Assembly of Three Chiral Binaphthyl Units into Multiheteromacrocycles

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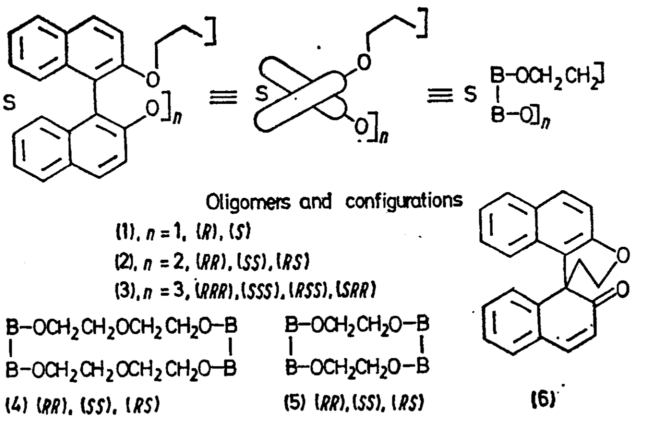
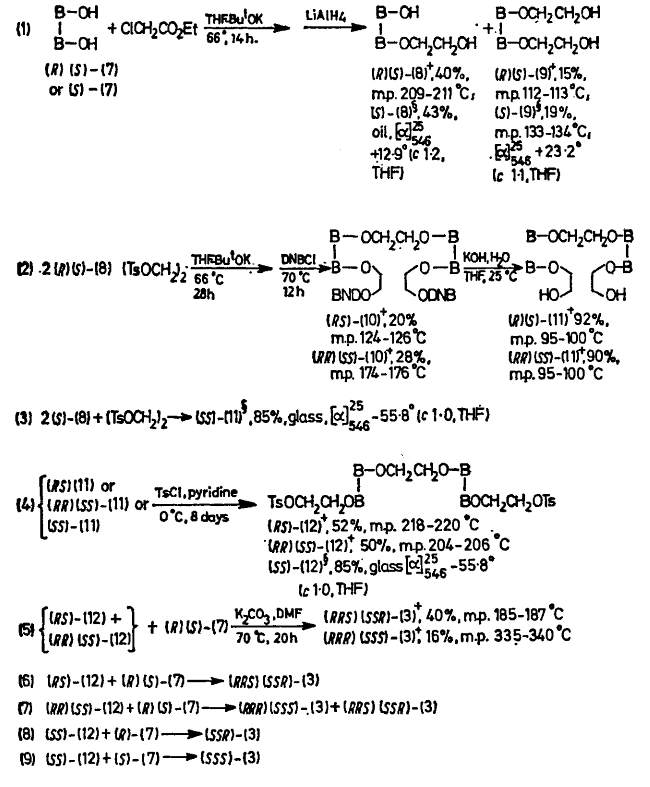
Summary The syntheses, configurational identification, and thermal equilibration of the stereoisomers of the 24-crown-6 ether containing three chiral 2,2′-substituted-1,1′-binaphthyl units are described.

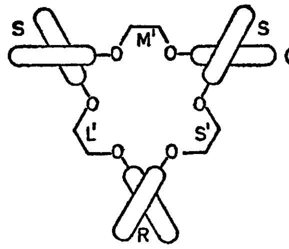
The syntheses and configurational identifications of the stereoisomers of (**1**)–(**3**) were undertaken since these compounds represent an extreme example of molecular shaping of potential host compounds for chiral recognition in molecular complexation. Although successive substitution of 2,2′-disubstituted-1,1′-binaphthyl for ethylene units in 18-crown-6 decreased the oxygen's basicity,[1] introduction of two such units as in (**4**) and (**5**) provided compounds that exhibited substantial chiral recognition in differential complexation of the enantiomers of aminoester salts.[2,3]

Treatment of racemic 2,2′-dihydroxy-1,1′-binaphthyl (**7**) with ethyleneglycol ditosylate in tetrahydrofuran (THF)–KOBu^t (44 h at reflux under nitrogen) gave a mixture of five compounds separated by chromatography (silica gel) and by fractional crystallization. Compound (*R*)(*S*)-

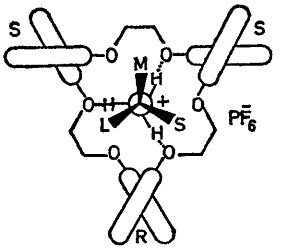


(**1**)†‡[4] (23%) had m.p. 222—223 °C, (*RS*)-(**2**)†‡ (*ca* 1%) had m.p. 355 °C (decomp.), (*RRR*)(*SSS*)-(**3**)†‡ (*ca.* 1%) had m.p. 338—342 °C (decomp.), (*RSS*)(*RRS*)-(**3**)†‡ (*ca* 1%) had m.p. 188—190 °C and the ketonic compound (**6**)†‡ (44%) gave m.p. 198—200 °C. The ^{1}H n.m.r. spectra of the diastereomeric racemates of (**3**) were distinctly different. The structure of (**6**)[4] was established by its Rast molecular weight and spectra; u.v.: λ_{max} (CH_2Cl_2) 278 (log ϵ 4·00), 289 (log ϵ 4·10), and shoulders at 268 and 331 nm (log ϵ 4·08); i.r.: (KBr), 1660 s cm^{-1} (C=O); ^{1}H n.m.r.: δ ($CDCl_3$), 2·22 (2H, m, CCH_2C), 4·18 (2H, m, CCH_2O) 6·22—6·50 (2H, m, COCH=CH), and 6·68—7·70 (10H, m, ArH). When optically pure (—)-(*S*)-(**7**)[1,2] was used as starting material, only three products were produced, (+)-(*S*)-(**1**)§ (25%), m.p. 216·5—217 °C, $[\alpha]^{25}_{546}$ + 628° (*c* 0·93, CH_2Cl_2); (—)-(*SSS*)-(**3**)§ (*ca.* 1%), glass, phase transition 185—200 °C, $[\alpha]^{25}_{546}$ — 175° (*c* 1·0, THF); (+)-(**6**)§ (45%) m.p. 187—188 °C $[\alpha]^{25}_{546}$ + 314° (*c* 0·97, CH_2Cl_2). The absence of (*SS*)-(**2**) in the reaction mixture suggests that (**2**) isolated with racemic (**7**) as starting material possessed the (*RS*)-configuration. When dimethylformamide (DMF) was substituted for THF as solvent, a 65% yield of (**1**) and a trace of (*RS*)-(**2**) was observed, but no (**3**) or (**6**) was detected (t.l.c.).

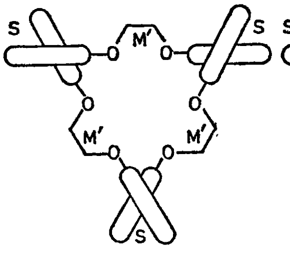




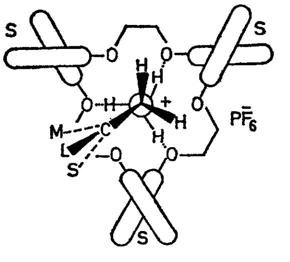
(*RSS*)-(**3**), C_2 point group.



(**13**), envisioned stable complex between (*RSS*)-(**3**) and LMS$\overset{*}{C}$NH$_3$PF$_6$ enantiomer



(*SSS*)-(**3**), D_3 point group (three C_2 axes and one C_3 axis)



(**14**), envisioned stable complex between (*SSS*)-(**3**) and LMS$\overset{*}{C}$CH$_2$NH$_3$PF$_6$ enantiomer

Reaction sequences (1)—(9) firmly establish the configurations of all the intermediates, and the diastereoisomers of (**3**). Compounds (**8**) and (**9**) were separated by extracting (**8**) with 1·3 M KOH in 2 : 1 water–MeOH from an ether solution of (**8**) and (**9**). Racemic-(**11**) and *meso*-(**11**) were separated by silica gel chromatography and crystallization of their 3,5-dinitrobenzoates (DNB), (*RS*)-(**10**) and (*RR*)(*SS*)-(**10**), respectively. The production of a single racemate (*RRS*)(*SSR*)-(**3**) in reaction (6) and both racemates (*RRS*)(*SSR*)-(**3**) and (*RRR*)(*SSS*)-(**3**) (separated by silica gel chromatography and crystallization) in (7) uniquely identifies the relative configurations of the isomers of (**12**) and those of (**3**). The step-by-step assemblies of (*SSS*)-(**3**) [reactions (3), (4), and (9)] and of (*SSR*)-(**3**) [reactions (3), (4), and (8)] identify the absolute configurations of these compounds. Enantiomer to racemate relationships among the stereoisomers of (**3**) were confirmed by the identity or non-identity of their ^{1}H n.m.r. spectra and t.l.c. behaviour.

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† Carbon and hydrogen analyses were within theory. The ^{1}H n.m.r. spectra in $CDCl_3$ were as expected.

‡ The 78 eV mass spectrum contained the molecular ion.

§ The enantiomer and racemate gave the same ^{1}H n.m.r. spectra and t.l.c. behaviour.

Compound (*RSS*)-(**3**) possesses a C_2 axis, and the naphthlene walls divide the space above and peripheral to the central hole into a large (L′), medium (M′), and small (S′) cavity. Corey-Pauling–Koltun (CPK) molecular models of complex (**13**) indicated a complementary relationship between host and guest. Compound (*SSS*)-(**3**) belongs to the rarely encountered D_3 point group. Its naphthalene walls divide the space above and peripheral to the central hole into three medium sized cavities (M′). Molecular models of complex (**14**) indicated a complementary relationship between host and guest. Unfortunately, the naphthalene groups attached to the oxygens of these potential host compounds reduced their basicity to below the point where any complexation could be detected by ^{1}H n.m.r. in partitioning experiments.[1,2] Work is in progress with amino-ester racemates with one enantiomer tritium- and the other ^{14}C-labelled that will provide a more sensitive scale for testing (*RSS*)-(**3**) and (*SSS*)-(**3**) as chiral hosts. The possibility also exists that the substances will exhibit stereoselectivity in clathrate formation as was observed with tri-*o*-thymotide.[5]

When heated to 340 °C in an inert atmosphere for 7 min, (*RRS*)(*SSR*)-(**3**) and (*RRR*)(*SSS*)-(**3**) both produced an approximately equal mixture of the two isomers. Thus $\Delta\Delta G = ca.\ 0$ for the two equilibrations. The difference in symmetry between the isomers (D_3 vs. C_2) should produce a $\Delta\Delta G = RT\ln 3 = 1340\ \text{cal mol}^{-1}$ for the two isomers. Apparently the (*RRR*)(*SSS*)-(**3**) isomer is slightly more compressed than its (*RRS*)(*SSR*)-isomer.

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