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## Note

# Chiral macrocycles incorporating lactitol and 4-*O*-(1-deoxy-D-galactitol-1-yl)-D-glucitol residues

MANUEL ALONSO-LOPEZ, MANUEL MARTIN-LOMAS, AND SOLEDAD PENADES
*Instituto de Química Orgánica, C.S.I.C., Juan de la Cierva 3, 28006 Madrid (Spain)*

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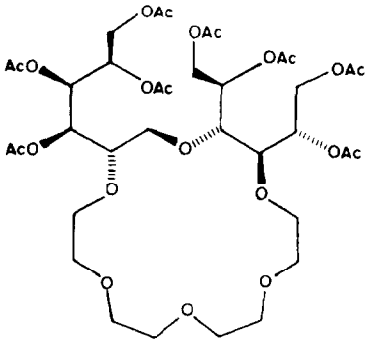
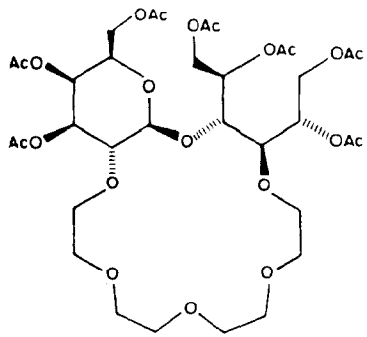


1



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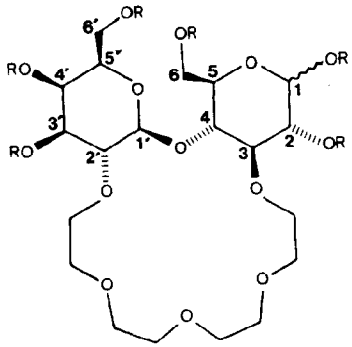
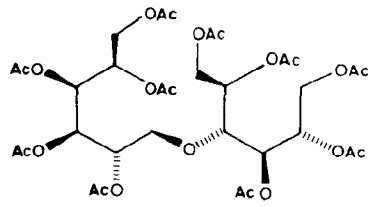


3 R = H
4 R = $BEt_2$



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0008-6215/88/$ 03.50 

The complexing properties of molecular receptors depend on the organization of binding sites which can be achieved within the context of relative structural rigidity or flexibility[1]. Hole and cavity sizes seem to be the primary factors that influence binding strength in rigid receptors[2]. However, complexation by flexible ligands largely depends on the number of donors in an appropriate topography[3].

We have reported the synthesis of chiral macrocyclic compounds from lactose derivatives[4,5]. These products are more rigid than those synthesised using monosaccharides and alditols[6]. Flexible, chiral macrocylic polyhydroxy ethers have also been prepared by reduction of cyclomalto-oligosaccharides ($\alpha$- and $\beta$-CD)[7] and by condensation of D-mannitol with tetraethyleneglycol ditosylate[8].

We now report on the chiral macrocycles **1** and **2**, which have different degrees of flexibility and bear chiral arms. The synthesis of **1** and **2** was based on the alkyldiborane reduction[9] of 3,2′-*O*-(3,6,9-trioxaundecane-1,11-diyl)lactose[4] (**3**) with alkyldiborane catalysed by 9-borabicyclo[3.3.1]non-9-yl mesylate (9-BBN-mesylate).

Treatment of the hexa-*O*-diethylboryl derivative **4** with ethyldiborane in the presence of 9-BBN-mesylate gave, after deboronation, acetylation, and chromatography, **1** (20%). The mass spectrum of **1** contained a peak for the molecular ion at *m/z* 840, the $^{13}$C-n.m.r. spectrum did not show any signal attributable to anomeric carbons, and the $^{1}$H-n.m.r. spectrum was completely analysed by using a homonuclear 2D-correlation (COSY) experiment. Compound **1** was formed by reductive cleavage of both *endo*-acetalic bonds of **3** and incorporates a 4-*O*-(1-deoxy-D-galactitol-1-yl)-D-glucitol residue.

When **3** was first treated with 1 equiv. of potassium iodide in dry methanol, then perborylated, and reacted with ethyldiborane in the presence of 9-BBN-mesylate, followed by deboronation and acetylation, 36% of **2** was isolated by chromatography. The mass spectrum of **2** contained a peak for the molecular ion at *m/z* 796, the $^{13}$C-n.m.r. spectrum contained a signal for C-1′ at 101.6 p.p.m., and the $^{1}$H-n.m.r. spectrum could be analysed completely. Compound **2** was formed by reductive cleavage of the C-1–O-5 bond of **3**, incorporates a lactitol residue, and is the product to be expected when the diborane reduction is carried out in the absence of catalyst. This result could be rationalised by considering that complexation of potassium iodide by the macrocycle enhances the nucleophilicity of the iodide ion[10] which neutralises the Lewis acid character of 9-BBN-mesylate. In accord with this assumption, the reduction of per-*O*-diethylboryl-lactose in the presence of potassium iodide yielded the expected reaction product 1,2,3,5,6-penta-*O*-acetyl-4-*O*-(2,3,4,5,6-penta-*O*-acetyl-1-deoxy-D-galactitol-1-yl)-D-glucitol (**5**), although in lower yield (20%) than obtained under usual conditions[9,11].

Comparison of the complexing properties of the structurally related macrocycles **1**–**3**, which have different degrees of flexibility, may give some insight into the influence of the flexibility on complexation.

EXPERIMENTAL

*General methods.* — All reactions were carried out under argon. T.l.c. was performed on Silica Gel $GF_{254}$ (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Merck silica gel (70–230 mesh). $^1H$- and $^{13}C$-n.m.r. spectra were recorded for solutions in $C_6D_6$ ($^1H$) or $CDCl_3$ ($^{13}C$), using a Varian XL-300 spectrometer. The COSY spectrum was recorded with a Bruker AM-200 spectrometer. The 2D-map was composed of 512–1024 data points, each incremented by 0.6 ms. A delay of 3 s was allowed between each pulse sequence. The data were acquired with quadrature phase detection in both dimensions and the final data were symmetrised. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. G.l.c. was performed on a Perkin–Elmer 3920 gas chromatograph equipped with an SE-30 capillary column. The mass spectra were recorded on a VG 12-250 spectrometer by electron impact.

*Reduction of 3,2'-O-(3,6,9-trioxaundecane-1,11-diyl)lactose* (**3**). — A suspension of **3** (92 mg, 0.184 mmol) in dry hexane (1 mL) and triethylborane (1 mL, with 0.1–1 mol% of diethylboryl pivalate) was stirred for 48 h at room temperature and then concentrated. Ethylborane[12] (0.339 g, 15.8%, $H^-$, 5.35 mmol) and 9-BBN-mesylate[13] (19.9 mg, 0.09 mmol) were then added to the residue, the mixture was heated for 10 h at 120° and then cooled to room temperature, and the volatile components were removed *in vacuo*. The residue was treated with boiling methanol (1 mL) which was evaporated, and then with ethane-1,2-diol (1 mL) which was evaporated at 70°/$10^{-3}$ Torr. The latter treatment was repeated until a boron-free residue was obtained. The residue was acetylated conventionally with acetic anhydride (0.5 mL) and pyridine (2 mL). Column chromatography (ethyl acetate) of the product yielded **1** (30 mg, 20%), isolated as a syrup, $[\alpha]_D$ +34° (*c* 0.3, chloroform). N.m.r. data: $^1H$ ($C_6D_6$), $\delta$ 5.93 (dd, 1 H, $J_{4',5'}$ 2.0, $J_{3',4'}$ 9.5 Hz, H-4'), 5.77 (m, 1 H, H-2), 5.68 (m, 1 H, H-5'), 5.64 (m, 1 H, H-5), 5.56 (dd, 1 H, $J_{2',3'}$ 1.4 Hz, H-3'), 4.95 (dd, 1 H, $J_{6a,6b}$ 12.5, $J_{5,6a}$ 2.8 Hz, H-6a), 4.67 (dd, 1 H, $J_{1a,1b}$ 12.0, $J_{1a,2}$ 2.7 Hz, H-1a), 4.62 (dd, 1 H, $J_{5,6b}$ 7.7 Hz, H-6b), 4.46 (dd, 1 H, $J_{6'a,6'b}$ 11.4, $J_{5',6'a}$ 5.1 Hz, H-6'a), 4.39 (dd, 1 H, $J_{1b,2}$ 7.7 Hz, H-1b), 4.03 (m, 2 H, H-4,6'b), 3.86 (m, 1 H, H-2'), 3.69 (dd, 1 H, *J* 5.4 and 4.1 Hz, H-3), and 1.92–1.70 (s, 24 H, 8 Ac); $^{13}C$ ($CDCl_3$), 170.6–169.8 (8 signals, C=O), 78.8, 78.6, 76.5 (C-3,4,2'), 72.7, 72.5, 71.6 (double intensity), 70.8, 70.7, 70.6 (double intensity), 70.5 (double intensity), 70.2, 68.3, 68.2, 68.1, 62.9, 62.5, 62.2 (C-1,6,6'), and 21.1–20.7 ($CH_3CO$). Mass spectrum: *m/z* 840 $M^+$, 781 [$M^+$ − AcO].

*Anal.* Calc. for $C_{36}H_{56}O_{22}\cdot H_2O$: C, 50.34; H, 6.81. Found: C, 50.30; H, 6.60.

*Reduction of* **3** *in the presence of KI.* — To a solution of **3** (70 mg, 0.14 mmol) in dry methanol (2 mL) was added KI (25 mg, 0.15 mmol). The mixture was stirred until all the KI had dissolved and was then concentrated, the residue was treated with hexane (1 mL) and triethylborane (1 mL, 0.1–1 mol% of diethylboryl pivalate), and the mixture was stirred for 48 h and concentrated. Ethyldiborane (0.339 g, 15.8%; $H^-$, 5.35 mmol) and 9-BBN-mesylate (24.7 mg, 0.11 mmol) were added and the mixture was processed as in the preparation of **1**. Column chromatography (ethyl acetate) of the residue yielded **2** (40 mg, 36%), isolated as a syrup, $[\alpha]_D$

+17.5° (*c* 0.4, chloroform). N.m.r. data: $^1$H ($C_6D_6$), $\delta$ 5.92 (m, 1 H, H-2), 5.76 (m, 1 H, H-5), 5.45 (d, 1 H, $J_{3',4'}$ 3.4 Hz, H-4'), 5.38 (dd, 1 H, $J_{6a,6b}$ 12.8, $J_{5,6a}$ 2.2 Hz, H-6a), 5.11 (dd, 1 H, $J_{2',3'}$ 10.1 Hz, H-3'), 4.91 (m, 2 H, H-1b,6b), 4.86 (d, 1 H, $J_{1',2'}$ 7.7 Hz, H-1'), 4.57 (dd, 1 H, $J_{1a,1b}$ 12.8, $J_{1a,2}$ 1.8 Hz, H-1a), 4.43 (dd, 1 H, $J_{4,5}$ 5.4, $J_{3,4}$ 1.3 Hz, H-4), 4.24 (dd, 1 H, $J_{6'a,6'b}$ 11.5, $J_{5',6'a}$ 7.1 Hz, H-6'a), 4.12 (dd, 1 H, $J_{5',6'b}$ 5.3 Hz, H-6'b), 3.89 (dd, 1 H, $J_{2,3}$ 8.1 Hz, H-3), and 1.82–1.72 (s, 21 H, 7 Ac); $^{13}$C ($CDCl_3$), 170.6–169.8 (7 signals, C=O), 101.6 (C-1'), 77.5, 77.0 (C-3,2'), 74.7, 73.3, 73.2, 73.0, 72.9, 72.5, 70.9, 70.8, 70.6, 70.5, 70.3, 70.2 (double intensity), 67.4, 62.8, 61.8, 61.7 (C-1,6,6'), and 21.2–20.6 ($CH_3$COO). Mass spectrum: *m/z* 796 $M^+$ 737 [$M^+$ − AcO], 677 [$M^+$ − AcOH–AcO].

*Anal.* Calc. for $C_{34}H_{52}O_{21}$: C, 51.25; H, 6.58. Found: C, 51.32; H, 6.95.

*Reduction of lactose in the presence of KI.* — To a solution of lactose (95 mg, 0.28 mmol) in dry methanol (2 mL) was added KI (48 mg, 0.29 mmol), and the mixture was stirred until all the KI had dissolved. The solution was concentrated, and the residue was stirred with hexane (1 mL) and triethylborane (1 mL, 0.1–1 mol% of diethylboryl pivalate) for 48 h and then concentrated. Ethyldiborane (0.678 g, 15.8%; $H^-$, 10.70 mmol) and 9-BBN-mesylate (43 mg, 0.20 mmol) were added and the mixture was processed as indicated for **1**. Column chromatography (hexane–ethyl acetate, 1:1) of the residue yielded **5** (ref. 11) (40 mg, 20%) isolated as a syrup.

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REFERENCES

1 J. F. Stoddart, *Top. Stereochem.*, 17 (1987) 207–288.
2 J. M. Lehn, *Science*, 227 (1985) 849–856.
3 R. D. Gandour, F. R. Fronczek, V. J. Gatto, C. Minganti, R. A. Schultz, B. D. White, K. A. Arnold, D. Mazzocchi, S. R. Miller, and G. W. Gokel, *J. Am. Chem. Soc.*, 108 (1986) 4078–4088.
4 M. Alonso-Lopez, M. Bernabe, A. Fernandez-Mayoralas, J. Jimenez-Barbero, M. Martin-Lomas, and S. Penades, *Carbohydr. Res.*, 150 (1986) 103–109.
5 M. Alonso-Lopez, J. Barbat, E. Fanton, A. Fernandez-Mayoralas, J. Gelas, D. Horton, M. Martin-Lomas, and S. Penades, *Tetrahedron*, 43 (1987) 1169–1176.
6 J. F. Stoddart, *Chem. Soc. Rev.*, 8 (1978) 85–142.
7 M. Bernabe, M. Martin-Lomas, S. Penades, R. Köster, and W. V. Dahlhoff, *Chem. Commun.*, (1985) 1001–1002.
8 M. Alonso-Lopez, M. Martin-Lomas, S. Penades, C. Bosso, and J. Ulrich, *J. Carbohydr. Chem.*, 5 (1986) 705–710.
9 R. Köster, S. Penades, and W. V. Dahlhoff, *Angew. Chem., Int. Ed. Engl.*, (1985) 519–521.
10 E. Weber and F. Vögtle, in E. Weber, and F. Vögtle (Eds.), *Host Guest Complex Chemistry. Macrocycles, Synthesis, Structures, Applications*, Springer-Verlag, Berlin, 1985, pp. 30–32.
11 M. Alonso-Lopez, M. Bernabe, M. Martin-Lomas, and S. Penades, *Carbohydr. Res.*, 142 (1985) 135–140.
12 R. Köster and P. Binger, *Inorg. Synth.*, (1974) 143–146.
13 R. Köster, *Houben-Weyl: Methoden der Organischen Chemie*, Vol. 13/3b, G.T. Verlag, Stuttgart, 1983, pp. 829–830.