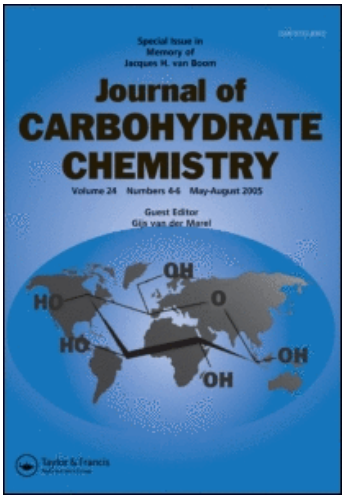

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New Chiral Macrocyclic Compounds from D-Mannitol

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Communication

NEW CHIRAL MACROCYCLIC COMPOUNDS FROM D-MANNITOL

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We have recently reported the synthesis of new chiral macrocyclic polyhydroxyethers by reduction of cyclodextrins[1]. These compounds display appreciable conformational freedom in solution as it occurs with the ionophores. Our chiral macrocycles may be considered as built by units of alditol (1 → 4) alditols. Such units, conveniently substituted, prepared by us by reduction of disaccharide derivatives[2], are possible synthons for the synthesis of other macrocyclic polyhydroxyethers in which the nature and number of alditol (1 → n) alditol components can be varied at will. We are interested in the preparation and the structural studies of these type of receptors since the synthesis of new chiral macrocycles is a topic of interest and

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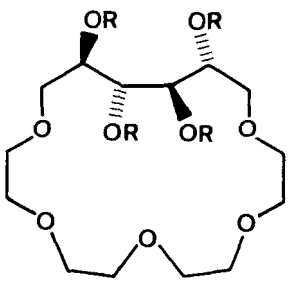
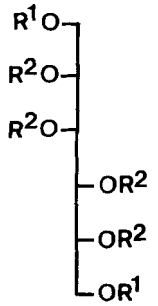
the building of chiral cavities may be of importance in the study of host-guest interactions. We now report on the preparation, from D-mannitol, a readily available starting material with C_2 symmetry, and tetraethylene glycol, of the chiral macrocycles 1, 2, and 3, as model compounds in exploring the synthesis of more complex macrocyclic polyhydroxyethers derived from alditol (1 → n) alditol. Other macrocyclic compounds from D-mannitol have been previously synthesised[3].





1 , R = Bzl

2 , R = H

3 , R = Ac

4 , R^1 = Tr , R^2 = H

5 , R^1 = Tr , R^2 = Bzl

6 , R^1 = H , R^2 = Bzl

Tritylation of D-mannitol with trityl chloride in pyridine (molar ratio 1:2, 25° C, 72 h) gave 1,6-di-O-trityl-D-mannitol 4, $[\alpha]_D$ = -1° (c 0.9, EtOH), in 89% yield[4]. Benzylation of 4 with sodium hydride-benzyl bromide, and tetrabutyl ammonium iodide[5] in THF gave 2,3,4,5-tetra-O-benzyl-1,6-di-O-trityl-D-mannitol 5 in 81% yield[6]. Selective deprotection of the trityl group in 5 was achieved with NaI-TMSCl[7] (3 1/2 h, 0° C) to give 2,3,4,5-tetra-O-benzyl-D-mannitol 6, $[\alpha]_D$ = +1° (c, 2.1, $CHCl_3$) in 80% yield[8]. Condensation of 6 with tetraethylene glycol ditosylate in THF in the presence of NaH afforded

macrocycle 1 in 20% yield after column chromatography. The use of K Bu^{t}O instead of NaH as a base did not improve the yield of the reaction (22 %). Hydrogenolysis of 1 with Pd/C in methanol gave 2 in 67%, acetylation of which yielded 3. ^{1}H-, ^{13}C-n.m.r. and f.a.b.-m.s. data were in agreement with the proposed structures[9].

Positive f.a.b.-mass spectra of compounds 1, 2 and 3[10] exhibited both their pseudomolecular ions $(M + H)^+$ and their cationised ions $(M + Na)^+$ or $(M + K)^+$. Addition into the matrix of equimolar amounts of alkaline chlorides led to the corresponding cationised ions. The relative intensities were more important for Na^+, K^+ or Rb^+ ions. Furthermore, the presence in the matrix of excess of any alkaline ion, as showed in fig. 1, enhanced the intensity of the signal corresponding to this ion.

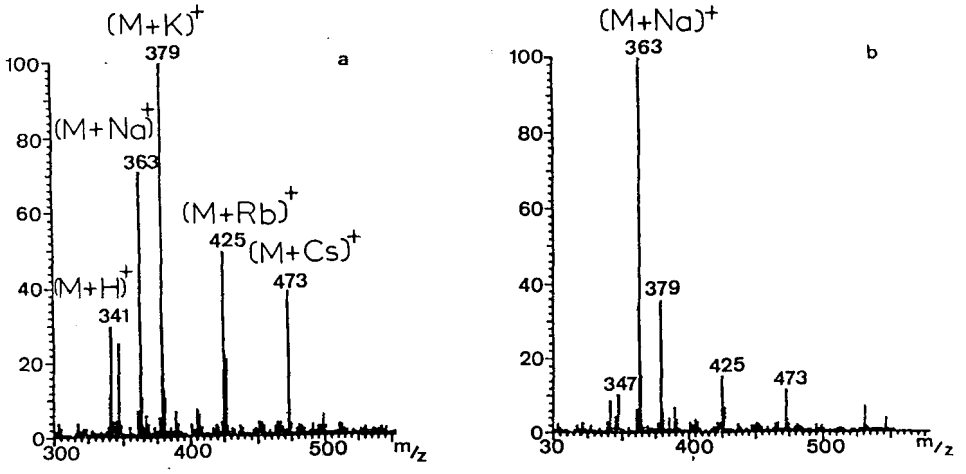


Fig.1 FAB(+) spectra of compound 2: a) at equimolar mixture of ions
b) in the presence of excess of NaCl

The presence of NH_4OH or NH_4Cl gave additional signals corresponding to the $(M + NH_4)^+$ ion.

Evidence for host-guest complex formation of 3 with benzyl ammonium thiocyanate was obtained by ^1H-n.m.r. spectroscopy. The ammonium salt was appreciably soluble in chloroform in the presence of 3. Integration of the signals for the benzylic protons of the guest molecule indicated the formation of a 1:1 host-guest complex. No appreciable change in the chemical shifts of the protons of 3 could be observed.

ACKNOWLEDGMENTS

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4. ^{13}C-n.m.r., $CDCl_3$ δ (ppm): 143.6 (C-ipso), 128.6 - 127.1 (Ph), 87.1, (Ph_3C), 72.0, 70.7, 64.9.

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6. ^1H-n.m.r., $CDCl_3$ δ (ppm): 7.40 - 6.90 (m, 50 H, Ph), 4.76-4.30 (m, 8H, Ph-CH_2-O), 4.27 (d, 2H, J = 7.3 Hz, H-3, 4), 3.85 (m, 2H, H-2, 5), 3.66 (dd, 2H, J = 2 Hz, J = 10.4 Hz, H-1, 6), 3.28 (dd, 2H, J = 4.3 Hz, H-1', 6'). ^{13}C-n.m.r., $CDCl_3$ δ (ppm): 144.0, 138.8, 138.7 (C-ipso), 128.8 - 126.8 (Ph), 86.6 (Ph_3C), 78.8, 78.0, 73.5, 71.6, 62.6 (C-1, C-6).

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8. Compound 6 was obtained from 5 as follows: Compound 5, (16 g, 0.015 mol) in acetonitrile (500 mL) under argon atmosphere at 0°C was treated, after 10 min, with NaI (11.67 g, 0.078 mol) and TMSCl (9 mL, 0.076 mol). After 30 min, NaI (1.16 g, 0.0078 mol) and TMSCl (1 mL) were added again, and the reaction mixture was stirred during 3 1/2 h. The reaction was worked as indicated in reference 7. ^{1}H-n.m.r., $CDCl_3$ δ (ppm): 7.40 - 7.20 (m, 20H, Ph), 4.78 - 4.37 (m, 8H, Ph-CH_2-O), 3.94 - 3.91 (m, 4H, H-1, 6, 3, 4), 3.86 (bd, 2H, H-1', 6'), 3.66 (m, 2H, H-2, 5), ^{13}C-n.m.r., $CDCl_3$ δ (ppm): 138.8, 138.0 (C-ipso), 129.9 - 127.0 (Ph), 79.8, 78.9, 74.3, 71.5, 60.5 (C-1, C-6).

9. Compound 1 was obtained from 6 as follows: Under argon atmosphere, 6 (310 mg, 0.572 mmol) was dissolved in THF (7 mL) and NaH (120 mg, 5 mmol) was added. The mixture was refluxed for 20 - 30 min, and tetraethylene glycol ditosylate (314 mg, 0.626 mmol) in THF (5 mL) was added dropwise during 4 h. Heating was continued for 72 h, and the mixture was then cooled. The excess of NaH was destroyed with methanol-water, and the mixture was extracted with chloroform. The organic layer was dried on Na_2SO_4. Column chromatography (hexane : ethyl acetate 1 : 1) gave 1 (80 mg, 20 %) as a syrup. $[\alpha]_D$ = +45.5° (c 0.2, $CHCl_3$). ^{1}H-n.m.r., $CDCl_3$ δ (ppm): 7.35 - 7.15 (m, 20H, Ph), 4.75 - 4.53 (m, 8H, Ph-CH_2-O), 3.99 (m, 2H, H-3, 4), 3.87 (m, 2H, H-2, 5), 3.78 (dd, 2H, J = 3.9, J = 10.8, H-1 , 6), 3.73 (dd, 2H, J = 5.4, H-1', 6'), 3.65 - 3.55 (m, 16H, ethylene moiety). ^{13}C-n.m.r., $CDCl_3$ δ (ppm): 139.2, 138.9 (C-ipso), 128.5 - 127.2 (Ph), 79.9, 74.3, 71.9, 70.9, 70.8, 70.7, 70.6, 70.5. Mass spectrum (f.a.b.): $[M + Na]^+$ m/z = 723.

Analytical data for 2: $[\alpha]_D$ = -4.8° (c = 1.3, MeOH). ^{1}H-n.m.r., (D_2O, DSS int. ref.) δ (ppm): 3.93 (d, 2H, J = 5.68, H-3, 4), 3.71 (m, 2H, H-2, 5), 3.68 (m, 20H, H-1, 1', 6, 6' , ethylene moiety). ^{13}C-n.m.r., CD_3OD δ (ppm): 73.1, 72.9, 71.8, 71.6, 71.3. Mass spectrum (f.a.b.): $[M + Na]^+$ m/z = 363.

Analytical data for 3: $[\alpha]_D$ = +29.5° (c = 0.6, $CHCl_3$). ^{1}H-n.m.r., $CDCl_3$ δ (ppm): 5.52 (d, 2H, J = 4.35, H-3, 4), 5.21 (m, 2H, H-2, 5), 3.79 - 3.59 (m, 20H, H-1, 1', 6, 6', ethylene moiety), 2.07 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO). ^{13}C-n.m.r., $CDCl_3$ δ (ppm): 169.9, 169.5 (CH_3CO), 71.3, 71.1, 70.9, 70.7, 70.6, 68.5, 20.9, 20.7 (CH_3CO). Mass spectrum (f.a.b.): $[M + Na]^+$ m/z = 531.

10. The f.a.b.-mass spectra were recorded by using a polyethylene glycol 200 matrix (1 and 3) or glycerol matrix (2) with a MS-50 Kratos instrument fitted with a 1,2 T magnet, having a mass range up to 1.300 u.m.a., and a f.a.b. 11 NF Ion Tech atomgun.