Carbohydrate Research, 55 (1977) C1–C4

Preliminary communication

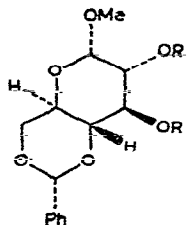
Chiral asymmetrical crown-ethers*

DALE A. LAIDLER and J. FRASER STODDART
Department of Chemistry, The University, Sheffield S3 7HF (Great Britain)
(Received February 2nd, 1977; accepted for publication February 18th, 1977)

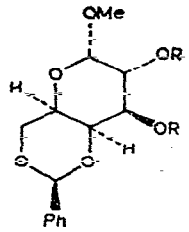
Chiral, symmetrical, macrocyclic polyethers have been derived from (*R*)- and (*S*)-binaphthol[1,2], L-threaric acid[3–5], D-mannitol[3,6], and L-iditol[7] as precursors containing C_2 symmetry and as both sole[1,3–7] and mixed[2] sources of chirality. Many of these macrocycles have been shown (*i*) to complex with primary alkylammonium salts[1–11] and (*ii*) to exhibit chiral recognition when the salt is racemic[1,2,8,10,11]. We now report on the synthesis of four chiral, asymmetrical 18-crown-6 macrocycles incorporating either D-glucose or D-galactose residues and assess the abilities of these macrocycles to complex with primary alkylammonium salts.

Treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[12] D-(1) with an excess of allyl bromide and potassium hydroxide in toluene gave the diallyl ether[13] D-(2) having m.p. 62–63° and $[\alpha]_D$ +60.0° (*c* 0.46, chloroform) in good yield. Ozonolysis of D-(2) in methanol, followed by borohydride reduction, afforded the "half-crown" diol D-(3), m.p. 114°, $[\alpha]_D$ +12.1° (*c* 0.13, chloroform). Treatment of D-(3) with sodium hydride and 1.1 molar equivalents of triethylene glycol bis(toluene-*p*-sulphonate)[14] (4) in dimethyl sulphoxide gave the D-*gluco*-18-crown-6 derivative D-(5) [m.p. 52–56°, $[\alpha]_D$ +37.6° (*c* 0.42, chloroform); ^{1}H n.m.r. data ($CDCl_3$): δ 7.60–7.14 (m, 5H, aromatic protons), 5.51 (s, 1H, benzylidene CH), 4.81 (d, *J* 3.5 Hz, 1H, anomeric proton), 4.42–3.47 (m, 26H, other CH and CH_2 protons), and 3.42 (s, 3H, OCH_3)] in 45% yield after chromatography on alumina (ether). By a similar procedure, methyl 4,6-*O*-benzylidene-α-D-galactopyranoside[15] D-(6) was converted via its diallyl ether D-(7) [m.p. 65–67°, $[\alpha]_D$ +140° (*c* 0.81, chloroform)] into the "half-crown" diol D-(8) [m.p. 134–136°, $[\alpha]_D$ +136.9° (*c* 0.8, chloroform)]. Treatment of D-(8) with sodium hydride and 1.0 molar equivalents of (4) in dimethyl sulphoxide afforded the D-*galacto*-18-crown-6 derivative D-(9) [m.p. 115°, $[\alpha]_D$ + 102.9° (*c* 0.47, chloroform); ^{1}H n.m.r. data ($CDCl_3$): δ 7.60–7.12 (m, 5H, aromatic protons), 5.52 (s, 1H, benzylidene CH), 4.95 (d, *J* 3.0 Hz, 1H, anomeric proton), 4.37–3.48 (m, 26H, other CH and CH_2 protons), and 3.42 (s, 3H, OCH_3)] in 16% yield after chromatography on alumina (ether–chloroform).

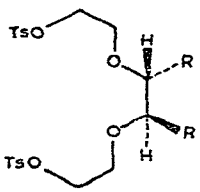
*Dedicated to the memory of Professor J.K.N. Jones, F.R.S.



D-(1) R = H
D-(2) R = $CH_2CH{=}CH_2$
D-(3) R = CH_2CH_2OH

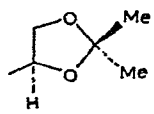


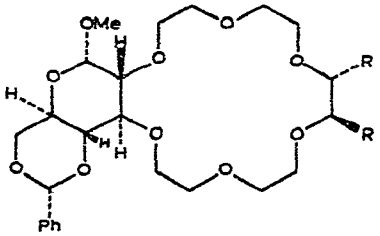
D-(6) R = H
D-(7) R = $CH_2CH{=}CH_2$
D-(8) R = CH_2CH_2OH



(4) R = H

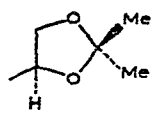
D-(10) R =

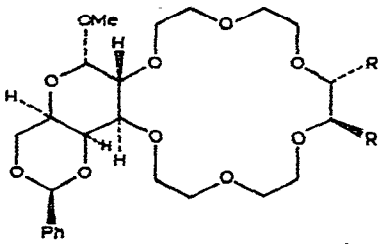




D-(5) R = H

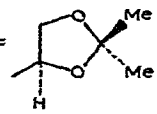
DD-(11) R =





D-(9) R = H

DD-(12) R =



It is possible to introduce additional chirality – in the form of a second carbohydrate residue – into asymmetrical 18-crown-6 derivatives incorporating either D-glucose or D-galactose residues, without encountering the synthetic problems associated with the formation of diastereoisomers, provided the second carbohydrate residue possesses C_2 symmetry. The "half-crown" bis(toluene-*p*-sulphonate)[3] D-(10) derived from D-mannitol fulfils

this requirement. Condensation of D-(3) and D-(10) in equimolar proportions in dimethyl sulphoxide in the presence of sodium hydride gave the D-*gluco*-D-*manno*-18-crown-6 derivative DD-(11) [m.p. 44–46°, $[\alpha]_D$ +69.4° (*c* 0.32, chloroform); ^{1}H n.m.r. data ($CDCl_3$): δ 7.56–7.24 (m, 5H, aromatic protons), 5.52 (s, 1H, benzylidene CH), 4.79 (d, *J* 3.5 Hz, 1H, anomeric proton), 4.40–3.30 (m, 33H, other CH and CH_2 protons, OCH_3), and 1.39 and 1.35 (2 X s, 12H, 4 X CH_3)] in 40% yield after chromatography on alumina (ether). Condensation of D-(9) and D-(10) in equimolar proportions in dimethyl sulphoxide in the presence of sodium hydride gave the D-*galacto*-D-*manno*-18-crown-6 derivative DD-(12) [$[\alpha]_D$ +90.0° (*c* 0.5, chloroform); ^{1}H n.m.r. data ($CDCl_3$): δ 7.60–7.22 (m, 5H, aromatic protons), 5.53 (s, 1H, benzylidene CH), 4.94 (d, *J* 3 Hz, 1 H anomeric proton), 4.40–3.45 (m, 30H, other CH and CH_2 protons), 3.43 (s, 3H, OCH_3), and 1.39 and 1.34 (2 X s, 12H, 4 X CH_3)] in 29% yield after chromatography on alumina [ether–light petroleum (b.p. 60–80°)] and silica gel (ether–methanol–ammonia).

The crown ethers D-(5), D-(9), DD-(11), and DD-(12) all dissolved alkali metal and primary alkylammonium salts in organic solvents. The formation of complexes with *tert*-butyl- and benzyl-ammonium thiocyanates in $CDCl_3$ was accompanied by substantial changes in the ^{1}H n.m.r. spectra of the crown ethers. For complexes with *tert*-butylammonium thiocyanate, a quantitative assessment of complexing power was obtained by measuring stability constants [defined as equilibrium constants (K_a in litre · mol^{-1}) for the equilibrium (*1*) in $CDCl_3$] by a ^{1}H n.m.r.-spectroscopic method[9]. The values of the stability constants:

$$^t\text{BuNH}_3{}^+\text{SCN}^- + \text{Crown} \overset{K_a}{\rightleftharpoons} {}^t\text{BuNH}_3\text{Crown}^+\text{SCN}^- \qquad (1),$$

for complexation with D-(5), (K_a 300), D-(9) (K_a 22,000), DD-(11) (K_a 87), and DD-(12) (K_a 1,100) indicates that these derivatives form weaker complexes than 18-crown-6 (K_a 750,000)[9] itself. There are two additional features of interest that follow from a comparison of the stability constants associated with these chiral, asymmetrical crown-ethers: (*i*) Factors of ~3 and 20, respectively, in K_a are sacrificed on disubstitution of the D-*gluco*- and D-*galacto*-18-crown-6 derivatives D-(5) and D-(9) with bulky 2,2-dimethyl-1,3-dioxolanyl groups. This trend is to be expected on steric grounds. (*ii*) The 18-crown-6 derivatives [D-(9) and DD-(12)] in the D-*galacto* series exhibit larger values for K_a in both cases than the comparable 18-crown-6 derivatives [D-(5) and DD-(11), respectively] in the D-*gluco* series. A cursory inspection of molecular models reveals that this is an unexpected observation, assuming that complex formation between the *tert*-butylammonium cation and the 18-crown-6 derivatives involves hydrogen bonding of all three[10,11], or at least two of the three[16], ammonium hydrogen atoms of the cation to ether oxygen atoms in the macrocycle so as to afford a face-to-face complex. Steric factors would be expected to mitigate more against complex formation involving D-(9) and DD-(12) than against complex formation involving D-(5) and DD-(11). However, the axial orientation of the C–O bond at C-4 of the galactosidic ring in both D-(9) and DD-(12) renders O-4 available to participate, together with the ether oxygen atoms of the macrocycle, in hydrogen bonding with the ammonium

hydrogen atoms of the cation in a *distorted* face-to-face complex. There is some ^{1}H n.m.r. spectroscopic evidence to support this proposal. On formation of the complex, both D-(9) and DD-(12) exhibit significant downfield shifts for H-4 and the benzylidene methine proton, which are not observed when either D-(5) or DD-(11) form complexes. For example, in the complex (salt : crown-ether ratio of 0.91) between D-(9) and *tert*-butylammonium thiocyanate in $CDCl_3$, the singlet for the benzylidene methine proton is shifted by 0.20 p.p.m., and the broadened doublet for H-4 by 0.49 p.p.m., both to lower field.

The ability of these chiral, asymmetrical crown-ethers (*i*) to exhibit enantiomeric differentiation towards racemic primary alkylammonium salts, and (*ii*) to form the basis from which enzyme analogues may be constructed (compare ref. 17) in the near future, is under investigation.

REFERENCES

1 D. J. Cram and T. L. Tarnowski, *Chem. Commun.*, (1976) 661–663, and earlier communications in this series.
2 W. D. Curtis, R. M. King, J. F. Stoddart, and G. H. Jones, *Chem. Commun.*, (1976) 284–285.
3 W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *Chem. Commun.*, (1975) 833–835.
4 J.-M. Girodeau, J.-M. Lehn, and J.-P. Sauvage, *Angew. Chem. Int. Ed. Engl.*, 14 (1975) 764.
5 J.-P. Behr, J.-M. Lehn, and P. Vierling, *Chem. Commun.*, (1976) 621–623.
6 D. A. Laidler and J. F. Stoddart, *Chem. Commun.*, (1976) 979–980.
7 W. D. Curtis, D. A. Laidler, J. F. Stoddart, J. B. Wolstenholme, G. H. Jones, and G. Jones, unpublished results.
8 W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *Chem. Commun.*, (1975) 835–837.
9 J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Am. Chem. Soc.*, 96 (1974) 7097–7099.
10 D. J. Cram and J. M. Cram, *Science*, 183 (1974) 803–809.
11 D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newcomb, P. Moreau, F. de Jong, G. W. Gokel, D. H. Hoffman, L. A. Domeier, S. C. Peacock, K. Madan, and L. Kaplan, *Pure Appl. Chem.*, 43 (1975) 327–349.
12 D. S. Mathers and G. J. Robertson, *J. Chem. Soc.*, (1933) 696–698.
13 J. S. Brimacombe, B. D. Jones, M. Stacey, and J. J. Willard, *Carbohydr. Res.*, 2 (1966) 167–169.
14 J. Dale and P. O. Kristiansen, *Acta Chem. Scand.*, 26 (1972) 1471–1478.
15 D. J. Bell and G. D. Greville, *J. Chem. Soc.*, (1955) 1136–1140.
16 L. C. Hodgkinson, S. J. Leigh, and I. O. Sutherland, *Chem. Commun.*, (1976) 640–642.
17 Y. Chao and D. J. Cram, *J. Am. Chem. Soc.*, 98 (1976) 1015–1017.