Oligosaccharide recognition by antibodies: Synthesis and evaluation of talose oligosaccharide analogues

T.L. Lowary, E. Eichler, and D.R. Bundle

Abstract: A series of monosaccharide **(4**–**6)**, disaccharide **(3**, **7**–**12),** and trisaccharide (**13**–**15)** analogs of the native ligand **2,** which fills the binding site of monoclonal antibody Se 155.4, have been synthesized and their bioactivity measured by solid- and solution-phase assays. The syntheses of disaccharide analogs sought to replace galactose by various alkyl groups at the O-2 position of mannose. The activity of one of these O-2 alkyl analogs was 75% of that observed for the trisaccharide and points to only weak net bonding between the solvent exposed galactose residue and the antibody binding site. The synthesis of talose analogs **13** and **14**, where the mannose or galactose residues of **2** were replaced by talose produced ligands with activities from one-third to one-half of that seen for the native ligand **2**. These activity changes did not exhibit discernable correlations with the ability of talose to disrupt water of solvation.

Key words: abequose, 3,6-dideoxy-D-*xylo*-hexose, talose disaccharide and trisaccharide, antibody oligosaccharide interactions, molecular recognition of carbohydrates, water in antibody complexes, *Salmonella* LPS, monoclonal antibody Se 155.4, bacterial *O*-antigen.

Résumé : On a réalisé la synthèse d'une série de monosaccharides (**4**–**6**), de disaccharides (**3, 7**–**12**) et de trisaccharides (**13**–**15**), des analogues du ligand naturel **2** qui remplit le site de liaison de l'anticorps monoclonal Se 155.4 et on a mesuré leur bioactivité par des essais en phase solide ainsi qu'en solution. Dans les synthèses des analogues de la série des disaccharides, on a tenté de remplacer le galactose par divers groupes alkyles en position O-2 du mannose. L'activité de l'un de ces analogues O-2 alkylés est égale à 75% de celle observée pour le trisaccharide et elle suggère qu'il n'existe qu'une faible liaison nette entre le résidu de galactose exposé au solvant et le site de liaison de l'anticorps. Les synthèses des analogues **13** et **14** dans lesquels les résidus de mannose ou de galactose du composé **2** ont été remplacés par du talose conduisent à des ligands dont les activités varient entre un tiers et une demie de celle observée avec le ligand **2** naturel. Ces changements d'activité ne donnent pas lieu à des corrélations qui pourraient avoir une corrélation avec l'habilité du talose à désorganiser l'eau de solvatation.

Mots clés : abéquose, 3,6-didésoxy-D-*xylo*-hexose, disaccharide et trisaccharide du talose, interactions anticorps-oligosaccharide, reconnaissance moléculaire des hydrates de carbone, eau dans des complexes d'anticorps, *Salmonella* LPS, anticorps monoclonal Se 155.4, *O*-antigène bactérien.

[Traduit par la Rédaction]

Introduction

The binding of carbohydrates by proteins is a biologically significant event, known to play a critical role in a diverse number of physiological processes such as viral (1, 2) and bacterial (3–5) infection and inflammation arising from cell adhesion (6–9). Consequently, in recent years interest in developing oligosaccharide-based therapeutics that inhibit carbohydrate–protein recognition has increased (3, 10, 11). However, to realize the potential of carbohydrate-based drugs, the milli- to micromolar K_ds characteristic of sugar–protein interactions must be improved (enhanced). This in turn requires a deeper appreciation of the origins of the free energy of binding. A significant body of three-dimensional structural data has been accumulated for oligosaccharide–protein complexes (12, 13). Despite supporting studies by NMR and thermodynamic measurements, the relative importance of competing processes that contribute to ΔG remains a subject of controversy (14, 15). Recent work suggests that solvation effects may make a far greater contribution to ΔG then was previously realized (16, 17). Possibly linked to the role of water is the observation by Lemieux that modification of functional groups located at or near the periphery of oligosaccharide–protein complexes can result in large swings in the enthalpy and entropy of binding, while the free energy changes by only small values. This observation led to

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We dedicate this paper to the memory of Professor Raymond U. Lemieux.

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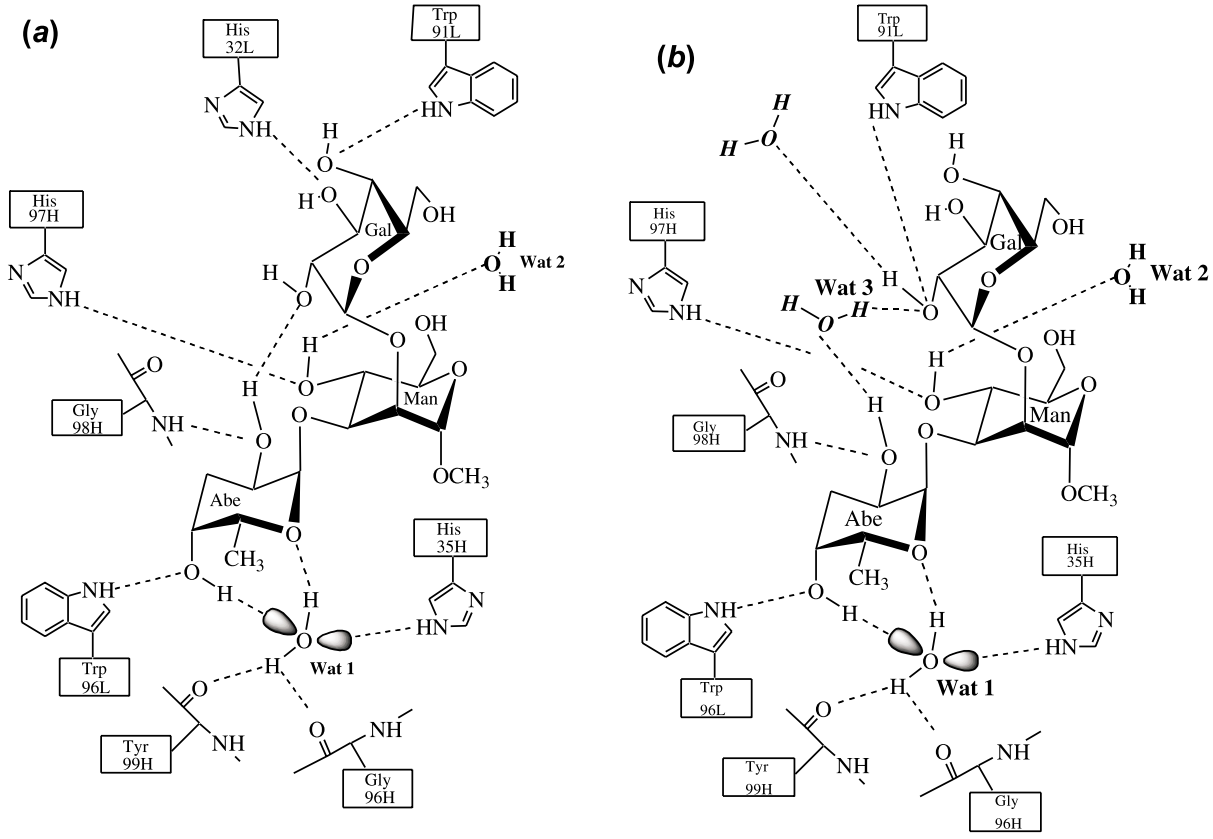
Fig. 1. (*a*) Bound conformation I (20) with a direct Abe O-2 to Man O-2 H-bond; (*b*) bound conformation II (21) with a water mediated Abe O-2 to Man O-2 H-bond. Note also the different H-bonding between the antibody and the galactose residue.



the proposal (18) (so far not realized) that significant gains in free energy might be achieved by concentrating on modification of groups in these positions. Here we focus on the synthesis of a carbohydrate epitope that should significantly disrupt structure of solvent, at least about the unbound carbohydrate ligand.

For this purpose we chose as a model system the monoclonal antibody Se 155.4 which recognizes a bacterial lipopolysaccharide antigen via the Gal[Abe]Man trisaccharide epitope (**2**). It is part of the tetrasaccharide α-D-Gal*p*-(1→2)[α-D-[Abe*p*-(1→3)]-α-D-Man*p*-(1→4)-α-L-Rha*p* (**1**) that comprises the repeating unit of the *O*-polysaccharide component of LPS (19). The structural (20, 21) and energetic (22–24) aspects of antigen binding to Se 155.4 have been well characterized, and an efficient *Escherichia coli* expression system has permitted extensive binding site mutagenesis (25) and antibody engineering studies (26, 27).

Functional group replacements of hydroxyl groups of the mannose (Man) and galactose (Gal) residues are reported here together with modification of the abequose (Abe) residue. The structural changes of the epitope are designed to probe the relative importance of hydrogen groups that are accessible to solvent water. The abequose C-2 hydroxyl group accepts a hydrogen bond from Gly 98 and donates a hydrogen bond to the Gal C-2 hydroxyl either directly (Fig. 1*a*) or via a water molecule (Fig. 1*b*). At the monosaccharide level, this was probed by methylation (**5**) or inversion of configuration (**6**) (Fig. 2). The relative importance of hydrogen bonds to the Man O-4 and Gal O-2 centres in trisaccharide **2** were investigated by synthesis of oligosaccharides in which a mannose or galactose residue is replaced by the corresponding talopyranoside: disaccharides **11** and **12** and trisaccharides **13** and **14** (Fig. 2). An additional rationale for investigating the activity of talopyranose containing structures derives from the observation that talose, more than other hexoses, disrupts the structure of water of solvation (28–31). Recently, the importance of solvent effects on protein binding of amphiphilic ligands has received attention (15, 32) and has been shown to make a large contribution to ΔG via enthalpic and entropic terms (16). Further information about the importance of the galactosyl residue in **2** was provided by the replacement of this moiety with small alkyl chains in compounds **7**–**10** (Fig. 2).

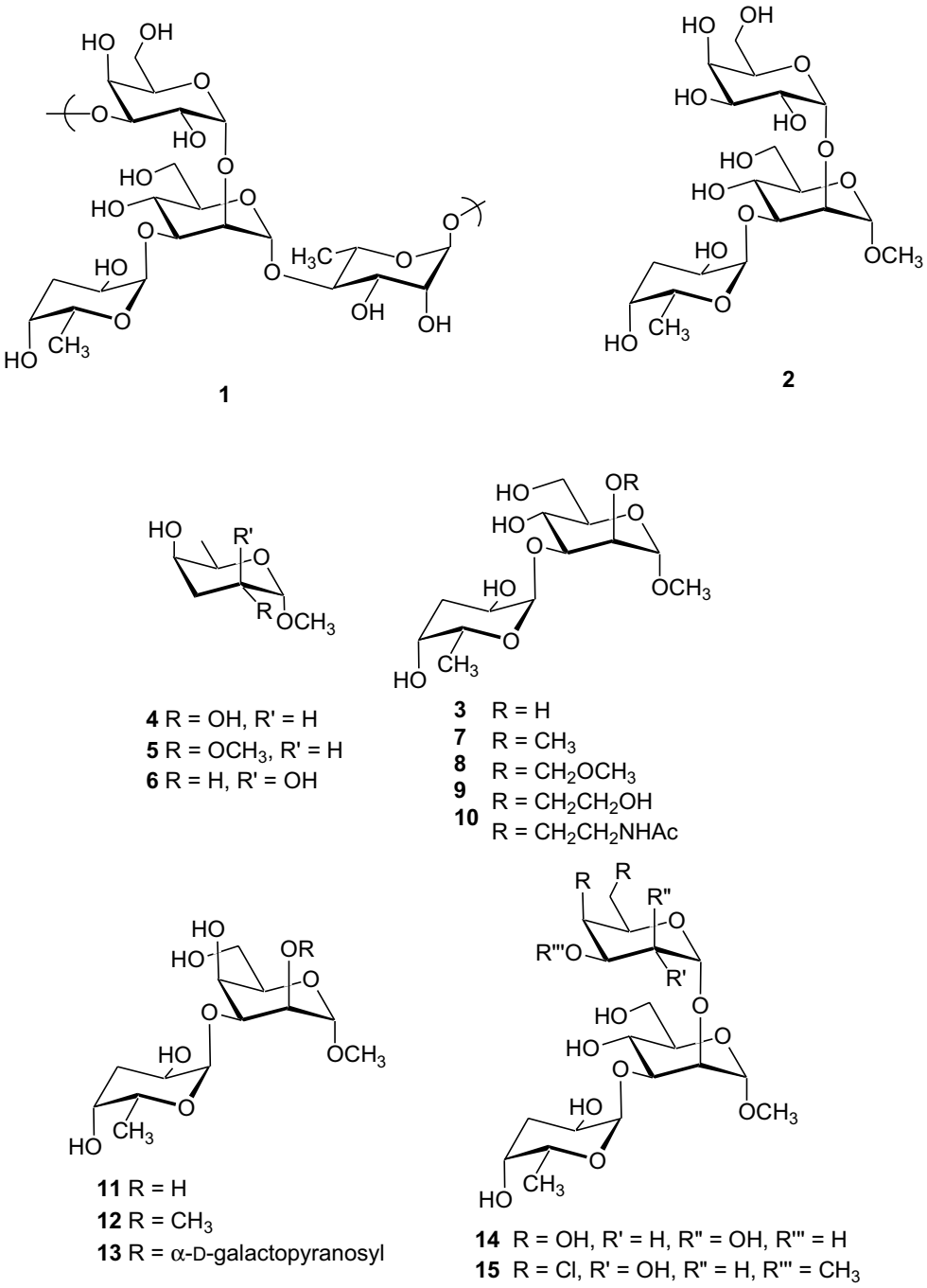
The results also raise questions about the strength of hydrogen bonds between protein and solvent exposed ligand-OH groups, the existence of which is based on the proximity and geometry of heavy atoms observed in high resolution crystal structures (20, 21). Two such hydrogen bonds involve the Gal O-3 and Gal O-4 atoms. Replacement of these hydroxyl groups by -OMe and -Cl, as in compound **15**, should abolish the hydrogen bond donor capability of the functionalities (33).

Results and discussion

Synthesis of methyl 2-*O*-methyl-3,6-dideoxy-α-D-*xylo*-hexopyranoside (5)

Treatment of methyl 3,6-dideoxy-α-D-*xylo*-hexopyranoside (**4**) (34) with barium oxide and a limiting amount of methyl iodide provided, in 45% yield, the 2-*O*-methyl derivative **5**.

Fig. 2. Tetrasaccharide repeating unit of the *Salmonella* LPS (**1**) and the native trisaccharide epitope (**2**). Synthetic targets **3**–**15**.



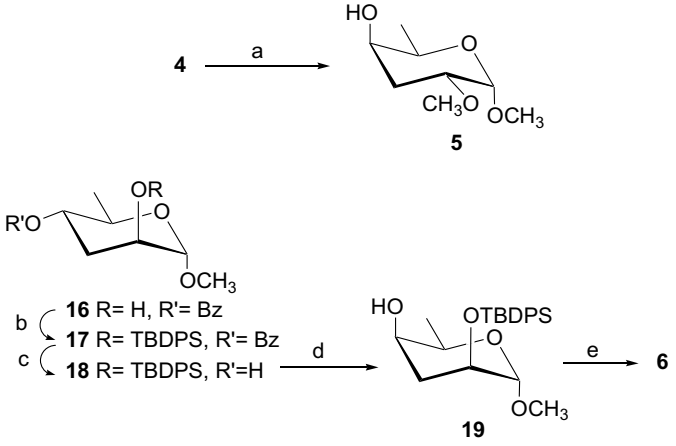
The regiochemistry of methylation was established by comparing the ^{1}H NMR chemical shifts of product **5** with those of starting material **4** (Scheme 1).

Synthesis of methyl 3,6-dideoxy-α-D-*lyxo*-hexopyranoside (6)

Treatment of methyl 3,6-dideoxy-D-*arabino*-hexopyranoside (**16**) (35) with *tert*-butyldiphenylsilyl chloride in pyridine with catalysis by DMAP resulted in the formation of the silyl ether **17** in 80% yield. Silylation of this alcohol proved to be extremely sluggish, possibly owing to steric hindrance resulting from the size of the silyl protecting group. Consequently, attempts were made to prepare the less bulky *tert*-butyldimethylsilyl ether. However, protection with this group was equally slow and this approach was therefore abandoned. It was hoped that a large protecting group on O-2 would facilitate the stereoselectivity of a later reduction (see below) and for this reason the use of smaller protecting groups was not investigated.

Subsequent treatment of **17** with sodium methoxide to remove the benzoate ester provided alcohol **18** in 94% yield (Scheme 1). The stereochemistry at C-4 was then inverted, first by oxidation with pyridinium chlorochromate and then by reduction with sodium borohydride, to provide, in 76% yield over the two steps, the 3,6-dideoxy-D-*lyxo*-hexopyranoside derivative **19**. The reduction was not, however,

Scheme 1. (*a*) CH_3I, BaO, $Ba(OH)_2$, DMF; (*b*) TBDPSCI, pyridine, DMAP; (*c*) $NaOCH_3$, CH_3OH; (*d*) PCC, CH_2Cl_2, then $NaBH_4$, CH_3OH; (*e*) TBAF, THF.



completely stereoselective and thus a small amount (16%) of methyl-3,6-dideoxy-D-*arabino*-hexopyranoside (**18**) was also obtained. Removal of the silyl ether in **19** with tetrabutylammonium fluoride provided the desired product **6** in 95% yield. Interestingly, compound **6** is a volatile liquid; attempts to dry the compound while heating under vacuum resulted in complete evaporation overnight.

Synthesis of 2-*O*-alkylated disaccharides (Scheme 2) (7–10)

Methylation of the previously reported (36) disaccharide **20** provided methyl ether **21** in 87% yield. Hydrogenation of the benzyl protecting groups provided the deprotected disaccharide **7** (66%).

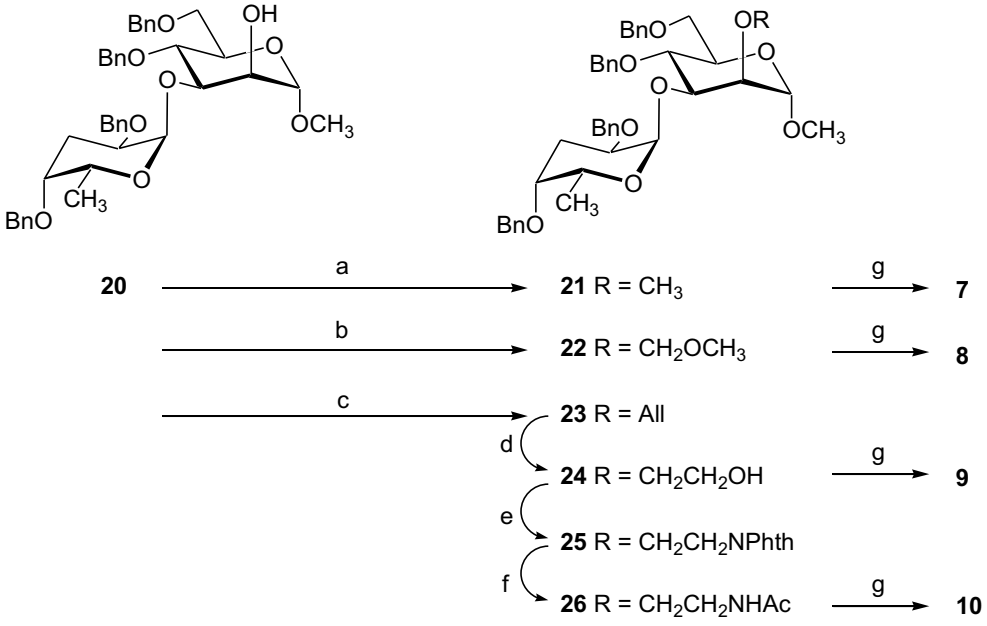
The 2-methoxymethyl derivative **8** could be prepared after prolonged reaction of disaccharide alcohol **20** with chloromethyl methyl ether. The MOM-protected disaccharide **22** was obtained in 80% yield and then converted to the target compound **8** by hydrogenation (88% yield).

Protection of **20** as a 2-*O*-allyl ether was achieved by reaction with allyl bromide to give **23** (92%). Ozonolysis of the allyl double bond and reductive work-up with sodium borohydride gave, in 70% yield, the 2′-hydroxyethyl ether disaccharide **24**. A portion of this alcohol was then deprotected (H_2, Pd/C) to give disaccharide **9** (74%). The remainder of alcohol **24** was converted to the phthlamido derivative **25** under Mitsunobu conditions (37) in 91% yield. Removal of the phthalimide group with hydrazine acetate and acetylation of the resulting amino group gave the protected *N*-acetyl disaccharide **26**. After deprotection, the disaccharide **10** was obtained in 62% yield from **25**.

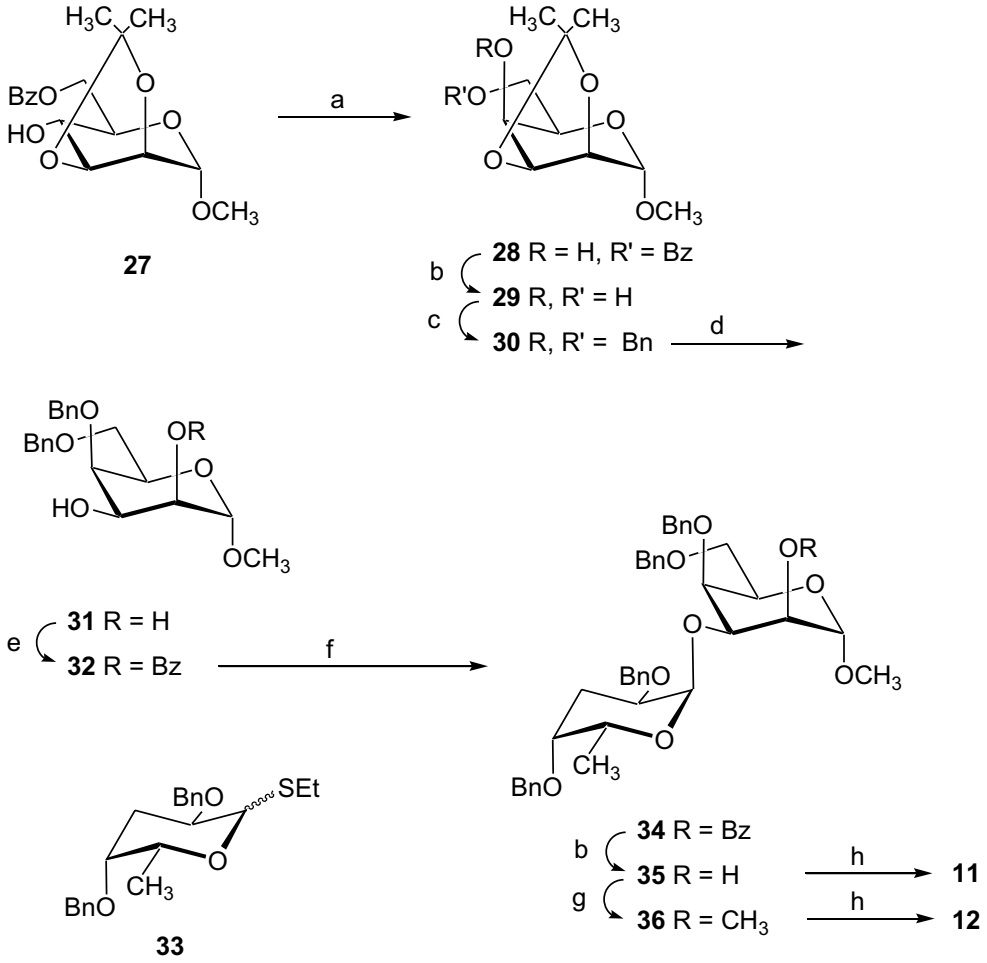
Synthesis of talopyranosyl-containing disaccharides (Scheme 3) (11, 12)

Preparation of the two disaccharides containing talopyranosyl residues began with the known mannoside **27** (38), which was subjected to an oxidation–reduction protocol to provide the talopyranoside alcohol **28** in 85% yield. The benzoate ester was removed by transesterification (92%) and the resulting diol protected as benzyl ethers (97%) to give **30**. Hydrolysis of the isopropylidene acetal from **30** gave methyl 4,6-di-*O*-benzyl-talopyranoside (**31**) in 91% yield. Transient protection of the diol as an orthobenzoate was achieved by reaction of **31** with trimethylorthobenzoate and was followed immediately by treatment with acid to afford the 2-*O*-benzoate **32** (81%). Glycosylation of **32** with the abequose thioglycoside **33** (39) provided the fully protected disaccharide **34** in 83% yield. Treatment of **34** with sodium methoxide gave the disaccharide alcohol **35** in 96% yield. A portion of this alcohol was hydrogenated to provide disaccharide **11** (84%). Methylation of the remainder of **35**

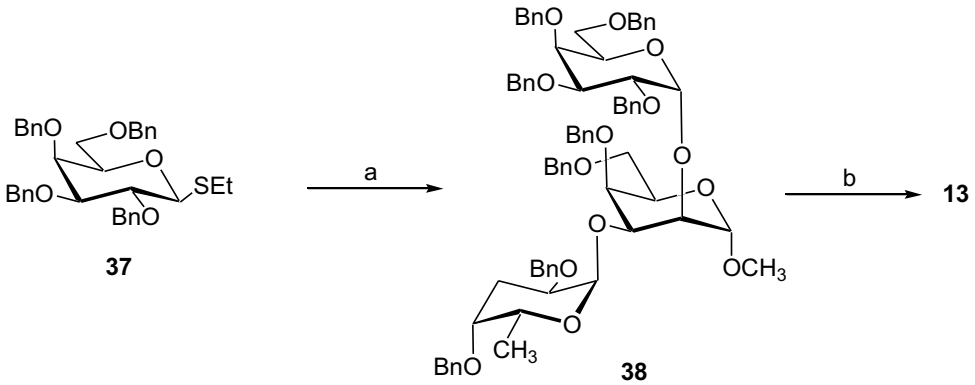
Scheme 2. (*a*) CH_3I, NaH, DMF; (*b*) MOMCl, Hunig's base, acetone; (*c*) AllBr, NaH, DMF; (*d*) O_3, CH_2Cl_2–CH_3OH, then $NaBH_4$; (*e*) $(Ph_3)_3P$, DEAD, phthalimide, THF; (*f*) H_2NNH_2–HOAc, CH_3OH, then Ac_2O, pyridine; (*g*) H_2, 10% Pd/C, HOAc.



Scheme 3. (*a*) PCC, CH_2Cl_2, then $NaBH_4$, CH_3OH; (*b*) $NaOCH_3$, CH_3OH; (*c*) BnBr, NaH, DMF; (*d*) 80% HOAc–H_2O; (*e*) $PhC(OCH_3)_3$, *p*-TsOH, CH_2Cl_2, then 80% HOAc–H_2O; (*f*) **33**, NIS, AgOTf, CH_2Cl_2; (*g*) CH_3I, NaH, DMF; (*h*) H_2, 10% Pd/C, HOAc.



Scheme 4. (*a*) **35**, NIS, AgOTf, CH_2Cl_2; (*b*) H_2, 10% Pd/C, HOAc.



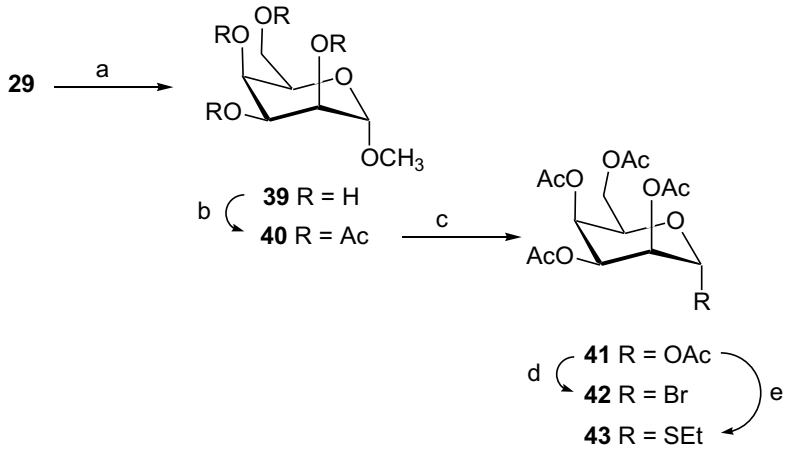
gave the 2-*O*-methyl disaccharide **36** (90%), which was deprotected by hydrogenation to disaccharide **12** in 78% yield.

Synthesis of talopyranosyl-containing trisaccharides (13, 14)

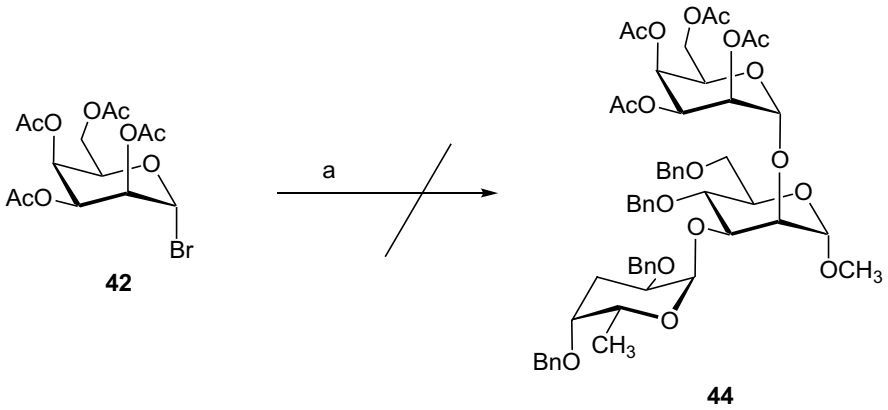
Alcohol **35** was glycosylated with the galactose thioglycoside **37** (40) to provide the trisaccharide **38** in modest (35%) yield. The desired product, **13**, was obtained in 86% yield upon hydrogenation (Scheme 4).

The synthesis of trisaccharide **14** required first the preparation of a suitable talopyranosyl donor that could be coupled to disaccharide alcohol **20**. To this end, the acetal protected methyl talopyranoside **29** was converted to methyl α-D-talopyranoside (**39**) by acid hydrolysis (Scheme 5). Acetylation then gave **40** in 76% yield (from **29**). Acetolysis provided the peracetate **41** (41) (95%), which in turn was

Scheme 5. (*a*) 95% TFA–H_2O; (*b*) Ac_2O, pyridine; (*c*) Ac_2O, H_2SO_4; (*d*) 48% HBr–HOAc, Ac_2O; (*e*) EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2.



Scheme 6. (*a*) **20**, AgOTf, collidine, CH_2Cl_2.



converted to the unstable talosyl-bromide **42** in quantitative yield. Unfortunately, when the disaccharide acceptor **20** was treated with an excess of bromide **42**, no trisaccharide product **44** could be isolated (Scheme 6). Decomposition of the bromide upon addition of the promoter (AgOTf) was virtually instantaneous. In hopes of circumventing this problem, attempts were made to prepare the more stable thioglycoside donor **43** from the peracetate using ethanethiol and boron trifluoride etherate. These attempts failed as well; despite prolonged reaction times and elevated temperatures, only small amounts (<10%) of **43** could be obtained. Therefore, another route to a more stable talopyranose donor was investigated.

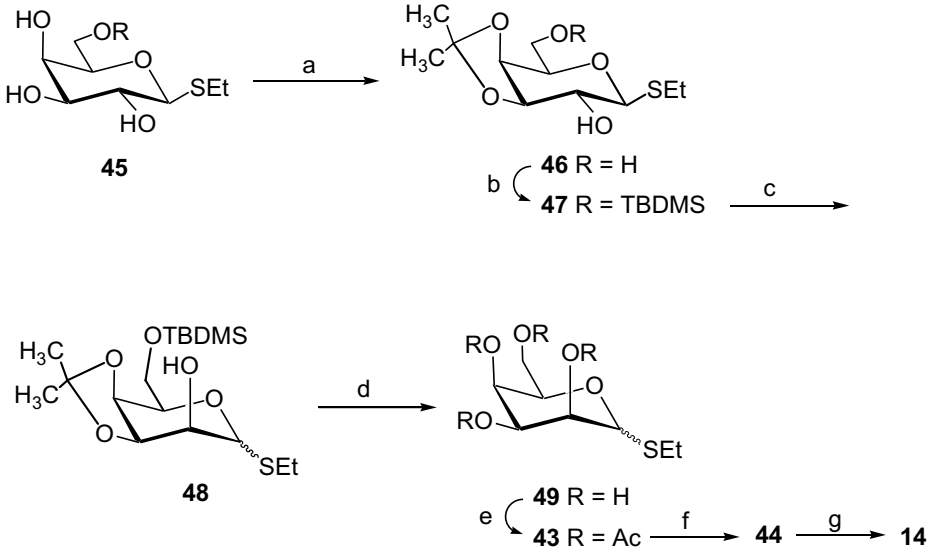
Acetonation of galactoside **45** (42) with dimethoxypropane provided, in 66% yield, **46** (Scheme 7). Regioselective protection of this acetonide as a 6-*O*-silyl ether (**47**) could be achieved in 85% yield. Oxidation of the C-2 hydroxyl group under Swern conditions and subsequent reduction with sodium borohydride gave, in 85% yield, an anomeric mixture of thioglycosides **48** with the talo-configuration. Presumably the basic conditions of the oxidation resulted in the anomerization of the product ketone. Removal of the isopropylidene and silyl protecting groups was achieved by acid hydrolysis to give ethyl 1-thio-talopyranoside (**49**) which was immediately acetylated to give thioglycoside **43** in 89% yield. Either anomer of **43** could be used in the ensuing glycosylation reaction. When the acceptor **20** was treated with the glycosyl donor **43**, trisaccharide **44** was obtained in 47% yield. Final deprotection of **44** by transesterification and hydrogenation afforded the desired trisaccharide **14** (87%) (Scheme 7).

Synthesis of the dichlorogalactosyl containing trisaccharide (15) (Scheme 8)

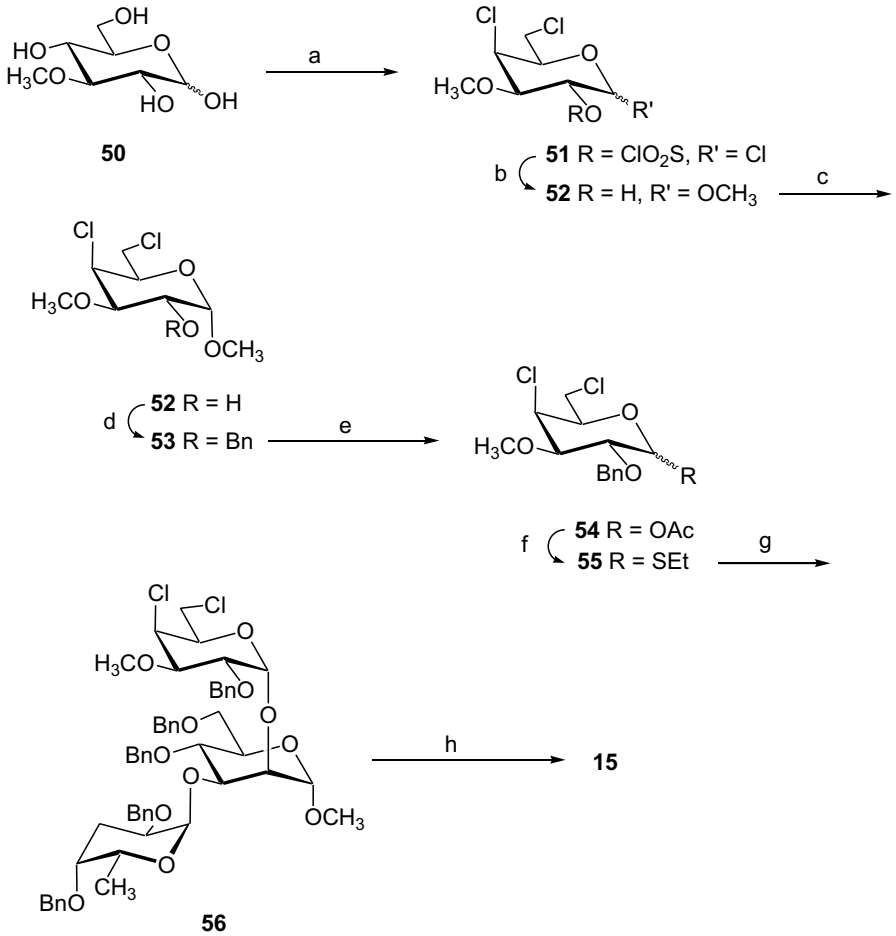
Synthesis of the galactose thioglycoside donor **55** required for the preparation of trisaccharide **15**, began with the treatment of 3-*O*-methyl glucose (**50**) (43) with sulfuryl chloride. The dichlorinated galactosyl chloride **51** was obtained as a mixture of anomers (1:1.7 (α:β), total yield 65%). Conversion to the methyl glycoside and concurrent removal of the chlorosulfate group gave **52** as an anomeric mixture of methyl glycosides (1.7:1 (α:β), total yield 67%). Proceeding only with the α-anomer, the hydroxyl group in glycoside **52** was protected as a benzyl ether (71%) and then **53** was subjected to acetolysis affording **54** in an 80% yield. Reaction of acetate **54** with ethanethiol gave the desired thioglycoside **55** (42%). Finally, glycosylation of disaccharide alcohol **20** with **55** provided the trisaccharide **56** (73%). The target trisaccharide **15** was obtained in 66% yield upon hydrogenation.

Talopyranosides in the $^4C_1$ conformation experience a strong destabilizing interaction between axial hydroxyl groups at C-2 and C-4. However, adoption of the $^1C_4$ chair is not likely, since an even stronger destabilizing interaction

Scheme 7. (*a*) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, CH_3CN, then CH_3OH, HOAc; (*b*) TBDMSCI, DMAP, pyridine; (*c*) $(CO)_2Cl_2$, DMSO, Et_3N, then $NaBH_4$, CH_3OH; (*d*) 80% HOAc–H_2O; (*e*) Ac_2O, pyridine; (*f*) **20**, NIS, AgOTf, CH_2Cl_2; (*g*) $NaOCH_3$, CH_3OH, then H_2, 10% Pd/C, HOAc.

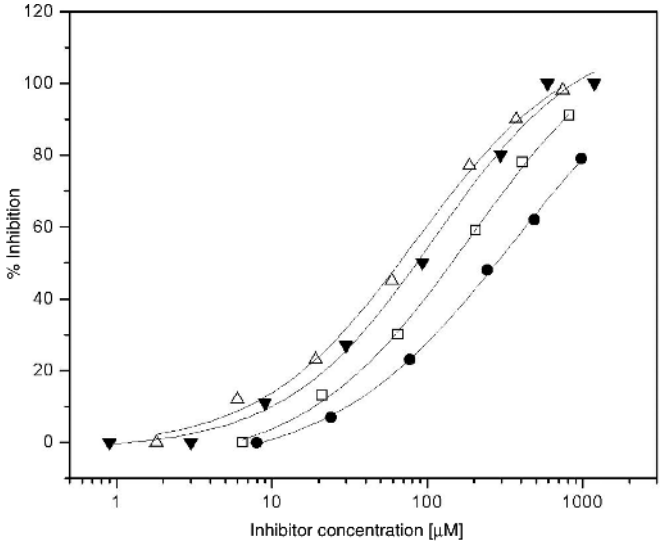


Scheme 8. (*a*) $SOCl_2$, pyridine, $CHCl_3$; (*b*) I_2, CH_3OH, then $NaOCH_3$, CH_3OH; (*c*) anomer separation; (*d*) BnBr, NaH, DMF; (*e*) Ac_2O, HOAc, H_2SO_4; (*f*) EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (*g*) **20**, NIS, AgOTf, CH_2Cl_2; (*h*) H_2, 10% Pd/C, HOAc.



then arises between axial substituents at C-3 and C-6. Distortion of the $^4C_1$ chair to skew conformations could occur and it is likely that such conformations could be readily sampled. Coupling constants (^3J) for the $^4C_1$ chair are expected

Fig. 3. Solid-phase inhibition assays for selected compounds. Trisaccharide **15** (△), trisaccharide **13** (□), disaccharide **7** (▼), disaccharide **10** (●).



to be small since there are no vicinal diaxial hydrogens. Flattening of the ring or skewing would lead to high ^3J values as neighbouring protons change from ~60° toward 0°. Observed values, especially for $J_{2,3}$ and $J_{3,4}$ show no clear trend toward such larger coupling constants. In several instances these coupling constants are lower than the expected 3–5 Hz for equatorial–axial hydrogens. A complete analysis of this conformational issue is beyond the scope of this paper, but there is no strong evidence to suggest that the α-talopyranosides reported here adopted conformations that deviate significantly from the $^4C_1$ chair.

The activity of the synthetic mono- (**4**–**6**), di- (**3**,**7**–**12**) and trisaccharides (**13**–**15**) as inhibitors of antibody binding were initially evaluated in a previously described solid-phase binding assay (24, 44). In brief, affinity purified Se 155.4 antibody is absorbed onto microtitre plates and the binding of biotinylated *O*-polysaccharide antigen to the solid-phase antibody is measured in the presence and absence of inhibitors. The data for representative oligosaccharides are shown (Fig. 3). The association constants were determined by titration microcalorimetry (Table 1) for all compounds except **6** and **15**[2]. Data for compounds **3**–**5** and **8** are taken from ref. 24 and were determined at an earlier date and on different equipment. Disaccharide **7** (^{13}C labeled in the 2-*O*-methyl group) has been used to derive kinetic data for ligand antibody interactions and to observe ligand–protein NOEs (45).

A detailed analysis of the full calorimetry data will be reported together with molecular modeling[2]. However, several points emerge from the data (Table 1). The relatively high activities of 2-*O*-alkylated disaccharides **7** and **9** are consistent with earlier interpretations that in solution any hydrogen bonds between the galactose residue and the antibody site are very weak and of little net benefit. For disaccharide analogs substitution of mannose by talose results in a five- to 10-fold loss of binding energy, which correlates with the important hydrogen bond from a histidine residue to Man O-4 (Fig. 1). When talose is substituted for mannose and galactose in trisaccharides **13** and **14** a two- to threefold loss of binding occurs. As will be reported elsewhere, modeling of the antibody complex with each of these trisaccharides shows that the hydrogen bonding patterns of Fig. 1 can be maintained with only small movements about the glycosidic linkages. It is also apparent that initial hopes that the talose analogs would provide readily discernable trends to correlate with solvent reorganization about the ligand antibody complex have not been realized.

Table 1. Association constants and relative inhibitory power of the mono-, di-, and trisaccharides **3**–**15**.

Compound	$K_a \times 10^5$ (M^{-1})[a]	Relative inhibitory power[b]
2	2.1	100
3	0.24[c]	11
4	0.015[c]	0.7
5	0.019[c]	0.9
6	–ve	Inactive
7	1.43	68
8	0.69[c]	32
9	1.58	75
10	0.55	26
11	0.05	2
12	0.14	6
13	0.70	33
14	1.17	55
15	~1.5–1.8[d]	71–85

[a]Determined by calorimetry; the standard deviation for duplicate measurements of *K* was never greater than ±2%.
[b]Inhibition potency of **2** set as 100.
[c]Taken from ref. 24 and determined by calorimetry.
[d]Value taken from solid-phase immunoassay; estimated from the IC_{50} (44) determined with an accuracy of ±5%.

Experimental

Optical rotations were measured with a PerkinElmer 241 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 (40–60 μM, E. Merck, Darmstadt). Millex-GV (0.22 μM) filter units were from Millipore (Mississauga, ON). ^1H NMR were recorded at 360 MHz (Bruker AM-360) or at 500 MHz (Varian Unity 500) with either internal $CHCl_3$ (δ: 7.24, $CDCl_3$) or internal acetone (δ: 2.225, D_2O). ^{13}C NMR were recorded either at 75.5 MHz (Bruker AM-300) or 125.7 MHz (Varian Unity 500) with internal $CHCl_3$ (δ: 77.00, $CDCl_3$) or internal acetone (δ: 37.01, D_2O). ^1H NMR data are reported as though they were first order. Proton and carbon resonances for **7** and **9**–**15** were assigned using ^1H-^1H and ^1H-^{13}C correlation 4 carried out at room temperature. Organic solutions were

[2]M. Warwas and D.R. Bundle. Unpublished results.

dried prior to concentration under vacuum at <40°C (bath). Microanalyses were carried out by the analytical services at this department and all samples, except **6**, submitted for elemental analyses were dried overnight under vacuum with phosphorus pentoxide at 56°C (refluxing acetone). Compound **6** was dried at room temperature. High resolution mass spectra (HR-MS) of **6** were recorded on a Kratos MS-50 instrument using electron-impact ionization. For other compounds, FAB-HR-MS were recorded on samples suspended in Cleland's matrix using a Kratos MS-50B instrument with xenon as the bombarding gas. Inhibition assays were performed in 96 well microtiter plates as previously described (24), and inhibition curves were drawn using the software package Origin 5.0 (OriginLab, Northampton, MA). Titration microcalorimetry was performed as previously described (22, 24).

Methyl 2-*O*-methyl-3,6-dideoxy-α-D-*xylo*-hexopyranoside (5)

To a stirred suspension of **4** (33) (350 mg, 2.16 mmol), barium oxide (1.32 g, 8.64 mmol), and barium hydroxide octahydrate (350 mg, 1.08 mmol) in DMF (10 mL) was added methyl iodide (151 μL, 2.38 mmol). The reaction was stirred for 4 h, diluted with CH_2Cl_2, and filtered through Celite. The filtrate was concentrated under reduced pressure, diluted with CH_2Cl_2, and washed successively with saturated solutions of $KHCO_3$ and NaCl. After drying ($MgSO_4$) and evaporation of the solvent, the product was chromatographed (hexane–EtOAc, 1:1) to provide **5** (170 mg, 45%) as an oil. $[\alpha]_D$ +118.7 (*c* 1.7, $CHCl_3$). R_f = 0.40 (hexane–EtOAc, 1:3). The regiochemistry of methylation was established by ^{1}H decoupling experiments. ^{1}H NMR ($CDCl_3$) δ: 4.69 (d, $J_{1,2}$ = 3.0 Hz, 1H, H-1), 3.83 (q, $J_{5,6}$ = 6.5 Hz, 1H, H-5), 3.67 (br. s, 1H, H-4), 3.57 (ddd, $J_{2,3eq}$ = 5.0 Hz, $J_{2,3ax}$ = 12.0 Hz, 1H, H-2), 3.35 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 2.01 (ddd, $J_{3ax,3eq}$ = 13.0 Hz, $J_{2,3eq}$ = 5.0 Hz, $J_{3eq,4}$ = 3.0 Hz, H-3eq), 1.86 (ddd, $J_{3ax,4}$ = 3.0 Hz, 1H, H-3ax), 1.11 (d, $J_{5,6}$ = 6.5 Hz, 3H, H-6). Anal. calcd. for $C_8H_{16}O_4$ (176.21): C 54.53, H 9.15; found: C 54.10, H 9.29.

Methyl 4-*O*-benzoyl-2-*O*-*tert*-butyldiphenylsilyl-3,6-dideoxy-α-D-*arabino*-hexopyranoside (17)

Alcohol **16** (34) (1.0 g, 3.76 mmol) was dissolved in pyridine (25 mL) and then DMAP (500 mg) was added followed by *tert*-butyldiphenylsilyl chloride (2.0 mL, 7.9 mmol). The reaction was heated to 60°C and stirred for 6 days and then the solution cooled and partitioned between water and CH_2Cl_2. The organic layer was then washed in succession with 0.5 N HCl, water, and a saturated solution of NaCl, and then dried (Na_2SO_4). After evaporation, chromatography (pentane–ethyl acetate, 9:1) gave the product **17** (1.50 g, 80%) as an oil. $[\alpha]_D$ +83.2 (*c* 0.9, $CHCl_3$). R_f = 0.53 (pentane–ethyl acetate, 9:1). ^{1}H NMR ($CDCl_3$) δ: 7.30-8.05 (m, 15H, Ph), 5.32 (ddd, $J_{3ax,4}$ = 13.0 Hz, $J_{3eq,4}$ = 4.5 Hz, $J_{4,5}$ = 10.0 Hz, 1H, H-4), 4.39 (br. s, 1H, H-1), 3.90–3.98 (m, 2H, H-2, H-5), 3.28 (s, 3H, OCH_3), 2.20 (dt, $J_{3ax,3eq}$ = 12.5 Hz, $J_{2,3eq}$ = 4.5 Hz, H-3eq), 1.86 (ddd, $J_{3ax,4}$ = 13.0 Hz, $J_{2,3ax}$ = 3.0 Hz, 1H, H-3ax), 1.33 (d, $J_{5,6}$ = 6.5 Hz, 3H, H-6), 1.17 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$) δ: 165.57 (C=O), 100.20 (C-1), 54.74 (OCH_3), 32.45 (C-3), 26.98 (C(*C*H_3)$_3$), 19.26 (*C*(CH$_3$)$_3$), 18.07 (C-6). Anal. calcd. for $C_{30}H_{36}O_5Si$ (504.70): C 71.39, H 7.19; found: C 71.59, H 7.31.

Methyl 2-*O*-*tert*-butyldiphenylsilyl-3,6-dideoxy-α-D-*arabino*-hexopyranoside (18)

Benzoate **17** (950 mg, 1.88 mmol) was dissolved in CH_3OH (50 mL) and a small piece of sodium was added. After stirring for 36 h, the reaction was quenched by adding acetic acid until the pH was neutral. The solvent was evaporated and then the residue chromatographed (pentane–ethyl acetate, 6:1) to give the product **18** (710 mg, 94%) as an oil. $[\alpha]_D$ +19.1 (*c* 0.8, $CHCl_3$). R_f = 0.20 (pentane–ethyl acetate, 6:1). ^{1}H NMR ($CDCl_3$) δ: 7.20–7.70 (m, 10H, Ph), 4.30 (br. s, 1H, H-1), 3.88–3.92 (m, 1H, H-2), 3.73–3.84 (m, 1H, H-4), 3.49–3.58 (m, 1H, H-5), 3.21 (s, 3H, OCH_3), 1.93 (ddt, $J_{2,3eq}$ = 3.5 Hz, $J_{1,3eq}$ = 1.0 Hz, H-3eq), 1.64 (ddd, $J_{3ax,3eq}$ = 13.0 Hz, $J_{3ax,4}$ = 11.5 Hz, $J_{2,3ax}$ = 2.5 Hz, 1H, H-3ax), 1.39 (d, $J_{4,4\text{-OH}}$ = 6.0 Hz, 1H,), 1.34 (d, $J_{5,6}$ = 6.5 Hz, 3H, H-6), 1.10 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$) δ: 99.96 (C-1), 54.55 (OCH_3), 35.70 (C-3), 26.98 (C(*C*H_3)$_3$), 19.25 (*C*(CH$_3$)$_3$), 17.93 (C-6). Anal. calcd. for $C_{23}H_{32}O_4Si$ (400.59): C 68.96, H 8.05; found: C 68.60, H 7.85.

Methyl 3,6-dideoxy-2-*O*-*tert*-butyldiphenylsilyl-α-D-*lyxo*-hexopyranoside (19)

Compound **18** (674 mg, 1.61 mmol) was dissolved in CH_2Cl_2 (30 mL) and stirred with crushed 4 Å molecular sieves (500 mg) for 15 min. Pyridinium chlorochromate (1.74 g, 8.05 mmol) was added and the reaction stirred for 4 h at which point there was a complete conversion to the ketone (R_f = 0.89, pentane–ethyl acetate, 4:1). The reaction was filtered through Celite and washed with water and a saturated solution of NaCl and then dried (Na_2SO_4). After evaporation of the organic layer, the resulting residue was dried for 1 h under vacuum. The black solid was then dissolved in CH_3OH (50 mL) and $NaBH_4$ (100 mg, 2.66 mmol) added. After stirring for 10 min, the reaction was quenched by adding acetic acid until the pH was neutral. The solvent was evaporated and then the residue chromatographed (pentane–ethyl acetate, 9:1) to give the product **19** (488 mg, 76%) and some starting material **18** (108 mg, 16%) as oils. $[\alpha]_D$ –4.0 (*c* 0.9, $CHCl_3$). R_f = 0.67 (pentane–ethyl acetate, 9:1). ^{1}H NMR ($CDCl_3$) δ: 7.25–7.75 (m, 10H, Ph), 4.30 (br. s, 1H, H-1), 3.84 (dq, $J_{4,5}$ = 1.0 Hz, $J_{5,6}$ = 6.5 Hz, 1H, H-5), 3.74–3.80 (m, 2H, H-2, 4-OH), 3.45–3.52 (m, 1H, H-4), 3.16 (s, 3H, OCH_3), 2.07 (ddd, $J_{3ax,3eq}$ = 14.5 Hz, $J_{2,3ax}$ = 4.5 Hz, $J_{3ax,4}$ = 1.5 Hz, 1H, H-3ax), 1.89 (dt, $J_{2,3eq}$ = 3.0 Hz, H-3eq), 1.30 (d, $J_{5,6}$ = 6.5 Hz, 3H, H-6), 1.12 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$) δ: 100.35 (C-1), 54.76 (OCH_3), 31.71 (C-3), 26.93 (C(*C*H_3)$_3$), 19.01 (*C*(CH$_3$)$_3$), 17.09 (C-6). Anal. calcd. for $C_{23}H_{32}O_4Si$ (400.59): C 68.96, H 8.05; found: C 68.91, H 8.27.

Methyl 3,6-dideoxy-α-D-*lyxo*-hexopyranoside (6)

Silyl ether **19** (450 mg, 1.12 mmol) was dissolved in THF (7.5 mL) and then tetrabutyl ammonium flouride (2.5 mL of a 1 M solution in THF, 2.24 mmol) was added. The reaction was stirred for 30 min and then evaporated. Chromatography of the residue (pentane–ethyl acetate, 1:1) gave the product **6** (172 mg, 95%) as an oil. $[\alpha]_D$ +46.4 (*c* 0.9, H_2O). R_f = 0.34

(pentane–ethyl acetate, 1:1). ^{1}H NMR (D_2O) δ: 4.658 (br. s, 1H, H-1), 4.025 (dq, $J_{4,5}$ = 2.0 Hz, $J_{5,6}$ = 7.0 Hz, 1H, H-5), 3.72–3.74 (m, 1H, H-2), 3.72–3.70 (m, 1H, H-4), 3.420 (s, 3H, OCH_3), 2.036 (ddd, $J_{3ax,3eq}$ = 14.0 Hz, $J_{2,3a} \approx J_{3a,4}$ = 3.5 Hz, 1H, H-3ax), 1.960 (dddd, $J_{2,3eq}$ = 3.5 Hz, $J_{1,3eq}$ = 1.0 Hz, H-3eq), 1.224 (d, $J_{5,6}$ = 7.0 Hz, 3H, H-6). ^{13}C NMR (D_2O) δ: 101.463 (C-1), 68.155 (C-5), 67.868 (C-4), 66.256 (C-2), 55.614 (OCH_3), 31.523 (C-3), 16.379 (C-6). Anal. calcd. for $C_7H_{14}O_4$ (162.19): C 51.84, H 8.70; found: C 51.97, H 8.90. HRMS calcd.: 162.0892; found: 162.0886.

Methyl 3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-2-*O*-methyl-4,6-di-*O*-benzyl-α-D-mannopyranoside (21)

Sodium hydride (20 mg, 0.42 mmol, 50% dispersion in oil) was washed twice with petroleum ether under an N_2 atmosphere. The solvent was decanted and the solid suspended in DMF (4 mL). Methyl 3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-4,6-di-*O*-benzyl-α-D-mannopyranoside (35) (**20**, 102 mg, 0.15 mmol) was then added as a solid and the reaction mixture was cooled to 0°C, and methyl iodide (20 μL, 0.3 mmol) added. After 1 h the reaction was quenched by the addition of methanol and the solvent evaporated. The resulting residue was then taken up in CH_2Cl_2 and washed succesively with water, 1 N HCl, water, $NaHCO_3$, and a saturated solution of NaCl. After drying ($MgSO_4$) and evaporation of the solvent the product was purified by chromatography (hexane–EtOAc, 3:1) to give **21** (91 mg, 87%) as an amorphous solid. $[\alpha]_D$ +64.7 (*c* 0.7, $CHCl_3$). R_f = 0.45, (hexane–EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ: 7.10–7.30 (m, 20H, Ph), 5.13 (s, 1H, H-1′), 5.14 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 4.86 (br. s, 1H, H-1), 4.62, 4.57, 4.54, 4.49, 4.45, 4.41, 4.38 (7d, ^2J = 12.0 Hz, 7H, PhCH_2), 4.18 (dd, $J_{5',6'}$ = 6.5 Hz, 1H, H-5′), 4.11 (dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.5 Hz, 1H, H-3), 3.32–3.90 (m, 2H, H-2′, H-4), 3.77–3.80 (m, 1H, H-5), 3.69–3.75 (m, 2H, H-6a, H-6b), 3.64 (br. s, 1H, H-2), 3.49 (s, 3H, OCH_3), 3.48 (br. s, 1H, H-4′), 3.41 (s, 3H, OCH_3), 1.99–2.14 (m, 2H, H-3′eq, H-3′ax), 1.22 (d, $J_{5'6'}$ = 6.6 Hz, 3H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 99.26 (C-1′), 97.36 (C-1). Anal. calcd. for $C_{42}H_{50}O_9$ (698.86): C 72.18, H 7.21; found: C 72.35, H 7.27.

Methyl 3-*O*-(3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-2-*O*-methyl-α-D-mannopyranoside (7)

Disaccharide **21** (77 mg, 0.11 mmol) was dissolved in acetic acid (4 mL) and then 10% Pd/C (70 mg) was added and the reaction was stirred under an atmosphere of H_2 for 3 h. The reaction was filtered through Celite and the filtrate evaporated, coevaporating twice with toluene. Chromatography (water) on Biogel P-2 gave **7** (24.5 mg, 66%) as an amorphous white solid after lyophilization. $[\alpha]_D$ +38.1 (*c* 0.5, H_2O). ^{1}H NMR (D_2O) δ: 5.059 (d, $J_{1',2'}$ = 4.0 Hz, 1H, H-1′), 4.972 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.070 (dq, $J_{4',5'}$ = 1.0 Hz, $J_{5',6'}$ = 6.5 Hz, 1H, H-5′), 3.999 (ddd, $J_{2',3'eq}$ = 6.0 Hz, $J_{2',3'ax}$ = 12.0 Hz, 1H, H-2′), 3.87–3.91 (m, 3H, H-3, H-6a, H-4′), 3.72–3.76 (m, 2H, H-4, H-6b), 3.697 (dd, $J_{2,3}$ = 3.5 Hz, 1H, H-2), 3.650 (ddd, $J_{4,5}$ = 9.5 Hz, $J_{5,6a}$ = 2.0 Hz, $J_{5,6b}$ = 6.0 Hz, 1H, H-5), 3.477 (s, 3H, ether OCH_3), 3.434 (s, 3H, aglycon OCH_3), 1.95–2.06 (m, 2H, H-3′ax, H-3′eq), 1.193 (d, $J_{5',6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR (D_2O) δ: 101.452 (C-1′, $^1J_{C,H}$ = 169.6 Hz), 97.887 (C-1, $^1J_{C,H}$ = 170.7 Hz), 80.435 (C-2), 79.308 (C-3), 73.405 (C-5), 69.142 (C-4′), 67.759 (C-5′), 67.094 (C-4), 64.359 (C-2′), 61.682 (C-6), 58.819 (ether OCH_3), 55.724 (aglycon OCH_3), 33.755 (C-3′), 16.357 (C-6′). Anal. calcd. for $C_{14}H_{26}O_9$ (338.36): C 49.70, H 7.74; found: C 49.34, H 7.76.

Methyl 3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl-2-*O*-methoxymethyl-4,6-di-*O*-benzyl-α-D-mannopyranoside (22)

To a stirred solution of alcohol **20** (35) (68 mg, 0.1 mmol) in acetone (4 mL) was added ethyldiisopropylamine (40 μL, 0.21 mmol) and chloromethyl methyl ether (20 μL, 0.22 mmol). The reaction was stirred at room temperature for 1 h and then heated at 60°C for 48 h during which time ethyldiisopropylamine (40 μL, 0.21 mmol) and chloromethyl methyl ether (20 μL, 0.22 mmol) were added twice. The reaction was cooled, the solvent evaporated, and the crude material taken up in CH_2Cl_2, and washed succesively with water, 1 N HCl, water, $NaHCO_3$, and a saturated solution of NaCl. The organic layer was dried ($MgSO_4$) and the solvent evaporated to provide a residue that was chromatographed (hexane–EtOAc, 3:1) to give the product **22** (57.3 mg, 80%) as an oil. $[\alpha]_D$ +87.1 (*c* 0.9, $CHCl_3$). R_f = 0.35 (hexane–EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ: 7.10–7.30 (m, 20H, Ph), 5.23 (d, $J_{1',2'}$ = 3.0 Hz, 1H, H-1′), 5.12 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 4.89 (d, ^2J = 7.0 Hz, 1H, OCH_2O), 4.87 (br. s, 1H, H-1), 4.78 (d, ^2J = 7.0 Hz, 1H, OCH_2O), 4.65, 4.56, 4.54, 4.49, 4.47, 4.37, 4.36 (d, ^2J = 12.0 Hz, 7H, PhCH_2), 4.25 (dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.5 Hz, 1H, H-3), 4.08 (q, $J_{5',6'}$ = 6.5 Hz, 1H), 3.96 (t, $J_{3,4}$, $J_{4,5}$ = 9.5 Hz, 1H, H-4), 3.93 (br. s, 1H, H-2), 3.86 (ddd, $J_{2',3'eq}$ = 5.0 Hz, $J_{2',3'ax}$ = 12.0 Hz, 1H, H-2′), 3.81–3.72 (m, 3H, H-5, H-6a, H-6b), 3.40–3.45 (m, 7H, H-4′, 2 × OCH_3), 1.91–2.11 (m, 2H, H-3′eq, H-3′ax), 1.20 (d, $J_{5',6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 99.86 (OCH_2O), 98.83 (C-1′), 97.25 (C-1). Anal. calcd. for $C_{43}H_{52}O_{10}$ (728.88): C 70.86, H 7.19; found: C 70.88, H 7.26.

Methyl 3-*O*-(3,6-dideoxy-α-D-*xylo*-hexopyranosyl-2-*O*-methoxymethyl-α-D-mannopyranoside (8)

Glycoside **22** (39 mg, 0.05 mmol) was dissolved in ethanol (4 mL), and then 10% Pd/C (40 mg) was added and the reaction stirred under an atmosphere of H_2 for 24 h. At this point the reaction was still not complete and therefore additional 10% Pd/C (40 mg) and acetic acid (0.5 mL) were added. After 3 h the reaction was finished and the solution was filtered through Celite and the filtrate evaporated, coevaporating twice with toluene. Chromatography (water) on Biogel P-2 gave **8** (17.5 mg, 88%) as an amorphous white solid after lyophilization. $[\alpha]_D$ +27.7 (*c* 0.6, H_2O). ^{1}H NMR (D_2O) δ: 5.12 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 4.91 (br. s, 1H, H-1), 4.80–4.86 (m, 2H, 2 × OCH_2O), 4.06–4.00 (m, 2H, H-2′, H-5′), 3.95–3.99 (m, 2H, H-2, H-3), 3.88–3.93 (m, 2H, H-6a, H-4′), 3.84 (t, $J_{3,4} \approx J_{4,5}$ = 10.0 Hz, H-4), 3.77 (dd, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6b}$ = 6.0 Hz, 1H, H-5), 3.64–3.69 (m, 1H, H-4), 3.43 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 1.97–2.02 (m, 2H, H-3′eq, H-3′ax), 1.18 (d, $J_{5',6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR (D_2O) δ: 101.00 (C-1′), 99.83 (C-1), 97.28

(OCH_2O). Anal. calcd. for $C_{15}H_{28}O_{10}$ (368.86): C 48.91, H 7.66; found: C 48.70, H 7.53.

Methyl 2-*O*-allyl-4,6-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-α-D-mannopyranoside (23)

Disaccharide alcohol **20** (35) (500 mg, 0.73 mmol) was dissolved in DMF (20 mL) and then sodium hydride (76 mg, 2.5 mmol) was added and the reaction was stirred for 10 min. Allyl bromide (200 μL, 2.35 mmol) was then added and the solution stirred for 2 h. Methanol was added to quench the excess base and then the reaction was diluted with EtOAc and washed with water and a saturated solution of NaCl. After drying (Na_2SO_4), and solvent evaporation, the product was purified by chromatography (pentane–EtOAc, 3:1) to give **23** (488 mg, 92%) as an oil. $[\alpha]_D$ +64.3 (*c* 0.9, $CHCl_3$). R_f = 0.65 (pentane–EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ: 7.10–7.40 (m, 20H, Ph), 5.95 (dddd, $^3J_{trans}$ = 17.0 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 5.5 Hz, 1H, OCH_2CH=CH_2), 5.33 (dddd, ^2J = 1.5 Hz, 1H, OCH_2CH=CH_2), 5.12–5.19 (m, 2H, H-1′, 1 × OCH_2CH=CH_2), 5.11 (d, ^2J = 11.5 Hz, 1H, PhCH_2), 4.81 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.64, 4.54, 4.52, 4.47, 4.37, 4.36 (d, ^2J = 12.0 Hz, 7H, PhCH_2), 4.08–4.24 (m, 4H, 2 × OCH_2CH=CH_2, H-5′, H-3), 3.93 (t, $J_{3,4} \approx J_{4,5}$ = 9.0 Hz, 1H, H-4), 3.70–3.87 (m, 5H, H-2, H-5, H-6a, H-6b, H-2′), 3.43 (br. s, 1H, H-4′), 3.37 (s, 3H, OCH_3), 2.12 (dt, $J_{3'eq,3'ax}$ = 13.0 Hz, $J_{2',3'eq}$, $J_{3'eq,4'}$ = 3.5 Hz, 1H, H-3′eq), 1.96 (dt, $J_{2',3'ax}$ = 13.0 Hz, $J_{3'ax,4'}$ = 2.5 Hz, 1H, H-3′ax), 1.18 (d, $J_{5',6'}$ = 6.5 Hz, H 1H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 135.12 (OCH_2CH=CH_2), 116.50 (OCH_2CH=CH_2), 99.98 (C-1′), 98.25 (C-1), 69.42 (OCH_2CH=CH_2), 66.58 (C-6), 54.76 (OCH_3), 27.52 (C-3′), 16.56 (C-6′). Anal. calcd. for $C_{44}H_{52}O_9$ (724.89): C 72.90, H 7.23; found: C 72.95, H 7.43.

Methyl 4,6-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-2-*O*-(2′-hydroxyethyl)-α-D-mannopyranoside (24)

A solution of **23** (500 mg, 0.73 mmol) in 1:1 CH_2Cl_2:CH_3OH (20 mL) was cooled to –78°C and O_3 was bubbled through the solution until a blue color persisted. Then $NaBH_4$ (100 mg) was added and the reaction was allowed to come to room temperature. The solution was then neutralized with acetic acid, diluted with CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4), evaporated, and chromatographed (pentane–EtOAc, 1:1) to give **24** (278 mg, 70%) as an oil. $[\alpha]_D$ +65.4 (*c* 1.1, $CHCl_3$). R_f = 0.41 (pentane–EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ: 7.00–7.40 (m, 20H, Ph), 5.25 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 5.03 (d, ^2J = 11.5 Hz, 1H, PhCH_2), 4.81 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.33–4.65 (m, 7H, 7 × PhCH_2), 4.21 (dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.5 Hz, 1H, H-3), 4.07 (dq, $J_{4',5'}$ = 1.0 Hz, $J_{5',6'}$ = 6.5 Hz, 1H, H-5′), 3.99 (t, $J_{3,4} \approx J_{4,5}$ = 9.5 Hz, 1H, H-4), 3.59–3.87 (m, 9H, H-2, H-5, H-6a, H-6b, H-2′, 2 × OCH_2CH_2OH, 2 × OCH_2CH_2OH), 3.46 (br. s, 1H, H-4′), 3.38 (s, 3H, OCH_3), 3.03 (t, ^2J = 6.0 Hz, 1H, OH), 2.13 (dt, $J_{3'eq,3'ax}$ = 13.0 Hz, $J_{2',3'eq} \approx J_{3'eq,4'}$ = 3.5 Hz, 1H, H-3′eq), 1.92 (dt, $J_{2',3'ax}$ = 13.0 Hz, $J_{3'ax,4'}$ = 2.5 Hz, 1H, H-3′ax), 1.19 (d, $J_{5',6'}$ = 6.5 Hz, 1H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 98.63 (C-1′), 98.18 (C-1), 70.52 (OCH_2CH_2OH), 68.88 (C-6), 61.61 (OCH_2CH_2OH), 54.80 (OCH_3), 27.17 (C-3′), 16.53 (C-6′). Anal. calcd. for $C_{43}H_{52}O_{10}$ (728.88): C 70.86, H 7.19; found: C 70.74, H 6.71.

Methyl 2-*O*-(2′-hydroxyethyl)-3-*O*-(3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-α-D-mannopyranoside (9)

Alcohol **24** (100 mg, 0.13 mmol) was dissolved in acetic acid (5 mL) and 10% Pd/C (50 mg) added and the reaction stirred overnight under a flow of H_2. The catalyst was filtered, the solvent evaporated and the product was purified by chromatography on Iatrobeads (CH_2Cl_2–CH_3OH, 4:1). The product obtained was then redissolved in water, filtered through a 0.22 μM filter and lyophilized to give **9** (35 mg, 74%), as an amorphous white solid. $[\alpha]_D$ +73.4 (*c* 0.6, H_2O). R_f = 0.21 (CH_2Cl_2–CH_3OH, 4:1). ^{1}H NMR (D_2O) δ: 5.105 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 4.941 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.070 (q, $J_{5',6'}$ = 6.5 Hz, 1H, H-5′), 4.106 (ddd, $J_{1',2'}$ = 3.5 Hz, $J_{2',3'eq}$ = 7.0 Hz, $J_{2',3'ax}$ = 11.0 Hz, 1H, H-2′), 3.926 (dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.5 Hz, 1H, H-3), 3.87–3.91 (m, 2H, H-6a, H-4′), 3.860 (t, $J_{4,5}$ = 9.5 Hz, 1H, H-4), 3.70–3.83 (m, 6H, H-2, H-6b, 2 × CH_2CH_2OH, 2 × CH_2CH_2OH), 3.656 (ddd, $J_{4,5}$ = 9.5 Hz, $J_{5,6a}$ = 2.5 Hz, $J_{5,6b}$ = 6.0 Hz, 1H, H-5), 3.432 (s, 3H, OCH_3), 1.98–2.05 (m, 2H, H-3′ax, H-3′eq), 1.182 (d, $J_{5',6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR (D_2O) δ: 101.238 (C-1′, $^1J_{C,H}$ = 170.4 Hz), 98.906 (C-1, $^1J_{C,H}$ = 170.0 Hz), 79.425 (C-2), 78.799 (C-3), 73.485 (OCH_2CH_2OH), 73.064 (C-5), 69.126 (C-4′), 67.759 (C-5′), 67.258 (C-4), 64.301 (C-2′), 61.591 (OCH_2CH_2OH), 61.529 (C-6), 55.666 (OCH_3), 33.764 (C-3′), 16.306 (C-6′). HR-FABMS calcd. for $C_{15}H_{28}O_{10}$ $[M + Na]^+$: 391.1580; found: 391.1595.

Methyl 4,6-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-2-*O*-(2′-phthlamidoethyl)-α-D-mannopyranoside (25)

Compound **24** (300 mg, 0.41 mmol) was dissolved in THF (5 mL) and triphenylphosphine (215 mg, 0.82 mmol) and phthalimide (91 mg, 0.62 mmol) were added followed by diethylazodicarboxylate (141 μL, 0.82 mmol). The reaction was stirred overnight and evaporated. Chromatography (toluene–EtOAc, 9:1) provided **25** (320 mg, 91%) as an oil. $[\alpha]_D$ +57.6 (*c* 1.4, $CHCl_3$). R_f = 0.38 (toluene–EtOAc, 9:1). ^{1}H NMR ($CDCl_3$) δ: 7.00–7.80 (m, 24H, Ph), 5.09 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 4.99 (d, ^2J = 11.5 Hz, 1H, PhCH_2), 4.75 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.28–4.53 (m, 7H, 7 × PhCH_2), 4.06 (dd, $J_{2,3}$ = 2.5 Hz, $J_{3,4}$ = 8.5 Hz, 1H, H-3), 3.88–4.02 (m, 9H, H-2, H-4, H-5, H-6a, H-6b, H-2′, H-5′, 2 × OCH_2CH_2NPhth), 3.63 (dd, ^2J = 10.5 Hz, J_{vic} = 1.5 Hz, 1H, CH_2NPhth), 3.33 (s, 3H, OCH_3), 3.20 (br. s, 1H, H-4′), 1.94 (dt, $J_{3'eq,3'ax}$ = 13.0 Hz, $J_{2',3'eq}$, $J_{3'eq,4'}$ = 3.5 Hz, 1H, H-3′eq), 1.67 (dt, $J_{2',3'ax}$ = 13.0 Hz, $J_{3'ax,4'}$ = 2.5 Hz, 1H, H-3′ax), 1.15 (d, $J_{5',6'}$ = 6.5 Hz, 1H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 167.85 (C=O), 99.06 (C-1′), 97.71 (C-1), 69.48 (OCH_2CH_2NPhth), 66.50 (C-6), 54.67 (OCH_3), 37.79 (OCH_2CH_2NPhth), 27.29 (C-3′), 16.46 (C-6′). Anal. calcd. for $C_{51}H_{52}NO_{11}$ (854.98): C 71.65, H 6.13, N 1.64; found: C 71.50, H 6.44, N 1.63.

Methyl 2-*O*-(2′-acetamidoethyl)-4,6-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-α-D-mannopyranoside (26)

Phthalimide **25** (300 mg, 0.34 mmol) was dissolved in methanol (15 mL) and hydrazine acetate (805 mg,

10.2 mmol) was added. The reaction was heated at reflux for 3 h and then more hydrazine acetate (805 mg, 10.2 mmol) was added. After refluxing for another 20 h the solution was cooled and the solvent evaporated. Pyridine (20 mL) was added followed by acetic anhydride (10 mL), and the reaction stirred overnight. The mixture was then diluted with EtOAc and washed with 0.5 N HCl, water, and brine. Evaporation of the solvent followed by chromatography (pentane–EtOAc, 3:1) provided **26** which was characterized only by ^{1}H NMR and then immediately carried through to the next reaction. ^{1}H NMR ($CDCl_3$) δ: 7.10–7.40 (m, 20H, Ph), 6.55 (br. s, 1H, N*H*), 5.24 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 5.07 (d, ^2J = 11.5 Hz, 1H, PhCH_2), 4.74 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.34–4.64 (m, 7H, 7 × PhCH_2), 4.19 (dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.5 Hz, 1H, H-3), 4.01–4.09 (m, 2H, H-4, H-5′) 3.85 (dt, $J_{2',3'eq}$ = 3.5 Hz, $J_{2',3'ax}$ = 13.0 Hz, 1H, H-2′), 3.58–3.79 (m, 8H, H-2, H-5, ^2JH-6a, H-6b, 2 × OCH_2CH_2NHAc, 2 × OCH_2CH_2NHAc), 3.46 (br. s, 1H, H-4′), 3.37 (s, 3H, OCH_3), 2.12 (dt, $J_{3'eq,3'ax}$ = 13.0 Hz, $J_{3'eq,4'}$ = 3.5 Hz, 1H, H-3′eq), 1.83–1.93 (m, 4H, NHCOCH_3, H-3′ax), 1.19 (d, $J_{5',6'}$ = 6.5 Hz, 1H, H6′).

Methyl 2-*O*-(2′-acetamidoethyl)-3-*O*-(3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-α-D-mannopyranoside (10)

The protected *N*-acetyl disaccharide **26** (from above) was dissolved in acetic acid (5 mL) and 10% Pd/C (200 mg) added and the reaction stirred overnight under a flow of H_2. The catalyst was then filtered away and the solvent evaporated. Purified by chromatography on Iatrobeads (CH_2Cl_2–CH_3OH, 4:1) gave a product that was then redissolved in water, filtered through a 0.22 μM filter and lyophilized to give **10** (85 mg, 62% from **25**), as an amorphous white solid. $[\alpha]_D$ +76.4 (*c* 0.6, H_2O). R_f = 0.29 (CH_2Cl_2–CH_3OH, 4:1). ^{1}H NMR (D_2O) δ: 5.094 (d, $J_{1',2'}$ = 4.0 Hz, 1H, H-1′), 4.899 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.021 (ddd, $J_{2',3'eq}$ = 6.0 Hz, $J_{2',3'ax}$ = 11.5 Hz, 1H, H-2′), 4.006 (q, $J_{5',6'}$ = 7.0 Hz, 1H, H-5′), 3.912 (dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 10.0 Hz, 1H, H-3), 3.86–3.91 (m, 2H, H-6a, H-4′), 3.835 (t, $J_{4,5}$ = 10.0 Hz, 1H, H-4), 3.74–3.80 (m, 3H, H-2, H-6b, CH_2CH_2NHAc), 3.67–3.72 (m, 1H, CH_2CH_2NHAc), 3.648 (ddd, $J_{5,6a}$ = 2.5 Hz, $J_{5,6b}$ = 6.5 Hz, 1H, H-5), 3.426 (s, 3H, OCH_3), 3.33–3.42 (m, 2H, 2 × CH_2CH_2NHAc), 1.94–2.01 (m, 5H, H-3′ax, H-3′eq, NHCOCH_3), 1.174 (d, $J_{5',6'}$ = 7.0 Hz, 3H, H-6′). ^{13}C NMR (D_2O) δ: 174.986 (C=O), 101.297 (C-1′, $^1J_{C,H}$ = 169.9 Hz), 98.892 (C-1, $^1J_{C,H}$ = 170.7 Hz), 79.090 (C-3), 78.005 (C-2), 73.566 (C-5), 69.995 (OCH$_2$CH$_2$NHAc), 69.116 (C-4′), 67.841 (C-5′), 67.334 (C-4), 64.294 (C-2′), 61.669 (C-6), 55.712 (OCH$_3$), 40.305 (OCH$_2$CH$_2$NHAc), 33.853 (C-3′), 22.756 (NHCOCH$_3$), 16.346 (C-6′). HR-FABMS calcd. for $C_{17}H_{31}NO_{10}Na$ [M + Na]$^+$: 432.1846; found: 432.1847.

Methyl 6-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-talopyranoside (28)

The known mannoside **27** (37) (3.0 g, 8.88 mmol) was dissolved in CH_2Cl_2 (70 mL) and stirred with crushed 4 Å molecular sieves (10 g) for 15 min. Pyridinium chlorochromate (9.6 g, 44.37 mmol) was added and the reaction stirred for 4 h at which point there was a complete conversion to the ketone (R_f = 0.51, hexane–EtOAc, 2:1). The reaction was filtered through Celite and then washed with water and a saturated solution of NaCl. After drying (Na_2SO_4) and evaporation of the organic layer, the resulting residue was dried for 1 h under vacuum. The black solid was dissolved in CH_3OH (50 mL) and $NaBH_4$ (336 mg, 8.88 mmol) added. After stirring for 10 min, the reaction was quenched by adding acetic acid until the pH was neutral. The solvent was evaporated and then the residue chromatographed (hexane–EtOAc, 1:1) to give the product **28** (2.54 g, 85%) as a crystalline solid; mp 111 to 112°C. $[\alpha]_D$ +39.1 (*c* 1.0, $CHCl_3$). R_f = 0.40 (hexane–EtOAc, 2:1). ^{1}H NMR ($CDCl_3$) δ: 7.30–8.10 (m, 5H, Ph), 5.01 (s, 1H, H-1), 4.53–4.67 (m, 2H, H-6a, H-6b), 4.24 (t, $J_{5,6a}$, $J_{5,6b}$ = 5.0 Hz, H-5), 4.03–4.10 (m, 2H, H-2, H-3), 3.84 (t, $J_{3,4}$, $J_{4,4\text{-OH}}$ = 6.0 Hz, H-4), 3.42 (s, 3H, OCH_3), 2.41 (d, 1H, 4-OH), 1.59, 1.39 (s, 3H, C(CH_3)$_2$). ^{13}C NMR ($CDCl_3$) δ: 166.36 (C=O), 109.62 (O$_2$*C*(CH$_3$)$_2$), 98.50 (C-1), 66.43 (C-6), 55.19 (OCH$_3$), 25.90, 25.17 (O$_2$C(*C*H$_3$)$_2$). Anal. calcd. for $C_{17}H_{22}O_7$ (338.36): C 60.35, H 6.55; found: C 60.35, H 6.65.

Methyl 2,3-*O*-isopropylidene-α-D-talopyranoside (29)

Benzoate **28** (10.0 g, 29.58 mmol) was dissolved in CH_3OH (125 mL) and $NaOCH_3$ (200 mg) was added. After stirring overnight, the solution was neutralized with Amberlite IR-120 (H+) resin, filtered and evaporated. Chromatography (hexane–EtOAc, 1:1) gave **29** (6.37 g, 92%) as a white foam. $[\alpha]_D$ +42.2 (*c* 1.5, $CHCl_3$). R_f = 0.18 (hexane–EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ: 4.99 (s, $J_{1,2}$ = 1.0 Hz, 1H, H-1), 4.26 (dd, $J_{3,4}$ = 6.5 Hz, 1H, H-3), 4.07 (dd, $J_{2,3}$ = 5.0 Hz, 1H, H-2), 4.00 (ddd, $J_{5,6a}$ = 4.0 Hz, $J_{6a,6b}$ = 12.5 Hz, $J_{6a,6\text{-OH}}$ = 7.5 Hz, 1H, H-6a), 3.78–3.88 (m, 3H, H-4, H-5, H-6b), 3.44 (s, 3H, OCH_3), 2.50 (d, $J_{4,4\text{-OH}}$ = 5.5 Hz, 1H, 4-OH), 2.26–2.32 (m, 1H, 6-OH), 1.57, 1.39 (s, 3H, C(CH_3)$_2$). ^{13}C NMR ($CDCl_3$) δ: 109.63 (O$_2$*C*(CH$_3$)$_2$), 98.72 (C-1), 62.82 (C-6), 55.36 (OCH$_3$), 25.90, 25.08 (O$_2$C(*C*H$_3$)$_2$). Anal. calcd. for $C_{10}H_{18}O_6$ (234.25): C 51.27, H 7.74; found: C 51.21, H 7.69.

Methyl 4,6-di-*O*-benzyl-2,3-*O*-isopropylidene-α-D-talopyranoside (30)

Diol **29** (850 mg, 3.62 mmol) was dissolved in DMF (50 mL) and cooled to 0°C. Sodium hydride (400 mg, 80% dispersion in oil, 13.3 mmol) was added and the mixture stirred for 15 min. To this solution was added benzyl bromide (1.5 mL, 12.6 mmol) and the reaction stirred overnight while being allowed to warm to room temperature. The reaction was then quenched with CH_3OH and the solution partitioned between water with CH_2Cl_2. The organic layer was washed with water and a saturated solution of NaCl, and then dried (Na_2SO_4), and evaporated. Chromatography (pentane–EtOAc, 6:1) gave **30** (1.45 g, 97%) as an oil. $[\alpha]_D$ +1.1 (*c* 0.9, $CHCl_3$). R_f = 0.42 (pentane–EtOAc, 6:1). ^{1}H NMR ($CDCl_3$) δ: 7.25–7.35 (m, 10H, Ph), 4.88 (s, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 4.85, 4.52, 4.49, 4.43 (4d, ^2J = 11.5 Hz, 8H, PhCH_2), 4.36 (dd, $J_{3,4}$ = 7.0 Hz, 1H, H-3), 4.06 (dd, $J_{2,3}$ = 4.5 Hz, 1H, H-2), 3.96 (ddd, $J_{4,5}$ = 3.0 Hz, $J_{5,6a}$ = 4.0 Hz, $J_{5,6b}$ = 5.5 Hz, 1H, H-5), 3.81 (dd, $J_{4,5}$ = 3.0 Hz, 1H, H-4), 3.71 (dd, $J_{5,6a}$ = 7.0 Hz, $J_{6a,6b}$ = 10.0 Hz, 1H, H-6a), 3.55 (dd, $J_{5,6b}$ = 5.5 Hz, 1H, H-6b), 3.42 (s, 3H, OCH_3), 1.52, 1.36 (s, 3H, C(CH_3)$_2$). ^{13}C NMR ($CDCl_3$) δ: 110.06 (O$_2$*C*(CH$_3$)$_2$), 98.93 (C-1), 74.41, 73.40 (PhCH$_2$), 69.75 (C-6), 55.56 (OCH$_3$), 26.18, 25.37 (O$_2$C(*C*H$_3$)$_2$). Anal.

calcd. for $C_{24}H_{30}O_6$ (414.50): C 69.54, H 7.30; found: C 69.56, H 7.44.

Methyl 4,6-di-*O*-benzyl-α-D-talopyranoside (31)

Taloside **30** (1.40g, 3.37 mmol) was dissolved in 80% acetic acid (25 mL) and heated at 80°C for 30 min. The solution was cooled and evaporated leaving an oily residue that was chromatographed (pentane–EtOAc, 1:1) to provide the product **31** (1.15 g, 91%) as an oil that crystallized upon standing; mp 64–66°C. $[\alpha]_D$ +37.0 (*c* 0.8, $CHCl_3$). R_f = 0.33 (pentane–EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ: 7.20–7.40 (m, 10H, Ph), 4.78 (s, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.74, 4.62, 4.58, 4.48 (4d, ^2J = 11.5 Hz, 4H, PhCH_2), 3.96 (t, $J_{5,6a}$, $J_{5,6b}$ = 7.0 Hz, 1H, H-5), 3.91 (dd, $J_{2,3}$ = 3.5 Hz, 1H, H-2), 3.82 (dt, $J_{3,4}$ = 3.5 Hz, $J_{3,3\text{-OH}}$ = 10.0 Hz, 1H, H-3), 3.60–3.71 (m, 3H, H-4, H-6, H-6), 3.37 (s, 3H, OCH_3), 3.36 (s, 1H, 2-OH), 2.72 (d, 1H, 3-OH). ^{13}C NMR ($CDCl_3$) δ: 102.09 (C-1), 76.16, 73.57 (PhCH_2), 68.79 (C-6), 55.19 (OCH_3). Anal. calcd. for $C_{21}H_{36}O_6$ (374.44): C 67.36, H 7.00; found: C 69.43, H 7.07.

Methyl 2-*O*-benzoyl-4,6-di-*O*-benzyl-α-D-talopyranoside (32)

Compound **31** (500 mg, 1.34 mmol) was dissolved in CH_2Cl_2 (10 mL) and triethylorthoformate (2.3 mL, 13.4 mmol) was added followed by *p*-TsOH (20 mg). The reaction was complete after stirring for 5 h as indicated by the appearance of a new TLC spot (R_f = 0.55, pentane–EtOAc, 3:1). The acid was neutralized with triethylamine and the solvent evaporated. The residue was redissolved immediately in 80% acetic acid (25 mL), stirred for 30 min, and evaporated. Chromatography (pentane–EtOAc, 3:1) of the resulting oil provided the product **32** (520 mg, 81%) as an oil. ^{1}H NMR ($CDCl_3$) δ: 7.10–7.90 (m, 15H, Ph), 5.12 (ddd, $J_{2,3}$ = 4.5 Hz, $J_{2,4}$ = 0.5 Hz, 1H, H-2), 4.87 (d, $J_{1,2}$ = 1.0 Hz, 1H, H-1), 4.76, 4.66, 4.63, 4.48 (4d, ^2J = 11.5 Hz, 4H, PhCH_2), 4.08–4.16 (m, 2H, H-3, H-5), 3.91–3.96 (m, 2H, H-4, H-6a), 3.75 (dd, $J_{5,6a}$ = 6.0 Hz, $J_{6a,6b}$ = 9.5 Hz, 1H, H-6a), 3.41 (s, 3H, OCH_3), 2.72 (d, $J_{3,3\text{-OH}}$ = 10.0 Hz, 1H, 3-OH).

Methyl 2-*O*-benzoyl-4,6-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-α-D-talopyranoside (34)

Alcohol **32** (500 mg, 1.04 mmol) and donor **33** (38) (506 mg, 1.36 mmol) were dried with crushed 4 Å molecular sieves over P_2O_5 under vacuum overnight. The solids were suspended in CH_2Cl_2 (40 mL) and cooled to –40°C. *N*-Iodosuccinimide (310 mg, 1.36 mmol) and silver triflate (30 mg, 0.12 mmol) were then added. After 15 min, the reaction turned dark red and the reaction was allowed to proceed for another 15 min at which point it was quenched with triethylamine. After diluting with CH_2Cl_2 the solution was washed in succession with a saturated solution of sodium thiosulfate, water, a saturated solution of NaCl, and then dried (Na_2SO_4). Evaporation of the solvents and chromatography (pentane–EtOAc, 6:1) gave the product **34** (680 mg, 83%) as an oil. $[\alpha]_D$ +16.2 (*c* 0.9, $CHCl_3$). R_f = 0.38 (pentane–EtOAc, 6:1). ^{1}H NMR ($CDCl_3$) δ: 7.05–8.00 (m, 25H, Ph), 5.35 (m, 1H, H-2), 5.18 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 4.89 (d, $J_{1,2}$ = 1.0 Hz, 1H, H-1), 4.50–4.64 (m, 6H, PhCH_2), 4.41 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 4.16 (t, $J_{2,3} \approx J_{3,4}$ = 3.5 Hz, 1H, H-3), 4.09 (dt, $J_{4,5}$ = 1.0 Hz, $J_{5,6b}$ = 6.0 Hz, 1H, H-5), 3.90–3.98 (m, 2H, H-4, H-2′), 3.86 (dd, $J_{5,6a}$ = 6.0 Hz, $J_{6a,6b}$ = 9.5 Hz, 1H, H-6a), 3.78 (dd, $J_{5,6b}$ = 6.0 Hz, 1H, H-6b), 3.42 (s, 3H, OCH_3), 3.35 (br. s, 1H, H-4′), 2.11 (dt, $J_{2,3e'} \approx J_{3e',4}$ = 3.5 Hz, $J_{3'eq,3'ax}$ = 13.0 Hz, 1H, H-3′eq), 1.82 (dt, $J_{3'ax,4}$ = 13.0 Hz, $J_{2',3'ax}$ = 2.5 Hz, 1H, H-3′ax), 1.08 (d, $J_{5'6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 166.31 (C=O), 98.96 (C-1), 97.70 (C-1′), 74.38, 73.33, 71.07, 70.79 (PhCH_2), 69.24 (C-6), 54.86 (OCH_3), 27.42 (C-3′), 16.03 (C-6′). Anal. calcd. for $C_{48}H_{52}O_{10}$ (788.94): C 73.08, H 6.64; found: C 72.82, H 6.68.

Methyl 4,6-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-α-D-talopyranoside (35)

The protected disaccharide **34** (560 mg, 0.71 mmol) was dissolved in CH_3OH (50 mL) and a small piece of sodium was added. The reaction was stirred overnight and then neutralized with Amberlite IR-120 (H+) resin. After filtration of the resin and evaporation of the CH_3OH the product was purified by chromatography (pentane–EtOAc, 3:1) to give the product **35** (466 mg, 96%) as an oil. $[\alpha]_D$ +42.0 (*c* 1.0, $CHCl_3$). R_f = 0.30 (pentane–EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ: 7.20–7.40 (m, 20H, Ph), 5.05–5.10 (m, 2H, H-1′, PhCH_2), 4.76 (br. s, 1H, H-1), 4.37–4.66 (m, 5H, PhCH_2), 4.33 (q, $J_{5'6'}$ = 6.5 Hz, 1H, H-5′), 4.25 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 3.81–3.97 (m, 5H, H-4, H-2, H-3, H-5, H-2′), 3.55–3.63 (m, 2H, H-6a, H-6b), 3.50 (br. s, 1H, H-4), 3.37 (s, 3H, OCH_3), 2.22 (dt, $J_{2,3'eq} \approx J_{3'eq,4}$ = 3.5 Hz, $J_{3'eq,3'ax}$ = 13.0 Hz, 1H, H-3′eq), 2.02 (dt, $J_{3'ax,4}$ = 13.0 Hz, $J_{2',3'ax}$ = 2.5 Hz, 1H, H-3′ax), 1.20 (d, $J_{5'6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 102.72 (C-1), 98.59 (C-1′), 75.13, 73.50, 71.43, 71.05 (PhCH_2), 69.08 (C-6), 55.12 (OCH_3), 28.03 (C-3′), 16.53 (C-6′). Anal. calcd. for $C_{41}H_{48}O_9$ (684.83): C 71.91, H 7.07; found: C 71.76, H 7.23.

Methyl 3-*O*-(3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-α-D-talopyranoside (11)

To a solution of **35** (120 mg, 0.18 mmol) in acetic acid (5 mL) was added 10% Pd/C (100 mg) and the reaction was stirred overnight under a flow of H_2. After filtration of the catalyst and evaporation of the solvent the residue was subjected to chromatography (CH_2Cl_2–CH_3OH, 4:1) on Iatrobeads. The product obtained was then redissolved in water, filtered through a 0.22 μM filter and lyophilized to give the product **11** (49 mg, 84%) as an amorphous white solid. R_f = 0.27 (CH_2Cl_2–CH_3OH, 4:1). $[\alpha]_D$ +161.0 (*c* 0.6, H_2O). ^{1}H NMR (D_2O) δ: 5.066 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 4.882 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.130 (dd, $J_{3,4}$ = 1.5 Hz, 1H, H-3), 4.096 (dq, $J_{4',5'}$ = 0.5 Hz, 1H, H-5′), 4.041 (ddd, $J_{2',3'ax}$ = 13.0 Hz, $J_{2',3'eq}$ = 5.0 Hz, 1H, H-2′), 3.967 (ddd, $J_{2,3}$ = 3.0 Hz, $J_{2,4}$ = 1.5 Hz, 1H, H-2), 3.87–3.93 (m, 3H, H-4, H-5, H-4′), 3.858 (dd, $J_{5,6a}$ = 8.0 Hz, $J_{6a,6b}$ = 12.0 Hz, 1H, H-6a), 3.793 (dd, $J_{5,6b}$ = 4.5 Hz, 1H, H-6b), 3.438 (s, 3H, OCH_3), 2.099 (dt, $J_{2',3'ax}$ = 13.0 Hz, $J_{3'ax,3'eq}$ = 13.0 Hz, $J_{3'ax,4'}$ = 3.0 Hz, 1H, H-3′ax), 1.999 (dt, $J_{2',3'eq}$ = 5.0 Hz, $J_{3'eq,4'}$ = 5.0 Hz, 1H, H-H-3′eq), 1.158 (d, $J_{5',6'}$ = 7.0 Hz, 3H, H-6′). ^{13}C NMR (D_2O) δ: 102.146 (C-1, $^1J_{C,H}$ = 171.6 Hz), 97.263 (C-1′, $^1J_{C,H}$ = 168.4 Hz), 72.159 (C-5), 71.79 (C-4), 70.697 (C-2), 69.211 (C-4′), 67.718 (C-5′), 67.590 (C-3), 64.044 (C-2′), 62.316 (C-6), 55.663 (OCH_3), 33.696 (C-3′), 16.156

(C-6′). HR-FAB-MS calcd. for $C_{13}H_{24}O_9Na$ $[M + Na]^+$: 347.1318; found: 347.1320.

Methyl 4,6-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-2-*O*-methyl-α-D-talopyranoside (36)

Alcohol **35** (136 mg, 0.20 mmol) was dissolved in DMF (5 mL) and cooled to 0°C. Sodium hydride (18.0 mg, 80% dispersion in oil, 0.6 mmol) was added and the mixture stirred for 10 min. To this solution was added methyl iodide (20 μL, 0.60 mmol) and the reaction stirred overnight while being allowed to warm to room temperature. Upon quenching the reaction with CH_3OH, the solution was partitioned between water with CH_2Cl_2. The organic layer was then washed with water, a saturated solution of NaCl, dried (Na_2SO_4), and evaporated. Chromatography (pentane–EtOAc, 3:1) gave **36** (124 mg, 90%) as an oil. $[\alpha]_D$ +49.5 (*c* 1.0, $CHCl_3$). R_f = 0.25 (pentane–EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ: 7.15–7.40 (m, 20H, Ph), 5.09 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 4.92 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 4.83 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 4.68, 4.63 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 4.31–4.58 (m, 6H, PhCH_2), 4.23 (q, 1H, H-5′), 3.75–4.10 (m, 5H, H-3, H-4, H-5, H-6a, H-2′), 3.58 (dd, $J_{6a,6b}$ = 10.5 Hz, $J_{5,6b}$ = 5.0 Hz, 1H, H-6b), 3.53 (s, 3H, OCH_3), 3.48 (br. s, 1H, H-4′), 3.38–3.45 (m, 4H, OCH_3, H-2), 2.18 (dt, $J_{2,3'eq} \approx J_{3'eq,4}$ = 3.5 Hz, $J_{3'eq,3'ax}$ = 13.0 Hz, 1H, H-3′eq), 1.92 (dt, $J_{3'ax,4}$ = 13.0 Hz, $J_{2',3'ax}$ = 2.5 Hz, 1H, H-3′ax), 1.23 (d, $J_{5'6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 98.31 (C-1), 98.07 (C-1′), 73.90, 73.39, 71.28, 70.95 (PhCH_2), 69.30 (C-6), 59.19 (OCH_3), 55.18 (OCH_3), 27.73 (C-3′), 16.66 (C-6′). Anal. calcd. for $C_{42}H_{50}O_9$ (698.86): C 72.19, H 7.21; found: C 71.73, H 7.40.

Methyl 3-*O*-(3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-2-*O*-methyl-α-D-talopyranoside (12)

Methyl ether **36** (118 mg, 0.17 mmol) was dissolved in acetic acid (5 mL) and then 10% Pd/C (100 mg) was added. The reaction was stirred overnight under a flow of H_2. After filtration of the catalyst and evaporation of the solvent the residue was subjected to chromatography (CH_2Cl_2–CH_3OH, 9:1) on Iatrobeads. The product obtained was then redissolved in water, filtered through a 0.22 μM filter and lyophilized to give the product **12** (45 mg, 78%) as an amorphous white solid. R_f = 0.55 (CH_2Cl_2–CH_3OH, 4:1). $[\alpha]_D$ +143.4 (*c* 0.5, H_2O). ^{1}H NMR (D_2O) δ: 5.045 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 5.021 (d, $J_{1',2'}$ = 4.0 Hz, 1H, H-1′), 4.069 (dq, $J_{4',5'}$ = 1.5 Hz, $J_{5',6'}$ = 7.0 Hz, 1H, H-5′), 4.035 (dd, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 4.015 (ddd, $J_{1',2'}$ = 4.0 Hz, $J_{2',3'ax}$ = 13.0 Hz, $J_{2',3'eq}$ = 5.0 Hz, 1H, H-2′), 3.957 (t, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 3.0 Hz, 1H, H-3), 3.86–3.90 (m, 2H, 4–5, H-4′), 3.825 (dd, $J_{5,6a}$ = 8.0 Hz, $J_{6a,6b}$ = 11.5 Hz, 1H, H-6a), 3.752 (dd, $J_{5,6b}$ = 4.0 Hz, $J_{6a,6b}$ = 11.5 Hz, 1H, H-6b), 3.486 (s, 3H, aglycon OCH_3), 3.441 (ether OCH_3), 2.088 (dt, $J_{2',3'ax}$ = 13.0 Hz, $J_{3'ax,3'eq}$ = 13.0 Hz, $J_{3'ax,4'}$ = 3.0 Hz, 1H, H-3′ax), 1.998 (ddd, $J_{2',3'eq}$ = 5.0 Hz, $J_{3'ax,3'eq}$ = 13.0 Hz, $J_{3'eq,4'}$ = 4.0 Hz, 1H, H-3′eq), 1.184 (d, $J_{5',6'}$ = 7.0 Hz, 3H, H-6′). ^{13}C NMR (D_2O) δ: 98.530 (C-1, $^1J_{C,H}$ = 170.7 Hz), 97.895 (C-1′, $^1J_{C,H}$ = 168.6 Hz), 79.796 (C-2), 72.525 (C-3), 72.324 (C-5), 69.217 (C-4′), 67.773 (C-5′), 67.309 (C-4), 64.056 (C-2′), 62.264 (C-6), 59.319 (ether OCH_3), 55.675 (aglycon OCH_3), 33.715 (C-3′), 16.260 (C-6′). HR-FAB-MS calcd for $C_{14}H_{26}O_9Na$ $[M + Na]^+$: 361.1475; found: 361.1480.

Methyl 4,6-di-*O*-benzyl-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-talopyranoside (38)

Disaccharide **35** (170 mg, 0.25 mmol) and thioglycoside **37** (39) (297 mg, 0.51 mmol) were dried with crushed 4 Å molecular sieves (500 mg) over P_2O_5 under vacuum overnight. The solids were suspended in CH_2Cl_2 (10 mL) and cooled to 0°C. *N*-Iodosuccinimide (124 mg, 0.55 mmol) and silver triflate (14 mg, 0.055 mmol) were then added. After stirring for 40 min and warming to room temperature, the reaction was quenched with triethylamine. Dilution with CH_2Cl_2 was followed by washing with a saturated solution of sodium thiosulfate, water, and a saturated solution of NaCl. After drying (Na_2SO_4) and evaporation of the solvent, chromatography (toluene–EtOAc, 9:1) gave the product **38** (106 mg, 35%) as an oil. $[\alpha]_D$ +58.8 (*c* 0.9, $CHCl_3$). R_f = 0.31 (toluene–EtOAc, 9:1). ^{1}H NMR ($CDCl_3$) δ: 7.10–7.40 (m, 40H, Ph), 5.38 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 5.16 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 5.06 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 5.02 (d, $J_{1'',2''}$ = 3.5 Hz, 1H, H-1″), 4.83, 4.80 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 4.40–4.65 (m, 13H, PhCH_2), 4.23 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 3.54–4.15 (m, 14H, H-3, H-4, H-5, H-6a, H-6b, H-2′, H-5′, H-2″, H-3″, H-4″, H-5″, H-6a″, H-6b″), 3.26 (s, 3H, OCH_3), 2.63 (br. s, 1H, H-4′), 1.90 (dt, $J_{2',3'eq}$, $J_{3'eq,4'}$ = 3.5 Hz, $J_{3'eq,3'ax}$ = 13.0 Hz, 1H, H-3′eq), 1.77 (dt, $J_{3'ax,4}$ = 13.0 Hz, $J_{2',3ax}$ = 2.5 Hz, 1H, H-3′ax), 1.06 (d, $J_{5'6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 100.26 (C-1″), 99.93 (C-1), 99.01 (C-1′), 69.20 (C-6), 66.41 (C-1″), 54.91 (OCH_3), 27.75 (C-3′), 16.46 (C-6′). Anal. calcd. for $C_{75}H_{82}O_{14}$ (1207.47): C 74.60, H 6.84; found: C 74.81, H 7.29.

Methyl 3-*O*-(3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-2-*O*-(α-D-galactopyranosyl)-α-D-talopyranoside (13)

The protected trisaccharide **38** (78 mg, 0.06 mmol) was dissolved in acetic acid (5 mL) and then 10% Pd/C (100 mg) was added. The reaction was stirred overnight under a flow of H_2. After filtration of the catalyst and evaporation of the solvent, the residue was subjected to chromatography (CH_2Cl_2–CH_3OH–water, 65:35:5) on Iatrobeads. The product obtained was then redissolved in water, filtered through a 0.22 μM filter and lyophilized to give **13** (26 mg, 86%) as an amorphous white solid. $[\alpha]_D$ +176.8 (*c* 0.5, H_2O). R_f = 0.58 (CH_2Cl_2–CH_3OH–water, 65:35:5). ^{1}H NMR (D_2O) δ: 5.304 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 5.060 (d, $J_{1'',2''}$ = 4.0 Hz, 1H, H-1″), 5.056 (s, 1H, H-1), 4.01–4.15 (m, 6H, H-2, H-3, H-4, H-2′, H-5′, H-5″), 3.980 (d, $J_{3'',4''}$ = 3.5 Hz, 1H, H-4″), 3.919 (dd, $J_{3'',4''}$ = 3.5 Hz, 1H, H-3″), 3.85–3.90 (m, 3H, H-5, H-6a, H-4′), 3.826 (dd, $J_{2'',3''}$ = 10.0 Hz, 1H, H-2″), 3.750 (d, $J_{5'',6''}$ = 6.0 Hz, 1H, H-6″), 3.428 (s, 3H, OCH_3), 2.00–2.02 (m, 2H, H-3′ax, H-3′eq), 1.176 (d, $J_{5',6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR (D_2O) δ: 101.618 (C-1″, $^1J_{C,H}$ = 173.7 Hz), 100.858 (C-1, $^1J_{C,H}$ = 174.2 Hz), 95.856 (C-1′, $^1J_{C,H}$ = 169.9 Hz), 79.936 (C-2), 72.422 (C-5″), 72.052 (C-5), 70.944 (C-3), 70.136 (C-4″), 70.038 (C-3″), 69.260 (C-2″), 69.171 (C-4′), 67.911 (C-5), 66.372 (C-4), 63.992 (C-2′), 62.240 (2 C, C-6, C-6″), 55.626 (OCH_3), 33.896

(C-3′), 16.186 (C-6′). HR-FAB-MS calcd. for $C_{19}H_{31}O_{14}Na$ $[M + Na]^+$: 509.1846; found: 509.1833.

Methyl 2,3,4,6-tetra-*O*-acetyl-α-D-talopyranoside (40)

Acetal **29** (6.10 g, 26.07 mmol) was dissolved in trifluoroacetic acid:water (9:1, 50 mL), stirred overnight, and then evaporated to a thick oil. The residue was then dissolved in pyridine (50 mL), cooled to 0°C, and acetic anhydride (20 mL) added. After stirring overnight while warming to room temperature the reaction was quenched by adding CH_3OH and the solution evaporated. Chromatography (hexane–EtOAc, 3:1) gave **40** (7.17 g, 76%) as a an oil. $[\alpha]_D$ +64.7 (*c* 0.9, $CHCl_3$). R_f = 0.34 (hexane–EtOAc, 2:1). ^{1}H NMR ($CDCl_3$) δ: 5.31 (br. d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 5.28 (t, $J_{2,3}$ = 3.5 Hz, 1H, H-3), 5.08 (dt, $J_{2,4}$ = 1.5 Hz, $J_{2,3}$ = 3.5 Hz, 1H, H-2), 4.79 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.04–4.16 (m, 3H, H-5, H-6a, H-6b), 3.40 (s, 3H, OCH_3), 2.12, 2.13, 2.05, 1.98 (s, 3 H, OCOCH_3). ^{13}C NMR ($CDCl_3$) δ: 170.75, 170.50, 170.19, 170.01 (*C*=O), 99.33 (C-1), 62.10 (C-6), 55.30 (O*C*H_3), 20.89, 20.67, 20.58 (OCO *C*H_3). Anal. calcd. for $C_{15}H_{22}O_{10}$ (362.34): C 49.72, H 6.12; found: C 49.23, H 6.21.

1,2,3,4,6-Penta-*O*-acetyl-α-D-talopyranose (41)

Methyl glycoside **40** (5.5 g, 15.2 mmol) was dissolved in acetic anhydride (120 mL) and the solution cooled to 0°C. H_2SO_4 (400 μL) was added dropwise from a microsyringe and the reaction allowed to continue for 2 h at 0°C. The reaction was quenched by adding CH_2Cl_2 and then a solution of $NaHCO_3$ and stirring for 20 min. The reaction was diluted with more CH_2Cl_2 and then washed with $NaHCO_3$, water, and a saturated solution of NaCl. After drying (Na_2SO_4) and evaporation of the solvent, the product **41** (5.6 g, 95%) was obtained as a white crystalline solid; mp 103–105°C (lit. (40) value mp +104 to 105°C). $[\alpha]_D$ +68.8 (*c* 1.3, $CHCl_3$) (lit. (40) value $[\alpha]_D$ +68° (*c* 0.6)). R_f = 0.28 (hexane–EtOAc, 2:1). ^{1}H NMR ($CDCl_3$) δ: 6.12 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 5.34 (br. d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 5.29 (t, $J_{2,3}$ = 3.5 Hz, 1H, H-3), 5.08 (ddd, $J_{2,4}$ = 1.0 Hz, 1H, H-2), 4.30 (dt, $J_{4,5}$ = 1.5, 7.0 Hz, 1H, H-5), 4.18 (dd, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6a}$ = 7.0 Hz, 1H, H-6a), 4.12 (dd, $J_{5,6b}$ = 7.0 Hz, 1H, H-6b), 2.13 (s, 6H, 2 × OCOCH_3), 2.12, 2.02, 1.99 (s, 3H, OCOCH_3). ^{13}C NMR ($CDCl_3$) δ: 170.37, 170.07, 169.64, 169.65, 168.02 (*C*=O) 91.14 (C-1), 61.41 (C-6), 20.82, 20.72, 20.60, 20.52 (OCO*C*H_3). Anal. calcd. for $C_{16}H_{22}O_{11}$ (390.35): C 49.23, H 5.68; found: C 49.26, H 5.63.

2,3,4,6-Tetra-*O*-acetyl-α-D-talopyranosyl bromide (42)

The peracetate **41** (500 mg, 1.28 mmol) was stirred with 45% HBr in acetic acid (10 mL) and acetic anhydride (1 mL) for 2 h. The solution was then evaporated to provide, in quantitative yield as determined by ^{1}H NMR, **42** as a yellow oil. Attempts to purify the product by flash chromatography resulted in complete decomposition of the bromide. ^{1}H NMR ($CDCl_3$) δ: 6.41 (s, 1H, H-1), 5.70 (t, $J_{2,3}$ = 3.5 Hz, 1H, H-3), 5.53 (br. d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 5.42 (d, $J_{2,3}$ = 3.5 Hz, 1H, H-2), 4.49 (br. t, $J_{5,6a}$, $J_{5,6b}$ = 6.0 Hz, 1H, H-5), 4.26 (dd, $J_{6a,6b}$ = 10.5 Hz, 1H, H-6a), 4.20 (dd, $J_{5,6b}$ = 6.5 Hz, 1H, H-6b), 2.03, 2.00, 1.90, 1.85 (s, 3H, OCOCH_3).

Ethyl 3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (46)

The deprotected thioglycoside **45** (41) (285 mg, 1.28 mol) was suspended in dry CH_3CN (5 mL) and dimethoxypropane (785 μL, 6.40 mmol) was added followed by *p*-TsOH (15 mg). After 10 min the solid was dissolved and the reaction was allowed to proceed for 2 h. Water (1 mL) was added and the reaction stirred for 30 min before being neutralized with triethylamine and evaporated. Chromatography (EtOAc) gave the product **46** (222 mg, 66%) as a white crystalline solid; mp 88–91°C. $[\alpha]_D$ +13.9 (*c* 0.9, $CHCl_3$). R_f = 0.55 (EtOAc). ^{1}H NMR ($CDCl_3$) δ: 4.21 (dd, $J_{4,5}$ = 2.0 Hz, 1H, H-4), 4.27 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 4.09 (dd, $J_{3,4}$ = 5.5 Hz, 1H, H-3), 3.76–4.01 (m, 3H, H-6a, H-6b, H-5), 3.56 (ddd, $J_{2,3}$ = 7.0 Hz, $J_{2,2\text{-OH}}$ = 2.0 Hz, 1H, H-2), 2.70–2.80 (m, 2H, SCH_2CH$_3$), 2.45 (d, 1H, 2-OH), 2.10 (dd, $J_{6a,6\text{-OH}}$ = 4.0 Hz, $J_{6b,6\text{-OH}}$ = 9.5 Hz, 1H), 1.51, 1.35 (s, 3H, (CH_3)$_2$CO$_2$), 1.32 (t, ^3J = 6.5 Hz, 1H, SCH$_2$CH_3). ^{13}C NMR ($CDCl_3$) δ: 110.18 ((CH$_3$)$_2$*C*O$_2$), 85.23 (C-1), 62.25 (C-6), 28.03, 26.21 ((*C*H$_3$)$_2$CO$_2$), 24.30 (S*C*H$_2$CH$_3$), 15.18 (SCH$_2$*C*H$_3$). Anal. calcd. for $C_{11}H_{20}O_5S$ (264.34): C 49.98, H 7.63, S 12.13; found: C 50.16, H 7.96, S 12.04.

Ethyl 3,4-*O*-isopropylidene-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-galactopyranoside (47)

Diol **46** (600 mg, 2.26 mole) was dissolved in dry pyridine (30 mL) and then *tert*-butyldimethylsilyl chloride (408 mg, 2.71 mmol) was added followed by DMAP (15 mg). The reaction was stirred overnight and then diluted with CH_2Cl_2 and washed successively with 0.5 N HCl, water, and a saturated solution of NaCl. After drying (Na_2SO_4), the organic layer was evaporated. Chromatogaphy (hexane–EtOAc, 2:1) gave the product **47** (700 mg, 85%) as an oil. $[\alpha]_D$ –5.1 (*c* 0.9, $CHCl_3$). R_f = 0.68 (hexane–EtOAc, 2:1). ^{1}H NMR ($CDCl_3$) δ: 4.25 (dd, $J_{3,4}$ = 5.5 Hz, $J_{4,5}$ = 2.5 Hz, 1H, H-4), 4.24 (d, $J_{1,2}$ = 10.0 Hz, 1H, H-1), 4.04 (dd, $J_{2,3}$ = 7.0 Hz, 1H, H-3), 3.78–3.89 (m, 3H, H-6a, H-6b, H-5), 3.55 (ddd, $J_{2,2\text{-OH}}$ = 2.0 Hz, 1H, H-2) 2.65–2.80 (m, 2H, SCH_2CH$_3$), 2.37 (d, $J_{2,2\text{-OH}}$ = 2.0 Hz, 1H, 2-OH), 1.53, 1.35 (s, 3H, (CH_3)$_2$CO$_2$), 1.32 (t, ^3J = 6.5 Hz, 1H, SCH$_2$CH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$) δ: 109.97 ((CH$_3$)$_2$*C*O$_2$), 85.58 (C-1), 62.10 (C-6), 28.28, 26.29 ((*C*H$_3$)$_2$CO$_2$), 25.82 (SiC(*C*H$_3$)$_3$), 24.46 (S*C*H$_2$CH$_3$), 18.26 (Si*C*(CH$_3$)$_3$), 15.39 (SCH$_2$*C*H$_3$), –5.34, –5.50 (Si(*C*H$_3$)$_2$). Anal. calcd. for $C_{17}H_{34}O_5SSi$ (378.60): C 53.93, H 9.05, S 8.47; found: C 54.06, H 8.95, S 8.52.

Ethyl 3,4-*O*-isopropylidene-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-talopyranoside (48)

Oxalyl chloride (220 μL, 1.98 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to –78°C. To this solution was added dropwise DMSO (310 μL, 4.36 mmol) in CH_2Cl_2 (10 mL). When the solution had stirred for 30 min, **47** (500 mg, 1.32 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise over 10 min. After stirring for another 20 min and warming to –60°C, triethylamine (1.2 mL, 8.85 mmol) was added and the reaction brought to room temperature. After 40 min, water was added and the layers separated. The organic layer was washed with water, a saturated solution of NaCl, and then dried (Na_2SO_4). Evaporation of the solvent provided a residue that was immediately

dissolved in methanol (50 mL) and then $NaBH_4$ (100 mg, 2.64 mmol) was added. After stirring for 20 min, the reaction was quenched with acetic acid and the solvent evaporated. TLC indicated a mixture of two easily separable products (R_f = 0.66 and 0.61 (hexane–EtOAc, 2:1)), which were later shown to be an anomeric mixture of talopyranosides. The residue was coevaporated with CH_3OH (3 × 50 mL) and the residue chromatographed (hexane–EtOAc, 3:1). The two products **48** were isolated as oils, the β-glycoside (343 mg, 69% yield) and the α-glycoside (81 mg, 16% yield). Only the β-glycoside was fully characterized. $[\alpha]_D$ –34.6 (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 4.52 (d, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.16–4.22 (m, 2H, H-3, H-4), 3.76–3.94 (m, 4H, H-5, H-6a, H-6b, H-2), 2.65–2.76 (m, 2H, SCH_2CH_3), 2.42 (d, $J_{2,2\text{-OH}}$ = 8.5 Hz, 1H, 2-OH), 1.58, 1.36 (s, 3H, $(CH_3)_2CO_2$), 1.30 (t, ^3J = 6.5 Hz, 1H, SCH_2CH_3), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ: 109.80 ($(CH_3)_2CO_2$), 84.42 (C-1), 62.13 (C-6), 25.81 ($SiC(CH_3)_3$), 25.74 ($(CH_3)_2CO_2$), 25.71 (SCH_2CH_3), 25.49 ($(CH_3)_2CO_2$), 18.25 ($SiC(CH_3)_3$), 15.24 (SCH_2CH_3), –5.36, –5.50 ($Si(CH_3)_2$). Anal. calcd. for $C_{17}H_{34}O_5SSi$ (378.60): C 53.93, H 9.05, S 8.47; found: C 53.97, H 9.02, S 8.48.

Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-talopyranoside (43)

Acetal **48** (279 mg, 0.74 mmol) was dissolved in 80% acetic acid (35 mL) and the solution heated for 1 h at 80°C. The solution was cooled, the solvent evaporated and the residue immediately dissolved in pyridine (20 mL). Following the addition of acetic anhydride (5 mL) and DMAP, the reaction was stirred overnight before being quenched by cooling to 0°C and adding CH_3OH. The mixture was then diluted with CH_2Cl_2 and washed with 0.5 N HCl, water, and a saturated solution of NaCl. After drying (Na_2SO_4) and evaporation, chromatography (hexane–EtOAc, 2:1) gave the product **43** (258 mg, 89%) as an oil. $[\alpha]_D$ –53.8 (*c* 1.0, $CHCl_3$). R_f = 0.33 (hexane–EtOAc, 2:1). ^{1}H NMR ($CDCl_3$) δ: 5.37 (dd, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.5 Hz, 1H, H-4), 5.27 (dd, $J_{2,3}$ = 3.5 Hz, 1H, H-2), 5.08 (t, 1H, H-3), 4.76 (d, $J_{1,2}$ = 1.0 Hz, 1H, H-1), 4.21 (dd, $J_{5,6a}$ = 7.0 Hz, $J_{6a,6b}$ = 11.5 Hz, 1H, H-6a), 4.15 (dd, $J_{5,6b}$ = 7.0 Hz, 1H, H-6b), 3.92 (dt, $J_{4,5}$ = 1.5 Hz, 1H, H-5), 2.73 (q, ^3J = 6.5 Hz, 2H, SCH_2CH_3), 2.13, 2.09, 2.01, 1.94 (s, 3H, $OCOCH_3$), 1.28 (t, 1H, ^3J = 6.5 Hz, SCH_2CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.37, 170.15, 170.03, 169.52 (C=O), 83.24 (C-1), 61.81 (C-6), 25.75 (SCH_2CH_3), 20.61, 20.53, 20.47, 20.35 ($OCOCH_3$), 14.96 (SCH_2CH_3). Anal. calcd. for $C_{10}H_{18}O_5S$ (392.42): C 48.97, H 6.16, S 8.17; found: C 49.18, H 6.09, S 8.22.

Methyl 2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-talopyranosyl)-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-4,6-di-*O*-benzyl-α-D-mannopyranoside (44)

Talose donor **43** (114 mg, 0.292 mmol) and disaccharide **20** (35) (50 mg, 0.73 mmol) were dried with crushed 4 Å molecular sieves (300 mg) under vacuum with P_2O_5. The solids were suspended in CH_2Cl_2 (5 mL) and the solution cooled to 0°C. Upon stirring for 30 min, *N*-iodosuccinimide (65 mg, 0.292 mmol) and silver triflate (7.5 mg, 0.029 mmol) were added. The reaction was quenched with triethylamine after 1 h and the reaction mixture diluted with CH_2Cl_2, filtered, and then the organic layer washed with a saturated solution of sodium thiosulfate, water and a saturated solution of NaCl. After drying (Na_2SO_4) and evaporation of the solvent, the product was purified by chromatography (hexane–EtOAc, 1:1) to give **44** (35 mg, 47%) as an oil. $[\alpha]_D$ +69.1 (*c* 1.1, $CHCl_3$). R_f = 0.54 (hexane–EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ: 7.10–7.50 (m, 20H, Ph), 5.27 (t, $J_{2'',3''}$, $J_{3'',4''}$ = 3.5 Hz, 1H, H-3″), 5.24 (br. s, 1H, H-2″), 5.17 (br. s, 1H, H-4″), 5.11 (br. s, 1H, H-1′), 5.06 (d, J_{gem} = 11.5 Hz, 1H, $PhCH_2$), 5.05 (s, 1H, H-1″), 4.93 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 4.34–4.60 (m, 7H, 7 × $PhCH_2$, H-5′), 4.20 (dd, $J_{5'',6a''}$ = 6.0 Hz, $J_{6a'',6b''}$ = 11.5 Hz, 1H, H-6a″), 4.15 (dd, $J_{2,3}$ = 2.5 Hz, $J_{3,4}$ = 9.5 Hz, 1H, H-3), 4.04 (dd, $J_{5'',6b''}$ = 7.0 Hz, 1H, H-6b″), 3.93–4.00 (m, 2H, H-4, H-2), 3.88 (dd, $J_{5'',6a''}$ = 6.0 Hz, 1H, H-5″), 3.81 (dt, $J_{2',3'eq}$ = 3.5 Hz, $J_{2',3'ax}$ = 12.5 Hz, 1H, H-2′), 3.70–3.76 (m, 1H, H-5), 3.60–3.69 (m, 2H, H-6a, H-6b), 3.54 (br. s, 1H, H-4′), 3.37 (s, 3H, OCH_3), 1.90–2.15 (m, 14H, 12 × $OCOCH_3$, H-3′ax, H-3′eq), 1.12 (d, $J_{5',6'}$ = 6.5 Hz, 1H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 170.48, 170.10, 169.78, 169.32 (C=O), 100.35 (C-1), 99.78 (C-1″), 99.00 (C-1′), 74.69 ($PhCH_2$), 73.20 ($PhCH_2$), 71.43, 70.81 ($PhCH_2$), 69.21 (C-6), 62.58 (C-6″), 54.96 (OCH_3), 27.56 (C-3′), 20.89, 20.74, 20.69 ($OCOCH_3$), 16.47 (C-6′). Anal. calcd. for $C_{55}H_{66}O_{18}$ (1015.12): C 65.08, H 6.55; found: C 64.54, H 6.40.

Methyl 2-*O*-(α-D-talopyranosyl)-3-*O*-(3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-α-D-mannopyranoside (14)

Trisaccharide **44** (51 mg, 0.05 mmol) was dissolved in CH_3OH (5 mL) and then $NaOCH_3$ (15 mg) was added. The reaction was stirred overnight and neutralized with Amberlite IR-120 (H+) resin. The solution was filtered, the filtrate evaporated and the residue immediately redissolved in acetic acid (10 mL). 10% Pd/C (30 mg) was added, and the reaction was stirred under a flow of H_2 overnight. The catalyst was filtered off and the solvent evaporated to yield a yellow residue. The colored impurities were removed by redissolution in water and filtration through a C-18 reverse-phase cartridge. The filtrate was evaporated and then passed through a Biogel P-2 column using water as the eluant. Concentration of the product by evaporation, filtration through a 0.22 μM filter and lyophilization gave the product **14** (21.2 mg, 87%) as an amorphous white solid. $[\alpha]_D$ +99.0 (*c* 0.7, H_2O). ^{1}H NMR (D_2O) δ: 5.205 (s, 1H, H-1″), 5.097 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 5.028 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 4.101 (dd, $J_{2,3}$ = 3.0 Hz, 1H, H-2), 4.01–4.07 (m, 3H, H-2′, H-5′, H-5″), 3.983 (dd, $J_{3,4}$ = 10.0 Hz, 1H, H-3), 3.91–3.97 (m, 3H, H-2″, H-3″, H-4″), 3.88–3.97 (m, 2H, H-6a, H-4′), 3.871 (t, $J_{4,5}$ = 10.0 Hz, 1H, H-4), 3.820 (dd, $J_{5,6'a}$ = 8.0 Hz, $J_{6''a,6''b}$ = 12.0 Hz, 1H, H-6″a), 3.74–3.79 (m, 2H, H-6b, H-6″b), 3.653 (ddd, $J_{5,6a}$ = 2.0 Hz, $J_{5,6b}$ = 6.0 Hz, 1H, H-5), 3.438 (s, 3H, OCH_3), 1.90–2.04 (m, 2H, H-3′ax, H-3′eq), 1.194 (d, $J_{5',6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR (D_2O) δ: 103.273 (C-1″, $^1J_{C,H}$ = 172.2 Hz), 101.15 (C-1′, $^1J_{C,H}$ = 170.8 Hz), 100.916 (C-1, $^1J_{C,H}$ = 174.5 Hz), 79.868 (C-3), 78.453 (C-2), 73.539 (C-5), 72.950 (C-5″), 71.085 (C-4″), 70.481 (C-2″), 69.037 (C-4′), 68.021 (C-5′), 67.404 (C-4), 65.976 (C-3″), 64.245 (C-2′), 62.426 (C-6″), 61.629 (C-6), 55.681 (OCH_3), 33.776 (C-3′), 16.324 (C-6′). Anal. calcd. for $C_{19}H_{34}O_{14}$-H_2O (504.29): C 45.24, H 7.19;

found: C 45.48, H 7.11. HR-FAB-MS calcd. for $C_{19}H_{31}O_{14}Na$ $[M + Na]^+$: 509.1846; found: 509.1843.

4,6-Dichloro-2-*O*-chlorosulfo-4,6-dideoxy-3-*O*-methyl-α/β-D-galactopyranosyl chloride (51)

3-*O*-Methyl-α-D-glucopyranose (42) (**50**, 194 mg, 1.0 mmol) was dissolved in pyridine (1 mL) and $CHCl_3$ (5 mL) and the flask purged with N_2. The solution was cooled to –78°C and sulfuryl chloride (0.5 mL, 6.25 mmol) was added slowly and then the bath was removed and the reaction was stirred for 24 h. The reaction was then diluted with $CHCl_3$ and washed successively with 1 N H_2SO_4, water, 1 N $KHCO_3$, water, and a saturated solution of NaCl. The organic phase was then dried ($MgSO_4$), evaporated and chromatographed (hexane–EtOAc, 4:1) to provide **51** as two separable anomers. The α-anomer (70 mg, 20%) was obtained as a liquid and the β-anomer (120 mg, 35%) as an amorphous solid. α-Anomer: $[\alpha]_D$ +180.8 (*c* 0.4, $CHCl_3$). R_f = 0.75 (hexane–EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ: 6.36 (d, $J_{1,2}$ = 4.0 Hz, 1H, H-1), 5.13 (dd, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 4.76 (br. d, $J_{3,4}$ = 2.5 Hz, 1H, H-4), 4.46 (dd, $J_{5,6a}$ = 8.5 Hz, $J_{5,6b}$ = 5.5 Hz, 1H, H-5), 3.98 (dd, 1H, H-3), 3.74 (dd, $J_{6a,6b}$ = 11.0 Hz, 1H, H-6a), 3.66 (dd, 1H, H-6′), 3.51 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 89.58, (C-1, $^1J_{C,H}$ = 186.0 Hz). Anal. calcd. for $C_7H_{10}Cl_4O_5S$ (352.03): C 23.88, H 2.86, S 9.11; found: C 24.20, H 2.83, S 9.29. β-Anomer: $[\alpha]_D$ +55.4 (*c* 0.9, CHCl3). R_f = 0.40 (hexane–EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ: 5.28 (d, $J_{1,2}$ = 8.5 Hz, 1H, H-1), 5.10 (dd, $J_{2,3}$ = 9.5 Hz, 1H, H-2), 4.73 (dd, $J_{4,5}$ = 1.0 Hz, 1H, H-4), 3.93 (dd, $J_{5,6a}$ = 7.5 Hz, $J_{5,6b}$ = 6.0 Hz, 1H, H-5), 3.78 (m, 2H, H-6a, H-6b), 3.65 (dd, 1H, $J_{3,4}$ = 3.5 Hz, H-3), 3.54 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 86.62 (C-1, $^1J_{C,H}$ = 174.0 Hz). Anal. calcd. for $C_7H_{10}Cl_4O_5S$ (352.03): C 23.88, H 2.86, S 9.11; found: C 24.41, H 2.91, S 9.45.

Methyl 4,6-dichloro-4,6-dideoxy-3-*O*-methyl-α/β-D-galactopyranoside (52)

Glycosyl chloride **51** (150 mg, 0.43 mmol) was dissolved in CH_3OH (5 mL), a few crystals of I_2 were added, and the reaction stirred for 48 h. Water (200 μL) was added and the reaction stirred for an additional 4 h. The solvent was then evaporated, coevaporating twice with toluene. The residue was then dissolved in 1 M $NaOCH_3$ (300 μL) and stirred overnight at which point the reaction pH had become slightly acidic. The solvent was evaporated and chromatographed (1:1 hexane–EtOAc) to give **52** as two separable anomers. Both the α-anomer (44 mg, 42%) and β-anomer (26 mg, 25%) were obtained as amorphous solids. α-Anomer: $[\alpha]_D$ +192.8 (*c* 0.7, $CHCl_3$). R_f = 0.25 (hexane–EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ: 4.83 (d, $J_{1,2}$ = 3.5 Hz, 1H, H-1), 4.56 (d, $J_{3,4}$ = 2.5 Hz, 1H, H-4), 4.09 (br. t, $J_{5,6a}$, $J_{5,6b}$ = 6.5 Hz, 1H, H-5), 3.97 (dd, $J_{2,3}$ = 9.5 Hz, 1H, H-2), 3.66–3.68 (m, 2H, H-6a, H-6b), 3.60 (dd, 1H, H-3), 3.47 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 99.41 (C-1). Anal. calcd. for $C_8H_{14}O_4Cl_2$ (247.10): C 39.89, H 5.71; found: C 39.32, H 5.75. β-Anomer: $[\alpha]_D$ +32.8 (*c* 0.4, $CHCl_3$). R_f = 0.20, (hexane–EtOAc, 1:1). ^{1}H NMR ($CDCl_3$) δ: 4.56 (d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 4.24 (d, $J_{1,2}$ = 7.5 Hz, 1H, H-1), 3.69–3.80 (m, 4H, H-5, H-2, H-6a, H-6b), 3.55 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.39 (dd, $J_{2,3}$ = 9.5 Hz, 1H, H-3). ^{13}C NMR ($CDCl_3$) δ: 104.25 (C-1). Anal. calcd. for $C_8H_{14}O_4Cl_2$ (247.10): C 39.89, H 5.71; found: C 39.12, H 5.85.

Methyl 2-*O*-benzyl-4,6-dichloro-4,6-dideoxy-3-*O*-methyl-α-D-galactopyranoside (53)

To a stirred suspension of **52** (49 mg, 0.2 mmol) and powdered NaOH (12 mg, 0.3 mmol) in DMF (3 mL) was added benzyl bromide (31 μL, 0.26 mmol). The reaction was instantaneous and was immediately quenched with CH_3OH. The reaction was diluted with toluene and washed with water and then a saturated solution of NaCl. After drying ($MgSO_4$) and solvent evaporation, the product was titrated with hexane to give **53** (48 mg, 71%) as an amorphous white solid. $[\alpha]_D$ +83.3 (*c* 0.7, $CHCl_3$). R_f = 0.60 (hexane–EtOAc, 3:1). ^{1}H NMR ($CDCl_3$) δ: 7.14–7.25 (m, 5H, Ph), 4.74, 4.50 (d, ^2J = 12.0 Hz, 1H, PhCH_2), 4.48 (d, $J_{1,2}$ = 4.0 Hz, 1H, H-1), 4.46 (br. s, 1H, H-4), 3.98 (br. t, $J_{5,6a}$, $J_{5,6b}$ = 6.5 Hz, 1H, H-5), 3.69 (m, 2H, H-2, H-3), 3.52 (m, 2H, H-6a, H-6b), 3.41 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 98.9 (C-1). Anal. calcd. for $C_{15}H_{20}Cl_2O_4$ (337.23): C 53.43, H 5.98; found: C 53.58, H 5.87.

1-*O*-Acetyl-2-*O*-benzyl-4,6-dichloro-4,6-dideoxy-α/β-D-galactopyranose (54)

Methyl glycoside **53** (250 mg, 0.75 mmol) was dissolved in acetic anhydride:HOAc:H_2SO_4 (50:20:0.5, 10 mL) and stirred at 0°C for 1 h and then at room temperature for 30 min. The reaction was quenched by pouring the solution into an ice cold $KHCO_3$ solution and then the product was extracted with CH_2Cl_2. The organic layer was washed with water and a saturated solution of NaCl and then dried ($MgSO_4$) and evaporated. Chromatography (hexane–EtOAc, 6:1) of the residue afforded **53** as two separable anomers. Both the α-anomer (185 mg, 68%) and the β-anomer (34 mg, 12%) were obtained as solids. α-Anomer: $[\alpha]_D$ +156.3 (*c* 0.5, $CHCl_3$). R_f = 0.35 (hexane–EtOAc, 4:1). ^{1}H NMR ($CDCl_3$) δ: 7.25–7.35 (m, 5H, Ph), 6.22 (d, $J_{1,2}$ = 4.0 Hz, 1H, H-1), 4.69 (d, ^2J = 11.5 Hz, 1H, PhCH_2), 4.66 (d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 4.60 (d, ^2J = 11.5 Hz, 1H, PhCH_2), 4.14 (ddd, $J_{5,6a}$ = 8.5 Hz, $J_{5,6b}$ = 5.5 Hz, $J_{4,5}$ = 0.5 Hz, 1H, H-5), 3.90 (dd, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 3.76 (dd, 1H, H-3), 3.64 (dd, $J_{6a,6b}$ = 11.0 Hz, 1H, H-6a), 3.55 (dd, 1H, H-6b), 3.50 (s, 3H, OCH_3), 2.15 (s, 3H, OCOCH_3). ^{13}C NMR ($CDCl_3$) δ: 90.22 (C-1). Anal. calcd. for $C_{16}H_{20}Cl_2O_5$ (365.24): C 52.62, H 5.52; found: C 52.86, H 5.60. β-Anomer: $[\alpha]_D$ +25.5 (*c* 0.5, $CHCl_3$). R_f = 0.5 (hexane–EtOAc, 4:1). ^{1}H NMR ($CDCl_3$) δ: 7.26–7.33 (m, 5H, Ph), 5.56 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.83, 4.66 (d, ^2J = 11.5 Hz, 1H, PhCH_2), 4.60 (d, $J_{3,4}$ = 3.5 Hz, 1H, H-4), 3.87 (ddd, $J_{4,5}$ = 0.5 Hz, $J_{5,6a}$ = 8.0 Hz, $J_{5,6b}$ = 5.5 Hz, 1H, H-5), 3.71–3.76 (m, 2H, H-2, H-6a), 3.66 (d, $J_{6a,6b}$ = 11.0 Hz, 1H, H-6b), 3.50–3.64 (m, 4H, H-3, OCH_3), 2.01 (s, 3H, OCOCH_3). ^{13}C NMR ($CDCl_3$) δ: 93.87 (C-1). Anal. calcd. for $C_{16}H_{20}Cl_2O_5$ (365.24): C 52.62, H 5.52; found: C 52.89, H 5.50.

Ethyl 2-*O*-benzyl-4,6-dichloro-4,6-dideoxy-3-*O*-methyl-1-thio-α-D-galactopyranoside (55)

Compound **54** (40 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (3 mL) and crushed 4 Å molecular sieves (40 mg) were added. Ethanethiol (50 μL, 0.65 mmol) and boron trifluoride etherate (50 μL, 0.4 mmol) were added and the

reaction stirred for 6 h. At this point additional ethanethiol (50 μL, 0.65 mmol) and boron trifluoride etherate (50 μL, 0.4 mmol) were added and the reaction was stirred overnight. The reaction was quenched by the addition of triethylamine (110 μL, 0.8 mmol), and the mixture filtered through Celite and evaporated. Chromatography (hexane–EtOAc, 6:1) of the residue gave **55** (4 mg, 10% and 13 mg, 32%) as an α/β mixture, both as solids. α-Anomer: $[\alpha]_D$ +205.7 (*c* 0.5, $CHCl_3$). R_f = 0.55 (hexane–EtOAc, 6:1). ^{1}H NMR ($CDCl_3$) δ: 7.24–7.37 (m, 5H, Ph), 5.28 (d, $J_{1,2}$ = 5.5 Hz, 1H, H-1), 4.71, 4.66 (d, ^2J = 12.0 Hz, 1H, PhC*H*$_2$), 4.57 (d, $J_{3,4}$ = 2.5 Hz, 1H, H-4), 4.54 (d, $J_{5,6}$ = 6.5 Hz, 1H, H-5), 4.06 (dd, $J_{2,3}$ = 9.5 Hz, 1H, H-2), 3.68–3.59 (m, 3H, H-3, H-6a, H-6b), 3.48 (s, 3H, OC*H*$_3$), 2.50–2.62 (m, 2H, SC*H*$_2$CH$_3$), 1.26 (d, 3H, ^3J = 7.5 Hz, SCH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$) δ: 83.56 (C-1). Anal. calcd. for $C_{16}H_{22}Cl_2O_3S$ (367.32): C 52.32, H 6.04, S 8.73; found: C 52.12, H 6.22, S 8.56.

Methyl 2-*O*-(2-*O*-benzyl-4,6-dichloro-4,6-dideoxy-3-*O*-methyl-α-D-galactopyranosyl)-3-*O*-(2,4-di-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-4,6-di-*O*-benzyl-α-D-mannopyranoside (56)

Thioglycoside donor **55** (22 mg, 0.06 mmol) and alcohol **20** (35) (38 mg, 0.06 mmol) were dissolved in CH_2Cl_2 (10 mL) and the flask purged with N_2. Crushed 4 Å molecular sieves (300 mg) were added and the mixture stirred for 2 h. *N*-Iodosuccinimide (31 mg, 13.8 mmol) was added followed by the dropwise addition of a previously prepared 0.13 M solution of TfOH in CH_2Cl_2. After adding 100 μL of this solution, the reaction was complete. Triethylamine (100 μL) was added and the suspension diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed successively with a saturated solution of $NaHCO_3$, 10% sodium thiosulfate, water, and a saturated solution of NaCl. After drying ($MgSO_4$) and evaporation of the solvent, the residue was chromatographed (hexane–EtOAc, 9:1) to provide **56** (39 mg, 73%) as a thick syrup. $[\alpha]_D$ +107.3 (*c* 0.9, $CHCl_3$). R_f = 0.40 (hexane–EtOAc, 9:1). ^{1}H NMR ($CDCl_3$) δ: 5.45 (d, $J_{1'',2''}$ = 2.0 Hz, 1H, H-1″), 5.21 (d, $J_{1',2'}$ = 3.0 Hz, 1H, H-1′), 5.02, 4.92 (d, ^2J = 11.5 Hz, 1H, PhC*H*$_2$), 4.89 (br. s, $J_{1,2}$ = 1.5 Hz, 1H, H-1), 4.78, 4.64, 4.50 (d, ^2J = 11.5 Hz, 3H, PhC*H*$_2$), 4.49 (br. s, 1H, H-4″), 4.20–4.29 (m, 7H, H-5″, H-3, 5 × PhC*H*$_2$), 4.11–4.17 (m, 1H, H-4), 4.04 (br. s, 1H, H-2), 4.03–4.08 (m, 1H, H-5′), 3.90 (m, 2H, H-2″, H-3″), 3.78 (m, 3H, H-2′, H-5, H-6a), 3.60–4.70 (m, 3H, H-6b, H-6″a, H-6″b), 3.44 (s, 3H, OC*H*$_3$), 3.40 (s, 3H, OC*H*$_3$), 3.05 (s, 1H, H-4′), 1.95–1.96 (dt, $J_{2',3'eq}$, $J_{3'eq,4'}$ = 3.5 Hz, $J_{3'eq,3'ax}$ = 13.0 Hz, 1H, H-3′eq), 1.73 (ddd, $J_{3'ax,4'}$ = 12.5 Hz, $J_{2',3'ax}$ = 2.0 Hz, 1H, H-3′ax), 1.15 (d, $J_{5',6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR ($CDCl_3$) δ: 99.38 (C-1), 98.95 (C-1′), 97.67 (C-1″). Anal. calcd. for $C_{55}H_{64}Cl_2O_{12}$ (990.02): C 66.73, H 6.52; found: C 66.91, H 6.70.

Methyl 2-*O*-(4,6-dichloro-4,6-dideoxy-3-*O*-methyl-α-D-galactopyranosyl)-3-*O*-(3,6-dideoxy-α-D-*xylo*-hexopyranosyl)-α-D-mannopyranoside (15)

Trisaccharide **56** (39 mg, 0.04 mmol) was dissolved in acetic acid (10 mL) and 10% Pd/C (40 mg) added. The reaction was stirred under an atmosphere of H_2 for 4 h and then was filtered through Celite and the filtrate evaporated. Chromatography (water) on Bio-Gel P-2 gave, after lyophilization, **15** (14 mg, 66%) as a foam. $[\alpha]_D$ +146.6 (*c* 0.5, H_2O). ^{1}H NMR (D_2O) δ: 5.332 (d, $J_{1'',2''}$ = 3.5 Hz, 1H, H-1″), 5.112 (d, $J_{1',2'}$ = 3.5 Hz, 1H, H-1′), 5.052 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 4.855 (dd, $J_{3'',4''}$ = 3.0 Hz, $J_{4'',5''}$ = 1.0 Hz, 1H, H-4″), 4.415 (ddd, $J_{5'',6''a}$ = 5.0 Hz, $J_{5'',6''b}$ = 6.5 Hz, 1H, H-5″), 4.106 (t, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 4.072 (dq, $J_{4',5'}$ = 1.0 Hz, 1H, H-5′), 3.99–4.06 (m, 2H, H-2′, H-3), 3.979 (t, $J_{3,4} \approx J_{4,5}$ = 9.5 Hz, 1H, H-4), 3.948 (dd, 3.5, $J_{2'',3''}$ = 10.0 Hz, 1H, H-2″), 3.86–3.92 (m, 3H, H-6a, H-4′, H-3″), 3.76–3.85 (m, 3H, H-6b, H-6″a, H-6″b), 3.674 (ddd, $J_{5,6a}$ = 2.0 Hz, $J_{5,6b}$ = 5.5 Hz, 1H, H-5), 3.473 (s, 3H, OC*H*$_3$), 3.434 (s, 3H, OC*H*$_3$), 1.90–2.02 (m, 2H, H-3′eq, H-3′ax), 1.183 (d, $J_{5',6'}$ = 6.5 Hz, 3H, H-6′). ^{13}C NMR (D_2O) δ: 101.110 (C-1′, $^1J_{C,H}$ = 171.2 Hz), 100.799 (C-1″, $^1J_{C,H}$ = 173.3 Hz), 100.356 (C-1, $^1J_{C,H}$ = 173.2 Hz), 77.206 (C-3), 77.920 (C-2), 77.767 (C-3″), 73.796 (C-5), 70.952 (C-5″), 69.108 (C-4′), 68.156 (C-2″), 67.738 (C-5′), 67.460 (C-4), 64.160 (C-2′), 61.423 (C-6), 59.945 (C-4″), 57.174 (OCH_3), 55.712 (OCH_3), 44.489 (C-6″), 33.733 (C-3′), 16.251 (C-6′). Anal. calcd. for $C_{20}H_{34}Cl_2O_{12}$ (539.39): C 44.54, H 6.35; found: C 44.49, H, 6.55.

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