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A NEW CYCLOGLUCOHEXAOSE DERIVATIVE

THE CHEMICAL SYNTHESIS OF

Cyclo{→3-[β-D-Glc*p*-(1→ 3)-]$_5$-D-Glc*p*-(1→)

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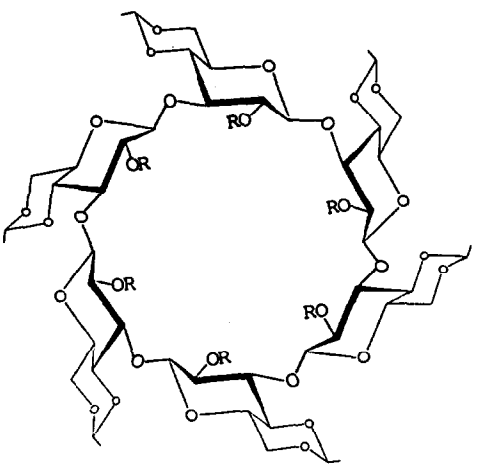
ABSTRACT : *The new 1→3 β-linked cycloglucohexaose derivatives (1) and (2) have been prepared from 1,2-O benzylidene-4,6-O-ethylidene-α-D-glucopyranose and its derivatives as the monomeric building blocks, using as a key reaction their photobrominative conversion into 2-O-benzoyl-glucosyl bromides.*

1,2-*O*-Benzylidene-4,6-*O*-ethylidene-glucopyranose(3) and galactopyranose derivatives are excellent building blocks for the synthesis of some oligosaccharides because of the ease with which they can be photobrominatively converted into glycosyl bromides[1] . In this letter we deploy this reaction on the *gluco*-derivative to prepare 1,3-β-linked homoglucans. Moreover be-

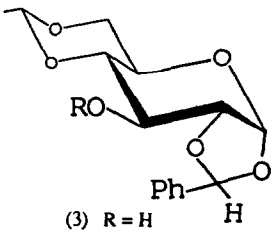


(1) R = H (2) R = Bz

cause the bromination may be carried out on 1,2-benzylidene oligosaccaccharides possessing a free hydroxyl group the formation of cycloglycans is possible.

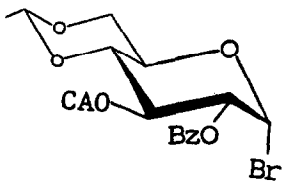
Interest in these molecules[2] stems from the ability of the naturally occurring cyclodextrins (1,4-α-linked glucopyranoses) CDs to form within their highly structured cavities inclusion complexes[3], investigations of which have been aided by chemically

modified CDs[4] . Recently CDs have been chemically synthesised[5] including those with an unnatural *manno*-configuration[6] There is however interest in cycloglycans formed by alternatively linked pyranose rings, with enclosed spaces of a similar size and flexibility that are topologically different. The cycloglycan derivative (1) represents the first such example and the synthesis+ of it is different in that we propose to generate a glycosylating agent at the 'head' of an oligosaccharide in the presence of one free hydroxyl in its 'tail'. Others [5,6,8] have used the reverse process.



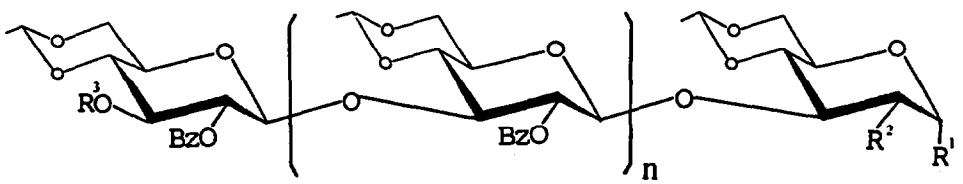
(3) R = H

(4) R = CA



(5) R=CA

CA = CH_2ClCO



n=0

(6) R^1,R^2=$PhCHO_2$, R^3=CA

(7) R^1,R^2=$PhCHO_2$, R^3=H

(8) R^1=Br, R^2=OBz, R^3=CA

n=1

(9) R^1,R^2=$PhCHO_2$, R^3=CA

(10) R^1,R^2=$PhCHO_2$, R^3=H

(11) R^1=Br, R^2=OBz, R^3=CA

n=2

(12) R^1,R^2=$PhCHO_2$, R^3=CA

(13) R^1=Br, R^2=OBz, R^3=CA

n=4

(14) R^1,R^2=$PhCHO_2$, R^3=CA

(15) R^1,R^2=$PhCHO_2$, R^3=H

(16) R^1=Br, R^2=OBz, R^3=H

(17) R^1= β-OMe, R^2=OBz, R^3=H

Glycosylation of (3) in the presence of silver triflate with the α-bromo sugar (5), which is readily prepared from the 1,2-benzylidene monochloroacetate (4) by sequential photobromination and anomerisation[1] gave the β-linked disaccharide (6) in 84%

+ There are examples where the cavities will be less structured. For example, the 1,2-linked glucans from Rhizobia and Agrobacteria[7] and the synthetic 1,6-linked glucofuranoses[8]. These are more flexible structures because of the size (heptadecamer) of the former and the exocyclic linkages involved on the latter.

yield. Photobromination and subsequent anomerisation of this material gave in 76% yield the α-bromo-disaccharide (8), which was 'head' extended by further treatment with (3) under the same glycosylating conditions to give in 92% yield a trisaccharide (9) in which the new intersaccharide linkage was again expected to be β as shown in (9). However the measured $J_{1',2'}$ value of 5.2Hz was surprisingly small and consequently the configuration anticipated was not confirmed. The presence of the neighbouring benzoyloxy group at C-2 makes an α-glycosidic link at C-1 improbable but a linkage through an ortho - ester at C-1′,-2′ appeared a possibility. However this was excluded since the ^{13}C-nmr spectrum exhibited two benzoyl carbonyl carbons and no signal for an orthoester quaternary carbon which occurs at δ120ppm in authentic orthoester containing oligosaccharides. These were prepared by glycosylating in the presence of *sym*-collidine, but otherwise under the conditions previously described.

Therefore the configuration of intersaccharide linkages had to be established by an alternative synthetic route which involved 'tail extension' of a disaccharide. Thus the hydroxy β-linked disaccharide (7) obtained by dechloracetylation of disaccharide (6) in 80% yield was glycosylated with the α-bromo monosaccharide (5). A trisaccharide was obtained in 95% yield identical with the material under investigation. Consequently it must have the β,β-intersaccharide linkages as shown in (9). This material was then used to produce the tetrasaccharide (12) by extending the chain at its head. Thus (9) was α-brominated and the bromide (11) formed in 74% yield was used to glycosylate the 3-hydroxy monomer (3) in 86% yield. By coupling the bromodisaccharide (8) with the 3′-hydroxydisaccharide (7) an identical tetrasaccharide was produced in 85% yield, thus confirming that the tetramer (13) was β,β,β-linked.

Hexasaccharide (14) was reached in two ways. The 1,2-benzylidene tetrasaccharide (12) was converted in the usual fashion into the α-bromotetrasaccharide (13) in 73% yield. This was then used to glycosylate the 3′-hydroxy-disaccharide (7) giving after chromatography material in 88% yield that was identical with the product obtained by the coupling of two trisaccharides : the 3″-hydroxy trimer (10), obtained by selective deacylation of (9), and the bromotrisaccharide (11). Thus the hexasaccharide (14) is all β-linked.

Up to this stage all the photobrominations / anomerizations have been carried out on fully protected 1,2-O-benzylidenated sugars. It was now necessary to ascertain if a 1,2-*O*-benzylidene oligosaccharide with one free hydroxyl in the tail, but otherwise fully protected, could be α-brominated at its 'head'. To this end the chloroacetylhexasaccharide (14) was selectively deprotected and the 3-hydroxyhexamer (15) was photobrominated and subsequently anomerized in the usual way. The product obtained was chromatographed and shown to be α-bromo-hydroxy-hexasaccharide (16). This was verified by converting it to its β-methyl glycoside (17) with methanol in the presence of silver triflate in 78% yield from (14). The same material was also produced in similar yield from the crude bromination product. Its structure was derived from its m.s., and ^{1}H-and ^{13}C-nmr spectra.

The crucial intramolecular glycosylation of the hydroxybromide (16) was then carried out on a dilute solution (1.0%) in dichlormethane in the presence of silver triflate which gave after chromatography the fully protected cyclohexaose (2) mp 221-3^{o} in 30% yield. The structure of (2) rests on its elemental composition, FAB ms and its very simple ^{1}H- and ^{13}C- nmr

spectra, reminiscent of that of a monomer thus indicating the anticipated six fold symmetry in molecule (2). Debenzoylation of compound (2) under Zemplen conditions gave the 2-hydroxy-4,6-ethylidene cyclohexaose (1) mp 206-8°. The sodium iodide doped FAB-ms suggests that this material is able to associate with three sodium atoms. This and other host/guest properties possessed by compound(1) are currently being investigated before its final deprotection to the trihydroxyhexaose.

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9. Physical data for new compounds is given below. $\delta_{H,C}$ were measured at 270 and 68 MHz respectively in $CDCl_3$ unless stated otherwise. (6) δ_H 5.42 (d,$J_{1,2}$ 4.7Hz), 5.06 (d,$J_{1,2'}$ 7.4Hz). (8) δ_H 6.54 (d,$J_{1,2}$ 4.2Hz), 4.99 (d,$J_{1',2'}$ 7.0Hz). (9) δ_H (400MHz) 5.25(d,$J_{1'',2''}$ 7.4 Hz), 5.13(d,$J_{1',2'}$ 5.2Hz), 5.19(d,$J_{1,2}$ 5.0Hz), 5.80 (s, PhCHO)$_2$. (11) δ_H 6.47 (d,$J_{1,2}$ 2.7Hz,HC_1Br). (12) δ_H (400 MHz), four anomeric proton doublets : 5.13 (d, 5.0Hz), 5.05(d, 7.2Hz), 4.94 (d, 7.5 Hz), ~4.97(partially obscured by other signals). (13) δc(C_6D_6) 100.0, 99.7 [3C], 99.4[2C], 98.8(seven acetal carbons of which three are anomerics), 88,8 (C_1Br); δ_H(C_6D_6) 6.45 (d,3.7Hz, HC_1Br). (14) FAB.ms m/z 1832 (M^++1). (16) $\delta_H C_6D_6$ 6.42 (d,2.7 Hz, HC_1Br). (17, where R_1 has the β-configuration) FAB,ms with NaI, m/z 1808 (M^+ + Na + 1, due to the ^{13}C isotope effect [10]); δ_H (400MHz) 3.00 (s, OMe), all groups of signals integrate satisfactorily but signal resolution is low. (2) mp 221-3°; $[\alpha]_D$ + 8.8° (c,0.5 CH_2Cl_2); Nmr spectra appear like those of a monomer.δ_H (C_6D_6) 5.04 (d, $J_{1,2}$ 6.2Hz), 5.26 (t, $J_{2,1}$ 6.2, $J_{2,3}$ 6.4Hz), 4.0-4.1(m, 2H), 3.38-3.58(m,3H), 1.22(d, J 5.1Hz) and 4.52 (q, J 5.1Hz) [*MeCH* respective ly];δ(400 MHz) 4.77-4.84(m 2H, H-1 and -2), 3.80 (dd, $J_{3,2}$ 6.7, $J_{3,4}$ 8.1Hz), 3.98 (dd, $J_{6,6}$ 10.0, $J_{6,5}$ 4.0Hz, H-6e), 3.41(t, J 10 and 9.5Hz, H-6a), 3.20-3.40(m, 2H, H-4, -5), 1.21(d, J 4.9 Hz) and 4.55 (q, J 4.9 Hz) [*MeCH* respectively]; δc 99.3, 78.1, 76.2, 77.2, 65.7 and 68.3(C-1 to -6), 20.5 and 97.7 (*MeCH*O_2), 133.2, 129.6, 129.4, 128.5, and 164.4 (PhCO); FAB.ms with NaI: $C_{90}H_{96}O_{36}$ Rqd.1752 Fnd : 1776 (M^+ + Na + 1, due to ^{13}C isotope effect [10]). (1) mp 206-8°; dec., $[\alpha]_D$ -9.1° (c 0.5 CH_2Cl_2); δ_H all signals are broad, with some sharpening seen on elevating temperature 4.80 - 4.55 (2H, H-1 and Me*CH*), 4.3 - 3.1 (6H), 1.28 - 1.32 (3H, Me), FAB.ms with NaI : $C_{48}H_{72}O_{30}$ Rqd 1128, Fnd: 1151(M^+ + Na) and 963, 775, and 587 formed by sequential loss of monomer units (188). In addition Fnd: 1195 (M^+ +3Na -2H) and 1007, 819 and 631.
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