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

Koichiro Naemura,* Yasushi Nishikawa, Junichi Fuji, Keiji Hirose[†] and Yoshito Tobe Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan

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 ¹H 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 ¹H n.m.r. spectroscopic method in CDCl₃.

Results and discussion

The chiral subunit (S)-7, $[\alpha]_D$ +58.9 (CHCl₃) 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 (CHCl₃) 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 KBF₄ gave (S,S)-9, $[\alpha]_D$ +94.3 (CHCl₃), 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 DMF⁴ to give (S,S)-6, $[\alpha]_D$ +99.2 (CHCl₃) 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. H₂SO₄ to give (S,S)-1, $[\alpha]_D$ +63.3 (CHCl₃), mp 81–83°C in 57% yield.

^{*} Corresponding author.

[†] Email: hirose@chem.es.osaka-u.ac.jp

Ring closure of (S,S)-8 with 1,3-bis(bromomethyl)-2-methoxy-5-bromobenzene in the presence of NaH and KBF₄ in boiling THF under high-dilution conditions gave (S,S)-10, $[\alpha]_D$ +83.5 (CHCl₃), 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 (CHCl₃), mp 41–43°C in 87% yield, which was subsequently converted into (S,S)-5, $[\alpha]_D$ +96.6 (CHCl₃) in 95% yield by demethylation. With dil. HNO₃ containing NaNO₂, the phenol moiety of (S,S)-5 was selectively nitrated to give (S,S)-2, $[\alpha]_D$ +91.0 (CHCl₃), mp 52–54°C in 49% yield. Demethylation of (S,S)-10 with sodium ethanethiolate gave (S,S)-4, $[\alpha]_D$ +83.5 (CHCl₃), 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 (CHCl₃), mp 46–48°C in 98% yield. Formylation of (S,S)-13 with *n*-butyl lithium and DMF⁵ at -78°C followed by deprotection with methanol and hydrochloric acid gave (S,S)-3, $[\alpha]_D$ +89.5 (CHCl₃), mp 105–107°C in 54% overall yield for two steps.



The pKa-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 CDCl₃ at 25°C. The pKa-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; *Ka*-values of the complexes increased with decreasing pKa-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

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

Table 1. pKa-Values of crown ethers and association constant Ka (dm³ mol⁻¹)-values for the complexes with achiral and chiral amines

 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 Ka-value was so small that it was difficult to get accurate data by ¹H NMR titration.

d) The relative ratio of Ka-values was not calculated.

amines, Ka-values of the complexes of (S,S)-6 with amines were so small that it was difficult to get accurate data by ¹H 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 assumption⁷ 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.



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 mode⁹ 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 ethers(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

¹H n.m.r. spectra were recorded at 270 MHz on a JASCO JNM-MH-270 spectrometer for solutions in CDCl₃ with SiMe₄ 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 cm² 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 LiAlH₄. 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, CHCl₃) as the mixture of two diastereoisomers; δ H (270 MHz; CDCl₃) 1.46–1.89 (6H, m, CH₂), 2.15 and 3.00 (1H, br s, OH), 3.25–4.06 (4H, m, OCH₂), 4.51–4.95 (2H, m, CH), (5H, m, C₆H₅). The mixture of two diastereoisomers was used for the next reaction without further separation.

(IS,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 cm³) was added to a suspension of sodium hydride (4.32 g, 180 mmol) in dry THF (250 cm³) 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 cm³) 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 (MgSO₄) and evaporated under reduced pressure to give the oily residue. The residue was dissolved in ethanol (400 cm³) 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, CHCl₃); vmax (neat film)/cm⁻¹ 3880, 2890, 1730, 1450, 1350, 1250, 1200, 1110, 910, 760 and 700; δ H (270 MHz; CDCl₃) 3.57–3.97(12H, m, CH₂ and OH), 4.95 (2H, dd *J* 2.72 and 9.15, CH), 7.22–7.39 (10H, m, C₆H₅); 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 cm³) 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 cm³) 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 (MgSO₄) 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, CHCl₃); vmax (KBr)/cm⁻¹ 2820, 1590, 1465, 1435, 1415, 1330, 1230, 1210, 1175, 1090, 1035, 1005, 880, 850, 740, 680; δ H (270 MHz; CDCl₃) 3.37–3.79 (12H, m, CH₂), 3.73 (3H, s, OCH₃), 4.26 (2H, d J 10.4, benzylic CH₂), 4.30 (3H, s, OCH₃), 4.59 (2H, d J 10.4, benzylic CH₂), 4.70 (2H, dd J 2.35 and 9.52, CH), 6.61 (2H, s, MeOArH), 7.31–7.44 (10, m, C₆H₅); 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 cm³) 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 cm³) 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 (MgSO₄) 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, CHCl₃); vmax (KBr)/cm⁻¹ 3420, 2990, 1485, 1350, 1340, 1210, 1110, 1080, 1060, 1030, 760, 700; δ H (270 MHz; CDCl₃) 3.53–3.94 (12H, m, CH₂), 4.56 (2H, d *J* 11.1, benzylic CH₂), 4.74 (2H, dd *J* 2.60 and 9.27, CH), 7.96 (2H, s, phenol moiety CH), 7.32–7.40 (10, m, C₆H₅); 8.02 (1H, s, OH). Found: C, 70.65; H, 7.02. C₂₉H₃₄O₇ requires C, 70.43; H, 6.93%.

(4\$,14\$)-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 cm³) was added to a solution of CAN (443 mg, 0.809 mmol) in acetonitrile (10 cm³) 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 (MgSO₄) 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; CDCl₃) 3.46–3.76 (12H, m, CH₂), 4.44 (2H, d J 15.5, benzylic CH₂), 4.69 (2H, dd J 3.71 and 7.67, CH), 4.71 (2H, d J 15.5, benzylic CH₂), 6.72 (2H, s, benzoquinone moiety CH), 7.28–7.41 (10, m, C₆H₅). 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 cm³) and conc. H_2SO_4 (1.5 cm³) was added to a solution of (*S*,*S*)-**12** (170 mg, 0.355 mmol) in a mixture of methylene dichloride (10 cm³) and ethanol (10 cm³) and the mixture was then stirred for 2 h at

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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 (MgSO₄) 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, CHCl₃); vmax (KBr)/cm⁻¹ 3280, 2880, 1600, 1535, 1470, 1415, 1350, 1295, 1120, 905, 840, 760, 705; δ H (270 MHz; CDCl₃) 3.59–4.00 (12H, m, CH₂), 4.64 (2H, d *J* 11.1, benzylic CH₂), 4.78 (2H, dd *J* 2.23 and 9.15, CH), 4.80 (2H, d *J* 11.1, benzylic CH₂), 7.32–7.42 (10, m, C₆H₅); 7.71 (2H, s, phenol moiety CH), 7.77 (1H, d *J* 8.66, 2,4-dinitrophenyl ArH), 8.46 (1H, dd *J* 2.22 and 8.66, 2,4-dinitrophenyl ArH), 8.74 (1H, d *J* 2.22, 2,4-dinitrophenyl ArH), 9.30 (1H, s, OH). Found: C, 61.87; H, 5.22; N, 8.25. C₃₄H₃₄N₄O₁₀ 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 cm³) 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 cm³) 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 (MgSO4) 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, CHCl₃); vmax (KBr)/cm⁻¹ 2880, 1470, 1460, 1440, 1350, 1250, 1230, 1100, 1030, 870, 860, 760, 700; δH (270 MHz; CDCl₃) 3.37–3.67 (12H, m, CH₂), 4.23 (2H, d J 10.4, CH), 4.35 (3H, s, OCH₃), 4.56 (2H, d J 10.4, CH), 4.65 (dd J 2.23 and 9.64, CH), 7.18 (2H, s, MeOArH), 7.31-7.46 (10, m, $C_{6}H_{5}$); 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. C₂₉H₃₃O₆Br 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 cm³) was added a 1.6 M solution of *n*-butyl lithium (17.3 cm³, 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 (MgSO₄) 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, CHCl₃); vmax (KBr)/cm⁻¹ 2870, 1465, 1450, 1350, 1220, 1100, 1025, 900, 780, 755, 700; δ H (270 MHz; CDCl₃) 3.36–3.77 (12H, m, CH₂), 4.29 (2H, d J 10.4, CH), 4.37 (3H, s, OCH₃), 4.63 (2H, d J 10.4, CH), 4.68 (2H, dJ 2.47 and 9.64, CH), 6.97 (1H, t J 7.30, MeOArH), 7.07 (2H, d, J 7.30, MeOArH), 7.28–7.45 (10, m, C₆H₅); 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, CHCl₃); vmax (KBr)/cm⁻¹ 3360, 2880, 1600, 1465, 1350, 1255, 1100, 900, 760, 705; δ H (270 MHz; CDCl₃) 3.54–3.97 (12H, m, CH₂), 4.56 (2H, d *J* 10.8, CH), 4.69 (2H, d *J* 10.8, CH), 4.76 (2H, dd *J* 2.23 and 9.15, CH), 6.74 (1H, t *J* 7.42, phenol moiety CH), 7.00 (2H, d, *J* 7.42, phenol moiety CH), 7.27–7.46 (10, m, C₆H₅); 8.01 (1H, s, OH); 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 cm³) was added successively a solution of sodium nitrite (630 mg, 8.83 mmol) in water (100 cm³) and 2% nitric acid (200 cm³) 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 (MgSO₄). 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, CHCl₃); vmax (KBr)/cm⁻¹ 3290, 2870, 1595, 1520, 1455, 1340, 1280, 1195, 1095, 965, 745, 695; δ H (270 MHz; CDCl₃) 3.57–3.97(12H, m, CH₂), 4.59 (2H, d J 11.0, benzylic CH₂), 4.75 (2H, s, CH), 4.76 (2H, d J 11.0, benzylic CH₂), 7.28–7.45 (10H, m, C₆H₅), 7.96 (2H, s, phenol moiety CH), 9.33 (1H, s, OH); 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, CHCl₃); vmax (KBr)/cm⁻¹ 3360, 2880, 1470, 1355, 1250, 1100, 875, 765, 700; δ H (270 MHz; CDCl₃) 3.53–3.97 (12H, m, CH₂), 4.51 (2H, d J 11.1, CH), 4.63 (2H, d J 11.1, CH), 4.73 (2H, dd J 2.60 and 9.27, CH), 7.12 (2H, s, phenol moiety CH), 7.31–7.43 (10H, m, C₆H₅); 8.03 (1H, s, OH). Found: C, 62.01; H, 5.69. C₂₈H₃₁O₆Br 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 cm³) was added a solution of (*S*,*S*)-4 (200 mg, 0.368 mmol) in dry THF (5 cm³) 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 cm³) 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 (Mg₂SO₄). 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, CHCl₃); vmax (KBr)/cm⁻¹ 2880, 1470, 1450, 1200, 1090, 1030, 920, 870, 760, 700; δ H (270 MHz; CDCl₃) 3.51–3.80 (12H, m, CH₂), 3.82 (3H, s, OCH₃), 4.10 (2H, d *J* 8.90, benzylic CH₂), 4.61 (2H, d *J* 8.90, benzylic CH₂), 4.51 (1H, br s, CH); 4.64 (1H, br s, CH); 6.96 (1H, s, BrArH); 6.97 (1H, s, BrArH); 7.28–7.46 (10H, m, C₆H₅); The high-resolution mass spectrum could not be recorded because of the vary weak molecular ion peak; FABMS: *mlz* 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 cm³, 0.341 mmol) in hexanes was added to a solution of (S,S)-13 (100 mg, 0.178 mmol) in dry THF (10 cm³) 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 (MgSO₄) 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 (MgSO4) 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, CHCl₃); vmax (KBr)/cm⁻¹ 3300, 2860, 1685, 1600, 1480, 1450, 1340, 1290, 1195, 1140, 1095, 885, 760; δH (270 MHz; CDCl₃) 3.56-3.99 (12H, m, CH₂), 4.60 (2H, d J 11.0, benzylic CH₂), 4.76 (2H, d J 11.0, benzylic CH₂), 4.77 (2H, dd J 2.84 and 9.27, CH), 7.29–7.44 (10H, m, C₆H₅), 7.56 (2H, s, phenol moiety CH), 9.17 (1H, s, OH), 9.77 (1H, s, CHO); 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. C₂₉H₃₂O₇ requires C, 70.85; H, 7.13%.

Determination of pKa values

According to the equation; $pKa=pH+log(D_B--D_{obs})-log(D_{obs}-D_{HB})$, pKa-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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