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Formation of disaccharides related to heparin and heparan sulfate by chemical modification of maltose*

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ABSTRACT

Maltose has been converted into 4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-idopyranuronic acid, 4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-glucopyranose, and 4-*O*-α-D-glucopyranosyl-L-idopyranose, the first two disaccharides being related structurally to biose sequences in heparin and heparan sulfate. Used as the starting material was a major product of the kinetic acetonation of maltose, namely, 2,3:5,6-di-*O*-isopropylidene-4-*O*-(4,6-*O*-isopropylidene-α-D-glucopyranosyl)-*aldehydo*-D-glucose dimethyl acetal. It was subjected to a sequence of transformations that included the introduction of a 2'-amino-2'-deoxy function into the glucosyl group, the inversion of C-5 in the glucose residue to give the L-*ido* configuration, oxidation at position 6, and cyclisation of the acyclic dimethyl acetal to give the desired pyranuronic acid. In the formation of the latter, the 5-*O*-levulinoyl substituent was found to be less prone to acyl migration to O-6 than more conventional ester groups. The relative acid labilities of the *O*-isopropylidene and dimethyl acetal groups are compared, and conformations of the acyclic residues of some disaccharide derivatives are discussed.

INTRODUCTION

Disaccharides that are readily available in quantity, most notably sucrose[1,2], have been modified in a variety of ways. The chemical transformation of maltose (4-*O*-α-D-glucopyranosyl-D-glucopyranose) into diasaccharide derivatives that are structurally related to heparin and heparan sulfate is now described. Although analogous compounds and higher oligosaccharides of greater complexity in this series have been succesfully synthesized[3–5], the work described involved substantially different methodology. Hence, some aspects of the chemistry may find use in further syntheses associated with these glycoaminoglycans and, possibly, other polysaccharides.

The major disaccharide sequences in heparin and heparan sulfate consist of 4-substituted residues of 2-amino-2-deoxy-α-D-glucopyranose 4-linked to α-L-idopyranuronic acid or/and β-D-glucopyranuronic acid. Sulfate substituents are located on the residues in various arrangements[6]. These basic types of repeating units have been prepared in a sequence of regio- and stereo-selective transformations of maltose, with the objective of using them in block-polymerization reactions.

* Dedicated to Professor Leslie Hough in the year of his 65th birthday.

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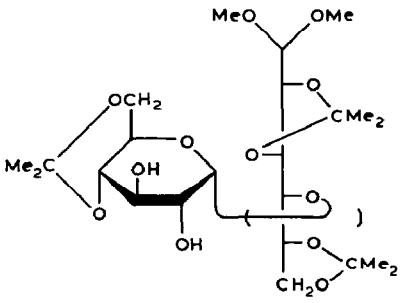
RESULTS AND DISCUSSION

2,3:5,6-Di-*O*-isopropylidene-4-*O*-(4,6-*O*-isopropylidene-α-D-glucopyranosyl)-*aldehydo*-D-glucose dimethyl acetal (**1**), which is readily accessible[7] by kinetic acetonation of maltose, served as an appropriate starting material. Taking advantage of differential acid labilities[8,9] of the four acetal functions in **1**, the first modification entailed conversion of the glucosyl group selectively into a 2-amino-2-deoxy-α-D-glucose moiety. Then, the configuration at C-5 of the acyclic glucose was inverted to give a 4-substituted L-iduronic acid.



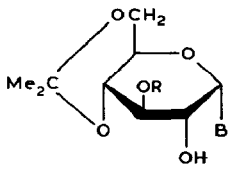
1 (B)

Formation of the 2-amino-2-deoxyglucosyl group. — A well known[10–13] procedure for introducing an aminodeoxy function into a glycoside involves the sequence alcohol →ketone→imine→amine. The application of this sequence to **1** required selective substitution of HO-3'*. Attempted partial benzoylation or benzylation of **1** gave mixtures of products, but the reaction with *tert*-butyldimethylsilyl chloride produced 80% of the 3'-*O*-*tert*-butyldimethylsilyl derivative **2**. This result contrasts with the finding[14] that, in the analogous reaction with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, the ratio of 2- and 3-substituents was 3:2. N.m.r. data (see below) suggest that the higher reactivity of HO-3' in **1** stems from steric hindrance of HO-2' by the acyclic acetal moiety.

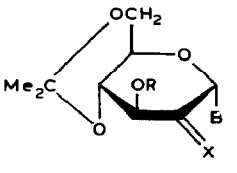
Oxidation at position 2' of **2** with reagents based[15–18] on pyridinium chlorochromate or dichromate, chosen to avoid either strong acidic or basic conditions, gave the ketone **3** (60–75%), the ^{13}C-n.m.r. spectrum of which contained a carbonyl resonance at δ 197.4. With hydroxylamine, **3** afforded the 2'-deoxy-2'-oxime derivative **4** (δ 154, imine C-2'). Based on a large downfield shift ($\sim$ 1 p.p.m.) of the H-1 signal of **4** relative to that of **2**, the oxime was taken to have the *Z* configuration by analogy with alicyclic oximes. As found by others[13,19,20], attempts to hydrogenate **4** over a palladium catalyst or at borane reduction were ineffective. However, as reported[21], the oxime was reduced by lithium aluminium hydride in oxolane, to afford a 2:1 mixture of the 2-amino-2-deoxy-α-D-*gluco* (**6**) and -α-D-*manno* (**7**) derivatives. This reaction was accompanied by loss of

* Primed numbers refer to the "non-reducing" moiety.

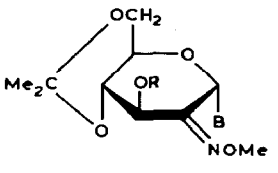
the 3′-substituent due, possibly[21], to silyl migration from O-3′ to the oximino group, followed by hydrogenolysis.



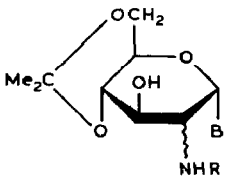
2 R = ^{t}BuMe$_2$Si



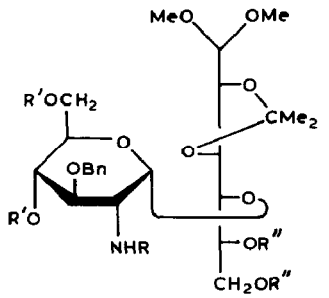
3 X = O, R = ^{t}BuMe$_2$Si
4 X = NOH, R = ^{t}BuMe$_2$Si



5 R = ^{t}BuMe$_2$Si



6 R = H, *gluco*
7 R = H, *manno*
8 R = Ac, *gluco*



9 R = Ac, R′,R′ = R″,R″ = Me$_2$C
10 R = Ac, R′ = H, R″,R″ = Me$_2$C
11 R = Ac, R′ = allyl, R″,R″ = Me$_2$C

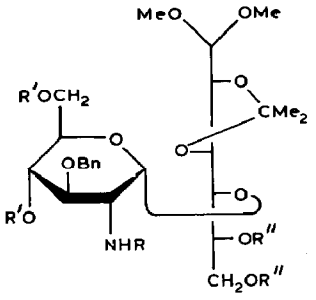
A marked improvement in the 2:1 epimeric ratio of **6**:**7**, to a value of ~10:1 was effected by methylation of **4** to give the methoxime **5** (δ 61.9, NOMe) prior to the reduction step, which again occurred with simultaneous loss of the 3′-substituent. The formation of a *cis*-1,2-amino (*gluco*) derivative **6** is expected to be favored[11,13,20] due to hindrance by the axial aglycon group. However, as methylation of the oxime so markedly alters the stereochemistry of the reduction step, it is likely that coordination between the aluminum and the oxime was a factor in determining an equatorial approach of the hydride ion to give the *manno* epimer. *N*-Acetylation of the mixture facilitated the isolation of the *gluco* isomer **8** (44% from **3**). Among characteristic n.m.r. data for **8** was the $J_{1',2'}$ value of 3.9 Hz (*cf.* <1 Hz for the *manno* epimer) and the acetamido C-2′ signal at δ 54.5. Finally, the 3-*O*-benzyl derivative (**9**) was prepared from **8**, not only to block HO-3′ but also to allow for enhanced reactivity[22] at HO-4′ in the subsequent coupling steps envisaged.

Of the *O*-isopropylidene groups in **1**, the 4′,6′-acetal was found in preliminary experiments to be the least stable. Consequently, partial hydrolysis of **9** afforded **10** as the major product (73%), which was converted into the 4′,6′-di-*O*-allyl derivative **11**.

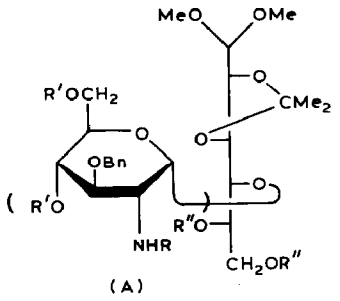
Formation of an L-*iduronic acid residue.* — Selective hydrolysis of the 5,6-*O*-isopropylidene group of **11** with aqueous 80% acetic acid at 40° gave the diol **12**, characterised as the 5,6-diacetate **13**. The dimesylate (**14**) of **12**, on heating under reflux with potassium acetate in acetic anhydride to effect[23] an inversion of C-5, afforded the 5,6-di-*O*-acetyl-L-*ido* product **15**.

O-Deacetylation of **15** gave the diol **16**, which was selectively 6-substituted with a *p*-methoxyphenyldiphenylmethyl (*p*-anisyldiphenylmethyl) group (→**17**) then 5-substituted with an *O*-levulinoyl group (→**18**). The levulinic ester was specifically chosen over *O*-acetyl or *O*-benzoyl since it is less prone to acyl migration[24]. Consequently, hydrolysis of **18** with aqueous 80% acetic acid at room temperature gave the 6-hydroxy derivative **19** (96%).

Oxidation of **19** with methyl sulfoxide–dicyclohexylcarbodi-imide[25] gave the aldehyde **20**, which was reacted with buffered sodium chlorite[26] and then diazomethane to afford the L-iduronate derivative **22** (67% from **19**). The *O*-levulinoyl group was then removed from **21** with hydrazine hydrate, to give **22**. Cyclisation of the uronate moiety

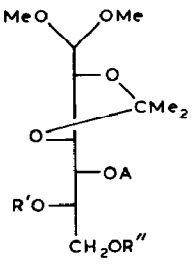


12 R = Ac, R′ = allyl, R″ = H
13 R = Ac, R′ = allyl, R″ = Ac
14 R = Ac, R′ = allyl, R″ = Ms

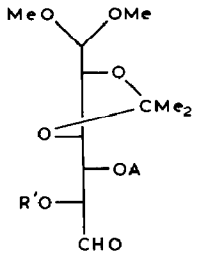


(A)

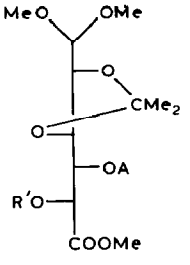
15 R = Ac, R′ = allyl, R″ = Ac
16 R = Ac, R′ = allyl, R″ = H



17 R′ = H, R″ = *p*MeOPh(Ph)$_2$C
18 R′ = Lv, R″ = *p*MeOPh(Ph)$_2$C
19 R′ = Lv, R″ = H

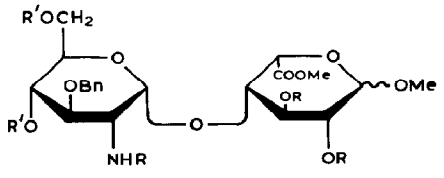


20 R′ = Lv

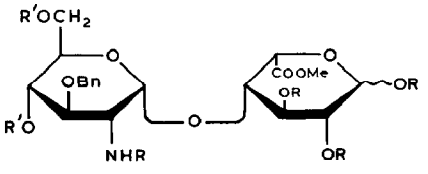


21 R′ = Lv
22 R′ = H

Lv = levulinoyl



23 R = Ac, R′ = allyl, α
24 R = Ac, R′ = allyl, β



25 R = Ac, R′ = allyl

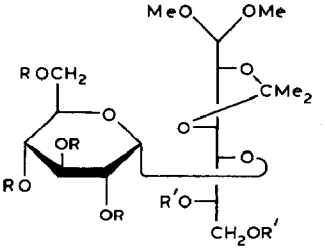
and hydrolysis of the 2,3-*O*-isopropylidene group was effected in aqueous 90% trifluoroacetic acid, to give a mixture of the methyl *α*- and *β*-pyranosides (40%) and *α*- or *β*-pyranose (20%), which were isolated as the diacetates **23** or **24**, and the triacetate **25**, respectively.

The anomeric designations of these glycosides were based on n.m.r. and optical rotation data[27]. Since $J_{1,2}$ for methyl *α*-D-idopyranosiduronic acid is larger than that of its *β* anomer, the fact that the glucoside **23** has the larger $J_{1,2}$ value (4.9 Hz, *cf.* 3.6 for **24**) suggests that it is *α*-L. The $[\alpha]_D$ values of +32° and +92°, respectively, for **23** and **24** are consistent[27] with these designations. Nevertheless, as these comparisons are dependent upon the conformational population of the idopyranuronic acid rings, it is worth noting that the ^3J values observed[27,28] for H-2,3,4,5 of **23** and **24** are similar (within the range 4.1–6.9 Hz), indicating that similar conformational species are being compared.

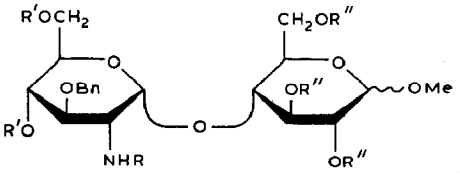
Additional observations and comments. — As already noted, the 4′,6′-acetal group of **1** and related derivatives is more acid-labile than the 5,6-acetal which, in turn, is far less stable than the 2,3-acetal. Indeed, as part of an *α-threo* ring, the latter is expected[8] to be moderately stable. Its removal is necessary, however, if the acyclic glycose dimethyl acetal residue is to be transformed into a pyranose ring, because the latter (in a chair conformation) would be highly strained by a *trans*-1,3-dioxolane structure.

Preliminary experiments with derivatives of 4-*O*-α-D-glucopyranosyl-2,3-*O*-isopropylidene-*aldehydo*-D-glucose or -L-idose dimethyl acetal (**26**, R = benzyl or acetyl) showed that the corresponding aldoses were obtained readily by hydrolysis with refluxing aqueous 80% acetic acid. However, in compounds containing the 2′-acetamido function, hydrolysis was accompanied by a rearrangement, and a mixture of methyl glucosides and aldoses was produced. This complication also occurred in aqueous 90% trifluoroacetic acid, as found for **23**, as well as for the 2′-oxo analogs (**26**). By contrast, methyl pyranosides were formed exclusively on methanolysis, as shown by the conversion of dimethyl acetal **9** into the methyl glucopyranoside **27**, which was characterised as its penta-acetate (**28**; *α*,*β*-ratio 2:1).

The acid-catalysed rearrangement of dimethyl acetal derivatives into methyl glycosides is well know[29] and preferentially yields methyl furanosides as the kinetic products. Since this possibility is excluded for 4-linked disaccharide derivatives, the slow formation of a pyranoside, in the presence of water, should allow for the formation of the aldopyranose. Although this reaction occurs under some circumstances, it is



26 R = Bn or Ac, R′ = Ac or H



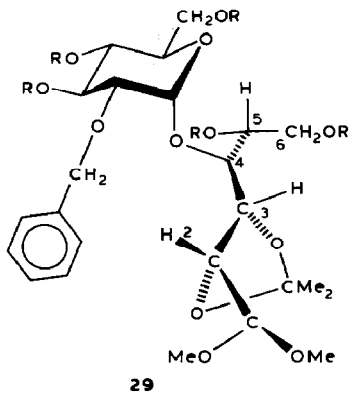
27 R = Ac, R′ = R″ = H

28 R = R′ = R″ = Ac

unclear as to why methyl pyranosides are produced when the (seemingly) remote 2′-acetamido function is present.

Conformational features of some of the disaccharide derivatives examined also deserve comment.

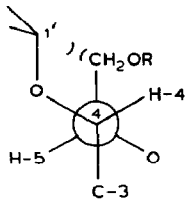
The more ready *tert*-butyldimethylsilylation of HO-3′ of **1** than of HO-2′ is the converse of the relative reactivities in monosaccharide analogs, and raised the possibility that HO-2′ is sterically hindered by the acyclic glycose residue. Evidence to that effect comes from ^{1}H chemical shift data for **26**, derivatives of **1** that contain 2′- and 3′-*O*-benzyl and -*O*-acetyl substituents. Whereas the change from *O*-acetyl to *O*-benzyl in **26** has almost no effect (variations of <0.15 p.p.m.) on the chemical shifts of the resonances of H-1,3,4,5,6,6′ of the acyclic residue, its H-2 signal is displaced markedly downfield (δ 4.65) when the 2′-substituent is *O*-benzyl, relative to its 2′-*O*-acetyl counterpart (δ 4.16). Not only does this imply a close proximity between the 2′-positions and the acyclic moiety, but also an orientation of the latter (corresponding to angle ψ) in which conformation **29** is a prominent species.



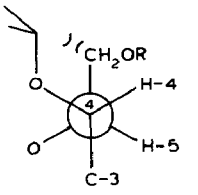
29

N.m.r. data support the view that acyclic aldohexose derivatives adopt planar zigzag conformations in which *gauche* interactions are minimised. The presence in the disaccharides of the glycosyl group at O-4, however, appears to alter substantially the orientations about the C-3–C-4 and C-4–C-5 bonds that are normally ascribed to monomeric acyclic *gluco* and *ido* derivatives. These latter orientations, represented in the Newman projection **30–33** as if they were portions of disaccharides, are characterised[30,31] by $^3J_{H,H}$ values that are distinctive for each configuration and bond. Widely different, however, are the corresponding couplings for the maltose derivatives, which are more consistent with the dihedral angles depicted in the rotamers **34–37**.

An examination of molecular models suggests some possible reasons for these differences, which are most directly apparent for the rotamers **30** and **34**. It is inferred that, if the "normal" conformation were to be retained, there would be crowding between the hydroxymethyl group and the 4-*O*-glycosyl group. Hence, a reorientation about the C-4–C-5 bond, as in **29** and **34**, should be favorable. Thus, it is concluded that the acyclic residues are well represented by the rotamers **34** and **35** (*gluco*), and **36** and **37** (*ido*).

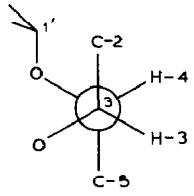


30 $J_{4,5}$ 6-10 Hz (D-*gluco*)

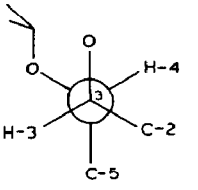


32 $J_{4,5}$ 1-5 Hz (L-*ido*)

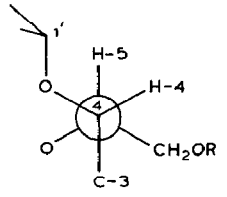
Expected major rotamers, based on acyclic monosaccharides



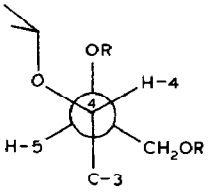
31 $J_{3,4}$ 1-5 Hz (D-*gluco*)



33 $J_{3,4}$ 6-10 Hz (L-*ido*)

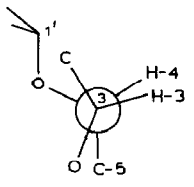


34 $J_{4,5}$ 1-5 Hz (D-*gluco*)

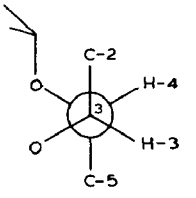


36 $J_{4,5}$ 6-10 Hz (L-*ido*)

Proposed major rotamers, based on measured spacings



35 $J_{3,4}$ 6-10 Hz (D-*gluco*)



37 $J_{3,4}$ 1-5 Hz (L-*ido*)

EXPERIMENTAL

General methods. — Optical rotations were determined at room temperature with a Jasco-DIP 140 Digital Polarimeter. N.m.r. spectra (^1H and ^{13}C) were recorded with Varian XL-200 and XL-300 spectrometers; chemical shifts (δ) are reported for solutions in $CDCl_3$, with reference to Me_4Si. Mass spectrometry was performed by the Biomedical Mass Spectrometry Unit, using an HP 5980 A instrument at 70 eV and 210° in the e.i.

mode, or a ZAB-HS instrument at 7 kV, 1 mA, and with either a diethanolamine or glycerol matrix for the f.a.b. mode. Silica gel (Merck, 400 mesh) was used for column chromatography. Microanalyses were performed by Guelph Analytical Laboratories, Guelph, Ont.

*2,3:5,6-Di-*O*-isopropylidene-4-*O*-(4,6-*O*-isoplropylidene-α-*D*-glucopyranosyl)*-aldehydo-*D*-*glucose dimethyl acetal* (**1**) *and 4-*O*-α-*D*-glucopyranosyl-2,3:5,6-di-*O*-isopropylidene*-aldehydo-*D*-*glucose dimethyl acetal*. — Compound **1** was prepared by the method of Ueno *et al.*[7]. Maltose monohydrate was dehydrated azeotropically with toluene, followed by heating at 45–60° under diminished pressure. To a solution of anhydrous maltose (11.5 g, 36 mmol) in 1,4-dioxane (100 mL) were added 2,2-dimethoxypropane (40 mL, 0.33 mol) and *p*-toluenesulfonic acid (100 mg), and the mixture was stirred for 20 h at 80°. Concentrated ammonia was added dropwise until the solution was neutral (pH paper), and the solvents were evaporated. The residue was chromatographed (1:1 ethyl acetate–hexane) to give, first, **1** as oily crystals (9 g, 18 mmol, 51%). N.m.r. data: ^{1}H, δ 5.08 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), 4.42 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1), 4.28–3.19 (m, 13 H, H-2,3,4,5,6a,6b,2',3',4',5',6'a,6'b and OH), 3.46–3.44 (2 s, 6 H, 2 OMe), 1.51, 1.46, 1.43, 1.35 (4 s, 18 H, 3 CMe_2); ^{13}C, δ 110.2, 109.1 (CMe_2), 105.8 (C-1), 101.4 (C-1'), 99.9 (4',6'-CMe_2), 66.5 (C-6), 64.4 (C-6'), 62.5 (C-5'), 56.8, 54.2 (OMe), 29.3, 27.5, 27.3, 26.6, 25.2, 19.4 (CMe_2).

Further elution with ethyl acetate provided the second title product (3 g, 6 mmol; 17%) as oily crystals. ^{1}H-n.m.r. data: δ 5.1 (d, 1 H, $J_{1',2'}$ ~4 Hz, H-1'), 4.4–3.4 (m, 13 H, H-1,2,3,4,5,6a,6b,2',3',4',5',6'a,6'b), 3.46, 3.43 (2 s, 6 H, 2 OMe), ~3.3 (b, 1 H, OH), 2.2 (b, 1 H, OH), 1.44, 1.42, 1.39, 1.30 (4 s, 12 H, 2 CMe_2).

*4-*O*-(3-*O*-tert-Butyldimethylsilyl-4,6-*O*-isopropylidene-α-*D*-glucopyranosyl)-2,3:5,6-di-*O*-isopropylidene*-aldehydo-*D*-*glucose dimethyl acetal* (**2**) *and its 2'-acetate*. — To a solution of compound **1** (12 g, 24 mmol) and imidazole (4.0 g, 60 mmol) in *N*,*N*-dimethylformamide (25 mL) at 0° was added *tert*-butyldimethylsilyl chloride (4.1 g, 2.7 mmol), and the mixture was left for 5 h with gradual warming to room temperature. Ice and water were added, followed by extraction with ether (3 × 70 mL), the extract was dried, filtered, and concentrated, and the residue was chromatographed (1:4 ethyl acetate–hexane) to give syrupy **2** (12 g, 19 mmol, 80%), $[\alpha]_D^{20}$ +75° (*c* 2, chloroform). In repeat preparations, the crude residue was suitable for oxidation after a solution in 1:4 ethyl acetate–hexane had been filtered through silica gel.

Compound **2** (50 mg, 0.1 mmol) was acetylated, and the product was chromatographed (1:4 ethyl acetate–hexane) to give the syrupy 2'-acetate (60 mg, 0.09 mmol), $[\alpha]_D^{20}$ +42° (*c* 6.4, chloroform). ^{1}H-N.m.r. data: δ 5.10 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1'), 4.82 (dd, 1 H, $J_{2',3'}$ 9.7 Hz, H-2'), 4.31 (d, 1 H, $J_{1,2}$ 5.7 Hz, H-1), 4.25–3.4 (11 H, H-2,3,4,5,6a,6b,3',4',5',6'a,6'b), 3.44 (s, 6 H, 2 OMe), 2.13 (s, 3 H, OAc), 1.46, 1.38, 1.35 (4 s, 18 H, 3 CMe_2), 0.85 (s, 9 H, Si^{t}Bu), 0.06, 0.03 (2 s, 6 H, $SiMe_2$). E.i.-mass spectrum: *m/z* 649 [(M^+ − Me), 100%], 607 [(M^+ − ^{t}Bu), 15].

Anal. Calc. for $C_{31}H_{56}O_{13}Si$: C, 56.00; H, 8.49 Found: C, 55.62; H, 8.16.

*4-*O*-(3-*O*-tert-Butyldimethylsilyl-4,6-*O*-isopropylidene-α-*D*-*arabino*-hexopyranosyl-2-ulose)-2,3:5,6-di-*O*-isopropylidene*-aldehydo-*D*-*glucose dimethyl acetal* (**3**). — To

a solution of **2** (5 g, 7.5 mmol) in benzene (200 mL) was added finely ground pyridinium chlorochromate (3 g, 14 mmol) and potassium acetate (1 g). The mixture was heated under reflux for 2 h, recharged with oxidant until no change was observed in t.l.c. (1:2 ethyl acetate–hexane), then filtered, and concentrated. The residue was chromatographed (1:4 ethyl acetate–hexane) to give **3** (3.2 g, 5.1 mmol; 68%), $[\alpha]_D^{20}$ +26.5° (*c* 2.5, chloroform). ^{1}H-N.m.r. data: δ 5.04 (s, 1 H, H-1′), 4.65 (d, 1 H, $J_{3',4'}$ 10 Hz, H-3′), 4.43 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1), 3.43, 3.42 (2 s, 6 H, 2 OMe), 1.47, 1.41, 1.37, 1.26 (4 s, 18 H, 3 CMe_2), 0.90 (s, 9 H, Si^{t}Bu), 0.12, 0.04, (2 s, 6 H, $SiMe_2$).

4-O-(*3*-O-tert-*Butyldimethylsilyl-2-deoxy-2-hydroxyimino-4,6*-O-*isopropylidene*-α-D-arabino-*hexopyranosyl)-2,3:5,6-di*-O-*isopropylidene*-aldehydo-D-*glucose dimethyl acetal* (**4**). — To a solution of **3** (240 mg, 0.39 mmol) in methanol (7 mL) was added a 1:2:10 mixture of hydroxylamine hydrochloride, sodium acetate, and water (3 mL, buffered to pH 4.5 with acetic acid). After 4 h, the methanol was evaporated, the aqueous residue was extracted with chloroform (4 ×), and the extract was washed with aqueous sodium hydrogen carbonate and water, dried, and concentrated. The residue was chromatographed (1:4 ethyl acetate–hexane) to give **4** (243 mg, 0.38 mmol; 97%) as a clear syrup, $[\alpha]_D^{20}$ +44° (*c* 3.1, chloroform). ^{1}H-N.m.r. data: δ 6.14 (s, 1 H, H-1′), 4.53 (d, 1 H, $J_{3',4'}$ 8.4 Hz, H-3′), 4.5–3.6 (m, 11 H, H-1,2,3,4,5,6a,6b,4′,5′,6a′,6b′), 3.43, 3.41 (2 s, 6 H, 2 OMe), 1.47, 1.46, 1.42, 1.39, 1.37, 1.31 (6 s, 18 H, 3 CMe_2), 0.90 (s, 9 H, Si^{t}Bu), 0.10, 0.07 (2 s, 6 H, $SiMe_2$). F.a.b.-mass spectrum (glycerol): *m/z* 636 [$(M+H)^+$, 100%], 6.20 [$(M^+ - Me)$, 98], 578 [$(M - {}^tBu)$, 43].

4-O-(*3*-O-tert-*Butyldimethylsilyl-2-deoxy-4,6*-O-*isopropylidene-2-methoxyimino*-α-D-arabino-*hexopyranosyl)-2,3:5,6-di*-O-*isopropylidene*-aldehydo-D-*glucose dimethyl acetal* (**5**). — A solution of compound **4** (506 mg, 0.8 mmol) in tetrahydrofuran (5 mL) was added to a suspension of sodium hydride (50 mg, 2 mmol) in tetrahydrofuran (5 mL) at 0°. After 10 min, methyl iodide was added, and the mixture was then held at room temperature for a total reaction time of 4 h. Wet tetrahydrofuran was added to destroy the excess of sodium hydride, followed by water, and the mixture was extracted with chloroform. The extract was washed with water, dried, and concentrated. The residue was chromatographed (1:6 ethyl aceate–hexane) to give **5** as a clear syrup (440 mg, 0.68 mmol; 85%), $[\alpha]_D^{20}$ +46° (*c* 2.1, chloroform). ^{1}H-N.m.r. data: δ 5.92 (s, 1 H, H-1′), 4.49 (d, 1 H, $J_{3',4'}$ 9.4 Hz, H-3′), 3.89 (s, 3 H, NOMe), 4.38–3.45 (m, 11 H, H-1,2,3,4,5,6a,6b,4′,5′,6a′,6b′), 3.44 (s, 6 H, 2 OMe), 1.46, 1.45, 1.42, 1.39, 1.36, 1.30 (6 s, 18 H, 3 CMe_2), 0.91 (s, 9 H, Si^{t}Bu), 0.13, 0.07 (2 s, 6 H, $SiMe_2$). F.a.b.-mass spectrum (thioglycerol): *m/z* 650 [$(M+H)^+$, 100%], 592 [$(M - {}^tBu)$, 88].

4-O-(*2-Amino-2-deoxy-4,6*-O-*isopropylidene*-α-D-*gluco*-(**6**) *and* -D-*manno-pyranosyl)-2,3:5,6-di*-O-*isopropylidene*-aldehydo-D-*glucose dimethyl acetal* (**7**). — A solution of **5** (4.2 g, 6.5 mmol) in tetrahydrofuran (50 mL) was slowly added to a suspension of lithium aluminium hydride (1.2 g) in tetrahydrofuran (100 mL) at 0°, and the mixture was then slowly heated to 65°. After 18 h, unreacted hydride was decomposed by the addition of ethyl acetate, ethanol, and water in succession, and the white slurry was filtered. The filtrate was concentrated and the aqueous solution was extracted with chloroform (5 × 100 mL). The extrect was washed with water, dried, and concentrated.

Chromatography (2.5% methanol in chloroform) of the residue gave a syrupy mixture of **6** and **7** (2.0 g, 3.9 mmol, 60%). ^{1}H-N.m.r. data: δ ~5.12 (d, 1 H, $J_{1',2'}$ <1 Hz, Man H-1'), 5.05 (d, 1 H, $J_{1',2'}$ 3.8 Hz, Glc H-1'), 3.46, 3.45 (2 s, 6 H, 2 OMe), 1.51, 1.48, 1.43, 1.41, 1.36 (5 s, 18 H, 3 CMe_2).

*4-O-(2-Acetamido-2-deoxy-4,6-O-isopropylidene-α-*D*-gluco-* (**8**) *and -*D*-manno-pyranosyl)-2,3:5,6-di-O-isopropylidene-*aldehydo-D*-glucose dimethyl acetal.* — Acetic anhydride (0.5 mL, 4.9 mmol) was added to a stirred solution of **6**,**7** (1.8 g, 3.5 mmol) in methanol (100 mL). After 2 h, the solvents were removed and the residue was chromatographed (2.5% methanol in chloroform) to give, first, the *gluco* isomer **8** (1.66 g, 3.0 mmol, 86%), followed by the *manno* isomer (200 mg, 0.36 mmol; 10%). N.m.r. data: ^{1}H, δ 4.97 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), 4.38 (d, 1 H, $J_{1,2}$ 6.1 Hz, H-1), ~4.15 (m, H-2'), 3.46, 3.44 (2 s, 6 H, 2 OMe), 2.07 (s, 3 H, NAc), ~1.8 (b, OH), 1.52, 1.48, 1.46, 1.45, 1.42, 1.35 (6 s, 18 H, 3 CMe_2); ^{13}C, δ 172.17 (N*C*OCH$_3$), 110.60, 108.89, (*C*Me$_2$), 105.43 (C-1), 99.70 (C-1'), 98.44 (*C*Me$_2$), 79.88 (C-4), 78.58 (C-3), 76.81, 74.90, 74.66 (C-2,5,4'), 71.01 (C-3'), 65.72 (C-6), 63.75 (C-6'), 61.89 (C-5'), 56.64, 54.67 (OMe), 54.49 (C-2'), 22.90 (NCO*C*H$_3$), 28.98, 27.42, 26.29, 24.92, 19.07 (C*Me*$_2$). F.a.b.-mass spectrum (glycerol): *m/z* 550 [(M + H)$^+$, 44%].

Anal. Calc. for $C_{25}H_{43}NO_{12}\cdot H_2O$: C, 52.90; H, 7.99; N, 2.47. Found: C, 52.76; H, 8.08; N, 2.35.

^{1}H-N.m.r. data for the *manno* isomer: δ 5.13 (s, 1 H, H-1'), 4.42 (d, 1 H, $J_{1,2}$ 6.2 Hz, H-1), 3.46, 3.44 (2 s, 6 H, 2 OMe), 2.77 (bs, 1 H, OH), 2.08 (s, 3 H, NAc), 1.64, 1.55, 1.49, 1.43, 1.36 (5 s, 18 H, 3 CMe_2).

*4-O-(2-Acetamido-3-O-benzyl-2-deoxy-4,6-O-isopropylidene-α-*D*-glucopyranosyl)-2,3:5,6-di-O-isopropylidene-*aldehydo-D*-glucose dimethyl acetal* (**9**). — A solution of **8** (1.25 g, 2.3 mmol) in tetrahydrofuran (20 mL) was added to a stirred suspension of sodium hydride (125 mg) in tetrahydrofuran (20 mL) at 0°. After 10 min, benzyl bromide (0.4 mL, 3.4 mmol) and tetrabutylammonium bromide (~10 mg) were added, and the mixture was stirred for 12 h. After the addition of ethanol, the solvents were removed, and a solution of the residue in chloroform was washed with water, dried, and concentrated to give a syrup. Chromatography (2:1 ethyl acetate–hexane) provided **9** (1.15 g, 1.8 mmol, 78%), $[\alpha]_D^{20}$ +79° (*c* 2.1, chloroform). N.m.r. data: ^{1}H, δ 7.31 (s, 5 H, Ph), 5.84 (d, 1 H, $J_{NH,2'}$ 9.7 Hz, N*H*Ac), 4.90 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), 4.87, 4.81, 4.61, 4.55 (AB, 2 H, PhC*H*$_2$), 4.32 (d, 1 H, $J_{1,2}$ 6.6 Hz, H-1), 4.28 (ddd, 1 H, $J_{2',3'}$ 8.3, $J_{2',NH}$ 10 Hz, H-2'), 4.23 (dd, 1 H, $J_{3,2}$ 5.9, $J_{3,4}$ 2.7 Hz, H-3), 4.19 (ddd, 1 H, $J_{5,4} = J_{5,6a} = J_{5,6b} = 6.1$ Hz, H-5), 4.04 (dd, 1 H, H-6b), 3.96 (dd, 1 H, $J_{6a,5}$ 6.1 Hz, H-6a), 3.93 (dd, 1 H, H-2), 3.84–3.73 (m, 4 H, H-4',5',6a',6b'), 3.68 (dd, 1 H, H-4), 3.49 (dd, 1 H, $J_{3',4'}$ 10.5 Hz, H-3'), 3.41, 3.38 (2 s, 6 H, 2 OMe), 1.94 (s, 3 H, NAc), 1.50, 1.46, 1.43, 1.40, 1.35, 1.30 (6 s, 18 H, 3 CMe_2); ^{13}C, δ 170.08 (N*C*OCH$_3$), 139.4–128 (Ph), 110.79, 109.09 (*C*Me$_2$), 105.77 (C-1), 101.17 (C-1'), 99.72 (*C*Me$_2$), 80.45 (C-4), 78.85 (C-3), 76.95 (C-2), 76.56 (C-3'), 75.55 (C-4',5), 73.81 (Ph*C*H$_2$), 66.62 (C-6), 64.52 (C-6'), 62.53 (C-5'), 56.68, 54.70 (OMe), 52.70 (C-2'), 23.32 (NCO*C*H$_3$), 29.36, 27.60, 27.56, 26.62, 25.18, 19.33 (C*Me*$_2$). F.a.b.-mass spectrum (glycerol): *m/z* 640 [(M + H)$^+$, 100%], 624 [(M$^+$ − Me), 23].

Anal. Calc. for $C_{32}H_{49}NO_{12}$: C, 60.08; H, 7.72. Found: C, 59.85; H, 7.74.

4-O-(2-Acetamido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-2,3:5,6-di-O-isopropylidene-aldehydo-D-*glucose dimethyl acetal* (**10**). — A solution of **9** (10.5 g, 16.4 mmol) and pyridinium *p*-toluenesulfonate (25 mg) in methanol (125 mL) was stirred for 8 h. A few drops of ammonium hydroxide were added to neutralise the solution, the solvent was removed, and the residue was chromatographed (3% methanol in chloroform) to give **10** (7.0 g, 12 mmol; 73%), $[\alpha]_D^{20}$ +88° (*c* 0.7, chloroform). ^{13}C-N.m.r. data: δ 138.2–128.0 (Ph), 110.40, 108.76 (CMe_2), 105.65 (C-1), 99.98 (C-1'), 79.63 (C-4), 78.55 (C-3), 73.8 (PhCH_2), 72.73, 70.74 (C-5,5'), 65.51 (C-6), 62.39 (C-6'), 56.92, 54.72 (OMe), 52.37 (C-2'), 27.30, 27.24, 26.01, 24.47 (CMe_2), 23.19. F.a.b.-mass spectrum (glycerol): *m/z* 600 [(M+H)$^+$, 40%].

Further elution (1:10 methanol, chloroform) afforded the 2,3-*O*-isopropylidene derivative (1.3 g, 2.3 mmol; 14%), $[\alpha]_D^{20}$ +57° (*c* 3.2, chloroform). ^{13}C-N.m.r. data: δ 170.56 ($NCOCH_3$), 139.03–128.11 (Ph), 110.90 (CMe_2), 105.73 (C-1), 101.08 (C-1'), 82.93 (C-4), 80.24, 78.93, 77.89, 74.55, 73.64, 73.60, 71.45 (C-2,3,5,3',4',5' and PhCH_2), 63.41 (C-6), 62.37 (C-6'), 56.91 (OMe), 55.17, 52.87 (C-2'), 27.58 (CMe_2), 23.29 ($NCOCH_3$). F.a.b.-mass spectrum (diethanolamine): *m/z* 665 [(M+DEAH)$^+$].

4-O-(2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl-2,3:5,6-di-O-isopropylidene-aldehydo-D-*glucose dimethyl acetal* (**11**). — A solution of **10** (1.24 g, 2.07 mmol) in tetrahydrofuran (10 mL) was added to a stirred suspension of sodium hydride (200 mg) in tetrahydrofuran (20 mL). After 10 min, allyl bromide (0.43 mL, 5 mmol) was added and the mixture was heated for 18 h at 60°. Ethanol was added, the mixture was neutralised with aqueous 5% hydrogen chloride and concentrated, and a solution of the residue in chloroform was washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated. Chromatography (1% methanol in chloroform) gave **11** (1.07 g, 1.6 mmol; 76%), $[\alpha]_D^{20}$ +66° (*c* 0.9, chloroform). N.m.r. data: ^{1}H, δ 7.3 (Ph), 6.0–5.8, 5.3–5.1 (m, 7 H, CH_2=CHCH_2O and NHAc), 4.92 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1'), 4.83, 4.80, 4.67, 4.58 (AB, 2 H, PhCH_2), 4.33 (d, 1 H, $J_{1,2}$ 6.6 Hz, H-1), 4.31–3.96 (m, 9 H, H-3,5,6a,6b,2', CH_2=CHCH_2O), 3.95 (dd, 1 H, $J_{2,3}$ 6 Hz, H-2), 3.83, 3.41 (2 s, 6 H, 2 OMe), 1.88 (s, 3 H, NAc), 1.41, 1.35 (2 s, 6 H, CMe_2); ^{13}C, δ 170.13 ($NCOCH_3$), 134.70, 134.45 (CH_2=CHCH$_2$O), 127.13 (Ph), 117.09, 116.91 (CH_2=CHCH$_2$O), 110.57, 108.94 (CMe_2), 105.09 (C-1), 100.73 (C-1'), 80.60 (C-4), 79.58 (C-3'), 78.40 (C-3), 78.03 (C-4'), 76.29 (C-2), 75.25 (C-5), 74.69 (PhCH_2), 73.71, 72.47 (CH_2=CHCH$_2$O), 71.55 (C-5'), 68.25 (C-6'), 66.73 (C-6), 56.30, 54.11 (OMe), 52.52 (C-2'), 27.47, 26.58, 25.07 (CMe_2), 23.18 ($NCOCH_3$). F.a.b.-mass spectrum (diethanolamine): *m/z* 786 [(M + DEAH)$^+$, 13.7%], 680 [(M + H)$^+$, 4.7].

4-O-(2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-2,3-O-isopropylidene-aldehydo-D-*glucose dimethyl acetal* (**12**). — Compound **11** (170 mg, 0.25 mmol) was hydrolysed with aqueous 80% acetic acid for 5 h at 40°. Chromatography (ethyl acetate) of the product gave **12** (106 mg, 0.17 mmol; 68%), $[\alpha]_D^{20}$ +57° (*c* 1.3, chloroform). N.m.r. data: ^{1}H, δ 7.32–7.26 (Ph), 5.98–5.84, 5.33–5.16 (m, 7 H, NHAc and 2 CH_2=CHCH$_2$O), 4.86 (d, 1 H, $J_{1',2'}$ 4.2 Hz, H-1') 4.83, 4.80, 4.64, 4.60 (AB, 2 H, PhCH_2), 4.34 (d, 1 H, $J_{1,2}$ 5.9 Hz, H-1), 4.27 (dd, 1 H, $J_{3,2}$ 5.9, $J_{3,4}$ 4.4 Hz, H-3), 4.34–4.23

(m, 2 H, H-2′ and $CH_2=CHCH_2O$), 3.98 (dd, 1 H, $J_{2,1} = J_{2,3} = 5.9$ Hz, H-2), 4.34–3.96 (m, 4 H, H-5 and $CH_2=CHCH_2O$), 3.57 (dd, 1 H, $J_{3',2'} = J_{3',4} = 10.3$ Hz, H-3′), 3.44, 3.41 (2 s, 6 H, OMe), 3.8–3.3 (m, 7 H, H-4, 6a,6b,4′,5′,6′a,6′b), 1.87 (s, 3 H, NAc), 1.41, 1.36 (2 s, 6 H, CMe_2); ^{13}C, δ 170.05 ($NCOCH_3$), 138.28–127.8 (Ph, $CH_2=CHCH_2O$), 117.68, 117.39 ($CH_2=CHCH_2O$), 110.72 (CMe_2), 105.07 (C-1), 101.23 (C-1′), 84.38 (C-4), 80.10 (C-3′), 78.51 (C-3), 78.37 (C-4′), 77.45 (C-2), 74.87 ($PhCH_2$), 73.83, 73.08 ($CH_2=CHCH_2O$), 72.53 (C-5′), 72.09 (C-5), 68.97 (C-6′), 62.98 (C-6), 56.68, 54.68 (OMe), 52.64 (C-2′), 27.44 (CMe_2), 23.24 ($NCOCH_3$).

Anal. Calc. for $C_{32}H_{49}NO_{12}\cdot H_2O$: C, 58.43; H, 8.04; N, 2.13. Found: C, 58.30; H, 7.95; N, 2.10.

4-O-(2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-5,6-di-O-acetyl-2,3-O-isopropylidene-aldehydo-D-*glucose dimethyl acetal* (**13**). — A portion of **12** was acetylated to give, after chromatography (2:1 ethyl acetate–hexane), **13**, $[\alpha]_D^{20}$ +75° (*c* 0.5, chloroform). ^{13}C-N.m.r. data: δ 170 ($COCH_3$), 135–130 ($PhCH_2$ and $CH_2=CHCH_2O$), 117.19, 117.09 ($CH_2=CHCH_2O$), 110.66 (CMe_2), 104.79 (C-1′), 99.87 (C-1), 80.57 (C-4), 79.42 (C-3′), 77.87 (C-4′), 78.49 (C-2,3), 76.66, 74.80 ($PhCH_2$), 73.91, 72.52 (CH_2CHCH_2O), 72.12 (C-5′), 71.94 (C-5), 68.33 (C-6′), 62.29 (C-6), 56.90, 53.62 (OMe), 52.60 (C-2′), 27.37 (CMe_2), 27.10, 23.32, 21.21, 20.84 ($NCOCH_3$, $OCOCH_3$). F.a.b.-mass spectrum (diethanolamine): *m/z* 829 [(M + DEAH)$^+$, 3.8%].

Anal. Calc. for $C_{36}H_{53}NO_{14}$: C, 59.74; H, 7.38; N, 1.94. Found: C, 59.34; H, 7.58; N, 1.83.

4-O-(2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-2,3-O-isopropylidene-5,6-di-O-methanesulfonyl-aldehydo-D-*glucose dimethyl acetal* (**14**). — A solution of **12** (300 mg, 0.47 mmol) in dichloromethane (5 mL) was added to a stirred solution of methanesulfonyl chloride (0.1 mL, 1.3 mmol) and pyridine (1 mL) in dichloromethane (10 mL). After 3 h, the solution was poured onto an ice–water mixture and extracted with chloroform, and the extract was washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated. Chromatography (2:1 ethyl acetate–hexane) of the residue gave syrupy **14** (277 mg, 0.35 mmol; 74%). ^1H-N.m.r. data: δ 7.30 (Ph), 6.0–5.8, 5.28–5.1 (m, 6 H, 2 $CH_2=CHCH_2O$), 5.52 (d, 1 H, $J_{NH,2'}$ 9 Hz, NHAc), ~5.03 (m, 1 H, H-5), 5.03 (d, 1 H, $J_{1',2'}$ 3.4 Hz, H-1′), 4.81, 4.77, 4.62, 4.58 (AB, 2 H, $PhCH_2$), 4.57 (dd, 1 H, $J_{6b,5}$ 2.4, $J_{6b,6a}$ 11.7 Hz, H-6b), 4.34 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 4.36–4.3 (H-6a), 3.44, 3.37 (2 s, 6 H, 2 OMe), 3.06, 3.04 (2 s, 6 H, 2 MsO), 180 (s, 3 H, NAc), 1.33, 1.29 (2 s, 6 H, CMe_2).

4-O-(2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-5,6-di-O-acetyl-2,3-O-isopropylidene-aldehydo-L-*idose dimethyl acetal* (**15**). — A solution of **14** (230 mg, 0.28 mol) and potassium acetate (200 mg) in acetic anhydride (8 mL) was heated for 20 h at 120°, then concentrated under high vacuum. A solution of the black residue in ethyl acetate was washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated to give a crude syrup. Chromatography (1:1 ethyl acetate–hexane) then gave **15** as an oil, $[\alpha]_D^{20}$ +49° (*c* 1.5, chloroform). N.m.r. data: ^1H, δ 7.33 (Ph), 6.0–5.85 (m, 2 H, 2 $CH_2=CHCH_2O$), 5.52 (d, 1 H, $J_{NH,2'}$ 9.0 Hz, NHAc), ~5.28 (m, 1 H, H-5), 5.32–5.14 (m, 4 H, 2 $CH_2=CHCH_2O$), 4.94 (d, 1 H, $J_{1',2'}$ 3.9 Hz,

H-1'), 4.86, 4.82, 4.63, 4.59 (AB, 2 H, PhCH_2), 4.39 (dd, 1 H, $J_{6b,5}$ 2.7, $J_{6a,6b}$ 12.5 Hz, H-6b), 4.30 (d, 1 H, $J_{1,2}$ 6.4 Hz, H-1), 4.29 (dd, 1 H, $J_{6a,5}$ 7.3, $J_{6a,6b}$ 12.7 Hz, H-6a), 4.17 (dd, 1 H, $J_{3,2}$ 6.3, $J_{3,4}$ 2.3 Hz, H-3), 4.2–4.12 (m, 1 H, H-2'), 4.36–3.94 (m, 4 H, 2 CH_2=CHCH_2O), 3.88 (dd, 1 H, H-2), 3.82 (ddd, 1 H, $J_{5',4'}$ 10, $J_{5',6'a}$ 2.2, $J_{5',6'b}$ 2.7 Hz, H-5'), 3.72 (dd, 1 H, $J_{6'b,5'}$ 3.2, $J_{6'b,6'a}$ 10.7 Hz, H-6'b), 3.70 (dd, 1 H, $J_{4,3}$ 2.2, $J_{4,5}$ 5.4 Hz, H-4), 3.66 (dd, 1 H, $J_{4',3'}$ 9 Hz, H-4'), 3.63 (dd, 1 H, H-6'a), 3.56 (dd, 1 H, $J_{3',2'}$ 10.5, $J_{3',4'}$ 8.8 Hz, H-3'), 3.39, 3.36 (2 s, 6 H, 2 OMe), 2.07, 2.03, 1.81 (3 s, 9 H, NAc and 2 OAc), 1.38 (2 s, 6 H, CMe_2), 1.33; ^{13}C, δ 134.6–128 (*Ph*CH_2, CH_2=*C*HCH_2O), 116.96, 116.88 (*C*H_2=CHCH_2O), 110.71 (*C*Me_2), 105.09 (C-1), 100.76 (C-1'), 79.16 (C-3'), 77.89 (C-4'), 76.70 (C-3), 76.61 (C-2), 74.51 (PhCH_2), 74.51, 73.71 (CH_2=CHCH_2O), 72.04 (C-5,5'), 68.02 (C-6'), 63.25 (C-6), 56.43, 54.21 (OMe), 52.74 (C-2'), 27.38, 27.30 (C*Me*$_2$), 23.08, 20.96, 20.79 (OCO*C*H_3, NCO*C*H_3). F.a.b.-mass spectrum (diethanolamine): *m/z* 829 [(M + DEAH)$^+$, 4.3%].

4-O-(2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-2,3-O-isopropylidene-aldehydo-L-*idose dimethyl acetal* (**16**). — Compound **15** was *O*-deacetylated with sodium methoxide in methanol to provide, after chromatography (ethyl acetate), syrupy **16**, $[\alpha]_D^{20}$ +56° (*c* 2.4, chloroform). ^{13}C-N.m.r. data: δ 138.78–127.79, 117.55, 117.33 (*C*H_2=*C*HCH_2O, Ph), 110.59 (*C*Me_2), 105.36 (C-1), 100.52 (C-1'), 82.59 (C-4), 79.84 (C-3'), 78.43 (C-4'), 77.54 (C-3), 77.27 (C-2), 74.79 (PH*C*H_2), 73.83 (CH_2=CH*C*H_2O), 72.51, 71.96 (C-5'), 71.69 (C-5), 68.97 (C-6'), 62.25 (C-6), 56.68, 54.95 (OMe), 52.66 (C-2'), 27.41, 27.34 (C*Me*$_2$), 23.15 (NCO*C*H_3). F.a.b.-mass spectrum (diethanolamine): *m/z* 745 [(M + DEAH)$^+$, 11.8%], 6.40 [(M + H)$^+$, 3.5].

4-O-(2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-6-O-p-anisyldiphenylmethyl-2,3-O-isopropylidene-aldehydo-L-*idose dimethyl acetal* (**17**). — *p*-Anisyldiphenylchloromethane (463 mg, 1.5 mmol) was added to a solution of **16** (770 mg, 1.2 mmol) and 2,2'-dimethylaminopyridine (10 mg) in pyridine (3 mL) and dichloromethane (20 mL). After 8 h, the solvents were removed, and a solution of the residue in chloroform (20 mL) was washed with aqueous sodium hydrogencarbonate and water, dried, and evaporated. The residue was chromatographed (2:1 ethyl acetate–hexane) to give syrupy **17** (1.04 g, 1.14 mmol; 95%). ^{1}H-N.m.r. data: δ 7.48–6.83 (Ph), 5.94–5.89 (m, 2 H, CH_2=C*H*CH_2O), 5.80 (d, 1 H, $J_{NH,2'}$ 9 Hz, N*H*Ac), 5.35–5.15 (m, 4 H, 2 CH_2CHCH_2O), 4.95 (d, 1 H, $J_{1',2'}$ 3.2 Hz, H-1'), 4.84, 4.80, 4.62, 4.58 (AB, 2 H, PhCH_2), 3.79 (s, 3 H, PhO*Me*), 3.33, 3.23 (2 s, 6 H, 2 OMe), 1.85 (s, 3 H, NAc), 1.38, 1.27 (2 s, 6 H, CMe_2).

4-O-2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-6-O-p-anisyldiphenylmethyl-2,3-O-isopropylidene-5-O-levulinoyl-aldehydo-L-*idose dimethyl acetal* (**18**). — To a stirred solution of **17** (1.02 g, 1.2 mmol) and 2,2'-dimethylaminopyridine (10 mg) in tetrahydrofuran (30 mL) were added dicyclohexylcarbodi-imide (412 mg, 2 mmol) and levulinic acid (0.16 mL, 175 mg, 1.5 mmol). After 4 h, the solution was concentrated, and a solution of the residue in chloroform was washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated. The residue was chromatographed (2:1 ethyl acetate–hexane) to give **18** (1.16 g, 1.1 mmol; 92%), $[\alpha]_D^{20}$ +40.1° (*c* 2, chloroform). ^{13}C-N.m.r. data: δ 206.15 (Lv*C*O), 172.09, 170.09 (N*C*OCH$_3$ and

Lv*C*O$_2$), 110.00 (*C*Me$_2$), 104.99 (C-1), 99.83 (C-1′), 86.01 (Ph$_3$*C*), 77.81 (C-3′), 76.95, 76.92 (C-3,4′), 76.02 (C-2), 74.77 (C-5), 74.47 (Ph*C*H$_2$), 73.55, 72.38 (CH$_2$=CH*C*H$_2$O), 71.80 (C-5′), 68.08 (C-6′), 63.18 (C-6), 55.19 (PhO*Me*), 56.38, 53.76 (OMe), 52.75 (C-2′), 28.22 (C*Me*$_2$), 24.88, 23.08 (N*C*OCH$_3$ and Lv*C*H$_3$).

*4-O-(2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-*D*-glucopyranosyl)-2,3-O-isopropylidene-5-O-levulinoyl*-aldehydo-L-*idose dimethyl acetal* (**19**). — A solution of **18** (1.07 g, 1.06 mmol) in aqueous 80% acid (5 mL) was stirred at room temperature for 10 h. The solvents were evaporated and the residue was chromatographed (4:1 ethyl acetate–hexane) to give **19** (750 mg, 1.02 mmol; 96%), $[\alpha]_D^{20}$ +64° (*c* 2.3, chloroform). ^{1}H-N.m.r. data: δ 7.31 (m, 5 H, Ph), 6.0–5.78 (m, 2 H, 2 CH$_2$=C*H*CH$_2$O), 5.63 (d, 1 H, AcN*H*-2′), 5.64–5.15 (m, 4 H, 2 C*H*$_2$=CHCH$_2$O), 5.10 (d, 1 H, $J_{5,4}$ 4.4 Hz, H-5), 4.95 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1′), 4.83, 4.79, 4.62, 4.59 (AB, 2 H, PhC*H*$_2$), 4.32 (d, 1 H, $J_{1,2}$ 6.4 Hz, H-1), 4.23 (dd, $J_{3,2}$ 6.4, $J_{3,4}$ 2.9 Hz, H-3), 4.3–4.0 (m, 6 H, H-2′, H-3, and 2 CH$_2$=CHC*H*$_2$O), 4.2–4.0 (m, H-2′), 3.87 (dd, 1 H, $J_{2,1}$ = $J_{2,3}$ = 6.4 Hz, H-2), 3.8–3.75 (m, 4 H, H-4,6a,6b,5′), 3.61 (dd, 1 H, $J_{6'b,5'}$ ~5.5, $J_{6'b,6'a}$ 10.8 Hz, H-6′b), 3.59 (dd, 1 H, $J_{6'a,5'}$ ~2 Hz, H-6′a), 3.55 (dd, 1 H, $J_{3',2'}$ = $J_{3',4'}$ = 8.9 Hz, H-3′), 3.45 (dd, 1 H, $J_{4',5'}$ 8.9 Hz, H-4′), 3.40, 3.36 (2 s, 6 H, 2 OMe), ~2.7 (m, 4 H, Lv*C*H$_2$), 2.17 (s, 3 H, Lv*C*H$_3$), 1.83 (s, 3 H, NAc), 1.39, 1.33 (2 s, 6 H, CMe$_2$). F.a.b.-mass spectrum (diethanolamine): *m/z* 843 [(M + DEAH)$^+$, 14.7%], 738 [(M + H)$^+$, 2.8].

*Methyl 4-O-(2-Acetamido-4,6-di-O-allyl-3-O-benzyl-2-deoxy-α-*D*-glucopyranosyl)-2,3-O-isopropylidene-5-O-levulinoyl*-aldehydo-L-*iduronate dimethyl acetal* (**21**) *and the 6-aldehydo intermediate* (**20**). — To a solution of **19** (90 mg, 0.12 mmol) in methyl sulfoxide (1.5 mL) were added dicyclohexylcarbodi-imide (130 mg, 0.63 mmol) and pyridinium trifluoroacetate (10 mg), and the mixture was stirred for 6 h until t.l.c. (ethyl acetate) showed complete loss of **19** and the formation of a less polar compound. Water (5 mL) was added, the mixture was extracted with chloroform (5 × 20 mL), and the extract was washed with aqueous sodium hydrogencarbonate and water, dried, and concentrated. The crude syrupy aldehyde (**20**) was dissolved in 1,4-dioxane (5 mL) and 2M sulfamic acid (0.15 mL, buffered with potassium acetate to pH 3), and then 2M sodium chlorite (0.1 mL) was added. After 2 h, the solution was evaporated to dryness repeatedly with toluene, followed by the addition of dichloromethane (2 mL) and ethereal diazomethane (3 mL). After 2 h, the solvent was removed, and a solution of the residue in chloroform was washed successively with aqueous sodium hydrogencarbonate and water, dried, and concentrated. The syrupy residue was chromatographed (3:1 ethyl acetate–hexane) to give **21** (58 mg, 0.8 mmol; 67% from **19**), $[\alpha]_D^{20}$ +41° (*c* 1.9, chloroform). N.m.r. data: ^{1}H, δ 7.33–7.26 (m, Ph), 6.15 (d, 1 H, $J_{NH,2'}$ 9.3 Hz, N*H*Ac), 5.97–5.82 (m, 2 H, 2 CH$_2$=C*H*CH$_2$O), 5.32–5.09 (m, 5 H, H-5 and 2 C*H*$_2$=CHCH$_2$O), 5.26 (d, 1 H, $J_{5,4}$ ~2.0 Hz, H-5), 4.94 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1′), 4.85, 4.81, 4.67, 4.63 (AB, 2 H, PhC*H*$_2$), 4.34 (d, 1H, $J_{1,2}$ 5.1 Hz, H-1), 4.31 (dd, 1 H, $J_{3,2}$ 5.4, $J_{3,4}$ 6.3 Hz, H-3), 4.29–4.13 (m, 1 H, H-2′), 4.05 (dd, 1 H, $J_{4,5}$ 1.8 Hz, H-4), 3.94 (dd, 1 H, H-2), 3.74 (s, 3 H, CO$_2$Me), 3.83–3.63 (m, 4 H, H-4′,5′,6′a,6′b), 3.59 (dd, 1 H, $J_{3',2'}$ = $J_{3',4'}$ = 9.5 Hz, H-3′), 3.41, 3.37 (2 s, 6 H, 2 OMe), 2.8–2.7 (m, 4 H, Lv*C*H$_2$), 2.20 (s, 3 H, Lv*C*H$_3$), 1.90 (s, 3 H, NAc), 1.40, 1.35 (2 s, 6 H, CMe$_2$); ^{13}C, δ 206.15 (Lv*C*O), 171.34 (Lv*C*O$_2$), 169.90 (NAc),

167.91 (CO_2Me), 138.63–127.58 (Ph, $CH_2=CHCH_2O$), 116.99, 116.74 ($CH_2=CHCH_2O$), 104.67 (C-1), 101.29 (C-1'), 80.51 (C-4), 80.23 (C-3'), 77.88 (C-2), 77.61 (C-4'), ~77.4 (C-3), 74.77 ($PhCH_2$), 73.7, 72.39 ($CH_2=CHCH_2O$), 72.02 (C-5'), 71.19 (C-5), 56.83, 54.58 (OMe), 52.74 (C-2'), 52.59 (CO_2Me), 37.87, 29.79, 27.84 ($LvCH_2$ and $LvCH_3$), 27.47 (CMe_2), 34.37 ($NCOCH_3$). F.a.b.-mass spectrum (diethanolmine): *m/z* 871 [$(M + DEAH)^+$, 3%].

*Methyl 4-*O*-(2-acetamido-4,6-di-*O*-allyl-3-*O*-benzyl-2-deoxy-α-*D*-glucopyranosyl)-2,3-*O*-isopropylidene*-aldehydo-*L*-*iduronate dimethyl acetal* (**12**). — To a solution of the ester **21** (500 mg, 0.67 mmol) in 2:1 pyridine–acetic acid (5 mL) was added hydrazine hydrate (0.03 mL in 1 mL of 2:1 pyridine–acetic acid, 0.9 mmol), and the mixture was stirred for 10 min at room temperature. Acetone (15 mL) was added, stirring was continued for 20 min, then the solution was concentrated. An extract of the residue in ethyl acetate was filtered through a thin bed of silica gel and concentrated. The syrupy residue was chromatographed (2:1 ethyl acetate–hexane) to give **22** (345 mg, 0.52 mmol; 77%), $[\alpha]_D^{20}$ +48.4° (*c* 1.8, chloroform). ^{1}H-N.m.r. data: δ 4.91 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1'), 4.83, 4.79, 4.64, 4.60 (AB, 2 H, $PhCH_2$), 4.40 (bd, 1 H, $J_{5,4}$ ~2.0 Hz, H-5), 4.37 (d, 1 H, $J_{1,2}$ 5.4 Hz, H-1), 4.32 (dd, 1 H, $J_{3,2} = J_{3,4}$ = 6.1 Hz, H-3), 4.21 (ddd, 1 H, $J_{2',1'}$ 3.7, $J_{2',3'}$ 9.5, $J_{2',NH}$ 9.8 Hz, H-2'), 4.06 (dd, 1 H, H-2), 4.3–3.97 (m, 4 H, 2 $CH_2=CHCH_2O$), 3.95 (dd, 1 H, $J_{4,3}$ 6.3, $J_{4,5}$ 2.2 Hz, H-4), 3.79 (s, 3 H, CO_2Me), 3.76–3.5 (m, 5 H, H-3',4',5',6'a,6'b), 3.45, 3.43 (2 s, 6 H, 2 OMe). F.a.b.-mass spectrum (diethanolamine): *m/z* 668 [$(M + H)^+$, 20%].

*Methyl [methyl 4-*O*-(2-acetamido-4,6-di-*O*-allyl-3-*O*-benzyl-2-deoxy-α-*D*-gluco-pyranosyl-2,3-di-*O*-acetyl-α-* (**23**) *and -β-*L*-idopyranosid]uronate* (**24**). — Aqueous 90% trifluoroacetic acid (5 mL) was added to **22** (345 mg, 0.52 mmol). After 40 min, the solvent was removed by evaporation under high vacuum. The residue was chromatographed (2% then 4% methanol in chloroform) to give fraction I (60 mg, 0.1 mmol; 20%), which contained the free pyranose, and then fraction II (120 mg, 0.2 mmol; 40%), which contained a mixture of methyl glycosides. A portion of fraction I was acetylated to provide, after chromatography (1:1 ethyl acetate–hexane), an α,β-anomeric mixture of 1-acetates (**25**). Fraction II was acetylated and the anomers were separated by chromatography (1:1 ethyl acetate–hexane).

The α anomer **23** had $[\alpha]_D^{20}$ +32° (*c* 1.5, chloroform). N.m.r. data: ^{1}H, δ 7.3 (m, 5 H, Ph), 6.0–5.8 (m, 2 H, 2 $CH_2=CHCH_2O$), 5.53 (d, 1 H, $J_{NH,2'}$ 9.5 Hz, *H*NAc), 5.32 (dd, 1 H, $J_{3,2} = J_{3,4}$ = 6.6 Hz, H-3), 5.4–5.1 (m, 4 H, 2 $CH_2=CHCH_2O$), 4.99 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 4.88 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1'), 4.80 (dd, 1 H, H-2), 4.72 (d, 1 H, $J_{5,4}$ 5.1 Hz, H-5), 4.80, 4.76, 4.58, 4.55 (AB, 2 H, $PhCH_2$), 4.16 (ddd, 1 H, $J_{2',3'}$ 10 Hz, H-2'), 4.08 (dd, $J_{4,3}$ 6.7 Hz, H-4), 4.3–3.87 (m, 4 H, 2 $CH_2=CHCH_2O$), 3.82 (s, 3 H, CO_2Me), 3.75 (ddd, 1 H, $J_{5',4'}$ 9.8, $J_{5',6'a} = J_{5',6'b}$ = 3.2 Hz, H-5'), 3.63 (d, 2 H, H-6'a,6'b), 3.49 (dd, 1 H, $J_{4',3'}$ 9.8 Hz, H-4'), 3.42 (s, 3 H, OMe), 3.40 (dd, 1 H, $J_{3',2'}$ 10, $J_{3',4'}$ 9 Hz, H-3'), 2.03, 2.02, 1.88 (3 s, 9 H, 2 OAc and NAc); ^{13}C, δ 169.53, 169.43 (CO_2Me, OAc, $NCOCH_3$), 138.8, 116.3 (Ph, $CH_2=CHCH_2O$), 97.58 (C-1), 98.54 (C-1'), 80.52 (C-3'), 78.11 (C-4'), 75.25 ($PhCH_2$), 73.75, 72.46 ($CH_2=CHCH_2O$), 72.34 (C-5'), 71.92 (C-4), 70.73 (C-5), 69.89 (C-2), 69.36 (C-3), 68.85 (C-6'), 56.67 (OMe), 52.48 (CO_2Me), 52.25 (C-2'), 23.38, 20.88 ($OCOCH_3$ and $NCOCH_3$).

The β anomer **24** had $[\alpha]_D^{20}$ +92° (*c* 2.2, chloroform). N.m.r. data: ^{1}H, δ 7.3 (m, 5 H, Ph), 5.96–5.85 (m, 3 H, NHCOCH$_3$ and 2 CH$_2$=CHCH$_2$O), 5.59 (dd, 1 H, $J_{3,2} = J_{3,4}$ = 6.9 Hz, H-3), 5.34–5.12 (m, 4 H, 2 CH$_2$=CHCH$_2$O), 4.94 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), ~4.89 (m, 2 H, $J_{1,2}$ ~3.6 Hz, H-1,2), 4.80, 4.76, 4.61, 4.57 (AB, 2 H, PhCH$_2$), 4.50 (d, 1 H, $J_{5,4}$ 4.6 Hz, H-5), ~4.17 (m, 1 H, H-2'), 4.31–3.96 (m, 4 H, 2 CH$_2$=CHCH$_2$O), 3.98 (dd, 1 H, $J_{4,5}$ 4.2 Hz, H-4), 3.60 (d, 2 H, $J_{6',5'}$ 3 Hz, H-6'a,6'b), 3.58–3.4 (m, 3 H, H-3',4',5'), 3.39 (s, 3 H, OMe), 2.03, 2.01, 1.87 (3s, 9 H, 2 OAc and NAc); ^{13}C, δ 170.23, 170.11, 169.95, 168.88 (CO$_2$Me, OCOCH$_3$, and NCOCH$_3$), 138.85–115.91 (Ph and CH$_2$=CHCH$_2$O), 98.80 (C-1'), 98.63 (C-1), 80.67 (C-3'), 78.20 (C-4'), 75.31 (PhCH$_2$), 73.94, 73.69 (CH$_2$=CHCH$_2$O), 72.48 (C-5'), 72.35 (C-4), 71.59 (C-5), 70.17 (C-2), 68.88 (C-3), 68.57 (C-6'), 57.11 (OMe), 52.39, 52.35 (C-2', CO$_2$*Me*), 23.29, 20.99, 20.79 (COCH$_3$ and NCOCH$_3$). F.a.b.-mass spectrum (diethanolamine): *m/z* 785.3625 [(M + DEAH)$^+$] (Calc.: *m/z* 785.3717).

Methyl 4-O-(2-acetamido-4,6-di-O-acetyl-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-2,3,6-tri-O-acetyl-α,β-D-glucopyranoside (**28**). — Acetyl chloride (0.05 mL) was added to a solution of **9** (60 mg, 0.9 mmol) in methanol (30 mL). After 23 h, Amberlite IRA-400 (HO$^-$) resin was added, and the solution was filtered and concentrated to dryness. The residue was chromatographed (10% methanol in chloroform) to give **27** (36.6 mg, 83%), which was acetylated, and the product was chromatographed (1:1 ethyl acetate–hexane) to give **28** (49 mg, 0.7 mmol; 78%; α,β-ratio 2:1). ^{1}H-N.m.r. data: δ 4.87 (d, $J_{1,2}$ 3.7 Hz, H-1α), 4.81 (dd, $J_{2,1}$ 7.9, $J_{2,3}$ 9.6 Hz, H-2β), 4.76 (dd, $J_{2,1}$ 3.7, $J_{2,3}$ 10.4 Hz, H-2α), 4.44 (d, $J_{1,2}$ 7.9 Hz, H-1β), 4.38 (m, H-2α'), 3.62 (dd, 1 H, *J* 9.4 and 10.7 Hz, H-3α'), 3.48 (s, β-OMe), 3.41 (s, α-OMe), 2.14–1.68 (6 s, 18 H, 5 OAc and NAc).

Anal. Calc. for C$_{32}$H$_{43}$NO$_{16}$·H$_2$O: C, 53.70; H, 6.34. Found: C, 53.21; H, 6.33.

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