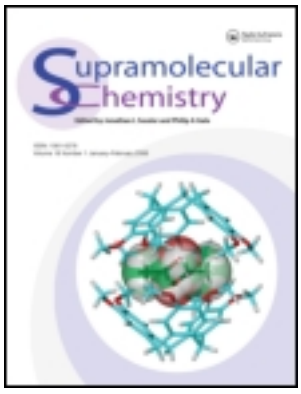

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Calix[4]bis(spirodienone) as a versatile synthon for upper rim alkoxylation of calixarenes and synthesis of novel triazole-based biscalixarene by 'CuAAC' chemistry

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Calix[4]bis(spirodienone) as a versatile synthon for upper rim alkoxylation of calixarenes and synthesis of novel triazole-based biscalixarene by 'CuAAC' chemistry

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The spiro rings of calix[4]bis(spirodienone) have been opened up using various bromofunctionalised alcohols employing a novel *ipso* nucleophilic substitution of *tert*-butyl groups by alkoxy groups. Additionally, a route has been paved towards the preparation of triazole-linked biscalixarene *via* the copper(I)-catalysed modern version of classical Huisgen 1,3-dipolar cycloaddition of alkynyl calixarene and azidocalixarene, derived from the above-mentioned bromo-substituted calixarene.

Keywords: calixarene; calix[4]bis(spirodienone); *p*-TSA; biscalixarenes; CuAAC

Introduction

Biscalixarenes have garnered considerable interest as fascinating calixarene derivatives for the study of various aspects of their supramolecular chemistry from simple host–guest interactions (*1*) to application as artificial sensors (*2*), synthetic receptors for biological agents (*3*), antibody mimetics (*4*) or building blocks for molecular boxes (*5*). Biscalixarenes may be constructed through upper rim–upper rim (*6*), lower rim–lower rim (*7*) and upper rim–lower rim linkage or non-covalently generated through hydrogen bonding (*8*). Rebek et al. (*9*) reported the synthesis and encapsulation behaviour of biscalixarenes linked by one bridge at the upper rim and bearing urea groups in the same rims. A series of biscalixarene derivatives linked through their upper rim with different aromatic and heteroaromatic units as spacers between them has also been reported (*10*). However, in most of the above-mentioned reports, there is one limitation or another such as the poor availability of starting materials, drastic reaction conditions, longer reaction times and poor yield of the products.

Our work in this direction was stimulated by the tremendous impact exerted by copper-assisted azide–alkyne cycloaddition (CuAAC) (*11*) (click reaction) (*12*) in numerous areas of the material and life sciences (*13*) and the belief that the use of this formidable reaction with calixarenes will furnish the opportunity for new applications. Besides the advantage of efficiency, regioselectivity and compatibility with reaction conditions, the unique properties of the 1,4-disubstituted 1,2,3-triazole ring, in terms of participation in hydrogen bonding and dipole–dipole interactions, have made click chemistry even more attractive (*14*). Click concept has been ingeniously utilised by Bew et al. (*15*) for making upper rim triazole-appended calixarenes bearing α-amino acids and carbohydrates for performing chemo-enzymatic procedures. Zhao and Chung et al. (*14c,d*) have validated the use of this synthetic strategy for preparing triazole-coupled calixarenes for binding of metal ions. Recently, Gonzalez et al. (*14f*) have reported the synthesis of calixarene-based cavitands and nanotubes by click chemistry. In this context, we would like to report in this article the systematic study on the selective monoalkoxylation of the upper rim of *p-tert*-butylcalix[4]arene using bifunctional alcohols and a further demonstration of the viability of CuAAC in the synthesis of a new head-to-head-linked biscalixarene.

As part of our ongoing research on the chemistry of bis(spirodienones) (*16*) **1a**, **1b** and **1c** (Figure 1) – the highly versatile molecules obtained by the oxidative cyclisation of *p-tert*-butylcalix[4]arene – we have recently come across an interesting reaction in which the bis(spirodienone) can be transformed into calix[4]arenes, locked in the cone conformation, that are selectively substituted with alkoxy/aryloxy groups at the upper rim (*17*). The synthetic methodology adapted involved an acid-mediated reaction of bis(spirodienone) with primary alcohols to afford upper rim-substituted mono- and 1,3-dialkoxy calix[4]arenes in a single step.

Results and discussion

With the aim of introducing additional functional groups at the upper rim of calixarenes, we extended this newly developed strategy using bifunctional alcohols. Initially, we reacted bis(spirodienone) **1a** with 3-bromopropan-1-ol **2a** under conditions that have been optimised for alcohols

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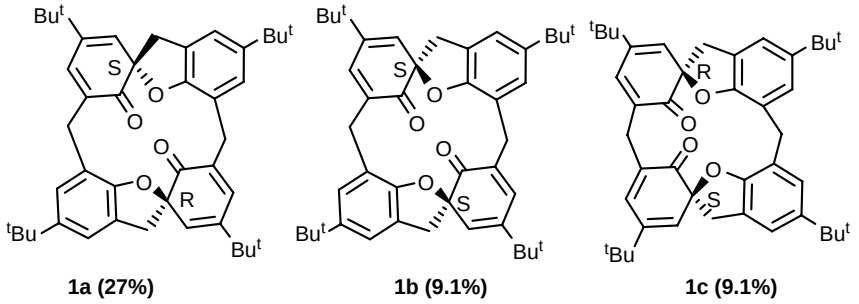
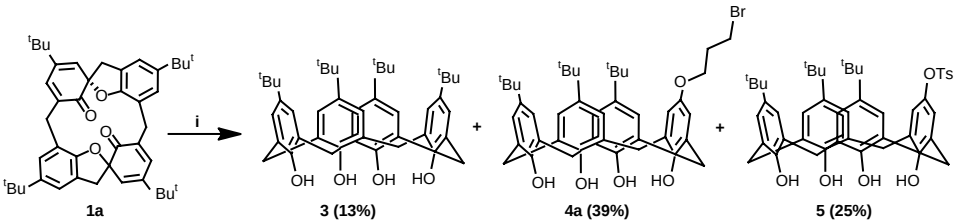


Figure 1. Oxidative cyclisation products of *p-tert*-butylcalix[4]arene.



Scheme 1. *p*-TSA-mediated reaction of calix[4]bis(spirodienone) **1a** with bromopropanol.

(Scheme 1) (*17*). The optimised condition involved in conducting the reaction in the presence of 5.0 equiv. of *p*-TSA in toluene is 110°C for 6 h. The reaction afforded a mixture of three products.

Although products **3** and **5** were identified as *p-tert*-butylcalix[4]arene and upper rim monotosylated calixarene on comparison with literature data (*17*), the structure of **4a** was established by various spectroscopic techniques. In the ^{1}H NMR spectrum, the hydroxyl proton was displayed as a singlet at δ 10.21 in units of parts per million (ppm). The aromatic protons were discernible as a multiplet and a singlet at δ 7.03 and 6.55 ppm, respectively. The methylene protons resonated as two broad doublets at δ 4.23 ($J = 14.3$ Hz) and 3.49 ppm. An uneven triplet at δ 3.93 ppm was observed for the OCH_2 protons. The *tert*-butyl group appeared as two singlets at δ 1.21 and 1.19 ppm in a 2:1 ratio with one *tert*-butyl group missing. The proposed structure was further supported by ^{13}C NMR spectrum showing an OCH_2 peak at δ 65.5 ppm. The aromatic carbon to which OH was attached resonated at δ 152.9 ppm. The aliphatic signals were observed in δ 34.1 – 15.1 ppm region. The cone conformation was confirmed from ^{13}C values obtained for methylene bridges and by comparison with literature precedents (*18*). The structure was further confirmed by CHN analysis (anal. calcd for $C_{43}H_{53}BrO_5$: C, 70.77; H, 7.32. Found: C, 70.73; H, 7.35).

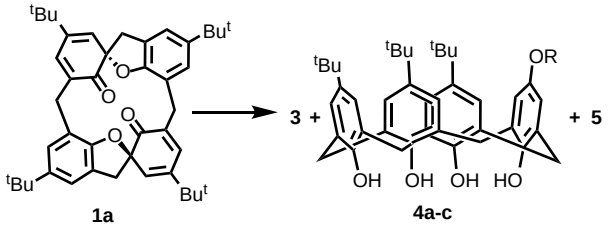
To establish the general nature of the reaction, we further reacted substrate **1a** with various bromoalcohols and an aminoalcohol under the optimised conditions. The results are summarised in Table 1. In the case of bromofunctionalised alcohols, the reaction proceeded smoothly affording mono-substituted products in acceptable yields.

When the reaction was carried out with 4-aminobutan-1-ol **2d**, to our disappointment no reaction took place and the starting material was recovered as such. To understand more about the non-reactivity of aminoalcohols, we decided to investigate the reaction with highly nucleophilic aliphatic amines. When substrate **1a** was subjected to the same reaction with diethylamine in the presence of *p*-TSA (5.0 eqiuv.) in toluene at reflux temperature, reaction failed to occur. The action of other Lewis acids such as AgOTf and $Sc(OTf)_2$ was also investigated but to no benefit. Thus, the non-reactive nature of aminoalcohols was attributed to the presence of amino group in the molecule. Under the reaction conditions employed, the amino group gets protonated owing to its high basicity.

The possibility of facile conversion of bromo derivative to azide functionality prompted us to utilise the phenomenon of click chemistry in the construction of multivalent structures such as biscalixarenes. The alkyne partner for the click reaction was also prepared by the same synthetic methodology (*17*).

Preliminary endeavours towards click reaction focused on utilising one-pot *in situ* azide synthesis/'click' protocol reported by Van der Eycken et al. (*19*). Treating bromofunctionalised calixarene **4a**, sodium azide and upper rim propargylated calixarene **4e** in DMSO at 80°C for 12 h did not yield the desired click calixarene adducts. All of the starting materials were recovered in good mass

Table 1. Generalisation of the reaction with various functionalised alcohols.



1a **4a-c**

Entry	ROH 2(a-d)	Yield (%) 3	4	5
1	Br–(CH2)3–OH (2a)	13	4a/39	25
2	Br–(CH2)4–OH (2b)	20	4b/35	23
3	Br–(CH2)6–OH (2c)	20	4c/28	27
4	H2N–(CH2)3–OH (2d)		No Reaction	

Reaction conditions: 2, 5.0 equiv. *p*-TSA, toluene, 110°C, 6h.

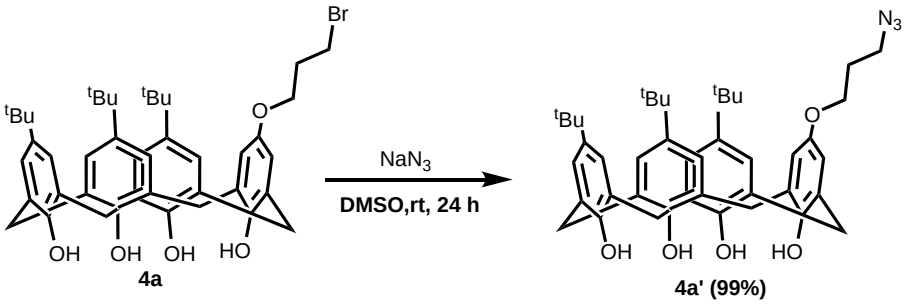
balances. Switching to a stepwise protocol, we readily undertook the synthesis of the core starting material **4a**′ *via* S_N2 displacement on bromofunctionalised calixarene (Scheme 2).

Having both the partners for the cycloaddition in hand, we next turned our attention to clicking between the two. Utilising a procedure reported by Sharpless et al. (*11a*), we attempted a copper(I)-catalysed [3 + 2]-dipolar cycloaddition reaction between calix[4]arene derivatives. Accordingly, an aqueous *tert*-butyl alcohol (1:1 v/v) solution of **4a**′ and **4e** was stirred (96 h) at ambient temperature with copper(II) sulphate and sodium ascorbate. However, the reaction failed to afford any product due to solubility problems, and the starting materials were recovered unchanged. Even though the solubility problem was alleviated by changing the solvent to aqueous DMF, no reaction ensued, both at ambient and reflux temperature. Solvents such as THF and CH_3CN were also used in the presence of CuI and $CuSO_4$/Na ascorbate combination but without much success. Interestingly, employing $CuSO_4$/Na ascorbate in aqueous ethanol at 60°C gave solely the 1,5-disubstituted triazole-linked biscalixarene in 77% yield (Scheme 3). The structure of compound **6** was characterised by NMR analysis and MALDI-TOF spectral data (Table 2).

The ^{1}H NMR of **6** exhibited the triazole proton at δ 7.51 ppm as a singlet. Moreover, the fixed cone conformation of the calix[4]arene scaffolds was substantiated by the presence of signals for the equatorial and axial protons of the methylene bridges as doublets at *ca* 4 and 3 ppm, respectively. The OH protons of the two calixarene units appeared as two singlets close to each other at δ 10. 23 and 10.21 ppm. The various CH_2 protons appeared as corresponding signals at δ 5.03 (singlet), 4.45 (triplet), 3.81 (triplet), 2.29 (multiplet) ppm. The ^{13}C NMR of **6** exhibited a peak at δ 153 ppm attributable to carbon to which OH is attached. The aliphatic carbon cluster representing *t*-Bu and bridging methylenes appeared within 34–29 ppm range. An HMQC experiment was run to assign carbons due to various CH_2s and triazole CH, which allowed the assignment of peaks at 64.3 and 62.1 ppm to $-NCH_2$ and $-OCH_2$ (near to triazole ring), respectively. The $-OCH_2$ near the calixarene moiety was seen at 49.9 ppm whereas the triazole CH appeared immersed in a cluster of aromatic carbon around 127 ppm.

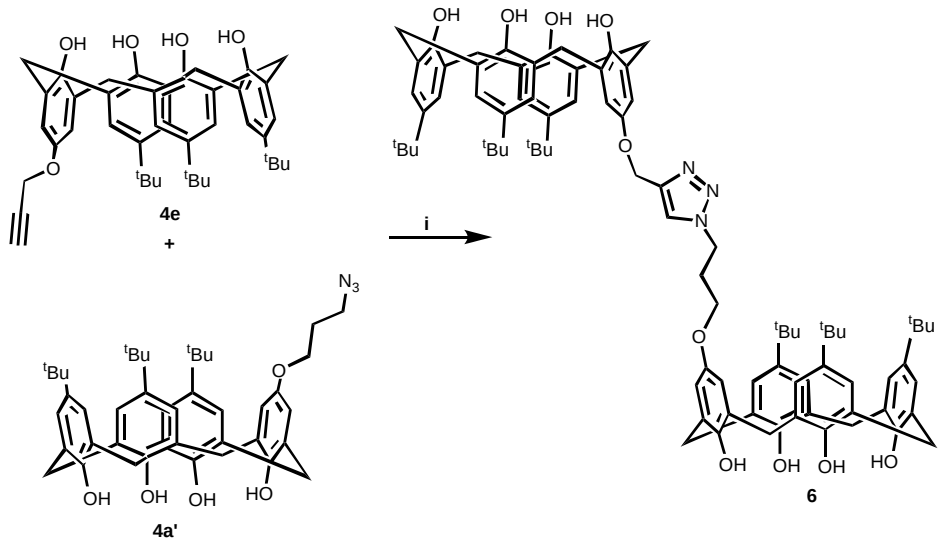
As a follow-up of the investigation described above, it was of interest to study the [2 + 3]-cycloaddition of azidocalixarene with various phenylacetylenes, which were prepared by the Sonogashira reaction of respective bromobenzenes and TMS acetylene using literature procedures (*20*). Interestingly, on reacting **4a**′ with phenyl acetylene **7** using $CuSO_4$/sodium ascorbate in *aqueous* ethanol at ambient temperature gave solely the triazole-linked calixarene **8** in 85% yield (Scheme 4).

This result obtained with phenylacetylene encouraged us to extend the Cu(I)-catalysed cycloaddition reaction of azidocalixarene **4a**′ to diacetylene and triacetylene benzenes. Accordingly, we attempted the reaction of azidocalixarene with diacetylene benzene **9** and triacetylene benzene **11** under similar conditions. Results revealed



4a **4a' (99%)**

Scheme 2. Reaction of **4a** with NaN_3.



Scheme 3. [3 + 2] Cycloaddition of alkynyl calixarene **4e** with azidocalixarene **4a′**.

that in the above cases the respective triazole-appended calixarenes **10** and **12** were obtained as the sole products in excellent yields. The gross structures of both the products were determined by IR, ^{1}H, ^{13}C NMR and MALDI-TOF analyses.

The host–guest properties of biscalixarene **6** were investigated in the presence of metal ions (Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Ag^+, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} and Pb^{2+}), organic anions (^{t}BuNCl, ^{t}BuNBr, ^{t}BuNHSO$_4$ and ^{t}BuNClO$_4$) and small molecules (CH_3OH and CH_3NH_2). The compound was found to be inactive in binding towards the various guests examined. The studies of other multicalixarenes are going on and will be duly reported.

Conclusion

In summary, we have employed bromoalcohols, in the presence of *p*-TSA, to open up the spiro rings of calix[4]bis(spirodienone) to furnish upper rim bromoalkyl-substituted calix[4]arenes. Furthermore, we have utilised this new upper rim bromo-substituted calixarene as a starting point in the synthesis of biscalixarene linked in an upper rim–upper rim fashion together with propargyl-substituted calixarene (obtained using the same synthetic methodology) *via* CuAAC. The high yield and exclusive formation of 1,4-disubstituted triazole highlight the efficiency of the approach.

Experimental

General procedures and materials

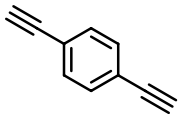
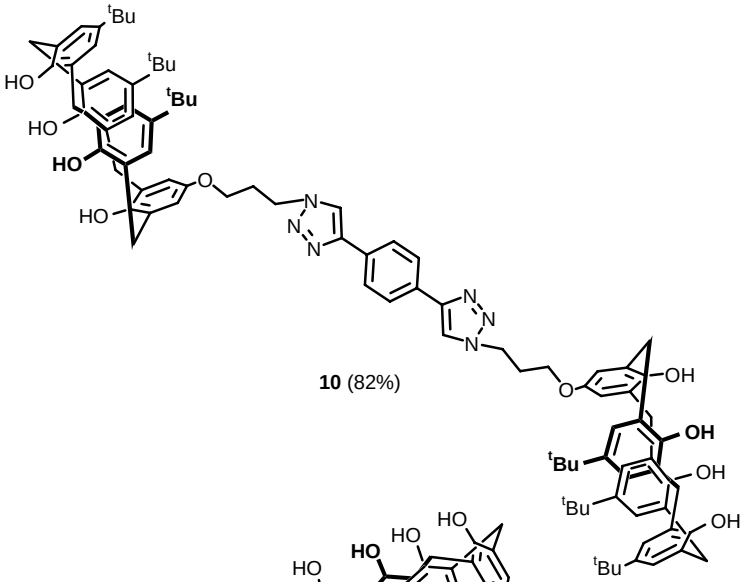
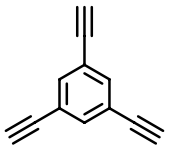
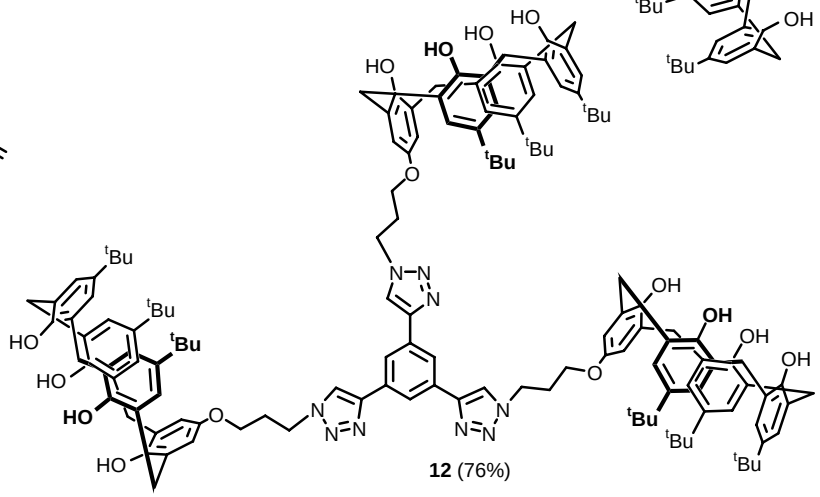
All the chemicals were of the best grade commercially available and were used without further purification. All the solvents were purified according to the standard procedure; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulphate binder. Gravity column chromatography was performed using 100–200 mesh silica gel and mixtures of hexane–ethyl acetate were used for elution.

NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C), respectively, on a Bruker Avance DPX-300 MHz. Chemical shifts are reported in δ (ppm) relative to TMS (^{1}H) or $CDCl_3$ (^{13}C) as internal standards. IR spectra were recorded on Bomem MB series FT-IR spectrometer; absorptions are reported in cm^{-1}. Mass spectra were recorded under MALDI-TOF mechanism in Axima-CFR Plus spectrometer. Elemental analysis was done using Perkin-Elmer 2400 CHNS analyser. Chemical shifts for ^{1}H NMR spectra are reported as δ (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.25, singlet). Multiplicities were given as s (singlet), br s (broad singlet), d (doublet), t (triplet) and dd (doublets of doublet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03, triplet). Elemental analysis was done using Perkin-Elmer 2400 CHN analyser.

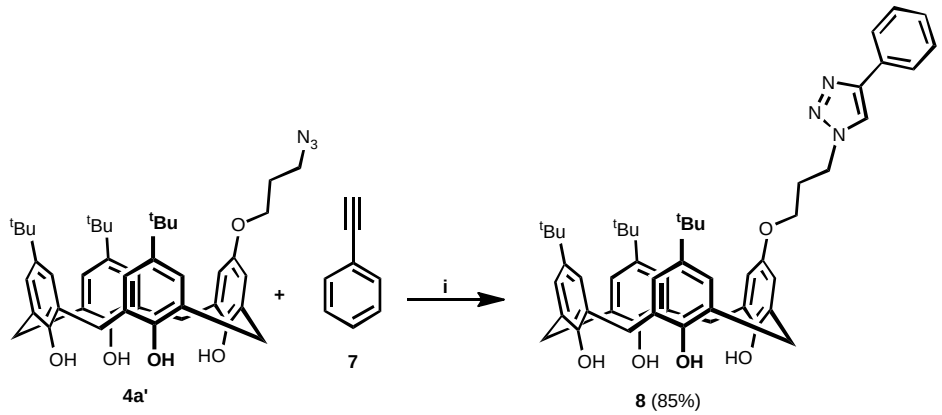
General procedure for the reaction of calix[4]bis(spirodienone) with bromoalcohols

A mixture of bis(spirodienone) **1a** (50 mg, 0.08 mmol), bromoalcohol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was taken in a 50 ml R.B. flask and was stirred at 110°C.

Table 2. Triazole-linked calix[4]arene frameworks from **4a′**.

Entry	Acetylenes	Products (yield)
1	 **9**	 **10** (82%)
2	 **11**	 **12** (76%)

Reaction conditions: 4a′, $CuSO_4$/Na ascorbate, DIPEA, EtOH/H_2O (2:1), rt, 2h



i = $CuSO_4$/Na ascorbate, DIPEA, EtOH/H_2O (2:1), rt, 2h.

Scheme 4. Reaction of azidocalixarene with phenylacetylene under 'click' protocol.

The reaction was continued till the reaction was complete as shown by TLC (~6 h). The solvent was removed under reduced pressure. The reaction mixture was worked up using dichloromethane–water mixture and the solid mass obtained was purified by column chromatography.

*5-(3-Bromoprop-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (**4a**)*

Yield: 39% as a white solid. R_f: 0.86 (90:10 hexane–ethyl acetate). Mp: Decomposed >230°C. IR (KBr) ν_{max}: 3172, 2960, 2862, 1814, 1258, 1050 cm^{-1}. ^1H NMR: δ 10.21 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.55 (s, ArH, 2H), 4.23 (broad s, $ArCH_2Ar$, 4H), 3.93 (uneven t, $-OCH_2$, 2H), 3.49 (m, $ArCH_2Ar$, $-CH_2$, 6H), 2.16 (m, $-CH_2$, 2H), 1.21 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR: δ 152.9 (C–OH), 146.8, 146.7, 146.3, 144.4, 144.2, 142.8, 129.4, 127.9, 127.7, 127.2, 126.0, 125.9, 125.6, 114.6 (Ar-C), 65.5 ($-OCH_2$), 56.9 ($-CH_2Br$), 34.1, 31.5, 30.8, 29.9, 29.4, 22.7, 14.1 ($ArCH_2Ar$, $-CH_2$, *t*-Bu). MS (FAB): calcd for $C_{43}H_{53}BrO_5$, $[M+1]^+$: 729.31; found: 729.64, 730.58. Elemental analysis calculated for $C_{43}H_{53}BrO_5$: C, 70.77; H, 7.32. Found: C, 70.73; H, 7.35.

*5-(4-Bromobut-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (**4b**)*

Yield: 35% as a white solid. R_f: 0.83 (90:10 hexane–ethyl acetate). Mp: Decomposed >230°C. IR (KBr) ν_{max}: 3171, 2957, 2860, 1810, 1258, 1050 cm^{-1}. ^1H NMR: δ 10.21 (s, OH, 4H), 7.02 (m, ArH, 6H), 6.54 (s, ArH, 2H), 4.24 (d, $J = 13.5$ Hz, $ArCH_2Ar$, 4H), 3.81 (t, $J = 6.0$ Hz, $-OCH_2$, 2H), 3.44 (m, $ArCH_2Ar$, $-CH_2$, 6H), 1.98 (m, $-CH_2$, 2H), 1.84 (s, $-CH_2$, 2H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR: δ 157.6 (C–OH), 146.8, 144.3, 129.3, 127.9, 127.7, 127.2, 126.0, 125.8, 125.6, 114.5 (Ar-C), 66.8 ($-OCH_2$), 52.4 ($-CH_2Br$), 34.0, 33.2, 32.5, 31.5, 31.4, 29.4, 27.9 ($ArCH_2Ar$, $-CH_2$, *t*-Bu). MS (FAB): calcd for $C_{44}H_{55}BrO_5$, $[M+1]^+$: 743.81; found: 743.95, 744.84. Elemental analysis calculated for $C_{44}H_{55}BrO_5$: C, 71.05; H, 7.45. Found: C, 71.08; H, 7.48.

*5-(7-Bromohept-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (**4c**)*

Yield: 28% as a white pasty mass. R_f: 0.82 (90:10 hexane–ethyl acetate). IR (KBr) ν_{max}: 3171, 2957, 2860, 1810, 1258, 1050 cm^{-1}. ^1H NMR: δ 10.20 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.54 (s, ArH, 2H), 4.22 (broad s, $ArCH_2Ar$, 4H), 3.77 (t, $J = 6.5$ Hz, $-OCH_2$, 2H), 3.38 (m, $ArCH_2Ar$, $-CH_2$, 6H), 1.85 (m, $-CH_2$, 2H), 1.22 (m, *t*-Bu, $-CH_2$, 33H), 0.88 (m, $-CH_2$, 2H). ^{13}C NMR: δ 157.9 (C–OH), 146.2, 144.2, 129.2, 125.9, 125.8, 125.6, 114.4 (Ar-C), 60.8 ($-OCH_2$), 44.3 ($-CH_2Br$), 34.0, 33.6, 32.7, 31.5, 29.7, 29.2, 28.6, 28.1 ($ArCH_2Ar$, $-CH_2$, *t*-Bu). MS (MALDI-TOF): calcd for $C_{47}H_{61}BrO_5$, $[M+Na]^+$: 807.37; found: 807.45.

General procedure for the reaction of calix[4]bis(spirodienone) with propargyl alcohol

A mixture of bis(spirodienone) **1a** (50 mg, 0.08 mmol), alcohol (4.0 equiv.) and *p*-TSA (5.0 equiv.) in toluene was taken in a 50 ml R.B flask and was stirred under reflux temperature (110°C). The refluxing was continued till the reaction was complete as shown by TLC (~10 min). The solvent was removed under reduced pressure. The reaction mixture was worked up using dichloromethane–water mixture and the solid mass obtained was purified by column chromatography.

*5-(Prop-3-yn-1-oxy)-11,17,23-tris(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (**4e**)*

Yield: 33% as a white powder. R_f: 0.88 (90:10 hexane–ethyl acetate). Mp: Decomposed >240°C. IR (KBr) ν_{max}: 3175, 2960, 2858, 2135, 1259, 1053 cm^{-1}. ^1H NMR: δ 10.23 (s, OH, 4H), 7.03 (m, ArH, 6H), 6.65 (s, ArH, 2H), 4.51 (s, $-OCH_2$, 2H), 4.23 (d, $J = 14.3$ Hz, $ArCH_2Ar$, 4H), 3.46 (broad s, $ArCH_2Ar$, 4H), 2.42 (s, acetylenic H, 1H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR: δ 152.0 (C–OH), 146.9, 146.3, 144.5, 144.4, 143.4, 130.9, 129.4, 128.9, 128.4, 127.9, 127.6, 127.1, 125.9, 125.7, 115.1 (Ar-C), 78.9, 75.4 (acetylenic carbons), 56.1 ($-OCH_2$), 34.1, 34.0, 32.6, 31.6, 29.8, 14.2 ($ArCH_2Ar$, *t*-Bu). MS (FAB): calcd for $C_{43}H_{50}O_5$, $[M+1]^+$: 647.36; found: 647.37. Elemental analysis calculated for $C_{43}H_{50}O_5$: C, 79.84; H, 7.79. Found: C, 79.80; H, 7.76.

*Procedure for the synthesis of azidocalixarene (**4a′**)*

To a solution of **4a** (50 mg, 0.07 mmol) in 2 ml dichloromethane, a 0.5 M solution of NaN_3 in DMSO (20 ml) was added and stirred at 25°C for 2 days. The reaction was quenched with water (10 ml) and stirred until it cooled to room temperature. The reaction mixture was washed with water (2 × 20 ml) and once with brine (10 ml). The organic layer was dried (anhydrous Na_2SO_4), filtered and the solvent removed under vacuum to alkyl azide **4a′** in almost quantitative yield (93 mg, 99%). R_f: 0.86 (80:20 hexane–ethyl acetate). Mp: Decomposed >230°C. IR (KBr) ν_{max}: 2960, 2102, 1814, 1358, 1060 cm^{-1}. ^1H NMR: δ 10.22 (s, OH, 4H), 7.06 (m, ArH, 6H), 6.43 (s, ArH, 2H), 4.23 (broad s, $ArCH_2Ar$, 4H), 3.86 (uneven t, $-OCH_2$, 2H), 3.50 (m, $ArCH_2Ar$, CH_2, 6H), 2.13 (m, $-CH_2$, 2H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR: δ 156.2 (C–OH), 149.8, 149.1, 146.2, 144.3, 131.1, 129.7, 129.5, 129.1, 128.8, 127.7, 127.4, 116.3 (Ar-C), 63.4, 56.9, 34.1, 32.6, 31.6, 31.5, 15.1 ($ArCH_2Ar$, $-CH_2$s, t-Bu). MS (FAB): calcd for

$C_{43}H_{53}N_3O_5$, $[M + 1]^+$: 692.89; found: 692.96. Elemental analysis calculated for $C_{43}H_{53}N_3O_5$: C, 74.64; H, 7.72; N, 6.07. Found: C, 74.83; H, 7.35; N, 5.98.

Typical procedure for the preparation of phenylacetylenes

To a mixture of bromobenzene, $PdCl_2(PPh_3)_2$ (10 mol %), CuI (20 mol %) and PPh_3 (20 mol %) under an argon atmosphere were added Et_3N (30 ml) and then a solution of TMS acetylene in Et_3N (10 ml). The resulting mixture was stirred at refluxing temperature for 24 h. After evaporation of Et_3N, the residue was triturated with $CHCl_3$ and filtered. The filtrate was partitioned between $CHCl_3$ and H_2O, where the aqueous layer was neutralised with diluted HCl. The organic layer was washed with H_2O and brine and dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was subjected to column chromatography on silica gel eluted with hexane–$CHCl_3$ (1.7:1) to give slightly crude phenylacetylenes substituted by TMS. The TMS group was deprotected using tetrabutylammonium fluoride to afford phenylacetylenes in excellent yield.

Procedure for the synthesis of triazole-functionalised biscalixarene 6

A mixture of calix[4]arene azide **4a′** (76 mg, 0.10 mmol), alkynyl calixarene **4e** (110 mg, 0.20 mmol), freshly distilled *N,N*-diisopropylethylamine (175 μl, 1.00 mmol), $CuSO_4$ (8.0 mg, 0.05 mmol), sodium ascorbate (99 mg, 0.5 mmol) and EtOH/H_2O (20 ml, 1:2) was magnetically stirred at 60°C for 2 h, diluted with AcOEt, washed with water, dried (Na_2SO_4) and concentrated. The solid mass obtained was purified by column chromatography.

Compound ***6***

R_f: 0.54 (70:30 hexane–ethyl acetate). Mp: Decomposed >230°C. IR (KBr) ν_{max}: 3467, 1640, 1484, 1296, 1203, 1123, 1064 cm^{-1}. ^1H NMR: δ 10.23 (s, OH, 4H), 10.21 (s, OH, 4H), 7.51 (s, triazole CH, 1H), 7.03 (m, ArH, 12H), 6.68 (s, ArH, 2H), 6.55 (s, ArH, 2H), 5.03 (s, —OCH_2, 2H), 4.45 (t, $J = 7.5$ Hz, —OCH_2, 2H), 4.24 (d, $J = 13.5$ Hz, $ArCH_2Ar$, 8H), 3.81 (t, $J = 5.0$ Hz, —NCH_2, 2H), 3.47 (m, $ArCH_2Ar$, 8H), 2.29 (m, —CH_2, 2H), 1.22 and 1.19 (s, t-Bu, 54 H). ^{13}C NMR: δ 152.7 (C–OH), 146.8, 146.3, 144.5, 143.2, 143.0, 129.4, 127.9, 127.7, 127.1, 126.1, 125.9, 125.8, 114.9, 114.6 (Ar-C), 64.3, 62.1, 49.9 (—CH_2), 34.1, 34.0, 32.5, 31.5, 31.4, 29.7, 22.7 ($ArCH_2Ar$, —CH_2, t-Bu). MS (MALDI-TOF): calcd for $C_{86}H_{103}N_3O_{10}$, $[M]^+$: 1337.76; found: 1337.26.

General procedure for the click reaction between azidocalixarene and phenylacetylenes

Phenylacetylene, $CuSO_4{\cdot}5H_2O$, sodium ascorbate and DIPEA were added to a solution of azidocalixarene **4a′** in 2:1 EtOH/H_2O (20 ml) mixtures. The mixture was stirred at ambient temperature for 2 h, when the TLC indicated the absence of azidocalixarene. Evaporation of solvent followed by work up using $CHCl_3$/H_2O yielded a crude mixture. The solid mass obtained was purified by column chromatography in hexane–ethyl acetate solvent system.

Compound ***8***

R_f: 0.64 (70:30 hexane–ethyl acetate). Mp: >250°C. IR (KBr) ν_{max}: 3428, 3255, 1635, 1392, 1284, 1144, 984 cm^{-1}. ^1H NMR: δ 10.21 (s, OH, 4H), 7.41 (s, triazole CH, 1H), 7.04 (m, ArH, 11H), 6.54 (s, ArH, 2H), 4.25 (d, $J = 13.5$ Hz, $ArCH_2Ar$, 4H), 3.90 (t, $J = 6.0$ Hz, —OCH_2, 2H), 3.49 (m, $ArCH_2Ar$, —CH_2, 6H), 2.39 (m, —CH_2, 2H), 1.22 (s, *t*-Bu, 18 H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR: δ 152.9 (C–OH), 146.8, 146.7, 146.3, 144.4, 144.2, 129.4, 127.9, 127.7, 126.0, 125.8, 125.6, 114.6 (Ar-C), 65.5, 46.7, 34.1, 34.0, 32.8, 32.7, 32.5, 31.9, 31.5, 30.8, 29.8, 29.7, 29.4, 22.7, 14.2 ($ArCH_2Ar$, —CH_2s, t-Bu). MS (MALDI-TOF): calcd for $C_{51}H_{59}N_3O_5$, $[M + 23]^+$: 817.03; found: 817.27.

Compound ***10***

R_f: 0.57 (70:30 hexane–ethyl acetate). Mp: Decomposed >230°C. IR (KBr) ν_{max}: 3456, 2954, 1640, 1484, 1210, 1123, 909 cm^{-1}. ^1H NMR: δ 10.21 (s, OH, 8H), 7.85 (s, ArH, 4H), 7.76 (s, triazole CH, 2H), 7.03 (m, ArH, 12H), 6.58 (s, ArH, 4H), 4.56 (t, $J = 7.0$ Hz, —OCH_2, 4H), 4.25 (broad s, $ArCH_2Ar$, 8H), 3.86 (t, $J = 6.0$ Hz, —NCH_2, 4H), 3.46 (m, $ArCH_2Ar$, 8H), 2.29 (m, —CH_2, 4H), 1.23 (s, *t*-Bu, 36H), 1.19 (s, *t*-Bu, 18H). ^{13}C NMR: δ 152.8 (C–OH), 146.8, 146.2, 144.5, 129.5, 127.9, 127.7, 126.1, 125.9, 125.6, 120.2, 114.6 (Ar-C), 64.5, 62.1, 34.1, 32.5, 31.5, 31.4, 29.7, 23.7, 15.1 ($ArCH_2Ar$, —CH_2s, *t*-Bu). MS (MALDI-TOF): calcd for $C_{96}H_{112}N_6O_{10}$, $[M]^+$: 1531.84; found: 1532.29.

Compound ***12***

R_f: 0.48 (70:30 hexane–ethyl acetate). Mp: Decomposed >230°C. IR (KBr) ν_{max}: 3354, 1667, 1440, 1225, 1113, 1038, 788 cm^{-1}. ^1H NMR: δ 10.22 (s, OH, 12H), 7.91 (s, ArH, 3H), 7.79 (s, triazole CH, 3H), 7.14 (m, ArH, 18H), 6.62 (s, ArH, 6H), 4.58 (t, $J = 7.2$ Hz, —OCH_2, 6H), 4.26 (broad s, $ArCH_2Ar$, 12H), 3.92 (t, $J = 6.1$ Hz, —NCH_2, 2H), 3.50 (m, $ArCH_2Ar$, 12H), 2.35 (m, —CH_2, 6H), 1.25 (s, *t*-Bu, 54 H), 1.19 (s, *t*-Bu, 27H). ^{13}C NMR: δ 153.2 (C–OH), 147.3, 146.8, 145.3, 129.6, 128.1, 127.5, 126.5, 126.1, 125.1, 122.4, 116.3 (Ar-C), 65.3, 62.4, 34.0, 32.1, 31.2, 29.5, 22.1, 15.3 ($ArCH_2Ar$, —CH_2s, *t*-Bu). MS

(MALDI-TOF): calcd for $C_{141}H_{165}N_9O_{15}$, $[M + 1]^+$: 2225.26; found: 2225.54.

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