Synthesis of the C-Glycoside Analogue of a Novel Sialyl Lewis X Mimetic

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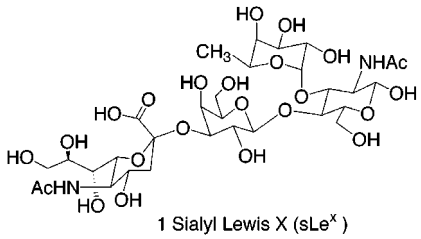
Sialyl Lewis X (sLe^x) mimetics that can function as selectin antagonists have received considerable attention in connection with the development of novel antiinflammatory therapies. An interesting structure that emerged from the studies of the Wong group is the 1,1-Gal-Man disaccharide **2**, reported to bind *E*-selectin 5 times more strongly than sLe^x. The *C*-glycoside derivative **3** is of interest both as a conformational probe for selectin binding and as a hydrolytically stable analogue. Herein we illustrate a novel methodology for β-*C*-galacto-disaccharides in the synthesis of **3.** The protocol has as a key step a novel oxocarbenium ion−enol ether cyclization to give a C1-substituted galactal.

The implication of sialyl Lewis X (sLe^x, **1**)−selectin interaction as an initial event in the inflammation response has led to innovative approaches to antiinflammatory therapies.[1,2] One area that has received considerable attention is the design of mimetics of sLe^x that can function as selectin antagonists.[2,3] Although non-carbohydrate structures have been examined, the majority of approaches have focused on carbohydrate-type ligands of varying degrees of similarity to sLe^x. An interesting structure that emerged from the studies of the Wong group is the 1,1-Gal-Man disaccharide (**2**), which was reported to bind *E*-selectin 5 times more strongly than sLe^x [4] (Figure 1).

The general model for sLe^x interaction with *E*-selectin assumes key contact points at the 4- and 6-OH groups of galactose, the COOH of sialic acid, and the hydroxyl groups of fucose. It is believed that the GlcNHAc residue acts as a conformationally restricted spacer that maintains the binding regions on the fucose and the COOH in a preferred spatial disposition. Accordingly, it has been suggested that the galactose sector in both sLe^x and **2** interacts with *E*-selectin in similar way and that the mannose residue of **2** acts as an isotere of the fucose moiety of sLe^x.[4] Although much simpler than sLe^x, **2** is still reasonably complex, a feature that is relevant to the issue of binding specificity. We were especially interested in the *C*-glycoside analogue **3**, since it is expected to be more flexible about the intersaccharide linkage[5] and therefore could serve as a conformational probe in the search for more effective ligands. Of course, the hydrolytic



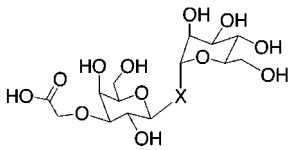


Figure 1.

stability of **3** presents an additional advantage for drug development.[6] Herein, we describe the details of our novel C-glycosidation methodology, as applied to the synthesis of **3**.[7]

Our strategy centers on the stereoselective hydroboration of a C1-substituted galactal **5**.[8] The concept of using a glycal as a precursor to 2-oxygenated C-glycosides is a known one, which was originally devised because of the high coupling efficiency of 1-lithio glycals with aldehydo aglycone partners.[8a] The more direct approach of using 2-O-substituted glycosyl anions is limited by problems of β-elimination.[9] Our synthesis of C1-substituted glycals is different from other methods[10−12] in that

(1) Springer, T. A.; Larsky, L. A. *Nature* **1991**, *349*, 196−197. Phillips, M. L.; Nudelman, E.; Gaeta, F. C. A.; Perez, M.; Singhal, A. K.; Hakomori, S.-I.; Paulson, J. C. *Science* **1990**, *250*, 1130−1135.

(2) Musser, J. H.; Anderson, M. B.; Levy, D. E. *Curr. Pharm. Design* **1995**, *1*, 221−232. Boschelli, D. H. *Drugs Future* **1995**, *20*, 805−816. Roy, R. In *Carbohydrates in Drug Design*; Witczak, Z. J., Nieforth, K. A., Eds.; Marcel Dekker: New York, 1997; pp 83−105.

(3) (a) Simanek, E. E.; McGarvey, G. J.; Jablonowski, J. A.; Wong, C.-H. *Chem. Rev.* **1998**, *98*, 833−862. (b) Kretzschmar, G.; Toepfer, A.; Huls, C.; Krause, M. *Tetrahedron* **1997**, *53*, 2485−2494.

(4) Hiruma, K.; Kajimoto, T.; Weitz-Schmidt, G.; Ollmann, I.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 9265−9270.

(5) For discussions on the conformational properties of *O*- vs *C*-glycosides: (a) Ravishankar, R.; Surolia, A.; Vijayan, M.; Lim, S.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 11297−11303. (b) Martín-Lomas, M.; Imberty, A.; Cañada, F. J.; Jimenez-Barbero, J. *J. Am. Chem. Soc.* **1998**, *120*, 1309−1318.

(6) (a) Nagy, J. O.; Wang, P.; Gilbert, J. H.; Schaefer, M. E.; Hill, T. G.; Callstrom, M. R.; Bednarski, M. D. *J. Med. Chem.* **1992**, *35*, 4501−02. (b) Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L. *J. Am. Chem. Soc.* **1996**, *118*, 2297−2298.

(7) Khan, N.; Cheng, X.; Mootoo, D. R. *J. Am. Chem. Soc.* **1999**, *121*, 4918−4919.

(8) (a) Schmidt, R. R.; Dietrich, H. *Liebigs Ann. Chem.* **1994**, 975−981. Eisele, T.; Ishida, M.; Hummel, G.; Schmidt, R. *Liebigs Ann. Chem.* **1995**, 2113−2121. (b) Postema, M. H. D.; Calimente, D. *Tetrahedron Lett.* **1999**, *40*, 4255−4259.

(9) (a) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1−54. (b) Mazeas, D.; Skrydstrup, T.; Beau, J.-M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 909−912. (c) Frey, O.; Hoffmann, M.; Wittmann, V.; Kessler, H.; Uhlmann, P.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 2060−2069.

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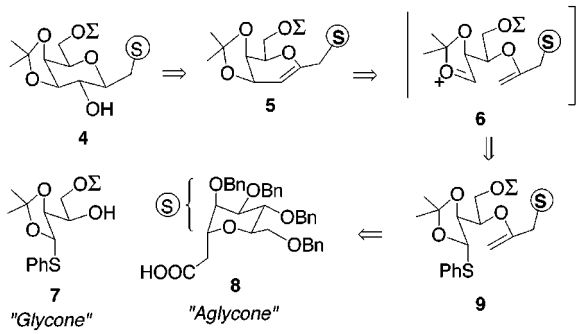
Scheme 1

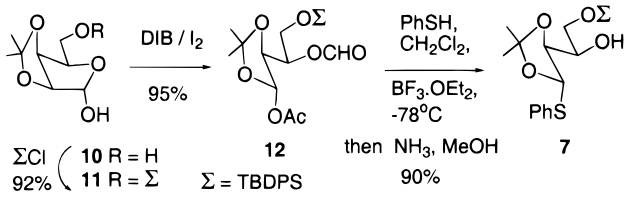


the glycal is formed via an intramolecular oxocarbenium ion−alkene cyclization in an acetal-enol ether precursor **9**. This idea was spawned from successes with related dioxolenium ion cyclizations.[13] An important aspect of this plan is that *β*-*C*-galactosides could be accessed in a convergent fashion from a 1-thio-1,2-*O*-isopropylidene acetal (TIA) **7** and a carboxylic acid **8** (Scheme 1).

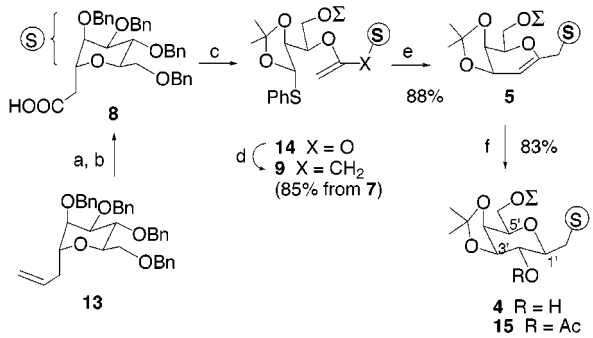
The key reaction in the synthesis of **7** was the Suarez fragmentation of an anomeric alkoxy radical.[14] The known D-lyxose derivative **10**[15] was converted to the monosilylated ether **11**. Treatment of **11** with iodobenzene diacetate (DIB) led to the 1-*O*-acetyl-1,2-*O*-isopropylidene acetal **12** in 90% yield. Acetal exchange on **12**, under controlled conditions with thiophenol and boron trifluoride etherate, followed by mild base treatment of the crude product, provided **7** in high yield. The overall synthesis of **7** from D-lyxose was achieved in 65% yield, spanned four "one-pot" operations, and involved simple procedures, thereby facilitating multigram batches of **7**. The acid component **8** was obtained via oxidative cleavage of the *C*-allyl mannoside **13**[16] via the published procedure.[17] (Scheme 2).

DCC-mediated coupling[18] of **7** and **8** (1.1 equiv) led to the ester **14**, which was treated with Tebbe reagent.[19]

Scheme 2



Scheme 3



(a) O_3 then DMS; (b) $NaClO_2$ or Jones reagent; (c) **7**, DCC, DMAP, PhH; (d) Tebbe; (e) MeOTf, DTBMP, CH_2Cl_2; (f) BH_3.DMS then Na_2O_2

The two-step operation provided enol ether **9** in 85% yield from **7**. The key cyclization reaction was carried out by treatment of **9** with methyl triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP). The glycal **5** was obtained in 88% yield as a single stereo- and regioisomer. No evidence was observed for isomers containing the *trans*-isopropylidene or the exocyclic alkene. The high efficiency of this reaction is presumably related to favorable entropy and ring strain effects of the cyclic oxocarbenium ion **6** on the cyclization step and regioselective deprotonation of the glycosyl cation derived therefrom. The latter selectivity may be a consequence of unfavorable $A^{(1,3)}$ interactions in the exocyclic alkene product.[20] Hydroboration of **5** provided the *C*-glycoside **4** as a single diastereomer in 83% yield. The structure of **4** was confirmed by ^{1}H COSY analysis of the acetate **15**. The coupling constants ($J_{1',2'} = 9.2$, $J_{2',3'} = 7.5$, $J_{3',4'} = 5.1$, and $J_{4',5'} = 2.2$ Hz) are in agreement with those expected for the 3,4-*O*-isopropylidene 1*β*-galacto residue.[21]

The alcohol **4** was next converted to the desired acid **3**. Acidic hydrolysis of **4** afforded the triol **16**, which was subjected to selective alkylation of the 3′-OH, using methyl bromoacetate and dibutyltin oxide.[4] Partial chromatographic purification of the crude product afforded an approximately 1:1 mixture. The ^{1}H NMR of this mixture did not show the methoxy signals for the expected alkylation product, and it was presumed that the components were the regiosomeric O-2 and O-4

(10) For reviews on *C*-glycoside synthesis: (a) Du, Y.; Linhardt, R. J.; Vlahov, J. R. *Tetrahedron* **1998**, *54*, 9913−9959. (b) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−717. (c) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995. (d) Levy, D.; Tang, C. *The Synthesis of C-Glycosides*; Elsevier/Pergamon: Oxford, 1995 and ref 9a.

(11) Recent examples of *C*-glycosides with less substituted aglycone segments: (a) Ben, R. N.; Orellana, A.; Arya, P. *J. Org. Chem.* **1998**, *63*, 4817−4820. (b) Griffin, F. K.; Murphy, P. V.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8179−8182. (c) Belica, P. S.; Franck, R. W. *Tetrahedron Lett.* **1998**, *39*, 8225−8228. (d) Evans, D. A.; Trotter, B. W.; Coté, B. *Tetrahedron Lett.* **1998**, *39*, 1709−1712. Johnson, C. R.; Johns, B. A. *Synlett* **1997**, 1406−1408. Spencer, R. P.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 4024−4025.

(12) Recent examples of *C*-glycosides with sugar-type aglycone segments: (a) Bazin, H. G.; Du, Y.; Polat, T.; Linhardt, R. J. *J. Org. Chem.* **1999**, *64*, 7254−7259. (b) Pham Huu, D.-P.; Petrusova, M.; BeMiller, J. N.; Petrus, L. *Tetrahedron Lett.* **1999**, *40*, 3053−3056. (c) Jarreton, O.; Skrydstrup, T.; Espinosa, J. F.; Jimmenéz-Barbero, J.; Beau, J.-M. *Chem. Eur. J.* **1999**, *5*, 430−441. (d) Dondoni, A.; Kleban, M.; Zuurmond, H.; Marra, A. *Tetrahedron* **1998**, *39*, 7991−7994. (e) Rubinstenn, G.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1998**, *39*, 3697−3700. (f) Rekai, El-D.; Rubinstenn, G.; Mallet, J.-M.; Sinaÿ, P. *Synlet* **1998**, 831−834. (g) Zhu, H.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 31−34. (h) Witczak, Z. J.; Chhabra, R.; Chojnacki, J. *Tetrahedron* **1997**, *38*, 2215−2218 (i) Sutherlin, D. P.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5267−5283. (j) Wei, A.; Haudrechy, A.; Audin, C.; Jun, H.; Bretel, H.-N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160−2169 and refs 8 and 9.

(13) Khan, N.; Xiao, H.; Zhang, B.; Cheng, X.; Mootoo, D. R. *Tetrahedron* **1999**, *55*, 8303−8312. Shan, W.; Wilson, P.; Liang, W.; Mootoo, D. R. *J. Org. Chem.* **1994**, *59*, 7986−7992.

(14) De Armas, P.; Francisco, C. G.; Suarez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772−774. Francisco, C. G.; Friere, R.; Gonzalez, C. C.; Suarez, E. *Tetrahedron Asymmetry* **1997**, *8*, 1971−1972.

(15) Levene, P. A.; Tipson, R. S. *J. Biol. Chem.* **1936**, *115*, 731−747

(16) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383−2386.

(17) Wong, C.-H.; Moris-Varas, F.; Hung, S.-C.; Marron, T. G.; Lin, C.-C.; Gong, K. W.; Weitz-Schmidt, G. *J. Am. Chem. Soc.* **1997**, *119*, 8152−8158.

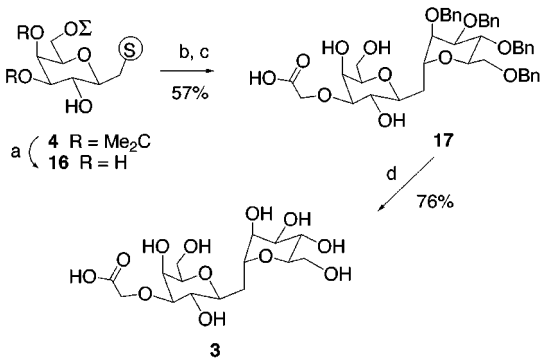
(18) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522−523.

(19) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212−1218.

(20) For a discussion of $A^{(1,3)}$ strain effects on the 1-methylcyclohexene/methylenecyclohexane equilibrium: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; p 737.

(21) For example, see: Barili, P. L.; Catelani, G.; D'Andrea, F.; Mastrorilli, E. *J. Carbohydr. Chem.* **1997**, *16*, 1001−1010.

Scheme 4



(a) MeOH, HCl; (b) Bu_2SnO then $BrCH_2CO_2Me$; (c) NaOH, EtOH-H_2O, then H^+; d) H_2, Pd/C, HCOOH, MeOH

lactone derivatives of **17**. Indeed, basic hydrolysis and acidification of the crude mixture afforded the desilylated acid **17** as a single product in 57% overall yield from **16**. Exhaustive hydrogenolysis of **17** provided, in 76% yield, a compound for which the physical data (^{1}H COSY, ^{13}C NMR, MS) was consistent with the title compound **3** (Scheme 4).

In summary, the *C*-glycoside analogue of a novel sLe^x mimetic has been prepared, via a highly convergent approach, from the readily available 1-thio-1,2-*O*-isopropylidene precursor **7**. Compound **7** is a general synthon for β-*C*-galactosides and is currently being applied to other *C*-glycoside targets. The conformational and biological properties of **3** are currently under investigation.[22]

Experimental Section

General. Unless otherwise noted, TLC was performed on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Flash column chromatography was performed using Kieselgel 60 (230−400 mesh, E. Merck) and usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. The spots were visualized by UV or charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous H_2SO_4 (500 mL). NMR spectra were recorded on 300, 400, or 500 MHz instruments with residual $CHCl_3$ or C_6H_6 as the internal standard.

1-Thio-1,2-*O*-isopropylidene Acetal 7. A solution of 2,3-*O*-isopropylidene-D-lyxofuranose **10**[15] (2.7 g, 14 mmol), TBDPSCl (3.7 mL, 14 mmol), and imidazole (1.9 g, 28 mmol) in anhydrous DMF (25 mL) was stirred at 50 °C for 1.5 h. The reaction mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography to give **11** (5.7 g, 95%): colorless oil; R_f = 0.20 (10% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.26, 1.35 (both s, 3H ea), 3.94 (m, 2H), 4.33 (m, 1H), 4.58 (d, J = 7.0 Hz, 1H), 4.75 (m, 1H), 5.35 (s, 1H), 7.38, 7.70 (both m, 10H).

A solution of **11** (9.5 g, 21.6 mmol) in anhydrous cyclohexane (120 mL) containing diacetoxyiodobenzene (8.54 g, 26.5 mmol) and iodine (5.89 g, 23.2 mmol) was stirred under an atmosphere of argon at room temperature for 3 h. The reaction mixture was then diluted with water and extracted with ether. The organic phase was washed with aqueous $Na_2S_2O_3$ and brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography to give **12** (10.0 g, 95%): clear oil; R_f = 0.45 (10% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.46, 1.505 (both s, 3H ea), 2.10 (s, 3H), 3.82 (m, 2H), 4.51 (m, 1H), 4.58 (d, J = 7.0 Hz, 1H), 5.25 (m, 1H), 6.21 (d, J = 1.5 Hz, 1H), 7.40, 7.60 (both m, 10H), 8.05 (s, 1H); ESMS 509 (M + Na).

BF_3·OEt_2 (1.3 mL, 12.4 mmol) was slowly added to a solution of **12** (5 g, 10.3 mmol) and thiophenol (2.12 mL, 20.6 mmol) in anhydrous CH_2Cl_2 (50 mL) at −78 °C under an atmosphere of argon. The reaction mixture was warmed to −40 °C and stirred at this temperature for 1 h or until TLC indicated complete disappearance of the starting material. Triethylamine (5 mL) was then added, and the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The organic phase was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude material was dissolved in methanolic ammonia (100 mL) and stirred at room temperature for 30 min. Most of the solvent was removed under reduced pressure, and the residue was diluted with water and extracted with ether. The organic phase was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Flash chromatography of the residue provided **7** (4.7 g, 90%): colorless oil; R_f 0.50 (10% EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.47, 1.49 (both s, 6H), 2.32 (br s, 1H, D_2O ex), 3.80 (m, 3H), 4.18 (dd, J = 2.0, 7.0 Hz, 1H), 5.44 (d, J = 7.0 Hz), 7.20−7.80 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 26.3, 27.1, 27.5, 65.3, 70.1, 80.4, 85.4, 111.5, 127.6, 127.9, 129.1, 129.9, 132.0, 133.3, 134.0, 135.7; ESMS 531 (M + Na). FABHRMS calcd for $C_{23}H_{31}O_4Si$ (M − SC_6H_5) 399.1992, found 399.1992.

Thioacetal Ester 14. DCC (1.20 g, 5.15 mmol) was added at 0 °C to a solution of alcohol **7** (2.00 g, 3.94 mmol), acid **8**[17] (3.00 g, 5.15 mmol), and DMAP (48.3 mg, 0.40 mmol) in anhydrous benzene (50 mL). The reaction mixture was warmed to room temperature and stirred for 1.5 h. The mixture was then diluted with ether (15 mL) and filtered. The filtrate was washed with 0.1 N aqueous HCl and brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography to give **14** (4.1 g, 97.2% from **7**): colorless oil; R_f 0.60 (15% EtOAc/petroleum ether); IR (neat) 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.38, 1.43 (both s, 3H ea), 2.52 (dd, J = 8.0, 14.0 Hz, 1H), 2.65 (dd, J = 4.8, 14.0 Hz, 2H), 3.63 (m, 2H), 3.75 (m, 4H) 3.86 (m, 1H), 4.30−4.60 (m, 11H), 5.24 (m, 1H), 5.30 (d, J = 6.6 Hz), 7.10−7.70 (m, 35H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 27.2, 27.7, 28.1, 37.3, 63.0, 69.6, 69.7, 72.2, 72.6, 72.9, 73.9, 74.1, 75.0, 76.3, 76.4, 80.0, 85.7, 112.3, 128.2, 128.4, 128.5, 128.7, 129.0, 129.1, 129.7, 130.5, 133.4, 133.7, 133.8, 134.2, 136.3, 136.4, 138.7, 138.8, 139.0, 139.3, 170.8. FABHRMS: calcd for $C_{65}H_{72}O_{10}SSiNa$ (M + Na) 1095.4513, found 1095.4514.

Thioacetal Enol Ether 9. A solution of Tebbe reagent in THF (15 mL, 0.5 M, 7.5 mmol) was added dropwise under an argon atmosphere at −78 °C to a solution of ester **14** (4.1 g, 3.8 mmol) and pyridine (0.3 mL) in anhydrous 3:1 toluene/THF (80 mL). The reaction mixture was warmed to room temperature, stirred at this temperature for 1 h, and then slowly poured into a solution of 1 N aqueous NaOH at 0 °C. The resulting suspension was extracted with ether, and the organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography of the residue on basic alumina (Brockmann I, 150 mesh) provided enol ether **9** (3.6 g, 88%): colorless oil; R_f 0.65 (15% EtOAc/petroleum ether); $[\alpha]_D$ 21.6 (c 1.44, $CHCl_3$); IR (neat) 1667, 1626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.38, 1.44 (both s, 3H ea), 2.20 (dd, J = 6.4, 14.3 Hz, 1H), 2.34 (dd, J = 8.4, 14.3 Hz, 1H), 3.54−3.94 (m, 10H), 4.19 (m, 1H), 4.36 (m, 1H), 4.38−4.55 (m, 8H), 4.77 (d, J = 9.8 Hz, 1H), 5.45 (d, J = 7.0 Hz, 1H), 7.10−7.75 (m, 35H); ^{13}C NMR (75 MHz, C_6D_6) δ 19.9, 27.1, 27.6, 28.1, 36.8, 62.4, 70.8, 71.7, 72.3, 72.4, 74.1, 74.7, 74.8, 75.4, 76.1, 77.2, 79.3, 80.9, 85.3, 112.3, 127.8, 128.2, 129.5, 130.4, 130.5, 132.7, 133.8, 134.0, 135.0, 136.4, 139.6, 139.7, 139.9, 140.1, 159.0; FABHRMS calcd for $C_{66}H_{74}O_9SSiNa$ (M + Na) 1093.4721, found 1093.4719.

3,4-*O*-Isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-D-arabino-hex-1-enopyranosyl 1-Carba-2,3.4,6-

(22) For a preliminary analysis of the solution conformation of deprotected **4**: Asensio, J. L.; Cañada, F. J.; Cheng, X.; Khan, N.; Mootoo, D. R.; Jiménez-Barbero, J. *Chem. Eur. J.*, in press.

tetra-*O*-benzyl-α-D-mannopyranoside 5. Enol ether **9** (3.6 g, 3.4 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (6.3 g, 40 mmol), and freshly activated, powdered 4A molecular sieves (1.0 g) in anhydrous CH_2Cl_2 (100 mL) were stirred for 15 min at room temperature under an argon atmosphere and then cooled to 0 °C. Methyl triflate (3.7 mL, 33 mmol) was then introduced, and the mixture was warmed to room temperature and stirred for an additional 18 h, at which time triethylamine (5 mL) was added. The mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Flash chromatography of the residue on basic alumina (Brockmann I, 150 mesh) provided **5** (2.8 g, 88%): clear oil; R_f 0.55 (15% EtOAc/petroleum ether); $[\alpha]_D$ 17.6 (*c* 1.28, $CHCl_3$); IR (neat) 1689, 1682 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.18 (s, 9H), 1.35, 1.54 (both s, 3H ea), 2.25 (m, 2H), 3.73 (dd, J = 2.9, 4.0 Hz, 1H), 3.80 (dd, J = 2.9, 7.7 Hz, 1H), 3.9 (m, 4H), 4.14 (m, 2H), 4.21 (t, J = 7.3 Hz, 1H), 4.29 (d, J = 6.2 Hz, 1H), 4.42−4.58 (m, 9H), 4.64 (d, J = 2.6 Hz, 1H), 4.74 (apparent d, J = 12 Hz, 1H), 7.00−7.40 (m, 26H), 7.70 (m, 4H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 19.5, 27.0, 28.6, 35.0, 63.0, 69.6, 69.7, 71.4, 71.6, 71.7, 72.1, 73.6, 74.0, 74.4, 75.1, 75.4, 75.7, 77.9, 100.0, 110.2, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 128.5, 130.0, 135.7, 135.8, 138.5, 138.6, 152.5; FABHRMS calcd for $C_{60}H_{69}O_9Si$ (M + H) 961.4711, found 961.4708.

3,4-*O*-Isoproplylidene-6-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl 1-Carba-2,3.4,6-tetra-*O*-benzyl-α-D-mannopyranoside 4. BH_3·Me_2S (10 mL of a 1 M solution in CH_2Cl_2, 10 mmol) was added at 0 °C to a solution of glycal **5** (2.3 g, 2.5 mmol) in anhydrous THF (50 mL) under an atmosphere of argon. The mixture was warmed to room temperature and stirred for an additional 1 h at this temperature. At that time the solution was recooled to 0 °C and treated with a mixture of 3 N NaOH (10 mL) and 30% aqueous H_2O_2 (10 mL) for 30 min. The mixture was then diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Flash chromatography of the residue provided **4** (2.0 g, 83%): white solid; R_f 0.30 (15% EtOAc/petroleum ether); $[\alpha]_D$ 22.9 (*c* 2.10, $CHCl_3$); IR (neat) 3391 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.41 (s, 3H), 1.56 (m, buried under s at δ1.58), 1.58 (s, 3H), 2.22 (m, 1H), 3.19 (m, 1H), 3.56 (m, 2H), 3.64−4.22 (m, 9H), 4.12 (d, J = 5.5 Hz, 1H, D_2O ex), 4.36 (d, J = 5.5 Hz, 1H), 4.42−4.84 (m, 9H), 7.10−7.85 (m, 30H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 27.3, 27.6, 29.3, 30.4, 63.7, 70.2, 70.5, 72.2, 72.5, 72.9, 73.6, 74.1, 74.6, 74.9, 76.1, 76.9, 77.6, 77.8, 78.9, 80.7, 109.9, 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.1, 130.3, 134.2, 134.4, 136.3, 136.4, 138.3, 138.8, 138.9; FABHRMS calcd for $C_{60}H_{71}O_{10}Si$ (M + H) 979.4817, found 979.4818.

2-*O*-Acetyl-3,4-*O*-isoproplylidene-6-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl 1-Carba-2,3.4,6-tetra-*O*-benzyl-α-D-mannopyranoside 15. ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.28, 1.61 (both s, 3H ea), 1.70 (s, 3H), 2.08 (m, 1H), 3.58 (dt, J = 4.8, 9.4 Hz, 1H), 3.73 (dd, J = 2.6, 5.5 Hz, 1H), 3.76−3.92 (m, 4H), 3.98 (dd, J = 5.1, 7.3 Hz, 1H), 4.08 (m, 3H), 4.17 (dd, J = 7.7, 9.5 Hz, 1H), 4.2 (dd, J = 2.2, 5.1 Hz, 1H), 4.34−4.54 (m, 8H), 4.59 (apparent d, J = 12.1 Hz, 1H), 5.38 (dd, J = 7.7, 9.2 Hz, 1H), 7.10−7.90 (m, 26H), 7.82 (m, 4H).

6-*O*-*tert*-Butyldiphenylsilyl-β-D-galactopyranosyl 1-Carba-2,3.4,6-tetra-*O*-benzyl-α-D-manno-pyranoside 16. A solution of 1 M HCl in ether (3 mL) was added to a solution of **4** (500 mg, 0.51 mmol) in dry methanol (50 mL). The reaction mixture was stirred at room temperature for 20 min, and then neutralized by addition of a solution of sodium methoxide in methanol. Removal of the volatiles under reduced pressure and flash chromatography of the residue provided **16** (300 mg, 63%): clear oil; R_f 0.50 (50% EtOAc/petroleum ether); IR (neat) 3369 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.39 (br d, J = 14 Hz, 1H), 2.20 (m, partially hidden under br s at δ 2.24, 1H), 2.24 (br s, 1H, D_2O ex), 2.52 (br s, 1H, D_2O ex), 3.17 (m, 1H), 3.31 (br d, J = 9.2 Hz, 1H), 3.46 (t, J = 5.5 Hz, 1H), 3.50 (br s, 1H), 3.65 (m, 3H), 3.72−3.98 (m, 5H), 4.10 (m, 2H, D_2O ex 1H), 4.40−4.70 (m, 8H), 4.80 (apparent d, J = 11 Hz, 1H), 7.15−7.55 (m, 26H), 7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 27.5, 27.6, 29.9, 61.1, 64.1, 69.7, 69.9, 70.6, 70.7, 70.8, 71.0, 72.5, 72.6, 72.7, 72.8, 73.0, 73.3, 73.4, 74.4, 75.0, 75.7, 75.9, 76.1, 76.3, 76.5, 76.6, 78.2, 78.5, 78.9, 79.2, 128.2, 128.3, 128.5, 128.6, 128.7, 128.9, 129.1, 129.1, 129.3, 129.4, 129.5, 130.3, 133.9, 134.2, 136.2, 136.3, 136.6, 136.7, 138.0, 138.8; ESMS 961.5 (M + Na).

3-*O*-Carboxymethyl-6-*O*-*tert*-butyldiphenylsilyl-β-D-galactopyranosyl 1-Carba-2,3.4,6-tetra-*O*-benzyl-α-D-mannopyranoside 17. A mixture of triol **16** (130 mg, 0.14 mmol), dibutyltin oxide (32 mg, 0.14 mmol), and anhydrous toluene (5 mL) was heated at reflux in a Dean−Stark apparatus for 1 h. The solvent was evaporated in vacuo, and the residue was dissolved in dry toluene (3 mL). *n*-Bu_4NI (40 mg, 0.14 mmol) and methyl 2-bromoacetate (0.1 mL, 0.42 mmol) were added, and the solution was heated at reflux for 1 h, at which time the volatiles were removed under reduced pressure to give a brown syrup. Partial purification of this material by flash chromatography provided an approximately 1:1 mixture (100 mg) of two components, R_f 0.45 and 0.35 (30% EtOAc/petroleum ether).

The mixture obtained in the previous step was treated with a 1:1 mixture of aqueous 3 N NaOH/ethanol (2 mL). After 1 h, the reaction mixture was neutralized with aqueous 2 N HCl. The solvent was then removed under reduced pressure, and the residue was purified by chromatography to give **17** (60 mg, 57% from **16**): clear oil; R_f 0.20 (30% methanol/EtOAc); IR (neat) 3368, 1729 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.86 (m, 1H), 2.14 (m, 1H), 3.14 (br t, J = 7.0 Hz, 1H), 3.30 (m, 1H partially hidden under residual CD_2HOD), 3.38 (t, J = 6.5 Hz, 1H), 3.64−3.86 (m, 9H), 4.08 (d, J = 3.0 Hz, 1H), 4.19 (ABq, $\Delta\delta$ = 0.13 ppm, J = 14.4 Hz, 2H), 4.36 (m, 1H), 4.45−4.58 (m, 6H), 4.63, 4.72 (both apparent d, J = 12, 11 Hz resp, 1H ea), 7.30 (m, 20H); ^{13}C NMR (75 MHz, CD_3OD) δ 35.0, 64.9, 70.4, 72.4, 73.3, 74.3, 74.5, 74.9, 76.2, 76.6, 77.1, 78.1, 78.9, 80.7, 81.3, 81.4, 87.0, 87.3, 130.4, 130.9, 130.9, 130.9, 131.1, 141.2, 141.4, 141.5, 179.5; FABHRMS calcd for $C_{48}H_{50}O_{12}Na$ (M + Na) 781.3200, found 781.3202.

3-*O*-Carboxymethyl-β-D-galactopyranosyl 1-Carba-α-D-mannopyranoside 3. A mixture of acid **17** (35 mg, 0.05 mmol), 20% Pd on carbon (35 mg), formic acid (0.1 mL), and methanol (2 mL) was stirred under an atmosphere of hydrogen (balloon) for 12 h. The reaction mixture was then purged with argon and filtered through a bed of Celite. The filtrate was concentrated in vacuo, and the residue was purified by Sephadex LH-20 chromatography (H_2O). Lyophilization of the column extracts provided **3** (14 mg, 76%): white powder; $[\alpha]_D$ +57 (*c* 0.75, 1:1 methanol/H_2O); ^1H NMR (500 MHz, D_2O) δ 1.90 (dt, J = 7.5, 15 Hz, 1H), 2.11 (ddd, J = 1.5, 7.5, 15 Hz, 1H), 3.31 (dt, J = 3.0, 8.0 Hz, 1H), 3.4 (dt, J = 3.0, 9.5 Hz, 1H), 3.53−3.74 (m, 7H), 3.79 (m, 2H), 3.91 (br s, 1H), 4.08 (d, J = 3.0 Hz, 1H), 4.11 (ABq, $\Delta\delta$ = 0.04 ppm, J = 12 Hz, 2H), 4.19 (t, J = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 34.1, 64.7, 65.0, 69.4, 70.8, 71.6, 73.2, 73.9, 74.3, 77.5, 79.1, 80.8, 81.7, 86.6, 181.5; FABMS 421 (M + Na).

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Supporting Information Available: ^1H and ^{13}C NMR data for compounds **3**, **4**, **9**, and **14**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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