Enantiomeric Differentiation by Chiral Macrocyclic Polyethers Derived from D-Mannitol and Binaphthol

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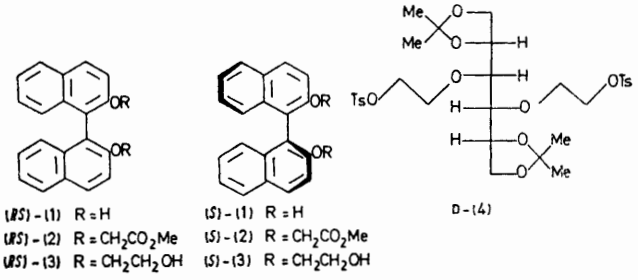
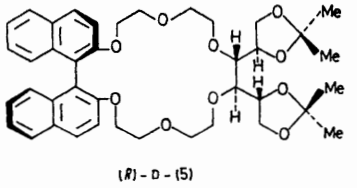
Summary The chiral macrocyclic polyethers (*R*)-D-(**5**) and (*S*)-D-(**5**) derived from D-mannitol and (*R*)- and (*S*)-binaphthol respectively exhibit comparable enantiomeric selectivities in complexing (±)-(*RS*)-α-phenylethylammonium hexafluorophosphate under equilibrium conditions.

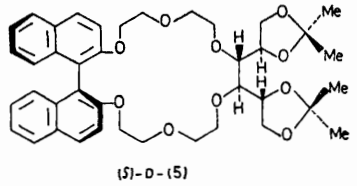
CHIRAL macrocyclic polyethers derived from (*R*)- and (*S*)-binaphthol,[1] L-tartaric acid,[2,3] and D-mannitol[2] as *singular* sources of chirality have been shown[1,4] to exhibit chiral recognition in complexation equilibria towards various racemic primary alkylammonium salts. The 'resolution' of the binaphthyl unit by incorporating (*RS*)-binaphthol[5] and 1,2:5,6-di-*O*-isopropylidene-D-mannitol[6] into the synthesis of diastereoisomeric macrocyclic polyethers has now been achieved.

Condensation of 2,2′-dihydroxy-1,1′-binaphthyl (*RS*)-(**1**) with $BrCH_2CO_2Me$ in the presence of K_2CO_3 and refluxing Me_2CO afforded (80%) the diester (*RS*)-(**2**), m.p. 133—134 °C, which was reduced to the diol (*RS*)-(**3**),[1] m.p. 108—109 °C, with $LiAlH_4$ in THF (85% yield). Reaction of equimolar proportions of the diol (*RS*)-(**3**) and the bistosylate D-(**4**),[2] m.p. 91—92 °C, $[\alpha]_D$ + 12·1° (*c* 0·7, $CHCl_3$), with NaH in Me_2SO at 50 °C for 40 h gave two diastereoisomeric di-*O*-isopropylidene derivatives (**5**) which were separated by preparative t.l.c. (Et_2O) on silica gel and identified as the faster moving component {isomer A, $[\alpha]_D$ + 68·2° (*c* 0·51, $CHCl_3$), τ ($CDCl_3$) 2·00—2·26 and 2·48—3·00 (4H and 8H, t and m, ArH), 5·61—6·83 (24H, m, CH_2 and CH), and 8·61 and 8·68 (2 × 6H, 2 × s, 4 × Me)} and the slower moving component {isomer B, $[\alpha]_D$ — 46·6° (*c* 0·53, $CHCl_3$), τ ($CDCl_3$) 1·96—2·22 and 2·42—3·00 (4H and 8H, t and m, ArH), 5·62—6·72 (24H, m, CH_2 and CH), and 8·61 (12H, s, 4 × Me)} in 7 and 6% yields, respectively. The diastereoisomers were also separated preparatively by high performance liquid chromatography (Et_2O–C_6H_{14}) on silica gel.

Configurational assignments were made to isomers A and B on the basis of a stereospecific synthesis of the di-*O*-isopropylidene derivative (*S*)-D-(**5**). Optically active (—)-2,2′-dihydroxy-1,1′-binaphthyl, (*S*)-(**1**), $[\alpha]_D$ — 30·8° (*c* 1·1, THF), obtained after resolution of its phosphoric acid derivative with cinchonine,[7] was converted (51%) into the







diester (*S*)-(**2**), $[\alpha]_D$ − 28·1° (*c* 0·42, $CHCl_3$), which was reduced to the diol (*S*)-(**3**),[1] $[\alpha]_D$ + 23·5° (*c* 0·98, $CHCl_3$), in 80% yield. Reaction of equimolar proportions of (*S*)-(**3**) and D-(**4**) with NaH and Me_2SO at 50 °C for 40 h gave (13%) only isomer B, $[\alpha]_D$ − 43·0° (*c* 0·1, $CHCl_3$), after preparative t.l.c. (Et_2O) on silica gel. Hence, isomer A is assigned to (*R*)-D-(**5**) and isomer B to (*S*)-D-(**5**).

Significant changes were observed in the ^1H n.m.r. spectra of (*R*)-D-(**5**) and (*S*)-D-(**5**) in $CDCl_3$ in the presence of primary alkyl ammonium salts indicating that both these diastereoisomers are capable of acting as chiral hosts towards suitable guest salts. In complexation experiments involving (+)-(*R*)-, (−)-(*S*)-, and (±)-(*RS*)-α-phenylethylamine [(*R*)-(**6**), (*S*)-(**6**), and (*RS*)-(**6**) respectively] salts under equilibrium conditions, both hosts were found to exhibit chiral recognition, a phenomenon which was demonstrated most convincingly by the noise-decoupled ^{13}C n.m.r. spectra of (*R*)-D-(**5**)–(*RS*)-(**6**).HPF_6 and (*S*)-D-(**5**)–(*RS*)-(**6**).HPF_6 in $CDCl_3$. The quaternary phenyl carbons in the diastereoisomeric complexes between (*R*)-D-(5) and (*RS*)-(**6**).HPF_6 are the only carbons in the guest salts which are sufficiently influenced by their chiral environment to exhibit different chemical shifts [$\delta(CDCl_3)$ 137·48 for (*R*)-(**6**).HPF_6 and 137·05 for (*S*)-(**6**).HPF_6]. Comparison of the relative peak areas associated with the two signals gives an (*R*):(*S*) ratio of 62:38.† In the diastereoisomeric complexes between (*S*)-D-(**5**) and (*RS*)-(**6**).HPF_6 the methyl carbons [$\delta(CDCl_3)$ 20·08 for (*R*)-(**6**).HPF_6 and 20·69 for (*S*)-(**6**).HPF_6] as well as the quaternary phenyl carbons [$\delta(CDCl_3)$ 136·69 for (*R*)-(**6**).HPF_6 and 136·81 for (*S*)-(**6**).HPF_6] show chemical shift nonequivalences. Comparison of the relative peak areas for the methyl carbons gives an (*R*):(*S*) ratio of 63:37.†

The macrocycle (*R*)-D-(**5**) has two homotopic faces. The macrocycle (*S*)-D-(**5**) also has two homotopic faces which are necessarily diastereotopic to those of (*R*)-D-(**5**). Their comparable selectivities towards (*RS*)-(**6**).HPF_6 are therefore unexpected.

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† By comparison with results obtained from ^1H n.m.r. spectroscopy it was established previously[1] that noise-decoupled ^{13}C n.m.r. spectra of complexes can be treated in a quantitative fashion. In the case of (*R*)-(D)-(**5**)–(*RS*)-(**6**).HPF_6 and (*S*)-(D)-(**5**)–(*RS*)-(**6**).HPF_6 the guest signals were obscured by host signals in their ^1H n.m.r. spectra.

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