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Asymmetrically Substituted Tetrahomodioxa *p*-Phenylcalix[4]arene

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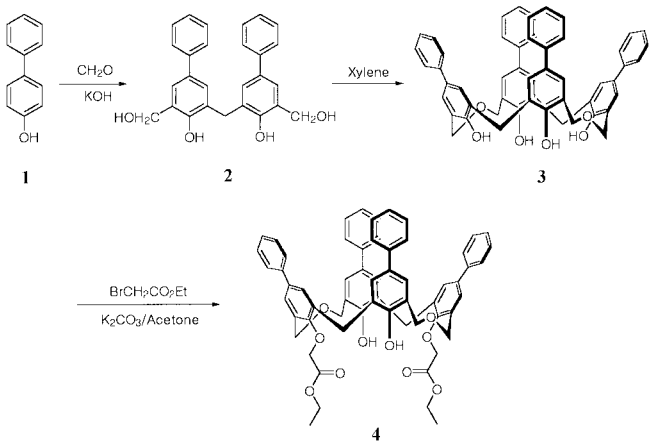
Calixarenes, a class of synthetic macrocycles having phenolic residues in a cyclic array linked by methylene groups at the position "ortho" to the hydroxy groups, have cavities of sufficient size to form host-guest complexes, thus, are particularly attractive compounds for attempting to construct systems that mimic the catalytic activity of the enzyme and have received a great deal of attention in recent years.[1-4]

In contrast to the calix[4]arenes, homooxacalix[4]arenes, containing extra oxygen in the macrocyclic ring, have received little attention mainly because they can only be synthesized in relatively low yield.[5-7] Recently we reported the simple one-step synthesis of tetrahomodioxa *p*-phenylcalix[4]arene in satisfactory yield,[8] which has enabled us to engage in a project to develop the functions of tetrahomodioxacalix[4]arene as high-performance materials.

One of the main features of naturally occurring host molecules is their capacity for enantioselective recognition. Various attempts have therefore been made to obtain chiral host molecules based on calixarenes. Chiral derivatives can be obtained by the introduction of chiral residues either at the upper or lower rim of the calixarene framework.[9-11] However, more interest has been focused on the possibility of synthesizing "inherently" chiral calix[4]arenes, which are built up of nonchiral subunits and consequently owe their chirality to the fact that the calixarene molecule is not planar.[12-15] The attempts for asymmetric molecules of this type involved the synthesis of calix[4]arenes with three (in AABC pattern) or four different *p*-substituted phenol units or the introduction of *m*-substituted phenol units. The same asymmetric pattern can be achieved by *O*-alkylation or *O*-acylation at the lower rim of calix[4]arene. Tetrahomodioxacalix[4]arene has only two plane of symmetry compared to calix[4]arene which has four, therefore selective mono *O*-alkylation or 1,3-di-*O*-alkylation will eliminate the remaining symmetry of tetrahomodioxacalix[4]arene and the resulting compound is chiral. Therefore this paper deals with the first synthesis of asymmetrically substituted homooxa calix[4]arene **4** by the selective introduction of two ester functions into the lower rim of the tetrahomodioxacalix[4]arene **3** as shown in following Scheme 1.



Scheme 1

When the mixture of *p*-phenyl phenol and 35% formaldehyde was stirred for 4 days at 40 °C in the presence of potassium hydroxide, the dimer diol **2** was prepared in 55% yield.[17,18] Compound **2** (3.02 g, 7.32 mmole) was refluxed in xylene (180 mL) for 20 h to remove water in a Dean-Stark moisture trap to afford the tetrahomodioxacalix[4]arene **3** in 79% yield[8]. When the homooxacalix[4]arene **3** was refluxed with a limited amount of ethyl bromoacetate in acetone in the presence of K_2CO_3, only two ester groups were introduced into two distal OH groups and compound **4** was isolated in 42% yield as crystalline solid.[18] The absence of symmetry elements in compound **4** is evident from its NMR spectra, which show characteristic line patterns for the chiral calix[4]arene skeleton and the groups attached to it. The ^{1}H NMR spectrum of compound **4** is extremely complex and shows the one conformer, which is stable in the NMR time

scale under measurement condition (0 to 50 °C). The methylenic protons from $ArCH_2Ar$ and $ArCH_2O$ bridges appear as six partly overlapping AX systems and these peak patterns are not changed at 50 °C. The methylene protons from two OCH_2CO groups also appear as two sets of AB quartet. ^{13}C NMR spectrum shows two peaks from carbonyl carbons, 36 peaks from aromatic carbons, 8 peaks from methylene carbons of $ArCH_2O$ and OCH_2CO, and two peaks at 31.37 and 31.31 ppm from $ArCH_2Ar$ bridge methylenic carbons. This complex ^{13}C NMR spectral pattern also supports the asymmetric structure of compound **4**. The position of the methylenic bridge carbons of $ArCH_2Ar$ at 31.37 and 31.31 ppm indicates that these two adjacent benzene rings are in a syn orientation.[19] In FT-IR spectrum, the OH stretching band which was appeared at 3353 cm^{-1} and shifted to higher frequency by 100 cm^{-1} from that of starting material (3251 cm^{-1}), indicates the reduced intramolecular hydrogen bonding of OH groups.[20]

We have demonstrated by this example that asymmetrically substituted tetrahomodioxacalix[4]arene is readily available by the selective 1,3-di-*O*-alkylation at lower rim. Experiments are underway to separate the derivatives into the pure enantiomers and to introduce further functional groups.

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18. A solution of compound **3** (1.00 g, 1.27 mmole) in acetone (100 mL) was treated with 174 mg (1 mole equivalent of **3**) of anhydrous K_2CO_3. To this suspension ethyl bromoacetate (0.5 mL) was added, then the reaction mixture was refluxed 24 hr. After removal of acetone by evaporation, the residue was acidified with dilute HCl, then extracted with methylene chloride. The organic layer was collected, washed with water, dried over anhydrous $MgSO_4$, and evaporated solvent to dryness to yield the slightly colored solid. The crude product was boiled with ethyl acetate (50 mL) and collected the insoluble material which was recrystallized from CH_2Cl_2 and methanol to give 420 mg (42%) of the product **4** as crystalline solid. mp 220 °C; IR(KBr) 3353, 1751 cm^{-1}; ^1H NMR($CDCl_3$, 25 °C) δ 8.09 (s, 2, OH) 7.59-7.22 (m, 28, ArH), 5.22 (d, 1, CH_2, J = 10.7 Hz), 5.06 (d, 1, CH_2, J = 11.7 Hz), 5.00 (d, 1, CH_2, J = 15.6 Hz), 4.82 (d, 1, CH_2, J = 15.6 Hz), 4.74 (d, 1, CH_2, J = 10.7 Hz), 4.70 (d, 1, CH_2, J = 11.7 Hz), 4.68 (d, 1, CH_2, J = 10.7 Hz), 4.64 (d, 1, CH_2, J = 14.7 Hz), 4.62 (d, 1, CH_2, J = 14.7 Hz), 4.39 (d, 1, CH_2, J = 10.7 Hz), 3.64 (d, 1, CH_2, J = 14.7 Hz), 3.59 (d, 1, CH_2, J = 14.7 Hz), 4.29 (AB q, 2, OCH_2CO J = 7.0 Hz), 4.28 (AB q, 2, OCH_2CO J = 7.0 Hz), 3.82 (q, 2, OCH_2, J = 7.3 Hz), 3.81 (q, 2, OCH_2, J = 7.3 Hz), 1.32 (t, 3, CH_3, J = 7.3 Hz), 0.81 (t, 3, CH_3, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 171.12, 169.53 (C=O), 155.64, 154.98, 153.79, 153.17, 140.97, 140,84, 140.28, 140.19, 137.65, 137.47, 135.04, 133.95, 132.81, 132.45, 130.23, 129.90, 129.73, 129.47, 128.95, 128.67, 128.64, 128.62, 128.57, 127.57, 127.15, 127.04, 127.00, 126.76, 126.59, 126.55, 126.48, 126.46, 123,92, 123.87 (Ar), 71.86, 71.66, 70.44, 70.35, 69.71, 68.17, 61.22, 61.19 (CH_2), 31.37, 31.31 ($ArCH_2Ar$), 14.18, 13.59 (CH_3); Anal. Calcd for $C_{62}H_{56}O_{10}$: C, 77.48; H, 5.87. Found: C, 77.33; H, 5.90.
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