Synthesis of Chiral Crown Ethers from (1*S*,2*S*)-(+)-2-Amino-1-phenyl-1,3-propanediol

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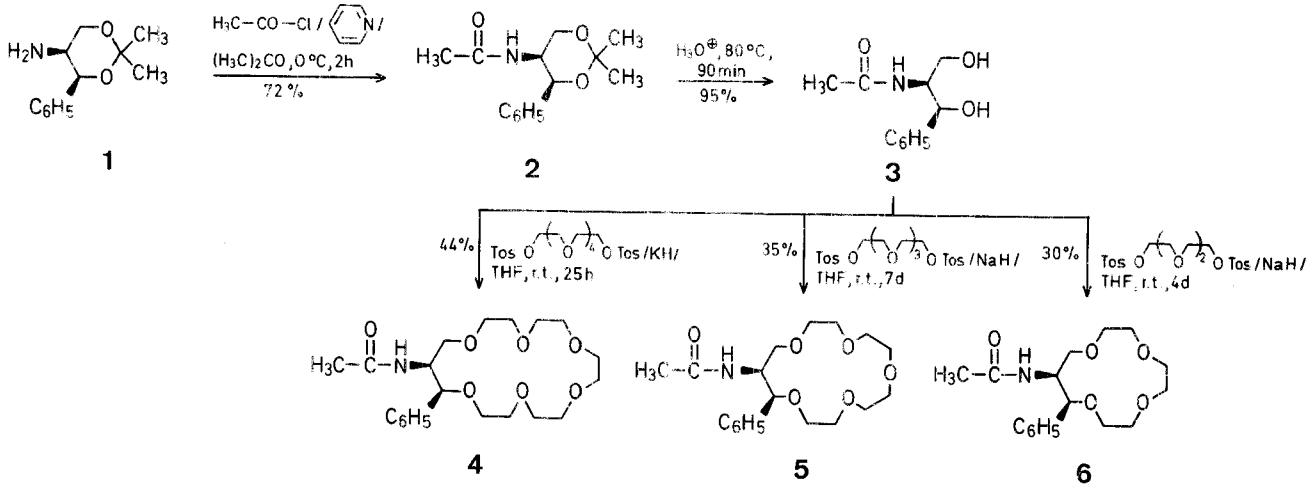
Numerous examples of the use of crown ethers and other macrocyclic compounds have been reported recently; chiral crown compounds can be used as enzyme-analog models, drug-receptor models, stereoselective catalysts and as agents for optical resolution of racemic substrates[1-7]. A large number of crown ethers have been prepared, but only a limited number of chiral crown ethers are available[8,9]. We report here the preparation of chiral crown derivatives from (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol.

Acetylation of commercially available (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (**1**) with acetyl chloride in acetone and pyridine gives compound **2** in 72% yield. The acetal function in compound **2** is hydrolysed almost quantitatively to diol **3** by means of warm 75% acetic acid. The substituted 19-crown-6 **4** is obtained in 44% yield by condensation between the diol **3** and pentaethylene glycol ditosylate in tetrahydrofuran with potassium hydride as base and template. Similarly, substituted 16-crown-5 **5** and 13-crown-4 **6** are obtained in 35% and 30% yield respectively, by condensation between the diol **3** and tetraethylene glycol ditosylate or triethylene glycol ditosylate in tetrahydrofuran with sodium hydride as base and template. The chiral crowns reported here are currently being used in phase transfer asymmetric induction.



Tri-, tetra-, and pentaethylene glycol were purchased from Aldrich Chem. Co. and (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane from Sigma Chem. Co. Tri-, tetra-, and pentaethylene glycol ditosylates were prepared according to known procedures[10,11].

(4*S*,5*S*)-(+)-5-Acetamido-2,2-dimethyl-4-phenyl-1,3-dioxane (2):
A solution of (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (**1**; 18 g, 84 mmol) in anhydrous pyridine (30 ml) and acetone (120 ml) is stirred under a nitrogen atmosphere at 0 °C. Acetyl chloride (8.4 g, 120 mmol) is added dropwise and the solution is stirred at 0 °C for 2 h. Acetone is distilled under vacuum and the residue is dissolved in water (50 ml) and extracted with ether (3 × 100 ml). The organic phase is washed successively with 10% acetic acid (100 ml), water (100 ml), aqueous sodium hydrogen carbonate, dried with potassium carbonate and evaporated. The crude product is purified by flash column chromatography (silica gel, Woelm 32–63, activity I). The eluent is ether under a 10 p.s.i. pressure. The compound **2** is an oil which crystallises on standing; yield 14.4 g (72%); $[\alpha]_D^{29}$: + 18.0° (*c* 34, $CHCl_3$) (Lit.[12], $[\alpha]_D^{21}$: + 15.8°). m.p. 74–76 °C.

M.S.: *m/e* = 234 (M^+).

I.R. (neat): ν = 3440, 3205, 3060, 3030, 2990, 2870, 1655, 1515, 1200, 1090 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.38 (s, 6H, 2 CH_3); 1.63 (s, 3H, CH_3—CO); 3.77 (dd, 1H, H-axial of CH_2—O, *J* = 2.5 and 13 Hz); 4.10–4.29 (m, 2H, H-equatorial of CH_2—O + N—CH); 5.09 (d, 1H, C_6H_5—CH—O, *J* = 2 Hz); 6.71 (d, 1H, NH, *J* = 9 Hz); 7.26 ppm (s, 5H, H_{arom}).

(1*S*,2*S*)-(+)-2-Acetamido-1-phenyl-1,3-propanediol (3):
A solution of compound **2** (12 g, 100 mmol) in 75% aqueous acetic acid (200 ml) is stirred at 80 °C for 90 min. The solvent is distilled under vacuum to afford product **3** as a yellow oil which is used as such without further purification; yield: 9.9 g (95%); $[\alpha]_D^{29}$: + 13.5° (*c* 2.7, CH_3OH).

M.S.: *m/e* = 209.

I.R. (neat): ν = 3200, 1600, 1300, 1150–900, 700 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$ + DMSO-d_6): δ = 1.87 (s, 3H, CH_3—CO); 3.62 (m, 2H, CH_2—O); 4.09 (m, 1H, N—CH); 4.98 (d, 1H, C_6H_5—CH, *J* = 4 Hz); 5.69 (s, 2H, OH, exchanged with D_2O); 7.04 (d, 1H, NH, *J* = 9 Hz, exchanged with D_2O); 7.19–7.53 ppm (m, 5H, H_{arom}).

(1*S*,2*S*)-(+)-2-Acetamido-1-phenyl-4,7,10,13,16,19-hexaoxacyclononadecane (4):
A mixture of diol **3** (1.0 g, 5 mmol), potassium hydride (0.6 g, 15 mmol), and dry tetrahydrofuran (300 ml) is stirred under a nitrogen atmosphere at room temperature for 1 h. Pentaethylene glycol ditosylate (4.1 g, 7.5 mmol) in tetrahydrofuran (150 ml) is added and the mixture is stirred at room temperature for 24 h. Water (150 ml) is added, tetrahydrofuran is evaporated, and the aqueous phase is extracted with dichloromethane (3 × 100 ml), the organic phase is dried with magnesium sulfate, and evaporated. The crude product is purified by column chromatography (alumina, neutral, grade I, chloroform/methanol 50:1 as eluent). The compound **4** is an oil; yield: 920 mg (44%); $[\alpha]_D^{29}$: + 34.7 (*c* 4.2, $CHCl_3$).

$C_{21}H_{33}NO_7$	calc.	C 61.30	H 8.08	N 3.40
(411.5)	found	60.97	8.01	3.54

M.S.: *m/e* = 352 (M^+ – 59).

I.R. (neat): ν = 3480, 2860, 1650, 1095, 725, 700 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 2.00 (s, 3H, CH_3—CO); 3.40–3.94 (m, 22H, CH_2—O); 4.06–4.40 (m, 1H, N—CH); 4.71 (d, 1H, C_6H_5—CH, *J* = 7.5 Hz); 6.72 (d, 1H, NH, *J* = 8.5 Hz); 7.36 ppm (s, 5H, H_{arom}).

(1*S*,2*S*)-(+)-2-Acetamido-1-phenyl-4,7,10,13,16-pentaoxacyclohexadecane (5):

A mixture of diol **3** (1.0 g, 5 mmol), sodium hydride (0.36 g, 15 mmol), and dry tetrahydrofuran (200 ml) is stirred under a nitrogen atmosphere at room temperature for 1 h. Tetraethylene glycol ditosylate (3.75 g, 7.5 mmol) in tetrahydrofuran (150 ml) is added and the mixture is stirred at room temperature for 7 days. Water (150 ml) is added, tetrahydrofuran is evaporated and the aqueous phase is extracted with dichloromethane (3 × 100 ml). The organic phase is dried with magnesium sulfate, and evaporated. The crude product is purified by column chromatography (alumina, neutral, grade I, chloroform/ether 10:1 as eluent) to give **5** as an oil; yield: 615 mg (35%); $[\alpha]_D^{25}$: +48.2° (*c* 1.0, $CHCl_3$).

$C_{19}H_{29}NO_6$	calc.	C 62.11	H 7.96	N 3.81
(367.4)	found	61.81	8.02	3.87

M.S.: *m/e* = 367 (M^+).

I.R. (neat): ν = 3420, 3055, 2910, 2865, 1650, 1100 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 2.00 (s, 3H, CH_3—CO); 3.28–3.89 (m, 16H, CH_2—O); 4.00–4.36 (m, 3H, N—CH—CH_2—O), 4.74 (d, 1H, C_6H_5—CH, *J* = 10 Hz); 7.03 (d, 1H, NH, *J* = 9 Hz); 7.20–7.51 ppm (m, 5H, H_{arom}).

(1*S*,2*S*)-(+)-2-Acetamido-1-phenyl-4,7,10,13-tetraoxacyclotridecane (6):

A mixture of diol **3** (1.0 g, 5 mmol), sodium hydride (0.36 g, 15 mmol), and dry tetrahydrofuran (200 ml) is stirred under a nitrogen atmosphere at room temperature for 1 h. Triethylene glycol ditosylate (3.40 g, 7.5 mmol) in tetrahydrofuran (150 ml) is added and the mixture is stirred at room temperature for 4 days. Water (150 ml) is added, tetrahydrofuran is evaporated, and the aqueous phase is extracted with dichloromethane (3 × 100 ml), the organic phase is dried with magnesium sulfate, and evaporated. The crude product is purified by column chromatography (alumina, neutral, grade I, chloroform as eluent) to give **6** as an oil; yield: 480 mg (30%); $[\alpha]_D^{27}$: +60.3° (*c* 0.5, $CHCl_3$).

$C_{17}H_{25}NO_5$	calc.	C 63.14	H 7.79	N 4.33
(323.4)	found	63.03	7.84	4.37

M.S.: *m/e* = 323 (M^+).

I.R. (neat): ν = 3420, 3320, 3425, 3055, 3010, 2900, 2855, 1665, 1110, 730, 700 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.88 (s, 3H, CH_3—CO); 3.21–3.96 (m, 12H, CH_2—O); 3.97–4.49 (m, 3H, N—CH—CH_2—O); 5.07 (d, 1H, C_6H_5—CH, *J* = 5 Hz); 6.46 (d, 1H, NH, *J* = 10 Hz); 7.22–7.55 ppm (m, 5H, H_{arom}).

We thank the Natural Sciences and Engineering Research Council of Canada and the Ministère de l'Education du Québec for financial support.

Received: February 19, 1985

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