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Synthesis of Lewis X and three Lewis X trisaccharide analogues in which glucose and rhamnose replace *N*-acetylglucosamine and fucose, respectively

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Abstract—Three analogues of the Le^x trisaccharide: α-L-Fuc*p*-(1→3)-[β-D-Gal*p*-(1→4)]-D-GlcNAc*p* as well as the Le^x trisaccharide itself were synthesized as methyl glycosides. In the analogues, either only the fucose residue is replaced by rhamnose or both the *N*-acetylglucosamine and the fucosyl residues are replaced by glucose and rhamnose, respectively. Our synthetic strategy relied on the use of lactoside and 2-azido lactoside derivatives as disaccharide acceptors, which were submitted to either fucosylation or rhamnosylation. Our results confirm that the reactivity of lactose in protection and glycosylation reactions is greatly affected by (1) the structure of the aglycone and (2) the presence of an azido substituent at C-2 of the glucose moiety. Thus, a methyl lactoside acceptor was easily glycosylated at O-3 with perbenzylated β-thiophenyl fucoside and rhamnoside to give anomerically pure α-fucosylated and α-rhamnosylated trisaccharides, respectively. In contrast, the same reactions on a 2-azido methyl lactoside acceptor led to the formation of anomeric mixtures. While the α- and β-fucosylated 2-azido trisaccharides could be separated by RP-HPLC, such separation was not possible for the rhamnosylated anomers. The desired rhamnosylated trisaccharide was finally obtained anomerically pure using an isopropylidene-protected rhamnosyl donor. The deprotection sequences also showed that the presence of a 2-azido substituent at C-2 of the glucose residue conferred stability to the vicinal fucosidic linkage at C-3. To test their relative affinity for anti-Le^x Abs the Le^x analogues will be used as competitive inhibitors against methyl Le^x. In addition, their conformational behavior will be studied by NMR spectroscopy and molecular modeling experiments.

Keywords: Lewis X analogues; Oligosaccharide synthesis; Reversed-phase HPLC; Lactosides; 2-Azido lactosides

1. Introduction

Since it was first characterized,[1] the Le^x antigenic determinant: α-L-Fuc*p*-(1→3)-[β-D-Gal*p*-(1→4)]-D-GlcNAc*p* has been found on numerous normal cells and tissues such as kidney tubules, gastrointestinal epithelial cells, and cells of the spleen and brain.[2] In contrast, the hexasaccharide dimLe^x **1** (Chart 1) has been identified as a tumor associated carbohydrate antigen (TACA).[3] Interestingly, monoclonal antibodies raised and selected against dimLe^x (**1**) were shown to bind specifically to epitopes displayed by dimLe^x on colorectal tumor tissues while they only weakly recognized the Le^x trisaccharide antigen.[3a,f] The observation that these MAbs are able to distinguish between the polyfucosylated type 2 chains, such as dimeric Le^x, accumulating in cancer cells and the monofucosylated type 2 chains displaying Le^x and present in normal cells opens the possibility of using dimeric Le^x as a vaccine candidate. However, if used directly as a vaccine candidate, the dimLe^x hexasaccharide is likely to trigger anti-dimLe^x antibodies, as well as antibodies binding to the non-reducing trisaccharide Le^x.

Because such reactions could lead to the destruction of normal cells displaying Le^x,[2] we are proposing to investigate as vaccine candidates analogues of hexasaccharide **1** in which one of the sugar units defining the Le^x epitope is replaced by other sugar residues,

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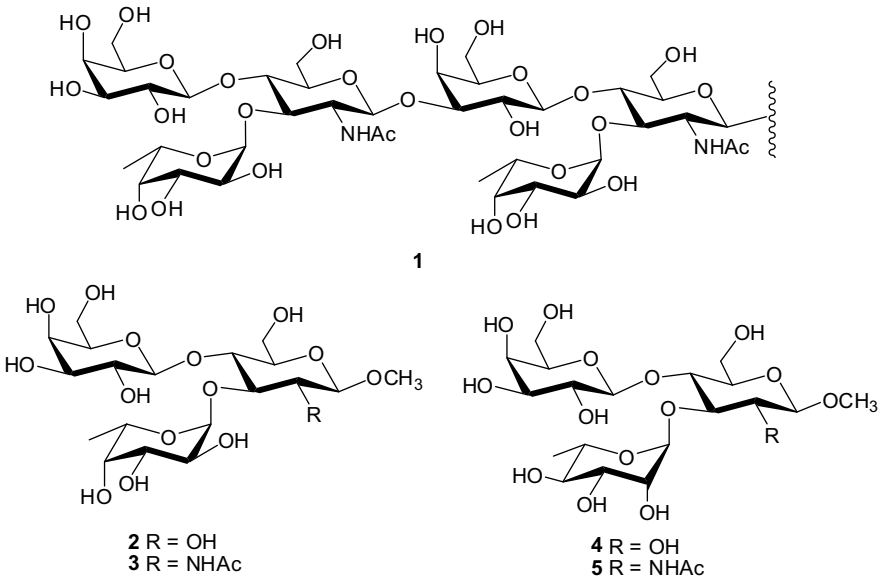


Chart 1.

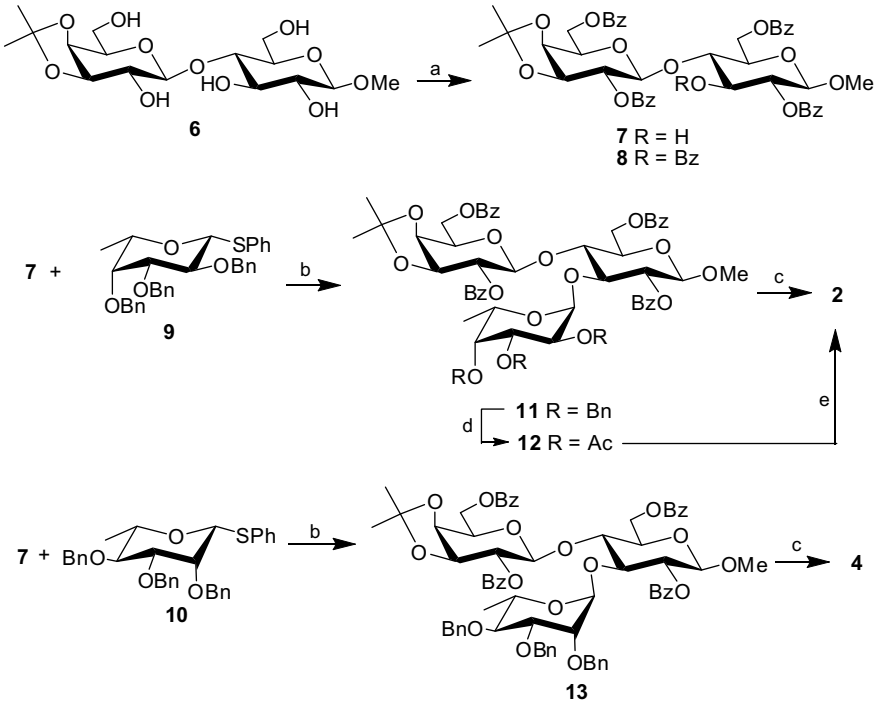
i.e., *N*-acetylglucosamine (A′) by glucose, fucose (B′) by rhamnose, or galactose (C′) by glucose. These analogues are expected to retain the internal epitopes presented on the surface of colorectal cancer cells by dimLe^x but no longer possess epitopes associated with the Le^x trisaccharide. To identify analogues that loose cross-reactivity with the natural Le^x antigen, we have first embarked on the chemical synthesis of trisaccharide analogues to be used in competitive binding experiments with the Le^x antigen (**3**). We are reporting here the chemical synthesis of three trisaccharide analogues of Le^x (**2**, **4**, **5**) in which either only the *N*-acetylglucosamine is replaced by glucose or in which both the *N*-acetylglucosamine and the fucosyl residues are replaced by glucose and rhamnose, respectively. Numerous syntheses of Le^x analogues and Le^x intermediate building blocks have been reported in the literature.[4–6] These syntheses usually follow one of three synthetic strategies: (1) a stepwise approach involving the successive galactosylation then fucosylation of a glucosamine acceptor;[4] (2) a stepwise approach in which the sequence of glycosylation of the glucosamine acceptor is reversed, that is, the fucosylation is followed by the galactosylation;[5] (3) a block approach in which a lactosamine derivative prepared from lactose is subjected to fucosylation at O-3.[6] Expanding on our previous work that used an allyl β-lactoside as key intermediate in the synthesis of allyl Le^x analogues,[7] we report here the preparation of the methyl trisaccharides **2** and **4** from methyl β-lactoside. Similarly, applying the strategy developed by Windmüller and Schmidt,[6a] we report here the synthesis of the known[5e] methyl Le^x trisaccharide **3** and that of the rhamnosylated analogue **5** via the glycosylation of a methyl 2-azido-2 deoxy β-lactoside acceptor that was prepared from lactal.[8]

2. Results and discussion

The lactose containing analogues **2** and **4** were prepared from the known[9] 3′,4′-*O*-isopropylidene methyl lactoside **6** (Scheme 1).

Lactoside **6** was treated with benzoyl chloride using the conditions established by Tsukida et al. for the selective benzoylation of benzyl or thiophenyl lactosides.[10] While the benzyl and phenyl lactosides gave a high yield of the analogous tetra-benzoates,[10] the desired methyl lactoside acceptor **7** was isolated in only 53% yield. This mediocre yield was explained by the concomitant formation of the known[11] penta-benzoate **8**, which was isolated in 22% yield. Thus it appears that the presence of a methyl group at the anomeric position increased the reactivity of the lactoside toward benzoylation thus reducing the selectivity of the reaction. However, since enough acceptor **7** was obtained, this reaction was not investigated further.

The disaccharide acceptor **7** was glycosylated with the known thiophenyl fucoside[12] **9** and thiophenyl rhamnoside[13] **10** under NIS–TfOH promotion. To prevent the degradation of the reactants and products, these reactions were allowed to proceed for 15 min at −30 °C in anhydrous chloroform containing activated 4 Å powdered molecular sieves. In these conditions and after HPLC purification as we previously described for similar compounds,[7] the fucosylated trisaccharide **11** and rhamnosylated trisaccharide **13** were isolated in 73% and 70% yields, respectively. The configuration of the fucosidic linkage in trisaccharide **11** was established using the vicinal coupling constant measured between H-1′ and H-2′ (3.8 Hz) that corresponded to an axial–equatorial relative orientation of these hydro-



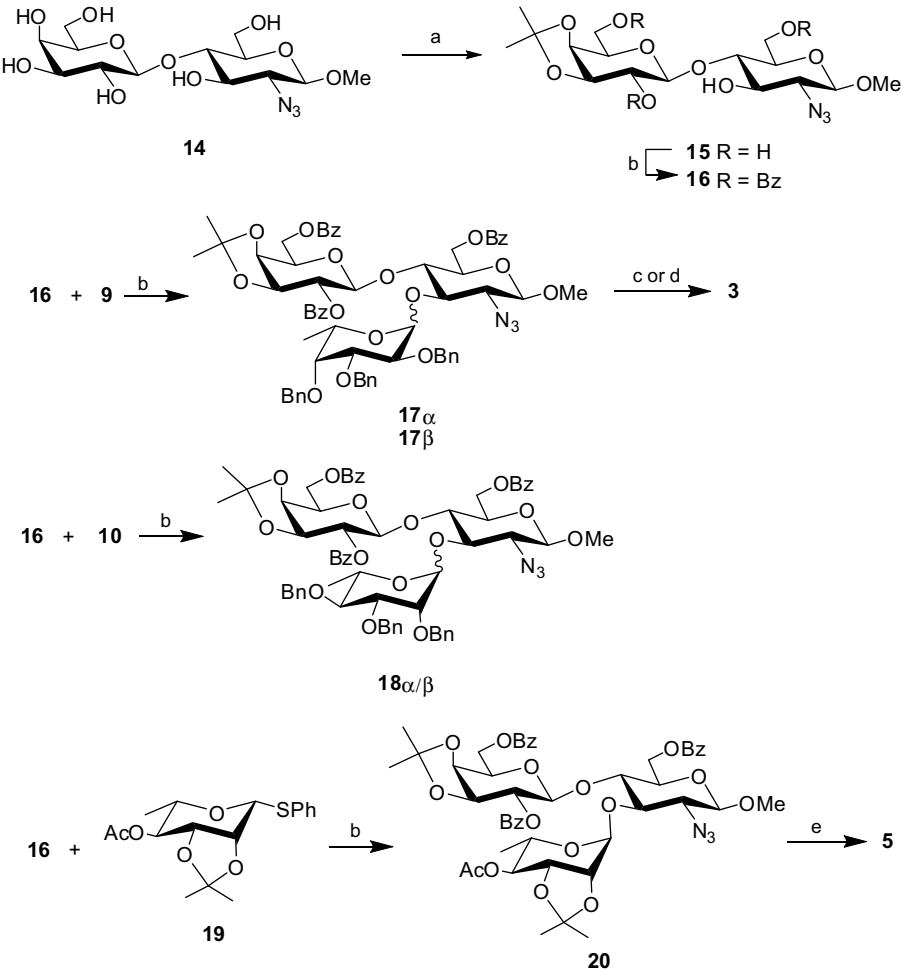
Scheme 1. Reagents and conditions: (a) 8 equiv BzCl, toluene, C_5H_5N, 0 °C, 2.5 h, **7** 53% and **8** 22%; (b) NIS, TfOH, $CHCl_3$, MS 4 Å, −30 °C, **11** (73%) and **13** (70%); (c) (1) MeONa, MeOH; (2) 90% aq AcOH 80 °C, 1 h; (3) 10% Pd–C, $H_{2(g)}$; **2** (45%) and **4** (75%); (d) (1) 10% Pd–C, $H_{2(g)}$ 100 psi; (2) Ac_2O, C_5H_5N; (e) (1) 90% aq AcOH 80 °C, 3 h; (2) MeONa, MeOH; **2** (85% from **10**).

gens consistent with an α-fucosidic bond. The configuration of the newly formed glycosidic linkage in the rhamnosylated trisaccharide **13** was deduced from the $J_{C,H}$ coupling constant at C-1 of rhamnose (169 Hz) that was consistent with that of an α linkage.[7,14] It is important to point out that while preparing trisaccharides **11** and **13**, we did not observe nor detect any formation of the β-fucosylated or β-rhamnosylated trisaccharide analogues.

Deprotection of trisaccharides **11** and **13** was first attempted in three steps: Zemplén deacylation was followed by the acid hydrolysis (AcOH aq) of the isopropylidene group and subsequent hydrogenolysis of the benzyl groups. While the deprotected rhamnosylated trisaccharide **4** was isolated in 75% over three steps, the final fucosylated analogue was only obtained in 45% yield. Indeed, TLC analysis during the isopropylidene hydrolysis showed a considerable amount of degradation consistent with the loss of the fucosyl residue. Thus the deprotection strategy for trisaccharide **11** was revised and accomplished in four steps. Hydrogenolysis of the benzyl protecting groups was followed by the acetylation of the fucosyl hydroxyl groups to stabilize the fucosidic linkage.[7,15] In turn, the trisaccharide intermediate **12** was first submitted to acid hydrolysis of the isopropylidene group then deacylated in Zemplén conditions. Following this deprotection sequence, the desired trisaccharide **2** was isolated pure in 85% yield over four steps.

Because methyl 2-azido-2-deoxy-lactoside (**14**) is easily available from lactose via the azido-nitration of peracetylated lactal,[8] it was chosen as a precursor to make trisaccharides **3** and **5** (Scheme 2). While lactoside derivatives can be selectively protected at the 3′ and 4′-hydroxyl groups of the galactose residue through the formation of thermodynamically more stable 3′,4′-*O*-isopropylidenes,[9,16] it has been observed that such reactions are more difficult to achieve on 2-azido lactosides,[4l,17,18] which often lead to considerable amounts of the kinetic 4′,6′-protected isomers. However, we found that the known[18] 3′,4′-*O*-isopropylidene derivative **15** could be obtained in a 66% yield when the reaction was carried out at 80 °C in DMF adding 2,2-dimethoxypropane (up to 6 equiv) and camphorsulfonic acid (up to 5 mg/mL) portion-wise over a 24-hour reaction time. This result constitutes a considerable improvement over the 47% yield reported by Zhu et al.[18] for the synthesis of **15**. Selective benzoylation of disaccharide **15**, once again employing the conditions developed by Tsukida et al.,[10] gave the 2-azido-2-deoxy-lactoside acceptor **16** in 67% yield; a considerably higher yield than that reported above for the synthesis of lactoside **7** (53%). Thus, it appears that the presence of the azido substituent at C-2 of the glucose residue in disaccharide **15** impacts greatly the reactivity of lactoside derivatives.

Acceptor **16** was glycosylated with the thiophenyl glycoside donors **9** and **10** using the same conditions as described above for the synthesis of trisaccharides



Scheme 2. Reagents and conditions: (a) 2–6 equiv DMP, CSA (2–5 mg/mL), DMF, 80 °C, 1.5 d, 66%; (b) 6 equiv BzCl, toluene, C_5H_5N, 0 °C, 4 h, 67%; (b) NIS, TfOH, $CHCl_3$, MS 4 Å, −30 °C, 15–30 min, **17** (74%, α/β = 7:3), **18** (70%, α/β = 65:35), **20** (95%); (c) (1) 10% Pd–C, $H_{2(g)}$ 100 psi; (2) Ac_2O, C_5H_5N; (3) 90% aq AcOH 80 °C, 3 h; (4) MeONa, MeOH; **3** (55% from **17α**); (d) (1) MeONa, MeOH; (2) 90% aq AcOH 80 °C, 1 h; (3) 10% Pd–C, $H_{2(g)}$; **3** (76% from **17α**); (e) (1) 10% Pd–C, $H_{2(g)}$ then in situ Ac_2O, C_5H_5N; 2. 90% aq AcOH 80 °C, 18 h; (3) MeONa, MeOH; **5** (72% from **20**).

11 and **13**. Once again showing the impact of the 2-azido substituent on the chemistry and reactivity of acceptor **16** versus that of acceptor **8**, the outcome of these reactions was unexpected. Indeed, in both fucosylation and rhamnosylation, we observed the formation of both α- and β-anomers in essentially identical ratios assessed by ^{1}H NMR of 7:3 in favor of the α-anomers. Hence, the mixture of the fucosylated anomers **17α,β** was isolated in 74% yield while the anomeric mixture of the rhamnosylated anomers was obtained in 70% yield. The structure of the newly formed fucosidic bonds in trisaccharides **17α** and **17β** was established using the vicinal coupling constants measured between H-1′ and H-2′ and that corresponded to an axial–equatorial (3.6 Hz) relative orientations of these hydrogens for **17α** and to a trans-diaxial orientation (8.4 Hz) for **17β**. Measurements of the $J_{C\text{-}1',H\text{-}1'}$ coupling constants for each product formed in the rhamnosylation reaction confirmed[7,14] that these indeed were the α($J_{C\text{-}1',H\text{-}1'}$ = 171 Hz) and β($J_{C\text{-}1',H\text{-}1'}$ = 161 Hz) anomers **18α,β**. Although RP-HPLC[7] was successfully used to separate the α- and β-fucosylated trisaccharide **17α** and **17β**, the rhamnolsylated anomers **18α,β** could not be separated. Thus we attempted to glycosylate acceptor **16** with the known[7] rhamnosyl donor **19** hoping for a better stereoselectivity. Indeed, in the same glycosylation conditions as used for the preparation of trisaccharide **18α,β**, the coupling of **16** with **19** gave the rhamnosylated trisaccharide **20** in 95% yield and as one single α rhamnoside confirmed by NMR as described above ($J_{C\text{-}1',H\text{-}1'}$ = 172 Hz).

Having in hand the pure trisaccharides **17α** and **20**, these were submitted to deprotection reactions to provide the desired trisaccharides **3** and **5**, respectively. Given the lability of the benzylated fucosidic residue observed in the deprotection of trisaccharide **11**, we first attempted to deprotect trisaccharide **17α** in four steps. Hydrogenolysis of the benzyl groups and reduction of the azido group were first accomplished with H_2(g) (100 psi) and 10% Pd–C catalyst and the intermediate

was N-acetylated in situ. After work-up, the triol was O-acetylated (Ac_2O–pyridine) to stabilize the fucosidic bond[7,15] and the triacetate was submitted to acid hydrolysis (AcOH aq) to remove the isopropylidene group. After silica gel chromatography, the diol was submitted to a Zemplén trans-esterification of the acyl groups and gave the deprotected Le^x trisaccharide **3** in 55% yield after Biogel P2 gel exclusion chromatography. We explain this relatively poor yield by the difficulties encountered in the first step (H_2, Pd–C), which required an extended reaction time and only proceeded to an acceptable degree following multiple work-ups and addition of fresh palladium catalyst.

To increase the yield of deprotection of trisaccharide **17α**, we attempted a three-reaction deprotection sequence. The benzoyl groups were first removed by trans-esterification, the isopropylidene was hydrolyzed, and the benzyl groups were removed by hydrogenolysis with the concomitant reduction of the azido group and the in situ acetylation of the resulting amino group. Following this sequence of reactions the deprotected Le^x trisaccharide **3** was obtained pure in 76% yield, and its analytical data were in total agreement with those reported in the literature.[5e] Although the deprotection of trisaccharide **11** following the same sequence of reactions (Scheme 1) led to some loss of the benzylated fucosidic residue during the aqueous hydrolysis, it is interesting to mention that we did not observe such degradation when deprotecting the azido trisaccharide **17α**. This result once again supports the assertion that the azido group at C-2 of the glucose residue confers a noticeably different reactivity to the molecule. The protected rhamnosylated trisaccharide **20** was easily deprotected in three steps. Reduction of the azido group (H_2, 10% Pd–C) and in situ acetylation of the amino group was followed by the acid catalyzed hydrolysis of the isopropylidene substituents and, finally, the *O*-acyl groups were removed in Zemplén conditions to give trisaccharide **5**, which was isolated pure in 72% yield after gel permeation chromatography.

The synthetic work described here illustrates some of the effects that an azido group at C-2 of a methyl lactoside derivative may have on its reactivity. When comparing the results obtained for the selective benzoylation of methyl lactoside **5** to that of the 2-azido 2-deoxy analogue **7**, it is reasonable to suggest that the azido substituent allowed a better selectivity of the reaction by reducing the reactivity at OH-3 of the lactoside. When comparing the deprotection of trisaccharide **11** to that of the 2-azido analogue **17α**, it appeared that, in contrast to a hydroxyl group, the 2-azido substituent reduced the lability of the fucosidic bond toward acid hydrolysis. In the glycosylation reactions using perbenzylated β-thiophenyl fuco- and rhamnoside donors, it appeared that the *O*-benzoyl group at C-2 of lactose in acceptor **8** favored the exclusive formation of the α-fucosidic and rhamnosidic bonds, while the azido group at C-2 of acceptor **16** led to the formation of anomeric mixtures in both reactions.

Given the fact that the β-thiophenyl glycosyl donors were activated by iodonium ions using only a catalytic amount of TfOH, we propose that the glycosylation of the 2-benzoate acceptor **8** with donors **9** and **10** proceeded mostly through fast S_N2-type displacements of the activated thiophenyl groups leading exclusively to α glycosidic bonds. In contrast, we propose that the 2-azido substituent at C-2 of acceptor **16** significantly reduced the reactivity of OH-3 and allowed the glycosylations to proceed through slower S_N1-type processes that led to the intermediate formation of oxocarbenium ions, which in turn gave anomeric mixtures of the desired trisaccharides. These results may be rationalized by the fact that, based on field inductive parameters,[19] the azido substituent is more inductively electron withdrawing than both hydroxyl and *O*-benzoyl groups. This greater inductive withdrawing effect may explain the reduced nucleophilicity of the 3-OH group toward benzoylation and glycosylation in the 2-azido lactoside **7** and 2-azido acceptor **16**, respectively. It also may explain the greater stability of the fucosidic bond toward acid hydrolysis in the deprotection of the 2-azido trisaccharide **17α**.

To test their relative affinity for the anti-Le^x monoclonal antibody SH1,[3f] the trisaccharide analogues **2**, **4**, and **5** will be used as competitive inhibitors with the methyl Le^x analogue **3**. In addition, the conformational behavior of these Le^x analogues will be studied by NMR spectroscopy and molecular modeling experiments.[20] The results obtained in these studies will be reported in due time and, hopefully, will lead to the discovery of an analogue of the TACA dimLe^x (**1**) that can be safely used in the design of an anti-cancer vaccine.

3. Experimental

3.1. General methods

^1H NMR (400.13 and 600.13 MHz) and ^{13}C NMR (75.5, 100.6 and 150.9 MHz) spectra were recorded in $CDCl_3$ (internal standard, for ^1H residual $CHCl_3$ δ 7.26; for ^{13}C: $CDCl_3$ δ 77.0), CD_3OD (internal standard, for ^1H residual CH_3OD δ 3.30; for ^{13}C: CD_3OD δ 49.0), or D_2O [external standard 3-(trimethylsilyl)-propionic acid-d_4, sodium salt (TSP) for ^1H δ 0.00, for ^{13}C δ 0.00]. ^1H NMR and ^{13}C NMR chemical shifts are reported in parts per million (ppm). Coupling constants (J) are reported in Hertz (Hz). Chemical shifts and coupling constants were obtained from a first-order analysis of one-dimensional spectra. Assignments of proton and carbon resonances were based on two-dimensional ^1H–^1H and ^{13}C–^1H correlation experiments.

Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broadened (br). All NMR spectra were recorded at 300 K. All reagents were purchased from commercial suppliers and used without further purification. TLC was performed on precoated aluminum plates with Silica Gel 60 F_{254} and detected with UV light and/or charred with a solution of 10% H_2SO_4 in ethanol. Compounds were purified by flash chromatography with Silica Gel 60 (230–400 mesh) unless otherwise stated. Solvents were distilled and dried according to standard procedures,[21] and organic solutions were dried over Na_2SO_4 and concentrated below 40 °C, under reduced pressure. Reversed-phase HPLC purifications were carried out on a Prep Nova Pak® HR C18, 6 μm 60 Å (25 × 100 mm) column using mixtures of acetonitrile and water as eluants. Gel permeation purifications were carried out on a Biogel P2 column (100 × 1 cm) eluted with water. High-resolution electrospray-ionization mass spectra (ESIMS) were recorded at the McMaster Regional Centre for Mass Spectrometry.

3.2. Methyl 2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (7)

3.2.1. Methyl 4-*O*-(3,4-*O*-isopropylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (6). β-Methyl lactoside (2.02 g, 5.6 mmol)[9,22] was dissolved in 2,2-dimethoxypropane (45 mL) containing anhydrous *p*TsOH (253 mg). The mixture was stirred at room temperature for 39 h, and then diluted with MeOH (50 mL). Water (15 mL) was added to the mixture and the clear solution obtained was neutralized with Et_3N (1 mL). The solution was concentrated to produce isopropylidene derivative **6** (2.01 g, 89%). NMR data were in agreement with those reported previously,[9] and disaccharide **6** was used directly in the next reaction.

3.2.2. Methyl 2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*isopropylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (7) and methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (8). Benzoyl chloride (4.6 mL, 0.04 mol) was added to a solution of the isopropylidene derivative **6** (2.01 g, 5.1 mmol) in anhydrous pyridine (30 mL) and toluene (40 mL) stirred at 0 °C. After stirring at 0 °C for 2.5 h, the reaction was quenched with MeOH (0.1 mL) and the mixture was concentrated. The residue was dissolved in EtOAc (150 mL) and washed sequentially with water, satd aq $NaHCO_3$, M HCl, and water. The aqueous phases were re-extracted with EtOAc (2 × 100 mL), and the combined organic solutions were dried and concentrated. Flash chromatography (1:5, EtOAc–toluene) of the residue produced first the known[11] penta-benzoate **8** (1.05 g, 22%) and then acceptor **7** (2.19 g, 53%), both pure as a white powders.

3.2.2.1. Analytical data for 7. $[\alpha]_D$ +28.3 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.08–7.27 (m, 20H, Ar), 5.37 (t, 1H, $J = 7.8$ Hz, H-2′), 5.24 (dd, 1H, $J = 9.5$, 8.1 Hz, H-2), 4.87 (dd, 1H, $J = 12.5$, 2.5 Hz, H-6a′), 4.67 (d, 1H, $J = 8.2$ Hz, H-1′), 4.64 (d, 1H, $J = 1.4$ Hz, OH), 4.47 (d, 1H, $J = 8.1$ Hz, H-1), 4.42–4.38 (m, 3H, H-6a, H-6b′, H-3′), 4.29–4.25 (m, 2H, H-4′, H-5′), 4.21 (dd, 1H, $J = 12.1$, 4.3 Hz, H-6b), 4.01 (br t, 1H, $J = 8.7$, 1.1 Hz, H-3), 3.75 (t, 1H, $J = 9.8$ Hz, H-4), 3.74 (m, 1H, H-5), 3.40 (s, 3H, OCH_3), 1.64, 1.62 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.5, 165.5, 165.2 (CO), 133.4–128.2 (Ar), 111.2 ($C(CH_3)_2$), 101.6 (C-1), 101.5 (C-1′), 82.3 (C-4), 76.6 (C-3′), 73.4 (C-3, C-4′), 72.9 (C-2′), 72.8 (C-2), 72.0 (C-5, C-5′), 63.6 (C-6′), 62.5 (C-6), 56.7 (OCH_3), 27.6, 26.2 ($C(CH_3)_2$). ESIMS: $[M+Na]^+$ calcd for $C_{44}H_{44}O_{15}$, 835.2578; found, 835.2629.

3.2.2.2. Analytical data for 8. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13–7.27 (m, 25H, Ar), 5.73 (t, 1H, $J = 9.5$ Hz, H-3), 5.41 (dd, 1H, $J = 9.6$, 7.8 Hz, H-2), 5.14 (t, 1H, $J = 7.3$ Hz, H-2′), 4.65–4.54 (m, 3H, H-1, H-1′, H-6a′), 4.47 (dd, 1H, $J = 12.2$, 4.2 Hz, H-6b′), 4.28–4.18 (m, 3H, H-4, H-6a, H-3′), 4.07 (dd, 1H, $J = 5.6$, 2.0 Hz, H-4′), 3.81 (m, 2H, H-5, H-5′), 3.65 (dd, 1H, $J = 11.4$, 7.6 Hz, H-6b), 3.43 (s, 3H, OCH_3), 1.52, 1.25 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.8, 165.6, 165.2, 164.9 (CO), 133.4–128.1 (Ar), 110.8 ($C(CH_3)_2$), 101.9 (C-1), 100.1 (C-1′), 76.9 (C-3′), 75.3 (C-4), 73.6 (C-2′), 73.1 (C-4′), 72.9 (C-5 or C-5′), 72.6 (C-3), 71.8 (C-2), 71.3 (C-5 or C-5′), 62.6 (C-6, C-6′), 57.1 (OCH_3), 27.4, 26.1 ($C(CH_3)_2$). ESIMS: $[M+NH_4]^+$ calcd for $C_{51}H_{48}O_{16}$, 934.3265; found, 934.3286.

3.3. Methyl 2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-β-D-glucopyranoside (11)

A mixture of the known thiophenyl glycoside[12] **9** (278 mg, 523 μmol) and acceptor **7** (254 mg, 312 μmol) in anhydrous $CHCl_3$ (3 mL) containing activated 4 Å powdered molecular sieves (484 mg) was stirred under N_2 for 3 h at room temperature. The mixture was cooled to −30 °C and *N*-iodosuccinimide (158 mg, 700 μmol) followed by TfOH (22 μL, 248 μmol) was added. The reaction mixture was stirred for 15 min at −30 °C and the reaction was quenched with triethylamine (130 μL). The solids were filtered off and washed with CH_2Cl_2. The combined filtrate and washing were washed successively with satd aq $NaHCO_3$, satd aq $Na_2S_2O_3$, and water. The aqueous phases were re-extracted twice with CH_2Cl_2, and the combined organic solutions were dried

and concentrated. Flash chromatography (7:3 hexanes–EtOAc) of the residue followed by RP-HPLC (20 mL/min; 9:1 CH_3CN–H_2O) produced pure trisaccharide **11** (281 mg, 73%); $[\alpha]_D$ +6.7 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.23–6.99 (m, 20H, Ar), 5.49 (d, 1H, $J = 3.8$ Hz, H-1′), 5.46 (t, 1H, $J = 8.0$ Hz, H-2″), 5.29 (t, 1H, $J = 8.0$ Hz, H-2), 5.0 (d, 1H, $J = 11.6$ Hz, C*H*HPh), 4.94 (m, 1H, H-5′), 4.87–4.75 (m, 3H, H-6a″, 2C*H*HPh), 4.71 (d, 1H, $J = 11.6$ Hz, C*H*HPh), 4.62 (br d, 1H, $J = 11.7$ Hz, H-6a), 4.55 (m, 2H, H-1, H-6b), 4.40 (m, 2H, H-1″, C*H*HPh), 4.30 (m, 5H, H-3, H-3′, H-3″, H-6b″, C*H*HPh), 4.20 (br d, 1H, H-4″), 4.17 (t, 1H, $J = 9.3$ Hz, H-4), 3.98 (dd, 1H, $J = 10.1$, 3.7 Hz, H-2′), 3.88 (m, 1H, H-5″), 3.83 (br s, 1H, H-4′), 3.56 (m, 1H, H-5), 3.41 (s, 3H, OCH_3) 1.55, 1.36 (2s, 6H, $C(CH_3)_2$), 1.37 (d, 3H, $J = 7.4$ Hz, H-6′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.2, 166.0, 164.6, 164.5 (CO), 133.5–126.7 (Ar), 110.8 ($C(CH_3)_2$), 102.8 (C-1), 100.1 (C-1″), 97.3 (C-1′), 79.0, 77.4, 74.1 (C-3, C-3′, C-3″), 78.2 (C-4′), 75.6 (C-2′), 74.8 (CH_2Ph), 74.8 (C-2″), 73.3, 73.2 (C-2, C-5, C-4″), 72.6, 72.5 (2 × CH_2Ph), 71.4 (C-5″), 66.4 (C-5′), 62.5 (C-6″), 62.3 (C-6), 56.8 (OCH_3), 27.7, 26.2 ($C(CH_3)_2$), 16.8 (C-6′). ESIMS: $[M+NH_4]^+$ calcd for $C_{71}H_{72}O_{19}$, 1246.5012; found, 1246.5020.

3.4. Methyl 2,6-di-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-3-*O*-(2,3,4-tri-*O*benzyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (13)

A mixture of the known[13] thiophenyl rhamnoside **10** (115 mg, 218 μmol) and acceptor **7** (102 mg, 126 μmmol) in anhydrous $CHCl_3$ (1.5 mL) containing activated 4 Å powdered molecular sieves (165 mg) was stirred under N_2 for 3 h at room temperature. The mixture was cooled to −30 °C, then *N*-iodosuccinimide (64 mg, 280 μmol) and TfOH (9 μL, 100 μmol) were added to the mixture. After the reaction was stirred for 15 min, triethylamine (90 μL) was added to quench the reaction and the work-up of the reaction was performed as described for the preparation of **11**. Flash chromatography (7:3, hexanes–EtOAc) followed by RP-HPLC (20 mL/min; 9:1 CH_3CN–H_2O) gave trisaccharide **13** (107 mg, 70%) pure as an amorphous glass. $[\alpha]_D$ +65.6 (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.16–6.87 (m, 30H, Ar), 5.36 (dd, 1H, $J = 8.0$, 9.2 Hz, H-2), 5.32 (t, 1H, $J = 8.0$ Hz, H-2″), 5.21 (d, 1H, $J = 1.2$ Hz, H-1′), 4.95 (d, 1H, $J = 11.5$ Hz, C*H*HPh), 4.84 (dd, 1H, $J = 3.6$, 11.7 Hz, H-6a″), 4.78 (m, 1H, H-5′), 4.70–4.59 (m, 3H, H-6a, H-6b″, C*H*HPh), 4.49 (dd, 1H, $J = 3.8$, 12.0 Hz, H-6b), 4.47 (d, 1H, $J = 8.8$ Hz, H-1″), 4.41 (d, 1H, $J = 7.9$ Hz, H-1), 4.35 (d, 1H, $J = 11.8$ Hz, C*H*HPh), 4.23–4.17 (m, 3H, H-3, H-3″, C*H*HPh), 4.12 (dd, 1H, $J = 2.2$, 5.1 Hz, H-4″), 4.09–4.00 (m, 3H, H-4, H-3′, C*H*HPh), 3.81 (m, 2H, H-5″, C*H*HPh), 3.74 (m, 1H, H-2′), 3.55 (m, 2H, H-4′, H-5″), 3.37 (s, 3H, OCH_3), 1.48 (d, 3H, $J = 6.1$ Hz, H-6′), 1.47, 1.29 (2s, 6H, 2 × $C(CH_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.2, 164.9, 164.78 (CO), 133.6–126.7 (Ar), 110.9, 104.1 (2 × $C(CH_3)_2$), 101.1 ($^1J_{C-H} = 169$ Hz, C-1′), 99.8 (C-1″), 99.1 (C-1), 80.39 (C-4′ or C-5″), 79.9 (C-3′), 77.3 (C-3 or C-3″), 76.8 (C-2′), 76.4 (C-3 or C-3″), 75.1 (CH_2Ph), 74.8 (C-2), 74.7 (C-4), 73.5 (C-4″), 73.2 (C-4′ or C-5″), 72.9 (C-2″), 72.8 (CH_2Ph), 71.9 (C-5), 71.3 (CH_2Ph), 68.2 (C-5′), 62.9 (C-6″), 62.3 (C-6), 56.9 (OCH_3), 27.6, 26.2 (2 × $C(CH_3)_2$), 17.6 (C-6′). ESIMS: $[M+Na]^+$ calcd for $C_{71}H_{72}O_{19}$, 1251.4590; found, 1251.4503.

3.5. Methyl 3-*O*-α-L-fucopyranosyl-4-*O*-β-D-galactopyranosyl-β-D-galactopyranoside (2)

3.5.1. Method A. The protected trisaccharide **11** (158 mg, 128 μmol) was dissolved in 0.4 M methanolic sodium methoxide (15 mL). The mixture was stirred at room temperature overnight, diluted with MeOH (10 mL), and deionized with Dowex 50 (H^+) resin. The resin was filtered off, rinsed with MeOH, and the combined filtrate and washings were concentrated. Chromatography (hexanes then 1:9 MeOH–$CHCl_3$) of the residue produced the corresponding polyol (98 mg, 94%) that was dissolved in 90% aqueous acetic acid (10 mL). The solution was stirred at 80 °C for 1 h and co-concentrated with toluene. The dry residue was dissolved in MeOH (10 mL), 10% Pd–C (100 mg) was added, and the stirred mixture was subjected overnight at room temperature to hydrogenolysis under H_2 atmosphere. Additional 10% Pd–C (100 mg) was added and the mixture was again submitted to hydrogenolysis overnight. The catalyst was filtered off on Celite and the solids were rinsed thoroughly with MeOH. The combined filtrate and washings were concentrated and silica gel chromatography (0.5:3:6.5 H_2O–MeOH–EtOAc) followed by RP-HPLC (10 mL/min; 7:3 CH_3CN–H_2O) produced the pure trisaccharide **2** (29 mg, 45 % from **13**), which was isolated as an amorphous powder after freeze-drying.

3.5.2. Method B

3.5.2.1. Methyl 2,6-di-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (12). The protected trisaccharide **11** (20 mg, 16 μmol) was dissolved in EtOAc (2 mL), and 10% Pd–C (42 mg) was added. The reaction mixture was submitted to hydrogenolysis at 100 psi of H_2 overnight at room temperature. The catalyst was filtered off and rinsed thoroughly with a mixture of MeOH and EtOAc (1:1, 10 mL) followed by pure MeOH (10 mL). The combined filtrate and washings were concentrated, and the crude alcohol (12.3 mg) was submitted to acetylation overnight at room temperature in a 1:1 mixture of Ac_2O and pyridine (2 mL). The reaction mixture was co-concentrated

with toluene to produce the crude triacetate **12** (20 mg) that was used directly in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25–7.30 (m, 20H, Ar), 5.45–5.32 (m, 3H, H-11, H-3′, H-4′ H-2″), 5.27 (dd, 1H, $J = 7.5$, 8.5 Hz, H-2), 5.18 (m, 1H, H-5′), 5.10 (dd, 1H, $J = 4.0$, 10.1 Hz, H-2′), 4.98 (dd, 1H, $J = 4.1$, 12.1 Hz, H-6a″), 4.80 (dd, 1H, $J = 8.9$, 11.9 Hz, H-6b″), 4.61 (dd, 1H, $J = 1.3$, 12.1 Hz, H-6a), 4.51 (d, 1H, $J = 8.7$ Hz, H-1″), 4.44 (dd, 1H, $J = 3.4$, 12.3 Hz, H-6b), 4.35 (d, 1H, $J = 7.9$ Hz, H-1), 4.29–4.10 (m, 4H, H-3, H-4, H-3″, H-4″), 3.84 (m, 1H, H-5″), 3.53 (m, 1H, H-5), 3.34 (s, 3H, OCH_3), 2.13, 1.87, 1.86 (3s, 3 × 3H, $3CH_3CO$), 1.60, 1.35 (2s, 2 × 3H, $C(CH_3)_2$), 1.35 (d, 3H, H-6′).

3.5.2.2. Methyl 3-*O*-α-L-fucopyranosyl-4-*O*-β-D-galactopyranosyl-β-D-galactopyranoside (2). The crude triacetate **12** was dissolved in 90% aqueous AcOH (2 mL), stirred at 80 °C for 3 h, and co-concentrated with toluene to give the corresponding crude diol which was dissolved in methanolic (0.4 M) sodium methoxide (2 mL). The solution was stirred overnight at room temperature and deionized with Dowex 50 (H^+) resin. The resin was filtered off, rinsed with MeOH, and the combined filtrate and washings were concentrated. Gel permeation chromatography of the residue on a Biogel P2 column eluted with water produced the pure trisaccharide **2** (7 mg, 85% from **11**), which was isolated as an amorphous powder after freeze-drying.

3.5.3. Analytical data for trisaccharide 2. $[\alpha]_D$ −5.3 (*c* 0.3, MeOH); ^{1}H NMR (600 MHz, D_2O): δ 5.29 (d, 1H, $J = 3.9$ Hz, H-1′), 4.68 (m, 1H, H-5′), 4.29 (d, 1H, $J = 7.8$ Hz, H-1″), 4.24 (m, 1H, $J = 8.0$ Hz, H-1), 3.86 (dd, 1H, $J = 2.0$, 12.3 Hz, H-6a), 3.81 (dd, 1H, $J = 3.3$, $J_{3',4'}$ 10.4 Hz, H-3′), 3.75 (br d, 1H, $J = 3.3$ Hz, H-4″), 3.71 (t, 1H, $J = 9.5$ Hz, H-4), 3.68 (dd, 1H, $J = 4.8$, 12.3 Hz, H-6b), 3.66–3.62 (m, 3H, H-3, H-2′, H-4′), 3.61–3.55 (m, 2H, H-6a″, H-6b″), 3.50 (dd, 1H, $J = 3.3$, 10.4 Hz, H-3″), 3.45–3.43 (m, 2H, H-5, H-5″), 3.42 (s, 3H, OCH_3), 3.37–3.33 (m, 2H, H-2, H-2″), 1.03 (d, 3H, $J = 6.6$ Hz, H-6′); ^{13}C NMR (150.9 MHz, D_2O): δ 103.6 (C-1), 101.8 (C-1″), 98.8 (C-1′), 77.3 (C-3 or C-2′ or C-4′), 75.3, 75.0 (C-5, C-5″), 74.5 (C-2), 72.8 (C-4′), 72.5 (C-3″), 72.0 (C-3 or C-2′ or C-4′), 71.2 (C-2″), 69.3 (C-3′), 68.4 (C-4″), 68.1 (C-3 or C-2′ or C-4′), 66.6 (C-5′), 61.7 (C-6″), 59.8 (C-6), 57.5 (OCH_3), 15.2 (C-6′). ESIMS: $[M+Na]^+$ calcd for $C_{19}H_{34}O_{15}$, 525.1801; found, 525.1792.

3.6. Methyl 4-*O*-β-D-galactopyranosyl-3-*O*-α-L-rhamnopyranosyl-β-D-galactopyranoside (3)

The protected trisaccharide **13** (82 mg, 60 μmol) was dissolved in 0.4 M methanolic sodium methoxide (5 mL) and the reaction was allowed to proceed overnight at rt. Work-up and purification by chromatography were carried out as described in Section 3.5.1 for the deprotection of trisaccharide **11** following method A. The intermediate polyol (51 mg, 93%) was then dissolved in 90% aqueous acetic acid (5 mL) and the hydrolysis as well as work-up of the reaction and subsequent hydrogenolysis of the remaining benzyl groups (H_2, 10% Pd–C) were also carried out as described in Section 3.5.1. Purification by chromatography (0.5:3:6.5, H_2O–MeOH–EtOAc) followed by RP-HPLC (10 mL/min; 7:3, CH_3CN–H_2O) gave the pure trisaccharide **3** (25 mg, 75% from **13**), which was isolated as an amorphous powder upon freeze-drying. $[\alpha]_D$ −33.5 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, D_2O): δ 5.14 (d, 1H, $J = 1.5$ Hz, H-1′), 4.29 (m, 1H, H-5′), 4.26 (d, 1H, $J = 7.9$ Hz, H-1″), 4.23 (d, 1H, $J = 8.0$ Hz, H-1), 3.83 (dd, 1H, $J = 1.75$, 3.3 Hz, H-2′), 3.81 (dd, 1H, $J = 2.0$, 12.3 Hz, H-6a), 3.73 (dd, 1H, $J = 3.4$, 9.7 Hz, H-3′), 3.71 (br d, 1H, $J = 3.5$ Hz, H-4″), 3.69 (t, 1H, $J = 9.3$ Hz, H-3), 3.67–3.61 (m, 3H, H-4, H-6b, H-6a″), 3.58 (dd, 1H, $J = 4.2$, 11.9 Hz, H-6b″), 3.49 (br dd, 1H, $J = 4.0$, 8.1 Hz, H-5″), 3.45 (dd, 1H, $J = 3.4$, 9.9 Hz, H-3″), 3.40 (m, 1H, H-5), 3.38 (s, 3H, OCH_3), 3.25 (m, 2H, H-2, H-2″), 3.21 (t, 1H, $J = 9.7$ Hz, H-4′), 1.09 (d, 3H, $J = 6.3$ Hz, H-6′); ^{13}C NMR (150.9 MHz, D_2O): δ 103.0 (C-1), 102.3 (C-1″), 99.7 (C-1′), 76.3 (C-3), 75.3, 75.2 (C-5, C-5″), 74.4 (C-2), 72.9 (C-4), 72.9 (C-4), 72.5 (C-3″), 72.3 (C-4′), 71.4 (C-2″), 70.1 (C-2′), 69.9 (C-3′), 68.9 (C-4″), 68.2 (C-5′), 61.1 (C-6″), 59.5 (C-6), 57.2 (OCH_3), 16.0 (C-6′). ESIMS: $[M + H]^+$ calcd for $C_{19}H_{34}O_{15}$, 503.1976; found, 503.1978.

3.7. Methyl 2-azido-6-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranoside (16)

3.7.1. Methyl 2-azido-4-*O*-(3,4-*O*-isopropylidene-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranoside (15). The known[8] methyl 2-azido lactoside **14** (224 mg, 590 μmol) was dissolved in DMF (3 mL) containing CSA (3 mg). The mixture was stirred at 80 °C for 5 min, and then 2,2-dimethoxypropane (150 μL, 1.2 mmol) was added to the mixture. The stirring was continued overnight and additional CSA (total 14.5 mg) and 2,2-dimethoxypropane (total 450 μL) were added portion-wise over the next 24 h. The reaction was quenched with triethylamine (30 μL) and the mixture was co-concentrated with toluene. Chromatography (1:9 MeOH–$CHCl_3$) of the residue produced the known[18] isopropylidene derivative **15** (163 mg, 66%), which was taken directly to the next step. ^{1}H NMR (400 MHz, D_2O): δ 4.49 (d, 1H, $J = 8.4$ Hz, H-1′), 4.47 (d, 1H, $J = 8.3$ Hz, H-1), 4.34 (dd, 1H, $J = 1.7$, 5.3 Hz, H-4′), 4.21 (dd, 1H, $J = 5.5$, 7.5 Hz, H-3′), 4.08 (m, 1H, H-5′), 3.96 (dd, 1H, $J = 2.3$, 12.4 Hz, H-6a), 3.87–

3.77 (m, 3H, H-6b, H-6a′, H-6b′), 3.71–3.47 (m, 8H, H-3, H-4, H-5, H-2′, H-5′, OCH_3), 3.34 (br t, 1H, H-2), 1.53, 1.38 (2s, 2 × 3H, $C(CH_3)_2$).

3.7.2. Methyl 2-azido-6-*O*-benzoyl-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranoside (16). Benzoyl chloride (270 μL, 2.3 mmol) was added to a solution of the isopropylidene derivative **15** (163 mg, 0.39 mmol) in anhydrous pyridine (2.4 mL) and toluene (3.3 mL) stirred at 0 °C. After stirring at 0 °C for 4 h, the reaction was quenched with MeOH (0.1 mL), concentrated, and the work-up was performed as described for the synthesis of acceptor **7**. Purification of the residue by centrifugal chromatography (7:3 hexanes–EtOAc) gave the 2-azido acceptor **16** (189 mg, 67%) as a white powder. $[\alpha]_D$ +28.3 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.18–7.26 (m, 15H, Ar), 5.34 (t, 1H, $J = 7.5$ Hz, H-2′), 4.92 (dd, 1H, $J = 2.8$, 12.3 Hz, H-6a′), 4.63 (br s, 1H, OH), 4.62 (d, 1H, $J = 7.9$ Hz, H-1′), 4.49 (dd, 1H, $J = 8.9$, 12.2, H-6b′), 4.39 (dd, 1H, $J = 5.4$, 7.1 Hz, H-3′), 4.32–4.26 (m, 3H, H-6a, H-4′, H-5′), 4.20 (dd, 1H, $J = 4.0$ 12.0 Hz, H-6b), 4.13 (d, 1H, $J = 8.2$ Hz, H-1), 3.69 (dd, 1H, $J = 7.7$, 9.6 Hz, H-3), 3.55–3.47 (m, 2H, H-4, H-5), 3.48 (s, 3H, OCH_3), 3.25 (dd, 1H, $J = 8.3$, 9.7 Hz, H-2), 1.64, 1.36 (2s, 2 × 3H, $C(CH_3)_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.5, 165.5, 165.1 (CO), 133.4–128.3 (Ar), 111.3 ($C(CH_3)_2$), 102.2 (C-1), 101.4 (C-1′), 81.7 (C-4 or C-5), 76.8 (C-3′), 73.9 (C-3), 73.3 (C-4′ or C-5′), 72.8 (C-2′), 72.0, 72.0 (C-4 or C-5 and C-4′ or C-5′), 65.5 (C-2), 63.6 (C-6′), 62.5 (C-6), 57.1 (OCH_3), 27.5, 26.2 (($C(CH)_3)_2$). ESIMS: $[M+NH_4]^+$ calcd for $C_{37}H_{39}O_{13}N_3$, 751.2827; found, 751.2860.

3.8. Methyl 2-azido-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-6-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-deoxy-β-D-glucopyranoside (17α) and methyl 2-azido-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-6-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-benzyl-β-L-fucopyranosyl)-2-deoxy-β-D-glucopyranoside (17β)

A mixture of known[12] donor **9** (257 mg, 490 μmol, 1.8 equiv) and acceptor **16** (201 mg, 275 μmol) in anhydrous $CHCl_3$ (4 mL) containing activated 4 Å powdered molecular sieves (345 mg) was stirred under N_2 for 3 h at room temperature. The mixture was cooled to −30 °C, then *N*-iodosuccinimide (161 mg, 710 μmol) and TfOH (23 μL, 260 μmol) were added to the mixture. The reaction was stirred at −30 °C for 15 min and quenched with triethylamine (150 μL). Work-up of the reaction was performed as described for the preparation of **11**. Flash chromatography followed by centrifugal chromatography (2:8 then 7:3, hexanes–EtOAc) produced the desired trisaccharide **17α** contaminated with 30% β-anomer **17β** (**17α,β**, 232 mg, 74%) as assessed by ^1H NMR. The two anomers were eventually separated by RP-HPLC (8:2 CH_3CN–H_2O). The wanted trisaccharide **17α** was isolated pure in 48% yield (150 mg) while trisaccharide **17β** was isolated in 8% yield (31 mg).

3.8.1. Analytical data for 17α. $[\alpha]_D$ +0.001 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.15–7.23 (m, 30H, Ar), 5.63 (d, 1H, $J = 3.6$ Hz, H-1′), 5.22 (dd, 1H, $J = 7.5$, 8.5 Hz, H-2″), 5.02 (d, 1H, $J = 11.6$ Hz, C*H*HPh), 4.93–4.78 (m, 5H, 2 CH_2Ph, H-5′), 4.71 (m, 2H, C*H*HPh, H-6a″), 4.54 (dd, 1H, $J = 1.6$, 12.3 Hz, H-6a), 4.49 (d, 1H, $J = 8.7$ Hz, H-1″), 4.45 (dd, 1H, $J = 3.6$, 12.3 Hz, H-6b), 4.39 (dd, 1H, $J = 7.6$, 11.2 Hz, H-6b″), 4.24 (dd, 1H, $J = 2.6$, 10.3, H-3′), 4.19 (d, 1H, $J = 7.9$ Hz, H-1), 4.19–4.15 (m, 3H, H-2′, H-3″, H-4″), 3.92–3.85 (m, 2H, H-4, H-5″), 3.81 (br s, 1H, H-4′), 3.69 (t, 1H, $J = 9.5$ Hz, H-3), 3.48 (s, 3H, OCH_3), 3.43 (dd, 1H, $J = 8.1$, 9.9 Hz, H-2), 3.37 (m, 1H, H-5), 1.51, 1.31 (2s, 6H, $C(CH_3)_2$), 1.29 (d, 3H, $J = 6.5$ Hz, H-6′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.0, 165.9 164.6 (CO), 139.2–126.9 (Ar), 110.7 ($C(CH_3)_2$), 103.4 (C-1), 101.1 (C-1″), 97.3 (C-1′), 79.4 (C-3′), 78.1 (C-4′), 77.0, 76.0 (2 of C-2′, C-3″, C-4″), 74.8 (CH_2Ph), 74.7 (C-4 or C-5″), 73.9 (C-3), 73.3 (CH_2Ph), 73.2 (C-2′ or C-3″ or C-4″), 73.0 (C-4 or C-5″), 72.6 (CH_2Ph), 71.1 (C-4 or C-5″), 66.5 (C-2), 66.3 (C-5′), 62.7 (C-6″), 62.3 (C-6), 57.2 (OCH_3), 27.7, 26.2 ($C(CH_3)_2$), 16.8 (C-6′). ESIMS: $[M+Na]^+$ calcd for $C_{64}H_{67}O_{17}N_3$, 1172.4368; found, 1172.4379.

3.8.2. Analytical data for 17β. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10–7.20 (m, 30H, Ar), 5.15 (t, 1H, $J = 8.0$ Hz, H-2″), 5.01 (d, 1H, $J = 10.9$ Hz, C*H*HPh), 4.97 (d, 1H, $J = 10.8$ Hz, C*H*HPh), 4.92 (d, 1H, $J = 8.4$ Hz, H-1″), 4.86 (d, 1H, $J = 11.2$ Hz, C*H*HPh), 4.85 (d, 1H, $J = 7.5$ Hz, H-1′), 4.78, 4.72 (2d, 2H, CH_2Ph), 4.61 (m, 2H, C*H*HPh, H-6a″), 4.53 (m, 2H, H-6a, H-6b″), 4.24 (dd, 1H, $J = 4.9$, 11.9 Hz, H-6b), 4.15 (d, 1H, $J = 7.7$ Hz, H-1), 4.12 (m, 1H, H-5″), 4.07 (t, 1H, $J = 9.4$ Hz, H-4), 4.00 (t, 1H, $J = 9.5$ Hz, H-3), 3.85 (dd, 1H, $J = 7.7$, 9.6 Hz, H-2′), 3.80 (dd, 1H, $J = 2.1$, 5.2 Hz, H-4″), 3.62–3.51 (m, 4H, H-2, H-5, H-3′, H-3″), 3.48 (br s, 1H, H-4′), 3.39 (s, 3H, OCH_3), 3.37 (m, 1H, H-5′), 1.36, 1.21 (2s, 2 × 3H, $C(CH_3)_2$), 1.22 (d, 3H, $J = 5.8$ Hz, H-6′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.7, 165.0 (CO), 139.0–127.0 (Ar), 110.4 ($C(CH_3)_2$), 102.5 (C-1), 101.2 (C-1″), 98.9 (C-1′), 83.1 (C-5 or C-3″), 79.8 (C-2′), 79.2 (C-3), 77.0 (C-3′), 76.7 (C-4′), 76.3 (C-4), 75.2, 74.7 (2 CH_2Ph), 74.0 (C-2″), 73.3 (C-4″), 73.0 (CH_2Ph), 72.6 (C-5 or C-3″), 70.6 (C-5″), 70.4, (C-5′), 64.5 (C-2), 63.2 (C-6″), 62.9 (C-6), 56.9 (OCH_3), 27.3, 26.2 ($C(CH_3)_2$), 16.8 (C-6′). ESIMS: $[M+H]^+$ calcd for $C_{64}H_{67}O_{17}N_3$, 1150.4549; found, 1150.4554.

3.9. Methyl 2-azido-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-6-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-benzyl-α/β-L-rhamnopyranosyl)-2-deoxy-β-D-glucopyranoside (18α/β)

A mixture of known[13] donor **10** (149 mg, 283 μmol, 2 equiv) and acceptor **16** (100 mg, 136 μmol) in anhydrous $CHCl_3$ (1.5 mL) containing activated 4 Å powdered molecular sieves (170 mg) was stirred under N_2 for 3 h at room temperature. The mixture was cooled to −30 °C, then NIS (81 mg, 359 μmol) and TfOH (11 μL, 127 μmol) were added to the mixture. The reaction was stirred at −30 °C for 30 min and quenched with triethylamine (100 μL). Work-up of the reaction was performed as described for the preparation of **11**. Flash chromatography (7:3, hexanes–EtOAc) produced a mixture of the anomeric trisaccharides **18α,β** that could not be distinguished by TLC (109 mg, 70%). The α/β ratio was estimated to be 65:35 by ^{1}H NMR.

Selected NMR data for **18α**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62 (d, 1H, $J = 3.7$ Hz, H-1′), 5.21 (dd, 1H, $J = 7.6$, 8.5, H-2″), 4.8 (H-5′), 4.48 (H-1″), 4.18 (H-1), 3.48 (s, 3H, OCH_3), 1.50, 1.30 (2s, 2 × 3H, $C(CH_3)_2$), 1.29 (d, 3H, $J = 6.6$ Hz, H-6′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 103.4 ($^1J_{C-H} = 161$ Hz, C-1), 100.2 ($^1J_{C-H} = 159$ Hz, C-1″), 97.3 ($^1J_{C-H} = 171.5$ Hz, C-1′), 57.2 (OCH_3), 27.7, 26.2 ($C(CH_3)_2$), 16.9 (C-6′).

Selected NMR data for **18β**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15 (t, 1H, $J = 8.0$, H-2″), 4.92 (H-1″), 4.85 (H-1′), 4.14 (H-1), 3.40 (s, 3H, OCH_3), 3.36 (H-5′), 1.35, 1.22 (2s, 2 × 3H, $C(CH_3)_2$), 1.23 (d, 3H, $J = 6.0$ Hz, H-6′); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 102.5 ($^1J_{C-H} = 160$ Hz, C-1), 101.3 ($^1J_{C-H} = 161$ Hz, C-1′), 99.0 ($^1J_{C-H} = 163$ Hz, C-1″), 56.9 (OCH_3), 27.7, 26.2 ($C(CH_3)_2$), 16.8 (C-6′).

3.10. Methyl 2-azido-4-*O*-(2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-6-*O*-benzoyl-2-deoxy-3-*O*-(2,3-*O*-isopropylidene-4-*O*-acetyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (20)

A mixture of the known[7] rhamnosyl donor **19** (91 mg, 269 μmol) and acceptor **16** (100 mg, 136 μmol) in anhydrous $CHCl_3$ (1.5 mL) containing activated 4 Å powdered molecular sieves (173 mg) was stirred under N_2 for 3 h at room temperature. The mixture was cooled to −35 °C and NIS (81 mg, 360 μmol) followed by TfOH (12 μL, 135 μmol) was added to the mixture. The reaction mixture was stirred for 30 min at −35 °C, and triethylamine (150 μL) was added to quench the reaction. The work-up of the reaction was performed as described for the preparation of **11**. Flash chromatography (8:2 hexanes–EtOAc) of the residue produced the pure trisaccharide **20** (124 mg, 95 %). $[\alpha]_D$ +19.1 (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13–7.39 (m, 15H, Ar), 5.60 (br s, 1H, H-1′), 5.25 (t, 1H, $J =$ 8.05 Hz, H-2″), 4.89 (dd, 1H, $J = 8.3$, 10.3 Hz, H-4′), 4.77 (dd, 1H, $J = 3.9$, 11.7 Hz, H-6a″), 4.70–4.61 (m, 2H, H-5′, H-6b″), 4.52 (m, 2H, H-6a, H-6b), 4.46 (d, 1H, $J = 8.7$ Hz, H-1″), 4.24 (m, 2H, H-3′, H-3″), 4.18 (m, 2H, H-1, H-4″), 4.18 (br d, 1H, $J = 8.7$ Hz, H-2′), 3.99 (m, 1H, H-5″), 3.76–3.67 (m, 2H, H-3, H-4), 3.48 (s, 3H, OCH_3), 3.38 (m, 1H, H-5), 3.27 (br t, 1H, $J = 9.1$ Hz, H-2), 2.16 (s, 3H, $COCH_3$), 1.59, 1.56, (2s, 2 × 3H, $C(CH_3)_2$), 1.34 (1s, 3H, CCH_3), 1.28 (d, 1H, $J = 6.2$ Hz, H-6′), 1.26 (1s, 3H, CCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.2, 166.07, 165.8, 164.6 (CO), 133.5–128.5 (Ar), 110.8, 109.5 (2 × $C(CH_3)_2$), 102.8 (C-1), 100.4 (C-1″), 96.6 ($^1J_{C,H} = 172.4$ Hz, C-1′), 77.3 (C-3′ or C-3″), 76.0 (C-2′), 75.6 (C-3 or C-4), 75.5 (C-3′ or C-3″), 74.5 (C-4′), 73.8 (C-3 or C-4), 73.5 (C-4″), 73.0 (C-5), 72.8 (C-2″), 71.5 (C-5″), 66.9 (C-2), 64.1 (C-5′), 63.1 (C-6″), 62.4 (C-6), 57.2 (OCH_3), 27.8, 27.6, 26.3 (2 × $C(CH_3)_2$), 21.0 ($COCH_3$), 16.6 (C-6′). ESIMS: $[M+NH_4]^+$ calcd for $C_{48}H_{55}O_{18}N_3$, 979.3824; found, 979.3862.

3.11. Methyl 2-acetamido-2-deoxy-3-*O*-α-L-fucopyranosyl-4-*O*-β-D-galactopyranosyl-β-D-galactopyranoside 3

3.11.1. Method A. The protected trisaccharide **17α** (21 mg, 19 μmol) was dissolved in EtOAc (2 mL) and 10% Pd–C (41 mg) was added. The reaction mixture was submitted to hydrogenolysis at 100 psi of H_2 48 h at room temperature. The catalyst was centrifuged down, the supernatant decanted, and the catalyst rinsed thoroughly through re-suspension/centrifugation/decantation with a mixture of MeOH and EtOAc. After concentration of the combined supernatant and washings, the crude residue was submitted to hydrogenolysis a second time in the same conditions described above. Once again the catalyst was centrifuged down and washed carefully with MeOH and EtOAc. After concentration of the combined supernatant and washings, the residue was this time dissolved in a mixture of EtOAc and MeOH (2:1, 2 mL), Ac_2O (200 μL) and 10% Pd–C (63 mg) were added and the mixture was submitted to hydrogenolysis at 100 psi for 2 days at room temperature. Work-up and hydrogenolysis were carried out as described immediately above one more time for an additional 2 days at room temperature. Work-up as above gave a crude residue (13 mg) that was submitted to acetylation overnight at room temperature in a 1:1 mixture of Ac_2O and pyridine (3 mL). The reaction mixture was co-concentrated with toluene to produce the crude acetylated intermediate (13 mg) that was used directly in the next reaction. It was dissolved in 90% aqueous AcOH (2 mL), the mixture was stirred at 80 °C for 4 h, and co-concentrated with toluene to give the corresponding crude diol (13 mg) which was submitted to flash chromatography (7:3 EtOAc–hexanes). The purified diol was dissolved in methanolic (0.4 M) sodium

methoxide (1.5 mL) and the solution was stirred overnight at room temperature and deionized with Dowex 50 (H^+) resin. The resin was filtered off, rinsed with MeOH, and the combined filtrate and washings were concentrated. Gel permeation chromatography of the residue on a Biogel P2 column eluted with water produced the pure trisaccharide **3** (5.7 mg, 55% from **17α**), which was isolated as an amorphous powder after freeze-drying.

3.11.2. Method B. Trisaccharide **17α** (70 mg, 60.9 μmol) was dissolved in 0.4 M methanolic sodium methoxide (5 mL). The mixture was stirred at room temperature overnight, diluted with MeOH (10 mL), and deionized with Dowex 50 (H^+) resin. The resin was filtered off, rinsed with MeOH, and the combined filtrate and washings were concentrated. Chromatography (1:9 MeOH–$CHCl_3$) produced the triol intermediate (46 mg), which was dissolved in 90% aqueous acetic acid (4 mL). The solution was stirred at 80 °C for 2 h and co-concentrated with toluene. The residue was dissolved in MeOH (4 mL), 10% Pd–C (40 mg) was added, and the mixture was submitted to hydrogenolysis at room temperature for 5 h. Ac_2O (16 μL) was added and the mixture was stirred under H_2 atmosphere overnight at room temperature. Additional 10% Pd–C (total 122 mg) and Ac_2O (total 300 μL) were added portion-wise during the following 2 days while hydrogenolysis at room temperature was continued. Once the reaction was seen to be complete by TLC (6:1:3 EtOAc–MeOH–H_2O) the catalyst was filtered off, the solids were rinsed thoroughly with MeOH, and the combined filtrate and washings were concentrated. Gel filtration on a Biogel P2 column eluted with H_2O produced trisaccharide **3** pure (25 mg, 76%) that was isolated as an amorphous white powder upon freeze-drying.

3.11.3. Analytical data for trisaccharide 3. The analytical data for **3** were in agreement with that reported previously.[5e] $[\alpha]_D$ −66.4 (*c* 0.3, MeOH); ^{1}H NMR (600 MHz, D_2O): δ 4.95 (d, 1H, $J = 4.0$ Hz, H-1′), 4.68 (m, 1H, H-5′), 4.32 (d, 1H, $J = 8.1$ Hz, H-1), 4.30 (d, 1H, $J = 7.8$ Hz, H-1″), 3.86 (dd, 1H, $J = 2.1$, 12.2 Hz, H-6a), 3.80–3.70 (m, 6H, H-2, H-3, H-4, H-6b, H-3′, H-4″), 3.64 (br d, 1H, $J = 3.4$ Hz, H-4′), 3.62–3.56 (m, 2H, H-6a″, H-6b″), 3.54 (dd, 1H, $J = 4.0$, 10.3 Hz, H-2′), 3.51 (dd, 1H, $J = 3.4$, 9.9 Hz, H-3″), 3.45 (m, 2H, H-5, H-5″), 3.35 (m, 4H, H-2″, OCH_3), 1.87 (s, 3H, $COCH_3$), 1.02 (d, 3H, $J = 6.6$ Hz, H-6′); ^{13}C NMR (150.9 MHz, D_2O): δ 174.5 ($COCH_3$), 101.9 (C-1″), 101.7 (C-1), 98.7 (C-1′), 75.4, 75.0 (2 C, C-5, C-5″), 74.9 (C-4 or C-3′ or C-4″), 73.5 (C-3), 72.5 (C-3″), 71.9 (C-4′), 71.1 (C-2″), 69.3, 68.4 (2 of C-4, C-3′, C-4″), 67.7 (C-2′), 66.7 (C-5′), 61.5 (C-6″), 59.8 (C-6), 57.1 (OCH_3), 55.6 (C-2), 22.2 ($COCH_3$), 14.2 (C-6′). ESIMS: $[M+Na]^+$ calcd for $C_{21}H_{37}O_{15}N$, 566.2061; found, 566.2054.

3.12. Methyl 2-acetamido-2-deoxy-4-*O*-β-D-galactopyranosyl-3-*O*-α-L-rhamnopyranosyl-β-D-galactopyranoside (5)

10% Pd–C (64 mg) was added to a solution of trisaccharide **20** (54 mg, 56 μmol) in EtOAc (2.5 mL). The reaction mixture was stirred at room temperature under H_2 atmosphere overnight. Pyridine (100 μL) and Ac_2O (100 μL) was added to the reaction mixture that was stirred at room temperature for 3 h. The catalyst was filtered off and rinsed with EtOAc (20 mL) and MeOH (10 mL) and the combined filtrate and washings were concentrated to dryness. The residue was dissolved in 80% aqueous acetic acid (3 mL) and the solution was stirred at 80 °C overnight. The mixture was co-concentrated with toluene and gave a residue (47 mg) that was dissolved in 0.4 M methanolic sodium methoxide (3 mL). The mixture was stirred overnight at room temperature and deionized with Dowex 50 (H^+) resin. The resin was filtered off, rinsed with MeOH, and the combined filtrate and washings were concentrated. Chromatography (6:3:1 EtOAc–MeOH–H_2O) of the crude product followed by gel permeation chromatography on Biogel P2 (water) gave trisaccharide **5** (22 mg, 72%) pure, which was isolated as an amorphous powder upon freeze-drying. $[\alpha]_D$ −43.6 (*c* 1.1, MeOH); ^{1}H NMR (600 MHz, D_2O): δ 4.82 (s, 1H, H-1′), 4.36 (m, 1H, H-1), 4.32 (d, 1H, $J = 7.9$ Hz, H-1″), 4.32 (m, 1H, H-5′), 3.86 (dd, 1H, $J = 2.0$, 12.3 Hz, H-6a), 3.78–3.73 (m, 4H, H-2, H-3, H-4, H-4″), 3.73–3.68 (m, 3H, H-6, H-3′, H-6″), 3.67 (br s, 1H, H-2′), 3.60 (dd, 1H, $J = 4.1$, 11.9 Hz, H-6b″), 3.53 (m, 1H, H-5), 3.49 (dd, 1H, $J = 3.4$, 9.9 Hz, H-3″), 3.46 (m, 1H, H-5), 3.37 (s, 3H, OCH_3), 3.28 (dd, 1H, $J = 8.0$, 9.8 Hz, H-2″), 3.23 (t, 1H, $J = 9.7$ Hz, H-4′), 1.87 (s, 3H, $COCH_3$), 1.12 (d, 3H, $J = 6.3$ Hz, H-6′); ^{13}C NMR (150.9 MHz, D_2O): δ 102.3 (C-1″), 101. 3 (C-1), 99.8 (C-1′), 75.3 (C-5, C-5″), 75.2, 73.6 (2 of C-3, C-4, C-4″), 72.7 (C-3″), 72.3 (C-4′), 71.4 (C-2″), 70.5 (C-2′), 70.0 (C-3′), 68.9 (C-3 or C-4 or C-4″), 68.4 (C-5′), 61.2 (C-6″), 59.7 (C-6), 57.2 (OCH_3), 55.7 (C-2), 21.8 ($COCH_3$), 16.5 (C-6′). ESIMS: $[M+H]^+$ calcd for $C_{21}H_{37}O_{15}N$, 544.2241; found, 544.2263.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.04.017.

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