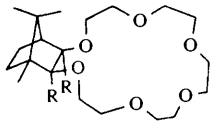
Synthesis of camphor based chiral crown ethers and their interactions with amino acid derivatives

Brian J. Brisdon,* Richard England, Mary F. Mahon, Khalid Reza and Malcolm Sainsbury
School of Chemistry, University of Bath, Claverton Down, Bath, UK BA2 7AY

Three camphor based crown ethers have been prepared, starting from (−)-(1*R*)-camphorquinone, in which 2- and 3-*endo*-substituents are used to regulate the availability of the *endo*-18-crown-6 face for binding organic guests and the bridge head methyl group is available to impart enantioselectivity at the *exo*-face. The stereochemistry of the key intermediate 2-*endo*-3-*endo*-dimethyl bornane-2,3-diol (**6**) has been confirmed by a single crystal X-ray structure determination. Interactions between these crowns and antipodal phenylglycine salts have been probed using NMR and modelling techniques.

The chemistry of chiral crown ethers has become the focus of considerable interest in the last two decades, following the discovery that enantiodifferentiation and asymmetric catalytic activity, two important properties of natural enzymes, can be induced by these macrocycles.[1] Cram[2–4] and others[5] have shown that chiral ligands derived from 18-crown-6 are able to discriminate between the enantiomers of guest alkylammonium salts to which they hydrogen-bond, and the chiral recognition process has been explored using NMR spectroscopy,[5] and exploited in solvent extraction and chromatographic techniques,[3] as well as in liquid membrane based separations.[4] Chiral crown ethers have also been used successfully as chiral catalysts in a range of asymmetric synthetic procedures which include Michael reactions,[6] reduction[7] and hydrogen cyanide addition,[8] but despite these efforts the intramolecular interactions which affect complexation of chiral crown ethers with specific guest molecules are still not fully understood.[9]

Although a considerable number of chiral macrocycles have been synthesised to provide a range of suitable substrates for enhanced structural selectivity and diastereomeric transient studies, most of these are based on a restricted number of easily accessible chiral building blocks which feature binaphthols,[10] *vic*-cyclohexanediol derivatives,[11] or natural products such as carbohydrates,[12] tartaric acid[13] and amino acids.[14]



1 R = H
2 R = Me
3 R = Ph

In this paper, which is the second from our laboratories on chiral crown ethers,[15] we present the synthesis of camphor based chiral crown ethers **1**–**3**, in which the nature of the substituent R can be used to regulate the availability of the *endo*-face for binding a guest species, and the bridge-head methyl group can be used to impart enantioselectivity on binding guests at the *exo*-face. The results of a preliminary NMR study of the ability of **2** and **3** to complex enantioselectivity with antipodal α-amino acid salts is also described. The only other report[16] of a camphor-containing crown ether is centred on monoaza-crowns, in which camphor was a substituent rather than an integral part of the macrocycle.

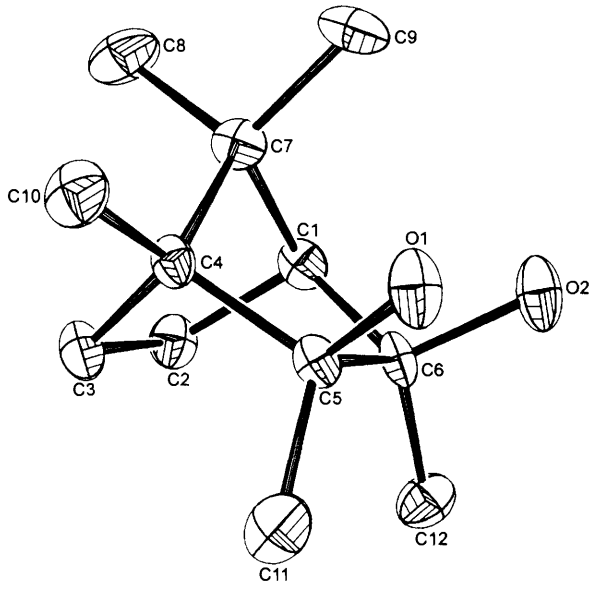
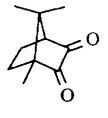


Fig. 1 Molecular structure of **6** together with the labelling scheme used (the thermal ellipsoids are drawn at the 50% level in the ORTEP representation)

Results and discussion

Synthesis of crowns 1–3

The requisite *cis*-diols needed for the synthesis of the crowns were obtained from (−)-(**R**)-camphorquinone **4**, which is readily available commercially. Thus reaction of **4** with L-Selectride affords the *cis*-diol **5** in good yield;[16] similarly, reactions of **4** with methyllithium and phenyllithium at low temperature produced the diols **6** and **7**, respectively.



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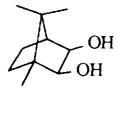

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In order to confirm the stereochemistry of the diols, a crystal structure determination was carried out on compound **6**, the results of which are shown in Figs. 1 and 2 and tabulated in Table 1. Intramolecular bond lengths and angles are unexceptional compared to related compounds[17] and are not

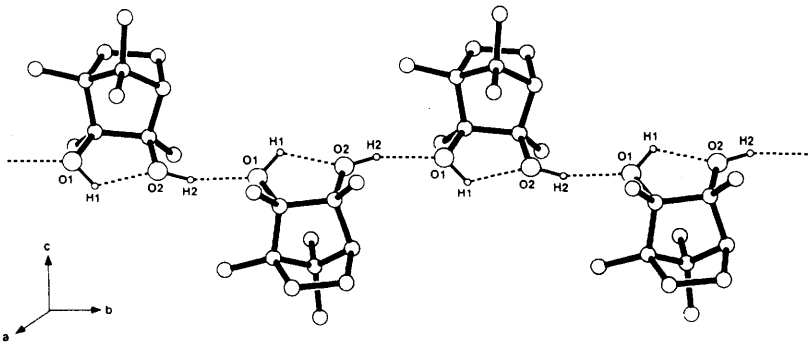


Fig. 2 Lattice domination by one-dimensional polymeric chains parallel to the *b*-axis, consequent upon two types of alternating hydrogen-bonding in **6**

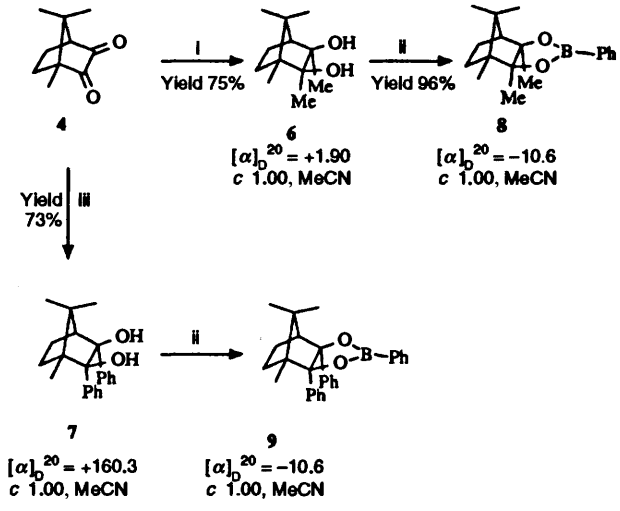
Table 1 Selected bond lengths and bond angles for **6**

C(5)–O(1)	1.438(9)	C(6)–O(2)	1.445(10)
C(2)–C(1)	1.522(11)	C(6)–C(1)	1.537(13)
C(7)–C(1)	1.557(12)	C(3)–C(2)	1.559(13)
C(4)–C(3)	1.532(11)	C(5)–C(4)	1.544(12)
C(7)–C(4)	1.583(11)	C(10)–C(4)	1.511(11)
C(6)–C(5)	1.571(11)	C(11)–C(5)	1.548(13)
C(12)–C(6)	1.534(13)	C(8)–C(7)	1.530(13)
C(9)–C(7)	1.557(11)	H(1)–O(1)	0.983(20)
H(2)–O(2)	0.970(21)		
C(6)–C(1)–C(2)	108.4(7)	C(7)–C(1)–C(2)	100.4(6)
C(7)–C(1)–C(6)	105.5(6)	C(3)–C(2)–C(1)	102.5(6)
C(4)–C(3)–C(2)	104.2(6)	C(5)–C(4)–C(3)	107.0(7)
C(7)–C(4)–C(3)	99.8(6)	C(7)–C(4)–C(5)	103.1(6)
C(10)–C(4)–C(3)	114.6(7)	C(10)–C(4)–C(5)	114.7(7)
C(10)–C(4)–C(7)	115.9(7)	C(4)–C(5)–O(1)	109.5(6)
C(6)–C(5)–O(1)	111.0(7)	C(6)–C(5)–C(4)	103.6(6)
C(11)–C(5)–O(1)	103.7(7)	C(11)–C(5)–C(4)	113.7(7)
C(11)–C(5)–C(6)	115.5(7)	C(1)–C(6)–O(2)	110.6(7)
C(5)–C(6)–O(2)	106.5(6)	C(5)–C(6)–C(1)	102.4(7)
C(12)–C(6)–O(2)	106.3(6)	C(12)–C(6)–C(1)	114.4(7)
C(12)–C(6)–C(5)	116.5(8)	C(4)–C(7)–C(1)	92.3(6)
C(8)–C(7)–C(1)	115.0(7)	C(8)–C(7)–C(4)	113.2(7)
C(9)–C(7)–C(1)	115.1(7)	C(9)–C(7)–C(4)	116.5(6)
C(9)–C(7)–C(8)	105.0(7)	C(5)–O(1)–H(1)	101.5(50)
C(6)–O(2)–H(2)	110.8(53)		

commented upon further, but scrutiny of the gross structure (Fig. 2) reveals lattice domination by one-dimensional polymeric chains parallel to the *b*-axis, which are a consequence of two types of alternating hydrogen-bonding. These consist of an intramolecular interaction between H(1) and O(2) [H(1)–O(2), 1.88(7) Å], and longer, intermolecular hydrogen-bonds between symmetry related molecules, with H(2)–O(1) separations of 1.95(4) Å.

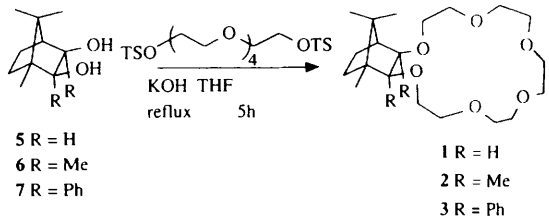
Diols are noted for their ability to form stable inclusion compounds when crystallised from common solvents,[18,19] in which the guest solvent molecules are contained in a series of parallel canals within the lattice. As a consequence the solid-state structures of many diols have been determined and the differing modes of hydrogen-bonding elucidated and classified in an attempt to rationalise this behaviour.[20] To date six distinct diol structural types have been identified based upon (*a*) helical tabulated, (*b*) double-stranded, (*c*) layer, (*d*) pillar, (*e*) helical and (*f*) hydrate structures. The lattice structure of **6** does not fall into any of these classifications and we have no evidence that **6** forms stable inclusion compounds under the conditions employed in our experiments. Each diol, **6** and **7**, formed a single boronate ester, **8** and **9** respectively (Scheme 1), in near quantitative yield, proving that in each diol there is a *cis*-relationship of hydroxy groups.

It seems evident that methyllithium and phenyllithium attack



Scheme 1 *Reagents and conditions:* i, MeLi, THF, −78 to 20 °C; ii, $PhB(OH)_2$, CH_2Cl_2; iii, PhLi, Et_2O, 0 °C to reflux

the carbonyl of camphorquinone **4** from the sterically less hindered *endo*-face, as does L-Selectride. The crown ethers **1**–**3** were then readily prepared by the cyclisation of their corresponding diols with pentaethylene glycol ditosylate in the presence of either potassium hydroxide or potassium *tert*-butoxide (Scheme 2). The parent crown **1** was found to be

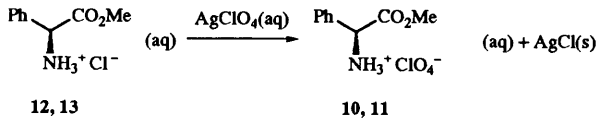


Scheme 2

unstable to silica and was purified successfully on an alumina column.

Preparation of amino acid derivatives.

The chiral phenylglycine salts (*R*)- and (*S*)-[$PhCHNH_3CO_2Me$]ClO_4, **10** and **11**, were prepared by treating their respective chloride salts **12** and **13**[21] with silver(I) perchlorate, filtering the silver(I) chloride formed during the reaction and carefully evaporating the solvent (Scheme 3). Pure **10** {$[\alpha]_D$ −100.2 (*c* 1.00, 6 mol dm^{-3} HCl)} and **11** {$[\alpha]_D$ +100.5 (*c* 1.00, 6 mol dm^{-3} HCl)} were acquired as colourless crystalline solids by crystallising from a mixture of acetonitrile and chloroform.



12, 13 10, 11

Scheme 3

Table 2 ^{1}H NMR chemical shifts (δ) of selected protons

Host + guest	4-H	9-CH_3	10-CH_3	OCH_3	C*H*NH_3^+
2	2.69	0.80	0.76		
10 or **11**				3.82	5.20
2 + **10**	2.72	0.77	0.77	3.73	5.07
2 + **11**	2.70	0.77	0.77	3.74	5.06
3		1.03	0.76		
3 + **10**		1.04	0.78	3.74	5.02[a]
3 + **11**		1.04	0.77	3.81	5.01

[a] In an NOE experiment, irradiation at 5.02 ppm caused a 7% enhancement of the bridge-head 8-CH_3 signal at 1.50 ppm.

Binding interactions between chiral crowns and phenylglycine salts

The strength and specificity of host–guest hydrogen-bonding interactions in solution involving neutral and polar organic molecules have been investigated by several techniques.[22] NMR spectroscopy has been shown to provide a facile method for investigating in suitable cases both the stoichiometry and strength of complex formation [23] and we have used this method for a preliminary study of chiral camphor–crown ether–phenyl glycine interactions. ^{1}H NMR measurements carried out on 1:1 molar mixtures of **2** and **3** with salts **10**–**13** dissolved in CD_3OD or CD_3CN failed to show chemical shift differences from the sum of the spectra of individual components in these solvents. However, some small but reproducible chemical shift differences were observed (Table 2) for the perchlorate salts of the two enantiomers of phenylglycine, **10** and **11**, in the presence of either crown on using a less polar solvent mix ($CDCl_3$–CD_3CN, 2:1 v/v). Attempts to determine the stoichiometry or association constants of the interacting pairs by NMR titration were not successful because of the small chemical shift differences observed. Extraction of aqueous racemic phenylglycine perchlorate salt by **2** or **3** dissolved in $CDCl_3$–CD_3CN (2:1 v/v) established a 1:1 stoichiometry within experimental error for the host–guest pair. No enantiomeric enrichment was noted under the conditions of the extraction experiments and pure chloroform solutions of the crowns failed to extract the salt at all. The phenylglycine salts **12** and **13**, which contained Cl^- as counterions, showed no change in chemical shift data on addition of the camphor–crowns, nor were they extracted by the crowns into a $CDCl_3$–CD_3CN mixture. It has been recognised previously [10] that Cl^- forms a sufficiently strong hydrogen bond with the RNH_3^+ group to prevent an 18-crown-6 host from developing the three O···H–N^+ hydrogen bonds with the guest which are required for effective complexation. The crown ether **1** decomposed in solution in the presence of the salts **10**–**13** and so it was not included in the NMR or extraction studies.

Molecular modelling

In order to understand the host–guest interactions involved on our systems, molecular modelling using the Program Discover [24] was carried out. A model of crown **3** was built and its interaction with salt **10** docked normal to the crown ring and within N–H···O hydrogen bonding distance was studied. The glycine was rotated in increments about first the *exo*- and then the *endo*-face of the crown ring. The complex was represented by a semi-empirical molecular mechanics forcefield and minimised to obtain the minimum energy structure of each configuration. Nine energy minima within the energy difference of 3 kJ mol^{-1} were found, with the lowest energy configuration involving complexation *via* the *exo*-face of the crown with the hydrogen of the glycine pointing towards the camphane. However, the modelling studies do not take into account any solvent effects and consequently NOE studies were also carried out. These confirmed an interaction between the glycine α-hydrogen in **10** and a bridge-head methyl group on the bornane fragment in **3**, so indicating that binding to the *exo*-face is also preferred in solution in chloroform–acetonitrile (2:1).

Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ with Me_4Si as internal standard unless stated otherwise. EI Mass spectra were determined with an ionisation potential of 70 eV, but for CI spectra isobutane was used as the reagent gas. Petrol refers to light petroleum, bp 60–80 °C, and silica gel (Merck 9385) was used for column chromatography. All $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}.

Bornane-2-*exo*-3-*exo*-diol (5) †

A solution of lithium tri-*sec*-butylborohydride ‡ (1.0 mol dm^{-3} in THF; 15.6 cm^3, 15.6 mmol) was added dropwise to a stirred solution of (1*R*)-camphorquinone § (1.0 g, 6.0 mmol) in dry THF (tetrahydrofuran) (20 cm^3) at −78 °C under a N_2 atmosphere. After 2 h the solution was warmed to ambient temperature. Excess reagent was quenched with saturated aq. NH_4Cl (30 cm^3) and the product was extracted with ethyl acetate (3 × 75 cm^3). The combined organic extracts were washed with water, dried over magnesium sulfate, concentrated and the residue purified by chromatography eluting with dichloromethane–hexane (1:1). This gave compound **5** [25] as a colourless oil (0.9 g, 92%); $[\alpha]_D^{20}$ −22.1 (*c* 1.00, CH_3CN) and $[\alpha]_D^{20}$ −17.1 (*c* 1.00, EtOH); ν_{max}(neat)/cm^{-1} 3350, 2925 and 1460; δ_H 0.84 (3 H, s), 0.91 (3 H, s), 1.01 (3 H, s), 1.28 (1 H, m), 1.49 (2 H, m), 1.72 (1 H, m), 2.00 (1 H, d, *J* 5.3 Hz), 4.08 (1 H, d, *J* 7.0 Hz) and 4.30 (1 H, d, *J* 7.0 Hz); δ_C 10.6 (C-10), 14.8 (C-8 or C-9), 19.85 (C-9 or C-8), 25.6 (C-5), 31.9 (C-6), 46.4 (C-1 or C-7), 47.7 (C-7 or C-1), 48.7 (C-4), 84.8 (C-3) and 89.1 (C-2); *m*/*z* (CI) (%) 277 (3), 237 (100), 135 (70), 110 (39) and 95 (78) (Found: C, 70.9; H, 10.9. Calc. for $C_{10}H_{18}O_2$: C, 70.6; H, 10.7%).

2-*endo*-3-*endo*-Dimethylbornane-2,3-diol (6)

A solution of (1*R*)-camphorquinone (1.0 g, 6.0 mmol) in dry THF (20 cm^3) under dry N_2 was stirred at −78 °C and treated dropwise over a period of 20 min with methyllithium in diethyl ether (13 cm^3, 18.0 mmol; 1.4 mol dm^{-3}). The mixture was stirred at −78 °C for 1 h and then allowed to warm to ambient temperature. Excess reagent was quenched with saturated NH_4Cl (30 cm^3) and the product extracted into ethyl acetate (3 × 50 cm^3). The combined organic fractions were washed with saturated NaCl (30 cm^3) and then water (30 cm^3). Evaporation of the solvent gave an oil which was purified by chromatography eluting with ethyl acetate and hexane (1:1). Traces of undesired diastereoisomers were finally removed by crystallisation of the colourless solid product from acetonitrile. This gave compound **6** (0.9 g, 75%) as prisms; $[\alpha]_D^{20}$ +1.9 (*c* 1.00, CH_3CN); mp 132–133 °C (lit.,[26] 131 °C); ν_{max}(neat)/cm^{-1} 3400(br), 2920 and 1460; δ_H 0.84 (3 H, s), 0.86 (3 H, s), 1.16 (3 H, s), 1.27 (6 H, s), 1.30 (3 H, m), 1.58 (1 H, m), 1.64 (1 H, d, *J* 4.6 Hz), 2.90 (1 H, br s, OH) and 3.20 (1 H, br s, OH); δ_C 10.7

† Bornane = 1,7,7-trimethylbicyclo[2.2.1]heptane.
‡ Lithium tri-*sec*-butylborohydride = lithium tri-*sec*-butylboranuide.
§ Camphorquinone = 1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-dione.

(C-10), 21.4 (C-8 or C-9), 22.8 (C-5), 23.19 (C-9 or C-8), 23.32 (C-3'), 24.26 (C-2'), 30.94 (C-6), 48.29 (C-1 or C-7), 53.1 (C-7 or C-1), 56.8 (C-4), 80.5 (C-3) and 82.3 (C-2); *m/z* (EI) (%) 198 (M^+, 3), 137 (22), 99 (39), 98 (62), 85 (50), 83 (20), 71 (22), 55 (20), 43 (100) and 41 (24); *m/z* (CI) (%) 198 (M^+, 2), 181 (100), 163 (11), 137 (13), 123 (14), 109 (10), 98 (18) and 88 (12) (Found: C, 72.6; H, 11.6. Calc. for $C_{12}H_{22}O_2$: C, 72.7; H, 11.2%).

2-*endo*-3-*endo*-Diphenylbornane-2,3-diol (7)

A solution of (1*R*)-camphorquinone (2.0 g, 12.0 mmol) in diethyl ether (30 cm^3) at 0 °C, under N_2, was treated with phenyllithium (2 mol dm^{-3} in hexane; 18.0 cm^3, 36 mmol). After the addition, the mixture was allowed to warm to room temperature and then heated under reflux for 4 h. After cooling, aq. saturated ammonium chloride (30 cm^3) was added dropwise and the aqueous phase was extracted with ethyl acetate (3 × 100 cm^3). The combined extracts were dried, filtered and the solvent evaporated to give a gum which was chromatographed (ethyl acetate–petrol 15:85). This afforded compound **7** as colourless prisms (2.8 g, 73%), mp 162 °C (lit.,[27] 161–163); $[\alpha]_D^{20}$ +160.3 (*c* 1.00, CH_3CN); ν_{max}(Nujol)/cm^{-1} 3380; δ_H 0.74 (3 H, s), 0.97 (3 H, s), 2.38 (1 H, d, *J* 5.1 Hz), 2.47 (1 H, s, OH), 4.57 (1 H, s, OH) and 6.90–7.20 (10 H, m); δ_C 23.0 (C-8 or C-9), 23.5 (C-9 or C-8), 23.6 (C-5), 30.75 (C-6), 52.9 (C-1 or C-7), 52.95 (C-8), 54.4 (C-7 or C-1), 86.7 (C-3) and 88.2 (C-2); *m/z* (CI) (%) 321 (M − 1, 11), 305 (100), 289 (12), 247 (58), 219 (41), 193 (23), 160 (32) and 105 (90) (Found: C, 82.1; H, 8.2. Calc. for $C_{22}H_{26}O_2$: C, 82.0; H, 8.1%).

2-*endo*-3-*endo*-Dimethylbornane-2,3-diyl phenylboronate (8)

Phenylboronic acid (0.94 g, 1.08 mmol) was added at room temperature to a stirred solution of the bornanediol **6** (0.214 g, 1.08 mmol) in dry dichloromethane (10 cm^3) under N_2. After the addition activated molecular sieves 4 Å (6 g) were added and the mixture was stirred at room temperature for 8 h. The sieves were removed and the solvent evaporated to give an oil which was then chromatographed using hexane–ethyl acetate (8:2) as the eluent. The product (**8**) was obtained as a colourless hygroscopic solid, mp 70 °C (0.25 g, 96%); ν_{max}(Nujol)/cm^{-1} 2925 and 1460; δ_H 0.84 (3 H, s), 0.95 (3 H, s), 1.10 (3 H, s), 1.24 (3 H, s), 1.35 (3 H, s), 1.22–1.41 (2 H, m), 1.53–1.62 (2 H, m) and 7.69–7.73 (2 H, m); δ_C 10.2 (C-10), 19.5 (C-9 or C-8), 22.2 (C-8 or C-9), 22.3 (C-3), 22.8 (C-5), 25.0 (C-2'), 30.4 (C-6), 48.1 (C-1 or C-7), 52.4 (C-7 or C-1), 54.4 (C-4), 127.7, 131.0 and 134.6; *m/z* (CI) (%) 265 (M + 1, 76), 174 (100), 163 (76), 109 (40), 95 (39), 85 (21) and 69 (37); $[\alpha]_D^{20}$ −10.6 (*c* 1.00, MeCN) (Found: C, 76.3; H, 9.0. $C_{18}H_{25}BO_2$ requires: C, 76.1; H, 8.9%).

2-*endo*-3-*endo*-Diphenylbornane-2,3-diyl phenylboronate (9)

Anhydrous phenyl boronic acid (0.64 g, 5.2 mmol) was added in small quantities to a solution of the bornanediol **7** (0.21 g, 1.1 mmol) in dry dichloromethane under N_2. Molecular sieves (4 Å, 5 g) were added and the mixture was stirred at room temperature for 48 h. After filtration, the filtrate was evaporated leaving an oil from which the pure product was obtained as hydroscopic colourless crystals (0.31 g, 95%) after chromatography (dichloromethane–hexane, 3:7); mp 118 °C; $[\alpha]_D^{20}$ +60.6 (*c* 0.5, MeOH); ν_{max}(Nujol)/cm^{-1} 2940; δ_H 0.89 (3 H, s), 1.84 (1 H, m), 2.02 (1 H, m), 2.77 (1 H, d, *J* 5.2 Hz) and 7.06–7.80 (15 H, m); δ_C 9.8 (C-10), 22.65 (C-9 or C-8), 24.0 (C-5), 25.8 (C-9 or C-8), 30.0 (C-6), 49. 0 (C-1 or C-7), 50.96 (C-4), 53.7 (C-7 or C-1), 86.6 (C-3), 99.3 (C-2), 125.4, 125.6, 126.0, 126.2, 126.5, 126.8, 127.0, 127.1, 127.7, 129.3, 129.4, 129.7 131.2, 134.8, 139.6 and 141.0; *m/z* (CI) (%) 285 (M + 1, 71), 174 (100), 163 (82), 109 (39), 95 (39) and 69 (37) (Found: C, 85.7; H, 7.1. $C_{28}H_{29}BO_2$ requires: C, 85.7; H, 7.4%).

General method for the hydrolysis of the phenylboronates 8 and 9

A solution of the phenylboronate (0.6 g) in ethanol (20 cm^3) was stirred with aqueous KOH (4 mol dm^{-3}; 15 cm^3) and then heated under reflux for 14 h. The reaction mixture was then cooled, neutralised (2 mol dm^{-3} HCl) and the volume of the solution reduced to 10 cm^3, prior to extraction of the liberated diol into ethyl acetate (4 × 40 cm^3). The combined extracts were evaporated and the residue purified by chromatography using the same eluents as detailed above. Physical and spectroscopic properties of the products were found to be identical with those described above for **6** and **7**, respectively.

2-*endo*-3-*endo*-Dimethyl-2,3-(3,6,9,12-tetraoxatetradecane-1,14-diyldioxy)bornane (2)

Method A. Potassium *tert*-butoxide (0.46 g, 4.1 mmol) under N_2 was added to a stirred solution of compound **6** (0.41 g, 2.05 mmol) in dry THF at 0 °C. After 20 min, pentaethylene glycol ditosylate (1.1 g, 2 mmol) in dry THF (15 cm^3) was added and the mixture was allowed to warm to room temperature over a period of 1 h. After this time the reaction mixture was heated under reflux for 5 h. Next the solvent was evaporated under reduced pressure and the residue shaken with water (30 cm^3) and dichloromethane (100 cm^3). The organic layer was separated, washed with brine, dried and evaporated to yield a gum. This was chromatographed (ethyl acetate–petrol 3:7) to give a colourless oil (0.6 g, 73%); $[\alpha]_D^{20}$ −0.4 (*c* 1.00, CH_3CN); ν_{max}(neat)/cm^{-1} 3000, 1640 and 1100; δ_H 0.76 (3 H, s), 0.80 (3 H, s), 1.12–1.43 (12 H, m), 1.51 (1 H, m), 1.82 (1 H, d, *J* 4.8 Hz), 3.45–3.62 (16 H, m), 3.66 (2 H, m), 3.77 (2 H, m), 3.92 (1 H, dd, *J* 2.0 Hz, 6.8 Hz) and 4.12 (1 H, dd, *J* 2.0 Hz, 13.4 Hz); *m/z* (CI) (%) 400 (M^+, 4), 383 (16), 357 (17), 221 (52), 203 (23), 177 (100), 163 (18), 133 (50), 109 (24) and 89 (48) (Found: C, 65.6; H, 10.2. $C_{22}H_{40}O_6$ requires: C, 65.9; H, 10.1%).

Method B. A stirred mixture of compound **6** (0.5 g, 2.6 mmol) in dry THF (25 cm^3) and potassium hydroxide (85%, 0.4 g, 515 mmol) under N_2 was heated under reflux and treated with pentaethylene glycol ditosylate (1.4 g, 2.6 mmol). After heating for 8 h, the reaction mixture was cooled and the solvent was removed to afford an oil. This was partitioned between water (20 cm^3) and dichloromethane (60 cm^3) and the aqueous phase was extracted with dichloromethane (2 × 30 cm^3). The combined organic phases were evaporated to yield a viscous oil which was chromatographed with ethyl acetate–hexane (1:1) giving compound **2** as a colourless oil (0.7 g, 67%); $[\alpha]_D^{20}$ −0.4 (*c* 1.00, CH_3CN) with physical and spectroscopic properties identical to compound **2** obtained by method A.

2-*endo*-3-*endo*-Diphenyl-2,3-(3,6,9,12-tetraoxatetradecane-1,14-diyldioxy)bornane (3)

Method A. Solid potassium *tert*-butoxide (0.75 g, 6.7 mmol) was added to compound **7** (1.0 g, 3.2 mmol) in dry THF (30 cm^3) at −15 °C under N_2. After 30 min, a solution of pentamethylene glycol ditosylate (1.7 g, 3.2 mmol) in dry THF (15 cm^3) was added dropwise and the mixture was then warmed to room temperature over 1 h and then heated under reflux for 6 h. After cooling, water (10 cm^3) was added and the reaction mixture was extracted with ethyl acetate (4 × 100 cm^3). The combined organic extracts were washed, dried and evaporated to give an oil which was chromatographed eluting with ethyl acetate–petrol (1.5:8.5). This gave the title compound as a colourless liquid (1.0 g, 63%); $[\alpha]_D^{20}$ +534 (*c* 0.27, $CHCl_3$); ν_{max} 3010, 1635 and 1115; δ_H 0.81 (3 H, s), 1.03 (3 H, s) 1.11–1.21 (2 H, m), 1.50 (3 H, s), 1.85 (1 H, m), 2.03 (1 H, m), 2.66 (1 H, d, *J* 5.2 Hz), 3.32 (2 H, m), 3.42 (4 H, m), 3.53 (2 H, m), 3.65 (6 H, m), 3.74 (2 H, m), 3.84 (2 H, m), 4.20 (1 H, m), 4.19 (1 H, m) and 7.00–7.21 (10 H, m); *m/z* (CI) (%) 524 (M^+, 3), 307 (100), 289

(12), 247 (42), 219 (38), 177 (11), 105 (18) and 89 (19) (Found: C, 73.6; H, 8.8. $C_{32}H_{46}O_6$ requires: C, 73.3; H, 8.5%).

Method B. Potassium hydroxide (0.23 g, 3.5 mmol) was added to compound **7** (0.51 g, 1.6 mmol) in THF (20 cm^3) under N_2 at −15 °C. After 1 h at 0 °C pentaethylene glycol ditosylate (0.87 g, 1.6 mmol) in THF (10 cm^3) was added and the mixture was heated under reflux for 8 h. The solvent was removed and the residue was partitioned between ethyl acetate (30 cm^3) and water (20 cm^3). The aqueous phase was extracted further with ethyl acetate (3 × 30 cm^3) and the combined organic extracts were dried and evaporated to give crude (**3**), which was purified as in method A above; yield, 0.55 g 55%.

2-*exo*-3-*exo*-(3,6,9,12-Tetraoxatetradecane-1,14-diyldioxy)bornane (1)

A mixture of compound **5** (0.22 g, 1.3 mmol) and potassium *tert*-butoxide (0.31 g, 2.55 mmol) in dry THF (25 cm^3) was heated at reflux for 1 h under an atmosphere of N_2. The mixture was cooled to 30 °C, treated with a solution of pentaethylene glycol ditosylate (0.7 g, 1.3 mmol) in THF (10 cm^3) and then heated under reflux for 6 h. The solvent was removed and the residue was shaken with water (10 cm^3). It was then extracted with dichloromethane (3 × 20 cm^3) and the extracts were dried and evaporated to give an oil which was chromatographed on alumina (eluent dichloromethane) to give compound **1** (0.4 g, 81%) as a colourless liquid which decomposed on contact with silica, or on standing at ambient temperatures for *ca.* 4 days; ν_{max}(neat)/cm^{-1} 2915, 1440 and 1065; δ_H 0.68 (3 H, s), 0.81 (3 H, s), 0.71–1.03 (4 H, m), 0.99 (3 H, s), 1.72 (1 H, d, *J* 4.5 Hz) and 3.42–3.81 (18 H, m); *m/z* (CI) (%) 373 (M + 1¶, 47), 237 (20), 221 (100), 135 (34), 133 (75) and 89 (38); $[\alpha]_D^{20}$ −2.5° (*c* 1.00, $CHCl_3$) (Found: C, 64.2; H, 10.0. $C_{20}H_{36}O_6$ requires: C, 64.5; H, 9.7%).

Complexation of crowns 2 and 3 with either (*S*)- or (*R*)-2-phenylglycinium methyl ester perchlorate

The crown (0.03 mmol) (host) in $CDCl_3$–CD_3CN (2:1) (1 cm^3) was added to 2-phenylglycinium methyl ester perchlorate (0.03 mmol) (guest) in the same solvent mixture (1 cm^3). ^1H NMR spectra were then compared with data for those of the parent crowns recorded in the same solvent.

Extraction studies on crowns 2 and 3 with 2-phenylglycinium methyl ester perchlorate

A solution of the given crown (0.119 mmol) in 2.0 cm^3 of $CDCl_3$–CD_3CN (2:1) was stirred for 2 h at 0 °C with a solution of D_2O (1.0 cm^3) containing racemic 2-phenylglycinium methyl ester perchlorate (0.632 g, 0.238 mmol). The lower organic layer was withdrawn with a syringe, the solvent removed and the residue dried under vacuum. Complete dissolution of the solid was effected by the addition of $CDCl_3$–CD_3CN (2:1) (0.75 cm^3) and the ^1H NMR spectrum of the solution recorded. Integration revealed that the crown to racemic amino acid ratio was 1:0.9 ± 0.1 in both cases. The mixed organic solvent–aqueous phase volume ratio could be varied between 2:1 and 2:3, and the molar ratio of crown–amino ester salt from 1:2 to 1:1.5 without affecting greatly the crown–amino ester salt ratio in the extract. The ester salt was not extracted from D_2O using either crown dissolved in an equal volume of pure $CDCl_3$. Residual crown was recovered from the aqueous layer by extraction with dichloromethane (2 × 5 cm^3), the extracts combined with the NMR solution and the solvent evaporated. Pure crown was obtained from the residue following elution from a silica column using ethyl acetate–hexane (1:1).

¶ For details of the CCDC deposition scheme, see 'Instructions for Authors (1995), *J. Chem. Soc., Perkin Trans. 2*, 1995, issue 1.

Crystallographic studies

A crystal of compound **6** of approximate dimensions 0.5 × 0.5 × 0.2 mm was used for data collection.

Crystal data. $C_{12}H_{23}O_2$, M = 199.3, orthorhombic, a = 7.5769(9), b = 10.670(2), c = 14.392(2) Å, U = 1163.5 $Å^3$, space group $P2_12_12_1$, Z = 4, D_c = 1.14 g cm^{-3}, μ(Mo-Kα) = 0.70 cm^{-1}, F(000) = 444. Data were measured at room temperature on a CAD4 automatic four-circle diffractometer in the range $2 \leqslant \theta \leqslant 24°$. 1095 reflections were collected of which 569 were unique with $I \geqslant 2\sigma(I)$. Data were corrected for Lorentz and polarisation but not for absorption. The structure was solved by Direct methods and refined using the SHELX[28,29] suite of programs. In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions except for H1 and H2 (attached to O1 and O2 respectively). These protons were located in an advanced Difference Fourier and refined at a distance of 0.98 Å from the relevant parent atoms.

Final residuals after 12 cycles of least squares were R = 0.0557, R_w = 0.0552, for a weighting scheme of $w = 1.2161/[\sigma^2(F) + 0.006\,338(F)^2]$. Max. final shift/esd was 0.000. The max. and min. residual densities were 0.08 and −0.08 e $Å^{-3}$ respectively. Tables of fractional atomic coordinates, thermal parameters and complete listings of bond distances and bond angles have been deposited.† The asymmetric unit is shown in Fig. 1, along with the labelling scheme used and key bond lengths and bond angles are given in Table 1.

Acknowledgements

We thank SERC for their support of this work and Mr A. P. Lemon for assistance in the preliminary modelling studies.

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Paper 5/01240F
Received 1*st March* 1995
Accepted 12*th June* 1995