Tetrahedron 64 (2008) 7567–7573

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regio- and stereoselective 1(*S*)-camphorsulfonylation of monoalkoxycalix[4]arenes

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ARTICLE INFO

Article history:
Received 5 February 2008
Received in revised form 6 May 2008
Accepted 22 May 2008
Available online 27 May 2008

Keywords:
Alkoxycalix[4]arenes
1(*S*)-Camphorsulfonylation
Heterosubstituted calixarenes
Diastereomers

ABSTRACT

The reaction of calix[4]arene monoalkyl ethers with 1(*S*)-camphor-10-sulfonyl chloride yields 1,2- or 1,3-alkoxy-1(*S*)-camphorsulfonyloxycalixarenes depending on the nature of the base used. In the presence of triethylamine only 1,3-substituted derivatives are formed. Two diastereomers of the 1,2-substituted calixarenes with clockwise and anticlockwise arrangement of alkyl and camphorsulfonyl groups at the narrow rim are formed in the presence of sodium hydride or potassium carbonate. Due to chiral induction of the camphorsulfonyl group the 1,2-substitution is diastereoselective. The ratio of diastereomers formed is dependent on the alkyl groups at the calixarene narrow rim.

1. Introduction

The design of highly selective artificial receptors based on calixarenes is an intensively developed area of supramolecular chemistry.[1,2] Calix[4]arenes due to their unique cap-shaped architecture and their ability to be functionalized in various ways have been used as building blocks for the construction of a large variety of host molecules with different supramolecular functions. Utilization of calixarenes as chemical sensors, extractants for nuclear waste treatment, materials for non-linear optics and bio-active compounds has been reported.[1,3,4] Functionalization of phenolic hydroxy groups at the narrow (lower) rim of calix[4]arenes is a relevant stage in the design of such materials.

In spite of numerous efficient methods for chemical modification of calixarenes, the regio- and stereoselective introduction of functional groups, however, continues to be a challenge to the synthetic chemist. The regioselective substitution of calix[4]arenes at the narrow rim is mainly due to the different acidities of the phenolic OH groups, which can be selectively ionized by using an appropriate base.[5] While distal 1,3-di(hetero)functionalization may be considered as one of the standard reactions in calix[4]arene chemistry,[6–9] only a few examples of proximal 1,2-di(hetero)-functionalization are known. All these compounds were obtained by multistep synthesis involving a protection–deprotection sequence[6,10,11] or rearrangements.[12–15] The methods for synthesis of 1,2-heterofunctionalized calix[4]arenes attract considerable interest as the shortest way to inherently chiral calixarenes of the ABHH type, the chirality of which originates from the asymmetric array of achiral residues on the calixarene skeleton.

2. Results and discussion

In this paper, we investigate regio- and stereoselective reactions of monoalkoxycalixarenes with 1(*S*)-(+)-camphor-10-sulfonyl chloride. Sulfonylation of monoalkoxycalixarenes **1a–c** by 1.1 mol of 1(*S*)-camphorsulfonyl chloride with an excess of triethylamine (Scheme 1) in toluene is regioselective and gives exclusively 1,3-monoalkoxysulfonyloxycalixarenes **2a–c** in the cone conformation. The observed selectivity can be explained by the different acidities of the phenolic OH groups. The OH group in the distal position to the alkylated phenol moiety of monoalkoxycalixarenes **1** is more acidic than that in the proximal position. In the presence of a weak base (triethylamine) the reaction proceeds, seemingly, through the intermediate monoanion **A**, which is stabilized by two OH···O hydrogen bonds.[5]

The substitution pattern at the narrow rim of cone shaped calixarenes **2a–c** is proved by ^{1}H NMR spectra. All axial and equatorial protons of methylene bridges are diastereotopic. The signals of the axial protons reveal as three doublets at 4.0–4.5 ppm. The AB doublets for the equatorial protons of the methylene bridges

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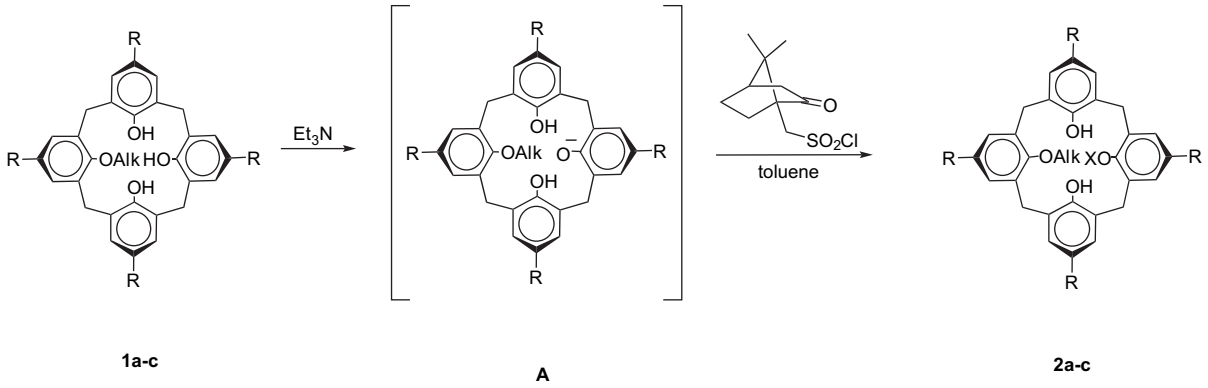
0040-4020/$ – see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tet.2008.05.106



1a R = H, Alk = i-Pr
1b R = t-Bu, Alk = Me
1c R = t-Bu, Alk = i-Pr

2a R = H, Alk = i-Pr, X = SO_2 - (1S)-Camphor
2b R = t-Bu, Alk = Me, X = SO_2 - (1S)-Camphor
2c R = t-Bu, Alk = i-Pr, X = SO_2 - (1S)-Camphor

Scheme 1.

strongly overlap to give a compact multiplets in the region 3.4–3.5 ppm. The pair of doublets for methylene protons of methylsulfonate group partially coincides with the signals of axial and equatorial protons of the methylene bridges. Methyl protons of the isopropyl group of the calixarenes **2a**,**c**, in spite of their diastereotopicity, are revealed as one doublet with coupling constant 6.2 Hz at 1.57 ppm (**2a**) and 1.53 ppm (**2c**), respectively. Single crystal X-ray difractometry for calixarenesulfoester **2b** reasonably accompanies the spectral data (Fig. 1). As may be observed from diffraction data, the compound **2b** has a cone conformation in two molecules (A and B) in the asymmetric part of the unit cell (Fig. 2). Both hydroxy groups of calixarene **2b** form intramolecular hydrogen bonds with the oxygen atoms of the methoxy group (O(1)–H(1O)···O(3)H···O 2.01 Å, O–H···O 168° in the molecule A and 1.95 Å, 179° in B; O(2)–H(2O)···O(3) H···O 1.99 Å, O–H···O 167° in molecule A 2.04 Å, 162° in molecule B). Formation of these intramolecular hydrogen bonds represents an additional factor stabilizing the cone conformation. The 1(*S*)-camphorsulfonyl substituent is oriented in such way that it locks the cavity of the calixarene on the narrow rim side. Such orientation of substituent results in the appearance of attractive intramolecular interactions between camphor fragment and methoxy/hydroxy groups. The geometric characteristics of these interactions (C(46)–H(46b)···O(1)H···O 2.59 Å, C–H···O 148° in molecule A and 2.57 Å, 146° in B; C(45)–H(45a)···O(7)H···O 2.50 Å, C–H···O 173° (molecule A), 2.58 Å, 171° (B)) allow to consider them as very weak intramolecular hydrogen bonds. One acetonitrile molecule is located inside the cavity of each calixarene, bound by C–H···π interactions with the aromatic rings: C(1SA)–H(1B)···C(22)(π)H···π 2.87 Å, C–H···π 159°, C(1SA)–H(1a)···C(11)(π)H···π 2.88 Å, C–H···π 165°, C(1SA)–H(1a)···C(12)(π)H···π 2.88 Å, C–H···π 167° in molecule A and C(1SB)–H(1b)···C(6)(π)H···π 2.88 Å, C–H···π 139°, C(1SB)–H(1a)···C(22)(π)H···π 2.87 Å, C–H···π 160° in molecule B.

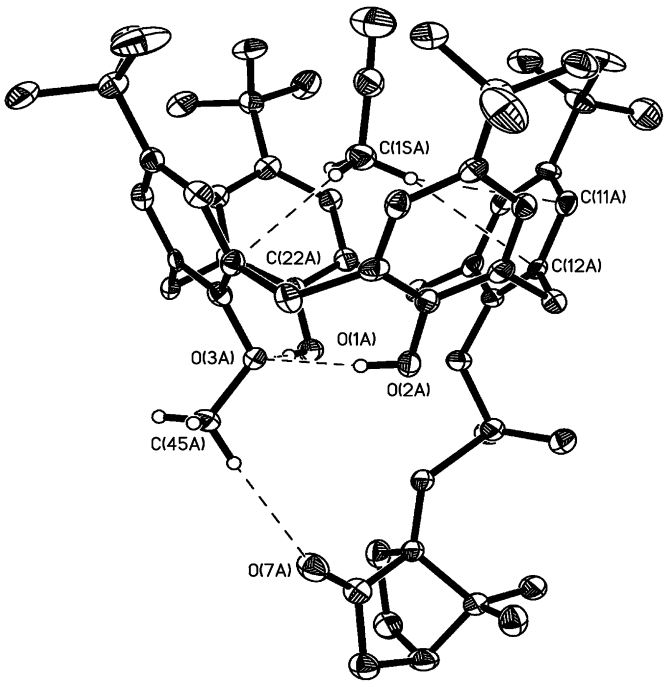


Figure 1. Molecular structure of calixarene **2b**–acetonitrile complex (grown from acetonitrile at 298 K).

In the crystal phase, molecules **2b** form a parquet-like packing motif along the (0 0 1) crystallographic direction. The camphor fragment of one molecule **2b** locks also the wide rim of the neighboring calixarene forming very weak intermolecular hydrogen bonds C(51)–H(51)···N(1S)′ (1+*x*, *y*, *z*) H···N 2.68 Å, C–H···N 136° (molecule A), C–H···N′ (*x*, *y*, *z*−1), H···N 2.69 Å, C–H···N 130° in molecule B. Besides that, the cavity from the side of the wide rim is locked also by a dimer of two additional acetonitrile molecules interacting with acetonitrile inside the cavity (weak intermolecular hydrogen bonds C(1SE)–H(1E) ···N(1S)H···N 2.56 Å, C–H···N 176° (A), (*x*, *y*, *z*−1) H···N 2.58 Å C-H···N 173° molecule B). In this dimer, acetonitrile molecules are almost parallel with each other (the N···C···N···C improper torsion angle is 16.5°) and oriented in a head-to-tail manner. The distance between the long axes of molecules is about 3.3 Å. This allows us to assume the existence of the stacking-like interaction between the π-systems of these molecules.

In contrast to triethylamine, the strong base NaH in polar solvents deprotonates the proximal OH groups of monoalkoxycalixarenes **1** forming dianionic species **B**, which have a reactive phenoxide anion in proximal positions.[5] As a result, the reaction of *iso*-propoxycalixarene **1a** with 1.08 equiv of 1(*S*)-(+)-camphor-10-sulfonyl chloride in the presence of sodium hydride in a THF–DMF (10:0.5) solution at room temperature gives proximally heterosubstituted diastereomers **3a** and **4a** with 85% total yield (Scheme 2). The diastereomers thus obtained contain the chiral camphorsulfonyl group attached to the asymmetrically substituted calixarene narrow rim. Noteworthy, due to the chiral induction of *S*-(+)-camphorsulfonyl residue, the reaction proceeds

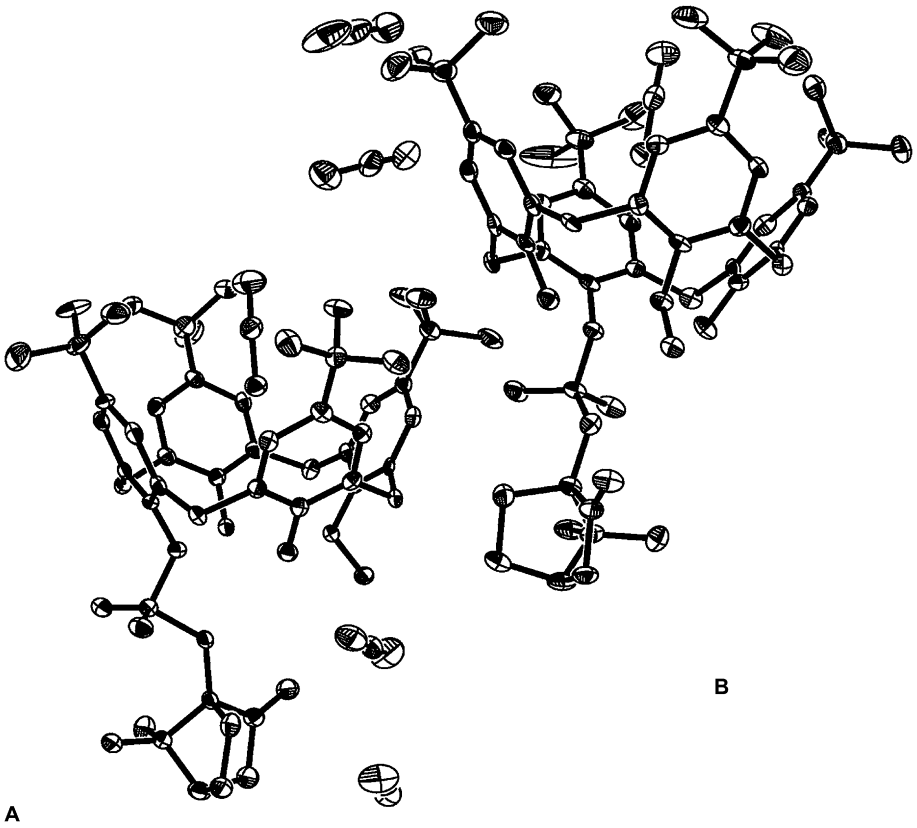


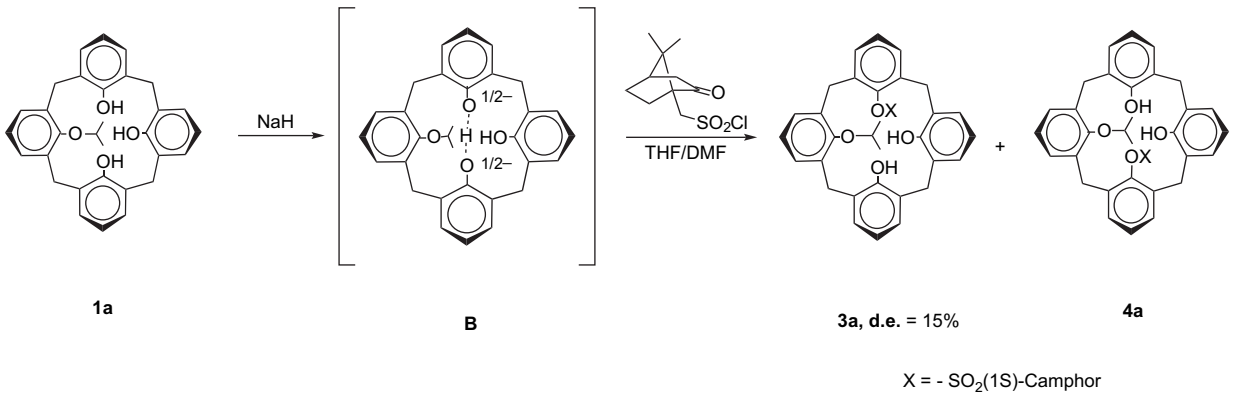
Figure 2. Two molecules (A and B) of compound **2b** observed in the asymmetric part of the unit cell.

stereoselectively with preferential formation of diastereomer **3a** (de 15%) in comparison with **4a**.

Diastereomer **3a** with 98% purity and 45% yield was obtained by simple crystallization of the diastereomeric mixture from benzene–hexane. The other diastereomer **4a** was obtained with 92% purity in 35% yield by crystallization of the residue from chloroform–hexane mixture. The ^{1}H NMR spectra of diastereomers **3a** and **4a** (Fig. 3) provide some structural evidence. For example, a set of seven doublets at 4.88, 4.53, 4.23, 4.09 ppm and 3.53, 3.43, 3.41 ppm in compound **3a** corresponds to axial and equatorial $ArCH_2Ar$ protons of the cone shaped macrocyclic skeleton. This splitting pattern suggests the 1,2-heterodisubstitution in the calix[4]arene narrow rim. Two doublets at 4.25 and 4.24 ppm correspond to the AB spin system of the methylenesulfonate group. The methyl groups of isopropyl ether residue, in contrast to 1,3-regioisomer **2a**, appear as two doublets at 1.74 and 1.60 ppm because of their diastereotopicity.

The cone conformation and the clockwise or anticlockwise orientation of the isopropyl and sulfonyl groups at the narrow rim of diastereomers **3a** and **4a** were recently proven by X-ray analysis.[16]

The reaction of monoalkoxycalixarenes **1a–c** with 1(*S*)-(+)-camphor-10-sulfonyl chloride in the presence of rather weak base K_2CO_3, which promotes only the distal substitution of monoalkoxycalixarenes,[5] unexpectedly results in proximally substituted diastereomers **3** and **4** (Scheme 3). It could be presumed, that at the first stage of this reaction the distally substituted calixarenesulfoesters **2** are formed, which in the presence of the base isomerize into proximally 1,2-disubstituted products analogously to known *O,O*-phosphorotropic,[12,13] sulfotropic[14] and acylotropic[15] rearrangements. However, our attempts to transform 1,3-disubstituted derivatives **2** into 1,2-disubstituted isomers **3** and **4** in the presence of potassium carbonate, or the stronger base sodium hydride, were unsuccessful.



Scheme 2.

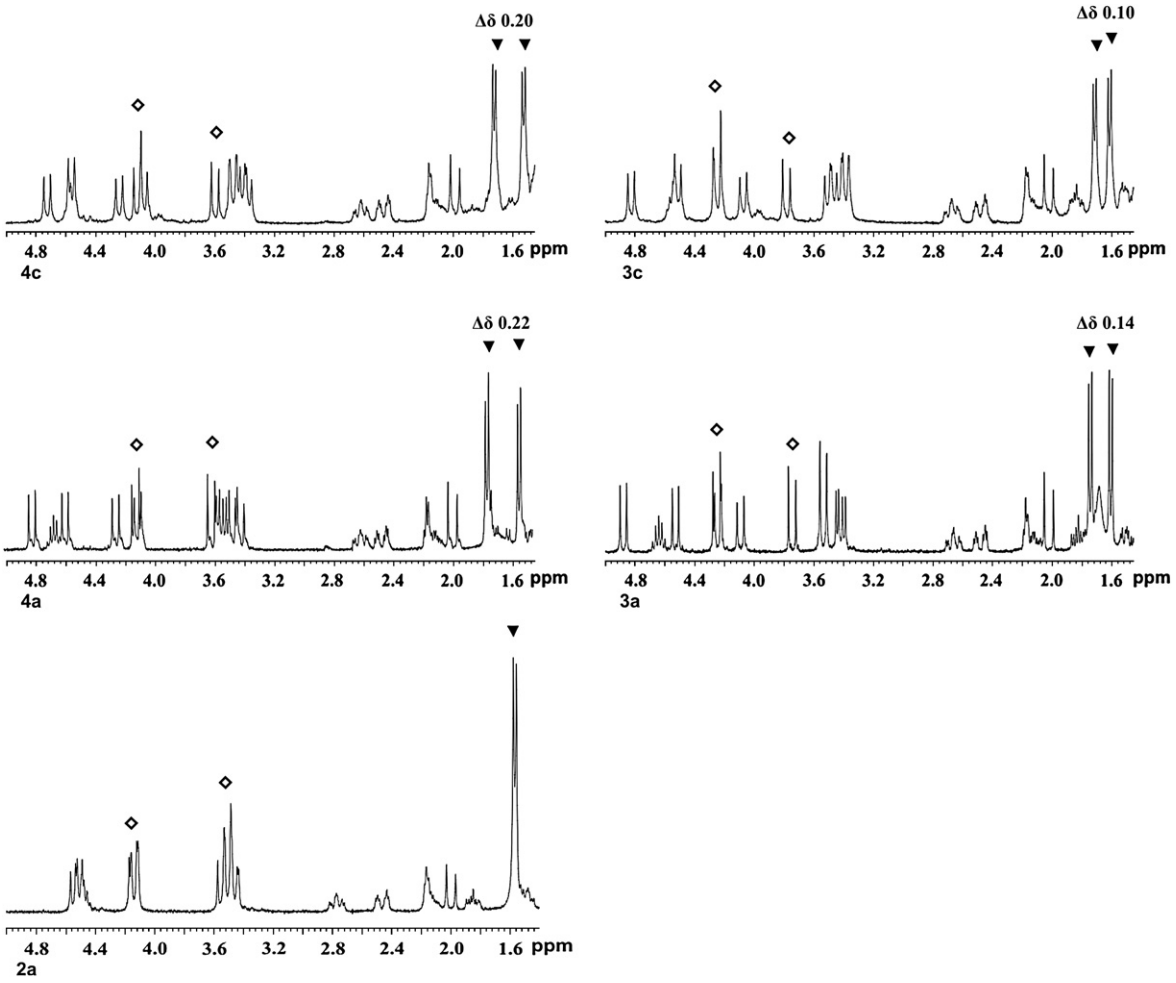
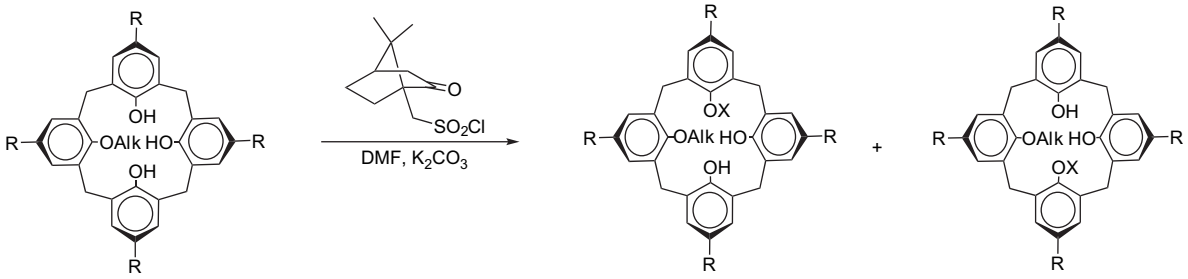


Figure 3. Representative sections of ^{1}H NMR spectra of diastereomers **3a**, **4a**, **3c**, **4c** and compound **2a**, 300 MHz, $CDCl_3$, 298 K (◇, SO_2–CH_2–camphor group; ▼, Me_2CH–O group).

The stereoselectivity of the 1,2-substitution in alkoxycalixarenes **1a–c** depends on the substituent nature as at the wide, so at the narrow rim. Integral intensity of the signals in the ^{1}H NMR spectrum of a crude mixture **3a** and **4a** indicates a 20% diastereomeric excess of **3a**. The methoxy derivatives **3b** and **4b** are formed with 17% diastereomeric excess of **3b**. Isopropoxy derivatives **3c** and **4c** are formed as an equimolar mixture. The total yield of the mixture: **3a** and **4a,** 34%; **3b** and **4b**, 67%; **3c** and **4c**, 81%.

Analytically pure diastereomers **3c** and **4c** were isolated from the mixture in semi-preparative scale with 40% and 42% yields, respectively, by HPLC, using achiral stationary phase Zorbax CN (250×4.6 mm) and hexane–THF (96:4) mixture as eluent.



1a-c **3a-c** **4a-c**

1a R = H, Alk = i-Pr
1b R = t-Bu, Alk = Me
1c R = t-Bu, Alk = i-Pr

a R = H, Alk = i-Pr, X = SO_2 - (1S)-Camphor
b R = t-Bu, Alk = Me, X = SO_2 - (1S)-Camphor
c R = t-Bu, Alk = i-Pr, X = SO_2 - (1S)-Camphor

Scheme 3.

The ^{1}H NMR spectrum of each diastereomer **3c** and **4c** (Fig. 3) contains four well-resolved doublets for the axial protons of the methylene bridges $ArCH_2Ar$ and four partially overlapped doublets for the equatorial ones and two doublets for the methylenesulfonyl group in the region 3.2–4.8 ppm. Such a splitting pattern proves the ABHH substitution type of compounds **3c** and **4c**.

An absolute configuration of diastereomers **3c** and **4c** has been established by comparison of their ^{1}H NMR spectra with the ^{1}H NMR spectra (Fig. 3) of *tert*-butyl depleted analogues **3a** and **4a**, examined by X-ray analysis.[16] As is evident from Figure 3, the signals of diastereotopic protons of SO_2–CH_2–camphor group (marked by diamonds) of **3c** at 3.78 and 4.24 ppm and diastereotopic CH_3 groups (marked by triangles) of the isopropyl moiety at 1.61 and 1.71 ppm with $\Delta\delta$ 0.1 ppm are very similar to that of calixarene **3a** with clockwise orientation of sulfonyl group relative to the isopropyl residue. The ^{1}H NMR spectrum of the diastereomer **4c** also conforms well to the spectrum of compound **4a** with anticlockwise orientation of sulfonyl group.

3. Conclusion

The regioselectivity of the reaction of monoalkoxycalix[4]arenes with 1(*S*)-camphor-10-sulfonyl chloride depends on the nature of the base used, and leads to 1,3-alkoxy-1(*S*)-camphorsulfonyloxycalixarenes or diastereomeric mixture of their 1,2-regioisomers. The ratio of diastereomers formed depends on the nature of the alkyl groups of the alkoxycalixarenes.

4. Experimental

4.1. General

Melting points were determined on a Boëtius apparatus and are uncorrected. All the reactions were carried out in anhydrous solvents, which were freshly distilled prior to use. ^{1}H NMR spectra were recorded on Varian VXR-300 spectrometer with frequency 300 MHz (TMS as internal standard). ^{13}C NMR spectra were recorded on Varian GEMINI 2000 spectrometer with frequency 100 MHz (TMS as internal standard). Monoalkoxycalixarenes **1a–c** were obtained according to the literature.[17]

4.2. General method for synthesis of distally substituted calixarenesulfoesters 2a–c

To the solution of monoalkoxycalixarene **1a**,**b** (1 mmol) and camphorsulfonyl chloride (1.5 mmol) in toluene (20 ml), triethylamine (0.4 ml, 2.8 mmol) was added. The reaction mixture was stirred at ambient temperature for 40 min, then refluxed for 10–15 min. After cooling to room temperature, the solvent was evaporated under reduced pressure. To the residue, chloroform (10 ml) and 10% HCl (10 ml) were added. The organic layer was separated, washed with a saturated solution of sodium bicarbonate (20 ml), then with water (2×20 ml) and dried over Na_2SO_4. Chloroform was removed under reduced pressure, the residue washed with warm methanol (20 ml) and dried under reduced pressure. Sulfoesters **2a–c** are colourless solids.

*4.2.1. 25-((1S)-10-Camphorsulfonyloxy)-27-iso-propoxy-26,28-dihydroxycalix[4]arene **2a***

Yield 85%. Mp>250 °C (decomp.). ^{1}H NMR ($CDCl_3$) δ: 0.99 and 1.26 (2s, 3H each, camphor Me), 1.47 (m, 1H, camphor CH), 1.57 (d, J=6.2 Hz, 6H, Me), 1.84 (m, 1H, camphor CH), 1.96–2.15 (m, 3H, camphor CH), 2.42 and 2.76 (2 m, 1H each, camphor CH), 3.50 (m, 5H, *e*-$ArCH_2Ar$+camphor CH_2), 4.13 (2d, J=13.5, 15.1 Hz, 3H, *a*-$ArCH_2Ar$+camphor CH_2), 4.51 (2d+m, 3H, *a*-$ArCH_2Ar$+CH), 6.74 (m, 8H, ArH+OH), 6.95, 7.07, 7.14 (3d, 2H each, ArH). Calcd, %: C, 72.33; H, 6.51; S, 4.71. $C_{41}H_{44}O_7S$ found, %: C 71.83, H 6.37, S 4.71.

*4.2.2. 5,11,17,23-Tetra-tert-butyl-25-((1S)-10-camphorsulfonyloxy)-27-methoxy-26,28-dihydroxycalix[4]arene **2b***

Yield 78%. Mp 165–166 °C (from acetonitrile). ^{1}H NMR ($CDCl_3$) δ: 0.73 (s, 9H, *t*-Bu), 0.97 and 1.27 (2s, 3H each, camphor Me), 1.01 (s, 9H, *t*-Bu), 1.31 (s, 18H, *t*-Bu), 1.43–1.50 (m, 1H, camphor CH), 1.73–1.82 (m, 1H, camphor CH), 1.99–2.16 (m, 3H, camphor CH), 2.38–2.47 (m, 1H, camphor CH), 2.73–2.84 (m, 1H, camphor CH), 3.33–3.45 (3d, 4H, *e*-$ArCH_2Ar$), 3.48 (d, J=14.9 Hz, 1H, camphor CH_2), 4.00 (d, J=14.0 Hz, 2H, *a*-$ArCH_2Ar$), 4.03 (d, J=14.9 Hz, 1H, camphor CH_2), 4.04 (s, 3H, OCH_3), 4.44 (2d, J=13.4 Hz, 2H, *a*-$ArCH_2Ar$), 6.32 and 6.33 (2s, 2H, OH), 6.56 and 6.86 (2s, 2H each, ArH), 7.05 and 7.16 (2 m, 2H each, ArH). Calcd, %: C, 75.31; H, 8.27; S, 3.66. $C_{55}H_{72}O_7S$ found, %: C, 75.48; H, 8.20; S, 3.53.

4.2.2.1. X-ray diffraction study. The colourless crystals of **2b** ($C_{55}H_{72}O_7S\cdot 3C_2H_3N$) are monoclinic. At 100 K a=14.604(1), b=18.161(2), c=22.542(2) Å, β=107.55(1)°, V=5700.2(7) Å^3, M_r=1000.35, Z=4, space group $P2_1$, d_{calcd}=1.166 g/cm^3, μ(Mo Kα)=0.110 mm^{-1}, F(000)=2160. Intensity of 25,107 reflections (16,763 independent, R_{int}=0.030) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scaning, $2\Theta_{max}$=55°). The structure was solved by direct method using SHELXTL package.[18] Absolute configuration was determined based on *S*-configuration of chiral centre in camphor substituent. Value of Flack parameter is 0.03. Position of the hydrogen atoms were located from electron density difference maps and refined by 'riding' model with U_{iso}=nU_{eq} of non-hydrogen atom bonded with given H-atom (n=1.5 for methyl group and n=1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation using 16,693 reflections was converged to wR_2=0.095 (R_1=0.043 for 1337 reflections with $F>4\sigma(F)$, S=0.859). The final atomic coordinates and crystallographic data for molecule **2b** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition number CCDC 674973.

*4.2.3. 5,11,17,23-Tetra-tert-butyl-25-((1S)-10-camphorsulfonyloxy)-27-iso-propoxy-26,28-dihydroxycalix[4]arene **2c***

Yield 62%. Mp 261–262 °C. ^{1}H NMR ($CDCl_3$) δ: 0.76 (s, 9H, *t*-Bu), 1.035 and 1.27 (2s, 3H each, camphor Me), 1.0–1.31 (2s, 9H+18H, *t*-Bu), 1.50 (m, 1H, camphor CH), 1.53 (d, J=6.2 Hz, 6H, CH_3), 1.85 (m, 1H, camphor CH), 1.95–2.14 (m, 3H, camphor CH), 2.47 and 2.82 (2 m, 1H each, camphor CH), 3.34–3.45 (3d, 4H, *e*-$ArCH_2Ar$), 3.48 (d, J=15.1 Hz, 1H, camphor CH_2), 4.04 and 4.06 (2d, J=14.0, 15.1 Hz, 3H, *a*-$ArCH_2Ar$+camphor CH_2), 4.37 (m, 1H, CH), 4.44 (2d, J=13.5, 13.2 Hz, 2H, *a*-$ArCH_2Ar$), 6.23 and 6.25 (2s, 2H, OH), 6.58 and 6.86 (2s, 2H each, ArH), 7.03 and 7.13 (2 m, 2H each, ArH). Calcd, %: C, 75.63; H, 8.46; S, 3.54. $C_{57}H_{76}O_7S$ found, %: C, 76.01; H, 8.32; S, 3.58.

4.3. Proximal sulfonylation of *iso*-propoxycalixarene 1a in the presence of NaH

To the solution of calixarene **1a** (1.0 g, 2.14 mmol) in THF–DMF mixture (16 ml:1.85 ml), the sodium hydride as 60% dispersion in mineral oil (0.094 g, 2.36 mmol) was added. The reaction mixture was stirred at ambient temperature for 1 h and the solution of camphorsulfonyl chloride (0.58 g, 2.31 mmol) in THF (2.5 ml) was added. The reaction mixture was stirred at ambient temperature for 18 h. The solvent was removed under reduced pressure and to the oily residue chloroform (35 ml) and saturated solution of NH_4Cl (35 ml) were added. The organic layer was separated and dried over

Na_2SO_4. The yield of diastereomeric mixture **3a**+**4a**—85%. Diastereomer **3a** was obtained by crystallization of the mixture **3a**+**4a** from benzene–hexane with 45% yield. The mother liquor was evaporated. The diastereomer **4a** was obtained by crystallization of the residue from chloroform–hexane with 35% yield.

4.4. 25-((1*S*)-10-Camphorsulfonyloxy)-26-*iso*-propoxy-27,28-dihydroxycalix[4]arene 3a

Mp 239–240 °C. $[\alpha]_D^{20}$ 11.7 (c 0.008, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.99 and 1.21 (2s, 3H each, camphor Me), 1.49 (m, 1H, camphor CH), 1.59 and 1.73 (2d, 3H each, CH_3), 1.82 (m, 1H, camphor CH), 1.99–2.20 (m, 3H, camphor CH), 2.48 and 2.66 (2 m, 1H each, camphor CH), 3.39, 3.41, 3.51 (3d, J=13.5, 12.8, 13.5 Hz, 1H, 1H, 2H, *e*-$ArCH_2Ar$), 3.77 (d, J=14.9 Hz, 1H, camphor CH_2), 4.07 (d, J=13.9 Hz, 1H, *a*-$ArCH_2Ar$), 4.22 (d, J=13.5 Hz, 1H, *a*-$ArCH_2Ar$), 4.23 (d, J=14.9 Hz, 1H, camphor CH_2), 4.51 and 4.86 (2d, J=12.8, 13.5 Hz, 1H each, *a*-$ArCH_2Ar$), 4.64 (m, 1H, CH), 6.66 (m, 2H, ArH), 6.82–7.09 (m, 10H, ArH), 8.87 and 9.72 (2s, 1H each, OH). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 19.85, 20.11, 21.64, 21.97, 25.11, 27.05, 31.39, 31.87, 32.58, 33.10, 42.59, 42.90, 48.03, 48.23, 58.19, 79.61, 120.01, 121.47, 125.77, 127.16, 127.42, 127.77, 127.86, 128.50, 128.55, 128.71, 128.76, 129.25, 129.39, 129.53, 129.78, 130.07, 134.33, 135.21, 135.82, 136.37, 142.68, 149.87, 149.92, 152.4. Calcd, %: C, 72.33; H, 6.51; S, 4.71. $C_{41}H_{44}O_7S$ found, %: C, 72.51; H, 6.21; S, 4.49.

4.5. 25-*iso*-Propoxy-26-((1*S*)-10-camphorsulfonyloxy)-27,28-dihydroxycalix[4]arene 4a

Mp 170–171 °C. $[\alpha]_D^{20}$ 3.0 (c 0.009, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.04 and 1.27 (2s, 3H each, camphor Me), 1.45 (m, 1H, camphor CH), 1.53 and 1.75 (2d, 3H each, CH_3), 1.96 (m, 1H, camphor CH), 2.06–2.18 (m, 3H, camphor CH), 2.43 and 2.61 (2 m, 1H each, camphor CH), 3.45, 3.49, 3.55, 3.58 (4d, J=13.7, 13.1, 13.9, 13.1 Hz, 4H, *e*-$ArCH_2Ar$), 3.59 (d, J=14.8 Hz, 1H, camphor CH_2), 4.08 (d, J=13.9 Hz, 1H, *a*-$ArCH_2Ar$), 4.09 (d, J=14.8 Hz, 1H, camphor CH_2), 4.23, 4.61, 4.79 (3d, J=13.7, 13.1, 13.1 Hz, 3H, *a*-$ArCH_2Ar$), 4.67 (m, 1H, CH), 6.65 (m, 2H, ArH), 6.83 (m, 1H, ArH), 6.92–7.12 (m, 8H, ArH), 7.25 (m, 1H, ArH), 8.94 and 9.80 (2s, 1H each, OH). Calcd, %: C, 72.33; H, 6.51; S, 4.71. $C_{41}H_{44}O_7S$ found, %: C, 72.00; H, 6.37; S, 4.31.

4.6. Proximal sulfonylation of monoalkoxycalixarenes 1a–c in the presence of K_2CO_3

4.6.1. General procedure

The mixture of monoalkoxycalixarenes **1a**–**c** (0.5 mmol) and K_2CO_3 (0.3 mmol) in dry DMF (15 ml) was stirred at 40–50 °C for 45 min. Then, camphorsulfonyl chloride (0.55 mmol) was added and the mixture was stirred under inert atmosphere at 65–70 °C for 2 h. After cooling to room temperature, the reaction mixture was poured in acidulous water (150 ml water and 2 ml 6 M HCl). The precipitate was filtered off, washed with water (20 ml), then with a saturated solution of sodium bicarbonate (20 ml) and again with water (20 ml). The mixture of diastereomers **3a** and **4a** with 20% excess of **3a** was obtained as colourless crystals by crystallization from acetonitrile with 34% yield. The mixture of diastereomers **3b**+**4b** with 17% excess of **3b** was obtained as colourless crystals by crystallization from acetonitrile with a yield of 67%. Calcd, %: C, 75.31; H, 8.27. $C_{55}H_{72}O_7S$ found, %: C, 75.28; H, 8.21.

The yield of diastereomers **3c**+**4c** mixture in ratio 1:1 (81%). Calcd, %: C, 75.63; H, 8.46; S, 3.54. $C_{57}H_{76}O_7S$ found, %: C, 75.40; H, 8.54; S, 3.52.

*4.6.2. Diastereomers **3c**+**4c** separation by HPLC method*

The HPL Chromatograph (Hitachi, LTD) consisted of a high-pressure pump connected to a Rheodyne sample 7120 injector with a 20 μL loop (Rheodyne, Berkeley, CA) and an UV–vis detector operated at 254 nm was used. The column (250×4.6 mm i.d.) was packed with Zorbax CN. The mobile phase was a mixture hexane–THF in ratio 96:4, v/v. The flow rate was 1.5 ml/min. The separation was performed at 20 °C.

For the chromatographic separation the 6% solution of the mixture **3c** and **4c** in hexane was used. The amount of the samples injected was 50×20 μL. About 40% of diastereomer **3c** and 42% of **4c** were evolved from initial mixture.

*4.6.3. 5,11,17,23-Tetra-tert-butyl-25-((1S)-10-camphorsulfonyloxy)-26-methoxy-27,28-dihydroxycalix[4]arene **3b**+**4b***

Mp 165–169 °C. ^1H NMR ($CDCl_3$) δ: 1.01 (s, camphor Me), 1.07 (s, camphor Me), 1.09 (s, *t*-Bu), 1.13 (s, *t*-Bu), 1.20–1.24 (6s, camphor Me+*t*-Bu), 1.28 (s, camphor Me), 1.65 (s, camphor CH), 1.92–2.21 (m, camphor CH), 2.43–2.69 (m, camphor CH), 3.36–3.55 (multiplet of doublets, *e*-$ArCH_2Ar$), 3.74 (d, J=14.9 Hz, OCH_2 camphor), 3.91 (d, J=14.9 Hz, OCH_2 camphor), 4.01–4.29 (multiplet of doublets, *a*-$ArCH_2Ar$), 4.17 (s, OMe), 4.25 (s, OMe), 4.57–4.82 (multiplet of doublets, *a*-$ArCH_2Ar$), 6.93–7.24 (m, ArH), 8.90 and 8.91 (2s, OH), 9.92 and 9.95 (2s, OH). Calcd, %: C, 75.31; H, 8.27. $C_{55}H_{72}O_7S$ found, %: C, 75.28; H, 8.21.

*4.6.4. 5,11,17,23-Tetra-tert-butyl-25-iso-propoxy-26-((1S)-10-camphorsulfonyloxy)-27,28-dihydroxycalix[4]arene **3c***

^1H NMR ($CDCl_3$) δ: 0.99 (s, 3H, camphor Me), 1.04 (s, 9H, *t*-Bu), 1.22 (s, 3H, camphor Me), 1.23–1.25 (3s, 27H, *t*-Bu), 1.52 (m, 1H, camphor CH), 1.61 and 1.71 (2d, 3H each, CH_3), 1.83 (m, 1H, camphor CH), 1.99–2.18 (m, 3H, camphor CH), 2.48 and 2.67 (2 m, 1H each, camphor CH), 3.36–3.52 (4d, J=12.6, 13.2, 13.2, 13.7 Hz, 1H each, *e*-$ArCH_2Ar$), 3.78 (d, J=14.9 Hz, 1H, camphor CH_2), 4.07 (d, J=13.7 Hz, 1H, *a*-$ArCH_2Ar$), 4.24 (2d, 2H, *a*-$ArCH_2Ar$+camphor CH_2), 4.51 and 4.55 (d+m, J=12.6 Hz, 2H, *a*-$ArCH_2Ar$ and CH, respectively), 4.82 (d, J=13.2 Hz, 1H, *a*-$ArCH_2Ar$), 6.91–7.24 (m, 8H, ArH), 8.89 and 9.90 (2s, 1H each, OH).

*4.6.5. 5,11,17,23-Tetra-tert-butyl-25-((1S)-10-camphorsulfonyloxy)-26-iso-propoxy-27,28-dihydroxycalix[4]arene **4c***

^1H NMR ($CDCl_3$) δ: 0.97 (s, 9H, *t*-Bu), 1.04 (s, 3H, camphor Me), 1.21–1.26 (4s, 30H, camphor Me+*t*-Bu), 1.53 (m+d, 4H, camphor CH+CH_3), 1.72 (m+d, 4H, camphor CH+CH_3), 1.95–2.16 (m, 3H, camphor CH), 2.42–2.67 (2 m, 1H each, camphor CH), 3.35–3.50 (4d, J=13.5, 12.4, 13.7, 12.8 Hz, 1H each, *e*-$ArCH_2Ar$), 3.60 (d, J=14.9 Hz, 1H, OCH_2), 4.09 (2d, J=12.4, 14.9 Hz, 2H, *a*-$ArCH_2$-Ar+camphor CH_2), 4.24 (d, J=13.5 Hz, 1H, *a*-$ArCH_2Ar$+camphor CH_2), 4.56 and 4.57 (d+m, J=12.8 Hz, 2H, *a*-$ArCH_2Ar$ and CH), 4.72 (d, J=13.4 Hz, 1H, *a*-$ArCH_2Ar$), 6.85–7.25 (m, 8H, ArH), 8.82 and 9.89 (2s, 1H each, OH).

Acknowledgements

The authors of the Kyiv team thank the Science and Technology Center in Ukraine for support of the work through the Grant #3594.

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