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Preliminary communication

The conversion of maltose into disaccharides having 2-amino-2-deoxy-α-D-glucose and L-idose as constituent sugars, for the synthesis of model compounds related to heparin

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Heparin[1] is a highly sulfated polymer that consists of (1→4)-linked, alternating residues of 2-amino-2-deoxy-α-D-glucopyranose and α-L-iduronic acid or, to a lesser extent, β-D-glucuronic acid. In studies on the synthesis of oligosaccharides containing the main structural elements of heparin and biosynthetic precursors of it, we have found that maltose (4-*O*-α-D-glucopyranosyl-D-glucopyranose, **1**) is a versatile, practical starting-material. That is, in a relatively few steps, the D-glucosyl group of **1** has been transformed into a 2-amino-2-deoxy-α-D-glucopyranosyl group, whereas its reducing residue has been inverted at C-5 to afford an L-*ido* derivative. These modifications ensured not only that the correct configuration of the aminodeoxy-D-glucosyl group was obtained, often a difficult step in oligosaccharide synthesis, but also that the L-idopyranose or D-glucopyranose residue to which it must be linked, was 4-*O*-substituted.

When acetal **2**, a compound readily accessible[2] by kinetic acetonation of maltose, was treated[3] with *tert*-butylchlorodiphenylsilane, it gave the 3′-*O*-silyl derivative (**3**)* selectively. Product **3** was oxidized with pyridinium chlorochromate on alumina[4] to the 2′-ketone (**4**), which was converted[5,6], *via* the oxime (**5**) and reduction of **5** with lithium aluminum hydride in oxolane, into a 2:1 mixture of the 2-amino-2-deoxy-α-D-*gluco* (**6**) and -α-D-*manno* (**8**) derivatives**, respectively. When acetylated, the mixture was separated chromatographically on silica gel, with 6.5:1 ethyl acetate–petroleum ether as the eluant, to give the D-*gluco* isomer as the diacetate (**7**); (M +1) 592 (10%). The ^{1}H-n.m.r. spectrum of **7** served to confirm the α-D-*gluco* configuration assigned to it; δ 4.98 (H-1′), 5.12 (H-3′), $J_{1,2}$ 3.7, $J_{2,3}$ 7.0 Hz.

*Product **3**, and all others cited, were chromatographically pure syrups that were characterized by ^{1}H-n.m.r. spectroscopy (200 MHz) and chemical ionization mass spectrometry.

As has been shown[7,8] in the reduction of C=X bonds (X = O or N) adjacent to an α-D-anomeric center, the α-D-*gluco* configuration is strongly favored. Attempts at the hydrogenolysis of **5 with palladium catalyst, which would be expected[8] to give a higher proportion of **6**, were unsuccessful. The loss of the *O*-silyl group during the reduction possibly entailed migration of the silicon atom from O-3′ to the oximino-oxygen atom, followed by hydrogenolysis of the N–O, rather than the Si–O, bond.

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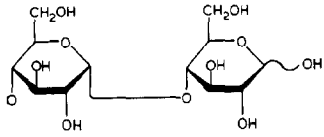
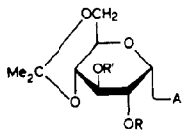
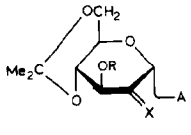


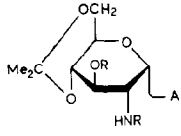
1



2 R = R' = H
3 R = H, R' = $(Me_3C)Ph_2Si$

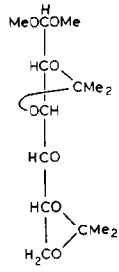


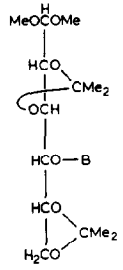
4 R = $(Me_3C)Ph_2Si$, X = O
5 R = $(Me_3C)Ph_2Si$, X = NOH



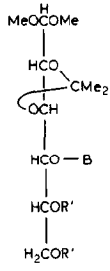
6 R = H
7 R = Ac
8 C-2 epimer of 6

A =

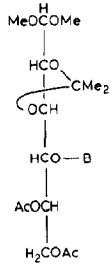




9 R = H
10 R = Bn
Bn = $PhCH_2$

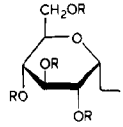


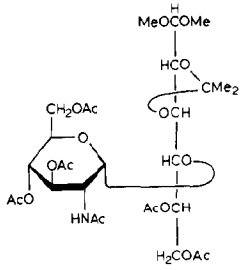
11 R = Bn, R' = H
12 R = Bn, R' = Ms



13 R = Bn

B =





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For modification of the reducing residue of **1*****, acetal **9**, another prominent product[2] of the kinetic acetonation of maltose, was used. Its tetra-*O*-benzyl derivative (**10**) was prepared by reaction with benzyl bromide/sodium hydride and, when subjected to hydrolysis in 80% acetic acid at 50°, the 5,6-*O*-isopropylidene group of **10** was selectively removed to the extent of 70% in 4 h (other products were detected on more-

***In a complementary transformation[9], the β-D-glucosyl group of cellobiose has been isomerized to an α-L-*ido* group.

prolonged treatment). The 5,6-diol (**11**) produced was separated chromatographically from residual **10** on silica gel, with 1:1 ethyl acetate–hexane as the eluant, and converted with mesyl chloride in pyridine into the di-*O*-mesyl derivative (**12**), which was heated under reflux with acetic anhydride/potassium acetate, affording the 5,6-di-*O*-acetyl L-*ido* product (**13**); (M − 15) 857 (100%). The isolation of 1,6-anhydro-β-L-idopyranose from an acid hydrolyzate of **13** helped to confirm the structure depicted.

Finally, the two individual reaction-sequences were combined for the synthesis of **14**, containing both 2-amino-2-deoxy-α-D-glucose and L-idose as constituent sugars. That is, the 4′,6′-*O*-isopropylidene group of **7**, the most labile[2] of its three *O*-isopropylidene substituents, was removed at r.t. with 0.004% HCl in methanol; this treatment was followed by acetylation. Having thereby protected the aminodeoxy-D-glucosyl group, the sequence of reactions depicted by **10** → **13** was then utilized to isomerize the D-glucose acetal portion into the corresponding L-idose residue of product **14**; (M − 15) 664 (100%).

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