Partial Functionalisation of C_4-Symmetric Tetramethoxyresorcinarenes

Daniel A. Tan[a], Chiara Massera[b], Mauro Mocerino[a]*

[a]*Chemistry, School of Molecular and Life Sciences, Curtin University, GPO Box U1987, Perth, Australia, 6845;* [b]*Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale, Università degli Studi di Parma, Parco Area delle Scienze 17/A, Parma, Italy, 43124*

* M.Mocerino@curtin.edu.au

Partial Functionalisation of C_4-Symmetric Tetramethoxyresorcinarenes

Investigations into the distal-functionalisation of the phenols of racemic C_4-symmetric tetramethoxyresorcinarene has led to a simple, single-step procedure that allows the isolation of gram quantities of partially silylated derivatives, with the targeted distally-silylated resorcinarene being obtained in a yield of 31%. These partially-silylated derivatives would serve as versatile intermediates for the selective functionalisation of this elegant architecture. The solid state structures of many of these derivatives have been determined by single crystal X-ray crystallography.

Keywords: resorcinarene; chiral; selective; partial; silylation

Introduction

Calixarenes are molecules with a cavity that is readily synthesised and functionalised. This has enabled researchers to design a wide range of calixarenes that can act as hosts for various smaller guest species, leading to some practical applications (*1-3*). A calixarene in the cone conformation has a cavity which could be tailored to host a particular guest depending on the type of functional groups present, as well as their arrangement around the wide rim of the calixarene. The functional group(s) at the wide rim of a calixarene could be arranged in a manner which endows chirality to the cavity. Chiral cavities are of interest for potential chiral recognition of racemic guests (*4*). Calixarenes with chiral cavities have been reported but their synthesis requires multiple steps, typically involving the construction of the calixarene macrocycle, followed by selective functionalisation, then installation of a group at the *meta* position (*5-9*). However, resorcinarenes, being constructed from resorcinol subunits, have existing hydroxy groups at the *meta* positions, which makes their cavities more readily modifiable to have chirality (*10, 11*). More conveniently, a resorcinarene with a chiral

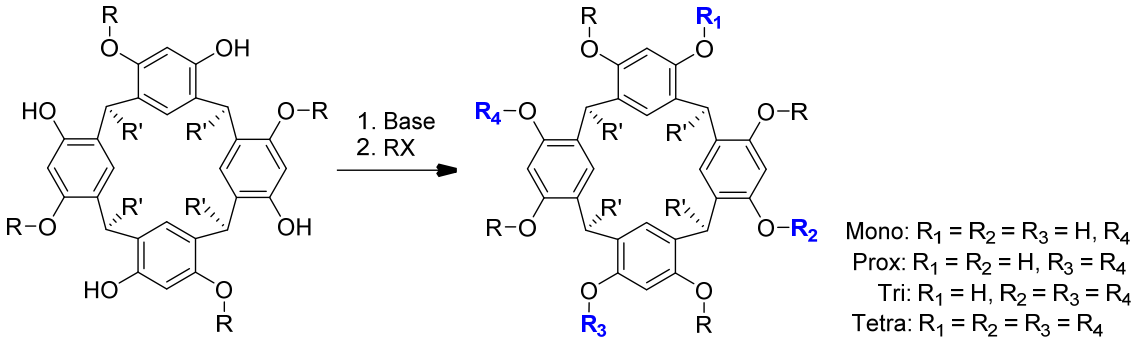
cavity has been assembled from 3-methoxyphenol subunits in a single step in high yields. In this case, the tetramethoxyresorcinarene product possesses C_4-symmetry with the four methoxy groups at the wide rim endowing the cavity with chirality (*6, 12*). The convenient synthesis of a chiral cavity has much potential for further functionalisation to suit a chiral recognition application. Functionalisation of the tetramethoxyresorcinarene in a C_4-symmetric manner can be easily accomplished via standard methods. Nevertheless, partial functionalisation of the wide rim of the resorcinarene cavity would present fewer reactive sites, enabling the construction of interesting architectures around the cavity that would modify its utility. We were particularly interested in the distal functionalisation of tetramethoxyresorcinarene with the goal of constructing a bridge over the cavity of the resorcinarene from distal aromatic rings.

A commonly utilised method for obtaining distally-functionalised calixarenes is by distal *O*-alkylation of the phenols on the narrow rim (*13*). The distal *O*-alkylated calixarene has enabled the synthesis of other partially-functionalised calixarenes (*14, 15*). The distal selectivity of the calixarene *O*-alkylation arises from the stabilisation of a phenoxide ion via intramolecular hydrogen bonds from the two adjacent phenols. However, resorcinarenes are disqualified from this method, since the phenols are on the wide rim and are in a different arrangement to that of calixarenes. Hence, the chemistry involved in partial functionalisation of calixarenes is different to that of resorcinarenes. Comparing calixarenes and tetramethoxyresorcinarenes in particular, the four phenolic reactive sites on the wide rim of a tetramethoxyresorcinarene spatially prevents their interaction, thus complicating the partial functionalisation of the macrocycle. Other literature methods for distally-functionalising calixarenes and derivatives on the wide rim include: selective bromine-lithium exchange (*16, 17*), selective partial lithiation

(*18*), and tetrasulfonylation (*19, 20*). Unfortunately, based on our previous investigations (*21, 22*), none of these methods for achieving distal selectivity on the wide rim of calixarenes are readily applicable to the tetramethoxyresorcinarenes. Therefore, the distal functionalisation of tetramethoxyresorcinarene appears to be a unique case, which necessitates a new strategy.

In the literature there are very few reports describing the partial functionalisation of the C_4-symmetric tetramethoxyresorcinarenes. The synthesis of a difunctionalised C_4-symmetric resorcinarene has been reported in the literature by Heaney and co-workers, who were making camphorsulfonates of tetraalkoxyresorcinarenes for diastereomeric resolution of the enantiomers. During their investigations, using either butyllithium or pyridine as base, they reported the selective production of dicamphorsulfonates of the chiral resorcinarene despite using an excess of base and camphorsulfonyl chloride (**Table 1**) (*23*). This selective dicamphorsulfonylation only occurred for derivatives of the resorcinarene bearing bulky alkoxy groups like isopropyl and cyclopentyl; methoxy derivatives could be readily tetrasubstituted. This result suggests that the steric bulk of the alkoxy group on the neighbouring ring was impacting the camphorsulfonylation. Only one regioisomer of the dicamphorsulfonates was obtained, with the best yield of 82% being for the isopropoxy, *C*-pentyl resorcinarene derivative. However, close inspection of the NMR data suggests that the proximal dicamphorsulfonate regioisomer was obtained rather than the distal as proposed in the initial paper. In one unusual instance, a resorcinarene with methoxy groups was not completely tetrasubstituted, with the tricamphorsufonate resorcinarene being isolated in 23% together with the tetracamphorsulfonate in 29% yield (*23*).

Table 1. Partial *O*-functionalisation of chiral C_4-symmetric tetraalkoxyresorcinarenes in the literature.



Ref	R	Base (eq)		Derivatising agent (eq)		Yield %					
						Tetra	Tri	Distal	Prox	Mono	SM
(*23*)	*i*-propyl	Pyridine	Exc	CS-Cl	3.9	0	0	0	64	0	0
(*23*)	*i*-propyl	BuLi	10.2	CS-Cl	8.1	0	0	0	82	0	0
(*23*)	*c*-pentyl	Pyridine	Exc	CS-Cl	12	0	0	0	46	0	0
(*23*)	*c*-pentyl	BuLi	10	CS-Cl	8	0	0	0	56	0	0
(*23*)	Methyl	Pyridine	Exc	CS-Cl	12	29	23	0	0	0	0
(*24*)	Methyl	BuLi	1	CS-Cl	5	0	0	0	0	29	22
(*25*)	Methyl	K_2CO_3	8.1	CP	4.2	1	7	14	9	7	28

CS-Cl = Camphorsulfonyl chloride CP = 1-chloro-4-pentyne Exc = Excess
SM = Starting Material

In similar work, Mattay and co-workers, who were also investigating the diastereomeric resolution of the C_4-symmetric resorcinarene, reported the synthesis of a mono-functionalised tetramethoxyresorcinarene (*24*). The reaction of 1 equivalent of butyllithium, followed by camphorsulfonyl chloride gave the monocamphorsulfonate in 29% yield, after HPLC separation from unreacted starting material (**Table 1**).

Nissinen and co-workers also briefly investigated the partial alkylation of C_4-symmetric tetramethoxyresorcinarenes, obtaining mostly the tetraalkylated product using 4.2 equivalents of alkylating agent (*25*). The best yield for the distally-alkylated resorcinarene was 14% when 1-chloro-4-pentyne was used as alkylating agent (**Table 1**). The mono-crown resorcinarene described by Nissinen and co-workers qualifies as a proximally-functionalised derivative of the tetramethoxyresorcinarene (*26*). Treatment of the parent tetramethoxyresorcinarene with caesium carbonate, followed by

tetra(ethylene glycol) ditosylate afforded the mono-crown resorcinarene in 13%, together with the bis-crown resorcinarene in 10% yield (**Table 1**).

To the best of our knowledge, the preceding four literature reports are the only examples describing the partial functionalisation of the C_4-symmetric resorcinarene. As evident in **Table 1**, none of these have described a practical method for obtaining the distally-functionalised product. Here we report our investigations into the distal functionalisation of the phenols of racemic tetramethoxyresorcinarenes, which have also led to the discovery of a single-step synthesis that allows isolation of gram-quantities of the four partially-functionalised tetramethoxyresorcinarenes.

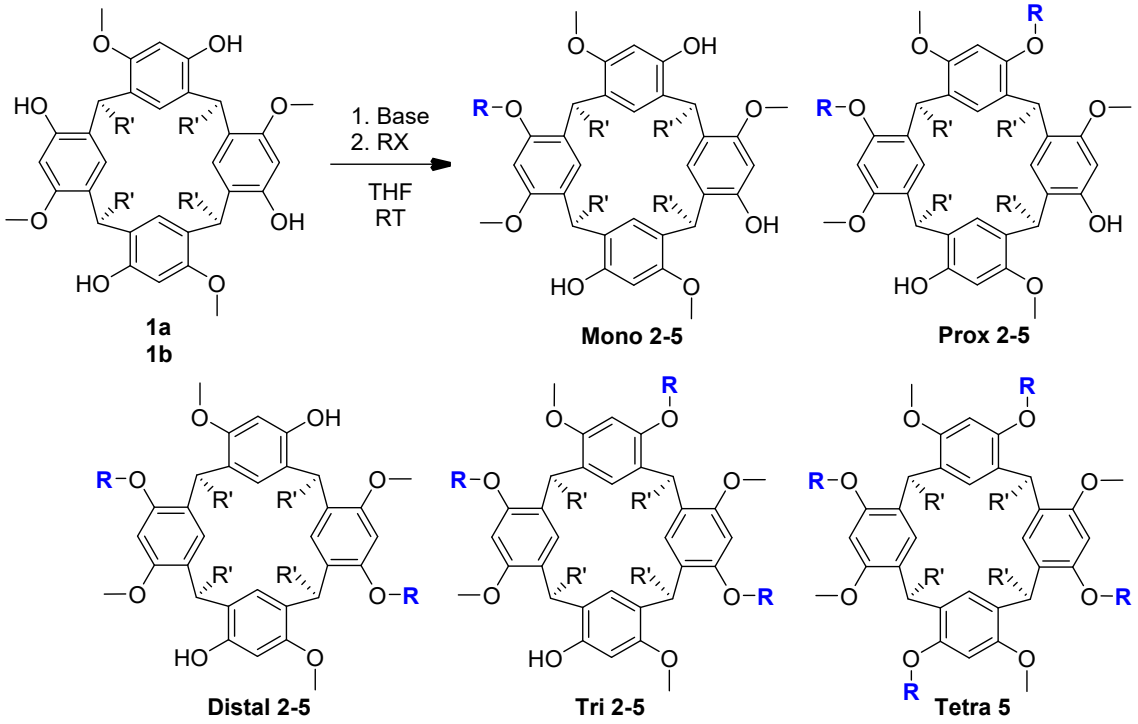
Results and Discussion

Our investigations began with the strategy of direct selective distal di-functionalisation of the phenols of the starting resorcinarene by deprotonation using two equivalents of base, followed by two equivalents of derivatising agent. By this method, it was envisioned that equilibrating the starting resorcinarene with two equivalents of base would form a di-phenoxide resorcinarene where the negative charges would form on the phenols furthest apart – the distal phenols – due to electrostatic repulsion. Subsequent treatment of the distal diphenoxide with a derivatising agent should give the desired distal di-functionalised resorcinarene. It was envisioned that the substituent group would be a bulky protecting group since that would enable potential cleavage to recover the phenol functionality. From a space perspective, a bulky protecting group should sterically-hinder proximal functionalisation, and thus aid in obtaining distal selectivity.

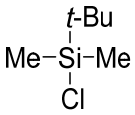
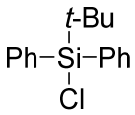
The first combination of base and protecting group that was investigated was butyllithium and *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (**Table 2**, entry I). Butyllithium was used as a base for the convenience of accurately adding two equivalents. Reaction with propyl and heptyl tetramethoxyresorcinarenes **1a** and **1b**

both yielded mostly unreacted starting material with a small amount of mono-TBDMS resorcinarene, as evident by TLC and NMR spectroscopy (**Table 2**, entries II-III). The number of equivalents of butyllithium and TBDMS-Cl were increased from two to up to ten equivalents, but still yielded a similar outcome with no additional products being observed in any of the TLC or ^{1}H NMR spectra of the crude mixtures (**Table 2**, entry IV). Interestingly, this lack of reaction appears to contradict a similar butyllithium reaction protocol employed by Heaney *et al*. for the tetracamphorsulfonylation of tetramethoxyresorcinarene (*23*). Nonetheless, it was thought that the lack of silylation may be due to the strong coordination between the small lithium cation of the butyllithium to the phenoxide anions, decreasing their nucleophilicity. Therefore, a base with a softer cation – potassium *tert*-butoxide – was investigated.

Table 2. *O*-functionalisation of tetramethoxyresorcinarenes with various protecting groups and bases in THF.



1a : R' = Pr
1b : R' = Heptyl
2 : R = TBDMS, R' = Pr
3 : R = TBDPS, R' = Pr
4 : R = Bn, R' = Pr
5 : R = TBDMS, R' = Heptyl

Entry	Starting material	Base	Eq	RX	Yield %					
					Tetra	Tri	Distal	Prox	Mono	Starting material
I	1a	BuLi	2		0	0	0	0	22*	78
II	1b	BuLi	2		0	0	0	0	26*	74
III	1b	BuLi	3		0	0	0	0	28*	72
IV	1a	BuLi	10.7		0	0	0	0	29*	71
V	1a	KOtBu	2.1		0	12	31	15	28	10
VI	1b	KOtBu	2.0		0	6	20	12	33	22
VII	1b	KOtBu	3.0		0	27	13	17	21	19
VIII	1a	NaH	2.0		0	7	23	12	37	18
IX	1a	KOtBu	2.0		0	0	16	7	32	39
X	1a	KOtBu	3.0		0	22*	25	9	12	Trace
XI	1a	KOtBu	2.0	BnBr	6	25	15	18	11[#]	5[#]

*Not separated; yield calculated based on approximated ^{1}H NMR integration.

#Incompletely separated

The reaction of the starting resorcinarene **1a** with potassium *tert*-butoxide followed by treatment with TBDMS-Cl gave a crude material with a TLC indicating five compounds. All five compounds were separated by chromatography and identified by NMR analysis to be the tri-, distal di-, proximal di-, mono- TBDMS, and unreacted starting resorcinarene (Entry V. Details, see SI). The major product was, the target distal product, **Distal-2**, which was afforded in a yield of 31%. This procedure is scalable, with all products being obtained in similar yields on a one-gram scale, while on a seven-gram scale, **Distal-2** was afforded in a 28% yield. The good chromatographic separation between the products enables efficient chromatography at large scales (SI, Figure S1.1). A key indicator enabling identification of the products by NMR spectroscopy was the rotational symmetry of the products, which was evident in the number of peaks in the NMR spectra (SI). Compared to the starting resorcinarene, there are many more peaks in the NMR spectra of the products, which was a result of a loss of the C_4 rotational symmetry. A clear indicator of the rotational symmetry of the resorcinarene products was the methoxy groups. For products where there was no rotational symmetry – tri, proximal, and mono – the four methoxy groups appear as four separate peaks in both ^{1}H and ^{13}C NMR spectra. The number of substituted phenols in a resorcinarene product can be determined by the number and integration of $SiCH_3$ or *tert*-butyl peaks in the NMR spectra. For example, the two di-TBDMS isomers, **Distal-2** and **Prox-2**, could be clearly differentiated by their rotational symmetry. **Distal-2**, having C_2 symmetry, has half the number of peaks compared to **Prox-2**, which has no symmetry (**Figure 1**).

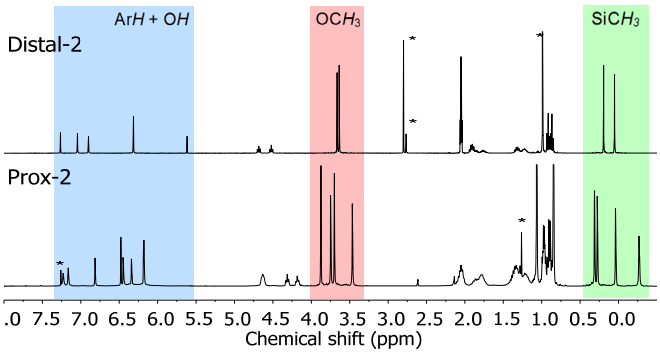


Figure 1. ^{1}H NMR spectra of TBDMS isomers **Distal-2** in acetone-d_6 and **Prox-2** in $CDCl_3$. Diagnostic signals have been highlighted. *Designates solvent peaks.

However, using the TBDMS peaks to judge the symmetry of the resorcinarene may be deceiving since the methyl groups on each silicon appear as two peaks, instead of one. This is because the silicon methyl groups, being in proximity to the chiral resorcinarene, have become diastereotopic.

The NMR spectrum of **Distal-2**, when acquired in $CDCl_3$, gave an unexpected and misleading ^{1}H NMR spectrum with very broad peaks. However, when the spectrum was acquired in acetone-d_6 or DMSO-d_6, the peaks were sharp (**Figure 2**).

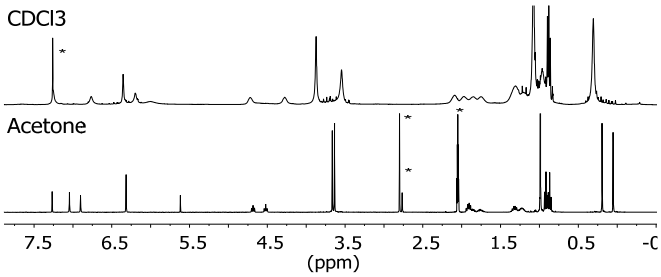


Figure 2. ^{1}H NMR spectra of **Distal-2** recorded in $CDCl_3$ (upper spectrum), and in acetone-d_6 (lower spectrum). *Denotes solvent peaks.

The assignment of the reaction products was confirmed at the solid state through X-ray diffraction analysis on single crystals. Crystals of good quality were obtained for **Mono-2**, **Prox-2**, **Distal-2** and **Tri-2** by crystallisation from DCM-MeOH, acetonitrile, THF-MeOH, and chloroform-MeOH, respectively. The ortep molecular structures of these compounds are reported in the SI, Figures S19.1-S19.4. **Figure 3** shows the crown conformations for **Mono-2**, **Prox-2**, **Distal-2** and **Tri-2**, which are influenced by the number and position of the TBDMS substituents. The geometry of the crowns can be expressed by reporting the angles formed between each of the mean planes passing through the phenyl rings of the wall (indicated with A, B, C, D and E, F, G and H in case of two independent molecules in the unit cell) and the mean plane passing through the four bridging carbon atoms of the lower rim (indicated with M, see Table S5 in the SI). In general, two opposite phenyl rings of the resorcinarene are roughly parallel to each other, forming with plane M angles in the range 62.75(7) - 89.43(8)°. On the contrary, the other two phenyl rings are more inclined outwards toward plane E, with **Tri-2** showing the most open crown conformation (angles A-M, C-M, E-M and G-M of 14.77(9), 5.34(8), 7.17(8) and 6.18(9)°, respectively).

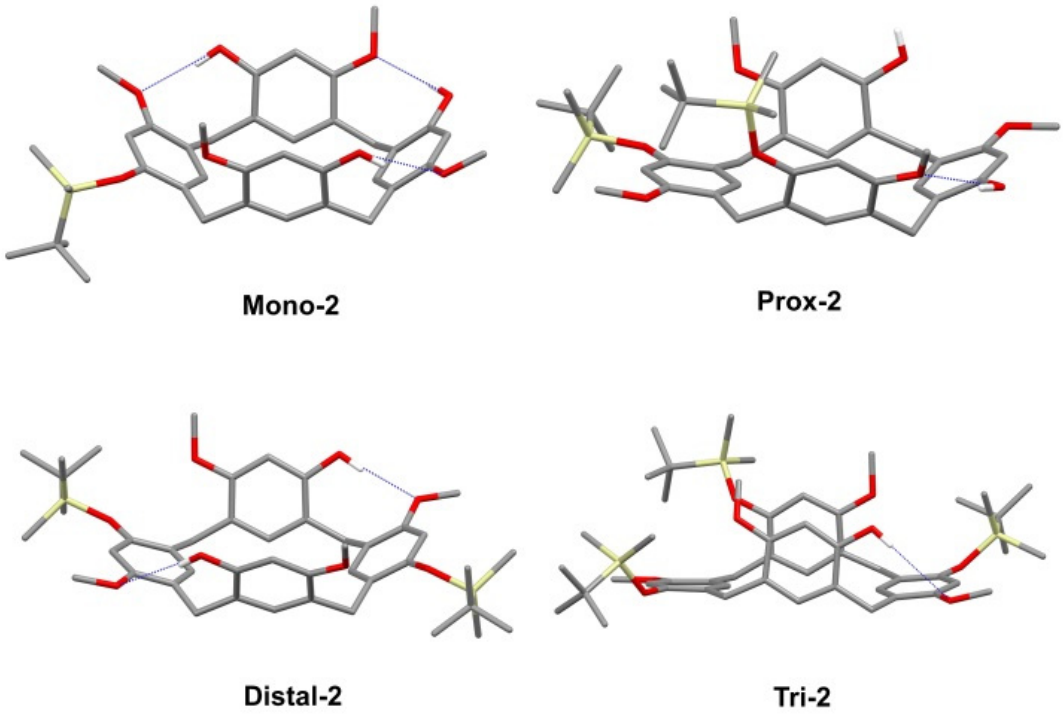


Figure 3. Crown conformation of the the TBDMS substituted resorcinarenes. Colour code: C, grey; O, red; Si, yellow. Alkyl chains and hydrogen atoms not involved in H-bonding have been omitted for clarity.

Changing the reaction conditions, i.e. using sodium hydride as base and other bulky protecting groups (*tert*-butyldiphenylsilyl chloride TBDPS-Cl or benzyl bromide Bn-Br) did not give a better yield of the distally-functionalised resorcinarene (**Table 2**, Entries VIII-XI). The crystal structures of **Mono-3**, **Distal-3** and **Distal-4** were also solved through X-ray diffraction analysis on single crystals obtained by crystallisation from DCM-petroleum spirits (**Mono-3**), chloroform-MeOH (**Distal-3 & -4**) (Figures S19.5-S19.7). The same silylation with TBDMS-Cl and potassium *tert*-butoxide, but in other reaction solvents such as DMF and acetonitrile did not favour the distal product, as apparent by TLC comparison (SI, Figure S1.1).

The crown conformation of the three resorcinarenes are shown in **Figure 4**. As in the case of the *tert*-butyldimethylsilyl derivatives, the phenyl rings of the wall are divided in two groups, those parallel to each other and those inclined outwards. The detailed geometrical parameters are reported in Table S6.

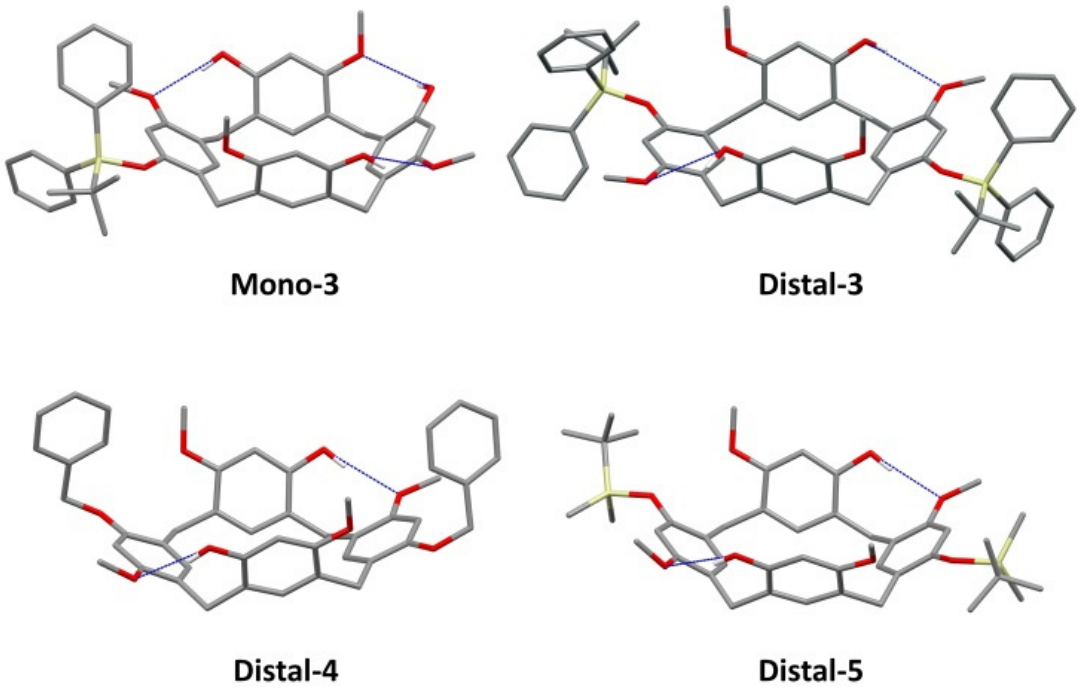


Figure 4. Crown conformation of the the TBDPS, Bn and long-chained TBDMS substituted resorcinarenes. Alkyl chains and hydrogen atoms not involved in H-bonding have been omitted for clarity.

Keeping in mind the potential applications of these partially-functionalised resorcinarenes, it could be useful to increase their solubility in non-polar solvents by increasing the hydrocarbon chain length at the narrower rim. It would also be interesting to briefly explore if the hydrocarbon chain length of the resorcinarene had any significant impact on the silylation reaction. Therefore, heptyl resorcinarene **1b** was reacted under the optimal conditions for **Distal-2**, but unexpectedly, the proportions of the products were significantly different. The selectivity for the distally-functionalised

product (**Distal-5**) was only 20%, with the yield being dominated by the **Mono-5** product (33%) (**Table 2**, entry VI). Increasing the equivalents of TBDMS-Cl and potassium *tert*-butoxide from two to three drastically increased the yield of **Tri-5** from 6% to 27%, while significant amounts of **Mono-5** and unreacted **1b** still remained (**Table 2**, entry VII). All four TBDMS heptyl resorcinarene products, **Mono-5**, **Prox-5**, **Distal-5**, and **Tri-5** were characterised by NMR methods, and had very similar spectra to their **1a** counterparts. However, the silyl ethers of the heptyl resorcinarene products were more unstable; attempts to crystallise the products via slow diffusion of methanol into chloroform effected hydrolysis of the pure products, as detected by the multiple spots on TLC. ^{1}H NMR evidence suggests that the silyl ether hydrolysis was caused by the chloroform, though it had been pre-treated with potassium carbonate (Figure S16.4). Only **Distal-5** could be crystallised (EtOAc-MeOH, see Figure S19.8 for the Ortep view of its molecular structure). The crown conformation of this compound is shown in **Figure 4**. As expected, the length of the alkyl chains does not influence the conformation of the resorcinarene, as can be seen from the comparison between the geometrical parameters of **Distal-5** and **Distal-2**. However, the long hydrophobic chains influence the crystal structure, since the resorcinarenes adopt a head-to-head / tail-to-tail packing along the *c*-axis direction, as shown in **Figure 5**. This is observation is consistent with the work by Nissinen and co-workers who reported the uniformed layered packing for bis-crown resorcinarenes with alkyl chains that were pentyl or longer (*27*).

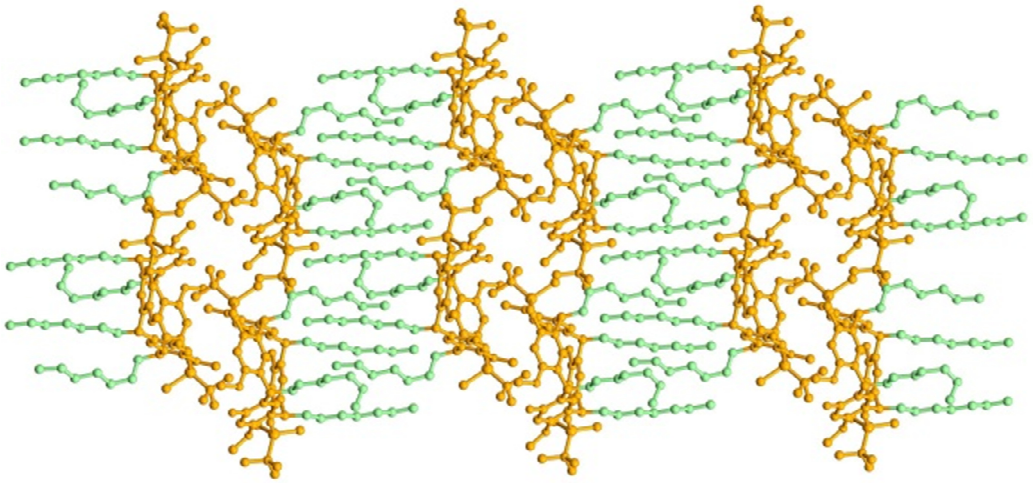


Figure 5. Ball-and-stick view of the crystal structure of **Distal-5.** The tails and the heads of the resorcinarene molecules are represented in green and orange, respectively.

In conclusion, we report the first practical synthesis and isolation of partially-functionalised derivatives of inherently-chiral tetramethoxyresorcinarenes **1a** and **1b** through *O*-functionalisation with various derivatising agents and bases. The products of these investigations were fully characterised by NMR spectroscopy, and where practical, X-ray crystallography. Though we targeted the distally-functionalised tetramethoxyresorcinarene, other partially-functionalised resorcinarenes could also be obtained in significant yields. The best yields for the partially-functionalised tetramethoxyresorcinarenes were: tri- (27%), distal- (31%), proximal- (18%), and mono- (37%). The ability to obtain practical amounts of partially-functionalised tetramethoxyresorcinarenes in a single synthetic step opens up many possibilities for the construction of interesting architectures at the wide rim of the resorcinarene that could be useful in applications such as chiral recognition.

Acknowledgments

CM wishes to thank the CNR of Trieste, and in particular Dr. Nicola Demitri, for the single crystal XRD data collected at the ELETTRA synchrotron facility. We thank Dr. Frankie Busetti of Edith Cowan University for performing the HRMS analyses.

Funding

We are grateful for support from the Australian Government Research Training Program Scholarship.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Experimental

General Methods

NMR spectra were recorded on a Bruker UltraShield Avance 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C). All chemical shifts were reported in parts per million (ppm). NMR spectra were calibrated to their respective solvents (*28*): chloroform-*d* ($CDCl_3$, δ 7.26 ppm; ^{13}C, δ 77.16 ppm); DMSO-d_6 (CD_3SOCD_3, δ 2.50 ppm; ^{13}C, δ 39.52 ppm); acetone-d_6 (CD_3COCD_3, δ 2.05 ppm; ^{13}C, δ 29.84 ppm). Multiplicity was assigned as follows: s = singlet, d = doublet, t = triplet, q = quartet, sxt = sextet, br = broad. A PureSolv MD5 solvent purification system from Innovative Technology Incorporated was used for the purification and drying of THF and DMF. IR spectra were acquired on a Perkin Elmer Spectrum 100 with ATR attachment and a scan range from 650 – 4000 cm^{-1}. Melting points were determined using an Electrothermal IA9300 melting point apparatus. Elemental composition of samples was analysed via a Perkin

Elmer 2400 Series II CHNS/O.

Thin layer chromatography was performed using 200 µm silica gel F-254 aluminium-backed sheets. Preparative TLC was performed using 20×20 cm, 1000 µm thick silica gel F-254 glass-backed plates. UV light (254 nm) was used to visualise TLC plates. Column chromatography was performed using 40-63 µm silica gel.

Starting resorcinarenes **1a** and **1b** were prepared according to the literature procedure.(*12, 21*)

Synthesis of Mono-2, Prox-2, Distal-2, Tri-2

To potassium *tert*-butoxide (23.0 mg, 0.205 mmol, 2.06 eq) was added resorcinarene **1a** (71.0 mg, 0.0996 mmol, 1.00 eq) with anhydrous THF (5 mL) to give a cloudy beige mixture which was stirred at room temperature under nitrogen for 45 min. Then TBDMS-Cl (30.3 mg, 0.201 mmol, 2.02 eq) was added to the mixture. After stirring at room temperature under nitrogen for 2 hours, the solvent was removed under reduced pressure to give a brown solid which was dissolved in DCM and washed with dilute HCl (1 M). The aqueous layer was extracted with DCM, and the combined organic extracts were dried ($MgSO_4$), filtered, and solvent removed under reduced pressure. The resultant crude solid was subjected to preparative TLC (EtOAc – petroleum spirits 40:60) to give the pure resorcinarenes: **Tri-2** (13 mg, 12%), **Distal-2** (29 mg, 31%), **Prox-2** (14 mg, 15%), **Mono-2** (23 mg, 28%) as beige solids as well as remaining resorcinarene **1a** (7 mg, 10%) in respective elution order. The beige products were recrystallised from the appropriate solvents to give white crystals suitable for analysis.

The procedure was repeated on a larger scale with resorcinarene **1a** (1.24 g, 1.74 mmol, 1.00 eq), anhydrous THF (50 mL), potassium *tert*-butoxide (0.390 g, 3.48 mmol, 2.00 eq), TBDMS-Cl (0.524 g, 3.47 mmol, 2.00 eq), and after column chromatography (EtOAc – petroleum spirits 5:95 to 40:60), gave pure resorcinarenes: **Tri-2** (0.267 g,

14%), **Distal-2** (0.403 g, 25%), **Prox-2** (0.217 mg, 13%), **Mono-2** (0.356 g, 25%) as beige solids as well as remaining resorcinarene **1a** (0.167 mg, 13%) in respective elution order.

The procedure was repeated on a larger scale with resorcinarene **1a** (6.99 g, 9.80 mmol, 1.00 eq), anhydrous THF (210 mL) potassium *tert*-butoxide (2.20 g, 19.6 mmol, 2.00 eq), TBDMS-Cl (2.97 g, 19.7 mmol, 2.01 eq), and after column chromatography (EtOAc – petroleum spirits 10:90 to 15:85), gave pure resorcinarenes **Tri-2** (1.73 g, 17%), and **Distal-2** (2.63 g, 28%) in respective elution order; the remaining compounds were not separated.

Mono-2: m.p. 255-256 °C (DCM/MeOH); IR 3420 cm^{-1} (OH phenol); ^{1}H NMR ($CDCl_3$) δ 0.26, 0.29 (2s, 2 × 3 H, $Si(CH_3)_2$), 0.87-1.03 (m, 12 H, CH_2CH_3), 1.06 (s, 9 H, $SiC(CH_3)_3$), 1.11-1.42 (m, 8 H, CH_2CH_3), 1.72-1.89, 1.93-2.08, 2.05-2.28 (3m, 1 H, 1 H, 6 H, CH_2CH), 3.59, 3.78, 3.857, 3.863 (4s, 4 × 3 H, OCH_3), 4.22-4.36 (m, 3 H, $CHCH_2$), 4.81 (t, J = 7.9 Hz, 1 H, $CHCH_2$), 6.23, 6.29, 6.41 (3s, 1 H, 2 H, 1 H, Ar*H*), 6.99 (overlapped, br s, 2 H, O*H*), 7.03, 7.11 (2s, 2 × 1 H, Ar*H*), 7.21 (overlapped, br s, 1 H, O*H*), 7.22, 7.33 (2s, 2 × 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ -4.0, -3.5 ($Si(CH_3)_2$), 14.16, 14.20, 14.6 (CH_2CH_3), 18.6 ($SiC(CH_3)_3$), 21.05, 21.12, 21.14, 21.3 (CH_2CH_3), 26.1 ($SiC(CH_3)_3$), 32.5, 32.8, 32.9, 33.0 ($CHCH_2$), 36.0, 36.7, 37.1, 39.4 (CH_2CH), 55.4, 55.9, 56.0, 56.0 (OCH_3), 99.4, 99.6, 100.2, 101.7 (*C*H, Ar), 121.9, 123.1 (*C*, Ar), 123.3, 123.4 (*C*H, Ar), 124.2, 124.4, 125.1, 125.2 (*C*, Ar), 125.3, 126.8 (*C*H, Ar), 130.3, 151.8, 152.4, 152.8, 153.1, 153.40, 153.44, 154.3, 156.6 (*C*, Ar) (note some signals are coincident). Found: C, 72.46; H, 8.37; $C_{50}H_{70}O_8Si$; requires C, 72.60; H, 8.53%.

Prox-2: m.p. 211 °C (MeCN); IR 3490 cm^{-1} (OH phenol); ^{1}H NMR ($CDCl_3$) δ -0.27, 0.04, 0.28, 0.31 (4s, 4 × 3 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.85-0.94, 0.94-1.03 (2m, 2 × 6 H, CH_2CH_3), 1.07 (s, 9 H, $SiC(CH_3)_3$), 1.14-1.46 (m, 8 H, CH_2CH_3),

1.68-1.94, 1.97-2.13 (2m, 2 × 4 H, C*H*$_2$CH), 3.47, 3.70, 3.75, 3.87 (4s, 4 × 3 H, OC*H*$_3$), 4.18, 4.31 (2t, *J* = 7.4 Hz, 2 × 1 H, C*H*CH$_2$), 4.57-4.70 (m, 2 H, C*H*CH$_2$), 6.18, 6.19, 6.34, 6.45, 6.48, 6.82, 7.16, 7.23 (8s, 8 × 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ -4.6, -4.1, -3.8, -3.5 (Si(*C*H$_3$)$_2$), 14.28, 14.29, 14.6 (CH$_2$*C*H$_3$), 18.3, 18.5 (Si*C*(CH$_3$)$_3$, 21.1, 21.3, 21.6 (*C*H$_2$CH$_3$), 25.9, 26.1 (SiC(*C*H$_3$)$_3$), 33.0, 33.9 (*C*HCH$_2$), 34.4, 35.1 (br, *C*HCH$_2$), 36.4, 36.6 (*C*H$_2$CH), 38.9, 39.2 (br, *C*H$_2$CH), 54.9, 55.1, 55.6, 56.0 (O*C*H$_3$), 99.0, 100.1, 101.4, 102.5 (*C*H, Ar), 121.3, 123.1 (br), 124.3 (*C*, Ar), 124.7 (*C*H, Ar), 125.2 (*C*, Ar), 125.5 (br, *C*H, Ar), 125.6 (*C*, Ar), 125.7 (*C*H, Ar), 126.1 (*C*, Ar), 127.1 (*C*H, Ar), 128.7 (br), 151.2, 152.1, 152.7, 153.0, 153.5, 154.0, 154.7, 156.9 (*C*, Ar) (note some signals are coincident). Found: C, 71.49; H, 9.01; $C_{56}H_{84}O_8Si_2$; requires C, 71.44; H, 8.99%.

Distal-2: m.p. 236-237 °C ($CHCl_3$/MeOH); IR 3470 cm^{-1} (OH phenol); ^{1}H NMR ($CDCl_3$) δ 0.31 (br s, 12 H, Si(C*H*$_3$)$_2$), 0.88 (t, *J* = 7.3 Hz, 6 H, CH$_2$C*H*$_3$), 0.90-1.02 (m, 6 H, CH$_2$C*H*$_3$), 1.07-1.47 (m, 8 H, C*H*$_2$CH$_3$), 1.08 (br s, 18 H, SiC(C*H*$_3$)$_3$), 1.62-1.88, 1.70-1.97, 1.85-2.10, 1.93-2.30 (4m, 4 × 2 H, C*H*$_2$CH), 3.54, 3.87 (2br s, 2 × 6 H, OC*H*$_3$), 4.28, 4.72 (2 br s, 2 × 2 H, C*H*CH$_2$), 6.01, 6.20, 6.35, 6.76 (4br s, 4 × 2 H, Ar*H*), 7.25 (overlapped with $CHCl_3$ br s, 2 H, O*H*); ^{13}C NMR ($CDCl_3$) δ -3.7 (Si(*C*H$_3$)$_2$), 14.3, 14.5 (CH$_2$*C*H$_3$), 18.5 (Si*C*(CH$_3$)$_3$), 21.0, 21.4 (*C*H$_2$CH$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 33.5 (*C*HCH$_2$), 36.9, 39.5 (*C*H$_2$CH), 55.3, 55.8 (O*C*H$_3$), 99.5, 101.1 (*C*H, Ar), 120.8, 123.6, 124.4 (*C*, Ar), 124.6, 127.5 (*C*H, Ar), 130.6, 151.8, 153.1, 153.4, 156.7 (*C*, Ar) (note some signals are coincident); ^{1}H NMR (DMSO-d_6) δ -0.11, 0.09 (2s, 2 × 6 H, Si(C*H*$_3$)$_2$), 0.79 (t, *J* = 7.3 Hz, 6 H, CH$_2$C*H*$_3$), 0.82 (t, *J* = 7.3 Hz, 6 H, CH$_2$C*H*$_3$), 0.89 (s, 18 H, SiC(C*H*$_3$)$_3$), 1.02-1.32 (m, 8 H, C*H*$_2$CH$_3$), 1.50-1.80 (m, 8 H, C*H*$_2$CH), 3.51, 3.60 (2s, 2 × 6 H, OC*H*$_3$), 4.39-4.53 (m, 4 H, C*H*CH$_2$), 6.16, 6.30, 6.55, 6.83 (4s, 4 × 2 H, Ar*H*), 8.74 (s, 2 H, O*H*); ^{13}C NMR (20% $CDCl_3$ in DMSO-d_6) δ -4.9,

-4.3 (Si(CH$_3$)$_2$), 13.9, 14.0 (CH$_2$$CH_3$), 17.7 (Si$C$(CH$_3$)$_3$), 20.7, 20.9 ($CH_2CH_3$), 25.4 (SiC($CH_3$)$_3$), 33.8, 34.2 ($CHCH_2$), 37.4, 38.0 ($CH_2$CH), 54.6, 55.2 (O$CH_3$), 98.3, 102.0 ($C$H, Ar), 122.3, 122.6, 125.0, 125.3 (C, Ar), 125.6, 126.3 (CH, Ar), 150.9, 152.8, 154.6, 154.8 (C, Ar); ^{1}H NMR (Acetone-d$_6$) δ 0.05, 0.19 (2s, 2 × 6 H, Si(CH_3)$_2$), 0.87 (t, J = 7.4 Hz, 6 H, CH$_2$CH_3), 0.92 (t, J = 7.4 Hz, 6 H, CH$_2$CH_3), 0.99 (s, 18 H, SiC(CH_3)$_3$), 1.16-1.27, 1.27-1.40 (2m, 2 × 4 H, CH_2CH$_3$), 1.68-1.82, 1.82-1.98 (2m, 2 H, 6 H, CH_2CH), 3.64, 3.66 (2s, 2 × 6 H, OCH_3), 4.52 (t, J = 7.6 Hz, 2 H, CHCH$_2$), 4.68 (t, J = 7.7 Hz, 2 H, CHCH$_2$), 6.32, 6.90, 7.04 (3s, 4 H, 2 H, 2 H, ArH), 7.27 (s, 2 H, OH); ^{13}C NMR (Acetone-d$_6$) δ -4.1, -3.7 (Si(CH$_3$)$_2$), 14.5, 14.6 (CH$_2$$CH_3$), 18.8 (Si$C$(CH$_3$)$_3$), 21.9, 22.2 ($CH_2CH_3$), 26.2 (SiC($CH_3$)$_3$), 35.27, 35.30 ($CHCH_2$), 38.2, 39.5 ($CH_2$CH), 55.4, 56.1 (O$CH_3$), 99.6, 103.2 ($C$H, Ar), 123.6, 124.9, 126.1 (C, Ar), 126.6 (CH, Ar), 127.5 (C, Ar), 127.9 (CH, Ar), 152.7, 154.1, 155.9, 156.6 (C, Ar). HRMS (ESI): calcd. for $C_{56}H_{85}O_8Si_2$ as $[M + H]^+$ 941.5778; found 941.5781. Found: C, 71.05; H, 9.15; $C_{56}H_{84}O_8Si_2$; requires C, 71.44; H, 8.99%.

Tri-2: m.p. 261-262 °C (CHCl$_3$/MeOH); IR 3544 cm^{-1} (OH phenol); ^{1}H NMR (CDCl$_3$) δ -0.10, 0.07, 0.15, 0.19, 0.26, 0.28, (6s, 6 × 3 H, Si(CH_3)$_2$), 0.84-0.98 (m, 12 H, CH$_2$CH_3), 0.84, 1.04, 1.02 (3s, 3 × 9 H, SiC(CH_3)$_3$), 1.19-1.48 (m, 8 H, CH_2CH$_3$), 1.66-2.02 (m, 8 H, CH_2CH), 3.46, 3.51, 3.70, 3.79 (4s, 4 × 3 H, OCH_3), 4.22 (t, J = 6.7 Hz, 1 H, CHCH$_2$), 4.42-4.50, 4.48-4.56 (2m, 1 H, 2 H, CHCH$_2$), 6.14, 6.21 (2s, 2 × 1 H, ArH), 6.30 (br s, 2 H, ArH), 6.33, 6.54, 6.96, 6.99 (4s, 4 × 1 H, ArH); ^{13}C NMR (CDCl$_3$) δ -4.3, -4.3, -4.1, -4.0, -3.7, -3.4 (Si(CH$_3$)$_2$), 14.37, 14.44, 14.5, 14.6 (CH$_2$$CH_3$), 18.2, 18.39, 18.40 (SiC(CH$_3$)$_3$), 21.2, 21.60, 21.63, 21.7 (CH$_2$CH$_3$), 25.86, 25.93, 26.0 (SiC(CH$_3$)$_3$), 34.7, 35.6, 36.00, 36.04 (CHCH$_2$), 37.2, 37.3, 37.70, 37.73 (CH$_2$CH), 54.8, 55.3, 55.5, 55.7 (OCH$_3$), 99.5, 101.4, 101.7, 103.0 (CH, Ar), 121.0, 123.5, 124.3, 124.5, 125.2 (C, Ar), 126.0, 126.2, 126.4 (CH, Ar), 127.4 (CCH, Ar), 127.7 (CH, Ar),

128.0, 129.6, 151.2, 152.1, 152.4, 154.2, 154.9, 155.8, 156.7 (*C*, Ar) (note some signals are coincident). Found: C, 70.51; H, 9.69; $C_{62}H_{98}O_8Si_3$; requires C, 70.54; H, 9.36%.

References

(1) Casnati, A., Calixarenes and cations: a time-lapse photography of the big-bang. *Chemical Communications* **2013,** *49*, (61), 6827-6830.

(2) Duncan, N.C.; Roach, B.D.; Williams, N.J.; Bonnesen, P.V.; Rajbanshi, A.; Moyer, B.A., N, N′-Dicyclohexyl-N″-Isotridecylguanidine as Suppressor for the Next Generation Caustic Side Solvent Extraction (NG-CSSX) Process. *Separation Science and Technology* **2012,** *47*, (14-15), 2074-2087.

(3) Mokhtari, B.; Pourabdollah, K.; Dallali, N., A review of calixarene applications in nuclear industries. *Journal of Radioanalytical and Nuclear Chemistry* **2011,** *287*, (3), 921-934.

(4) Gropp, C.; Quigley, B.L.; Diederich, F., Molecular Recognition with Resorcin[4]arene Cavitands: Switching, Halogen-Bonded Capsules, and Enantioselective Complexation. *Journal of the American Chemical Society* **2018,** *140*, (8), 2705-2717.

(5) Arnott, G.E., Inherently Chiral Calixarenes: Synthesis and Applications. *Chemistry – A European Journal* **2018,** *24*, (8), 1744-1754.

(6) McIldowie, M.J.; Mocerino, M.; Ogden, M.I., A brief review of Cn-symmetric calixarenes and resorcinarenes. *Supramolecular Chemistry* **2010,** *22*, (1), 13-39.

(7) Kundrat, O.; Lhoták, P., Meta Substitution of Calixarenes. In *Calixarenes and Beyond*; Neri, P., Sessler, J.L., Wang, M.-X., Eds. Springer International Publishing: Cham, 2016; pp 43-73.

(8) Li, S.-Y.; Xu, Y.-W.; Liu, J.-M.; Su, C.-Y., Inherently Chiral Calixarenes: Synthesis, Optical Resolution, Chiral Recognition and Asymmetric Catalysis. *International Journal of Molecular Sciences* **2011,** *12*, (1), 429-455.

(9) Zheng, Y.-S.; Luo, J., Inherently chiral calixarenes: a decade's review. *Journal of Inclusion Phenomena and Macrocyclic Chemistry* **2011,** *71*, (1), 35.

(10) Page, P.C.B.; Heaney, H.; Sampler, E.P., The First Enantioselective Syntheses of Axially Chiral Enantiomerically Pure Calix[4]resorcinarene Derivatives. *Journal of the American Chemical Society* **1999,** *121*, (28), 6751-6752.

(11) Wierzbicki, M.; Jędrzejewska, H.; Szumna, A., Chiral Calixarenes and Resorcinarenes. In *Calixarenes and Beyond*; Neri, P., Sessler, J.L., Wang, M.-X., Eds. Springer International Publishing: Cham, 2016; pp 13-41.

(12) McIldowie, M.J.; Mocerino, M.; Skelton, B.W.; White, A.H., Facile Lewis Acid Catalyzed Synthesis of C4 Symmetric Resorcinarenes. *Organic letters* **2000,** *2*, (24), 3869-3871.

(13) Van Loon, J.D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D.N., Selective functionalization of calix[4]arenes at the upper rim. *The Journal of Organic Chemistry* **1990,** *55*, (21), 5639-5646.

(14) Shu, C.-M.; Chung, W.-S.; Wu, S.-H.; Ho, Z.-C.; Lin, L.-G., Synthesis of Calix[4]arenes with Four Different "Lower Rim" Substituents. *The Journal of Organic Chemistry* **1999,** *64*, (8), 2673-2679.

(15) Markovsky, L.N.; Visotsky, M.A.; Pirozhenko, V.V.; Kalchenko, V.I.; Lipkowski, J.; Simonov, Y.A., Phosphorotropic rearrangement in synthesis of asymmetrically-substituted calix[4]arenes. *Chemical Communications* **1996**, (1), 69-71.

(16) Larsen, M.; Jørgensen, M., Selective Halogen−Lithium Exchange Reaction of Bromine-Substituted 25,26,27,28-Tetrapropoxycalix[4]arene. *The Journal of Organic Chemistry* **1996,** *61*, (19), 6651-6655.

(17) Barrett, E.S.; Irwin, J.L.; Turner, P.; Sherburn, M.S., Efficient Distal-Difunctionalization of Cavitand Bowls. *The Journal of Organic Chemistry* **2001,** *66*, (24), 8227-8229.

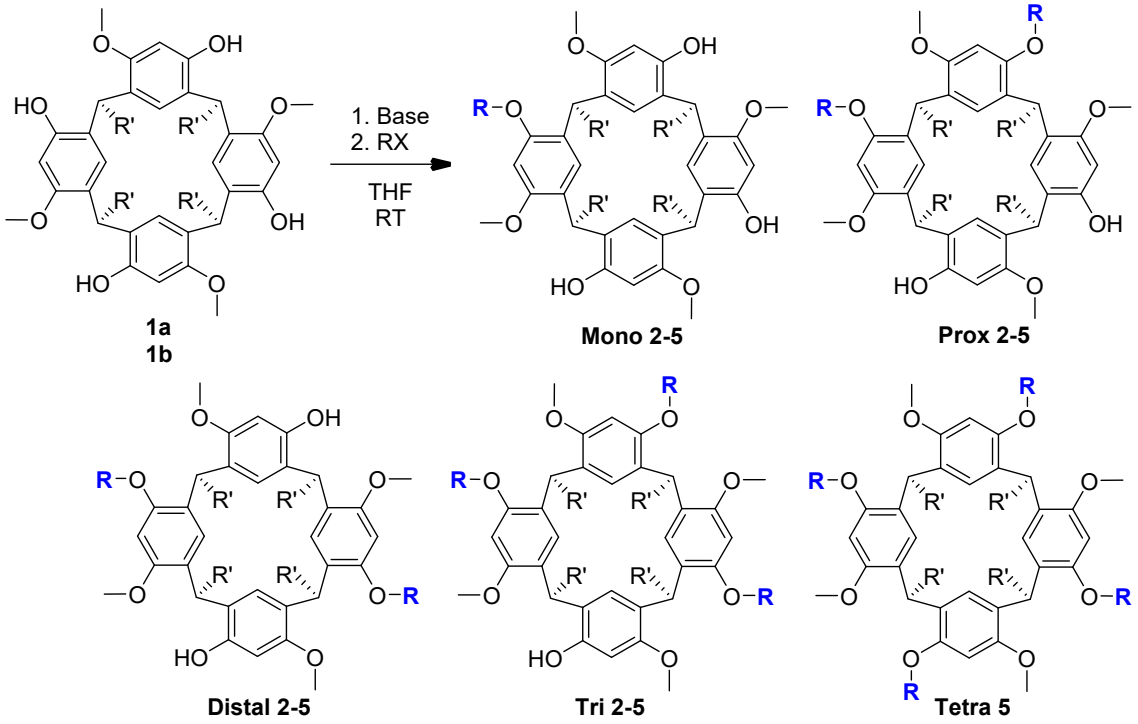
(18) Ngodwana, L.; Kleinhans, D.J.; Smuts, A.-J.; van Otterlo, W.A.L.; Arnott, G.E., Selective derivatisation of resorcinarene ethers via an ortholithiation approach. *RSC Advances* **2013,** *3*, (12), 3873-3876.

(19) Lukin, O.; Shivanyuk, A.; Pirozhenko, V.V.; Tsymbal, I.F.; Kalchenko, V.I., Synthesis, Conformation, and Binding Properties of Resorcarene Tetrasulfonates. Asymmetric Reorganization of Pendant Sulfonyl Groups via Intramolecular SO- - -H−O Hydrogen Bonds. *The Journal of Organic Chemistry* **1998,** *63*, (25), 9510-9516.

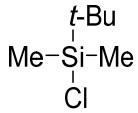
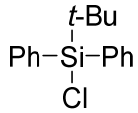
(20) Shivanyuk, A.; Paulus, E.F.; Böhmer, V.; Vogt, W., Selective Derivatizations of Resorcarenes. 4. General Methods for the Synthesis of C2v-Symmetrical Derivatives. *The Journal of Organic Chemistry* **1998,** *63*, (19), 6448-6449.

(21) Tan, D.A.; Mocerino, M., Distal functionalisation of C4 symmetric tetramethoxyresorcinarene by selective lithiation. *Journal of Inclusion Phenomena and Macrocyclic Chemistry* **2018,** *91*, (1), 71-80.
(22) Tan, D.A.; Mocerino, M., Unpublished work. In Curtin University.
(23) Buckley, B.R.; Page, P.C.B.; Chan, Y.; Heaney, H.; Klaes, M.; McIldowie, M.J.; McKee, V.; Mattay, J.; Mocerino, M.; Moreno, E., et al., The Preparation and Absolute Configurations of Enantiomerically Pure C4-Symmetric Tetraalkoxyresorcin[4]arenes Obtained from Camphorsulfonate Derivatives. *European Journal of Organic Chemistry* **2006,** *2006*, (22), 5135-5151.
(24) Klaes, M.; Agena, C.; Köhler, M.; Inoue, M.; Wada, T.; Inoue, Y.; Mattay, J., First Synthesis, Isolation and Characterization of Enantiomerically Pure and Inherently Chiral Resorc[4]arenes by Lewis Acid Cyclization of a Resorcinol Monoalkyl Ether. *European Journal of Organic Chemistry* **2003,** *2003*, (8), 1404-1409.
(25) Salorinne, K.; Nauha, E.; Nissinen, M.; Ropponen, J., Synthesis and Characterization of the *O*-Alkylation Products of Resorcinarene. *European Journal of Organic Chemistry* **2013,** *2013*, (8), 1591-1598.
(26) Salorinne, K.; Tero, T.-R.; Riikonen, K.; Nissinen, M., Synthesis and structure of mono-bridged resorcinarene host: a ditopic receptor for ammonium guests. *Organic & Biomolecular Chemistry* **2009,** *7*, (20), 4211-4217.
(27) Helttunen, K.; Salorinne, K.; Barboza, T.; Barbosa, H.C.; Suhonen, A.; Nissinen, M., Cation binding resorcinarene bis-crowns: the effect of lower rim alkyl chain length on crystal packing and solid lipid nanoparticles. *New Journal of Chemistry* **2012,** *36*, (3), 789-795.
(28) Gottlieb, H.E.; Kotlyar, V.; Nudelman, A., NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. *The Journal of Organic Chemistry* **1997,** *62*, (21), 7512-7515.

Table 2. *O*-functionalisation of tetramethoxyresorcinarenes with various protecting groups and bases in THF.



1a : R' = Pr **2** : R = TBDMS, R' = Pr **4** : R = Bn, R' = Pr
1b : R' = Heptyl **3** : R = TBDPS, R' = Pr **5** : R = TBDMS, R' = Heptyl

Entry	Starting material	Base	Eq	RX	Yield %					
					Tetra	Tri	Distal	Prox	Mono	Starting material
I	1a	BuLi	2		0	0	0	0	22*	78
II	1b	BuLi	2		0	0	0	0	26*	74
III	1b	BuLi	3		0	0	0	0	28*	72
IV	1a	BuLi	10.7		0	0	0	0	29*	71
V	1a	KOtBu	2.1		0	12	31	15	28	10
VI	1b	KOtBu	2.0		0	6	20	12	33	22
VII	1b	KOtBu	3.0		0	27	13	17	21	19
VIII	1a	NaH	2.0		0	7	23	12	37	18
IX	1a	KOtBu	2.0		0	0	16	7	32	39
X	1a	KOtBu	3.0		0	22*	25	9	12	Trace
XI	1a	KOtBu	2.0	BnBr	6	25	15	18	11#	5#

*Not separated; yield calculated based on approximated ^{1}H NMR integration.

#Incompletely separated

Figure 1. ^{1}H NMR spectra of TBDMS isomers **Distal-2** in acetone-d_6 and **Prox-2** in $CDCl_3$. Diagnostic signals have been highlighted. *Designates solvent peaks.

Figure 2. ^{1}H NMR spectra of **Distal-2** recorded in $CDCl_3$ (upper spectrum), and in acetone-d_6 (lower spectrum). *Denotes solvent peaks.

Figure 3. Crown conformation of the the TBDMS substituted resorcinarenes. Colour code: C, grey; O, red; Si, yellow. Alkyl chains and hydrogen atoms not involved in H-bonding have been omitted for clarity.

Figure 4. Crown conformation of the the TBDPS, Bn and long-chained TBDMS substituted resorcinarenes. Alkyl chains and hydrogen atoms not involved in H-bonding have been omitted for clarity.

Figure 5. Ball-and-stick view of the crystal structure of **Distal-5.** The tails and the heads of the resorcinarene molecules are represented in green and orange, respectively.