Macroheterocycles; XXX. Synthesis of Chiral Cryptands and Polynuclear Crown Ethers

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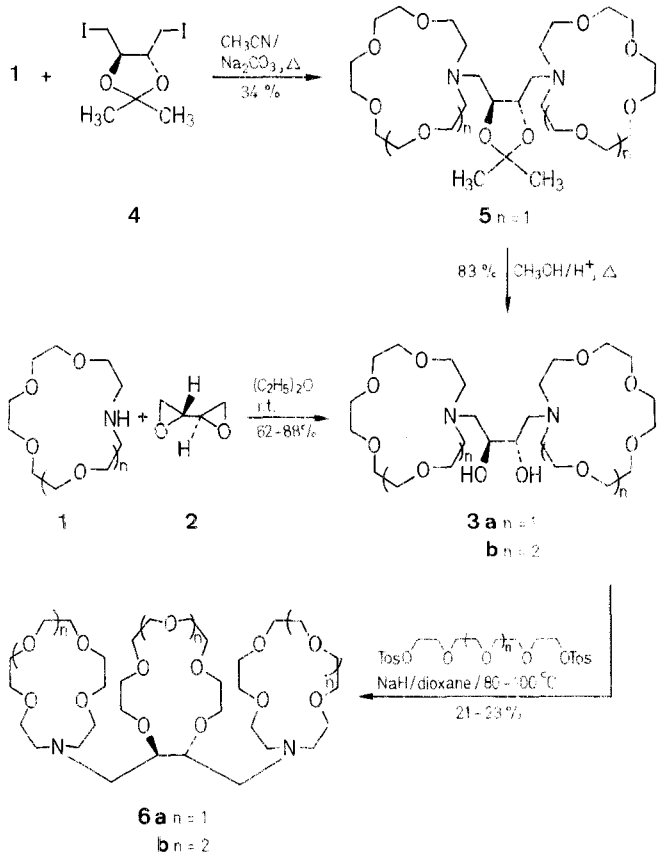
Syntheses of novel chiral bi- and trinuclear crown ethers and cryptands by alkylation of mono- and diazacrown ethers with L-1,2:3,4-diepoxybutane are described.

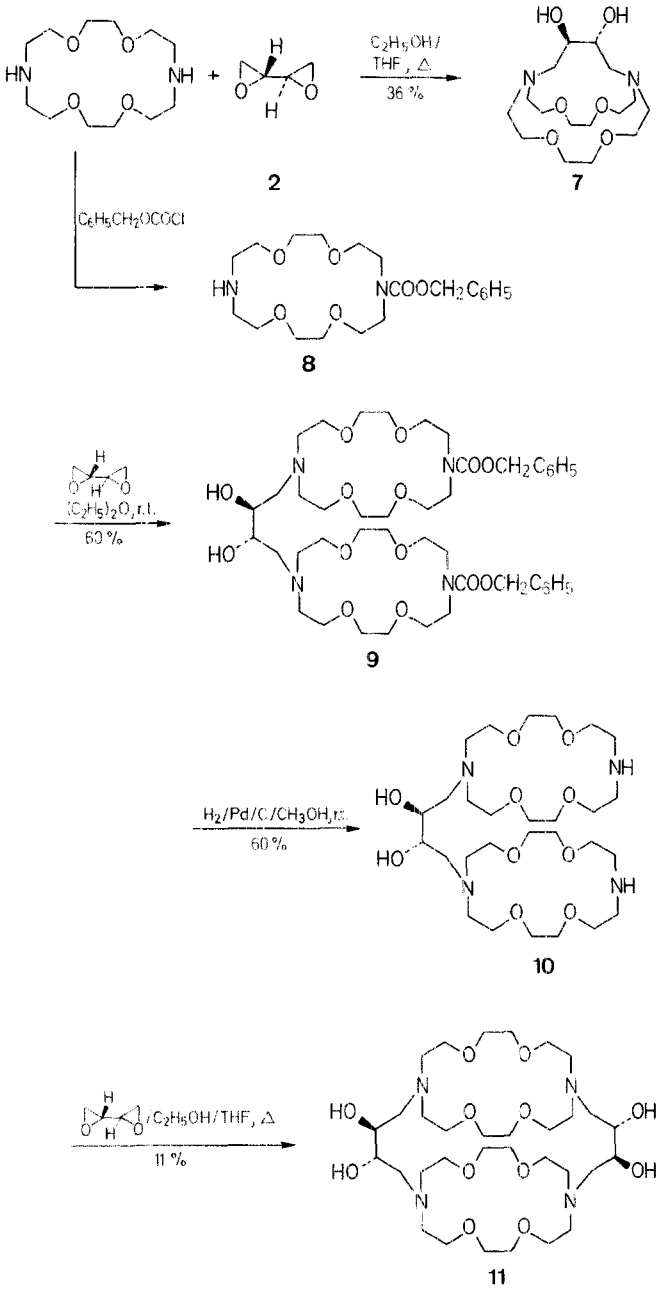
As a continuation of our studies of chiral crown ethers[1], we now describe a convenient synthesis of binuclear crown ethers with a chiral anchor group **3**, chiral trinuclear crown ethers **6**, and cryptands **7** and **11**. Chiral diepoxide **2**, prepared from 1,4-ditosyl-L-treitol as reported previously[2], was the starting material for this synthesis. Reaction of diepoxide **2** with monoazacrown ethers **1** resulted in crown ethers **3** with a good yield. We have carried out this reaction in water, methanol, tetrahydrofuran and ether. The best results were obtained in the latter case.



Cleavage of the epoxide rings in **2** occurs at the CH_2—O bonds that are sterically more accessible. We have demonstrated this by the independent synthesis of crown ether **3a**, achieved by the alkylation of monoaza-15-crown-5 (**1**, n = 1) with diiodide **4**[3] followed by cleavage of the acetal ring in product **5**. Acidic hydrolysis of 4,5-bis(aminoalkyl) dioxolanes is complicated and can't be realized under ordinary conditions[4]. We have successfully carried out the cleavage of the dioxolane ring in compound **5** using dry methanol saturated with hydrogen chloride.

Trinuclear chiral crown ethers **6** were prepared by the reaction of diols **3** with polyethylene glycol ditosylates in dioxane in the presence of sodium hydride. Analysis of CPK molecular models shows that compounds **6** may assume a cylindrical conformation in which the rings are situated one over another. In this conformation, trinuclear crown ethers **6** are similar to cascades[5] and are of interest for the resolution of substrates and for selective transport.

Alkylation of diaza-18-crown-6 with diepoxide **2** in a mixture of ethanol/tetrahydrofuran (1:1) gives chiral cryptand **7** in a yield of 36%, as shown in the scheme[6].



In this case, formation of cryptand **11** is not observed, as shown by mass spectra analysis of reaction mixture. This cryptand was obtained by the sequential alkylation of monosubstituted diaza-18-crown-6 **8**[7] and diamine **10** with diepoxide **2**, according to the above scheme.

We have obtained crystalline complexes of crown ethers **3a** and **5** and cryptand **7** with sodium perchlorate (in ratios of 2:1 and 1:1, respectively). It is interesting that the optical activity of these complexes is much higher than that for the free ligands {**3a** · $2NaClO_4$ $[\alpha]_D^{20}$: −48.1° (*c* 1.5, C_2H_5OH);

5·$2NaClO_4$ $[\alpha]_D^{20}$: −33.0° (*c* 2.2, C_2H_5OH); **7**·$NaClO_4$ $[\alpha]_D^{20}$: +32.9° (*c* 1.5, C_2H_5OH)}, which is probably due to conformational changes of the ligand during complexation.

Crown Ethers 3 and 9; General Procedure:
A solution of monoazacrown-ether **1** or 1-benzyloxycarbonyldiaza-18-crown-6 **8** (14 mmol) and diepoxide **2** {(0.6 g, 7 mmol) $[\alpha]_D^{20}$: +22.5° (*c* 2.0, $CHCl_3$), lit. $[\alpha]_D^{20}$: +23.6° (*c* 2.0, $CHCl_3$)} in ether (15 ml) is allowed to stand at room temperature for 10 days. After removal of the solvent the residue is dissolved in dry benzene (5 ml). Triethylamine (1 ml, 7 mmol) and benzyloxycarbonylchloride (0.32 ml, 2 mmol) in benzene (10 ml) are added[8]. The mixture is filtered, benzene is removed at reduced pressure. The residue is dissolved in 10% hydrochloric acid (10 ml) and extracted with chloroform (3 × 20 ml). The aqueous layer is alkalified to pH 12 by the addition of a saturated solution of lithium hydroxide and extracted with chloroform (5 × 20 ml). The resultant extract is dried with anhydrous magnesium sulphate. After removal of chloroform, crown ether **3 (9)** is obtained as a yellowish oil. Product **9** crystallizes upon standing.

(4*S*,5*S*)-2,2-dimethyl-bis[(1,4,7,10-tetraoxa-13-aza-13-cyclopentadecyl)methyl]-1,3-dioxolane (5):
A solution of diiodide **4** {(3 g, 78 mmol) $[\alpha]_D^{20}$: +17.3° (*c* 8.5, CH_3OH), lit. $[\alpha]_D^{20}$: +17.5° (*c* 8.5, CH_3OH)} in dry acetonitrile (15 ml) is added dropwise to a boiling mixture of monoaza-15-crown-5 (**1**, n = 1; 3.4 g, 16 mmol) in dry acetonitrile (10 ml) and anhydrous sodium carbonate (5.1 g, 48 mmol) over 2 hours with stirring. The reaction mixture is heated and stirred for 45 hours followed by filtration; the solvent is removed and the residue is dissolved in distilled water (10 ml). The aqueous solution is extracted with chloroform (2 × 20 ml); the extract is dried with magnesium sulphate followed by removal of solvent. The residue is purified by column chromatography (neutral alumina, hexane/isopropanol, 15:1, as eluent). Pure product **5** is obtained as a colorless oil; yield: 1.5 g (34%).

(2*S*,3*S*)-1,4-bis(1,4,7,10-tetraoxa-13-aza-13-cyclopentadecyl)butane-2,3-diol (3a from 5):
Acetal **5** (0.7 g, 12 mmol) is dissolved in methanol (10 ml), saturated by hydrogen chloride and refluxed for 5 hours. The solvent is removed; the residue is dissolved in 10% hydrochloric acid (5 ml) and extracted with chloroform (3 × 10 ml). The aqueous layer is alkalified to pH 12 with a saturated solution of lithium hydroxide and extracted with chloroform (5 × 20 ml). The resultant extracts are dried with anhydrous magnesium sulphate, and the solvent is removed. Crown ether **3a** is obtained as a colorless oil; yield: 0.53 g (83%).

Trinuclear crown ethers 6; General Procedure:
A solution of diol **3** (5.8 mmol) in dry dioxane (15 ml) is added dropwise at 60°C to a suspension of sodium hydride (1.4 g, 58 mmol) in dry dioxane (20 ml), and the mixture is stirred for 1 hour. A solution of polyethylene glycol ditosylate (5.8 mmol) in dry dioxane (40 ml) is slowly added dropwise to the mixture, which is then stirred at 80–100°C for 12 hours. The excess sodium hydride is destroyed by the addition of cold water (20 ml), and the solvent is removed. The residue is dissolved in 10% hydrochloric acid (10 ml) and extracted with chloroform (3 × 20 ml). The aqueous solution is alkalified to pH 12 with a saturated solution of lithium hydroxide, and is extracted in the continuous extractor with benzene for 5 hours. The resultant extracts are dried with anhydrous magnesium sulphate. After the removal of the solvent, crown ether **6** is obtained as a yellowish oil.

Cryptands 7 and 11; General Procedure:
Diaza-18-crown-6 or diamine **10** (10 mmol) and diepoxide **2** (0.9 g, 11 mmol) are dissolved in a mixture of dry ethanol and dry tetrahydrofuran (1:1, 30 ml) and refluxed for 10 hours. Solvents are removed, and the residue is treated as in case of crown ethers **3** and **9**. Cryptands are obtained: **7**, as a white crystalline material, and **11**, as a yellowish oil. Cryptand **7** is recrystallized from hexane.

(2*S*,3*S*)-1,4-bis(1,4,10,13-tetraoxo-7,16-diaza-7-cyclooctadecyl)butane-2,3-diol (10):
A solution of crown ether **9** (1.48 g, 2 mmol) in methanol (15 ml) is added to a suspension of activated palladium catalyst (10% of palladium/carbon, 0.2 g) in methanol (15 ml) and hydrogenolized for 8 hours at room temperature with stirring. The mixture is filtered, methanol is removed, and the residue is dissolved in 10% hydrochloric acid (5 ml) and extracted with chloroform (3 × 10 ml). The aqueous layer is alkalified to pH 12 with lithium hydroxide and extracted with chloroform (2 × 30 ml). The resultant extracts are dried with anhydrous magnesium sulphate, and the solvent is removed. Crown ether **10** is obtained as a yellowish oil; yield: 0.62 g (60%).

Complexes of Compounds 3a, 5 and 7 with Sodium Perchlorate; General Procedure:
A solution of sodium perchlorate (0.13 g, 1.1 mmol) in dry methanol (5 ml) is added to a solution of crown ether **3a** or **5** (0.5 mmol) or

Table. Crown Ethers and Cryptands Prepared

Product	n	Yield [%]	m.p. [°C]	$[\alpha]_D^{20}$ (*c*, ethanol)	Molecular Formula[a]	MS (70 eV) *m/e* (M^+)	^{1}H-NMR ($CDCl_3$) δ [ppm]
3a	1	88	oil	−17.7° (2.2)	$C_{24}H_{48}N_2O_{10}$ (524.8)	525	2.71–3.00 (m, 12H); 3.50–3.80 (m, 34H); 4.10 (s, 2H)
3b	2	62	oil	−10.9° (1.8)	$C_{28}H_{56}N_2O_{12}$ (612.8)	613	2.70–3.00 (m, 12H); 3.51–3.80 (m, 42H); 4.01 (s, 2H)
5	1	34	oil	−6.9° (1.8)	$C_{27}H_{52}N_2O_{10}$ (564.8)	565	1.35 (s, 6H); 2.77–3.00 (m, 12H); 3.50–3.80 (m, 34H)
6a	1	23	oil	−19.6° (1.9)	$C_{32}H_{62}N_2O_{13}$ (683.0)	683[b]	2.40–2.80 (m, 12H); 3.31–3.80 (m, 50H)
6b	2	21	oi	−3.8° (2.0)	$C_{38}H_{74}N_2O_{16}$ (815.1)	815	2.60–3.10 (m, 12H); 3.30–3.80 (m, 62H)
7	–	36	99–100	+18.3° (1.9)	$C_{16}H_{32}N_2O_6$ (348.5)	348	2.07–2.72 (m, 12H); 2.86 (s, 2H); 3.00–3.23 (m, 16H); 3.32–3.52 (m, 2H)
9	–	60	73–74	−6.7° (3.3)	$C_{44}H_{70}N_4O_{14}$ (879.2)	879	2.10–2.62 (m, 20H); 2.72 (s, 2H); 3.11–3.60 (m, 2H); 5.16 (s, 4H); 7.8 (s, 10H)
10	–	60	oil	−9.6° (2.0)	$C_{28}H_{58}N_4O_{10}$ (610.9)	611	2.55–2.95 (m, 20H); 3.35–3.78 (m, 38H)
11	–	11	oil	−24.0° (1.2)	$C_{32}H_{64}N_4O_{12}$ (697.0)	697	2.12–2.86 (m, 24H); 3.12–3.50 (m, 40H)

[a] Satisfactory microanalyses obtained: C ± 0.31, H ± 0.27, N ± 0.34.
TLC analysis (neutral alumina, chloroform/benzene/isopropanol 8:3:0.1; 8:3:0.5 or 8:3:1).
[b] By F.D. mass spectrometry; in E.I. mass spectrum there is no peak for the molecular ion.

cryptand **7** (1 mmol) in dry methanol (5 ml) and heated to boiling. The mixture is allowed to stand at room temperature for one hour, then ethyl acetate (0.5 ml) and ether (5 ml) are added. The mixture is allowed to stand for 10 hours. The white crystalline precipitate is filtered, washed with chloroform (1 ml) and recrystallized from dry ethanol.

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[8] This procedure readily separates the traces of starting azacrown ethers as N-benzyloxycarbonyl derivatives, which are then extracted from the solution aqueous acid.