Synthesis of a Pentasaccharide Epitope for the Investigation of Carbohydrate–Protein Interactions

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Pyranose residues of a polysaccharide that are not involved in the principal sugar–protein antibody combining site, filled by trisaccharide **1**, cause a 50-fold reduction in intrinsic affinity. The antibody is crystallographically characterized, and the residue responsible for the lost binding energy has been identified as the terminal disaccharide Rha→Gal of pentasaccharide **5**. This disaccharide segment of **5** may avoid protein contact by adopting the "*anti*" conformer about the preceding Man-Rha glycosidic linkage. Monosaccharide thioglycoside synthons **6**–**9** were used in NIS-promoted glycosylations to synthesize the pentasaccharide as a glycoside that was suitable for binding and solution conformational studies. Disaccharide **29** was obtained upon the addition of rhamnose building unit **6** to the (trimethylsilyl)ethyl galactopyranoside **10** followed by protecting group manipulation. The sequential addition of **7**–**9** to **29** afforded the pentasaccharide derivative **35** bearing a 2-*O*-benzoate group suited for subsequent 1,2-*trans*-glycoside synthesis following its conversion to a glycosyl imidate. In order to preserve the integrity of the 3,6-dideoxyhexopyranosyl glycosidic bond during cleavage of the (trimethylsilyl)ethyl group leading to the imidate **39**, it was essential to convert the benzylated pentasaccharide target **35** into its fully acylated derivative **37**. Pentasaccharide **5** was obtained by transesterification of the protected glycoside **40** formed via **39**. Qualitative NOE measurements suggest a predominant solution conformation for **5** that cannot be adopted in the bound state due to protein–oligosaccharide clashes at the periphery of the binding site.

Introduction

Carbohydrate-mediated adhesion events between distinct types of mammalian cells,[1–4] as well as viral[5,6] and bacterial[7–9] adhesion to mammalian cells has heightened interest in oligosaccharide-based inhibitors of carbohydrate–protein recognition for therapeutic intervention in cell–cell adhesion events.[7,10,11] However, several basic questions remain to be answered before the potential of this new class of drugs may be realized. Compared to other areas of molecular recognition (e.g., protein–protein or nucleic acid–nucleic acid), the origins of the highly stereospecific yet relatively low affinity (milli- to micromolar) carbohydrate–protein binding remains obscure.[12] Generally, a trisaccharide or its equivalently sized epitope provides almost all the free energy for binding sites, and inter-residue flexibility has been cited as the source of the unfavorable entropy that opposes an association process that is typically enthalpy driven.[13–15] An even larger question, which has only recently begun to be addressed, is the importance of water in these recognition processes.[16–18] This work describes the synthesis of a pentasaccharide **5**, which is designed to probe the mutual dependence of inter-residue flexibility and binding affinity.

High resolution crystal structures of oligosaccharide–protein complexes[19,20] provide the detailed structural insights necessary to probe the observation that micromolar activities appear to be the experimental ceiling that is seldom breached for univalent interactions. Detailed structural information of this type provides a unique opportunity to correlate binding energy changes that accompany ligand functional group modifications or mutagenesis of the binding site amino acids with three-dimensional data for the complex. This approach has been adopted for a trisaccharide carbohydrate epitope (**1**,

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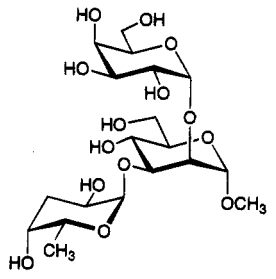
Chart 1



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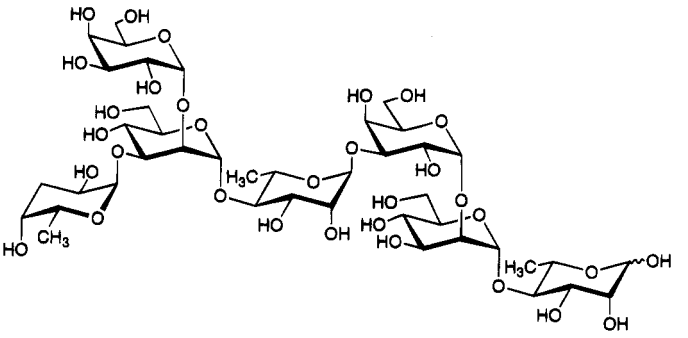

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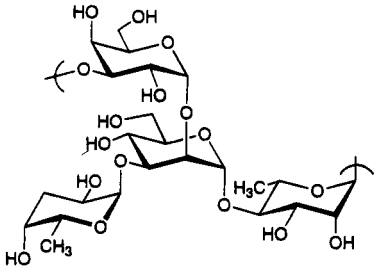

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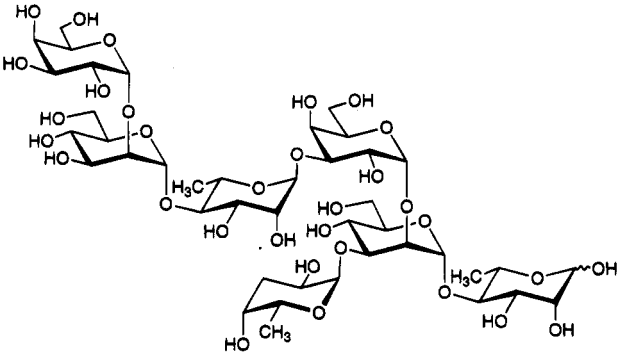

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Chart 1) that fills the binding site of antibody Se 155.4.[21-29] In this paper, we describe the synthesis of a pentasaccharide epitope (**5**) that is designed to probe entropically disfavored binding events that occur at the periphery of the contact surface between epitope **1** and the Se 155.4 binding site.

This oligosaccharide–antibody system has been characterized by several crystal structures of variously sized oligosaccharides complexed with Fab[21,23] and *E. coli* expressed Fab (unpublished) or single chain Fv[28] proteins derived by antibody enginneering techniques.[26,27] Extensive calorimetric studies have detailed the interactions between the Se 155.4 antibody and modified trisaccharide ligands.[22,24,25] While the native polysaccharide antigen possesses the tetrasaccharide repeating unit α-D-Gal*p*(1→2)[α-D-[Abe*p*-(1→3)]-α-D-Man*p*-(1→4)-α-L-Rha*p* (**2**), the rhamnose unit is not required for binding, and thus, the trisaccharide α-D-Gal*p*-(1→2)[α-D-[Abe*p*(1→3)]-α-D-Man*p*-OCH_3 (**1**) has been used as a reference compound in our studies.[22,25] Crystal structures of antibody crystallized with both the synthetic trisaccharide **1**[23] and a dodecasaccharide polymer fragment containing three repeating units **2**[21] show that **1** fills a binding cavity that is lined with hydrophobic amino acids (tyrosine, tryptophan) and that a bound water molecule occupies the bottom of the pocket. The immunodominant abequose residue is completely buried in the binding pocket and forms hydrogen bonds to the protein not only directly but also indirectly through the bound water molecule. The galactose and mannose residues of **1** are partially buried in the binding pocket but have significant surface exposed to solvent water.[21] Subsequent calorimetric studies have shown that almost all the enthalpy of binding derives from the abequose residue.[22]

More recent work[22,29] comparing the binding of two isomeric heptasaccharides,[30] Gal[Abe]ManRhaGalManRha (**3**) and GalManRhaGal[Abe]ManRha (**4**), suggests that there is an unfavorable steric interaction beyond the immediate boundary of the binding site. This occurs between the H-2 loop of the antibody and pyranose residues that extend the trisaccharide epitope (Gal[Abe]-Man) at its reducing terminus (Figure 1). The two heptasaccharides bind the antibody with a 50-fold difference in affinity.[22] Heptasaccharide **3** in which the abequose is at the nonreducing-end repeating unit binds weakly compared to **4**, where the abequose is linked to the reducing-end repeating unit. Since the orientation of binding is dictated by the position of the abequose residue, the differential binding was suggested to arise from the steric clash of the carbohydrate with the antibody in the former case but not the latter[22] (Figure 1). Modeling studies[31] involving the placement of ex-

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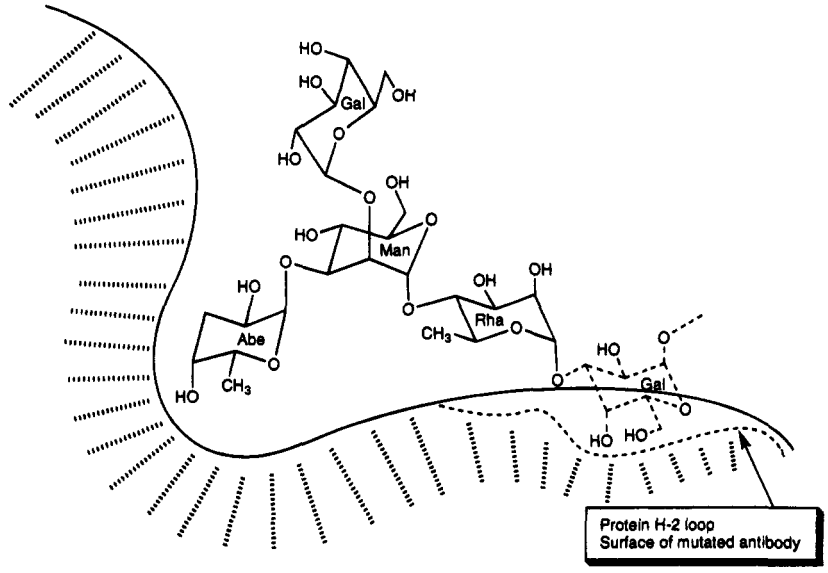

Figure 1. Schematic representation of a low energy pentasaccharide conformation interacting with the antibody binding site. The trisaccharide portion Gal[Abe]Man is accepted in the antibody binding pocket, while the lowest energy conformer for the pentasaccharide results in an oligosaccharide–protein clash (galactose residue shown in dashed lines). In this extended epitope the lowest potential energy conformers for the torsional angles of the Man-Rha and Rha-Gal glycosidic linkages would drive the Rha-Gal segment into the protein surface at the region of the heavy H-2 loop.

tended ligands into the binding site indicated that the residue clashing with the antibody was the galactose moiety of the next repeating unit located at the reducing end of the rhamnose in **3**. It was determined that in order to avoid the unfavorable contacts, the torsional angles about the Man-Rha and Rha-Gal glycosidic linkages had to adopt energetically less favored values that were also significantly different from those observed for the oligosaccharide in aqueous solution.[32] In fact, Kotchetkov and co-workers have concluded from potential energy calculations that a second minimima, corresponding to the so called "*anti*" conformer about the Rha to Gal linkage ($\varphi \approx 180°$ rather than $\approx 0°$), should be considered when modeling this antigen,[33] although our own NMR data indicated that this conformer was not significantly populated.[32] Recently, the population of the "*anti*" conformation has been detected for an unrelated disaccharide in DMSO solution.[34] It is therefore important to investigate the importance of such conformers in the bound state, when the steric demands of the protein receptor could be expected to bias the bound conformation toward such torsional angles. In the case of the Se 155.4 epitope, chemical synthesis is the only effective way to access the minimal, active structural element that can display antibody binding and potentially reveal the existence of the "*anti*" conformer in the bound state.

Protein engineering studies aimed at an enhanced association constant resulted in a 10-fold increase in antigen binding affinity for Fab or single chain Fv mutants[27] when mutations were made in the antibody H-2 peptide loop. This peptide segment did not make contact with trisaccharide **1** but would with the extended epitope **3**. It was postulated that the higher binding affinity was due to increased interaction of the oligosaccharide backbone with the antibody H-2 loop that became possible by reducing the steric bulk of the loop, thereby reducing the requirement for oligosaccharide conformational changes (Figure 1). In order to test such a hypothesis, we required an oligosaccharide larger than **1**. Since the previously used hydrolytic procedure to obtain **3** and **4** was not a practical route to anything but 1–2 mg amounts of material,[30] we set out to chemically synthesize an oligosaccharide probe in quantities that could be used for detailed calorimetric, NMR, and crystallographic studies. We report here the synthesis of pentasaccharide **5**, which includes the entire tetrasaccharide repeating unit **2** plus the additional galactose residue implicated in reducing antibody affinity for the polymeric antigen.

Results and Discussion

Synthetic Strategy. The retrosynthetic analysis for the preparation of **5** is shown in Figure 2. In designing the synthesis, we endeavored to pick a general route that would be amenable, at a later date, to the preparation of oligosaccharide analogs containing either modified or isotopically labeled sugar residues. Furthermore, the abilty to couple **5** to a variety of aglycons was taken into consideration. Consequently, the strategy chosen relied upon the stepwise addition of monosaccharides from the reducing end of the molecule, with the most expensive sugar, abequose, being added last. Thioglycosides were picked as the glycosyl donors due to their hydrolytic stability and wide range of activation methods.[35,36] Specifically, the suitably protected thioglycosides **6–9** were chosen as glycosyl donors and galactoside **10** as the initial acceptor alcohol. Our strategy involved first the preparation of the pentasaccharide as a protected 2-(trimethylsilyl)ethyl (TSMET) glycoside and then its conversion

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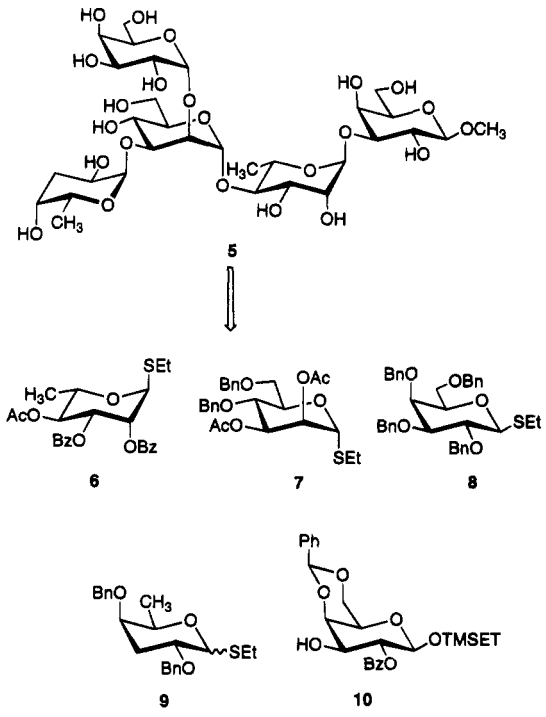

Figure 2.

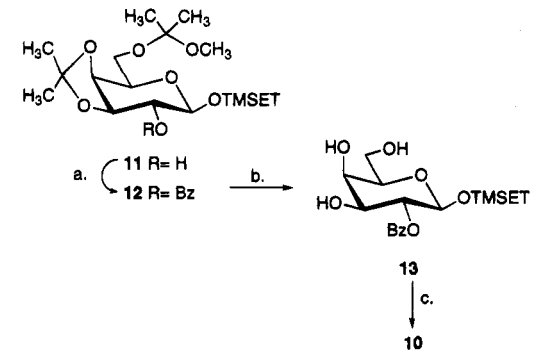

Figure 3. Key: (a) BzCl, pyridine, 62%; (b) 4:1 HOAc:H_2O, 80 °C, 89%; (c) $PhCH(OCH_3)_2$, CSA, CH_3CN, 92%.

to the methyl glycoside immediately prior to deprotection. Equally straightforward would be the coupling of this pentasaccharide block to alcohols other than methanol.

Preparation of Monosaccharide Building Blocks. The galactopyranoside acceptor **10** was synthesized (Figure 3) by first benzoylating the known[37] diisopropylidene derivative **11** under standard conditions to provide benzoate **12** in 62% yield. Alcohol **10** could then be readily prepared in two steps via the triol intermediate **13**, by acetal cleavage with aqueous acetic acid followed by benzylidenation with dimethoxytoluene and camphorsulfonic acid (82% from **12**).

For the preparation of the rhamnose donor **6** (Figure 4), ethyl 1-thio-α-L-rhamnopyranoside,[36] **14**, was protected as its 2,3-isopropylidene acetal **15** which was not isolated. Conventional acetylation followed by hydrolytic removal of the acetal group afforded the diol **17** (three steps, 87%). The synthesis was completed by di-*O*-benzoylation with benzoyl chloride and pyridine to give the donor **6** in 78% yield.

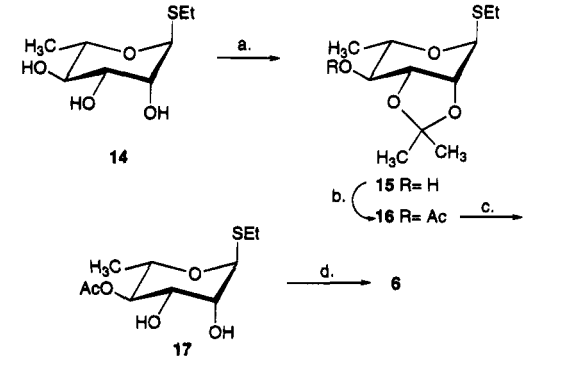

Figure 4. Key: (a) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH; (b) Ac_2O, pyridine, 92%; (c) 4:1 HOAc:H_2O, 80 °C, 95%; (d) BzCl, pyridine, 78%.

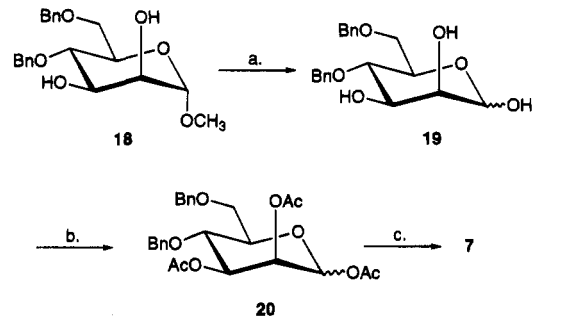

Figure 5. Key: (a) 3.76 M TFA, reflux, 74%; (b) Ac_2O, pyridine, 91%; (c) EtSH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C, 74%.

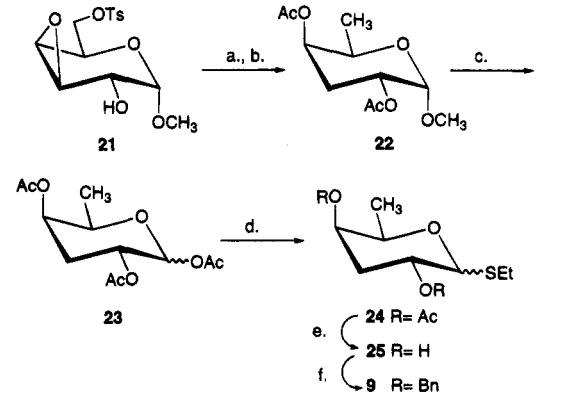

Figure 6. Key: (a) $LiEt_3BH$, THF, reflux; (b) Ac_2O, pyridine, 85%; (c) Ac_2O, H_2SO_4, 0 °C, 100%; (d) EtSH, $BF_3 \cdot OEt_2$, 0 °C, 91%; (e) $NaOCH_3$, CH_3OH, 87%; (f) BnBr, NaH, DMF, 81%.

In order to prepare the mannose donor **7** (Figure 5), the previously reported[38] methyl glycoside **18** was hydrolyzed with aqueous trifluoroacetic acid, giving the reducing sugar **19** in 74% yield. Acetylation then provided the triacetate **20** (91%) as a mixture of anomers (3:1 α:β). Finally, treatment of **20** with ethanethiol and boron trifluoroetherate afforded in 74% yield the thioglycoside **7**.

The galactose donor, ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside, **8**, has been previously synthesized.[39]

Synthesis of the abequose donor **9** (Figure 6) began with the reaction of epoxy tosylate **21**[40] with lithium

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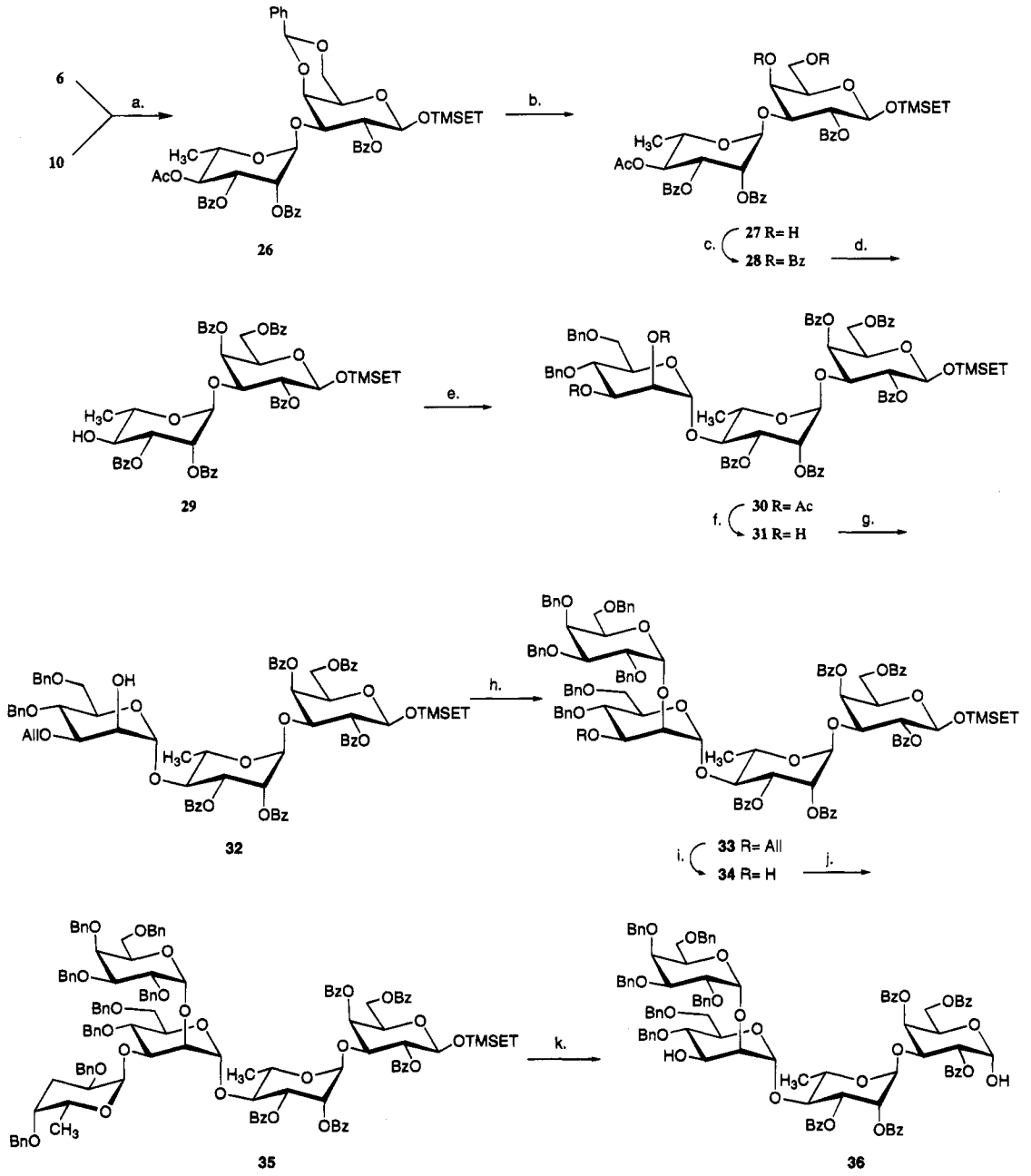

Figure 7. Key: (a) NIS, TfOH, CH_2Cl_2, 90%; (b) I_2, CH_3OH, reflux, 88%; (c) BzCl, pyridine, 87%; (d) AcCl, CH_3OH, 55%; (e) **7**, NIS, TfOH, CH_2Cl_2, 89%; (f) AcCl, CH_3OH, 94%; (g) Bu_2SnO, toluene, reflux, then allyl bromide, *n*-Bu_4NI, 60 °C, 76%; (h) **8**, NIS, AgOTf, CH_2Cl_2, 0 °C, 81%; (i) $(Ph_3P)_3RhCl$, DABCO, 7:3:1 EtOH:benzene;H_2O then $HgCl_2$, HgO, 9:1 acetone:H_2O, 87%; (j) **9**, NIS, AgOTg, CH_2Cl_2, 0 °C, 78%; (k) TFA-CH_2Cl_2, 0 °C or BF_3·OEt_2, 0 °C.

triethylborohydride using a known method[41] to provide the crude 3,6-dideoxy sugar. In order to facilitate product isolation, the product was not purified at this stage but was instead immediately acetylated and characterized as the diacetate **22** (85%, two steps). Acetolysis of the methyl glycoside provided an anomeric mixture of peracetates **23** in quantitative yield (3:1 α:β). Reaction of the peracetate with ethanethiol promoted by boron trifluoroetherate yielded a 1:1 anomeric mixture of ethyl thioglycosides **24** in 91% combined yield. Zemplén deacetylation of the mixture provided the chromatographically inseparable diols **25** (87%). Finally, protection of the hydroxyl groups as benzyl ethers gave the glycosyl donor **9** in 81% yield. Either anomer of **9** could be used in glycosylation reactions with indistinguishable results.

Assembly of the Pentasaccharide (Figure 7). Treatment of the galactose acceptor **10** and the rhamnose donor **6** with *N*-iodosuccinimide and triflic acid[42] gave the disaccharide **26** in 90% yield. The benzylidene acetal was removed in 88% yield using the method of Szarek,[43] by reaction with iodine in refluxing methanol. The resulting diol **27** was protected with benzoyl chloride (87%), affording the fully acylated disaccharide **28**. Selective deacetylation to provide **29** was achieved by treatment

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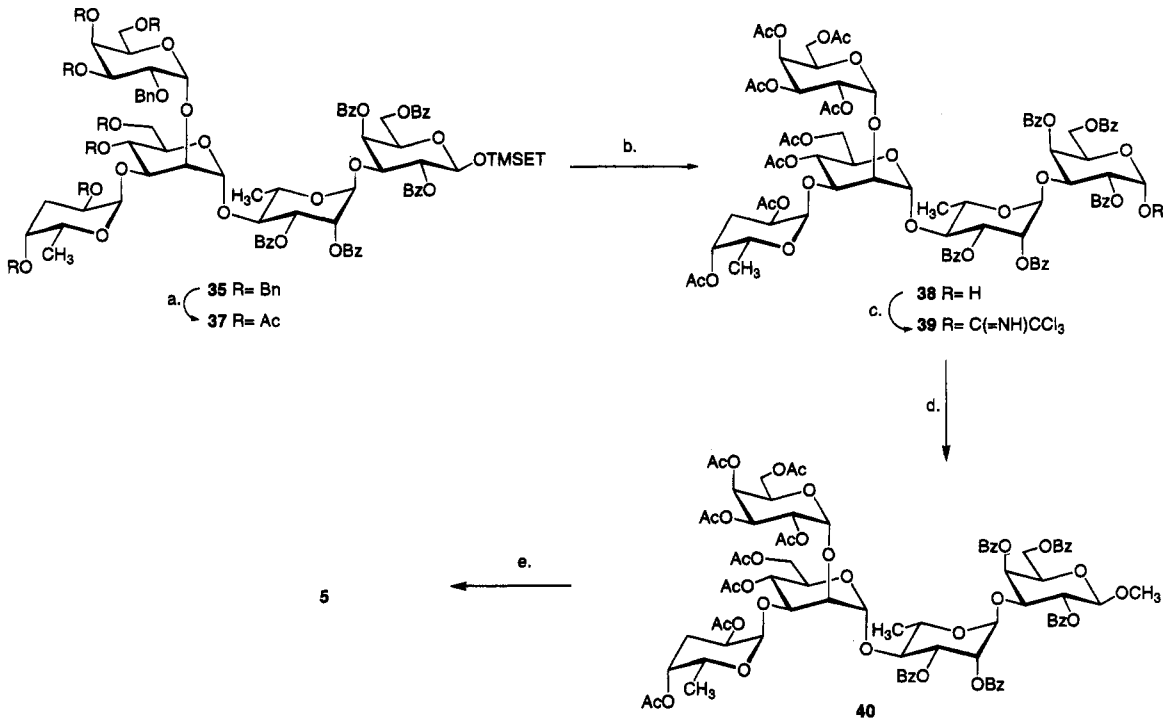

Figure 8. Key: (a) H_2, 10% Pd–C, HOAc, then Ac_2O, pyridine, 74%; (b) TFA, CH_2Cl_2, 0 °C, 98%; (c) CCl_3CN, DBU, CH_2Cl_2, 93%; (d) CH_3OH, TMSOTf, −78 °C; (e) $NaOCH_3$, CH_3OH, 73% over two steps.

with methanolic hydrogen chloride (55%). Reaction of this alcohol with the mannose thioglycoside **7** again with *N*-iodosuccinimide and triflic acid afforded the trisaccharide **30** (89%). The acetates were selectively removed under acidic conditions to give the diol **31** in 94% yield. Protection of Man *O*-3 as an allyl ether was achieved (76%) via the dibutylstannylidene acetal by treatment first with dibutyltin oxide and then allyl bromide to give **32**. Addition of the galactose residue was then achieved (81%) using donor **8** and *N*-iodosuccinimide, this time promoted by silver triflate (Figure 7b). The reaction could also be carried out using triflic acid; however, the use of silver triflate was found to be procedurally simpler. Removal of the allyl group from tetrasaccharide **33** under standard conditions gave the alcohol **34** in 87% yield. The protected pentasacharide was obtained by treatment of **34** with the abequose donor **9**, *N*-iodosuccinimide, and silver triflate, providing the pentasaccharide **35** in 78% yield. The presence of β-anomers was not detected during the chromatographic purification of compounds **33** and **35**. However, it is not known whether the reactions leading to **33** and **35** gave exclusively α-linked products, since no attempts were made to rigorously establish the possible presence of small amounts of β-anomer in crude reaction products.

We were next ready to convert the TSMET glycoside to a methyl glycoside via an activated glycosyl donor. A number of methods exist for the conversion of TSMET glycosides, either directly or indirectly, to glycosyl donors. Direct conversion to either the anomeric chlorides[44] or acetates[37] requires in the case of the chlorides a reagent often incompatible with benzyl protecting groups[44,45] or produces in the case of anomeric acetates a fairly unreactive glycosyl donor. We were, therefore, leery of using these methods and chose instead the indirect approach by first preparing the reducing sugar and then activating the pentasaccharide as an imidate.[46] Two methods exist for the cleavage of TMSET glycosides to oligosaccharides with a hemiacetal group: treatment with trifluoroacetic acid in dichloromethane[37] or treatment with boron trifluoroetherate in acetonitrile.[47] Both methods have been used successfully for cleavage of a large number of TMSET oligosaccharides, including those containing highly acid labile sialyl glycosidic linkages.[48] With this in mind, we were assured that the acid-sensitive 3,6-dideoxy sugar glycosidic linkage in **35** would also withstand these reaction conditions.

However, when **35** was treated under either condition we observed not only TMSET removal but also the concomitant loss of the abequose residue resulting in the formation of tetrasaccharide **36** (product not characterized) as the major product. Fortunately, the loss of the dideoxy sugar could be avoided by first converting the protecting groups on the abequose residue from benzyl ethers to acetate esters. To this end (Figure 8), **35** was hydrogenated and then acetylated to give the fully acylated pentasaccharide **37** (74%, two steps). Cleavage of the TMSET glycoside in **37** with trifluoroacetic acid afforded **38** in 98% yield, which was in turn converted to trichloroacetimidate **39** upon treatment with trichloroacetonitrile and DBU. This chromatographically stable imidate reacted sluggishly with methanol and trimethylsilyl trifluoromethanesulfonate. Nevertheless, the methyl glycoside **40** could be obtained as a mixture with the reducing sugar **38** arising from imidate hydrolysis. All attempts to purify the product at this stage failed, and thus, the mixture was deacylated with sodium methoxide

(44) Jansson, K.; Noori, G.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 3181–3185.
(45) Kovac, P.; Whittaker, N. F.; Glaudemans, C. P. J. *J. Carbohydr. Chem.* **1985**, *4*, 243–254.
(46) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–124.
(47) Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1990**, *10*, 549–560.
(48) Magnusson, G. *Trends. Glycosci. Glycotech.* **1992**, *4*, 358–367.

and then purified on Iatrobeads, affording the deprotected pentasaccharide **5** (73% from **39**).

Stereochemistry of newly established glycosidic linkages was monitored by NMR. Where appropriate, for galactopyranosyl and *xylo*-hexopyranosyl residues, homonuclear ^3J ^{1}H NMR coupling constants were used. The anomeric configuration of the mannopyranosyl and rhamnopyranosyl linkages were unambiguously established by measurement of the ^1J heteronuclear coupling constant[49] of the anomeric carbon atom for compounds **26** and **30**. The structure of the final compound **5** was confirmed by a full analysis and assignment of the ^{1}H and ^{13}C NMR spectra, including heteronuclear one-bond coupling constants for each of the five anomeric carbon atoms.

Solution Conformation of Pentasaccharide 5. Inter-residue NOEs across the glycosidic linkage and between $n + 1$ residues provide constraints that point to a preferred conformation for the pentasaccharide in solution. At 500 MHz, all anomeric protons in **5** are well resolved, thus simplifying quantitation of inter-residue NOEs and the determination of NOE buildup curves. Shown in Figure 9 is the preferred solution conformation of **5** in D_2O based on the observed NOE's. However, comparison of this preliminary NOE data with those previously reported for related oligosaccharides including the methyl glycoside of **2**,[32] and the trisaccharide methyl glycoside **1**,[23] indicates that all three molecules adopt similar solution conformations. The solution conformation of **5** cannot be adopted in the bound state, since the Rha and Gal residues would clash with the protein. Therefore, to avoid this steric clash, either the φ torsional angle of the Man→Rha glycosidic linkage must adopt the "*anti*" conformer, or the ϕ,φ torsional angles of both the Man→Rha and Rha→Gal may simultaneously change in the bound state. Whatever the precise conformers, the resultant exclusion of conformational space invokes an entropic penalty.[22] Detailed quantitative NMR and molecular modeling studies of the free and bound conformations of **5** with antibodies will be the subject of a separate paper.

Experimental Section

Optical rotations were measured with a polarimeter at 22 ± 2 °C. Analytical TLC was performed on silica gel 60-F_{254} (E. Merck, Darmstadt) with detection by quenching of fluorescence and/or by charring with sulfuric acid. Iatrobeads refers to a beaded silica gel 6RS-8060 manufactured by Iatron Laboratories (Tokyo). All commercial reagents were used as supplied, and chromatography solvents were distilled prior to use. Column chromatography was performed on silica gel 60 (E. Merck 40–60 μM, Darmstadt) or Iatrobeads. The ratio of silica gel to compound ranged between 100 and 50:1 (w/w). Millex-GV (0.22 μM) filter units were from Millipore (Mississuaga, ON). ^{1}H NMR spectra were recorded at 360 MHz or at 500 MHz, and first-order proton chemical shifts δ_H are referenced to either internal $CHCl_3$ (δ_H 7.24, $CDCl_3$) or internal acetone (δ_H 2.225, D_2O). ^{13}C NMR spectra were recorded either at 75.5 or 125.7 MHz, and ^{13}C chemical shifts δ_C are referenced to internal $CHCl_3$ (δ_C 77.00, $CDCl_3$) or internal acetone (δ_C 37.01, D_2O). The assignment of resonances for the target compound **5** was made by two-dimensional homonuclear and heteronuclear shift correlation experiments. Unless otherwise stated, all reactions were carried out at room temperature. Organic solutions were dried prior to concentration under vacuum at <40 °C (bath). Microanalyses were carried out by the analytical services at this department, and all samples submitted for elemental analyses were dried overnight under vacuum with phosphorus pentaoxide at 56 °C (refluxing acetone). Fast atom bombardment mass spectra were recorded on samples suspended in Cleland's matrix with xenon as the bombarding gas.

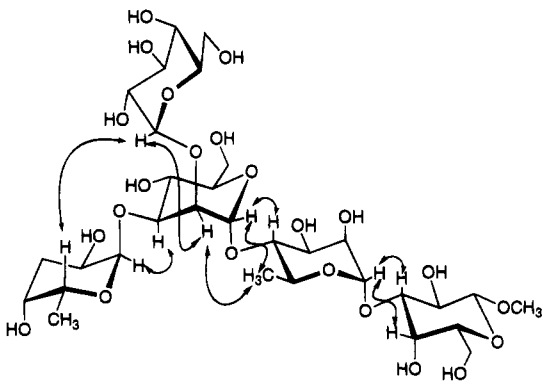

Figure 9. Arrows indicate inter-residue NOEs that define the preferred solution conformation of pentasaccharide **5**. In all glycosidic linkages a NOE is observed from H-1 across the glycosidic oxygen atom to the proton attached to the aglyconic carbon atom. This and additional NOEs from H-1 to other protons on the next ring (e.g., Man H-1 and Man H-2 to Rha H-6; Rha H-1 to Gal H-4 and H-3) point to very low population of conformers where the orientation of the next pyranose rings are flipped by 180° (refs 32 vs 33).

For NMR assignment purposes, the carbohydrate residues in all reaction products larger than monosaccharides have been designated by letters as follows: reducing end galactose, A; rhamnose, B; mannose, C; terminal galactose, D; and abequose, E.

2-(Trimethylsilyl)ethyl 2-*O*-Benzoyl-3,4-isopropylidene-6-*O*-(2-methoxyisopropyl)-β-D-galactopyranoside (12). 2-(Trimethylsilyl)ethyl 3,4-*O*-isopropylidene-6-*O*-(2-methoxyisopropyl)-β-D-galactopyranoside[37] (**11**, 4.4 g, 11.2 mmol) was dissolved in pyridine (50 mL) and cooled to 0 °C. Benzoyl chloride (1.6 mL, 14 mmol) was added dropwise and the reaction allowed to proceed for 1 h. The mixture was then diluted with CH_2Cl_2 and successively washed with saturated $NaHCO_3$, water, and saturated NaCl solution. The organic phase was dried ($MgSO_4$), filtered, and evaporated to give a residue that was coevaporated twice with toluene. Chromatography of the resulting syrup (3:1 hexane–EtOAc) afforded product **12** (3.4 g, 62%) as an oil: $[\alpha]_D$ +11.8° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ_H 7.30–8.03 (m, 5 H), 5.19 (t, 1 H, J = 8.0, 7.0 Hz), 4.48 (d, 1 H, J = 8.0 Hz), 4.29 (dd, 1 H, J = 7.0, 5.5 Hz), 4.22 (dd, 1 H, J = 5.5, 2.0 Hz), 3.89–3.96 (m, 2 H), 3.72–3.75 (m, 2 H), 3.48–3.53 (m, 1 H), 3.22 (s, 3 H), 1.59 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.31 (s, 3 H), 0.81–0.88 (m, 2 H), −0.11 (s, 9 H). Anal. Calcd for $C_{25}H_{40}O_8Si$ (496.68): C, 60.45; H, 8.12. Found: C, 60.65; H, 8.18.

2-(Trimethylsilyl)ethyl 2-*O*-Benzoyl-β-D-galactopyranoside (13). Compound **12** (3.3 g, 6.6 mmol) was dissolved in 80% acetic acid (100 mL) and the solution heated at 80 °C for 2 h. After the solution was cooled to room temperature, the solvent was evaporated, and the resulting residue was coevaporated twice with toluene. Chromatography (EtOAc) gave product **13** (2.26 g, 89%) as a white amorphous solid: $[\alpha]_D$ −32.4° (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ_H 7.41–8.02 (m, 5 H), 5.18 (dd, 1 H, J = 8.0, 8.5 Hz), 4.56 (d, 1 H, J = 8.0 Hz), 4.09 (br s, 1 H), 3.92–4.01 (m, 3 H), 3.78 (m, 1 H), 2.69–3.60 (m, 4 H), 2.69 (t, 1 H, J = 6.0, 6.0 Hz), 0.79–0.94 (m, 2 H), −0.10 (s, 9 H). Anal. Calcd for $C_{18}H_{28}O_7Si$ (384.50): C, 56.22; H, 7.34. Found: C, 56.19; H, 7.28.

2-(Trimethylsilyl)ethyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside (10). The triol **13** (1 g, 2.6 mmol) was dissolved in dry acetonitrile and dimethoxytoluene (0.58 mL, 3.9 mmol), and a few crystals of camphorsulfonic acid were added to the solution. The reaction was allowed to stir overnight, and it was quenched by the addition of triethylamine. The solvent was evaporated and the residue chro-

(49) Bock, K.; Pederson, C. *J. Chem. Soc., Perkin Trans. 2*, **1974**, 293.

matographed (7:3 hexane–EtOAc) to give the product **10** (1.13 g, 92%) as white solid: $[\alpha]_D$ −1.8° (*c* 0.5, $CHCl_3$); R_f 0.25 (3:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ_H 7.35–8.10 (m, 10 H), 5.58 (s, 1 H), 5.36 (dd, 1 H, *J* = 8.0, 10.0 Hz), 4.62 (d, 1 H, *J* = 8.0 Hz), 4.39 (dd, 1 H, *J* = 1.5, 12.5 Hz), 4.26 (dd, 1 H, *J* = 4.0, 1.0 Hz), 4.11 (dd, 1 H *J* = 2.0, 12.5 Hz), 4.01–4.09 (m, 1 H), 3.90 (dt, 1 H, *J* = 4.0, 10.0, 10.0 Hz), 3.55–3.63 (m, 1 H), 3.54 (br s, 1 H), 2.61 (d, 1 H, *J* =1 0.0 Hz), 0.82–1.00 (m, 2 H), −0.06 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 166.25, 101.56, 100.42, 75.76, 73.03, 72.04, 69.08, 67.04, 66.60, 17.99, −1.4. Anal. Calcd for $C_{25}H_{32}O_7Si$ (472.61) C, 63.53; H, 6.82. Found: C, 63.62; H, 6.95.

Ethyl 4-*O*-Acetyl-2,3-*O*-isopropylidene-1-thio-α-L-rhamnopyranoside (16). Ethyl 1-thio-α-L-rhamnopyranoside[36] (**14**, 5.6 g, 27 mmol) was dissolved in 2,2-dimethoxypropane (35 mL), and a catalytic amount of *p*-toluenesulfonic acid was added. The mixture was stirred at room temperature for 1.5 h and then neutralized with triethylamine. The solvent was evaporated and the residue immediately dissolved in pyridine (50 mL) and cooled to 0 °C. Acetic anhydride (5 mL) was added dropwise from a syringe. After the addition was complete, the reaction was warmed to room temperature and stirred for 3 h. The solvent was then evaporated and coevaporated twice with toluene. Crystallization of the syrup from hexane gave the product **16** (7.20 g, 92%): $[\alpha]_D$ −144.2° (*c* 1.0, $CHCl_3$); R_f 0.58 (4:1 pentane:EtOAc); ^1H NMR ($CDCl_3$) δ_H 5.51 (s, 1 H), 4.88 (dd, 1 H, *J* = 8.0, 10.0 Hz), 4.17 (d, 1 H, *J* = 5.5 Hz), 4.12 (dd, 1 H, *J* = 5.5, 8.0 Hz), 4.01–4.09 (m, 1 H), 2.53–2.64 (m, 2 H), 2.07 (s, 3 H), 1.54 (s, 3 H), 1.30 (s, 3 H), 1.27 (t, 3 H, *J* = 6.5 Hz), 1.13 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ_C 170.09, 109.84, 79.51, 76.80, 75.59, 74.85, 64.61, 27.72, 26.51, 24.51, 21.03, 16.96, 14.65. Anal. Calcd for $C_{13}H_{22}O_5S$ (290.38): C, 53.77; H, 7.63, S, 11.04. Found: C, 53.65; H, 7.38; S, 10.81.

Ethyl 4-*O*-Acetyl-1-thio-α-L-rhamnopyranoside (17). Acetate **16** (7.0 g, 24 mmol) was dissolved in 80% acetic acid (100 mL), and the mixture was heated in an oil bath at 80 °C for 4 h. The solution was cooled, the solvent was evaporated, and then the residue was coevaporated twice with toluene. The solid residue was triturated overnight with hexane to provide product **17** (5.8 g, 95%) as an amorphous solid: $[\alpha]_D$ −220.5° (*c* 1.6, $CHCl_3$); R_f 0.32 (1:1 CH_2Cl_2:CH_3OH); ^1H NMR ($CDCl_3$) δ_H 5.26 (s, 1 H), 4.81 (t, 1 H, *J* = 9.5, 9.5 Hz), 4.12–4.16 (m, 1 H), 4.01 (d, 1 H, *J* = 3.5 Hz), 3.81 (dd, 1 H, *J* = 9.5, 3.5 Hz), 2.53–2.65 (m, 2 H), 2.10 (s, 3 H), 1.26 (t, 3H, *J* = 6.5 Hz), 1.19 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ_C 171.90, 84.03, 75.29, 72.50, 70.56, 66.30, 25.13, 21.06, 17.26, 14.88. Anal. Calcd for $C_{10}H_{18}O_5S$ (250.31): C, 47.98; H, 7.25; S, 12.81. Found: C, 48.07; H, 7.35; S, 12.66.

Ethyl 4-*O*-Acetyl-2,3-di-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (6). A solution of compound **17** (5.6 g, 22 mol) in pyridine (40 mL) was cooled to 0 °C, and benzoyl chloride (7.6 mL, 66 mmol) was added dropwise from a syringe. The reaction was allowed to stir overnight while warming to room temperature. The reaction was quenched with CH_3OH and the solvent evaporated. The residue was dissolved in CH_2Cl_2 and washed sucessively with saturated $NaHCO_3$, water, and saturated NaCl solution. After drying ($MgSO_4$) and concentration, the crude mixture was purified by chromatography (3:1 hexane–EtOAc) to provide a syrup that solidified on standing. Trituration of this solid with hexane overnight afforded product **6** (8.04 g, 78%) as a crystalline solid: $[\alpha]_D$ −40.2° (*c* 1.1, $CHCl_3$); R_f 0.43 (4:1 pentane:EtOAc); ^1H NMR ($CDCl_3$) δ_H 7.24–8.05 (m, 10 H), 5.71 (dd, 1 H, *J* = 1.5, 3.5 Hz), 5.58 (dd, 1 H, *J* = 3.5, 10.0 Hz), 5.45 (t, 1 H, *J* = 10.0, 10.0 Hz), 5.43 (d, 1 H, *J* = 1.5 Hz), 4.36–4.44 (m, 1 H), 2.64–2.74 (m, 2 H), 2.00 (s, 3 H), 1.35 (t, 3 H, *J* = 7.0 Hz) 1.33 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$): δ_C 170.09, 165.59, 165.43, 82.19, 72.61, 71.56, 70.52, 67.14, 25.72, 20.84, 17.54, 14.97. Anal. Calcd for $C_{24}H_{26}O_7S$ (458.53): C, 62.86; H, 5.71; S, 6.99. Found: C, 62.59; H, 5.87; S. 6.87.

4,6-Di-*O*-benzyl-D-mannopyranose (19). Methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside[38] (**18**, 9.0 g, 24.0 mmol) was dissolved in aqueous 3.76 M trifluoroacetic acid (720 mL) and refluxed for 3 h. The mixture was cooled and evaporated and the residue chromatographed (3:1 EtOAc:hexane) to give the product **19** (7.8 g, 74%) as a white foam containing a mixture of anomers (α:β = 1:1): $[\alpha]_D$ +40.2° (*c* 1.0, $CHCl_3$); R_f 0.26 (3:1 EtOAc:hexane); ^1H NMR ($CDCl_3$) δ_H 5.27 (br s), 4.74 (br s); ^{13}C NMR ($CDCl_3$) δ_C 94.60, 94.17. Anal. Calcd for $C_{20}H_{24}O_6$ (360.41): C, 66.65; H, 6.71. Found: C, 66.66; H, 6.74.

1,2,3-Tri-*O*-acetyl-4,6-di-*O*-benzyl-D-mannopyranose (20). The partially protected hexose **19** (7.8 g, 21.7 mmol) was dissolved in pyridine (175 mL) and acetic anhydride (250 mL) added dropwise. The reaction was stirred for 90 min, concentrated, and then coevaporated twice with toluene. The residue dissolved in CH_2Cl_2 was washed successively with $NaHCO_3$, water, and saturated NaCl solution and dried ($MgSO_4$). Evaporation of the solvent gave the product **20** (9.6 g, 91%) as an oily mixture of anomers (α:β = 3:1); $[\alpha]_D$ +37.7° (*c* 1.6, $CHCl_3$), R_f 0.18 (4:1 EtOAc:hexane); ^1H NMR ($CDCl_3$) α-anomer δ_H 6.12 (d, 1 H, *J* = 2.0 Hz), 5.36 (dd, 1 H, *J* = 3.5, 9.5 Hz), 5.28 (dd, 1 H, *J* = 2.0, 3.5 Hz), 4.10 (t, 1 H, *J* = 9.5, 9.5 Hz), 3.90–3.96 (m, 1 H), 3.85 (dd, 1 H, *J* = 3.5, 11.5 Hz), 3.71 (dd, 1 H, *J* = 1.5 11.5 Hz), 2.16, 2.12, 1.98; ^{13}C NMR ($CDCl_3$) δ_C 90.83, β-anomer δ_H 5.84 (d, 1 H, *J* = 1.0 Hz), 5.49 (dd, 1 H, *J* = 1.0, 3.5 Hz), 5.12 (dd, 1 H, *J* = 3.5, 10.0 Hz), 4.03 (t, 1 H, *J* = 10.0, 10.0 Hz), 3.84 (dd, 1 H, *J* = 4.0, 11.0 Hz), 3.71 (dd, 1 H, *J* = 1.5 11.0 Hz), 3.62–3.67 (m, 1 H), 2.21, 2.07, 1.96; ^{13}C NMR ($CDCl_3$) δ_C 90.53. Anal. Calcd for $C_{26}H_{30}O_9$ (486.52): C, 64.19; H, 6.21. Found: C, 64.15; H, 6.30.

Ethyl 2,3-*O*-Acetyl-4,6-di-*O*-benzyl-1-thio-α-D-mannopyranoside (7). Triacetate **20** (9.0 g, 18.5 mmol) was dissolved in CH_2Cl_2 (210 mL), and then ethanethiol (6.2 mL, 83.7 mmol) was added followed by $BF_3{\cdot}OEt_2$ (5.4 mL, 43.9 mmol). After 3.5 h, the reaction was quenched by the addition of triethylamine (6 mL), and the solution was filtered and then evaporated. Chromatography of the resulting oil (4:1 hexane:EtOAc) gave the product **7** (6.7 g, 74%) as an oil: $[\alpha]_D$ + 80.3° (*c* 1.0, $CHCl_3$); R_f 0.26 (4:1 hexane:EtOAc); ^1H NMR ($CDCl_3$) δ_H 7.00–7.30 (m, 10 H, 5.35 (dd, 1 H, *J* = 1.5, 3.5 Hz), 5.31 (d, 1 H, *J* = 1.5 Hz), 5.28 (dd, 1 H, *J* = 3.5, 9.5 Hz), 4.73, 4.63, 4.50, 4.49 (d, 1 H, *J* = 11.5 Hz), 4.21–4.28 (m, 1 H), 4.03 (t, 1 H, *J* = 9.5, 9.5 Hz), 3.86 (dd, 1 H, *J* = 4.0, 10.5 Hz), 3.67 (dd, 1 H, *J* = 2.0 10.5 Hz), 2.54–2.70 (m, 2 H), 2.16, 1.96, 1.29 (t, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ_C 170.07, 169.72, 82.17, 68.65, 25.34, 21.00, 20.84, 14.80. Anal. Calcd for $C_{26}H_{32}O_7S$ (488.60): C, 63.91; H, 6.60; S, 6.56. Found: C, 63.88; H, 6.78; S, 6.49.

Methyl 2,4-Tri-*O*-acetyl-3,6-dideoxy-α-D-*xylo*-hexopyranoside (22). Epoxide **21**[40] (3.62 g, 10.96 mmol) was dissolved in THF (44 mL) and the solution cooled to 0 °C. Lithium triethylborohydride (110 mL, 1 M solution in THF) was added slowly with a syringe. Immediately following the addition, the reaction was removed from the ice bath and refluxed for 30 min. The reaction was cooled, the hydride reagent was quenched with CH_3OH, and the mixture was poured into ice–water (500 mL). After the mixture was stirred for 2 h, H_2O_2 (30% solution, 41 mL) was added, and stirring was continued overnight. The reaction mixture was then evaporated to dryness, and the solid residue was suspended in dry pyridine (100 mL) and DMF (100 mL), to which were added Ac_2O (10 mL) and DMAP (50 mg). After 24 h, the reaction was evaporated and the residue was suspended in CH_2Cl_2 and then washed successively with cold 0.5 M HCl, $NaHCO_3$, water, and saturated NaCl solution. The aqueous extracts were extracted with CH_2Cl_2 until no product was detected by TLC in the organic layer. The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by chromatography (3:1 hexane: EtOAc) to give the product **22** (2.29 g, 85%) as an oil: $[\alpha]_D$ +101.8° (*c* 0.7, $CHCl_3$); R_f 0.38 (3:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ_H 5.00 (ddd, 1 H, *J* = 3.5, 5.0 12.5 Hz), 4.49 (m, 1 H), 4.77 (d, 1 H, *J* = 3.5 Hz), 3.95 (dq, 1 H, *J* = 6.5, 1.5 Hz), 3.37 (s, 3 H), 2.07 (s, 3 H), 2.06 (ddd, 1 H, *J* = 13.5, 12.5, 3.5 Hz), 2.02 (s, 3 H), 1.93 (dddd, 1 H, *J* = 13.5, 5.0, 3.0, 1.5 Hz), 1.07 (d, 3 H, *J* = 6.5 H); ^{13}C NMR ($CDCl_3$) δ_C 170.42, 170.22, 99.66, 70.62, 66.50, 64.59, 55.07, 28.45, 20.94, 20.87, 16.03. Anal. Calcd for $C_{11}H_{18}O_6$ (246.26): C, 53.65; H, 7.37. Found: C, 53.78; H, 7.33.

1,2,4-Tri-*O*-acetyl-3,6 dideoxy-D-*xylo*-hexopyranose (23). Glycoside **22** (2.2 g, 8.94 mmol) was dissolved in Ac_2O (60 mL) and the solution cooled to 0 °C. H_2SO_4 (200 μL) was added

dropwise with a microsyringe and the reaction allowed to continue for 40 min at 0 °C. The reaction was quenched by adding CH_2Cl_2 and then $NaHCO_3$ and stirring for 20 min. The reaction was diluted with more CH_2Cl_2 and then washed with $NaHCO_3$, water, and a saturated NaCl solution. The aqueous extracts were extracted with CH_2Cl_2 until no product was detected by TLC in the organic layer. The combined organic extracts were dried with Na_2SO_4, and the solvent was evaporated to give the product **23** (2.41 g, 98%) as a mixture of anomeric acetates (α:β 3:1): ^{1}H NMR ($CDCl_3$) δ_H 6.25 (d, J = 3.5 Hz), 5.70 (d, J = 8.5 Hz), 1.20 (d, J = 6.5 Hz), 1.14 (d, J = 6.5 Hz).

Ethyl 2,4-Di-*O*-acetyl-3,6-dideoxy-1-thio-α/β-D-*xylo*-hexopyranoside (24). The peracetate **23** (2.41 g 8.80 mmol) was dissolved in 50 mL of CH_2Cl_2, and EtSH (850 μL, 11.48 mmol) was added. The solution was cooled to 0 °C and BF_3·OEt_2 (5.4 mL, 43.98 mmol) added. After being stirred for 30 min, the reaction was quenched by the careful addition of triethylamine (3 mL). The reaction mixture was evaporated and then chromatographed (3:1 hexane–EtOAc) to provide the product **24** (2.05 g, 91%) as two separable anomers in a 1:1 ratio. α-Isomer: $[\alpha]_D$ +180.4° (*c* 1.1, $CHCl_3$); R_f 0.62 (3:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 5.58 (d, 1 H, J = 5.5 Hz), 5.21 (ddd, 1 H, J = 5.5, 4.0, 10.5 Hz), 5.00 (br s, 1 H), 4.35 (dq, 1 H, J = 6.5, 1.5 Hz), 2.49–2.63 (m, 2 H), 2.13, 2.06 (s, 3 H), 1.99–2.05 (m, 2 H), 1.27 (t, 3 H, J = 6.5 Hz), 1.12 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ_C 170.55, 170.21, 82.75, 70.58, 66.43, 64.85, 30.11, 23.99, 21.03, 16.15, 15.06. Anal. Calcd for $C_{12}H_{20}O_5S$ (276.35): C, 52.16; H, 7.29; S, 11.60. Found: C, 52.14; H, 7.37; S, 12.35.

β-Isomer: $[\alpha]_D$ −53.0° (*c* 1.5, $CHCl_3$); R_f 0.45 (3:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 4.95–5.10 (m, 2 H), 4.47 (d, 1 H, J = 10 Hz), 3.74 (q, 1 H, J = 6.5 Hz), 2.63–2.80 (m, 2 H), 2.35 (dt, 1 H, J = 13.5, 4.5, 3.0 Hz), 2.13, 2.06 (s, 3 H), 1.77 (ddd, 1 H, J = 13.5, 11.5, 2.5 Hz), 1.28 (t, 3 H, J = 6.5 Hz), 1.19 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ_C 170.69, 169.77, 85.12, 75.31, 70.09, 66.19, 34.88, 24.03, 21.11, 21.05, 16.82, 14.91. Anal. Calcd for $C_{12}H_{20}O_5S$ (276.35): C, 52.16; H, 7.29; S, 11.60. Found: C, 51.77; H, 7.33; S, 12.31.

Ethyl 3,6-Dideoxy-1-thio-α/β-D-xylo-hexopyranoside (25). The anomeric mixture of acetylated thioglycosides **24** (1.60 g, 5.79 mmol) was dissolved in CH_3OH (50 mL) and then $NaOCH_3$ (100 mg) added and the reaction stirred overnight. By morning, the reaction was still not complete and the pH was <6, so more $NaOCH_3$ (100 mg) was added, and the solution stirred again overnight. The cloudy solution was neutralized with Amberlite IR-120 (H+) resin, filtered, and evaporated. Chromatography (EtOAc) gave the diol **25** as a mixture of inseparable isomers (970 mg, 87% yield). α-Isomer: ^{1}H NMR ($CDCl_3$) δ_H 5.30 (dd, 1 H, J = 5.0, 1.5 Hz), 4.15–4.28 (m, 2 H), 3.71–3.78 (m, 1 H), 2.61–2.71 (m, 2 H), 2.18 (dddd, 1 H, J = 13.5, 4.5, 3.0, 1.5 Hz), 1.79 (br. s, 2 H), 1.64 (ddd, 1 H, J = 13.5, 12.0, 3.0 Hz), 1.32 (t, 3 H, J = 6.5 Hz), 1.25 (d, 3 H, J = 6.5 Hz). β-Isomer: ^{1}H NMR ($CDCl_3$) δ_H 4.29 (d, 1 H, J = 9.5 Hz), 3.63–3.79 (m, 3 H), 2.71–2.82 (m, 2 H), 2.44 (ddd, 1 H, J = 13.5, 4.5, 3.0 Hz), 2.08 (br. s, 2 H), 1.66 (ddd, 1 H, J = 13.5, 11.5, 2.5 Hz), 1.32 (t, 3 H, J = 6.5 Hz), 1.27 (d, 3 H, J = 6.5 Hz).

Ethyl 2,4-Di-*O*-benzyl-3,6-dideoxy-1-thio-α-D-*xylo*-hexopyranoside and Ethyl 2,4-Di-*O*-benzyl-3,6-dideoxy-1-thio-β-D-*xylo*-hexopyranoside (9). The anomeric mixutre of diols **25** (502 mg, 2.61 mmol) was dissolved in dry DMF (25 mL) and cooled to 0 °C. Then NaH (313.5 mg, 10.45 mmol) was added and the solution stirred for 20 min, after which point benzyl bromide (1.24 mL, 10.45 mmol) was added dropwise. The reaction was stirred overnight as it came to room temperature. The reaction was quenched with CH_3OH, diluted with CH_2Cl_2, and then washed with water and a saturated NaCl solution. Chromatography (9:1 hexane–EtOAc) gave the product **9** (785 mg, 81%) as two separable anomers in a 1:1 ratio.

α-Isomer: $[\alpha]_D$ +124.9° (*c* 1.0, $CHCl_3$); R_f 0.34 (9:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 7.20–7.50 (m, 10 H), 5.55 (d, 1 H, J = 5.0 Hz), 4.71, 4.64, 4.51, 4.41 (d, 1 H, J = 11.5 Hz), 4.27 (br q, 1 H, J = 6.5 Hz), 4.17 (dt, 1 H, J = 5.0, 5.0, 12.0 Hz), 3.47 (br s, 1 H), 2.52–2.71 (m, 2 H), 2.20 (dt, 1 H, J = 13.0, 5.0, 5.0 Hz), 1.81 (ddd, 1 H, J = 13.0, 12.0, 2.5 Hz), 1.35 (t, 3 H, J = 6.5 Hz), 1.24 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ_C 84.10, 75.52, 71.29, 70.70, 70.62, 66.33, 29.81, 23.58, 16.38, 15.12. Anal. Calcd for $C_{22}H_{28}O_3S$ (372.52): C, 70.93; H, 7.58; S, 8.61. Found: C, 71.23; H, 7.71; S, 8.58. β-Isomer: $[\alpha]_D$ −69.9° (*c* 1.2, $CHCl_3$); R_f 0.23 (9:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 7.20–7.50 (m, 10 H), 4.73, 4.57 4.56 (d, 1 H J = 11.5 Hz), 4.48 (d, 1 H, J = 9.0 Hz), 4.40 (d, 1 H J = 11.5 Hz), 3.55–3.66 (m, 2 H,), 3.41 (br s, 1 H), 2.66–2.84 (m, 2 H), 2.43 (dt, 1 H, J = 13.5, 4.5, 3.0 Hz), 1.47 (ddd, 1 H, J = 13.5, 11.5, 2.5 Hz), 1.32 (t, 3 H, J = 6.5 Hz), 1.26 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ_C 86.57, 76.29, 75.14, 72.77, 72.52, 71.14, 34.26, 24.33, 16.98, 14.95. Anal. Calcd for $C_{22}H_{28}O_3S$ (372.52): C, 70.93; H, 7.58. Found: C, 70.87; H, 7.65.

2-(Trimethylsilyl)ethyl 2-*O*-Benzoyl 4,6-*O*-benzylidene-3-*O*-(2,3-di-*O*-benzoyl-4-*O*-acetyl-α-L-rhamnopyranosyl)-β-D-galactopyranoside (26). Alcohol **10** (1.18 g, 2.5 mmol) and donor **6** (1.32 g, 2.9 mmol) were dissolved in dry CH_2Cl_2 (80 mL), and powdered 4 Å molecular sieves (5 g, freshly activated) were added. The mixture was stirred for 2 h at room temperature, and then *N*-iodosuccinimide (1.40 g, 6.25 mmol) was added and the suspension stirred for 10 min before a saturated solution of triflic acid in CH_2Cl_2 (ca. 0.15 M) was added rapidly, dropwise. After the addition of 0.15 equiv of acid, all the thioglycoside had been consumed. The reaction was quenched with triethylamine, and then the reaction was filtered through Celite. The filtrate was washed with $NaHCO_3$, 10% $Na_2S_2O_3$, water, and a saturated NaCl solution. After evaporation of the solvent, chromatography (3:1 hexane–EtOAc) gave the product **26** (1.98 g, 90%) as a white foam: $[\alpha]_D$ +122.4° (*c* 0.9, $CHCl_3$); R_f 0.33 (2:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 7.24–8.15 (m, 16 H), 5.68 (dd, 1 H, J = 7.5, 10.0 Hz), 5.60 (s, 1 H), 5.57 (dd, 1 H, J = 3.5, 10.0 Hz), 5.25–5.33 (m, 2 H), 5.19 (br s, 1 H), 4.70 (d, 1 H, J = 7.5 Hz), 4.45 (d, 1 H, J = 3.5 Hz), 4.41 (d, 1 H, J = 12.0 Hz), 4.28 (dd, 1 H, J = 10.0, 6.5 Hz), 4.14 (d, 1 H, J = 12.0 Hz), 4.04–4.09 (dd, 1 H, J = 10.0, 3.5 Hz), 3.99–4.04 (m, 1 H), 3.56–3.65 (m, 1 H), 3.54 (br s, 1 H), 1.90 (s, 3 H), 1.09 (d, 3 H, J = 6.5 Hz), 0.83–1.09 (m, 2 H), −0.05 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 170.08, 165.29, 165.21, 164.68, 101.23, 100.65 ($^1J_{C,H}$ = 157.8 Hz), 98.99 ($^1J_{C,H}$ = 170.2 Hz), 69.19, 66.69, 20.70, 17.98, 17.51, −1.40. Anal. Calcd for $C_{47}H_{52}O_{14}Si$ (869.01): C, 64.96; H, 6.03. Found: C, 64.73; H, 5.96.

2-(Trimethylsilyl)ethyl 2-*O*-Benzoyl-3-*O*-(2,3-di-*O*-benzoyl-4-*O*-acetyl-α-L-rhamnopyranosyl)-β-D-galactopyranoside (27). Disaccharide **26** (400 mg 0.46 mmol) was dissolved in a 1% solution of I_2 in CH_3OH (w/v, 8 mL) and the solution heated at reflux for 6 h. The solution was cooled, a few crystals of $Na_2S_2O_3$ were added, and the suspension was stirred until the dark red solution went colorless. The solvent was evaporated and the residue chromatographed (1:1 hexane–EtOAc) to give the product **27** (315 mg 88%) as a syrup: $[\alpha]_D$ + 85.4° (*c* 0.8, $CHCl_3$); R_f 0.21 (1:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 7.25–8.03 (m, 15 H), 5.53–5.59 (m, 2 H), 5.34 (m, 1 H), 5.30 (t, 1 H, J = 10.0, 10.0 Hz), 5.13 (s, 1 H), 4.59 (d, 1 H, J = 8.0 Hz), 4.22 (dd, 1 H, J = 10.0, 6.5 Hz), 3.93–4.03 (m, 4 H), 3.67 (t, 1 H, J = 5.5, 5.5 Hz), 3.53–3.58 (m, 1 H), 3.28 (t, 1 H, J = 4.0, 4.0 Hz), 3.04 (d, 1 H, J = < 4.0 Hz), 2.39 (dd, 1 H, J = 4.5, 7.5 Hz), 1.92 (s, 3 H), 1.26 (d, 3 H, J = 6.5 Hz), 0.79–0.92 (m, 2 H), −0.10 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 170.09, 165.29, 165.06, 164.82, 100.93, 98.88, 67.33, 62.13, 20.70, 18.01, 17.57, −1.50. Anal. Calcd for $C_{40}H_{48}O_{14}Si$ (780.90): C, 61.52; H, 6.19. Found: C, 61.52; H, 6.04.

2-(Trimethylsilyl)ethyl 2,4,6-Tri-*O*-benzoyl-3-*O*-(2,3-di-*O*-benzoyl-4-*O*-acetyl-α-L-rhamnopyranosyl)-β-D-galactopyranoside (28). Diol **27** (300 mg, 0.38 mmol) was dissolved in dry pyridine (10 mL), and few crystals of DMAP were added. The mixture was cooled to 0 °C, and benzoyl chloride (175 μl, 1.52 mmol) was added dropwise from a microsyringe. The reaction was stirred at room temperature overnight and quenched by the addition of methanol, and the solvent evaporated to give a residue that was coevaporated twice with toluene. The reaction product was taken up in CH_2Cl_2 and washed with 1 M HCl, saturated $NaHCO_3$, water, and a saturated NaCl solution. The solution was then dried over $MgSO_4$, filtered, evaporated, and chromatographed (3:1 hex-

ane–EtOAc) to give the product **28** (330 mg, 87%) as a white foam: $[\alpha]_D$ +76.3° (*c* 0.7, $CHCl_3$); R_f 0.54 (2:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ_H 7.19–8.31 (m, 25 H), 5.84 (br d, 1 H, J = 3.5, < 1.0 Hz), 5.69 (dd, 1 H, J = 8.0, 10.0 Hz), 5.36 (dd, 1 H, J = 3.5, 10.0 Hz), 5.22–5.31 (m, 2 H), 5.14 (d, 1 H, J = 1.5 Hz), 4.72 (d, 1 H, J = 8.0 Hz), 4.60 (dd, 1 H, J = 7.5, 11.5 Hz), 4.52 (dd, 1 H, J = 5.5, 11.5 Hz), 4.27 (dd, 1 H, J = 10.0, 3.5 Hz), 4.12–4.23 (m, 2 H), 3.98–4.08 (m, 1 H), 3.57–3.66 (m, 1 H), 1.91 (s, 3 H), 1.21 (d, 3 H, J = 6.0 Hz), 0.85–1.01 (m, 2 H), −0.07 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 170.20, 166.22, 166.16, 165.08, 164.81, 164.55, 101.01, 99.13, 67.50, 62.79, 20.81, 18.05, 17.41, −1.49. Anal. Calcd for $C_{54}H_{56}O_{16}Si$ (989.12): C, 65.57; H, 5.71. Found C, 65.36; H, 5.96.

2-(Trimethylsilyl)ethyl 2,4,6-Tri-*O*-benzoyl-3-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-β-D-galactopyranoside (29). Compound **28** (850 mg, 0.86 mmol) was dissolved in 3% methanolic hydrogen chloride (50 mL) and the mixture stirred for 6 h. The solution was partially concentrated, diluted with CH_2Cl_2, and washed sucessively with saturated $NaHCO_3$, water, and a saturated NaCl solution. The organic phase was dried with $MgSO_4$, filtered, and concentrated and the residue chromatographed (3:1 hexane–EtOAc) to afford **29** (446 mg, 55%) as a white amorphous solid: $[\alpha]_D$ + 86.7° (*c* 1.3, $CHCl_3$); R_f 0.23 (2:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ_H 7.20–8.30 (m, 25 H), 5.84 (dd, 1 H, J = 3.5, 1.0 Hz), 5.64 (dd, 1 H, J = 8.0, 10.0 Hz), 5.17–5.24 (m, 2 H), 5.07 (d, 1 H, J = 1.5 Hz), 4.70 (d, 1 H, J = 8.0 Hz), 4.64 (dd, 1 H, J = 7.0, 11.5 Hz), 4.50 (dd, 1 H, J = 5.5, 11.5 Hz), 4.27 (dd, 1 H, J = 10.0, 3.5 Hz), 4.11–4.24 (m, 2 H), 3.98–4.07 (m, 1 H), 3.65–3.77 (m, 1 H), 3.56-3.65 (m, 1 H), 2.51 (d, 1 H, J = 7.0 Hz), 1.37 (t, 3 H, J = 6.5 Hz), 0.85–1.00 (m, 2 H), −0.08 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 166.16, 164.75, 100.99, 98.79, 67.58, 62.85, 18.06, 17.70, −1.48. Anal. Calcd for $C_{52}H_{54}O_{15}Si$ (947.08): C, 65.95; H, 5.75. Found: C, 65.98; H, 5.71.

2-(Trimethylsilyl)ethyl 2,4,6-Tri-*O*-benzoyl-3-*O*-[2,3-di-*O*-benzoyl-4-*O*-(2,3-di-*O*-acetyl-4,6-di-*O*-benzyl-α-D-mannopyranosyl)-α-L-rhamnopyranosyl]-β-D-galactopyranoside (30). Disaccharide alcohol **29** (152 mg, 0.16 mmol) and mannopyranoside donor **7** (90 mg, 0.18 mmol) were dissolved in dry CH_2Cl_2 (10 mL). The solution was stirred under N_2 for 2 h with activated, powdered 4 Å molecular sieves (2.5 g), and then *N*-iodosuccinimide (90 mg, 0.4 mmol) was added and the mixture stirred for 10 min. To this solution was added triflic acid in CH_2Cl_2 (0.12 mL of 0.135 molar solution). After being stirred for 30 min, the reaction was quenched with triethylamine, diluted with CH_2Cl_2 and filtered. The filtrate was washed successively with saturated $NaHCO_3$, a 10% solution of $Na_2S_2O_3$, water, and a saturated NaCl solution. After drying ($MgSO_4$), the solution was filtered and evaporated and the residue chromatographed (7:3 hexane–EtOAc) to provide the product **30** (195 mg, 89%) as a white amorphous solid: $[\alpha]_D$ +104.5° (*c* 0.7, $CHCl_3$); R_f 0.29 (2:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ_H 7.12–8.25 (m, 35 H), 5.85 (dd, 1 H, J = 3.5, <1.0 Hz), 5.66 (dd, 1 H, J = 8.0, 10.0 Hz), 5.37 (dd, 1 H, J = 3.5, 9.5 Hz), 5.22 (dd, 1 H, J = 3.5, 10.0 Hz), 5.20 (dd, 1 H, J = 1.0, 3.5 Hz), 5.15 (dd, 1 H, J = 1.5, 3.5 Hz), 5.07 (d, 1 H, J = 1.5 Hz), 4.94 (d, 1 H, J = 2.0 Hz), 4.72 (d, 1 H, J = 8.0 Hz), 4.65 (dd, 1 H, J = 7.5, 11.0 Hz), 4.53 (d, 1 H, J = 11.5 Hz), 4.51 (dd, 1 H, J = 5.5, 11.0 Hz), 4.41, 4.30 (d, 1 H, J = 11.5 Hz), 4.24 (dd, 1 H, J = 10.0, 3.5 Hz), 4.13–4.22 (m, 2 H), 3.97–4.06 (m, 1 H), 3.97 (t, 1 H, J = 10.0, 10.0 Hz), 3.90 (d, 1 H, J = 11.5 Hz), 3.80 (t, 1 H, J = 9.5, 9.5 Hz), 3.56–3.66 (m, 2 H), 3.35 (dd, 1 H, J = 11.5, 2.0 Hz), 2.98 (dd, 1 H, J = 11.5, 1.5 Hz), 2.05, 1.96 (s, 3 H), 1.38 (d, 3 H, J = 6.0 Hz), 0.85–1.00 (m, 2 H), −0.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C 170.55, 169.83, 166.44, 166.24, 165.19, 164.83, 164.59, 101.16, ($^1J_{C,H}$ = 159.2 Hz), 99.16 ($^1J_{C,H}$ = 173.2 Hz), 99.11 ($^1J_{C,H}$ = 173.5 Hz), 74.59, 73.52, 67.91, 67.65, 62.95, 21.16, 21.11, 18.26, 18.22, −1.29. Anal. Calcd for $C_{76}H_{80}O_{22}Si$ (1373.55): C, 66.46; H, 5.87. Found: C, 66.28; H, 5.88.

2-(Trimethylsilyl)ethyl 2,4,6-Tri-*O*-benzoyl-3-*O*-[2,3-di-*O*-benzoyl-4-*O*- (4,6-di-*O*-benzyl-α-D-mannopyranosyl)-α-L-rhamnopyranosyl]-β-D-galactopyranoside (31). Trisaccharide **30** (2.5 g, 1.82 mmol) was dissolved in 49:1 methanol: acetyl chloride (50 mL), and the solution was stirred for 10 h. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution and then diluted with CH_2Cl_2. After being washed with water and a saturated NaCl solution, the organic layer was dried with Na_2SO_4 and evaporated. Chromatography (1:1 hexane–EtOAc) gave the de-*O*-acetylated product **31** (2.20 g, 94%) as a white foam: $[\alpha]_D$ +120.50° (*c* 1.0, $CHCl_3$); R_f 0.22 (1:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ_H 7.10–8.30 (m, 35 H), 5.80 (br d, 1 H, J = 3.5 Hz), 5.68 (dd, 1 H, J = 9.0, 7.5 Hz), 5.35, (dd, 1 H, J = 3.5, 8.5 Hz), 5.17 (dd, 1 H, J = 2.0, 3.0 Hz), 5.06 (d, 1 H, J = 2.0 Hz), 4.92 (br. s, 1 H), 4.70, (d, 1 H, J = 7.5 Hz), 4.59 (dd, 1 H J = 7.0, 11.0 Hz), 4.51 (dd, 1 H, J = 5.0, 11.0 Hz), 4.46, 4.39, 4.32 (d, 1 H, J = 11.5 Hz), 4.22 (dd, 1 H, J = 9.5, 3.5 Hz,), 4.14–4.25 (m, 1 H), 3.91–4.07 (m, 3 H), 3.55–3.87 (m, 5 H), 3.40-3.45 (m, 1 H), 3.18 (dd, 1 H, J = 2.0, 10.5 Hz), 2.95 (dd, 1 H, J = 1.5, 10.5 Hz), 2.13 (d, 2 H, J = 4.0 Hz), 1.29 (d, 1 H, J = 6.5 Hz), 0.85–1.00 (m, 2 H), −0.09 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 166.23, 166.13, 164.99, 164.69, 164.52, 100.93, 100.90, 98.99, 74.02, 73.35, 67.78, 67.46, 62.78, 18.36, 17.98, −1.54. Anal. Calcd for $C_{72}H_{77}O_{20}Si$ (1289.47): C, 67.01; H, 6.01. Found: C, 66.79; H, 5.92.

2-(Trimethylsilyl)ethyl 2,4,6-Tri-*O*-benzoyl-3-*O*-[2,3-di-*O*-benzoyl-4-*O*- (3-*O*-allyl-4,6-di-*O*-benzyl-α-D-mannopyranosyl)-α-L-rhamnopyranosyl]-β-D-galactopyranoside (32). A mixture of trisaccharide diol **31** (1.45 g, 1.123 mmol) and dibutyltin oxide (336 mg, 1.35 mmol) was refluxed in dry toluene (100 mL) through a column of 4 Å molecular sieves overnight. The reaction mixture was cooled to 60 °C, and allyl bromide (1 mL, 11.2 mmol) and tetra-*N*-butylammonium iodide (414 mg, 1.12 mmol) were added. The reaction mixture was heated overnight, cooled to room temperature, and washed successively with $Na_2S_2O_3$, water, and saturated NaCl solution. The organic layer was dried (Na_2SO_4) and evaporated. Chromatography of the residue (2:1 hexane–EtOAc) gave the product **32** (1.13 g, 76%) as a white foam: $[\alpha]_D$ +133.56° (*c* 1.2, $CHCl_3$); R_f 0.60 (1:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ_H 7.00–8.30 (m, 35 H), 5.90 (1 H, J = 17.0, 10.5, 5.5 Hz), 5.82 (d, 1 H, J = 3.5 Hz), 5.66 (dd, 1 H, J = 8.0, 10.0 Hz), 5.35 (dd, 1 H, J = 3.5, 9.5 Hz), 5.27 (1 H, J = 10.5, 1.5, 1.5 1.5 Hz), 5.14–5.21 (m, 2 H, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.07 (d, 1 H, J = 1.0 Hz), 4.98 (br s, 1 H), 4.70 (d, 1 H, J = 8.0 Hz), 4.63 (d, 1 H, J = 11.5 Hz), 4.49–4.60 (m, 2 H), 4.33, 4.31 (d, 1 H, J = 11.5 Hz), 4.28 (dd, 1 H, J = 3.5, 10.0 Hz), 3.99–4.20 (m, 5 H, J = 13.5, 5.5, 1.5 Hz), 3.96 (d, J = 11.5 Hz), 3.87–3.90 (m, 1), 3.84 (t, 1 H, J = 9.5, 9.5 Hz), 3.76 (t, 1 H, J = 10.0, 10.0 Hz), 3.56–3.65 (m, 1 H), 3.55 (dd, 1 H, J = 3.5, 10.0 Hz), 3.42–3.47 (m, 1 H), 3.17 (dd, 1 H, J = 2.5, 11.5 Hz), 2.93 (dd, 1 H, J = 1.5, 11.5 Hz), 2.31 (d, 1 H, J = 2.5 Hz), 1.30 (d, 3 H, J = 6.5 Hz), 0.85–1.00 (m, 2 H), −0.09 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 166.10, 166.03, 164.94, 164.65, 164.47, 100.89, 100.64, 98.99, 117.18, 73.17, 74.47, 71.02, 67.75 (C–6C), 67.35, 62.76, 18.26, 17.92, −1.58. Anal. Calcd for $C_{75}H_{81}O_{20}Si$ (1330.55): C, 67.70; H, 6.14. Found C, 67.83; H, 6.07.

2-(Trimethylsilyl)ethyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→2)-*O*-(3-*O*-allyl-4,6-di-*O*-benzyl-α-D-mannopyranosyl)-(1→4)-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranoside (33). Trisaccharide alcohol **32** (1.43 g, 1.07 mmol) and donor **8** (941 mg, 1.61 mmol) were dried in vacuo with crushed 4 Å molecular sieves (5 g) over P_2O_5 overnight. The solids were suspended in CH_2Cl_2 (50 mL), and the mixture was cooled to 0 °C and stirred for 20 min. *N*-Iodosuccinimide (362 mg, 1.61 mmol) and then silver triflate (41 mg, 0.1612 mmol) were added to the mixture, and after being stirred for 15 min, the reaction was quenched with triethylamine. The suspension was diluted with CH_2Cl_2 and then filtered and the filtrate was washed successively with $Na_2S_2O_3$, water, and a saturated NaCl solution. After drying (Na_2SO_4), the residue was purified by chromatography (4:1 hexane–EtOAc) to give the product **33** (1.61 g, 81%) as a white foam: $[\alpha]_D$ +100.71° (*c* 1.3, $CHCl_3$); R_f 0.19 (4:1 hexane–EtOAc); ^1H NMR ($CDCl_3$) δ_H 6.90–8.20 (m, 55 H), 5.89 (1 H, J = 17.0, 10.5, 5,5 Hz), 5.84 (d, 1 H, J = 3.5 Hz), 5.63 (dd, 1 H, J = 8.0, 10.0 Hz), 5.47 (d, 1 H, J = 3.5 Hz), 5.36 (dd, 1 H, J = 3.5, 9.5 Hz), 5.26 (1 H, J = 10.5, 1.5, 1.5, 1.5 Hz), 5.21 (dd, 1 H, J = 2.0, 3.5 Hz), 5.13 (1 H, J = 17.0, 1.5, 1.5, 1.5 Hz), 5.08 (d, 1 H, J = 2.0 Hz), 5.00 (br s, 1 H), 4.98, 4.90 (d, 1 H, J = 11.5 Hz), 4.72 (d, 1 H, J =

8.0 Hz), 4.65, 4.62 (d, 1 H, J = 11.5 Hz), 4.52–4.59 (m, 2 H), 4.50 (d, 1 H, J = 11.5 Hz), 4.38–4.47 (m, 4 H), 4.33 (d, 1 H, J = 11.5 Hz), 4.24 (dd, 1 H, J = 3.5, 10.0 Hz), 3.81–4.21 (m, 12 H), 3.56–3.65 (m, 1 H), 3.51 (dd, 1 H, J = 9.5, 8.0 Hz), 3.36–3.44 (m, 2 H), 3.13 (dd, 1 H, J = 2.5, 10.5 Hz), 2.94 (d, 1 H, J = 11.5 Hz), 1.28 (d, 3 H, J = 6.5 Hz), 0.85–1.00 (m, 2 H), −0.08 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 166.21, 166.07, 165.02, 164.75, 164.51, 116.95, 100.96, 100.67, 99.07, 97.25, 74.82, 74.28, 73.36, 73.34, 73.38, 71.88, 71.35, 68.74, 68.23, 67.44, 62.69, 18.06, 18.00, −1.51. Anal. Calcd for $C_{109}H_{115}O_{25}Si$ (1853.19): C, 70.65; H, 6.25. Found: C, 70.65; H, 6.24.

2-(Trimethylsilyl)ethyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→2)-*O*-(4,6-di-*O*-benzyl-α-D-mannopyranosyl)-(1→4)-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranoside (34). To the tetrasaccharide **33** (1.04 g, 0.56 mmol) dissolved in ethanol:benzene:water 7:3:1 (v/v) (110 mL) was added tris(triphenylphosphine)rhodium(I) chloride (74 mg, 0.08 mmol) and DABCO (27 mg, 0.24 mmol). The reaction was refluxed overnight, cooled, and evaporated and the residue immediately redissolved in 9:1 acetone:water (100 mL). Mercuric chloride (6 g) and mercuric oxide (50 mg) were added and the solution stirred for 4 h. The solvent was then evaporated and the resulting solid taken up in CH_2Cl_2 and successively washed with saturated potassium iodide, water, and saturated NaCl solution. Evaporation of the organic layer and chromatography (3:1 hexane–EtOAc) gave the product **34** (880 mg, 87%) as a white foam: $[\alpha]_D$ +88.5° (c 1.2, $CHCl_3$); R_f 0.20 (3:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 7.00–8.30 (m, 55 H), 5.80 (d, 1 H, J = 3.5 Hz), 5.65 (dd, 1 H, J = 8.0, 10.0 Hz), 5.33 (dd, 1 H, J = 3.5, 9.5 Hz), 5.19 (dd, 1 H, J = 2.0, 3.5 Hz), 5.05 (d, 1 H, J = 2.0 Hz), 5.01 (br s, 1 H), 4.94 (d, 1 H, J = 3.5 Hz), 4.87, 4.84 (d, 1 H, J = 11.5 Hz), 4.71 (d, 1 H, J = 8.0 Hz), 4.67 (d, 1 H, J = 11.5 Hz), 4.61 (dd, 1 H, J = 7.5, 11.5 Hz), 4.54 (d, 1 H, J = 11.5 Hz), 4.52 (dd, 1 H J = 5.5, 11.5 Hz), 4.47, 4.42 (d, 1 H, J = 11.5 Hz), 4.36–4.40 (m, 4 H), 4.15–4.25 (m, 2 H), 3.97–4.07 (m, 4 H), 3.91 (d, 1 H, J = 11.5 Hz), 3.70–3.85 (m, 4 H), 3.52–3.65 (m, 3 H), 3.47 (d, 1 H, J = 11.5 Hz), 3.36–3.48 (m, 3 H), 3.24 (dd, 1 H, J = 2.5, 11.5 Hz), 2.94 (d, 1 H, J = 11.5 Hz), 1.24 (d, 3 H, J = 6.5 Hz), 0.85–1.00 (m, 2 H), −0.08 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 166.22, 166.09, 164.96, 164.66, 164.48, 101.63, 100.90, 100.25, 99.00, 74.71, 74.22, 73.31, 72.93, 72.27, 68.67, 68.26, 67.40, 62.77, 18.16, 17.99, −1.52. Anal. Calcd for $C_{106}H_{111}O_{25}Si$ (1813.13): C, 70.22; H, 6.17. Found: C, 70.36; H, 6.26.

2-(Trimethylsilyl)ethyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-(1→2)-*O*-[2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-(1→3)]-*O*-(4,6-di-*O*-benzyl-α-D-mannopyranosyl)-(1→4)-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranoside (35). The tetrasaccharide alcohol **34** (500 mg, 0.276 mmol) and the 3,6-dideoxyhexose thioglycoside **9** (408 mg, 1.095 mmol) were dried in vacuo with crushed 4 Å molecular sieves (5 g) over P_2O_5 overnight. The mixture was suspended in CH_2Cl_2 and the solution cooled to 0 °C and stirred for 20 min. *N*-Iodosuccinimide (252 mg, 1.12 mmol) and silver triflate (20 mg, 0.078 mmol) were added, and after 30 min the reaction was quenched with triethylamine. The reaction was then diluted with CH_2Cl_2 and filtered, and the filtrate was washed successively with $Na_2S_2O_3$, water, and saturated NaCl solution and dried (Na_2SO_4). After removal of the solvent, chromatography of the residue (3:1 hexane–EtOAc) gave the protected pentasaccharide **35** (458 mg, 78%) as a syrup: $[\alpha]_D$ +98.27° (c 0.8, $CHCl_3$); R_f 0.33 (3:1 hexane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 6.90–8.30 (m, 65 H), 5.83 (d, 1 H, J = 3.0 Hz), 5.67 (dd, 1 H, J = 8.0, 10.0 Hz), 5.56 (d, 1 H, J = 3.5 Hz), 5.37 (dd, 1 H, J = 3.5, 9.5 Hz), 5.25 (dd, 1 H, J = 1.5, 3.5 Hz), 5.21 (d, 1 H, J = 3.5 Hz), 5.09 (d, 1 H, J = 1.5 Hz), 5.07 (d, 1 H, J = 1.0 Hz), 5.04, 4.90, 4.87 (d, 1 H, J = 11.5 Hz), 4.72 (d, 1 H, J = 8.0 Hz), 4.64 (dd, 1 H, J = 7.5, 11.5 Hz), 4.56, 4.54 (d, 1 H, J = 11.5 Hz), 4.51 (dd, 1 H, J = 5.5, 11.5 Hz), 3.94–4.45 (m, 18 H), 3.72–3.88 (m 5 H), 3.56–3.66 (m, 1 H), 3.37–3.52 (m, 3 H), 3.27 (dd, 1 H, J = 2.5, 11.5 Hz), 2.93 (d, 1 H, J = 11.5 Hz), 1.96 (dt, 1 H, J = 13.0, 2.5, 2.5 Hz), 1.72 (dt, 1 H, J = 13.0, 13.0, 2.5 Hz), 1.34 (d, 3 H, J = 6.5 Hz), 1.16 (d, 3 H, J = 6.5 Hz), 0.85–1.01 (m, 2 H), −0.06 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 166.15, 165.92, 164.89, 164.54, 164.36, 100.94, 100.92, 99.16, 98.95, 98.04, 74.70, 73.73, 73.26, 73.13, 73.02, 71.72, 71.06, 70.70, 68.52, 68.26, 67.37, 62.66, 27.52, 17.96, 17.94, 16.44, −1.55. Anal. Calcd for $C_{126}H_{133}O_{28}Si$ (2123.52): C, 71.26; H, 6.31. Found: C, 71.24; H, 6.55.

2-(Trimethylsilyl)ethyl *O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→2)-*O*-[2,4-di-*O*-acetyl-3,6-dideoxy-α-D-xylo-hexopyranosyl)-(1→3)]-*O*-(4,6-di-*O*-acetyl-α-D-mannopyranosyl)-(1→4)-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranoside (37). A stirred solution of pentasaccharide **35** (228 mg, 0.107 mmol) was dissolved in acetic acid (20 mL) and hydrogenated over 10% Pd/C (150 mg) under a flow of H_2 for 6 h. The catalyst was removed by filtration, and the solvent was evaporated. The residue dissolved in pyridine (15 mL) was reacted with acetic anhydride (5 mL), and the solution was stirred overnight. The reaction was cooled to 0 °C, quenched with CH_3OH, and evaporated. Chromatography of the residue (1:1 EtOAc–pentane) gave the peracylated product **37** (138 mg, 74%) as a white amorphous solid: $[\alpha]_D$ +123.3° (c 0.7, $CHCl_3$); R_f 0.29 (1:1 pentane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 7.20–8.30 (m, 25 H), 5.83 (d, 1 H, J = 3.0 Hz), 5.63 (dd, 1 H, J = 8.0, 10.0 Hz), 5.51 (d, 1 H, J = 3.5 Hz), 5.42 (d, 1 H, J = 2.5 Hz), 5.38 (dd, 1 H, J = 3.5, 9.5 Hz), 5.22–5.31 (m, 2 H), 5.20 (dd, 1 H, J = 1.5, 3.5 Hz), 5.10 (dd, 1 H, J = 3.5, 10.5 Hz), 4.92–5.07 (m, 5 H), 4.71 (d, 1 H, J = 8.0 Hz), 4.57 (dd, 1 H, J = 7.5, 11.5 Hz), 4.48 (dd, 1 H, J = 5.5, 11.5 Hz), 3.82–4.27 (m, 11 H), 3.50–3.65 (m, 3 H), 3.40 (d, 1 H, J = 12.5 Hz), 1.77–2.18 (m, 26 H), 1.38 (d, 3 H, J = 6.5 Hz), 1.16 (d, 3 H, J = 6.5 Hz), 0.85–1.01 (m, 2 H), −0.06 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ_C 170.71, 170.56, 170.51, 170.35, 170.07, 169.82, 169.68, 169.24, 166.09, 165.95, 164.92, 164.52, 164.40, 100.94, 99.82, 99.29, 97.02, 96.48, 67.44, 62.61, 61.30, 61.22, 27.95, 20.93, 20.87, 20.71, 20.58, 20.38, 20.24, 18.06, 17.96, 16.12, -1.55. Anal. Calcd for $C_{86}H_{100}O_{36}Si$ (1737.82): C, 59.44; H, 5.80. Found: C, 59.56 H, 5.87.

***O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→2)-*O*-[2,4-di-*O*-acetyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-(1→3)]-*O*-(4,6-di-*O*-acetyl-α-D-mannopyranosyl)-(1→4)-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranose (38).** Compound **37** (125 mg, 0.072 mmol) was dissolved in CH_2Cl_2 (500 μL) and cooled to 0 °C. Trifluoroacetic acid (1 mL) was added, and the reaction mixture was stirred for 1 h at 0 °C. The solution was diluted with toluene (3 mL) and evaporated. Chromatography of the residue (3:2 EtOAc–pentane) gave the product **38** (115 mg, 98%) as a white amorphous solid: R_f 0.45 (2:3 pentane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 7.20–8.20 (m, 25 H), 5.91 (d, 1 H, J = 3.0 Hz), 5.88 (t, 1 H, J = 3.5, 3.5 Hz), 5.52 (d, 1 H, J = 3.5 Hz), 5.46 (dd, 1 H, 3.5, J = 10.0 Hz), 5.43 (d, 1 H, J = 2.5 Hz), 5.20–5.40 (m, 6 H), 4.93–5.04 (m, 4 H), 4.73 (t, 1 H, J = 6.5, 6.5 Hz), 4.66 (dd, 1 H, J = 10.0, 3.5 Hz), 4.51 (dd, 1 H, J = 6.5, 11.5 Hz), 4.41 (dd, 1 H, J = 6.5, 11.5 Hz), 3.85–4.35 (m, 10 H), 3.35–3.57 (m, 4 H), 1.78–2.19 (m, 26 H), 1.45 (d, 3 H), 1.14 (d, 3 H, J = 6.5 Hz).

***O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→2)-*O*-[2,4-di-*O*-acetyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-(1→3)]-*O*-(4,6-di-*O*-acetyl-α-D-mannopyranosyl)-(1→4)-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranosyl Trichloroacetimidate (39).** The reducing sugar **38** (113.8 mg, 0.069 mmol) was dissolved in CH_2Cl_2 (5 mL) and then cooled to 0 °C. Tricholoroacetonitirile (50 μL, 0.499 mmol) was added followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (2.5 μL, 0.0173 mmol), and the reaction was stirred for 3 h while being warmed to room temperature. The solvent was evaporated and the product chromatographed (3:2 EtOAc–pentane) to give the product **39** (120 mg, 93%) as a white amorphous solid: R_f 0.45 (2:3 pentane–EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 8.59 (s, 1 H), 6.93 (d, 1 H, J = 3.5 Hz).

Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-(1→2)-*O*-[2,4-di-*O*-acetyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-(1→3)]-*O*-(4,6-di-*O*-acetyl-α-D-mannopyranosyl)-(1→4)-*O*-(2,3-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→3)-2,4,6-tri-*O*-benzoyl-α-D-galactopyranoside (40). The pentasaccharide imidate **39** (120 mg, 0.64 mmol) was dissolved

in CH_2Cl_2 (3 mL) and then cooled to −78 °C. Methanol (13 μL, 0.321 mmol) was added followed by trimethylsilyl trifluoromethanesulfonate (1.5 μL, 7.8 μmol), and the reaction was stirred for 40 min. The reaction mixture was removed from the cooling bath and then quenched with a drop of triethylamine. The solvent was evaporated and then chromatographed (3:2 EtOAc−pentane) to give the impure methyl glycoside **40** contaminated with reducing sugar **38** as a white amorphous solid: R_f 0.45 (2:3 pentane−EtOAc); ^{1}H NMR ($CDCl_3$) δ_H 7.20−8.20 (m, 25 H), 5.84 (d, 1 H, J = 3.5 Hz), 5.65 (dd, 1 H, J = 8.0, 10.0 Hz), 5.51 (d, 1 H J = 3.5 Hz), 5.42 (d, 1 H, J = 3.5 Hz), 5.37 (dd, 1 H, J = 3.5, 9.5 Hz), 5.23−5.30 (m, 2 H), 5.19 (dd, 1 H, J = 2.0, 3.5 Hz), 5.07−5.13 (m, 2 H), 4.93−5.05 (m, 4 H), 4.61 (d, 1 H, J = 8.0 Hz), 4.59 (dd, 1 H, J = 7.0, 11.5 Hz), 4.47 (dd, 1 H, J = 5.5, 1.5 Hz), 3.83−4.27 (m, 11 H), 3.50−3.60 (m, 6 H), 3.40 (dd, 1 H, J = 2.5, 12.5 Hz), 1.79−2.17 (m, 26 H), 1.38 (d, 3 H, J = 6.5 Hz), 1.14 (d, 3 H, J = 6.5 Hz).

Methyl *O*-(α-D-Galactopyranosyl)-(1→2)-*O*-[3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-(1→3)]-*O*-(α-D-mannopyranosyl)-(1→4)-*O*-(α-L-rhamnopyranosyl)-(1→3)-α-D-galactopyranoside (5). The impure methyl glycoside **40** was dissolved in methanol (5 mL), a small piece of sodium added, and the reaction stirred for 16 h. The solution was neutralized and concentrated, and the residue was purified by chromatography on Iatrobeads (60:35:5 CH_2Cl_2:CH_3OH:H_2O). The product was then dissolved in water, filtered, and lyophilized to provide the product **5** (37 mg, 73% from **39**) as a fluffy white solid: $[\alpha]_D$ +93.9° (c 0.2, H_2O); R_f 0.29 (60:35:5 CH_2Cl_2:CH_3OH:H_2O); ^{1}H NMR (D_2O) δ_H 5.32 (d, 1 H, $J_{1C,2C}$ = 1.5 Hz, H-1C), 5.16 (d, 1 H, $J_{1D,2D}$ = 4.0 Hz, H-1D), 5.10 (d, 1 H, $J_{1E,2E}$ = 4.0 Hz, H-1E), 5.03 (d, 1 H, $J_{1B,2B}$ = 2.0 Hz, H-1B), 4.36 (d, 1 H, $J_{1A,2A}$ = 8.0 Hz, H-1A), 4.12 (dq, 1 H, $J_{4E,5E}$ = 11.5 Hz, $J_{5E,6E}$ = 6.5 Hz, H-5E), 3.67−4.05 (m, 22H, H-3A, H-4A, H-5A, H-6A, H-6'A, H-2B, H-3B, H-5B, H-2C, H-3C, H-4C, H-5C, H-6C, H-6'C, H-2D, H-3D, H-4D, H-5D, H-6D, H-6'D, H-2E, H-4E), 3.61 (dd, 1 H, $J_{1A,2A}$ = 8.0 Hz, $J_{2A,3A}$ = 9.5 Hz, H-2A), 3.58 (s, 3 H, OCH_3), 3.55 (t, 1 H, $J_{3B,4B}$ = $J_{3B,4B}$ = 9.5 Hz, H-6B), 1.94−2.02 (m, 2H, H-3E$_{eq}$, H-3E$_{ax}$), 1.33 (d, 3 H, $J_{5B,6B}$ = 6.5 Hz, H-6B), 1.18 (d, 3 H, $J_{5E,6E}$ = 6.5 Hz, H-6E); ^{13}C NMR ($CDCl_3$) δ_C 104.56 (C-1A, $^1J_{C,H}$ = 160.8 Hz), 103.05 (C-1B, $^1J_{C,H}$ = 172.0 Hz), 102.17 (C-1D, $^1J_{C,H}$ = 171.1 Hz), 101.46 (C-1E, $^1J_{C,H}$ = 171.5 Hz), 100.63 (C-1C,$^1J_{C,H}$ = 173.4 Hz), 82.47 (C-4B), 71.10 (C-2A), 67.83 (C-5E), 58.13 (OCH_3) 33.89 (C-3E), 18.07 (C-6B), 16.49 (C-6E); HR-FABMS calcd for $C_{31}H_{54}O_{23}$ $[M + H]^+$ 795.3134, found 795.3132.

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Supporting Information Available: NMR peak assignments (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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