

CHEMISTRY

A European Journal

A Journal of



Accepted Article

Title: Upper-rim monofunctionalisation in the synthesis of triazole- and disulfide-linked multicalix[4]- and -[6]arenes.

Authors: William Gardiner, Matthew Camilleri, Luis Angel Martinez Lozano, Sean Bew, and G. Richard Stephenson

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Chem. Eur. J.* 10.1002/chem.201804755

Link to VoR: <http://dx.doi.org/10.1002/chem.201804755>

Supported by
ACES

WILEY-VCH

DOI: 10.1002/chem.201xxxxxx

Macrocycles

Upper-rim monofunctionalisation in the synthesis of triazole- and disulfide-linked multicalix[4]- and -[6]arenes.

William H. Gardiner,^[a] Matthew Camilleri,^[a,b] Luis A. Martinez-Lozano,^[a] Sean P. Bew,^{*[a]} and G. Richard Stephenson^{*[a]}

Abstract: Covalently linked multiple calixarenes are valued in supramolecular chemistry. We report an easy and versatile synthetic route to covalently linked double and triple calix[4]arene and calix[6]arenes by a novel DMF-controlled selective alkylation of a convenient and readily available upper-rim dimethylaminomethyl-substituted tetrahydroxy calix-

[4]arene and -[6]arenes. Synthetic routes to upper-rim functionalised redox active disulfide-linked double-, tetra- and peptidohybrid-calixarenes employing either redox chemistry (CH₂SH) or thiolates (CH₂S⁻) are also opened up from the same key starting material.

Introduction

Monosubstituted calix[4]arenes are less plentiful than their 1,3-di- and tetra-functionalized counterparts.¹ They are, however, derivatives to form linear multi-calixarenes. They also serve as building blocks to form di-calixarenes. These possibilities are exemplified in this paper with examples of double and triple calixarenes. The products are easily accessible by two new and highly efficient synthetic procedures. Relatively few mono-substituted calix[4]arenes have been reported. This observation is all the more surprising when their versatility and critical use as components of electron-switches,² supramolecular calixpeptides,³ enzyme mimics,⁴ catalysts,⁵ molecular recognition,⁶ ESR probes,⁷ organocatalysts,⁸ and nucleoside motifs,⁹ and in procedures for asymmetric hydrogenation,¹⁰ and chiral lithiation,¹¹ are taken into consideration. The explanation is that it is easier to fully substitute (i.e. tetrasubstitute) a calix[4]arene than it is to perform the reaction exclusively at just one of the four identical rings of the macrocycle. Although di- and tetra-substituted calix[4]arenes are valuable, sought after commodities, it is clear that what is currently lacking in the supramolecular / macrocyclic chemists

synthetic route to monofunctionalised calix[4]arenes. Examples bearing valued upper-rim functionality e.g. halide, amine, aldehyde, thiol, alkyne or azide are notably missing. There are for example no general routes to mono-azide cone-**12**, nor monothiol cone-**13** (Table 1).

It is important to note that the widespread utility of calix[4]arenes derives from their straightforward synthesis. Furthermore, it is also possible when specific reaction conditions are employed, to generate with high chemoselectivity one of four different, i.e. 1,2-alternate, 1,3-alternate, cone or partial cone, conformations.¹²

These issues have attracted the attention of a number of research groups, but despite much effort, the existing procedures to access upper-rim mono-substituted calix[4]arenes often lack simplicity and generality, or are restricted by practical difficulties. For example, the useful thermal *para*-Claisen rearrangement of mono-allyloxycalix[4]arenes requires high temperatures (~210 °C) and is limited to simple O-allyl ethers.¹³ In specific cases, however, there have been significant individual successes, for example with the mono-nitration¹⁴ and mono-formylation¹⁵ of tetra-O-alkylated calix[4]arenes. The availability of *ortho*-alkylation¹⁶ or simple S_N2 chemistry¹⁷ have also proved useful. In some cases, there have been crucial advances, as exemplified by the research groups of Hof^{1h} and Sherburn (the latter example providing the ground-state *para*-Claisen rearrangement¹⁸). None-the-less, despite this progress, there still remains a need for simple, general synthetic methods to access cone-locked upper-rim monosubstituted calix[4]arenes, particularly those bearing strategically important functional groups such as CH₂N₂ (for dynamic-covalent chemistry (DCvC) linking).

Strategies to link macrocycles are currently topical but successful examples tend to be in the resorcinarene and pillararene series,

[a] Dr's S. P. Bew, G. R. Stephenson, W. H. Gardiner and L. A. Martinez-Lozano
School of Chemistry
University of East Anglia
Norwich Research Park, Norwich, NR4 7TJ, UK
Fax: (+) 44 1603 592003
E-mail: s.bew@uea.ac.uk; g.r.stephenson@uea.ac.uk

[b] Mr M. Camilleri
School of Chemistry, University of Bath, Bath, BA2 7AY, UK.

Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author.

DOI: 10.1002/chem.201xxxxxx

not with simple calixarenes themselves. There are some notable exceptions. Fischer and Weber¹⁹ have reported a bis-calix[4]arene with a triazole-based connection between bridge positions on the two calix[4]arene rings. In general, examples of heterocycle-linked multi-calix[4]arenes are rare, but pyridine,²⁰ and porphyrin²¹ have previously been used as linkers for this purpose. In the case of disulfide-linked calix[4]arenes, as far as the authors are aware, there is only one example of a structure of this type,²² and that, one formed accidentally from an unexpected reaction. Notably, the two reviews on DCvC linking²³ focus on resorcinarenes, not the true calixarenes that are the subject of our work. Recently, the best progress with disulfide-linking has been with pillar[5]arene structures. In these elegant examples, two 2018 papers²⁴ wonderfully demonstrate the importance in real-world applications of these disulfide-linked products, and the introduction to an earlier 2016 paper²⁵ spells out the importance of having easy synthetic access and also the strategic value of the redox chemistry. Other DCvC examples are similarly distinct from main-stream calixarene chemistry. A diselenide-linked structure,²⁶ for example, substitutes one of the methylene bridges for Se-Se links, and another very recent example (2018) of DCvC uses **lower** rim acylhydrazine substituents.

A valuable entry point to synthetically versatile monofunctionality in simple calix[4]arenes was provided many years ago by Gutsche.²⁷ Working with the conformationally mobile lower-rim tetrahydroxy series, the conveniently-installed upper-rim *N,N*-dimethylaminomethyl group in **3** was converted into a selection of other examples. We were surprised to discover, however, that the synthesis of corresponding examples with *cone*-confining lower-rim tetrapropoxy groups had not been reported. We describe here how this limitation can be overcome. We also demonstrate the utility of the *N,N*-dimethylaminomethyl substituent to access other *cone*-locked mono-substitution patterns in the tetrapropoxy series, including -CH₂N₃ and -CH₂SH groups that enable the synthesis of multi-calixarenes. Finally, based on this approach, we report covalently linked and dynamic covalently linked multi-calixarenes. *ChemCatChem* 10(12): 201804755, 2018. DOI: 10.1002/cssc.201804755

Results and Discussion

Our first objective was the seemingly simple task of introducing *O*-(*n*-propyl) groups on the lower rim of **3**, to lock it into the *cone*-locked conformation. It soon became apparent, however, that there is an intrinsic difficulty with this reaction (controlling the reactivity of competing nucleophilic sites, see Figure 1, box) when performed in the conventional way with *n*-propyl iodide as the electrophile. It seems the nucleophilic *N,N*-

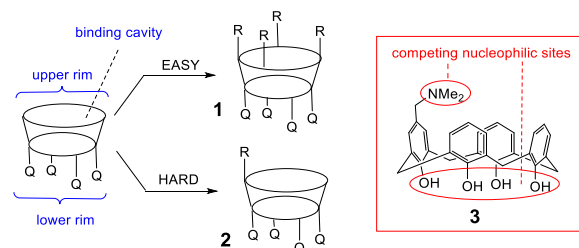
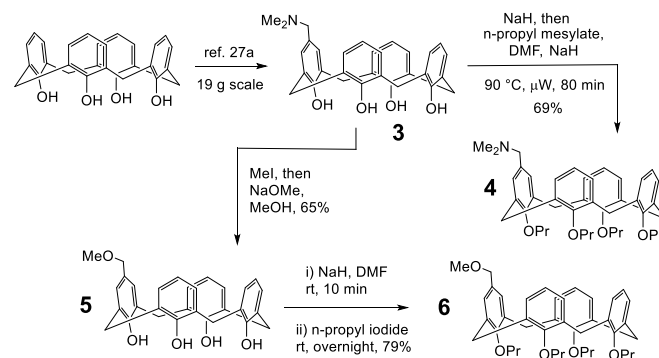


Figure 1. Upper- and lower-rim substitution sites in conformationally labile (e.g. Q = OH) and *cone*-locked (e.g. **1** or **2**, Q = OPr) calix[4]arenes; box: the problem of competing nucleophilic sites in the Gutsche *N,N*-dimethylaminomethylcalix[4]arene **3**.

dimethylamino group competes with the nucleophilic lower-rim phenoxides (i.e. Q = O⁻, generated by the use of a base). In our initial experiments, the standard *O*-alkylation methods,²⁸ that are widely used with great success with other calix[4]arenes, generated no viable quantities of *cone*-**4**. Instead, highly coloured reaction mixtures comprising what appeared to be complex oligomers were produced. This problem probably arises because the undesired *N*-propylation reaction generates an *N*-quaternised species. Such structures are prone to intramolecular elimination, forming a reactive *para*-quinone methide (not shown). Furthermore, in the presence of sodium hydride, an intramolecular [2,3]-sigmatropic Sommelet-Hauser rearrangement or Hoffman elimination reaction might occur. Interestingly, neither of the latter reactions, as far as the authors are aware, have been reported on calixarenes.

To overcome this problem, we have developed a novel approach to avoid the unwanted nucleophilicity of the 3° amine on the upper-rim, whilst at the same time increasing the nucleophilicity of the phenoxide anions on the lower-rim. The key to success proved to be the use of DMF as solvent, and the choice of *n*-propyl mesylate as the electrophile in place of the conventional *n*-propyl iodide. When the anion is generated from **3** with sodium hydride (Scheme 1), the ring of lower-rim oxygen atoms can be expected to provide an excellent binding site for the Na⁺ counterion; an effect that has been exploited to hold calix[4]arenes in the *cone*-conformation during *O*-alkylation.²⁹



Scheme 1. Convenient access to the mono(*N,N*-dimethylaminomethyl)calix[4]arene **4** and the mono(methoxymethyl)calix[4]arene **5**.

Hevey and Ling have demonstrated³⁰ that mesylates become better leaving groups when bound to Na⁺. Thus, with the sodium ion located at the lower-rim, and by choosing *n*-propyl mesylate as our electrophile, we anticipated its interaction with Na⁺ would increase its electrophilicity exactly where it is needed, resulting in enhanced *O*-propylation on the lower-rim phenoxides. No such activation would be expected near the competing nitrogen atom of the upper-rim substituent.

Monofunctionalised calix[4]arene synthesis

Gratifyingly, when this approach was tried in practice, addition of *n*-propyl mesylate initially afforded *cone*-**4** in an unoptimised 52% isolated yield. To establish the importance of DMF, the reaction was repeated using THF or DMSO as the solvent. In both cases the yield of *cone*-**4** was much lower.

DOI: 10.1002/chem.201xxxxxx

Indeed, the O-propylation reaction failed to proceed at all when attempted using sodium hydride in THF at ambient temperature. Interestingly, switching to n-propyl iodide under these conditions afforded a complex mixture of oligomers. Employing DMSO in place of THF, again with sodium hydride, but at 100 °C and with n-propyl mesylate afforded *cone-4* in only a 15% yield.

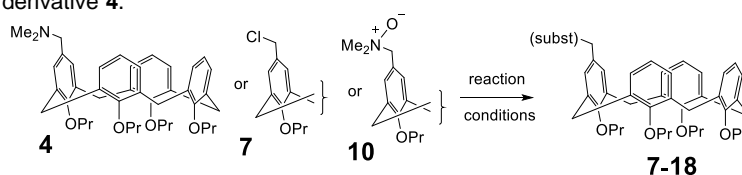
To explore the possibility that a molecule of DMF might be present as a guest in the cavity of **3**, and based on an observation by Harrowfield *et al.*,³¹ we added tetraethylammonium chloride (TEAC) to the reaction mixture in an attempt to displace the DMF from the calixarene. Stirring a solution of **3** in DMF for 1 hour was followed by addition of TEAC (1 equivalent) and stirring for a further 30 minutes before commencing our normal sodium hydride / n-propyl mesylate O-alkylation procedure. ¹H-NMR analysis indicated a complex mixture of *N*- and *O*-alkylated products as well as oligomers. This important result suggests that DMF does indeed play a pivotal role in blocking the nucleophilic properties of the tertiary *N,N*-dimethylammonium group.

Alternative sulfonate esters were also examined, but with n-propyl tosylate, *cone-4* was isolated in a poor 34% yield. n-Propyl

triflate failed to produce *cone-4* at all. Optimisation of the uniquely effective n-propyl mesylate / DMF / NaH combination quickly established that with 5 equivalents of sodium hydride and 4.6 equivalents of n-propyl mesylate, *cone-4* was produced in an increased 69% isolated yield (c.f. 52% from our initial attempt). The reaction is convenient, efficient, reliable and scaleable. Indeed, starting with 10 g of **3** we obtained more than 8 g of *cone-4*.

Next we compared the reactivity of methoxymethyl and *N,N*-dimethylaminomethyl substituents on the upper-rim. The starting material **3** was *N*-quaternised with methyl iodide. The product was treated at room temperature with sodium methoxide in methanol to provide the mono-substituted methoxymethyl calix[4]arene **5** (Scheme 1). Using sodium hydride as base and n-propyl iodide as electrophile, the lower-rim tetrahydroxy calix[4]arene **5** was now successfully converted into the *cone*-locked lower-rim tetrapropoxy derivative **6**. This further supports our proposal that the difficulty with the *O*-alkylation of **3** is a consequence of the presence of its nucleophilic *N,N*-dimethylamine group.

Table 1. Examples of simple preparations of valuable mono-substituted calix[4]arenes from newly available *N,N*-dimethylaminomethyl derivative **4**.



Entry	Starting material		Product		Reaction conditions	Yield (%)
	No.	(-subst)	No.	(-subst)		
1	<i>cone-4</i>	-NMe ₂	<i>cone-7</i>	-Cl ³²	EtOCOCI, CHCl ₃ , rt	76
2	<i>cone-4</i>	-NMe ₂	<i>cone-8</i> and <i>cone-9</i>	-CHO ³³ and -CO ₂ H ³⁴	KMnO ₄ , wet THF, reflux	20 and 27 ^[a]
3	<i>cone-4</i>	-NMe ₂	<i>cone-10</i>	-N ⁺ Me ₂ O ⁻	MCPBA, CHCl ₃ , rt	70
4	<i>cone-6</i>	-OMe	<i>cone-11</i>	-I ^[b]	NaI, MeCN, toluene, BF ₃ OEt ₂ , 0 °C	~85 ^[b]
5	<i>cone-10</i>	-N ⁺ Me ₂ O ⁻	<i>cone-8</i>	-CHO ³³	(Ac) ₂ O, DCM, 80 °C, aW	69
6	<i>cone-7</i>	-Cl	<i>cone-12</i>	-N ₃	NaN ₃ , DMF, 100 °C, aW	84
7	<i>cone-11</i>	-I	<i>cone-12</i>	-N ₃	NaN ₃ , DMF, 100 °C, aW	10 ^[c]
8	<i>cone-7</i>	-Cl	<i>cone-13</i>	-SH	thiourea, THF, 90 °C, aW, then 1 M KOH, THF, 90 °C, aW	82
9	<i>cone-7</i>	-Cl	<i>cone-14</i>	-CN	NaCN, DMF, 100 °C, aW	81
10	<i>cone-7</i>	-Cl	<i>cone-15</i>	-PO(OMe) ₂	P(OMe) ₃ (neat), 95 °C	39
11	<i>cone-7</i>	-Cl	<i>cone-16</i>	-NCO ³⁵	KCNO, DMF, 100 °C, aW	30
12	<i>cone-7</i>	-Cl	<i>cone-17</i>	-SCN	KCNS, DMF, 100 °C, aW	30
13	<i>cone-7</i>	-Cl	<i>cone-18</i>	-NCS	KCNS, DMF, 100 °C, aW	20

[a] after separation by chromatography on silica gel, dichloromethane / diethyl ether 4:1.

[b] this compound was unstable, but was identified by its conversion, albeit in low a yield (see [c]), into the fully characterized azidomethyl compound **12**.

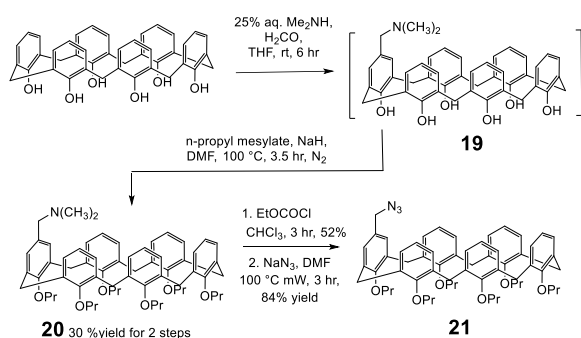
[c] polymeric material was also formed; the chloromethyl compound **7** is the better starting material for the synthesis of the azide **12**.

DOI: 10.1002/chem.201xxxxxx

As expected, the *N,N*-dimethylamino substituted calix[4]arene **cone-4** is easily converted into other *cone*-locked upper-rim monosubstituted calix[4]arenes (see Table 1). For example, efficient access to the useful chloromethyl derivative *cone-7*³² was possible using ethyl chloroformate (Table 1, entry 1). The corresponding iodomethyl derivative *cone-11* was obtained by reaction of **6** with NaI and BF₃·OEt₂ (Table 1, entry 4). This compound, however, was relatively unstable, turning pink on storage (see Table 1, footnote b). Access to the upper-rim monoformyl calix[4]arene *cone-8* is also more convenient from *cone-4* than by previously reported methods.^{11,21,33} Conversion into the *N*-oxide *cone-11* followed by reaction with acetic anhydride (entries 3 and 5, respectively) proved more efficient than direct oxidation with potassium permanganate, which gave a mixture aldehyde *cone-8* and the carboxylic acid *cone-9*³⁴ (entry 2). With the upper-rim chloromethyl derivative *cone-7* in hand, attention turned to the synthesis of the azide (*cone-12*, entry 6) and thiol (*cone-13*, entry 8) derivatives. Surprisingly, in view of their simple structures and potential value in the synthesis of *bis*-calixarenes, both these products are reported for the first time in this paper. Similarly, the nitrile *cone-14* was generated from chloromethylcalix[4]arene *cone-7* by a simple nucleophilic substitution (entry 9). In preliminary experiments, a selection of other nucleophiles were tested (entries 10-13), including the use of trimethylphosphite in an Arbuzov reaction (entry 10) extending the series of new upper-rim monosubstituted calix[4]arenes **15-18**, but in modest yields.

Monofunctionalised calix[6]arene synthesis

We wanted to further establish the versatility of our monofunctionalisation protocol by expanding it to include larger calixarenes (Scheme 2). A THF solution containing aqueous dimethylamine, formaldehyde and calix[6]arene³⁶ afforded gram quantities of our new core starting material mono-*N,N*-dimethylaminomethyl calix[6]arene (**19**).

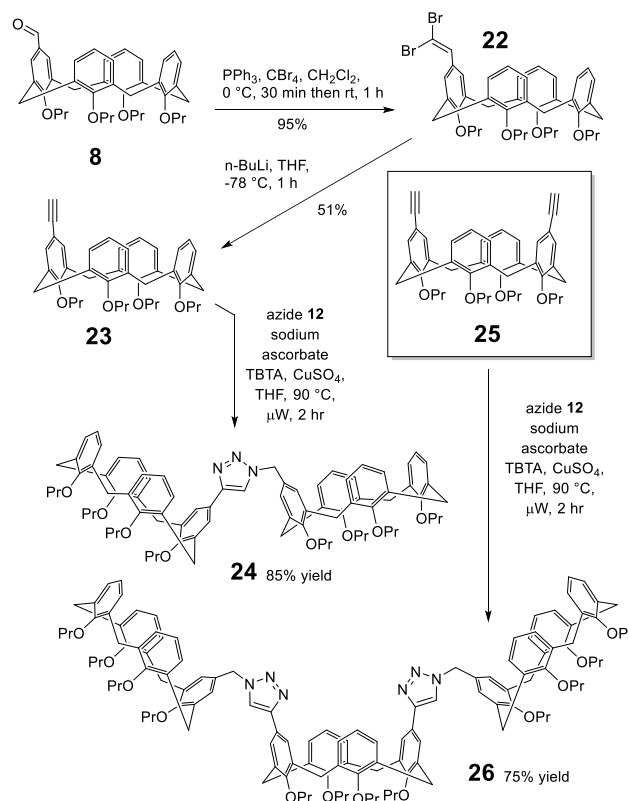


Scheme 2. Synthesis of monosubstituted calix[6]arenes

Based on our method described above for the calix[4]arene series, *O*-propylation generated **20** in a 59% yield. Subsequent chloromethylation (EtOCOCI) was followed by azide displacement (NaN₃, 100 °C, aW, 3 hr) affording the previously unknown azidomethylcalix[6]arene **21** in an 84% yield.

Heterocycle-linked multi-calixarene synthesis

The improved availability of the aldehyde *cone-8* (Table 1, entry 3 then entry 5) as a core starting material gave us easy access to mono-alkyne *cone-23*.³⁷ The formation of **22** (Scheme 3) was followed by a Corey-Fuchs reaction which gave *cone-23*. With the azide *cone-12* and the alkyne *cone-23* in hand, it was simple to produce the heterocycle-linked double calixarene **24**.

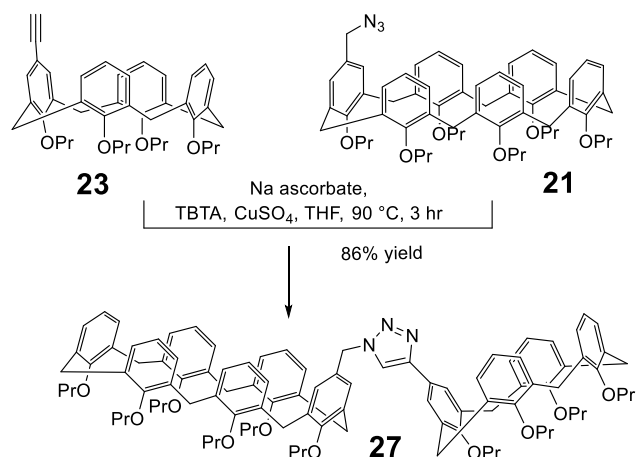


Scheme 3. Synthesis of heterocycle-linked double calixarene **24** and triple calixarene **26**.

Using a mild microwave-assisted CuAAC reaction (Scheme 3) we were delighted that *bis*-1,4-(*cone*-calix[4]arene)-1,2,3-triazole-linked *bis*-calixarene **24** was formed. The diyne *cone-25* (Scheme 3, box) was synthesized in two-steps from the corresponding and readily available 1,3-dialdehyde.³⁸ A double CuAAC reaction with 2 equivalents of the azide *cone-12* gave the triple calixarene cavitand **26** in a 75% yield.

The first example of a heterocycle-linked calix[6]arene-based multi-calixarene, **27** (Scheme 4), was obtained by combining *cone*-calix[4]arene alkyne *cone-23* with the newly available *cone*-calix[6]arene azide **21** using the same microwave-assisted CuAAC procedure that we had employed to form **24**.

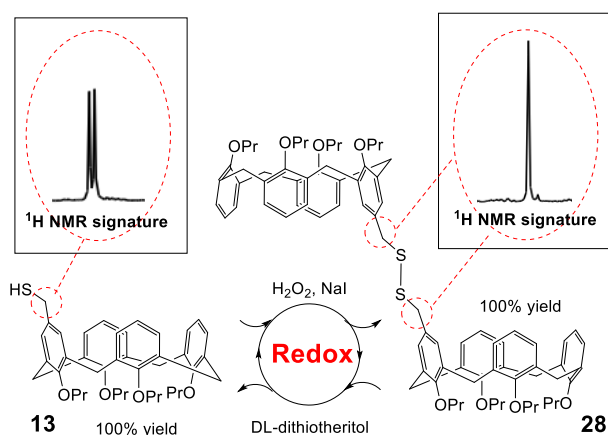
DOI: 10.1002/chem.201xxxxxx



Scheme 4. Synthesis of the new covalently linked double calixarene **27** combining calix[4]- and calix[6]-arene rings.

Redox active multi-calixarene synthesis

Redox-switchable multi-calixarenes that undergo predictable changes in response to an external stimuli are at the cutting edge of new molecular systems.³⁹ Based on the availability of thiol *cone*-**13**, we envisaged the synthesis of a redox-switchable *cone*-calix[4]arene-derived double calixarene **28** (Scheme 5) using a disulfide-centered DCvC linker.

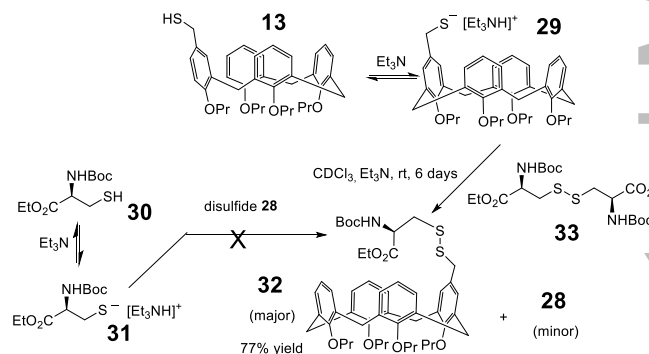


Scheme 5. Preparation of the redox-switchable DCvC-linked double calixarene **28** from *cone*-**13**.

Mild oxidation (H_2O_2 , NaI) of *cone*-**13** afforded our first example of a potentially reversible disulfide-linked double calixarene. $^1\text{H-NMR}$ analysis of the disulfide **28** confirmed that the $-\text{CH}_2\text{SH}$ doublet of *cone*-**13** ($J = 7$ Hz, left-hand box, Scheme 5) at 3.35 ppm had been replaced, after oxidation and intermolecular S-S bond-formation, with a singlet at 3.43 ppm (**28**, right-hand box, Scheme 5). This doublet \rightarrow singlet transition is an important spectroscopic marker. It should allow us to readily observe the proposed reversible/dynamic nature of the double calixarene formation. Indeed, $^1\text{H-NMR}$ spectroscopy promptly confirmed our ability to reform mono-

calix[4]arene *cone*-**13** via a quick and efficient reduction using DL-ascorbic acid (Scheme 5). Our successful direct O-alkylation of **3** has in this way, and through a series of now readily available compounds using simple reactions, made available both permanently covalently linked e.g. **24** and the reversible⁴¹ i.e. dynamically covalently linked⁴² e.g. **28** bis-calix[4]arenes.

Cysteine is an important thiol-containing α -amino acid⁴³ and is a component of the bioactive peptide glutathione (biomarker of cell oxidative stress⁴⁴). Both readily undergo redox chemistry. Thus cysteine and glutathione when oxidized are transformed into homodimeric S-S linked cystine⁴⁵ and glutathione disulfide (GSSG)^{44b,46} (not shown), respectively. Confident in our ability to generate redox-active calix[4]arene-based multi-calixarenes cf. **13** **8** **28** (Scheme 5), we were intrigued by the possibility of employing disulfide / thiol exchange chemistry on the upper-rim of calixarenes to generate cysteine- and glutathione-calix[4]arene peptidohybrids. Despite significant interest in peptido-calixarene-based chemistry, biology and medicinal chemistry,⁴⁷ as far as the authors are able to determine, there are no examples of their use in calixarene-based disulfide / thiol DCvC.⁴⁸ Exploiting our new, easy and quantitative access to the disulfide-linked double calixarene **28** (Scheme 5), we probed the synthesis of the non-symmetric S-S-linked cysteine-calix[4]arene *cone*-**32** and glutathione-calix[4]arene (*cone*-**35**) peptidohybrids (Schemes 6 and 7).

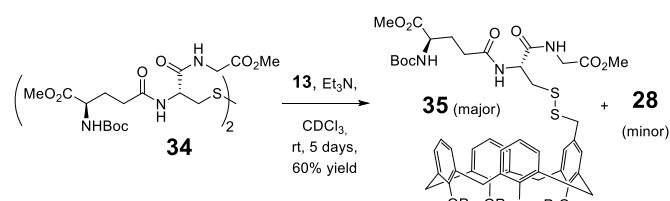


Scheme 6. Application of disulfide exchange chemistry for the efficient DCvC synthesis of S-S-linked peptidocalixarene **32**.

Meijer *et al.*⁴⁹ have exalted the practical importance and convenience, of using triethylamine as a weak organic base to promote the thiolate-disulfide exchange reactions (not shown).^{49,50} Probing the requirement for base and employing CDCl_3 as a convenient reaction / NMR solvent, a mixture of *N*-*boc*-(*R*)-cysteine ethyl ester (**30**) and our S-S-linked bis-calixarene **28** was analyzed by $^1\text{H-NMR}$ after 48 hours. As expected, in the absence of base, no observable reaction was identified. However, following the addition of triethylamine (2 equivalents) to **30** in an attempt to generate triethylammonium thiolate **31** and so promote the thiolate-disulfide exchange (Scheme 6), we were surprised that the reaction still did not proceed, even after 144 hours.

DOI: 10.1002/chem.201xxxxxx

An alternative route to **32** was devised. Our new approach, cone-13 and the disulfide **33** were first stirred in the absence of triethylamine for 48 hours. Similar to disulfide **28** and thiol **30**, and as expected, no reaction was observed ($^1\text{H-NMR}$). When triethylamine was added to form small quantities of the more nucleophilic thiolate **29** (Scheme 6) derived from *cone-13*, the disulfide / thiol exchange reaction was now observed, albeit slowly. Indeed, after 10 hours, $^1\text{H-NMR}$ spectroscopy indicated that approximately 8% of the desired peptidocalixarene **32** (Scheme 6) rising to a 60% yield after 144 hours at which point the majority of starting materials had been consumed (< 5% remaining) so the reaction was stopped.



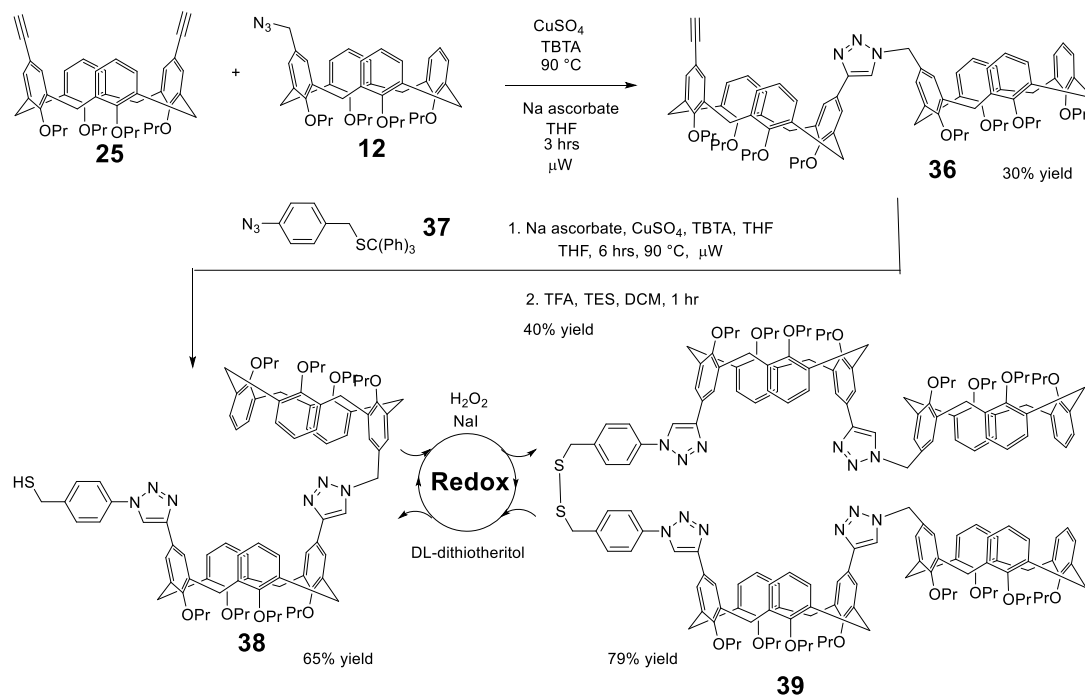
Scheme 7. Application of DCvC for the efficient dynamic synthesis of S-S-linked peptidocalixarene **35**.

We turned our attention next to the installation of a tripeptide on the upper-rim of mono-functionalized *cone*-calix[4]arene **13** (Scheme 7). This would demonstrate the generality of our peptidocalixarene-based disulfide exchange DCvC. Using the protected GSSG derivative **34** and 2 equivalents of triethylamine, reaction progress was again monitored using $^1\text{H-NMR}$. The reaction was stopped after 120

hours, and the desired tripeptide (GSSG)-S-S-linked-calix[4]arene peptidohybrid **35** was isolated. Similar to the synthesis of peptidocalix[4]arene **32**, only a small percentage of bis-calixarene **28** was observed. Although in both examples we chose not to isolate **28**, it could, if desired, be recycled after reduction to **13**.

Finally, with generally-applicable procedures now in place for the easy synthesis of covalent (i.e. heterocycle-linked) and dynamic covalent (i.e. disulfide-linked) multi-calixarenes, we turned to the synthesis of larger tetracalixarenes that contained both types of linkages. We started (Scheme 8) by varying the stoichiometry of our successful microwave-assisted double CuAAC reaction conditions (i.e. copper sulfate / TBTA / sodium ascorbate, 90 °C) to access the unsymmetrically-substituted calix[4]arene **36**, by reacting **12** and **25** together in a ca. 1:1 ratio. Executing a second CuAAC using the same catalysts, but with a slightly longer reaction time, allowed (4-azidobenzyl)-S-tritylsulfane **37** to be incorporated onto the precursor for **38**. Subsequent S-deprotection (trityl-group) using a combination of trifluoroacetic acid and triethylsilane generated the first example of a *cone*-locked 1,3-difunctionalised calix[4]arene appended, on the upper-rim, with both a thiol group and a heterocycle-linked mono-functionalised calix[4]arene (i.e. **38**).

We next established the potential of **38** to undergo the redox chemistry that we had demonstrated earlier with **13** (Scheme 5) by oxidation with hydrogen peroxide to form the S-S-dimer **39**. The dynamic nature of **38** / **39** was then confirmed by its subsequent reduction with DL-dithioerithol to reform the thiol containing calix[4]arene **38**.



Scheme 8. Synthesis of thiol derived multi-calixarene **38** and the easily reversible DCvC oxidative synthesis of S-S-linked tetracalixarene homodimer **39**

DOI: 10.1002/chem.201xxxxx

Conclusions

We report the first straightforward multi-gram synthesis of a new C_{60} -cone-calix[4]arene (*cone-4*). We have established that this simple 3° amine product opens the way to synthesise a raft of alternative, and hitherto unknown, but important mono-functionalised *cone*-calix[4]arenes (Table 1, entries 1, 3, 5, 6, 8, 9, 69-84% yield). Interestingly, the critical formation of **4** is far from trivial, but eventually provided an efficient and scalable O-alkylation reaction of **3**. This specifically required the combined use of DMF and *n*-propyl mesylate. These specialized reaction conditions were then successfully employed in the calix[6]arene series. Demonstrating the generality of our procedure and synthetic utility of our methodology, we report here the application of our mono-functionalised calixarenes for the synthesis of an S-S-linked redox-active double and tetra-calixarenes. We also report new examples of double and triple heterocycle-linked (*via* CuAAC chemistry) multi-calixarenes. Similarly, the first application of dynamic covalent chemistry using thiolate / disulfide exchange to access was successful affording, in preference to calixarene dimerisation, new peptidocalixarene hybrids. The C_{60} -cone-calix[4]arene (**4**) they generate *i.e.* redox active and DCVC augmented calixarenes, will significantly strengthen the supramolecular, macrocyclic, material and bio[...]. Interesting architectures to be constructed and novel properties investigated.

Experimental Section

Large scale synthesis of 5-(dimethylamino)methyl-25,26,27,28-tetrapropoxycalix[4]arene cone-4:²⁷ To a stirred solution of 5-(dimethylamino)methyl-25,26,27,28-tetrahydroxycalix[4]arene **3** (10 g, 20.76 mmol) in *N,N*-dimethylformamide (400 mL) under nitrogen was added sodium hydride (4.15 g, 60% in mineral oil, 104 mmol). The resulting suspension was stirred for 30 min at rt and then *n*-propyl methanesulfonate (13.06 g, 94 mmol) was added. The solution was heated and stirred at 100 °C for 3.5 h, allowed to cool to rt, and then poured into distilled water (300 mL). The aqueous layer was separated and extracted with diethyl ether (3 x 150 mL) and the combined organic phases were washed with brine (3 x 100 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford a yellow oil. The oil was dissolved in dichloromethane (50 mL) and filtered through silica gel (eluting with dichloromethane first, to remove the excess of sulfonate, and then dichloromethane / methanol, 9:1 V/V) to afford, after removal of the solvent under reduced pressure the title compound as a pale yellow foam (8.17 g, 60%).

Synthesis of 5-(dimethylamino)methyl-37,38,39,40,41,42-hexapropoxycalix[6]arene **20, step 1:** To a solution of calix[6]arene³⁶ (2.23 g, 3.5 mmol) in tetrahydrofuran (50 mL) was added dimethylamine (1.2 mL, 5.53 mmol, 25 % aq. solution) and formaldehyde (0.4 mL, 5.25 mmol, 37 % aq. solution). The mixture was stirred at room temperature for 6 h, after which time the fine white precipitate was collected by suction filtration to

afford the aminomethyl derivative **19** as a white solid (1.23 g, 1.77 mmol, 50 %). Its extremely low solubility in a wide range of organic solvents required its characterisation as the propyl ether **20**, as described in step 2. **Step 2:** A 20 mL capacity microwave vial was charged with the calixarene obtained from step 1 (0.500 g, 0.721 mmol), Anhydrous *N,N*-dimethylformamide (15 mL) was added under nitrogen, and then sodium hydride (0.221 g, 5.77 mmol, 60% in mineral oil) was added. The resulting suspension was stirred for 30 min at rt before the addition of *n*-propyl methanesulfonate (747 μL , 6.13 mmol) from a syringe. The vial was sealed with a PTFE-lined crimp cap and the mixture heated in the microwave synthesiser at 90 °C for 1.5 h. On cooling to rt, the aqueous layer was extracted with diethyl ether (3 x 30 ml), and the combined organic phase was washed with aqueous 1% potassium carbonate (2 x 30 mL), dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to leave a pale yellow oil. The oil was dissolved in dichloromethane (5 mL) and filtered through silica gel (eluting with dichloromethane first to remove the excess of electrophile and then dichloromethane / methanol, 9:1 V/V) to yield the desired title compound as a pale yellow oil (0.400 g, 0.423 mmol, 59 %). R_f 0.42 (15% methanol in dichloromethane); $^1\text{H NMR}$ (C_6D_6 , 500 T P: δ 7.85 (m, 5H), 4.07 (s, 12H), 3.39 (brs, 8H), 3.29 (s, 2H), 3.23 (brs, 4H), 2.10 (brs, 6H), 1.49 (brs, 6H), 1.32 (brs, 6H), 0.82 (t, J 6.1 Hz, 6H), 0.78-0.70 (m, 12H) ppm. $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 155.3, 135.2, 135.0, 134.7, 123.9, 123.8, 74.84, 74.76, 44.8, 31.2, 31.01, 30.97, 23.95, 23.94, 23.86, 23.84, 10.88, 10.83, 10.77 ppm. FT-IR (neat) 3361, 2963, 2935, 2875, 2281, 1750, 1588, 1454, 1385, 1250, 1215, 1194, 1084, 1063, 1042, 1006, 963, 889 cm^{-1} . MS (MALDI) m/z 988.02 $[\text{M}+\text{CO}_2]^+$; HRMS $[\text{M} + \text{H}]^+$ Calculated for: $\text{C}_{63}\text{H}_{80}\text{N}_1\text{O}_6$; 946.5980 Found: 946.5978.

Synthesis of 4-[5-(25,26,27,28-tetrapropoxycalix[4]arenyl)]-1H-1,2,3-triazol-1-yl]methyl-25,26,27,28-tetrapropoxycalix[4]arene **24:** A 5 mL capacity microwave vial was charged with a solution of the azide *cone-12* (30 mg, 0.05 mmol), the alkyne *cone-23* (38 mg, 0.06 mmol), copper(II) sulfate pentahydrate (4 mg, 0.19 mmol), sodium ascorbate (19 mg, 0.1 mmol) and tris(benzyltriazolylmethyl)amine (10 mg, 0.02 mmol) in tetrahydrofuran (1 mL). The vial was sealed with a PTFE-lined crimp cap and heated at 90 °C in the microwave synthesiser for 2 h. TLC analysis (dichloromethane) indicated the starting material had been consumed. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (diethyl ether / petrol, 7:1 V/V) to afford the title compound as a clear oil (52 mg, 0.04 mmol, 85 %). R_f 0.34 (30% diethyl ether in petrol); $^1\text{H NMR}$ (CDCl_3) δ 5.0 (d, J 7.4 Hz, 3H), 6.84 (dd, J 7.4, 1.4 Hz, 4H), 6.81-6.78 (m, 4H), 6.71 (t, J 7.4 Hz, 2H), 6.67 (d, J = 7.5 Hz, 2H), 6.51 (dd, J = 6.4, 2.8 Hz, 2H), 6.47-6.42 (m, 6H), 6.37 (t, J 7.5 Hz, 1H), 6.28 (s, 2H), 5.03 (s, 2H), 4.50-4.42 (m, 8H), 3.97-3.86 (m, 8H), 3.82-3.72 (m, 8H), 3.24-3.08 (m, 8H), 1.98-1.86 (m, 16H), 1.06-1.00 (m, 12H), 0.98-0.91 (m, 12H) ppm. $^{13}\text{C NMR}$ (CDCl_3) δ 157.1, 156.6, 156.3, 136.4, 136.2, 135.8, 135.7, 135.4, 134.7, 134.6, 134.4, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 126.0, 124.4, 122.2, 122.1, 121.9, 121.6, 118.8, 77.0, 76.8, 76.7, 54.0, 31.2, 31.1, 23.5, 23.5, 23.3, 23.2, 10.7, 10.6, 10.4, 10.3, 10.2 ppm. FT-IR (neat) 2960, 2932, 2874, 1586, 1456, 1384, 1246, 1214, 1194, 1006, 966 cm^{-1} . MS (MALDI) m/z 1287.32

DOI: 10.1002/chem.201xxxxxx

[M+Na]⁺; HRMS [M + H]⁺ Calculated for: C₈₃H₉₈N₃O₈; 1263.7348
Found: 1263.7348.

Synthesis of 5,5-(bis-25,26,27,28-tetra-propoxycalix[4]-arenyl)methyl disulfide 28: To a solution of *cone-13* (15 mg, 0.023 mmol) in ethyl acetate (0.5 mL) was added sodium iodide (1 mg, 7 μmol) then hydrogen peroxide (3 μL, 0.023 mmol) using a syringe. The mixture was stirred at rt for 1 h. The mixture was diluted with ethyl acetate (8 mL), and then washed with a sat. aq. sodium thiosulfate (5 mL) and water (5 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the title compound as a clear oil (15 mg, 0.023 mmol, 100%). ¹H NMR (500 MHz, CDCl₃) δ 6.47 (m, 22H), 4.44 (d, *J* = 13.3 Hz, 4H), 4.43 (d, *J* = 13.3 Hz, 4H), 3.88-3.77 (m, 16H), 3.43 (s, 4H), 3.14 (d, *J* = 13.4 Hz, 4H), 3.12 (d, *J* = 13.4 Hz, 4H), 1.96-1.85 (m, 16H), 1.01-0.92 (m, 24H) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 135.1, 134.9, 130.4, 129.3, 128.3, 128.2, 122.1, 121.9, 76.8, 76.8, 43.8, 31.1, 29.9, 23.41, 23.36, 10.5, 10.4 ppm. FT-IR (neat): 2961, 2923, 2875, 1732, 1586, 1462, 1455, 1263, 1210, 1195, 1086, 1007, 966, 758, 739 cm⁻¹. MS (MALDI): *m/z* 1298.66 [M + Na]⁺; HRMS: [M + NH₄]⁺ Calculated for: C₈₂H₁₀₂NO₈S₂ 1292.7041; Found: 1292.7005.

Acknowledgements

The authors acknowledge financial support from the EU Interreg IV Manche / Channel cross-border projects IS:CE-chem (4061) and Alcc (4196) and the EPSRC Mass Spectrometry Service at the University of Swansea for HRMS measurements and for their help and advice.

Keywords: supramolecular chemistry; host-guest chemistry; catalysis; molecular recognition; supramolecular catalysis; supramolecular catalysis; supramolecular catalysis

References

- [1] 1,3-Di- and tetra-functionalized are widely used and in some cases, are available in gram quantities, see: a) D. Zhang, W. Wang, *ARKIVOC* **2011**, 496-551; b) T. Haino, H. Iwamoto, *Science of Synthesis* **2010**, 45b, 1193; c) V. Boehmer, *Angew. Chem. Int. Ed.* **1995**, 34, 713-745; d) X.-Q. Sun, H. Zheng, Z.-Y. Li, M. O. Vysotsky, *Int. Res. J. Pure Appl. Chem.* **2014**, 4, 352-361; e) X. Cao, L. Luo, F. Zhang, Miao, D. Tian, H. Li, *Tetrahedron Lett.* **2014**, 55, 2029-2032; f) M. H. Dueker, H. Schaefer, M. Zeller, V. A. Azov, *J. Org. Chem.* **2013**, 78, 4905-4912; g) R. Sharma, R. Margani, S. M. Mobin, R. Misra, *RSC Advances* **2013**, 3, 5785-5788; h) K. D. Daze, M. C. F. Ma, F. Pineux, F. Hof, *Org. Lett.* **2012**, 14, 1512-1515; i) S. P. Bew, S. V. Sharma, *J. Org. Chem.* **2011**, 76, 7076-7083; j) S. P. Bew, A. W. J. Barter, S. V. Sharma, *J. Inclusion Phenom. Macrocyclic Chem.* **2010**, 66, 195-208; k) S. P. Bew, R. A. Brimage, G. Hiatt-Gipson, S. V. Sharma, S. Thurston, *Org. Lett.* **2009**, 11, 2483-2486; l) S. P. Bew, M. R. Cheesman, S. V. Sharma, *Chem. Commun.* **2008**, 5731-5733; m) S. P. Bew, R. A. Brimage, N. L'Hermite, S. V. Sharma, *Org. Lett.* **2007**, 9, 3713-1242.
- [2] J. R. Siekierzycka, C. Hippus, F. Würthner, R. M. Williams, A. M. Brouwer, *J. Am. Chem. Soc.* **2010**, 132, 1240-1242.
- [3] L. Baldini, F. Sansone, G. Faimani, C. Massera, A. Casnati, R. Ungaro, *Eur. J. Org. Chem.* **2008**, 869-886.
- [4] a) R. Cacciapaglia, A. Casnati, L. Mandolini, A. Peracchi, D. N. Reinhoudt, R. Salvio, A. Sartori, R. Ungaro, *J. Am. Chem. Soc.* **2007**, 129, 12512-12520; b) P. Molenveld, J. F. J. Engbersen, D. N. Reinhoudt, *Angew. Chem. Int. Ed.* **1999**, 38, 3189-3192.
- [5] a) Fahlbusch, M. Frank, G. Maas, J. Schatz, *Organometallics* **2009**, 28, 6183-6193; b) M. E. Amato, F. P. Ballistreri, A. Pappalardo, G. A. Tomaselli, R. M. Toscano, D. J. Williams, *Eur. J. Org. Chem.* **2005**, 3562-3570; c) L. Monnereau, D. Sémeril, D. Matt, L. Toupet, *Chem. Eur. J.* **2010**, 16, 9237-9247.
- [6] I. Stibor, J. Budka, V. Michlová, M. Tkadlecová, M. Pojarová, M. Curinová, P. Lhoták, *New J. Chem.* **2008**, 32, 1597-1607.
- [7] X. Hu, Y. Li, H. Yang, Y. Luo, *Tetrahedron Lett.* **2006**, 47, 7463-7465.
- [8] S. Shirakawa, T. Kimura, S.-I. Murata, S. Shimizu, *J. Org. Chem.* **2009**, 74, 1288-1296.
- [9] C.-C. Zeng, Y.-L. Tang, Q.-Y. Zheng, L.-J. Huang, B. Xi Z.-T. Huang, *Tetrahedron Lett.* **2001**, 42, 6179-6181.
- [10] N. Khiri, E. Bertrand, M.-J. Ondel-Eymin, Y. Rousselin, J. Bayardon, P. D. Harvey, S. Juge, *Organometallics* **2010**, 29, 3622-3631.
- [11] S. A. Herbert, G. E. Arnott, *Org. Lett.* **2010**, 12, 4600-4603.
- [12] a) T. Komori, S. Shinkai, *Chem. Lett.* **1992**, 901-904; b) P. Lhotak, S. Shinkai, *Tetrahedron Lett.* **1996**, 37, 645-6488.
- [13] D. C. Gutsche, J. A. Levine, P. K. Sujeeth, *J. Org. Chem.* **1985**, 50, 5802-5806.
- [14] a) K. C. Nam, D. S. Kim, *Bull. Korean Chem. Soc.* **1994**, 15, 284-286; b) C.-C. Zeng, Q.-Y. Zheng, Y.-L. Tang, Z.-T. Huang, *Tetrahedron* **2003**, 59, 2539-2548; c) F. Stejskal, V. Eigner, H. Dvorakova, P. Curinova, P. Lhotak, *Tetrahedron Lett.* **2015**, 56, 5357-5361.
- [15] A. Ikeda, M. Yoshimura, P. Lhotak, S. Shinkai, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1945-1950.
- [16] S. Thulasi, A. Savithri, R. L. Varma, *Supramolecular Chem.* **2011**, 23, 501-508.
- [17] In a tetra-bromomethyl example: a) L.-M. Yang, Y.-S. Zhen, Z.-T. Huang, *Synth. Commun.* **1999**, 29, 4451-4455; In a dichloromethyl example: b) Z.-T. Huang, G.-Q. Wang, L.-M. Yang, Y.-X. Lou, *Synth. Commun.* **1995**, 25, 1109-1118.
- [18] E. S. Barrett, J. L. Irwin, A. J. Edwards, M. S. Sherburn, *J. Am. Chem. Soc.* **2004**, 126, 16747-16749.
- [19] C. Fischer, E. Weber, *J. Incl. Phenom. Macrocycl. Chem.* **2014**, 79, 151-160.
- [20] P. Beer, M. Shade, Z. Chen, PCT Int. Appl. (1995), WO 9511449 A1 19950427.
- [21] M. Dudic, P. Lhotak, V. Kral, K. Lang, I. Stibor, *Tetrahedron Lett.* **1999**, 40, 5949-5952.
- [22] F. Üçü, *Tetrahedron* **2016**, 72, 760-766.
- [23] a) K. Kobayashi, M. Yamanaka, *Chem. Soc. Rev.* **2015**, 44, 449-446; b) M. Yamanaka, K. Kobayashi, *Asian J. Org. Chem.* **2013**, 2, 276-289.
- [24] a) C.-L. Sun, Z. Gao, K.-X. Teng, L.-Y. Niu, Y.-Z. Chen, Y. S. Zhao, Q.-Z. Yang, *ACS App. Mat. Interfaces* **2018**, 10, 26526-26532; b) C.-L. Sun, H.-Q. Peng, L.-Y. Niu, Y.-Z. Chen, L.-Z. Wu, C.-H. Tung, Q.-Z. Yang, *Chem. Commun.* **2018**, 54, 1117-1120.

DOI: 10.1002/chem.201xxxxxx

- [25] C.-L. Sun, J.-F. Xu, Y.-Z. Chen, L.-Y. Niu, L.-Z. Wu, C.-H. Tung, Q.-Z. Yang, *Polymer Chem.* **2016**, *7*, 2057-2061.
- [26] J. Thomas, L. Dobrzanska, L. Van Meervelt, M. A. Quevedo, K. Wozniak, M. Stachowicz, M. Smet, W. Maes, W. Dehaen, *Chem. Eur. J.* **2016**, *22*, 979-987.
- [27] a) C. D. Gutsche, K. C. Nam, *J. Am. Chem. Soc.* **1988**, *110*, 6153-6162; b) I. Alam, S. K. Sharma, C. D. Gutsche, *J. Org. Chem.* **1994**, *59*, 3716-3720.
- [28] O-alkylation calix[4]arene chemistries, see a) K. Iwamoto, K. Araki, S. Shinkai, *J. Org. Chem.* **1991**, *56*, 4955-4962; b) G. Ferguson, J. F. Gallagher, L. Giunta, P. Neri, S. Pappalardo, M. Parisi, *J. Org. Chem.* **1994**, *59*, 42-53; c) S. Shimizu, A. Moriyama, K. Kito, Y. Sasaki, *J. Org. Chem.* **2003**, *68*, 2187-2194.
- [29] K. Iwamoto, K. Fujimoto, T. Matsuda, S. Shinkai, *Tetrahedron Lett.* **1990**, *31*, 7169-7172.
- [30] R. Hevey, C.-C. Ling, *Org. Biomol. Chem.* **2013**, *11*, 1887-1895.
- [31] J. M. Harrowfield, M. I. Ogden, W. R. Richmond, B. W. Skelton, A. H. White, *J. Chem. Soc., Perkin Trans 2* **1993**, 2183-2190.
- [32] T. Fahlbusch, M. Frank, J. Schatz, T. D. Schuehle, *J. Org. Chem.* **2006**, *71*, 1688-1691.
- [33] a) E. Kelderman, L. Derhaeg, W. Verboom, J. F. J. Engbersen, S. Harkema, A. Persoons, D. N. Reinhoudt, *Supramolecular Chem.* **1993**, *2*, 183-190; b) K. Araki, K. Hisaichi, T. Kanai, S. Shinkai, *Chem. Lett.* **1995**, 569-570; c) using Cl₂HCOMe and SnCl₄, A. Casnati, A. Sartori, L. Pirondini, F. Bonetti, N. Pelizzi, F. Sansone, F. Ugozzoli, R. Ungaro, *Supramol. Chem.* **2006**, *18*, 199-218; Synthesis from the mono-bromo derivative: d) see ref. 15
- [34] Alternative synthesis from the aryl bromide: see ref. [11].
- [35] Previously synthesised from the CH₂NH₂ derivative: K. H. Krawinkler, N. M. Maier, R. Ungaro, F. Sansone, A. Casnati, W. Lindner, *Chirality* **2003**, *15*, S17-29.
- [36] a) C. D. Gutsche, L. G. Lin, *Tetrahedron* **1986**, *42*, 1633-1640; see also: b) E. Nomura, H. Taniguchi, S. Tamura, *Chem. Lett.* **1989**, 1125-1126; c) V. Percec, T. K. Bera, B. B. De, Y. Sanai, J. Smith, M. N. Holerca, B. Barboiu, R. B. Grubbs, J. M. Frechet, *J. Org. Chem.* **2001**, *66*, 2104-2117; d) H. M. Chawla, S. Kumar, N. Pant, A. Santra, K. Srinivas, N. Kumar, D. St. C. Black, *J. Inclusion Phenom. Macrocycl. Chem.* **2011**, *71*, 169-178; e) S. Sayin, M. Yilmaz, *Tetrahedron*, **2014**, *70*, 6669-6676; f) L. An, L.-L. Han, Y.-G. Zheng, X.-N. Peng, Y.-S. Xue, X.-K. Gu, J. Sun, C.-G. Yan, *Eur. J. Med. Chem.* **2016**, *123*, 21-30; h) J. V. de Assis, P. A. S. Abranches, I. B. Braga, O. M. P. Zuniga, A. G. Sathicq, G. P. Romanelli, A. G. Sato, S. A. Fernandes, *RSC Advances* **2016**, *6*, 24285-24289; i) S. Sayin, M. Yilmaz, *Tetrahedron* **2016**, *72*, 6528-6535.
- [37] For an alternative synthesis, see: F. Elaieb, A. Hedhli, D. Semeril, D. Matt, J. Harrowfield, *Eur. J. Org. Chem.* **2016**, 3103-3108.
- [38] a) M. Larsen, M. Jørgensen, *J. Org. Chem.* **1996**, *61*, 6651-6655; b) Q. Lin, A. D. Hamilton, *Comptes Rendus Chim.* **2002**, *5*, 441-450.
- [39] a) I. Pochorovski, F. Diederich, *Acc. Chem. Res.* **2014**, *47*, 2096-2105; b) I. Pochorovski, M.-O. Ebert, J.-P. Gisselbrecht, C. Boudon, W. B. Schweizer, F. Diederich, *J. Am. Chem. Soc.* **2012**, *134*, 14702-14705.
- [40] W. W. Cleland, *Biochemistry* **1964**, *8*, 480-482.
- [41] For a dynamic covalent disulfide-linked carceplex, see: a) J. Sun, B. O. Patrick, J. C. Sherman, *Tetrahedron* **2009**, *65*, 7296-7302; see also: b) C. Naumann, S. Place, J. C. Sherman, *J. Am. Chem. Soc.* **2002**, *124*, 16-17; for an example of combined covalent and dynamic covalent, see: c) G. Sforazzini, E. Orentas, A. Bolag, N. Sakai, S. Matile, *J. Am. Chem. Soc.* **2013**, *135*, 12082-12090.
- [42] Y. Jin, C. Yu, R. J. Denmana, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634-6654.
- [43] For a review of the redox chemistry of cysteine, see: L. J. Alcock, M. V. Perkins, J. M. Chalker, *Chem. Soc. Rev.* **2018**, *47*, 231-268.
- [44] a) M. Valko, D. Leibfritz, J. Moncol, M. T. Cronin, M. Mazur, J. Telser, *Int. J. Biochem. Cell Biol.* **2007**, *39*, 44-84; b) A. Meister, M. E. Anderson, *Ann. Rev. Biochem.* **1983**, *52*, 711-760; c) H. J. Forman, D. A. Dickinson, *Biofactors* **2003**, *17*, 1-12; d) H. Olguin, G. Juarez, D. Calderon, in *Glutathione: Biochemistry, Mechanisms of Action and Biotechnological Implications*, (Eds: N. Labrou, E. Fliemetakis), Nova Science Publishers, Inc. Hauppauge, New York, **2013**, pp. 55-75; e) P. Monostori, G. Wittmann, E. Karg, S. Turi, *J. Chromatography B* **2009**, *877*, 3331-3346.
- [45] M. D. Chaney, L. K. Steinrauf, *Acta Cryst. B* **1974**, *30*, 711-716.
- [46] L. Flohé, *Biochim. Biophys. Acta* **2013**, *1830*, 3139-3142.
- [47] Y. Hamuro, M. C. Calama, P. Crego, H. S. Park, A. D. Hamilton, *Angew. Chem. Int. Ed.* **1997**, *36*, 2680-2683.
- [48] Examples of dynamic covalent chemistry using alternative approaches: a) J. Thomas, L. Dobrzanska, M. Smet, W. Maes, W. Dehaen, *Supramolecular Chem.* **2014**, *26*, 591-600; b) M. Rissanen, A. Szumna, *Angew. Chem. Int. Ed.* **2014**, *53*, 13760-13764; c) H. Kudo, K. Shigematsu, K. Mitani, T. Nishikubo, N. C. Kasuga, H. Uekusa, Y. Ohashi, *Macromolecules* **2008**, *41*, 2030-2036; Alternative approaches using alternative approaches: d) M. Ciaccia, I. Tosi, L. Baldini, R. Cacciapaglia, L. Mandolini, S. Di Stefano, C. A. Hunter, *Chem. Sci.* **2015**, *6*, 144-151; e) M. Taniguchi, H. Du, J. S. Lindsey, *J. Chem Inform. Modeling* **2013**, *53*, 2203-2216; f) A. Le-Gresley, N. Kuhnert, *J. Chem. Res.* **2010**, *34*, 61-67; g) J. M. C. A. Kerckhoffs, M. A. Mateos-Timoneda, D. N. Reinhoudt, M. Crego-Calama, *Chem. Eur. J.* **2007**, *13*, 2377-2385; h) M. Crego-Calama, D. N. Reinhoudt, M. G. J. Cate, *Topics in Current Chemistry*, **2005**, *249*, 285-316; i) F. Cardullo, M. Calama, M. Crego; B. H. M. Snellink-Ruel, J.-L. Weidmann, A. Bielejewska, P. Timmerman, D. N. Reinhoudt, R. Fokkens, N. M. M. Nibbering, *Chem. Commun.* **2000**, 367-368; j) L. J. Prins, P. Timmerman, D. N. Reinhoudt, *Pure Appl. Chem.* **1998**, *70*, 1459-1468.
- [49] A. T. ten Cate, P. W. D. Dankers, R. P. Sijbesma, E. W. Meijer, *J. Org. Chem.* **2005**, *70*, 5799-5803.
- [50] H. Hioki, W. C. Still, *J. Org. Chem.* **1998**, *63*, 904-905.

6

Received: ((will be filled in by the editorial staff))

Revised: ((will be filled in by the editorial staff))

Published online: ((will be filled in by the editorial staff))

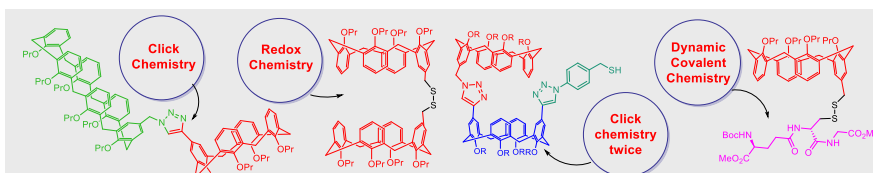
DOI: 10.1002/chem.201xxxxx

Accepted Manuscript

DOI: 10.1002/chem.201xxxxxx

Layout 2:

FULL PAPER



Double and triple calix[4]- and calix[6]arenes are easily accessible by a novel selective alkylation reaction employing *n*-propyl mesylate in DMF. Disulfide-linked double- and peptidohybrid-calixarenes and a tetra-calixarene, formed either redox chemistry (CH₂SH) or thiolate (CH₂S⁻) addition, are also described.

Multi-calixarenes

W. H. Gardiner, M. Camilleri, L. A. Martinez-Lozano, S. P. Bew,* G. R. Stephenson*

È

Monofunctionalisation in the synthesis of triazole- and disulfide-linked multicalix[4]- and -[6]arenes.

Accepted Manuscript