Chiral Crown Ether Synthesis by Catalysis in a Two Phases System

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Chiral crown ethers are being studied with growing interest, mainly as models for the study of enzyme-like reactions. Such crown ethers, containing binaphthyl groups, have been prepared and their capacity to resolve racemic amino acids or chiral amine salts has been studied[1-5]. More recently, the osidic substrates, as an inexpensive source of chiral bis[methylenedioxy]moieties, have been used[6-10].

Many of the preparative methods described so far give mixtures, involve the preparation of ditosylate derivatives and their subsequent condensation with a diol. These reactions often proceed in poor yields.

The results that we have obtained in the synthesis of ethers and of acetals in the sugar series[11] led us to study the reactions between the bis[2-chloroethyl] ether or the 1,2-bis[2-chloroethoxy]ethane (used as solvent and reagent) and sugars having two free adjacent hydroxy groups. When the reaction is carried out in the presence of a concentrated

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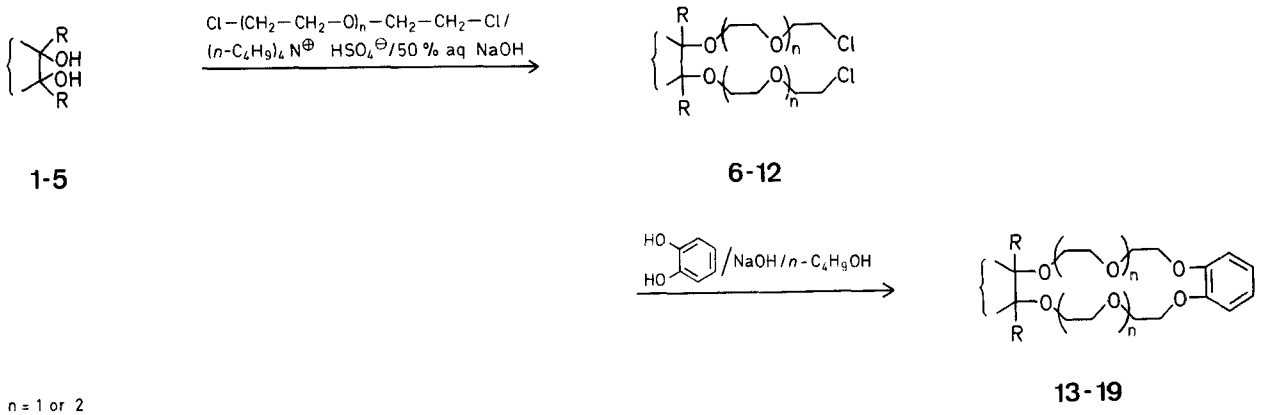


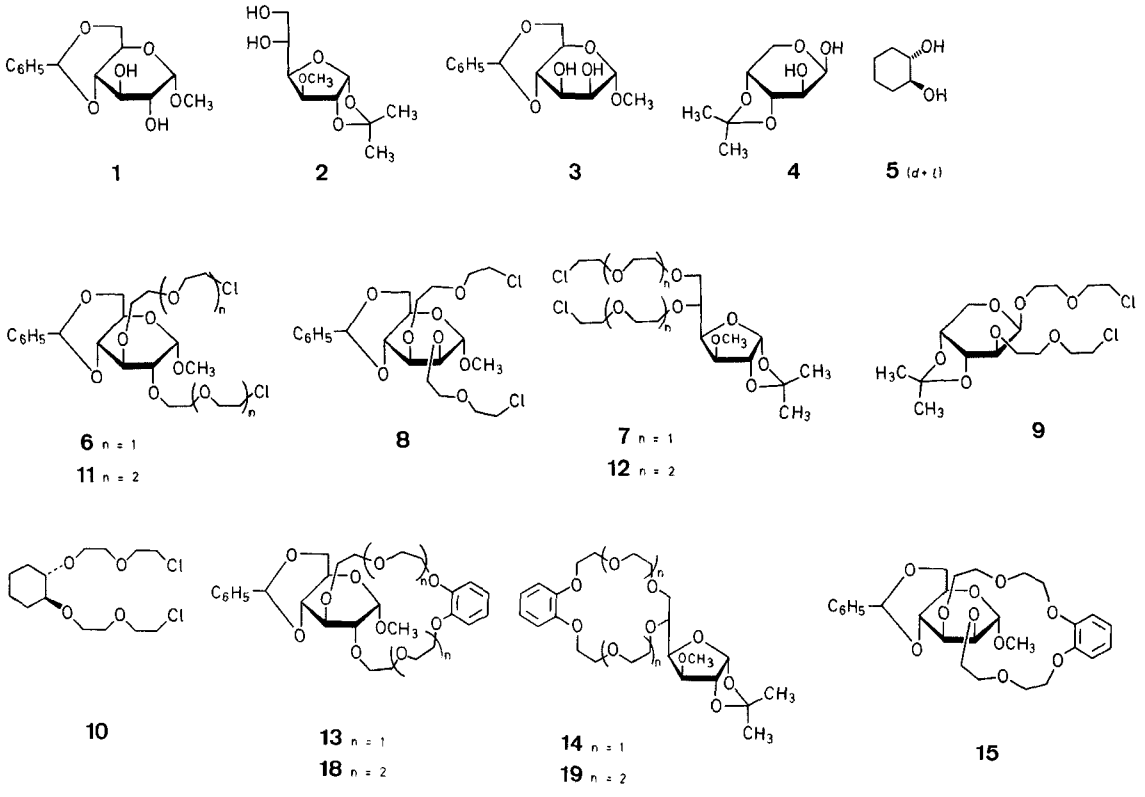
Scheme **A**

aqueous sodium hydroxide solution containing a small amount of an ammonium salt, we have been able to prepare bis[chloroalkoxy] derivatives of sugars in good yields.

Thus, the substrates **1** to **5** (see Scheme **B**) react at room temperature with the bis[2-chloroethyl] ether in the presence of tetrabutylammonium hydrogen sulfate and 50% aqueous sodium hydroxide to give bis[2-chloroethoxyethoxy] derivatives **6** to **10** according to Scheme **A**.

The substrates **1** and **2** react under the same conditions with the 1,2-bis[2-chloroethoxy]ethane to give the compounds **11** and **12** (Scheme **B**). The best yields are obtained with a 0.5 molar quantity (based on free hydroxy group) of ammonium salt. If this quantity is lowered, the reaction is slower and does not go to completion.

The bis[2-chloroethoxyethoxy] derivatives have been cyclized with catechol according to a method described[12] which requires dry sodium hydroxide in *n*-butanol as a solvent. We thus obtained the crown ethers **13** to **19** (Scheme **B**) in good overall yields. All attempts to accomplish the cyclization by catalysis in a two phase system resulted in elimination of two molecules of hydrochloric acid from the bis[2-chloroethoxyethoxy] derivatives.



Scheme **B**

The compounds involved are given in Scheme **B** and their physical characteristics are listed in the Table.

Table. Chiral Crown Ethers **13–19** and Bis[2-chloroethoxy] Precursors **6–12** (see Scheme B)

Substrate	Product	Reaction time [h]	Yield [%]	m.p.	$[\alpha]_D^{20}$ (*c* in $CHCl_3$)	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
1[13]	**6**	8	80	62–63°	+42.9° (1.42)	$C_{22}H_{32}Cl_2O_8$ (495.4)	3.38 (s, 3H); 4.35–3.45 (m, 22H); 4.8 (d, 1H, $J_{1,2}$ = 3.3 Hz); 5.47 (s, 1H); 7.2–7.4 (m, 5H)
2[b]	**7**	24	85	gum	+41.6° (2.3)	$C_{18}H_{32}Cl_2O_8$ (447.4)	1.29 (s, 3H); 1.45 (s, 3H); 3.35 (s, 3H); 3.45–4.40 (m, 21H); 4.52 (d, 1H, J = 4.2 Hz); 5.85 (d, 1H, J = 4.2 Hz)
3[13]	**8**	18	72	gum	+23.2° (1.13)	$C_{22}H_{32}Cl_2O_8$ (495.4)	3.35 (s, 3H); 3.45–4.40 (m, 22H); 4.75 (m, 1H); 5.5 (s, 1H); 7.2–7.6 (m, 5H)
4[14]	**9**	12	90	gum	+74.8° (2.72)	$C_{16}H_{28}Cl_2O_7$ (403.3)	1.34 (s, 3H); 1.52 (s, 3H); 3.5–4.5 (m, 21H); 4.90 (d, 1H, J_{1-2} = 4 Hz)
5	**10**	12	70	gum	—	$C_{14}H_{26}Cl_2O_4$ (329.3)	1.0–2.3 (m, 8H); 3.1–3.4 (m, 2H); 3.5–4.0 (m, 16H)
1	**11**	24	65	gum	+31.1° (1.59)	$C_{26}H_{40}Cl_2O_{10}$ (583.5)	3.38 (s, 3H); 3.45–4.35 (m, 30H); 4.8 (d, 1H, J = 3.3 Hz); 5.47 (s, 1H); 7.2–7.4 (m, 5H)
2	**12**	24	72	gum	+57.2° (1.34)	$C_{22}H_{46}Cl_2O_{10}$ (535.5)	1.29 (s, 3H); 1.45 (s, 3H); 3.35 (s, 3H); 3.45–4.40 (m, 29H); 4.52 (d, 1H, J = 4.2 Hz); 5.85 (d, 1H, J = 4.2 Hz)
6	**13**	8	68	129–130°	+14.1° (2.6)	$C_{28}H_{36}O_{10}$ (532.6)	3.37 (s, 3H); 3.45–4.4 (m, 22H); 4.80 (d, 1H, J = 3.3 Hz); 5.48 (s, 1H); 6.86 (s, 4H); 7.2–7.6 (m, 5H)
7	**14**	8	65	gum	+53.8° (1.85)	$C_{24}H_{36}O_{10}$ (484.6)	1.29 (s, 3H); 1.45 (s, 3H); 3.37 (s, 3H); 3.45–4.40 (m, 21H); 4.52 (d, 1H, J = 4.2 Hz); 5.85 (d, 1H, J = 4.2 Hz); 6.83 (s, 4H)
8	**15**	8	70	gum	+41.2° (0.9)	$C_{28}H_{36}O_{10}$ (532.6)	3.05 (s, 3H); 3.4–4.4 (m, 22H); 4.60 (m, 1H); 5.55 (s, 1H); 6.85 (s, 4H); 7.15–7.60 (m, 5H)
9	**16**	8	72	gum	+84.4° (2.5)	$C_{22}H_{32}O_9$ (440.5)	1.34 (s, 3H); 1.52 (s, 3H); 3.4–4.5 (m, 21H); 4.90 (d, 1H, J = 4 Hz)
10	**17**	8	70	73–74°	—	$C_{20}H_{30}O_6$ (366.5)	0.9–2.2 (m, 8H); 3.0–3.35 (m, 2H); 3.6–4.3 (m, 16H); 6.87 (s, 4H)
11	**18**	8	70	105–107°	+32.7° (1.81)	$C_{32}H_{44}O_{12}$ (620.7)	3.38 (s, 3H); 3.45–4.4 (m, 30H); 4.81 (d, 1H, J = 3.3 Hz); 5.47 (s, 1H); 6.86 (s, 4H); 7.2–7.6 (m, 5H)
12	**19**	8	75	gum	+93.4° (1.07)	$C_{28}H_{44}O_{12}$ (572.6)	1.29 (s, 3H); 1.45 (s, 3H); 3.38 (s, 3H); 3.5–4.3 (m, 30H); 4.52 (d, 1H, J = 4.2 Hz); 6.87 (s, 4H); 5.85 (d, 1H, J = 4.2 Hz)

[a] All products gave satisfactory microanalysis (C ±0.2; H ±0.3; Cl ±0.3); performed by Centre de Microanalyse du CNRS, Lyon.
[b] Prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose; methylation according to Ref. [11] and partial deprotection by aqueous acetic acid[15].

Methyl 4,6-*O*-Benzylidene-2,3-bis-*O*-[(2-chloroethoxy)-ethyl]-α-D-glucopyranoside (6):
A solution of **1** (1.12 g, 4 mmol) and of tetrabutylammonium hydrogen sulfate (1.3 g, 4 mmol) in bis[2-chloroethyl] ether (10 ml) is vigorously stirred at room temperature with a 50% aqueous sodium hydroxide solution (10 ml). The reaction is monitored by T.L.C. (eluent: ether/chloroform, 1/1) and is complete after 8 h. Dichloromethane (50 ml) and water (50 ml) are added to the reaction mixture. The organic phase is decanted and the aqueous phase is washed with dichloromethane (2 × 30 ml). The organic phases are combined and washed with water (2 × 20 ml), dried with magnesium sulfate, filtered, and concentrated under vacuum. The resultant gum is eluted through a silica gel column with ether to yield a white solid which is recrystallized from ethanol; yield: 1.57 g (80%); m.p. 62–63°; $[\alpha]_D^{20}$: +42.9° (*c* 1.42, $CHCl_3$).

Methyl 4,6-*O*-benzylidene-2,3-*O*-{1,2-bis[ethoxyethoxy]-benzenediyl}-α-D-glucopyranoside (13):
Catechol (330 mg, 3 mmol) is dissolved in *n*-butanol (6 ml). Argon is bubbled through this solution in order to remove oxygen and then dry sodium hydroxide powder (240 mg, 6 mmol) is added. The mixture is stirred and heated under reflux. After 0.5 h, a solution of **6** (1.5 g, 3 mmol) dissolved in *n*-butanol (4 ml) is added under an inert atmosphere. The resultant reaction mixture is stirred and heated under reflux for 8 h. After cooling, the mixture is extracted with chloroform (50 ml), the extract is washed with water (3 × 20 ml), dried with magnesium sulfate, and evaporated. The residue is eluted through a neutral alumina column (80 g, ether/chloroform, 1:1) and crystallized from a mixture of benzene and petroleum ether; yield: 1.09 g (68%); m.p. 129–130°; $[\alpha]_D^{20}$: +14.1° (*c* 2.6, $CHCl_3$).

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