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Synthesis and characterisation of 5,11,17,23,29-penta(*tert*-butyl)-32,33,35-tri[((1*S*)-camphor-10-sulfonyl)-oxy]-34,36-dihydroxy-calix[5]arene

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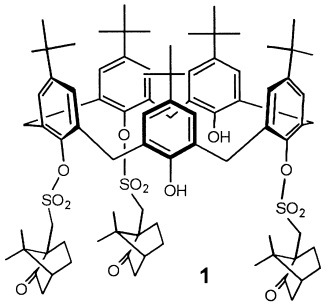
Abstract

The reaction of (1*S*)-camphor-10-sulfonyl chloride with the *p*-*tert*-butylcalix[5]arene afforded the corresponding 1,3,4-triester, which was fully characterised by high-resolution NMR techniques. © 2000 Published by Elsevier Science Ltd.

Keywords: calix[5]arene; camphorsulfonate; podand.

The introduction of the chiral camphor-10-sulfonyl group at the lower rim of calixarenes has been poorly studied since the synthesis of camphorsulfonylcalix[8]arenes described by Gutsche.[1] More recently, we have reported the synthesis of the 1,3-bis-((1*S*)-camphor-10-sulfonyl)-*p*-*tert*-butylcalix[4]arene and the crystal structure of its 1:2 complex with toluene.[2] The original synthetic approaches used pyridine as solvent and base; we preferred to employ a safer and cheaper medium. Toluene as solvent and triethylamine as base gave good results, with a simpler workup and a slightly increased yield (40% vs 30%).



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In order to obtain a larger chiral cavity, we adapted this procedure to the *p-tert*-butylcalix[5]arene. Thus, reacting in these conditions, the penta-phenolic macrocycle with an excess of (1*S*)-camphor-10-sulfonyl chloride afforded the triester **1** in 49% yield. This stoichiometry was confirmed by electrospray mass spectrometry, elemental analysis and ^{1}H NMR spectroscopy.[3] The latter showed, in the middle-field region, the expected resonance signals of the bridging and the anchoring methylene groups; two singlets at 5.734 and 6.166 ppm were assigned to the two residual hydroxyl groups, HO^1 and HO^2, respectively. Ten well-separated singlets found in the aromatic region and integrating for 1H each indicated that the molecule should be distorted. As no crystals suitable for an X-ray diffraction analysis were obtained, we attempted to determine the structure of **1** by high-resolution NMR techniques at 500 MHz.

TOCSY experiment allowed us to build back the low- and middle-field regions. The spin systems were labeled from high to low field. In the middle-field region, eight AB systems integrating for 2H each were found at 3.43, 3.94 ([AB]^1), 3.43, 3.87 ([AB]^2), 3.50, 4.60 ([AB]^3), 3.53, 4.41 ([AB]^4), 3.53, 4.50 ([AB]^5), 3.59, 4.64 ([AB]^6), 3.78, 4.61 ([AB]^7) and 3.81, 4.28 ppm ([AB]^8). We considered that, as for calix[4]arenes, the upfield and downfield parts of the bridging methylene AB resonance signals correspond to the equatorial and axial protons, respectively.

In the aromatic part, five couples of singlets assigned to the phenolic units were found at 6.36, 6.61 (Ha′ and Ha″, cycle **a**), 6.85, 7.05 (Hb′ and Hb″, cycle **b**), 7.06, 7.29 (Hc′ and Hc″, cycle **c**), 7.11, 7.34 (Hd′ and Hd″, cycle **d**) and 7.15, 7.19 ppm (He′ and He″, cycle **e**).

At a lower level of the TOCSY spectrum (Fig. 1), the long range couplings allowed us to chain the building blocks in the macrocyclic structure. It appears that cycle **a** is bound to the bridging methylene groups 4 and 7, cycle **b** to 7 and 5, and cycle **e** to 3 and 6. Weaker correlations were found between **c** and 5, and between **d** and 4. In addition, through the strong correlations observed between the resonance signals of cycle **d** and HO^1, then **c** and HO^2, **c** and **d** were labelled

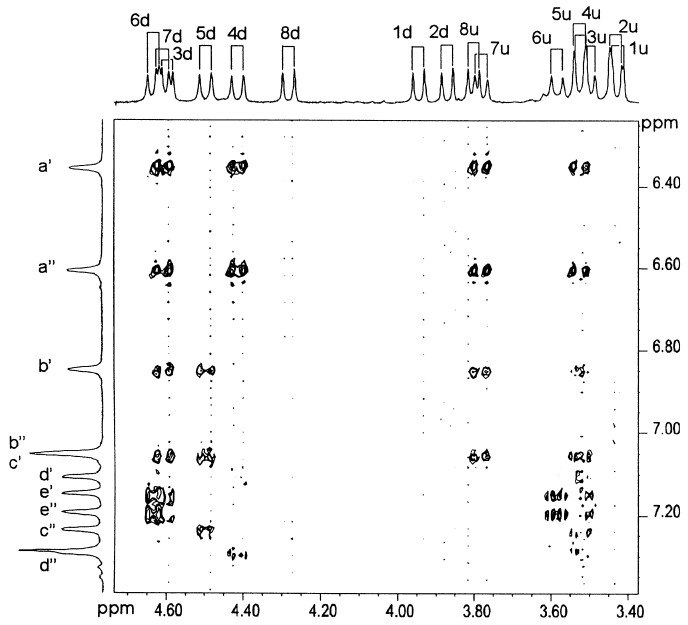


Figure 1. Low-level TOCSY correlations between aromatic and methylene protons in **1**: d, downfield; u, upfield

as the unsubstituted phenol units. By deduction, the three residual AB systems 1, 2 and 8 were assigned to the sulfo-methylene groups attached to cycles **a**, **b** and **e**.

The NOESY correlations observed between *tert*-butyl and aromatic resonance signals allowed us to precisely attribute the former. As shown in Fig. 2, HO^1 is strongly correlated to the downfield parts of $[AB]^6$ and $[AB]^4$, and, at a lower level, to the upfield parts of $[AB]^6$ and the downfield part of $[AB]^1$. Similarly, HO^2 is strongly correlated to the downfield parts of $[AB]^5$ and $[AB]^3$, and, at a lower level, to the upfield parts of $[AB]^8$ and $[AB]^5$. Cycles **c** and **d** where thus definetely positioned between **b** and **e** then **a** and **e**, respectively. This was confirmed by the NOESY correlations observed in the aromatic part of the spectrum, between Ha′ and Hb′, Ha″ and Hd′, then He′ and Hd″. No correlations were observed between the resonance signals of Hb″ and Hc′, then Hc″ and He″.

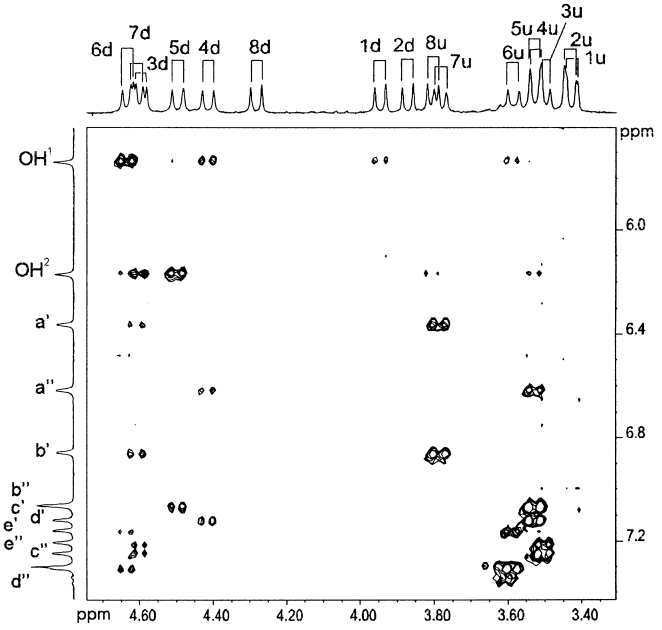


Figure 2. NOESY correlations between aromatic and methylene protons in **1**: d, downfield; u, upfield

In the middle- to low-field cross-region (Fig. 2), strong NOESY correlations were found between Ha′, Hb′ and the upfield parts of $[AB]^7$, Ha″, Hd′ and $[AB]^4$, Hb″, Hc′ and $[AB]^5$, Hd″, He′ and $[AB]^6$, then Hc″, He″ and $[AB]^3$. At a much lower level, each aromatic proton is correlated to the downfield part of the adjacent methylene AB resonance signals. Among them, Hc′ and Hd′ are strongly correlated with the downfield parts of $[AB]^5$ and $[AB]^4$, respectively, suggesting that the corresponding phenol rings are strongly inclined.

Attempts to localise unambiguously the camphorsulfonyl groups with NOESY failed; the interaction observed between HO^1 and the downfield part of $[AB]^1$ suggests that the corresponding camphorsulfonyl group is brought by the cycles **a** or **e**.

A ROESY experiment showed that HO^1 correlates with $[AB]^1$ and very slightly with $[AB]^8$. On the other hand, HO^2 correlates with $[AB]^8$ and the downfield part of $[AB]^2$. In the middle- to high-field cross-region (Fig. 3), the most intense correlations allowed us to assign more precisely the methyl resonance signals of the camphor subunits CS1, CS2 and CS8, attached to $[AB]^1$,

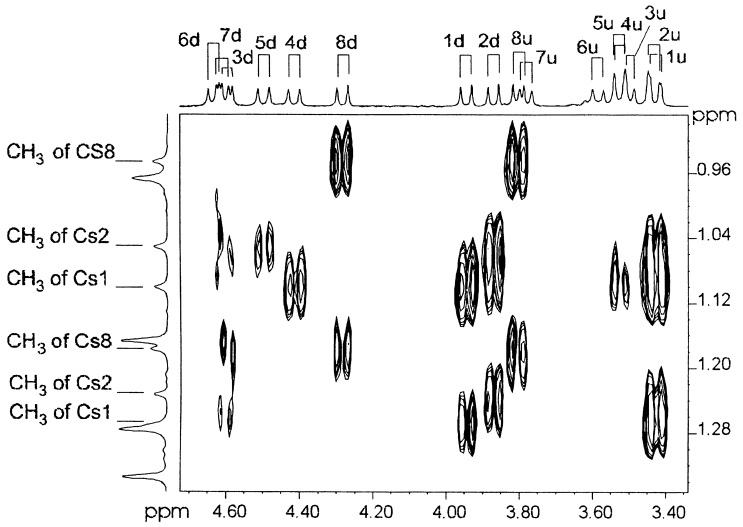
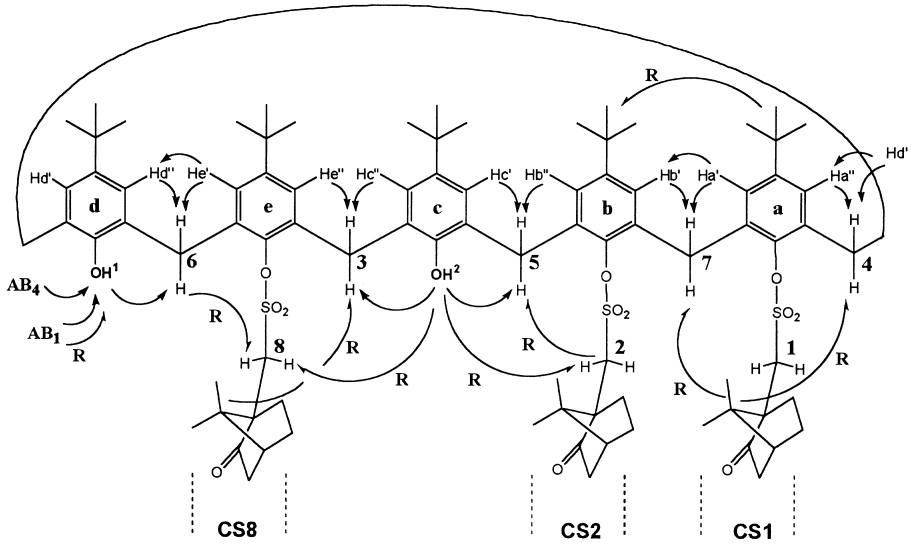


Figure 3. ROESY experiment in the middle field–high field cross-region: d, downfield; u, upfield

$[AB]^2$ and $[AB]^8$, respectively. At slightly lower levels, we found that the methyl group of CS1 correlates with $[AB]^4$ and the downfield part of $[AB]^7$, that one of the methyl groups of CS2 correlates with $[AB]^5$ and that one of those of CS8 correlates with $[AB]^3$. These through-space interactions allow us to assign $[AB]^1$ to the camphorsulfonyl group brought by **a**, $[AB]^2$ by **b** and $[AB]^8$ by **e** (Scheme 1).



Scheme 1. Molecular structure of **1** and main NOESY and ROESY (R) correlations

The above-mentioned through-space correlations shown in Scheme 1 suggest that **1** exists in a distorded cone conformation, illustrated by ^{13}C NMR. HSQC showed that the Ar–CH_2–Ar resonance signals appear as five singlets located at 30.91, 31.35, 31.63, 32.09 and 33.69 ppm, for

the systems 6, 3, 5, 4 and 7, respectively. These values are in the range 30–33 ppm, which corresponds, in accordance with de Mendoza,[4] Gutsche[5] and Pappalardo,[6] to a cone conformation.

A short and simple process allowed us to prepare a new calix[5]arene displaying three bulky and lipophilic chiral substituents at the lower rim. The complexation properties of this podand towards chiral substances such as amino acids are under current investigation.

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3. *General aspects*. All commercially available products were used without further purification unless specified otherwise. ^{1}H, ^{13}C, HSQC, TOCSY, NOESY and ROESY spectra were recorded on a Bruker DRX 500 (TMS as internal standard, chemical shifts in ppm, *J* in hertz). IR (ν in cm^{-1}). UV: λ_{max} in nm, ε in dm^3 mol^{-1} cm^{-1}. **5,11,17,23,29-Penta(*tert*-butyl)-32,33,35-tris-[((1*S*)-camphor-10-sulfonyl)-oxy]-34,36-dihydroxy-calix[5]arene (1).** A solution of *p-tert*-butylcalix[5]arene (0.33 g, 0.40 mmol) in toluene (20 ml) was heated at 90°C. (1*S*)-Camphor-10-sulfonyl chloride (0.82 g, 3.27 mmol) was added, followed by NEt_3 (4 ml, 28.5 mmol). The mixture was heated at 90°C during 2 h and solvents were evaporated. The product was dissolved in CH_2Cl_2 and washed with 1 M HCl (20 ml), saturated aqueous $NaHCO_3$ (30 ml) and brine (30 ml). The organic phase was chromatographed (SiO_2, CH_2Cl_2:hexane 4:1) to give **1**. White powder (0.29 g, 49%). M.p.: 280°C. UV (CH_2Cl_2): 276 (8193). IR (KBr): 3515 (OH), 1740 (C=O); ^{1}H NMR: δ 0.524 (s, 9H, C(CH_3)$_3$ of **a**), 0.947 (s, 3H, CH_3 camph. 8), 0.968 (s, 9H, C(CH_3)$_3$ of **b**), 1.053 (s, 3H, CH_3 camph. 2), 1.100 (s, 3H, CH_3 camph. 1), 1.168 (s, 9H, C(CH_3)$_3$ of **e**), 1.178 (s, 3H, CH_3 camph. 8), 1.234 (s, 3H, CH_3 camph. 2), 1.277 (s, 12H, CH_3 camph. 1 and C(CH_3)$_3$ of **c**), 1.335 (s, 9H, C(CH_3)$_3$ of **d**), 1.56–2.60 (m, 21H, C*H* and CH_2 camph.), 3.425, 3.943 ([AB]^1, J_{AB} = 15.6, SO_2–CH_2), 3.432, 3.870 ([AB]^2, J_{AB} = 14.4, SO_2–CH_2), 3.500, 4.597 ([AB]^3, J_{AB} = 14.6, Ar **c**–CH_2–Ar **e**), 3.525, 4.414 ([AB]^4, J_{AB} = 15.7, Ar **b**–CH_2–Ar **c**), 3.527, 4.498 ([AB]^5, J_{AB} = 15.5, Ar **a**–CH_2–Ar **d**), 3.587, 4.636 ([AB]^6, J_{AB} = 15.0, Ar **d**–CH_2–Ar **e**), 3.783, 4.605 ([AB]^7, J_{AB} = 17.0, Ar **a**–CH_2–Ar **b**), 3.808, 4.284 ([AB]^8, J_{AB} = 15.3, SO_2–CH_2), 5.734 (s, 1H, *H*O^1), 6.166 (s, 1H, *H*O^2), 6.356 (s, 1H, Ha′), 6.607 (s, 1H, Ha″), 6.847 (s, 1H, Hb′), 7.050 (s, 1H, Hb″), 7.055 (s, 1H, Hc′), 7.109 (s, 1H, Hd′), 7.149 (s, 1H, He′), 7.193 (s, 1H, He″), 7.289 (s, 1H, Hc″), 7.340 (s, 1H, Hd″). ^{13}C NMR: δ 19.70 (*C*H$_3$ camph. 8, 2 and 1), 19.89 (*C*H$_3$ camph. 1), 19.92 (*C*H$_3$ camph. 2), 19.98 (*C*H$_3$ camph. 8), 25.17, 25.65, 26.77, 26.89, 27.00 (*C*H$_2$–*C*H$_2$ camph.), 30.73, 31.03, 31.13, 31.51, 31.60 (C(*C*H$_3$)$_3$), 30.92 (Ar–*C*H$_2$–Ar 6), 31.35 (Ar–*C*H$_2$–Ar 3), 31.63 (Ar–*C*H$_2$–Ar 5), 32.09 (Ar–*C*H$_2$–Ar 4), 33.69 (Ar–*C*H$_2$–Ar 7), 33.68, 33.89, 33.91, 34.16, 34.28 (*C*(CH$_3$)$_3$), 42.49, 42.53, 42.55 (*C*H$_2$–CO camph.), 42.77, 42.97, 43.33 (*C*H camph.), 47.87, 48.03, 48.26 (*C*(CH$_3$)$_2$ camph.), 48.03, 48.46, 48.87 (*C*H$_2$–SO$_2$), 58.20, 58.27, 58.4739 (*C*–CH$_2$–SO$_2$), 125.27, 125.58, 125.68, 125.95, 126.18, 126.31, 126.70, 126.77 (*C*ar–H), 125.46, 125.87, 127.17, 127.93, 133.50, 134.10, 134.18, 134.80, 135.30, 141.26, 142.27, 142.40, 142.45, 142.48, 148.81, 148.95, 149.25, 149.61, 150.02 ($C_{o,p,ipso}$), 213.84, 214.65, 215.15 (*C*=O). ES-MS (pos. mode) 1476.9 [**1**+Na]$^+$, 1261.8 [**1**–CS+Na]$^+$. Anal. calc. for $C_{85}H_{112}O_{14}S_3$ (1452.0): C, 70.21; H, 7.76; S, 6.61; O, 15.40. Found: C, 69.97; H, 7.63; S, 6.73; O, 15.44.
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