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On the Use of the Haloetherification Method to Synthesize Fully Functionalized Disaccharides

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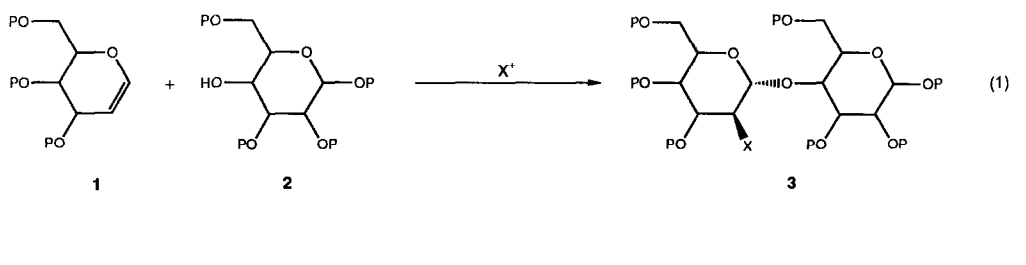
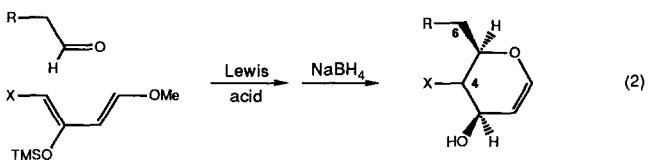
Synthetic routes to the fully functionalized, α-linked disaccharides **19**, **21** and **25** are described starting from a common intermediate, the iodo acetate **15**. This substance was in turn prepared via a haloetherification reaction between the allal derivative **13**, the galactose alcohol **14** and an "iodonium" equivalent.

In the most important of the glycosylation protocols used to date, the oxidation levels of both the glycosyl donor and glycosyl acceptor are not altered.[1] An interesting exception to this pattern is the strategy of coupling a glycal (**1**) to a suitably differentiated glycosyl acceptor (**2**) through a haloetherification reaction of the type discovered and developed by Lemieux[2] and Thiem[3]. In this process the glycosyl donor (i.e., the glycal) is oxidized en route to dissacharide **3** (see eq. 1).

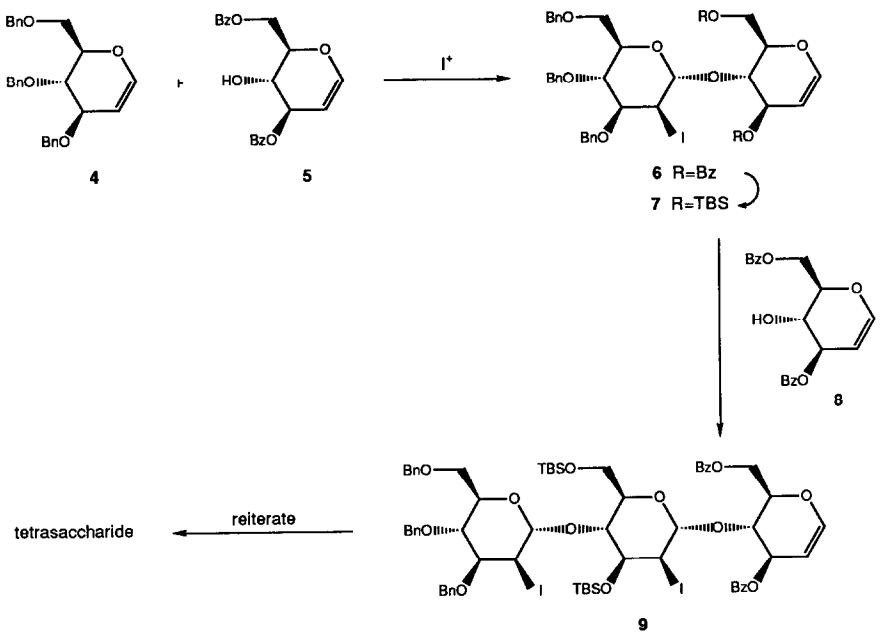
Our interest in this sort of reaction initially arose from our research on the Lewis acid catalyzed diene-aldehyde cyclocondensation reaction. As a consequence of those studies, glycals which are susceptible to a wide range of structural modification at C_6 and C_4, can be synthesized in two steps (see eq. 2).[4] In our total synthesis of avermectin A_{1a}, the cyclocondensation methodology was used to generate the L-oleandrose residues.[5a,b,c] These residues were combined and joined (in two ways) to the aglycone using haloetherification strategies.





One of the attractions of the haloetherification approach is that it leads quite stereoselectivity to the formation of a 2-β-halo-1-α-glycoside through the apparent *trans* diaxial addition of "halonium" and alkoxy residues across the glycal double bond. Recently a major advance in the haloetherification was achieved in our laboratory.[6] *By judicious selection of the protecting groups, it is possible to order the sense of oxidative coupling of two different glycals.* This is seen in the coupling of glycals **4** and **5** to afford **6** (Scheme 1). The principle seems to be that the iodonium equivalent attacks that glycal which bears ether rather than ester protecting groups. Since only glycal **5** has the free hydroxyl function which allows it to serve as the glycosyl acceptor, the sense of disaccharide formation is, in effect, dictated. Compound **6** upon conversion (two steps) to di-TBS ether **7** functions exclusively as the glycosyl donor with respect to glycal **8**. Trisaccharide **9** is the sole product.

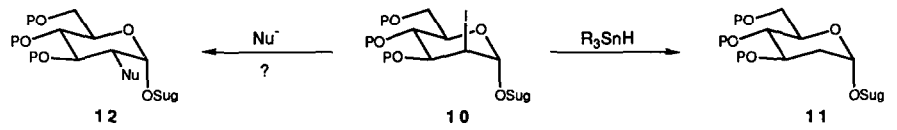
Scheme I



The one feature of the iodoglycosylation route which has proven to be unsatisfactory is the difficulty associated with converting the 2-β-iodo-1-α-glycoside product (cf. **10**) to a disaccharide bearing a 2-hetero function (Scheme II). The only generally encountered products derived from the transformation of systems of the type **10** have been 2-desoxydisaccharides (cf. **11**) (via the action of various

tinhydrides).[7] For reasons which are not completely clear, attempted S_N2-like displacements (cf. **10** to**12**) of the C_2-β-iodo function by oxygen or nitrogen based nucleophiles have been either totally unproductive or have been attended by unacceptably low yields.[8,9]

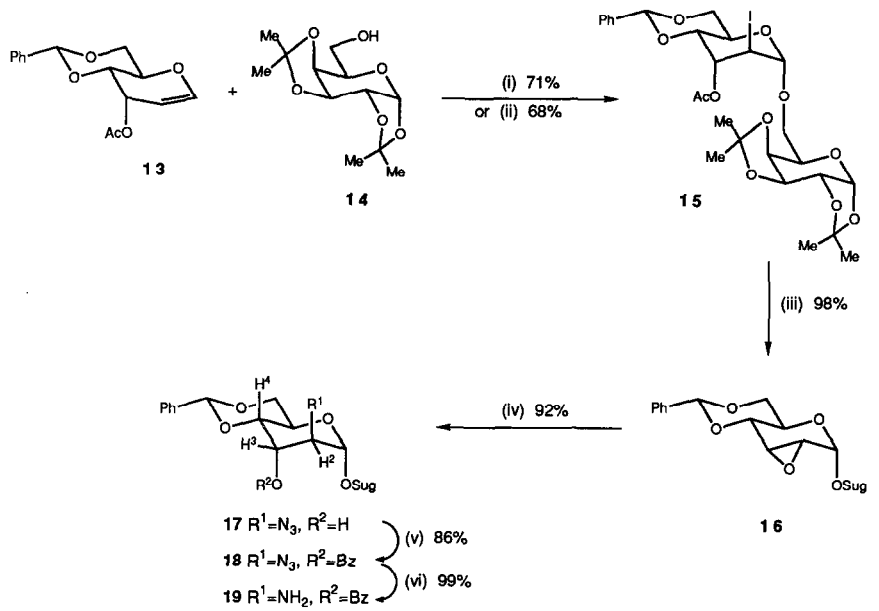
Scheme II



12 10 11

In this paper we present an approach which circumvents the apparent non-susceptibility of systems of the type **10** to intermolecular displacement. Two lines of inquiry were investigated. For each of these departures the starting material was the D-allal derivative **13**.[10] Reaction of **13** with N-iodosuccinimide and glycosyl acceptor **14**[11] afforded **15** (71%, Scheme III). A comparable result (68%) was achieved using

Scheme III[a]



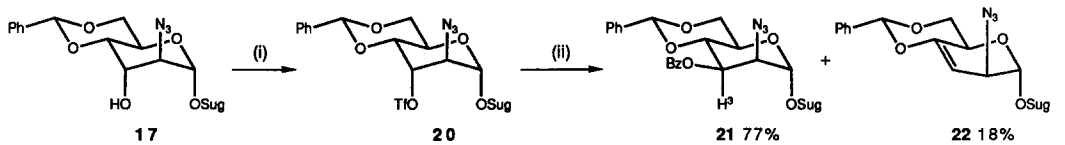
13 14 15 16

[a]Reaction Conditions: (i) NIS, MeCN, 4A powdered molecular sieves; (ii) I(*sym*-collidine)$_2$ClO$_4$, CH_2Cl_2, 4A sieves; (iii) NaOMe, MeOH, 0°C to rt; (iv) NaN_3, DMF, 90-95°C, 3 days; (v) PhCOCl, pyridine, 50°C; (vi) H_2, Pd/C, EtOAc.

I(*sym*-collidine)$_2$ClO$_4$ as the oxidative coupling reagent.[12] Treatment of **15** with sodium methoxide-methanol gave, in 98% yield, the α-oxirane **16**.[13] The latter undergoes smooth azidolysis to provide **17** (92%). That nucleophilic attack of azide on the oxirane had indeed occurred at C_2 in accord with the Furst-Plattner rules[14] was confirmed by inspection of the ^{1}H NMR spectrum of **18** (in C_6D_6). H^3 was observed as a triplet (δ 5.62) with J = 2.9 Hz. Had S_N2 epoxide opening been effected at C_3, the resulting methine proton at C_3 would be expected to have a much larger coupling to the vicinal protons at C_4 and C_2 (*trans*-diaxial relationships). Compound **17** was converted via **18** to the novel α-linked 2-deoxy-2-aminoaltrose derivative **19** (85%).

An alternative sequence leading to the α-linked mannose precursor **21** started with the reaction of **17** with triflic anhydride to afford **20** (Scheme IV). The axial triflate suffered smooth displacement through the action of sodium benzoate in the presence of tetra-N-butylammonium bisulfate in benzene/water. Compound **21** was thus obtained in 77% yield, accompanied by ca. 18% of **22**. The methine proton, H^3, exhibited the expected doublet of doublets (δ 5.76, J = 3.9, 10.2 Hz) in the ^{1}H NMR spectrum of **21** (in $CDCl_3$).

Scheme IV[a]

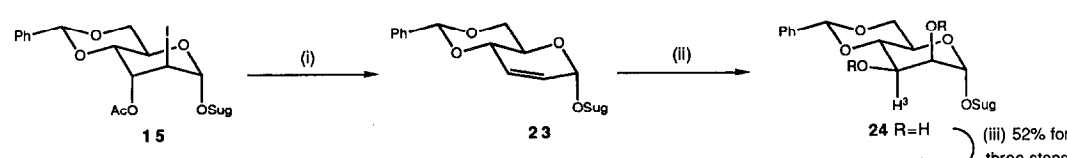


17 **20** **21** 77% **22** 18%

[a]Reaction Conditions: (i) Tf_2O, pyridine, 0°C to rt; (ii) $PhCO_2Na$, $^nBu_4NHSO_4$, PhH, H_2O, reflux.

A route was also developed to the α-linked mannose disaccharide **24** (Scheme V). This started with the treatment of **15** with zinc in ethanol to give a 95% yield of the reductive elimination product **23**. The latter, on treatment with catalytic osmium tetroxide, afforded a single diol **24**, which upon acetylation gave rise to **25**. Inspection of the ^{1}H NMR spectrum of **25** (in C_6D_6) indicated that the bis-hydroxylation had occurred stereoselectively on the β-face of the C_2-C_3 olefin. Thus, the C_3 proton (δ 5.92) is coupled to H^2 and H^4 with coupling constants of 3.5 and 9.8 Hz, respectively. A much smaller $J_{3,4}$ value would be expected (axial-equatorial relationship) had α-face functionalization been operative.

Scheme V[a]



15 **23** **24** R=H, **25** R=Ac (iii) 52% for three steps

[a]Reaction Conditions: (i) Zn, EtOH(95%), reflux; (ii) OsO_4(catalytic), NMO, acetone, H_2O; (iii) Ac_2O, Et_3N, DMAP, CH_2Cl_2.

In summary, it has been demonstrated here that the use of allal derivative **13** is a promising one in terms of synthesizing certain kinds of oligosaccharides. It allows one to take advantage of the stereospecificity and operational simplicity of the iodoetherification route to disaccharides, while providing a capability to introduce common hetero based functionalities in common stereochemical patterns at C_2 and C_3.

Of course, we well recognize that it would be preferable if technology could be developed to achieve the oxidative coupling of glycals wherein the axial substituent entered at C_2 could be directly replaced with external nucleophiles. This goal is being addressed, as are additional applications of the oxidative coupling of glycals.

Experimental Section

General Procedure. Combustion analyses were performed by Galbraith Laboratories, Inc. Infrared spectra were recorded on a Perkin Elmer 1420 Ratio Recording Infrared Spectrophotometer. Low resolution and high resolution mass spectra were determined on a Hewlett-Packard 5985 quadrapole mass spectrometer and a Kratos MS80RFA spectrometer, respectively. High field NMR spectra were recorded on a Bruker WM-250 NMR instrument. Flash chromatography was performed on EM Science Kieselgel 60 (230-400 mesh) eluting with the indicated solvent systems. I(*sym*-collidine)$_2$ClO$_4$ was prepared according to the procedure of Lemieux[12]. N-iodosuccinamide was recrystallized from dioxane-CCl_4.

1,2;3,4-Di-*O*-isopropylidene-6-*O*-(3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-altropyranosyl)-α-D-galactopyranose **15**.

To a stirred solution of 3-*O*-acetyl-4,6-*O*-benzylidene-D-allal **13** (344.4 mg, 1.25 mmol) and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose **14** (356.9 mg, 1.37 mmol) in dry acetonitrile (7 mL, 0.18M) was added approximately 350 mg of 4A powdered molecular sieves. The mixture was stirred for 30 min at room temperature and then N-iodosuccinamide (421.9 mg, 1.87 mmol) was added. After being stirred for 15h, the mixture was filtered and ethyl acetate (100 mL) and 10% aqueous $Na_2S_2O_3$ (100 mL) were added. The organic phase was removed and the aqueous phase was extracted with ethyl acetate (2X50 mL). The combined organics were dried ($MgSO_4$) and concentrated. Chromatography of the residual oil (hexanes:ethyl acetate, 2:1 v/v) provided the iodo acetate **15** (590.2 mg; 71%) as a foam: $[\alpha]_D^{23}$ -10.1° (c 0.51, $CHCl_3$); IR ($CHCl_3$) 3010, 1735, 1380, 1235, 1125, 1070, 1005 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33, 1.35, 1.46 and 1.54 (s each, 3H each), 2.13 (s, 3H), 3.62 (dd, 1H, J=6.3, 10.5 Hz), 3.82 (dd, 1H, J=6.3, 10.4 Hz), 3.83 (t, 1H, J=9.5 Hz), 3.96 (ddd, 1H, J=1.9, 6.3, 6.3 Hz), 4.22 (dd, 1H, J=1.9, 8.0 Hz), 4.32-4.39 (m, 2H), 4.46 (dd, 1H, J=4.8, 9.5 Hz), 4.50-4.55 (m, 2H), 4.64 (dd, 1H, J=2.6, 8.0 Hz), 5.13 (s, 1H), 5.27 (t, 1H, J=2.6 Hz), 5.55 (d, 1H, J=5.0 Hz), 5.65 (s, 1H), 7.35-7.52 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.9, 22.4, 24.5, 24.9, 26.0, 26.1, 59.5, 66.3, 67.0, 69.1, 70.5, 70.7, 71.1, 71.2, 73.2, 96.4, 101.8, 102.0, 108.5, 109.4, 126.2, 128.2, 129.1, 137.2, 170.5; Anal. calcd. for $C_{27}H_{35}IO_{11}$: C, 48.95; H, 5.32; Found: C, 48.95; H, 4.93.

In a similar procedure , employing 595.8 mg (2.16 mmol) of glycal **13**, 673.5 mg (2.59 mmol) of alcohol **14** and 1.12 g of I(*sym*-collidine)$_2$ClO$_4$ in CH_2Cl_2 (30 mL, 0.07M), 976.9 mg (68%) of the iodo acetate **15** was obtained.

1,2;3,4-Di-*O*- isopropylidene-6-*O*-(2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranosyl)-α-D-galactopyranose **16**.

To a cold (0°C) stirred solution of the iodo acetate **15** (200.0 mg, 0.30 mmol) in anhydrous methanol (5 mL) was added sodium methoxide (32.4 mg, 0.60 mmol) and the resulting solution was stirred for 1h at 0°C and 1h at room temperature. The mixture was concentrated and subjected to chromatography (hexanes:ethyl acetate, 3:2 v/v) to provide the epoxide **16** (146.2 mg; 98%) as a colorless foam: $[\alpha]_D^{23}$ +21.9° (c 0.72, $CHCl_3$); IR ($CHCl_3$) 3010, 1380, 1070 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34, 1.37, 1.46 and 1.56 (s each, 3H each), 3.52-3.56 (m, 2H), 3.68 (t, 1H, J=10.0 Hz), 3.81 (dd, 1H, J=8.6, 10.3 Hz), 3.86 (dd, 1H, J=6.2, 10.3 Hz), 3.96 (d, 1H, J=9.1 Hz), 4.05-4.17 (m, 2H), 4.26 (dd, 1H, J=5.0, 10.0 Hz), 4.33 (dd, 1H, J=2.4, 5.0 Hz), 4.37 (dd, 1H, J=1.8, 8.0 Hz), 4.64 (dd, 1H, J=2.4, 8.0 Hz), 5.10 (m, 1H), 5.52 (d, 1H, J=5.0 Hz), 5.58 (s, 1H), 7.33-7.57 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.5, 24.8, 26.0, 26.1, 50.5, 53.1, 60.1, 65.9, 66.9, 68.8, 70.56, 70.64, 70.8, 77.9, 94.8, 96.3, 102.6, 108.5, 109.1, 126.2, 128.2, 129.1, 137.2; Anal. calcd. for $C_{25}H_{32}O_{10}$: C, 60.97; H, 6.55; Found: C, 61.11; H, 6.83.

1,2;3,4-Di-*O*-isopropylidene-6-*O*-(2-azido-2-deoxy-4,6-*O*-benzylidene-α-D-altropyranosyl)-α-D-galactopyranose **17**.

A stirred solution/suspension of epoxide **16** (80.0 mg, 0.16 mmol) and sodium azide (52.7 mg, 0.81 mmol) in dry DMF (1 mL) was heated at 90-95°C for 72h. After 24h and 48h, respectively, more sodium azide (21.1 mg, 0.32 mmol) was added. The mixture was cooled to room temperature, water (10 mL) and ether (10 mL) were added, and the organic phase was separated. The aqueous phase was extracted with ether (3X20 mL) and the combined organics were washed with water (2X5 mL), dried ($MgSO_4$) and concentrated. Chromatography of the residual oil (hexanes:ethyl acetate, 2:1 v/v) provided the azido alcohol **17** (80.1 mg; 92%) as a colorless foam: $[\alpha]_D^{23}$ +6.2° (c 0.64, $CHCl_3$); IR ($CHCl_3$) 3500, 3010, 2110, 1380, 1070 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.34, 1.36, 1.47 and 1.54 (s each, 3H each), 3.22 (d, 1H, J=8.7 Hz), 3.70 (dd, 1H, J=5.0, 10.1 Hz), 3.79-4.05 (m, 5H), 4.16 (dm, 1H, J=8.7 Hz), 4.24-4.37 (m, 4H), 4.64 (dd, 1H, J=2.4, 7.8 Hz), 4.92 (s, 1H), 5.56 (d, 1H, J=5.0 Hz), 5.65 (s, 1H), 7.33-7.57 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.4, 24.8, 25.9, 26.0, 58.4, 61.9, 65.9, 66.7, 67.7, 68.9, 70.6, 70.8, 71.1, 75.9, 96.2, 98.0, 102.2, 108.6, 109.5, 126.2, 128.1, 129.0, 137.2; FAB-MS, m/e 536 $(M+H)^+$; Anal. calcd. for $C_{25}H_{33}N_3O_{10}$: C,56.07; H, 6.21; N, 7.85; Found: C, 55.88; H, 6.13; N, 7.68.

1,2;3,4-Di-*O*-isopropylidene-6-*O*-(2-azido-2-deoxy-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-altropyranosyl)-α-D-galactopyranose **18**.

A stirred solution of the azido alcohol **17** (117.0 mg, 0.22 mmol) and benzoyl chloride (0.13 mL, 1.1 mmol) in pyridine (5 mL) was heated at 50°C for 2h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous copper(II) sulfate (2X30 mL). The aqueous phase was extracted with CH_2Cl_2 (3X10 mL) and the combined organics were dried ($MgSO_4$) and concentrated. Chromatography of the residual oil (hexanes:ethyl acetate, 3:1 v/v) provided the benzoate **18** (119.5 mg; 86%) as a colorless foam: $[\alpha]_D^{23}$ +14.8° (c 0.23, $CHCl_3$); IR ($CHCl_3$) 3010, 2920, 2110, 1720, 1385, 1270, 1070 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 1.02, 1.06, 1.34 and 1.42 (s each, 3H each), 3.50 (t, 1H, J=10.4 Hz), 3.74 (dd, 1H, J=7.9, 9.4 Hz), 3.88-3.94 (m, 3H), 4.00 (dd, 1H, J=5.9, 9.5 Hz), 4.10-4.19 (m, 3H), 4.36 (dd, 1h, J=2.3, 7.9 Hz), 4.57 (dt, 1H, J=5.1, 10.0 Hz), 4.71 (s, 1H), 5.28 (s, 1H), 5.45 (d, 1H, J=5.0 Hz), 5.62 (t, 1H, J=2.9 Hz), 7.00-7.20 (m, 6H), 7.51 (m, 2H), 8.27 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.4, 24.9, 26.0, 26.1, 59.5, 60.2, 65.7, 66.5, 68.2, 69.2, 70.5, 70.6, 70.7, 74.1, 96.3, 98.3, 102.2, 108.6, 109.3, 126.1, 128.2, 128.5, 129.1, 129.87, 129.92, 133.2, 137.2, 165.9; Exact mass calcd. for $C_{32}H_{38}O_{11}N_3$ [$(M+H)^+$,CI-HRMS]: 640.2507; Found: 640.2510.

1,2;3,4-Di-*O*-isopropylidene-6-*O*-(2-amino-2-deoxy-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-altropyranosyl)-α-D-galactopyranose **19**.

A solution/suspension of the azido benzoate **18** (55.5 mg, 0.087 mmol) and 10% palladium on carbon (22 mg) in ethyl acetate (3 mL) was stirred under an atmosphere of hydrogen (1 atm) for 1h. The mixture was filtered through Celite, washing with ether. The filtrate was dried ($MgSO_4$) and concentrated. Chromatography of the residual oil (ethyl acetate) provided the amino benzoate **19** (52.6 mg; 99%) as a colorless foam: $[\alpha]_D^{23}$ +54.9° (c 0.82, $CHCl_3$); IR ($CHCl_3$) 3385, 3310, 2995, 2940, 1715, 1600, 1450, 1385, 1278, 1115, 1074 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22, 1.34, 1.41 and 1.50 (s each, 3H each), 1.40-1.65 (br, 2H), 3.52 (d, 1H, J=2.6 Hz), 3.64 (t, 1H, J=8.7 Hz), 3.79-4.02 (m, 4H), 4.18 (dd, 1H, J=3.0, 9.5 Hz), 4.29 (dd, 1H, J=2.3, 5.0 Hz), 4.35-4.53 (m, 3H), 4.75 (s, 1H), 5.36 (t, 1H, J=2.6 Hz), 5.51 (d, 1H, J=5.0 Hz), 5.63 (s, 1H), 7.27-7.60 (m, 8H), 8.10 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.3, 24.9, 25.9, 26.2, 52.7, 59.6, 65.8, 66.1, 69.4, 70.36, 70.44, 70.7, 71.4, 74.2, 96.2, 101.9, 102.1, 108.5, 109.1, 126.1, 128.2, 128.4, 129.0, 129.7, 130.4, 132.8, 137.3, 165.9; Exact mass calcd. for $C_{32}H_{40}O_{11}N$ [$(M+H)^+$, CI-HRMS]: 614.2602; Found: 614.2618.

1,2;3,4-Di-*O*-isopropylidene-6-*O*-(2-azido-2-deoxy-3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-α-D-galactopyranose **21**.

To a cold (0°C), stirred solution of the azido alcohol **17** (110.0 mg, 0.21 mmol) and pyridine (0.2 mL, 2.5 mmol) in CH_2Cl_2 (5 mL) was added triflic anhydride (0.1 mL, 0.59 mmol). The solution was stirred at 0°C for 10 min and 30 min at room temperature and then water (10 mL) was added. The organics were separated and the aqueous phase was extracted with CH_2Cl_2 (2X10 mL). The combined organics were dried ($MgSO_4$) and concentrated. The crude triflate **20** exhibited: IR ($CHCl_3$) 3010,

2110, 1725, 1220, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.35, 1.37, 1.47 and 1.56 (s each, 3H each), 3.70-3.90 (m, 3H), 3.99-4.06 (m, 2H), 4.13 (d, 1H, J=3.1 Hz), 4.27-4.40 (m, 4H), 4.66 (dd, 1H, J=2.5, 8.0 Hz), 4.96 (s, 1H), 5.10 (br t, 1H, J=2.5 Hz), 5.54 (d, 1H, J=5.0 Hz), 5.63 (s, 1H), 7.35-7.51 (m, 5H).

The crude material was dissolved in benzene (10 mL) and water (2 mL). Sodium benzoate (200 mg, 1.39 mmol) and tetra-N-butylammonium bisulfate (100 mg, 0.29 mmol) were added. The resulting mixture was refluxed for 21h and then cooled to room temperature. Water (10 mL) was added and the mixture was extracted with ether (3X20 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated. Chromatography of the residual oil (hexanes:ethyl acetate, 4:1 v/v) provided two compounds. The less polar material, the enol ether **22** (19.6 mg; 18%) was not fully characterized but exhibited: IR ($CHCl_3$) 3010, 2110, 1725, 1685, 1385, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.35, 1.36, 1.47 and 1.57 (s each, 3H each), 3.65 (br d, 1H, J=5.5 Hz), 3.74-3.94 (m, 3H), 4.00 (br t, 1H, J=6.6 Hz), 4.25 (dd, 1H, J=1.7, 7.8 Hz), 4.35 (dd, 1H, J=2.5, 5.1 Hz), 4.40-4.51 (m, 2H), 4.64 (dd, 1H, J=2.8, 8.1 Hz), 5.00 (s, 1H), 5.35 (d, 1H, J= 5.5 Hz), 5.55 (d, 1H, J=5.4 Hz), 5.60 (s, 1H), 7.35-7.60 (m, 5H).

The more polar substance, the azido benzoate **21** (100.6 mg; 77%), was obtained as a colorless foam: $[\alpha]_D^{23}$ +17.8° (c 0.59, $CHCl_3$); IR ($CHCl_3$) 3010, 2110, 1725, 1270, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.35, 1.37, 1.46 and 1.59 (s each, 3H each), 3.75 (dd, 1H, J=7.6, 10.0 Hz), 3.82-3.91 (m, 2H), 4.00-4.09 (m, 2H), 4.22 (t, 1H, J=9.7 Hz), 4.29-4.36 (m, 4H), 4.66 (dd, 1H, J=2.4, 7.9 Hz), 4.95 (d, 1H, J=1.1 Hz), 5.55 (d, 1H, J=5.0 Hz), 5.61 (s, 1H), 5.77 (dd, 1H, J=3.9, 10.1 Hz), 7.29-7.50 (m, 7H), 7.60 (m, 1H), 8.13 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.6, 24.9, 26.0, 26.2, 62.5, 64.2, 65.9, 66.7, 68.7, 70.5, 70.68, 70.73, 70.9, 76.3, 96.3, 99.3, 101.8, 108.7, 109.5, 126.1, 128.1, 128.4, 128.9, 129.4, 130.0, 133.3, 137.2, 165.6; FAB-MS, m/e 640 $(M+H)^+$; Anal. calcd. for $C_{32}H_{37}N_3O_{11}$: C, 60.09; H, 5.83; N, 6.57; Found: C, 60.07; H, 6.15; N, 6.25.

1,2;3,4-Di-*O*-isopropylidene-6-*O*-(2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-manno-pyranosyl)-α-D-galactopyranose **25**.

To a stirred solution of the iodo acetate **15** (24.8 mg, 0.037 mmol) in 95% ethanol (2 mL) was added powdered zinc (45 mg, 0.67 mmol) and the resulting mixture was refluxed for 18h. After cooling to room temperature, the mixture was filtered through Celite, washing with ether. The filtrate was concentrated and redissolved in ether and washed with 10% aqueous $Na_2S_2O_3$. The ethereal layer was dried ($MgSO_4$) and concentrated. The crude olefin **23** exhibited: IR ($CHCl_3$) 3010, 1720, 1380, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.34, 1.37, 1.47 and 1.56 (s each, 3H each), 3.75-3.94 (m, 4H), 4.04-4.16 (m, 2H), 4.28-4.34 (m, 3H), 4.63 (dd, 1H, J=2.4, 7.9 Hz), 5.08 (br s, 1H), 5.52 (d, 1H, J=5.0 Hz), 5.58 (s, 1H), 5.75 (dt, 1H, J=10.3, 2.4 Hz), 6.12 (br d, 1H, J= 10.3 Hz), 7.34-7.54 (m, 5H).

To a stirred solution of the crude olefin **23** and NMO (5 mg, 0.043 mmol) in acetone (1 mL) was added 0.01 mL of a 0.157 M aqueous solution of osmium tetroxide (0.0016 mmol). The resulting mixture was stirred for 22h and then 2 drops of water, 2 drops of saturated aqueous sodium bisulfite and fluorisil were added and stirred for 45min.

The mixture was filtered through Celite, washing with ethyl acetate. The filtrate was dried ($MgSO_4$), concentrated and redissolved in CH_2Cl_2 (1 mL). Triethylamine (0.03 mL, 0.22 mmol), DMAP (0.5 mg, 0.004 mmol) and acetic anhydride (0.02 mL, 0.21 mmol) were added and the resulting solution was stirred for 1h. Water (10 mL) and CH_2Cl_2 (10 mL) were added and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2X10 mL) and the combined organics were dried ($MgSO_4$) and concentrated. Chromatography of the residual material (hexanes:ethyl acetate, 3:1 v/v) provided the bis acetate **25** (11.6 mg; 52%) as a colorless foam: $[\alpha]_D^{23}$ -12.2° (c 0.50, $CHCl_3$); IR ($CHCl_3$) 3010, 2920, 1745, 1373, 1250, 1070 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 1.07, 1.19, 1.46, 1.50, 1.69 and 1.77 (s each, 3H each), 3.65 (t, 1H, J=9.7 Hz), 3.84 (dd, 1H, J=6.9, 10.2 Hz), 3.97 (dd, 1H, J=6.0, 10.2 Hz), 4.06 (dd, 1H, J=1.8, 9.7 Hz), 4.17-4.31 (m, 5H), 4.49 (dd, 1H, J=2.3, 7.9 Hz), 4.97 (d, 1H, J=1.4 Hz), 5.44 (s, 1H), 5.49 (d, 1H, J=5.0 Hz), 5.83 (dd, 1H, J=1.5, 3.5 Hz), 5.92 (dd, 1H, J=3.5, 9.8 Hz), 7.10-7.25 (m, 3H), 7.60 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.8, 24.4, 24.9, 25.9, 26.1, 63.9, 65.8, 66.1, 66.9, 68.4, 68.7, 70.0, 70.6, 70.7, 76.1, 96.2, 99.0, 101.9, 108.7, 109.3, 126.2, 128.2, 129.0, 137.2, 169.7; Anal. calcd. for $C_{29}H_{38}O_{13}$: C, 58.58; H, 6.44; Found: C, 58.63; H, 6.40.

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