Synthesis of Chiral Crown Ethers Having Bromoarylene Moieties on Their Rim. Anomalous Behavior of Racemic Substrates in Cyclization to Crown Ethers

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Bis(binaphtho)-22-crown-5 and bis(binaphtho)-22-crown-4, having bromoarylene moities on their rim, were prepared from (*R*)- and (*S*)-2,2′-dihydroxy-1,1′-binaphthyl. An acyclic diol, bridged by two (*R*)-binaphthyl moieties, underwent cyclization reaction with diethylene glycol ditosylate to afford the corresponding (*R,R*)-bis(binaphtho)-22-crown-5 in a good yield (69%). A one-pot cyclization reaction of (*R*)-2,2′-dihydroxy-1,1′-binaphthyl with 2,6-bis(bromomethyl)bromobenzene resulted in a good yield (45%) of (*R,R*)-bis(binaphtho)-22-crown-4, having two symmetrical bromoarylene units. In contrast to the cases started with (*R*)- and (*S*)-2,2′-dihydroxy-1,1′-binaphthyl, the racemate in cyclization reactions did not give the corresponding crown products in the expected proportion.

Developing new methods for designing chiral molecules has become an important aspect of efforts to create interesting host molecules for molecular recognition[1] and effective auxiliaries for asymmetric reactions.[2] Macrocyclic crown ethers, developed by Pedersen, Cram, and Lehn, represent promising prototypes for such chiral molecules.[3] In addition to the introduction of Lewis base properties induced by hetero atoms in the macrocyclic ring, the introduction of effective functional groups onto the ring might considerably enhance the capturing ability of guests such as compounds involving boron[4] and phosphorus.[5] On the basis of the original crown ether **1**,[6] chiral crown ethers **2** and **3**, containing a bromoarylene function on their rim, seem to be interesting synthetic intermediates to such effective functional crown ethers (Fig. 1). In this report, after briefly reviewing Cram's synthesis of crown ether **1**, we will focus on the synthesis of **2** and **3** from (*R*)-, (*S*)-, and (*R*),(*S*)-2,2′-dihydroxy-1,1′-binaphthyl **4** and disclose some interesting anomalous behavior of racemic substrates in cyclization to the crown ethers.

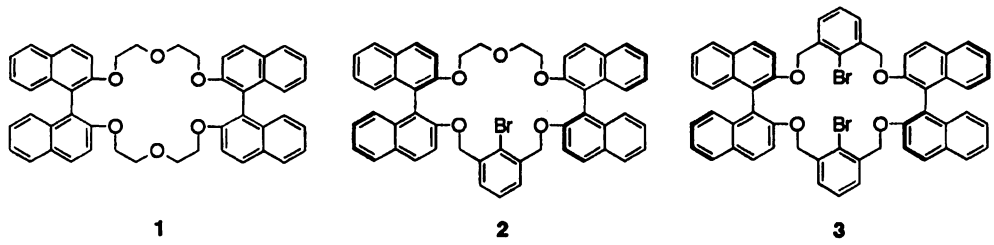
Results and Discussion

The direct synthesis of crown ether **1** from binaphthyl **4**, originally reported by Cram,[7,8] was carried out as follows: When (*S*)-binaphthyl **4** was used as the starting material, (*S,S*)-**1** (31%) and (*S*)-**5** (5%) were obtained. Our initial experiments involved a reinvestigation of the direct synthesis of **1** from **4**, which was originally described by Cram. In our case the reaction afforded compound **6** as the major product rather than the reported products (**1** and **5**) under the reaction conditions used (Scheme 1). Isolation of **6** was not previously reported for this reaction. The reaction of (*R*)-**4** with diethylene glycol ditosylate in the presence of 2 mole equivalents of *t*-BuOK in refluxing tetrahydrofuran gave (*R,R*)-**6** in 49% yield, and the yield of **6** was increased to 88% when sodium hydride was used as the base (Table 1). The enantiomer (*S,S*)-**6** was obtained from (*S*)-**4**. Racemate **4** was readily transformed to a mixture of (*R,R*)-, (*S,S*)-, and (*R,S*)-**6** in statistical proportions without any special selection.

Synthesis of Crown Ether 2. The facile and straightforward preparation of **6** encouraged us to attempt a synthesis of crown ether **2** by inserting a bromoarylene unit into **6**, since it seemed likely that condensation of **6** with 2,6-bis(bromomethyl)bromobenzene **7** would give compound **2** as the product. Bromination of 2-bromo-1,3-xylene with *N*-bromosuccinimide (NBS) in the presence of α,α'-azoisobutyronitrile (AIBN) in refluxing carbon tetrachloride afforded compound **7**. The reaction of (*R,R*)-**6** with **7** (NaH–DMF) yielded (*R,R*)-**2** but only in 30% yield (Scheme 2). In order to improve the yield of **2**, we adopted an alternative route, which involved the condensation of diol **8** with diethylene glycol ditosylate in the reverse order. Treatment of 2 mole equivalents of the mono protected (*R*)-**9** with **7** (NaH–THF) yielded

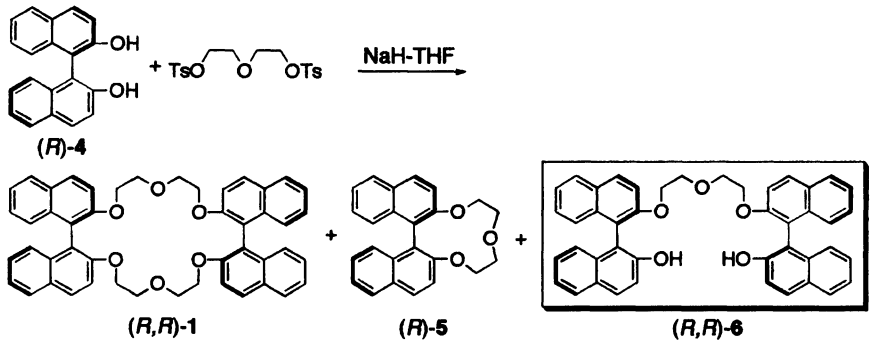
Table 1. Preparation of **6** from 2,2′-Dihydroxy-1,1′-binaphthyl (**4**) (Scheme 1)

2,2′-Dihydroxy-1,1′-binaphthyl	Base	Reaction time	% yield		
			1	**5**	**6**
(*R*)-**4**	*t*-BuOK	5 h	40	3	49
(*R*)-**4**	NaH	8 h	3	2	88
(*R*),(*S*)-**4**	NaH	9 h	11	2	76

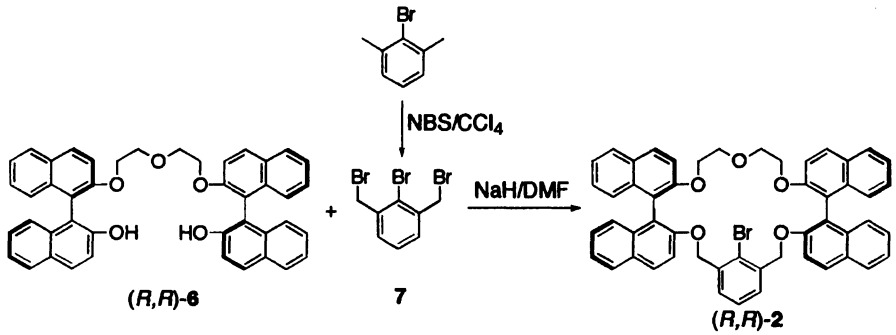


1 **2** **3**

Fig. 1. The structure of target molecules **2** and **3**.



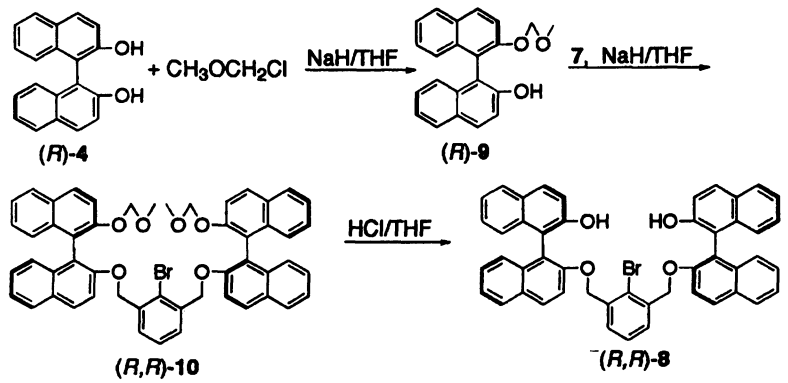
Scheme 1.



Scheme 2.

(*R*,*R*)-**10**, which, after hydrolysis, afforded (*R*,*R*)-**8** in good yield (Scheme 3). Using this procedure, the enantiomer (*S*,*S*)-**10** was obtained from (*S*)-**9** while racemate **9** resulted in a mixture of (*R*,*R*)-, (*S*,*S*)-, and (*R*,*S*)-**10**. The optical purity of each **8** was determined by HPLC using a chiral column (Daicel Chiralcel OD). Both (*R*,*R*)- and (*S*,*S*)-**8** were optically pure and a mixture of **8** from racemate **4** consisted of (*R*,*R*)-, (*S*,*S*)-, and (*R*,*S*)-**8** in the statistically expected ratio of 1 : 1 : 2.

Cyclization of **8** with diethylene glycol ditosylate by refluxing (NaH–THF) overnight gave **2** in ca. 30% yield. Changing the solvent from THF to *N*,*N*-dimethylformamide

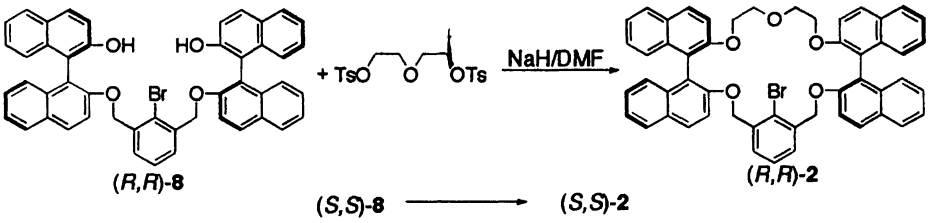


Scheme 3.

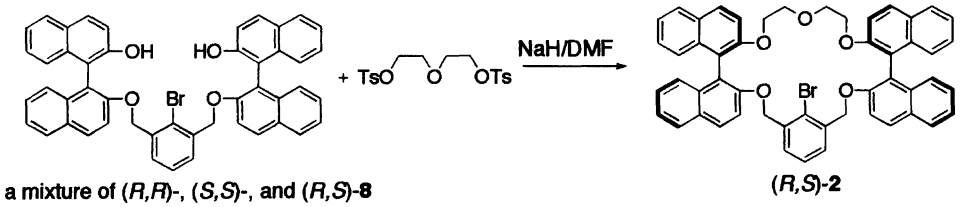
(DMF), however, significantly improved the yield; (*R*,*R*)- and (*S*,*S*)-**8** gave the corresponding (*R*,*R*)-**2** and (*S*,*S*)-**2**, in 70—80% yield, respectively (Scheme 4). For a reaction involving a mixture of **8** produced from (*R*), (*S*)-**4**, *to our great surprise*, only one cyclic product was isolated in 27% yield. This was later shown to be (*R*,*S*)-**2** (Scheme 5). To identify the isolated product, we explored another way of synthesizing the compound (*R*,*S*)-**2**. The mono-substituted (*R*)-**11** was obtained from a mixture (1 : 1) of (*R*)-**9** and **7** in 40% yield, along with the disubstituted (*R*,*R*)-**10** (31%). Condensation of (*R*)-**11** with (*S*)-**9** afforded (*R*,*S*)-**10** in 84% yield, followed by cyclization to (*R*,*S*)-**2** (Scheme 6). It is surprising that on starting with a mixture of **8**, only (*R*,*S*)-**2** was obtained without (*R*,*R*)-**2** and (*S*,*S*)-**2**. This is a very anomalous phenomenon. Why did the mixture of **8** not give the corresponding products **2** in proportion to the statistical ratio of **8**? Since the optically active **2** and the *meso* **2** can be obtained from (*R*,*R*)-**8**, (*S*,*S*)-**8**, and (*R*,*S*)-**8**, respectively, with the same level of yield, the feasibility for the ring formation should not differ so much. This suggests that the ionic species obtained from (*R*,*R*)- and (*S*,*S*)-**8**, and diethylene glycol ditosylate were more likely to be consumed than those from (*R*,*S*)-**8** while undergoing oligomerization and/or polymerization during the cyclization process, because of some advantageous mutual interaction between the ionic species from (*R*,*R*)- and (*S*,*S*)-**8**. We can understand the phenomenon as an interesting chiral recognition involving biaryl compounds, although further studies on the mechanism are now under way concerning some template effects.

Synthesis of Crown Ether 3. The synthesis of macrocyclic compound **3** having two bromoarylene units was achieved by a direct cyclization of 2,2′-dihydroxy-1,1′-binaphthyl with bromide **7** as follows. Treatment of (*R*)-2,2′-dihydroxy-1,1′-binaphthyl with **7** in DMF–NaH produced (*R*,*R*)-**3** in 45% yield (Scheme 7). The enantiomer (*S*,*S*)-**3** was obtained from (*S*)-2,2′-dihydroxy-1,1′-binaphthyl. The reaction with (*R*), (*S*)-2,2′-dihydroxy-1,1′-binaphthyl, however, resulted in no production of any cyclic dimers. This behavior of the racemate also seems to be attributed to complex and intermolecular interactions among isomeric anionic species which might be involved in stepwise processes of the dimeric cyclization.

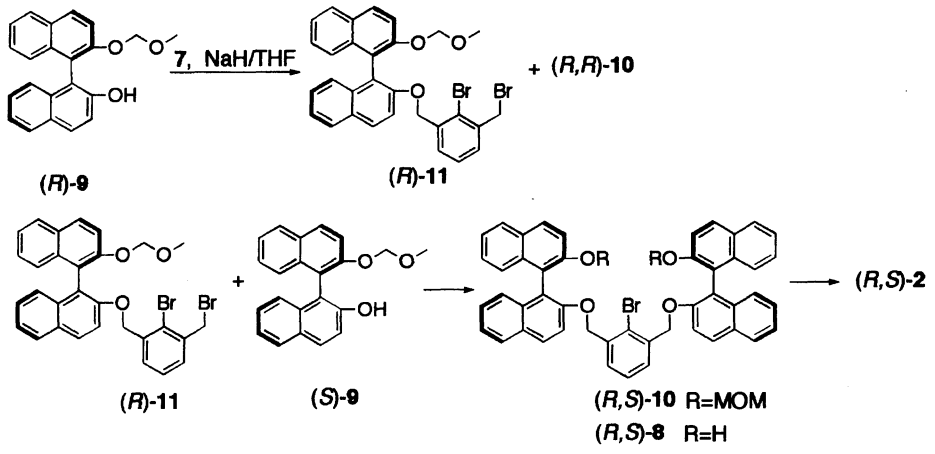
On Structure of (*R*,*S*)-2, (*R*,*R*)-2, and (*R*,*R*)-3. The ^{1}H NMR spectra (500 MHz) of (*R*,*S*)- and (*R*,*R*)-**2** were



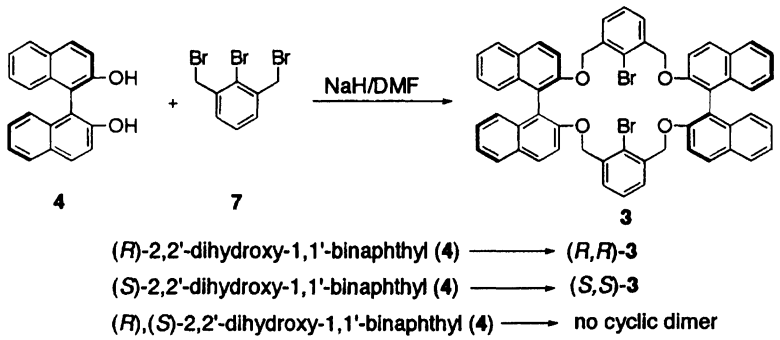
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

analyzed in detail with the assistance of H–H COSY and H–C COSY measurements. The observation of 27 peaks (one peak is overlapping) in the ^{13}C NMR (125 MHz) spectra of (*R*,*S*)-**2** supports the conclusion that a facial symmetry is maintained over the entire cyclic molecule. The H–H NOESY experiments of (*R*,*S*)-**2** revealed nuclear Overhauser effects (NOE) between protons **a** and **b** and between protons **c** and **d**, respectively, as indicated in the partial planar structure **16** (Fig. 2). NOEs were not observed between proton **e** and protons **d** or **c**, however. Despite the bridged bromoarylene moiety of (*R*,*R*)-**2**, which represents the presence of an additional chiral component for the chiral ring system, only 27 peaks were observed in the ^{13}C NMR spectra. This peak reduction does not indicate the existence of overall molecular asymmetry and can be rationalized by taking account of the conformational equilibrium achieved on the NMR time scale. The NOEs between protons **e** and **d** and between protons **e** and **c** were obtained in addition to that between protons **a** and **b**, as shown in **17** (Fig. 3). It is not possible, however, for the three types of NOE to be simultaneously

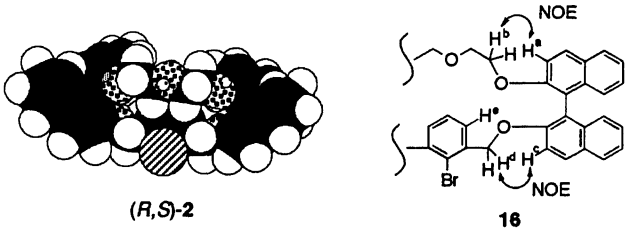


Fig. 2. The Dreiding model of (*R*,*S*)-**2** and the partial planar structure indicating the observed NOE interactions in (*R*,*S*)-**2**.

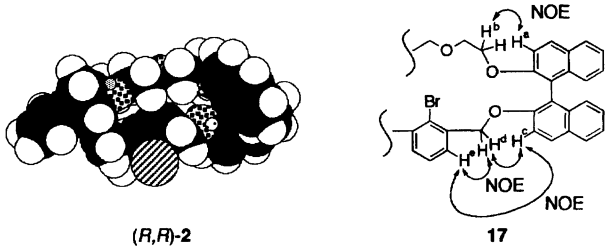


Fig. 3. The Dreiding model of (*R*,*R*)-**2** and the partial planar structure indicating the observed NOE interactions in (*R*,*R*)-**2**.

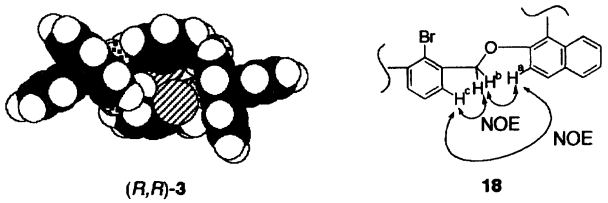


Fig. 4. The Dreiding model of (*R*,*R*)-**3** and the partial planar structure indicating the observed NOE interactions in (*R*,*R*)-**3**.

observed in half of the molecule, based on a consideration of its stereomodel. This crossed NOE observation is best explained based on an equilibrium between unsymmetrically distorted ring conformers. However, spectral changes could not be detected at −40 °C.

The ^{13}C NMR spectrum of (*R*,*R*)-**3** showed fifteen peaks. It is probable, however, that the ring system of (*R*,*R*)-**3** exists in several conformations at equilibration in much the same manner as for **18** (Fig. 4). For the former compound, we concluded this was so by observing three types of NOE, which are impossible for a fixed ring. The NMR experiments at −40 °C showed an increasing chemical-shift difference of proton **b** (AB quartet) and signal broadening of both protons **b** and **c**, indicating appreciable NOE interactions with each other. This strongly suggests that, at this temperature, much less conformational equilibration was occurring.

Conclusion

We could develop versatile synthetic routes to chiral crown ethers **2** and **3** having bromoarylene substituents and could confirm their structures. An interesting anomalous behavior of racemic substrates was found in cyclization to the crown ethers. Our next goals are to investigate further syntheses to compounds having boron and phosphorus, available for molecular recognition and to investigate the mutual interaction between stereoisomeric, ionic species in cyclization in order to explain the anomalous behavior of racemates.

Experimental

Unless otherwise noted, materials were obtained from a commercial supplier and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. *N*,*N*-Dimethylformamide (DMF) and carbon tetrachloride were distilled from calcium hydride prior to use. All reactions

involving organometallic reagents were conducted under an argon atmosphere. Upon work-up, solvents were evaporated using a rotary evaporator, unless otherwise indicated. Melting points were determined with a Yanako Micro Melting-point apparatus. Melting points are uncorrected. Infrared spectra (IR) were determined with a JASCO FT/IR-5300 fourier transform infrared spectrometer. ^{1}H NMR spectra were determined with the following spectrophotometers: JNM A-500, JEOL RX-400, and Hitachi R-90H (superconducting, FT instruments operating at 500, 400, and 90 MHz, respectively). ^{13}C NMR spectra were measured at 125 MHz with the JNM A-500. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in Hertz. High-performance liquid chromatography (HPLC) was done with a JASCO 875-UV/880-PU with a Daicel CHIRALCEL OD column. Optical rotations were determined with a JACSO DIP-370 digital polarimeter. Merck silica-gel 60 (230—400 mesh) was used for flash column chromatography; for thin-layer chromatography Merck Silica-gel 60 TLC aluminum sheets were used.

(*R*,*R*)-Oxybis[2-(ethyleneoxy)-2′-hydroxy-1,1′-binaphthyl] ((*R*,*R*)-6): A suspension of 1.4 g (35 mmol) of 60% sodium hydride in oil was added dropwise to a solution of 5 g (17.46 mmol) of (*R*)-2,2′-dihydroxy-1,1′-binaphthyl ((*R*)-**4**) in 100 ml of THF. The resulting solution was stirred at room temperature for 1 h and then a solution of 7.25 g (17.46 mmol) of diethylene glycol ditosylate in THF was added dropwise. The reaction mixture was refluxed for 8 h. After the solvent was evaporated, the residue was shaken with CH_2Cl_2/water. The extracted organic layer was washed with water and aqueous $NaHCO_3$ and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (200 g silica gel; 3/7 ethyl acetate/hexane) to afford 187 mg (3%) of bis(binaphtho)-22-crown-6, 126 mg (2%) of bis(binaphtho)-11-crown-3, 4.91 g (88%) of (*R*,*R*)-**6**. $[\alpha]_D^{25}$ −61.1° (*c* 0.9, $CHCl_3$); mp 77—80 °C; IR (KBr) 3495, 3055, 1265, 1593, 1174, 812, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 3.05 (2H, ddd, *J* = 3, 6, 11 Hz), 3.12 (2H, ddd, *J* = 3, 6, 11 Hz), 3.75 (2H, ddd, *J* = 3, 6, 11 Hz), 3.86 (2H, ddd, *J* = 3, 6, 11 Hz), 5.15 (2H, s), 6.96 (2H, d, *J* = 8 Hz), 7.10—7.13 (2H, m), 7.14 (2H, d, *J* = 8 Hz), 7.24 (6H, m), 7.29 (2H, d, *J* = 9 Hz), 7.35 (2H, d, *J* = 9 Hz), 7.77 (2H, d, *J* = 8 Hz), 7.78 (2H, d, *J* = 8 Hz), 7.82 (2H, d, *J* = 9 Hz), 7.93 (2H, d, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ = 69.3, 69.5, 115.6, 116.7, 117.9, 123.2, 124.3, 125.0, 125.1, 126.3, 127.1, 127.9, 128.1, 129.1, 129.6, 129.6, 129.9, 130.7, 133.9, 134.0, 151.3, 155.1. Found: C, 82.01; H, 5.52%. Calcd for $C_{44}H_{34}O_5$: C, 82.22; H, 5.33%.

(*S*,*S*)-**6** was prepared from (*S*)-2,2′-dihydroxy-1,1′-binaphthyl ((*S*)-**4**), according to a similar procedure: $[\alpha]_D^{25}$ 59.1° (*c* 0.9, $CHCl_3$).

2,6-Bis(bromomethyl)bromobenzene (7): To a solution of 2 g (10.8 mmol) of 2-bromo-1,3-xylene in 20 mL of carbon tetrachloride were added 4.23 g (23.8 mmol) of *N*-bromosuccinimide and a trace of benzoyl peroxide. The reaction mixture was heated at reflux for 12 h. After filtration of the resulting precipitate, the solvent was removed with a rotary evaporator. The residue was purified by flash column chromatography (40 g silica gel; hexane) to afford 1.52 g (41%) of 2,6-bis(bromomethyl)bromobenzene (**7**). Mp 109.5—120 °C (lit, mp 97—98 °C);[9] IR (KBr) 1425, 1209, 723, 580 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ = 4.637 (4H, s), 7.15—7.45 (3H, m).

(*R*,*R*)-8,9,10-(1,3-Benzo)-9-bromo-2,3 : 4,5 : 13,14 : 15,16-tetra-(1,2-naphtho)-1,6,12,17,20-pentaoxacyclodocosa-2,4,8,13,15-pentaene ((*R*,*R*)-2) from (*R*,*R*)-6: A suspension of 36 mg (0.9 mmol) of 60% sodium hydride in oil was added dropwise to a solution of 150 mg (0.233 mmol) of (*R*,*R*)-**6** in 50 ml of DMF. The resulting solution was stirred at room temperature for 1 h and then a solution of 80 mg (0.233 mmol) of 2,6-bis(bromomethyl)-bromobenzene (**7**) in 10 ml of DMF was added dropwise. The reaction mixture was heated at 90 °C for 48 h. After the DMF was evaporated, the residual mixture was extracted with CH_2Cl_2/water. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (8 g silica gel; 1/9 ethyl acetate/hexane) to afford 53 mg (28%) of (*R*,*R*)-**2**. $[\alpha]_D^{25}$ 3.6° (*c* 0.9, $CHCl_3$); mp 181—183 °C; IR (KBr) 1622, 1591, 1508, 1271, 1244, 1088, 806, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.81 (2H, ddd, *J* = 5.5, 5.5, 10.5 Hz), 2.98 (2H, ddd, *J* = 5.5, 5.5, 10.5 Hz), 3.72 (2H, ddd, *J* = 5.5, 5.5, 10.5 Hz), 3.75 (2H, ddd, *J* = 5.5, 5.5, 10.5 Hz), 5.05 (4H, ABq, *J* = 12.5, 16 Hz), 6.84 (3H, s), 7.11 (2H, brd, *J* = 8.5 Hz), 7.13 (2H, brd, *J* = 8.5 Hz), 7.18 (2H, ddd, *J* = 1, 7, 8.5 Hz), 7.21 (2H, ddd, *J* = 1, 7, 8.5 Hz), 7.26 (2H, d, *J* = 8.5 Hz), 7.31 (2H, ddd, *J* = 1, 7, 8.5 Hz), 7.32 (2H, ddd, *J* = 1, 7, 8.5 Hz), 7.59 (2H, d, *J* = 8.5 Hz), 7.86 (2H, d, *J* = 8.5 Hz), 7.87 (2H, d, *J* = 8.5 Hz), 7.94 (2H, d, *J* = 8.5 Hz), 7.97 (2H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ = 67.1, 68.9, 70.7, 114.4, 115.9, 119.7, 121.1, 123.5, 123.8, 124.0, 125.4, 125.5, 126.3, 126.4, 126.4, 127.8, 127.9, 129.1, 129.1, 129.2, 129.2, 129.5, 134.2, 134.3, 137.0, 153.3, 153.7. Found: C, 75.76; H, 4.75%. Calcd for $C_{52}H_{39}BrO_5$: C, 75.81; H, 4.77%.

(*R*,*R*)-2,6-Bis[1-(2-methoxymethoxy-1-naphthyl)-2-naphthyloxymethyl)]bromobenzene ((*R*,*R*)-10): A suspension of 58 mg (1.45 mmol) of 60% sodium hydride in oil was added dropwise to a solution of 400 mg (1.21 mmol) of (*R*)-2-hydroxy-2′-methoxymethoxy-1,1′-binaphthyl ((*R*)-**9**) in 15 ml of THF. The resulting solution was stirred at room temperature for 1 h and a solution of 190 mg (0.605 mmol) of 2,6-bis(bromomethyl)bromobenzene (**7**) in 5 ml of THF was then added dropwise. The reaction mixture was refluxed overnight. After the THF was evaporated, the residual mixture was shaken with CH_2Cl_2/water. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of solvent, the residue was purified by flash column chromatography (35 g silica gel; 8/92 ethyl acetate/hexane) to afford 413 mg (81%) of (*R*,*R*)-**10**. $[\alpha]_D^{25}$ 61.6° (*c* 0.9, $CHCl_3$); mp 170—171 °C; IR (KBr) 1591, 1508, 1271, 1240, 1150, 1034, 1015, 808 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 3.08 (6H, s), 4.98 (4H, ABq, *J* = 7, 43 Hz), 5.00 (4H, ABq, *J* = 14, 31.5 Hz), 6.61—6.67 (3H, m), 7.08 (2H, brd, *J* = 8.5 Hz), 7.13 (2H, ddd, *J* = 1.5, 6.5, 8.5 Hz), 7.18 (2H, brd, *J* = 8.5 Hz), 7.22 (2H, ddd, *J* = 1.5, 6.5, 8.5 Hz), 7.23 (2H, ddd, *J* = 1.5, 6.5, 8 Hz), 7.32 (2H, ddd, *J* = 1.5, 6.5, 8 Hz), 7.37 (2H, d, *J* = 9 Hz), 7.54 (2H, d, *J* = 9 Hz), 7.83 (2H, d, *J* = 8 Hz), 7.85 (2H, d, *J* = 8 Hz), 7.915 (2H, d, *J* = 9 Hz), 7.918 (2H, d, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ = 55.8, 70.6, 95.2, 115.6, 117.1, 120.4, 120.6, 121.1, 123.9, 124.0, 125.5, 125.5, 126.3, 126.4, 126.8, 127.0, 127.8, 127.9, 129.4, 129.4, 129.5, 129.9, 134.1, 134.1, 136.6, 152.8, 153.6. Found: C, 74.57; H, 4.98%. Calcd for $C_{52}H_{41}BrO_6$: C, 74.19; H, 4.90%.

(*S*,*S*)-**10** was prepared from (*S*)-**9**, according to a similar procedure: $[\alpha]_D^{25}$ −63.6° (*c* 0.9, $CHCl_3$).

A mixture of (*R*,*R*)-, (*S*,*S*)-, and (*R*,*S*)-**10** was prepared from (*R*), (*S*)-**9**: Mp 184—188 °C.

(*R*,*R*)-2,6-Bis[1-(2-hydroxy-1-naphthyl)-2-naphthyloxymethyl]bromobenzene ((*R*,*R*)-8): A solution of 110 mg (0.13 mmol) of (*R*,*R*)-**10** in 5 ml of THF with a small amount of 10% HCl was stirred at room temperature for 18 h. The reaction mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (8 g silica gel; 15/85 ethyl acetate/hexane) to afford 90.7 mg (93%) of (*R*,*R*)-**8**. $[\alpha]_D^{25}$ −2.00° (*c* 0.9, $CHCl_3$); mp 115—121 °C; IR

(KBr) 3505, 1620, 1591, 1507, 1269, 1208, 1146, 812, 748 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 5.03 (4H, s), 5.14 (2H, s), 6.62—6.67 (3H, m), 7.00—7.48 (16H, m), 7.75—8.03 (8H, m). Found: C, 76.11; H, 4.40%. Calcd for $C_{48}H_{33}BrO_4$: C, 76.49; H, 4.41%.

(*S,S*)-**8** was prepared from (*S,S*)-**10**, according to a similar procedure: $[\alpha]_D^{25}$ 1.67° (*c* 0.9, $CHCl_3$); mp 108—115 °C.

A mixture of **8** was prepared from a mixture of (*R,R*)-, (*S,S*)-, and (*R,S*)-**10** : Mp 125—135 °C.

Determination of Optical Purity of 8: Each **8** was optically pure and the ratio of the mixture was determined (*R,R*)-**8** : (*S,S*)-**8** : (*R,S*)-**8** = 1 : 1 : 2 with HPLC (Daicel CHIRALCEL OD column; 1/9 2-propanol/hexane), as depicted in Fig. 5.

(*R,R*)-8,9,10-(1,3-Benzo)-9-bromo-2,3 : 4,5 : 13,14 : 15,16-tetra-(1,2-naphtho)-1,6,12,17,20-pentaoxacyclodocosa-2,4,8,13,15-pentaene ((*R,R*)-2) from (*R,R*)-8: A suspension of 42.4 mg (1.06 mmol) of 60% sodium hydride in oil was added dropwise to a solution of 200 mg (0.265 mmol) of (*R,R*)-**8** in 50 ml of DMF. The resulting solution was stirred at room temperature for 1 h, then a solution of 110 mg (0.265 mmol) of diethylene glycol ditosylate in 10 ml of DMF was added. The reaction mixture was heated at 90 °C for 48 h. After the DMF was evaporated, the resulting mixture was extracted with CH_2Cl_2/water. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (8 g silica gel; 1/9 ethyl acetate/hexane) to afford 150 mg (69%) of (*R,R*)-**2**.

(*S,S*)-**2** was prepared from (*S,S*)-**8**: $[\alpha]_D^{25}$ −4.1° (*c* 0.9, $CHCl_3$).

(*RS,SR*)-8,9,10-(1,3-Benzo)-9-bromo-2,3 : 4,5 : 13,14 : 15,16-tetra(1,2-naphtho)-1,6,12,17,20-pentaoxacyclodocosa-2,4,8,13,15-pentaene ((*R,S*)-2) from a Mixture of (*R,R*)-, (*S,S*)-, and (*R,S*)-8 (Racemate-8): A suspension of 25.5 mg (1.06 mmol) of 60% sodium hydride in oil was added dropwise to a solution of 200 mg (0.265 mmol) of a mixture of **8** in 50 ml of DMF. The resulting solution was stirred at room temperature for 1 h, then a solution of 110 mg (0.265 mmol) of diethylene glycol ditosylate in 10 ml of DMF was added. The reaction mixture was heated at 90 °C for 48 h. After the DMF was evaporated, the resulting mixture was extracted with CH_2Cl_2/water. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (8 g silica gel; 1/9 ethyl acetate/hexane) to afford 75 mg (34%) of (*R,S*)-**2**; mp 251—252 °C; IR (KBr) 1622, 1591, 1508, 1269, 1248, 1096, 799, 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.79 (2H, ddd, *J* = 7, 7, 10 Hz), 3.13 (2H, ddd, *J* = 7, 7, 10 Hz), 3.72—3.79 (4H, m), 5.10 (4H, ABq, *J* = 13, 30.5 Hz), 6.41 (2H, d, *J* = 7.5 Hz), 6.61 (1H, t, *J* = 7.5 Hz), 7.15 (4H, brd, *J* = 8.5 Hz), 7.22 (2H, ddd, *J* = 1, 7, 8.5 Hz), 7.25 (2H, ddd, *J* = 1, 7, 8.5 Hz), 7.30 (2H, d, *J* = 9 Hz), 7.35 (2H, ddd, *J* = 1, 7, 8.5 Hz), 7.35 (2H, ddd, *J* = 1, 7, 8.5 Hz), 7.58 (2H, d, *J* = 9 Hz), 7.88 (2H, d, *J* = 8.5 Hz), 7.90 (2H, d, *J* = 8.5 Hz), 7.92 (2H, d, *J* = 9 Hz), 7.98 (2H, d, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ = 67.0, 69.3, 72.3, 115.1, 117.3, 119.5, 120.3, 121.7, 123.6, 124.1, 125.4, 125.7, 126.4, 126.8, 127.34 127.9, 127.93, 129.15, 129.17, 129.50, 129.92, 133.95, 134.23, 136.76, 153.91, 154.65. Found: C, 75.89; H, 4.75%. Calcd for $C_{52}H_{39}BrO_5$: C, 75.81; H, 4.77%.

(*R,S*)-2,6-Bis[1-(2-methoxymethoxy-1-naphthyl)-2-naphthyloxymethyl]bromobenzene ((*R,S*)-10): A suspension of 49 mg (1.23 mmol) of 60% sodium hydride in oil was added dropwise to a solution of 413 mg (1.21 mmol) of (*R*)-2-hydroxy-2′-methoxymethoxy-1,1′-binaphthyl ((*R*)-**9**) in 20 ml of THF. The resulting solution was stirred at room temperature for 1 h. Then a solution of 534 mg (1.48 mmol) of 2,6-bis(bromomethyl)bromobenzene (**7**) in 10 ml of THF was added. The reaction mixture was refluxed overnight. After the THF was evaporated, the resulting mixture was extracted with CH_2Cl_2/water. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (35 g silica gel; 5/95 ethyl acetate/hexane) to afford 300 mg (40%) of (*R*)-2-bromomethyl-6-[1-(2-methoxymethoxy-1-naphthyl)-2-naphthyloxymethyl]bromobenzene ((*R*)-**11**) and 170 mg (31%) of (*R,R*)-**10**. A suspension of 13 mg (0.325 mmol) of 60% sodium hydride in oil was added dropwise to a solution of 106 mg (0.321 mmol) of (*S*)-**9** in 10 ml of THF. The resulting solution was stirred at room temperature for 1 h and a solution of 190 mg (0.321 mmol) of (*R*)-**11** in 5 ml of THF was added. The reaction mixture was refluxed overnight. After the THF was evaporated, the resulting mixture was extracted with CH_2Cl_2/water. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (8 g silica gel; 8/92 ethyl acetate/hexane) to afford 210 mg (78%) of (*R,S*)-**10**. Mp 215—220 °C; IR (KBr) 1591, 1508, 1265, 1240, 1148, 1034, 1015, 806 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.10 (6H, s), 5.00 (4H, ABq, *J* = 7, 34.8 Hz), 5.02 (4H, s), 6.61—6.68 (3H, m), 7.09 (2H, brd, *J* = 8.4 Hz), 7.15 (2H, ddd, *J* = 1.2, 6.4, 8.4 Hz), 7.19 (2H, brd, *J* = 8.4 Hz), 7.23 (2H, ddd, *J* = 1.2, 6.4, 8.4 Hz), 7.29 (2H, ddd, *J* = 1.2, 6.4, 7.9 Hz), 7.33 (2H, ddd, *J* = 1.2, 6.4, 8.2 Hz), 7.37 (2H, d, *J* = 8.9 Hz), 7.55 (2H, d, *J* = 9.2 Hz), 7.85 (2H, d, *J* = 7.9 Hz), 7.85 (2H, d, *J* = 8.2 Hz), 7.92 (2H, d, *J* = 8.6 Hz), 7.93 (2H, d, *J* = 9.2 Hz). Found: C, 74.23; H, 4.88%. Calcd for $C_{52}H_{41}BrO_6$: C, 74.19; H, 4.90%.

(*R,S*)-8,9,10-(1,3-Benzo)-9-bromo-2,3 : 4,5 : 13,14 : 15,16-tetra-(1,2-naphtho)-1,6,12,17,20-pentaoxacyclodocosa-2,4,8,13,15-pentaene ((*R,S*)-2) from (*R,S*)-8 Obtained from (*R,S*)-10 by Hydrolysis (HCl/THF): A suspension of 24 mg (0.596 mmol) of 60% sodium hydride in oil was added dropwise to a solution of 150 mg (0.199 mmol) of (*R,S*)-**8** in 40 ml of DMF. The resulting solution was stirred at room temperature for 1 h. Then a solution of 82.28 mg (0.199 mmol) of diethylene glycol ditosylate in 10 ml of DMF was added. The reaction mixture was heated at 90 °C for 48 h. After the DMF was evaporated, the residual mixture was extracted with CH_2Cl_2/water. The organic layer was washed with

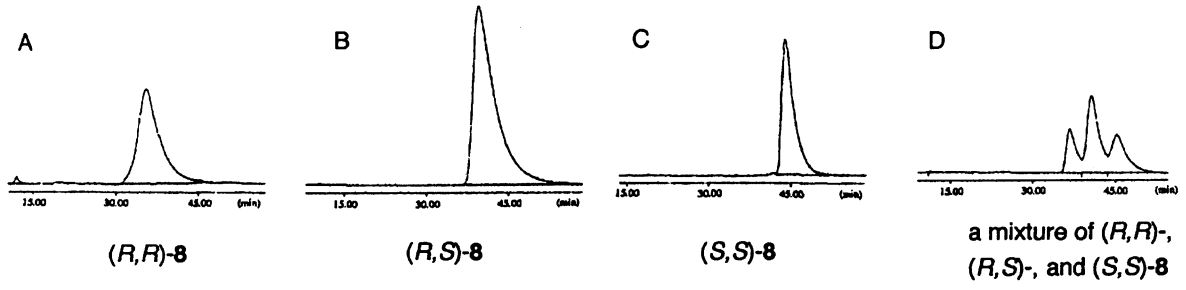


Fig. 5. HPLC patterns of isomers **8** with Daicel chiralcel OD column.

water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (8 g silica gel; 1/9 ethyl acetate/hexane) to afford 92 mg (56%) of (*R,S*)-**2**.

(*R,R*)-8,9,10 : 19,20,21-bis(1,3-Benzo)-9,20-dibromo-2,3 : 4, 5 : 13, 14 : 15, 16- tetra(1, 2- naphtho)- 1, 6, 12, 17- tetraoxacyclodocosa-2,4,8,13,15,19-hexaene ((*R,R*)-3): A suspension of 84 mg (2.09 mmol) of 60% sodium hydride in oil was added dropwise to a solution of 200 mg (0.699 mmol) of (*R*)-2,2′-dihydroxy-1,1′-binaphthyl in 50 ml of DMF. The resulting solution was stirred at room temperature for 1 h and a solution of 239.47 mg (0.699 mmol) of 2,6-bis(bromomethyl)bromobenzene in 10 ml of DMF was added. The reaction mixture was heated at 90 °C for 48 h. After the DMF was evaporated, the residual mixture was extracted with CH_2Cl_2/water. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (8 g silica gel; 1/9 ethyl acetate/hexane) to afford 136 mg (42%) of (*R,R*)-**3**. $[\alpha]_D^{25}$ −230° (*c* 0.9, $CHCl_3$); mp 219—221 °C; IR (KBr) 1622, 1591, 1508, 1240, 1213, 1098, 802, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.93 (8H, ABq, J = 13.5, 64 Hz), 6.25 (4H, d, J = 7.5 Hz), 6.34 (2H, t, J = 7.5 Hz), 7.14 (4H, d, J = 8 Hz), 7.19 (4H, ddd, J = 1, 6, 8 Hz), 7.29 (4H, ddd, J = 1, 6, 8 Hz), 7.60 (4H, d, J = 8.5 Hz), 7.88 (4H, d, J = 8 Hz), 8.00 (4H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ = 68.6, 114.2, 120.1, 123.5, 123.5, 125.2, 126.4, 126.4, 127.9, 128.2, 128.9, 129.1, 134.4, 136.1, 152.7. Found: C, 71.87; H, 4.12% Calcd for $C_{56}H_{38}Br_2O_4$: C, 71.95; H, 4.09%.

(*S,S*)-**3** was prepared from (*S*)-2,2′-dihydroxy-1,1′-binaphthyl, according to a similar procedure: $[\alpha]_D^{25}$ 221° (*c* 0.9, $CHCl_3$).

The data of ^1H NMR and ^{13}C NMR spectra with COSY and NOESY for (*R,R*)-**2**, (*R,S*)-**2**, and (*R,R*)-**3** are deposited as Document No. 69044 at the Office of the Editor of Bull. Chem. Soc. Jpn.

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