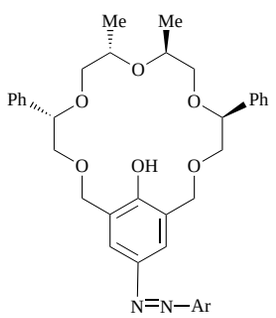
Preparation of optically active azophenolic crown ethers containing 1-phenylethane-1,2-diol and 2,4-dimethyl-3-oxapentane-1,5-diol as a chiral subunit: temperature-dependent enantiomer selectivity in the complexation with chiral amines [1]

Kazuko Ogasahara, Keiji Hirose, Yoshito Tobe and Koichiro Naemura *

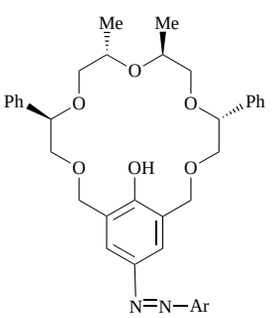
Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560 Japan

With (2*S*,4*S*)-2,4-dimethyl-3-oxapentane-1,5-diol and (*S*)- or (*R*)-1-phenylethane-1,2-diol as chiral subunits, optically active azophenolic crown ethers (*S*,*S*,*S*,*S*)-1, (*R*,*S*,*S*,*R*)-2, (*S*,*S*,*S*,*S*)-3 and (*R*,*S*,*S*,*R*)-4 possessing two phenyl and two methyl substituents together with the *p*-(2,4-dinitrophenylazo)phenol moiety have been prepared in enantiomerically pure forms. Temperature-dependent enantiomer selectivity in the complexation of these crown ethers with chiral amines has been studied by the UV–visible spectroscopic method in chloroform and from the observed association constants, thermodynamic parameters for the complexation have been calculated.

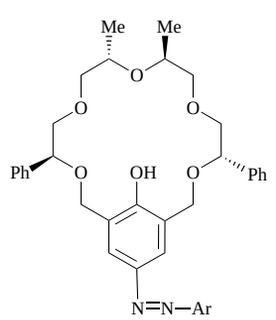
Complexation of chiral and achiral molecular receptors possessing a well-defined three-dimensional cavity with guests has been widely studied,[2] while complexation of chiral crown ethers of an 18-crown-6 type possessing a planar binding cavity are still of interest for obtaining basic information on chiral recognition behaviour. We have prepared optically active crown ethers of this type by using various types of chiral subunits, examined the enantiomer recognition behaviour in complexation with chiral amines and given an explanation for the observed enantiomer selectivities on the basis of CPK molecular model examination.[3] Recently, we found that the sign of the $\Delta_{R,S}\Delta G$ values for the complexation of the azophenolic crown ethers with 2-aminopropan-1-ol in $CDCl_3$ reversed at *ca.* 6 °C; the enantiomer selectivities observed at the ordinary temperature were governed by $-\Delta_{R,S}\Delta S$.[4] The facts show that it is important to know whether the observed enantiomer selectivity in complexation is governed by $-\Delta_{R,S}\Delta H$ or $-\Delta_{R,S}\Delta S$ in order to discuss structural complementarity between a chiral crown ether and guest enantiomers on the basis of CPK molecular model examination of complexes and the observed enantiomer selectivity. Herein, we report the preparation of the optically active azophenolic crown ethers (*S*,*S*,*S*,*S*)-**1**, (*R*,*S*,*S*,*R*)-**2**, (*S*,*S*,*S*,*S*)-**3** and (*R*,*S*,*S*,*R*)-**4** by using (*S*)- or (*R*)-1-phenylethane-1,2-diol and (2*S*,4*S*)-2,4-dimethyl-3-oxapentane-1,5-diol as a chiral subunit. These crown ethers contain the phenol moiety which possesses an intraannular OH group as a binding site for neutral amines and the 2,4-dinitrophenylazo group at the *para*-position which is not only a chromophore but also increases the binding ability of the compounds towards a neutral amine.[5] Their enantiomer selectivities in complexation with chiral amines were evaluated at various temperatures by the UV–visible spectroscopic method in $CHCl_3$ and from the observed association constants, thermodynamic parameters for the complexation were calculated.



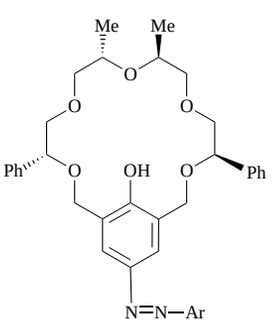
(*S*,*S*,*S*,*S*)-**1**



(*R*,*S*,*S*,*R*)-**2**



(*S*,*S*,*S*,*S*)-**3**

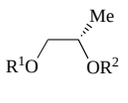


(*R*,*S*,*S*,*R*)-**4**

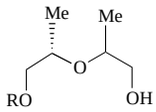
Results and discussion

The chiral diethylene glycol unit (*S*,*S*)-**10**[6] was prepared from ethyl (*S*)-lactate. According to a published route,[7] by protection of the hydroxy group as a tetrahydropyranyl ether (THP) followed by $LiAlH_4$ reduction, ethyl (*S*)-lactate was transformed to (*S*)-**5** in 90% yield. The primary hydroxy group of (*S*)-**5** was blocked by treatment with benzyl chloride and sodium hydride to give (*S*)-**6**, the THP blocking group of which was then removed to give (*S*)-**7** in 72% overall yield. Condensation of (*S*)-**7** with racemic ethyl 2-bromopropionate in the presence of sodium hydride gave **8** as a mixture of (*S*,*S*)- and (*S*,*R*)-diastereoisomers in 51% yield. After hydrogenolysis of **8** with H_2 and 10% Pd on carbon in ethanol, the resulting diol **9** was tosylated to give a 1 : 1 mixture of (*S*,*S*)-**10** and (*S*,*R*)-**10**, the ^1H NMR spectrum of which exhibited two doublet signals of equal intensity due to the methyl groups at δ 1.04 and 1.07 for (*S*,*S*)-**10** and (*S*,*R*)-**10**, respectively. The mixture was recrystallized from methanol until the signal at δ 1.07 disappeared completely to give diastereoisomerically and enantiomerically pure (*S*,*S*)-**10** in 19% yield based on **8**.

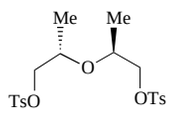
The chiral subunits (*S*)-**11** and (*R*)-**11** were prepared from



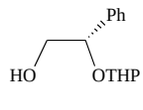
(*S*)-**5** R^1 = H R^2 = THP
(*S*)-**6** R^1 = CH_2Ph R^2 = THP
(*S*)-**7** R^1 = CH_2Ph R^2 = H



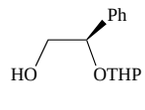
8 R = CH_2Ph
9 R = H



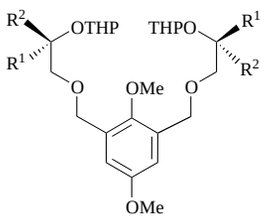
(*S*,*S*)-**10**



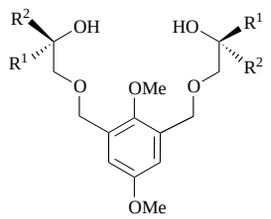
(*S*)-**11**



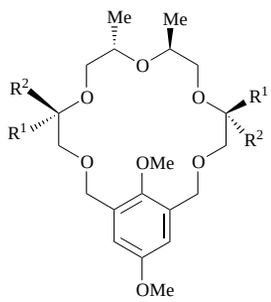
(*R*)-**11**



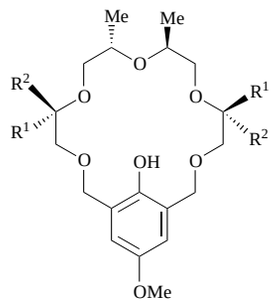
(*S*,*S*)-**12** R^1 = Ph R^2 = H
(*R*,*R*)-**13** R^1 = H R^2 = Ph



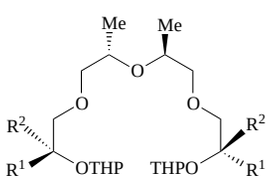
(*S*,*S*)-**14** R^1 = Ph R^2 = H
(*R*,*R*)-**15** R^1 = H R^2 = Ph



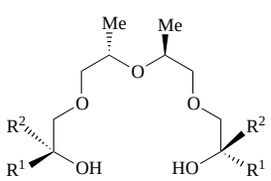
(*S*,*S*,*S*,*S*)-**16** R^1 = Ph R^2 = H
(*R*,*S*,*S*,*R*)-**17** R^1 =H R^2 = Ph



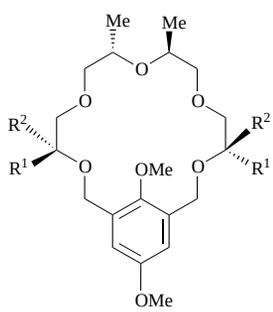
(*S*,*S*,*S*,*S*)-**18** R^1 = Ph R^2 = H
(*R*,*S*,*S*,*R*)-**19** R^1 = H R^2 = Ph



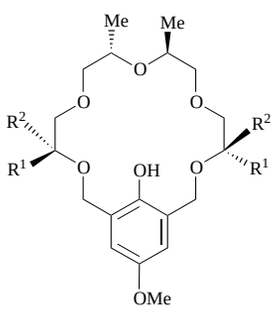
(*S*,*S*,*S*,*S*)-**20** R^1 = Ph R^2 = H
(*R*,*S*,*S*,*R*)-**21** R^1 = H R^2 = Ph



(*S*,*S*,*S*,*S*)-**22** R^1 = Ph R^2 = H
(*R*,*S*,*S*,*R*)-**23** R^1 = H R^2 = Ph



(*S*,*S*,*S*,*S*)-**24** R^1 = Ph R^2 = H
(*R*,*S*,*S*,*R*)-**25** R^1 = H R^2 = Ph



(*S*,*S*,*S*,*S*)-**26** R^1 = Ph R^2 = H
(*R*,*S*,*S*,*R*)-**27** R^1 = H R^2 = Ph

(*S*)- and (*R*)-mandelic acid, respectively, according to a published route:[5,8] esterification, protection of the hydroxy group and $LiAlH_4$ reduction.

The preparation of (*S*,*S*,*S*,*S*)-**1** having C-5 and C-13 phenyl substituents and homotopic faces was carried out stepwise; that is, condensation of (*S*)-**11** with a *m*-phenylene unit and then ring closure with a chiral diethylene glycol unit. Treatment of 2 mol equiv. of (*S*)-**11** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in the presence of sodium hydride in tetrahydrofuran (THF) gave (*S*,*S*)-**12**, which was deprotected with methanol containing a small amount of hydrochloric acid to give (*S*,*S*)-**14** in 57% overall yield. High-dilution condensation of (*S*,*S*)-**14** with (*S*,*S*)-**10** in the presence of sodium hydride and potassium tetrafluoroboranuide in *N*,*N*-dimethylformamide (DMF) gave (*S*,*S*,*S*,*S*)-**16** in 37% yield. For easy conversion of the dimethoxyphenyl moiety to the *p*-benzoquinone moiety, the inner methoxy group of (*S*,*S*,*S*,*S*)-**16** was selectively cleaved by treatment with sodium ethanethiolate in DMF[9] to give (*S*,*S*,*S*,*S*)-**18** in 80% yield. Oxidation of (*S*,*S*,*S*,*S*)-**18** with cerium(IV) ammonium nitrate (CAN) in acetonitrile[10] followed by treatment with 2,4-dinitrophenylhydrazine in a mixture of conc. H_2SO_4, ethanol and methylene dichloride gave (*S*,*S*,*S*,*S*)-**1** in 81% overall yield. By the same sequence of the reactions described above, (*R*,*R*)-**15** was derived from (*R*)-**11** and 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in 58% overall yield *via* (*R*,*R*)-**13**. Ring closure of (*R*,*R*)-**15** with (*S*,*S*)-**10** gave (*R*,*S*,*S*,*R*)-**17**, which was transformed to (*R*,*S*,*S*,*R*)-**2** in 31% overall yield *via* (*R*,*S*,*S*,*R*)-**19**.

For the preparation of (*S*,*S*,*S*,*S*)-**3** having C-4 and C-14 phenyl groups, two chiral subunits (*S*)-**11** were first linked with a chiral diethylene glycol unit and then with a *m*-phenylene unit. Condensation of 2 mol equiv. of (*S*)-**11** with (*S*,*S*)-**10** in the presence of sodium hydride in DMF followed by removal of the blocking group gave (*S*,*S*,*S*,*S*)-**22** in 28% overall yield *via* (*S*,*S*,*S*,*S*)-**20**. High-dilution condensation of (*S*,*S*,*S*,*S*)-**22** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in the presence of sodium hydride and potassium tetrafluoroboranuide in DMF gave (*S*,*S*,*S*,*S*)-**24** in 36% yield. The inner methoxy group of (*S*,*S*,*S*,*S*)-**24** was cleaved to give (*S*,*S*,*S*,*S*)-**26**, which was transformed to (*S*,*S*,*S*,*S*)-**3** in 55% overall yield by oxidation with CAN followed by treatment with 2,4-dinitrophenylhydrazine. In a similar manner, condensation of 2 mol equiv. of (*R*)-**11** with (*S*,*S*)-**10** followed by deprotection gave (*R*,*S*,*S*,*R*)-**23** in 21% overall yield, which was transformed to (*R*,*S*,*S*,*R*)-**4** in 21% overall yield *via* (*R*,*S*,*S*,*R*)-**25** and (*R*,*S*,*S*,*R*)-**27**, successively.

The association constants for the complexes of the crown ethers (*S*,*S*,*S*,*S*)-**1**, (*R*,*S*,*S*,*R*)-**2**, (*S*,*S*,*S*,*S*)-**3** and (*R*,*S*,*S*,*R*)-**4** with chiral amines (2-aminopropan-1-ol **28**, 2-amino-3-methylbutan-1-ol **29**, 2-amino-2-phenylethan-1-ol **30**, 1-aminopropan-2-ol **31** and 1-phenylethylamine **32**) were determined at various temperatures by the Rose–Drago method[11] on the basis of the absorption in UV–visible spectrum of the complexes; the crown ethers showed an absorption maximum at 400–406 nm in chloroform and that of the complexes with amines appeared in the region 560–580 nm. The K_a values for the complexes of (*S*,*S*,*S*,*S*)-**1** with (*R*)-**28**, (*R*)-**30** and (*R*)-**31** were so large at 4 °C that it was difficult to get accurate data; these were, therefore, evaluated over the temperature range 15–45 °C. The observed K_a values of the complexes and thermodynamic parameters for the complexation calculated from the K_a values are summarized in Table 1. The predictive isoenantioselective temperatures ($T_{iso} = \Delta_{R,S}\Delta H/\Delta_{R,S}\Delta S$) are also calculated and listed in Table 1.

Table 1 Association constants for the complexes and thermodynamic parameters for complexation of crown ethers in $CHCl_3$

Crown ether	Amine	K_a/mol^{-1} at 4 °C	at 15 °C	at 25 °C	at 38 °C	at 45 °C	ΔH kJ mol^{-1}	ΔS J deg^{-1} mol^{-1}	T_{iso}[a]/°C
(*S*,*S*,*S*,*S*)-**1**	(*R*)-**28**		(2.64 ± 0.50) × 10^4	(1.04 ± 0.35) × 10^4	(2.99 ± 0.31) × 10^3	(1.53 ± 0.12) × 10^3	−70.5 ± 6.8	−160 ± 22	—[b]
(*S*,*S*,*S*,*S*)-**1**	(*S*)-**28**		(3.69 ± 0.24) × 10^3	(1.57 ± 0.09) × 10^3	(4.77 ± 0.55) × 10^2	(2.53 ± 0.33) × 10^2	−66.4 ± 7.9	−162 ± 26	
(*S*,*S*,*S*,*S*)-**1**	(*R*)-**29**	(1.74 ± 0.05) × 10^4	(3.54 ± 0.29) × 10^3	(1.59 ± 0.16) × 10^3	(4.73 ± 0.58) × 10^2		−78.2 ± 0.7	−202 ± 2	124
(*S*,*S*,*S*,*S*)-**1**	(*S*)-**29**	(1.75 ± 0.10) × 10^3	(6.02 ± 0.21) × 10^2	(2.94 ± 0.33) × 10^2	(1.05 ± 0.11) × 10^2		−61.4 ± 0.6	−159 ± 2	
(*S*,*S*,*S*,*S*)-**1**	(*R*)-**30**		(1.20 ± 0.07) × 10^4	(4.47 ± 1.16) × 10^3	(1.38 ± 0.12) × 10^2	(5.89 ± 0.54) × 10^2	−75.7 ± 6.2	−183 ± 20	356
(*S*,*S*,*S*,*S*)-**1**	(*S*)-**30**		(7.32 ± 0.30) × 10^2	(3.00 ± 0.21) × 10^2	(1.20 ± 0.03) × 10^2	(5.8 ± 0.3) × 10	−63.1 ± 6.5	−164 ± 21	
(*S*,*S*,*S*,*S*)-**1**	(*R*)-**31**		(1.58 ± 0.23) × 10^4	(5.96 ± 1.29) × 10^3	(1.98 ± 0.11) × 10^3	(8.51 ± 0.31) × 10^2	−70.6 ± 4.3	−165 ± 14	—[b]
(*S*,*S*,*S*,*S*)-**1**	(*S*)-**31**		(6.08 ± 1.41) × 10^3	(2.54 ± 0.16) × 10^3	(7.91 ± 0.90) × 10^2	(3.72 ± 0.78) × 10^2	−68.4 ± 9.2	−165 ± 30	
(*S*,*S*,*S*,*S*)-**1**	(*R*)-**32**	(6.19 ± 0.19) × 10^2	(2.61 ± 0.35) × 10^2	(1.44 ± 0.03) × 10^2	(4.7 ± 0.2) × 10		−53.5 ± 5.4	−139 ± 18	412
(*S*,*S*,*S*,*S*)-**1**	(*S*)-**32**	(1.74 ± 0.17) × 10^3	(7.20 ± 0.17) × 10^2	(4.05 ± 0.12) × 10^2	(1.07 ± 0.04) × 10^2		−57.7 ± 10.5	−145 ± 36	
(*R*,*S*,*S*,*R*)-**2**	(*R*)-**28**	(8.80 ± 0.64) × 10^3	(2.85 ± 0.16) × 10^3	(1.69 ± 0.42) × 10^3	(5.17 ± 0.35) × 10^2		−59.9 ± 2.8	−141 ± 10	263
(*R*,*S*,*S*,*R*)-**2**	(*S*)-**28**	(3.11 ± 0.15) × 10^4	(8.80 ± 0.73) × 10^3	(4.71 ± 1.82) × 10^3	(1.40 ± 0.16) × 10^3		−65.8 ± 1.4	−152 ± 5	
(*R*,*S*,*S*,*R*)-**2**	(*R*)-**29**	(1.08 ± 0.04) × 10^3	(4.30 ± 0.16) × 10^2	(2.15 ± 0.11) × 10^2	(7.6 ± 0.5) × 10		−54.7 ± 0.4	−139 ± 1	205
(*R*,*S*,*S*,*R*)-**2**	(*S*)-**29**	(6.64 ± 0.51) × 10^3	(2.17 ± 0.21) × 10^3	(9.48 ± 0.25) × 10^2	(2.92 ± 0.20) × 10^2		−64.6 ± 0.3	−160 ± 1	
(*R*,*S*,*S*,*R*)-**2**	(*R*)-**30**	(2.80 ± 0.21) × 10^3	(1.03 ± 0.05) × 10^3	(3.80 ± 0.43) × 10^2	(1.55 ± 0.08) × 10^2		−60.9 ± 9.3	−154 ± 32	—[b]
(*R*,*S*,*S*,*R*)-**2**	(*S*)-**30**	(2.33 ± 0.13) × 10^4	(8.31 ± 0.21) × 10^3	(2.91 ± 0.19) × 10^3	(9.91 ± 0.25) × 10^2		−66.1 ± 10.0	−155 ± 34	
(*R*,*S*,*S*,*R*)-**2**	(*R*)-**31**	(8.95 ± 0.66) × 10^3	(3.49 ± 0.18) × 10^3	(1.50 ± 0.27) × 10^3	(5.33 ± 0.67) × 10^2		−60.2 ± 10.6	−141 ± 36	81
(*R*,*S*,*S*,*R*)-**2**	(*S*)-**31**	(2.76 ± 0.27) × 10^4	(7.45 ± 0.32) × 10^3	(3.11 ± 0.07) × 10^3	(9.41 ± 0.15) × 10^2		−71.5 ± 3.1	−173 ± 11	
(*R*,*S*,*S*,*R*)-**2**	(*R*)-**32**	(1.78 ± 0.04) × 10^3	(6.83 ± 0.18) × 10^2	(3.08 ± 0.13) × 10^2	(1.12 ± 0.08) × 10^2		−59.6 ± 4.3	−153 ± 15	230
(*R*,*S*,*S*,*R*)-**2**	(*S*)-**32**	(5.83 ± 0.15) × 10^2	(2.56 ± 0.28) × 10^2	(1.22 ± 0.10) × 10^2	(4.8 ± 0.6) × 10		−54.0 ± 5.6	−142 ± 19	
(*S*,*S*,*S*,*S*)-**3**	(*R*)-**28**	(2.43 ± 0.24) × 10^4	(8.89 ± 0.30) × 10^3	(3.19 ± 0.15) × 10^3	(1.38 ± 0.12) × 10^3		−61.5 ± 2.4	−138 ± 8	131
(*S*,*S*,*S*,*S*)-**3**	(*S*)-**28**	(9.07 ± 0.99) × 10^3	(3.75 ± 0.18) × 10^3	(1.59 ± 0.07) × 10^3	(7.04 ± 0.39) × 10^2		−54.4 ± 2.9	−120 ± 10	
(*S*,*S*,*S*,*S*)-**3**	(*R*)-**29**	(5.04 ± 0.22) × 10^3	(1.99 ± 0.09) × 10^3	(8.19 ± 0.66) × 10^2	(3.26 ± 0.35) × 10^2		−58.6 ± 0.3	−141 ± 1	93
(*S*,*S*,*S*,*S*)-**3**	(*S*)-**29**	(2.69 ± 0.11) × 10^3	(1.69 ± 0.03) × 10^3	(6.11 ± 0.30) × 10^2	(2.24 ± 0.21) × 10^2		−53.0 ± 0.5	−125 ± 2	
(*S*,*S*,*S*,*S*)-**3**	(*R*)-**30**	(5.67 ± 0.15) × 10^3	(2.26 ± 0.13) × 10^3	(9.84 ± 0.57) × 10^2	(4.10 ± 0.24) × 10^2		−56.3 ± 4.6	−131 ± 16	296
(*S*,*S*,*S*,*S*)-**3**	(*S*)-**30**	(1.68 ± 0.08) × 10^3	(7.13 ± 0.09) × 10^2	(3.65 ± 0.23) × 10^2	(1.53 ± 0.12) × 10^2		−50.8 ± 5.9	−122 ± 20	
(*S*,*S*,*S*,*S*)-**3**	(*R*)-**31**	(1.80 ± 0.26) × 10^4	(6.94 ± 0.57) × 10^3	(3.98 ± 0.11) × 10^3	(1.23 ± 0.05) × 10^3		−56.3 ± 3.6	−122 ± 12	90
(*S*,*S*,*S*,*S*)-**3**	(*S*)-**31**	(5.29 ± 0.55) × 10^3	(2.46 ± 0.21) × 10^3	(1.68 ± 0.19) × 10^3	(6.28 ± 0.36) × 10^2		−44.4 ± 3.5	−89 ± 12	
(*S*,*S*,*S*,*S*)-**3**	(*R*)-**32**	(8.23 ± 0.19) × 10^2	(3.66 ± 0.03) × 10^2	(2.02 ± 0.11) × 10^2	(8.7 ± 0.4) × 10		−47.8 ± 3.3	−116 ± 11	—[b]
(*S*,*S*,*S*,*S*)-**3**	(*S*)-**32**	(7.52 ± 0.19) × 10^2	(3.54 ± 0.11) × 10^2	(1.80 ± 0.05) × 10^2	(8.1 ± 0.5) × 10		−47.8 ± 3.7	−117 ± 13	
(*R*,*S*,*S*,*R*)-**4**	(*R*)-**28**	(3.35 ± 0.24) × 10^3	(1.62 ± 0.10) × 10^3	(5.92 ± 0.20) × 10^2	(2.81 ± 0.26) × 10^2		−57.4 ± 7.5	−138 ± 26	288
(*R*,*S*,*S*,*R*)-**4**	(*S*)-**28**	(7.91 ± 0.36) × 10^3	(3.68 ± 0.24) × 10^3	(1.13 ± 0.86) × 10^3	(5.88 ± 0.30) × 10^2		−61.3 ± 7.8	−145 ± 27	
(*R*,*S*,*S*,*R*)-**4**	(*R*)-**29**	(8.65 ± 0.45) × 10^2	(3.71 ± 0.47) × 10^2	(1.94 ± 0.11) × 10^2	(7.3 ± 0.7) × 10		−54.5 ± 0.6	−140 ± 2	57
(*R*,*S*,*S*,*R*)-**4**	(*S*)-**29**	(1.82 ± 0.11) × 10^3	(6.98 ± 0.26) × 10^2	(3.22 ± 0.09) × 10^2	(9.1 ± 2.7) × 10		−66.0 ± 1.1	−174 ± 4	
(*R*,*S*,*S*,*R*)-**4**	(*R*)-**30**	(4.70 ± 0.17) × 10^2	(2.20 ± 0.22) × 10^2	(1.09 ± 0.02) × 10^2	(4.7 ± 0.4) × 10		−53.0 ± 1.7	−139 ± 6	209
(*R*,*S*,*S*,*R*)-**4**	(*S*)-**30**	(2.40 ± 0.04) × 10^3	(9.70 ± 0.21) × 10^2	(4.32 ± 0.66) × 10^2	(1.62 ± 0.7) × 10^2		−62.0 ± 1.2	−157 ± 4	
(*R*,*S*,*S*,*R*)-**4**	(*R*)-**31**	(3.25 ± 0.17) × 10^3	(1.58 ± 0.07) × 10^3	(6.13 ± 0.70) × 10^2	(1.98 ± 0.24) × 10^2		−63.7 ± 15	−162 ± 52	−61
(*R*,*S*,*S*,*R*)-**4**	(*S*)-**31**	(6.89 ± 0.60) × 10^3	(3.20 ± 0.16) × 10^3	(1.42 ± 0.07) × 10^3	(5.22 ± 0.42) × 10^2		−58.4 ± 8.4	−137 ± 28	
(*R*,*S*,*S*,*R*)-**4**	(*R*)-**32**	(6.72 ± 0.32) × 10^2	(2.91 ± 0.17) × 10^2	(1.45 ± 0.09) × 10^2	(6.3 ± 0.3) × 10		−49.6 ± 2.4	−125 ± 8	—[b]
(*R*,*S*,*S*,*R*)-**4**	(*S*)-**32**	(4.39 ± 0.07) × 10^2	(1.96 ± 0.13) × 10^2	(9.3 ± 0.4) × 10	(4.3 ± 0.1) × 10		−49.1 ± 2.9	−126 ± 10	

[a] The predictive isoenantioselective temperatures are calculated from ΔH and ΔS values. [b] The T_{iso} value was not calculated because of the small $\Delta\Delta S$ value.

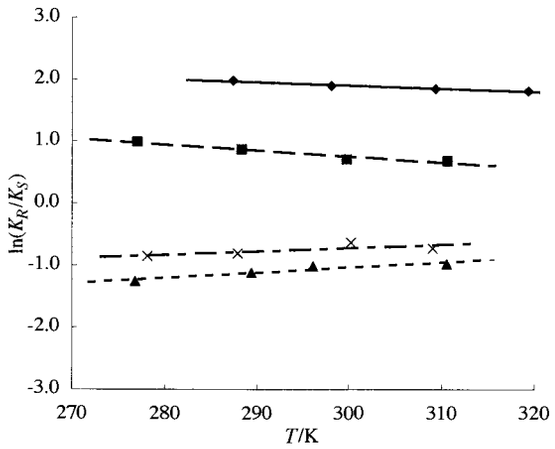


Fig. 1 Temperature dependence of $\ln(K_R/K_S)$ for the complexation of 2-aminopropan-1-ol **28** with crown ethers; ◆ (*S*,*S*,*S*,*S*)-**1**, ▲ (*R*,*S*,*S*,*R*)-**2**, ■ (*S*,*S*,*S*,*S*)-**3** and × (*R*,*S*,*S*,*R*)-**4**

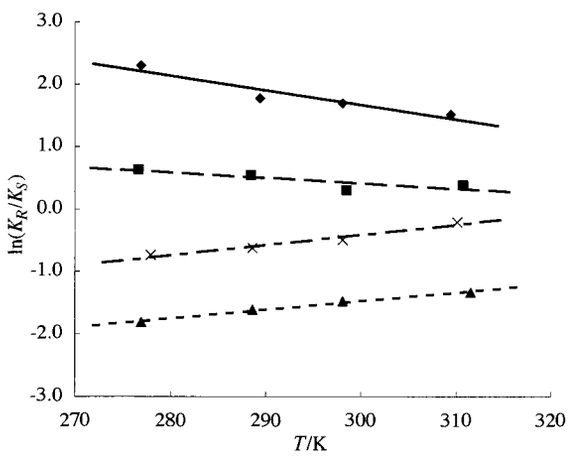
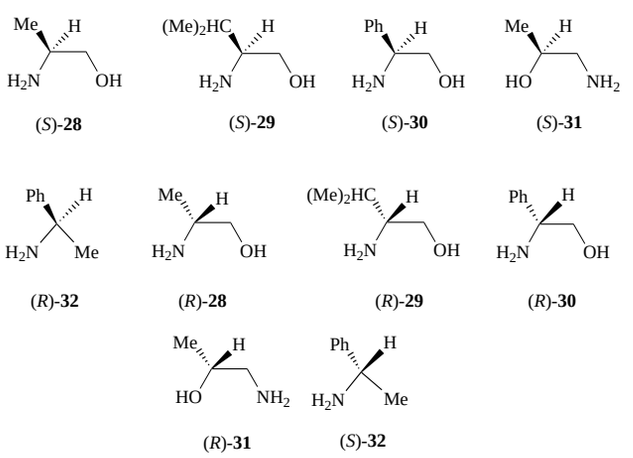


Fig. 2 Temperature dependence of $\ln(K_R/K_S)$ for the complexation of 2-amino-3-methylbutan-1-ol **29** with crown ethers; ◆ (*S*,*S*,*S*,*S*)-**1**, ▲ (*R*,*S*,*S*,*R*)-**2**, ■ (*S*,*S*,*S*,*S*)-**3** and × (*R*,*S*,*S*,*R*)-**4**



In Figs. 1, 2, 3, 4 and 5, we have plotted $\ln(K_R/K_S)$ values of complexation for the amines **28**, **29**, **30**, **31** and **32**, respectively, with the four crown ethers as a function of temperature. The enantiomer selectivities for formation of the (*S*,*S*,*S*,*S*)-**1**:**28**, the (*S*,*S*,*S*,*S*)-**1**:**31**, the (*S*,*S*,*S*,*S*)-**3**:**32** and the (*R*,*S*,*S*,*R*)-**4**:**32** complexes scarcely changed during the experiment. On the other hand, in all the other combinations of the crown ether and the amine, unambiguous temperature-dependent enantiomer selectivities were observed. The plot in Fig. 4 shows that the *S*-selectivity of (*R*,*S*,*S*,*R*)-**4** towards **31** increased with increasing temperature over the experimental temperature; the T_{iso} value is calculated to be −61 °C.

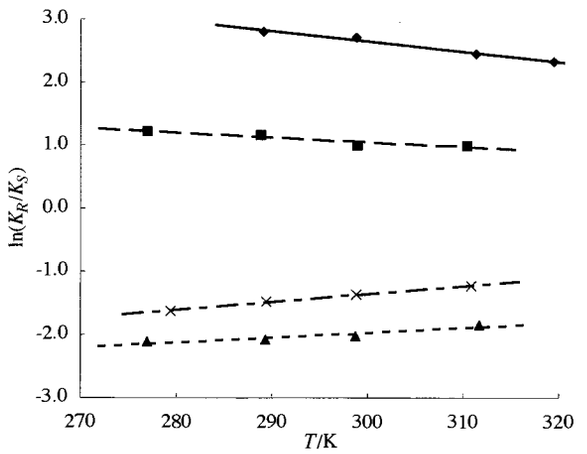


Fig. 3 Temperature dependence of $\ln(K_R/K_S)$ for the complexation of 2-amino-2-phenylethanol **30** with crown ethers; ◆ (*S*,*S*,*S*,*S*)-**1**, ▲ (*R*,*S*,*S*,*R*)-**2**, ■ (*S*,*S*,*S*,*S*)-**3** and × (*R*,*S*,*S*,*R*)-**4**

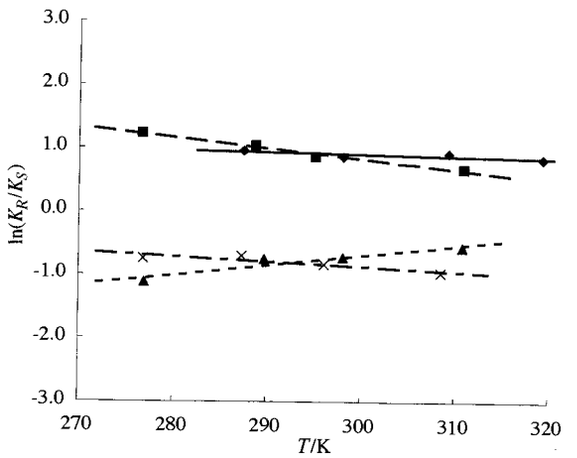


Fig. 4 Temperature dependence of $\ln(K_R/K_S)$ for the complexation of 1-aminopropan-2-ol **31** with crown ethers; ◆ (*S*,*S*,*S*,*S*)-**1**, ▲ (*R*,*S*,*S*,*R*)-**2**, ■ (*S*,*S*,*S*,*S*)-**3** and × (*R*,*S*,*S*,*R*)-**4**

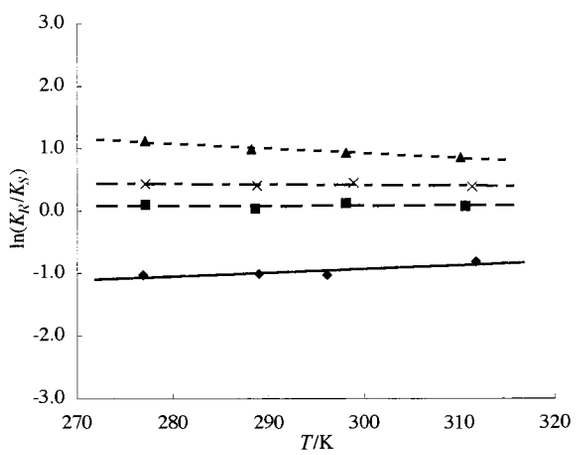
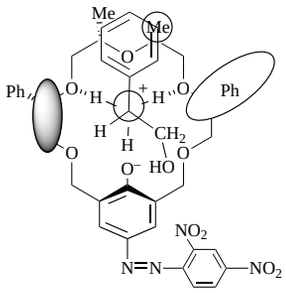
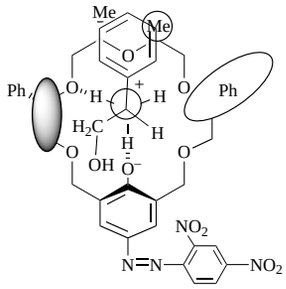


Fig. 5 Temperature dependence of $\ln(K_R/K_S)$ for the complexation of 1-phenylethylamine **32** with crown ethers; ◆ (*S*,*S*,*S*,*S*)-**1**, ▲ (*R*,*S*,*S*,*R*)-**2**, ■ (*S*,*S*,*S*,*S*)-**3** and × (*R*,*S*,*S*,*R*)-**4**

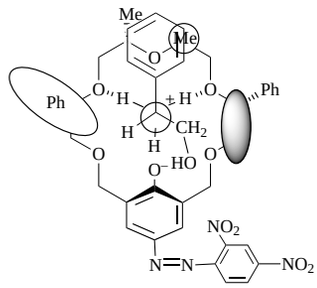
The crown ethers (*S*,*S*,*S*,*S*)-**1** and (*S*,*S*,*S*,*S*)-**3** showed *R*-selectivity towards the 2-substituted 2-aminoethanol derivatives **28**, **29** and **30** whilst the crown ethers having the *R*,*S*,*S*,*R*-configuration showed *S*-selectivity towards these amines. Since these selectivities, except for that of (*S*,*S*,*S*,*S*)-**1** towards **28**, are obviously found below T_{iso} (governed by $-\Delta_{R,S}\Delta H$), we explain these selectivities in terms of steric interactions between the steric barriers of the crown ether and the ligands of the amine. On the basis of CPK molecular model examination of the complexes and with the assumptions[12] that the phenolate



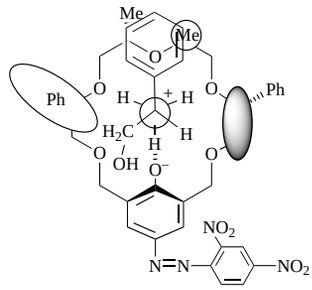
33



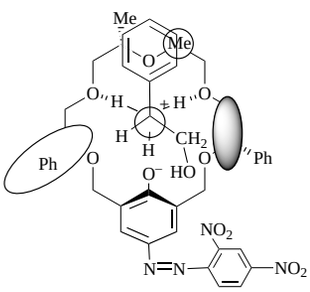
34



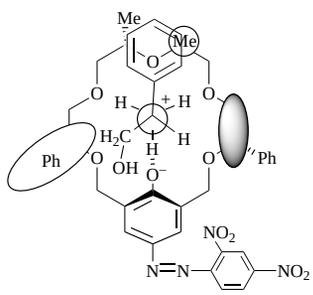
35



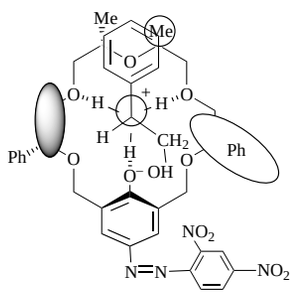
36



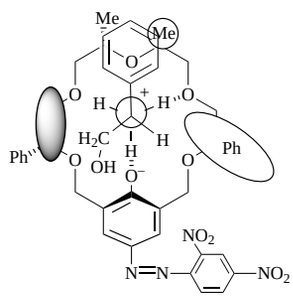
37



38



39



40

oxygen atom necessarily participates in binding to an amine and the hydroxymethyl group of 2-aminoethanol derivatives occupies preferentially the site near the phenol moiety making the additional hydrogen bonding between the phenolate oxygen atom and the hydroxy group, the predicted geometries **33**, **34**, **35** and **36** are illustrated for the (*S*,*S*,*S*,*S*)-**1**:(*R*)-**30**, the (*S*,*S*,*S*,*S*)-**1**:(*S*)-**30**, the (*R*,*S*,*S*,*R*)-**2**:(*R*)-**30** and the (*R*,*S*,*S*,*R*)-**2**:(*S*)-**30** complexes, respectively. Judging from the steric requirements of CPK molecular models of the complexes of (*S*,*S*,*S*,*S*)-**1** and the observed enantiomer selectivities, we assume that the area over the hydrogen atom at the 12 o'clock position is the less hindered site and that the C-5 phenyl substituent occupies a pseudo-equatorial position; this makes the C-4 methylene and the C-5 methine groups effective chiral barriers. 'The ethyleneoxy barrier' (shaded ellipse in the geometries) functions as the more effective chiral barrier on the β-face of the complex compared with the C-13 phenyl substituent (open ellipse in the geometries). Similarly, the C-13 methine and the C-14 methylene groups serve as 'the ethyleneoxy barrier' in the complexes of (*R*,*S*,*S*,*R*)-**2**.

With the assumptions described above, the *R*-selectivity of the combination (*S*,*S*,*S*,*S*)-**1**:**30** is interpreted as arising from steric repulsion between 'the ethyleneoxy barrier' and the hydroxymethyl group of (*S*)-**30** and making the (*S*,*S*,*S*,*S*)-**1**:(*S*)-**30** complex with the geometry **34** less stable than the (*S*,*S*,*S*,*S*)-**1**:(*R*)-**30** complex. The *S*-selectivity of the combination (*R*,*S*,*S*,*R*)-**2**:**30** is analogously rationalized; the (*R*,*S*,*S*,*R*)-**2**:(*R*)-**30** complex with the geometry **35** was destabilized by steric repulsion between 'the ethyleneoxy barrier' and the hydroxymethyl group of the amine.

The predicted geometries **37**, **38**, **39** and **40** are illustrated for the (*S*,*S*,*S*,*S*)-**3**:(*R*)-**30**, the (*S*,*S*,*S*,*S*)-**3**:(*S*)-**30**, the (*R*,*S*,*S*,*R*)-**4**:(*R*)-**30** and the (*R*,*S*,*S*,*R*)-**4**:(*S*)-**30** complexes, respectively. On the basis of the steric requirements of CPK molecular models of the complexes of (*S*,*S*,*S*,*S*)-**3**, it is assumed that the pseudo-equatorial C-14 phenyl substituent makes the C-13 methylene and the C-14 methine groups 'the ethyleneoxy barrier'; but the phenyl substituent at C-4 position is the more effective chiral barrier on the β-face of the complex and thus plays a more important role in chiral discrimination. The *R*-selectivities of the combination (*S*,*S*,*S*,*S*)-**3**:**30** is interpreted as arising from steric repulsion between the C-4 phenyl chiral barrier and the hydroxymethyl group of (*S*)-**30** and thus making the (*S*,*S*,*S*,*S*)-**3**-(*S*)-**30** complex with the geometry **38** less stable than the (*S*,*S*,*S*,*S*)-**3**-(*R*)-**30** complex. Analogously, steric repulsion between the C-14 phenyl chiral barrier and the hydroxymethyl group of (*R*)-**30** made the (*R*,*S*,*S*,*R*)-**4**:**30** complex with the geometry **39** less stable than the (*R*,*S*,*S*,*R*)-**4**:(*S*)-**30** complex.

Fig. 4 demonstrates that the most stable complexes for (*R*,*S*,*S*,*R*)-**2** and (*S*,*S*,*S*,*S*)-**3** were formed with (*S*)-**31** and with (*R*)-**31**, respectively, below T_{iso}. Although the *S*-selectivity of the combination (*R*,*S*,*S*,*R*)-**4**:**31** was found above T_{iso}, it is not clear whether the *R*-selectivity of the combination (*S*,*S*,*S*,*S*)-**1**:**31** was observed above or below T_{iso}. The predicted geometries **41**, **42**, **43** and **44** where the hydroxymethyl group occupies the less hindered site near the phenolate oxygen atom are illustrated for the (*R*,*S*,*S*,*R*)-**2**:(*R*)-**31**, the (*R*,*S*,*S*,*R*)-**2**:(*S*)-**31**, the (*S*,*S*,*S*,*S*)-**3**:(*R*)-**31** and the (*S*,*S*,*S*,*S*)-**3**:(*S*)-**31** complexes, respectively. It is assumed that the *S*-selectivity of the combination (*R*,*S*,*S*,*R*)-**2**:**31** is due to steric repulsion between the methyl group of (*R*)-**31** and the phenyl substituent which destabilizes the (*R*,*S*,*S*,*R*)-**2**:(*R*)-**31** complex, whilst steric repulsion between the methyl group of (*S*)-**31** and 'the ethyleneoxy barrier' made the (*S*,*S*,*S*,*S*)-**3**:(*S*)-**31** complex less stable than its diastereoisomeric complex.

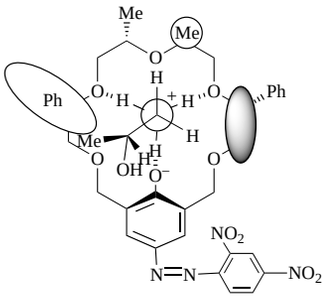
In the case of complexation with **32**, the *S*-selectivity of (*S*,*S*,*S*,*S*)-**1** and the *R*-selectivity of (*R*,*S*,*S*,*R*)-**2** were unambiguously found below T_{iso}. The predicted geometries **45**, **46**, **47** and **48** are illustrated for the (*S*,*S*,*S*,*S*)-**1**:(*S*)-**32**, the (*S*,*S*,*S*,*S*)-**1**:(*R*)-**32**, the (*R*,*S*,*S*,*R*)-**2**:(*S*)-**32** and the (*R*,*S*,*S*,*R*)-**2**:(*R*)-**32** complexes, respectively. It is assumed that steric repulsion between the 'ethyleneoxy barrier' and the methyl group of **32** made the (*S*,*S*,*S*,*S*)-**1**:(*R*)-**32** and the (*R*,*S*,*S*,*R*)-**2**:(*S*)-**32** complexes less stable than the corresponding diastereoisomeric complexes.

As mentioned here, the results demonstrated that arrangement of substituents on the crown ether ring affects enantiomer selectivity: the enantiomer selectivities of the crown ethers having the phenyl substituents located near the diethylene glycol bridge were higher than those of the crown ethers having the same substituents located near the phenol moiety.

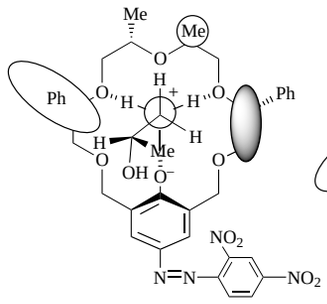
Experimental

General procedure

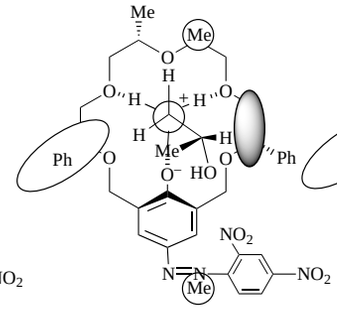
^{1}H NMR spectra were recorded at 270 MHz on a JASCO JNM-MH-270 spectrometer for solutions in $CDCl_3$ with



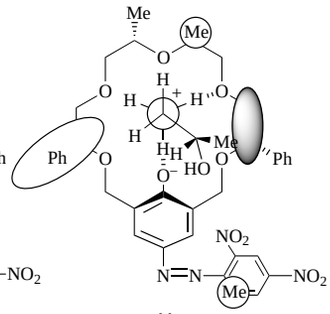
41



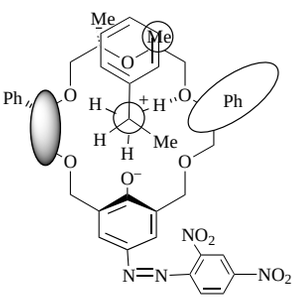
42



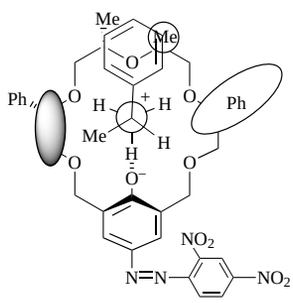
43



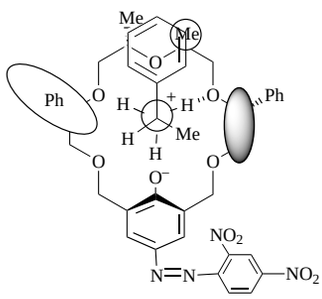
44



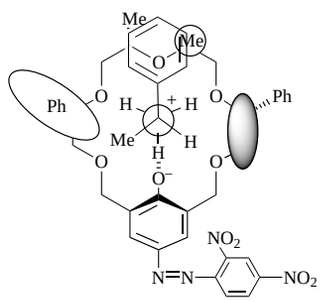
45



46



47



48

$SiMe_4$ as internal standard and *J* values are given in Hz. Mass spectra were recorded on a JEOL-DX-303-HF spectrometer using *m*-nitrobenzyl alcohol as a matrix. Elemental analyses were carried out by Yanagimoto CHN-Corder, Type 2. Mps were measured on a Yanagimoto micro melting point apparatus and are uncorrected. UV and visible spectra were recorded on a Hitachi 330 spectrometer. IR spectra were measured on a Hitachi 260-10 spectrometer. Optical rotations were measured using a JASCO DIP-40 polarimeter at ambient temperature and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. The chiral amines: (*R*)-**28**, (*S*)-**28**, (*R*)-**29**, (*S*)-**29**, (*R*)-**31**, (*S*)-**31**, (*R*)-**32** and (*S*)-**32** were purchased from Aldrich Chemical Company, Inc. and (*R*)-**30** from Tokyo Kasei Kogyo Co., Ltd. These amines were used without further purification. (*S*)-2-Amino-2-phenylethanol **30** purchased from Aldrich Chemical Company, Inc. was used after recrystallization from benzene–hexane.[13]

(2*S*)-2-Tetrahydropyranyloxypropan-1-ol 5

A mixture of ethyl (*S*)-lactate (100 g, 0.847 mol), 3,4-dihydro-2*H*-pyran (142 g, 1690 mol) and a few drops of hydrochloric acid was stirred at room temperature for 12 h after which it was washed with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure to give oily products. These, dissolved in dry THF (700 cm^3), were added slowly to a suspension of $LiAlH_4$ (25.0 g, 0.659 mol) in dry THF (1200 cm^3). After the mixture had been refluxed for 4 h, it was cooled to 0–5 °C and diluted with acetone (80 cm^3) and water (10 cm^3). Deposited solids were filtered off and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure to give (*S*)-**5** (122 g, 90%) as a mixture of diastereoisomers, which was used for the next reaction without further purification.

(2*S*)-3-Benzyloxypropan-2-ol 7

A solution of (*S*)-**5** (131 g, 0.819 mol) in dry THF (600 cm^3) was carefully added to a suspension of sodium hydride (28.8 g, 1.20 mol) in dry THF (700 cm^3) after which the mixture was refluxed for 1.5 h. After the reaction mixture had been cooled to 0–5 °C, it was treated with benzyl chloride (154 g, 1.22 mol), added slowly and then refluxed for 32 h. After this, the reaction mixture was treated with a small amount of water, added carefully with ice-cooling, and then concentrated under reduced pressure. The residue was extracted with chloroform. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give (*S*)-**6**, which was dissolved in methanol (300 cm^3). The solution was stirred with a few drops of hydrochloric acid for 12 h at room temperature after which it was neutralized with aq. sodium hydrogen carbonate and evaporated. The residue was extracted with benzene. The combined extracts were washed with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure. Distillation of the residue gave (*S*)-**7** (97.8 g, 72%); bp 123–125 °C (14 mmHg); $[\alpha]_D^{22}$ +13.2 (*c* 1.05, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3400, 3030, 2975, 2870, 1458, 1370, 1100, 1030, 1000, 965, 855, 742 and 710; δ_H($CDCl_3$) 1.14 (3H, d, *J* 6.4, CH_3), 2.33 (1H, s, OH), 3.29 (1H, dd *J* 7.9 and 9.4, CH_2), 3.46 (1H, dd *J* 3.2 and 9.4, CH_2), 3.95–4.04 (1H, m, CH), 4.51 (2H, s, benzylic CH_2) and 7.25–7.36 (5H, m, C_6H_5) (Found: C, 72.08; H, 8.5. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%).

A diastereoisomeric mixture of 2,4-dimethyl-3-oxapentane-1,5-diol 9

A solution of (*S*)-**7** (45.7 g, 0.275 mol) in dry THF (600 cm^3) was slowly added to a suspension of sodium hydride (7.92 g, 0.330 mol) in dry THF (800 cm^3) after which the mixture was stirred for 3 h under reflux. After the reaction mixture had been cooled to room temperature, it was treated with ethyl (±)-2-bromopropionate (100 g, 0.552 mol), added slowly, and then stirred for 19 h at room temperature. A small amount of water was carefully added to the reaction mixture with ice-cooling, after which the volatile materials were evaporated under reduced pressure. The residue was extracted with chloroform. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give oily products, which were dissolved in dry THF (600 cm^3). The THF solution was added slowly to a suspension of $LiAlH_4$ (16.0 g, 0.422 mol) in dry THF (1000 cm^3) and the mixture was stirred for 24 h at room temperature. Saturated aq. ammonium chloride was carefully added to the reaction mixture with ice-cooling, to give a solid which was filtered off. The filtrate was evaporated under reduced pressure and the residue extracted with methylene dichloride. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give oily products, which were distilled to give **8** (62.5 g, 51%); bp 125–127 °C (0.4 mmHg). A solution of **8** (61.0 g, 0.272 mol) and toluene-*p*-sulfonic acid monohydride (1.00 g, 5.26 mmol) in ethanol (1000 cm^3) was vigorously stirred at room temperature

over 10% Pd-on-carbon (5.80 g) under 1 atm of hydrogen. After hydrogen uptake had ceased, the catalyst was filtered off. The filtrate was neutralized with aq. sodium hydrogen carbonate and concentrated under reduced pressure. The residue was extracted with methylene dichloride and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give **9** (35.4 g, 97%) as a mixture of diastereoisomers, which was used for the next reaction without further purification.

(2*S*,4*S*)-2,4-Dimethyl-1,5-di-*p*-tosyloxy-3-oxapentane 10

Toluene-*p*-sulfonyl chloride (130 g, 0.682 mol) was added to a solution of **9** (40.8 g, 0.304 mol) in pyridine (220 cm^3) at 0–5 °C, after which the mixture was stirred at the same temperature for 3.5 h and then poured into ice–water, acidified (pH 2.0) with hydrochloric acid and extracted with chloroform. The combined extracts were washed successively with dil. hydrochloric acid, aq. sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure to give a white solid, whose ^1H NMR spectrum showed two sets of signals; δ_H($CDCl_3$) 1.04 [6H, d *J* 7.3, CH_3 for (*S*,*S*)-**10**], 1.07 [6H d *J* 6.3, CH_3 for (*S*,*R*)-**10**], 2.45 [12H, s, $ArCH_3$ for (*S*,*S*)-**10** and (*S*,*R*)-**10**], 3.60–3.85 [6H, m, CH and OCH_2 for (*S*,*S*)-**10**], 3.78–3.91 [6H, m, CH and OCH_2 for (*S*,*R*)-**10**], 7.32–7.36 [8H, m, ArH for (*S*,*S*)-**10** and (*S*,*R*)-**10**] and 7.75–7.80 [8H, m, ArH for (*S*,*S*)-**10** and (*S*,*R*)-**10**]. The solid was recrystallized seven times from methanol until the doublet signal at δ 1.07 had disappeared to give diastereoisometrically and enantiomerically pure (*S*,*S*)-**10** (26.8 g, 20%); mp 82.0–82.5 °C; $[a]_D^{29}$ +3.4 (*c* 0.990, $CHCl_3$). HPLC analysis [Opti-Pak XC, 250 mm × 4.6 mm column, hexane–ethanol (98:2, 0.1 cm^3 min^{-1})] showed only a single peak for (*S*,*S*)-**10** [R_t/min 59.9], that for (*R*,*R*)-**10** [R_t/min 67.8] being absent; ν_{max}(KBr)/cm^{-1} 2980, 2960, 2940, 2920, 1595, 1365, 1342, 1200, 1180, 1120, 995, 975, 858, 850, 820, 790, 705 and 665; δ_H($CDCl_3$) 1.04 (6H, d, *J* 7.3, CH_3), 2.45 (6H, s, $ArCH_3$), 3.60–3.82 (2H, m, CH), 3.85 (4H, d, *J* 5.2, OCH_2), 7.34 (4H, d, *J* 8.4, ArH) and 7.77 (4H, d, *J* 8.4, ArH) (Found: C, 54.00; H, 5.8; S, 14.44. $C_{20}H_{26}O_7S_2$ requires C, 54.28; H, 5.92; S, 14.49%).

1,3-Bis[(4*S*)-4-hydroxy-4-phenyl-2-oxabutyl]-2,5-dimethoxybenzene 14

A solution of (*S*)-**11** {$[a]_D^{25}$ +58.0 (*c* 1.00, $CHCl_3$); 30.8 g, 139 mmol} which had been prepared from (*S*)-mandelic acid as the mixture of two diastereoisomers[5] in dry THF (150 cm^3) was slowly added to a suspension of sodium hydride (15.2 g, 0.633 mol) in dry THF (150 cm^3). After the mixture had been refluxed for 1.5 h, it was cooled to room temperature and treated with a solution of 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (22.3 g, 68.8 mmol) in dry THF (100 cm^3). The mixture was refluxed for 12 h, after which it was treated with a small amount of water with ice-cooling, and concentrated under reduced pressure. The residue was extracted with ethyl acetate and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to give (*S*,*S*)-**12** (32.3 g, 87%) [hexane–ethyl acetate (9:1)] as a yellow oil, which was dissolved in methanol (150 cm^3). The solution was stirred with a few drops of hydrochloric acid at room temperature for 12 h and then evaporated under reduced pressure. The residue was extracted with ethyl acetate. The combined extracts were washed with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to give (*S*,*S*)-**14** (17.3 g, 65%) [hexane–ethyl acetate (2:1)]; $[a]_D^{22}$ +39.3 (*c* 1.467, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3440, 2900, 1605, 1480, 1250, 1210, 1110, 1065, 1015, 756 and 702; δ_H($CDCl_3$) 2.87 (2H, d, *J* 2.3, OH), 3.56 (2H, dd, *J* 8.9 and 9.8, OCH_2), 3.70 (2H, dd, *J* 3.1 and 9.8, OCH_2), 3.71 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.63 (4H, s, benzylic CH_2), 4.94 (2H, ddd, *J* 2.3, 3.1 and 8.9, C*H*Ph), 6.89 [2H, s, $(MeO)_2ArH$] and 7.27–7.40 (10 m, C_6H_5) (Found: C, 70.88; H, 6.9. $C_{22}H_{30}O_6$ requires C, 71.21; H, 6.90%).

1,3-Bis[(4*R*)-4-hydroxy-4-phenyl-2-oxabutyl]-2,5-dimethoxybenzene 15

In a manner similar to that described for the preparation of (*S*,*S*)-**14**, reaction of (*R*)-**11** (10.1 g, 0.188 mol) which was prepared from (*R*)-mandelic acid as a mixture of two diastereoisomers[8] with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (7.41 g, 22.9 mmol) followed by silica gel chromatography of the products gave (*R*,*R*)-**13** [hexane–ethyl acetate (2:1)]. Deprotection of (*R*,*R*)-**13** with methanol containing a few drops of hydrochloric acid gave (*R*,*R*)-**15** (5.79 g, 58%) after silica gel chromatography [hexane–ethyl acetate (2:1)]; $[a]_D^{25}$ −3.73 (*c* 0.346, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3430, 2902, 1605, 1482, 1250, 1110, 1065, 1012, 908, 765 and 705; δ_H($CDCl_3$) 2.86 (2H, d, *J* 2.6, OH), 3.56 (2H, dd, *J* 8.7 and 9.7, OCH_2), 3.70 (2H, dd, *J* 3.1 and 9.7, OCH_2), 3.71 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.63 (4H, s, benzylic CH_2), 4.94 (2H, ddd, *J* 2.6, 3.1 and 8.7, C*H*Ph), 6.89 [2H, s, $(MeO)_2ArH$] and 7.28–7.41 (10, m, C_6H_5) (Found: M^+, 438.2072. $C_{26}H_{30}O_6$ requires *M*, 438.2042).

(5*S*,8*S*,10*S*,13*S*)-19,21-Dimethoxy-8,10-dimethyl-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene 16

A solution of (*S*,*S*)-**14** (660 mg, 1.51 mmol) and (*S*,*S*)-**10** (705 mg, 1.59 mmol) in dry DMF (150 cm^3) was added dropwise to a mixture of sodium hydride (147 mg, 6.13 mmol) and potassium tetrafluoroboranuide (228 mg, 1.63 mmol) in dry DMF (150 cm^3) over a 9 h period at 90 °C, after which the mixture was heated for further 48 h at the same temperature. After the mixture had been cooled to 0–5 °C, it was treated with a small amount of water and then evaporated under reduced pressure. The residue was extracted with ethyl acetate and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to give (*S*,*S*,*S*,*S*)-**16** (300 mg, 37%) [hexane–ethyl acetate (4:1)] as a colourless glass; $[a]_D^{22}$ +143 (*c* 0.495, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2905, 2895, 2884, 1598, 1475, 1442, 1360, 1238, 1190, 1000, 760 and 700; δ_H($CDCl_3$) 0.97 (6H, d, *J* 6.4, CH_3), 3.18 (2H, dd, *J* 2.7 and 10.0, OCH_2), 3.26 (2H, dd, *J* 7.2 and 10.1, OCH_2), 3.63–3.68 (6H, m, OCH_2 and C*H*Me), 3.81 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 4.47 (2H, br s, C*H*Ph), 4.48 (2H, d, *J* 10.0, benzylic CH_2), 4.85 (2H, d, *J* 10.0, benzylic CH_2), 6.88 [2H, s, $(MeO)_2ArH$] and 7.28–7.36 (10H, m, C_6H_5) (Found: M^+, 536.2747. $C_{32}H_{40}O_7$ requires *M*, 536.2774).

(5*R*,8*S*,10*S*,13*R*)-19,21-Dimethoxy-8,10-dimethyl-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene 17

By a procedure similar to that described for the preparation of (*S*,*S*,*S*,*S*)-**16**, reaction of (*R*,*R*)-**15** (3.22 g, 7.35 mmol) with (*S*,*S*)-**10** (3.62 g, 8.17 mmol) followed by silica gel chromatography of the products gave (*R*,*S*,*S*,*R*)-**17** (1.70 g, 43%) [hexane–ethyl acetate (4:1)] as a colourless viscous oil; $[a]_D^{24}$ +133 (*c* 0.489, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2890, 2850, 1600, 1482, 1452, 1362, 1250, 1222, 1090, 1000, 760 and 700; δ_H($CDCl_3$) 0.91 (6H, d, *J* 6.3, CH_3), 3.10 (2H, dd, *J* 6.6 and 9.6, OCH_2), 3.22 (2H, dd, *J* 5.4 and 9.6, OCH_2), 3.61–3.67 (6H, m, OCH_2 and C*H*Me), 3.83 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.49 (2H, dd, *J* 4.5 and 11.0 C*H*Ph), 4.50 (2H, d, *J* 10.9, benzylic CH_2), 4.69 (2H, d, *J* 10.9, benzylic CH_2), 6.90 [2H, s, $(MeO)_2ArH$] and 7.28–7.34 (10H, m, C_6H_5) (Found: M^+, 536.2817. $C_{32}H_{40}O_7$ requires *M*, 536.2774).

(*S*,*S*,*S*,*S*)-21-Hydroxy-19-methoxy-8,10-dimethyl-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene 18

Ethanethiol (1.18 g, 19.0 mmol) was added slowly to a suspension of sodium hydride (482 mg, 20.1 mmol) in dry DMF (16

cm^3) at 0–5 °C after which a solution of (*S*,*S*,*S*,*S*)-**16** (535 mg, 0.997 mmol) in dry DMF (15 cm^3) was added dropwise to the resulting clear solution of sodium ethanethiolate in dry DMF with ice-cooling. The mixture was heated at 100 °C for 2 h, and then cooled to 0–5 °C, neutralized with hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residue on silica gel gave (*S*,*S*,*S*,*S*)-**18** (418 mg, 80%) [hexane–ethyl acetate (3:1)] as a colourless viscous oil; $[\alpha]_D^{22}$ +133 (*c* 0.489, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3350, 2902, 2850, 1600, 1482, 1455, 1370, 1258, 1220, 1120, 1100, 1055, 760 and 702; δ_H($CDCl_3$) 1.10 (6H, d, *J* 6.7, CH_3), 3.25–3.45 (4H, m, OCH_2), 3.65–3.78 (4H, m, OCH_2), 3.74 (3H, s, OCH_3), 4.40–4.45 (2H, m, C*H*Me), 4.60 (2H, dd, *J* 3.5 and 8.7 (C*H*Ph), 4.65 (2H, d, *J* 10.1, benzylic CH_2), 4.76 (2H, d, *J* 10.1, benzylic CH_2), 6.74 (2H, s, HOAr*H*), 7.27–7.38 (10H, m, C_6H_5) and 7.93 (1H, s, OH) (Found: M^+, 522.2595. $C_{31}H_{38}O_7$ requires *M*, 522.2618).

(5*R*,8*S*,10*S*,13*R*)-21-Hydroxy-19-methoxy-8,10-dimethyl-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene 19

In a manner similar to that described for the preparation of (*S*,*S*,*S*,*S*)-**18**, treatment of (*R*,*S*,*S*,*R*)-**17** (535 mg, 0.997 mmol) with sodium ethanethiolate in DMF gave (*R*,*S*,*S*,*R*)-**19** (418 mg, 85%) as a colourless viscous oil after silica gel chromatography [hexane–ethyl acetate (4:1)]; $[\alpha]_D^{22}$ −183 (*c* 0.203, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3460, 2900, 2860, 1600, 1485, 1450, 1370, 1250, 1220, 1100, 1062, 760 and 702; δ_H($CDCl_3$) 1.15 (6H, d, *J* 6.3, CH_3), 3.25 (2H, dd, *J* 7.4 and 8.7, OCH_2), 3.53 (2H, dd, *J* 4.3 and 8.7, OCH_2), 3.62–3.72 (4H, m, OCH_2), 3.75 (3H, s, OCH_3), 4.00–4.06 (2H, m, C*H*Me), 4.66 (2H, dd, *J* 4.0 and 7.9, C*H*Ph), 4.72 (4H, s, benzylic CH_2), 6.73 (2H, s, HOAr*H*), 7.24–7.39 (10H, m, C_6H_5) and 7.75 (1H, s, OH) (Found: M^+, 522.2675. $C_{31}H_{38}O_7$ requires *M*, 522.2618).

(1*S*,5*S*,7*S*,11*S*)-5,7-Dimethyl-1,11-diphenyl-3,7,9-trioxaundecane-1,11-diol 22

A solution of (*S*)-**11** (11.2 g, 50.4 mmol) in dry THF (70 cm^3) was slowly added to a suspension of sodium hydride (1.90 g, 79.2 mmol) in dry THF (40 cm^3) after which the mixture was refluxed for 1.5 h and then treated with a solution of (*S*,*S*)-**10** (11.0 g, 24.8 mmol) in dry THF (70 cm^3) added at room temperature. After the mixture had been refluxed for 30 h, it was cooled to 0–5 °C and treated with a small amount of water, added carefully. After evaporation of the mixture under reduced pressure, the residue was extracted with ethyl acetate and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel chromatography of the residue gave (*S*,*S*,*S*,*S*)-**20** [hexane–ethyl acetate (9:1)], which was dissolved in methanol (100 cm^3) containing a few drops of hydrochloric acid. The solution was stirred for 12 h at room temperature after which it was evaporated under reduced pressure. The residue was extracted with ethyl acetate and the combined extracts were washed with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel chromatography of the residue gave (*S*,*S*,*S*,*S*)-**22** (2.73 g, 28%) [hexane–ethyl acetate (4:1)]; $[\alpha]_D^{25}$ +94.0 (*c* 0.792, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3350, 2950, 2900, 1438, 1180, 1062, 995, 960, 748 and 685; δ_H($CDCl_3$) 1.20 (6H, d, *J* 6.4, CH_3), 3.46–3.68 (8H, m, OCH_2), 3.76–3.89 (2H, m, C*H*Me), 4.13 (2H, br s, OH), 4.93 (2H, dd, *J* 2.6 and 8.9, C*H*Ph) and 7.22–7.64 (10, m, C_6H_5) (Found: C, 70.48; H, 8.1. $C_{22}H_{30}O_5$ requires C, 70.56; H, 8.07%).

(1*R*,5*S*,7*S*,11*R*)-5,7-Dimethyl-1,11-diphenyl-3,7,9-trioxaundecane-1,11-diol 23

In a manner similar to that described for the preparation of (*S*,*S*,*S*,*S*)-**22**, reaction of (*R*)-**11** (4.89 g, 22.0 mmol) with (*S*,*S*)-**10** (4.81 g, 10.9 mmol) gave (*R*,*S*,*S*,*R*)-**21** after silica gel chromatography [hexane–ethyl acetate (2:1)]. Treatment of (*R*,*S*,*S*,*R*)-**21** with methanol (50 cm^3) and a few drops of hydrochloric acid gave (*R*,*S*,*S*,*R*)-**23** (874 mg, 21%) after silica gel chromatography [hexane–ethyl acetate (4:1)]; $[\alpha]_D^{25}$ −59.6 (*c* 0.286, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3400, 2900, 1455, 1380, 1338, 1120, 910, 762 and 705; δ_H($CDCl_3$) 1.18 (6H, d, *J* 6.4, CH_3), 3.42–3.53 (4H, m, OCH_2), 3.62 (2H, dd, *J* 3.5 and 10.4, OCH_2), 3.71 (2H, dd, *J* 3.0 and 10.4, OCH_2), 3.77–3.89 (2H, m, C*H*Me), 4.13 (2H, br s, OH), 4.85–4.95 (2H, m, C*H*Ph) and 7.22–7.39 (10H, m, C_6H_5); the high-resolution mass spectrum could not be recorded because of the weak molecular ion peak; *m*/*z* (EI) (relative intensity) 375 (M^+ + H, 26), 255 (38), 237 (110) and 117 (34).

(4*S*,8*S*,10*S*,14*S*)-19,21-Dimethoxy-8,10-dimethyl-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene 24

A solution of (*S*,*S*,*S*,*S*)-**22** (1.51 g, 4.02 mmol) and 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (1.37 g, 4.23 mmol) in dry THF (430 cm^3) was added to a mixture of sodium hydride (298 mg, 12.4 mmol) and potassium tetrafluoroboranuide (290 mg, 2.29 mmol) in dry THF (170 cm^3) over a 15 h period at 50 °C, after which the mixture was refluxed for further 48 h. After the reaction mixture had been cooled to room temperature, it was treated with a small amount of water added carefully and then concentrated under reduced pressure. The residue was extracted with ethyl acetate and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel chromatography of the residue gave (*S*,*S*,*S*,*S*)-**24** (774 mg, 36%) [hexane–ethyl acetate (4:1)] as a colourless viscous oil; $[\alpha]_D^{24}$ +113 (*c* 0.671, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2860, 1605, 1490, 1460, 1225, 1100, 1018, 765 and 710; δ_H($CDCl_3$), 1.01 (6H, d, *J* 6.4, CH_3), 3.29–3.79 (10H, m, OCH_2 and C*H*Me), 3.77 (3H, s, OCH_3), 4.11 (3H, s, OCH_3), 4.27 (2H, d, *J* 10.0, benzylic CH_2), 4.67 (2H, dd, *J* 2.5 and 9.4 C*H*Ph), 4.68 (2H, d, *J* 10.0, benzylic CH_2), 6.73 [2H, s, $(MeO)_2ArH$] and 7.30–7.43 (10H, m, C_6H_5) (Found: M^+, 536.2747. $C_{32}H_{40}O_7$ requires *M*, 536.2774).

(4*R*,8*S*,10*S*,14*R*)-19,21-Dimethoxy-8,10-dimethyl-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene 25

In a manner similar to that described for the preparation of (*S*,*S*,*S*,*S*)-**24**, reaction of (*R*,*S*,*S*,*R*)-**23** (784 mg, 2.09 mmol) with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (737 mg, 2.27 mmol) followed by silica gel chromatography of the products gave (*R*,*S*,*S*,*R*)-**25** (450 mg, 40%) [hexane–ethyl acetate (4:1)] as a colourless viscous oil; $[\alpha]_D^{24}$ +150 (*c* 0.453, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 2900, 1610, 1490, 1460, 1245, 1100, 1018, 762 and 705; δ_H($CDCl_3$) 1.00 (6H, d, *J* 6.3, CH_3), 3.22–3.59 (8H, m, OCH_2), 3.74–4.59 (2H, m, C*H*Me), 3.79 (3H, s, OCH_3), 4.14 (3H, s, OCH_3), 4.24 (2H, d, *J* 10.9, benzylic CH_2), 4.61–4.69 (4H, m, C*H*Ph and benzylic CH_2), 6.75 [2H, s, $(MeO)_2ArH$] and 7.37–7.43 (10H, m, C_6H_5); the high-resolution mass spectrum could not be recorded because of the weak molecular ion peak; *m*/*z* (EI) (relative intensity) 536 (M^+, 36), 417 (28), 297 (100), 237 (26), 181 (34) and 165 (26).

(4*S*,8*S*,10*S*,14*S*)-21-Hydroxy-19-methoxy-8,10-dimethyl-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene 26

In a manner similar to that described for the preparation of (*S*,*S*,*S*,*S*)-**18**, treatment of (*S*,*S*,*S*,*S*)-**24** (561 mg, 1.05 mmol) with sodium ethanethiolate in DMF gave (*S*,*S*,*S*,*S*)-**26** (373 mg, 68%) as a colourless viscous oil after silica gel chromatography [hexane–ethyl acetate (3:1)]; $[\alpha]_D^{22}$ +75.1 (*c* 0.599, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3350, 2900, 1590, 1470, 1440, 1335, 1242, 1080, 1015, 745 and 690; δ_H($CDCl_3$) 1.19 (6H, d, *J* 6.7, CH_3), 3.35–3.76 (8H, m, OCH_2), 3.69 (3H, s, OCH_3), 4.23–4.30 (2H, m, C*H*Me), 4.50 (2H, d, *J* 10.9, benzylic CH_2), 4.60 (2H, d,

J 10.9, benzylic CH_2), 4.74 (2H, dd, *J* 3.0 and 9.6, C*H*Ph), 6.59 (2H, s, HOAr*H*), 7.33–7.41 (10H, m, C_6H_5) and 7.96 (1H, s, OH) (Found: M^+, 522.2597. $C_{31}H_{38}O_7$ requires *M*, 522.2618).

(4*R*,8*S*,10*S*,14*R*)-21-Hydroxy-19-methoxy-8,10-dimethyl-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene 27

In a manner similar to that described for the preparation of (*S*,*S*,*S*,*S*)-**18**, treatment of (*R*,*S*,*S*,*R*)-**25** (437 mg, 0.814 mmol) with sodium ethanethiolate gave (*R*,*S*,*S*,*R*)-**27** (281 mg, 66%) as a colourless viscous oil after silica gel chromatography [hexane–ethyl acetate (3:1)]; $[\alpha]_D^{22}$ −108 (*c* 0.161, $CHCl_3$); ν_{max}(neat film)/cm^{-1} 3400, 2900, 1605, 1480, 1450, 1240, 1090, 762 and 705; δ_H($CDCl_3$) 1.17 (6H, d, *J* 6.3, CH_3), 3.41–3.73 (8H, m, OCH_2), 3.69 (3H, s, OCH_3), 4.04–4.16 (2H, m, C*H*Me), 4.57 (2H, d, *J* 11.2, benzylic CH_2), 4.64 (2H, d, *J* 11.2, benzylic CH_2), 4.69 (2H, dd, *J* 2.8 and 10.1, C*H*Ph), 6.59 (2H, s, HOAr*H*), 7.32–7.40 (10H, m, C_6H_5) and 7.68 (1H, s, OH); the high-resolution mass spectrum could not be recorded because of the weak molecular ion peak; *mz* (EI) (relative intensity) 522 (M^+, 7), 503 (7), 403 (100), 373 (15), 283 (35), 253 (37), 237 (17), 165 (35) and 151 (27).

(5*S*,8*S*,10*S*,13*S*)-19-(2′,4′-Dinitrophenylazo)-21-hydroxy-8,10-dimethyl-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]-henicosane-1(21),17,19-triene 1

A solution of (*S*,*S*,*S*,*S*)-**18** (317 mg, 0.607 mmol) in acetonitrile (30 cm^3) was added to a solution of CAN (1.03 g, 1.87 mmol) in acetonitrile (12 cm^3). The mixture was stirred for 2 h at room temperature and then cooled to 0–5 °C, when it was treated with water and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to give the quinone derivative (279 mg, 91%) (chloroform) as a yellow oil; δ_H($CDCl_3$) 1.04 (6H, d, *J* 6.3, CH_3), 3.10 (2H, dd, *J* 2.5 and 9.7, OCH_2), 3.28 (2H, dd, *J* 9.4 and 9.7, OCH_2), 3.72 (2H, dd, *J* 8.9 and 11.9, OCH_2), 3.75 (2H, dd, *J* 2.0 and 11.9, OCH_2), 3.81–3.87 (2H, m, C*H*Me), 4.35 (2H, d, *J* 15.2 benzylic CH_2), 4.45 (2H, dd, *J* 2.0 and 8.9, C*H*Ph), 4.38 (2H, d, *J* 15.2 benzylic CH_2), 6.79 (2H, s, the quinone moiety CH) and 7.28–7.37 (10H, m, C_6H_5). To a solution of the quinone derivative (275 mg, 0.543 mmol) in a mixture of methylene dichloride (12 cm^3) and ethanol (12 cm^3) was added a solution of 2,4-dinitrophenylhydrazine (545 mg, 2.75 mmol) in a mixture of ethanol (12 cm^3) and conc. H_2SO_4 (2 cm^3). The mixture was stirred for 1.5 h at room temperature after which it was diluted with water and extracted with chloroform. The combined extracts were washed with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel to give a solid [hexane–ethyl acetate (2:1)], which was further purified by preparative recycling HPLC (JAIGEL 1H and JAIGEL 2H column, chloroform) to give (*S*,*S*,*S*,*S*)-**1** (308 mg, 81%) as a red amorphous solid; λ_{max}($CHCl_3$)/nm 405 (ε 2.34×10^4); ν_{max}(KBr)/cm^{-1} 3250, 2860, 1600, 1535, 1348, 1295, 1130, 1115, 905, 830, 760 and 700; δ_H($CDCl_3$) 1.12 (6H, d, *J* 6.6, CH_3), 3.27 (2H, dd, *J* 2.5 and 10.3, OCH_2CHMe), 3.46 (2H, dd, *J* 9.1 and 9.5, OCH_2CHPh), 3.70 (2H, t, *J* 10.3, OCH_2CHMe), 3.84 (2H, dd, *J* 2.6 and 9.5, OCH_2CHPh), 4.11–4.50 (2H, m, C*H*Me), 4.60 (2H, dd, *J* 2.5 and 9.1 C*H*Ph), 4.78 (2H, d, *J* 11.1, benzylic CH_2), 4.88 (2H, d, *J* 11.1, benzylic CH_2), 7.28–7.37 (10H, m, C_6H_5), 7.83 [1H, d, *J* 8.9, $(NO_2)_2$Ar*H*], 7.85 (2H, s, HOAr*H*), 8.49 [1H, dd, *J* 2.3 and 8.9, $(NO_2)_2$Ar*H*], 8.75 [1H, d, *J* 2.3, $(NO_2)_2$Ar*H*] and 9.45 (1H, s, OH) (Found: C, 62.64; H, 5.6; N, 8.22. $C_{36}H_{38}O_{10}N_4$ requires C, 62.97; H, 5.58; N, 8.16%).

(5*R*,8*S*,10*S*,13*R*)-19-(2′,4′-Dinitrophenylazo)-21-hydroxy-8,10-dimethyl-5,13-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]-henicosane-1(21),17,19-triene 2

By a procedure similar to that described for the preparation of (*S*,*S*,*S*,*S*)-**1**, oxidation of (*R*,*S*,*S*,*R*)-**19** (776 mg, 1.48 mmol) with CAN (2.49 g, 4.53 mmol) in acetonitrile gave the quinone derivative (692 mg, 84%) as a yellow oil after silica gel chromatography (chloroform); δ_H($CDCl_3$) 1.02 (6H, d, *J* 6.4, CH_3), 3.14 (2H, dd, *J* 5.9 and 9.4, OCH_2), 3.26 (2H, dd, *J* 5.9 and 9.4, OCH_2), 3.57–3.67 (4H, m, OCH_2 and C*H*Me), 3.72 (2H, dd, *J* 8.4 and 11.7, OCH_2), 4.52 (2H, d, *J* 14.8 benzylic CH_2), 4.54 (2H, dd, *J* 2.5 and 8.4, C*H*Ph), 4.67 (2H, d, *J* 14.8 benzylic CH_2), 6.79 (2H, s, the quinone moiety CH) and 7.28–7.38 (10H, m, C_6H_5). Treatment of the quinone derivative (690 mg, 1.36 mmol) with 2,4-dinitrophenylhydrazine (1.01 g, 5.12 mmol) gave (*R*,*S*,*S*,*R*)-**2** (788 mg, 84%) as a red amorphous solid after silica gel column chromatography [hexane–ethyl acetate (2:1)] followed by preparative recycling HPLC (chloroform); λ_{max}-($CHCl_3$)/nm 400 (ε 2.46×10^4); ν_{max}(KBr)/cm^{-1} 3250, 2850, 1590, 1530, 1460, 1338, 1290, 1125, 900, 830 and 700; δ_H($CDCl_3$), 1.16 (6H, d, *J* 6.3, CH_3), 3.28 (2H, dd, *J* 7.3 and 8.9, OCH_2CHMe), 3.54 (2H, dd, *J* 4.0 and 8.9, OCH_2CHMe), 3.70 (2H, dd, *J* 8.9 and 11.2, OCH_2CHPh), 3.77 (2H, dd, *J* 3.0 and 11.2, OCH_2CHPh), 4.00–4.70 (2H, m, C*H*Me), 4.68 (2H, dd *J* 3.0 and 8.9 C*H*Ph), 4.82 (2H, d, *J* 10.6, benzylic CH_2), 4.87 (2H, d *J* 10.6, benzylic CH_2), 7.29–7.41 (10H, m, C_6H_5), 7.81 [1H, d, *J* 8.9, $(NO_2)_2$ArH], 7.84 (2H, s, HOAr*H*), 8.48 [1H, dd, *J* 2.5 and 8.9, $(NO_2)_2$Ar*H*], 8.75 [1H, d, *J* 2.5, $(NO_2)_2$ArH] and 9.53 (1H, s, OH) (Found: C, 62.63; H, 5.6; N, 8.21. $C_{36}H_{38}O_{10}N_4$ requires C, 62.97; H, 5.58; N, 8.16%).

(4*S*,8*S*,10*S*,14*S*)-19-(2′,4′-Dinitrophenylazo)-21-hydroxy-8,10-dimethyl-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]-henicosane-1(21),17,19-triene 3

By a procedure similar to that described for the preparation of (*S*,*S*,*S*,*S*)-**1**, oxidation of (*S*,*S*,*S*,*S*)-**26** (317 mg, 0.607 mmol) with CAN (1.03 g, 1.87 mmol) in acetonitrile followed by silica gel chromatography of the products gave the quinone derivative (289 mg, 94%) (chloroform) as a yellow oil; δ_H($CDCl_3$) 1.10 (6H, d, *J* 6.3, CH_3), 3.27–3.61 (8H, m, OCH_2), 3.76–3.83 (2H, m, C*H*Me), 4.30 (2H, d, *J* 15.2 benzylic CH_2), 4.64 (2H, dd, *J* 4.0 and 7.9, C*H*Ph), 4.79 (2H, d, *J* 15.2 benzylic CH_2), 6.76 (2H, s, the quinone moiety CH) and 7.29–7.42 (10H, m, C_6H_5). Treatment of the quinone derivative (279 mg, 0.551 mmol) with 2,4-dinitrophenylhydrazine (861 mg, 4.35 mmol) gave (*S*,*S*,*S*,*S*)-**3** (487 mg, 81%) as a red amorphous solid after silica gel column chromatography [hexane–ethyl acetate (2:1)] followed by preparative recycling HPLC (chloroform); λ_{max}($CHCl_3$)/nm 406 (ε 2.38×10^4); ν_{max}(KBr)/cm^{-1} 3250, 2850, 1590, 1535, 1345, 1290, 1110, 1030, 900, 835, 758 and 700; δ_H($CDCl_3$) 1.22 (6H, d, *J* 6.6, CH_3), 3.40 (2H, dd, *J* 4.5 and 9.6, OCH_2CHMe), 3.55 (2H, dd, *J* 2.7 and 10.9, OCH_2CHPh), 3.69 (2H, t, *J* 9.6, OCH_2CHMe), 3.71 (2H, dd, *J* 5.8 and 10.9, OCH_2CHPh), 4.28–4.39 (2H, m, C*H*Me), 4.61 (2H, dd, *J* 2.7 and 10.9 C*H*Ph), 4.61 (2H, d, *J* 11.1, benzylic CH_2), 4.71 (2H, d, *J* 11.1, benzylic CH_2), 7.34–7.47 (10H, m, C_6H_5), 7.78 [1H, d, *J* 8.9, $(NO_2)_2$Ar*H*], 7.71 (2H, s, HOAr*H*), 8.46 [1H, dd, *J* 2.5, 8.9, $(NO_2)_2$Ar*H*], 8.73 [1H, d, *J* 2.5, $(NO_2)_2$Ar*H*] and 9.53 (1H, s, OH) (Found: C, 62.79; H, 5.5; N, 8.05. $C_{36}H_{38}O_{10}N_4$ requires C, 62.97; H, 5.58; N, 8.16%).

(4*R*,8*S*,10*S*,14*R*)-19-(2′,4′-Dinitrophenylazo)-21-hydroxy-8,10-dimethyl-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]-henicosane-1(21),17,19-triene 4

By a procedure similar to that described for the preparation of (*S*,*S*,*S*,*S*)-**1**, oxidation of (*R*,*S*,*S*,*R*)-**27** (279 mg, 0.534 mmol) with CAN (888 mg, 1.62 mmol) in acetonitrile gave the quinone derivative (228 mg, 84%) as a yellow oil after silica gel chromatography (chloroform); δ_H($CDCl_3$) 1.10 (6H, d, *J* 6.2, CH_3), 3.28 (2H, dd, *J* 4.6 and 9.3, OCH_2), 3.43 (2H, dd, *J* 6.3 and 9.3, OCH_2), 3.49–3.63 (4H, m, OCH_2), 3.67–3.74 (2H, m, C*H*Me), 4.42 (2H, d, *J* 15.2 benzylic CH_2), 4.66 (2H, dd, *J* 2.7 and 8.9, C*H*Ph), 4.73 (2H, d, *J* 14.8 benzylic CH_2), 6.75 (2H, s, the quinone moiety CH) and 7.31–7.38 (10H, m, C_6H_5). Treatment of the quinone derivative (220 mg, 0.436 mmol) with 2,4-

dinitrophenylhydrazine (431 mg, 2.18 mmol) gave (*R*,*S*,*S*,*R*)-**4** (246 mg, 81%) as a red amorphous solid after silica gel column chromatography [hexane–ethyl acetate (2:1)] followed by preparative recycling HPLC (chloroform); $\lambda_{max}(CHCl_3)$/nm 404 (ε 2.23×10^4); ν_{max}(KBr)/cm^{-1} 3250, 2900, 1598, 1530, 1460, 1340, 1285, 1125, 1110, 905, 830, 760 and 700; $\delta_H(CDCl_3)$ 1.12 (6H, d, *J* 6.4, CH_3), 3.46 (2H, dd, *J* 4.9 and 9.2, OCH_2CHMe), 3.58–3.77 (6H, m, OCH_2), 4.07–4.11 (2H, m, C*H*Me), 4.73–4.76 (6H, m, C*H*Ph and benzylic CH_2), 7.33–7.42 (10H, m, C_6H_5), 7.72 (2H, s, HOAr*H*), 7.79 [1H, d, *J* 8.9, $(NO_2)_2ArH$], 8.47 [1H, dd, *J* 2.5, 8.9, $(NO_2)_2ArH$], 8.74 [1H, d, *J* 2.5, $(NO_2)_2ArH$] and 9.53 (1H, s, OH) (Found: C, 62.74; H, 5.6; N, 8.07. $C_{36}H_{38}O_{10}N_4$ requires C, 62.97; H, 5.58; N, 8.16%).

References

1 A preliminary communication of part of this work has appeared: K. Naemura, K. Ogasahara, K. Hirose and Y. Tobe, *Tetrahedron Asymm.*, 1997, **8**, 19.

2 J.-M. Lehn, *Supramolecular Chemistry*, VCH Verlagsgesellschaft, Weinheim, 1995 and references cited therein.

3 K. Naemura and R. Fukunaga, *Chem. Lett*., 1985, 1651; K. Naemura, R. Fukunaga and M. Yamanaka, *J. Chem. Soc., Chem. Commun.*, 1985, 1560; K. Naemura, M. Komatsu, K. Adachi and H. Chikamatsu, *J. Chem. Soc., Chem. Commun.*, 1986, 1675; K. Naemura, T. Matsumura, M. Komatsu, Y. Hirose and H. Chikamatsu, *J. Chem. Soc., Chem. Commun.*, 1988, 239; K. Naemura, R. Fukunaga, M. Komatsu, M. Yamanaka and H. Chikamatsu, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 83; K. Naemura, S. Takeuchi, K. Hirose, Y. Tobe, T. Kaneda and Y. Sakata, *J. Chem. Soc., Perkin Trans. 1*, 1995, 213; K. Naemura, K. Ueno, S. Takeuchi, K. Hirose, Y. Tobe, T. Kaneda and Y. Sakata, *J. Chem. Soc., Perkin Trans. 1*, 1996, 383.

4 K. Naemura, T. Fuji, K. Ogasahara, K. Hirose and Y. Tobe, *Chem. Commun.*, 1996, 2749.

5 K. Naemura, Y. Nishikawa, J. Fuji, K. Hirose and Y. Tobe, *Tetrahedron: Asymmetry*, 1997, **8**, 873.

6 K. Naemura, M. Asada, K. Hirose and Y. Tobe, *Tetrahedron: Asymmetry*, 1995, **6**, 1873.

7 P. Huszthy, M. Oue, J. S. Bradshaw, C. Y. Zhu, T. Wang, N. K. Dalley, J. C. Curtis and R. M. Izatt, *J. Org. Chem.*, 1992, **57**, 5383.

8 P. Huszthy, J. S. Bradshaw, C. Y. Zhu and R. M. Izatt, *J. Org. Chem.*, 1991, **56**, 3330.

9 G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1970, **16**, 1327.

10 P. Jacob, P. S. Callery, A. T. Shulgin and N. Castagnoli, Jr., *J. Org. Chem.*, 1976, **41**, 3627.

11 N. J. Rose and R. S. Drago, *J. Am. Chem. Soc.*, 1959, **81**, 6138.

12 T. Kaneda, K. Hirose and S. Misumi, *J. Am. Chem. Soc.*, 1989, **111**, 742; K. Naemura, K. Ueno, S. Takeuchi, Y. Tobe, T. Kaneda and Y. Sakata, *J. Am. Chem. Soc.*, 1993, **115**, 8475.

13 K. Saigo, H. Miura, K. Ishizaki and H. Nohira, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 1188.

Paper 7/03452K
Received 19*th May* 1997
Accepted 5*th August* 1997