Syntheses of model oligosaccharides of biological significance. 4. Synthesis of a fucosylated *N,N'*-diacetylchitobioside and related oligosaccharides[1]

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This paper is dedicated to Professor Peter Yates on the occasion of his 60th birthday

DAVID A. SCHWARTZ, HO-HUAT LEE, JEREMY P. CARVER, and JIRI J. KREPINSKY. Can. J. Chem. **63**, 1073 (1985).

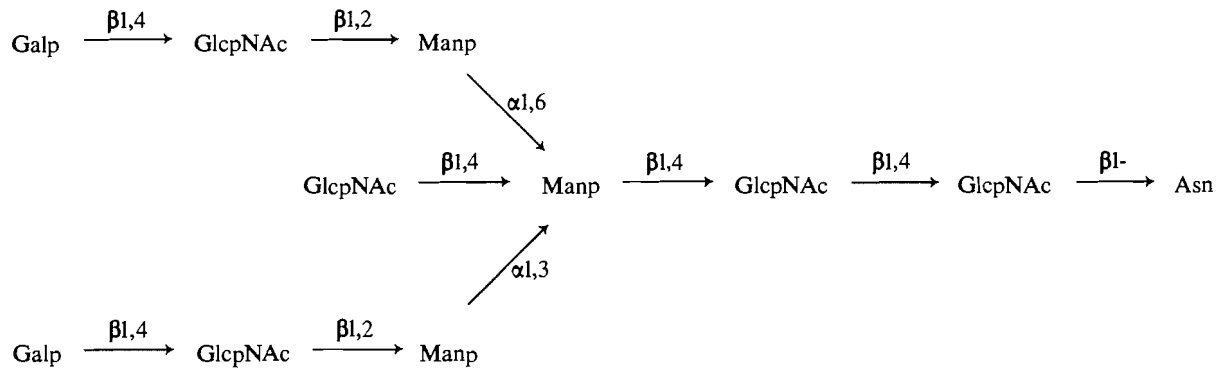
The synthesis of two trisaccharides and one disaccharide containing L-fucose and 2-acetamido-2-deoxy-D-glucose is reported. Methyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside was glycosylated with a 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide. Removal of the phthalimido protecting groups by hydrazinolysis followed by *N*-acetylation and debenzylation yielded methyl *N,N'*-diacetylchitobioside 3',4',6'-triacetate. The latter was selectively fucosylated at the 6-position with 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide to yield, after debenzylation and de-*O*-acetylation, methyl 2-acetamido-4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-6-*O*-(α-L-fucopyranosyl)-β-D-glucopyranoside. When methyl 3-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside was fucosylated, its 6-*O*- and 4,6-di-*O*-(α-L-fucopyranosyl) derivatives were obtained by use of 1 and 2 equivalents, respectively, of the protected fucosyl bromide.

DAVID A. SCHWARTZ, HO-HUAT LEE, JEREMY P. CARVER et JIRI J. KREPINSKY. Can. J. Chem. **63**, 1073 (1985).

On rapporte la synthèse de deux trisaccharides et d'un disaccharide contenant du L-fucose et de l'acétamido-2 déoxy-2 D-glucose. On a glycosylé le di-*O*-benzyl-3,6 déoxy-2 phtalimido-2 β-D-glucopyrannoside de méthyle avec le bromure de tri-*O*-acétyl-3,4,6 déoxy-2 phtalimido-2 β-D-glucopyrannosyle. L'hydrazinolyse du groupe protecteur phtalimido, suivie d'une *N*-acétylation et d'une débenzylation, conduit au N triacétate-3',4',6' du *N,N'*-diacétylchitobioside de méthyle. La fucolisation sélective de ce dernier en position 6 à l'aide du bromure de tri-*O*-benzyl-2,3,4 α-L-fucopyrannosyle, conduit, après débenzylation et dé-*O*-acétylation, à l'acétamido-2 *O*-(acétamido-2 déoxy-2 β-D-glucopyrannosyl)-4 déoxy-2 *O*-(α-L-glucopyrannosyl)-6 β-D-glucopyrannoside de méthyle. La fucosylation du *O*-benzyl-3 déoxy-2 phtalimido-2 β-D-glucopyrannoside par 1 ou 2 équivalents de bromure de fucosyle protégé de méthyle permet d'obtenir les dérivés *O*-6 ou di-*O* (α-L-fucopyranosyle)-4,6.

[Traduit par le journal]

Glycoproteins containing N-linked oligosaccharides are ubiquitous on cell surfaces. All such oligosaccharides contain a core structure which is invariably attached through an *N,N'*-diacetylchitobiosyl linkage to L-asparagine (1), and in some cases this disaccharide moiety is glycosylated with L-fucose (2). We are studying the role of the three-dimensional structure of oligosaccharides such as **1** and **2** in biosynthetic pathways as well as in cell–cell recognition. In addition to this, the complete structures or their fragments can be used as determinants of artificial antigens which may be useful for the prep-



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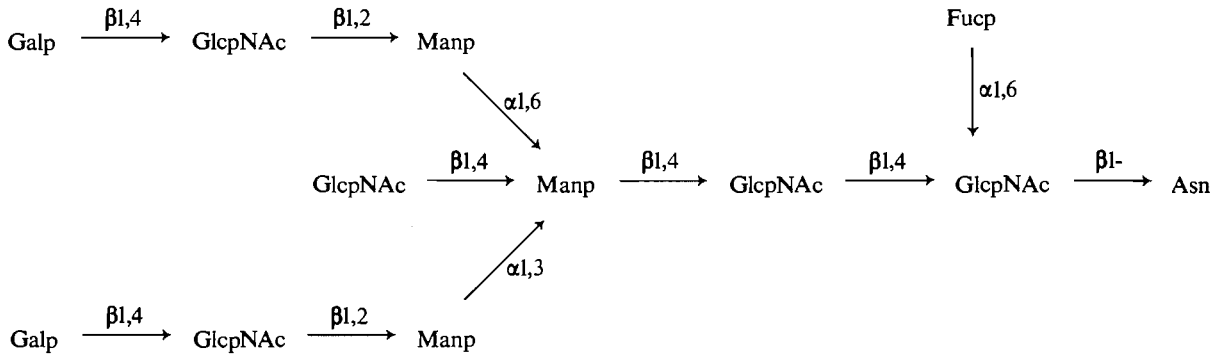
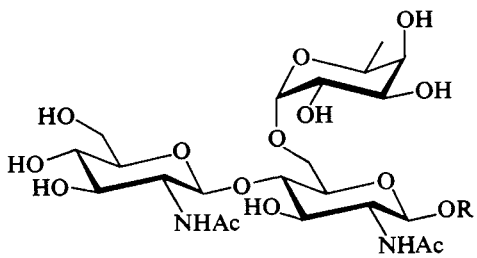


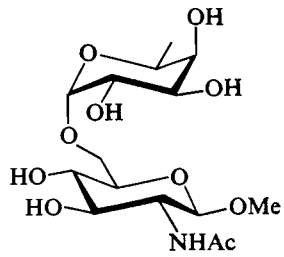
2

aration of diagnostic reagents (2, 3). In our overall synthetic strategy we sought to develop a methodology for the efficient syntheses of smaller oligosaccharides which can be linked together to form **1** or **2**. Thus we have previously reported the syntheses of the mannose-containing portion of the core (4, 5), and herein we describe an efficient and simple synthesis of the chitobiose-fucose part of **2**, i.e. the model trisaccharide **3***a*. We also wanted to prepare the disaccharide **4**, and in the course of this synthesis we observed that the reactivities of OH-6 and OH-4 differ sufficiently to allow a simple preparation of either **4** or **5**.

Trisaccharide **3***b* has already been synthesized (6) in a fairly complicated procedure employing 1,6-anhydro derivatives (20 steps in 1% overall yield). Since OH-4 is much more reactive in the latter than in the conventional $^4C_1$ conformation it seems advantageous to utilize this property for the formation of the 1,4-linkage of chitobiose. However, the use of 1,6-anhydro sugars is also extremely time-consuming, so we set out to design a shorter route which would allow the preparation of substantial quantities of **3***a* and related oligosaccharides relatively rapidly. The efficiency of the synthetic sequence is of particular importance because, eventually, isotopically labelled



3*a* R = Me
b R = H



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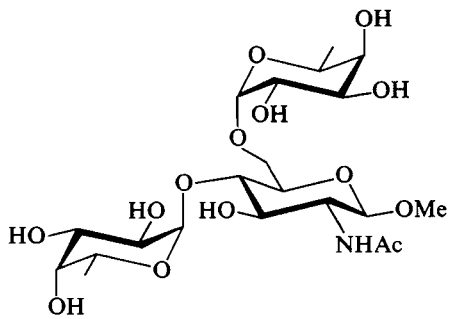

5

fucose is to be incorporated.

Lemieux *et al.* (7) have shown that the OH-4 in 2-amino-2-deoxyglucose is not so unreactive in the $^4C_1$ conformation as to warrant the use of 1,6-anhydro derivatives (8, 9). It was also shown previously (7, 11) that the protection of the amino function as its *N*-phthalimido derivative in glycosylating agents leads to exclusive formation of the desired β-anomer in similar situations. Moreover, in an aglycon moiety, the *N*-phthalimido group cannot participate in an imidate formation as the acetamido group does (10). We have therefore adopted the *N*-phthalimido approach to form a chitobiosyl derivative as, for instance, in the condensation of the aglycon **6***a* with the bromide **7** using silver triflate/collidine as a promoter, which resulted in a 60% yield of the disaccharide **8***a* (11).

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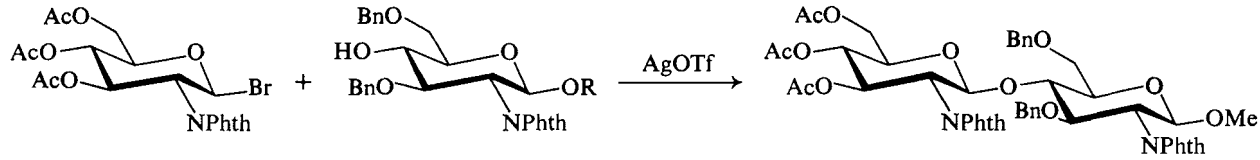
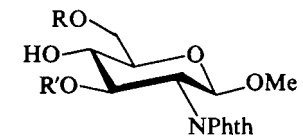


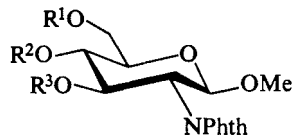
7 6*a* R = CH_2CCl_3; *b* R = Me 8*a* R = CH_2CCl_3; *b* R = Me

The aglycon required for the synthesis of trisaccharide **3***a* should be a derivative of **8** in which the OH-6 is free. Therefore, any protection of this OH group should be removable in the presence of other blocking groups. First we considered the combinations **9** (R = Bn, R^1 = Ac) and **10** (R = *tert*-butyldimethylsilyl, R^1 = Ac).

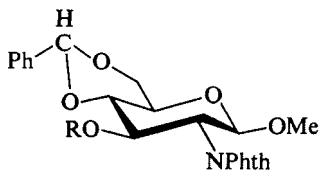
Glycosylation of bromide **7** with methanol using silver triflate/collidine as promoter yielded **11** in 79% yield, with complete β-anomeric specificity (as determined by 360-MHz ^{1}H nmr spectroscopy). This glycosylation was subsequently accomplished more readily and in higher yield (95%) using silver zeolite (13) as the promoter with no loss of anomeric specificity.



9 R = Bn; R^1 = Ac
10 R = Me_2tBuSi—; R = Ac



11 R^1 = R^2 = R^3 = Ac
12 R^1 = R^2 = R^3 = H
15 R^1 = R^2 = H; R^3 = Ac
16 R^1 = Ac; R^2 = R^3 = H
17 R^1 = Bn; R^2 = R^3 = H
18 R^1 = R^3 = Bn; R^2 = H
23 R^1 = R^2 = H; R^3 = Bn



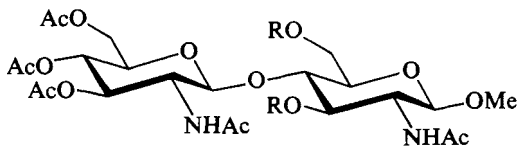
13 R = H
14 R = Ac
19 R = Bn

Zemplén deacetylation gave in 85% yield the triol **12** which after benzylidenation with α,α-dimethoxytoluene/*p*-toluenesulphonic acid gave **13** in 85% yield. Acetylation followed by hydrolysis of the benzylidene moiety gave the 3-acetyl derivative **15** in 80% yield. The structure of **15** was confirmed by its ^{1}H nmr spectrum which exhibited a signal at δ 5.63 characteristic of an acetylated H-3 (dd, J = 10.6 and 9.1 Hz).

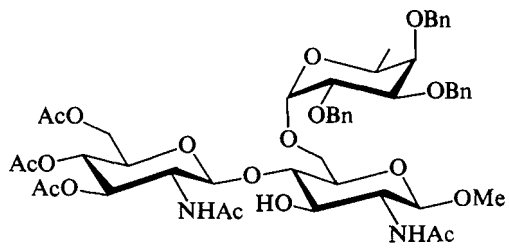
An attempt to synthesize **9** from diol **15** using phase transfer catalysis (14) resulted in isolation of **16** formed by migration of the secondary acetate group to the primary hydroxyl group. The stannylation technique of benzylation (11) yielded only the 6-benzyl derivative **17**, as the acetate was labile under the reaction conditions. We could not obtain the 3,6-dibenzyl derivative by this procedure as has been reported previously (15) for methyl α-D-mannopyranoside.

Unable to synthesize alcohol **9** we turned our attention to alcohol **10**. Direct silylation of diol **15** with *tert*-butyldimethylsilyl chloride and imidazole in DMF gave the desired alcohol **10** in 66% yield. Attempted glycosylation of alcohol **10** with bromide **7** using silver triflate/3,4-dihydro-2*H*-pyrido[1,2-*a*]-pyridinone-2-one (11, 16) in dichloroethane was unsuccessful, presumably because of the steric encumbrance of the bulky silyl protecting group.

Stymied by our previous approaches to make monosaccharides **9** and **10** with differential protection at the 3- and 6-positions of the glycon, we felt that the synthesis of disaccharide **20** (cf. ref. 11) or **8***b*, followed by their debenzylation, would lead to diols which could be selectively fucosylated at the desired, and more accessible, primary 6-position. Acetamido groups in **20** could be a potential problem as they can form an imidate in glycosidation reactions using strong promoters (10). However, it has been shown previously that in glycosidations in which mild promoters were used, certain bases present in the reaction mixture could be responsible for the imidate formation (e.g. Hünig's base, ref. 7*c*). The avoidance of such bases, particularly when the hydroxyl group to be glycosylated is the more reactive primary one (as would be the case in the standard, bromide ion-catalyzed fucosylation (12) of an *N,N'*-diacetylchitobiose derivative by tri-*O*-benzyl-α-L-fucopyranosyl bromide) should therefore suppress the imidate formation.



20 R = Bn
21 R = H



22

The synthesis of the starting alcohol **18** began from the benzylidene derivative **13** which was alkylated in 86% yield with sodium hydride and benzyl bromide in diethoxyethane to give **19** (11). Selective reduction of the benzylidene acetal in **19** using sodium cyanoborohydride (17) gave the desired alcohol **18** in 95% yield. The overall yield of **18** from **7** was 50%.

Glycosylation of alcohol **18** with bromide **7** to give the desired disaccharide **8***b* was accomplished in 46% yield using

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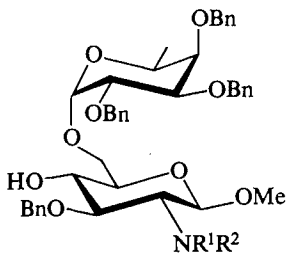
silver triflate/collidine in nitromethane. The ^{1}H nmr spectrum of **8***b* exhibited a doublet at δ 5.53, (J = 8.4 Hz, H-1) and a doublet at 4.87, (J = 8.3 Hz, H-1′). These assignments were confirmed by decoupling experiments (cf. also ref. 11).[3]

In order to synthesize the trisaccharide **3***a* starting from **8***b* we considered two approaches differing in whether the fucosylation would be performed on *N*-phthalimido or *N*-acetyl derivatives. As it as desirable to keep the number of synthetic steps after fucosylation to a minimum because, eventually, isotopically labelled fucose is to be incorporated, the latter was preferred.

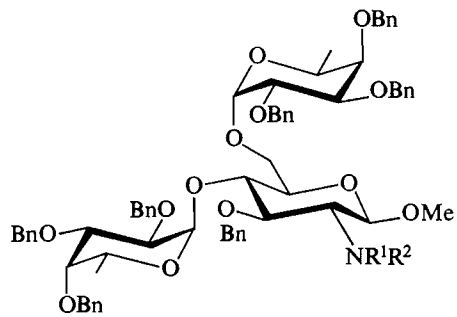
Hydrazinolysis of **8***b* and subsequent acetylation gave the desired *N,N′*-diacetylchitobiose derivative **20** in 75% yield. This disaccharide was debenzylated by hydrogenolysis over palladium-on-charcoal in methanol to give diol **21**. Diol **21** was selectively fucosylated in 65% yield with 1.2 equivalents of 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide (18) using the halide ion-catalyzed procedure (12), i.e., tetraethylammonium bromide and 4A molecular sieves in dichloromethane/DMF. Trisaccharide **22** was deprotected by hydrogenolysis followed by Zemplén deacetylation to give trisaccharide **3***a* in 55% yield.

The structure of **3***a* was confirmed by its ^{1}H nmr spectrum, which exhibited three anomeric doublets: δ 4.91, (J = 3.8 Hz, H-1, α-fucopyranosyl moiety), 4.64, (J = 7.6 Hz, H′) and 4.43 (J = 8.0 Hz, H-1). The broadened quartet at δ 4.13, J = 6.3 Hz and <0.5 Hz is assigned to H-5 on the fucose moiety and is characteristic for a fucose substituted at the 6-position of *N,N′*-diacetylchitobiose (19).

Synthesis of saccharides **4** and **5** began with the hydrolysis of **19** in 60% aqueous acetic acid to give diol **23** in 88% yield. The protected disaccharide **24** was prepared from **23** by taking advantage of the higher reactivity of the primary hydroxyl group in **23** towards 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide **28** (18) in comparison with the secondary hydroxyl. Consequently, the use of 1.2 equivalents of **28** for shorter periods of time leads to almost exclusive formation of **24**, while 2.4 equivalents or more of **28** and prolonged reaction times yield mostly the trisaccharide derivative **25**. It is, however, easy to separate **24** from **25** by chromatography.



24 R¹, R² = Phth
26 R¹ = Ac, R² = H



25 R¹, R² = Phth
27 R¹ = Ac, R² = H

Deprotection of both **24** and **25** by hydrazinolysis followed by *N*-acetylation and hydrogenolysis gave disaccharide **4** and trisaccharide **5**, respectively. The ^{1}H nmr spectra of **4** and **5** were in complete agreement with their structures. Thus, for example, **4** showed two anomeric proton resonances at δ 4.49 (d, J = 3.9 Hz, H-1′) and δ 4.45 (d, J = 8.5 Hz, H-1), a one-proton quartet at δ 4.14 (J = 6.5 Hz, J_2 < 0.5 Hz, H-5′), and a three-proton doublet at δ 1.23 (J = 6.6 Hz, H-6′). Similarly, **5** showed three anomeric proton resonances at δ 5.00 (J = 3.6 Hz, H-1′), 4.91 (J = 3.9 Hz, H-1″), and at 4.44 (J = 8.3, H-1), as well as two three-proton doublets at δ 1.22 and δ 1.14 (J = 6.6 Hz, H-6′ and H-6″).

Complete analysis of the nmr spectra of **3***a*, **4**, and **5** will be published elsewhere in connection with our conformational studies of these oligosaccharides.

Experimental

General methods

Melting points were determined on a Reichert Thermovar melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer polarimeter (Model 140) at 26 ± 1°C. Microanalyses were performed by the Microanalytical Laboratory Ltd., Markham, Ontario. The ^{1}H nmr spectra were recorded at 360 MHz with a Nicolet spectrometer at the Toronto Biomedical NMR Centre, University of Toronto. They were obtained at 23 ± 2°C either in $CDCl_3$ containing 1% TMS as the internal standard or in D_2O (99.996%, Merck, Sharp, and Dohme) with acetone (0.1%, 2.225 ppm relative to internal DSS) as the internal standard. FAB mass spectrometry was performed with a VG Analytical ZAB HF reverse geometry instrument (for general conditions cf. ref. 22 and references therein) at the Institute of Physiological Chemistry, University of Bonn.

Thin layer chromatography (tlc) was performed on silica gel $60F_{254}$ (Merck) plastic plates using the following solvent systems: A, hexane/ethyl acetate (1 : 1); B, ethyl acetate (100%); and visualized by quenching of ultraviolet fluorescence and (or) spraying with 50% aqueous sulfuric acid and heating at 100°C. Silica gel 60 (230–400 mesh; Merck was used for flash chromatography. All glycosylation reactions were performed under an argon atmosphere. All starting materials were dried overnight under vacuum (10^{-3} Torr; 1 Torr = 133.3 Pa) prior to use and all solvents were distilled from appropriate drying agents. Solutions were concentrated at water aspirator pressure unless indicated *in vacuo* (10^{-3} Torr).

The symbols ′ and ″ are used as follows:

$$\text{G}' \text{ (or F}') \xrightarrow[1,6]{1,4 \text{ or}} \text{G} \rightarrow \text{aglycon}$$

$$\text{G}' \xrightarrow{1,4} \text{G} \xrightarrow{1,6} \text{aglycon}, \quad \text{G} \downarrow \text{F}''$$

[3] Symbols used to distinguish monosaccharide units in oligosaccharides are defined in the experimental part.

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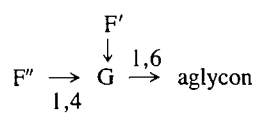

where G represents an *N*-acetylglucosamine unit and F represents a fucose unit.

*Methyl 3,4,5-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**11**)*

Method A

To a cooled solution (−30°C) of methanol (0.9 mL), collidine (3.0 mL; 22.9 mmol), and silver triflate (5.80 g; 22.6 mmol) in nitromethane (25 mL) was added a solution of bromide **7**[4] (9.96 g; 20.0 mmol) in nitromethane (15 mL). The reaction mixture was stirred at −30°C for 1 h (tlc monitored), warmed to room temperature, and filtered through Celite. The filtrate was washed successively with 0.5 *N* aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic extract was dried ($MgSO_4$) and concentrated to give a yellow oil from which **11** was crystallized after dilution with hexane/ethyl acetate (1:1) as a white solid (6.15 g in two crops; 79% yield).

Method B

To a stirred mixture of silver zeolite (20 g) (ref. 13), methanol (6 mL), and dichloromethane (75 mL) was added a solution of bromide (α or β) **7** (20.4 g; 40.9 mmol) in dichloromethane (50 mL). The reaction mixture was protected from light and was stirred at room temperature for 1 h, filtered through Celite, and the filtrate was concentrated to give a syrup (18.0 g) which after recrystallization from hexane/ethyl acetate (1:1) gave microcrystalline **11** (17.0 g; 95% yield from three crops); mp 155–157°C; $[\alpha]_D$ +42.2° (*c* 1.0, chloroform) (lit. (20) mp 160.5–162.0°C; $[\alpha]_D$ +44.7° (*c* 1.1, chloroform); (lit. (21) mp 156–157°C; $[\alpha]_D$ +45.5° (*c* 3.23, chloroform)); R_f(A) 0.3; ^{1}H nmr δ: 7.75–7.90 (m, 4H, $N(CO)_2C_6H_4$), 5.78 (dd, 1H, *J* = 10.6, 9.2 Hz, H-3), 5.30 (d, 1H, *J* = 8.5 Hz, H-1), 3.45 (s, 3H, OCH_3), 2.15, 2.05, and 1.88 (s, 9H, $COCH_3$).

*Methyl 2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**12**)*

This compound was prepared in 85% yield from triacetate **11** and sodium methoxide in methanol according to ref. 20; mp 200–202°C; $[\alpha]_D$ −9.1° (*c* 1.0, methanol) (lit. (20) mp 202.5–204.5°C; $[\alpha]_{589}$ −8.62° (*c* 1.0, methanol)); R_f(A) 0.0, (B) 0.3; ^{1}H nmr δ: 7.85–7.95 (m, 4H, $N(CO)_2C_6H_4$), 5.17 (d, 1H, *J* = 8.3 Hz, H-1), 3.43 (s, 3H, OCH_3).

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**13**)*

Compound **13** was prepared in 85% yield from triol **12**, α,α-dimethoxytoluene, and *p*-toluenesulphonic acid in acetonitrile (7). After recrystallization from hexane/ethyl acetate (1:1) a colourless microcrystalline solid was isolated; mp 192–194°C; $[\alpha]_D$ +63.2° (*c* 1.0, chloroform); R_f(A) 0.43; ^{1}H nmr δ: 7.72–7.88 (m, 4H, $N(CO)_2C_6H_4$), 7.36–7.51 (m, 5H, C_6H_5CH), 5.60 (s, 1H, CHC_6H_5CH), 5.21 (d, 1H, *J* = 8.4 Hz, H-1), 3.45 (s, 3H, OCH_3), 2.38 (s, 1H, D_2O exch., O*H*). *Anal.* calcd. for $C_{22}H_{21}NO_7$: C 64.23, H 5.14, N 3.40; found: C 64.44, H 5.20, N 3.46.

*Methyl 3-*O*-acetyl-4,6-benzylidene-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**14**)*

Acetic anhydride (12.5 mL) was mixed with a cooled solution (0°C) of **13** (5.95 g; 14.4 mol) in pyridine (25 mL) and the reaction mixture was stirred overnight at room temperature. The colourless solution was poured onto crushed ice; the separated solid was collected by filtration, and dried *in vacuo*, to give **14** as an amorphous solid (5.90 g; 90% yield); $[\alpha]_D$ +4.0° (*c* 1.0, chloroform); R_f(A) 0.46; ^{1}H nmr δ: 7.7–7.9 (m, 4H, $N(CO)_2C_6H_4$)), 7.3–7.5 (m, 5H, C_6H_5CH), 5.88 (dd, 1H, *J* = 10.2 and 9 Hz, H-3), 5.55 (s, 1H, C_6H_5CH), 5.37 (d, 1H, *J* = 8.4 Hz, H-1), 3.45 (s, 3H, OCH_3). *Anal.* calcd. for $C_{24}H_{23}NO_8$: C 63.57, H 5.11, N 3.09; found: C 63.44, H 5.26, N 3.14.

*Methyl 3-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**15**)*

A solution of **14** (1.05 g; 2.31 mmol) in 60% acetic acid (50 mL) was heated at 100°C for 30 min (tlc monitored). The solvent was removed *in vacuo* to give diol **15** as a colourless solid (748 mg; 88% yield). Recrystallization from hexane/ethyl acetate gave **15** as a microcrystalline solid; mp 84–86°C; $[\alpha]_D$ +74.4° (*c* 1.0, chloroform); R_f(B) 0.45; ^{1}H nmr δ: 7.85–7.95 (m, 4H, $N(CO)_2C_6H_4$), 5.63 (dd, 1H, *J* = 10.6 and 9.1 Hz, H-3), 5.30 (d, 2H, *J* = 8.4 Hz, H-1), 3.45 (s, 3H, OCH_3), 2.8 (br s, 2H, O*H*), 1.95 (s, 3H, $COCH_3$).

*Methyl 6-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**16**)*

A solution of diol **15** (200 mg; 0.54 mmol), tetra-*n*-butylammonium hydrogen sulfate (40 mg; 0.11 mmol), and benzyl bromide (0.1 mL; 0.82 mmol) in dichloromethane was added to a solution of aqueous NaOH (1 *M*; 0.65 mL; 0.65 mmol) in water (5 mL), and heated under reflux for 16 h. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated to a colourless oil. Flash chromatography on silica gel (hexane/ethyl acetate (35:65)) gave **16** as an amorphous solid; R_f(B) 0.44; ^{1}H nmr δ: 7.85–7.95 (m, 4H, $N(CO)_2C_6H_4$), 5.15 (d, 1H, *J* = 8.4 Hz, H-1), 4.67 (dd, 1H, *J* = 12.4 and 3.5 Hz, H-6), 4.29 (dd, *J* = 12.4 and 2.2 Hz, H-6'), 3.44 (s, 3H, OCH_3), 2.05 (s, 3H, $COCH_3$).

*Methyl 6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**17**)*

A solution of diol **15** (200 mg; 0.55 mmol) and bis(tri-*n*-butyl tin) oxide (0.30 mL; 0.58 mmol) in toluene (8 mL) was heated under reflux with continuous removal of water for 3 h. The solution was cooled to room temperature, the solvent was removed *in vacuo*, and the residue was dissolved in benzyl bromide (5 mL) and heated at 85°C for 18 h. After processing as described (11), the colourless residual oil was purified by flash chromatography on silica gel (ethyl acetate) to give **17** as an oil; R_f(B) 0.55; ^{1}H nmr δ: 7.85–7.95 (m, 4H, $N(CO)_2C_6H_4$), 6.82–7.03 (m, 5H, $C_6H_5CH_2$), 5.15 (d, 1H, *J* = 8.4 Hz, H-1), 3.85 (m, 2H, H-6), 3.43 (s, 3H, OCH_3).

*Methyl 3-*O*-acetyl-6-*O*-(tert-butyl)dimethylsilyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**10**)*

A solution of diol **14** (560 mg; 3.83 mmol) in DMF (5 mL) containing *tert*-butyldimethylsilyl chloride (277 mg; 1.84 mmol) and imidazole (260 mg; 3.83 mmol) was stirred overnight at room temperature. The colourless solution was diluted with ether, washed successively with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residual oil was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:1) as eluant; a colourless solid was isolated which was crystallized from hexane/ethyl acetate (490 mg; 66% yield); mp 138.5–140°C; $[\alpha]_D$ +0.6 (*c* 1.0, chloroform); R_f(A) 0.45; ^{1}H nmr δ: 7.85–7.95 (m, 4H, $N(CO)_2C_6H_4$), 5.65 (dd, 1H, *J* = 10.7, 8.3 Hz, H-3), 5.28 (d, 1H, *J* = 8.5 Hz, H-1); 3.45 (s, 3H, OCH_3), 1.95 (s, 3H, $COCH_3$), 1.6 (s, 1H, D_2O exch., O*H*), 0.95 (s, 9H, $(CH_3)_3C$), 0.10 (s, 6H, $SiCH_3$). *Anal.* calcd. for $C_{23}H_{33}NO_8Si$: C 57.60, H 6.93, N 2.92; found: C 57.71, H 7.04, N 2.90.

*Methyl 3-*O*-benzyl-4,6-benzylidene-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**19**)*

Compound **19** was prepared in 86% yield from alcohol **13**, sodium hydride, and benzyl bromide in dimethoxyethane as described (11). Following work-up, the residual oil was crystallized from hexane/ethyl acetate (1:1); mp 124–125°C; $[\alpha]_D$ +58.0° (*c* 1.0, chloroform); R_f(A) 0.55; ^{1}H nmr δ: 7.72 (br s, 4H, $N(CO)_2C_6H_4$), 7.42–7.6 (m, 5H, C_6H_5CH), 6.85–7.05 (m, 5H, $C_6H_5CH_2$), 5.63 (s, 1H, C_6H_5CH), 5.15 (d, 1H, *J* = 8.5 Hz, H-1), 4.20 (dd, 1H, *J* = 10.4 and 8.5 Hz, H-2), 3.40 (s, 3H, OCH_3). *Anal.* calcd. for $C_{29}H_{27}NO_7$: C 69.45, H 5.43, N 2.79; found: C 69.28, H 5.23, N 2.82.

*Methyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (**18**)*

To a mixture of compound **19** (1.0 g; 2.0 mmol), powdered molecular sieves (3A Linde; 25 g), and sodium cyanoborohydride (385 mg;

[4] This compound and some other intermediates were purchased from Toronto Research Chemicals, 100 College St., Toronto, Ont., Canada M5G 1L5.

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6.0 mmol) in THF (50 mL) was added dropwise a saturated solution of HCl in dry diethyl ether until the gas evolution ceased (17). The reaction mixture was stirred at room temperature until the starting material completely disappeared (1 h; tlc monitored). When compound **19** was present after 1 h, a small amount of ethereal HCl was added and stirring was continued. After the work-up as described (17), a colourless oil was isolated; $[\alpha]_D$ 39.4° (*c* 1.9, chloroform); R_f(A) 0.40; ^{1}H nmr δ: 7.6–7.75 (m, 4H, $N(CO)_2C_6H_4$), 7.2–7.4 (m, 5H, $C_6H_5CH_2$), 6.9–7.1 (m, 5H, $C_6H_5CH_2$), 5.06 (d, 1H, *J* = 8.3 Hz, H-1) 4.23 (dd, 1H, *J* = 10.7 and 8.3 Hz, H-3), 4.13 (dd, 1H, *J* = 10.7 and 8.3 Hz, H-2), 3.38 (s, 3H, OCH_3), 2.95 (s, 1H, D_2O exch., O*H*). *Anal.* calcd. for $C_{29}H_{29}NO_7$: C 69.17, H 5.80, N 2.78; found: C 68.92, H 5.63, N 2.69.

*Methyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-4-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)-*β*-D-glucopyranoside (8*b*)*

To a solution of silver triflate (479 mg; 1.86 mmol), collidine (0.250 mL; 1.90 mmol), and alcohol **18** (875 mL; 1.74 mmol) in dry nitromethane (5 mL) cooled to −25°C was added a solution of bromide **7** (942 mg; 1.89 mmol) in dry nitromethane (3 mL). The reaction mixture was stirred at −25°C for 4 h, allowed to warm to room temperature, and a second equivalent of silver triflate (480 mg; 1.86 mmol) and collidine (0.250 mL; 1.90 mmol) was added followed by the addition of a solution of bromide **7** (950 mg; 1.97 mmol) in nitromethane (5 mL). The reaction mixture was protected from light, stirred overnight, and then filtered through Celite. The filtrate was diluted with dichloromethane (25 mL) and washed successively with 1 *N* aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated to a brown syrup (2.8 g). Further purification by flash chromatography on silica gel using hexane/ethyl acetate (1:1) gave starting alcohol **18** (470 mg) and disaccharide **8***b* as an oil (742 mg; 46% yield); $[\alpha]_D$ −8.6, (*c* 2.1, chloroform); R_f(A) 0.26; ^{1}H nmr δ: 7.75–7.95 (m, 4H, $N(CO)_2C_6H_4$), 7.65 (br s, 4H, $N(CO)_2C_6H_4$), 7.30–7.35 (m, 5H, $C_6H_5CH_2$), 6.80–7.05 (m, 5H, $C_6H_5CH_2$), 5.79 (dd 1H, *J* = 11.0 and 9.0 Hz, H-3′), 5.53 (d, 1H, *J* = 8.4 Hz, H-1), 4.87 (d, 1H, $J_{1,2}$ = 8.3 Hz, H-1′), 3.28 (s, 3H, OCH_3), 2.00, 1.97, and 1.84 (3s, 9H, $COCH_3$). *Anal.* calcd. for $C_{49}H_{48}N_2O_{16}$: C 63.91, H 5.25, N 3.04; found: C 63.70, H 5.41, N 2.90.

*Methyl 2-acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-*β*-D-glucopyranoside (20)*

A solution of disaccharide **8***b* (248 mg; 0.27 mmol), hydrazine hydrate (85%; 2 mL), and 95% aqueous ethanol (10 mL) was gently heated under reflux for 30 min. After cooling to 0°C the reaction mixture was filtered and the filtrate was evaporated to dryness (pale yellow solid, 230 mg). The residue was dissolved in pyridine (5 mL) and acetic anhydride (2 mL) and stirred overnight at room temperature. After the usual work-up the residue was triturated with hexane/ethyl acetate (1:1), the solid **20** was isolated by filtration (75 mg), and another portion of **20** (75 mg) was isolated by concentration of the filtrate followed by crystallization from hexane/ethyl acetate (1:1). The total yield of **20** was 75%; mp 246–248°C; $[\alpha]_D$ −10.6° (*c* 1.0, methanol); R_f(B) 0.64; ^{1}H nmr δ: 7.3–7.5 (m, 10H, $C_6H_5CH_2$), 6.15 (d, 1H, *J* = 9 Hz, N*H*$COCH_3$), 5.19 (d, 1H, *J* =9 Hz, N*H*$COCH_3$), 4.49 (d, 1H, *J* = 6.0 Hz, H-1), 4.36 (d, 1H, *J* = 8.4 Hz, H-1′), 3.43 (s, 3H, OCH_3), and 2.09, 2.04, 2.03, 2.01, and 1.96 (5s, 15H, $COCH_3$). *Anal.* calcd. for $C_{37}H_{48}N_2O_{14}$: C 59.67, H 6.50, N 3.76; found: C 59.50, H 6.39, N 3.69.

*Methyl 2-acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-2-deoxy-*β*-D-glucopyranoside (21)*

Compound **20** (300 mg; 0.40 mmol) was hydrogenolyzed over palladium-on-carbon in methanol (10 mL) at atmospheric pressure for 16 h. After the usual work-up **21** was obtained as a colourless solid (235 mg; 87% yield). This product was used without further purification; $[\alpha]_D$ −21.7° (*c* 1.0, methanol); ^{1}H nmr δ: 5.10 (t, 1H, *J* = 8.6 Hz, H-3′), 5.04 (t, 1H, *J* = 8.6 Hz, H-4′), 4.62 (d, 1H, *J* = 8.6 Hz, H-1′), 4.42 (d, 1H, *J* = 8.3 Hz, H-1), 3.48 (s, 3H, OCH_3), 2.09, 2.04, 2.03, 2.01, and 1.96 (5s, 15H, $COCH_3$). *Anal.* calcd. for $C_{23}H_{36}N_2O_{14}$: C 48.93, H 6.43, N 4.96; found: C 49.03, H 6.55, N 5.03.

*Methyl 2-acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-6-*O*-(2,3,4-tri-*O*-benzyl-*α*-L-fucopyranosyl)-2-deoxy-*β*-D-glucopyranoside (22)*

To a mixture of diol **21** (290 mg; 0.51 mmol), tetraethylammonium bromide (323 mg; 1.53 mmol), and powdered molecular sieves (4A Linde; 1.5 g) in dry dichloromethane (5 mL) and DMF (5 mL) was added a solution of tribenzylfucopyranosyl bromide (ref. 18) (310 mg; 0.624 mmol) in dichloromethane (5 mL). After stirring at room temperature for 16 h, the solids were removed by filtration and the filtrate was washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness to give an amorphous white solid (600 mg) which after trituration with hexane/ethyl acetate (1:1) gave crystalline **22** (325 mg; 65% yield); mp 258–260°C; $[\alpha]_D$ −60.3° (*c* 1.0, methanol); R_f(B) 0.14; ^{1}H nmr δ: 7.2–7.6 (m, 15H, $C_6H_5CH_2$), 6.6 (d, 1H, *J* = 10.5 Hz, N*H*$COCH_3$), 5.42 (d, 1H, *J* = 10.5 Hz, N*H*$COCH_3$), 4.69 (d, 1H, *J* = 3.5 Hz, H-1″), 4.41 (d, 1H, *J* = 8.6 Hz, H-1′), 4.30 (d, 1H, *J* = 8.3 Hz, H-1), 3.41 (s, 3H, OCH_3), 2.09 (s, 3H, $COCH_3$), 2.0 (s, 6H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 1.77 (s, 3H, $COCH_3$), 1.12 (d, 3H, *J* = 6.4 Hz, H-6″). *Anal.* calcd. for $C_{50}H_{64}N_2O_{18}$: C 61.21, H 6.58, N 2.85; found: C 61.09, H 6.73, N 2.92.

*Methyl 2-acetamido-4-*O*-(2-acetamido-2-deoxy-*β*-D-glucopyranosyl)-2-deoxy-6-*O*-(*α*-L-fucopyranosyl)-*β*-D-glucopyranoside (3*a*)*

Compound **21** (280 mg; 0.48 mmol) was debenzylated by hydrogenolysis as described for **22**. The product was de-*O*-acetylated with sodium methoxide in methanol and neutralized with 10% aqueous acetic acid. Following evaporation of the solvent, the residue was dissolved in distilled water and passed through a column (150 mm × 15 mm) of mixed bed resin (BioRad AG501-X8). Trisaccharide **3***a* was isolated as a white crystalline solid (85 mg, 55% yield). Recrystallization from ethanol/water gave an analytical sample; mp 298–300°C (dec.); $[\alpha]_D$ −4.3° (*c* 0.57, H_2O); ^{1}H nmr δ: 4.91 (d, 1H, *J* = 8.0 Hz, H-1″), 4.64 (d, 1H, *J* = 7.6 Hz, H-1′), 4.43 (d, 1H, *J* = 8.0 Hz, H-1), 4.13 (br q, 1H, *J* = 6.5, J_2 < 0.5 Hz, H-5″), 2.08 (s, 3H, $COCH_3$), 2.03 (s, 3H, $NHCOCH_3$), 1.23 (d, 3H, *J* = 6.6 Hz, H-6″); *m/e*: 583, $(M - 1)^-$. *Anal.* calcd. for $C_{23}H_{40}N_2O_{15}$: C 47.25, H 6.90, N 4.79; found: C 47.19, H 6.82, N 4.83.

*Methyl 3-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranoside (23)*

A solution of **19** (4.10 g; 8.15 mmol) in 60% aqueous acetic acid (50 mL) was heated at 100°C for 30 min (tlc monitored). The solvents were removed *in vacuo* to give diol **23** accompanied by a small amount of the 6-acetate derivative. Pure **23** was obtained by flash chromatography on silica gel using ethyl acetate as a microcrystalline solid (2.90 g; 88% yield); mp 120.5–122°C; $[\alpha]_D$ +57.2° (*c* 1.0, chloroform); R_f(A) 0.12; ^{1}H nmr δ: 7.75 (br s, 4H, $N(CO)_2C_6H_4$), 7.0–7.15 (m, 5H, $C_6H_5CH_2$), 5.10 (d, 1H, *J* = 8.4 Hz, H-1), 3.40 (s, 3H, OCH_3). *Anal.* calcd. for $C_{22}H_{23}NO_7$: C 63.92, H 5.61, N 3.39; found: C 63.78, H 5.80, N 3.34.

*Methyl 3-*O*-benzyl-2-deoxy-2-phthalimido-6-*O*-(2,3,4-tri-*O*-benzyl-*α*-L-fucopyranosyl)-*β*-D-glucopyranoside (24)*

To a mixture of diol **23** (450 mg; 1.09 mmol), tetraethylammonium bromide (1.14 g; 5.4 mmol), and powdered molecular sieves (4A Linde; 2.5 g) in dichloromethane (10 mL) was added a solution of tribenzylfucosyl bromide (ref. 18) (650 mg; 1.3 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 6 h and filtered through Celite. The filtrate was washed with water, dried ($MgSO_4$), filtered, and concentrated to give a colourless oil (1.2 g). Flash chromatography on silica gel (hexane/ethyl acetate (2:1)) gave **24** as a colourless oil (380 mg; 42% yield); $[\alpha]_D$ −7.0° (*c* 0.86, chloroform); R_f(A) 0.42; ^{1}H nmr δ: 7.6–7.8 (m, 4H, $N(CO)_2C_6H_4$), 7.2–7.6 (m, 15H, $C_6H_5CH_2$), 6.9–7.1 (m, 5H, $C_6H_5CH_2$), 5.01 (d, 1H, *J* = 8.4 Hz, H-1) 4.82 (d, 1H, *J* = 4.4 Hz, H-1′), 3.33 (s, 3H, OCH_3), 1.16 (d, 1H, *J* = 6.5 Hz, H-5′). *Anal.* calcd. for $C_{49}H_{51}NO_{11}$: C 70.91, H 6.19, N 1.69; found: C 70.80, H 6.22, N 1.73.

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Methyl 3-O-benzyl-2-deoxy-2-phthalimido-4,6-di-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-β-D-glucopyranoside (25)

To a mixture of diol **23** (625 mg; 1.51 mmol), tetraethylammonium bromide (1.59 g; 7.57 mmol), and powdered freshly activated molecular sieves (4A Linde; 1.50 g) in dichloromethane (10 mL) was added a solution of tribenzylfucosyl bromide (ref. 18) (1.45 g; 2.91 mmol) in dichloromethane (5 mL). The reaction mixture was stirred overnight at room temperature and filtered through Celite. The filtrate was washed with water, dried ($MgSO_4$), filtered, and concentrated to 2.2 g of a brown oil. Flash chromatography on silica gel using hexane/ethyl acetate (2:1) as eluant gave two major fractions. The more polar fraction, R_f(A) 0.42, was disaccharide **24** (365 mg; 30% yield).

The less polar fraction, R_f(A) 0.61, was trisaccharide **25** (425 mg) as a colourless oil; $[\alpha]_D$ −38.2° (*c* 0.6, chloroform); ^{1}H nmr δ: 7.6–7.8 (m, 4H, $N(CO)_2C_6H_4$), 7.2–7.5 (m, 30H, $C_6H_5CH_2$), 7.0 (m, 5H, $C_6H_5CH_2$), 5.35 (d, 1H, *J* = 3.2 Hz, H-1), 3.26 (s, 3H, OCH_3), 1.04 (d, 3H, *J* = 6.5 Hz, H-6′ or H-6″), 0.82 (d, 3H, *J* = 6.5 Hz, H-6′ or H-6″). *Anal.* calcd. for $C_{76}H_{79}NO_{15}$: C 73.23, H 6.39, N 1.12; found: C 73.11, H 6.45, N 1.01.

Methyl 2-acetamido-3-O-*benzyl-2-deoxy-6-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-β-D-glucopyranoside (26)*

A solution of **24** (250 mg; 0.31 mmol) and hydrazine hydrate (85%; 2 mL) in 95% aqueous ethanol (10 mL) was gently heated under reflux for 20 min. The reaction mixture was concentrated to dryness to give a non-crystalline yellowish residue which was dissolved in a mixture of 50% aqueous methanol (10 mL) and acetic anhydride (3 mL) and sitrred at room temperature overnight. The precipitate which formed was isolated by filtration and dried *in vacuo* to give crystalline **26** (133 mg; 60% yield); mp 197–200°C; $[\alpha]_D$ −44.5° (*c* 0.7, chloroform); R_f(B) 0.48; ^{1}H nmr δ: 7.2–7.5 (m, 20H, $C_6H_5CH_2$), 5.37 (d, 1H, *J* = 9 Hz, N*H*COCH$_3$, 3.42 (s, 3H, OCH_3), 1.90 (s, 3H, NHCOCH_3), 1.17 (d, 3H, *J* = 6.5 Hz, H-6′). *Anal.* calcd. for $C_{43}H_{51}NO_{10}$: C 69.61, H 6.94, N 1.89; found: C 69.82, H 7.11, N 1.94.

Methyl 2-acetamido-2-deoxy-6-O-(α-L-fucopyranosyl)-β-D-glucopyranoside (4)

Compound **26** (210 mg; 0.28 mmol) was stirred with 10% palladium-on-charcoal (50 mg) in 75% aqueous methanol (10 mL) under hydrogen (1 atm (= 101.3 kPa)) for 18 h. Following filtration through Celite the filtrate was concentrated *in vacuo* and the resulting colourless solid was dissolved in water and passed through a column (150 mm × 15 mm) of mixed bed resin (BioRad AG501-X8) to give a desalted solution of disaccharide **4**. Pure **4** was obtained following lyophilization as an amorphous solid (89 mg; 83% yield); $[\alpha]_D$ −20.6° (*c* 0.38; H_2O); ^{1}H nmr δ: 4.94 (d, 1H, *J* = 3.9 Hz, H-1′), 4.45 (d, 1H, *J* = 8.5 Hz, H-1), 4.14 (br q, 1H, *J* = 6.5, $J_2 < 0.5$ Hz, H-5′), 3.50 (s, 3H, OCH_3), 2.04 (s, 3H, NHCOCH_3), 1.23 (d, 3H, *J* = 6.5 Hz, H-6′); *m/e*: 380 $(M-1)^-$. *Anal.* calcd. for $C_{15}H_{27}NO_{10}$: C 47.24, H 7.14, N 3.69; found: C 7.01, H 7.02, N 3.58.

Methyl 2-acetamido-3-O-benzyl-2-deoxy-4,6-di-O-(2,3,4-tri-O-benzyl-α-D-fucopyranosyl)-β-D-glucopyranoside (27)

A solution of compound **25** (248 mg; 0.21 mmol) and hydrazine hydrate (85%; 1 mL) in 95% aqueous ethanol (5 mL) was gently heated under reflux for 20 min. The reaction mixture was evaporated to dryness *in vacuo* and the resulting yellow amorphous residue was treated at room temperature with pyridine (5 mL) and acetic anhydride (1 mL). After the usual work-up a colourless oil (220 mg) was isolated. Flash chromatography on silica gel using hexane/ethyl acetate (2:3) gave **27** as a colourless oil (110 mg; 48% yield); $[\alpha]_D$ −41.5° (*c* 1.0, chloroform); R_f(A) 0.25; ^{1}H nmr δ: 7.1–7.5 (m, 35H, $C_6H_5CH_2$), 6.29 (d, 1H, *J* = 9.2 Hz, N*H*COCH$_3$, 5.29 (d, 1H, *J* = 3.1 Hz, H-1), 3.38 (s, 3H, OCH_3), 1.63 (s, 3H, NHCOCH_3), 1.03 (d, 3H, *J* = 6.4 Hz, H-6′ or H-6″), 0.96 (d, 3H, *J* = 6.4 Hz, H-6′ or H-6″).

Methyl 2-acetamido-2-deoxy-4,6-di-O-(α-L-fucopyranosyl-β-D-glucopyranoside (5)

Compound **27** (200 mg; 0.17 mmol) was deprotected to give **5** in a similar manner as it was used to prepare **4**. Trisaccharide **5** was a colourless amorphous solid (77 mg; 85% yield); $[\alpha]_D$ −3.8° (*c* 0.63, H_2O); ^{1}H nmr δ: 5.00 (d, 1H, *J* = 3.6 Hz, H-1′ or H-1″), 4.91 (d, 1H, *J* = 3.9 Hz, H-1′ or H-1″), 4.44 (d, 1H, *J* = 8.3 Hz, H-1), 4.34 (br q, 1H, *J* = 6.6 Hz, H-5′ or H-5″), 4.13 (br q, 1H, *J* = 6.6 Hz, H-5′ or H-5″), 3.49 (s, 3H, OCH_3), 1.22 (d, 3H, *J* = 6.6 Hz, H-6′ or H-6″), 1.14 (d, 3H, *J* = 6.6 Hz, H-6′ or H-6″).

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