Synthesis and Chiral Recognition of Optically Active Crown Ethers Incorporating a 9,9′-Biphenanthryl Moiety as the Chiral Center

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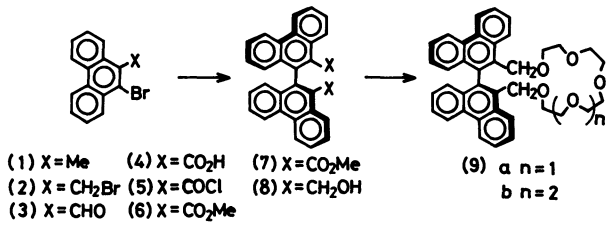
Synopsis. Two chiral crown ethers incorporating a 9,9′-biphenanthryl moiety as the chiral center have been prepared, and their chiral recognition properties in transport of methyl (±)-phenylglycinate hydrochloride, (±)-1-phenylethylamine hydrochloride, and (±)-1,2-diphenylethylamine hydrochloride were examined.

As an extension of our recent synthetic studies on optically active crown ethers incorporating axially dissymmetric molecules,[1] we report here the preparation and chiral recognition properties of optically active crown ethers (**9**) having a 9,9′-biphenanthryl moiety as the chiral center.

Preparation of **9** was carried out according to the sequence of reactions illustrated in Scheme 1. In the



Scheme 1.

initial step 9-bromo-10-methylphenanthrene (**1**)[2] was converted into the corresponding bromomethyl derivative (**2**) by a side chain bromination, followed by a Sommelet reaction[3] and an oxidation to give the acid (**4**) (30% yield from 1). The latter was transformed into the corresponding acid chloride (**5**) and esterified to produce **6** (86.8% yield from **4**). The coupling of the bromo ester (**6**) to give the biphenanthryl diester (**7**) was effected under Ullmann conditions,[4] and the lithium aluminium hydride reduction of this ester gave the alcohol (**8**) (64.4% yield from **6**). Optical resolution of (±)-(**8**) was achived by HPLC with a column packed with (+)-poly(triphenylmethyl methacrylate);[5] elution with methanol gave optically pure (−)-(*S*)-(**8**)[6] and (+)- (*R*)-(**8**) with $[\alpha]_D$ (acetone) −70.0° and +69.7°, respectively. Condensation of (−)-(**8**) with tetraethylene glycol ditosylate (NaH–THF) afforded the (−)-(*S*)-9,9′-biphenanthryl-crown-5 (**9a**), mp 223—225 °C (55% yield). The (+)-(*R*)-biphenanthryl-crown-6 (**9b**) was prepared in the same way from (+)-(**8**). The (+)-alcohol (**8**) was condensed with pentaethylene glycol ditosylate to afford (+)-(*R*)-(**9b**), mp 201—203 °C (47% yield).

Table 1. Differential Transport of Enantiomeric Molecules

Host	Guest	Transport %	Configuration of dominant entiomer	Optical purity %
(−)-(*S*)-(**9a**)	a	1.4	*R*	21
	b	3.1	*S*	88
	c	3.5	*S*	49
(+)-(*R*)-(**9b**)	a	1.8	*S*	15
	b	4.1	*R*	20
	c	3.9	*R*	19

a) Methyl (±)-phenylglycinate hydrochloride. b) (±)-1,2-Diphenylethylamine hydrochloride. c) (±)-1-Phenylethylamine hydrochloride.

Table 1 gives the chiral recognition behavior of (−)-(*S*)-(**9a**) and (+)-(*R*)-(**9b**) with methyl (±)-phenylglycinate hydrochloride, (±)-1-phenylethylamine hydrochloride, and (±)-1,2-diphenylethylamine hydrochloride.

A few of the typical enantiomer selective crown ethers (**10**) prepared by Cram et al.[8] are shown in

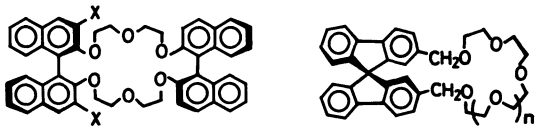


Figure. One of the most enantiomer selective of these compounds is the dimethyl derivative of the bis-(α,α′-binaphthyl)-22-crown-6 (**10**). With methyl (±)-phenylglycinate at 0 °C, a 90% optical purity was found for this crown by differential transport. Our results (Table 1) show that **9a** containing five oxygens has a higher enantiomer selectivity than **9b** containing six oxygens towards all substrates, and 1,2-diphenylethylamine of as high as 88% optical purity was 3.1% transported by (−)-(*S*)-(**9a**). These results are compatible with Prelog's experiment[9] which reveal that 9,9′-spiro-bifluorene-22-crown-5 (**11**) (n=1) possesses the highest enantiomer selectivity for several ammonium cations with a chiral substituent in a 9,9′-spiro-bifluorenocrown series (**11**).

Experimental

Melting points are uncorrected. IR and NMR spectra were recorded on a Hitachi 260-10 and a JNM-MH-100 spectrometer, respectively.

9-Bromo-10-(bromomethyl)phenanthrene (2). A stirred and refluxed solution of **1** (21.7 g, 80 mmol), *N*-bromosuccinimide (15.8 g, 80 mmol), and benzoyl peroxide (0.1 g) in CCl_4 (150 mL) was irradiated with a tungsten lamp (100 W) for 4 h. After a usual workup, the resulting solid was recrystallized from hexane to give **2** (19.6 g, 70% yield), mp 141—142 °C; ^{1}H-NMR (CCl_4) δ=5.13 (s, 2H), 7.48—8.60 (m, 8H) (Found: C, 51.42; H, 2.86%).

9-Bromo-10-formylphenanthrene (3). The aldehyde (**3**)

(4 g, 11.4 mmol) was synthesized from **2** under Sommelet conditions as described.[3] The crude product was recrystallized from benzene to yield **3** (2.4 g, 95%), mp 160—161 °C; IR (KBr) 1700 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=7.54—9.05 (m, 8H), 10.92 (s, 1H) (Found: C, 63.26; H, 3.13; Br, 28.10%).

9-Bromo-10-phenanthrenecarboxylic Acid (4). The oxidation of **3** (8 g, 28 mmol) was carried out according to literature[10] using potassium permanganate (12 g). The resulting product was recrystallized from toluene to afford **4** (4.8 g, 56.8%), mp 221—223 °C; IR (KBr) 1710 cm^{-1} (C=O) (Found: C, 59.68; H, 2.96; Br, 26.66%).

Methyl 9-Bromophenanthrene-10-carboxylate (6). A mixture of **4** (5 g, 16.6 mmol), thionyl chloride (8.3 ml, 114 mmol), and toluene (20 ml) was gradually heated to boiling, whereupon the acid chloride dissolved. After refluxing for 3 h, the solvent was removed by vacuum distillation. The solid residue was recrystallized from benzene–hexane to give **5** (4.7 g, 88.6%), mp 73—74 °C; IR (KBr) 1780 cm^{-1} (C=O). A suspension of **5** (4.5 g, 14 mmol) in absolute methanol (20 ml) was stirred at room temperature untill dissolution had occured. The solution was then heated to reflux for 5 h, followed by evaporation under reduced pressure to give a crystalline solid. Recrystallization from benzene–hexane afforded **6** (4.2 g, 98%), mp 228—229 °C; IR (KBr) 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=4.07 (s, 3H), 7.54—8.68 (m, 8H) (Found: C, 60.95; H, 3.54; Br, 25.31%).

Dimethyl 9,9′-Biphenathryl-10,10′-dicarboxylate (7). The Ullmann coupling of **6** (1.0 g, 3.17 mmol) was carried out according to literature[11] using activated copper bronze (1.6 g), and dry DMF (15 ml). The resulting product was recrystallized from methanol to yield **7** (0.52 g, 69.7%), mp 226—227 °C; IR (KBr) 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ=3.35 (s, 6H), 7.20—8.95 (m, 16H) (Found: C, 81.65; H, 4.71%).

10,10′-Bis(hydroxymethyl)-9,9′-biphenanthryl (8). A solution of **7** (3.3 g, 7 mmol) in dry THF (50 ml) was added to a suspension of $LiAlH_4$ (0.6 g, 15.8 mmol) in dry THF (90 ml). The mixture was refluxed for 0.5 h with stirring and cooled in an ice-bath. After a usual workup, the product was recrystallized from chloroform to give **8** (2.9 g, 92.4%), mp 292—294 °C; IR (KBr) 3450 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) δ=1.57 (s, 2H), 4.72 (q, J=12 Hz, 4H), 7.16—8.90 (m, 16H) (Found: C, 81.75; H, 4.71%).

Optical Resolution of (±)-(8). Optical resolution of (±)-(**8**) was achieved by HPLC with a column packed with (+)-poly(triphenylmethyl methacrylate) as descrived.[12] A solution of (±)-(**8**) (15 mg) in methanol (15 ml) was injected on the column and eluted with methancl to give the first eluted (−)-isomer followed by (+)-isomer. The procedure was repeated to process a total of 1 g of **8**, and recrystallization of the resolved enantiomeric compounds from chloroform afforded optically pure (*S*)-(−)-(**8**) and (*R*)-(+)-(**8**) respectively. (*S*)-(−)-(**8**): 0.45 g (45%), mp 280—281 °C, $[\alpha]_D^{25}$ −70.0° (acetone); (*R*)-(+)-(**8**): 0.46 g (46%), mp 281—282 °C, $[\alpha]_D^{26}$ +69.7° (acetone).

(−)-(*S*)-Decahydrodiphenanthro[9,10-*o*:9′,10′-*q*][1,4,7,10,13]-pentaoxacyclononadecin (9a). To a boiling suspension of NaH (36 mg, 1.5 mmol) in dry THF (15 ml) was added a solution of (−)-(**8**) (170 mg, 0.41 mmol) and tetraethylene glycol ditosylate (180 mg, 0.41 mmol) in dry THF (30 ml) dropwise over 8 h period under N_2. The reaction mixture was refluxed for further 12 h, cooled in an ice-bath, and quenched with water (12 ml). After a usual workup, the crude product was chromatographed on alumina (benzene eluent) to give a solid which was recrystallized from benzene–hexane to furnish (−)-(**9a**) (130 mg, 55%), mp 223—225 °C, $[\alpha]_D^{23}$ −143.9° ($CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ=3.05—3.78 (m, 16H), 4.70 (s, 4H), 7.15—9.10 (m, 16H); Found: C, 79.48; H, 6.35%. Calcd for $C_{38}H_{36}O_5$: C, 79.69; H, 6.34%.

(+)-(*R*)-Dodecahydrodiphenanthro[9,10-*r*:9′,10′-*t*][1,4,7,10,13,16]hexaoxacyclodocosin (9b). Condensation of (+)-(**8**) (400 mg, 0.965 mmol) with pentaethylene glycol ditosylate (480 mg, 0.965 mmol) was carried out by the same procedure as described for **9a**. The product was chromatographed on alumina (benzene eluent) followed by recrystallization from benzene–hexane to give (+)-(**9b**) (280 g, 47%), mp 201—203 °C, $[\alpha]_D^{25}$ +166° ($CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ=3.10—3.75 (m, 20H), 4.69 (s, 4H), 7.20—8.97 (m, 16H); Found: C, 77.76; H, 6.48%. Calcd for $C_{40}H_{40}O_6$: C, 77.90; H, 6.54%.

Enantiomer Differential Transport. Differential transport was carried out in a conventional apparatus which consisted of an outer cylindrical gass vessel (24.5 mm inner diameter) and a central glass tube (15.5 mm inner diameter). The 0.01 M (1 M=1 mol dm^{-3}) $CHCl_3$ solution of the host separated the inner aqueous phase (0.1 M HCl) and the outer aqueous phase (0.08 M HCl) which contained $LiPF_6$ (0.4 M) and the racemic guest (0.08 M). The organic layer was stirred at 20 °C for 1 h, and transport was followed by monitoring the absorbance at 262 nm and $[\theta]_{262}$ of the inner aqueous phase.

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6) Absolute configuration of (−)-(**8**) was determined by the chiral recognition method developed by Miyano and coworkers.[7] Intramolecular Ullmann reaction of (+)-2,2′-bis(10-bromo-9-phenanthrylcarbonyloxy)-1,1′-binaphthyl (prepared from **5** by reaction with optically pure (−)-(*S*)-1,1′-binaphthyl-2,2′-diol) followed by $LiAlH_4$ reduction gave recovered (−)-(*S*)-1,1′-binaphthyl-2,2′-diol and (−)-(**8**) ($[\alpha]_D^{25}$ −59.5° (acetone), 85% optical yield). This result unequvocally indicate that (−)-(**8**) has a same *S*-configuration.

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