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# Preparation of homochiral phenolic crown ethers containing *para*-substituted phenol moiety and chiral subunits derived from (*S*)-1-phenylethane-1,2-diol: their chiral recognition behaviour in complexation with neutral amines

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***Abstract:*** Crown ethers **1–6** containing two chiral subunits derived from (*S*)-1-phenylethane-1,2-diol and a phenol moiety bearing an intra-annular OH group and an additional *para*-substituent have been prepared in enantiomerically pure forms and their enantiomer recognition behaviour in complexation with neutral amines has been examined by the $^1$H n.m.r. spectroscopic method. © 1997 Elsevier Science Ltd. All rights reserved.

Binding cavities of crown ethers have been variously designed to provide a favorable environment for binding guest species selectively and their structural and chiral selectivities in complexation have been extensively studied.[1] Crown ethers containing the phenol moiety bearing the intra-annular OH group possess a cavity capable of binding neutral amines and the introduction of the additional substituent at its *para*-position makes the phenolic crown ether of special interest because the electronic nature of the *para*-substituent varies the acidity of the phenolic group resulting in the variation of their complexing behaviour.[2] In order to seek information on how the acidity of the phenolic group might affect the enantiomer selectivity in complexation of crown ethers with amines as well as the binding ability, using (*S*)-1-phenylethane-1,2-diol as a homochiral building block, we prepared enantiomerically pure crown ethers **1–6** possessing the phenyl chiral barriers and the phenol moiety bearing the *para*-substituent. Their chiral recognition behaviour in complexation with neutral amines was also examined by the $^1$H n.m.r. spectroscopic method in $CDCl_3$.

## Results and discussion

The chiral subunit (*S*)-**7**, $[\alpha]_D$ +58.9 ($CHCl_3$) was prepared from (*S*)-(+)-mandelic acid as the mixture of two diastereoisomers using the reported route.[3] Condensation of 2 mol equiv. of (*S*)-**7** with diethylene glycol bis(*p*-toluenesulfonate) in the presence of NaH followed by deprotection with pyridinium *p*-toluenesulfonate and ethanol gave (*S,S*)-**8**, $[\alpha]_D$ +53.9 ($CHCl_3$) in 76% overall yield for the two steps, which was the common precursor of phenolic crown ethers **1–6**. High-dilution condensation of (*S,S*)-**8** with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in boiling tetrahydrofuran (THF) containing NaH and $KBF_4$ gave (*S,S*)-**9**, $[\alpha]_D$ +94.3 ($CHCl_3$), mp 121–123°C in 65% yield, which was transformed to phenolic crown ethers (*S,S*)-**1** and (*S,S*)-**6**. The intra-annular methyl ether of (*S,S*)-**9** was selectively cleaved with sodium ethanethiolate in DMF[4] to give (*S,S*)-**6**, $[\alpha]_D$ +99.2 ($CHCl_3$) in 74% yield. Oxidation of (*S,S*)-**6** with cerium(IV) ammonium nitrate (CAN) in acetonitrile gave (*S,S*)-**12** in 98% yield, which was immediately treated with 2,4-dinitrophenylhydrazine in a mixture of ethylene dichloride, ethanol and conc. $H_2SO_4$ to give (*S,S*)-**1**, $[\alpha]_D$ +63.3 ($CHCl_3$), mp 81–83°C in 57% yield.

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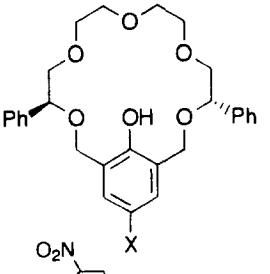
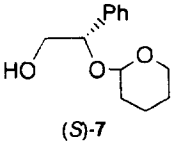
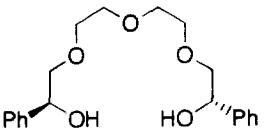
Ring closure of (*S,S*)-**8** with 1,3-bis(bromomethyl)-2-methoxy-5-bromobenzene in the presence of NaH and $KBF_4$ in boiling THF under high-dilution conditions gave (*S,S*)-**10**, $[\alpha]_D$ +83.5 ($CHCl_3$), mp 118–119°C in 67% yield, from which phenolic crown ethers (*S,S*)-**2**, (*S,S*)-**3**, (*S,S*)-**4** and (*S,S*)-**5** were derived. Treatment of (*S,S*)-**10** with *n*-butyl lithium in hexane followed by quenching with water at −78°C gave (*S,S*)-**11**, $[\alpha]_D$ +107.2 ($CHCl_3$), mp 41–43°C in 87% yield, which was subsequently converted into (*S,S*)-**5**, $[\alpha]_D$ +96.6 ($CHCl_3$) in 95% yield by demethylation. With dil. $HNO_3$ containing $NaNO_2$, the phenol moiety of (*S,S*)-**5** was selectively nitrated to give (*S,S*)-**2**, $[\alpha]_D$ +91.0 ($CHCl_3$), mp 52–54°C in 49% yield. Demethylation of (*S,S*)-**10** with sodium ethanethiolate gave (*S,S*)-**4**, $[\alpha]_D$ +83.5 ($CHCl_3$), mp 105–107°C in 96% yield. The hydroxy group of (*S,S*)-**4** was protected by treatment with chloromethyl methyl ether and NaH to give (*S,S*)-**13**, $[\alpha]_D$ +87.3 ($CHCl_3$), mp 46–48°C in 98% yield. Formylation of (*S,S*)-**13** with *n*-butyl lithium and DMF[5] at −78°C followed by deprotection with methanol and hydrochloric acid gave (*S,S*)-**3**, $[\alpha]_D$ +89.5 ($CHCl_3$), mp 105–107°C in 54% overall yield for two steps.



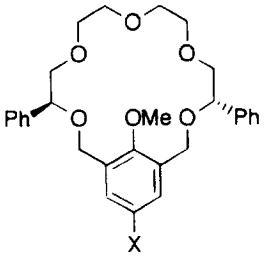

(*S,S*)-**1** X = N=N
(*S,S*)-**2** X = $NO_2$
(*S,S*)-**3** X = CHO
(*S,S*)-**4** X = Br
(*S,S*)-**5** X = H
(*S,S*)-**6** X = $OCH_3$



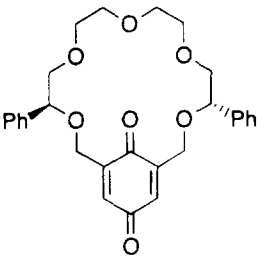

(*S*)-**7**



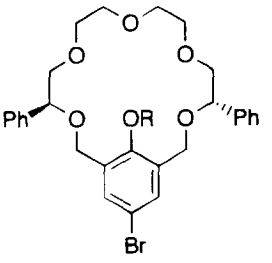

(*S,S*)-**8**




(*S,S*)-**9** X = $OCH_3$
(*S,S*)-**10** X = Br
(*S,S*)-**11** X = H




(*S,S*)-**12**




(*S,S*)-**13** R = $CH_2OCH_3$

The p*K*a-values of crown ethers **1–6** were measured by spectrophotometric method in a mixture of dioxane and water (1/1 volume) at 25°C.[6] The association constants of the complexes with achiral and chiral amines were determined by the $^1H$ n.m.r. spectroscopic method in $CDCl_3$ at 25°C. The p*K*a-values of crown ethers and the association constants of the complexes with achiral amine and chiral amines are summarized in Table 1.

The data listed in Table 1 suggest that the acidity of the crown ether is varied through the electronic nature of the *para*-substituent and the increase in the acidity of the phenolic group through the electron withdrawing *para*-substituent enhanced the conversion of neutral amines to the corresponding ammonium species and the equilibrium between the neutral crown ether and the complex with the ammonium species was shifted in the direction of increased complexation; *K*a-values of the complexes increased with decreasing p*K*a-values of the crown ethers. Since the electron donative *para*-substituent, on the contrary, decreased markedly the binding ability of the phenolic crown ether towards neutral

**Table 1.** p*K*a-Values of crown ethers and association constant *K*a ($dm^3$ $mol^{-1}$)-values for the complexes with achiral and chiral amines

| Crown ether | p*K*a | Amine[a] | $Ka^{achiral}$ | $Ka^{R}$ [b] | $Ka^{S}$ [b] | $Ka^{R}$ / $Ka^{S}$ |
|---|---|---|---|---|---|---|
| (*S*,*S*)-**1** | 7.3 | **14** | $6.3 \times 10^3$ | | | |
| (*S*,*S*)-**2** | 7.7 | **14** | $4.5 \times 10^3$ | | | |
| (*S*,*S*)-**3** | 8.3 | **14** | $5.1 \times 10^2$ | | | |
| (*S*,*S*)-**4** | 10.8 | **14** | $1.9 \times 10^1$ | | | |
| (*S*,*S*)-**5** | 11.8 | **14** | 5.0 | | | |
| (*S*,*S*)-**6** | 12.0 | **14** | -[c] | | | |
| (*S*,*S*)-**1** | | **15** | | $7.7 \times 10^3$ | $2.2 \times 10^3$ | 3.5 |
| (*S*,*S*)-**2** | | **15** | | $5.4 \times 10^3$ | $2.0 \times 10^2$ | 2.7 |
| (*S*,*S*)-**3** | | **15** | | $6.2 \times 10^2$ | $3.1 \times 10^2$ | 2.0 |
| (*S*,*S*)-**4** | | **15** | | $1.7 \times 10^1$ | 8.8 | 1.9 |
| (*S*,*S*)-**5** | | **15** | | 3.9 | 3.1 | 1.3 |
| (*S*,*S*)-**1** | | **16** | | $8.4 \times 10^3$ | $2.6 \times 10^3$ | 3.2 |
| (*S*,*S*)-**2** | | **16** | | $7.4 \times 10^3$ | $2.1 \times 10^3$ | 3.5 |
| (*S*,*S*)-**3** | | **16** | | $8.8 \times 10^2$ | $2.4 \times 10^2$ | 3.7 |
| (*S*,*S*)-**4** | | **16** | | $3.3 \times 10^1$ | 7.6 | 4.3 |
| (*S*,*S*)-**5** | | **16** | | 5.0 | <1 | -[d] |
| (*S*,*S*)-**1** | | **17** | | $2.2 \times 10^3$ | $7.1 \times 10^2$ | 3.1 |
| (*S*,*S*)-**2** | | **17** | | $2.6 \times 10^3$ | $8.1 \times 10^2$ | 3.2 |
| (*S*,*S*)-**3** | | **17** | | $1.8 \times 10^2$ | $5.6 \times 10^1$ | 3.2 |
| (*S*,*S*)-**4** | | **17** | | 4.6 | <1 | -[d] |
| (*S*,*S*)-**5** | | **17** | | -[c] | -[c] | |
| (*S*,*S*)-**1** | | **18** | | $4.0 \times 10^2$ | $5.1 \times 10^2$ | 0.78 |
| (*S*,*S*)-**2** | | **18** | | $2.1 \times 10^2$ | $2.9 \times 10^2$ | 0.72 |
| (*S*,*S*)-**3** | | **18** | | $2.2 \times 10^1$ | $2.9 \times 10^1$ | 0.76 |
| (*S*,*S*)-**4** | | **18** | | 2.2 | 2.9 | 0.76 |
| (*S*,*S*)-**5** | | **18** | | -[c] | -[c] | |
| (*S*,*S*)-**1** | | **19** | | $2.6 \times 10^2$ | $3.0 \times 10^2$ | 0.87 |
| (*S*,*S*)-**2** | | **19** | | $1.6 \times 10^2$ | $1.9 \times 10^2$ | 0.84 |
| (*S*,*S*)-**3** | | **19** | | $1.6 \times 10^1$ | $1.9 \times 10^1$ | 0.84 |
| (*S*,*S*)-**4** | | **19** | | -[c] | 1.1 | -[d] |

a) **14**: 2-aminoethanol, **15**: 1-amino-2-propanol, **16**: 2-amino-1-propanol, **17**: 2-amino-3-methyl-1-butanol, **18**: 1-phenylethylamine, **19**: 1-α-naphthylethylamine

b) $Ka^R$ for the complex with (*R*)-amine and $Ka^S$ for the complex with (*S*)-amine

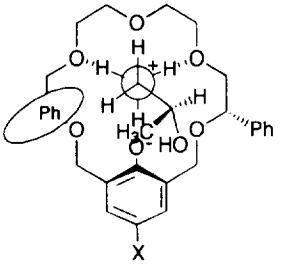
c) The *K*a-value was so small that it was difficult to get accurate data by $^1$H NMR titration.

d) The relative ratio of *K*a-values was not calculated.

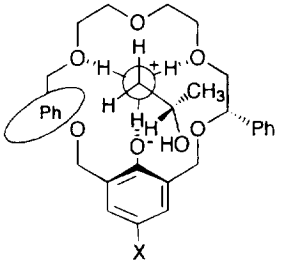
amines, *K*a-values of the complexes of (*S*,*S*)-**6** with amines were so small that it was difficult to get accurate data by $^1$H n.m.r. titration.

We next give an explanation for the enantiomer selectivities in complexation observed at 25°C in terms of steric interactions between the substituents of the amine and the steric barriers of the crown ether. On the basis of CPK molecular model examination of the diastereoisomeric complexes using the assumption[7] that the phenolate oxygen atom necessarily acts as a primary binding site and the hydroxymethyl group of 2-aminoethanol derivatives occupies the less hindered site near the phenol moiety of the crown ether making the fourth hydrogen bonding between the phenolate oxygen atom and the hydroxy group of the amine. The predicted geometries **20** and **21** are illustrated for the complexes of (*S*,*S*)-crown ethers **1**–**5** with (*R*)-**15** and with (*S*)-**15**, respectively. On the basis of the steric requirements of CPK molecular models of the complexes of (*S*,*S*)-crown ethers with the amines,

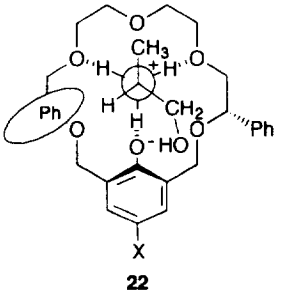
it is assumed that the phenyl substituent at C-14 occupies pseudo-equatorial position making the C-13 methylene and the C-14 methine groups of the crown ether the effective chiral barrier on the β-face of the complex; 'the ethyleneoxy barrier'.[8] The observed enantiomer discrimination towards **15** would be due to a steric replusion between the methyl group of (*S*)-**15** and 'the ethyleneoxy barrier' making the (*S*,*S*)-crown ether:(*S*)-**15** complexes with the geometry **21** less stable than the corresponding diastereoisomeric complexes with the geometry **20** in which significant steric interactions between the methyl group of the amine and the crown ether are not appreciable.



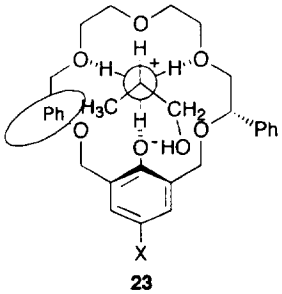

**20**



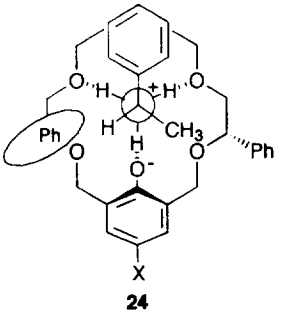

**21**



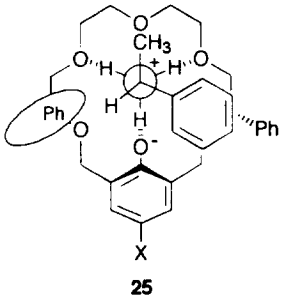

**22**




**23**




**24**




**25**

The predicted geometries **22** and **23** are illustrated for the (*S*,*S*)-crown ether:(*R*)-**16** complexes and the (*S*,*S*)-crown ether:(*S*)-**16** complexes, respectively. The observed *R*-selectivities towards **16** are interpreted in terms of a steric replusion between the methyl group of the amine and the phenyl chiral barrier making the (*S*,*S*)-crown ether:(*S*)-**16** complexes with the geometry **23** less stable than the (*S*,*S*)-crown ether:(*R*)-**16** complexes with the geometry **22** in which the methyl group of the amine occupies the less hindered site over the oxygen atom at the 12 o'clock position. The observed *R*-selectivities of (*S*,*S*)-crown ethers **1**–**4** towards **17** are similarly interpreted.

On the assumption that the ethylamine derivative binds to the phenolic crown ethers in three-point binding mode[9] and the hydrogen atom at the stereogenic center of the amine occupies preferentially the most hindered site near the phenyl chiral barrier in the complex, the predicted geometries **24** and **25** are illustrated for the complexes of (*S*,*S*)-crown ethers **1**–**4** with (*S*)-**18** and with (*R*)-**18**, respectively. The observed enantiomer discrimination is assumed to be due to a steric replusion between the phenyl group of **18** and 'the ethyleneoxy barrier' making the (*S*,*S*)-crown ether:(*R*)-**18** complexes with the

geometry **25** less stable than its diastereoisomeric complexes with the geometry **24** in which the phenyl group of (*S*)-**18** is placed at the less hindered site. Similarly, the observed *S*-selectivities of (*S,S*)-crown ethers **1–3** towards **19** are rationalized in terms of a steric replusion between the naphthyl group of **19** and 'the ethyleneoxy barrier'.

The present results showed that the stabilities of the complexes of phenolic crown ethers with neutral amines were markedly made to vary by changes in the acidity of the phenolic group controlled through the *para*-substituent and it is necessary for binding strongly a wide variety of neutral amines that crown ethers of this type possess the rather strong electron withdrawing group such as a 2,4-dinitrophenylazo group or a nitro group at the *para*-position of the phenol moiety.

## Experimental section

*General procedure*

$^1$H n.m.r. spectra were recorded at 270 MHz on a JASCO JNM-MH-270 spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as internal standard and *J*-values are given in Hz. Mass spectra were recorded on a JEOL-DX-303-HF spectrometer. Elemental analyses were carried out by Yanagimoto CHN-Corder, Type 2. Mps were measured on a Yanagimoto micro melting point apparatus and are uncorrected. 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$^{-1}$. pH-Values were measured by a digital pH meter HM-12A combined with TOA pH electrode GST-152C (TOA Electronics Ltd.). The homochiral guest compounds: (*R*)- and (*S*)-2-amino-1-propanol **19**, (*R*)- and (*S*)-2-amino-3-methyl-1-butanol **20**, (*R*)- and (*S*)-1-amino-2-propanol **21** and (*R*)- and (*S*)-1-phenylethylamine **22** were purchased from Aldrich Chemical Company, Inc. and used without further purification.

*(S)-(+)-2-Phenyl-2-(tetrahydropyranyloxy)ethanol 7*

According to the procedure reported in the literature,[3] (*S*)-**7** was prepared from (*S*)-(+)-mandelic acid by esterification of the carboxyl group, protection of the hydroxy group and reduction with $LiAlH_4$. Silica gel chromatography of the products gave (*S*)-**7** (75% yield for the three steps), [hexane/ethyl acetate (3/1–1/1) as eluent], $[\alpha]_D^{25}$ +58.9 (c 1.48, $CHCl_3$) as the mixture of two diastereoisomers; δH (270 MHz; $CDCl_3$) 1.46–1.89 (6H, m, C*H*$_2$), 2.15 and 3.00 (1H, br s, O*H*), 3.25–4.06 (4H, m, OCH$_2$), 4.51–4.95 (2H, m, C*H*), (5H, m, $C_6H_5$). The mixture of two diastereoisomers was used for the next reaction without further separation.

*(1S,11S)-1,11-Diphenyl-3,6,9-trioxaundecane-1,11-diol 8*

A solution of (*S*)-**7** (20.0 g, 90.0 mmol) in dry THF (250 cm$^3$) was added to a suspension of sodium hydride (4.32 g, 180 mmol) in dry THF (250 cm$^3$) and the mixture was then stirred for 1 h at 60°C. The mixture was cooled to the room temperature and then a solution of diethylene glycol bis(*p*-toluenesulfonate) (22.4 g, 54.0 mmol) in dry THF (450 cm$^3$) was added to the mixture. The mixture was refluxed for 7 h, cooled to 0–5°C, neutralised with hydrochloric acid and concentrated under reduced pressure. The residue was extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give the oily residue. The residue was dissolved in ethanol (400 cm$^3$) and stirred for 7 h at 60°C with pyridinium *p*-toluenesulfonate (1.13 g, 4.50 mmol). After removal of the solvent under reduced pressure, silica gel chromatography of the products gave (*S,S*)-**8** (11.8 g, 76% yield) [hexane/ethyl acetate (1/1) as eluent] as an oil, $[\alpha]_D^{26}$ +53.9 (*c* 1.04, $CHCl_3$); νmax (neat film)/cm$^{-1}$ 3880, 2890, 1730, 1450, 1350, 1250, 1200, 1110, 910, 760 and 700; δH (270 MHz; $CDCl_3$) 3.57–3.97(12H, m, C*H*$_2$ and OH), 4.95 (2H, dd *J* 2.72 and 9.15, C*H*), 7.22–7.39 (10H, m, $C_6H_5$); The high-resolution mass spectrum could not be recorded because of the vary weak molecular ion peak; FABMS: *m/z* 347[($MH^+$), 100%] and 369[($M+Na^+$), 42%].

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

A solution of (*S,S*)-**8** (2.00 g, 5.77 mmol) and 1,3-bis(bromomethyl)-2,5-dimethoxybenzene (1.87 g, 5.77 mmol) in dry THF (600 $cm^3$) was slowly added to a mixture of sodium hydride (554 mg, 23.1 mmol) and potassium tetrafluoroboranuide (730 mg, 5.77 mmol) in dry THF (200 $cm^3$) over a 9 h period under reflux and the mixture was then refluxed for an additional 20 h. After the reaction mixture had been cooled to 0–5°C, a small amount of water was added to the chilled mixture. The mixture was neutralised with hydrochloric acid and extracted with ethyl acetate. 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*)-**9** (1.90 g, 65%) [hexane/ethyl acetate (1/1) as eluent] as a solid, mp 121–123°C; $[\alpha]_D^{26}$ +94.3 (*c* 0.548, $CHCl_3$); νmax (KBr)/$cm^{-1}$ 2820, 1590, 1465, 1435, 1415, 1330, 1230, 1210, 1175, 1090, 1035, 1005, 880, 850, 740, 680; δH (270 MHz; $CDCl_3$) 3.37–3.79 (12H, m, C*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.26 (2H, d *J* 10.4, benzylic C*H*$_2$), 4.30 (3H, s, OC*H*$_3$), 4.59 (2H, d *J* 10.4, benzylic C*H*$_2$), 4.70 (2H, dd *J* 2.35 and 9.52, C*H*), 6.61 (2H, s, MeOAr*H*), 7.31–7.44 (10, m, $C_6H_5$); The high-resolution mass spectrum could not be recorded because of the vary weak molecular ion peak; FABMS: *m/z* 508[($MH^+$), 100%] and 531[($M+Na^+$), 21%].

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

Ethanethiol (2.92 g, 47.0 mmol) was added slowly to a suspension of sodium hydride (1.62 g, 67.6 mmol) in dry DMF (100 $cm^3$) at room temperature. After evolution of hydrogen had ceased, a solution of (*S,S*)-**9** (1.72 g, 3.38 mmol) in dry DMF (30 $cm^3$) was then added to the reaction mixture. The reaction mixture was stirred for 3 h at 100°C, cooled to 0–5°C, nertralised with hydrochloric acid and extracted with diethyl ether. 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*)-**6** (723 mg, 74%) [hexane/ethyl acetate (2/1) as eluent] as a solid, mp 140–142°C; $[\alpha]_D^{23}$ +99.2 (*c* 0.915, $CHCl_3$); νmax (KBr)/$cm^{-1}$ 3420, 2990, 1485, 1350, 1340, 1210, 1110, 1080, 1060, 1030, 760, 700; δH (270 MHz; $CDCl_3$) 3.53–3.94 (12H, m, C*H*$_2$), 4.56 (2H, d *J* 11.1, benzylic C*H*$_2$), 4.65 (2H, d *J* 11.1, benzylic C*H*$_2$), 4.74 (2H, dd *J* 2.60 and 9.27, C*H*), 7.96 (2H, s, phenol moiety C*H*), 7.32–7.40 (10, m, $C_6H_5$); 8.02 (1H, s, OH). Found: C, 70.65; H, 7.02. $C_{29}H_{34}O_7$ requires C, 70.43; H, 6.93%.

*(4S,14S)-4,14-Diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(20),17-diene-19,21-dione* ***12***

A solution of (*S,S*)-**6** (200 mg, 0,404 mmol) in acetonitrile (20 $cm^3$) was added to a solution of CAN (443 mg, 0.809 mmol) in acetonitrile (10 $cm^3$) and the mixture was then stirred for 30 min at room temperature. After water had been added to the reaction mixture, the mixture was extracted with chloroform. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give the residue, which was chromatographed on silica gel to give (*S,S*)-**12** (196 mg, 98%) [chloroform as eluent] as a yellow solid, δH (270 MHz; $CDCl_3$) 3.46–3.76 (12H, m, C*H*$_2$), 4.44 (2H, d *J* 15.5, benzylic C*H*$_2$), 4.69 (2H, dd *J* 3.71 and 7.67, C*H*), 4.71 (2H, d *J* 15.5, benzylic C*H*$_2$), 6.72 (2H, s, benzoquinone moiety C*H*), 7.28–7.41 (10, m, $C_6H_5$). As the quinone was unstable, it was immediately used for the next reaction without further purification.

*(4S,14S)-21-Hydroxy-19-(2′,4′-dinitrophenylazo)-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]-henicosane-1(21),17,19-triene* ***1***

A solution of 2,4-dinitrophenylhydrazine (324 mg, 1.78 mmol) in a mixture of ethanol (10 $cm^3$) and conc. $H_2SO_4$ (1.5 $cm^3$) was added to a solution of (*S,S*)-**12** (170 mg, 0.355 mmol) in a mixture of methylene dichloride (10 $cm^3$) and ethanol (10 $cm^3$) and the mixture was then stirred for 2 h at

room temperature. After water had been added to the reaction mixture, the mixture was extracted with chloroform. The combined extracts were washed with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure to give a red solid. Silica gel chromatography of the products [chloroform as eluent] followed by purification by a preparative recycling HPLC (column; JAIGEL 2H and 1H, chloroform as eluent) gave (*S,S*)-**1** (133 mg, 57%) as a red solid; mp 81–83°C; $[\alpha]_D^{23}$ +63.3 (*c* 0.055, $CHCl_3$); νmax (KBr)/$cm^{-1}$ 3280, 2880, 1600, 1535, 1470, 1415, 1350, 1295, 1120, 905, 840, 760, 705; δH (270 MHz; $CDCl_3$) 3.59–4.00 (12H, m, C*H*$_2$), 4.64 (2H, d *J* 11.1, benzylic C*H*$_2$), 4.78 (2H, dd *J* 2.23 and 9.15, C*H*), 4.80 (2H, d *J* 11.1, benzylic C*H*$_2$), 7.32–7.42 (10, m, $C_6H_5$); 7.71 (2H, s, phenol moiety C*H*), 7.77 (1H, d *J* 8.66, 2,4-dinitrophenyl Ar*H*), 8.46 (1H, dd *J* 2.22 and 8.66, 2,4-dinitrophenyl Ar*H*), 8.74 (1H, d *J* 2.22, 2,4-dinitrophenyl Ar*H*), 9.30 (1H, s, O*H*). Found: C, 61.87; H, 5.22; N, 8.25. $C_{34}H_{34}N_4O_{10}$ requires C, 62.00; H, 5.20; N, 8.51%.

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

A solution of (*S,S*)-**8** (5.00 g, 14.4 mmol) and 1,3-bis(bromomethyl)-2-methoxy-5-bromobenzene (5.38 g, 14.4 mmol) in dry THF (1200 $cm^3$) was slowly added to a mixture of sodium hydride (1.38 g, 57.5 mmol) and potassium tetrafluoroboranuide (1.81 g, 14.4 mmol) in dry THF (500 $cm^3$) over a 12 h period under reflux and the mixture was then refluxed for an additional 10 h. After the reaction mixture had been cooled to 0–5°C, a small amount of water was added to the chilled mixture. The reaction mixture was neutralised with hydrochloric acid and extracted with ethyl acetate. 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 products gave (*S,S*)-**10** (5.40 g, 67%) [hexane/ethyl acetate (1/1) as eluent] as a solid, mp 118–119°C; $[\alpha]_D^{26}$ +83.5 (*c* 0.682, $CHCl_3$); νmax (KBr)/$cm^{-1}$ 2880, 1470, 1460, 1440, 1350, 1250, 1230, 1100, 1030, 870, 860, 760, 700; δH (270 MHz; $CDCl_3$) 3.37–3.67 (12H, m, C*H*$_2$), 4.23 (2H, d *J* 10.4, C*H*), 4.35 (3H, s, OC*H*$_3$), 4.56 (2H, d *J* 10.4, CH), 4.65 (dd *J* 2.23 and 9.64, C*H*), 7.18 (2H, s, MeOAr*H*), 7.31–7.46 (10, m, $C_6H_5$); The high-resolution mass spectrum could not be recorded because of the vary weak molecular ion peak; FABMS: *m/z* 557[($MH^+$), 56%], 559[($MH^+$), 47%], 579[($M+Na^+$), 84%], 581[($M+Na^+$), 100%], 595[($M+K^+$), 27%] and 597[($M+K^+$), 32%]. Found: C, 61.76; H, 5.61. $C_{29}H_{33}O_6Br$ requires C, 62.48; H, 5.97%.

*(4S,14S)-21-Methoxy-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene* ***11***

To a solution of (*S,S*)-**10** (14.0 g, 25.1 mmol) in dry THF (100 $cm^3$) was added a 1.6 M solution of *n*-butyl lithium (17.3 $cm^3$, 27.7 mmol) in hexanes over a 40 min period at −78°C under nitrogen atmosphere and the mixture was then stirred for 1 h at the same temperature. Water (10.0 g, 555 mmol) was added dropwise to the reaction mixture at −78°C and the mixture was stirred for an additional 2 h at the same temperature. The reaction mixture was warmed to room temperature and extracted with ethyl acetate. The combined extracts were washed water, dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel chromatography of the residue gave (*S,S*)-**11** (10.5 g, 87%) [hexane/ethyl acetate (1/1) as eluent] as a solid, mp 41–43°C; $[\alpha]_D^{26}$ +107.2 (*c* 0.653, $CHCl_3$); νmax (KBr)/$cm^{-1}$ 2870, 1465, 1450, 1350, 1220, 1100, 1025, 900, 780, 755, 700; δH (270 MHz; $CDCl_3$) 3.36–3.77 (12H, m, C*H*$_2$), 4.29 (2H, d *J* 10.4, C*H*), 4.37 (3H, s, OC*H*$_3$), 4.63 (2H, d *J* 10.4, C*H*), 4.68 (2H, dd *J* 2.47 and 9.64, C*H*), 6.97 (1H, t *J* 7.30, MeOAr*H*), 7.07 (2H, d, *J* 7.30, MeOAr*H*), 7.28–7.45 (10, m, $C_6H_5$); The high-resolution mass spectrum could not be recorded because of the vary weak molecular ion peak; FABMS: *m/z* 479[($MH^+$), 34%], 501[($M+Na^+$), 100%] and 517[($M+K^+$), 35%].

*(4S,14S)-21-Hydroxy-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene* ***5***

By the same procedure described for the preparation of (*S,S*)-**6**, demethylation of (*S,S*)-**11** (10.5 g, 21.9 mmol) followed by silica gel chromatography of the products gave (*S,S*)-**5** (9.70 g, 95%)

[hexane/ethyl acetate (2/1) as eluent] as a white glass; $[\alpha]_D^{23}$ +96.6 (*c* 1,053, $CHCl_3$); νmax (KBr)/$cm^{-1}$ 3360, 2880, 1600, 1465, 1350, 1255, 1100, 900, 760, 705; δH (270 MHz; $CDCl_3$) 3.54–3.97 (12H, m, C*H*$_2$), 4.56 (2H, d *J* 10.8, C*H*), 4.69 (2H, d *J* 10.8, C*H*), 4.76 (2H, dd *J* 2.23 and 9.15, C*H*), 6.74 (1H, t *J* 7.42, phenol moiety C*H*), 7.00 (2H, d, *J* 7.42, phenol moiety C*H*), 7.27–7.46 (10, m, $C_6H_5$); 8.01 (1H, s, O*H*); The high-resolution mass spectrum could not be recorded because of the vary weak molecular ion peak; FABMS: *m/z* 465[($MH^+$), 28%], 487[($M+Na^+$), 100%] and 503[($M+K^+$), 34%].

*(4S,14S)-21-Hydroxy-19-nitro-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene* **2**

To a solution of (*S,S*)-**5** (1.00 g, 2.15 mmol) in chloroform (60 $cm^3$) was added successively a solution of sodium nitrite (630 mg, 8.83 mmol) in water (100 $cm^3$) and 2% nitric acid (200 $cm^3$) and the mixture was then stirred vigorously for 20 h at room temperature. The reaction mixture was neutralized with aq. sodium hydrogen carbonate, faintly acidified with a small amount of hydrochloric acid and extracted with chloroform. The combined extracts were washed with aq. sodium hydrogen carbonate and water and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on silica gel to give (*S,S*)-**2** (540 mg, 49% yield) [hexane/ethyl acetate (2/1) as eluent] as a solid, mp 52–54°C; $[\alpha]_D^{25}$ +91.0 (*c* 0.519, $CHCl_3$); νmax (KBr)/$cm^{-1}$ 3290, 2870, 1595, 1520, 1455, 1340, 1280, 1195, 1095, 965, 745, 695; δH (270 MHz; $CDCl_3$) 3.57–3.97(12H, m, C*H*$_2$), 4.59 (2H, d *J* 11.0, benzylic C*H*$_2$), 4.75 (2H, s, C*H*), 4.76 (2H, d *J* 11.0, benzylic C*H*$_2$), 7.28–7.45 (10H, m, $C_6H_5$), 7.96 (2H, s, phenol moiety C*H*), 9.33 (1H, s, O*H*); The high-resolution mass spectrum could not be recorded because of the vary weak molecular ion peak; FABMS: *m/z* 510[($MH^+$), 69%], 532[($M+Na^+$), 100%] and 548[($M+K^+$), 33%].

*(4S,14S)-19-Bromo-21-hydroxy-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene* **4**

By the same procedure described for the preparation of (*S,S*)-**6**, demethylation of (*S,S*)-**10** (4.00 g, 7.18 mmol) followed by silica gel chromatography of the products gave (*S,S*)-**4** (3.73 g, 96%) [hexane/ethyl acetate (2/1) as eluent] as a solid; mp 105–107°C; $[\alpha]_D^{26}$ +83.5 (*c* 0.773, $CHCl_3$); νmax (KBr)/$cm^{-1}$ 3360, 2880, 1470, 1355, 1250, 1100, 875, 765, 700; δH (270 MHz; $CDCl_3$) 3.53–3.97 (12H, m, C*H*$_2$), 4.51 (2H, d *J* 11.1, C*H*), 4.63 (2H, d *J* 11.1, C*H*), 4.73 (2H, dd *J* 2.60 and 9.27, C*H*), 7.12 (2H, s, phenol moiety C*H*), 7.31–7.43 (10H, m, $C_6H_5$); 8.03 (1H, s, O*H*). Found: C, 62.01; H, 5.69. $C_{28}H_{31}O_6Br$ requires C, 61.88; H, 5.75%.

*(4S,14S)-19-Bromo-21-(methoxymethoxy)-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]-henicosane-1(21),17,19-triene* **13**

To a suspension of sodium hydride (18 mg, 0.74 mmol) in dry THF (5 $cm^3$) was added a solution of (*S,S*)-**4** (200 mg, 0.368 mmol) in dry THF (5 $cm^3$) and the mixture was then stirred 1 h at room temperature. A solution of chloromethyl methy ether (148 mg, 1.84 mmol) in dry THF (5 $cm^3$) was added to the reaction mixture and the mixture was then refluxed for 3 h. After the reaction mixture had been cooled to 0–5°C, a small amount of water was added to the chilled reaction mixture and the reaction mixture was evaporated under reduced pressure. The residue was extracted with ethyl acetate and the combined extracts were washed with water and dried ($Mg_2SO_4$). After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on silica gel to give (*S,S*)-**13** (216 mg, 98% yield) [hexane/ethyl acetate (5/1) as eluent] as a solid, mp 46–48°C; $[\alpha]_D^{29}$ +87.3 (*c* 0.739, $CHCl_3$); νmax (KBr)/$cm^{-1}$ 2880, 1470, 1450, 1200, 1090, 1030, 920, 870, 760, 700; δH (270 MHz; $CDCl_3$) 3.51–3.80 (12H, m, C*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 4.10 (2H, d *J* 8.90, benzylic C*H*$_2$), 4.61 (2H, d *J* 8.90, benzylic C*H*$_2$), 4.51 (1H, br s, C*H*); 4.64 (1H, br s, C*H*); 6.96 (1H, s, BrAr*H*); 6.97 (1H, s, BrAr*H*); 7.28–7.46 (10H, m, $C_6H_5$); The high-resolution mass spectrum could not be recorded because of the vary weak molecular ion peak; FABMS: *m/z* 586[($MH^+$), 90%], 588[($MH^+$), 100%], 609[($M+Na^+$), 58%], 611[($M+Na^+$), 59%], 625[($M+K^+$), 25%] and 627[($M+K^+$), 28%].

*(4S,14S)-19-Formyl-21-hydroxy-4,14-diphenyl-3,6,9,12,15-pentaoxabicyclo[15.3.1]henicosane-1(21),17,19-triene* **3**

A 1.6 M solution of *n*-butyl lithium (213 $cm^3$, 0.341 mmol) in hexanes was added to a solution of (*S,S*)-**13** (100 mg, 0.178 mmol) in dry THF (10 $cm^3$) at −78°C and dry DMF (132 ml, 1.70 mmol) was then added to the mixture at the same temperature. The mixture was stirred for 1 h at −78°C under nitrogen atmosphere, allowed to warm to 0°C and diluted with water. The mixture was extracted with diethyl ether and the combined extracts were washed with water, dried ($MgSO_4$) and evaporated under pressure to give a solid. The residual solid was dissolved in methanol (5 $cm^3$) and stirred with a few drops of hydrochloric acid for 9 h at room temperature. After the reaction mixture had been concentrated under reduced pressure, the residue was extracted with diethyl ether. The combined extracts were washed with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel hromatography of the residue gave (*S,S*)-**3** (45 mg, 54%) [chloroform as eluent] as a solid, mp 105–107°C; $[\alpha]_D^{25}$ +89.5 (*c* 0.452, $CHCl_3$); vmax (KBr)/$cm^{-1}$ 3300, 2860, 1685, 1600, 1480, 1450, 1340, 1290, 1195, 1140, 1095, 885, 760; δH (270 MHz; $CDCl_3$) 3.56–3.99 (12H, m, $CH_2$), 4.60 (2H, d *J* 11.0, benzylic $CH_2$), 4.76 (2H, d *J* 11.0, benzylic $CH_2$), 4.77 (2H, dd *J* 2.84 and 9.27, C*H*), 7.29–7.44 (10H, m, $C_6H_5$), 7.56 (2H, s, phenol moiety C*H*), 9.17 (1H, s, O*H*), 9.77 (1H, s, C*H*O); The high-resolution mass spectrum could not be recorded because of the vary weak molecular ion peak; FABMS: *m/z* 493[($MH^+$), 76%], 515[($M+Na^+$), 100%] and 531[($M+K^+$), 29%]. Found: C, 70.40; H, 6.32. $C_{29}H_{32}O_7$ requires C, 70.85; H, 7.13%.

*Determination of pKa values*

According to the equation; $pK_a = pH + \log(D_{B^-} - D_{obs}) - \log(D_{obs} - D_{HB})$, p*K*a-values were calculated from pH and electronic spectral data. The $D_{obs}$, $D_{B^-}$ and $D_{HB}$-values are the observed absorbances in 1:1 dioxane–buffer solution, in 1:1 dioxane–0.01 molar aqueous NaOH and in 1:1 dioxane–0.01 molar hydrochloric acid, respectively, at 260, 270, 280, 310, 320 and 330 nm at 25°C. The suitable buffer solution for $D_{obs}$ of crown ethers is listed as following, 1:1 dioxane–phosphate pH standard equimolar solution (pH 8.30) for crown ethers **1**, **2** and **3**, 1:1 dioxane–Tetraborate pH standard solution (pH 11.37) for crown ethers **4** and **5** and 1:1 dioxane–carbonate pH standard solution (pH 11.81) for crown ether **6**.

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