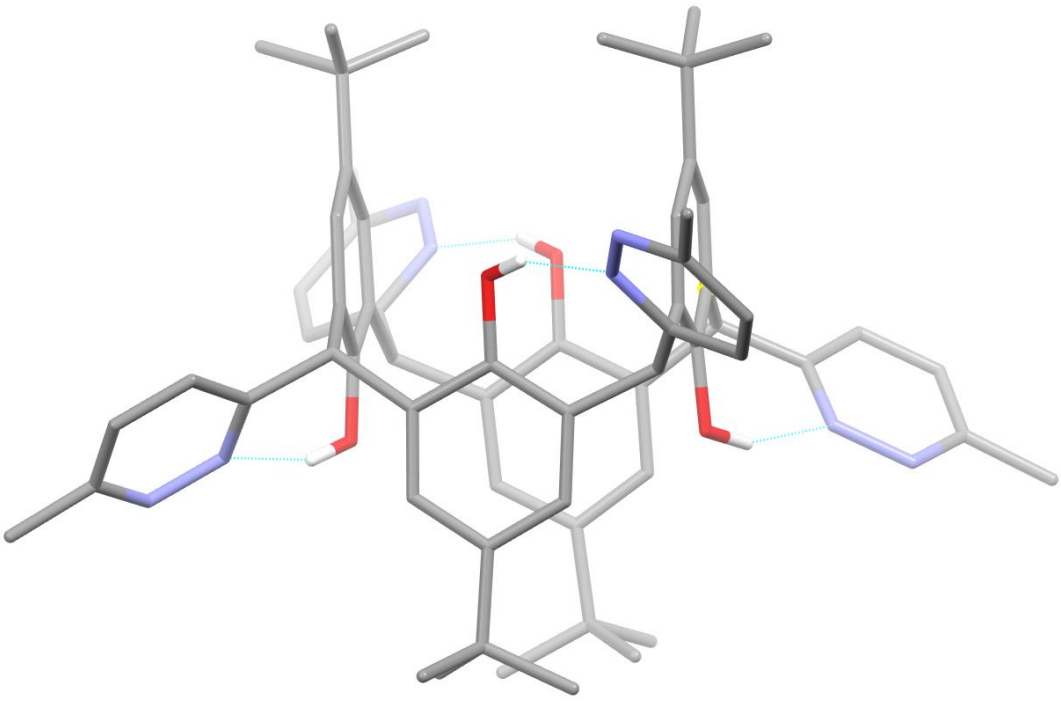


Figure 3.9. Sticks representation of the single crystal X-ray structure of **26** showing the fully demethylated species in the 1,3 alternate conformation due to hydrogen bonding interactions indicated with blue dotted lines. Colour code C - Grey; O - Red; N - Blue, H atoms (apart from those involved in H-bonding) are omitted for clarity.

3.4.2. Deprotection of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(1-hexyl-2-methyl-1H-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 19.

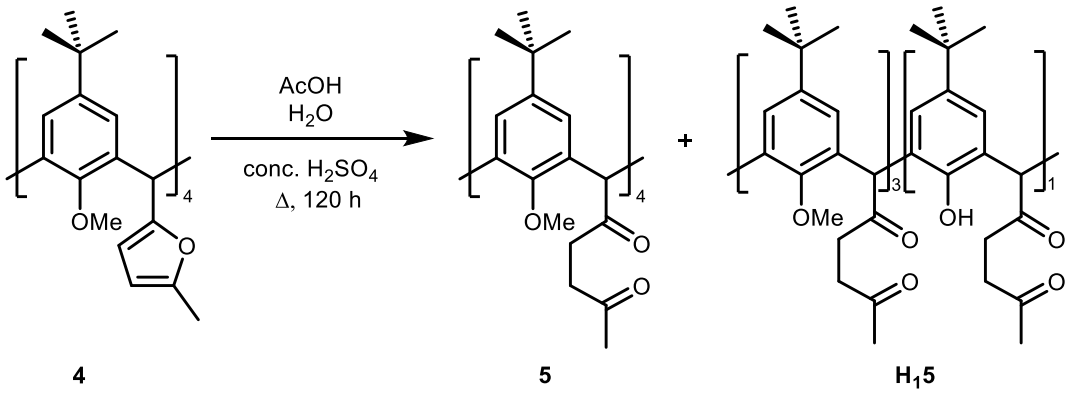
The deprotection of a pyrrole appended C[4] was attempted. The hexyl derivative **19** was chosen due to high yield during its synthesis, easier purification, and given that only one product was seen to form during the reaction. It was thought that solubility and steric bulk was interfering with the deprotection step outlined above, and that the alkyl chain in **19** may assist in reducing these issues; alkane chains are more flexible than the phenyl derivatives which should allow easier access to the methoxy groups and facilitate the deprotection step.

Firstly, the deprotection was attempted using iodocyclohexane as previously utilised. Following a 48-hour reflux in DMF the reaction was worked-up and analysed using ^{1}H

NMR spectroscopy. Unfortunately, this was unsuccessful as no deprotection could be seen. No starting material was observed or able to be recovered, suggesting that the C[4] was potentially degrading. It was theorised that the high temperature could be interfering with the pyrrole and breaking down, and therefore the reaction conditions were too harsh. Having achieved deprotection of the pyridazine using BBr_3 this was then trialled next. The reaction of **19** with 20 equivalents of BBr_3 in dry DCM for 24 hours was attempted. Analysis of the ^1H NMR showed multiple different signals indicating a reaction had taken place, however it was also abundantly clear that the major product was starting material. Work-up and column chromatography afforded a mixed fraction containing starting material **19** and what was believed to be small amounts of the monohydroxy derivative (**$H_1$19)**. This was followed by another fraction isolated in yields < 5% of the dihydroxy derivative **$H_2$19**. This was characterised by inspection of the ^1H NMR spectrum which displayed only one methoxy peak at 3.95 ppm integrating to 6 protons, and a new broad singlet at 5.41 ppm integrating to 2 protons indicative of the OH signal. Subsequent IR analysis showed a broad OH stretch at 3512 cm^{-1}, confirming demethylation. However due to the small yield, no observation of tri/tetra hydroxy products, and mostly unreacted starting material being returned it was decided to explore alternative reaction conditions. An experiment was performed in which the same general reaction conditions were employed, but stirring time increased to seven days with a aliquot being taken and analysed using ^1H NMR spectroscopy periodically. Similar results were observed between 24 and 72 hours with mostly starting material being observed. Additional time resulted in similar demethylation as before, however the spectrum became much more broad, indicating that the compound was degrading. Moseev *et al* avoided using BBr_3 to demethylate a mono-substituted bridge calix[4]arene, instead favouring the previously attempted iodocyclohexane as they found it to either form complex mixtures of various isomers or decomposition of starting material due to the C-C bond on the bridge breaking.[24] A two-step protocol with BBr_3 was also trialled as this was seen to work for the previous demethylation of **25**. However, this was also seen to mostly return starting material and small amounts of **$H_1$19** or **$H_2$19**. It was therefore determined that BBr_3 was unsuitable for the demethylation of compound **19** and so other prospective routes to isolated demethylated species were investigated. Knowing that it was difficult to deprotect once the pyrrole derivative had formed, it should be possible to deprotect before forming the pyrrole as the Paal-Knorr conditions shouldn't impact on hydroxyl functionality. Demethylation of **5** where the saturated diketone was appended should

therefore allow any deprotected pyrrole to form by reversing the order in which the steps are undertaken, performing a Paal-Knorr reaction on a demethylated species. The demethylation of compound **5** was first attempted with using BBr_3 and iodocyclohexane, however limited success was achieved and no demethylated species could be obtained following column chromatography.

Previous work showed that a side product was being formed during the acidic ring opening of **4** using acetic acid, sulfuric acid and water. This side product was discovered to be the mono-hydroxy version of **5** (referred to as **H$_1$5**) and so that reaction was stopped after a 20-hour reflux to avoid the formation of this side product. It is seen in the literature that highly acidic conditions can be used to dealkylate ethers, with Li *et al* reporting that heating a solution of 2-bromo-3,5-dimethoxybenzaldehyde in conc. H_2SO_4 for 14 hours resulted in removal of one methoxy group.[25] It was theorised that this discovery could be utilised and was then trialled to explore whether longer reaction times would lead to formation of other demethylated products. Therefore, the reaction of **4** in acetic acid, conc. sulfuric acid and water was carried out at reflux for 5 days (Scheme 3.10).



Scheme 3.10. Synthetic scheme for the prolonged acidic ring opening reaction of **4** forming a mixture of **5** and the monohydroxy derivative **H$_1$5**.

Following work-up and analysis using ^{1}H NMR spectroscopy it was clear that the reaction had progressed further and **H$_1$5** was now the major product by comparison of the integrals of both the *t*-butyl and OMe signals of the two products. However, no other demethylated species could be identified. The reaction was then purified via column chromatography to afford two products, the major **H$_1$5** in 34 % yield and the minor **5** in 14 % yield equating to an overall yield of 48 % which is comparable to that achieved for the 20-hour reflux of

4 in which the major product obtained is **5**. The synthesis of **H$_1$5** was identified by comparison of the ^{1}H NMR spectrum previously obtained by Fong *et al*.[21]

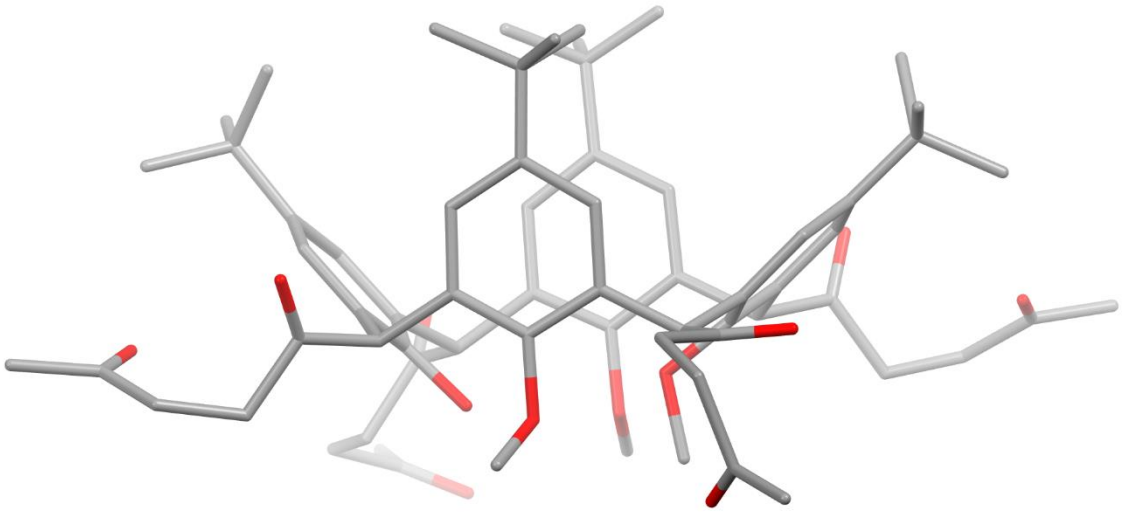


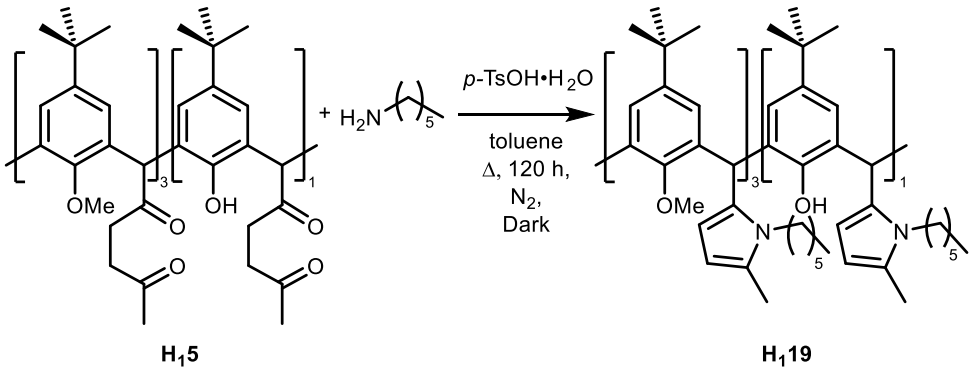
Figure 3.10. Single crystal X-ray structure of **H$_1$5** previously obtained by Fong *et al*[2] in stick representation showing a partially demethylated product in the pinched cone conformation. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.[2]

The *t*-butyl signal which is displayed as a singlet in the ^{1}H NMR spectrum of **5** can now be seen as a set of three individual singlets with an integral ratio of 1:1:2. This aligns with the structure as there are now three distinct *t*-butyl environments. The OMe signals are also seen to appear at two different shifts with integral ratio of 1:2 equalling a total of 9 protons conforming to the structure. Finally, the CH_3 group at the end of the 1,4 diketone of the methylene bridge was noticed to have split into 2 singlets with an equal integral ratio totalling 12 protons. This is due to the mirror plane through the centre of the calix[4]arene passing through the hydroxyl group and the opposite methoxy. The reaction was repeated for a longer period to understand if further demethylated products could be obtained. Following a 10-day reflux a black solid could be seen floating in the reaction vessel, the reaction yield was significantly lower, and no additional demethylation could be identified. It was therefore determined that the reaction conditions were unsuitable to achieve further demethylated products and instead the calixarene was being broken down accounting for the loss in yield and black solid formed. Other reaction conditions were

explored including increasing the concentration of H_2SO_4, using different acids such as HBr or HCl, but these only showed degradation of the calixarene and little to no evidence for ring opening of the furan.

3.4.3. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20- tetrakis(tert-butyl(1-hexyl-2-methyl-1H-pyrrole)-25,26,27,-trismethoxy-28,-monohydroxycalix[4]arene, $H_1$19.

Once the monohydroxy species had been isolated the next reaction investigated was between the monohydroxy diketone **$H_1$5** and hexyl amine. This would allow a functional group tolerance check to determine if the hydroxyl groups being present interfered with the Paal-Knorr reaction. Compound **$H_1$5**, hexyl amine and catalytic amounts of *p*-TsOH·H_2O were heated at reflux in toluene for 5 days whilst also being wrapped in aluminium foil, thus mimicking the reaction conditions for the synthesis of **19** (Scheme 3.11).



$H_1$5 **$H_1$19**

Scheme 3.11. Synthetic scheme for the synthesis of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(tert-butyl(1-hexyl-2-methyl-1H-pyrrole)-25,26,27 tetramethoxy-28-hydroxycalix[4]arene, **$H_1$19**.

Following reflux and purification via column chromatography, analysis of the ^{1}H NMR spectrum showed that the distinctive diketone peaks had disappeared with peaks aligning to the hexyl chain and pyrrole backbone appearing. Two signals for the *t*-butyl environments can be seen with integrals totalling to 36 protons. Interestingly there are three different *t*-butyl environments present, however it is thought that upon pyrrole formation and the conformation adopting the pinched cone the *t*-butyl signals become indistinguishable and so overlap in the spectra; there is evidence for this as one peak is

slightly broader than the other. A similar observation can be seen for the CH_3 of the pyrrole in which it would be expected to display as two singlets, but instead is seen as one slightly broader singlet indicating that the environments whilst different, cannot be resolved on the 400 MHz spectrometer. There are two OMe peaks present at 4.31 and 3.51 ppm with integrals ratio of 1:2 respectively totalling 9 protons due to the mirror plane discussed previously. A suitable single crystal grown from a saturated solution of DCM was analysed using single crystal X-ray diffraction. The unit cell was found to be triclinic, and the structure solution carried out in space group $P\bar{1}$ (Figure 3.11).

The crystal structure shows that the diketones have ring closed, forming four hexyl substituted pyrroles off the methylene bridge with one molecule of DCM sitting in the pseudo cavity. It is noted that the hydroxyl group occupies the splayed position of the calix[4]arene pointing inwards, towards to the lower-rim rather than the parallel 'pinched' position conforming to what is seen previously in **H$_1$5**.

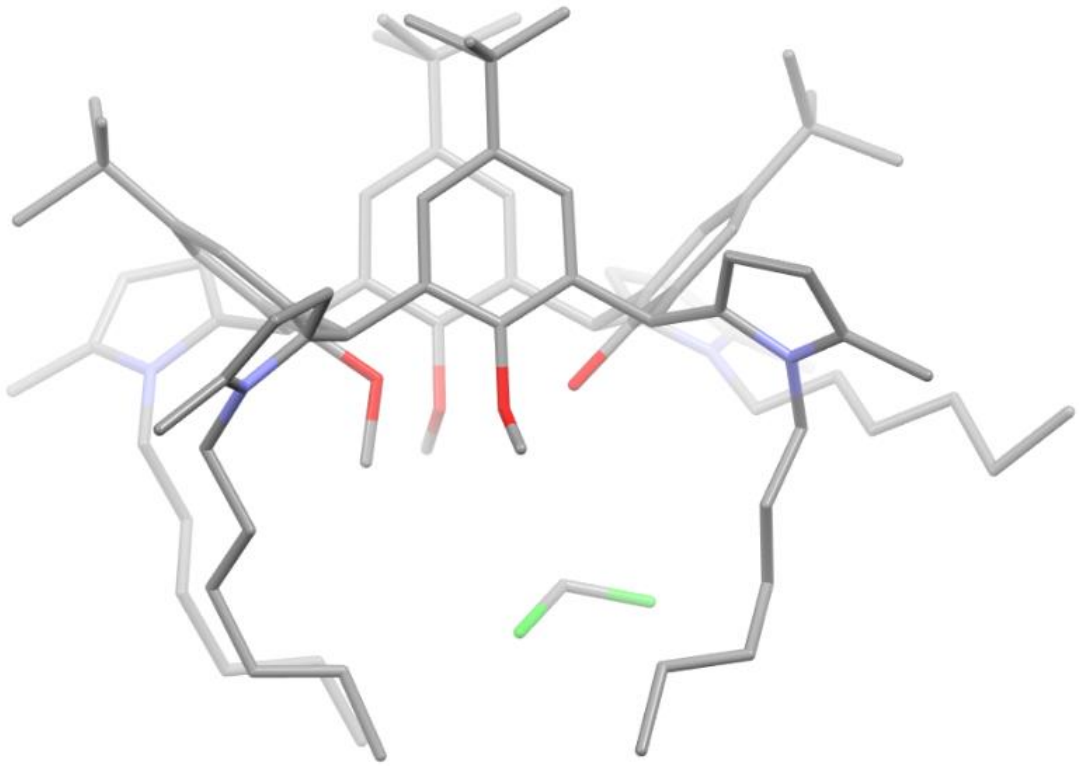
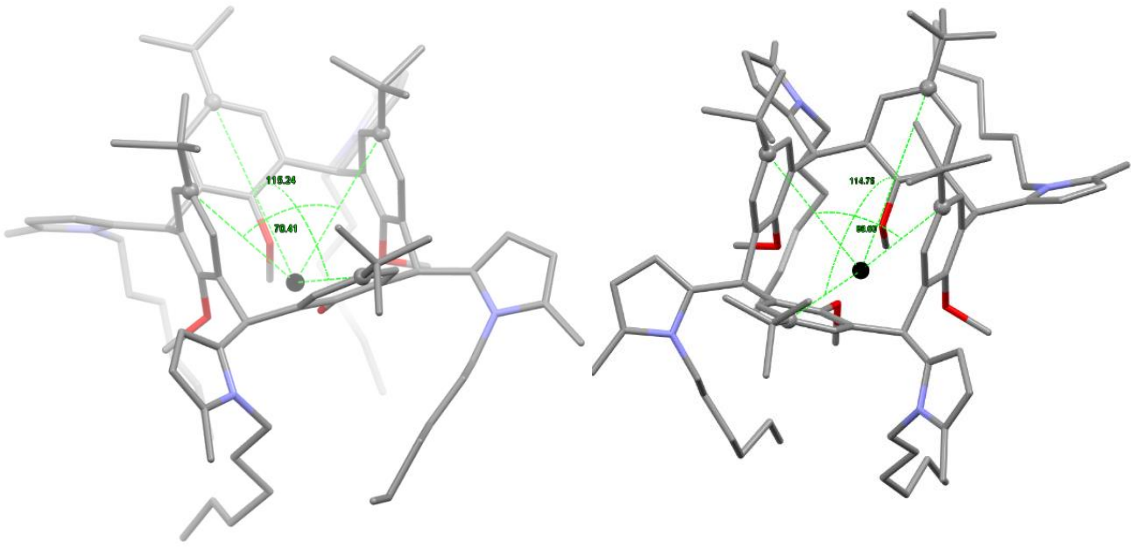


Figure 3.11. Sticks representation of the single crystal X-ray structure of **H$_1$19** showing the partially demethylated species in pinched cone conformation with one molecule of DCM. Colour code C - Grey; O - Red; N - Blue, Cl - Green, H atoms omitted for clarity.

Generating a centroid in the plane of the lower-rim oxygens allows the measurement of an angle which describes the extent to which each C[4] is pinched and we can compare this to that of the fully methylated species **19**. The splayed angle in **$H_1$19** was found to be 115.24°, whilst the pinched angle was measured as 70.41° (Figure 3.12). In comparison to the fully methylated species, **19** has values of 114.75° for the splayed angle and 68.60° for the pinched. There is only a small difference in the pinched and splayed nature of the monohydroxy species. However, one would expect that as more methoxy groups are removed and hydrogen bonding interactions begin to dominate lower-rim behaviour, with reduction in splaying. Future work in this area should focus on the deprotection of **5** as this has proved to be more stable than the pyrrole derivatives, and work in this chapter has indicated that the Paal-Knorr synthesis is viable on the demethylated species. It is believed that compound **5** can be fully demethylated under the correct reaction conditions, although starting from **4** and ring opening whilst also performing the demethylation is almost certainly more difficult. Even though using the standard methods of BBr_3 and iodocyclohexane didn't work, many other deprotection methods are left to investigate[26] and so work on the deprotection the of **5** should be continued.



$H_1$19 **19**

Figure 3.12. Single crystal X-ray structure of **$H_1$19** and **19** showing the different splayed and pinched angles between the top of the phenyl ring and a centroid in the plane of the oxygen atoms. Colour code C - Grey; O - Red; N - Blue, Centroid - Black; H atoms omitted for clarity.

3.4.4. Deprotection of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(2-methylthiophene)-25,26,27,28-tetramethoxycalix[4]arene, 23.

Due to limited time on this project the deprotection of compound **23** has not been fully investigated. However, due to the analogous nature of this compound to furan derivative **4**, which was deprotected without any complications using iodocyclohexane, this was trialed. Following a 48-hour reflux of **23** and iodocyclohexane in DMF a very small amount of a monohydroxy product could be observed forming through ^{1}H NMR spectroscopy analysis. Increasing the time to 72 hours resulted in a very similar spectrum and so it was decided that iodocyclohexane was unsuitable for the deprotection of **23**. If more time were available, other reagents such as BBr_3 would have been trialed.

3.5. Decomposition of Pyrrole Appended Methylene Bridge Calix[4]arenes.

The idea of decomposition has been mentioned throughout the thesis without much explanation up to this point, but a small section on the stability of these compounds is presented here. It is worth noting that the cause or decomposition pathway is not yet fully understood and so the hypothesis in this section is based on observations made during the course of the project.

It was discovered that during the project that the pyrrole appended C[4]s were decomposing. This was first noticed upon attempting to grow single crystals of the products. Multiple vials were set up in different solvent mixtures, using different crystallisation techniques, however when the crystals didn't grow the mixtures were recombined re-analysed via ^{1}H NMR spectroscopy. This showed that no discernable compound product could be identified, and the spectrum was typically very broad and could not be interpreted. An example of a before and after spectrum stacked onto of one another can be seen in Figure 3.13.

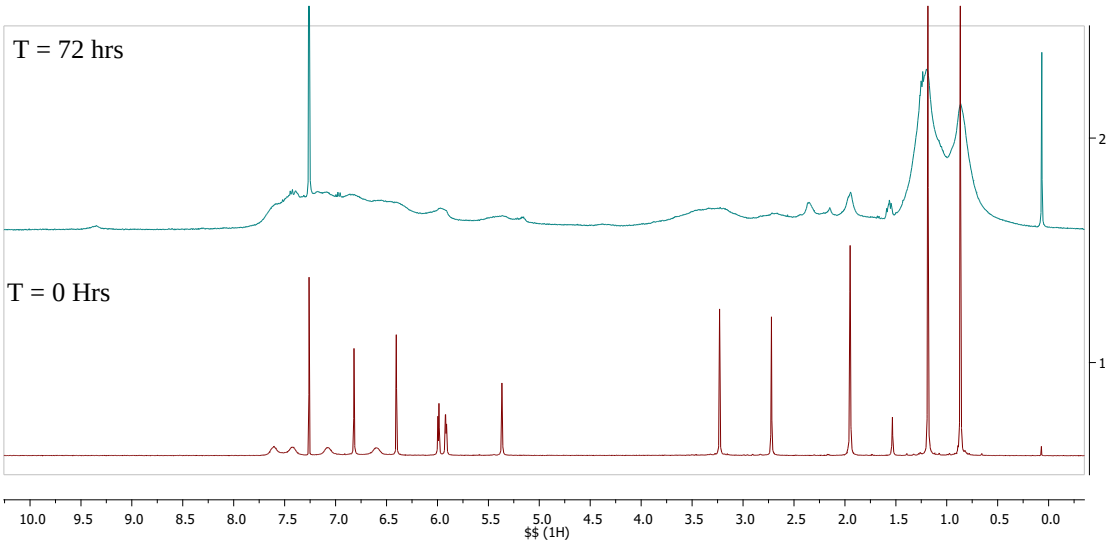


Figure 3.13. A ^{1}H NMR stacked spectrum spectra of **6** before and after being left in solution at ambient temperature and pressure without avoiding any natural light.

Following this discovery, a set of control experiments were carried out to test degradation in light. A set of vials containing 10 mg of a pyrrole appended C[4], in this case a 4-bromophenyl derivative (**6**, due to the high synthetic yield), were set up and a range of solvent added to them ($CHCl_3$, DCM, EtOAc, Et_2O, toluene, acetone) to afford clear solutions in each case. Another set of solvents in which **6** was insoluble in (ACN, MeOH and hexane) was also chosen and these were added to different vials. Finally one vial was left with no solvent added. The vials were then left in direct sunlight for 72 hours (over a weekend). Following the 72 hours the chlorinated vials had darkened to black and the other solvent colour had remained unchanged. Removal of solvent and analysis via ^{1}H NMR spectroscopy showed that every sample in which solvent was added had degraded, even those in which **6** was insoluble. The compound with no solvent added had remained unchanged. Following this a new set of experiments was conducted in which all samples were wrapped in aluminium foil to avoid exposure to light. Following 72 hours the solvents were removed and analysis showed very little degradation, thus confirming that exposure to light was causing degradation to **6**.

It is seen in the literature that pyrroles can undergo, oxidation reactions[27] through autooxidation[28] or ariel oxidation reactions[29] forming a magnitude of different products. Oxidation of pyrroles can form known products, however, due to their reactive nature

they often undergo decomposition or uncontrollable polymerisation. It was theorised that a similar event was occurring here, and that light was initiating the reaction. This would help explain the inability to interpret any of the data as the pyrroles were most likely decomposing or forming a large range of different products.[27] Knowing that oxidation products were possible it was decided to do another experiment using a dry solvent under an inert atmosphere of N_2. Compound **6** (10 mg) was placed in a Schlenk flask which was evacuated and backfilled 5 times. Following this dry DCM was added and the flask left in sunlight for 72 hours. Following the 72 hours the mixture had again turn dark, and following removal of solvent and analysis via ^{1}H NMR spectroscopy the product had clearly degraded. Due to the known stability out of solution and a being able to prolong the lifetime by using aluminium foil to reduce light it was decided to move on with the project. Two compounds synthesised did show prolonged stability in the presence of light. These were **15** and **16** which were the naphthalene and pyrene appended derivatives. Naphthalene and pyrene groups are known for their photoelectronic and optical properties[30] and it is therefore theorised to be stabilising the pyrrole by absorbing the visible light and reducing the rate of decomposition. However, additional experiments would be required to make any concrete conclusions.

3.6. Summary and Conclusions.

In summary, the Paal-Knorr synthesis with methylene bridge modified calix[4]arenes has been further in this study. All routes displayed in Figure 3.5 have been explored with success, isolating pyrrole, thiophene and pyridazine methylene bridged C[4]s. The deprotection of these compounds was then investigated, isolating a tetra-hydroxy pyridazine C[4], **25**, demonstrating that lower-rim deprotection can be achieved, albeit in low yields. Future work should focus on optimisation of this step and allow further investigation into how this compound behaves in areas such as catalysis or cluster formation.

Deprotection was then trialled on the hexyl-pyrrole C[4], **19**, however with significant complications. It was shown that iodocyclohexane was an unsuitable deprotecting agent as no demethylated species could be observed. BBr_3 was also trialled with limited success as it could be observed that the product was decomposing before the fully demethylated species was formed. Therefore, other deprotection routes were attempted whilst utilising **5**. Use of both BBr_3 and iodocyclohexane to demethylate **5** was unsuccessful. Previous work had shown that a monohydroxy species of **5**, **$H_1$5**, was isolated as a side product in the ring opening of **4** and efforts to isolate further demethylated products by increasing time or acidity of the reaction were unsuccessful. The monohydroxy **$H_1$5** was then isolated in a moderate yield and further reaction through a Paal-Knorr pyrrole condensation with hexylamine forming **$H_1$19** proved that reacting a demethylated diketone under Paal-Knorr conditions is possible to obtain the desired product.

The decomposition of functionalised pyrroles has been discussed and control experiments show that the compounds are stable in the solid form. They were found to decompose in solution in the presence of light, the hypothesis being that this is occurring via a light-mediated oxidation reaction. It was found that reducing the amount of light by wrapping the products in aluminium foil would decrease the decomposition and therefore this was utilised throughout the project upon identification of this phenomenon.

3.7. Experimental

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-propyl-2-methyl-1H-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 18.

Compound **5**, (0.250 g, 0.228 mmol), propylamine (0.085 mL, 1.025 mmol) and p-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 3 days under N_2 wrapped in aluminium foil. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and washed three times with water (3 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by column chromatography (EtOAC/Hex 1:9) to yield (0.085 g, 31.3 %) of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-propyl-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 4H), 6.55 (s, 4H), 5.98 (s, 4H), 5.82 (d, *J* = 3.3 Hz, 4H), 5.79 (d, *J* = 3.3 Hz, 4H), 4.26 (s, 6H), 3.64 (t, *J* = 8.0 Hz, 8H), 3.44 (s, 6H), 2.24 (s, 12H), 1.82 – 1.67 (m, 4H), 1.57 (dt, *J* = 15.1, 7.3 Hz, 4H), 1.08 (s, 18H), 0.87 (s, 18H), 0.85 (t, *J* = 10.2 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.16, 153.79, 145.51, 143.60, 137.95, 132.65, 132.08, 128.02, 125.22, 122.49, 108.53, 104.85, 62.70, 59.80, 45.46, 36.21, 34.17, 33.78, 31.44, 31.14, 24.17, 12.73, 11.32. ESI-MS: 1189.8420 $[M+H]^+$, 1211.8280 $[M+Na]^+$.

Crystal Data for $C_{80}H_{108}N_4O_4$ (*M* =1189.70 g/mol): monoclinic, space group P2/c (no. 13), *a* = 15.3725(2) Å, *b* = 11.00180(10) Å, *c* = 22.1599(3) Å, *β* = 107.6050(10)°, *V* = 3572.27(8) Å^3, *Z* = 2, *T* = 100(2) K, μ(CuKα) = 0.513 mm^{-1}, *Dcalc* = 1.106 g/cm^3, 106228 reflections measured (8.372° ≤ 2Θ ≤ 149.092°), 7316 unique (R_{int} = 0.0508, R_{sigma} = 0.0212) which were used in all calculations. The final R_1 was 0.0393 (I > 2σ(I)) and wR_2 was 0.1071 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(1-hexyl-2-methyl-1H-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 19.

Compound **5**, (0.600 g, 0.5645 mmol), hexylamine (0.343 mL, 2.37 mmol) and p-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 5 days under N_2. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and washed three times with water (3 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by column chromatography (EtOAC/Hex 1:9) to yield (0.4507 g, 58.7 %) of **19.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 4H), 6.54 (s, 4H), 5.98 (s, 4H), 5.80 (dd, *J* = 14.3, 3.3 Hz, 8H), 4.25 (s, 6H), 3.66 (t, *J* = 8.0 Hz, 8H), 3.44 (s, 6H), 2.24 (s, 12H), 1.75 (br. m, 4H), 1.60 – 1.47 (br. m, 4H), 1.33 – 1.20 (br. m, 24H), 1.08 (s, 18H), 0.90 (t, *J* = 6.6 Hz, 12H), 0.87 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.23, 153.72, 145.50, 143.59, 137.94, 132.55, 132.10, 127.91, 125.19, 122.48, 108.58, 104.86, 62.70, 59.87, 44.02, 36.20, 34.18, 33.78, 31.80, 31.47, 31.23, 31.14, 26.86, 22.58, 14.03, 12.74.

ASAP MS 1359.20 $[M+H]^+$

Crystal Data for $C_{47.499}H_{69}N_2O_{2.5}$ (*M* =708.03 g/mol): triclinic, space group P-1 (no. 2), *a* = 14.7586(2) Å, *b* = 15.6878(2) Å, *c* = 22.8186(3) Å, *α* = 98.3560(10)°, *β* = 98.1520(10)°, *γ* = 116.1390(10)°, *V* = 4564.78(11) Å^3, *Z* = 4, *T* = 100(2) K, μ(CuKα) = 0.475 mm^{-1}, *Dcalc* = 1.030 g/cm^3, 154190 reflections measured (6.454° ≤ 2Θ ≤ 140.13°), 17276 unique (R_{int} = 0.0495, R_{sigma} = 0.0257) which were used in all calculations. The final R_1 was 0.0650 (I > 2σ(I)) and wR_2 was 0.1978 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-hexadecyl-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 20.

Compound **5**, (0.200 g, 0.188 mmol), hexadecyl amine (0.190 mL, 0.7904 mmol) and *p*-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 5 days under N_2 wrapped in aluminium foil. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and washed three times with water (3 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by column chromatography (DCM/Hex 1:1) to yield (0.137 g, 38 %) of **20**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 4H), 6.54 (s, 4H), 5.97 (s, 4H), 5.83 – 5.76 (dd, 8H), 4.25 (s, 6H), 3.66 (t, *J* = 7.9 Hz, 8H), 3.44 (s, 6H), 2.24 (s, 12H), 1.72 (br. m, *J* = 8.0 Hz, 4H), 1.53 (br. m, 4H), 1.26 (br. m, 96H), 1.08 (s, 18H), 0.89 (ddd, *J* = 6.6, 1.1 Hz, 20H), 0.87 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.36, 153.88, 145.65, 143.75, 138.11, 132.73, 132.25, 128.06, 125.37, 122.65, 108.73, 105.04, 77.16, 62.83, 60.00, 44.16, 36.37, 34.32, 33.92, 32.10, 31.62, 31.39, 31.29, 29.91, 29.85, 29.54, 27.38, 22.85, 14.26, 12.88. ESI-MS: 1916.66 $[M+H]^+$

5,11,17,23-tetra-tert-butyl-2,8,14,-tris(1-hexadecyl-2-methyl-1*H*-pyrrole)-20-1-(pentane-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, 21

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 2.3 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.67 – 6.61 (m, 3H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.47 (dd, *J* = 7.4, 2.5 Hz, 2H), 6.00 (s, 1H), 5.94 (s, 1H), 5.91 (s, 2H), 5.82 – 5.75 (m, 8H), 4.23 (s, 3H), 4.22 (s, 3H), 3.73 – 3.59 (m, 8H), 3.54 (s, 3H), 3.43 (s, 3H), 2.99 – 2.94 (m, 3H), 2.74 – 2.66 (m, 1H), 2.24 (d, *J* = 4.5 Hz, 9H), 2.19 (s, 3H), 1.83 – 1.65 (br. m, 4H), 1.62 – 1.46 (br. m, 4H), 1.27 (br. s, 96H), 1.19 (s, 9H), 1.07 (s, 9H), 0.91 – 0.85 (m, 29H), 0.82 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.06, 207.22, 154.96, 154.11, 153.60, 145.93, 145.59, 143.94, 143.64, 138.80, 138.02, 132.36, 132.24, 132.24, 132.15, 132.11, 131.80, 128.10, 128.02, 127.95, 127.94, 125.39, 125.31, 124.79, 123.58, 122.52, 122.40, 121.94, 115.35, 108.67, 105.01, 104.92, 62.82, 62.74, 60.61, 60.40, 59.75, 51.15, 44.10, 44.06, 44.02, 37.56, 36.41, 36.35, 36.29, 36.26, 34.34, 34.16, 33.82, 33.71, 31.94, 31.53, 31.45, 31.13, 31.10, 29.76, 29.74, 29.70, 29.39, 22.70, 14.13, 12.73. ESI-MS: 1752.40 m/z $[M+K]^+$. **IR** ν_{max} 2922 cm^{-1} and 2852 cm^{-1} (C-H), 1717 cm^{-1} (C=O).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(2-methyl-1H pyrrole)carbamate)-25,26,27,28-tetramethoxycalix[4]arene, 22.

Compound **5**, (0.500 g, 0.456 mmol), boc-hydrazide (0.362 g, 2.723 mmol) and *p*-TsOH·H_2O (0.015 g) in toluene (50 mL) was heated at reflux for 72 hours. The orange solution was cooled to room temperature and toluene removed under reduced pressure. The crude solid was dissolved in $CHCl_3$ (50 mL) and then washed with water (2 × 50 mL) and brine (1 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure. Crude was purified by column chromatography (1:3 EtOAc/Hex) to afford (0.287 g, 42%) of **22**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (br. m, *J* = 36.4 Hz, 10H), 6.13 (br. m, *J* = 36.3 Hz, 2H), 5.81 (br. m, 10H), 4.13 (br. s, 6H), 3.47 (br. s, 6H), 2.16 (m, *J* = 11.8 Hz, 12H), 1.51 (m, *J* = 33.4 Hz, 36H), 1.09 (s, 18H), 0.85 (s, 18H). **IR** ν_{max} 3230 cm^{-1} (N-H stretch)

ESI-MS:1503.9019 $[M+Na]^+$

Crystal Data for $C_{88}H_{120}N_8O_{12}$ (*M* =1570.02 g/mol): orthorhombic, space group Pbcn (no. 60), *a* = 19.3698(4) Å, *b* = 25.8061(5) Å, *c* = 18.7571(4) Å, *V* = 9375.9(3) $Å^3$, *Z* = 4, *T* = 100(2) K, μ(CuKα) = 0.597 mm^{-1}, *Dcalc* = 1.112 g/cm^3, 123915 reflections measured (7.4° ≤ 2Θ ≤ 140.414°), 8908 unique (R_{int} = 0.0966, R_{sigma} = 0.0446) which were used in all calculations. The final R_1 was 0.0580 (I > 2σ(I)) and wR_2 was 0.1684 (all data).

5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(2-methylthiophene)-25,26,27,28-tetramethoxycalix[4]arene, 23.

Compound **5**, (0.400 g, 0.3644 mmol) and Lawesson's reagent (0.588 g, 1.458 mmol) in toluene (65 mL) was heated at reflux overnight under N_2. The reaction mixture was cooled to room temperature, filtered to remove left over Lawesson's reagent. The solvent was then removed under reduced pressure. Dissolved in $CHCl_3$ and washed with saturated $NaHCO_3$ (1 × 100 mL), water (2 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified via column chromatography (1:1 DCM/Hex) and recrystalised from EtOAc to yield 0.184 g (46.6 %) of **23**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 8H), 6.66 (dd, J = 3.4, 1.0 Hz, 4H), 6.59 (dd, J = 3.3, 1.1 Hz, 4H), 6.20 (s, 4H), 3.85 (s, 12H), 2.46 (s, 12H), 1.03 (s, 36H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.30, 145.67, 144.85, 138.28, 136.11, 126.34, 124.50, 123.97, 62.10, 39.05, 34.28, 31.46, 15.59. ASAP-MS: 1089.50 $[M]^+$, 1090.50 $[M+H]^+$

Crystal Data for $C_{68}H_{80}O_4S_4$ (*M* =1089.56 g/mol): monoclinic, space group $P2_1/m$ (no. 11), *a* = 10.6277(3) Å, *b* = 22.1383(6) Å, *c* = 13.4241(4) Å, *β* = 107.2860(10)°, *V* = 3015.76(15) $Å^3$, *Z* = 2, *T* = 100(2) K, μ(CuKα) = 1.808 mm^{-1}, *Dcalc* = 1.200 g/cm^3, 7003 reflections measured (7.97° ≤ 2Θ ≤ 144.304°), 6071 unique (R_{int} = 0.0464, R_{sigma} = 0.0294) which were used in all calculations. The final R_1 was 0.0593 (I > 2σ(I)) and wR_2 was 0.1720 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(pent-2-ene-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, 24.

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(2-methylfuranyl)-25,26,27,28-tetramethoxycalix[4]arene, **4** (1.805 g) and mCPBA (2.403 g) in dry DCM (60 mL) was stirred at room temperature under N_2 for 18 hours. A white precipitate formed overnight which was removed by filtration and washed with DCM. The filtrate was washed with Na_2SO_3 (1 × 50 mL), NaHCO3 (aq) (1 × 50 mL) and water (1 × 50 mL). The organic phase was collected and dried over $MgSO_4$ before removal of the solvent under reduced pressure. The crude product was purified by column chromatography (3:2 EtOAc/PET) to yield 0.659 g (34%) of **24**. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.05 (s, 36 H), 2.36 (s, 12 H), 3.86 (s, 12 H), 5.83 (s, 4 H), 6.31 (d, J=11.98 Hz, 4 H), 6.52 (d, J=11.98 Hz, 4 H), 6.82 (s, 8 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ ppm 201.5, 199.9, 154.9, 146.0, 139.0, 133.1, 130.8, 125.3, 62.1, 51.2, 34.2, 31.2, 29.6. ESI-MS: 1111.6 $[M+Na]^+$.

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(3-methylpyridazine)-25,26,27,28-tetramethoxycalix[4]arene, 25.

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(pent-2-ene-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, **24** (0.501 g) and hydrazine hydrate (1.0 mL) in acetic acid (120 mL) was heated at reflux overnight. After this time, water (100 mL) was added to the brown solution and extracted with $CHCl_3$ (3 × 100 mL). The combined organic phase was washed with water (3 × 100 mL) before it was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude was purified by column chromatography (9:1 $CHCl_3$/MeOH) to yield 0.329 g (67%) of **25**. ^{1}H NMR (300 MHz, CD_2Cl_2) δ ppm 0.99 (s, 36 H) 2.69 (s, 12 H) 3.85 (s, 12 H) 6.54 (s, 4 H) 6.78 (s, 8 H) 7.29 (d, *J*=8.80 Hz, 4 H) 7.53 (d, *J*=8.44 Hz, 4 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ ppm 162.2, 157.7, 155.2, 145.1, 134.6, 127.0, 126.4, 124.7, 62.1, 34.1, 31.3, 22.0. ESI-MS: 1095.6, $[M+Na]^+$.

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(3-methylpyridazine)-25,26,27,28-tetrahydroxycalix[4]arene, 26.

Compound **25** (0.350 g) was dissolved in dry DCM (10 mL) under N_2 in a Schlenk flask. The solution was cooled to -78°C using dry ice/acetone before adding 1M BBr_3 in DCM

(6.52 mL 6.52 mmol, 20 equivalents) very slowly. Immediately, a solid precipitates. The reaction mixture was stirred at -78°C for 1 hour before it was warmed to RT and stirred for 24h. The brown solution was quenched with water (50 mL) before pouring into a separating funnel. Any residue still in Schlenk flask was dissolved in DCM and added to the aqueous solution. Solution was extracted with DCM and the combined organic phases washed with water (3 × 30 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford a brown solid (0.265 g). The procedure was then repeated using the crude product and purified via gradient column chromatography (100% $CHCl_3$→ 9:1 $CHCl_3$/MeOH in 1% increments). The columned product was then washed with cold ACN to afford 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(3-methylpyridazine)-25,26,27,28- tetrahydroxycalix[4]arene, **26** as an off white powder (0.018 g, 5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (br. s, 4H), 7.42 (d, J = 8.5 Hz, 4H), 7.33 (d, J = 8.5 Hz, 4H), 6.91 (br. s, 8H), 5.55 (s, 4H), 2.72 (s, 12H), 1.06 (s, 36H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ ppm 162.44, 157.15, 150.34, 138.04, 127.52, 127.34, 127.26, 51.73, 32.71, 30.58, 30.43, 30.36, 28.69, 20.91. ESI-MS: 1039.5 $[M+Na]^+$. **Crystal Data** (CCDC 2126920): $C_{64}H_{72}N_8O_4$ (M =1017.29 g/mol), tetragonal, space group *I-4* (no. 82), a = 12.0951(5) Å, c = 22.4894(10) Å, V = 3290.0(3) Å 3 , Z = 2, T = 100(2) K, μ(Synchrotron) = 0.068 mm-1 , Dcalc = 1.027 g/cm3 , 42098 reflections measured (3.92° ≤ 2Θ ≤ 52.224°), 3026 unique (Rint = 0.0526, Rsigma = 0.0294) which were used in all calculations. The final R1 was 0.0534 (I > 2σ(I)) and wR2 was 0.1523 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(pentane-1,4-dione)-25,26,27, trismethoxy-28,-monohydroxycalix[4]arene, $H_1$5.

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(2-methylfuranyl) 25,26,27,28-tetramethoxycalix[4]arene, **4** (1.00 g, 2.44 mmol) in acetic acid (300 mL), water (120 mL) and conc. sulfuric acid (20 mL) was heated at reflux for 5 days. The solution was cooled to room temperature and diluted with water (150 mL) before extraction with $CHCl_3$ (3 × 100 mL). The combined organic phase was washed with water (3 × 150 mL), then dried over $MgSO_4$ before the solvent was removed under reduced pressure. The crude solid was purified by column chromatography (8:2 → 7:3 → 6:4 → 1:1→ 100% $CHCl_3$/EtOAc) to yield 0.358 g (34 %) of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(pentane-1,4-dione)- 25,26,27,-trismethoxy-28,-monohydroxycalix[4]arene **$H_1$5**

and 0.136 g (13.6 %) of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(pentane-1,4-dione)-25,26,27,28 tetramethoxycalix[4]arene **5.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 2H), 6.91 (s, 2H), 6.65 (d, *J* = 2.4 Hz, 2H), 6.61 (d, *J* = 2.4 Hz, 2H), 5.85 (s, 2H), 5.84 (s, 2H), 4.20 (s, 3H), 3.80 (s, 6H), 2.95 – 2.84 (m, 12H), 2.77 – 2.63 (m, 4H), 2.18 (s, 6H), 2.18 (s, 6H), 1.25 (s, 9H), 1.24 (s, 9H), 0.82 (s, 18H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ ppm 207.8, 207.6, 206.9, 206.7, 155.1, 152.4, 150.3, 147.2, 145.6, 143.3, 133.9, 128.7, 128.4, 128.1, 126.9, 126.5, 123.3, 122.4, 63.7, 61.8, 51.1, 50.5, 37.6, 37.4, 36.3, 36.2, 34.5, 34.2, 33.9, 31.5, 31.4, 30.9, 29.8. ESI-MS: 1105.6, [M+Na]+.

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(tert-butyl(1-hexyl-2-methyl-1H-pyrrole)-25,26,27,-tetramethoxy-28-monohydroxycalix[4]arene, $H_1$19.

Compound **5**, (0.257 g, 0.3295 mmol), hexylamine (0.183 mL, 1.384 mmol) and *p*-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 5 days under N_2, wrapped in aluminium foil to avoid light ingress. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and washed three times with water (3 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by column chromatography (DCM/Hex 1:1) to yield (0.130 g, 29.3 %) of **$H_1$19.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 – 6.67 (m, 4H), 6.65 – 6.62 (m, 4H), 6.08 (s, 2H), 6.00 (s, 2H), 5.86 (d, *J* = 3.3 Hz, 2H), 5.83 (d, *J* = 3.3 Hz, 2H), 5.82 – 5.79 (m, 4H), 4.31 (s, 3H), 4.24 (s, 1H), 3.67 – 3.55 (m, 8H), 3.52 (d, *J* = 10.6 Hz, 6H), 2.24 (s, 12H), 1.77 – 1.68 (m, 2H), 1.66 – 1.58 (m, 2H), 1.56 – 1.48 (m, 2H), 1.46 – 1.37 (m, 2H), 1.25 (m, 32H), 1.08 (s, 18H), 0.90 (t, *J* = 6.8 Hz, 12H), 0.88 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.00, 152.61, 148.86, 146.57, 144.94, 143.38, 138.07, 134.67, 132.69, 132.37, 131.93, 131.84, 128.45, 128.33, 126.23, 125.80, 122.81, 122.15, 108.78, 108.48, 105.16, 105.05, 77.16, 63.27, 60.86, 53.56, 44.20, 44.05, 36.20, 34.36, 34.15, 34.01, 31.95, 31.92, 31.61, 31.52, 31.41, 31.19, 31.08, 27.02, 26.90, 22.78, 22.70, 14.27, 14.17, 12.97, 12.85. ASAP MS 1342.95 $[M-H]^-$

Crystal Data for $C_{91.5}H_{131}ClN_4O_4$ (*M* =1386.45 g/mol): triclinic, space group P-1 (no. 2), *a* = 14.4968(8) Å, *b* = 15.5599(8) Å, *c* = 23.0298(12) Å, *α* = 98.765(2)°, *β* =

99.105(2)°, γ = 115.493(2)°, V = 4486.0(4) Å^3, Z = 2, T = 100(2) K, μ(CuKα) = 0.734 mm^{-1}, *Dcalc* = 1.026 g/cm^3, 104107 reflections measured (8.026° ≤ 2Θ ≤ 141.614°), 16912 unique (R_{int} = 0.0433, R_{sigma} = 0.0312) which were used in all calculations. The final R_1 was 0.1021 (I > 2σ(I)) and wR_2 was 0.3679 (all data).

3.7. References.

1 M. Helmstädter, J. Vietor, J. Sommer, S. Schierle, S. Willems, A. Kaiser, J. Schmidt and D. Merk, *ACS Med. Chem. Lett.*, 2021, **12**, 267–274.

2 A. Fong, Heriot-Watt, 2019.

3 A. Fong, C. L. Campbell, S. Huynh, L. J. McCormick McPherson, S. J. Teat, M. W. P. Bebbington and S. J. Dalgarno, *Chem. Commun.*, 2022, **58**, 3302–3305.

4 J. Klimentová and P. Vojtíšek, *J. Mol. Struct.*, 2007, **826**, 48–63.

5 B. Jeragh and A. A. El-Asmy, *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.*, 2014, **129**, 307–313.

6 B. Jeragh, M. S. Ali and A. A. El-Asmy, *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.*, 2015, **150**, 504–513.

7 K. Hemming, *Chem. Educ.*, 2001, **6**, 396–398.

8 F. Duus, *Tetrahedron*, 1976, **32**, 2817–2825.

9 E. Campaigne and W. O. Foye, *J. Org. Chem.*, 1952, **17**, 1405–1412.

10 M. Jesberger, T. P. Davis and L. Barner, *Synthesis (Stuttg).*, 2003, **13**, 1929–1958.

11 F. W. Lichtenthaler, A. Brust and E. Cuny, *Green Chem.*, 2001, **3**, 201–209.

12 X. Hang and Y. Bi, *Dalt. Trans.*, 2021, **50**, 3749–3758.

13 R. J. Flood, K. O. Ramberg, D. B. Mengel, F. Guagnini and P. B. Crowley, *Cryst. Growth Des.*, 2022, **22**, 3271–3276.

14 M. Yuguchi, M. Tokuda and K. Orito, *J. Org. Chem.*, 2004, **69**, 908–914.

15 G. Barbarella, M. Zambianchi, A. Bongini and L. Antolini, *Adv. Mater.*, 1993, **5**, 834–838.

16 F. Benetollo, G. Bombieri, A. Del Pra, F. Orsini, T. Previtera and M. G. Vigorita, *J. Mol. Struct.*, 1998, **443**, 131–139.

17 G. Minetto, L. F. Raveglia, A. Sega and M. Taddei, *European J. Org. Chem.*, 2005, **2005**, 5277–5288.

18 I. Columbus, *J. Org. Chem.*, 2008, **73**, 2598–2606.

19 M. Hofmann, N. Hampel, T. Kanzian and H. Mayr, *Angew. Chemie Int. Ed.*, 2004, **43**, 5402–5405.

20 L. Zuo, S. Yao, W. Wang and W. Duan, *Tetrahedron Lett.*, 2008, **49**, 4054–4056.

21 A. Fong, L. McCormick, S. J. Teat, E. K. Brechin and S. J. Dalgarno, *Supramol. Chem.*, 2018, **30**, 504–509.

22 M. J. Hardman, A. M. Thomas, L. T. Carroll, L. C. Williams, S. Parkin and J. L. Fantini, *Tetrahedron*, 2011, **67**, 7027–7034.

23 L. T. Carroll, P. A. Hill, C. Q. Ngo, K. P. Klatt and J. L. Fantini, *Tetrahedron*, 2013, **69**, 5002–5007.

24 T. D. Moseev, I. A. Lavrinchenko, M. V Varaksin, D. Y. Pobedinskaya, O. P. Demidov, I. V Borovlev, V. N. Charushin and O. N. Chupakhin, *RSC Adv.*, 2021, **11**, 6407–6414.

25 C. Li, E. Lobkovsky and J. A. Porco, *J. Am. Chem. Soc.*, 2000, **122**, 10484–10485.

26 S. A. Weissman and D. Zewge, *Tetrahedron*, 2005, **61**, 7833–7863.

27 J. K. Howard, K. J. Rihak, A. C. Bissember and J. A. Smith, *Chem. – An Asian J.*, 2016, **11**, 155–167.

28 R. A. Jones, G. P. Bean, A. T. Blomquist and H. H. Wasserman, *The Chemistry of Pyrroles: Organic Chemistry: A Series of Monographs, Vol. 34*, Elsevier Science, 2013.

29 V. Ji Ram, A. Sethi, M. Nath and R. Pratap, eds. V. Ji Ram, A. Sethi, M. Nath and R. B. T.-T. C. of H. Pratap, Elsevier, 2019, pp. 149–478.

30 T. M. Figueira-Duarte and K. Müllen, *Chem. Rev.*, 2011, **111**, 7260–7314.

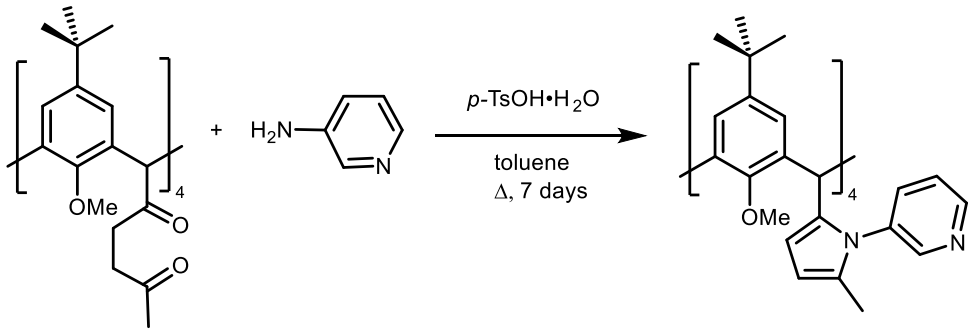
Chapter 4
Methylene-Bridge Substituted Pyridyl Calix[4]arenes

4.1. Introduction.

This chapter discusses the continuation of previous work in the group investigating the synthesis of calix[4]arenes functionalised at the methylene bridge with pyridyl groups. Metal organic cage formation using pyridyl moieties has been widely studied by many research groups due to the ability of nitrogen to donate strongly to metal centres. Pioneering work in this area came from the groups of Fujita and Stang, but these species are now employed in multiple areas of chemistry such as sensing[1,2] and catalysis[3]. Therefore it is of interest to synthesise calix[4]arenes bearing this functionality at the bridge positions for use in constructing metal-organic cages such as those by Zhong *et al.*, who used 4-pyridyl groups on the upper-rim of a calix[4]arene to form calixarene bases molecular capsules with Pd(II) which exploited the pyridyl-palladium type interaction.[4]

Previous attempts in this area aimed to mimic the type of cage formation pioneered by Fujita and Zhong by placing pyridyl groups off the periphery at the methylene bridges. Work by Fong,[5] utilising the same procedure as discussed in the previous chapter(s), sought first to obtain the saturated diketone **5** and then ring close to form the desired substituted pyrrole. The reaction of **5** with 2-, 3-, and 4-aminopyridine was undertaken. However, the reaction of 2- and 4-amino pyridine proved unsuccessful using these standard conditions. The reflux of **5** with an appropriate aniline (2- or 4-aminopyridine) in toluene with *p*-TsOH·H_2O present as an acid catalyst only returned starting material, indicating that no reaction had taken place. The reaction, albeit not on a calixarene framework, has been seen to work in the literature and so it was theorised that this procedure required more forcing conditions in this case. Other methods trialled employed a solvent with a higher boiling point (mesitylene), different catalysts (pyridinium *p*-toluenesulfonate, PPTS), or utilising different reaction conditions (microwave reaction / sealed tube), however all proved to be unsuccessful.

Although the reaction of 2 and 4- aminopyridine was unsuccessful, the reaction of 3-aminopyrine with **5** using the standard reaction conditions returned the desired product. (Scheme 4.1). This allowed access to pyridyl functionality off the bridge that could be further investigated.



Scheme 4.1. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(3-(2-methyl-1Hpyrrole) pyridine)-25,26,27,28-tetramethoxy-calix[4]arene by Fong *et al*[6].

Subsequent metal coordination using a variety of metal salts (Pd, Zn and Co) in varying stoichiometries was investigated. It was seen through analysis of the ^{1}H NMR spectrum of all the complexes formed that the best stoichiometry for the reactions was a 1:2 ratio of ligand to complex, as this displayed sharp and distinct signals. However, through single crystal x-ray diffraction analysis it was shown that these conditions were producing chelating structures and indicated that the compounds were not rigid enough to prevent the chelation from two pyridyl moieties towards one metal centre (Figure 4.1). Zhong *et al.* proved that avoiding chelation was vital to self-assembly of metal-organic capsules.[4] To circumvent these issues, it was theorised that the introduction of a phenyl spacer between the pyridyl and amine would add more rigidity along with a gap between the pyridyl and amine functionality. This would reduce the effects of the electronics, the mesomeric effect for the 2- and 4- aminopyridine places extra electron density on the ring nitrogen which can stabilise the protonated resonance form. This makes the 2- and 4-aminopyridines more acidic than 3-amino pyridine. Introducing a phenyl spacer would still cause a similar resonance however a reduced effect should occur promoting a complete reaction. This chapter discusses the different methods trialled for introducing 2-,3- and 4- pyridyl groups to the calix[4]arene at the methylene bridge positions. The synthesis of 4-(pyridin-3-yl)aniline and 4-(pyridin-4-yl)aniline are first discussed prior to

their reaction with **5**. 4-(pyridin-2-yl)aniline was commercially available and was used as supplied.

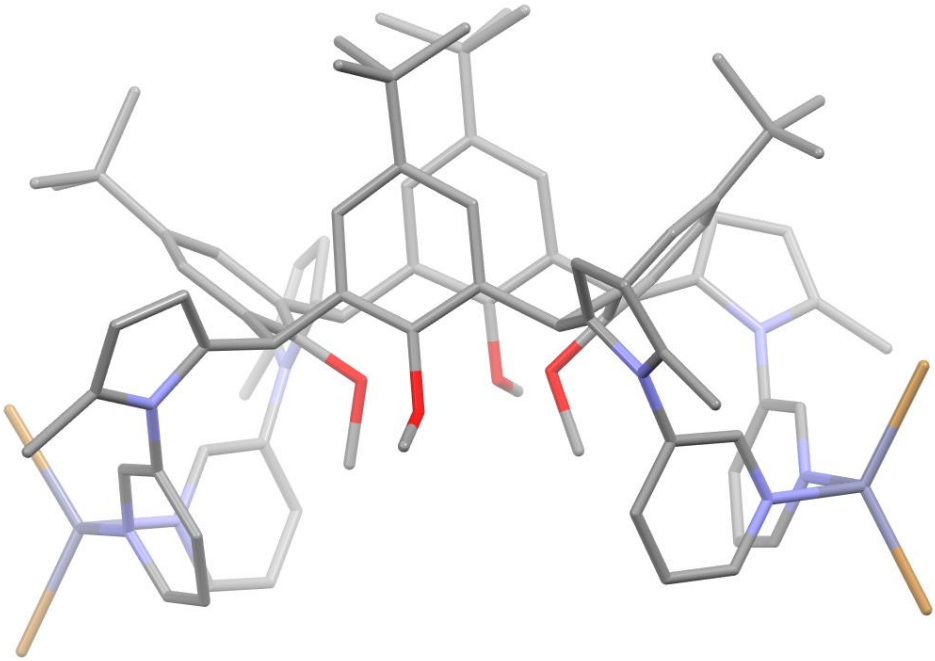


Figure 4.1. Single crystal X-ray structure of the product from the reaction of a previously synthesised calix[4]arene bearing a 3-pyridyl substituent with $CoBr_2$. The crystal shows binding of two $CoBr_2$ units in a chelating nature. Crystal is represented in ball and stick representation. Colour code: C - Grey; O - Red; N - Blue; Co - Purple; Br - Gold. H atoms are omitted for clarity.[5]

4.2. Investigation of Different Routes to Pyridyl Methylene-Bridged Calix[4]arenes.

It was decided that the most facile method for building an extended pyridyl off the bridge of a calix[4]arene would be to use the well understood Suzuki-Miyaura coupling which have been utilised on the upper-rim of a calix[4]arene to great effect.[7] This can be seen to have two different approaches for the addition of different functional groups via coupling onto the calix[4]arene (Figure 4.2). Figure 4.2 a) shows direct coupling onto

the calix[4]arene utilising a previously synthesised compound such as **6** or a boronic acid. The second route shown in Figure 4.2b would require syntheses of anilines via a cross coupling with a substrate such as 4-bromoaniline and a boronic acid or 2-/4-aminophenylboronic acid with an aryl or alkyl halide, followed by ring closure using the Paal-Knorr pyrrole synthesis utilised in Chapters 2 and 3.

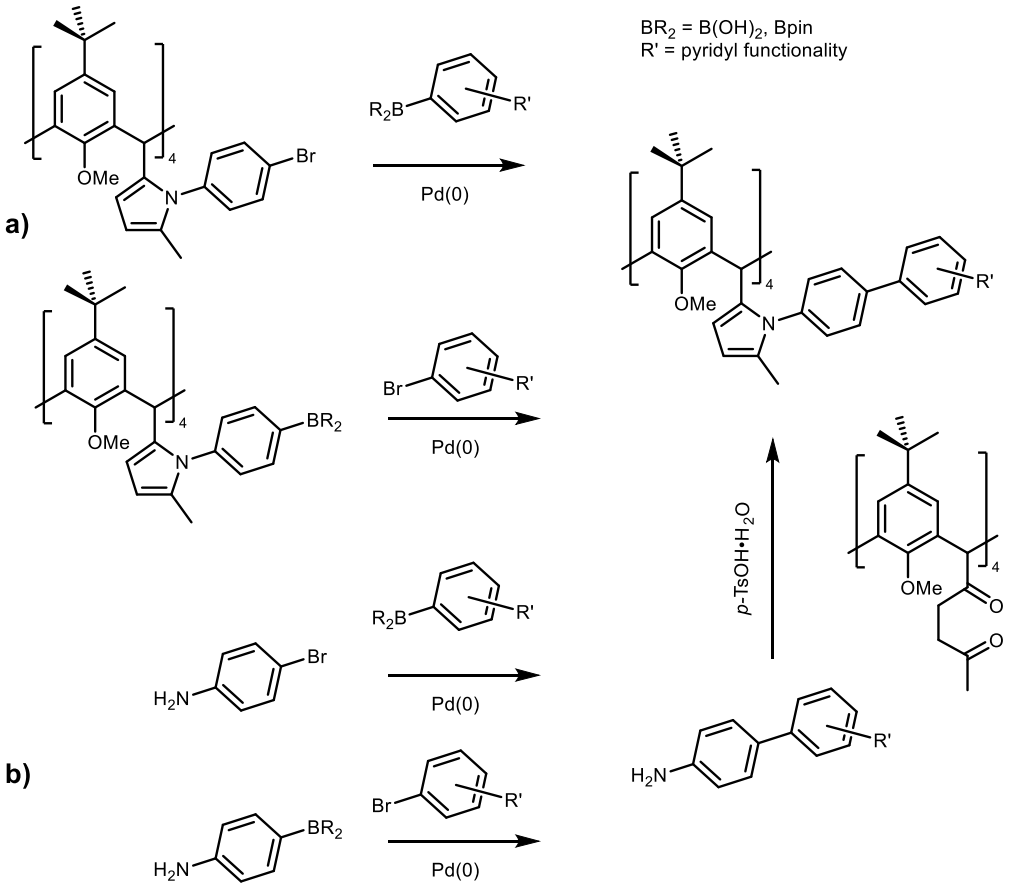
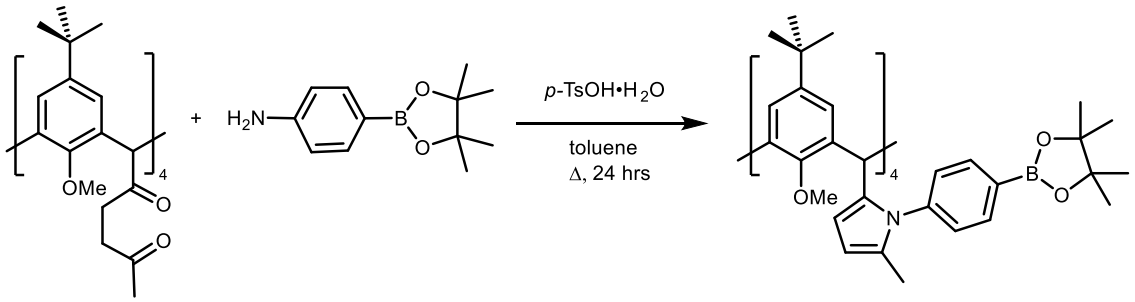


Figure 4.2. Different synthetic routes to synthesise a methylene bridge extended pyridyl calix[4]arene utilising Suzuki Miyaura cross coupling.

With compound **6** having been synthesised previously, this route was investigated first. Due to the large number of commercially available boronic acids used for forming Ar-C bonds this would allow to use **6** as a building block. The reaction of **6** was first tested with phenyl boronic and 4-formyl boronic acid to explore whether the reaction would proceed. Using literature conditions, compound **6** was reacted with reach boronic acid as a mixture of toluene or THF and water, using potassium carbonate as a base and $Pd(PPh_3)_4$ as the catalyst. Analysis of both reactions via ^1H NMR and mass spectroscopy showed

no evidence of product formation and only starting material was recovered. Suzuki-Miyaura couplings usually require much optimisation as many different catalysts, solvents and bases can be used. However, in this instance, as no evidence of any coupling had been observed it was decided to instead move forward and trial another method. The next reaction to be investigated was that of **5** with 4-aminoboronic pinacol ester. This would swap the coupling partners with the boron species on the periphery of the calixarene. A boronic ester was chosen as they are easier to handle, more stable and avoids any oxidation products that boronic acids can form.[8] The reaction of **5** with 4-aminoboronic pinacol was carried out using the same conditions as previously employed (Scheme 4.2).

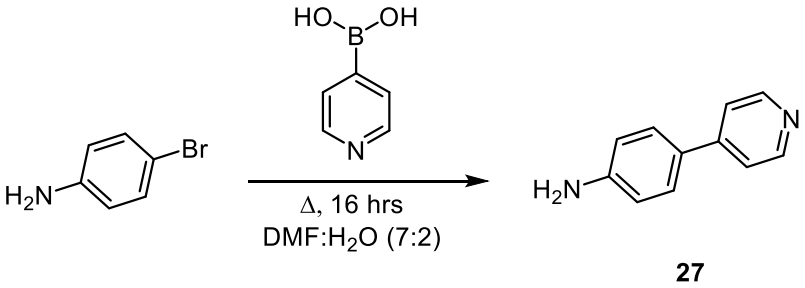


Scheme 4.2. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-4-boronic acid pinacol ester)(2-methyl-1Hpyrrole))-25,26,27,28 tetramethoxycalix[4]arene.

Following a 24 hr reflux, the reaction was worked up and analysed by ^{1}H NMR spectroscopy. Initial inspection showed that there were no distinctive diketone peaks indicating a completed reaction, however, *t*-butyl, OMe and 2-methylpyrrole peaks were split so the product had clearly desymmetrised. Mass spectrometry indicated that the desired product had not been formed as no peaks were found to correspond to the m/z value of 1829.68. A partial crystal structure with poor data was obtained, showing that one of the boronic esters was potential degrading so it was decided not to investigate this further and to move onto the direct synthesis of the extended pyridyl anilines. However, if time permitted it would be interesting to trail different conditions such as lower temperature, disparate solvents or the use of more stable borate esters such as MIDA borates.

4.2.1. Synthesis of 4-(4-pyridyl) aniline, 27

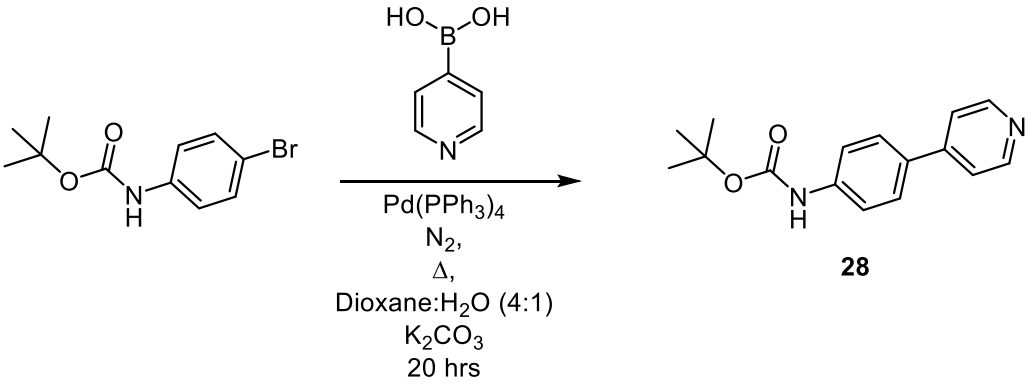
Using a literature procedure reported by Wasielewski and co-workers,[9] 4-pyridineboronic acid was heated at reflux overnight with 4-bromoaniline, $Pd(PPh_3)_4$, Na_2CO_3 in a 7:2 mixture of DMF/H_2O (Scheme 4.3). The reaction mixture was then diluted with DCM/Hexanes and the organic layer was removed under reduced pressure. Pure **27** was isolated from precipitation from DCM. The product was confirmed by comparison of the ^1H NMR spectrum with literature values.



27

Scheme 4.3. Synthetic scheme for the preparation of 4-(pyridin-4-yl)aniline **27** from 4-bromoaniline and 4-pyridylboronic acid.

The literature paper referenced reports a yield of 58%, however when following the procedure, the average isolated yield obtained from a series of two reactions was 33%. This was much lower than expected and so therefore a different route was trialled. It is known that electron withdrawing groups are better coupling partners when bound to the aryl halide due to facilitating the oxidative addition step.[10] Knowing that amines are strongly electron donating it was thought that using a boc-protected amine would improve yields. *Tert*-butyl 4-bromophenylcarbamate was instead employed as the aryl halide and 4-pyridyl boronic acid as the coupling partner. It should be noted here that 4 amino phenyl boronic acid with bromoaniline could have been used, but due to the cost of the boronic acid this route was not explored. Therefore the reaction of tert-butyl 4-bromophenylcarbamate with 4-pyridylboronic acid was carried out following the literature procedure reported by Li *et al.*[11] *Tert*-butyl 4-bromophenylcarbamate was reacted with 4-pyridyl boronic acid in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in dioxane/H_2O 4:1 at 90 °C overnight (scheme 4.4).



Scheme 4.4. Synthetic scheme for the preparation of *tert*-butyl(4-pyridin-4-yl)phenyl)carbamate **28**.

The product was then purified by column chromatography and analysis using ^{1}H NMR spectroscopy confirmed product synthesis. No crystallographic data on this compound were found in the Cambridge Structural Database (CSD) and therefore a single crystal grown from slow evaporation of DCM was analysed via X-ray diffraction. The unit cell was found to be monoclinic and structure solution was carried out in space group *C*2/*c* (Figure 4.3).

Figure 4.3. Sticks representation of the single crystal X-ray structure of **28.** Colour code C - Grey; O - Red; N – Blue. H atoms are omitted for clarity.

To access the amine, the boc protecting group needs to be removed. This was performed by stirring compound **28** in a mixture of TFA:DCM 1:1 overnight before removal of solvent (scheme 4.4).

28 **27**

Scheme 4.5. Synthetic scheme for the deprotection of *tert*-butyl(4-pyridin-4-yl)phenyl)carbamate **28** to 4-(pyridin-4-yl)aniline **27**.

After following the literature procedure, the ^{1}H NMR of the product did not match that of the previous reaction shown in scheme 4.3 and of that reported by Wasielewski and co-workers. The tert-butyl peak had fully disappeared indicating that the deprotection of the boc group was successful and the peaks displayed in the spectrum were of the correct multiplicity, and integrations. However, they were shifted downfield and no broad peak for the amine could be seen. A single crystal suitable for X-ray diffraction was grown from an ethyl acetate solution. The unit cell was triclinic, and the structure solution carried out in space group $P\bar{1}$ (figure 4.4).

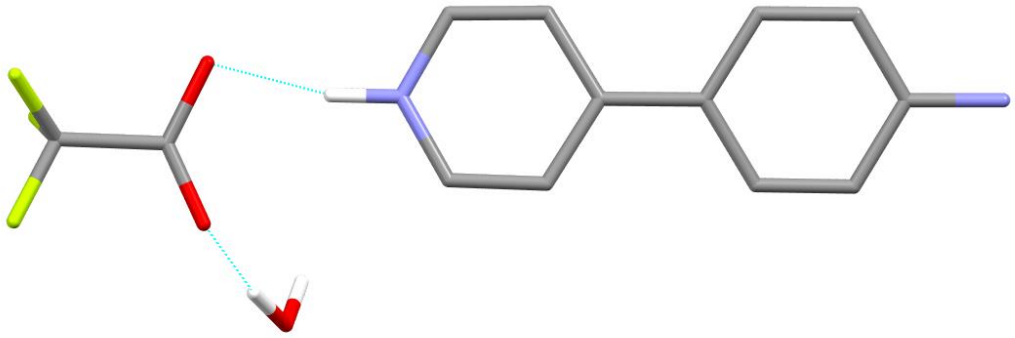


Figure 4.4. Sticks representation of the single crystal X-ray structure of **27** as the TFA salt. H-Bonding indicated by a blue dotted line. Colour code C - Grey; O - Red; N - Blue; F - Green; H -White, H atoms (apart from those involved in H-bonding) are omitted for clarity.

Inspection of the crystal structure shows that the TFA salt of **27** has formed whereby the 4-pyridyl group has been protonated by proton transfer from the carboxylic acid to the pyridyl. Water can also be seen H-bonding to the other oxygen on the carboxylic acid.

Knowing that the TFA salt was forming, this was removed by dissolving in DCM and washing with $NaHCO_3$ until the solution was pH ~ 7. Removal of solvent afforded yellow

crystals and the ^{1}H NMR spectrum analysed. The signals present in the sprectum now conformed to that synthesised previously and what has been reported in the literature. Single crystals were analysed via single crystal X-ray diffraction. The unit cell was found to be of monoclinic symmetry and structure solution carried out in space group *C*2/*c* (Figure 4.4).

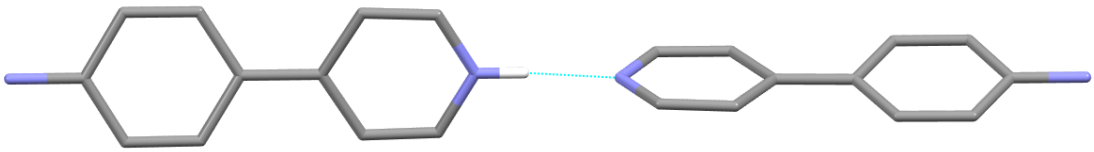
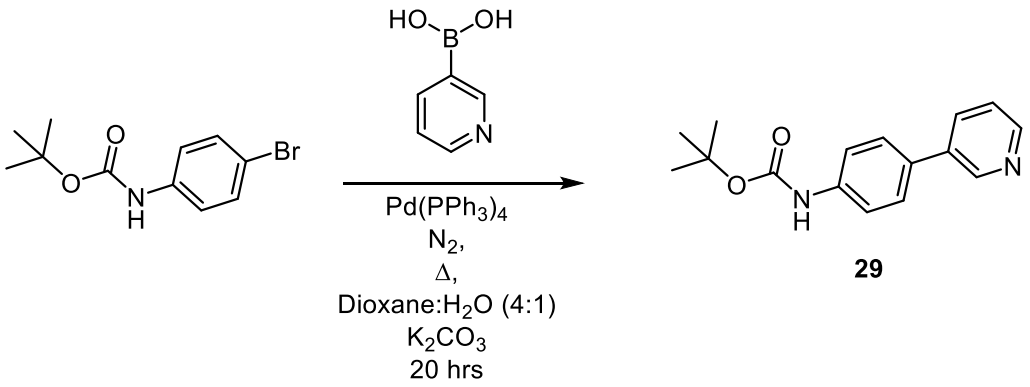


Figure 4.5. Sticks representation of the single crystal X-ray structure of two molecules of **27** with H bonding interactions between the two pyridyl groups. H-Bonding indicated by a blue dotted line. Colour code C - Grey; O - Red; N - Blue; H -White. H atoms (apart from those involved in H-bonding) are omitted for clarity.

From Figure 4.5 it can be seen that 4-(4-pyridyl) aniline **27** was successfully deprotected and the TFA removed. Two pyridyl groups are seen to orientate head to head with a hydrogen bonding interaction from one to the other, of length 1.75(3) Å and N···N of 2.673(2) Å common for this type of interaction.[12] The ASU contains one molecule of **27** and so the hydrogen on the pyridyl was set to 0.5 occupancy when refining to account for this interaction. The overall yield for this two-step process was 81% which is higher than the reported 75% from the literature and significantly higher than that found using the previous method; because of this the same procedure was used for the preparation of 4-(3-pyridyl) aniline.

4.2.2. Synthesis of 4-(3-pyridyl) aniline, 30

Following the same procedure as used for the synthesis of **27,** starting from the boc protected aryl halide, compound **30** was synthesised in two steps. The first step was the Suzuki Miyaura coupling between 3-pyridyl boronic acid with 4-bromophenylcarbamate using $Pd(PPh_3)_4$ synthesising *tert*-butyl(3-pyridin-4-yl)phenyl)carbamate **29**, Scheme 4.6).



Scheme 4.6 Synthetic scheme for the preparation of *tert*-butyl(3-pyridin-4-yl)phenyl)carbamate (**29**) using the Suzuki-Miyaura coupling.

The reaction was worked up and the crude purified using column chromatography to afford compound **29.** The product was analysed via ^{1}H NMR spectroscopy to confirm product synthesis and compared to the literature.[13] No CSD data had previously been obtained for the compound and therefore a crystal grown from a saturated DCM solution was obtained and analysed via X-ray diffraction studies. The unit cell was found to be orthorhombic and the structure solution carried out in space group *Pna*2$_1$ (Figure 4.6).

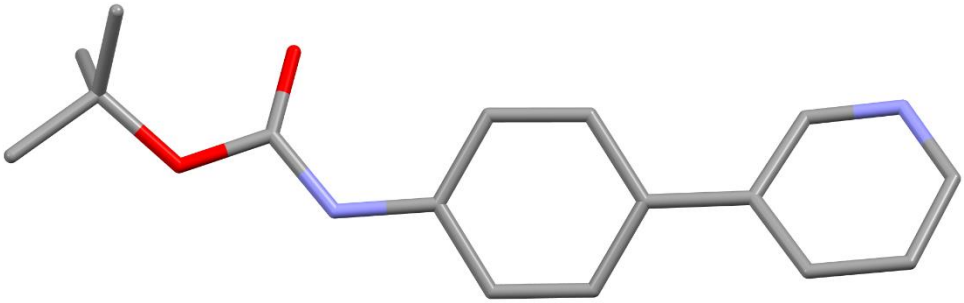


Figure 4.6. Sticks representation of the single crystal X-ray structure of **29**. H-Bonding indicated by a blue dotted line. Colour code C - Grey; O - Red; N - Blue; H atoms are omitted for clarity.

Following synthesis of **29**, the boc group was deprotected to form the amine. This was performed in the same method as before, but knowing the TFA salt forms the reaction was worked up and neutralised before removal of solvent (scheme 4.7).

(**29**) (**30**)

Scheme 4.7. Synthetic scheme for the deprotection of *tert*-butyl(4-pyridin-4-yl)phenyl)carbamate **29** to 4-(pyridin-3-yl)aniline, **30**.

Compound **30** was isolated in 53 % yield over a two-step process and analysed via ^{1}H NMR spectroscopy to confirm product formation by comparison to literature. No crystallographic data were found in a search of the CSD and so therefore a crystal grown from a saturated solution of DCM was analysed. The unit call was orthorhombic and the structure solution carried out in space group *Pbca* (Figure 4.7).

Figure 4.7. Sticks representation of the single crystal X-ray structure of **30**. H-Bonding indicated by a blue dotted line. Colour code C - Grey; O - Red; N - Blue; H -White.

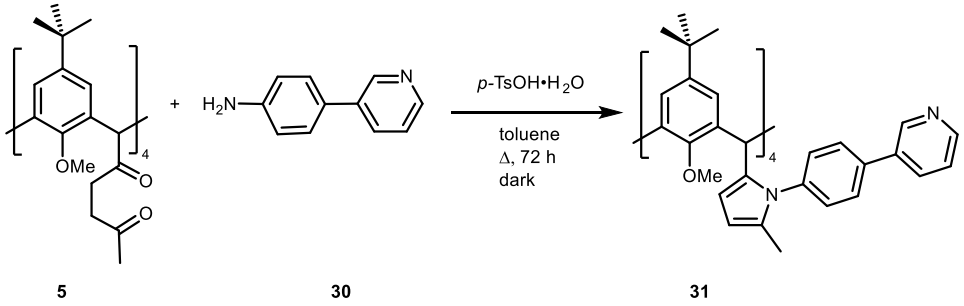
Figure 4.6 shows that the boc group has been successfully removed and the amine formed. It also shows interactions of the 3-pyridyl group to one molecule of water through a hydrogen bonding interaction. The hydrogen bond distance was calculated to be 1.897(12) Å which is comparable to a regular pyridine N···H-O bond length.[14]

4.3. Synthes of Extended Pyridyl Methylene-Bridged Calix[4]arenes.

Once the extended pyridyl anilines had been synthesised, the next step was to attach these to the calix[4]arene through the Paal-Knorr synthesis using previous conditions used in chapters 2 and 3 by reacting the relevant aniline with **5**. The first aniline to be trailed was **33** due to the previous work showing that 3-Aminopyridine with **5** produced the desired product.

4.3.1. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-3-pyridyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 31.

Extended 3-pyridyl aniline **30** was refluxed with **5** in toluene using *p*-TsOH·H_2O as a catalyst under N_2 wrapped in aluminium foil to mimic a dark reaction (scheme 4.8).



5 30 31

Scheme 4.8. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-3-pyridyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetra-methoxycalix[4]arene, **31**.

Previously the reaction of **5** with 3-amino pyridine was performed over 7 days. This timeframe this was used as the standard reaction period, however after 3 days an aliquot was taken and analysed using ^{1}H NMR spectroscopy. It was seen that the distinctive diketone peaks had disappeared, a set of doublets corresponding to the backbone of the pyrrole had grown in along with splitting of the *t*-butyl, OMe and Ar-H peaks. It was therefore decided to work up the reaction and the crude was purified via column chromatography to afford **31** in 30% yield. The ^{1}H NMR spectrum shows two signals for

the *t*-butyl, OMe and calix-Ph-H environments, indicative of the pinched cone formation previously observed upon successful pyrrole formation. Eight additional signals are seen in the aromatic region and can be assigned to the extended pyridyl group. Two of these environments are shifted downfield at 8.51 and 8.42 ppm integrating to 4 protons each. These were assigned to the Ph-H on the 3-pyridyl ring closest to the nitrogen. It is known that nearby electronegative atoms cause a shift on the hydrogen atom signals due to withdrawing electron density, and in turn the hydrogen is less shielded from the magnetic field and so therefore the signal will appear more downfield. The ^{13}C NMR spectrum showed no evidence of carbonyls and so confirming that all diketones had reacted. ASAP-MS showed clear peaks at 1634.15 and 1635.10 relating to $[M]^+$ and $[M+H]^+$ peaks for the tetrasubstituted product, confirming synthesis of **31**. Suitable single crystals grown from a saturated chloroform solution were analysed using X-ray diffraction. The unit cell was found to be of monoclinic symmetry and structure solution carried out in space group *P*2. The ASU contained two separate halves of the calix[4]arene which, upon symmetry generation, afford two full molecules of **31** in the pinched cone conformation (Figure 4.8). The symmetry expanded crystal structure shows two full calix[4]arenes appended with 3-pyridyl groups separated from the pyrrole with a phenyl spacer. Disorder in adjacent pyridyl substituents was observed and modelled over two positions at partial occupancies of 0.5. The two molecules of chloroform were also disordered and were modelled at occupancies of 0.6 and 0.4 over two positions.

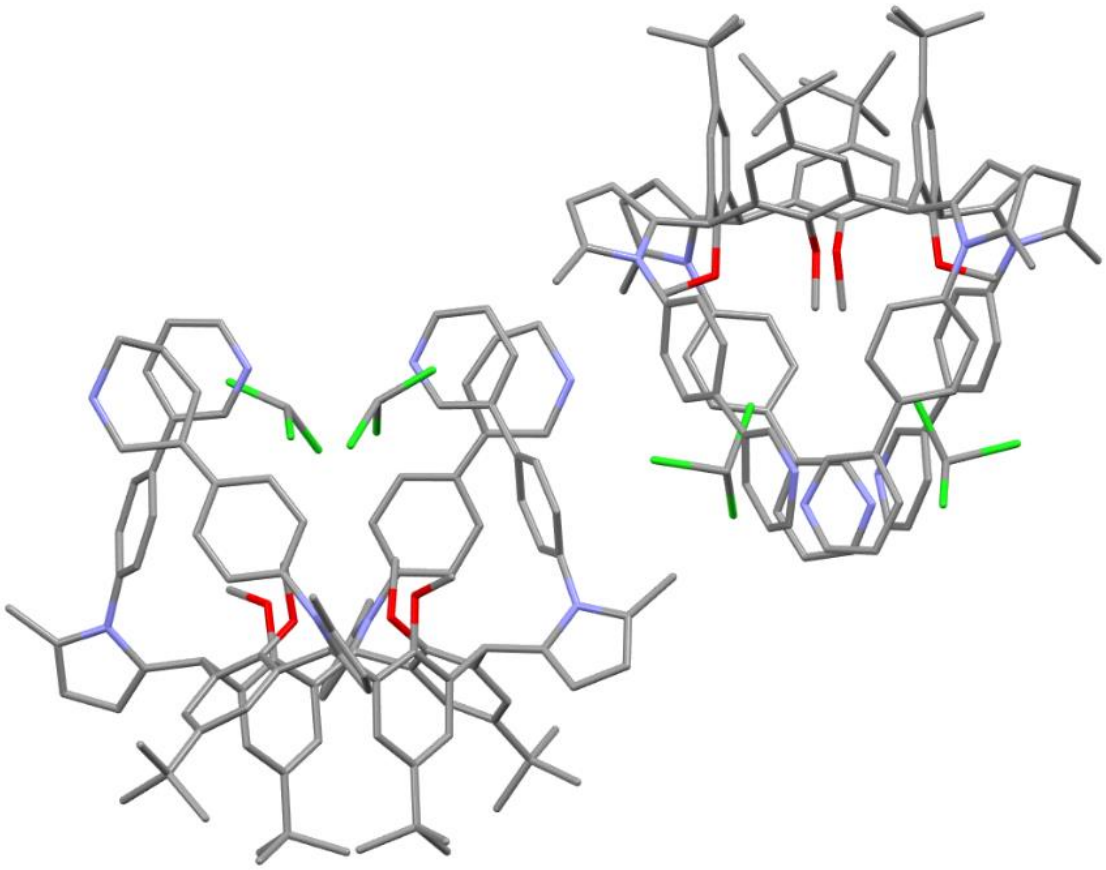
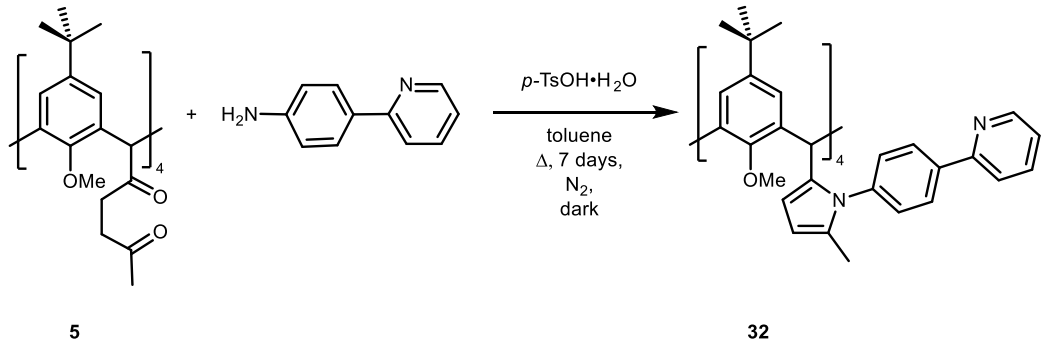


Figure 4.8. Sticks representation of the single crystal X-ray structure of **31** displaying two tetra-substituted 3-pyridyl calix[4]arene units containing chloroform. Colour code C- Grey; O -Red; N – Blue. H atoms omitted for clarity.

4.3.2. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-2-pyridyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 32.

The next compound to be investigated was the 2-pyridyl derivative. 2-pyridyl aniline was commercially available and so was used as supplied. Compound **5**, 2-pyridyl aniline and catalytic amounts of *p*-TsOH·H_2O were refluxed in toluene wrapped in aluminium foil, thus mimicking a dark reaction (Scheme 4.9).



Scheme 4.9. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-2-pyridyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, **32**.

Following a 7-day reflux the reaction was worked up and analysed. The ^{1}H NMR spectrum showed multiple products identified by the number of signals present in the *t*-butyl and OMe ranges. Following purification using column chromatography two major products were identified as the tris- and tetra-substituted calix[4]arenes. Characterisation of these two compounds will be discussed as **32** and **33**, respectively. Firstly, the tetra-substituted product **32** was isolated in 33% yield following column chromatography. The ^{1}H NMR spectrum displayed a symmetrical nature showing two signals for both the *t*-butyl, OMe and Ph-H environments, indicative of product formation whereby the diketone ring closes forming a pyrrole and the calix[4]arene adopts the pinched cone conformation. Further analysis using IR and ^{13}C NMR spectroscopy showed no evidence for carbonyls being present indicating that reaction had taken place at all four positions. ESI-MS confirmed presence of a tetrasubstituted product showing clear signals at 1634.89 and 1656.88 m/z relating to the $[M+H]^+$ and $[M+Na]^+$ peaks respectively. A suitable single crystal grown from a saturated toluene solution was obtained. The unit cell was found to be orthorhombic and the structure solution carried out in space group $P2_12_12$. The ASU contained one half of the calix[4]arene with one molecule of toluene disordered over two positions (Figure 4.10).

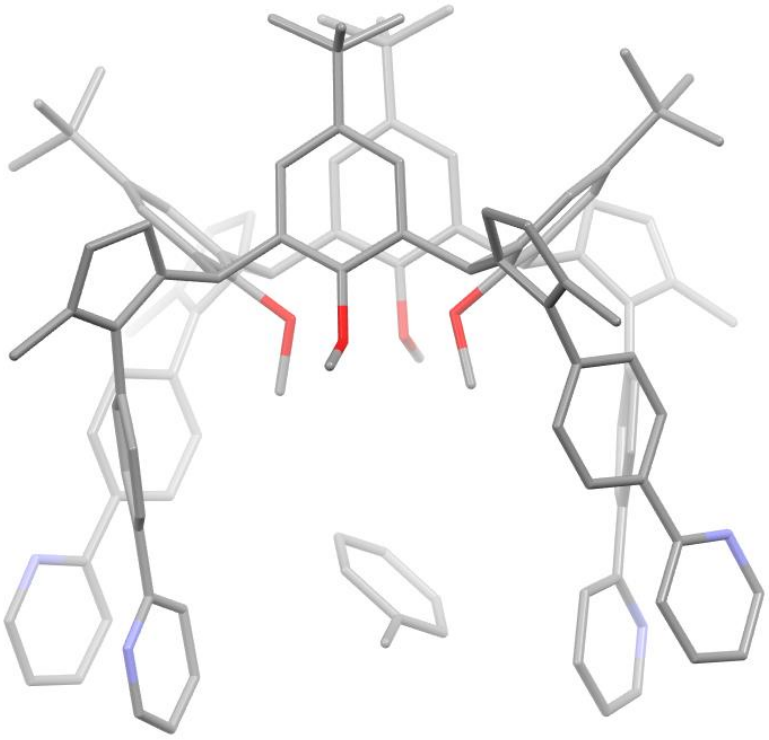
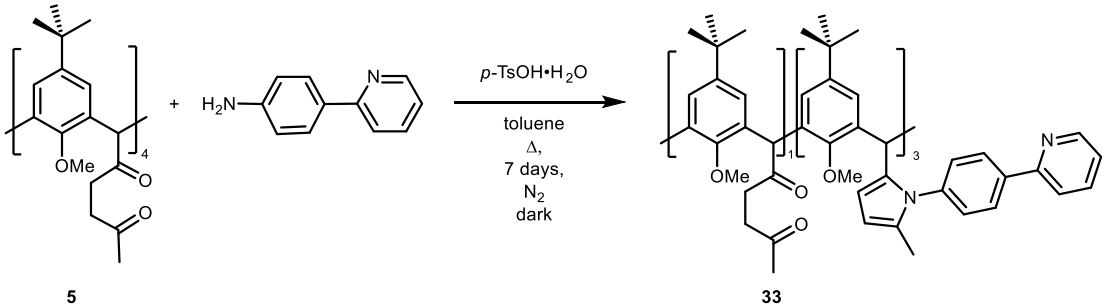


Figure 4.10. Sticks representation of the partial single crystal X-ray structure of **32** displaying a tetra-substituted 2-pyridyl-pyrrole calix[4]arene. Toluene is disordered over multiple positions, however only one position is shown. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

From Figure 4.10 it can be seen that all four diketone positions on the calix[4]arene have been ring closed to form the desired tetra-substituted pyrrole. The calix[4]arene is again seen to adopt the pinched cone conformation. Two of the pyridyl groups opposite to one another are shown to point further down into the lower cavity whilst two are positioned pointing into the splayed region of the calix[4]arene. One molecule of toluene is seen to be positioned on the symmetry plane and split over two positions within the ASU. This was modelled and the occupancy of each was assigned as 0.25 each.

The second product isolated through column chromatography was the tris-substituted species in which three positions on the calix[4]arene had ring closed forming the respective 2-pyridyl-phenyl pyrrole and one remained unreacted as the 1,4 diketone (scheme 4.10).



5 33

Scheme 4.10. Synthetic scheme for the secondary product of **5** with 4-(pyridin-2-yl)aniline affording 5,11,17,23-tetra-tert-butyl-2,8,14,-tris(1-(phenyl-2-pyridyl)-2-methyl-1*H*-pyrrole)-20- (pentane-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene **33**.

Compound **33** was isolated in 30% yield which is significant when compared to the 33% yield for the fully substituted analogue. Compound **33** was analysed using ^{1}H NMR spectroscopy to reveal a clearly de-symmetrised product with a vast array of signals in the aromatic region and the distinctive *t*-butyl, OMe and 2-methylpyrrole environments displayed as 4 signals. Two multiplets were observed at 2.70 and 2.52 ppm, indicative of the diketone still being present. Further analysis using IR spectroscopy displayed a distinctive carbonyl stretch at 1715 cm^{-1} and the presence of a diketone was further confirmed using ^{13}C NMR spectroscopy whereby two carbonyl signals at 209.24 and 207.33 ppm were observed. Mass spectrometry using ESI-MS displayed a peak 1521.96 m/z corresponding to the $[M+Na]^{+}$ values for **33**. A single crystal grown from slow evaporation of DCM was analysed using single crystal X-ray diffraction studies. The unit cell was found to be monoclinic and the structure solution was carried out in the space group $P2_1/c$ (Figure 4.11).

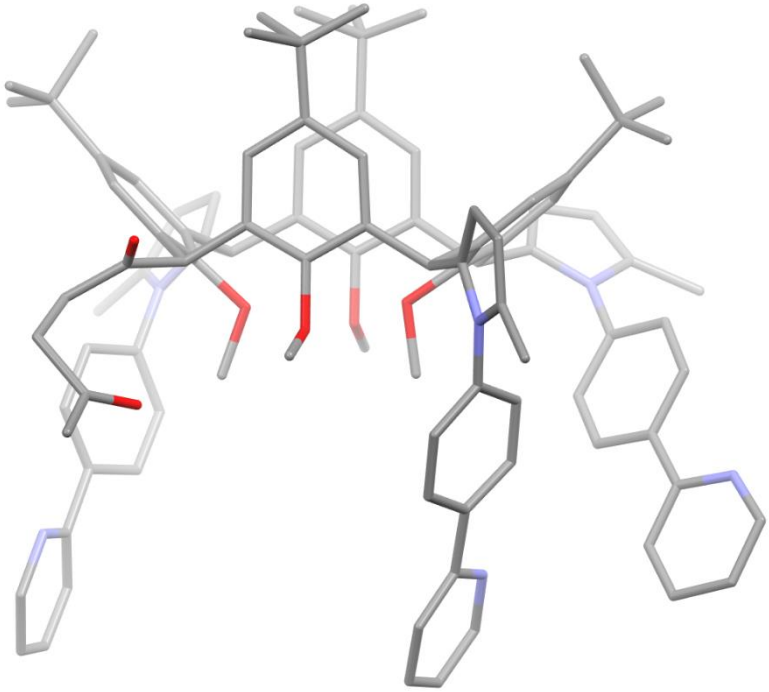
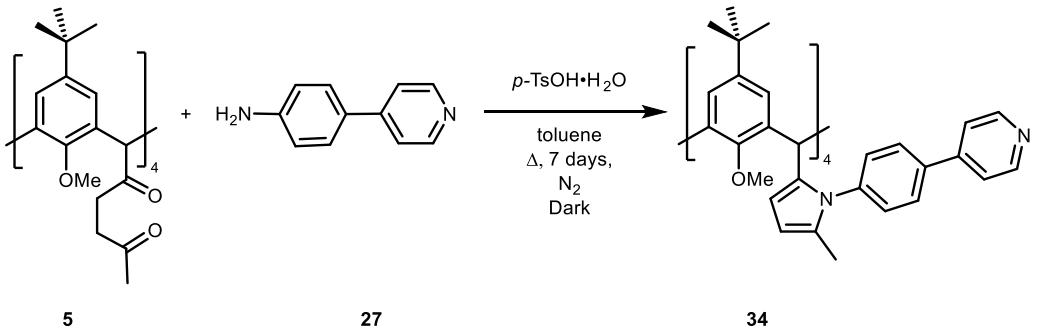


Figure 4.11. Sticks representation of the single crystal X-ray structure of **33** displaying a tris-substituted 2-pyridyl calix[4]arene. Colour code C- Grey; O -Red; N – Blue. H atoms omitted for clarity. Some solvent has been masked (DCM) due to inability to model sufficiently.

Inspection of Figure 4.11 shows that three calix[4]arene diketone bridge positions have been ring closed to form the respective 2-pyridyl extended pyrrole. One diketone position is observed to be unreacted which aligns with the other characterisation data outlined above. The calix[4]arene has adopted the pinched cone conformation and the extended 2-pyridyl groups are seen pointing downwards and oriented towards the splayed side of the structure. The solvent of crystallisation of DCM was unable to be modelled and so a solvent mask was utilised in this instance.

4.3.3. Synthesis of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-4-pyridyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 34.

The final compound to be investigated in this series was the 4-pyridyl analogue and therefore reaction of **5** with the previously synthesised 4-(4-pyridyl)aniline **27** was investigated by refluxing in toluene under N_2 for 7 days using *p*-TsOH·H_2O as a catalyst and wrapping in aluminium foil to mimic a dark reaction (Scheme 4.11).



5 **27** **34**

Scheme 4.11. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-4-pyridyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene **34**.

Following a 7-day reflux the reaction was worked up and purified using column chromatography, affording compound **34** in 13% yield. Analysis using ^{1}H NMR confirmed that the product had ring closed as the distinctive diketone signals for the backbone had disappeared whilst two new set of doublets can be seen further downfield, indicating a different compound is present. The calix[4]arene was clearly symmetrical due to the number of signals present, with only 2 signals for *t*-butyl and OMe environments and 1 signal for the 2-methyl pyrrole environment. IR and ^{13}C NMR spectroscopy showed no evidence of carbonyl stretches. ESI-MS confirmed product synthesis as peaks at 1634.74 m/z and 1656.93 corresponding to $[M+H]^+$ and $[M+Na]^+$ respectively. Single crystals suitable for X-ray diffraction were grown from a saturated solution of acetone. The unit cell was found to be triclinic and the structure solution carried out in $P\bar{1}$ (Figure 4.12). Inspection of Figure 4.12 clearly shows the desired product has formed with a reaction occurring at every diketone position on the calix[4]arene forming the desired pyrrole. The calix[4]arene is also seen to adopt the pinched cone conformation with 3 of the 4-pyridyl groups facing downwards towards the

lower-rim cavity and one angled out towards the splayed area of the cone. This is mostly likely due to the acetone sitting in the cavity occupying the space in which this substituent would usually inhabit. Two molecules of acetone are found within the structure, both of which reside near the periphery of the calixarene and are seen to occupy pockets between calix[4]arene units in the expanded structure. Two of the pyridyl rings were discovered to be disordered over two positions and were subsequently modelled at 0.6 and 0.4 occupancy.

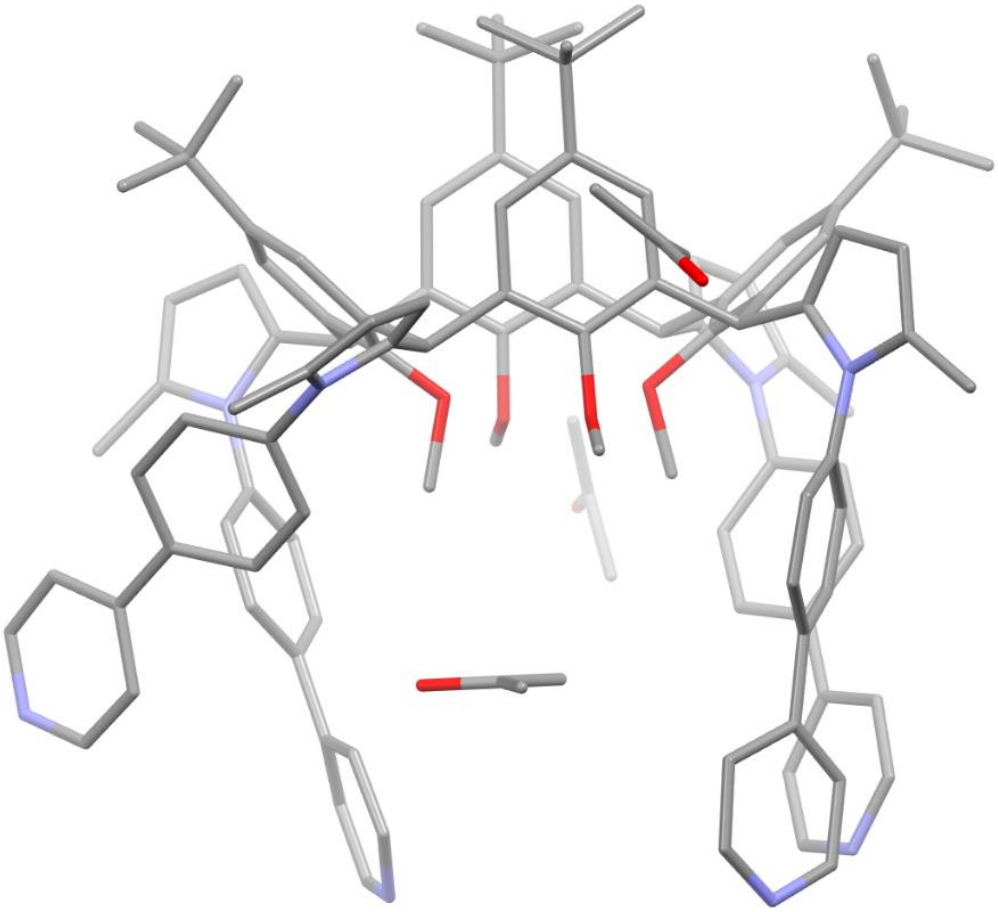
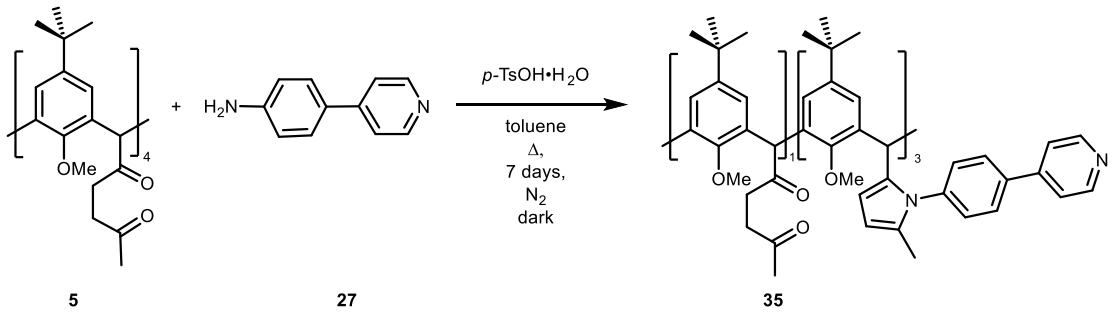


Figure 4.12. Sticks representation of the single crystal X-ray structure of **34** displaying a tetra-substituted 4-pyridyl-pyrrole calix[4]arene with acetone contained in the crystal lattice. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

Just as was the case with the reaction of **5** with 4-(2-pyridyl) aniline, a secondary product was isolated from the column in 22% yield. This was found to be the partially substituted tris-pyrrole, **35** (Scheme 4.12).



5 27 35

Scheme 4.12. Synthetic scheme for the secondary product of **5** with 4-(pyridin-4-yl)aniline affording 5,11,17,23-tetra-tert-butyl-2,8,14,-tris(1-(phenyl-4-pyridyl)-2-methyl-1*H*-pyrrole)-20- (pentane-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, **35**.

Analysis through ^{1}H NMR spectroscopy showed a typical de-symmetrised calix[4]arene observing the *t*-butyl and OMe environments as 4 signals. A multiplet at 2.78 – 2.50 ppm integrating to 4H was observed indicating the presence of the diketone backbone. Carbonyl stretches were observed in the ^{13}C NMR spectrum at 209.12 and 207.22 ppm. ESI-MS displayed signals at 1500.83 and 1521.98 m/z relating to $[M+H]^+$ and $[M+Na]^+$ confirming the synthesis. Single crystals suitable for X-ray diffraction analysis were grown from a saturated acetone solution. The unit cell was monoclinic and the structure solution carried out in space group *C*2/*c* (Figure 4.13). From Figure 4.13 it can be observed that three diketone positions have ring closed to the pyrrole whilst one is left unreacted. The diketone position was found to be disordered within the crystal and was modelled over two positions at 0.6 and 0.4 occupancy although only one position is shown in the Figure. Three acetone molecules are modelled within the crystal structure. One can be seen at the front of Figure 4.13 sitting close to the lower-rim cavity and two are located at the back.

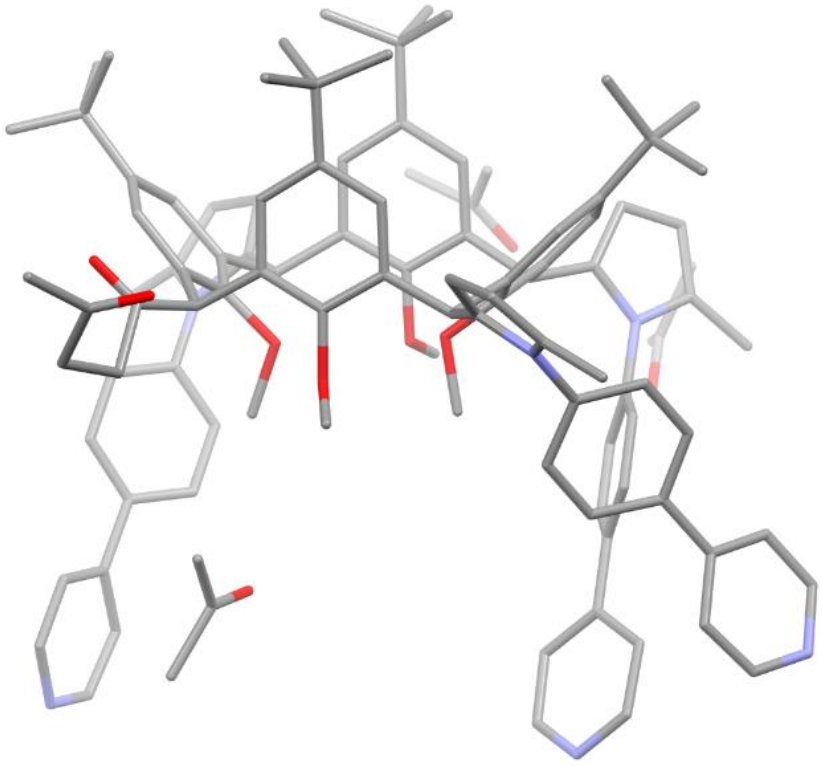
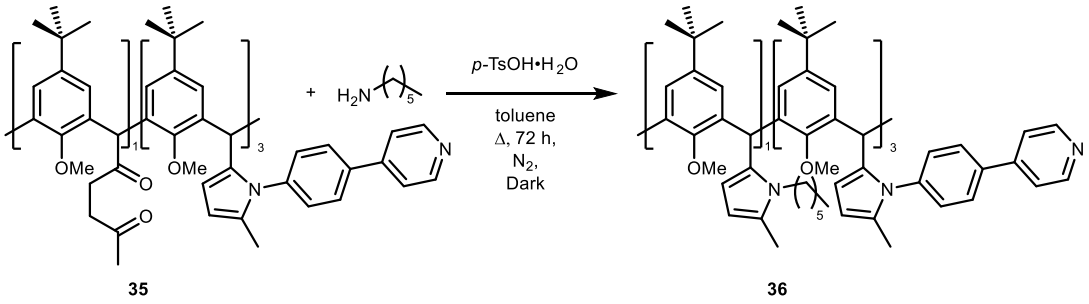


Figure 4.13. Sticks representation of the partial single crystal X-ray structure of **35** displaying a tris-substituted 4-pyridyl calix[4]arene. Disorder was observed within two of the pyridyl rings and modelled over two positions however only one position is shown in the Figure. Colour code C - Grey; O - Red; N - Blue. H atoms omitted for clarity.

As seen in both the reaction of **5** with 2-/4-pyridyl aniline a mixture of products are forming. Initial studies from the crude reaction of **5** with 2-pyridyl aniline were analysed using ESI-MS to determine if product formation was occurring. From the mass spectrum 4 clear peaks could be identified with m/z values of 1114.67, 1231.71, 1365.76 and 1500.83. These correspond to starting material, mono-, di- and tri-substituted pyrrole, respectively. This demonstrates that all that partially substituted derivatives are being formed and could therefore be isolated. It is theorised that if reaction was stopped after varying lengths of time the major product would differ. This discovery could be utilised to form asymmetrical calix[4]arenes with 2-/4- pyridyl groups at differing number of positions and alternative groups at other bridge positions. To trail this idea using the limited time left on this project the reaction of the tris-substituted 4-pyridyl **35** with

hexylamine was investigated. Compound **35** was refluxed with hexylamine, *p*-TsOH·H_2O as a catalyst under N_2 wrapped in foil to mimic a dark reaction (Scheme 4.13).



Scheme 4.13. Synthetic scheme for the preparation of 5,11,17,23-tetra-tert-butyl-2,8,14,-tris(1-(phenyl-4-pyridyl)-2-methyl-1*H*-pyrrole)-20-1-hexyl-2-methyl-1H-pyrrole 25,26,27,28-tetramethoxycalix[4]arene **36**.

Following a three-day reflux, the reaction was worked-up and analysed via ^{1}H NMR spectroscopy. The spectrum showed loss of the diketone multiplet, shifting of the *t*-butyl and OMe peaks and introduction of an additional set of doublets at 5.71 and 5.68 ppm with ^3J coupling values of 3.3 Hz. This would indicate that a reaction has taken place and the diketone has ring closed to form the pyrrole. Analysis using ^{13}C NMR and IR spectroscopy displayed no carbonyl signals, adding further evidence that a reaction had occurred. ASAP-MS was used and confirmed product formation displaying signals at 1566.00 and 1565.10 relating to the $[M]^-$ and $[M-H]^-$ peaks. A crystal of this compound is currently trying to be obtained, however up to this point attempts have been unsuccessful. This reaction displays another future possibility that could be investigated bringing about a new variety of methylene bridge substituted calix[4]arenes introducing multiple different functionalities.

Now the tetra-substituted pyridyl pyrroles have all been synthesised, and if time permitted on this project, the next step would be to react with a variety of metal salts and investigate the differences to those previously synthesised by Fong[5] to determine if by adding a phenyl spacer, the chelation displayed in Figure 4.1 still occurred.

4.4. Summary and Conclusion.

This chapter has discussed the synthesis of methylene bridge substituted calix[4]arenes possessing pyridyl groups in the 2-,3- and 4- positions. The different methodologies trialled for forming extended pyridyl systems was investigated before discussing aniline synthesis, and the subsequent reaction with **5** through the Paal-Knorr synthesis. The reaction of 4-(3-pyridyl) aniline with **5** was shown to be complete after 72 hours and the tetra-substituted pyrrole was isolated, and full characterisation obtained. The 2- and 4-pyridyl analogues showed longer reaction times were necessary to obtain the tetra-substituted analogue, however even after 7 days the major product varied between the tetra and tri-substituted derivatives, thus indicating that the reaction was still being hindered in comparison to the 3-pyridyl, and that longer reaction times could be required to increase conversion to the fully substituted product. It would also be of interest to trail different higher boiling point solvents such as *m*-xylene to observe if this had any effect on product formation. The long reaction times could, however, be a useful advantage by enabling the synthesis of other substituted derivatives by just reducing reaction time. By monitoring the reaction, it should be possible to formulate procedures which produce major products of the mono, di, tri and tris substituted analogues based on the length of reaction.

All five of the pyridyl compounds isolated were fully characterised and crystal structures obtained and modelled. The discovery of partially substituted calix[4]arenes led to the idea of synthesising asymmetrical methylene bridge calix[4]arenes. Compound **35** was chosen to trail the idea and the reaction with hexylamine was undertaken, affording the asymmetrical calix[4]arene **36**.

The lower-rim deprotection of the compounds discussed in chapter **3** has proved to be challenging. Due to this, future work in this area would focus around testing the tetra methoxy pyridyl species for metal coordination comparing to work previously performed within the group. Another area worthy of investigation would be reaction times or temperature for the synthesis of partially substituted pyrroles calix[4]arenes, as well as onward reaction with a variety of anilines to form asymmetrically substituted molecules.

4.5. Experimental.

4-(pyridin-4-yl)phenylcarbamate, 28.

Suzuki-Miyaura coupling reaction of tert-butyl 4-bromophenylcarbamate (800 mg, 2.95 mmol) with 4-pyridineboronic acid (300 mg, 2.46 mmol) in the presence of $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) and K_2CO_3 (678 mg, 4.9 mmol) in dioxane:H_2O (4:1, 10 mL) at 90 ºC for 14 hrs. *tert*-butyl 4-(pyridin 4-yl)phenylcarbamate (561 mg, 84.4 %) was obtained after column chromatography (DCM:MeOH, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 4.5, 1.7 Hz, 2H), 7.62 – 7.57 (m, 2H), 7.52 – 7.45 (m, 4H), 6.64 (br. s, 1H), 1.54 (s, 9H).

Crystal Data for $C_{16}H_{18}N_2O_2$ (*M* =270.32 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 5.6961(8) Å, *b* = 18.536(2) Å, *c* = 13.639(3) Å, *β* = 101.716(6)°, *V* = 1410.1(4) Å^3, *Z* = 4, *T* = 100(2) K, μ(CuKα) = 0.682 mm^{-1}, *Dcalc* = 1.273 g/cm^3, 35406 reflections measured (8.16° ≤ 2Θ ≤ 144.86°), 2759 unique (R_{int} = 0.0410, R_{sigma} = 0.0172) which were used in all calculations. The final R_1 was 0.0353 (I > 2σ(I)) and wR_2 was 0.0890 (all data).

4-(pyridine-4-yl)aniline, 27.

Tert-butyl 4-(pyridin-4-yl)phenylcarbamate (561 mg, 1.58 mmol) was treated with DCM:TFA (5:1, 2.5 mL) and stirred overnight at room temperature followed by dissolution in EtOAc, aqueous work up, washing with $NaHCO_3$ (3 × 50 mL) and water (2 × 50 mL), dried over $MgSO_4$ before removal of solvent. Work up was necessary due to formation of TFA salt which could not be removed under vacuum. 4-(pyridine-4-yl)aniline (340 mg, 98 %) as a yellow solid.

Overall yield for two steps: 81.2%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.52 – 7.47 (m, 2H), 7.44 (dd, *J* = 4.5, 1.7 Hz, 2H), 6.80 – 6.74 (m, 2H), 3.87 (br. s, 2H).

Crystal Data for $C_{22}H_{22}ClN_4$ (M =377.88 g/mol): monoclinic, space group C2/c (no. 15), a = 22.6652(6) Å, b = 7.4583(2) Å, c = 11.0266(3) Å, β = 96.2017(9)°, V = 1853.07(9) Å^3, Z = 4, T = 100(2) K, μ(CuKα) = 1.926 mm-1, Dcalc = 1.354 g/cm^3, 18188 reflections measured (7.848° ≤ 2Θ ≤ 148.978°), 1882 unique (Rint = 0.0336,

Rsigma = 0.0220) which were used in all calculations. The final R1 was 0.0295 ($I > 2\sigma(I)$) and wR2 was 0.0800 (all data).

TFA salt of 27.

Crystal Data for $C_{13}H_{13}F_3N_2O_3$ (M =302.25 g/mol): triclinic, space group P-1 (no. 2), a = 7.8836(3) Å, b = 7.9262(3) Å, c = 10.7932(4) Å, α = 86.3850(10)°, β = 89.4960(10)°, γ = 83.6410(10)°, V = 668.95(4) Å^3, Z = 2, T = 100(2) K, μ(CuKα) = 1.175 mm^{-1}, *Dcalc* = 1.501 g/cm^3, 17168 reflections measured (8.208° ≤ 2Θ ≤ 144.148°), 2586 unique (R_{int} = 0.0344, R_{sigma} = 0.0305) which were used in all calculations. The final R_1 was 0.0767 ($I > 2\sigma(I)$) and wR_2 was 0.2718 (all data).

***Tert*-butyl 4-(pyridin-3-yl)phenylcarbamate, 29.**

Suzuki coupling reaction of tert-butyl 4-bromophenylcarbamate (800 mg, 2.95 mmol) with 3-pyridineboronic acid (300 mg, 2.46 mmol) in the presence of $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) and K_2CO_3 (678 mg, 4.9 mmol) in dioxane:H_2O (4:1, 10 mL) at 90 ºC for 14 hr. *tert*-Butyl 4-(pyridin 3-yl)phenylcarbamate (426 mg, 64 %) was obtained after column chromatography (DCM:MeOH, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, J = 2.3, 0.7 Hz, 1H), 8.55 (dd, J = 4.8, 1.6 Hz, 1H), 7.83 (ddd, J = 7.9, 2.3, 1.7 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.33 (ddd, J = 7.9, 4.8, 0.8 Hz, 1H), 6.73 (br. s, 1H), 1.53 (s, 9H).

Crystal Data for $C_{16}H_{18}N_2O_2$ (M =270.32 g/mol): orthorhombic, space group $Pna2_1$ (no. 33), a = 20.1193(3) Å, b = 9.77180(10) Å, c = 7.14350(10) Å, V = 1404.42(3) Å^3, Z = 4, T = 100(2) K, μ(CuKα) = 0.685 mm^{-1}, *Dcalc* = 1.278 g/cm^3, 27398 reflections measured (8.79° ≤ 2Θ ≤ 149.134°), 2833 unique (R_{int} = 0.0371, R_{sigma} = 0.0189) which were used in all calculations. The final R_1 was 0.0255 ($I > 2\sigma(I)$) and wR_2 was 0.0692 (all data).

4-(Pyridin-3-yl)aniline, 30.

Tert-butyl 4-(pyridin-4-yl)phenylcarbamate (426 mg, 1.58 mmol) was treated with DCM:TFA (5:1, 2.5 mL) and stirred overnight at room temperature followed by dissolution in EtOAc, aqueous work up, washing with $NaHCO_3$ (3 × 50 mL) and water (2 × 50 mL), dried over $MgSO_4$ before removal of solvent. Work up was necessary due to

formation of TFA salt which could not be removed under vacuum. 4-(pyridine-3-yl)aniline was obtained in (263 mg, 98 %) yield as a yellow solid.

Overall yield of two steps: 62.8%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 2.4, 0.7 Hz, 1H), 8.44 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.74 (ddd, *J* = 7.9, 2.4, 1.7 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.24 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 6.74 – 6.69 (m, 1H), 3.63 (s, 2H).

Crystal Data for $C_{11}H_{12}N_2O$ (*M* =188.23 g/mol): orthorhombic, space group Pbca (no. 61), *a* = 10.08790(10) Å, *b* = 8.36980(10) Å, *c* = 22.6208(3) Å, *V* = 1909.96(4) Å^3, *Z* = 8, *T* = 100(2) K, μ(CuKα) = 0.690 mm^{-1}, *Dcalc* = 1.309 g/cm^3, 31799 reflections measured (7.816° ≤ 2Θ ≤ 149.12°), 1926 unique (R_{int} = 0.0420, R_{sigma} = 0.0206) which were used in all calculations. The final R_1 was 0.0323 (I > 2σ(I)) and wR_2 was 0.0901 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-3-pyridyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene 31.

Compound **5**, (0.200 g, 0.1824 mmol), 3-pyridylaniline (0.1375 g, 0.766 mmol) and *p*-TsOH·H_2O (0.010 g) in toluene (50 mL) wrapped in foil and was heated at reflux for 3 days, under N_2. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed once 1M HCl, twice with water (2 × 50 mL) and once with brine (1 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by column chromatography (DCM:MeOH 98: 2 → 90:10 in 2 % increments) to obtain **31** as an off white powder (90 mg, 30 %)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 1.9 Hz, 4H), 8.42 (dd, *J* = 4.8, 1.5 Hz, 4H), 7.57 (d, *J* = 7.6 Hz, 4H), 7.54 – 7.49 (m, 4H), 7.29 (d, *J* = 7.6 Hz, 4H), 7.10 (dd, *J* = 7.8, 4.8 Hz, 4H), 7.01 (d, *J* = 7.5 Hz, 4H), 6.90 (s, 4H), 6.77 (d, *J* = 7.5 Hz, 4H), 6.46 (s, 4H), 6.02 (d, *J* = 3.3 Hz, 4H), 5.96 – 5.93 (m, 4H), 5.44 (s, 4H), 3.23 (s, 6H), 2.82 (s, 6H), 1.99 (s, 12H), 1.25 (s, 18H), 0.89 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.57, 153.15, 148.57, 147.93, 144.57, 143.43, 139.55, 137.64, 136.53, 135.18, 133.96, 133.86, 132.66, 129.90, 129.37, 129.24, 127.31, 126.85, 124.64, 123.39, 122.59, 109.77, 106.24, 62.15,

58.85, 36.24, 34.37, 33.75, 31.73, 31.17, 13.29. ASAP-MS: $[M]^+$ 1634.15, $[M+H]^+$ 1635.10.

Crystal Data for $C_{114}H_{113.4}Cl_6N_8O_4$ (M =1872.22 g/mol): monoclinic, space group P2 (no. 3), a = 15.8974(3) Å, b = 15.7057(2) Å, c = 19.5699(3) Å, β = 90.1040(10)°, V = 4886.20(13) $Å^3$, Z = 2, T = 100(2) K, μ(CuKα) = 2.061 mm-1, Dcalc = 1.273 g/cm3, 93665 reflections measured (5.626° ≤ 2Θ ≤ 144.904°), 18979 unique (Rint = 0.0515, Rsigma = 0.0397) which were used in all calculations. The final R1 was 0.0719 (I > 2σ(I)) and wR2 was 0.2168 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-2-pyridyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 32.

Compound **5**, (0.250 g, 0.228 mmol), 4-(2-Pyridyl)aniline (0.162 g, 0.956 mmol), *p*-TsOH·H_2O (0.010 g) toluene (50 mL) was heated at reflux for 7 days under N_2. The apparatus was wrapped with aluminium foil to avoid any potential light degradation. Following reflux reaction mixture was cooled to room temperature and solvent removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed once with 1M HCl (1 × 50 mL, twice with water (2 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified via column chromatography (DCM/EtOAc 4:1) to yield 0.122 mg (33%) of **32**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.47 (m, 4H), 8.11 (br. s, 4H), 7.52 – 7.47 (m, 4H), 7.48 (br. s, 4H), 7.32 (d, J = 7.9 Hz, 4H), 7.26 – 7.23 (m, 4H), 7.05 (ddd, J = 7.4, 4.9, 0.8 Hz, 4H), 6.94 (s, 4H), 6.78 (s, 4H), 6.46 (s, 4H), 6.03 (d, J = 3.3 Hz, 4H), 5.94 (d, J = 3.1 Hz, 4H), 5.44 (s, 4H), 3.18 (s, 6H), 2.77 (s, 6H), 1.96 (s, 12H), 1.24 (s, 18H), 0.88 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.47, 153.83, 153.31, 149.72, 144.45, 143.49, 140.29, 138.32, 137.72, 136.80, 134.22, 132.97, 129.28, 124.66, 122.75, 122.21, 120.61, 109.58, 106.23, 62.37, 59.03, 36.28, 34.51, 33.87, 31.87, 31.33, 13.38. ESI-MS: 1634.89, $[M+H]^+$, 1656.88, $[M+Na]^+$.

Crystal Data for $C_{119}H_{118.5}N_8O_4$ (*M* =1724.71 g/mol): orthorhombic, space group $P2_12_12$ (no. 18), *a* = 15.9627(10) Å, *b* = 19.6253(10) Å, *c* = 15.8255(10) Å, *V* = 4957.7(5) $Å^3$, *Z* = 2, *T* = 100(2) K, μ(CuKα) = 0.540 mm^{-1}, *Dcalc* = 1.155 g/cm^3, 76327 reflections measured (5.584° ≤ 2Θ ≤ 127.952°), 8244 unique (R_{int} = 0.0783, R_{sigma} =

0.0356) which were used in all calculations. The final R_1 was 0.0778 ($I > 2\sigma(I)$) and wR_2 was 0.2199 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,-tris(1-(phenyl-2-pyridyl)-2-methyl-1*H*-pyrrole)-20- (pentane-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, 33.

Compound **5**, (0.250 g, 0.228 mmol), 4-(2-Pyridyl)aniline (0.162 g, 0.956 mmol), *p*-TsOH·H_2O (0.010 g) toluene (50 mL) was heated at reflux for 7 days under N_2. The apparatus was wrapped with aluminium foil to avoid any potential light degradation. Following reflux reaction mixture was cooled to room temperature and solvent removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed once with 1M HCl (1 × 50 mL), twice with water (2 × 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure to yield a crude. The crude was purified via column chromatography (DCM/EtOAc 4:1) to yield 0.102 mg (30%) of **33**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.1 Hz, 1H), 8.60 – 8.54 (m, 2H), 8.23 – 8.05 (m, 3H), 7.77 – 7.64 (m, 3H), 7.60 – 7.47 (m, 4H), 7.45 – 7.30 (m, 5H), 7.22 (dd, *J* = 6.8, 5.3 Hz, 1H), 7.14 – 7.06 (m, 2H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.83 – 6.78 (m, 3H), 6.76 (d, *J* = 2.2 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.10 (d, *J* = 3.3 Hz, 1H), 6.00 (dd, *J* = 9.3, 3.1 Hz, 3H), 5.93 (s, 2H), 5.55 (d, *J* = 7.6 Hz, 2H), 5.46 (d, *J* = 7.2 Hz, 2H), 3.34 (s, 3H), 3.27 (s, 3H), 3.03 (s, 3H), 2.94 (s, 3H), 2.85 – 2.70 (m, 3H), 2.65 – 2.55 (m, 1H), 2.14 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.25 (s, 9H), 1.23 (s, 9H), 0.87 (s, 9H), 0.84 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.24, 207.33, 156.61, 156.48, 156.40, 154.52, 153.92, 153.78, 153.32, 149.86, 149.76, 145.38, 144.58, 143.80, 140.27, 140.22, 140.17, 138.87, 138.81, 138.46, 138.37, 137.70, 137.59, 137.02, 136.82, 134.04, 133.92, 133.84, 133.40, 133.35, 133.07, 132.00, 129.64, 129.44, 129.25, 128.03, 126.98, 125.77, 125.05, 124.76, 123.88, 122.88, 122.47, 122.29, 121.43, 120.66, 120.57, 109.83, 109.58, 109.30, 106.40, 106.27, 105.69, 62.61, 62.56, 59.79, 58.99, 50.95, 37.60, 36.46, 36.37, 36.24, 34.54, 34.47, 33.89, 33.83, 31.86, 31.77, 31.33, 31.24, 30.11, 13.43, 13.38, 13.16, 1.16. ESI-MS: 1521.97, $[M+Na]^+$.

Crystal Data for $C_{102.5}H_{109}Cl_3N_6O_6$ (*M* =1627.30 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 14.5827(4) Å, *b* = 27.9149(10) Å, *c* = 23.2007(9) Å, *β* = 106.110(2)°, *V* = 9073.6(5) Å^3, *Z* = 4, *T* = 100(2) K, μ(CuKα) = 1.361 mm^{-1}, *Dcalc* = 1.191 g/cm^3, 96195

reflections measured (5.074° ≤ 2Θ ≤ 117.732°), 12953 unique (R_{int} = 0.1530, R_{sigma} = 0.1010) which were used in all calculations. The final R_1 was 0.0999 (I > 2σ(I)) and wR_2 was 0.3311 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrakis(1-(phenyl-4-pyridyl)-2-methyl-1*H*-pyrrole)-25,26,27,28-tetramethoxycalix[4]arene, 34.

Compound **5,** (0.522 g, 0.1824 mmol), 4-(pyridine-4-yl)aniline (0.3404 g, 0.766 mmol) and *p*-TsOH·H_2O (0.020 g) in toluene (125 mL) wrapped in foil and was heated at reflux for 7 days, under N_2. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed once with twice with water (2 × 50 mL) and once with $NaHCO_3$ (1 × 50 mL). The organic phase was dried over MgSO4 and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by column chromatography (DCM/MeOH 2% → 10%) to obtain 0.094 (13%) of **34**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 3.2 Hz, 8H), 7.58 (br. s, 4H), 7.28 (br. s, 4H), 7.17 (d, J = 5.3 Hz, 8H), 7.05 (br. s, 4H), 6.91 (s, 4H), 6.79 (br. s, 4H), 6.45 (s, 4H), 6.02 (d, J = 3.2 Hz, 4H), 5.96 (d, J = 3.0 Hz, 4H), 5.43 (s, 4H), 3.21 (S, 6H), 2.83 (s, 6H), 1.98 (s, 12H), 1.25 (s,18H), 0.88 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.56, 153.05, 150.40, 146.80, 144.61, 143.55, 140.43, 137.49, 136.81, 133.89, 132.63, 129.25, 124.69, 122.68, 121.13, 109.98, 106.48, 77.35, 77.23, 77.03, 76.71, 62.21, 58.74, 36.21, 34.39, 33.76, 31.72, 31.16, 13.31. ESI-MS: 1634.74, $[M+H]^+$.

Crystal Data for $C_{121}H_{131}N_8O_7$ (*M* =1809.33 g/mol): triclinic, space group P-1 (no. 2), *a* = 14.3757(3) Å, *b* = 15.6881(3) Å, *c* = 26.2958(5) Å, *α* = 95.4750(10)°, *β* = 95.4550(10)°, *γ* = 117.0340(10)°, *V* = 5193.87(18) Å^3, *Z* = 2, *T* = 100(2) K, μ(CuKα) = 0.557 mm^{-1}, *Dcalc* = 1.157 g/cm^3, 164827 reflections measured (6.404° ≤ 2Θ ≤ 144.452°), 20476 unique (R_{int} = 0.0519, R_{sigma} = 0.0278) which were used in all calculations. The final R_1 was 0.0806 (I > 2σ(I)) and wR_2 was 0.2517 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,-tris(1-(phenyl-2-pyridyl)-2-methyl-1*H*-pyrrole)-20- (pentane-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene, 35.

Compound **5**, (0.522 g, 0.1824 mmol), 4-(pyridine-4-yl)aniline (0.3404 g, 0.766 mmol) and *p*-TsOH·H_2O (0.020 g) in toluene (125 mL) wrapped in foil and was heated at reflux for 7 days, under N_2. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and then washed once with twice with water (2 × 50 mL) and once with $NaHCO_3$ (1 × 50 mL). The organic phase was dried over MgSO4 and then the solvent was removed under reduced pressure to yield a crude. The crude was purified by Column Chromatography (DCM:MeOH 2% → 10%) to obtain 0.0158 g (22%) of **35**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 – 8.49 (m, 6H), 7.66 (br. s, 3H), 7.42 (d, *J* = 5.6 Hz, 2H), 7.40 – 7.32 (br. s, 3H), 7.24 (d, *J* = 6.0 Hz, 2H), 7.18 (d, *J* = 5.5 Hz, 2H), 7.15 (br. s, 1H), 7.06 (br s, 1H), 6.95 (s, 2H), 6.89 (d, *J* = 1.8 Hz, 1H), 6.84 (br. s, 1H), 6.76 (d, *J* = 1.9 Hz, 1H), 6.81 – 6.73 (br. s, 3H), 6.55 (d, *J* = 2.1 Hz, 1H), 6.46 (s, 2H), 6.35 (d, *J* = 2.1 Hz, 1H), 6.09 – 5.93 (m, 6H), 5.55 (s, 1H), 5.54 (s, 1H), 5.46 (s, 1H), 5.42 (s, 1H), 3.38 (s, 3H), 3.27 (s, 3H), 3.08 (s, 3H), 2.95 (s, 3H), 2.86 – 2.57 (m, 4H), 2.16 (s, 3H), 2.00 (m, 9H), 1.25 (s, 9H), 1.24 (s, 9H), 0.86 (s, 9H), 0.84 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.99, 207.09, 154.26, 153.70, 153.52, 153.19, 150.46, 150.39, 147.25, 146.81, 145.41, 144.71, 143.88, 143.78, 140.44, 140.37, 140.24, 138.50, 137.54, 137.38, 136.91, 136.84, 133.84, 133.77, 133.57, 133.28, 132.93, 132.88, 131.62, 129.59, 129.28, 129.16, 127.90, 127.08, 126.83, 125.55, 125.19, 124.81, 124.72, 123.83, 122.84, 122.73, 121.44, 121.20, 109.99, 109.46, 106.58, 105.76, 62.53, 62.42, 59.56, 58.70, 51.08, 37.46, 36.44, 36.21, 36.14, 36.03, 34.42, 34.34, 33.77, 33.71, 31.70, 31.62, 31.16, 31.09, 29.98, 13.34, 13.30, 13.04. ESI-MS: 1500.83, $[M+H]^+$, 1521.98, $[M+Na]^+$.

Crystal Data for $C_{108.5}H_{121}N_6O_{8.5}$ (*M* =1645.11 g/mol): monoclinic, space group C2/c (no. 15), *a* = 23.6399(9) Å, *b* = 18.1324(8) Å, *c* = 46.3176(17) Å, *β* = 94.5216(13)°, *V* = 19792.2(14) Å^3, *Z* = 8, *T* = 100(2) K, μ(CuKα) = 0.544 mm^{-1}, *Dcalc* = 1.104 g/cm^3, 34230 reflections measured (3.828° ≤ 2Θ ≤ 144.976°), 18213 unique (R_{int} = 0.0562, R_{sigma} = 0.0783) which were used in all calculations. The final R_1 was 0.0981 (I > 2σ(I)) and wR_2 was 0.3130 (all data).

5,11,17,23-tetra-tert-butyl-2,8,14,-tris(1-(phenyl-4-pyridyl)-2-methyl-1*H*-pyrrole)-20- 1-hexyl-2-methyl-1H-pyrrole 25,26,27,28-tetramethoxycalix[4]arene, 36.

5,11,17,23-tetra-tert-butyl-2,8,14,-tris(1-(phenyl-2-pyridyl)-2-methyl-1H-pyrrole)-20-(pentane-1,4-dione)-25,26,27,28-tetramethoxycalix[4]arene **35** (0.158 g, 0.105 mmol), Hexylamine (0.0146 mL, 0.110 mmol) and *p*-TsOH·H_2O (0.010 g) in toluene (50 mL) was heated at reflux for 3 days under N_2 wrapped in aluminium foil. The reaction mixture was cooled to room temperature and then the solvent was removed under reduced pressure. The solid was dissolved in $CHCl_3$ and washed three times with water (3 x 50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was removed under reduced pressure. A yellow solid was crashed out of Acetone/pet ether and washed with cold pet ether to afford **36** (0.0509, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, *J* = 4.5, 1.6 Hz, 2H), 8.59 – 8.53 (m, 4H), 7.65 (br. s, 3H), 7.43 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.34 (br. s, 3H), 7.24 – 7.21 (m, 4H), 7.11 (br. s, 3H), 6.96 (dd, *J* = 14.1, 2.4 Hz, 2H), 6.82 (br. s, 3H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 8.5, 2.5 Hz, 2H), 6.47 – 6.44 (t, 2H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.12 (d, *J* = 3.3 Hz, 1H), 6.05 – 5.92 (m, 5H), 5.69 (dd, *J* = 13.4, 3.1 Hz, 2H), 5.56 – 5.49 (m, 4H), 3.39 (s, 3H), 3.27 (t, *J* = 7.4 Hz, 2H), 3.20 (s, 3H), 3.14 (s, 3H), 2.97 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H), 1.99 (s, 6H), 1.62 – 1.48 (m, 2H), 1.35 – 1.21 (m, 6H), 1.26 (s, 9H), 1.12 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.75 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.79, 153.73, 153.41, 150.57, 150.55, 150.52, 147.18, 147.06, 147.02, 145.16, 144.73, 143.83, 143.59, 140.70, 140.65, 140.61, 137.79, 137.71, 137.64, 137.55, 137.14, 136.94, 136.88, 134.28, 134.16, 132.95, 132.68, 132.38, 132.10, 131.95, 130.11, 129.61, 129.31, 128.04, 127.14, 126.95, 125.32, 125.09, 124.83, 124.66, 122.98, 122.94, 122.79, 121.86, 121.33, 121.29, 110.09, 110.03, 109.48, 108.69, 106.68, 106.60, 105.89, 104.98, 62.50, 62.47, 58.95, 58.88, 43.39, 36.52, 36.31, 36.26, 36.11, 34.54, 34.28, 33.91, 33.82, 31.85, 31.74, 31.67, 31.28, 31.24, 26.34, 24.06, 22.30, 17.65, 14.13, 13.47, 13.42, 13.17, 12.90. ASAP-MS: 1566.00, $[M]^-$; 1565.10, $[M-H]^-$

4.6. References.

1 R. Kumar, A. Sharma, H. Singh, P. Suating, H. S. Kim, K. Sunwoo, I. Shim, B. C. Gibb and J. S. Kim, *Chem. Rev.*, 2019, **119**, 9657–9721.

2 M. Fujita, *Chem. Soc. Rev.*, 1998, **27**, 417–425.

3 R. Saha, B. Mondal and P. S. Mukherjee, *Chem. Rev.*, 2022, **122**, 12244–12307.

4 Z. Zhong, A. Ikeda, M. Ayabe, S. Shinkai, S. Sakamoto and K. Yamaguchi, *J. Org. Chem.*, 2001, **66**, 1002–1008.

5 A. Fong, Heriot-Watt, 2019.

6 A. Fong, C. L. Campbell, S. Huynh, L. J. McCormick McPherson, S. J. Teat, M. W. P. Bebbington and S. J. Dalgarno, *Chem. Commun.*, 2022, **58**, 3302–3305.

7 R. K. Juneja, K. D. Robinson, C. P. Johnson and J. L. Atwood, *J. Am. Chem. Soc.*, 1993, **115**, 3818–3819.

8 H. R. Snyder, J. A. Kuck and J. R. Johnson, *J. Am. Chem. Soc.*, 1938, **60**, 105–111.

9 V. L. Gunderson, A. L. Smeigh, C. H. Kim, D. T. Co and M. R. Wasielewski, *J. Am. Chem. Soc.*, 2012, **134**, 4363–4372.

10 A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020–4028.

11 R. Li, M. P. Martin, Y. Liu, B. Wang, R. A. Patel, J.-Y. Zhu, N. Sun, R. Pireddu, N. J. Lawrence, J. Li, E. B. Haura, S.-S. Sung, W. C. Guida, E. Schonbrunn and S. M. Sebti, *J. Med. Chem.*, 2012, **55**, 2474–2478.

12 A. A. Gurinov, S. B. Lesnichin, H.-H. Limbach and I. G. Shenderovich, *J. Phys. Chem. A*, 2014, **118**, 10804–10812.

13 A. Hooper, A. Zambon and C. J. Springer, *Org. Biomol. Chem.*, 2016, **14**, 963–969.

14 K. K. Zborowski and J. Poater, *ACS Omega*, 2021, **6**, 24693–24699.

Chapter 5

Conclusions and Future Work.

Since the discovery of the first synthetic polymer by Adolf von Baeyer in 1907, a magnitude of research has gone into the investigation of the phenol-formaldehyde procedure. It is without doubt that the work performed by Gutsche and co-workers, in which they were able to produce what are now standard optimised procedures for the synthesis of calix[*n*]arenes in varying ring sizes, has propelled the use and application of C[*n*]s in modern chemistry. Many other research groups have used these procedures, and with that have gained fantastic insight into the composition, structure, and properties of these molecules through a range of different analytical techniques including NMR and Infrared spectroscopies, and single crystal X-ray diffraction (amongst others). This combined knowledge has paved a way for calix[*n*]arenes to play a key role in advancement of supramolecular chemistry over several decades.

The calix[*n*]arene scaffold has widely been explored and thus modification is of particular interest to synthetic and supramolecular chemists. This involves building specific functionality directly onto the framework, therefore allowing versatile macrocycles to be synthesised from the same initial building block. The calix[*n*]arene building block has seen use in many diverse areas of chemistry including enzyme mimicry, sensing, analytical chemistry, medicine, and gas sorption/storage, resulting in a large diversity of downstream possibilities. Modification of calix[*n*]arenes can be performed at three positions, the upper- and lower-rims along with the methylene bridge. The upper- and lower-rims have not been discussed in detail in this thesis although there is an extraordinary amount of research performed in these regions due to the well-known and understood acyl or alkylation reactions. The methylene bridge has received significantly less attention, a fact which is likely due to the need for more complicated synthetic pathways as seen in the introductory chapter. Calix[4]arene methylene bridge modification was most commonly performed using stepwise convergent synthesis. Lithiation methods were also used to great effect, however this is limited to modification at just one methylene bridge position. Mono functionalisation at every methylene bridge position has been achieved via two main starting points, the tetra-bromo and tetra-keto calix[4]arenes due to their ease of synthesis and ability to undergo nucleophilic

substitution. That said, work in this area is limited to a small number of research groups and so remains in its infancy. This thesis set out to explore the possibilities of a specific route to methylene bridge modified C[4]s utilising the tetra-bromo analogue in a multi-step procedure to form various heterocycles. The C[4] and its substituents all remain in the rccc isomer and the cone conformation is retained.

Chapter 2 presents one method for modification at the framework, replicating work previously done in this research group and introducing a 1,4 saturated diketone functionality at all the methylene bridge positions. The scope of using this as an intermediate in the Paal-Knorr pyrrole synthesis with a wide variety of anilines has been investigated, producing a library of pyrrole-appended methylene bridge C[4]s. The majority of reactions attempted proceeded towards the desired product, including the introduction of halogenated phenyls, phenyl ethers and large polycyclic aromatics at the methylene bridge positions. The reaction of **5** with 4-nitroaniline afforded a near equal quantity of two products. The first was the desired tetra-substituted product, **14**, followed by a tris-substituted, mono-furanyl C[4], **15**. It was discussed that furans can be synthesised from saturated 1,4 diketones in acidic media, and 4-nitroaniline possesses a low pKa value of 1.01. However, it is interesting that this is the only example in the scope explored that has identified furan formation through Paal-Knorr pyrrole reaction conditions, and notably in comparable yields to the desired product. This was also the first example in this study to form an asymmetric C[4] in which two different functionalities are present at the methylene bridge positions. These compounds have a wide variety of possible future work associated with them as nitro groups are used in many areas of chemistry. Although nitro groups are known to be poor hydrogen bond acceptors in the solid state, they are observed to play a key role in crystal packing and engineering through dipole-dipole interactions. This should help facilitate co-crystallisation with variety of guests, more notably those also possessing a nitro group due to key N-O···N-O type interactions. Guests of large interest in this area would be the common energetic moieties such as tri-nitrotoluene (TnT) or tri-nitrobenzene (TnB) as co-crystallisation has been shown to demonstrate decreased thermal decomposition.[1] Further derivation of this species could be attempted through reduction of the nitro group to a versatile amine which could be reacted further (or used in crystal engineering itself); this could be an interesting route to forming capsules by reaction with e.g. another equivalent of diketone **5**. Potential issues that could arise would be forming oligomers due to the number of available reaction sites, but classical approaches such as high

dilution may help avoid these pitfalls. The chapter finalises by forming napthyl and pyrene appended pyrrole C[4]s. These are large polycyclic aromatics and the use of 1-aminonapthalene and 1-aminopyrene introduces horizontal directional bulk rather than vertical when using para substituted anilines. This was shown to restrict the rotation of the groups appended at the pyrrole and 'lock' the conformation. Three different isomers were observed in the case of the napthyl derivative, one of which displayed two naphthalene groups splayed outwards and two pinched inwards (**16-1**). The other two isomers were unable to be separated via column chromatography and repeat re-crystallisations resulted in slightly better separation indicating that this could be achieved on larger scales. Using this slight separation, differences in the *t*-butyl, OMe and 2-methylpyrrole environments in the ^{1}H NMR spectrum were analysed in order to identify the isomer. A single crystal of **16-2** was obtained and analysed showing a symmetrical C_{2v} structure. The other structure **16-3** was identified as having 1-fold rotational axis due to four individual signals for the three key environments mentioned previously. Using this information, the isomer was predicted and similar properties were found for the pyrene derivative, however in this case only two isomers were identified and were unable to be separated via column chromatography (although small amounts of one isomer was isolated by washing with cold solvent). The isomers were determined to show similarities to **16-2** and **16-3** therefore the same analysis process was employed. No crystal structure was able to be obtained in this instance and so future work in this area should focus on separation of individual isomers for characterisation. Once pure isomers of each are obtained, UV-vis absorption and emission experiments should be performed. This could be a useful determination of host-guest chemistry as binding inside the lower cavity should impact the UV-vis absorbance and fluorescence.

Chapter 3 continues research into the scope of the Paal-Knorr synthesis by investigating alkyl amines and a boc-protected hydrazine. In all of these, the major product was identified as the desired tetra-substituted derivative. Other work in this chapter revolved around investigating alternative routes to methylene bridge modified C[4]s using the furan, **4**. Saturated diketone **5** was investigated for thiophene formation using different thiolating agents including H_2S, P_2S_5 and Lawessons reagent. The latter was the only one shown to successfully form the desired product (**23**) along with small impurities of other derived C[4]s. Despite being closely related to the furan analogue (**4**) which had been previously reported to undergo demethylation using cyclohexyl iodide, only small scale mono-demethylation was observed after a 72-hour reflux and therefore

the demethylating agent was deemed inappropriate. Work involving the use of BBr_3 to deprotect the lower-rim would be interesting to trial if time on the project permitted. This could then be investigated for metal cluster formation and compared with results obtained previously for the furan derivative. Other previous work identified a methylene bridge appended pyridazine C[4] (**25**) could be formed through oxidative ring opening of the furan to form an unsaturated 1,4 diketone and subsequent ring closure using hydrazine. The pyridazine species was fully deprotected utilising a two-step procedure involving BBr_3. The desired product (**26**) was isolated, and a crystal structure obtained displaying a 1,3 alternate conformation. The yield of the final product was low and future work should focus on improving this before investigation into potential uses such as in metal cluster formation or catalysis continues. Demethylation of a pyrrole appended C[4], **19**, was also investigated using BBr_3, however only small amounts of mono demethylation could be observed. Longer reaction times led to decomposition of the starting material and therefore BBr_3 was determined unsuitable for this deprotection. It is theorised that demethylation was hindered by the pyrrole group, so demethylation of saturated diketone **5** was attempted using standard conditions though this proved to be unsuccessful. Previous work had shown that leaving the furan C[4], **4**, refluxing in acidic conditions when synthesising **5** for long periods of time resulted in production of a mono-hydroxyl C[4], **$H_1$5**, which could be obtained in a reasonable yield. To determine if the Paal-Knorr synthesis was viable with a demethylated species, **$H_1$5** was reacted with hexylamine and the desired product (**$H_1$19**) was successfully formed. Having concluded that the presence of a hydroxyl group does not impact the pyrrole formation, future work should involve deprotecting the diketone derivative **5**, or potentially **4**, prior to formation of the pyrrole as a way to produce methylene bridged C[4]s with hydroxyl groups present at the lower-rim, thus circumventing the deprotection issue. Finally, chapter 3 concludes by discussing the stability of pyrrole appended C[4]s formed during the project, in particular that these were shown to be decomposing in solution due to the presence of light. The decomposition pathway and product are not yet understood, and more rigorous testing is required to elucidate this, however it was shown that remaining as a solid and avoiding light when in solution helped the product remain stable. Working on stabilising the pyrrole moiety is of high priority when synthesising methylene bridge pyrrole appended C[4]s.

Chapter 4 presents a route to forming methylene bridged C[4]s with pyridyl groups attached. In previous studies, only 3-aminopyridine was successful in the Paal-

Knorr synthesis, and so the chapter discusses alternate pathways to introduce pyridyl functionality in desired locations. It was concluded that Suzuki-Miyaura coupling directly onto the C[4] bridge where the halogenated aryl resided was unsuccessful with simple boronic acids. The Paal-Knorr pyrrole synthesis using pyridyl anilines was attempted, and the synthesis of 4- and 3-pyridylaniline is discussed before the reaction with saturated diketone, **5**. Reaction of 3-pyridyl aniline afforded the desired tetra-substituted product in moderate yields after 3 days and was the only isolated product. Reaction of 2- and 4-amino pyridine were similar to one another, and after a 7-day reflux two products were isolated and determined to be the tetra- and tris-substituted C[4]s. This showed that, although a phenyl spacer has been introduced, longer reaction times are required in comparison to the 3-pyridyl analogue (possibly indicating that the reaction is still hindered). Long reaction times could be utilised to form asymmetrical calix[4]arenes whereby the reaction could be stopped after certain periods of time to afford major products with varying amounts of substitution. Investigating this, **35** was reacted with hexylamine and identified as forming the desired asymmetrical product and indicating another route for future work. The tetra-substituted pyrrole derivatives with pyridyl functionality, **31**, **32**, and **34**, should be investigated for metal organic cage formation and compared to the results obtained by Fong previously whereby chelation occurred. Another possible route would be to investigate formation of asymmetrical C[4]s, allowing multiple groups to be added to the same framework which should be able to tune the peripheral groups for specific host-guest interactions.

Overall this thesis has greatly expanded the number of methylene bridge C[4]s by utilising the Paal-Knorr pyrrole synthesis with a previously reported bridged C[4], **5**, and a variety of amines. The method has been used to great effect and the desired product was formed in most cases, although more investigation is needed to fully understand the scope. This method has enormous space for exploration due to the number of commercially available anilines available, but also that one can synthesise building blocks if required. However, the stability of these compounds is an issue and a limiting factor that would need to be overcome if these compounds are to be widely utilised in the future.

5.1. References.

1 D. Guo, Q. An, S. V Zybin, W. A. Goddard III, F. Huang and B. Tang, *J. Mater. Chem. A*, 2015, **3**, 5409–5419.

Inclusion of Published Works Form

Declaration

This thesis contains one or more multi-author published works. I hereby declare that the contributions of each author to these publications is as follows:

Citation details	A. Fong, , C. L. Campbell, S. Huynh, L. J. McCormick McPherson, S. J. Teat, M. W. P. Bebbington & S. J. Dalgarno, 'Facile synthetic routes to bridge-functionalised calix[4]arenes', ***Chem. Commun.***, 2022, **58**, 3302-3305
Author 1 and 2	Synthesis and Characterisation
Author 3	Synthesis
Author 4 and 5	Crystallography
Author 6 and 7	Supervisors

Citation details	e. g. Author 1 and Author 2, Title of paper, Title of Journal, X, XX-XX (20XX)
Author 1	Contribution….
Author 2	Contribution….

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Author 1	Contribution….
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Facile synthetic routes to bridge-functionalised calix[4]arenes†

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Ring-opening of furans at the equatorial methylene bridge positions of a calix[4]arene gives access to a range of new molecules (in good yield) that have widespread potential impact in supramolecular chemistry amongst other areas.

Calix[*n*]arenes are cyclic host molecules (general notation C[*n*]s herein, where *n* represents the number of aryl rings present) that have played a pivotal role in the development of supramolecular chemistry over the past 30–40 years. Reasons for such widespread application include (but are not limited to) tuneable ring size,[1] structural flexibility associated with conformational interconversion,[2] cavities or clefts that can house suitable guest species,[3] and versatility towards synthetic alteration at the upper- or lower-rims.[4–7] Of the family of C[*n*]s, the cyclic tetramers have arguably been most widely studied as their conformation can be readily controlled.[8] In addition, synthetic modification of C[4]s at either the upper- or lower-rims (or both) is well explored.[9,10] Although this is the case, the synthesis of exhaustively methylene bridge-functionalised species remains a significant challenge.[11,12] Access to a wide range of such species would be of tremendous benefit as one could exploit many of the characteristic C[4] properties whilst simultaneously imparting new functionality on the periphery of this extremely versatile scaffold. This contribution addresses this challenge in part, presenting a new and versatile route to exhaustively methylene bridge-functionalised C[4]s.

Access to C[4] chemistry is typically *via* a one-pot synthesis of *p-tert*-butylcalix[4]arene (TBC[4]) from *p-tert*-butylphenol and formaldehyde under well-established reaction conditions.[13] Literature concerned with synthetic C[4] upper-/lower-rim alteration is vast, but reports of functionalisation at all methylene bridge positions are limited. Several examples have shown substitution at one or two positions around the C[4] framework[11,12,14,15] and in some cases this methodology has been used to tether C[4]s with linkers of varying length and/or composition (*e.g.* alkyl *vs.* aryl linkers).[16] However, monosubstitution at all methylene bridges presents a major challenge as these groups can be introduced either axial or equatorial (Fig. 1); this can give rise to isomers that can be difficult to separate. Rather than explore this particular step further, we sought to utilise a previously reported compound in which all four groups at the methylene bridge were known to occupy equatorial positions, thus allowing us to preserve the C[4] cone conformation whilst undertaking subsequent synthetic transformations. The compound in question, 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrakis(2-methylfuranyl)-25,26,27,28-tetramethoxycalix[4]arene (**1**, Fig. 1), was previously reported by Biali and co-workers and is isolated by methylation of the lower-rim of TBC[4],[17] mono-bromination at each methylene bridge, and solvolytic reaction with 2-methylfuran in the presence of butylene oxide. The authors reported a Diels–Alder reaction of **1** with benzyne to afford a tetra-naphthyl derivative, but to our knowledge this exhaustively bridge-substituted calixarene has not been further exploited.

Ring-opening of the furan moieties in **1** to afford either unsaturated or saturated 1,4-diketones gives numerous possibilities for the introduction of functionalities to the C[4]

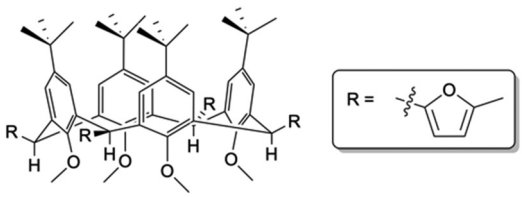

Fig. 1 Schematic of **1** showing 2-methylfuranyl moieties monosubstituted equatorially at all four methylene bridge positions of the TBC[4] framework.

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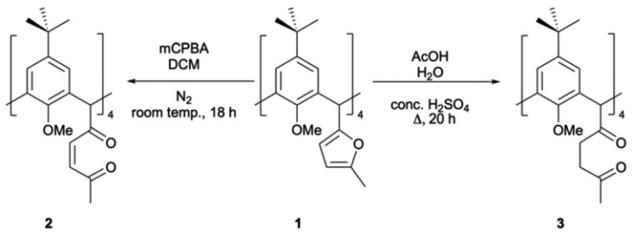
† Electronic supplementary information (ESI) available: Synthetic, analytical and crystallographic information (CIFs). CCDC 2126914–2126920. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc06889j



Scheme 1 Synthesis of C[4]s with unsaturated (**2**) and saturated (**3**) diketones at each methylene bridge of a *p*-*tert*-butylcalix[4]arene.

methylene bridge. Here we report formation of both diketones, but also their use in the synthesis of a range of C[4]s that are mono-substituted at all four methylene bridges. We also report preliminary work in lower-rim deprotection following alteration of methylene bridge functionality, as reintroducing hydroxyl groups in that region of the scaffold will be immensely beneficial (*e.g.* for use in coordination chemistry whilst also exploiting peripheral groups present at the methylene bridges).

Introduction of a 2-methylfuranyl moiety at each C[4] methylene bridge position presents a range of opportunities for synthetic transformation. Furans are known as synthetically diverse species that can be modified through various reactions including electrophilic aromatic substitution, Diels–Alder and nucleophilic addition.[18,19] One reaction of interest to us was ring-opening,[19,20] as it provides the opportunity to isolate other equatorial heterocycles at each C[4] methylene bridge. This was achieved by oxidation using a peroxy acid (mCPBA) or *via* acid-catalysed hydrolysis, affording unsaturated or saturated diketones respectively (**2** and **3**, Scheme 1).

Reaction of **1** with mCPBA in DCM afforded **2** in 34% yield upon purification by column chromatography (3 : 2 EtOAc/PET). Colourless single crystals were grown by recrystallisation from acetonitrile and the structure of **2** is shown in Fig. 2A. Each furan moiety on the C[4] scaffold has been ring-opened as indicated by four carbon–carbon bond lengths (in the 1,4-diketone backbones) in the range of 1.318(5)–1.325(5) Å. The presence of carbonyl groups was also confirmed by both IR and ^{13}C NMR spectroscopies, with introduction of a band at 1696 cm^{-1} and signals at 201.5 and 199.9 ppm respectively.

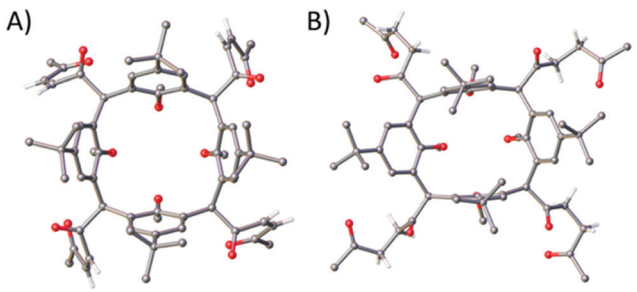


Fig. 2 Top down views of single crystal X-ray structures of C[4]s with unsaturated (**2**) and saturated (**3**) diketones at the methylene bridge positions. Colour code: C – grey, H – white, O – red. H atoms (except those in the diketone backbones) and solvent of crystallisation omitted for clarity. Figures not to scale.

Alternatively, heating **1** at reflux in a mixture of acetic acid, conc. sulfuric acid and water for 20 h, followed by purification *via* column chromatography (7 : 3 $CHCl_3$/EtOAc) afforded **3** in 53% yield. Colourless single crystals of **3** were grown from methanol, the structure of which is shown in Fig. 2B. Inspection of the structure shows that the furan group has been ring-opened to give the saturated diketone species, with C–C bond lengths (of the diketone backbone) in the range of 1.508(2)–1.5191(18) Å. Compound **3** has an extremely useful NMR handle associated with the methylene groups of the saturated diketones. These present as two very distinct triplets in the ^{1}H NMR at 2.81 and 2.91 ppm and can be used to monitor consumption of **3** in further reactions (*vide infra*). As for **2**, the presence of carbonyl groups in **3** was also confirmed by both IR and ^{13}C NMR spectroscopies, with the introduction of a band at 1713 cm^{-1} and signals at 208.8 and 207.4 ppm respectively.

With these new compounds in hand, we began to explore exhaustive formation of new heterocycles at the methylene bridge positions. Starting with **2**, reaction with hydrazine hydrate in acetic acid at reflux gave the tetra pyridazine analogue **4** in 67% yield. IR spectroscopy conveniently confirmed reaction completion upon consumption of the unsaturated diketones at the methylene bridges. Single crystals of **4** were grown by vapour diffusion of chloroform/acetonitrile and the structure is shown in Fig. 3. Inspection of the structure shows successful formation of a pyridazine moiety at each bridge and retention of equatorial positioning. Following the successful isolation of **4**, we attempted to react **2** to form the tetrathiophene C[4] analogue,[21] however all attempts were unsuccessful and returned starting material.

We expected **3** to be a more versatile reagent, as the saturated diketones can be exploited in the formation of a vast array of *N*-substituted pyrrole analogues through Paal–Knorr synthesis.[22] We selected the reagents in Fig. 4A as a starting point with a view to forming pyrroles **5A–E** (Fig. 4B).

Reaction of **3** with ammonium acetate in acetic acid afforded compound **5A** in 69% yield following purification by column chromatography (9 : 1 $CHCl_3$/EtOAc), which is appreciable when one considers the reaction is occurring four times per C[4] scaffold. Inspection of the ^{1}H NMR spectrum showed loss of the 1,4-diketone NMR handle with concomitant introduction of a set of doublets at 5.82 ppm and a broad singlet at 7.68 ppm corresponding to the CH and NH protons of the pyrrole moiety, respectively. Colourless single crystals of **5A** were grown from vapour diffusion of methanol into a saturated DCM solution and structural analysis also confirmed successful Paal–Knorr

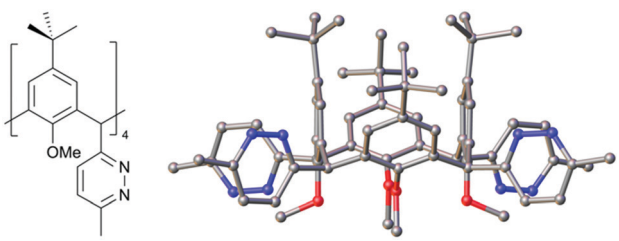


Fig. 3 Schematic and side-on view of the single crystal X-ray structure of **4**. Colour code: C – grey, N – blue, O – red.

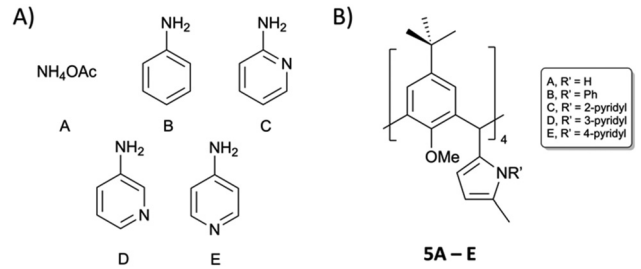


Fig. 4 Reagents (A) selected for reaction with **3** with the aim of isolating tetra pyrrolic C[4]s **5A–E** (B).

pyrrole synthesis (Fig. 5A). Inspection of the structure of **5A** showed that all pyrrole groups remained equatorial as expected, and that the C[4] is in a pinched cone conformation.

Reaction of **3** with aniline at reflux in toluene and in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) for 24 hours resulted in formation of **5B** in 55% yield. As in the synthesis of **5A**, loss of the signals for the 1,4-diketone NMR handle occurred with the introduction of a set of doublets at 5.93 and 5.99 ppm corresponding to the CH protons of the pyrrole moieties in **5B**, and multiple additional peaks in the aromatic region for the *N*-phenyl groups. The latter signals were broad, a feature that may be related to hindered rotation or C[4] conformational locking due to the bulk of the *N*-phenyl groups at the methylene bridge. Unfortunately, it was not possible to study this further (*e.g.* through VT experiments) as **5B** has limited solubility. It was, however, possible to obtain colourless single crystals of **5B** upon crystallisation from $CHCl_3$, in which it is sparingly soluble. Subsequent structural analysis confirmed pyrrole formation at each methylene bridge, with the C[4] again adopting a pinched-cone conformation (Fig. 5B).

Following successful formation of **5A**/**B**, we turned our attention to aminopyridines as these would afford interesting scaffolds for coordination chemistry/metal-directed assembly (*e.g.* to afford metal–organic cages[23]). Replacement of aniline with 2-, 3-, or 4-aminopyridine (2-, 3-, or 4-AP respectively) in the above reaction was successful in only one case. Reaction of **3** with 3-AP at reflux for seven days afforded **5D** a white solid in 55% yield following purification by column chromatography (9 : 1 DCM/MeOH). As was the case for **5B**, the RT ^{1}H NMR spectrum of **5D** also displayed broad aromatic signals. This was again thought to be due to hindered rotation of the pyridine moieties, but in this case it was possible to carry out VT NMR analysis to investigate whether the compound would display thermally induced rotation of the pyridine moieties (and therefore lead to much sharper and distinct NMR signals). Upon warming from 25 °C to 75 °C it was possible to see significant peak sharpening, and it is interesting to note the broad peaks around 8.4 and 8.0 ppm coalesce as the temperature is raised. This peak would be expected to be much sharper and distinct if heating beyond 75 °C, but it was not possible to reach higher temperatures. The same phenomenon occurred for the two broad peaks at 7.58 and 6.99 ppm, and again, much sharper signals would be expected if higher temperatures were accessible. This process is reversible, and signal broadening is reintroduced upon returning to RT. Colourless single crystals were grown upon vapour diffusion from chloroform/methanol and structure analysis confirmed pyrrole formation at each methylene bridge (Fig. 5C).

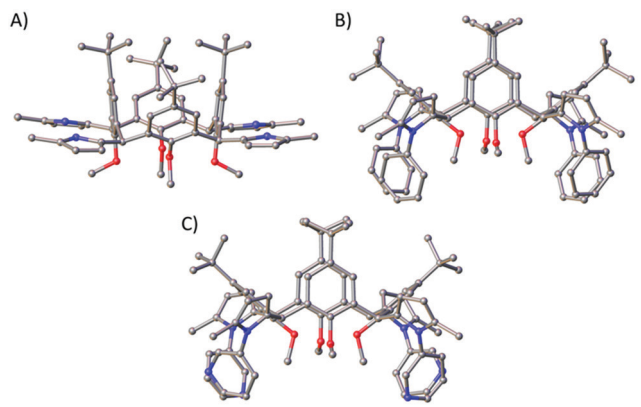


Fig. 5 Single crystal X-ray structures of **5A** (A), **5B** (B) and **5D** (C). Colour code: C – grey, N – blue, O – red. H atoms and solvent of crystallisation omitted for clarity. Figures not to scale.

As stated above, we were unable to introduce 2- and 4-pyridyl functionality to the C[4] platform *via* standard reaction conditions of reflux in toluene in the presence of TsOH. Given this, we explored the use of higher boiling solvent (*e.g.* mesitylene), microwave syntheses, and pressurised vessels, but in every case these reactions returned starting materials. This likely relates to differences in nucleophilicity compared to 3-AP, and is unfortunate as the 4-pyridyl appended C[4] is a desirable compound for metal directed assembly,[23] but work to isolate these (or structurally related compounds) will continue.

One of the key parameters controlling C[4] conformation or behaviour is lower-rim alkylation. Reintroducing the lower-rim hydroxyl groups is a desirable outcome for the new C[4]s reported here, particularly as the polyphenolic pocket can act as a binding site for a range of transition and lanthanide metal ion.[24,25] With this goal in mind we have begun preliminary experiments on deprotecting the lower-rim of **4** (as it is isolable in the highest yield from all new compounds reported here). Removal of *O*-methyl groups at the C[4] lower-rim, including those in **1**, can be achieved with relative ease using iodocyclohexane.[24,26] Surprisingly, initial attempts under these conditions with **4** were unsuccessful, returning only starting material. Subsequent use of BBr_3 was found to de-protect the lower-rim,[27] though this gave a relatively poor yield of the target tetrahydroxy tetra-pyridazinyl C[4], **6**. Reaction of **4** with 40 equiv. of BBr_3 in dry DCM under N_2 at RT for 24 h showed partial demethylation; this was evaluated by comparing integrals of the lower-rim methoxy ^{1}H-NMR signals to those of the methyl groups on pyridazine moieties. Hardman *et al.* previously used 6.5 equiv. of BBr_3 to fully deprotect a lower-rim methylated C[4] with one chloroalkyl chain at a methylene bridge,[27] suggesting that the processes may be somewhat hindered. We therefore propose that the same problem may be occurring here, but to a greater extent given that all methylene bridges are functionalised with relatively bulky groups.

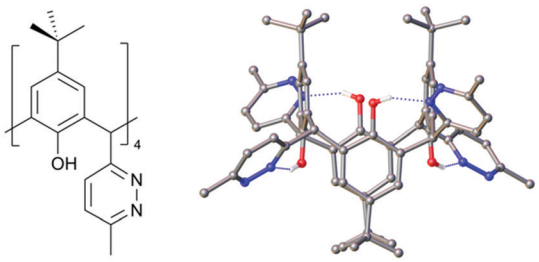


Fig. 6 Schematic and single crystal X-ray structure of **6**. Colour code: C – grey, H – white, N – blue, O – red. H atoms (except those H-bonding) omitted for clarity.

Purification of this crude product *via* column chromatography, followed by NMR and mass spectroscopy, confirmed that 4 distinct products were formed. These were identified as the mono-, di- (distal and vicinal) and tri-methoxy pyridazine C[4]s. Increasing the reaction time to 48 h showed near-identical results upon workup, so alternative approaches were sought. Fantini and co-workers have utilised a two-step protocol when deprotecting a bis-calix[4]arene comprising two C[4]s tethered directly through a methylene bridge.[28] This was found to avoid partially demethylated products and it is proposed that borate esters produced in the reaction are removed, thus preventing them from interfering with the demethylation. Inspired by this, compound **4** was dissolved in dry DCM, cooled to −78 °C, and 20 equiv. of BBr_3 was added dropwise over 15 minutes. This was left to stir under N_2 at −78 °C for 1 h before warming to RT stirring for 24 h. Analysis of the crude revealed that the major products after 24 h were tri- and di-methoxy species. The procedure was thus repeated and with a further 24 h stirring. Upon workup, the ^{1}H-NMR spectrum showed the reaction had proceeded further, with only one methoxy signal present; this corresponded to tri-hydroxy pyridazine C[4] as a mixture with **6**. Compound **6** was isolated in 5% yield *via* column chromatography, recrystallised from $CHCl_3$, and structural analysis confirmed full deprotection (Fig. 6); this also shows the molecule has adopted a 1,3-alternate conformation due to H-bonding interactions, but one would expect this to revert to a cone conformer upon lower-rim deprotonation or metal ion binding in the polyphenolic pocket, though this will be the subject of future studies.

In summary, we have reported new C[4] scaffolds that are monosubstituted at all methylene bridge positions with a range of functional groups. The use of a starting material in which all reactive groups are equatorial leads to retention of this arrangement in the final products, a feature that should ultimately lead to the widespread application of these molecules. Preliminary work shows that lower-rim deprotection can be achieved, though this is a priority area for optimisation. Reintroduction of key lower-rim hydroxyl functionality will allow for use of these molecules in areas such as coordination cluster formation or catalysis. Conformational changes may also lead to fascinating host–guest chemistry associated with the C[4] cavity, whilst extensive functionalisation of the appended moieties will likely lead to application in metal-directed assembly.

A. F., C. L. C. and S. H. performed experimental and analytical work. S. J. T. and S. J. D. collected XRD data. A. F., C. L. C. and S. J. D. solved the crystal structures. A. F., M. W. P. B. and S. J. D. designed the work.

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Conflicts of interest

There are no conflicts to declare.

References

1 C. D. Gutsche, B. Dhawan, K. H. No and R. Muthukrishnan, *J. Am. Chem. Soc.*, 1981, **103**, 3782–3792.
2 A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713–1734.
3 J. L. Atwood, G. A. Koutsantonis and C. L. Raston, *Nature*, 1994, **368**, 229–231.
4 C. D. Gutsche, B. Dhawan, J. A. Levine, K. Hyun No and L. J. Bauer, *Tetrahedron*, 1983, **39**, 409–426.
5 A. Arduini, A. Casnati, L. Dodi, A. Pochini and R. Ungaro, *J. Chem. Soc., Chem. Commun.*, 1990, 1597–1598.
6 A. Arduini, A. Pochini, A. Rizzi, A. R. Sicuri and R. Ungaro, *Tetrahedron Lett.*, 1990, **31**, 4653–4656.
7 C. D. Gutsche and L.-G. Lin, *Tetrahedron*, 1986, **42**, 1633–1640.
8 C. D. Gutsche and L. J. Bauer, *J. Am. Chem. Soc.*, 1985, **107**, 6052–6059.
9 C. D. Gutsche, *Calixarenes: An Introduction*, The Royal Society of Chemistry, Cambridge, 2nd edn, 2008, ch. 5. pp. 116–146.
10 P. Jose and S. Menon, *Bioinorg. Chem. Appl.*, 2007, **2007**, 65815.
11 M. Deska, B. Dondela and W. Sliwa, *ARKIVOC*, 2014, **2015**, 29–47.
12 S. E. Biali, in *Calixarenes and Beyond*, ed. P. Neri, J. L. Sessler and M.-X. Wang, Springer International Publishing, Switzerland, 2016, ch. 4, pp. 75–93.
13 C. D. Gutsche, M. Iqbal and D. Stewart, *J. Org. Chem.*, 1986, **51**, 742–745.
14 K. Agbaria and S. E. Biali, *J. Am. Chem. Soc.*, 2001, **123**, 12495–12503.
15 S. Simaan and S. E. Biali, *Org. Lett.*, 2005, **7**, 1817–1820.
16 M. Coletta, R. McLellan, P. Murphy, B. T. Leube, S. Sanz, R. Clowes, K. J. Gagnon, S. J. Teat, A. I. Cooper, M. J. Paterson, E. K. Brechin and S. J. Dalgarno, *Chem. – Eur. J.*, 2016, **22**, 8791–8795; M. Coletta, R. McLellan, J.-M. Cols, K. J. Gagnon, S. J. Teat, E. K. Brechin and S. J. Dalgarno, *Supramol. Chem.*, 2016, **28**, 557–566.
17 I. Columbus and S. E. Biali, *Org. Lett.*, 2007, **9**, 2927–2929; I. Columbus and S. E. Biali, *J. Org. Chem.*, 2008, **73**, 2598–2606.
18 M. V. Sargent and F. M. Dean, in *Comprehensive Heterocyclic Chemsitry*, ed. C. W. Bird and G. W. H. Cheeseman, Pergamon, Oxford, 1984, vol. 4, pp. 599–656.
19 H. Hart and Y. Takehira, *J. Org. Chem.*, 1982, **47**, 4370–4372.
20 F. W. Lichtenthaler, A. Brust and E. Cuny, *Green Chem.*, 2001, **3**, 201–209.
21 F. Duus, *Tetrahedron*, 1976, **32**, 2817–2825; M. Yuguchi, M. Tokuda and K. Orito, *J. Org. Chem.*, 2004, **69**, 908–914.
22 V. F. Ferreira, M. C. B. V. de Souza, A. C. Cunha, L. O. R. Pereira and M. L. G. Ferreira, *Org. Prep. Proced. Int.*, 2001, **33**, 411–454.
23 P. J. Stang, D. H. Cao, S. Saito and A. M. Arif, *J. Am. Chem. Soc.*, 1995, **117**, 6273–6283; M. Fujita, S. Nagao and K. Ogura, *J. Am. Chem. Soc.*, 1995, **117**, 1649–1650; Z. Zhong, A. Ikeda, M. Ayabe, S. Shinkai, S. Sakamoto and K. Yamaguchi, *J. Org. Chem.*, 2001, **66**, 1002–1008.
24 A. Fong, L. McCormick, S. J. Teat, E. K. Brechin and S. J. Dalgarno, *Supramol. Chem.*, 2018, **30**, 504–509.
25 M. Coletta, E. K. Brechin and S. J. Dalgarno, in *Calixarenes and Beyond*, ed. P. Neri, J. L. Sessler and M.-X. Wang, Springer International Publishing, Switzerland, 2016, ch. 25, pp. 671–690.
26 L. Zuo, S. Yao, W. Wang and W. Duan, *Tetrahedron Lett.*, 2008, **49**, 4054–4056.
27 M. J. Hardman, A. M. Thomas, L. T. Carroll, L. C. Williams, S. Parkin and J. L. Fantini, *Tetrahedron*, 2011, **67**, 7027–7034.
28 L. T. Carroll, P. A. Hill, C. Q. Ngo, K. P. Klatt and J. L. Fantini, *Tetrahedron*, 2013, **69**, 5002–5007.