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Synthesis of 4-substituted-2-acetamido-2,4-dideoxy-mannopyranoses using 1,6-anhydro sugar chemistry ☆

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Abstract

The introduction of nitrogen, sulfur, and bromine substituents at C-4 of 2-acetamido-2-deoxy-D-mannopyranose has been readily achieved through opening of the 3,4-epoxide of 2-acetamido-1,6:3,4-dianhydro-2-deoxy-β-D-talopyranose.

Keywords: 1,6-Anhydro sugar; Azido sugar; Mannopyranose; Mitsunobu reaction

1. Introduction

The role of sialic acids in a wide range of biological processes, ranging from immunological events to cell recognition, has generated a great deal of interest in the chemistry of this class of carbohydrate in recent times [1–4]. Sialic acid, or *N*-acetylneuraminic acid, can be prepared enzymatically by the action of the enzyme Neu5Ac aldolase (*N*-acylneuraminate pyruvate lyase; EC 4.1.3.3) on 2-acetamido-2-deoxy-D-mannopyranose [5]. This enzyme has also been shown to convert other *manno* monosaccharides into modified sialic acids, both naturally occuring and unnatural [6–8].

We have been interested in the synthesis and biological activity of structurally modified sialic acids [8–11], and to this end we have undertaken the preparation of a range of compounds which may be substrates for Neu5Ac aldolase. As part of this work

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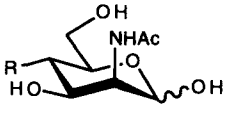
we required a straightforward route to C-4-substituted 2-acetamido-2-deoxy-D-mannopyranoses (**1**).

A variety of methods have been previously reported for the synthesis of 4-substituted hexopyranoses, in particular glucopyranoses and galactopyranoses [12–16]. The introduction of substituents at C-4 by all of these methods required selective protection chemistry and suitable activation of the 4-hydroxyl group by triflate formation [12], Mitsunobu chemistry [13] or 3,4-anhydro sugar formation [14]. Furthermore, the introduction of nitrogen at the C-4 position of glucopyranoses has also been achieved by nucleophilic attack at C-4 on the 1,6:3,4-dianhydro sugars **2** [15,16].



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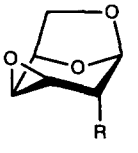


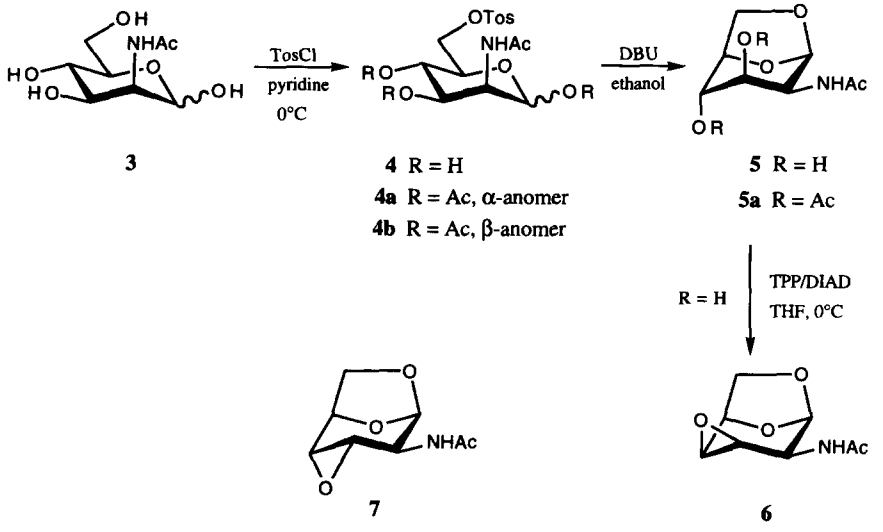
2

R = OBn [15]
R = OTos [15, 16]
R = N_3 [16]

A convenient synthesis of 4-substituted-2-acetamido-2,4-dideoxy-D-mannopyranoses is noticeably absent from the literature, and we required a number of analogues of this type. We found the prospect of using 1,6-anhydro sugar chemistry for the preparation of C-4-substituted D-mannopyranoses appealing because of its relative ease as well as its known increase in selectivity in subsequent reactions [17].

2. Results and discussion

The synthesis of the key intermediate, 2-acetamido-1,6:3,4-dianhydro-2-deoxy-β-D-talopyranose (**6**), was achieved according to Scheme 1. 2-Amino-1,6-anhydro-2-deoxy-β-D-mannopyranose has previously been prepared by internal substitution of a nitrogen functional group at C-2 through opening of a 2,3-aziridine ring [18] or a [2,3-*d*]oxazolidin-2-one [19]. We have prepared 2-acetamido-1,6-anhydro-2-deoxy-β-D-mannopyranose (**5**) directly from 2-acetamido-2-deoxy-D-mannopyranose (**3**) using known chemistry [20]. Reaction of the 6-*O*-tosylate of 2-acetamido-2-deoxy-D-mannopyranose (**4**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethanol gave **5** in good yield (77%). The 1,6-anhydro sugar was then treated, initially at 0°C, with triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran to yield the 3,4-epoxide with the D-*talo* configuration, **6**, in greater than 70% isolated yield. The alternative epoxide with the D-*altro* configuration, **7**, was not observed.

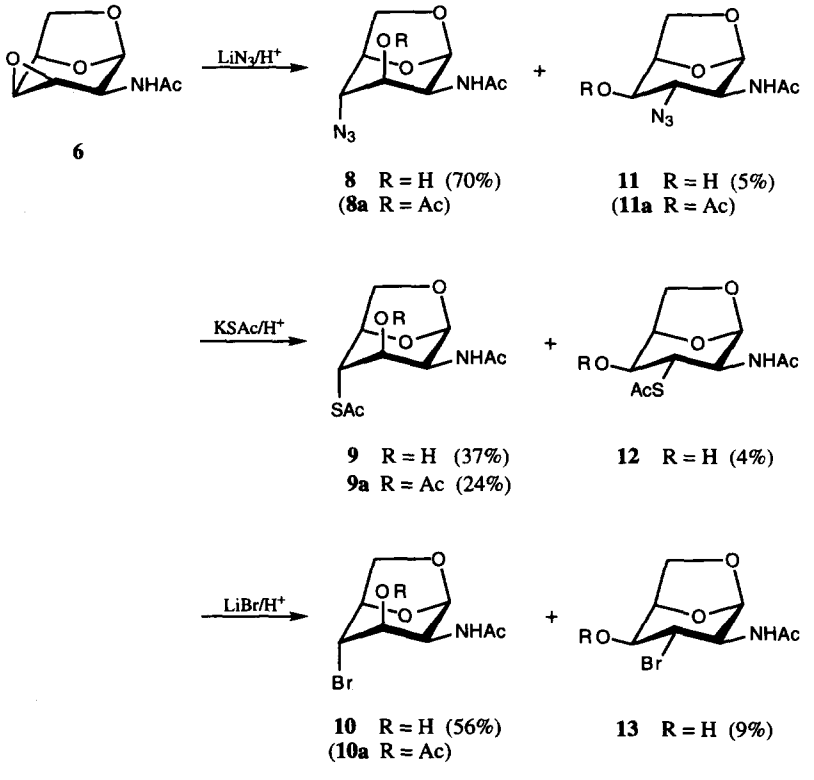


Scheme 1.

The introduction of nitrogen, sulfur and bromine at C-4 (Scheme 2) was readily achieved by treatment of **6** with azide, thioacetate and bromide, respectively, in good yield and with high regioselectivity. Thus, **8**, **9** and **10** were prepared by the treatment of **6** in *N*,*N*-dimethylformamide with lithium azide, potassium thioacetate or lithium bromide, respectively, in the presence of Dowex-50 resin (H^+). In each case, small amounts of the other regioisomer (**11**, **12**, **13**) resulting from the opening of the 3,4-epoxide at C-3 were observed by ^1H NMR spectroscopy. The preparation of **8** and **9** could also be achieved in acetone giving similar yields, but longer reaction times were required.

Acetolysis of the 3-*O*-acetylated derivatives of the 4-substituted-2-acetamido-1,6-anhydro-2,4-dideoxy-β-D-mannopyranoses **8a**, **9a**, and **10a** (Scheme 3) was carried out using acetic anhydride and trimethylsilyl triflate as previously described [21] to yield the corresponding α and β peracetates **14a,b**, **15a,b**, and **16a,b**, respectively, in greater than 70% isolated yield. Under these conditions we also observed, not unexpectedly, some formation of the oxazoline analogues **17–19.** The 4-azido substituted sugar **14a,b** was deprotected under acidic conditions to give the free sugar **20** in 46% yield. Removal of the 3-*O*-acetate proved to be difficult and required long reaction times or elevated temperatures, which may have led to some *N*-deacetylation and, subsequently, the low yield. Base-catalysed deacetylation was avoided because of the risk of epimerisation at C-2.

We have found that access to a number of 4-substituted-2-acetamido-2,4-dideoxy-D-mannopyranoses is possible via 1,6-anhydro sugar chemistry. These analogues are prepared in good yield and should provide some useful templates for further manipulation. Indeed 4-substituted 1,6-anhydro sugars may be useful as glycosyl donors in a reiterative strategy for the stereospecific synthesis of α-linked ManNAc-containing



6

8 R = H (70%) (**8a** R = Ac)

11 R = H (5%) (**11a** R = Ac)

9 R = H (37%) **9a** R = Ac (24%)

12 R = H (4%)

10 R = H (56%) (**10a** R = Ac)

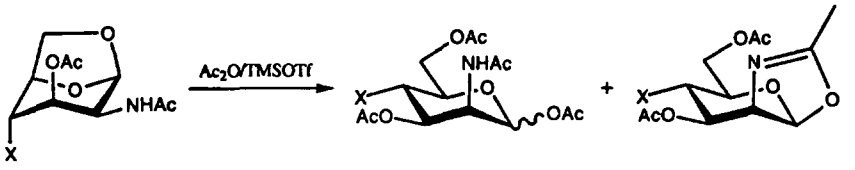
13 R = H (9%)

Scheme 2.

oligosaccharides as has been reported with α-1,2-anhydro sugars in the synthesis of β-linked oligosaccharides [22].

3. Experimental

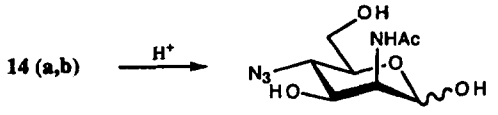
General.—Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured at 24°C using a Jasco DIP-370 polarimeter. Infrared spectra were recorded using a Hitachi 270–30 infrared spectrophotometer for samples prepared as KBr disks unless stated otherwise. ^{1}H and ^{13}C (JMOD) NMR spectra were recorded using a Bruker AM 300 spectrometer working respectively at 300 MHz and 75.5 MHz: a solution of $CDCl_3$–CD_3OD refers to a solution in $CDCl_3$ containing approximately 10% CD_3OD. In the assignment of ^{1}H NMR spectra "brd" refers to a broad doublet, and "brs" to a broad singlet. Assignment of ^{13}C NMR spectra is based on comparison with literature data [23], and where indicated (*) assignment is tentative. Low-resolution FAB (LRFAB) mass spectra (thioglycerol–glycerol matrix) and high-resolution FAB (HRFAB) mass spectra [poly(ethylene glycol) matrix] were obtained using a Jeol JMS-DX 300 mass spectrometer. All solvents were distilled prior



8a X = N_3
9a X = SAc
10a X = Br

14 (a,b) X = N_3
15 (a,b) X = SAc
16 (a,b) X = Br

17 X = N_3
18 X = SAc
19 X = Br



20 (a,b)

Scheme 3.

to use or were of analytical grade. 2-Acetamido-2-deoxy-D-mannopyranose (**3**) was either made in house[1] or obtained from Pfanstiehl Laboratories (Waukegan, IL, USA). Column chromatography was performed using E. Merck Silica Gel-60 (0.040–0.063 mm). Thin-layer chromatography (TLC) was performed on aluminium plates coated with Silica Gel-60 F_{254} (E. Merck) using the solvent combinations (v/v) as specified. The plates were developed by dipping in a solution of 10% H_2SO_4 in 95% EtOH and charring at approx 175°C for several minutes. Dowex 50WX8-400 resin (H^+ form) was dried by washing the resin three times with anhydrous methanol and drying under high vacuum, at approx 40°C, for several hours. All new compounds gave satisfactory NMR and mass spectroscopic data.

General procedure for acetylation.—The sugar (100 mg) was acetylated with acetic anhydride (0.5 mL) in pyridine (0.5 mL) at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel.

2-Acetamido-2-deoxy-6-O-p-tolylsulfonyl-D-mannopyranose (**4**).—A solution of 2-acetamido-2-deoxy-D-mannopyranose (**3**) (1.00 g, 4.52 mmol) in anhydrous pyridine (13 mL), cooled in an ice–water bath, was treated dropwise with a solution of *p*-toluenesulfonyl chloride (1.034 g, 5.42 mmol) in anhydrous pyridine (6.5 mL)[2]. The reaction was stirred at approx 0°C for 2.5 h. The reaction was quenched by the addition of

[1] 2-Acetamido-2-deoxy-D-glucopyranose was readily epimerised using Amberlite IRA-400 resin (OH^- form) [24].

[2] The formation of **4** from commercially available 2-acetamido-2-deoxy-D-mannopyranose monohydrate required the use of approx 2.2 mol-equiv of tosyl chloride. The reaction was monitored by TLC, and the additional tosyl chloride was added in 0.4 mol-equiv portions as required.

methanol (approx 5 mL), toluene was added, and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3:4 dichloromethane–acetone). The fractions with R_f 0.21 (1:2 dichloromethane–acetone) were combined and evaporated to dryness to give the product as a foam (0.98 g, 58%). ^{1}H NMR spectral data showed a 4.3:1 ratio of the α and β anomers (assignment based on δ values of the H-3 and H-5 protons [25] and reported conformational preference [26]). The product was fully characterised as its peracetate **4a,b**. ^{1}H NMR spectral data for (**4**α,β): ^{1}H NMR ($CDCl_3$–CD_3OD): δ 2.02 (s, 3 H, NHAc), 2.44 (s, 3 H, tosyl-CH_3), 3.58 (dd, 1 H, $J_{4,3}$ 9.6, $J_{4,5}$ 9.9 Hz, H-4), 3.99 (ddd, 1 H, $J_{5,4}$ 9.9, $J_{5,6}$ 2.1, $J_{5,6'}$ 4.4 Hz, H-5), 4.08 (dd, 1 H, $J_{3,2}$ 4.6, $J_{3,4}$ 9.6 Hz, H-3), 4.22–4.38 (m, 3 H, H-2, H-6, H-6′), 4.88 (d, 1 H, $J_{1,2}$ 1.4 Hz, H-1 β-anomer), 5.07 (d, 1 H, $J_{1,2}$ 1.1 Hz, H-1 α-anomer), 7.35 (d, 2 H, $J_{o\text{-ArH}}$ 8.1 Hz, ArH-3, ArH-5), 7.78 (d, 2 H, $J_{o\text{-ArH}}$ 8.1 Hz, ArH-2, ArH-6).

2-Acetamido-1,3,4-tri-O-*acetyl-2-deoxy-6*-O-p-*tolylsulfonyl*-D-*mannopyranose* (**4a,b**). —2-Acetamido-2-deoxy-6-*O*-*p*-tolylsulfonyl-D-mannopyranose (**4**) was acetylated according to the general procedure, and the crude product was purified by column chromatography on silica gel (8:1 dichloromethane–acetone). The fractions with R_f 0.29 (6:1 dichloromethane–acetone) were combined and evaporated to give a foam characterised by ^{1}H NMR spectroscopy as a 2:1 ratio of the α and β anomers of the title compound: mp 74–80°C. $[\alpha]_D$ +53.7° (*c* 1.33, $CHCl_3$). ν_{max} 1754, 1688, 1668, 1598, 1536, 1432, 1216, and 810 cm^{-1}. LRFAB mass spectrum: 502 [$(M + H)^+$, 35%], 443 (53), 442 (100), 382 (58), 340 (42), 322 (100), 281 (63), 280 (81), 251 (92), 250 (100), 186 (43), 168 (100). HRFAB mass spectrum: $C_{21}H_{28}NO_{11}S$ requires 502.13831; found 502.13942. Given the 2:1 ratio of anomers, analysis of the ^{1}H and ^{13}C NMR spectra of the mixture allowed the spectral peaks for each of the anomers to be identified.

NMR spectral data for 2-acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-6-*O*-*p*-tolylsulfonyl-α-D-mannopyranose (**4a**): ^{1}H NMR ($CDCl_3$): δ 2.00, 2.02, 2.06, 2.15 (4 s, 12 H, 3 OAc and NHAc), 2.46 (s, 3 H, tosyl-CH_3), 4.02–4.12 (m, 2 H, H-5, H-6), 4.27 (dd, 1 H, $J_{6',5}$ 2.2, $J_{6',6}$ 11.5 Hz, H-6′), 4.61 (ddd, 1 H, $J_{2,1}$ 1.8, $J_{2,3}$ 3.9, $J_{2,NH}$ 9.3 Hz, H-2), 5.18-5.31 (m, 2 H, H-3, H-4), 6.00 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 6.13 (brd, 1 H, N*H*Ac), 7.36 (d, 2 H, $J_{o\text{-ArH}}$ 8.1 Hz, ArH-3, ArH-5), 7.79 (d, 2 H, $J_{o\text{-ArH}}$ 8.1 Hz, ArH-2, ArH-6). ^{13}C NMR ($CDCl_3$): δ 20.5–23.2 [3 OC(O)*Me*, NC(O)*Me* and Ar*Me*], 49.1 (C-2), 65.3 (C-4), 67.6 (C-6), 68.8 (C-3*), 70.1 (C-5*), 91.6 (C-1), 128.0 (*Ar*), 129.8 (*Ar*), 167.9–170.8 [3 O*C*(O)Me and N*C*(O)Me].

NMR spectral data for 2-acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-6-*O*-*p*-tolylsulfonyl-β-D-mannopyranose (**4b**): ^{1}H NMR ($CDCl_3$): δ 1.99, 2.01, 2.09, 2.10 (4s, 12 H, 3 OAc and NHAc), 2.46 (s, 3 H, tosyl-CH_3), 3.77 (ddd, 1 H, $J_{5,4}$ 9.7, $J_{5,6}$ 3.8, $J_{5,6'}$ 2.5 Hz, H-5), 4.02–4.12 (m, 1 H, H-6), 4.31 (dd, 1 H, $J_{6',5}$ 2.5, $J_{6',6}$ 11.1 Hz, H-6′), 4.74 (ddd, 1 H, $J_{2,1}$ 1.7, $J_{2,3}$ 4.0, $J_{2,NH}$ 9.2 Hz, H-2), 5.02 (dd, 1 H, $J_{3,2}$ 4.0, $J_{3,4}$ 9.9 Hz, H-3), 5.18 (brdd, 1 H, H-4), 5.82 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 6.05 (brd, 1 H, N*H*Ac), 7.36 (d, 2 H, $J_{o\text{-ArH}}$ 8.1 Hz, ArH-3, ArH-5), 7.79 (d, 2 H, $J_{o\text{-ArH}}$ 8.1 Hz, ArH-2, ArH-6). ^{13}C NMR ($CDCl_3$): δ 20.5-23.2 [3 OC(O)*Me*, NC(O)*Me* and Ar*Me*], 49.3 (C-2), 65.1 (C-4), 67.1 (C-6), 71.3 (C-3*), 72.8 (C-5*), 90.5 (C-1), 128.0 (*Ar*), 129.8 (*Ar*), 167.9–170.8 [3 O*C*(O)Me and N*C*(O)Me].

2-Acetamido-1,6-anhydro-2-deoxy-β-D-mannopyranose (**5**).—A solution of 2-acetamido-2-deoxy-6-*O*-*p*-tolylsulfonyl-D-mannopyranose (**4**) (0.5 g, 1.33 mmol) in anhydrous ethanol (20 mL) at room temperature was treated dropwise with 1,8-diazabicyclo[5.4.0]undec-7-ene (98%; 0.41 mL, 2.69 mmol), and the reaction was stirred for approx 16 h. The reaction mixture was concentrated under reduced pressure, and the brown residue was subjected to column chromatography on silica gel (10:1 ethyl acetate–methanol). Fractions with R_f 0.29 (5:1 ethyl acetate–methanol) were combined and evaporated to give the product as a foam (0.21 g, 77%). Recrystallisation from ethanol–dichloromethane gave **5** as a colourless crystalline solid: mp 167–169.5°C. $[\alpha]_D$ − 108.0° (*c* 0.98, MeOH). ν_{max} 3524, 3380, 1646, 1554, 1436, 1340, 1138, 1110, 1066, 1044, 984 and 888 cm^{-1}. ^1H NMR ($CDCl_3$–CD_3OD): δ 1.98 (s, 3 H, NHAc), 3.65 (brd, 1 H, H-4), 3.68 (dd, 1 H, $J_{6exo,5}$ 6.1, $J_{6exo,6endo}$ 7.2 Hz, H_{6exo}), 3.76 (dd, 1 H, *J* 1.5, $J_{2,3}$ 5.4 Hz, H-2 or H-3), 4.03 (dd, 1 H, *J* 1.7, $J_{2,3}$ 5.4 Hz, H-2 or H-3), 4.20 (dd, 1 H, $J_{6endo,5}$ 0.7, $J_{6endo,6exo}$ 7.2 Hz, H_{6endo}), 4.45 (brd, 1 H, H-5), 5.28 (brs, 1 H, H-1). ^{13}C NMR ($CDCl_3$–CD_3OD): δ 21.9 [NHC(O)*Me*], 47.9 (C-2), 64.1 (C-6), 68.9 (C-3*), 71.5 (C-4*), 75.4 (C-5), 100.1 (C-1), 171.0 [NH*C*(O)Me]. LRFAB mass spectrum: 204 [$(M + H)^+$, 47%], 186 (32), 110 (62). HRFAB mass spectrum: $C_8H_{14}NO_5$ requires 204.08720; found 204.08799.

*Preparation of 2-acetamido-3,4-di-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-mannopyranose* (**5a**).—2-Acetamido-1,6-anhydro-2-deoxy-β-D-mannopyranose (**5**) was acetylated according to the general procedure, and the crude product was purified by column chromatography on silica gel (10:1 dichloromethane–acetone). The fractions with R_f 0.17 (6:1 dichloromethane–acetone) were combined and evaporated to give a colourless foam which was recrystallised from ethanol–diethyl ether to give **5a** as colourless crystals: mp 180–181°C (dec.) (lit. [19] 182–183°C). $[\alpha]_D$ −95.0° (*c* 1.33, $CHCl_3$) [lit. [19] −98°, (*c* 0.8, $CHCl_3$)]. ν_{max} 1752, 1736, 1674, 1522, 1378 and 1224 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.99, 2.14, 2.15 (3 s, 9 H, 2 OAc and NHAc), 3.80 (dd, 1 H, $J_{6exo,5}$ 5.9, $J_{6exo,6endo}$ 7.7 Hz, H_{6exo}), 4.08 (d, 1 H, $J_{6endo,6exo}$ 7.7 Hz, H_{6endo}), 4.47 (ddd, 1 H, $J_{2,1}$ 1.8, $J_{2,3}$ 5.8, $J_{2,NH}$ 9.7 Hz, H-2), 4.61 (brd, 1 H, H-5), 4.73 (brs, 1 H, H-4), 5.08 (brdd, 1 H, $J_{3,2}$ 5.8, $J_{3,4}$ 1.3 Hz, H-3), 5.34 (brs, 1 H, H-1), 5.75 (brd, 1 H, N*H*Ac). ^{13}C NMR ($CDCl_3$): δ 20.8 [2 OC(O)*Me*], 23.0 [NC(O)*Me*], 46.7 (C-2), 64.9 (C-6), 68.7 (C-3*), 70.5 (C-4*), 73.2 (C-5), 100.7 (C-1), 169.2, 169.8 [2 O*C*(O)Me and N*C*(O)Me]. LRFAB mass spectrum: 289 [$(M + 2)^+$, 16%], 288 [$(M + H)^+$, 100], 168 (50), 150 (33), 138 (43), 106 (42).

2-Acetamido-1,6:3,4-dianhydro-2-deoxy-β-D-talopyranose (**6**).—A mixture of 2-acetamido-1,6-anhydro-2-deoxy-β-D-mannopyranose (**5**) (0.8 g, 3.94 mmol) and triphenylphosphine (1.24 g, 4.73 mmol; 1.2 equiv) in anhydrous tetrahydrofuran (32 mL) under nitrogen, cooled in an ice–water bath, was treated dropwise with diisopropyl azodicarboxylate (97%; 0.96 mL, 4.73 mmol). The resulting orange–yellow solution was stirred at 0°C for 1 h and then allowed to warm to room temperature over a further 1 h. The reaction was monitored by TLC (30:1 dichloromethane–methanol): **5** (R_f 0.0), **6** (R_f 0.31). The reaction was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel. Elution with dichloromethane followed by 20:1 dichloromethane–acetone removed the hydrazine byproduct and a major proportion of the triphenylphosphine oxide. Elution with 10:1 dichloromethane–acetone

removed the product contaminated with triphenylphosphine oxide (up to 20% by mass). The yield of product after chromatography was approx 76%. Repeated recrystallisation from ethanol–diethyl ether–hexane freed the product from contamination by triphenylphosphine oxide and produced **6** as colourless needles: mp 114.6–115.5°C. $[\alpha]_D$ +13.6° (*c* 1.0, $CHCl_3$). ν_{max} 1640, 1536, 1376, 1140, 1080, 970 and 898 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.02 (s, 3 H, NHAc), 3.28 (dd, 1 H, $J_{3,2}$ 3.8, $J_{3,4}$ 4.6 Hz, H-3), 3.51 (dd, 1 H, $J_{6exo,5}$ 4.9, $J_{6exo,6endo}$ 6.5 Hz, H_{6exo}), 3.70 (dd, 1 H, $J_{4,3} = J_{4,5}$ = 4.6 Hz, H-4), 3.91 (d, 1 H, $J_{6endo,6exo}$ 6.5 Hz, H_{6endo}), 4.33 (ddd, 1 H, $J_{2,1}$ 3.3 Hz, $J_{2,3}$ 3.8, $J_{2,NH}$ 9.4 Hz, H-2), 4.81 (dd, 1 H, $J_{5,4}$ 4.6, $J_{5,6exo}$ 4.9 Hz, H-5), 5.20 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 5.96 (brd, 1 H, N*H*Ac). ^{13}C NMR ($CDCl_3$): δ 23.1 [NC(O)*Me*], 47.1 (C-2), 49.1 (C-3*), 55.8 (C-4*), 63.9 (C-6), 71.8 (C-5), 97.0 (C-1), 170.0 [N*C*(O)Me]. LRFAB mass spectrum: 186 [$(M + H)^+$, 85%], 155 (24), 154 (100), 136 (77). HRFAB mass spectrum: $C_8H_{12}NO_4$ requires 186.07663; found 186.07712.

*2-Acetamido-1,6-anhydro-4-azido-2,4-dideoxy-β-*D*-mannopyranose* (**8**) *and 2-acetamido-1,6-anhydro-3-azido-2,3-dideoxy-β-*D*-idopyranose* (**11**).—A mixture of 2-acetamido-1,6:3,4-dianhydro-2-deoxy-β-D-talopyranose (**6**) (0.70 g, 3.78 mmol), lithium azide (0.37 g, 7.56 mmol) and anhydrous Dowex 50WX8 resin (H^+ form; 350 mg) in anhydrous *N,N*-dimethylformamide (25 mL) was stirred and heated at an oil-bath temperature of approx 95°C for 16 h. The reaction was monitored by TLC (3:1 dichloromethane–acetone): **6** (R_f 0.31), **8**, **11** (R_f 0.15). The solvent was then removed under vacuum, the residue was taken up in 1:1 dichloromethane–ethyl acetate and filtered through a plug of Celite, and the filtrate was evaporated under reduced pressure. The crude product was subjected to column chromatography on silica gel (5:1 dichloromethane–acetone). Fractions with R_f 0.15 (3:1 dichloromethane–acetone) were combined and evaporated to give a foam (0.65 g, 75%). The product obtained after chromatography was still contaminated with traces of triphenylphosphine oxide from the previous reaction, and ^1H NMR analysis showed that 2-acetamido-1,6-anhydro-3-azido-2,3-dideoxy-β-D-idopyranose (**11**) was present as approx 5% of the mixture of azides. The two isomers were separable following acetylation, and therefore compound **8** was fully characterised as its acetate **8a**.

Spectral data for 2-acetamido-1,6-anhydro-4-azido-2,4-dideoxy-β-D-mannopyranose (**8**): ν_{max} 2100, 1640, 1534, 1112, 1032, 984 and 898 cm^{-1}. ^1H NMR ($CDCl_3$–CD_3OD): δ 1.97 (s, 3 H, NHAc), 3.50 (brs, 1 H, H-4), 3.73 (dd, 1 H, $J_{6exo,5}$ 5.8, $J_{6exo,6endo}$ 7.3 Hz, H_{6exo}), 3.87 (dd, 1 H, *J* 1.4, $J_{2,3}$ 5.4 Hz, H-2 or H-3), 4.05 (dd, 1 H, *J* 1.8, $J_{2,3}$ 5.4 Hz, H-2 or H-3), 4.24 (dd, 1 H, $J_{6endo,5}$ 0.7, $J_{6endo,6exo}$ 7.3 Hz, H-6_{endo}), 4.56 (brd, 1 H, H-5), 5.31 (brs, 1 H, H-1). ^{13}C NMR ($CDCl_3$–CD_3OD): δ 22.2 [NC(O)*Me*], 48.3 (C-2), 63.0 (C-4), 65.2 (C-6), 67.2 (C-3), 73.7 (C-5), 100.5 (C-1), 170.1 [N*C*(O)Me]. LRFAB mass spectrum: 229 [$(M + H)^+$, 48%], 186 (23).

*2-Acetamido-3-*O*-acetyl-1,6-anhydro-4-azido-2,4-dideoxy-β-*D*-mannopyranose* (**8a**) *and 2-acetamido-4-*O*-acetyl-1,6-anhydro-3-azido-2,3-dideoxy-β-*D*-idopyranose* (**11a**).—A mixture of 2-acetamido-1,6-anhydro-4-azido-2,4-dideoxy-β-D-mannopyranose (**8**) and 2-acetamido-1,6-anhydro-3-azido-2,3-dideoxy-β-D-idopyranose (**11**) was acetylated according to the general procedure, and the crude product was subjected to column chromatography on silica gel (1:2 hexane–ethyl acetate). Fractions with R_f 0.19 (ethyl

acetate) were combined and evaporated to give **8a** as a foam. Fractions with R_f 0.31 (ethyl acetate) were combined and evaporated to give **11a** as a foam.

Data for 2-acetamido-3-*O*-acetyl-1,6-anhydro-4-azido-2,4-dideoxy-β-D-mannopyranose (**8a**): $[\alpha]_D$ −135.3° (*c* 0.97, $CHCl_3$). ν_{max} 2104, 1744, 1660, 1532, 1434, 1376, 1228, 1140, 1104, 1034, 986, 898 and 878 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.01, 2.16 (2 s, 6 H, OAc and NHAc), 3.56 (brs, 1 H, H-4), 3.85 (dd, 1 H, $J_{6exo,5}$ 5.7, $J_{6exo,6endo}$ 7.7 Hz, H_{6exo}), 4.03 (dd, 1 H, $J_{6endo,5}$ 0.8, $J_{6endo,6exo}$ 7.7 Hz, H_{6endo}), 4.47 (ddd, 1 H, $J_{2,1}$ 1.8, $J_{2,3}$ 5.8, $J_{2,NH}$ 9.6 Hz, H-2), 4.60 (brd, 1 H, H-5), 5.07 (dd, 1 H, $J_{3,2}$ 5.8, $J_{3,4}$ 1.3 Hz, H-3), 5.36 (brs, 1 H, H-1), 5.78 (brd, 1 H, N*H*Ac). ^{13}C NMR ($CDCl_3$): δ 20.8 [OC(O)*Me*], 22.9 [NC(O)*Me*], 46.6 (C-2), 60.4 (C-4), 65.7 (C-6), 69.2 (C-3), 73.7 (C-5), 100.6 (C-1), 169.5 [N*C*(O)Me and O*C*(O)Me]. LRFAB mass spectrum: 271 [$(M + H)^+$, 95%]. HRFAB mass spectrum: $C_{10}H_{15}N_4O_5$ requires 271.10425; found 271.10580.

Spectral data for 2-acetamido-4-*O*-acetyl-1,6-anhydro-3-azido-2,3-dideoxy-β-D-idopyranose (**11a**): ν_{max} 2108, 1744, 1642, 1552, 1438, 1374, 1250, 1218, 1138, 1106, 1058, 1032, 952, 894, 616 and 474 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.04, 2.12 (2 s, 6 H, OAc and NHAc), 3.46 (dd, 1 H, $J_{3,2} = J_{3,4} = 9.5$ Hz, H-3), 3.76 (dd, 1 H, $J_{6exo,5}$ 4.9, $J_{6exo,6endo}$ 8.2 Hz, H_{6exo}), 4.02 (d, 1 H, $J_{6endo,6exo}$ 8.2 Hz, H_{6endo}), 4.16 (ddd, 1 H, $J_{2,1}$ 1.2, $J_{2,3} = J_{2,NH} = 9.5$ Hz, H-2), 4.62 (brdd, 1 H, H-5), 4.96 (dd, 1 H, $J_{4,3}$ 9.5, $J_{4,5}$ 4.1 Hz, H-4), 5.30 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 5.78 (brd, 1 H, N*H*Ac). ^{13}C NMR ($CDCl_3$): δ 20.7 [OC(O)*Me*], 23.2 [NC(O)*Me*], 54.3 (C-2), 61.8 (C-3), 65.4 (C-6), 71.2 (C-4*), 72.6 (C-5*), 100.9 (C-1), 170.0 [N*C*(O)Me and O*C*(O)Me]. LRFAB mass spectrum: 271 [$(M + H)^+$, 100%].

2-Acetamido-4-acetylthio-1,6-anhydro-2-deoxy-β-D-mannopyranose (**9**).—A mixture of 2-acetamido-1,6:3,4-dianhydro-2-deoxy-β-D-talopyranose (**6**) (0.17 g, 0.92 mmol), potassium thioacetate (0.21 g, 1.84 mmol) and anhydrous Dowex 50WX8 resin (H^+ form; 170 mg) in anhydrous *N,N*-dimethylformamide (5 mL) was stirred and heated at an oil-bath temperature of approx 85°C. The reaction was monitored by TLC (3:1 dichloromethane–acetone): **6** (R_f 0.31), **9**, **12** (R_f 0.19), **9a** (R_f 0.36). A further portion of resin (85 mg) was added after approx 24 h, and the reaction continued for a total of 48 h. The reaction was allowed to cool. It was then filtered through a plug of Celite, the residue was washed thoroughly with dichloromethane and ethyl acetate, and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (5:1 dichloromethane–acetone). Fractions with R_f 0.19 (3:1 dichloromethane–acetone) were combined and evaporated to give a brown foam which was found to be a mixture of **9** and **12** (98 mg, 41%). Fractions with R_f 0.36 (3:1 dichloromethane–acetone) were combined and evaporated to give the 3-*O*-acetylated derivative **9a** as a pale brown foam (67 mg, 24% of the theoretical yield of 3-*O*-acetylated product); the overall yield of thioacetylated product was approx 65%. The mixture of **9** and **12** obtained after chromatography was still contaminated with traces of triphenylphosphine oxide from the previous reaction, and ^1H NMR analysis showed that 2-acetamido-3-acetylthio-1,6-anhydro-2-deoxy-β-D-idopyranose (**12**) was present as approx 4% of the mixture. Compound **9** was fully characterised as its acetate **9a**.

Spectral data for 2-acetamido-4-acetylthio-1,6-anhydro-2-deoxy-β-D-mannopyranose (**9**): ν_{max} 1696, 1642, 1526, 1126, 1102 and 1034 cm^{-1}. ^1H NMR ($CDCl_3$–CD_3OD): δ

1.94 (s, 3 H, NHAc), 2.30 (s, 3 H, SAc), 3.71 (dd, 1 H, $J_{6exo,5}$ 5.7, $J_{6exo,6endo}$ 7.2 Hz, H_{6exo}), 3.73 (brs, 1 H, H-4), 3.75 (dd, 1 H, $J_{3,4}$ 1.4, $J_{3,2}$ 5.1 Hz, H-3), 4.01 (dd, 1 H, $J_{2,1}$ 1.7, $J_{2,3}$ 5.1 Hz, H-2), 4.38 (dd, 1 H, $J_{6endo,5}$ 0.8, $J_{6endo,6exo}$ 7.2 Hz, H_{6endo}), 4.44 (brdd, 1 H, H-5), 5.27 (brs, 1 H, H-1). ^{13}C NMR ($CDCl_3$–CD_3OD): δ 22.4 [NHC(O)*Me*], 30.1 [SC(O)*Me*], 48.4 (C-2*), 48.6 (C-4*), 67.0 (C-6), 69.4 (C-3), 74.5 (C-5), 100.7 (C-1), 170.9 [NH*C*(O)Me], 195.3 [S*C*(O)Me]. LRFAB mass spectrum: 263 [(M + 2)$^+$, 31%], 262 [(M + H)$^+$, 57], 257 (30), 215 (49), 202 (72), 201 (100), 186 (88).

*2-Acetamido-3-*O*-acetyl-4-acetylthio-1,6-anhydro-2-deoxy-β-*D*-mannopyranose* (**9a**). —A mixture of 2-acetamido-4-acetylthio-1,6-anhydro-2-deoxy-β-D-mannopyranose (**9**) and 2-acetamido-3-acetylthio-1,6-anhydro-2-deoxy-β-D-idopyranose (**12**) was acetylated according to the general procedure, and the crude product was subjected to column chromatography on silica gel (10:1 dichloromethane–acetone). Fractions with R_f 0.36 (3:1 dichloromethane–acetone) were combined and evaporated to give a foam which was recrystallised repeatedly from ethanol–diethyl ether–hexane to give **9a** as pale yellow crystals: mp 167–168°C. $[\alpha]_D$ −19.2° (*c* 0.24, $CHCl_3$). ν_{max} 1746, 1694, 1600, 1528, 1376, 1222, 1130, 1100 and 1026 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.99, 2.17 (2 s, 6 H, OAc and NHAc), 2.39 (s, 3 H, SAc), 3.80–3.88 (m, 2 H, H-4 and H_{6exo}), 4.24 (d, 1 H, $J_{6endo,6exo}$ 7.6 Hz, H_{6endo}), 4.35 (ddd, 1 H, $J_{2,1}$ 1.8, $J_{2,3}$ 5.5, $J_{2,NH}$ 9.6 Hz, H-2), 4.48 (brd, 1 H, H-5), 5.09 (dd, 1 H, $J_{3,2}$ 5.5, $J_{3,4}$ 1.3 Hz, H-3), 5.32 (brs, 1 H, H-1), 5.75 (brd, 1 H, N*H*Ac). ^{13}C NMR ($CDCl_3$): δ 20.9 [OC(O)*Me*], 23.0 [NC(O)*Me*], 30.3 [SC(O)*Me*], 45.9 (C-2*), 47.2 (C-4*), 67.4 (C-6), 70.8 (C-3), 75.1 (C-5), 100.8 (C-1), 169.0, 169.4 [N*C*(O)Me and O*C*(O)Me], 193.0 [S*C*(O)Me]. LRFAB mass spectrum: 304 [(M + H)$^+$, 99%], 202 (37), 186 (34). HRFAB mass spectrum: $C_{12}H_{18}NO_6S$ requires 304.08548; found 304.08689.

*2-Acetamido-1,6-anhydro-4-bromo-2,4-dideoxy-β-*D*-mannopyranose* (**10**).—A mixture of 2-acetamido-1,6:3,4-dianhydro-2-deoxy-β-D-talopyranose (**6**) (0.17 g, 0.92 mmol), lithium bromide (0.16 g, 1.84 mmol) and anhydrous Dowex 50WX8 resin (H$^+$ form; 120 mg) in anhydrous *N,N*-dimethylformamide (7 mL) was stirred and heated at an oil-bath temperature of approx 85°C. The reaction was monitored by TLC (2:1 dichloromethane–acetone): **6** (R_f 0.38), **10**, **13** (R_f 0.29). A further portion of resin (120 mg) was added after approx 24 h, and the reaction was continued for a total of 48 h. The reaction was allowed to cool. It was then filtered through a plug of Celite, the residue was washed thoroughly with dichloromethane and ethyl acetate, and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (10:1 dichloromethane–acetone). Fractions with R_f 0.29 (2:1 dichloromethane–acetone) were combined and evaporated to give a foam which was found to be a mixture of **10** and **13** (159 mg, 65%). The product obtained after chromatography was still contaminated with traces of triphenylphosphine oxide from the previous reaction, and ^{1}H NMR analysis showed that 2-acetamido-1,6-anhydro-3-bromo-2,3-dideoxy-β-D-idopyranose (**13**) was present as approx 9% of the mixture. Compound **10** was fully characterised as its acetate **10a**.

Spectral data for 2-acetamido-1,6-anhydro-4-bromo-2,4-dideoxy-β-D-mannopyranose (**10**): ν_{max} 3424, 3224, 1640, 1530, 1374, 1320, 1250, 1190, 1108, 1088, 1032, 976, 896, 888, 740 and 582 cm^{-1}. ^{1}H NMR ($CDCl_3$–CD_3OD): δ 2.03 (s, 3 H, NHAc), 3.79

(dd, 1 H, $J_{6exo,5}$ 5.7, $J_{6exo,6endo}$ 7.5 Hz, H_{6exo}), 4.20 (brs, 2 H, H-3 or H-5, and H-4), 4.32 (d, 1 H, $J_{6endo,6exo}$ 7.5 Hz, H_{6endo}), 4.40 (m, 1 H, H-2), 4.64 (brd, 1 H, H-5 or H-3), 5.42 (brs, 1 H, H-1), 6.47 (brd, 1 H, N*H*Ac). ^{13}C NMR ($CDCl_3$–CD_3OD): δ 23.1 [NHC(O)*Me*], 47.2 (C-2), 50.7 (C-4), 67.0 (C-6), 71.0 (C-3), 76.0 (C-5), 101.0 (C-1), 170.8 [NH*C*(O)Me]. LRFAB mass spectrum: 268 [(^{81}BrM + H)$^+$, 50%], 266 [(^{79}BrM + H)$^+$, 50].

*2-Acetamido-3-*O*-acetyl-1,6-anhydro-4-bromo-2,4-dideoxy-β-*D*-mannopyranose* (**10a**).—A mixture of 2-acetamido-1,6-anhydro-4-bromo-2,4-dideoxy-β-D-mannopyranose (**10**) and 2-acetamido-1,6-anhydro-3-bromo-2,3-dideoxy-β-D-idopyranose (**13**) was acetylated according to the general procedure, and the crude product was subjected to column chromatography on silica gel (10:1 dichloromethane–acetone). Fractions with R_f 0.36 (3:1 dichloromethane–acetone) were combined and evaporated to give a foam which was recrystallised from ethanol–diethyl ether–hexane to give **10a** as colourless crystals: mp 167.5–170.5°C. $[\alpha]_D$ −105.2° (*c* 1.68, $CHCl_3$). ν_{max} 1746, 1642, 1632 and 1214 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.01, 2.16 (2 s, 6 H, OAc and NHAc), 3.85 (dd, 1 H, $J_{6exo,5}$ 5.7, $J_{6exo,6endo}$ 7.8Hz, H_{6exo}), 4.08 (d, 1 H, $J_{6endo,6exo}$ 7.8 Hz, H_{6endo}), 4.10 (brs, 1 H, H-4), 4.63 (brd, 1 H, H-5), 4.70 (ddd, 1 H, $J_{2,1}$ 1.5, $J_{2,3}$ 5.5, $J_{2,NH}$ 9.7 Hz, H-2), 5.24 (brdd, 1 H, H-3), 5.38 (brs, 1 H, H-1), 5.78 (brd, 1 H, N*H*Ac). ^{13}C NMR ($CDCl_3$): δ 20.8 [OC(O)*Me*], 23.0 [NC(O)*Me*], 45.4 (C-2*), 46.1 (C-4*), 67.0 (C-6), 72.0 (C-3), 75.7 (C-5), 100.8 (C-1), 169.4 [*O*C(O)Me and N*C*(O)Me]. LRFAB mass spectrum: 310 [(^{81}BrM + H)$^+$, 74%], 308 [(^{79}BrM + H)$^+$, 79], 230 (100), 228 (99). HRFAB mass spectrum: $C_{10}H_{15}{}^{79}BrNO_5$ requires 308.01337; found 308.01203.

*2-Acetamido-1,3,6-tri-*O*-acetyl-4-azido-2,4-dideoxy-α-*D*-mannopyranose* (**14a**), *2-acetamido-1,3,6-tri-*O*-acetyl-4-azido-2,4-dideoxy-β-*D*-mannopyranose* (**14b**), *and 2-methyl-(3,6-di-*O*-acetyl-4-azido-2,4-dideoxy-β-*D*-mannopyrano)-[2,1-*d*]-2-oxazoline* (**17**).—A solution of 2-acetamido-3-*O*-acetyl-1,6-anhydro-4-azido-2,4-dideoxy-β-D-mannopyranose (**8a**) (100 mg, 0.37 mmol) in acetic anhydride (2 mL) under nitrogen, cooled in an ice-water bath, was treated with trimethylsilyl triflate (71 μL, 0.37 mmol). The reaction was stirred at 0–4°C for 16 h. The reaction was monitored by TLC (ethyl acetate): **8a** (R_f 0.25), **14a**, **14b**, **17** (R_f 0.37); TLC (30:1 dichloromethane–methanol): **8a** (R_f 0.24), **14a**, **14b** (R_f 0.24), **17** (R_f 0.30). The reaction was quenched by the addition of saturated sodium bicarbonate solution over a period of approx 30 min. The mixture was then extracted with ethyl acetate (3 × 40 mL), and the combined organic extracts were washed with saturated sodium bicarbonate solution (2 × 10 mL), saturated sodium chloride solution (20 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (40:1 dichloromethane–methanol). The overall yield of the three products was 95–98%; **14a** and **14b** in a ratio of 1.8:1 (75% yield), **17** (20% yield). The three products could not be properly separated; however, the mixture could be freed of the oxazoline compound **17** by hydrolysis in 20% aqueous acetic acid for 4 h at room temperature. After evaporation of the hydrolysis reaction and chromatography of the residue on silica gel (40:1 dichloromethane–methanol), a mixture of **14a** and **14b** alone could be obtained as a foam: $[\alpha]_D$ +99.1° (2.5:1 ratio of α and β anomers; *c* 1.06, $CHCl_3$). ν_{max} 2116, 1754, 1660, 1536, 1432, 1370, 1224, 1134, 1036 and 968 cm^{-1}. LRFAB mass spectrum: 390 [(M + 18)$^+$, 27%], 373 [(M + H)$^+$, 54], 314 (91), 313 (100), 279 (100),

253 (100), 183 (56), 168 (100), 138 (100), 123 (100). HRFAB mass spectrum: $C_{14}H_{21}N_4O_8$ requires 373.13593; found 373.13507. Given the approx 2:1 ratio of anomers, analysis of the ^1H and ^{13}C NMR spectra of the mixture allowed the spectral peaks for each of the anomers to be identified.

NMR spectral data for 2-acetamido-1,3,6-tri-*O*-acetyl-4-azido-2,4-dideoxy-α-D-mannopyranose (**14a**): ^1H NMR ($CDCl_3$): δ 2.06, 2.08, 2.13, 2.16 (4 s, 12 H, 3 OAc and NHAc), 3.68 (dd, 1 H, $J_{4,3}$ 10.3, $J_{4,5}$ 10.6 Hz, H-4), 3.81 (ddd, 1 H, $J_{5,4}$ 10.6, $J_{5,6}$ 2.5, $J_{5,6'}$ 4.4 Hz, H-5), 4.28 (dd, 1 H, $J_{6,5}$ 2.5, $J_{6,6'}$ 12.3 Hz, H-6), 4.34 (dd, 1 H, $J_{6',5}$ 4.4, $J_{6',6}$ 12.3 Hz, H-6'), 4.61 (ddd, 1 H, $J_{2,1}$ 1.7, $J_{2,3}$ 4.2, $J_{2,NH}$ 9.1 Hz, H-2), 5.26 (dd, 1 H, $J_{3,2}$ 4.2, $J_{3,4}$ 10.3 Hz, H-3), 5.71 (brd, 1 H, N*H*Ac), 5.99 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1). ^{13}C NMR ($CDCl_3$): δ 20.7 [3 OC(O)*Me*], 23.0 [NC(O)*Me*], 48.6 (C-2), 56.5 (C-4), 63.0 (C-6), 70.5 (C-3*), 70.6 (C-5*), 91.8 (C-1), 168.0–170.6 [3 O*C*(O)Me and N*C*(O)Me].

NMR spectral data for 2-acetamido-1,3,6-tri-*O*-acetyl-4-azido-2,4-dideoxy-β-D-mannopyranose (**14b**): ^1H NMR ($CDCl_3$): δ 2.06, 2.08, 2.13, 2.16 (4 s, 12 H, 3 OAc and NHAc), 3.55 (ddd, 1 H, $J_{5,4}$ 10.3, $J_{5,6}$ 2.5, $J_{5,6'}$ 4.4 Hz, H-5), 3.63 (dd, 1 H, $J_{4,3}$ 9.8, $J_{4,5}$ 10.3 Hz, H-4), 4.28 (dd, 1 H, $J_{6,5}$ 2.5, $J_{6,6'}$ 12.3 Hz, H-6), 4.34 (dd, 1 H, $J_{6',5}$ 4.4, $J_{6',6}$ 12.3 Hz, H-6'), 4.72 (ddd, 1 H, $J_{2,1}$ 1.6, $J_{2,3}$ 3.8, $J_{2,NH}$ 8.5 Hz, H-2), 4.97 (dd, 1 H, $J_{3,2}$ 3.8, $J_{3,4}$ 9.8 Hz, H-3), 5.75 (brd, 1 H, N*H*Ac), 5.77 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1). ^{13}C NMR ($CDCl_3$): δ 20.7 [3 OC(O)*Me*], 23.2 [NC(O)*Me*], 49.4 (C-2), 56.3 (C-4), 62.8 (C-6), 73.3 (C-3*), 73.6 (C-5*), 90.5 (C-1), 168.0-170.6 [3 O*C*(O)Me and N*C*(O)Me].

Spectral data for 2-methyl-(3,6-di-*O*-acetyl-4-azido-2,4-dideoxy-β-D-mannopyrano)-[2,1-*d*]-2-oxazoline (**17**): ν_{max} 2110, 1744, 1676, 1368 and 1230 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.10 (s, 3 H, Ac), 2.12 (d, 3 H, *J* 1.8 Hz, Ac), 2.24 (s, 3 H, Ac), 3.59 (ddd, 1 H, $J_{5,4}$ 9.2, $J_{5,6}$ 5.5, $J_{5,6'}$ 3.4 Hz, H-5), 3.70 (dd, 1 H, $J_{4,3}$ 10.3, $J_{4,5}$ 9.2 Hz, H-4), 4.18 (dd, 1 H, $J_{6,5}$ 5.5, $J_{6,6'}$ 12.0 Hz, H-6), 4.27 (dd, 1 H, $J_{6',5}$ 3.4, $J_{6',6}$ 12.0 Hz, H-6'), 4.39 (ddd, 1 H, $J_{2,1}$ 5.5, $J_{2,3}$ 5.5, *J* 1.8 Hz, H-2), 5.16 (dd, 1 H, $J_{3,2}$ 5.5, $J_{3,4}$ 10.3 Hz, H-3), 5.75 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1). LRFAB mass spectrum: 313 [$(M + H)^+$, 19%], 279 (60), 215 (26).

*2-Acetamido-1,3,6-tri-*O*-acetyl-4-acetylthio-2-deoxy-α-D-mannopyranose* (**15a**), *and 2-acetamido-1,3,6-tri-*O*-acetyl-4-acetylthio-2-deoxy-β-D-mannopyranose* (**15b**).—A solution of 2-acetamido-3-*O*-acetyl-4-acetylthio-1,6-anhydro-2-deoxy-β-D-mannopyranose (**9a**) (28 mg, 0.092 mmol) in acetic anhydride (1 mL) under nitrogen, cooled in an ice-water bath, was treated with trimethylsilyl triflate (70 μL, 0.36 mmol). The reaction was stirred at 0–4°C for 1 h. The reaction was monitored by TLC (ethyl acetate): **9a** (R_f 0.35), **15a**, **15b**, **18** (R_f 0.42), and a trace of material with R_f 0.21. The reaction was quenched by the addition of saturated sodium bicarbonate solution over a period of approx 30 min. The mixture was then extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts washed with saturated sodium bicarbonate solution (10 mL), water (10 mL), saturated sodium chloride solution (10 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. ^1H NMR spectral analysis of the crude product showed a 2:1 ratio of **15a** and **15b**. The mixture also contained approx 20% of the oxazoline **18** and the compound lacking an acetate at the anomeric position. The crude product was treated with 20% aq acetic acid at room temperature for 1 h to hydrolyse

the oxazoline present. The reaction was then evaporated to dryness with toluene, and the residue was reacetylated with acetic anhydride in pyridine. Evaporation of the acetylation reaction mixture gave a crude product which was subjected to column chromatography on silica gel (2:1 ethyl acetate–dichloromethane). Fractions with R_f 0.42 (ethyl acetate) were combined to give a mixture of **15a** and **15b** as a foam (34 mg, 91%): $[\alpha]_D$ +97.6° (2.2:1 mixture of α and β anomers; *c* 1.27, $CHCl_3$). ν_{max} 1752, 1702, 1685, 1666, 1536, 1430, 1370, 1226, 1134, 1104, 1036, 970, 622 and 600 cm^{-1}. LRFAB mass spectrum: 423 [$(M + 18)^+$, 19%], 406 [$(M + H)^+$, 49], 348 (30), 347 (64), 346 (100), 304 (32), 286 (64), 244 (45), 226 (42), 184 (100), 168 (39). The compound did not give a molecular ion or $(M + H)^+$ peak under high-resolution FAB mass spectroscopy conditions. Given the approx 2:1 ratio of anomers, analysis of the ^1H and ^{13}C NMR spectra of the mixture allowed the spectral peaks for each of the anomers to be identified.

NMR spectral data for 2-acetamido-1,3,6-tri-*O*-acetyl-4-acetylthio-2-deoxy-α-D-mannopyranose (**15a**): ^1H NMR ($CDCl_3$): δ 1.99, 2.08, 2.09, 2.16 (4 s, 12 H, 3 OAc and NHAc), 2.36 (s, 3H, SAc), 3.78 (dd, 1 H, $J_{4,3} = J_{4,5} = 11.6$ Hz, H-4), 4.0–4.2 (m, 2 H, H-5 and H-6), 4.37 (dd, 1 H, $J_{6',5}$ 5.3, $J_{6',6}$ 12.4 Hz, H-6'), 4.57 (ddd, 1 H, $J_{2,1}$ 1.6 Hz, $J_{2,3}$ 4.1, $J_{2,NH}$ 9.2 Hz, H-2), 5.26 (dd, 1 H, $J_{3,2}$ 4.1, $J_{3,4}$ 11.6 Hz, H-3), 5.92 (brd, 1 H, N*H*Ac), 6.04 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1). ^{13}C NMR ($CDCl_3$): δ 20.7 [3 OC(O)*Me*], 22.9 [NC(O)*Me*], 30.6 [SC(O)*Me*], 40.0 (C-2), 48.6 (C-4), 63.1 (C-6), 67.1 (C-3), 71.4 (C-5), 91.9 (C-1), 168–171 [3 O*C*(O)Me and N*C*(O)Me], 190.5 [S*C*(O)Me].

NMR spectral data for 2-acetamido-1,3,6-tri-*O*-acetyl-4-acetylthio-2-deoxy-β-D-mannopyranose (**15b**): ^1H NMR ($CDCl_3$): δ2.00 (s, 3 H, Ac), 2.09 (s, 6 H, 2Ac), 2.10 (s, 3 H, Ac), 2.35 (s, 3 H, SAc), 3.68 (dd, 1 H, $J_{4,3}$ 11.5, $J_{4,5}$ 11.2 Hz, H-4), 3.86 (ddd, 1 H, $J_{5,4}$ 11.2, $J_{5,6}$ 2.0, $J_{5,6'}$ 5.4 Hz, H-5), 4.16 (dd, 1 H, $J_{6,5}$ 2.0, $J_{6,6'}$ 12.3 Hz, H-6), 4.39 (dd, 1 H, $J_{6',5}$ 5.4, $J_{6',6}$ 12.3 Hz, H-6'), 4.71 (ddd, 1 H, $J_{2,1}$ 1.4 Hz, $J_{2,3}$ 3.8, $J_{2,NH}$ 9.0 Hz, H-2), 5.01 (dd, 1 H, $J_{3,2}$ 3.8, $J_{3,4}$ 11.5 Hz, H-3), 5.78 (d, 1 H, $J_{1,2}$ 1.4, H-1), 5.85 (brd, 1 H, N*H*Ac). ^{13}C NMR ($CDCl_3$): δ 20.7 [3 OC(O)*Me*], 22.9 [NC(O)*Me*], 30.6 [SC(O)*Me*], 39.7 (C-2), 49.3 (C-4), 62.9 (C-6), 70.0 (C-3), 74.8 (C-5), 90.7 (C-1), 168–171 [3 O*C*(O)Me and N*C*(O)Me], 190.5 [S*C*(O)Me].

*2-acetamido-1,3,6-tri-*O*-acetyl-4-bromo-2,4-dideoxy-α-D-mannopyranose* (**16a**), *and 2-acetamido-1,3,6-tri-*O*-acetyl-4-bromo-2,4-dideoxy-β-D-mannopyranose* (**16b**).—A solution of 2-acetamido-3-*O*-acetyl-1,6-anhydro-4-bromo-2,4-dideoxy-β-D-mannopyranose (**10a**) (28 mg, 0.091 mmol) in acetic anhydride (1 μL) under nitrogen, cooled in an ice–water bath, was treated with trimethylsilyl triflate (70 mL, 0.36 mmol). The reaction was stirred at 0–4°C for 1 h. The reaction was monitored by TLC (ethyl acetate): **10a** (R_f 0.26), **16a**, **16b**, **19** (R_f 0.41), and a trace of material with R_f 0.18; TLC (5:1 dichloromethane–acetone): **10a** (R_f 0.24), **16a**, **16b**, **19** (R_f 0.31), and a trace of material with R_f 0.07. The reaction was quenched by the addition of saturated sodium bicarbonate solution over a period of approx 30 min. The mixture was then extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts washed with saturated sodium bicarbonate solution (10 mL), water (10 mL), saturated sodium chloride solution (10 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. ^1H NMR spectral analysis of the crude product showed a 2:1 ratio of **16a** and **16b**. The mixture also contained approx 20% of the oxazoline **19** and the compound

lacking an acetate at the anomeric position. The crude product was treated with 20% aq acetic acid at room temperature for 1 h to hydrolyse the oxazoline present. The reaction was then evaporated to dryness with toluene, and the residue was reacetylated with acetic anhydride in pyridine. Evaporation of the acetylation reaction mixture gave a crude product which was subjected to column chromatography on silica gel (2:1 ethyl acetate–dichloromethane). Fractions with R_f 0.41 (ethyl acetate) were combined to give a mixture of **16a** and **16b** as a foam (28 mg, 75%): $[\alpha]_D$ +33.0° (3.3:1 ratio of α and β anomers; *c* 0.91, $CHCl_3$). ν_{max} 1750, 1662, 1536, 1434, 1368, 1224, 1132, 1078, 1038 and 970 cm^{-1}. LRFAB mass spectrum: 429 [(^{81}BrM + 18)$^+$, 13%], 427 [(^{79}BrM + 18)$^+$, 14], 412 [(^{81}BrM + H)$^+$, 37], 410 [(^{79}BrM + H)$^+$, 37], 352 (100), 350 (100), 292 (100), 290 (100), 272 (25), 250 (19), 248 (20), 232 (49), 230 (49), 212 (37), 190 (64), 188 (66), 168 (77). HRFAB mass spectrum: $C_{14}H_{21}{}^{79}BrNO_8$ requires 410.04504; found 410.04398. Given the approx 2:1 ratio of anomers, analysis of the ^{1}H and ^{13}C NMR spectra of the mixture allowed the spectral peaks for each of the anomers to be identified.

NMR spectral data for 2-acetamido-1,3,6-tri-*O*-acetyl-4-bromo-2,4-dideoxy-α-D-mannopyranose (**16a**): ^{1}H NMR ($CDCl_3$): δ 2.05, 2.07, 2.12, 2.19 (4 s, 12 H, 3 OAc and NHAc), 4.02 (dd, 1 H, $J_{4,3}$ 10.9, $J_{4,5}$ 10.6 Hz, H-4), 4.24 (ddd, 1 H, $J_{5,4}$ 10.6, $J_{5,6}$ 2.1, $J_{5,6'}$ 4.8 Hz, H-5), 4.38 (dd, 1 H, $J_{6,5}$ 2.1, $J_{6,6'}$ 12.3 Hz, H-6), 4.48 (dd, 1 H, $J_{6',5}$ 4.8, $J_{6',6}$ 12.3 Hz, H-6′), 4.58 (ddd, 1 H, $J_{2,1}$ 1.8, $J_{2,3}$ 4.2, $J_{2,NH}$ 9.2 Hz, H-2), 5.38 (dd, 1 H, $J_{3,2}$ 4.2, $J_{3,4}$ 10.9 Hz, H-3), 5.81 (brd, 1 H, N*H*Ac), 5.99 (brs, 1 H, H-1). ^{13}C NMR ($CDCl_3$): δ 20.6 [3 OC(O)*Me*], 22.9 [NC(O)*Me*], 44.0 (C-2), 49.8 (C-4), 63.6 (C-6), 70.7 (C-3), 72.4 (C-5), 91.9 (C-1), 168-170 [3 O*C*(O)Me and N*C*(O)Me].

NMR spectral data for 2-acetamido-1,3,6-tri-*O*-acetyl-4-bromo-2,4-dideoxy-β-D-mannopyranose (**16b**): ^{1}H NMR ($CDCl_3$): δ 2.05, 2.05–2.12 (4 s, 12 H, 3 OAc and NHAc), 3.92 (dd, 1 H, $J_{4,3}$ 10.3, $J_{4,5}$ 10.6 Hz, H-4), 3.95 (m, 1 H, H-5), 4.36–4.50 (m, 2 H, H-6 and H-6′) 4.71 (ddd, 1 H, $J_{2,1}$ 1.6, $J_{2,3}$ 3.8, $J_{2,NH}$ 9.2 Hz, H-2), 5.11 (dd, 1 H, $J_{3,2}$ 3.8, $J_{3,4}$ 10.3 Hz, H-3), 5.81 (brd, 1 H, N*H*Ac), 5.87 (brs, 1 H, H-1). ^{13}C NMR ($CDCl_3$): δ 20.6 [3 OC(O)*Me*], 22.9 [NC(O)*Me*], 43.3 (C-2), 50.7 (C-4), 63.3 (C-6), 73.8 (C-3), 75.7 (C-5), 90.7 (C-1), 168-170 [3 O*C*(O)Me and N*C*(O)Me].

2-Acetamido-4-azido-2,4-dideoxy-α-D-mannopyranose (**20a**) *and 2-acetamido-4-azido-2,4-dideoxy-β-D-mannopyranose* (**20b**).—A mixture of 2-acetamido-1,3,6-tri-*O*-acetyl-4-azido-2,4-dideoxy-α-D-mannopyranose (**14a**) and 2-acetamido-1,3,6-tri-*O*-acetyl-4-azido-2,4-dideoxy-β-D-mannopyranose (**14b**) (46 mg, 0.12 mmol), and Amberlyst 15 resin (H^+ form; 50 mg) in 25 mM aq HCl (4 mL) was heated at approx 70–80°C for 24 h. The reaction was monitored by TLC (10:1:0.25 ethyl acetate–methanol–water): **14a**, **14b** (R_f 0.60), **20a**, **20b** (R_f 0.27). The mixture was filtered through a Celite pad, the resin was washed several times with water and methanol, and the filtrate was evaporated to dryness under reduced pressure. Any traces of triphenylphosphine oxide carried through from previous reactions could be removed by extraction of an aqueous solution of the crude product with ethyl acetate. The crude product could be purified by chromatography on silica gel (10:1:0.25 ethyl acetate–methanol–water). The fractions with R_f 0.27 were combined, and evaporated, and the residue was lyophilised to give a mixture of **20a** and **20b** as a colourless, hygroscopic solid (14 mg, 46%): $[\alpha]_D$ +54.4° (1.27:1 mixture of α and β anomers; *c* 0.92, H_2O).

ν_{max} 3452, 2116, 1550, 1424, 1024, 658 and 614 cm^{-1}. LRFAB mass spectrum: 247 [$(M + H)^+$, 20%], 215 (66). HRFAB mass spectrum: $C_8H_{15}N_4O_5$ requires; 247.1042, found 247.1046. Given the approx 1.3:1 ratio of anomers, analysis of the ^1H and ^{13}C NMR spectra of the mixture allowed the spectral peaks for each of the anomers to be identified.

NMR spectral data for 2-acetamido-4-azido-2,4-dideoxy-α-D-mannopyranose (**20a**): ^1H NMR (D_2O): δ 2.04 (s, 3 H, NHAc), 3.56 (dd, 1 H, $J_{4,3} = J_{4,5} = 10.2$ Hz, H-4), 3.75–3.89 (m, 3 H, H-5, H-6 and H-6′), 4.16 (dd, 1 H, $J_{3,2}$ 4.5, $J_{3,4}$ 10.2 Hz, H-3), 4.30 (dd, 1 H, $J_{2,1}$ 1.3, $J_{2,3}$ 4.5 Hz, H-2), 5.12 (d, 1 H, $J_{1,2}$ 1.3 Hz, H-1). ^{13}C NMR ($CDCl_3$): δ 24.4 [NC(O)*Me*], 55.3 (C-2), 61.7 (C-4), 63.3 (C-6), 70.8 (C-3), 72.9 (C-5), 95.5 (C-1), 177.4 [N*C*(O)Me].

NMR spectral data for 2-acetamido-4-azido-2,4-dideoxy-β-D-mannopyranose (**20b**): ^1H NMR (D_2O): δ 2.08 (s, 3 H, NHAc), 3.35 (ddd, 1 H, $J_{5,4}$ 10.3, $J_{5,6}$ 2.4, $J_{5,6'}$ 4.0 Hz, H-5), 3.47 (dd, 1 H, $J_{4,3}$ 10.0, $J_{4,5}$ 10.3 Hz, H-4), 3.77–3.89 (m, 2 H, H-6 and H-6′), 3.97 (dd, 1 H, $J_{3,2}$ 4.3, $J_{3,4}$ 10.0 Hz, H-3), 4.43 (dd, 1 H, $J_{2,1}$ 1.6, $J_{2,3}$ 4.3 Hz, H-2), 4.96 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1). ^{13}C NMR ($CDCl_3$): δ 24.4 [NC(O)*Me*], 56.3 (C-2), 61.3 (C-4), 63.3 (C-6), 74.2 (C-3), 77.3 (C-5), 95.7 (C-1), 177.4 [N*C*(O)Me].

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References

[1] M.P. DeNinno, *Synthesis*, (1991) 583–593.
[2] R. Schauer, *Adv. Carbohydr. Chem. Biochem.*, 40 (1982) 131–234.
[3] A. Lubineau and J. Le Gallic, *J. Carbohydr. Chem.*, 10 (1991) 263–268.
[4] G. Estenne, A. Saroli, and A. Doutheau, *J. Carbohydr. Chem.*, 10 (1991) 181–195.
[5] D.G. Comb and S. Roseman, *J. Biol. Chem.*, 235 (1960) 2529–2537.
[6] C. Augé, S. David, C. Gautheron, A. Malleron, and B. Cavayé, *New J. Chem.*, 12 (1988) 733–744.
[7] M.A. Sparks, K.W. Williams, C. Lukacs, A. Schrell, G. Priebe, A. Spaltenstein, and G.M. Whitesides, *Tetrahedron*, 49 (1993) 1–12.
[8] D.C.M. Kong and M. von Itzstein, *Tetrahedron Lett.*, 36 (1995) 957–960.
[9] M. von Itzstein, W-Y. Wu, G.B. Kok, M.S. Pegg, J.C. Dyason, B. Jin, T.V. Phan, M.L. Smythe, H.F. White, S.W. Oliver, P.M. Colman, J.N. Varghese, D.M. Ryan, J.M. Woods, R.C. Bethell, V.J. Hotham, J.M. Cameron, and C.R. Penn, *Nature*, 363 (1993) 418–423.
[10] S. Bennett, M. von Itzstein, and M.J. Kiefel, *Carbohydr. Res.*, 259 (1994) 293–299.
[11] M. von Itzstein, W-Y. Wu, and B. Jin, *Carbohydr. Res.*, 259 (1994) 301–305.
[12] B. Leon, S. Liemann, and W. Klaffke, *J. Carbohydr. Chem.*, 12 (1993) 597–610.
[13] H.H. Brandstetter and E. Zbiral, *Helv. Chim. Acta*, 63 (1980) 327–343.
[14] E. Mark, E. Zbiral, and H.H. Brandstetter, *Monatsh. Chem.*, 111 (1980) 289–307.
[15] M. Černý, I. Černý, and J. Pacák, *Collect. Czech. Chem. Commun.*, 41 (1976) 2942–2951.
[16] H. Paulsen and H. Koebernick, *Chem. Ber.*, 109 (1976) 104–111.
[17] M. Černý and J. Staněk Jr, *Adv. Carbohydr. Chem. Biochem.*, 34 (1977) 23–177.
[18] M. Černý, T. Elbert, and J. Pacák, *Collect. Czech. Chem. Commun.*, 39 (1974) 1752–1767.

[19] M. Černý, H. Večerková, I. Černý, and J. Pacák, *Collect. Czech. Chem. Commun.*, 45 (1980) 1837–1844.
[20] D. Lafont, P. Boullanger, O. Cadas, and G. Descotes, *Synthesis*, (1989) 191–194.
[21] M. Zottola, B.V. Rao, and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, (1991) 969–970.
[22] D. M. Gordon and S.J. Danishefsky, *J. Org. Chem.*, 56 (1991) 3713–3715 and references therein; R. L. Halcomb and S.J. Danishefsky, *J. Am. Chem. Soc.*, 111 (1989) 6661–6666.
[23] (a) H-O. Kalinowski, S. Berger, and S. Braun, *^{13}C-NMR-Spektroskopie*, Thieme, Stuttgart, 1984, pp 400–401; (b) Y. Itoh and S. Tejima, *Chem. Pharm. Bull.*, 30 (1982) 3383–3385; (c) R.G.S. Ritchie, N. Cyr, and A.S. Perlin, *Can. J. Chem.*, 54 (1976) 2301–2309; (d) H. Paulsen, V. Sinnwell, and W. Greve, *Carbohydr. Res.*, 49 (1976) 27–35.
[24] M. von Itzstein, B. Jin, and W-Y. Wu, unpublished results.
[25] J.F. Stoddart, *Stereochemistry of Carbohydrates*, Wiley, New York, 1971, pp 129–145.
[26] S. Coffey (Ed.), *Rodd's Chemistry of Carbon Compounds*, Vol. I, Part F, 2nd ed., Elsevier, Amsterdam, 1967.