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A New Class of Chiral Calix[4]arenes as Receptors with Planar Chirality

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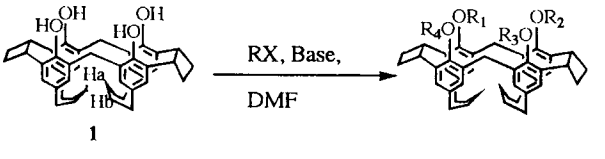
Abstract: The modification of title compounds to chiral receptors and their characterization are reported. The two synthetic methods were developed. The racemates obtained could be resolved to each stable enantiomer by a chiral HPLC column. Chiral calixarenes were designed as the receptors with planar chirality. The (-)-receptor strongly forms 1:1 complex with (*R*)-(+)-α-phenylethylammonium picrate. © 1997 Elsevier Science Ltd.

The chiral recognition is one of the most important and fascinating area in host-guest chemistry.[1] Chiral *centers*[2] of natural products and *axes*[3] of biaryl units have been used to construct semi-artificial and artificial receptors. *Planar* chiralities are also employed to design receptors, although there are only a few examples.[4] Generally speaking, the last kind of receptors with planar chirality are accompanying with the synthetic difficulties.[5] In order to add another example to the receptors, we were prompted to design and synthesize a new chiral receptor by using a calixarene-type structure. As well known, calix[n]arenes (n=4-8) have been developed to make the receptors for organic and inorganic guests in biomimetic chemistry,[6] although their conformational unstability prevents them from exhibiting any chiral recognition until now.[7] Recently, we developed bridged calix[4]arene analog **1**,[8] which has C_{2v} symmetry in a rigid structure. It can easily be converted to chiral calixarene skeletons by the introduction of one to three substituents on its four hydroxy groups. Moreover, its further functionalization on the remaining hydroxy groups is expected to afford chiral receptors, ionophores, organic catalysts, and so forth. As the first achievement along the research project, we report here the simple transformation of calixarene **1** to chiral receptors and their ability of chiral recognition.

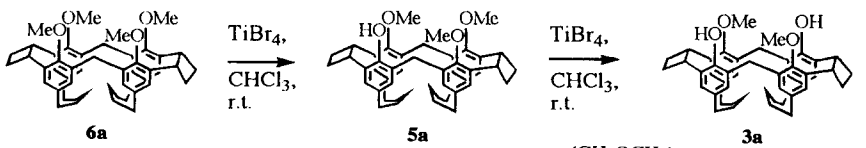
Calix[4]arene **1** has three bridges connecting its benzene rings and can never take any ring inversion even when it is dissolved in polar media.[8b,d] Hence, **1** can be said to hold the rigid structure perfectly. On the modification, we took two synthetic strategies as shown in Equations (1) and (2); *i.e.*, one is the direct method in a simple manner to ethers by the reaction with **1**, alkyl halides, and bases (Eq. (1)), whose results are summarized in Table 1. The other is the stepwise one which includes the regioselective cleavage of tetramethyl ether **6a** derived from **1** (Eq. (2)).



1

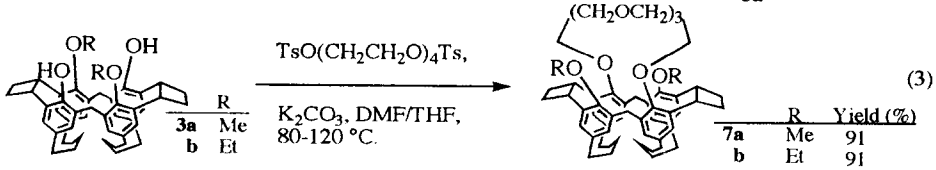
	R_1	R_2	R_3	R_4
2a	Me	H	H	H
b	Et	H	H	H
3a	Me	H	Me	H
b	Et	H	Et	H
4a	Me	H	H	Me
b	Et	H	H	Et
5a	Me	Me	Me	H
b	Et	Et	Et	H
6a	Me	Me	Me	Me
b	Et	Et	Et	Et

(1)



6a **5a** **3a**

(2)



	R
3a	Me
b	Et

	R	Yield (%)
7a	Me	91
b	Et	91

(3)

Table I Product Distribution of Williamson Ether Synthesis

Entry	R-X	equiv.	Base	equiv.	Temp. (℃)	Time (h)	Yield (%) 1	2	3	4	5	6
1	MeI	5	Li_2CO_3	5	0	12	56	28	2	2	--	--
2	MeI	5	Na_2CO_3	5	0	12	--	--	34	38	--	--
3	MeI	5	K_2CO_3	5	0	12	--	--	42	45	--	--
4	MeI	20	K_2CO_3	5	25	12	--	--	25	30	22	22
5	MeI	20	NaH	2	40	12	--	--	--	--	--	96
6	EtBr	2	Na_2CO_3	5	0	12	26	43	14	12	--	--
7	EtBr	1	K_2CO_3	5	0	12	41	--	20	16	8	--
8	EtBr	2	K_2CO_3	5	0	12	--	--	42	23	10	--
9	EtBr	20	K_2CO_3	5	0	12	--	--	12	28	35	13
10	EtBr	5	K_2CO_3	5	45	12	--	--	--	--	--	84

The typical direct method was performed with **1**, alkyl halide (1-20 equiv.), base (2-5 equiv.) in DMF at 0-45 ℃ for 12 h under a nitrogen atmosphere (see Table I). After an acidic extraction, pure compounds **2-6** were obtained by column chromatography (silica gel, benzene/ethyl acetate=1/1 as an eluent). When a strong base and severe conditions were applied (entry 5 and 10), tetra-substituted products **6** were obtained exclusively and in high yields. By using weak bases and mild conditions, the reactions proceeded stepwise and gave the partially substituted ethers in moderate yields. Chiral calixarenes, monoalkyl ethers **2** and trialkyl ones **5**, with C_1 symmetry were produced in 8-43% yields. And also, planar dissymmetric calixarenes **3** were produced in 2-42% yields.

The high regioselectivity was accomplished by the stepwise method with tetramethyl ether **6a** and $TiBr_4$ as a mild Lewis acid (Eq. (2)).[9] By the ether cleavage with $TiBr_4$ (4 equiv.) in $CHCl_3$ at room temperature, **6a** exclusively gave trimethyl ether **5a** as a chiral product with C_1 symmetry in 98% yield. It is of much interest that the reaction only gave dimethyl ether **3a** with C_2 symmetry and chiral plane in 41% yield at the disappearance of **5a**. Note that the stepwise method sufficiently gave the desired partially alkylated chiral isomer regioselectivity. Unfortunately, this method is useful only for tetramethyl ether **6a**.

Structural determination was mainly carried out from the spectral patterns and chemical shift change of isomers by ^1H NMR spectroscopy.[12] The aromatic protons of **1** and **6a** appear as two sets of fine doublets around δ 7.[8b,c] By introducing one or three methyl groups, the aromatic protons of **2a** and **5a** split into eight sets of doublet. And also, those of **3a** having two methyl groups split into four sets of doublet. These results show that the electronic environment around aromatic ring protons is largely affected by the methyl group substitution or the product symmetry. The methine protons of cyclobutane rings for **3a** split into two parts in the ratio of 1:1, appearing at δ 4.3 to 4.7. Interestingly, those of **2a** and **5a** split into four parts in the ratio of 1:1:1:1, appearing at δ 4.2 to 4.6. The inner protons Ha (see structure **1**) of pentamethylene bridges for **2a** and **5a** appear as two multiplets at δ -0.3 to -0.1 due to the environmental difference between two metacyclophane units. On the other hand, the outer protons Hb of the bridges for all isomers only show one multiplet peak at δ 0.5 to 0.8 because of the small environmental difference. The methoxy protons of **6a** shift to the up-field (δ 3.49) compared with those of anisol derivatives, whose origins were the remarkable repulsion between methoxy groups.[10] In fact, MM2 calculations show that the steric energy notably increases from 63.8 kcal/mol for parent arene **1** to 91.4 kcal/mol for tetramethyl ether **6a**. When the number of methoxy groups decreases from three for **5a** to one for **2a**, their chemical shift gradually approaches that of anisol (δ 3.80) because of the increase of freedom. The methylene bridge protons of **6a** and **3a** connecting two metacyclophane units, which have C_2 symmetry, appear as two doublets (AB type) at δ 2.98 and 4.25 (J=13 Hz) and δ 3.21 and 3.69 (J=13 Hz), respectively. This result shows that two CH_2 groups have the same environment of the cone conformation.

On the other hand, those of **2a** and **5a** splits four doublets, indicating C_1 chiral structures. The chemical shift difference ($\Delta\delta$) between their *quasi*-axial and equatorial protons is large 1.27 ppm for **6a** and small 0.69 ppm for **1**, while the number of methyl groups decreases. This behavior shows that the rigidity around methylene bridges is released during the removal of the methoxy groups. The hydroxy groups for each isomer show the down-field shift to δ 6.73 – 7.91 compared with those of phenol derivatives around δ 5,[8g] due to the different strength of hydrogen bonding. This result shows that the interaction between one or two hydroxy and methoxy groups has an original direction to make hydrogen bonding concerning with the steric hindrance or molecular dimension.[11] Judging from the chemical shifts of hydroxy groups for **1** and **3a**, the hydrogen bonding mode is almost same.[8b] On the other hand, the hydrogen bonding of **5a** is considered to be weak, judging from its chemical shift at δ 6.73. Interestingly, three hydroxy groups of **2a** appear at three different positions (δ 5.51, 7.16, and 7.91), reflecting its C_1 symmetry.

The racemates obtained could be resolved to each stable enantiomer by a chiral HPLC column (Chiralpak AD, Daicel Chemical Industries, Ltd; 25 x 2 cm, hexane/isopropanol=8/2 as a mobile phase). After the optical resolution, the optical purity (~100% *ee*) was checked by the same HPLC column (see Figure 1). The specific rotations ($[\alpha]_D$) of enantiomers obtained are in a range of ±7.65° to 41.1° in CH_2Cl_2. Based on the structure of **3** having C_2 symmetry, we designed receptors **7** with planar chirality. The receptors possessing tetraethylene glycol units as a binding site were prepared as follows; racemates **3** were allowed to react with K_2CO_3 and tetraethylene glycol ditosylate at 80-120 ℃ for 3 days in DMF/THF (9/1) as shown in Eq. (3). After an acidic extraction, pure receptors **7** were obtained in 91% yield, respectively, by column chromatography (silica gel, ethyl acetate as an eluent).

The typical features of ^{1}H NMR spectra of methylated derivative **7a**[12] were summarized as follows; the chemical shift of methoxy group is shifted to up-field about 0.11 ppm, compared with that of **3a** owing to the further repulsion between the groups by the bulkiness of polyether bridge.[8c] And also, by the same reason, the AB pattern of methylene bridge protons is widely spread from δ 3.21 and 3.69 for **3a** to δ 2.99 and 4.28 for receptor **7a**.

The optical resolution of receptors **7** was performed by the chiral HPLC column. The $[\alpha]_D$ values of **7a** and **b** are ±3.0° and 1.9°, respectively. These values are small compared with partially alkylated calixarenes **2**, **3**, and **5**, reflecting the structural similarity to achiral symmetrical tetraalkyl ethers **6**. The ability of chiral recognition for enantiomeric receptors **7** was evaluated by the interaction with chiral amines. First, the stoichiometry of interaction between receptor **7a** and phenethylamine was judged from Job's plots. When the mole fraction of receptor (-)-**7a** was 0.5, the complex concentration reached to maximum. This result obviously shows that receptor (-)-**7a** strongly forms 1:1 complex with (*R*)-(+)-α-phenylethylammonium picrate.

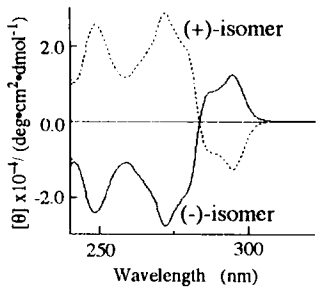


Figure 1 Circular dichroism spectra of **3a** in 1,4-dioxane at 25 °C.

Table II Extraction (%) of ammonium picrates by receptors[a]

receptor	α-phenylethylamine	
	(*R*)-(+)	(*S*)-(-)
(+)-**7a**	66.1	72.2
(-)-**7a**	72.0	67.6
(+)-**7b**	57.4	61.9
(-)-**7b**	61.5	58.7

a) Extraction conditions: 5.0 x 10^{-4} M of receptor in CH_2Cl_2; 5.0 x 10^{-6} M of ammonium picrate in H_2O. Receptor solution (5.0 ml) was shaken for 10 min with picrate solution (5.0 ml) and % extraction was measured by the absorbance of picrate in CH_2Cl_2. Experimental error was ± 2%.

Based on this result, the chiral recognition was estimated by the extraction with the same chiral ammonium picrate. The results are listed in Table II. The order of extraction, therefore chiral recognition, is **7a > 7b**. These results suggest that ethyl group is too large to bind an ammonium ion. Note that the (-)-receptor prefers (*R*)-guest to (*S*)-one to assemble the host-guest comlex with the opposite specific rotation in chiral selectivity. Hence, the methylated host **7a** is more suitable organic receptor than the ethylated one **7b**.

In conclusion, we successfully synthesized the unique chiral calixarenes by two methods. All racemates obtained could be resolved to each enantiomer by the chiral HPLC column. The chiral calixarenes recognized the chirality of α-phenylethylamine. Further investigation including X-ray crystallographic analysis is now in progress and will be reported elsewhere.

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References and Note

(1) Vögtle, F. *Supramolecular Chemistry*; John Wiley & Sons: New York, 1993.
(2) White, B. D.; Mallen, J.; Arnold. K. A.; Fronczek, F. R.; Gandour, R. D.; Gehrig, L. M. B.; Gokel, G. W. *J. Org. Chem.* **1989**, *54*, 937.
(3) Sousa, L. R.; Hoffman, D. H.; Kaplan, L.; Cram, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 7100.
(4) Harada, N.; Soutome, T.; Nehira, T; Uda, H.; Ui, S.; Okamura, A.; Miyano, S. *J. Am. Chem. Soc.* **1993**, *115*, 7547.
(5) Rozenberg, V.; Kharitonov, V.; Antonov, D.; Sergeeva, E.; Aleshkin, A.; Ikonnikov, N.; Orlova, S.; Belokon, Y. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 91.
(6) *Calixarenes 50th Anniversary*; Vicens, J.; Asfari, Z.; Harrowfield, J. M., Eds.; Kluwer: Dordrecht, 1994.
(7) Shinkai, S.; Arimura, T.; Kawabata, H.; Murakami, H.; Araki, K.; Iwamoto, K.; Matsuda, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1734; Okada, Y.; Kasai, Y.; Nishimura, J. *Tetrahedron Lett.* **1995**, *36*, 555.
(8) (a) Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Chem. Lett.* **1992**, 755; (b) Okada, Y.; Mabuchi, S.; Kurahayashi, M.; Nishimura, J. *Chem. Lett.* **1991**, 1345; (c) Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Tetrahedron Lett.* **1993**, *34*, 1971; (d) Okada, Y.; Kasai, Y.; Ishii, F.; Nishimura, J. *J. Chem. Soc., Chem. Commun.* **1993**, 976; (e) Okada, Y.; Sugitani Y.; Kasai, Y.; Nishimura, J. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 586; (f) Okada, Y.; Kasai, Y.; Nishimura, J. *Synlett* **1995**, 85; (g) Okada, Y.; Ishii, F.; Kasai, Y.; Nishimura, J. *Tetrahedron* **1994**, *50*, 12159;
(9) Arduini, A.; Casnati, A.; Dodi, L.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1597.
(10) Okada, Y.; Sugiyama, K.; Wada, Y.; Nishimura, J. *Tetrahedron Lett.* **1990**, *31*, 107.
(11) Groenen, L. C.; Steinwender, E.; Lutz, B. T. G.; van der Maas, J. H.; Reinhoudt, D. N. *J. Chem. Soc., Perkin Trans.2* **1992**, 1893.
(12) ^{1}H NMR (500 MHz) in $CDCl_3$, δ (intensity, multiplicity, *J* in Hz); **2a**, -0.32 (1H, m), -0.19 (1H, m), 0.58 (2H, m), 1.31 (4H, m), 1.68 (4H, m), 2.13 (1H, m), 2.20 - 2.60 (10H, m), 2.61 - 2.84 (5H, m), 3.14 (1H, d, 14), 3.22 (1H, d, 14), 3.64 (1H, d, 14), 3.81 (1H, d, 14), 3.82 (3H, s), 4.25 (1H, m), 4.40 (1H, m), 4.56 (1H, q-like), 4.58 (1H, m), 5.51 (1H, s), 6.59 (1H, d, 2.0), 6.66 (1H, d, 2.0), 6.67 (1H, d, 2.0), 6.70 (1H, d, 2.0), 6.94 (2H, d, 2.0), 6.98 (1H, d, 2.0), 7.15 (1H, d, 2.0), 7.16 (1H, s), 7.91 (1H, s); **2b**, -0.32 (1H, m), -0.17 (1H, m), 0.57 (2H, m), 1.30 (6H, m), 1.56 (3H, t, 7.0), 1.60 - 1.84 (4H, m), 2.09 (1H, m), 2.22 - 2.59 (8H, m), 2.70 (4H, m), 2.80 (1H, m), 3.14 (1H, d, 14), 3.21 (1H, d, 14), 3.64 (1H, d, 14), 3.82 (1H, d, 14), 3.88 (2H, q, 7.0), 4.26 (1H, m), 4.36 (1H, m), 4.55 (1H, q-like), 4.60 (1H, m), 5.61 (1H, s), 6.59 (1H, d, 1.8), 6.66 (1H, d, 1.8), 6.68 (1H, d, 1.8), 6.69 (1H, d, 1.8), 6.94 (2H, d, 1.8), 6.98 (1H, d, 1.8), 7.15 (1H, d, 1.8), 7.22 (1H, s), 7.95 (1H, s); **3a**, -0.20 (2H, m), 0.57 (2H, m), 1.26 (2H, m), 1.38 (2H, m), 1.72 (4H, m), 2.04 (2H, m), 2.32 (4H, m), 2.40 (2H, m), 2.69 (6H, m), 2.76 (2H, m), 3.21 (2H, d, 13), 3.69 (2H, d, 13), 3.78 (6H, s), 4.38 (2H, m), 4.61 (2H, q-like), 6.62 (2H, d, 2.1), 6.67 (2H, d, 2.1), 6.98 (2H, d, 2.1), 7.14 (2H, d, 2.1), 7.79 (2H, s); **3b**, -0.18 (2H, m), 0.53 (2H, m), 1.25 (2H, m), 1.38 (2H, m), 1.55 (6H, t, 7.0), 1.72 (4H, m), 1.98 (2H, m), 2.30 (4H, m), 2.40 (2H, m), 2.68 (6H, m), 2.81 (2H, m), 3.20 (2H, d, 13), 3.70 (2H, d, 13), 3.83 (2H, q, 7.0), 3.86 (2H, q, 7.0), 4.36 (2H, m), 4.60 (2H, q-like), 6.63 (2H, d, 1.8), 6.66 (2H, d, 1.8), 6.98 (2H, d, 1.8), 7.14 (2H, d, 1.8), 7.73 (2H, s); **5a**, -0.14 (2H, m), 0.64 (2H, m), 1.24 (2H, m), 1.43 (2H, m), 1.78 (4H, m), 2.10 - 2.83 (16H, m), 3.00 (1H, d, 14), 3.21 (1H, d, 14), 3.42 (3H, s), 3.63 (1H, d, 14), 3.66 (3H, s), 3.74 (3H, s), 4.39 (1H, d, 14), 4.39 (1H, m), 4.44 (1H, m), 4.54 (1H, q-like), 4.58 (1H, q-like), 6.65 (1H, d, 1.8), 6.73 (1H, s), 6.73 (1H, d, 1.8), 6.81 (1H, d, 1.8), 6.91 (1H, d, 1.8), 7.01 (1H, d, 1.8), 7.06 (1H, d, 1.8), 7.11 (1H, d, 1.8), 7.19 (1H, d, 1.8); **5b**, -0.15 (2H, m), 0.61 (2H, m), 1.26 (2H, m), 1.46 (2H, m), 1.52 (3H, t, 7.0), 1.53 (6H, m), 1.63 - 1.89 (4H, m), 2.05 (1H, m), 2.23 (1H, m), 2.27 - 2.58 (6H, m), 2.60 - 2.80 (8H, m), 3.00 (1H, d, 13), 3.13 (1H, m), 3.22 (1H, d, 14), 3.39 (1H, m), 3.62 (1H, d, 14), 3.67 (2H, q, 7.0), 3.82 (2H, m), 4.26 (1H, m), 4.43 (1H, d, 13), 4.43 (1H, m), 4.56 (2H, m), 6.65 (1H, d, 1.8), 6.74 (1H, s), 6.75 (1H, d, 1.8), 6.85 (1H, d, 1.8), 6.93 (1H, d, 1.8), 7.00 (1H, d, 1.8), 7.07 (1H, d, 1.8), 7.14 (1H, d, 1.8), 7.20 (1H, d, 1.8); **7a**, -0.07 (2H, m), 0.72 (2H, m), 1.32 (2H, m), 1.43 (2H, m), 1.56 (2H, m), 1.78 (4H, m), 2.27 - 2.53 (8H, m), 2.59 (4H, m), 2.63 - 2.80 (4H, m), 2.99 (2H, d, 14), 3.67 (6H, s), 3.72 (2H, m), 3.80 - 3.96 (10H, m), 4.12 (2H, m), 4.28 (2H, d, 14), 4.50 (4H, m), 6.91 (2H, d, 2.0), 6.94 (2H, d, 2.0), 7.03 (2H, d, 2.0), 7.09 (2H, d, 2.0); **7b**, 0.00 (2H, m), 0.77 (2H, m), 1.41 (2H, m), 1.51 (6H, t, 7.0), 1.79 (4H, m), 2.30 (2H, m), 2.39 (2H, m), 2.49 (8H, m), 2.64 - 2.80 (4H, m), 2.98 (2H, d, 13), 3.56 - 3.80 (10H, m), 3.85 (4H, q, 7.0), 3.92 (2H, m), 4.06 - 4.22 (4H, m), 4.31 (2H, d, 13), 4.46 (4H, m), 6.89 (2H, d, 2.0), 6.95 (2H, d, 2.0), 7.03 (2H, d, 2.0), 7.08 (2H, d, 2.0).

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