Pergamon

Tetrahedron Letters 39 (1998) 6057–6060

TETRAHEDRON LETTERS

Inherently Chiral Calix[4]arenes with Asymmetrical Superposition of Substituents at the Lower and the Upper Rims of Macrocycle†

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Received 9 April 1998; revised 10 June 1998; accepted 15 June 1998

Abstract: Three types of inherently chiral calix[4]arenes ($_{AAHH}^{BHBH}$, $_{AHHH}^{HBBH}$, $_{AAHH}^{HHBH}$) with asymmetrical superposition of ethyl, diethoxyphosphoryl groups at the lower rim of the macrocycle and bromine atoms at the upper rim, have been synthesized. The key steps of the synthesis are O,O'-phosphorotropic rearrangements of 1,3-distally disubstituted calix[4]arenes into 1,2-proximal isomers, regioselective bromination of the upper rim and hydrolytic removing of phosphoryl or benzoyl group from the lower rim.

Inherently chiral calixarenes[1] have attracted attention as host-molecules capable of enantioselective recognition.[2] Compounds of this type have been mainly obtained by asymmetric placement of substituents on the phenolic oxygen atoms (lower rim).[3] The upper rim (*para*- and *meta*-positions of benzene rings) have been less used for this purpose.[4]

In 1990 V. Böhmer *et al.*[5] proposed a synthesis of calix[4]arenes with chirality brought about by asymmetrical superposition of substituents at the lower and the upper rims of macrocycle ($_{AHAH}^{BBCC}$ type). **BBCC** substitution type at the upper rim was reached by step-by-step condensation of 4-phenylphenol or p-cresol with 4-tert-butylphenol into corresponding calix[4]arene tetrols. 1,3-Dialkylation of the tetrols then led to the lower rim **AHAH** substitution type. Up to now this is the only article describing calixarenes with chirality caused by lower/upper rim substituent superposition.

In this communication we report the synthesis of inherently chiral calix[4]arenes with three new asymmetrical combinations of substituents at the lower and the upper rims: $_{AAHH}^{BHBH}$, $_{AHHH}^{HBBH}$, $_{AAHH}^{HHBH}$.

This synthesis is based on recently developed O,O'-phosphorotropic rearrangement of 1,3-distally disubstituted calix[4]arenes into 1,2-proximal isomers,[3e] regioselective bromination[6] of the upper rim and hydrolytic removal of phosphoryl (benzoyl) groups from the lower rim.

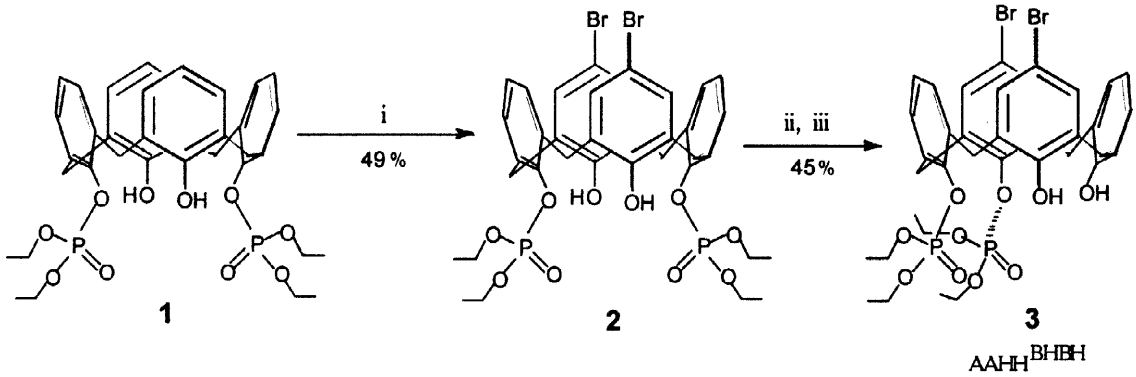
Calix[4]arene **3** of $_{AAHH}^{BHBH}$ type with two diethoxyphosphoryl groups at the proximal positions of the lower rim (**AAHH**) and two bromine atoms at the distal positions of the upper rim (**BHBH**), has been

† Dedicated to the memory of Academician of National Academy of Sciences of Ukraine, Prof. Dr. Leonid N. Markovsky

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01246-5

obtained in two steps from commercially available 1,3-diphosphoryloxycalix[4]arene **1**[7] in a *cone* conformation (Scheme 1). The first step is the bromination of *para*-positions of phenolic moieties. The second one is the migration of the phosphoryl group of dibromide **2** from the distal position to the proximal one under reaction with sodium hydride.

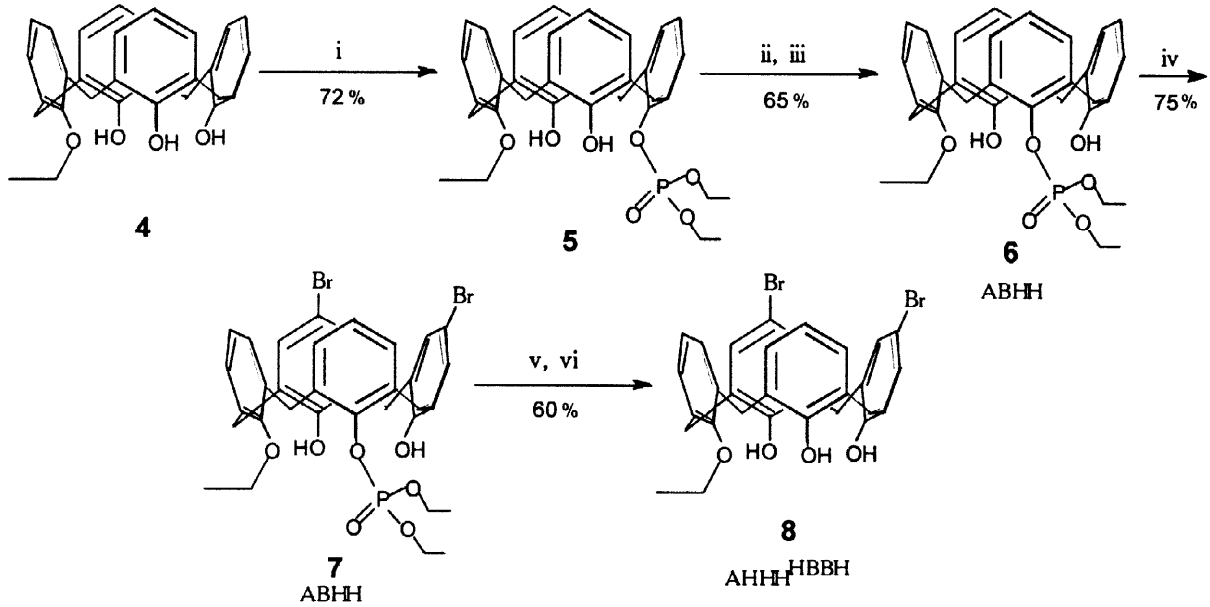
Scheme 1.



i Br_2, 2.2 eq. $CHCl_3$, 0 °C, 2 h; ii NaH, 1.2 eq., THF, 64 °C, 10 minutes; iii 10% HCl, 40 eq., $CHCl_3$, 20 °C.

Calix[4]arene **8** with $_{AHHH}^{HBBH}$ substitution type was synthesized as outlined on the Scheme 2. Firstly, phosphate **5** with distal position of substituents was obtained by phosphorylation of monoethylcalix[4]arene **4**[8] with diethylchlorophosphate in the presence of triethylamine. Then, phosphate **6** (**ABHH**) with proximal position of unsubstituted phenolic moieties, was obtained by O,O'-phosphorotropic migration of the phosphoryl group in **5**. The following bromination of the phenolic rings in **6** and hydrolytic cleavage of the diethoxyphosphoryl group in dibromo derivative **7**, led to monoethylcalix[4]arene **8**.

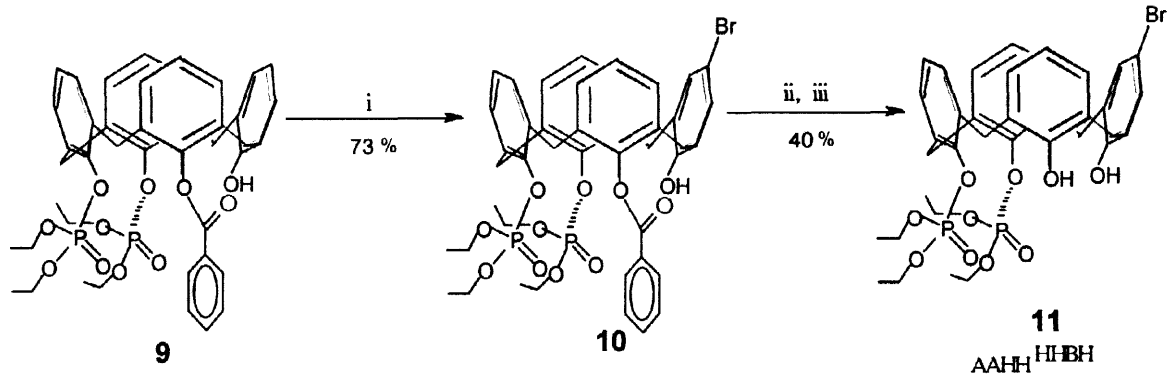
Scheme 2.



i $(EtO)_2P(O)Cl$ 1.23 eq., Et_3N 1.23 eq., $CHCl_3$, 60 °C, 6 h; ii n-BuLi (hexane solution, 1.3 M), 1.2 eq., THF, 20 °C, 72 h; iii 10% HCl, 5 eq., $CHCl_3$, 20 °C; iv NBS, 2.1 eq., acetone, 20 °C, 12 h; v LiOH, 8 eq., THF/H_2O, reflux, 12 h; vi 10% HCl, 16 eq., $CHCl_3$, 20 °C.

Calix[4]arene 11 of $_{AAHH}^{HHBH}$ type was readily obtained by bromination of the *para*-position of the phenolic moiety of 1,2-diphosphoryl-3-benzoylcalix[4]arene **9**[3e] and successive hydrolytic cleavage of benzoyl group in monobromo calixarene **10** (Scheme 3).

Scheme 3.



i Br_2, 1.1 eq. $CHCl_3$, 0 °C, 2 h; ii K_2CO_3, 2 eq., CH_3OH/H_2O, reflux, 2h; iii 10% HCl, 10 eq., CH_2Cl_2, 20 °C.

Four pairs of doublets of AX systems of methylene bridge protons Ar_2CH_2 in ^1H NMR spectra of **3, 6-8, 10, 11**[9] confirm C_1 symmetry of these compounds. The racemic nature of final products **3, 8, 11** is proved by doubling of signals of hydrogen and phosphorus atoms in ^1H, $^{31}P\{^1H\}$ NMR spectra ($CDCl_3$) after addition of chiral solvating Pirkle's reagent (S(+)-2,2,2-trifluoro-1-(9'-anthryl)-ethanol).

The differences of chemical shifts[2b] in each pair of doublets of AX systems of methylene bridge protons Ar_2CH_2 in ^1H NMR spectra correlated by COSY ^1H-^1H NMR, are within $\Delta\delta$ 0.80-1.50 ppm and shifts of carbon atom signals of these groups in $^{13}C\{^1H\}$ NMR spectra[9] are in a range of 30.95-32.19 ppm[10] that point out the *cone* conformation of the compounds obtained.

Acknowledgment. The authors are grateful to the Ukrainian Ministry of Science and Technologies (project 3.4/340) for financial support of this work.

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9. All compounds obtained have satisfactory elemental analyses. NMR determinations were carried out on a Varian XL-300 instrument ($CDCl_3$, 25 ^{0}C). Selected analytical data of new compounds are:

2: m. p. 250-251 ^{0}C (ethanol). ^{1}H NMR δ 1.36 (t, J = 6.3 Hz, $CH_2C\underline{H}_3$, 12H), 3.43, 4.40 (AXq, J = 14.4 Hz, $Ar_2C\underline{H}_2$, 8H), 4.24 (m, $C\underline{H}_2CH_3$, 8H), 5.33 (s, OH, 2H), 6.80 (m, C_6H_3, 6H), 7.29 (s, C_6H_2, 4H).

3: m. p. 90-92 ^{0}C (heptane). ^{1}H NMR δ 1.32, 1.34, 1.37, 1.39 (td, J = 7.2, 1.2 Hz, $CH_2C\underline{H}_3$, 3H each), 3.36, 4.20 (AXq, J = 12.9 Hz, $Ar_2C\underline{H}_2$, 2H), 3.40, 4.54 (AXq, J = 14.4 Hz, $Ar_2C\underline{H}_2$, 2H), 3.40, 4.57 (AXq, J = 14.1 Hz, $Ar_2C\underline{H}_2$, 2H), 3.40, 4.90 (AXq, J = 13.8 Hz, $Ar_2C\underline{H}_2$, 2H), 4.30 (m, $C\underline{H}_2CH_3$, 8H), 6.68 (t, J = 7.5 Hz, C_6H_3, 1H), 6.91 (ABXdd, J = 7.2, 0.9 Hz, C_6H_3, 3H), 6.95 (d, J = 7.8 Hz, C_6H_3, 2H,), 7.06, 7.10 (ABq, J = 2.1 Hz, C_6H_2, 2H), 7.06, 7.08 (ABq, J = 2.0 Hz, C_6H_2, 2H), 7.40 (br s, OH, 2H). ^{13}C{^{1}H} NMR δ 30.95, 31.14, 32.05, 32.08 (four s, $Ar_2\underline{C}H_2$).

5: m. p. 173-174 ^{0}C ($CHCl_3/CH_3OH$). ^{1}H NMR δ 1.39 (t, J = 7.2 Hz, $CH_2C\underline{H}_3$, 6H), 1.63 (t, J = 7.0 Hz, $ArOCH_2C\underline{H}_3$, 3H), 3.41, 4.12 (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 4H), 3.50, 4.58 (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 4H), 4.20 (q, $J_{HH} = J_{PH}$ = 7.0 Hz, $\underline{C}H_2OP$, 4H), 4.32 (q, J = 7.0 Hz, $ArOC\underline{H}_2$ 2H), 6.60-7.20 (m, Ar-H, 12 H).

6: m. p. 203-204 ^{0}C (methanol). ^{1}H NMR δ 1.25, 1.36 (td, J = 7.2, 1.2 Hz, $CH_2C\underline{H}_3$, 3H each), 1.77 (t, J = 7.0 Hz, $ArOCH_2C\underline{H}_3$, 3H), 3.30, 4.65, (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 2H), 3.30, 4.18, (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 2H), 3.47, 3.98, (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 2H), 3.47, 4.75 (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 2H), 4.24, 4.42 (q, $J_{HH} = J_{PH}$ = 7.0 Hz, $C\underline{H}_2OP$, 2H each), 4.43 (q, J = 7.0 Hz, $ArOC\underline{H}_2$ 2H), 6.63, 6.68 (t, J = 7.8 Hz, C_6H_3, 1H each), 6.74 (t, J = 6.9 Hz, C_6H_3, 1H), 6.80-7.20 (m, C_6H_3, 9 H), 8.89, 10.08 (s, OH, 1H each).

7: m. p. 222-223 ^{0}C (methanol). ^{1}H NMR δ 1.25, 1.36 (td, J = 7.2, 1.2 Hz, $CH_2C\underline{H}_3$, 3H each), 1.75 (t, J = 7.0 Hz, $ArOCH_2C\underline{H}_3$, 3H), 3.27, 4.18, (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 2H), 3.30, 4.18, (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 2H), 3.41, 4.65, (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 2H), 3.47, 3.98, (AXq, J = 13.0 Hz, $Ar_2C\underline{H}_2$, 2H), 4.24, 4.42 (q, $J_{HH} = J_{PH}$ = 7.0 Hz, $\underline{C}H_2OP$, 2H each), 4.43 (q, J = 7.0 Hz, $ArOC\underline{H}_2$ 2H), 6.80 (t, J = 8.4 Hz, C_6H_3, 1H), 6.90-7.15 (m, C_6H_3, 7 H), 7.05, 7.20 (ABq, J = 1.8 Hz, C_6H_2, 2H), 8.89, 9.88 (s, OH, 1H, each).

8: m. p. >250 ^{0}C (dec.). ^{1}H NMR δ 1.76 (t, J = 6.9 Hz, $CH_2C\underline{H}_3$, 3H), 3.35, 4.21, (AXq, J = 14.4 Hz, $Ar_2C\underline{H}_2$, 2H), 3.39, 4.41, (AXq, J = 12.8 Hz, $Ar_2C\underline{H}_2$, 2H), 3.43, 4.21, (AXq, J = 14.0 Hz, $Ar_2C\underline{H}_2$, 2H), 3.52, 4.25, (AXq, J = 13.2 Hz, $Ar_2C\underline{H}_2$, 2H), 4.30 (m, $C\underline{H}_2CH_3$, 2H), 6.73 (t, J = 7.5 Hz, C_6H_3, 1H), 6.93 (t, J = 7.2 Hz, C_6H_3, 1H), 7.03 (d, J = 7.2 Hz, C_6H_3, 1H), 7.00-7.14 (m, Ar-H, 5H), 7.10, 7.19 (ABq, J = 2.0 Hz, C_6H_2, 2H), 9.21, 9.57, 9.78 (s, OH, 1H, each). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 31.59, 31.70, 31.83, 31.88 (four s, $Ar_2\underline{C}H_2$).

10: m. p. 220-221 ^{0}C (ethanol). ^{1}H NMR δ 0.94, 1.29, 1.34, 1.40 (td, J = 6.9, 1.0 Hz, $CH_2C\underline{H}_3$, 3H each), 3.30, 4.57 (AXq, J = 14.1 Hz, $Ar_2C\underline{H}_2$, 2H), 3.30, 4.06 (AXq, J = 14.7 Hz, $Ar_2C\underline{H}_2$, 2H), 3.36, 5.01 (AXq, J = 14.4 Hz, $Ar_2C\underline{H}_2$, 2H), 3.39, 4.35 (AXq, J = 13.8 Hz, $Ar_2C\underline{H}_2$, 2H), 3.90 (m, $C\underline{H}_2CH_3$, 2H), 4.22 (m, $C\underline{H}_2CH_3$, 4H), 4.43 (m, $C\underline{H}_2CH_3$, 2H), 6.04 (s, OH, 1H), 6.22, 6.30, 6.34, 6.44 (d, J = 7.5 Hz, C_6H_3, 1H each), 6.44, 6.57, 6.94 (t, J = 7.5 Hz, C_6H_3, 1H each), 7.22 (d, J = 7.5 Hz, C_6H_3, 2H), 7.24, 7.29 (ABq, J = 2.0 Hz, C_6H_2, 2H), 7.52 (t, J = 7.5 Hz, C_6H_5, 2H), 7.66 (t, J = 7.5 Hz, C_6H_5, 1H), 8.50 (d, J = 7.2 Hz, C_6H_5, 2H).

11: m. p. 70-72 ^{0}C (heptane). ^{1}H NMR δ 1.35 (m, $CH_2C\underline{H}_3$, 12 H), 3.35, 4.60 (AXq, J = 13.8 Hz, $Ar_2C\underline{H}_2$, 2H), 3.35, 4.19 (AXq, J = 14.1 Hz, $Ar_2C\underline{H}_2$, 2H), 3.44, 4.94 (AXq, J = 13.5 Hz, $Ar_2C\underline{H}_2$, 2H), 3.48, 4.55 (AXq, J = 14.7 Hz, $Ar_2C\underline{H}_2$, 2H), 4.20-4.30 (m, $C\underline{H}_2CH_3$, 8H), 6.67 (t, J = 6.9 Hz, C_6H_3, 1H), 6.75-7.00 (m, C_6H_3, 8H), 7.02, 7.05 (ABq, J = 2.1 Hz, C_6H_2, 2H), 7.24, 7.47 (br s, OH, 1H, each). ^{13}C{^{1}H} NMR δ 31.05, 31.13, 32.11, 32.19 (four s, $Ar_2\underline{C}H_2$).

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