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25,27-Bis(benzoyloxy)calix[4]arenes: Synthesis and Structure Elucidation of *syn* and *anti* Isomers

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Introduction

It is well known that large phenolic substituents hinder the conformational freedom of the calix[4]arene system (*i.e.* restriction of the phenolic ring free rotation about the methylene linkages).[1–3] Therefore, unlike the parent calix[4]arene, the four "up/down" conformational isomers of tetra-*O*-substituted calix[4]arenes are not able to interconvert, and each isomer is isolable.[4,5] The structures of the four conformers are usually established by ^{1}H-NMR spectral methods.[6] Recently, Prados et al. reported that the ^{13}C-NMR spectrum of the methylene carbon chemical shift revealed more information about the conformations of calix[4]arenes.[7] However, these analysis methods are best applicable to the symmetrical tetra-*O*-substituted calix[4]arenes. The tri-*O*-substituted calix[4]arenes, which possesses four noninterconvertible conformers, and the 1,2- and 1,3-di-*O*-substituted calix[4]arenes, which possesses two conformers each,[8] are not amenable to exact structure determination by the same spectral analyses. Only recently have the synthesis and the structure assignment of tri-*O*-substituted and di-*O*-substituted calix[4]arenes been achieved by Gutsche[9] and Shinkai.[10–12] In this paper we report the one-step synthesis and the structure elucidation of two conformational isomers of 25,27-bis(benzoyloxy)-26,28-dihydroxycalix[4]arene and their tris(benzoyloxy) and tetrakis(benzoyloxy) derivatives.

Results and Discussion

1,3-Dibenzoate of Calix[4]arene (1 and 2). The calixarene ester derivatives are generally prepared by treating calixarenes with the corresponding acyl chloride in the presence of a weak base, whereas the calixarene ether derivatives are prepared by refluxing calixarenes and the corresponding alkyl halide in the presence of NaH. Recently, we found that the reaction of calix[4]arene with excess benzoyl chloride in the presence of NaH produced calix[4]arene 1,3-dibenzoates **1** and **2** (Scheme 1). We observed that the 1,3-dibenzoate **1** was produced in over 80% yield by refluxing the reaction mixture in toluene for 4 h, whereas the 1,3-dibenzoate **2** was produced by stirring the reaction mixture in THF in an ice bath for the same period of time. The FAB-MS spectrum displayed *m*/*e* values of 633 for both compounds **1** and **2**, indicating that only two benzoyl groups were attached to the calix[4]arene. The ^{1}H-NMR spectra of **1** and **2** displayed a pair of doublets for the methylene hydrogens, which suggested that the two benzoyl moieties were in the 1,3-position, and the remaining free phenolic hydroxy groups appeared singlets for both **1** and **2**. If the same reaction mixture was stirred at room temperature for 4 h, a mixture of compounds **1** and **2** was produced. The composition of the product mixture was evaluated as 40% **1** and 60% **2** from the integration ratio of the two hydroxy hydrogen singlets. This product mixture was not converted to compound **1** even if the product mixture was refluxed in toluene for another 4 h with excess benzoyl chloride and NaH. Moreover, **1** was not detected when compound **2** was refluxed under the same reaction conditions. These results indicated that the conversion of **2** to **1** had not occurred.

The structures of **1** and **2** were assigned as *anti* and *syn* isomers, respectively, on the basis of the chemical shift difference of the methylene hydrogen's doublet pairs. Compound **1** displayed a small chemical shift difference ($\Delta\delta = 0.15$ ppm) and was assigned as the *anti* isomer, whereas compound **2** displayed a larger chemical shift difference ($\Delta\delta = 0.47$ ppm) and was assigned as the *syn* isomer. The assignment was supported by the spectrum of the *anti* isomer of 25,27-bis(propyloxy)-26,28-dihydroxycalix[4]arene, which showed a chemical shift difference of $\Delta\delta = 0.22$ ppm,[11] and was further supported by other evidence, *vide infra*.

Tribenzoate of Calix[4]arene (3). Gutsche and Lin[13] reported that calix[4]arene reacts with excess benzoyl chloride in pyridine to yield the tribenzoate **3** (Scheme 2). When calix[4]arene was replaced by the 1,3-dibenzoate **2** under the same reaction conditions, the identical tribenzoate **3** was afforded as the only product in 78% yield. However, the 1,3-dibenzoate **1**, which is not soluble in most organic solvents, was not converted to tribenzoates under the same reaction conditions, and starting material was recovered in all cases.

The physical properties and the ^{1}H-NMR spectral data, which displayed two sets of double doublets for the methylene hydrogens, suggested that the tribenzoate **3** existed in only one of the four possible conformers. Although the X-ray crystallographic structure of the derivative of tribenzoate **3**, 5-allyl-25-methoxy-26,27,28-tris(benzoyloxy)calix[4]arene, was shown to possess an "up-down-up" arrangement of the three benzoyloxy moieties,[14] the exact structure for the tribenzoate **3** will be elucidated in a later section.

Tetrabenzoate of Calix[4]arene (4 and 5). Gutsche and Lin also showed that the tetrabenzoates **4** and **5** can be prepared directly by treating calix[4]arene or triben-

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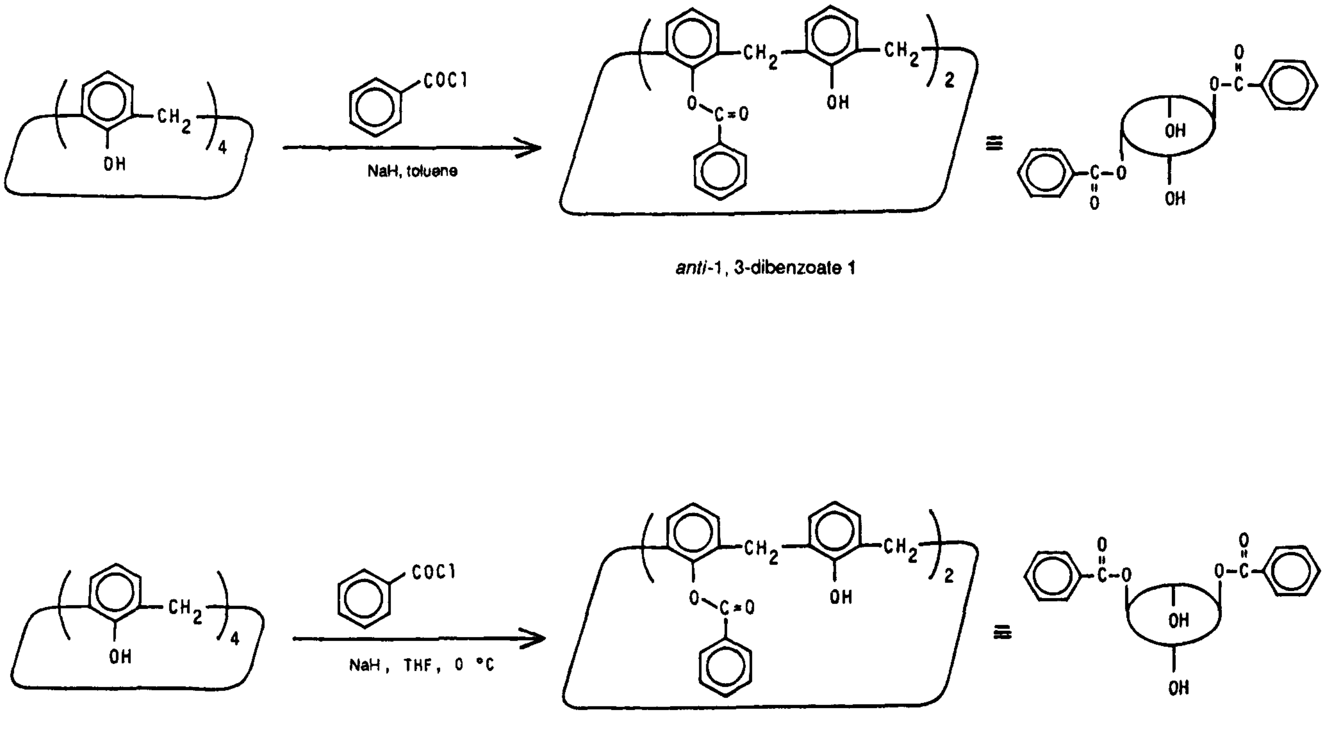
Scheme 1



anti-1, 3-dibenzoate **1**

syn-1, 3-dibenzoate **2**

zoate **3** with excess benzoyl chloride in the presence of $AlCl_3$.[14] When tribenzoate **3** was treated with benzoyl chloride and $AlCl_3$, a mixture of "1,3-alternate" tetrabenzoate **4** and "partial cone" tetrabenzoate **5** was obtained. The composition of this product mixture was greatly influenced by the reaction conditions. The amount of 1,3-alternate tetrabenzoate **4** was increased as the amount of $AlCl_3$ used was reduced. For example, 5% of **4** was isolated in pure form when 10 molar equiv of $AlCl_3$ was used, and **4** increased to 36% when half that amount of $AlCl_3$ was used. Furthermore, the partial cone tetrabenzoate **5** was the only isolated product if 30 molar equiv of $Alcl_3$ was used. The reason for these results is not clear.

When 1,3-dibenzoate **2** was treated under the same reaction conditions, the only product that could be isolated was the 1,3-alternate tetrabenzoate **4**. We attributed this to a strong bonding interaction between $AlCl_3$ and two free phenolic hydroxy groups in 1,3-dibenzoate **2**. Under such an assumption, the two free phenolic hydroxy groups were bonded to $AlCl_3$ on the less sterically hindered side (the opposite direction of benzoyloxy groups), and the formation of the ester linkage on that position produced only the 1,3-alternate tetrabenzoate **4**. The 1,3-dibenzoate **1**, which was expected to yield the partial cone tetrabenzoate **5** under the same assumption, failed to give any tetrabenzoates. The inertness of 1,3-dibenzoate **1** toward tribenzoylation and tetrabenzoylation may be due to the solubility of the compound.

Elucidation of Conformational Structure. The ^{1}H-NMR spectra and MS spectra of calix[4]arene benzoates strongly support the number and the position of the benzoyloxy moieties. However, the exact conformational structures of **1**, **2**, and **3** were not known. In the conversion of 1,3-dibenzoates to tribenzoates, the *syn*-1,3-dibenzoate would convert to an "all-up" ($H^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}$)[8] or an "up-down-up" ($H^{\alpha}R^{\alpha}R^{\beta}R^{\alpha}$) tribenzoate, whereas the *anti*-1,3-dibenzoate would produce a racemic pair of up-up-down ($H^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$ and $H^{\alpha}R^{\beta}R^{\beta}R^{\alpha}$) tribenzoates as shown in Figure 1. The *syn*-1,3-dibenzoate would yield the "cone" ($R^{\alpha}R^{\alpha}R^{\alpha}R^{\alpha}$), partial cone ($R^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$), and 1,3-alternate ($R^{\alpha}R^{\beta}R^{\alpha}R^{\beta}$) tetrabenzoate on further benzoylation, whereas, the *anti*-1,3-dibenzoate would yield partial cone ($R^{\alpha}R^{\alpha}R^{\alpha}R^{\beta}$) and 1,2-alternate ($R^{\alpha}R^{\alpha}R^{\beta}R^{\beta}$) tetrabenzoates.

We have shown that only 1,3-alternate tetrabenzoate **4** was produced when 1,3-dibenzoate **2** was treated with benzoyl chloride and $AlCl_3$. This result indicated that two original benzoyloxy moieties could not possess the *anti* arrangement, and the *syn* structure became the only possible solution for the 1,3-dibenzoate **2**. The other conformer, the *anti* structure, was assigned to 1,3-dibenzoate **1**. The tribenzoate **3** was shown to be identical to the tribenzoylate product produced from *syn*-1,3-dibenzoate **2**, and therefore, the tribenzoate **3** was limited to all-up or up-down-up isomers. We had also shown the formation of 1,3-alternate tetrabenzoate **4** from tribenzoate **3** which eliminated the all-up isomer from the possible conformers list. Therefore, the tribenzoate **3** was in the least sterically hindered up-down-up structure as may be expected.

Experimental Section[15]

***anti*-25,27-Bis(benzoyloxy)-26,28-dihydroxycalix[4]arene (1).** A solution of 2.12 g (5.0 mmol) of calix[4]arene, 1.20

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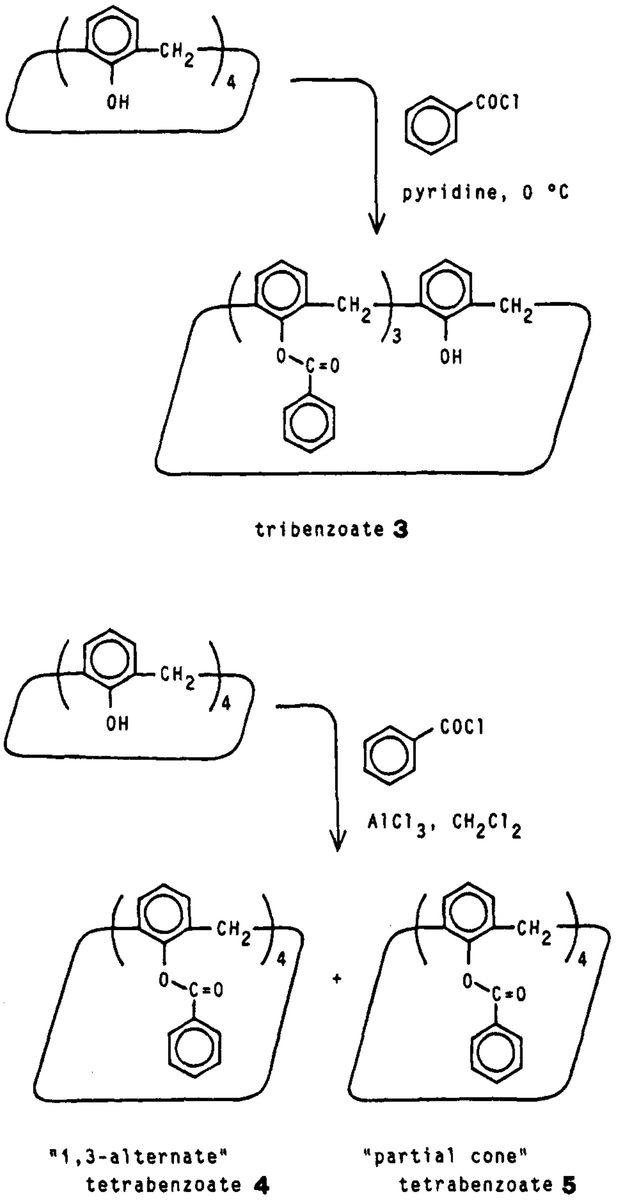
(15) All reagents were obtained from Merck Chemical Company and used without further purification. Melting points were taken in capillary tubes on a Mel-Temp apparatus (Laboratory Devices Cambridge, MA) and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 spectrometer, except for the ^{1}H-NMR spectra of compounds **1** and **2** which were recorded on a Bruker AM-300 WB spectrometer. Chemical shifts are reported as δ values in ppm relative to TMS ($\delta = 0.0$) as an internal standard. FAB-MS spectra were taken on a JOEL JMS-HX 110 spectrometer. TLC analyses were carried out on Merck silica gel 60 F_{254} aluminum-backed plates (absorbant thickness 0.2 mm).

Scheme 2



g (50 mmol) of NaH, and 10 mL (12.10 g, 86 mmol) of benzoyl chloride in 100 mL of toluene was refluxed for 4 h. The solvent was removed, and the oily residue was treated with CH_3OH to produce a white solid. Recrystallization from $CHCl_3$ and CH_3OH afforded 2.81 g (88%) of small colorless needle-like crystals: mp 303–305 °C; ^1H NMR ($CDCl_3$) δ 6.22–7.49 (m, 22H), 5.65 (s, 2H), 3.90–3.95 (d, 4H), 3.78–3.83 (d, 4H); ^{13}C NMR δ 164.2, 152.3, 146.9, 134.3, 133.8, 130.1, 129.7, 129.3, 128.7, 128.3, 127.3, 126.8, 121.1, 34.6; FAB-MS *m/e* 633 ($M^+ + 1$). Anal. Calcd for $C_{42}H_{32}O_6$: C, 79.75; H, 5.06. Calcd for $C_{42}H_{32}O_6 \cdot {}^1/_2CH_3OH$: C, 78.70; H, 5.25. Found: C, 78.85; H, 5.00.

***syn*-25,27-Bis(benzoyloxy)-26,28-dihydroxycalix[4]arene (2).** A solution of 2.12 g (5.0 mmol) of calix[4]arene and 1.20 g (50 mmol) of NaH in 100 mL of THF was chilled in an ice bath, and a portion of 10 mL (12.10 g, 86 mmol) of benzoyl chloride was added. The reaction mixture was allowed to stir for 4 h, the solvent was removed, and the oily residue was treated with CH_3OH to leave a white solid. Recrystallization from $CHCl_3$ and CH_3OH afforded 1.82 g (57.5%) of colorless needle-like crystals: mp 262–264 °C; ^1H NMR ($CDCl_3$) δ 6.68–8.39 (m, 22H), 5.47 (s, 2H), 3.97–4.02 (d, 4H), 3.51–3.56 (d, 4H); ^{13}C NMR δ 165.4, 153.3, 145.9, 134.4, 132.8, 131.1, 129.8, 129.7, 129.5, 128.6, 127.2, 120.4, 33.0; FAB-MS *m/e* 633 ($M^+ + 1$). Anal. Calcd for $C_{42}H_{32}O_6$: C, 79.75; H, 5.06. Found: C, 79.64; H, 5.11.

25,26,27-Tris(benzoyloxy)-28-hydroxycalix[4]arene (3). Method A. From Calix[4]arene. A solution of 2.12 g (5.00 mmol) of calix[4]arene in 25 mL of pyridine was cooled in an ice bath, and 3.50 mL (4.24 g, 30.1 mmol) of benzoyl chloride was added. The mixture was stirred at 0 °C for 1 h and was then allowed to slowly warm to room temperature for another hour. The mixture was poured into 300 mL of water, and solid material was collected by filtration. Recrystallization from $CHCl_3$ and CH_3OH afforded 2.97 g (81%) of colorless, thin plate-like crystals: mp 268–270 °C (lit.[14] mp 276–277 °C); ^1H NMR ($CDCl_3$) δ 6.52–8.10 (m, 27H), 5.44 (s, 4H), 3.83–3.90 (d, 2H), 3.75–3.82 (d, 2H), 3.63–3.71 (d, 2H), 3.43–3.50 (d, 2H); ^{13}C NMR δ 165.0, 164.4, 153.3, 148.8, 147.2, 134.3, 134.0, 133.7, 133.4, 133.1, 131.8, 131.3, 130.8, 130.0, 129.7, 129.3, 129.2, 128.6, 128.3, 128.2, 126.5, 125.6, 120.2, 37.9, 32.9; FAB-MS *m/e* 737 ($M^+ + 1$).

Method B. From *syn*-25,27-Bis(benzoyloxy)-26,28-dihydroxycalix[4]arene (2). A solution of 0.22 g (0.35 mmol) of **2** in 10 mL of pyridine was cooled in an ice bath, and 2.0 mL (2.42 g, 17 mmol) of benzoyl chloride was added. The mixture was stirred at 0 °C for 1 h and was allowed to slowly warm to rt for another hour. The mixture was poured into 100 mL of water, and solid material was collected by filtration. Recrystallization from $CHCl_3$ and CH_3OH afforded 0.20 g (78%) of colorless, thin plate-like crystals identical in chemical and spectral properties with compound **3**.

25,26,27,28-Tetrakis(benzoyloxy)calix[4]arene (4 and 5). Method A. From Calix[4]arene. A solution of 5.0 mL (6.05 g, 43.0 mmol) of benzoyl chloride and 1.34 g (10.0 mmol) of $AlCl_3$ in 20 mL of CH_2Cl_2 was added to a cold solution of 1.06 g (2.50 mmol) of calix[4]arene in 30 mL of CH_2Cl_2. The mixture was stirred for 24 h and poured into 300 mL of H_2O, and the organic portion was separated. The solvent was removed, and the residue was treated with CH_3OH to precipitate a pale yellow solid. The solid was treated with 50 mL of acetone and filtered to give 1.20 g of a colorless solid. This acetone-insoluble material was further recrystallized from $CHCl_3$ and CH_3OH to afford 0.87 g (41%) of **4** as colorless, plate-like crystals: mp over 400 °C (lit.[14] mp over 450 °C); ^1H NMR ($CDCl_3$) δ 6.70–8.00 (m, 32H), 3.60 (bs, 8H); ^{13}C NMR δ 164.8, 148.7, 134.5, 133.9, 132.1, 131.8, 129.1, 128.7, 125.1, 37.4.

The solvent was removed from the acetone-soluble portion, and the residue was recrystallized from $CHCl_3$ and CH_3OH to yield 0.09 g (4%) of **5** as colorless needle-like crystals: mp 298–300 °C (lit.[14] mp 301–303 °C); ^1H NMR ($CDCl_3$) δ 6.20–8.10 (m, 32H), 3.93–4.00 (d, 2H), 3.82–3.89 (d, 2H), 3.67–3.74 (d, 2H), 3.51–3.58 (d, 2H); ^{13}C NMR δ 196.2, 164.6, 164.6, 157.6, 148.8, 147.1, 138.8, 134.4, 134.1, 133.9, 133.7, 133.5, 132.4, 132.3, 132.2, 132.1, 131.8, 131.3, 131.2, 130.2, 129.9, 129.8, 129.3, 129.2, 128.7, 128.5, 128.3, 128.2, 126.7, 125.8, 38.0, 32.4.

Method B. From *syn*-25,27-Bis(benzoyloxy)-26,28-dihydroxycalix[4]arene (2). A solution of 1.0 mL (1.21 g, 8.60 mmol) of benzoyl chloride and 1.00 g (7.50 mmol) of $AlCl_3$ in 20 mL of CH_2Cl_2 was added to a cold solution of 0.13 g (0.21 mmol) of **2** in 20 mL of CH_2Cl_2. The mixture was stirred for 24 h and was then poured into 300 mL of H_2O. The organic portion was separated and dried with Na_2SO_4, and solvent was removed to give a light yellow solid. The solid was recrystallized from $CHCl_3$ and CH_3OH and yield 0.13 g (87.5%) of colorless, platelike crystals identical in chemical and spectral properties with compound **4**.

Method C. From 25,26,27-Tris(benzoyloxy)-28-hydroxycalix[4]arene (3). A solution of 0.60 mL (0.73 g, 5.20 mmol) of benzoyl chloride and 0.37 g (2.80 mmol) of $AlCl_3$ in 20 mL of CH_2Cl_2 was added to a cold solution of 0.37 g (0.50 mmol) of **3** in 30 mL of CH_2Cl_2. The mixture was stirred for 24 h and poured into 300 mL of H_2O. The organic portion was separated and dried with Na_2SO_4, and solvent was removed to give an oily residue. The residue was treated with CH_3OH to precipitate 0.32 g of pale yellow solid. The solid was dissolved in 50 mL of acetone and filtered to give 0.19 g of colorless solid. The acetone-insoluble material was recrystallized from $CHCl_3$ and CH_3OH to afford 0.15 g (36%) of colorless, platelike crystals identical in chemical and spectral properties with compound **4**.

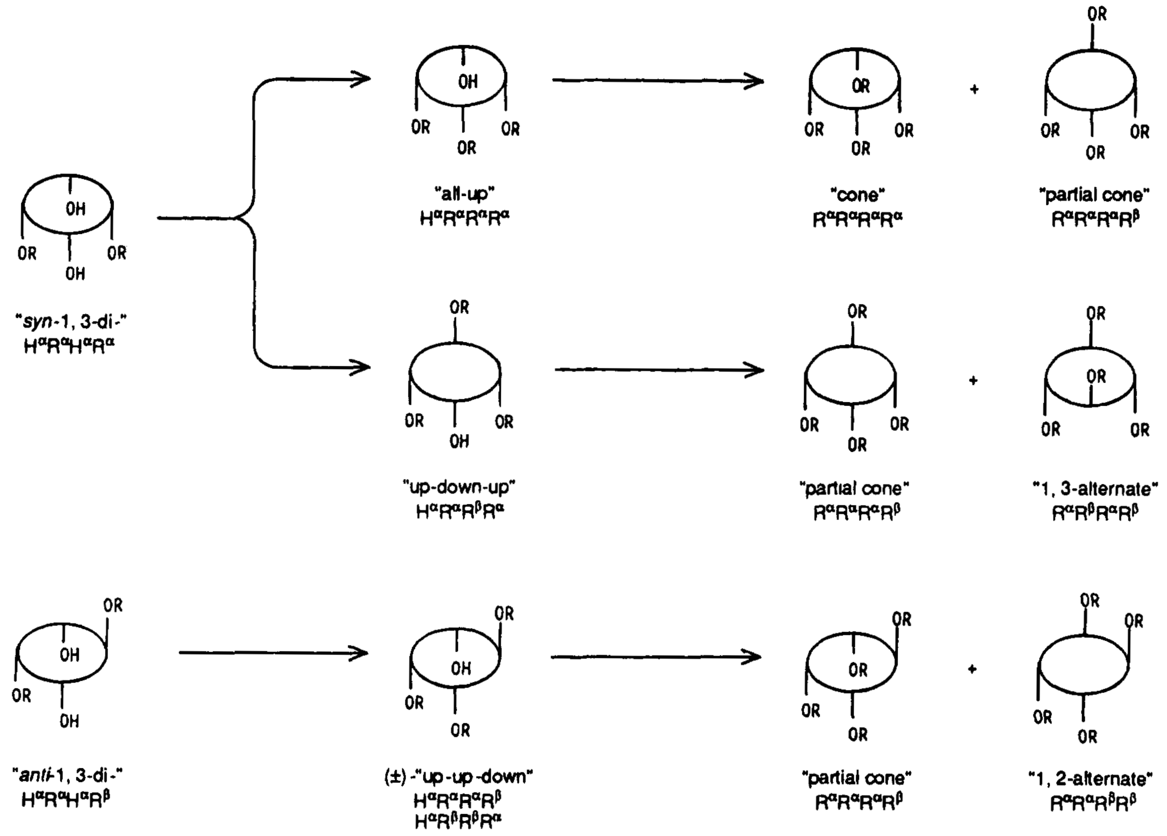


Figure 1. Possible conversion pathways of two 1,3-di-*O*-substituted calix[4]arenes.

The solvent was removed from the acetone-soluble portion and the residue was further recrystallized from $CHCl_3$ and CH_3OH to yield 0.06 g (14%) of colorless needle-like crystals identical in chemical and spectral properties with compound **5**.

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Supplementary Material Available: Copies of ^{1}H-NMR spectra of **1**–**5** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.