Synthesis and Optical Resolution of an *anti-O,O′*-Dialkylated Calix[4]arene

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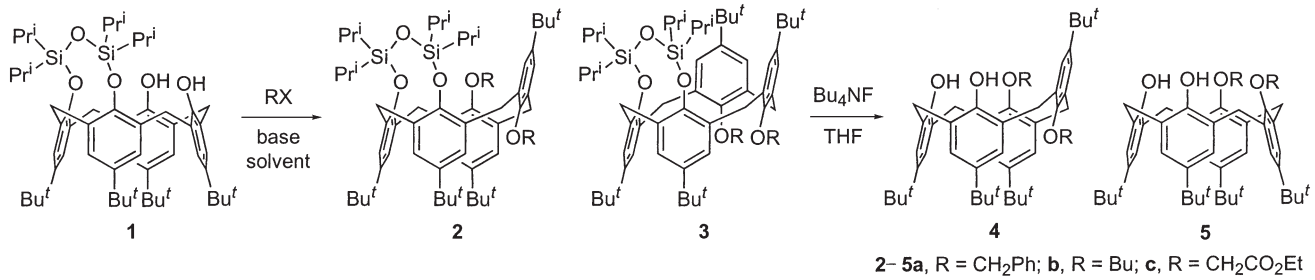
Proximally *O,O′*-disiloxane-bridged calix[4]arene (**1**) was treated with benzyl bromide in the presence of Cs_2CO_3 to afford, after desilylation, *anti-O,O′*-dibenzylcalix[4]arene (**4a**) in 90% yield. Chromatographic separation of its diastereomeric (*S*)-2-methoxy-2-(1-naphthyl)propionic esters allowed the first optical resolution of this kind of dialkylated calix[4]arenes.

Calix[4]arenes are one of the most useful building blocks for the construction of receptors of metal ions and neutral molecules, due to the feasibility of various modifications at the phenolic hydroxy groups (lower rim), as well as at the para positions (upper rim), to develop varying functions.[1] However, regioselective difunctionalization at the adjacent phenolic hydroxy groups has still not been sufficiently explored,[2] despite the potential usefulness of the resulting proximally disubstituted calix[4]arenes to design synthetic receptors.[3] Recently, we have succeeded in the selective protection of proximal two hydroxy groups of calix[4]-arenes with a tetraisopropyldisiloxane moiety (*e.g.* compound **1**),[4] which provided a versatile access to adjacently *syn-O,O′*-dialkylated calix[4]arenes, while it still remains a challenge to get *anti* counterparts. It should be noted that the *anti* diethers bearing the same alkyl moiety at the *O,O′*-positions are chiral molecules, being structurally the simplest among the inherently chiral calix[4]arenes modified at the lower rim.[3] Although there are several reports on the synthesis of this class of compounds, there have been, to the best of our knowledge, no precedent of their optical resolution. Herein, we report stereocontrol in dialkylation of disiloxane-protected calix[4]arene (**1**), which enables stereoselective synthesis of *anti* (**2**) and *syn* diethers (**3**) by the selection of the base and solvent. Also reported is the optical resolution of *anti*-dibenzyl ether **4a**.

1 was treated with an alkyl halide in THF in the presence of K_2CO_3 or Cs_2CO_3 to give the corresponding dialkyl ethers in good to excellent yields except the case of BuI with K_2CO_3 (entry 2) (Scheme 1, Table 1). Structures of the products were determined by NMR and MS spectra, according to the criteria as described in the previous paper.[4] It can be seen that K_2CO_3 was not so active but preferentially gave 1,2-alternate conformers (**3**) (entries 1–3). Replacement of the base from K_2CO_3 to Cs_2CO_3 dramatically altered the stereoselectivity of the reaction to give partial-cone conformers (**2**) as the major product (entries 4 and 5). Although the reaction of **1** with ethyl bromoacetate still preferred the formation of 1,2-alternate **3c** even by using Cs_2CO_3, an addition of DMF greatly improved the selectivity for **2c** (entries 6 and 7).

The origin of the high stereoselectivity in the dialkylation of **1** was deduced from a template effect of the alkali metal cations.[2e,5] Thus, a K^+ ion seems to ligate to the phenoxide oxygen of the monoanion of **1** in the 1,2-alternate conformation to avoid the



Scheme 1.

Table 1. Dialkylation of disiloxane-bridged calix[4]arene **1** with RX in THF at reflux

Entry	RX (mol equiv.)	Base (mol equiv.)	Time/h	Yield/%[Product]	
1[a]	$PhCH_2Br$ (20.0)	K_2CO_3 (20.0)	5 days	6 [**2a**]	61 [**3a**]
2[b]	BuI (20.0)	K_2CO_3 (20.0)	5 days	0 [**2b**]	13 [**3b**]
3	$BrCH_2CO_2Et$ (6.0)	K_2CO_3 (6.0)	12	16 [**2c**]	79 [**3c**]
4	$PhCH_2Br$ (8.0)	Cs_2CO_3 (6.0)	12	94 [**2a**]	2 [**3a**]
5	BuI (8.0)	Cs_2CO_3 (6.0)	18	85 [**2b**]	2 [**3b**]
6	$BrCH_2CO_2Et$ (6.0)	Cs_2CO_3 (6.0)	6	25 [**2c**]	69 [**3c**]
7[c]	$BrCH_2CO_2Et$ (6.0)	Cs_2CO_3 (6.0)	4	68 [**2c**]	28 [**3c**]

[a]A monoalkylated compound was obtained in 21% yield. [b]Two stereoisomers of monoalkylated compound were obtained in 64 and 13% yields. [c]The reaction was carried out in THF–DMF (4:1).

steric repulsion imposed by the bulky disiloxane bridge, with the aid of coordination of the adjacent phenolic hydroxy group and cation-π interaction with the two benzene rings bearing the disiloxane bridging group.[6] Therefore, the first alkylation should occur from the opposite side to the disiloxane group in regard to the mean plane of the macrocycle. On the other hand, Cs^+ ion is too large to locate in the vicinity of the deprotonated **1**, thus forming a loose ion pair with the phenoxide anion of cone conformation.[4] This may lead the first alkylation to occur from the same side to the disiloxane moiety. The second alkylation may be allowed only from the opposite side to the disiloxane moiety in both cases because of the steric congestion, yielding the products of *syn* (**3**) and *anti* (**2**) conformations for K^+ and Cs^+ ions, respectively.[2c] The 1,2-alternate conformer of **1** can be distinguished from the other conformers by ^{1}H NMR spectrum, where some of the methyl protons of the disiloxane bridge are strongly shielded by the facing benzene ring, appearing around 0.4 ppm.[4] Actually, the complex prepared in situ by treatment of **1** with 1.0 mol equiv. of *tert*-BuOK in THF-d_8 showed a broad methyl signal at 0.4 ppm,[7] while the Cs complex prepared with an excess of Cs_2CO_3 did not show any signals at this region. This observation will strongly support the reaction mechanism. Ethyl bromoacetate in THF seemed to coordinate to a Cs^+ ion to form a bulky alkylating agent, which could not approach the deprotonated **1** from the same side to the disiloxane bridge. Therefore, alkylation was forced to occur mainly from the opposite side to give *syn* product **3c** (entry 6). The addition of DMF, however, might liberate the bromide from the Cs^+ ion, leading to the preferential formation of *anti* product **2c** (entry 7).

Desilylation of the disiloxane-capped calixarenes **2a**–**c** was carried out by a simple treatment with tetrabutylammonium fluoride in THF to liberate *anti* diethers **4a**–**c** in 96, 98 and 92% yields, respectively (Scheme 1). Their ^{1}H NMR spectra showed one singlet for the hydroxy protons (2 H), two singlets for the *tert*-butyl protons (each 18 H), and four doublets for the aryl protons (each 2 H), the magnetic equivalences suggesting C_2-symmetric structures.[8] On the other hand, the ^{13}C NMR signal of one methylene carbon of diethers **4a**–**c** appeared around 32 ppm,[8] indicating that only two aryl unites adjacent to the methylene group statically adopted a *syn* conformation.[9] These observations indicate that diethers **4a**–**c** rapidly interconvert between two partial-cone conformers in solution.

Optical resolution of *anti*-dibenzyl ether **4a** could be achieved by deriving to diastereomeric esters. Thus, treatment of **4a** with (*S*)-2-methoxy-2-(1-naphthyl)propionic acid [(*S*)-MNPA][10] in the presence of *N*,*N*′-dicyclohexylcarbodiimide gave four diastereomeric monoesters. They could be separated by flash chromatography on silica gel with diethyl ether–hexane (1:19) and then dichloromethane–hexane (1:2) as the eluent in 9, 13, 38, and 29% isolated yields as the first to fourth fractions, respectively. Each fraction was hydrolyzed with MeONa in MeOH quantitatively to give (+)-**4a** {100% ee, $[\alpha]_D^{25} + 23.6$ (*c* 1.01, $CHCl_3$)} from the first and the third fractions and (−)-**4a** {100% ee, $[\alpha]_D^{25} - 23.6$ (*c* 1.02, $CHCl_3$)} from the second and the fourth fractions. The CD spectra of diethers **4a** are mirror images, showing that they are enantiomers (Figure 1).

In conclusion, we have shown here a facile route for the synthesis of proximal *syn*- and *anti*-*O*,*O*′-dialkylated calix[4]arenes. The optical resolution of *anti*-dibenzyl ether **4a** provided the first isolation of inherently chiral calix[4]arenes having only two *O*,*O*′-substituents of the same kind.

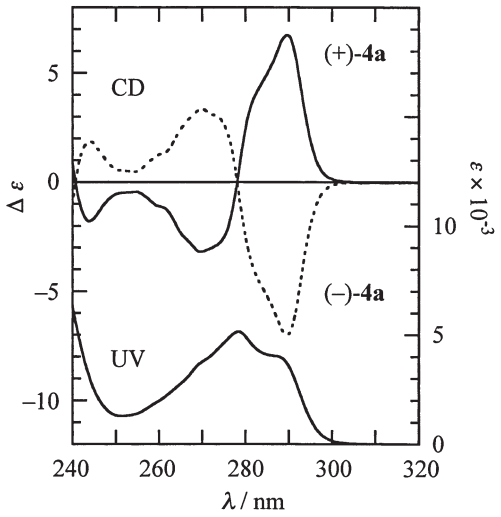


Figure 1. CD and UV spectra of *anti* diethers (+)- and (−)-**4a** in ethanol at 25 °C. Concn.: (+)-**4a**, 2.44 mM; (−)-**4a**, 2.45 mM.

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7 The alkoxide showed an exclusive *syn*-selectivity in dialkylation of **1** in THF, giving **3a**–**c** in 90, 67 and 52% yields, respectively.

8 **4a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (36 H, s, Bu^t × 4), 3.68 (2 H, s, CH_2), 3.81 (2 H, d, J = 15.4 Hz, CH × 2), 3.85 (2 H, d, J = 15.4 Hz, CH × 2), 4.07 (2 H, s, CH_2), 4.40 (2 H, d, J = 11.6 Hz, PhC*H* × 2), 4.71 (2 H, d, J = 11.6 Hz, PhC*H* × 2), 6.22 (4 H, d, J = 7.6 Hz, ArH), 6.78 (4 H, t, J = 7.6 Hz, ArH), 6.84 (2 H, d, J = 2.4 Hz, ArH), 6.87 (2 H, d, J = 2.3 Hz, ArH), 6.94 (2 H, t, J = 7.6 Hz, ArH), 6.94 (2 H, d, J = 2.3 Hz, ArH), 7.13 (2 H, d, J = 2.4 Hz, ArH), 8.29 (2 H, s, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.2, 31.3, 32.4, 33.6, 33.9, 35.9, 39.5, 72.1, 124.4, 125.1, 125.3, 125.6, 126.2, 126.6, 127.3, 127.8, 128.5, 132.1, 133.7, 136.3, 142.7, 147.1, 149.1, 151.5.

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