Facile Synthesis of Chiral 18-Crown-6 Derivatives from L-Tartaric Acid

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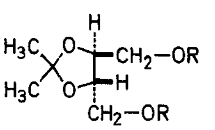
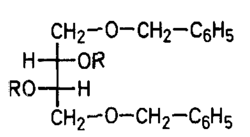
The ability of cyclic polyethers to solubilize organic or inorganic salts in non-polar and in polar aprotic solvents has made these compounds useful reagents in organic synthesis[1] and in mechanistic studies. While cyclic polyethers (crown ethers) are mainly used as phase-transfer catalysts, Cram has developed a so-called host-guest chemistry[2] which is based on the complex formation of cyclic polyethers with primary alkanaminium salts. The use of chiral cyclic polyethers as receptors is of particular interest in the field of enzyme-analog models. Chiral cyclic polyethers have been prepared using D-Ψ-ephedrine[3], (*R*)- and (*S*)-binaphthol[2], D-mannitol[4], L-tartaric acid[4,5], and optically pure (*S,S*)-cyclohexane-1,2-diol[6] as source of chirality.

We describe here a new simple procedure for incorporating an L-tartaric acid unit into an 18-crown-6 structure. The C_2 chirality of the whole molecule thus obtained is of potential interest with respect to chiral recognition and asymmetric induction. The procedure provides a facile access to a chirality source and affords good yields.

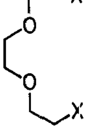
Four new chiral crown ethers were synthesized, two of them (**8**, **10**) without nitrogen in the ring, one with two amine functions (**12**), and one with two amide functions (**11**) in the ring. In three cases (**8**, **11**, **12**), the vicinal side chains are benzyloxymethyl groups; in one case (**10**), they are acetoxymethyl groups.



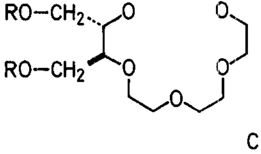
1 R = H
2 R = $-CH_2-C_6H_5$



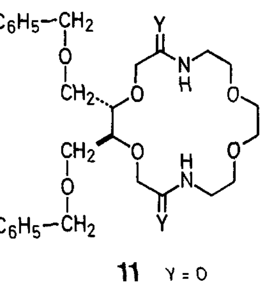
3 R = H
4 R = $-CH_2-COOH$
5 R = $-CH_2-CH_2-OH$



6 X = $-OTos$
7 X = $-NH_2$



8 R = $C_6H_5-CH_2-$
9 R = H
10 R = $H_3C-\overset{O}{\overset{\|}{C}}-$



11 Y = O
12 Y = H_2

In order to find a correlation between the type of functional groups present in the molecule and the binding properties of the crown ethers, we compared the stability constants of the complexes of these four crown ethers with *t*-butylammonium thiocyanate in deuterochloroform.

$$t\text{-}C_4H_9-\overset{\oplus}{N}H_3\ SCN^{\ominus} + \text{Host} \rightleftharpoons [t\text{-}C_4H_9-\overset{\oplus}{N}H_3\cdot\text{Host}]\,SCN^{\ominus}$$

The experiments were carried out using Cram's method[9] by measuring the equilibrium constants K [l/mol] at 25°

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(scale A, $K_d = 5.2 \cdot 10^{-5} \cdot mol^{-1}$). These constants which are a measure of the complexing power were found to be $3.2 \cdot 10^5$ for **8**, $5.2 \cdot 10^4$ for **10**, $1.7 \cdot 10^4$ for **11**, and $2.2 \cdot 10^4$ for **12**. Thus, (*S,S*)-1,2-bis[benzyloxymethyl]-18-crown-6 (**8**) exhibits the greatest complexing power.

The diol **1** was prepared from L-tartaric acid according to Carmack[7] and Feit[8]. Benzylation of **1** afforded the dibenzyl ether **2** in quantitative yield, which was hydrolyzed to dibenzyl-L-threitol (**3**) in 96% yield. Potassium *t*-butoxide-catalyzed reaction of bromoacetic acid with **3** in *t*-butanol gave the corresponding diacid **4** (43%) as an amorphous solid, which was then converted by lithium aluminum hydride reduction in tetrahydrofuran to the diol **5** (79%). The cyclic polyether **8** was obtained (26%) by reaction of the diol **5** with potassium hydroxide and the ditosylate **6**[10] in tetrahydrofuran. The dibenzyl ether **8** was hydrogenolyzed over 10% palladium-carbon to give the diol **9**, which was characterized by conversion to the diacetate **10**.

The diacid **4** was converted into the acid chloride by reaction with oxalyl chloride. The reaction of this acid chloride with the diamine **7**[11] in benzene under conditions of the dilution principle gave the cyclic diamide **11** as an oil in 23% yield. Compound **11** was reduced with lithium aluminum hydride in tetrahydrofuran to give the diamine **12** in 90% yield.

1,4-Di-*O*-benzyl-2,3-*O*-isopropylidene-L-threitol (2):

2,3-O-Isopropylidene-L-threitol (**1**; 75.3 g, 0.46 mol; $[\alpha]_D^{20}$: 4.9°, *c* 5.1, $CHCl_3$; Ref. [8], $[\alpha]_D^{20}$: 4.1°) in freshly distilled tetrahydrofuran (300 ml) is added dropwise, over a period of 1 h, to dry tetrahydrofuran (300 ml) containing sodium hydride (26 g). The mixture is stirred under a nitrogen atmosphere at room temperature for 90 min; then, benzyl bromide (181.8 g, 1.02 mol) is added dropwise, and the mixture is stirred at room temperature for a further 12 h and then heated under reflux for 2 h. After cooling and addition of water in an ice bath, the solution is evaporated, the residue is extracted with benzene, and the organic layer is dried and evaporated to give an oil (160 g), which is used in the next step without further purification. A portion of the product was distilled to give an analytical sample; b.p. 173–175°/0.2 torr; $[\alpha]_D^{25}$: −7.5° (*c* 2.6, $CHCl_3$).

I.R. (film): $\nu_{max} = 730$; 690 (phenyl) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.41$ (s, 6H, $2CH_3$); 3.50–4.23 (m, 6H, other protons); 4.50 (s, 4H, $2O-\underline{CH_2}-C_6H_5$); 7.26 ppm (s, $10H_{arom}$).

1,4-Di-O-benzyl-L-threitol (3):

The dibenzyl ether **2** (160 g, 0.47 mol) is dissolved in 0.5 normal hydrochloric acid (40 ml)/methanol (400 ml). Acetone and methanol are gently distilled off during 5 h. After another addition of 0.5 normal hydrochloric acid (20 ml) and methanol (50 ml), the mixture is concentrated, neutralized with sodium hydrogen carbonate, and extracted with benzene. The extract is dried and evaporated to give a white solid; yield: 136 g (96%); m.p. 58–59° (Ref. [4], m.p. 66°); $[\alpha]_D^{25}$: −5.0 (*c* 5.0, $CHCl_3$) (Ref. [4], −5.5°).

$C_{18}H_{22}O_4$	calc.	C 71.50	H 7.33
(302.4)	found	71.68	7.41

I.R. (nujol): $\nu_{max} = 3250$ (—OH); 730; 690 (phenyl) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.26$–2.93 (d, 2H, —OH); 3.40–4.00 (m, 6H, other protons); 4.46 (s, 4H, $-\underline{CH_2}-C_6H_5$); 7.21 ppm (s, $10H_{arom}$).

2,3-Bis-*O*-[carboxymethyl]-1,4-di-*O*-benzyl-L-threitol (4):

The diol **3** (10 g, 33 mmol) and potassium *t*-butoxide (15.6 g, 139 mmol) are stirred in *t*-butanol (100 ml) at 80° in a nitrogen atmosphere for 30 min. Bromoacetic acid (9.7 g, 69.8 mmol) in *t*-butanol (50 ml) is added dropwise during 1 h and the mixture is stirred under reflux for 8 h. After evaporation and basification with saturated aqueous sodium carbonate, the solution is extracted with benzene, the aqueous layer is acidified with conc. hydrochloric acid, and extracted with benzene. The organic layer is dried and evaporated to give a syrup (6 g, 43%), which on cooling solidifies as an amorphous powder; $[\alpha]_D^{25}$: 7.4° (*c* 2.4, $CHCl_3$).

$C_{22}H_{26}O_8$	calc.	C 63.15	H 6.26
(418.4)	found	64.11	6.50

I.R. (film): $\nu_{max} = 1730$ (C=O); 735; 695 (phenyl) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.33$–3.79 (m, 6H, other protons); 4.17 (s, 4H, $2O-CH_2-COO$); 4.40 (s, 4H, $-OCH_2-C_6H_5$); 7.17 (s, $10H_{arom}$); 8.56 ppm (s, 2H, —COOH).

2,3-Bis-*O*-(2-hydroxyethyl)-1,4-di-*O*-benzyl-L-threitol (5):

The diacid **4** (5.0 g, 12 mmol) in tetrahydrofuran (30 ml) is added dropwise to a suspension of lithium aluminum hydride (0.68 g, 17.8 mmol) in tetrahydrofuran (50 ml) under a nitrogen atmosphere and the mixture is stirred under reflux for 5 h. Aqueous sodium hydroxide is added with stirring and the mixture is filtered. The filtrate and the Soxhlet extract of the precipitate are combined, dried, and evaporated to give an oil; yield: 3.7 g (79%); $[\alpha]_D^{25}$: 2.5° (*c* 2.2, $CHCl_3$).

$C_{22}H_{30}O_6$	calc.	C 67.67	H 7.74
(390.5)	found	66.72	7.84

I.R. (film): $\nu_{max} = 3400$ (—OH); 730, 690 (phenyl) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.36$–3.83 (m, 16H, other protons); 4.46 (s, 4H, $2O-\underline{CH_2}-C_6H_5$); 7.25 ppm (s, $10H_{arom}$).

(*S,S*)-1,2-Bis[benzyloxymethyl]-18-crown-6 (8):

The mixture of the diol **5** (1.6 g, 4 mmol) and potassium hydroxide (567 mg) in tetrahydrofuran (4 ml) is heated under reflux for 30 min with stirring. To this mixture, triethyleneglycol ditosylate[10] (**6**; 2.07 g, 4.5 mmol) is added and the solution is stirred under reflux for 24 h. After cooling and the addition of dichloromethane (~50 ml), the mixture is filtered and the filtrate evaporated in vacuo. The residue is purified by column chromatography (silica gel, ether/methanol 20:1 as eluent) to give an oil; yield: 545 mg (26%); $[\alpha]_D^{25}$: 5.0° (*c* 2.1, $CHCl_3$).

$C_{28}H_{40}O_8$	calc.	C 66.64	H 7.99
(504.6)	found	66.42	8.48

M.S.: $m/e = 504$ (M^{+}).

I.R. (KBr): $\nu_{max} = 1100$ (C—O); 735; 690 (phenyl) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.40$–4.00 (m, 26H, other protons); 4.50 (s, 4H, $2O-\underline{CH_2}-C_6H_5$); 7.29 ppm (s, $10H_{arom}$).

(*S,S*)-1,2-Bis[acetoxymethyl]-18-crown-6 (10):

The dibenzyl ether **8** (333 mg) is hydrogenolyzed in methanol (15 ml) over 10% palladium carbon (50 mg) to give an oil (**9**; 208 mg) [^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.36$–4.10, m, all protons]. This oil is acetylated with acetic anhydride (1 ml) in pyridine (2 ml) at room temperature to give the diacetate **10**: yield: 164 mg (61%); $[\alpha]_D^{25}$: −9.6° (*c* 1.9, $CHCl_3$).

$C_{18}H_{32}O_{10}$	calc.	C 52.93	H 7.90
(408.5)	found	53.64	7.69

M.S.: $m/e = 409$ ($M^{+} + 1$).

I.R. (film): $\nu_{max} = 1740$ (C=O) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.07$ (s, 6H, $2H_3C-CO-O$); 3.46–3.97 (m, 22H, other protons); 4.09–4.43 ppm (m, 4H, $2\underline{CH_2}-OAc$).

(*S,S*)-1,2-Bis[benzyloxymethyl]-5,16-dioxo-6,15-diaza-18-crown-6 (11):

A solution of the diacid dichloride obtained from **4** (4.94 g, 11.8 mmol) and oxalyl chloride (7.0 g, 77.1 mmol) in absolute benzene (300 ml) and a solution of 1,2-bis[2-aminoethoxy]-ethane[11] (**7**; 3.5 g, 23.6 mmol) in absolute benzene (300 ml) are added simultaneously over a period of 9 h to vigorously stirred benzene (300 ml) at 40°. The resultant mixture is concentrated and filtered. The filtrate is evaporated and the residual product purified by column chromatography (silica gel 250 g chloroform/methanol 30:1 as eluent) to give an oil; yield: 1.45 g (23%); $[\alpha]_D^{25}$: 4.3 (*c* 1.3, $CHCl_3$).

$C_{28}H_{38}N_2O_8$	calc.	C 63.38	H 7.22	N 5.28
(530.6)	found	63.52	7.48	4.38

M.S.: $m/e = 530$ ($M^{\ddagger}$).

I.R. (KBr): $\nu_{max} = 3430$, 1675 (CONH); 735; 695 (phenyl) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.48$–4.20 (m, 24 H, other protons); 4.40 (s, 4 H, 2 O—C$\underline{H}_2$—C_6H_5); 7.28 ppm (s, 10 H_{arom}).

(*S*,*S*)-1,2-Bis[benzyloxymethyl]-6,15-diaza-18-crown-6 (12):
The mixture of the cyclic diamide **11** (365 mg, 0.7 mmol) and lithium aluminum hydride (157 mg, 4 mmol) in tetrahydrofuran (30 ml) is stirred under reflux for 66 h. The excess of hydride is destroyed by addition of ethyl acetate and water, the mixture is filtered, and the filtrate dried and evaporated to give an oil: yield: 314 mg (90%); $[\alpha]_D^{25}$: 17° (*c* 1.7, $CHCl_3$).

$C_{28}H_{42}N_2$ (502.7)

M.S.: $m/e = 503$ ($M^{\ddagger} + 1$).

I.R. (KBr): $\nu_{max} = 3300$ (NH); 730; 690 (phenyl) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.59$–2.92 (m, 8 H, —CH_2—N—CH_2—); 3.10 (br s, 2 H, —NH—); 3.33–4.10 (m, 18 H, other protons); 4.56 (s, 4 H, O—C$\underline{H}_2$—C_6H_5); 7.33 ppm (s, 10 H_{arom}).

The product was too hygroscopic to give a satisfactory microanalysis but the I.R., N.M.R., and M.S. spectrometric data fully substantiated the structure.

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