Total Synthesis and Proof of Structure of a Human Breast Tumor (Globo-H) Antigen

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Abstract: The total synthesis of the Hakomori MBr1 antigen, heavily expressed on human breast tumors, is related. The construction involved the assembly of four glycals: (**17** (twice), **18**, **20**, and **26**) and an L-fucose derivative, **34**. The sensitivity of the stereochemistry of sulfonamido galactosylation by a terminal galactose ring as a function of the state of protection status of its C_4 alcohol was exploited in a key step. (See the formation of compound **51**.) The synthesis served to confirm the Hakomori assignment of structure, and paves the way for immunoconjugation. (See compound **64**.)

Background

One need hardly dwell on the advantages which might accrue if the enormous powers of the human immune system could be mobilized to do battle against cancer.[1] It could be imagined that such a recruitment would be helpful in combating the onset of the formation of the cancerous cells, in attacking existing areas of cellular transformation, and in resisting metastasis.[2] This concept has often been discussed in the context of futuristic hopes and has been supported by some apparent tantalizing early successes.[3] However, at the present writing, no broadly based clinical application of active immunity against cancer through vaccination has been demonstrated.

Among the novel constellations, generated by transformed cells are anomalous glycosidic ensembles.[4] The degree to which particular carbohydrate patterns are indeed specific to cancer cells, or even to cancers of particular tissues or organs, remains to be properly and fully sorted out through the techniques of immunohistology. However, there is an emerging perception that certain consensus patterns are, minimally, overexpressed in transformed cells as glycoprotein or glycolipid conjugates.[5] Whether such accumulation arises from the coincidental abundance of particular glycosyl transferases, or whether it reflects the purposeful biosynthesis of these anomalous constellations to perform a function in the transformed cell, awaits clarification and may indeed vary, on a case to case basis.

In this regard, our attentions were drawn to a novel structure which seems to be associated with human breast cancer. Traces of the glycosphingolipid, **1** were isolated by Hakomori[6,7] and associates by processing human breast cancer cell line, MCF-7. The structure was assigned by spectroscopic measurements in combination with chemical and enzymatic degradative mapping. Another advance which facilitated study of this breast tumor antigen was its immunocharacterization via monoclonal antibody MBr1 by Colnaghi and associates.[8] This antibody had been obtained from mice immunized with intact MCF-7 cell lines. Thus, the isolation of **1** from these cell lines and its binding to MBr1 were taken to implicate this glycolipid as a breast tumor antigen.

The degree of specificity of antigen **1** to breast tumors has not been established. The criterion of isolation and characterization of **1** has, at this writing, only been met by the Hakomori experiment using the transformed (MCF-7) mammary cells.[7] By the criteria of immunohistology, as evidenced by binding of whole tissue to MBr1, the antigen seems to be present, to a lesser extent in normal mammary and other teratocarcinoma cells. However, caution is appropriate in drawing such a conclusion. As shown by our mapping studies at the end of this paper, and by earlier, as well as continuing investigations by Russo and co-workers,[9,10] truncated versions of **1** are also found to bind to MBr1. Hence, the criterion of immunohistology, as based on binding of MBr1 to define the presence of **1** as a total structural entity in a particular tissue, is lacking in rigor by the standards of chemistry.

While such uncertainties remain to be resolved, the clear association of compound **1** with mammary and other epithelial cancers[11] rendered it an important synthetic target. Aside from the inherent challenge to the field of complex oligosaccharide synthesis posed by this structure, there were additional incentives

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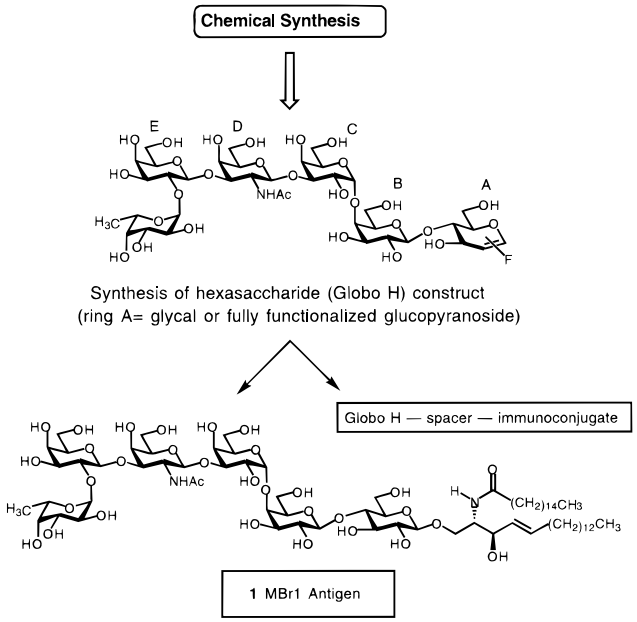
Scheme 1



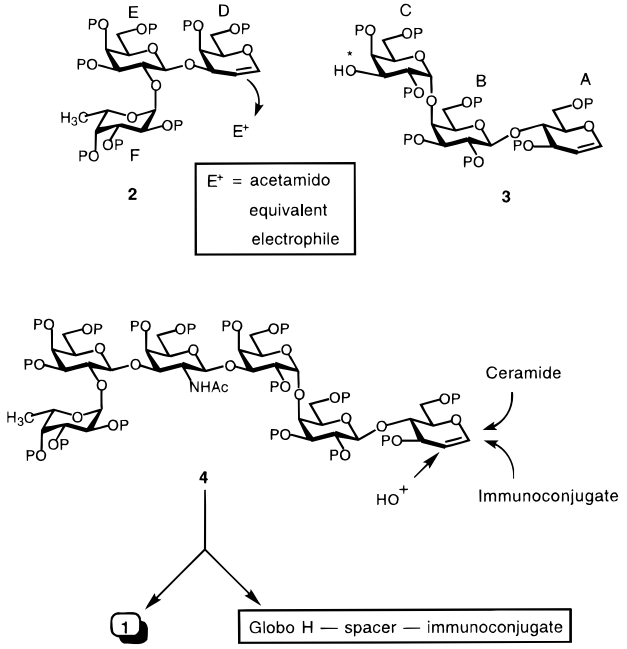
arising from the possibility of constructing a carbohydrate-based antitumor vaccine. Conceivably, an immunofostering conjugate of fully synthetic **1** might serve to stimulate antibody formation in patients. Through such studies, the prospects for magnifying active immunity against cancer could be evaluated experimentally. Clearly, such an undertaking would require access to substantial amounts of the carbohydrate domain in a form where it could be connected to an immunotriggering domain. Scheme 1 provides the structure of **1** and the governing paradigm for creating synthetically derived carbohydrate-based antitumor vaccines.

In this paper, we describe (i) the total syntheses of the MBr1 antigen,[12] (ii) a chemically rigorous proof of its structure, and (iii) the establishment of a linker domain for purposes of fashioning a functional vaccine.

Synthetic Planning

In studying structure **1** as to its amenability to chemical synthesis on a decent scale, the interior network of four galactose/galactosamine residues is quickly recognized. A principal retrosynthetic disconnection between ring C and D seemed attractive. Hence, a DEF glycal (cf. structure type **2**) emerges as a subgoal. In a similar vein glycal type **3** can serve as an ABC acceptor equivalent. System **2** would be converted to an "azaglycosylation donor"[13] upon suitable activation of its glycal linkage. For instance, we hoped to apply our own methodology wherein a 2β-iodo sulfonamide derived from a type 2 (DEF) glycal would function as the donor for β-sulfonamidoglycosylation.[14,15] Of course, the appropriate C_3 oxygen of the galactose residue at the nonreducing end of ABC glycal

Scheme 2



3 would have to be distinguished as the unique acceptor site. With hexasaccharide glycal **4** thus produced, provision for introduction of the ceramide via its glycal linkage would be available.[16,17] Alternatively, the terminal glycal linkage of the hexasaccharide could be exploited to lead, through a spacer sector, to suitable immunoconjugates in keeping with the biological goal of the program[18] (see Scheme 2).

Keeping in mind the realities of the availability of carbohydrate building blocks, it seemed clear from the outset that the DEF sector would be fashioned from the suitable melding of two galactal units to provide eventually the Gal-Gal glycal **5**, which upon fucosylation at C_2' would lead to **2**.

As to the ABC domain, we initially hoped to exploit the ready accessibility of lactal **6**.[19] In the early planning, it was conjectured that it could prove possible to differentiate the hydroxyl groups of **6** such as to identify the unique axial hydroxyl at C_4' as the acceptor site (see asterisk in structures **6** and **7**). We further envisioned the generation of galactal (**8**) wherein C_3 would be distinguished via a unique blocking group which would identify this center as the acceptor site.

Coupling of **7** with an α-galactosyl donor derived from **8** followed by deprotection of the unique P* blocking group would lead to the previously discussed **3** for coupling with an azaglycal donor derived from **2** (Scheme 3).

It is with the building of an ABC sector corresponding to **3** that our account begins.

Several initiatives were undertaken to evaluate the possibility of using lactal (**6**) as our starting material to fashion a usefully differentiated AB system. In accord with previous reports, it was a relatively straightforward matter to protect C_6 and C_6' as the di-TIPS derivative (see compound **9**). As described in an earlier finding, we could contain the 3′- and 4′-hydroxyl groups in the form of a cyclic carbonate.[20,21] The hydroxyl groups at C_3 and C_2' were thus exposed for silylation. Cleavage of the

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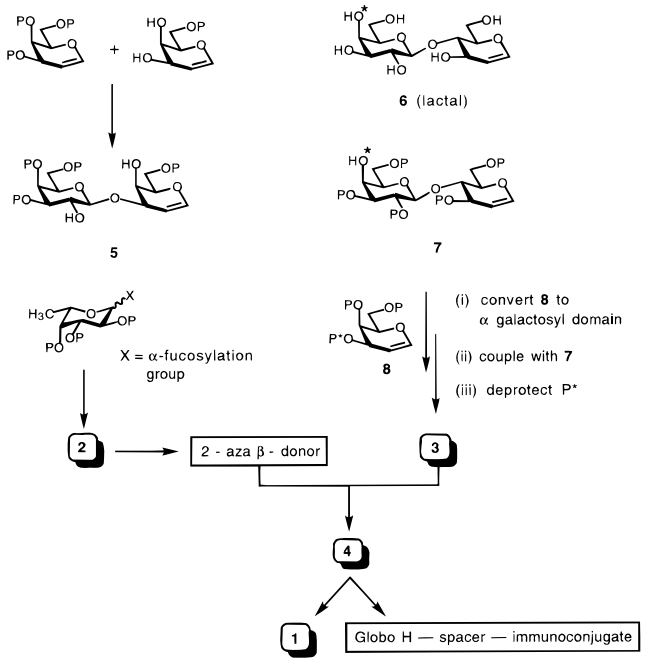
Scheme 3



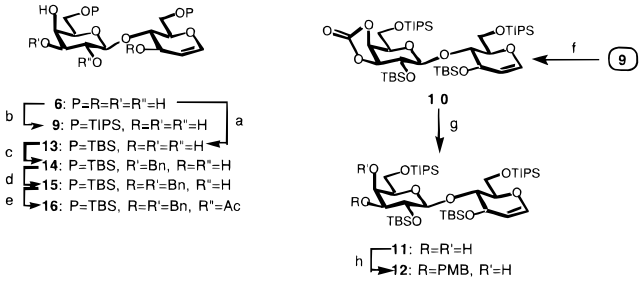
cyclic carbonate in **10** gave rise to **11**. We attempted to selectively protect C_3' with a durable blocking group. Unfortunately, we could only obtain a 28% yield of the *p*-methoxybenzyl ether **12** with 35% recovered **11**.

In another initiative, two *tert*-butyl dimethyl silyl groups were introduced at C_6 and C_6' of **6**. A high-yielding monobenzylation of compound **13** at C_3' was accomplished to afford **14** in high yield (Scheme 4). The next preferred site of benzylation was the C_3 hydroxyl. However, the selectivity margins were not acceptable. At best, a 35% yield of **15** was obtained. Furthermore, the selectivity margin for acetylation of C_2' and C_4' was poor. We could obtain, at best, a 56% yield of **16**. On the basis of these and other early difficulties of a similar character, we set aside the idea of using lactal (**6**) itself to fashion the AB sector, recognizing full well that several unexplored opportunities to realize this goal remain open for future study.

Fortunately, another route presented itself. In this route we would fashion our own lactal subunit corresponding to rings A and B in formal construct **3**. The advantage here would be that in the assembly process we could already have made provision for distinguishing the C_4' hydroxyl group corresponding to structure type **7**. The synthesis proceeded as follows. Galactal was silylated at C_6 to provide structure **17**. Engagement of the C_3 and C_4 hydroxyl groups, as previously described, provided the cyclic carbonate **18**. The α-epoxide **19**, obtained by the treatment of **18** with dimethyldioxirane, was to serve as the B ring. (See Scheme 5.)

The A ring equivalent was obtained from the dibenzylation of glucal, giving rise to the 3,6-dibenzyl compound **20**. Coupling of compounds **19** and **20** gave rise to A B intermediate **21**. The next subgoal was that of identifying the C_4' hydroxyl group of the B ring as the site of the α galactosylation. It was possible to introduce a single benzyl group at C_2' in **21** in 81% yield, to afford compound **22**. Desilyation followed by cleavage of the cyclic carbonate gave rise to **23**. Using stannylidene methodology,[22] two benzyl groups could be introduced on C_3' and C_6', giving rise to compound **24** *in which the only non benzylated hydroxyl group was, in fact, at the axial hydroxyl at C_4' destined to provide the linkage site of the B and C rings*.

Scheme 4[a]



[a] Reagents: (a) TBSCl, cat. DMAP, Et_3N, DMF, 62%; (b) TIPSCl, imidazole, DMF, 49%; (c) $(n\text{-}Bu_3Sn)_2O$, PhH, then BnBr, TBAI, 96%; (d) NaH, BnBr, DMF, 35%; (e) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 56%; (f) (i) 1,1′-carbonyldiimidazole, cat. DMAP, CH_2Cl_2, 67%; (ii) TBSCl, imidazole, DMF, 83%; (g) NaOMe, MeOH, THF, 75%; (h) $n\text{-}Bu_2SnO$, PhH, then PMBCl, TBABr, 28% (with 35% of **11**).

The C ring construct was fashioned from D-galactal. It was possible through stannylation to cleanly introduce a *p*-methoxybenzyl group at C_3 (see compound **25**). At this stage, 2-fold benzylation at the C_4 and C_6 centers gave rise to differentiated galactal **26**. The latter was converted to the β-anomeric fluoride **28** via its α epoxide **27**.[23] Benzylation of the C_2 hydroxyl group gave **29**, which was to function as our α galactosylating agent for introduction of ring C.

The stage was now set for the fateful coupling between acceptor **24** and donor **29**. Indeed, glycosylation was accomplished using Mukaiyama[24]−Nicolaou[25] conditions, as shown. This reaction gave rise to a 54% yield of **30**, as well as an 18% yield of its β anomer **31**. Upon discharge of the lone *p*-methoxybenzyl group in the C ring, formation of the ABC acceptor with its differentiated hydroxyl acceptor site was accomplished. (See compound **32** and asterisk.)

For fashioning of the DEF glycosyl donor corresponding to **2**, we began with a compound, described earlier, i.e., the TIPS cyclic carbonate α epoxide, **19**. This donor was, in turn, used to glycosylate the previously described acceptor **17**. No differentiation of the C_3 and C_4 hydroxyl groups of **17** was necessary in this coupling which occurred cleanly at C_3, under the influence of zinc chloride. Compound **33** was obtained in 87% yield.

The stage was now set to distinguish C_2' from C_4 in a fucosylation experiment. We hoped that fucosylation would occur at the equatorial rather than the axial alcohol. In the event this supposition proved to be correct. Using the previously described fucosyl donor **34**, under Mukaiyama[24]−Nicolaou[25] conditions, there was obtained a 47% yield of compound **35** accompanied by approximately 8% of monofucosylated product **36** where the L-fucosyl residue had penetrated at C_4 of the galactose. For purposes of advancing on our goal, this somewhat disappointing attrition in regioselectivity was accepted in deference to the convenience of the route. Compound **35** was acetylated to provide **37** which was converted to its iodo sulfonomide **38** in the usual way.[14,15]

The coupling of acceptor **32** and donor **38** was carefully studied because it loomed as a key step in the synthesis. This type of merger, though with much simpler substrates, had been the cornerstone of our azaglycosidation methodology.[13−15] Thus, we were surprised to find that under a variety of conditions, the union of these two substances could not be

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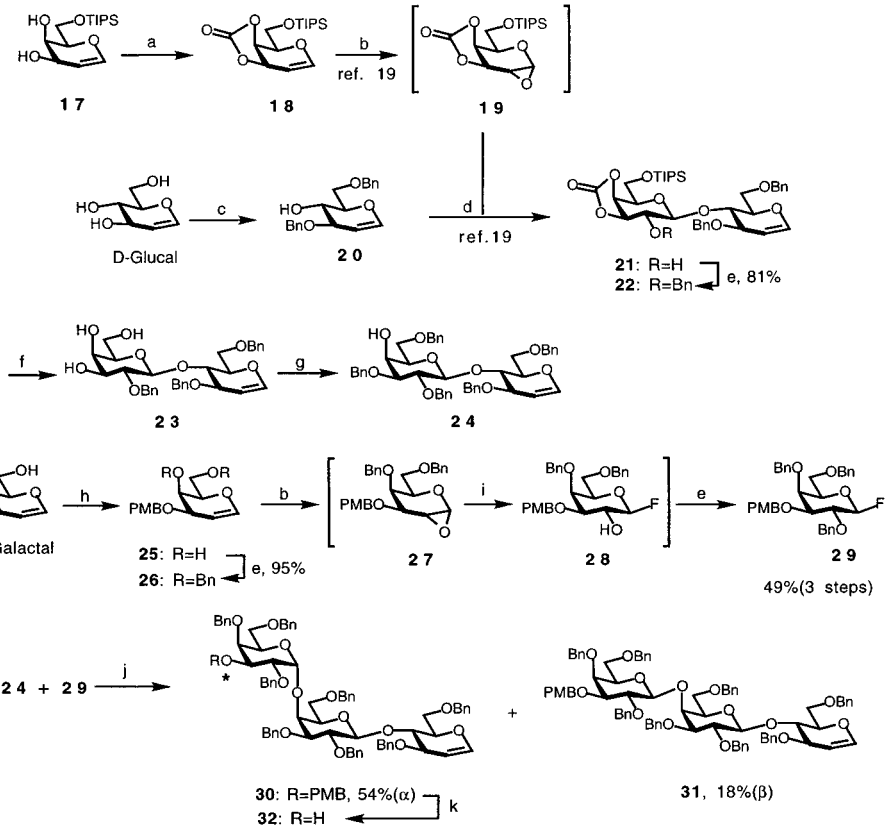
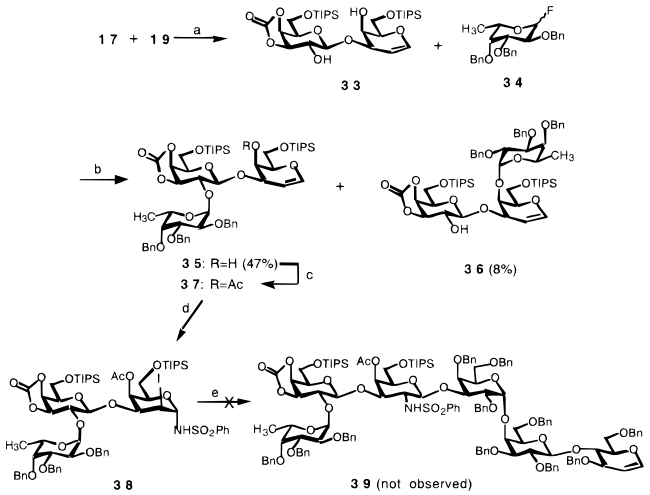
Scheme 5[a]



[a] Reagents: (a) 1,1′-carbonyldiimidazole, cat. DMAP, CH_2Cl_2, quant.; (b) 3,3′-dimethyldioxirane, CH_2Cl_2; (c) (n-$Bu_3Sn)_2O$, TBABr, BnBr, PhH, 65%; (d) $ZnCl_2$, THF; (e) BnBr, NaH, DMF; (f) TBAF, THF, then MeOH, MeONa, 93%; (g) (n-$Bu_3Sn)_2O$, Bu_2SnO, PhH, then TBABr, BnBr, 90%; (h) n-Bu_2SnO, TBABr, PMBCl, PhH, 70%; (i) TBAF, THF; (j) $AgClO_4$, $SnCl_2$, di-*tert*-butylpyridine, 4 Å molecular sieves, Et_2O; (k) DDQ, CH_2Cl_2, H_2O, 86%.

Scheme 6[a]



[a] Reagents: (a) $ZnCl_2$, THF, 87%; (b) $AgClO_4$, $SnCl_2$, di-*tert*-butylpyridine, Et_2O; (c) Ac_2O, Py, cat. DMAP, 91%; (d) $I(coll)_2ClO_4$, $PhSO_2NH_2$, 4 Å molecular sieves, THF, 82%; (e) **32**, (n-$Bu_3Sn)_2O$, PhH, then $AgBF_4$, THF.

achieved in a reasonable way. At best, one could detect traces of a presumed coupled product **39** by examination of NMR spectra of crude reaction mixtures. (See Scheme 6.) However, it did not prove feasible to obtain homogeneous product material necessary to demonstrate even this level of attainment in a rigorous way. This failure, in conjunction with other failures in more complicated cases, demonstrated that the azaglycosidation via "direct rollover" of iodo sulfonamides may not be reliable with seriously hindered substrates which are encountered in the context of coupling of oligomers. Difficulties can be further aggravated by what we have termed chiral mismatches, i.e., situations where the match of particular asymmetric contours of the donor and acceptor[26] influence the feasibility of coupling and its steric course. In a striking example, Spijker and van Boeckel[27] found out that the β-directing power of a C_2 benzoyl group was so overweighed by the chiral mismatch that it led to a complete α glycosylation.

In our earlier investigations on sulfonamidoglycosylation,[14] we had already explored a variation which might be effective in otherwise difficult cases. This is shown in the transformation of **40** + **41** → **42** (Scheme 7). In this two-step protocol, the acceptor for the first azaglycosidation is a thioethyl function, giving rise to a structure of the type **42**. The latent donor capacity of such a thioglycoside can be promoted through the action of methyl triflate.[28] In the cases previously studied,[13,15] very high preferences for β-glycoside in the second had been realized (cf. **42** + AH → **43**).

In principle, it might have been argued that whether one starts with **40** or **42**, after suitable promotion the actual glycosylating entity is the same *N*-sulfonylaziridine **44**. However, this need not necessarily be the case. A possibility deserving of consideration is that when starting with donor type **42**, the active glycosylating agent is actually a form in which the oxygen atom of the sulfonamide (rather than the nitrogen) had participated leading to structure type **45** (status of NH undefined). Such a

(26) For a striking example of matching effects in glycoside synthesis, see: Halcomb, R. L.; Boyer, H. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefksy, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5720 and references cited therein.

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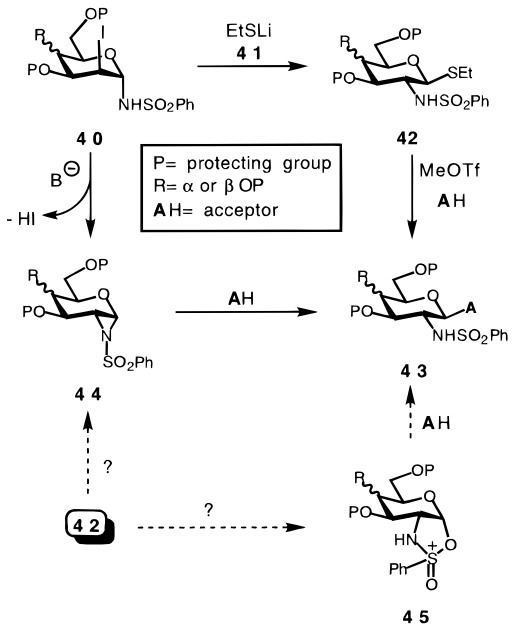
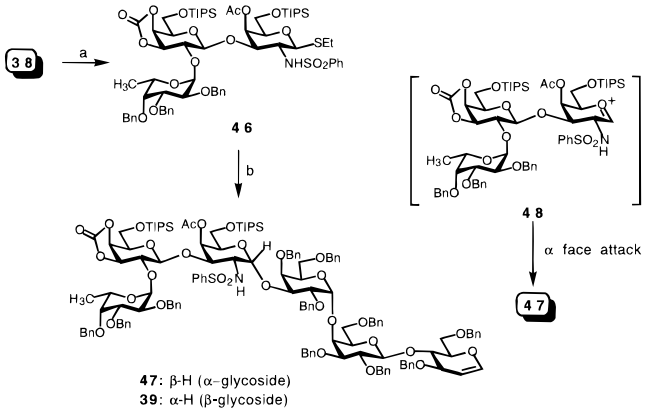
Scheme 7



Scheme 8[a]

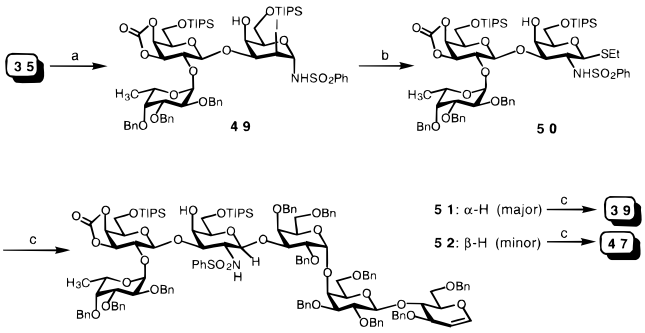


[a] Reagents: (a) **41** from EtSH, LHMDS, and DMF, 92%; (b) **32**, MeOTf, 4 Å molecular sieves, $Et_2O-CH_2Cl_2$ (2:1), 60% β-H (β-H:α-H = 5:1).

system could well display different characteristics of stability, and stereoselectivity patterns, relative to **44** in difficult glycosidations.

We decided to explore implementation of the two-stage protocol to the case at hand. The effort began on a favorable note when compound **38** reacted with lithium ethanethiolate under the specified conditions to afford compound **46** (Scheme 8). We now studied the all-critical glycosidation of acceptor **32** with donor **46**. Indeed, under promotion by methyl triflate, coupling occurred giving rise to a 5:1 mixture of glycosides. Naturally, on the basis of previous experience, we assumed that the major product was the β-glycoside **39**, while the minor one was assigned as **47**. At this stage, NMR analysis was complicated by interferences from the signals of the blocking group based protons. Our assignment was based solely on precedent and the perceived mechanistic logic of the reaction. Following introduction of the ceramide residue and global deprotection by schemes which will be described below, it was discovered that the major product of this glycosidation was the α-glycoside **47** while the minor one was actually the desired **39**. Clearly, the C_2-based sulfonamide had not provided β-directionality guidance for the glycosidation reaction. We took this breakdown to imply a failure in the participation effect of the sulfonamide resulting in intervention of an onium type specie (cf. **48**) as the active form of the donor, rather than

Scheme 9[a]



[a] Reagents: (a) $I(coll)_2ClO_4$, $PhSO_2NH_2$, 4 Å molecular sieves, THF, 50%; (b) **41** from EtSH, LHMDS, and DMF, 79%; (c) **32**, MeOTf, 4 Å molecular sieves, $Et_2O-CH_2Cl_2$ (2:1), 70−85% α-H (α-H:β-H = 10:1); (c) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2.

counterparts of 1,2 "cyclo" structures such as **44** or **45**, which would have assured β-galactoside formation.

It seemed possible that structural features in the terminal galactose ring, or elsewhere in the DEF ensemble, were encouraging onium ion formation and disfavoring the participating form (cf. **44** or **45**) of the active glycosyl donor. We naturally wondered whether the outcome favoring the α:β preponderance of 5:1 could be materially altered by effecting small changes in the nature of the donor ring. The area of the donor entity which might be most readily probed experimentally, without major restructuring of the synthesis, was the disposition of the oxygen at C_4 in the reducing terminus ring. In an earlier intermediate, **35**, this oxygen atom had appeared as an alcohol. The possibility that the free hydroxyl group at C_4 could be maintained in the fashioning of donor **49** was explored.

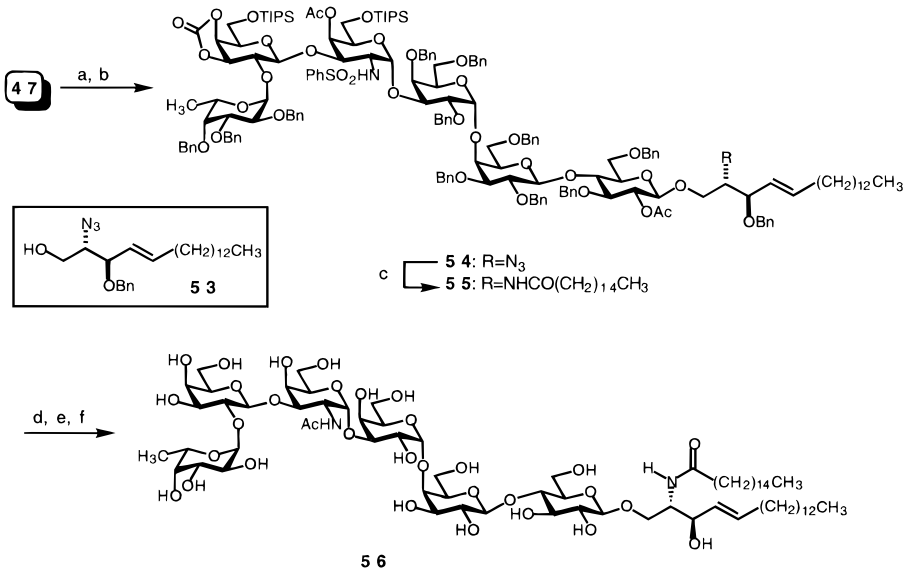
In the event, it was feasible to effect iodosulfonimidation on intermediate **35** to produce **49** (Scheme 9). This compound was, in turn, converted to the 1β-ethanethiolate donor **50** bearing a 2α-phenylsulfonamido function by the rearrangement shown. Coupling of **50** with **32** with methyl triflate gave rise to an 10:1 mixture of **51**:**52**. Acetylation of these two compounds quickly established that they did indeed correspond to the previously encountered **39** and **47**. *Most remarkably, the major product of the glycosidation via **50**, with the hydroxyl in free form, was **51** corresponding in stereochemistry to the minor product **39**, in the glycosidation of the C_4 acetoxy bearing donor **46**.* Similarly, the minor product **52**, arising from **50**, corresponded to the major product (**47**) of the C_4 acetoxy donor **46**. Thus, indeed, very substantial reversal of the directionality of the glycosylation had been achieved by the seemingly minor device of changing the character of the C_4 in the donor from acetate to alcohol. This trend has been verified in simpler substances. It played a key role in our recently completed total synthesis of asialo GM_1.[29]

We first demonstrate that our formulations of **39**, **47**, **51**, and **52** are correct. Treatment of presumed compound **47** with 3,3-dimethyldioxirane followed by coupling of the epoxide with azidohydrin **53** under the influence of anhydrous zinc chloride gave rise, after acetylation, to product **54** (Scheme 10). The capacity to introduce truncated precursors of the ceramide side chain in this way had been previously demonstrated in our laboratory.[16,17] Reduction of the azide linkage and palmitoylation of the resultant amine led to **55**. Treatment of the latter

(29) Danishefsky, S. J.; Kwon, O. Unpublished data. See also: Berresi, F.; Hindsgaul, O. *J. Carbohydr. Chem.* **1996**, *14*, 1043. For a review containing related observations on galactosylation, see: Paulson, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.

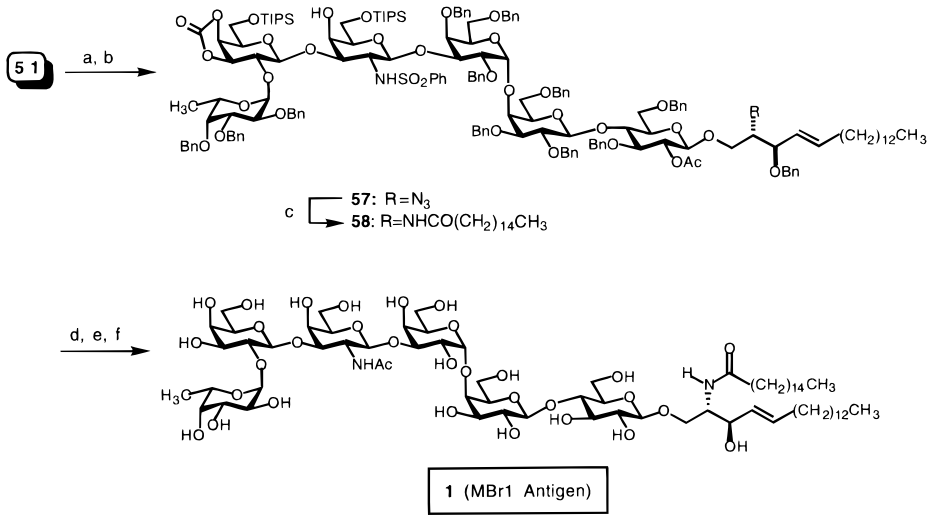
(30) Three characteristic α anomeric protons were observed through proton NMR: δ 5.19 (1H, d, J = 3.8 Hz), 5.11 (1H, d, J = 3.6 Hz), and 5.01 (1H, d, J = 3.6 Hz). This fact shows that the C−D glycosidic linkage is α.

Scheme 10[a]



[a] Reagents: (a) (i) 3,3-dimethyldioxirane, 4 Å molecular sieves, CH_2Cl_2; (ii) **53**, $ZnCl_2$, THF, 46%; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 96%; (c) Lindlar's catalyst, H_2, palmitic anhydride, EtOAc, 92%; (d) (i) TBAF, THF; (ii) NaOMe, MeOH; (e) (i) Na, NH_3, THF; (ii) Ac_2O, Et_3N, DMAP, DMF, THF; (f) NaOMe, MeOH, 68% (over five steps).

Scheme 11[a]



[a] Reagents: (a) (i) 3,3-dimethyldioxirane, 4 Å molecular sieves, CH_2Cl_2; (ii) **53**, $ZnCl_2$, THF, 53%; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 95%; (c) Lindlar's catalyst, H_2, palmitic anhydride, EtOAc, 90%; (d) (i) TBAF, THF; (ii) NaOMe, MeOH, 94%; (e) (i) Na, NH_3, THF; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 80%; (f) NaOMe, MeOH, quantitative.

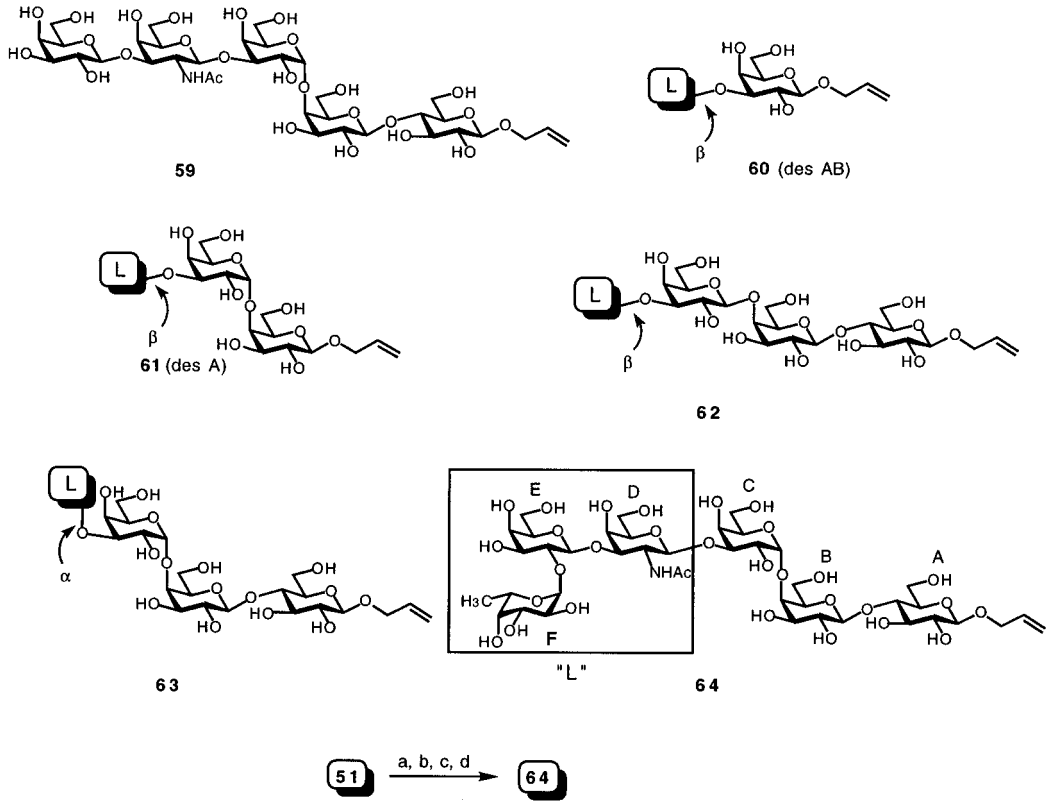
product with TBAF and then with sodium methoxide−methanol resulted in cleavage of the silyl and the two acetate protecting groups, as well as the cyclic carbonate. The 12 benzyl and sulfonamido protecting groups were discharged by reaction of sodium and ammonia. Exhaustive acetylation followed by deacetylation with sodium methoxide in methanol afforded compound **56**. This structure differed in its NMR spectrum in several notable respects from the MBr1 antigen itself.[4,30] On the basis of these data, as well as by virtue of its mass spectrum, we formulate it to be compound **56**, i.e., the C−D glycoside epimer of the desired compound **1**.

In a similar vein, starting with compound **51**, reaction with 3,3-dimethyldioxirane afforded the usual 1,2-epoxide derivative. The latter, on reaction with acceptor **53**, moderated by zinc chloride, gave rise to a 53% yield of the adduct **57** (Scheme 11). This glycosidation was soon followed by reduction of the azide linkage and palmitoylation of the resultant amine to afford **58**. The remaining steps were much the same as those used in the synthesis of **56**. Thus starting with substrate **58**, a cleavage sequence consisting of all silyl groups (TBAF), acyl groups (sodium methoxide−methanol), and benzyl groups (sodium and ammonia) followed by peracetylation and per-deacetylation of the oxygen-based acetates gave rise to the MBr1 antigen **1**. The compound thus synthesized in contrast with **56** binds very nicely to the MBr1 antigen. Moreover, its structure assignment, on purely chemical grounds, is in complete accord with its NMR,[31] its infrared and mass spectra, and the corresponding spectra of its precursor structures. The region of the spectrum of synthetic **1** reflecting anomeric resonances is identical with the corresponding spectrum displayed in the Hakomori paper.[7] *The structural proposal advanced by Hakomori for the MBr1 antigen has thus been fully supported and the total synthesis of the breast tumor antigen has been accomplished.*

It was well to determine the structural specificity involved in binding of target congeners to this MBr1 antigen. The

(31) Only the chemical shifts and coupling constants of anomeric protons were reported for the natural MBr-1 antigen (**1**) (see ref 7). Characterisitc anomeric protons of MBr-1 antigen (**1**) were observed at 4.95 (1H, br s), 4.81 (1H, d, $J = 3.7$ Hz), 4.48 (1H, d, $J = 8.4$ Hz), 4.44 (1H, d, $J = 8.1$ Hz), 4.25 (1H, d, $J = 7.6$ Hz), 4.16 (1H, d, $J = 7.8$ Hz) and is in complete agreement with reported data.

Scheme 12[a]



[a] Reagents: (a) TBAF, THF, 94%; (b) (i) Na, NH_3, THF; (ii) Ac_2O, Et_3N, DMAP, THF, DMF, 85%; (c) (i) 3,3-dimethyldioxirane, CH_2Cl_2; (ii) allyl alcohol, 66% (+29% of α-manno isomer); (d) NaOMe, MeOH, quantitative.

Table 1. Inhibition of MAb MBr1 Binding to an MCF-7 Cell Line by Synthetic Antigens (**59**−**64**)

compd	IC_{50} (mM)[a]	compd	IC_{50} (mM)[a]
59	>500[b]	**62**	27
60	26	**63**	200
61	10	**64**	16

[a] 50% inhibitory concentration. [b] IC_{50} not reached.

chemistry by which the targets had been synthesized followed the principles described above and led to compounds **59**−**64** as reported earlier.[32] The binding data with MBr1 antibody are summarized in Table 1. These data signify the crucial nature of the terminal fucose residue. In the absence of this residue, the structure known otherwise as the SSEA-3 (stage specific embryonic antigen-3, **59**) antigen[33] fails to bind to the MBr1 antibody at appropriate concentrations.

The data also indicate that the nature of the glycosidic bond in rings B and C is not critical. Indeed they point to the fact that rings A and B may be deleted entirely (see compound **60**, Scheme 12). Interestingly, pentacycle **61**, in which only the A ring of the MBr1 hexasaccharide epitope has been deleted, binds MBr1 antibody even slightly more avidly than does the full antigen.

We close by describing how the glycal domain (see compound **51**) was converted to allyl glycoside **64**, which is a major target site structure for commencement of the process of conjugation. The methodology we used here was similar to that used in the synthesis of our truncated constructs,[32] as well as that used in the fashioning of the reducing end of the Lewis blood group determinants.[19] Thus, the peracetylated version of glycal **51** (see steps a and b) was treated with dimethyldioxirane. The resulting epoxide was coupled with allyl alcohol. Surprisingly, this sequence led to an approximately 2.5:1 ratio of α:β epoxides. Deacylation through the action of sodium methoxide completed the synthesis of the allyl glycoside **64**. As discussed earlier,[18,19] oxidative cleavage of the double bond of such allyl glycosides leads to glycolic aldehyde glycosides which are eminently suitable for bioconjugations. Reports on these investigations as well as the immunoperformances of our synthetic constructs will be forthcoming in future disclosures.

Summary

The synthesis of compound **1** accomplished the goal of proof of structure and provided the basis for orderly immunoconjugation. Moreover it served to underscore the power of glycal assembly in reaching oligosaccharide ensembles. In particular we cite the conciseness in reaching systems of the type **32** and **35** using minimalist protection devices involving systems derived from the readily obtainable galactal **17** and glucal **20**. We also underscore the remarkable reversal in the stereochemistry of sulfonamidogalactosylation by fine tuning of the status of the axial C_4-based oxygen of the donor terminus.

Experimental Section

General. All commercial materials were used without further purifications unless otherwise noted. The following solvents were distilled under positive pressure of dry nitrogen immediately before use: THF from sodium benzophenone ketyl, ether from $LiAlH_4$, CH_2Cl_2, toluene and benzene from CaH_2. All the reactions were performed under N_2 atmosphere. NMR (^1H, ^{13}C) spectra were recorded on Bruker AMX-400 MHz, Bruker Avance DRX-500 MHz, referenced to TMS (^{1}H-NMR, δ 0.00) or $CDCl_3$ (^{13}C-NMR, δ 77.0) and CD3OD (^{13}C-NMR, δ 49.05) peaks unless otherwise stated. LB = 1.0 Hz was used before Fourier transformation for all of the ^{13}C-NMR. IR spectra were recorded with a Perkin-Elmer 1600 series-FTIR spectrometer, and optical rotations were measured with a JASCO DIP-370 digital

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(33) Shevinsky, L. H.; Knowles, B. B.; Damjanov., I.; Solter, D. *Cell* **1982**, *30*, 697. Andrews, P. W.; Goodfellow, P. N.; Shevinsky, L. H.; Bronson, D. L.; Knowles, B. B. *Int. J. Cancer* **1982**, *29*, 523. Nunomura, S.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 5681. Park, T. K.; Kim, I. J.; Danishefsky, S. J. *Tetrahedron Lett.* **1995**, *36*, 9089 (see also ref 6).

polarimeter using 10 cm pathlength cell. Low- and high-resolution mass spectral analyses were performed with a JEOL JMS-DX-303 HF mass spectrometer. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized by dipping the plates in a cerium sulfate−ammonium molybdate solution followed by heating. Flash column chromatography was performed using the indicated solvent on E. Merck silica gel 60 (40−63 μm) or Sigma H-Type silica gel (10−40 μm) for normal phase and EM Science Lichroprep RP-18 (15−25 μm) for reverse phase. Melting points are obtained with Electrothermal melting point apparatus (series no. 9100) and are uncorrected.

3,6-Di-*O*-benzyl-D-glucal (20). Triacetylglucal (from Aldrich) (30.7 g, 111 mmol) was dissolved in absolute methanol (300 mL), treated with NaOMe (25 wt % in MeOH, 1.5 mL), and stirred for 5 h at room temperature under N_2. The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatographed with 5−20% MeOH in CH_2Cl_2 to give 16.6 g (100.7%) of white crystalline, hygroscopic solid.

D-Glucal (8.0 g, 54.7 mmol) and $(Bu_3Sn)_2O$ (30.7 mL, 1.1 molar equiv) in dry C_6H_6 (150 mL) were refluxed for 20 h with Dean−Stark trap. The reaction mixture was cooled below boiling temperature and treated with BnBr (21 mL) and TBABr (35.3 g). The mixture was refluxed for 17 h. The reaction mixture was cooled and concentrated, and the residue was diluted with EtOAc (2 × 200 mL), washed with H_2O (3 × 300 mL) and brine (300 mL), dried over Na_2SO_4, filtered, and concentrated to dryness. Careful column chromatography of crude material with 15−20% EtOAc in hexanes gave **20** (11.68 g, 65%) as a colorless oil: $[\alpha]^{23}_D$ −25.0° (*c* 5.7, $CHCl_3$); IR ($CHCl_3$ film) 3432, 1646, 1453, 1234, 1096 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34−7.25 (m, 10H), 6.37 (1H, dd, J = 6.1, 1.4 Hz), 4.82 (1H, dd, J = 6.2, 2.3 Hz), 4.67 (1H, d, J = 11.8 Hz), 4.61−4.53 (m, 3H), 4.08−4.05 (m, 1H), 3.98−3.94 (m, 2H), 3.81−3.75 (m, 2H), 2.63 (1H, d, J = 3.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.6, 138.3, 137.7, 128.4 (two peaks), 127.7 (two peaks), 100.0, 76.9, 76.2, 73.6, 70.7, 69.1, 68.8; HRMS calcd for $C_{20}H_{26}NO_4$ ($[M + NH_4]^+$) 344.1862, found 344.1841.

Synthesis of Lactal Carbonate 22. 21 was prepared according to the procedure described in ref 19. To a mixture of lactal carbonate **21** (2.70 g, 4.02 mmol) and BnBr (574 μL, 4.83 mmol) in DMF (30 mL) was added 60% NaH at 0 °C. After being stirred at 0 °C for 5 min, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. Then, it was poured into cold water (70 mL), diluted with EtOAc (120 mL), washed with H_2O (2 × 70 mL) and brine (70 mL), dried over Na_2SO_4, filtered, and concentrated to dryness. Flash column chromatography of crude material with 10−12% EtOAc in hexanes afforded **22** (2.479 g, 81%) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35−7.25 (15H, m), 6.41 (1H, d, J = 6.0 Hz), 4.88 (1H, d, J = 5.5 Hz), 4.86−4.84 (1H, m), 4.65−4.58 (4H, m), 4.57 (1H, d, J = 12.2 Hz), 4.46 (1H, d, J = 11.4 Hz), 4.17−4.13 (2H, m), 4.11−4.09 (1H, m), 3.89 (1H, dd, J = 11.0, 4.7 Hz), 3.84 (1H, d, J = 5.1 Hz), 3.82 (1H, d, J = 1.6 Hz), 3.74 (1H, dd, J = 5.5, 1.7 Hz), 3.68 (1H, dd, J = 11.0, 2.8 Hz), 3.58 (1H, dd, J = 5.5, 4.7 Hz), 1.08−1.00 (21H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.06, 144.56, 138.55, 138.04, 137.01, 128.51, 128.37, 128.25, 128.13, 127.92, 127.77, 127.69, 127.52, 127.44, 100.28, 99.32, 77.06, 76.52, 75.91, 73.81, 73.73, 73.60, 73.49, 73.37, 71.23, 70.62, 67.93, 61.31, 17.89, 17.85, 11.76; LRMS (NH_3) 778 ($[M + NH_4]^+$, 100).

Synthesis of Lactal 23. A solution of TIPS carbonate lactal **22** (4.28 g, 5.62 mmol) in THF (25 mL)−MeOH (5 mL) was treated with TBAF solution (1.0 M, 6.75 mL, 1.2 equiv). After 6 h, additional TBAF (4 mL) was added, and the mixture was stirred an additional 3 h. The reaction mixture was concentrated and directly chromatographed with 4:1 EtOAc−hexanes to obtain 2.20 g of the triol. Remaining mixtures of cyclic carbonate and mixed carbonate were hydrolyzed in MeOH with MeONa (25 wt % in MeOH, 1.0 mL) and purified chromatographically. Total yield was 3.02 g (93%). This material was directly used for the dibenzylation step: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (15H, m), 6.43 (1H, d, J = 6.3 Hz), 4.87 (1H, dd, J = 6.3, 3.4 Hz), 4.84 (1H, d, J = 11.4 Hz), 4.63 (2H, apparent s), 4.61 (1H, d, J = 11.4 Hz), 4.53−4.47 (3H, m), 4.19−4.16 (3H, m), 3.87−3.84 (2H, m), 3.78−3.66 (3H, m), 3.46 (2H, apparent d, J = 4.6 Hz), 3.29 (1H, t, J = 5.5 Hz), 3.08 (1H, br), 2.73 (2H, br); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.70, 138.41, 138.22, 137.83, 128.45, 128.33 (2C), 128.12, 127.84, 127.73, 127.64, 127.57, 127.51, 102.28, 99.74, 78.99, 76.03, 74.64, 74.07, 73.24 (2C), 73.17, 72.64, 70.20, 69.10, 67.79, 62.15.

Synthesis of Disaccharide Acceptor 24. A mixture of triol glycal **23** (2.95 g, 5.1 mmol), Bu_2SnO (1.33 g, 1.05 equiv), and $(Bu_3Sn)_2O$ (1.69 mL, 0.65 equiv) in dry C_6H_6 (50 mL) under N_2 was refluxed for 5 h with azeotropic removal of water. The reaction mixture was cooled below boiling and treated with BnBr (2.43 mL, 4.0 molar equiv) and TBABr (3.29 g, 2.0 equiv). C_6H_6 (10 mL) was distilled off, and the reaction mixture was refluxed for 16 h. The reaction mixture was directly loaded on a silica column and eluted with 15−20% EtOAc−hexanes to give **24** (3.48 g, 90%) as a clear oil: $[\alpha]^{23}_D$ −3.3° (*c* 0.87, $CHCl_3$); IR ($CHCl_3$ film) 2867, 1652 1454, 1364, 1097, 736 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35−7.21 (25H, m), 6.45 (1H, d, J = 6.2 Hz), 4.88 (1H, dd, J = 6.2, 3.9 Hz), 4.83 (1H, d, J = 10.9 Hz), 4.69 (2H, apparent s), 4.68 (1H, d, J = 10.9 Hz), 4.59 (2H, apparent s), 4.55 (1H, d, J = 7.8 Hz), 4.49 (2H, apparent s), 4.47 (2H, apparent s), 4.29 (1H, dd, J = 9.6, 5.8 Hz), 4.18 (1H, t, J = 4.4 Hz), 4.13 (1H, m), 3.99 (1H, br s), 3.85 (1H, dd, J = 10.6, 6.4 Hz), 3.75−3.60 (4H, m), 3.47−3.41 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.43, 138.64, 138.42, 137.99, 137.84, 137.80, 128.40, 128.34, 128.26, 128.23, 128.18, 128.15, 127.82, 127.75, 127.69, 127.67, 127.65, 127.55, 127.51, 127.46, 127.3, 1102.56, 99.56, 80.57, 78.69, 75.72, 75.10, 73.57, 73.32, 73.13, 72.94, 72.28, 71.94, 70.12, 68.90, 67.85, 66.62; LRMS (NH_3) 776 ($[M + NH_4]^+$, 100).

3-*O*-(4-Methoxybenzyl)-D-galactal (25). A suspension of D-galactal (3.70 g, 25.3 mmol) and Bu_2SnO (6.30 g, 1.0 equiv) in dry C_6H_6 (150 mL) was heated to reflux for 2 h with azeotropic removal of water. The reaction mixture was cooled and treated with PMBCl (3.80 mL, 1.1 equiv) and TBABr (9.10 g, 1.1 equiv) and refluxed for 4 h. The reaction mixture was filtered through a silica column and eluted with EtOAc−hexanes (4:1). Fractions containing product were concentrated, and the residue was triturated in hexanes to give 4.50 g (70%) (generally 65−75%) of the product as white crystalline solid: mp (hexanes) 117−118 °C; $[\alpha]^{23}_D$ −23.0° (*c* 1.1, $CHCl_3$); IR (KBr) 3313 (br), 1645, 1513, 1228, 1082, 821 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, d, J = 8.4 Hz), 6.89 (2H, d, J = 8.4 Hz), 6.44 (1H, dd, J = 6.4, 1.6 Hz), 4.70 (1H, dt, J = 6.3, 1.9 Hz), 4.59−4.52 (2H, AB q, J = 11.4 Hz), 4.20−4.18 (1H, m), 4.09 (1H, m), 4.02−3.97 (1H, m), 3.90−3.82 (2H, m), 3.81 (3H, s), 2.73 (1H, d, J = 3.1 Hz, C4-OH), 2.54 (1H, dd, J = 8.2, 4.2 Hz, C6-OH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.46, 145.02, 142.05, 129.46, 113.95, 99.36, 76.12, 70.17, 70.14, 63.65, 62.74, 55.26; LRMS (NH_3) 284 $[M + NH_4]^+$, 266 $[M]^+$, 249.

4,6-Di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-D-galactal (26). A solution of 3-*O*-(4-methoxybenzyl)-D-galactal **25** (2.28 g, 8.56 mmol) and BnBr (3.75 mL, 3.68 molar equiv; passed through basic alumina) in DMF (30 mL) under N_2 at 0 °C was treated with 60% NaH (1.37 g, 4.0 molar equiv) in two portions. The reaction mixture was stirred 0.5 h at 0 °C and 1 h at room temperature. The reaction mixture was carefully poured into 50 g of crushed ice, diluted to 100 mL with water, and then extracted with EtOAc−hexanes (1:1, 3 × 100 mL). Organic extracts were washed with water (2 × 100 mL), dried over Na_2SO_4, and concentrated to dryness. Flash column chromatography of crude material with 15% EtOAc−hexanes gave **26** (3.58 g, 96%) as a clear liquid: $[\alpha]^{23}_D$ −48.2° (*c* 0.85, $CHCl_3$); IR (neat) 3030, 2867, 1645, 1613, 1513 1247, 1092, 821, 736 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34−7.23 (12H, m), 6.86 (2H, d, J = 8.4 Hz), 6.35 (1H, d, J = 6.4 Hz), 4.86 (1H, d, J = 12.0 Hz), 4.84−4.81 (1H, m), 4.62 (1H, d, J = 12.0 Hz), 4.59−4.51 (2H, AB q, J = 11.7 Hz), 4.50−4.39 (2H, AB q, J = 11.9 Hz), 4.15 (2H, m), 3.91 (1H, m), 3.78 (3H, s), 3.78−3.74 (1H, m), 3.63 (1H, dd, J = 10.2, 5.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.04, 143.99, 138.30, 137.90, 130.43, 128.95, 128.26, 128.20, 128.03, 127.77, 127.57, 127.56, 113.67, 100.00, 75.58, 73.28, 73.17, 71.13, 70.42, 70.28, 68.35, 55.15; LRMS (NH_3) 464 ($[M + NH_4]^+$, 100), 326 (18), 309 (48), 253 (17).

Synthesis of Fluoride 29. A solution of galactal **26** (3.20 g, 7.17 mmol) in dry CH_2Cl_2 (10 mL) under N_2 at 0 °C was treated with dimethyldioxirane (0.09 M, 80 mL), and the mixture was stirred until all of the glycal was consumed (0.5−1 h; TLC 30% EtOAc in hexanes). Most of the volatiles were removed at 0 °C with a stream of dry N_2. The residue was dissolved in dry THF (30 mL) under N_2 at 0 °C, treated with TBAF (36 mL, stored over molecular sieves), and then stirred at ambient temperature for 20 h. The dark brown solution was filtered

through a pad of silica (~4 cm depth) and washed with EtOAc (200 mL). The filtrate was washed with water (3 × 200 mL), dried ($MgSO_4$), and concentrated. The residue was redissolved in 30% EtOAc in hexanes (50 mL) and filtered through a short silica column (10 cm diameter × 4 cm height) and washed with the same solvent system (1 L). The filtrate was concentrated to give 2.59 g of fluorohydrin **28** with >90% purity. The residue was dissolved in dry DMF (30 mL) under N_2 at 0 °C, treated with benzyl bromide (958 μL, 1.5 equiv, freshly filtered through basic alumina) and finally with NaH (322 mg, 60% dispersion, 1.5 equiv), and stirred for 30 min at 0 °C and 30 min at room temperature. The reaction was quenched by pouring the mixture into 100 g of ice, and the mixture was extracted with 1:1 EtOAc−hexanes (150 mL × 2). The organic extracts were washed with water (150 mL × 2), dried ($MgSO_4$), and concentrated *in vacuo*. Flash column chromatography of residue with 10% EtOAc in hexanes gave 2.00 g (49%) (generally 35−50%) of the title compound as a yellowish liquid: $[\alpha]^{23}_D$ +15.3° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$ film) 2916, 1612, 1513, 1248, 1103, 1056, 734 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (17H, m), 6.84 (2H, d, J = 8.4 Hz), 5.15 (1H, dd, J = 53.2, 7.0 Hz), 4.92 (1H, d, J = 11.6 Hz), 4.84−4.74 (2H, AB q, J = 11.0 Hz), 4.68−4.61 (2H, AB q, J = 11.4 Hz), 4.56 (1H, d, J = 11.6 Hz), 4.48−38 (2H, AB q, J = 11.8 Hz), 3.96−3.89 (1H, m), 3.86 (1H, br s), 3.78 (3H, s), 3.65−3.56 (3H, m), 3.51 (1H, dd, J = 9.8, 2.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.22, 138.33, 138.11, 137.62, 130.16, 129.19, 128.40, 128.29, 128.21, 128.04 (2C), 127.90, 127.81, 127.69, 127.59, 113.77, 110.20 (d, J = 214 Hz), 80.60 (d, J = 11.3 Hz), 79.00 (d, J = 20.5 Hz), 74.92, 74.52, 73.59 (d, J = 5.0 Hz), 73.54, 72.99, 72.70, 68.34, 55.20; LRMS (NH_3) 454 ($[M + NH_4]^+$, 100).

Synthesis of Trisaccharide 30. Lactal **24** (600 mg, 0.791 mmol, 1.0 equiv) and fluoro sugar **29** (679 mg, 1.5 equiv) were combined in ether, concentrated, dried in vacuum for 2 h, and then treated with di-*tert*-butylpyridine (177 μL, 1.0 equiv) in a glovebag and dissolved in dry ether (8.5 mL) under a nitrogen atmosphere. In a separate 25 mL flask were placed 4 Å molecular sieves (2.0 g), and then these were flame-dried under vacuum and cooled to room temperature. Anhydrous silver perchlorate (163 mg, 1.0 equiv) and $SnCl_2$ (150 mg, 1.0 equiv) were added to the molecular sieves in a glovebag, and the system was flushed with N_2. The salt mixture was placed in a water bath, and the sugar solution was introduced via a double-tipped needle. The reaction vessel was wrapped with aluminum foil and stirred for 48 h at room temperature. The reaction mixture was diluted with ether and filtered through a pad of silica gel, rinsed with ether. The filtrate (70 mL) was washed with dilute $NaHCO_3$ solution (2 × 50 mL), dried over Na_2SO_4, and concentrated to dryness. Flash column chromatography with 20% EtOAc in hexanes gave a trisaccharides mixture. The trisaccharide portion was rechromatographed with 2% ether in methylene chloride to give 561 mg (54%) of the desired α-product **30** and 183 mg (18%) of β-product **31**.

30: $[\alpha]^{23}_D$ +41.8° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$ film) 2867, 1648, 1513, 1496, 1453, 1364, 1248, 1097, 735 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33−7.12 (42H, m), 6.83 (2H, d, J = 8.4 Hz), 6.45 (1H, d, J = 6.0 Hz), 5.03 (1H, d, J = 2.3 Hz), 4.91−4.76 (6H, m), 4.68−4.40 (12H, m), 4.23−3.97 (11H, m), 3.86−3.82 (1H, dd, J = 10.7, 6.2 Hz), 3.76 (3H, s), 3.69−3.64 (2H, m), 3.53 (1H, t, J = 8.7 Hz), 3.47−3.43 (1H, m), 3.40−3.36 (1H, m), 3.34−3.31 (1H, dd, J = 9.9, 2.8 Hz), 3.22 (1H, dd, J = 8.3, 4.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.93, 144.50, 138.98, 138.84, 138.78, 138.64, 138.58, 138.06, 138.02 (2C), 130.82, 129.04, 128.33, 128.24, 128.21, 128.15, 128.08, 128.05, 127.83, 127.81, 127.72, 127.64, 127.58, 127.55, 127.50, 127.44, 127.41, 127.36, 127.33, 127.31, 113.65, 103.02, 100.39, 100.01, 80.93, 78.93, 78.70, 76.53, 76.11, 75.14, 74.84, 74.79, 74.35, 73.91, 73.59, 73.36, 73.15, 73.10, 72.98, 72.15, 72.10, 71.99, 70.55, 69.25, 67.92 (2C), 67.69, 55.19; HRMS calcd for $C_{82}H_{86}O_{15}Na$ $(M + Na)^+$ 1333.5860, found 1333.5890.

31: $[\alpha]^{23}_D$ +6.8° (*c* 0.76, $CHCl_3$); IR ($CHCl_3$ film) 2863, 1648, 1513, 1453, 1363, 1247, 1100, 735 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, d, J = 7.45 Hz), 7.34−7.13 (40H, m), 6.83 (2H, d, J = 8.4 Hz), 6.43 (1H, d, J = 6.0 Hz), 5.07 (1H, d, J = 10.7 Hz), 5.00 (1H, d, J = 11.6 Hz), 4.98 (1H, d, J = 7.6 Hz), 4.85 (1H, dd, J = 6.1, 3.6 Hz), 4.72−4.40 (16H, m), 4.35 (2H, app s), 4.30 (1H, d, J = 2.2 Hz), 4.27 (1H, m), 4.18 (1H, t, J = 4.6 Hz), 4.14 (1H, m), 3.85−3.72 (4H, m), 3.78 (3H, s), 3.65 (1H, dd, J = 10.6, 3.3 Hz), 3.60−3.53 (2H, m), 3.49−3.43 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.01, 144.29, 139.07, 139.02, 138.67, 138.54, 138.45, 138.39, 138.00, 137.87, 130.77, 129.10, 128.36, 128.22, 128.17, 128.13, 128.07, 127.96, 127.83, 127.77, 127.70, 127.65, 127.59, 127.55, 127.45, 127.33, 127.25, 127.21, 113.63, 102.75, 102.46, 99.87, 82.09, 81.56, 79.85, 79.77, 76.02, 75.19, 74.85, 74.58, 74.23, 73.64, 73.41 (2C), 73.38, 73.08 (2C), 72.78, 72.48 (2C), 70.67, 69.68, 69.33, 68.68, 67.88, 55.16; HRMS (FAB) calcd for $C_{82}H_{86}O_{15}Na$ $(M + Na)^+$ 1333.5860, found 1333.5900.

Synthesis of Trisaccharide 32. A solution of PMB trisaccharide **30** (561 mg, 0.428 mmol) in CH_2Cl_2 (12 mL) at 0 °C was treated with 830 μL of water and DDQ (126 mg, 1.3 equiv) and stirred at 0 °C for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ solution (50 mL), extracted with EtOAc (2 × 50 mL), washed with saturated $NaHCO_3$ solution (2 × 50 mL) and water (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified with flash column chromatography (20% EtOAc in hexanes) to give 437 mg (86%) of the deprotected trisaccharide **32** as a colorless oil: $[\alpha]^{23}_D$ +45.6° (*c* 1.78, $CHCl_3$); IR ($CHCl_3$ film) 2866, 1648, 1496, 1453, 1365, 1248, 1097, 735 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36−7.15 (40H, m), 6.43 (1H, d, J = 6.2 Hz), 5.09 (1H, d, J = 3.3 Hz), 4.85 (1H, dd, J = 6.2, 3.6 Hz), 4.83−4.65 (5H, m), 4.61−4.41 (9H, m), 4.29−4.08 (8H, m), 4.02 (1H, d, J = 2.6 Hz), 3.97 (1H, d, J = 2.2 Hz), 3.93 (1H, t, J = 8.4 Hz), 3.86−3.78 (2H, m), 3.67−3.61 (2H, m), 3.53 (1H, t, J = 9.0 Hz), 3.48−3.42 (1H, m), 3.39−3.36 (1H, m), 3.33 (1H, dd, J = 10.0, 2.7 Hz), 3.25 (1H, dd, J = 8.5, 4.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.38, 138.78, 138.62, 138.47 (2C), 138.20, 138.00, 137.88 (2C), 128.31, 128.29, 128.23, 128.19, 128.16, 128.05, 127.88, 127.83, 127.62, 127.57, 127.49, 127.45, 127.43, 127.41, 127.37, 127.32, 127.23, 102.68, 99.89, 99.34, 80.82, 78.72, 77.49, 77.10, 75.88, 75.13, 75.03, 74.23, 73.62, 73.05, 73.01 (3C), 72.62, 72.19 (2C), 70.46, 69.66, 68.92, 67.85, 67.74, 67.54; HRMS calcd for $C_{74}H_{78}O_{14}Na$ $[M + Na]^+$ 1213.5290, found 1213.5270.

Synthesis of Disaccharide Glycal 33. TIPS galactal carbonate **18** (4.32 g, 3.14 mmol) was dissolved in CH_2Cl_2 (20 mL), and the mixture was cooled to 0 °C. It was then treated with dimethyldioxirane (219 mL, ~3.14 mmol) at 0 °C. The epoxidation was finished (to give **19**) within 20 min, and the reaction mixture was concentrated to dryness by a stream of N_2. The residue was dried azeotropically once with C_6H_6 (20 mL) and further dried on high vacuum for 30 min at 0 °C. It was then dissolved in THF (60 mL) and cooled to −78 °C. To the above solution was added azeotropically dried TIPS galactal **17** (3.32 g, 10.95 mmol) in THF (20 mL) via cannula and $ZnCl_2$ (26.3 mL, 1.0 M in ether). The reaction mixture was allowed to warm to room temperature and stirred overnight. After treatment with saturated $NaHCO_3$ (40 mL), the reaction mixture was concentrated and extracted with ether (500 mL). The combined organic phase was washed with brine (300 mL), dried over $MgSO_4$, and concentrated to dryness. The crude product was purified by flash column chromatography (20% EtOAc in hexanes) to give 6.20 g of **33** as a white foam (87%): $[\alpha]^{23}_D$ −31.4° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$ film) 3434, 2942, 2866, 1802, 1648, 1463, 1383, 1239, 1113, 1032, 882, 787, 685 cm^{-1}; ^{1}H-NMR (400 MHz) δ 6.54 (1H, dd, J = 6.4, 1.6 Hz), 4.85 (1H, dd, J = 6.4, 2.0 Hz), 4.72−4.68 (2H, m), 4.65 (1H, d, J = 7.2 Hz), 4.55 (1H, m), 4.08 (1H, dd, J = 9.6, 5.6 Hz), 3.96−3.82 (6H, m), 3.33 (1H, d, J = 3.2 Hz, OH), 3.27 (1H, d, J = 2.8 Hz, OH), 1.16−1.04 (42H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.45, 145.75, 99.27, 77.83, 76.59, 74.27, 72.04, 71.62, 70.86, 64.52, 62.57, 61.60, 17.84, 11.78, 11.77; HRMS (FAB) calcd for $C_{31}H_{59}O_{10}Si_2$ 647.3647, found 647.3671 (M + 1).

Synthesis of Trisaccharide Glycal 35. A mixture of disaccharide **33** (2.64 g, 4.08 mmol) and fucosyl fluoride **34** (1.64 g, 3.77 mmol) was azeotroped with C_6H_6 three times (3 × 10 mL) and further dried on high vacuum for 1 h. It was dissolved in THF (20 mL) and treated with 2,6-di-*tert*-butylpyridine (2.16 g, 11.31 mmol). The above mixture was added via cannula to a flask containing $AgClO_4$ (1.56 g, 7.54 mmol), $SnCl_2$ (1.43 g, 7.54 mmol), and 4 Å molecular sieves (4.0 g) in THF (15 mL) at −40 °C. The reaction mixture was stirred for 30 min at −40 °C and then for 34 h at 5 °C. After treatment with saturated $NaHCO_3$ solution (40 mL) at 5 °C, the reaction mixture was extracted with EtOAc (2 × 300 mL). The combined organic layer was washed with brine (200 mL), dried over $MgSO_4$, and concentrated to dryness. The crude product was purified by flash column chromatography (17% EtOAc in hexanes) to give the desired trisaccharide glycal **35** (1.93 g, 47%, based on fluorofucose) and regioisomer **36** (329 mg, 8%) with 500 mg of the recovered disaccharide **33**.

35: $[\alpha]^{23}_D$ −53.2° (*c* 1.30, $CHCl_3$); IR ($CHCl_3$ film) 2941, 2866, 1808, 1649, 1459, 1365, 1239, 1167, 1106, 1054, 882, 788, 738 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.30 (15H, m), 6.35 (1H, dd, J = 6.4, 1.6 Hz), 5.01 (1H, d, J = 4.0 Hz), 4.98 (1H, d, J = 11.6 Hz), 4.88 (1H, d, J = 4.8 Hz), 4.86 (1H, d, J = 3.7 Hz), 4.83 (2H, d, J = 9.6 Hz), 4.73 (1H, d, J = 11.4 Hz), 4.70 (1H, dd, J = 3.6, 8.2 Hz), 4.65 (2H, d, J = 11.7 Hz), 4.53 (1H, m), 4.43 (1H, m), 4.15−3.97 (5H, m), 3.92−3.82 (7H, m), 3.67 (1H, m), 2.66 (1H, d, J = 2.4 Hz), 1.13 (3H, d, J = 6.8 Hz), 1.09−1.00 (42H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.00, 145.30, 138.49, 138.30, 138.19, 128.43, 128.29, 128.16, 128.11, 127.87, 127.53, 127.49, 127.27, 98.34, 97.93, 97.81, 78.90, 77.32, 77.03, 76.13, 75.30, 74.75, 74.31, 73.92, 73.22, 72.99, 72.13, 71.09, 67.33, 63.44, 61.70, 17.80, 11.78, 11.72; HRMS (FAB) calcd for $C_{58}H_{86}O_{14}Si_2Na$ 1085.5450, found 1085.5480.

Synthesis of Trisaccharide Glycal 37. Trisaccharide glycal **35** (3.10 g, 2.91 mmol) was dissolved in pyridine (10 mL), and acetic anhydride (5 mL) and 4-(dimethylamino)pyridine (DMAP, 50 mg) were added. After being stirred at room temperature for 1.5 h, the mixture was concentrated *in vacuo* and loaded directly on silica gel column. Elution with 30% EtOAc in hexanes afforded the product (2.93 g, 91%) as a colorless oil: $[\alpha]^{23}_D$ −54.7° (*c* 0.89, $CHCl_3$); IR ($CHCl_3$ film) 2941, 2865, 1817, 1747, 1652, 1455, 1367, 1232, 1105, 1053, 882, 788, 735, 695 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41−7.23 (15H, m), 6.34 (1H, d, J = 6.4 Hz), 5.36 (1H, m), 4.99 (2H, m), 4.87−4.70 (6H, m), 4.68 (4H, m), 4.45 (1H, m), 4.07 (2H, m), 3.98 (1H, m), 3.91−3.71 (7H, m), 3.64 (1H, s), 2.09 (3H, s), 1.15−1.05 (42H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.07, 153.52, 145.26, 138.59, 138.39, 138.25, 128.49, 128.28, 128.27, 128.19, 127.53, 127.62, 127.57, 127.41, 98.81, 98.74, 98.26, 82.45, 78.95, 7.44, 77.19, 76.21, 75.73, 74.84, 74.81, 73.94, 73.22, 73.00, 71.43, 69.91, 67.27, 65.11, 62.12, 61.45, 20.83, 16.63; HRMS (FAB) calcd for $C_{60}H_{88}O_{15}Si_2K$ 1143.5300 $(M + K)^+$, found 1143.5250.

Synthesis of Iodo Sulfonamide 38. A mixture of trisaccharide glycal **37** (2.53 g, 2.3 mmol) and $PhSO_2NH_2$ (2.16 g, 13.7 mmol) was azeotroped with C_6H_6 and further dried on high vacuum for 1 h. It was dissolved in THF (20 mL), and freshly activated 4 Å molecular sieves (5.0 g) were added. I(*sym*-coll)$_2ClO_4$ was prepared by stirring I_2 (3.56 g, 13.7 mmol) with Ag(*sym*-coll)$_2ClO_4$ (6.18 g, 13.7 mmol) in THF (20 mL) at room temperature until the disappearance of the brown color of I_2. It was then added via a thick cannula to the flask containing glycal **37** and benzensulfonamide at 0 °C. The reaction mixture was stirred at 0 °C overnight and quenched with saturated $Na_2S_2O_3$ solution (50 mL). After filtration and extraction with EtOAc (2 × 200 mL), the combined organic layer was washed with saturated $CuSO_4$ (100 mL) and brine (100 mL) and dried ($MgSO_4$). Concentration and purification by silica gel chromatography (20% EtOAc in hexanes) afforded the iodo sulfonamide **38** (2.59 g, 82%): $[\alpha]^{23}_D$ −71.6° (*c* 1.58, $CHCl_3$); IR ($CHCl_3$ film) 2942, 2866, 1816, 1747, 1454, 1364, 1347, 1232, 1164, 1097, 822, 790, 733, 688 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, d, J = 7.6 Hz), 7.52 (1H, m), 7.45 (2H, m), 7.41−7.20 (15H, m), 5.36 (1H, t, J = 9.0 Hz), 5.04 (3H, m), 4.99 (1H, d, J = 11.5 Hz), 4.89 (2H, m), 4.79 (2H, dd, J = 14.4, 12.3 Hz), 4.73 (1H, m), 4.67 (3H, m), 4.38 (1H, m), 4.15−4.05 (3H, m), 4.08−3.93 (5H, m), 3.92−3.75 (5H, m), 1.99 (3H, s), 1.24 (3H, d, J = 6.4 Hz), 1.15−1.05 (42H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.65, 153.51, 141.29, 138.76, 138.60, 138.53, 132.69, 128.74, 128.49, 128.38, 128.18, 128.13, 127.96, 127.89, 127.46, 127.35, 127.28, 101.74, 96.82, 78.50, 77.39, 76.04, 75.81, 75.01, 74.41, 74.09, 73.27, 73.09, 72.33, 71.68, 68.00, 67.38, 60.57, 59.57, 20.87, 16.72; HRMS (FAB) calcd for $C_{66}H_{94}O_{17}INSSi_2K$ 1426.4460 $(M + K)^+$, found 1426.4420.

Synthesis of Ethylthio Sulfonamide 46. To a solution of EtSH (550 mg, 8.85 mmol) in DMF (30 mL) was added lithium bis(trimethylsilyl)amide (LHMDS, 1.0 M in THF, 3.54 mL, 3.54 mmol) at −42 °C. After being stirred for 5 min, it was then added via cannula to a flask containing iodo sulfonamide **38** (2.46 g, 1.77 mmol) in DMF (20 mL) at −42 °C. The reaction mixture was allowed to warm to room temperature and stirred for total 3 h. After dilution with diethyl ether (2 × 400 mL), it was washed with saturated $NaHCO_3$ solution (2 × 200 mL) and brine (200 mL) and dried ($MgSO_4$). Concentration and purification by silica gel chromatography (20% EtOAc in hexanes) afforded **46** (2.16 g, 92%) as a white solid (92%): $[\alpha]^{23}_D$ −23.8° (*c* 1.57, $CHCl_3$); IR ($CHCl_3$ film) 2941, 2865, 2359, 1809, 1745, 1456, 1363, 1325, 1232, 1159, 1092, 883, 689 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, J = 7.2 Hz), 7.50 (1H, m), 7.41 (2H, m), 7.38−7.26 (15H, m), 5.42 (1H, d, J = 3.1 Hz), 5.10 (1H, d, J = 3.2 Hz), 5.08 (1H, d, J = 3.6 Hz), 5.03 (1H, d, J = 6.3 Hz), 4.98 (1H, d, J = 11.5 Hz), 4.86−4.80 (3H, m), 4.74 (1H, d, J = 11.8 Hz), 4.66 (2H, m), 4.62 (2H, dd, J = 19.0, 10.4 Hz), 4.14−4.07 (3H, m), 4.04−3.90 (3H, m), 3.85 (3H, m), 3.68 (2H, m), 3.60 (1H, m), 3.55−3.45 (2H, m), 2.43 (2H, m), 2.10 (3H, s), 1.17 (3H, d, J = 6.4 Hz), 1.09 (18H, s), 1.08 (3H, s), 1.04 (18H, s), 1.02 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.85, 154.00, 141.55, 138.64, 138.43, 138.35, 132.38, 128.61, 128.47, 128.32, 128.25, 128.17, 127.90, 127.86, 127.57, 127.47, 127.36, 127.34, 101.16, 98.22, 83.37, 80.70, 79.09, 78.97, 77.42, 77.32, 77.00, 76.68, 76.34, 74.84, 73.82, 73.38, 72.96, 72.88, 72.72, 70.53, 68.98, 67.75, 62.77, 61.38, 56.22, 24.21, 20.84, 16.67, 14.34; HRMS (FAB) calcd for $C_{68}H_{99}O_{17}NS_2Si_2Na$ 1344.5790 $(M + Na)^+$, found 1344.5800.

Synthesis of Hexasaccharide 47 and 39. To a thoroughly dried mixture of acceptor **32** (75 mg, 0.063 mmol) and acetyl thioglycoside **46** (176 mg, 2.0 equiv) was added freshly activated 4 Å molecular sieves (450 mg), and the mixture was placed under nitrogen atmosphere. The mixture was suspended in dry ether (4 mL), stirred for 10 min, and then cooled to 0 °C. The mixture was treated with MeOTf (35.5 μL, 5.0 equiv) and stirred for 5 h at 0 °C, for 2 h while warming to room temperature, and finally for 1 h at room temperature. The reaction mixture was quenched with Et_3N (1 mL), and the mixture was diluted with ether, filtered through a pad of silica gel, and rinsed with ether. The filtrate (100 mL) was washed with dilute $NaHCO_3$ (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude products was purified with HPLC (21% EtOAc−hexanes, 15 mL/min, 260 nm UV detection) to give 94.1 mg of α-isomer **47** and ca. 1/5 of β-isomer **39** (judged by HPLC).

47: $[\alpha]^{23}_D$ +10.9° ($CHCl_3$, *c* 0.15); IR ($CHCl_3$ film) 2940, 2865, 1813, 1746, 1651, 1454, 1366, 1095, 735 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71−7.69 (2H, m), 7.43−7.14 (58H, m), 6.44 (1H, d, J = 6.2 Hz), 5.48 (1H, d, J = 2.4 Hz), 5.05 (2H, m), 4.95 (1H, d, J = 11.5 Hz), 4.87−4.58 (21H, m), 4.44 (2H, AB q, J = 12.2 Hz), 4.35−4.11 (7H, m), 4.10−4.01 (3H, m), 3.95−3.76 (11H, m), 3.72−3.61 (4H, m), 3.57−3.24 (9H, m), 2.07 (3H, s), 1.08 (3H, d, J = 6.4 Hz), 1.06−0.96 (42H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.65, 153.44, 144.48, 140.70, 138.94, 138.71, 138.63, 138.53, 138.28, 138.23, 138.05, 138.04, 137.86, 132.67, 129.15, 128.48, 128.28, 128.24, 128.18, 128.11, 128.04, 127.97, 127.89, 127.80, 127.64, 127.60, 127.56, 127.48, 127.44, 127.39, 127.36, 127.33, 127.19, 126.91, 103.18, 102.09, 99.20, 98.56, 98.28, 97.05, 80.89, 78.86, 78.80, 77.37, 76.55, 75.98, 75.87, 75.79, 75.65, 75.44, 75.04, 74.99, 74.85, 74.45, 74.41, 74.02, 73.55, 73.47, 73.16, 73.11, 73.06, 72.82, 72.64, 72.57, 72.22, 71.65, 70.66, 70.18, 70.13, 69.19, 69.07, 68.41, 68.01, 67.87, 67.74, 60.93, 60.33, 53.71, 20.82, 17.98, 17.94, 17.91, 17.78, 16.64, 11.82, 11.79; HRMS (FAB) calcd for $C_{140}H_{171}NO_{31}SSi_2Na$ $[M + Na]^+$ 2473.0990, found 2473.0990.

39: $[\alpha]^{23}_D$ +11.3° ($CHCl_3$, *c* 0.31); IR ($CHCl_3$ film) 2940, 2865, 1815, 1745, 1650, 1454, 1233, 1161, 1099, 735 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, m), 7.42−7.07 (58H, m), 6.41 (1H, d, J = 6.0 Hz), 5.30 (1H, d, J = 2.8 Hz), 5.03 (1H, d, J = 3.0 Hz), 5.00−4.94 (3H, m), 4.90−4.71 (9H, m), 4.67−4.61 (3H, m), 4.56 (1H, d, J = 12.2 Hz), 4.51−4.42 (8H, m), 4.36−4.29 (1H, m), 4.26 (1H, d, J = 12.1 Hz), 4.20 (2H, s), 4.14−3.96 (9H, m), 3.93−3.79 (9H, m), 3.69−3.37 (10H, m), 3.33−3.23 (3H, m), 2.05 (3H, s), 1.18 (3H, d, J = 6.5 Hz), 1.12−0.98 (42H, m).

Synthesis of Iodo Sulfonamide 49. A mixture of trisaccharide glycal **35** (118 mg, 0.11 mmol) and benzenesulfonamide (87 mg, 0.55 mmol) was azeotroped with C_6H_6 once and further dried on high vacuum for 1 h. It was dissolved in THF (5 mL), and freshly activated 4 Å molecular sieves (870 mg) was added. I(*sym*-coll)$_2ClO_4$ was prepared by stirring I_2 (57.5 mg, 0.22 mmol) with Ag(*sym*-coll)$_2ClO_4$ (100 mg, 0.22 mmol) in THF (1 mL) at room temperature until the disappearance of the brown color of I_2. It was then added via a thick cannula to the flask containing glycal **35** and benzensulfonamide at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and quenched with saturated $Na_2S_2O_3$ solution (10 mL). After filtration and extraction with EtOAc (80 mL), the combined organic layer was washed with saturated $CuSO_4$ (20 mL) and brine (20 mL) and dried ($MgSO_4$). Concentration and purification by silica gel chromatography (20% EtOAc in hexanes) afforded 74 mg (50%) of the iodo sulfonamide **49**, which was unstable under a variety of conditions: $[\alpha]^{23}_D$ −47.0° (*c*

1.35, $CHCl_3$); IR (CHC_3 film) 3263, 2942, 2865, 1817, 1454, 1344, 1164, 1098, 882, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (2H, d, $J = 7.2$ Hz), 7.56 (1H, m), 7.48 (2H, m), 7.41−7.24 (15H, m), 5.62 (1H, d, $J = 7.8$ Hz), 5.57 (1H, dd, $J = 7.8$, 3.7 Hz), 4.98 (2H, m), 4.89 (2H, m), 4.87−4.72 (4H, m), 4.70−4.63 (4H, m), 4.20 (1H, m), 4.14−4.03 (4H, m), 4.00−3.92 (4H, m), 3.90−3.75 (4H, m), 3.61 (2H, m), 3.19 (1H, dd, $J = 10.0$, 5.9 Hz), 2.69 (1H, d, $J = 5.1$ Hz), 1.20 (3H, d, $J = 6.5$ Hz), 1.05−1.01 (42H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.07, 140.45, 138.71, 138.51, 133.07, 128.99, 128.56, 128.44, 128.24, 128.21, 127.98, 127.58, 127.34, 127.24, 97.79, 96.98, 83.72, 78.61, 77.43, 76.26, 75.03, 74.26, 74.15, 73.00, 72.93, 72.62, 70.95, 67.83, 66.36, 61.5, 60.42, 16.73; HRMS (FAB) calcd for $C_{64}H_{92}O_{16}INSSi_2K$ 1384.4360 $(M + K)^+$, found 1384.4320.

Synthesis of Ethylthio Sulfonamide 50. To a solution of EtSH (102 mg, 1.7 mmol) in DMF (10 mL) was added lithium bis-(trimethylsilyl)amide (LHMDS, 1.0 M in THF, 0.81 mL, 0.81 mmol) at −42 °C. After 5 min of stirring, it was transferred via a cannula to a flask containing iodo sulfonamide **49** (448 mg, 0.33 mmol) in DMF (10 mL) at −42 °C. The reaction mixture was allowed to warm to room temperature and stirred for total 3 h. After dilution with diethyl ether (200 mL), it was washed with saturated $NaHCO_3$ solution (2 × 10 mL) and brine (10 mL) and dried ($MgSO_4$). Concentration and purification by silica gel chromatography (5% EtOAc in CH_2Cl_2) afforded **50** (338 mg, 79%) as a white solid: $[\alpha]^{23}_D$ −75.2° (*c* 0.99, $CHCl_3$); IR ($CHCl_3$ film) 3447, 2942, 2866, 1795, 1455, 1382, 1367, 1325, 1161, 1107, 883, 744, 688 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.89 (2H, d, $J = 6.8$ Hz), 7.50 (1H, m), 7.47 (2H, m), 7.40−7.25 (15H, m), 5.42 (1H, m), 5.00 (1H, d, $J = 3.7$ Hz), 4.97 (1H, d, $J = 11.6$ Hz), 4.90 (1H, m), 4.83 (1H, d, $J = 11.8$ Hz), 4.81 (1H, d, $J = 11.7$ Hz), 4.73 (1H, d, $J = 11.8$ Hz), 4.63 (4H, m), 4.35 (1H, d, $J = 10.2$ Hz), 4.09 (4H, m), 4.01 (1H, dd, $J = 6.6$, 13.1 Hz), 3.93−3.75 (6H, m), 3.70 (1H, d, $J = 1.7$ Hz), 3.55 (1H, m), 3.46 (1H, m), 2.81 (1H, m), 2.45 (1H, m), 2.30 (1H, m), 1.16 (3H, d, $J = 6.44$ Hz), 1.12−1.00 (42H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.26, 140.60, 138.66, 138.47, 132.55, 128.75, 128.49, 128.33, 128.24, 128.16, 127.93, 127.85, 127.65, 127.55, 127.48, 127.29, 99.40, 97.82, 83.60, 79.10, 77.49, 76.42, 74.86, 74.07, 72.92, 72.80, 71.48, 71.41, 70.25, 67.82, 67.76, 55.09, 23.51, 17.90, 17.90, 16.69, 14.37, 11.81; HRMS (FAB) calcd for $C_{66}H_{97}O_{16}NS_2Si_2K$ 1318.5420 $(M + K)^+$, found 1318.5470.

Synthesis of Hexasaccharide 51 and 52. A mixture of acceptor trisaccharide **32** (92 mg, 0.077 mmol, 1.0 equiv), thiogycoside **50** (198 mg, 2.0 equiv), and freshly activated 4 Å molecular sieves (560 mg) under N_2 at room temperature was suspended in CH_2Cl_2−Et_2O (1:2, 3.9 mL) and stirred for 10 min. The reaction mixture was cooled to 0 °C and then treated with methyl triflate (52.4 μL, 6.0 equiv). The reaction mixture was stirred for 4.5 h at 0 °C and for 1.5 h while warming to 15 °C. The reaction was quenched with TEA (1.0 mL), and the mixture was filtered through a pad of silica and rinsed with Et_2O. The filtrate (70 mL) was washed with saturated $NaHCO_3$ solution (2 × 50 mL), dried (Na_2SO_4), and concentrated to dryness. The crude product was purified by HPLC (MICROSORB Semi-prep Si 80-120-C5, 17% EtOAc in hexanes, 15 mL/min, 260 nm UV detection) to give 158 mg (85%) of the desired product **51** and 27.7 mg of corresponding α-isomer **52** (ca. 55% purity).

51: t_R 22 min; $[\alpha]^{23}_D$ −13.3° ($CHCl_3$, *c* 1.4); IR ($CHCl_3$ film) 2940, 2865, 1792, 1652, 1454, 1161, 1101, 734 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.8 (2H, m), 7.38−7.06 (58H, m), 6.43 (1H, d, $J = 6.1$ Hz), 5.15 (1H, br s), 5.07 (1H, d, $J = 3.6$ Hz), 5.03 (1H, d, $J = 3.6$ Hz), 4.99 (1H, d, $J = 11.6$ Hz), 4.89−4.61 (12H, m), 4.54−4.46 (4H, m), 4.42 (2H, app s), 4.38 (1H, d, $J = 11.9$ Hz), 4.34−4.26 (3H, m), 4.21−4.18 (4H, m), 4.13−4.03 (7H, m), 3.98−3.76 (14H, m), 3.70−3.61 (4H, m), 3.46−3.27 (7H, m), 2.84 (1H, OH), 1.16 (3H, d, $J = 6.4$ Hz), 1.13−1.02 (42H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.35, 144.55, 140.78, 138.99, 138.75, 138.68, 138.57, 138.54, 138.43, 138.13, 138.03, 137.94, 137.82, 132.31, 128.81, 128.52, 128.51, 128.38, 128.36, 128.27, 128.24, 128.20, 128.16, 128.02, 127.93, 127.72, 127.66, 127.58, 127.48, 127.43, 127.37, 127.20, 103.41, 102.75, 99.79, 99.55, 98.29, 97.76, 80.49, 80.39, 79.03, 78.91, 78.25, 77.68, 77.37, 76.51, 75.88, 75.09, 74.99, 74.91, 74.73, 74.15, 74.02, 73.92, 73.52, 73.19, 73.10, 72.94, 72.67, 72.25, 72.07, 71.76, 71.56, 71.33, 70.33, 69.45, 69.32, 68.48, 68.08, 67.88, 67.86, 67.75, 61.97, 61.60, 56.14, 17.99, 17.96, 17.95, 17.92, 16.75, 11.86; HRMS (FAB) calcd for $C_{138}H_{169}NO_{30}SSi_2Na$ (M + Na) 2431.0890, found 2431.0970.

52: t_R 17.7 min; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.74 (2H, d, $J = 7.2$ Hz), 7.37−7.15 (58H, m), 6.45 (1H, d, $J = 6.4$ Hz), 5.05 (1H, d, $J = 3.2$ Hz), 5.00 (1H, br s), 4.97 (1H, d, $J = 11.6$ Hz), 4.89−4.42 (24H, m), 4.34 (1H, m), 4.28−3.59 (28H, m), 3.53 (1H, m), 3.45−3.26 (5H, m), 1.11 (3H, d, $J = 6.5$ Hz), 1.06−0.86 (42H, m).

Synthesis of Azide 54. A mixture of hexasaccharide **47** and freshly activated 4 Å molecular sieves (200 mg) in CH_2Cl_2 (1 mL) was treated with dimethyldioxirane (ca. 0.07 M, 1 mL) at 0 °C. After the completion of reaction, most of the volatiles were removed by a stream of N_2. The residue was dried on high vacuum for 30 min. Then, a solution of azidohydrin **53** in 1.3 mL of THF was added to the reaction mixture by cannula. The reaction mixture was cooled to −30 °C, treated with 1 M $ZnCl_2$ in Et_2O (53 μL), slowly allowed to warm to room temperature, and stirred overnight. The reaction mixture was diluted with EtOAc (70 mL), washed with saturated $NaHCO_3$ solution (2 × 200 mL) and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified with HPLC (15% EtOAc−hexanes, 15 mL/min, 260 nm UV detection) to give 56 mg (46%) of the coupled product as a colorless oil. To a solution of coupled product (56 mg, 0.019 mmol), DMAP (2.8 mg, 0.023 mmol), and Et_3N (5.4 μL, 0.039 mmol) in CH_2Cl_2 (1.5 mL) was added Ac_2O (2.2 μL, 0.023 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After the solvent was evaporated, the residue was diluted with EtOAc (30 mL), washed with dilute $NaHCO_3$ solution (2 × 5 mL) and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (using 10−40 μm of silica gel, SIGMA) of crude material gave 54.7 mg (96%, 42% over two steps) of the desired product **54** as a colorless oil: $[\alpha]^{23}_D$ 11.6° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$ film) 3013, 2925, 2100, 1815, 1750, 1497, 1454, 1366, 1232, 1092 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.68 (2H, br d, $J = 7.2$ Hz), 7.42−7.14 (63H, m), 5.74−5.66 (1H, m), 5.43 (1H, d, $J = 2.0$ Hz), 5.38 (1H, br dd, $J = 15.4$ and 8.6 Hz), 5.11 (1H, br d, $J = 2.9$ Hz), 4.94−4.89 (3H, m), 4.85−4.79 (3H, m), 4.75 (1H, d, $J = 5.7$ Hz), 4.73 (1H, d, $J = 5.1$ Hz), 4.70−4.66 (4H, m), 4.64−4.51 (8H, m), 4.48−4.41 (5H, m), 4.35−4.30 (3H, m), 4.29−4.21 (3H, m), 4.16−4.08 (3H, m), 4.02−3.90 (8H, m), 3.88−3.83 (2H, m), 3.80−3.73 (6H, m), 3.68−3.64 (2H, m), 3.56−3.52 (4H, m), 3.47−3.25 (9H, m), 3.08 (1H, br s), 2.10−2.05 (5H, m), 1.83 (3H, s), 1.25 (22H, br s), 1.12−1.03 (24H, m), 0.97 (21H, br s), 0.88 (3H, t, $J = 7.1$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.23, 168.56, 153.40, 140.57, 139.25, 139.17, 138.67, 138.55, 138.47, 138.38, 138.34, 138.30, 138.25, 138.15, 138.08, 137.99, 137.91, 132.36, 128.97, 128.52, 128.38, 128.31, 128.28, 128.27, 128.25, 128.22, 128.21, 128.19, 128.13, 128.08, 127.97, 127.93, 127.84, 127.76, 127.63, 127.56, 127.51, 127.49, 127.43, 127.42, 127.40, 127.35, 127.21, 127.12, 127.09, 127.08, 103.32, 102.12, 100.72, 98.95, 98.42, 97.97, 81.53, 80.65, 79.38, 79.24, 78.85, 77.62, 76.25, 75.98, 75.73, 75.42, 75.17, 74.85, 74.80, 74.16, 74.13, 73.51, 73.12, 73.08, 73.01, 72.90, 72.66, 72.45, 72.40, 72.32, 72.27, 70.38, 70.15, 70.11, 69.54, 68.73, 68.25, 68.05, 68.04, 68.03, 67.99, 67.88, 63.78, 61.21, 60.89, 53.58, 32.32, 31.88, 29.64, 29.63, 29.61, 29.59, 29.41, 29.31, 29.13, 29.00, 22.65, 20.85, 20.79, 18.02, 17.97, 17.93, 17.88, 16.64, 14.08, 11.83 (several peaks); HRMS (FAB) calcd for $C_{167}H_{214}N_4O_{35}SSi_2Na$ $[M + Na]^+$ 2946.4250, found 2946.4150.

Synthesis of Amide 55. A mixture of azide **54** (50 mg, 0.017 mmol), Lindlar's catalyst (106 mg), and palmitic anhydride (25.4 mg, 0.051 mmol) in EtOAc (2.2 mL) was stirred at room temperature under a H_2 atmosphere for 18 h. The reaction mixture was filtered through a pad of silica gel, rinsed with EtOAc (20 mL), and concentrated *in vacuo*. Flash column chromatography of crude material with 20−23% EtOAc in hexanes provided **55** (32.7 mg, 92%) of amide as a colorless oil: $[\alpha]^{23}_D$ +12.1° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$ film) 3339, 2924, 2854, 1815, 1749, 1673, 1650, 1454, 1366, 1234, 1094, 734, 697 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.67 (2H, d, $J = 7.2$ Hz), 7.35−7.13 (63H, m), 5.65 (1H, d, $J = 9.0$ Hz), 5.63−5.57 (1H, m), 5.43 (1H, br s), 5.33−5.27 (1H, m), 5.11 (2H, t-like, $J = 4.0$ Hz), 4.94 −4.90 (2H, m), 4.88−4.79 (4H, m), 4.76−4.73 (2H, m), 4.71−4.64 (5H, m), 4.62−4.58 (3H, m), 4.56−4.49 (5H, m), 4.44 (1H, dd, $J = 8.6$ and 2.2 Hz), 4.40 (1H, d, $J = 7.0$ Hz), 4.36−4.32 (2H, m), 4.30−4.11 (9H, m), 4.02−3.88 (7H, m), 3.81−3.65 (8H, m), 3.60−3.50 (4H, m), 3.45−3.36 (4H, m), 3.34−3.23 (5H, m), 3.09 (1H, br s), 2.10−1.98 (4H, m), 2.04 (3H, s), 1.83 (3H, s), 1.51 (2H, m), 1.30−1.23 (49H, m), 1.10 −0.97 (42H, m), 0.88 (6H, t, $J = 6.9$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.41, 169.63, 168.58, 153.41, 140.58, 139.34, 139.21, 138.71,

138.60, 138.56, 138.50, 138.41, 138.39, 138.26, 138.20, 138.12, 138.02, 136.88, 132.36, 128.99, 128.54, 128.39, 128.32, 128.27, 128.23, 128.20, 128.19, 128.15, 128.10, 127.99, 127.94, 127.90, 127.85, 127.77, 127.65, 127.60, 127.58, 127.52, 127.49, 127.43, 127.38, 127.29, 127.23, 127.16, 127.12, 127.09, 103.27, 102.23, 101.11, 99.03, 98.47, 98.17, 79.41, 79.31, 78.88, 77.46, 76.50, 76.37, 76.00, 75.85, 75.22, 74.88, 74.82, 74.32, 74.20, 74.15, 73.58, 73.13, 73.11, 73.03, 72.93, 72.76, 72.47, 72.34, 72.26, 70.38, 70.24, 69.58, 68.75, 68.35, 68.12, 68.04, 67.92, 67.71, 61.25, 60.93, 53.62, 53.38, 51.52, 36.81, 32.27, 31.90, 29.69, 29.52, 29.44, 29.34, 29.27, 25.67, 22.66, 20.91, 20.79, 18.03, 17.98, 17.95, 17.90, 16.66, 14.09, 11.85; HRMS (FAB) calcd for $C_{183}H_{246}N_2O_{36}SSi_2Na$ $[M + Na]^+$ 3158.6640, found 3158.6740.

Synthesis of 56. A solution of amide **55** (82 mg, 0.026 mmol) in dry THF (5 mL) was treated with TBAF (1.0 M in THF, 260 μL, 10 molar equiv) under N_2 for 19 h at room temperature. Then, MeOH (3 mL) and NaOMe (25 wt % in MeOH, 200 μL) were added. After the mixture was stirred for 1 h, 200 mg of Dowex 50-X8 was added, and the reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (70 mL), washed with water (3 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to dryness. Flash column chromatography with 2−5% MeOH in CH_2Cl_2 gave 67 mg of the product. Na (87 mg) was added to liquid NH_3 (ca. 8 mL) at −78 °C, and the mixture was stirred for 2 min under N_2 to form a blue solution, into which was added the desilylated and decarbonated substrate (67 mg) in dry THF (2 mL). The resulting mixture was stirred for 45 min at −78 °C, and then the reaction was quenched with absolute MeOH (5 mL) at −78 °C. The ammonia was removed by a stream of N_2, and more MeOH was added to a final ca. 10 mL of solution in the reaction vessel. After neutralization with Dowex 50-X8 (810 mg, dried), the mixture was then filtered, rinsed with NH_3 in methanol (20 mL), and concentrated *in vacuo*. The crude product (83 mg) was further dissolved in DMF−THF (3 mL, 1:1), and DMAP (4 mg), Et_3N (1.0 mL), and finally Ac_2O (400 μL) were added. The mixture was stirred for 24 h at room temperature and then diluted to 60 mL with EtOAc. It was washed with water (2 × 50 mL) and saturated $NaHCO_3$ solution (2 × 50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Chromatography with 60% EtOAc−CH_2Cl_2 gave 41.2 mg (73%) of the peracetated product. It was then treated with NaOMe (25 wt %, 102 μL) in MeOH (10 mL) for 15 h at room temperature and neutralized with Dowex 50-X8. Filtration, concentration, and purification by reverse phase chromatography (Lichroprep, 6 g, 20−0% H_2O in MeOH) gave 27.2 mg of **56** (68% over three steps) as a white cotton: mp 203 °C dec; $[\alpha]^{23}_D$ +41.7° (*c* 1.09, DMSO); IR (KBr) 3396 (br), 2926, 2853, 1650, 1547, 1377, 1076, 820 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 5.68 (1H, dt, J = 15.2, 6.9 Hz), 5.44 (1H, dd, J = 15.2 and 7.7 Hz), 5.19 (1H, d, J = 3.8 Hz), 5.11 (1H, d, J = 3.6 Hz), 5.01 (1H, d, J = 3.6 Hz), 4.59−4.58 (1H, m), 4.41−4.36 (2H, m), 4.30 (1H, d, J = 7.8 Hz), 4.27−4.16 (5H, m), 4.13−4.08 (1H, m), 4.06−4.03 (2H, m), 3.99−3.88 (5H, m), 3.83−3.80 (3H, m), 3.79−3.64 (11H, m), 3.59−3.51 (6H, m), 3.42−3.40 (1H, m), 3.31−3.25 (3H, m), 2.17 (2H, t, J = 7.6 Hz), 2.01 (3H, s), 1.57 (2H, br s), 1.34−1.25 (51H), 0.90 (6H, t, J = 6.6 Hz); ^{13}C-NMR (100 MHz, CD_3OD) δ 175.99, 173.78, 135.13, 131.41, 105.45, 104.47, 103.90, 102.49, 101.54, 95.55, 80.88, 79.83, 79.49, 77.01, 76.72, 76.50, 76.28, 76.25, 75.29, 74.96, 74.72, 73.54, 73.05, 72.79, 72.59, 71.84, 71.66, 70.57, 70.36, 69.94, 68.98, 68.63, 67.49, 62.93, 62.68, 62.50, 61.77, 61.66, 54.74, 50.75, 49.90, 37.42, 33.51, 33.13, 30.92, 30.87, 30.84, 30.82, 30.80, 30.76, 30.68, 30.53, 30.51 (several peaks), 27.21, 26.70, 23.78, 23.07, 16.89, 14.51; HRMS (FAB) calcd for $C_{72}H_{130}N_2O_{32}Na$ $[M + Na]^+$ 1557.8500, found 1557.8440.

Synthesis of Azide 57. A mixture of hexasaccharide glycal **51** and freshly activated 4 Å molecular sieves (100 mg) in CH_2Cl_2 (1 mL) was treated with dimethyldioxirane (ca. 0.07 M, 1 mL) at 0 °C. After completion of the reaction, the volatiles were removed by a stream of N_2, and the residue was dried on high vacuum for 20 min. Then, a solution of azidohydrin **53** in THF (0.8 mL) was added to the epoxide via cannula and cooled to −40 °C. $ZnCl_2$ (1 M) in Et_2O (25 μL) was added, and the reaction mixture was allowed to warm up to room temperature and stirred for 12 h. It was then diluted with EtOAc (50 mL), washed with saturated $NaHCO_3$ solution (2 × 20 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated to dryness. The crude material was purified by flash column chromatography (10−22% EtOAc in hexanes) to give 31.3 mg (53%) of coupled product as a colorless oil. To a solution of the coupled product (31.1 mg, 0.0109 mmol), DMAP (1.6 mg, 0.013 mmol) and Et_3N (3.0 μL, 0.0219 mmol) in CH_2Cl_2 (1 mL) and Ac_2O (1.2 μL, 0.013 mmol) were added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After the solvent was evaporated, the residue was diluted with EtOAc (30 mL), washed with dilute $NaHCO_3$ solution (2x 5 mL) and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (20% EtOAc−hexanes) of the crude material gave 30.0 mg (95%) of the desired product **57** as a colorless oil: $[\alpha]^{23}_D$ −9.2° (*c* 0.50, CH_2Cl_2); IR ($CHCl_3$ film) 3344, 3030, 2924, 2864, 2101, 1789, 1754, 1496, 1453, 1366, 1232 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, J = 7.2 Hz), 7.46−7.05 (63H, m), 5.75 (1H, dt, J = 15.2, 6.8 Hz), 5.43 (1H, dd, J = 15.5, 8.6 Hz), 5.13 (2H, m), 5.09 (1H, d, J = 3.6 Hz), 5.05 (1H, d, J = 11.6 Hz), 5.00 (1H, d, J = 11.5 Hz), 4.94−4.86 (5H, m), 4.83−4.65 (14H, m), 4.59 (2H, d, J = 11.7 Hz), 4.53−4.43 (4H, m), 4.39−4.31 (4H, m), 4.23 (1H, d, J = 11.9 Hz), 4.18 (1H, d, J = 11.9 Hz), 4.15−4.08 (2H, m), 4.05−3.57 (31H, m), 3.54 (1H, d, J = 9.1 Hz), 3.49−3.45 (2H, m), 3.38 (1H, m), 3.31−3.23 (3H, m), 2.91 (2H, m), 2.75 (1H, dt, J = 6.0 Hz), 2.12 (2H, dq, J = 6.9 Hz), 1.85 (3H, s), 1.20−1.09 (42, m), 0.92 (3H, t, J = 6.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.1, 165.9, 155.5, 140.9, 139.2, 139.0, 138.8, 138.64, 138.47, 138.43, 138.3, 138.2, 138.10, 138.07, 138.0, 132.1, 129.1, 128.69, 128.65, 128.56, 128.43, 128.36, 128.35, 128.26, 128.17, 128.12, 128.08, 127.97, 127.77, 127.66, 127.64, 127.60, 127.54, 127.49, 127.45, 127.41, 127.3, 126.0, 103.0, 102.7, 100.8, 99.7, 99.2, 98.0, 81.2, 80.6, 79.5, 79.2, 79.0, 78.3, 77.7, 76.8, 76.5, 75.5, 75.1, 75.03, 74.97, 74.91, 74.87, 74.0, 73.2, 73.10, 73.07, 72.98, 72.93, 72.6, 72.3, 72.1, 72.0, 71.32, 71.25, 70.2, 69.4, 69.32, 69.25, 68.1, 67.9, 67.5, 68.3, 62.1, 56.1, 32.4, 31.9, 29.71, 29.68, 29.66, 29.48, 29.2, 29.1, 22.7, 20.7, 18.13, 18.11, 18.01, 17.98, 16.9, 14.2, 11.9; LRMS (FAB) calcd for $C_{165}H_{212}O_{34}N_4SSi_2Na$ $(M + Na)^+$ 2904.4140, found 2904.

Synthesis of Amide 58. A mixture of azide **57** (66 mg, 0.023 mmol), Lindlar's catalyst (66 mg), and palmitic anhydride (23 mg, 0.046 mmol) in EtOAc (1 mL) was stirred at room temperature under H_2 atmosphere for 24 h. The reaction mixture was filtered through a pad of silica gel, rinsed with EtOAc (20 mL), and concentrated *in vacuo*. The crude material was purified with HPLC (20% EtOAc in hexanes, 15 mL/min, 260 nm UV detection) to give **58** (64 mg, 90%) as a colorless oil: $[\alpha]^{23}_D$ −17.9° (*c* 0.65, CH_2Cl_2)**;** IR ($CHCl_3$ film) 3531, 3346, 3063, 3030, 2924, 2854, 1790, 1674, 1496, 1454, 1365, 1236 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, J = 7.2 Hz), 7.42−7.02 (63H, m), 5.65 (1H, d, J = 9.1 Hz), 5.62 (1H, dt, J = 15.3, 6.6 Hz), 5.31 (1H, dd, J = 15.3, 8.6 Hz), 5.10 (1H, m), 5.05 (1H, d, J = 3.6 Hz), 5.02 (1H, d, J = 11.5 Hz), 4.96 (1H, d, J = 11.4 Hz), 4.90−4.62 (13H, m), 4.57−4.38 (8H, m), 4.32−4.26 (3H, m), 4.21−4.07 (9H, m), 4.01−3.41 (31H, m), 3.30 (1H, m), 3.23 (3H, m), 2.87 (2H, m), 2.71 (1H, m), 2.07−1.97 (4H, m), 1.82 (3H, s), 1.52 (2H, m), 1.32−1.19 (53H, m), 1.15−1.08 (42H, m), 0.88 (6H, t, J = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.06, 165.86, 155.54, 140.94, 139.23, 139.01, 138.64, 138.47, 138.10, 138.00, 132.00, 128.56, 128.43, 128.40, 128.36, 125.35, 128.26, 128.17, 128.12, 127.66, 127.64, 127.60, 127.54, 127.49, 127.45, 127.41, 126.04, 102.99, 102.71, 100.80, 99.72, 99.15, 97.97, 8.19, 80.60, 79.60, 79.21, 79.02, 78.47, 77.67, 77.40, 76.90, 76.49, 75.03, 74.97, 74.91, 74.87, 74.03, 73.19, 73.10, 73.07, 72.98, 72.80, 72.51, 72.03, 71.83, 71.7, 70.16, 69.20, 68.29, 68.09, 67.86, 67.06, 63.77, 62.11, 62.04, 56.05, 32.39, 31.94, 29.71, 29.68, 29.66, 29.48, 29.38, 29.20, 29.07, 22.71, 20.70, 16.89, 14.16; LRMS (FAB) calcd for $C_{181}H_{244}O_{35}N_2SSi_2Na$ $(M + Na)^+$ 3116.6530, found 3116.

Synthesis of 1. A solution of **58** (20 mg, 0.0065 mmol) in THF (0.5 mL) was treated with TBAF solution (1.0 M in THF, 50 μL) and stirred for 2 h. Then it was filtered through a pad of silica gel, washed with EtOAc (30 mL), and concentrated *in vacuo*. The crude material was dissolved in MeOH (1 mL), treated with MeONa (10 mg), and stirred for 3 h. The reaction was neutralized with Dowex 50-X8 (40 mg), filtered, washed with EtOAc (10 mL), and concentrated *in vacuo*. Flash column chromatography of crude material with 0−5% MeOH in CH_2Cl_2 afforded the desired product (16.5 mg, 94%). To liquid NH_3 (ca. 8 mL) under N_2 at −78 °C was added Na (12 mg), and the mixture was stirred for 2 min. To the blue solution was added the desilylated and decarbonated substrate (16 mg) in THF (1 mL), and the mixture was stirred for 45 min at −78 °C. The reaction mixture was quenched by addition of MeOH (4 mL). Ammonia was removed

with a stream of N_2, and then the solution was diluted with MeOH to ca. 7 mL. The reaction mixture was neutralized with Dowex 50-X8 (115 mg), filtered, rinsed with NH_3 in MeOH (20 mL), and concentrated *in vacuo*. A mixture of the residue and DMAP (3 mg) were dissolved in DMF (1 mL), THF (1 mL), and Et_3N (0.2 mL), then treated with Ac_2O (50 μL), and stirred for 3 h. After the reaction mixture was concentrated, the residue was purified on 10−40 μm of silica gel using 10% hexanes in EtOAc to give the product (10.7 mg, 80%). A portion of the peracetate (2.3 mg) dissolved in MeOH (0.5 mL) under N_2 was treated with MeONa in MeOH (25 wt %, 5 μL), and the mixture was stirred for 4 h. The reaction mixture was neutralized with Dowex 50-X8 (4.5 mg), filtered, washed with MeOH (5 mL), and concentrated *in vacuo*. The residue was purified with reverse phase column chromatography (Lichroprep, MeOH) to give **1** (quantitative) as white cotton: $[\alpha]^{23}_D$ +9.1° (*c* 0.45, MeOH)**;** IR (KBr) 3356, 2920, 2851, 1734, 1652, 1547, 1466, 1372, 1260, 1075, 1042 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6/D_2O, 10:1) δ 5.53 (1H, dt, J = 15.3, 6.7 Hz), 5.35 (1H, dd, J = 15.2, 7.0 Hz), 4.95 (1H, br s), 4.81 (1H, d, J = 3.7 Hz), 4.48 (1H, d, J = 8.4 Hz), 4.44 (1H, d, J = 8.1 Hz), 4.25 (1H, d, J = 7.6 Hz), 4.16 (1H, d, J = 7.8 Hz), 4.07 (2H, m), 3.99−3.85 (5H, m), 3.81−3.72 (6H, m), 3.68−3.35 (22H, m), 3.29 (2H, m), 3.03 (1H, t, J = 7.9 Hz), 2.02 (2H, m), 1.93 (2H, m), 1.82 (3H, s), 1.44 (2H, m), 1.23 (46H, m), 1.08 (3H, d, J = 6.4 Hz), 0.84 (6H, t, J = 6.6 Hz); ^{13}C-NMR (125 MHz, CD_3OD) δ 176.02, 174.52, 135.21, 131.40, 105.55, 105.44, 104.44, 103.95, 102.86, 101.06, 81.18, 80.49, 80.05, 79.12, 77.97, 76.84, 76.57, 76.44, 76.27, 75.57, 74.96, 74.70, 73.59, 73.06, 72.61, 72.48, 71.56, 70.69, 70.66, 70.37, 69.99, 69.72, 69.73, 68.12, 62.69, 62.64, 61.77, 61.62, 54.89, 54.83, 53.14, 37.43, 33.55, 33.17, 30.96, 30.92, 30.89, 30.87, 30.85, 30.79, 30.73, 30.64, 30.59, 30.54, 30.49, 27.26, 23.83, 23.76, 16.76, 14.46; HRMS (FAB) calcd for $C_{72}H_{130}O_{32}N_2Na$ (M + Na)$^+$ 1557.8500, found 1557.8450.

Synthesis of Allyl Glycoside 64. A solution of hexasaccharide glycal **51** (85 mg, 0.035 mmol) in THF (6 mL) under N_2 at room temperature was treated with TBAF (1.0 M in THF, 353 μL, 10 equiv). After 38 h at room temperature, the reaction mixture was concentrated to ca. 1 mL, then dissolved in EtOAc (60 mL), washed with H_2O (2 × 30 mL), dried (Na_2SO_4), and concentrated to dryness. Flash column chromatography of the crude material with 4% MeOH in CH_2Cl_2 gave 70.0 mg (98%) of the desilyl decarbonated product. To liquid ammonia (ca. 8 mL) under N_2 at −78 °C was added sodium (95 mg). To the formed blue solution was added a solution of the above desilyl decarbonate compound (70 mg, 33.8 μmol) in dry THF (2 mL). After 45 min at −78 °C, the reaction was quenched with absolute methanol (4 mL). Most of the ammonia was removed with a stream of nitrogen (final volume was ca. 4 mL) and the reaction mixture diluted with methanol to ca. 10 mL. To the solution was added Dowex 50-X8 (890 mg, washed and dried), and the mixture was stirred for 5 min. The solution was filtered and rinsed with methanol and finally with NH_3 in methanol (5 mL), and the filtrate was concentrated *in vacuo*. The residue and DMAP (2.4 mg) were placed under N_2, suspended in DMF (1.0 mL), THF (1.0 mL), and Et_3N (1.0 mL), and then treated with Ac_2O (0.3 mL). After 20 h (TLC analysis with EtOAc), the reaction mixture was poured into water (40 mL), extracted with EtOAc (2 × 40 mL), washed with dilute $NaHCO_3$ solution (30 mL) and water (30 mL), dried over Na_2SO_4, and concentrated to dryness. Flash column chromatography of the crude material with 80% EtOAc in CH_2Cl_2 gave 52.0 mg (93%) of the peracetylhexasaccharide glycal as a white foam.

Peracetylhexasaccharide glycal: mp 132−134 °C; $[\alpha]^{23}_D$ +4.7° ($CHCl_3$, *c* 1.4); IR ($CHCl_3$ film) 1742, 1652, 1371, 1227, 1069 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, d, J = 6.8 Hz), 6.42 (1H, d, J = 6.0 Hz), 5.58 (1H, d, J = 3.2 Hz), 5.47 (1H, d, J = 3.4 Hz), 5.40−5.37 (2H, m), 5.29 (1H, dd, J = 10.9, 3.1 Hz), 5.25−5.15 (5H, m), 5.06 (1H, dd, J = 11.2, 3.3 Hz), 5.02 (1H, d, J = 3.6 Hz), 4.99−4.92 (2H, m), 4.84−4.81 (2H, m), 4.67 (1H, d, J = 7.8 Hz), 4.56−4.51 (2H, m), 4.45−4.38 (3H, m), 4.29 (1H, dd, J = 10.6, 3.4 Hz), 4.22−3.95 (13H, m), 3.90−3.77 (3H, m), 2.19−1.92 (51H, m), 1.15 (3H, d, J = 6.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.40, 171.45, 170.84, 170.54, 170.52, 170.48, 170.45, 170.40, 170.39, 170.34, 170.23, 169.99, 169.82, 169.74, 169.36, 169.00, 145.43, 102.01, 101.17, 98.83 (2C), 98.45, 94.24, 75.65, 74.95, 73.98, 73.64, 73.49, 72.32, 71.84, 71.53, 71.44, 70.81, 70.74, 70.66, 70.12, 69.77, 68.97, 68.71, 68.67, 68.02, 67.97, 67.88, 67.60, 67.35, 64.43, 61.88, 61.81, 61.42, 61.29, 61.04, 56.18, 23.06, 21.02, 20.81, 20.76, 20.68, 20.64, 20.62, 20.58, 20.57, 20.55, 20.49, 20.43, 15.88; LRMS (FAB), 1676 [M + Na]$^+$ (100), 1634 (18), 1594 (35), 1404 (10), 849 (95); HRMS (FAB) calcd for $C_{70}H_{95}NO_{44}Na$ [M + Na]$^+$ 1676.5120, found 1676.5160.

Peracetyl hexasaccharide glycal (52 mg) was divided into two portions (22 mg and 30 mg). A solution of hexasaccharide glycal (22.0 mg, 13.4 μmol) in dry CH_2Cl_2 (2 mL) under N_2 at 0 °C was treated with dimethyldioxirane solution (ca. 0.08 M, 500 μL) and stirred for 40 min at 0 °C. The reaction mixture was concentrated to ca. 100 μL with a stream of dry N_2 at 0 °C and then treated with allyl alcohol (5 mL). The mixture was stirred for 15 h at room temperature. Excess allyl alcohol was removed *in vacuo*. The other batch (30 mg) was treated similarly. The crude products were combined and chromatographed with 85% EtOAc in CH_2Cl_2 to give 35.8 mg (66%) of less polar product (β-allyl gluco) and 15.7 mg (29%) of more polar product (α-allyl manno). A 33.2 mg (19 μmol) portion of the less polar material under N_2 was dissolved in absolute MeOH (14 mL) and treated with MeONa (25% in MeOH, 165 μL). After 6 h, the reaction mixture was neutralized with Dowex 50-X8 (200 mg, washed and dried), filtered, and concentrated to give quantitative yield of the title compound. An analytical sample was prepared by RP column chromatography (Lichroprep, 6.0 g), eluting with water−5% methanolic water, followed by lyophilization to obtain white powder: mp 204−206 °C dec; $[\alpha]^{23}_D$ +5.5° (MeOH, *c* 0.67); IR (MeOH film) 3356 (br), 2923, 1658, 1374, 1071 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 5.99−5.93 (1H, m), 5.35−5.29 (1H, m), 5.24 (1H, d, J = 3.8 Hz), 5.18−5.14 (1H, m), 4.93 (1H, d, J = 3.9 Hz), 4.56−4.54 (2H, m), 4.42−4.06 (10H, m), 3.99 (1H, s), 3.91−3.47 (26H, m), 3.41−3.37 (1H, m), 3.27 (1H, t, J = 8.8 Hz), 2.01 (3H, s), 1.24 (3H, d, J = 6.5 Hz); ^{13}C-NMR (100 MHz, CD_3OD, ref = δ 49.05) δ 174.55, 135.73, 117.57, 105.48, 105.42, 103.94, 103.26, 102.79, 101.08, 81.21, 80.67, 80.05, 79.20, 78.09, 76.79, 76.56, 76.48, 76.44, 76.41, 75.54, 74.86, 74.68, 73.57, 72.63, 72.50, 71.57, 71.16, 70.64, 70.41, 69.68, 68.16, 62.67, 62.64, 62.57, 61.96, 61.63, 53.11, 23.58, 16.78; LRMS (FAB), 613 (100); HRMS (FAB) calcd for $C_{41}H_{69}NO_{30}Na$ [M + Na]$^+$ 1078.3800, found 1078.3780.

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Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for **9** → **16** and NMR spectra (^{1}H, ^{13}C) for most compounds (**1**, **22**, **23**, **24**, **28**, **32**, **35**, **37**, **38**, **46**, **47**, **49**−**51**, **55**, **56**, **58**, and **64**) (50 pages). See any current masthead page for ordering and Internet access instructions.

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