Synthesis of Asialo GM_1. New Insights in the Application of Sulfonamidoglycosylation in Oligosaccharide Assembly: Subtle Proximity Effects in the Stereochemical Governance of Glycosidation

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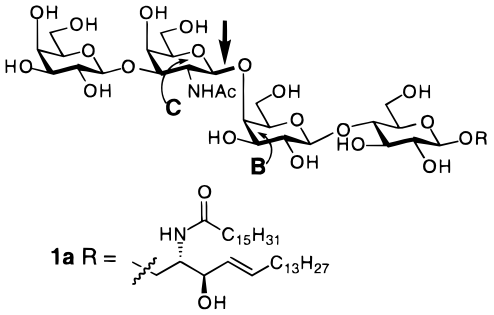
Received July 23, 1997[⊗]

Abstract: The total synthesis of asialo GM_1 (**1a**) has been accomplished. Using related chemistry, the methyl glycoside of the asialo compound (**1b**) has also been synthesized. These kinds of compounds have been identified as potential ligands for bacterial and viral infection sites. A simpler structure, which has also been identified for its infection attracting structure in the context of glycopeptides and glycolipids (methyl glycoside **2**), has also been synthesized. The key common phase in the syntheses involves the sulfonamidoglycosidation reaction which is used to create a β-linkage leading to a galNAc residue joined to the C_4 hydroxyl group of a galactose unit either as a monosaccharide (see compound **2**) or as C_4' in the context of a lactosyl moiety. During the course of these studies there was encountered an unusual "proximal hydroxyl" directing effect. Thus, when C_4 on the galactose ring of an azaglycosylating donor bears a free hydroxyl (see, for instance, compound **13**), β-glycoside formation predominates. When this hydroxyl group is blocked, the process tends in the direction of α-glycoside formation (see compound **32**). These findings were explained as arising from a critical intramolecular hydrogen bond between the C_4 axial hydroxyl of the galactose donor and its proximal pyranosidal ring oxygen. This interaction stabilizes conformations from which β-glycosidation predominates.

Background

It is now becoming clear that carbohydrate substructures of human cell surface glycoproteins or glycolipids constitute important binding sites for a variety of bacterial and viral infections.[1,2] From this perspective alone there would be a clear biological rationale for undertaking the synthesis of the title structure, asialo GM_1. One of the major causes of morbidity and mortality of victims of cystic fibrosis (CF) is infection of the lungs by microorganisms, particularly *Pseudomonas aeruginosa*.[3,4] Al Awquati and co-workers found that CF bronchial and pancreatic epithelia reversibly bind *P. aeruginosa*. Strong evidence was brought to bear to the effect that asialo GM_1 (**1a**, see Scheme 1), which is bound through a hydrophobic attraction to the apical membrane of CF epithelia, is a likely binding site for *P. aeruginosa* and that its increased abundance contributes to bronchial bacterial invasion. These findings also underscore the need to synthesize glycosides of the type **1b** where the core carbohydrate is retained, but the ceramide attachment is replaced by simple glycosidic linkages. The synthetic carbohydrate ligands should not be membrane bound. *In suitably bioavailable form, they could serve as "decoys" to prevent or clear up bacterial infection.* The understanding of how glycolipid "ligands" interact with protein receptors in infectious bacteria could well benefit from an insight as to structure activity relationships (SAR) of the carbohydrate domain. An early report from Krivan[5] suggests that the interior galNAcβ1-4gal disaccharide **2** functions as a recognition locus for a variety of common pathogenic attachments such as occur in influenza and pneumonia as well as CF-directed infection.[3]

Scheme 1. Target Structures



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[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1997.

(1) Idänpään-Heikkilä, I.; Simon, P. M.; Vullo, T.; Cahill, P.; Sokol, K.; Tuomanen, E. *J. Infect. Dis.,* in Press.

(2) Cundell, D. R.; Tuomanen, E. *Microb. Pathog.* **1994**, *17*, 361−374.

(3) Imundo, L.; barasch, J.; Prince, A.; Al-Awqati, Q. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 3019−3023.

(4) Barasch, J.; Kiss, B.; Prince, A.; Saiman, L.; Gruenert, D.; Al-Awqai, Q. *Nature* **1991**, *352*, 70−73. Barasch, J.; Al-Awqati, Q. *J. Cell. Sci. (Suppl.)* **1993**, *17*, 229- 233.

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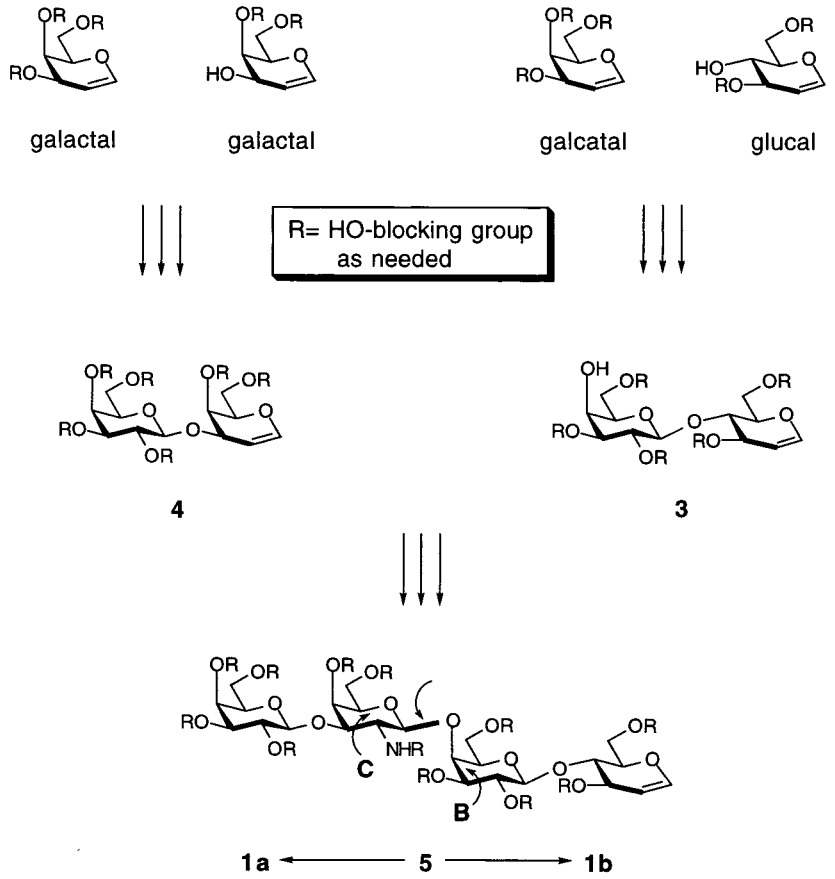
S0002-7863(97)02495-5 CCC: $15.00
Published on Web 02/04/1998

Scheme 2. Overall Synthetic Plan



Insights gained from the development of a stereoselective synthetic route to asialo GM$_1$[6,7] would undoubtedly find application in the preparation of glycosides of the type **1b** and of the basic Krivan motif **2**. In addition to the obvious biological ramifications of the asialo GM$_1$ problem, there were significant chemical issues to be faced if we were to adapt our general strategy of glycal assembly[8] to the synthetic problem at hand. Hence, the problem area was attractive to us in that it combined questions of high interest to our laboratory at the level of chemistry, with potential applications of consequence in anti-infective strategies.

On the basis of these broad considerations, we summarized the specific goals of our project to be (i) a total synthesis of asialo GM$_1$ in a concise fashion, (ii) the investigation of the range of applicability of sulfonamidoglycosylation to the assembly of complex and biologically useful oligosaccharides, (iii) the application of the lessons of these investigations to the assembly of analogues based on the Krivan ligand **2**, and (iv) the evaluation of the concept of using fully synthetic, circulating glycosides incorporating the motifs of **1** and **2** as potential antagonists of bacterial invasion in keeping with the findings of Tuomanen,[2] Al Awquati,[3] and Krivan.[5]

From a chemical standpoint, the most provocative structural feature of asialo GM$_1$ as a target for synthesis is the union of the B and C rings. In this key connection (see boldface arrow in Scheme 1), the sole axial oxygen center attached to the lactose is glycosidically linked in a β-sense to a galNAc residue, which through its C_3 hydroxyl is, in turn, linked (β) to a terminal galactose. Applying the logic of glycal assembly to this strategic bond,[8] and bearing in mind the biological thrust as expressed in goal iv above, we would hope to couple the generalized AB glycal (cf. **3**) with CD glycal (**4**) leading to an ABCD glycal **5**.

Continuing in the retrosynthetic vein, we first consider the CD sector. Of course, the bicyclic glycal **3**, in principle, corresponds to a lactose or lactal derivative. Therefore one might have started from the readily available lactose. However, as discussed earlier,[9] we had not yet developed a satisfactory method to distinguish the sole C_4' axial hydroxyl as the specific glycosidation site starting with lactal. Therefore, it would be necessary for us to fashion a system of the type **3**, through synthesis, possibly from monocylcic glycals.

An important subgoal would be a system of the type **5**, which we termed as an "asialo GM$_1$ glycal". We were confident that glycal **5** could be advanced to reach asialo GM$_1$ (**1a**) or to probe structures of the type **1b**. The synthetic "gestalt" which governed our experiments is broadly programmed in Scheme 2.

We first describe the synthesis of the azaglycosyl donor **13** (Scheme 3). The sequence started with triacetylgalactal **6**, which was converted to galactal and then to the mono-TIPS derivative **7** (TIPS = triisopropylsilyl). This having been accomplished, the hydroxyl groups at C_3 and C_4 were engaged as a cyclic carbonate (see compound **8**).[9] The olefin linkage was epoxi-

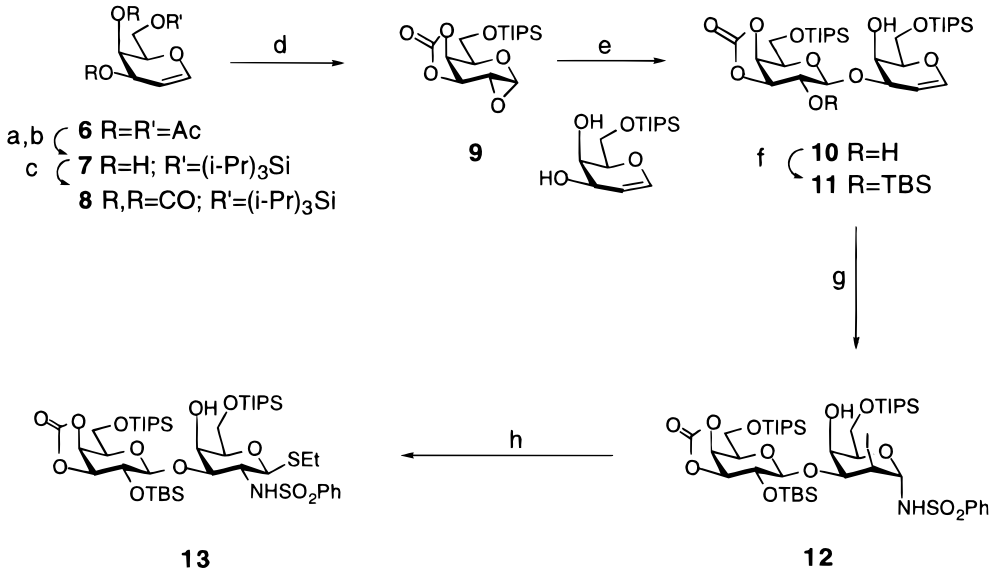
(6) (a) Sugimoto, M.; Horisaki, T.; Ogawa, T. *Glycoconjugate J.* **1985**, *2*, 11−15. (b) Sabesan, S.; Lemieux, R. U. *Can. J. Chem.* **1984**, *62*, 644−654. (c) Paulsen, S.; Paal, M.; Hadamczyk, D.; Steiger, K.-M. *Carbohydr. Res.* **1984**, *131*, c1−c5. Paulsen, S.; Paal, M. *Carbohydr. Res.* **1985**. *137*, 39−62.

(7) (a) Sugimoto, M.; Numata, M.; Koike, K.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *156*, c1. (b) Hasegawa, A.; Ishida, H.; Nagahama, T.; Kiso, M. *J. Carbohydr. Chem.* **1993**, *12*, 703−718. (c) Stauch, T.; Greilich, U.; Schmidt, R. R. *Liebigs Ann. Chem.* **1995**, 2101−2111.

(8) Danishefsky, S. D.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419.

(9) Bilodeau, M. T.; Park, T. K.; Hu, S.; Randolph, J. T.; Danishefsky, S. J.; Livingston, P. O.; Zhang, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7, 7840. Park, T. K.; Kim, I. J.; Hu, S.; Bilodeau, M. T.; Randolph, J. T.; Kwon, O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 11488.

Scheme 3[a]

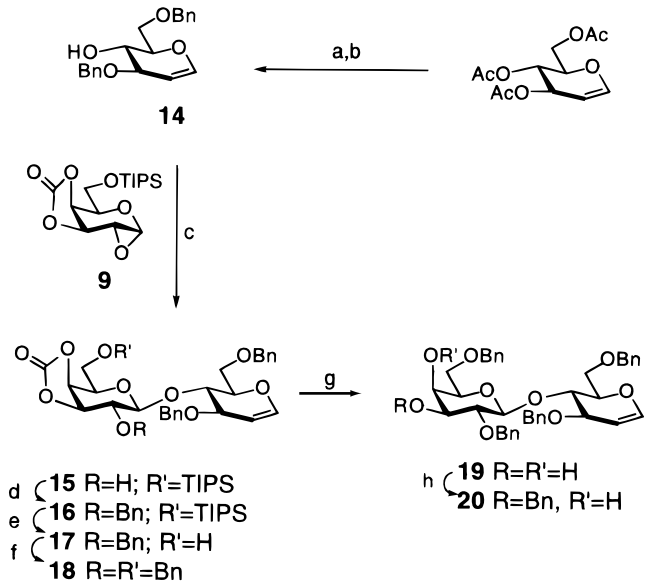


[a] Reagents: (a) NH_3/MeOH; (b) TIPSCl, Im, DMF, 74% (two steps); (c) 1,1′-carbonyldiimidazole (CDI), 4-dimethylaminopyridine (DMAP), CH_2Cl_2, 97%; (d) dimethyldioxirane, CH_2Cl_2, 0 °C; (e) **7**, $ZnCl_2$, THF, −78 °C to room temperature (rt), 78%; (f) *tert*-butyldimethylsilyl chloride (TBSCl), Im, DMF, 0 °C to rt, quantitative; (g) I(*sym*-coll)$_2$ClO$_4$, $PhSO_2NH_2$, 4 Å MS, CH_2Cl_2, 0 °C; (h) EtSH, LHMDS, DMF, −40 °C to rt, 42% (two steps).

dized through the action of dimethyldioxirane,[8] thereby affording epoxide **9**. The latter coupled smoothly with 6-*O*-TIPS-D-galactal (**7**)[10] under the influence of zinc chloride, specifically at C_3, to provide compound **10**. Of the two hydroxyl groups in this substance, the one which is equatorial (C_2' of the gal-gal residue) underwent selective silylation (see compound **11**). From this point, it was possible to introduce the 2β-iodo-1α-phenylsulfonamido arrangement through the reaction of **11** with benzenesulfonamide in the presence of bis(*sym*-collidinyl)-iodonium perchlorate.[11] Previous experience[8] had taught us that, with a hindered glycosyl acceptor, a system of the type **12** would not be effective as a glycosyl donor. Fortunately, methodology was already on hand for dealing with this type of situation in a complex setting.[12] In the event, reaction of **12** with lithium ethanethiolate gave rise to the donor system **13**, which was to function in a coupling reaction with a suitably differentiated lactal derivative (cf. **3**).

The specific lactal which we settled upon to correspond to the generalized structure **3** was the pentabenzyl compound **20** (Scheme 4), in which only the axial 4′ hydroxyl group is available to function as a glycosyl acceptor site. Actually, this very compound had been prepared as part of a synthesis of the human breast tumor antigen.[9] In the chemistry practiced here, some small variations were introduced with the view of allowing us to explore a range of new lactal analogues, which were not available via the previous protocols. We proceeded as follows: The cyclic carbonate epoxide **9**, synthesized as shown above from galactal, again served admirably for our purposes. This compound coupled smoothly under guidance by anhydrous zinc chloride with 3,6-*O*-dibenzyl-D-glucal (**14**), itself prepared in one step from the selective 2-fold benzylation of D-glucal, as shown. In this fashion we gained concise access to **15**. The latter underwent clean benzylation at its C_2' hydroxyl group, thus affording **16**. At this stage it proved possible to cleave the TIPS protecting group and to benzylate the resultant **17**,

Scheme 4[a]



[a] Reagents: (a) NaOMe, MeOH; (b) (i) $(Bu_3Sn)_2O$, PhH, Dean−Stark; (ii) BnBr, tetrabutylammonium bromide (TBABr), 86% (overall); (c) $ZnCl_2$, THF, −78 °C to rt, 86%; (d) NaH, BnBr, DMF, 90%; (e) tetrabutylammonium fluoride (TBAF), AcOH, THF, 90%; (f) NaH, BnBr, DMF, 0 °C to rt, 81%; (g) K_2CO_3, MeOH, 89%; (h) (i) $(Bu_3Sn)_2O$, toluene, Dean−Stark; (ii) BnBr, tetrabutylammonium iodide (TBAI), quantitative.

thus providing **18** as shown. Further cleavage of the cyclic carbonate gave **19**, in which the C_3' and C_4' are free. While this constellation in **19** could be exploited for other reasons, in the case at hand, we took recourse to stannylidine-mediated selective benzylation[13] to afford the desired **20**.

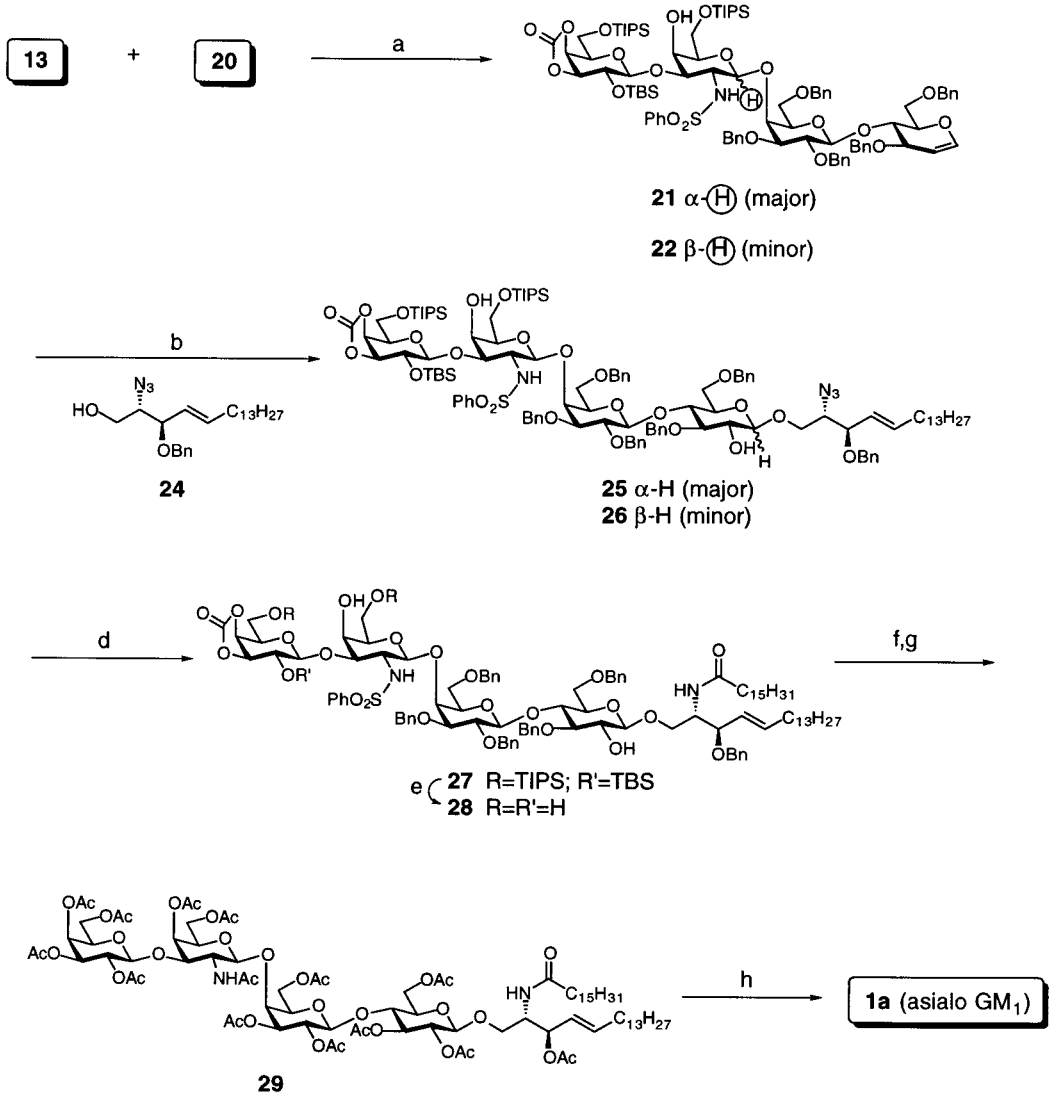
We first describe the total synthesis of the focusing target, asialo GM_1 (**1a**)[6] and then relate the results of some interesting and important accessory studies. Coupling of **13** and **20** could be carried out under mediation by methyl triflate under the conditions shown, to give the desired β-glycoside **21** (71% yield) (Scheme 5), as well as a 6% yield of the α-anomer (**22**). Glycal

(10) Danishefsky, S. J.; Behar, V.; Randolph, J. T.; Lioyd, K. O. *J. Am. Chem. Soc.* **1995**, *117*, 5701−5711.

(11) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811−5819.

(12) Griffith, D. A. Ph.D. Thesis, Yale University, 1992.

Scheme 5[a]



[a] Reagents: (a) MeOTf, 4 Å MS, Et_2O/CH_2Cl_2 2:1, 0 °C, 71−84% α-H (α-H:β-H = 13:1); (b) dimethyldioxirane, 4 Å MS, CH_2Cl_2, 0 °C; (c) **24**, $ZnCl_2$, THF, −50 °C to rt, 60% α-H, 6% β-H; (d) H_2, Lindlar's catalyst, palmitic anhydride, EtOAc, rt, 89%; (e) TBAF, AcOH, THF, 82%; (f) Na, NH_3, THF, −78 to −33 °C; MeOH, −78 °C to rt; (g) Ac_2O, pyridine, 75% (overall); (h) NaOMe, MeOH, 89%.

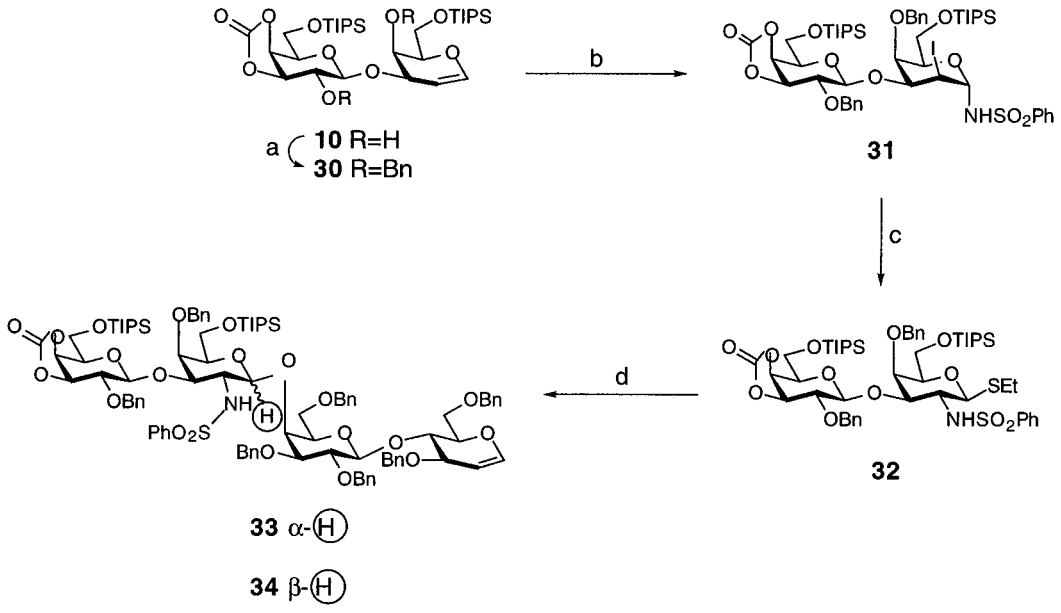
21 was to function as the specific equivalent of the hypothesized generalized structure **5**. All of our subsequent schemes were to pass through this kind of structure. The assignment of sterochemistry at the B−C glycoside linkage for these two compounds was initially based on extensive NMR analysis (including COSY, Hetcor, and J-res techniques) which identified the critical ring C anomeric protons to be as formulated. Coupling reactions, similar to that of **13** + **20** using a 1β-(thioethyl)-2α-sulfonamidogalactose-type donor, had been studied previously in our laboratory.[9] Their outcomes have been shown to be quite dependent on protecting group patterns[8] and are also markedly sensitive to the choice of reaction conditions. We shall return to issues pertinent to the 2 + 2 coupling shortly.

We first report the synthesis of asialo GM$_1$ (**1a**) from the tetracyclic glycal **21**. The sequence commenced with its reaction with dimethyldioxirane to generate oxirane **23**. The latter, on reaction with azido alcohol **24**,[14] under mediation by anhydrous zinc chloride, afforded a 60% yield of **25**. There was also obtained a 6% yield of the isomer **26**. At this stage, the formulation of stereochemistry at the pre-ceramide linkage of glycosides **25** and **26** was based to a considerable extent on well-established analogies rather than on unambiguous data on the compounds themselves. The azide linkage of **25** suffered reduction with Lindlar catalyst, and the resulting amine was palmitoylated to give rise to **27**.

The concluding deprotection sequence commenced with desilylation (see compound **28**). This step was followed by debenzylation and peracetylation to provide homogeneous **29** in 75% yield. Finally, cleavage of all acyl bonds afforded an 89% yield of asialo GM$_1$ (**1a**). Of course, there was no actual sample of asialo GM$_1$ (bearing the *N*-palmitoyl group in the ceramide domain) available to us. Our assignment of the structure was based on the extensive NMR analysis of the intermediates en route to the final structure, on the close correspondence on the four anomeric protons with NMR data in the recent literature,[15] and on the basis of the anomeric $^{13}C-$

(13) Davis, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643−663.
(14) Schmidt, R. R.; Zimmermann, P. *Tetrahedron Lett.* **1986**, *27*, 481−484. Zimmermann, P.; Schmidt, R. R. *Liebigs Ann. Chem.* **1988**, 663−667.
(15) Gasa, S.; Mitsuyama, T.; Makita, A. *J. Lipid Res.* **1983**, *24*, 174−182.
(16) Podlasek, C. A.; Wu, J.; Stripe, W. A.; Bondo, P. B.; Serianni, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 8635−8644.

Scheme 6[a]



[a] Reagents: (a) NaH, BnBr, DMF, 82%; (b) I(*sym*-coll)$_2$ClO$_4$, PhSO$_2$NH$_2$, 4 Å MS, CH$_2$Cl$_2$, 0 °C, 80%; (c) EtSH, LHMDS, DMF, −40 °C to rt, 84%; (d) **20**, MeOTf, 4 Å MS, THP, 0 °C, 39% β-H, 4% α-H.

^{1}H spin-coupling constants[16] (measuring 160.9, 158.2, 160.0, and 159.1). This structure is also supported by the agreement of its high-resolution mass spectrum with theory. (FAB-HRMS calcd for $C_6H_{110}O_{23}N_2Na$ 1249.7400, found 1249.7420).

Prior to our discovery that donor **13** functioned well with acceptor **20** to produce a highly favorable ratio of β:α glycosides of tetracyclic product (cf. **21** and **22**), we had evaluated other versions of subtype glycal **4** as potential glycosyl donors. One such study commenced with bicyclic diol **10**. In this variation, both hydroxyl groups were benzylated through the action of sodium hydride and benzyl bromide to produce bicyclic glycal **30** (Scheme 6). The latter was converted, in 80% yield, to iodosulfonomide **31** in the usual way. "Rollover"[8] of the sulfonamido function through the action of ethanethiol (deprotonated through the action of lithium hexamethyldisilazide (LHMDS)) gave rise to compound **32**. This compound differs from the previously noted donor **20** by the presence of a benzyl group (instead of a TBS group) on the C_2 hydroxyl of the terminal galactose and a benzyl group rather than a free hydroxyl group at C_4 of the donor ring.

The coupling of compound **32** and acceptor **20** was studied in some detail. Interestingly, through the use THF as solvent, a 20:1 ratio of α:β glycosides (see **33** and **34**) was obtained. However, since the yield in this experiment was only reproduced with difficulty due to the polymerization of tetrahydrofuran under the conditions (methyl triflate) of the coupling, we did not pursue the finding in detail. The experimental problem was alleviated through the use of tetrahydropyran (THP) as the solvent. A 10:1 ratio of **34** to **33** was obtained, this time in 43% yield. Attempted recourse to other solvent systems, such as ether−methylene chloride led to mixtures, in which the desired product **33** was favored, though only in ratios of approximately ∼1.5:1. The criteria for distinguishing the stereochemistry at the B:C connecting point between **33** and **34** were similar to those discussed above for glycals **21** and **22**.

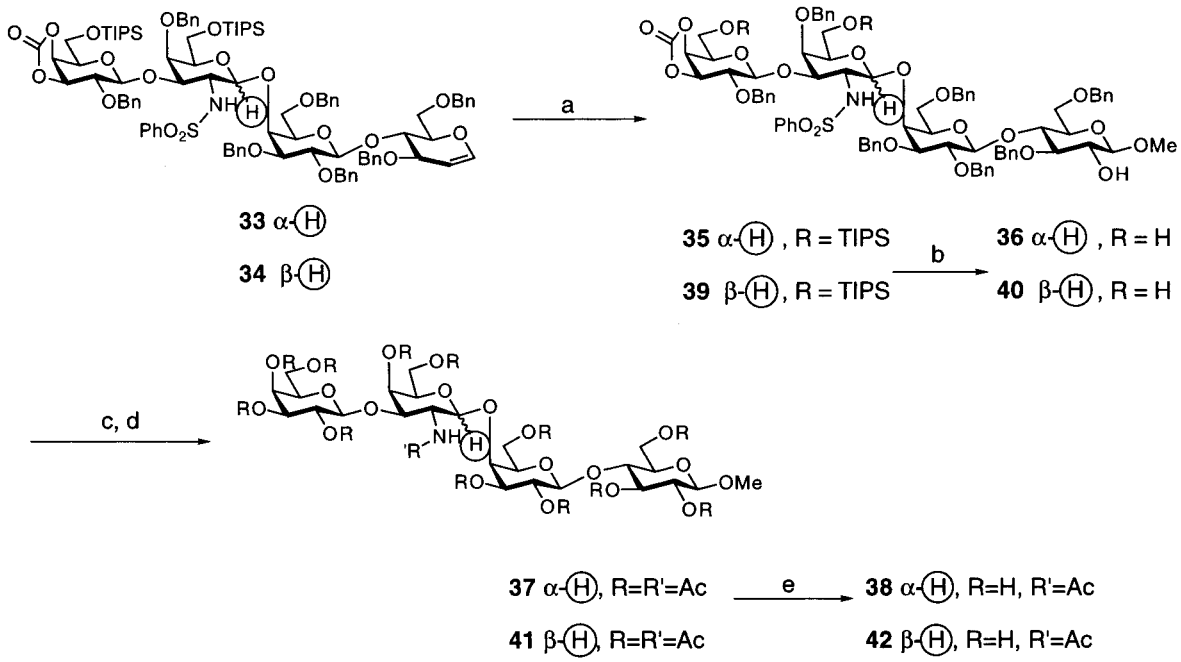
We shall return to the matter of the sharp dependency of the stereochemistry of the azaglycosylation reaction on the nature of C_4 hydroxyl group of the galactose donor ring. We first describe the sequences leading to the methyl glycoside goal systems (**38** and **42**). The former would have the natural asialo GM_1 stereochemistry in the merger of the B and C rings. In the latter structure, an unnatural glycosdic arrangement would be present. Glycals **33** and **34** served as the starting materials for the synthesis of methyl glycosides **38** and **42**.

Epoxidation of glycal **33** through the action of dimethyldioxirane, followed by methanolysis, gave rise to **35** (Scheme 7), albeit in a disappointing 43% yield. The deprotection phase was conducted as above. Desilylation with TBAF (see compound **36**) was followed by reductive debenzylation (Na/NH$_3$), methanolysis, and peracetylation. By following these steps, compound **37** was obtained in 80% yield. Finally, cleavage of all the acetate functions afforded the β-methyl glycoside **38**.

It is, eventually, our intention to pinpoint the structural dependencies for bacterial binding to ligands related to asialo GM_1 in the structures which lack the cell anchoring. Therefore, we also processed the tetracyclic glycal **34** which was epimeric at the ring B-ring C glycosidic bond. This compound, at the stereochemical level, departs from the central galNAcβ1-4gal motif (see structure **2**) identified by Krivan as a bacterial binding domain.[5] The synthesis of the epi-asialo GM_1 system commenced with the glycal **34**. This compound was advanced using protocols which are closely related to those described above. Epoxidation of **34** with dimethyldioxirane, followed by methanolysis, led to methyl glycoside **39**, this time in a more respectable 64% yield. Deprotection of the two primary TIPS groups gave rise to diol **40**. The next phase involved cleavage of the sulfonamide group, followed by exhaustive acylation (see compound **41**). Methanolysis of all of the oxygen bound acetates led to methyl glycoside **42**.

We proceeded to the synthesis of the disaccharide glycal **52** (Scheme 8). From such an intermediate we were confident that we could reach the methyl glycoside **57** that embodies the basic stereochemical motif identified by Krivan[5] in a variety of bacterial binding carbohydrate ligands. Once again, the effort began from galactal and proceeded through the mono-TIPS compounds (see structure **7**). An additional silicon protecting group was introduced at the C_3 alcohol, in the context of the 3,6-*O*-di-TIPS-D-galactal derivative **43**. The axial hydroxyl group in **43** was acetylated (see structure **44**). Once again, it

Scheme 7[a]



[a] Reagents: (a) dimethyldioxirane, CH_2Cl_2, 0 °C; MeOH, $ZnCl_2$, THF, 43% for **35**, 64% for **39**; (b) TBAF, AcOH, THF, quantitative for **36**, 93% for **40**; (c) Na, NH_3, THF, −78 to −33 °C; MeOH, −78 °C to rt; (d) Ac_2O, pyridine, 80% for **37**, 29% for **41**; (e) NaOMe, MeOH, 99%.

proved possible to add iodobenzenesulfonamide to the glycal linkage, even in the presence of the unprotected alcohol at C_4, thereby leading to trans-diaxial iodosulfonamide **45**. Rearrangement and thiolative trapping gave rise to potential donor **46**. In this compound, surprisingly, the TIPS group had migrated from C_3 to C_4. Apparently, the presence of the sulfonamide group, either due to hydrogen bonding or due to steric congestion, favors the presence of a free OH at C_3, even though the bulky silyl group takes up residence on the axial alcohol. Seemingly, the conditions of thiolate induced rearrangement of **45** trigger the equilibration of the silyl group from C_3 to C_4 .

Since we preferred to work in the series where C_3 was protected, we returned to the derived acetate **44**. We were able to carry out the addition of iodobenzenesulfonamide to the glycal linkage to provide **49**. Under the impact of lithium ethanethiolate (generated through the reaction of ethanethiol and LHMDS), the potential donor system **48**, with the acetate still in place, was obtained. Attempted deprotection of acetyl group using potassium cyanide or potassium carbonate facilitated TIPS group migration, providing **46** rather than desired **49**. However, it was possible to cleave this function through the action of lithium aluminum hydride in ether, without triggering silyl movement to afford donor **49**. It would seem that, in the reaction of **45**, either the LHMDS base or the ethanethiolate mediates this still mysterious rearrangement.

Donors **48** and **49** were coupled to acceptor **50**, in turn prepared from D-galactal by stannylidene-induced dibenzylation. These glycosidations led to disaccharides **51** (α/β = 1:3) and **52** (α/β = 1:11) as the major products, respectively. These results again highlight the dramatic dependency of the stereochemistry of glycosidation of such galactose-based donors on the C_4 protecting group. Before we discuss this issue in detail, we first describe the conversion of "galNAcβ1-4gal" glycal **52** to its fully deprotected methyl glycoside **57** (Scheme 9). The latter would be useful for the re-evaluation of the Krivan concept.[5]

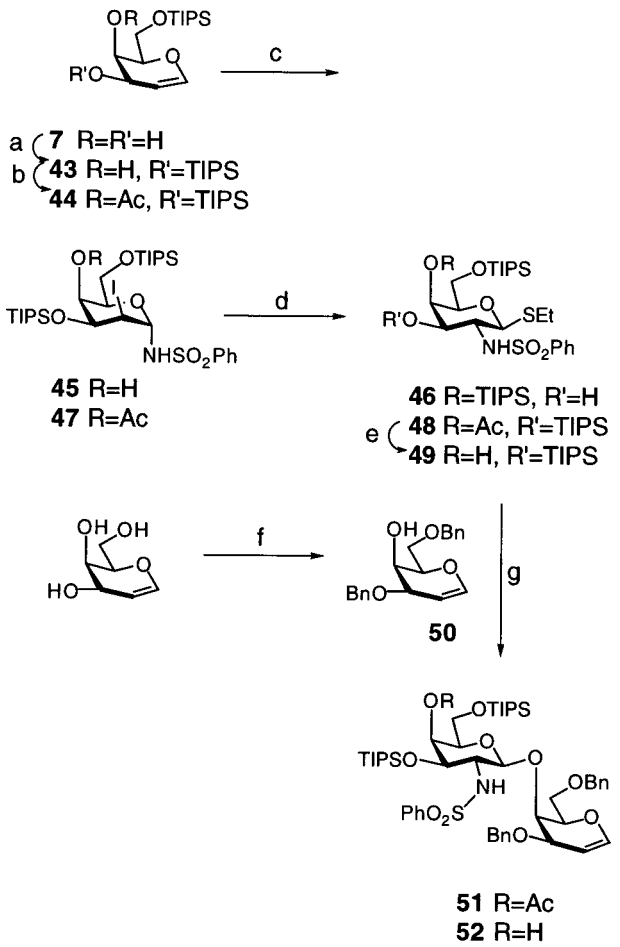
Reaction of glycal **52** with dimethyldioxirane and subsequent methanolysis supplied β-methyglycoside **53** in 64% yield accompanied by 17% of the α-methyl glycoside. The deprotection protocol followed the previous sequence for the asialo GM_1 methyl glycoside. Treatment of **53** with TBAF resulted in cleavage of all the silyl groups. The benzyl and sulfonamido groups were discharged by sodium in ammonia (see compound **55**). Exhaustive acetylation afforded the purifiable peracetate **56**. Deacetylation of all of the oxygen-bound acetates afforded methyl glycoside **57**.

The strong preference for the formation of β-galactoside in azaglycosidations with galactosyl donors possessing a C_4 free hydroxyl group appears to be quite general.[8,9] Where C_4 is protected, competition from α-azagalactoside formation can be very serious. For instance, in the course of the asialo GM_1 glycal synthesis described above, the ratio of β:α glycoside changed from 1:10 with donor **32**, containing a C_4 *O*-benzyl protecting group, to 13:1 for donor **13**, in which the C_4 hydroxyl group is unprotected. Moreover, the β:α ratio increased from 3:1 for a C_4 acetyl donor (**48**) to 11:1 in the case of donor **49**, in which this group is free. Similarly, in the synthesis of the MBr1 antigen,[9] the directionality of the glycosidation is reversed from 5:1, favoring α-glycoside for the C_4 *O*-acetyl protected donor, to 10:1 β:α for a corresponding case where the C_4 hydroxyl in the galactal-derived donor is free.

In analyzing this striking difference, we start with some assumptions about the nature of glycosidation reactions,[17,18] as applied to the cases at hand**.** It seems reasonable that β-glycoside would be produced from a conventional neighboring group participation of the C_2 sulfonamide, leading to a structure of the type **59** (Scheme 10). Inversion of configuration at C_1 in **59** by the nucleophilic acceptor gives rise to β-galactoside product **60**. At the other limit, there can be considered a structure of the type **61** corresponding to an anomeric "onium"

(17) Paulson, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155.
(18) Berresi, F.; Hindsgaul, O. *J. Carbohydr. Chem.* **1996**, *14*, 1043.

Scheme 8[a]



[a] Reagents: (a) TIPSCl, imidazole, DMF, 62% (+7% of **7**); (b) Ac_2O, pyridine, DMAP, 89%; (c) I(*sym*-coll)$_2$ClO$_4$, $PhSO_2NH_2$, 4 Å MS, CH_2Cl_2, 0 °C, 93% for **47**; (d) EtSH, LHMDS, DMF, −40 to −15 °C, 88% for **48**, 52% for **46** (two steps); (e) LAH, Et_2O, 0 °C, 78%; (f) (i) $(Bu_3Sn)_2O$, PhH, Dean−Stark; (ii) BnBr, TBABr, 80%; (g) MeOTf, 4 Å MS, Et_2O/CH_2Cl_2 2:1, 67% for **52**.

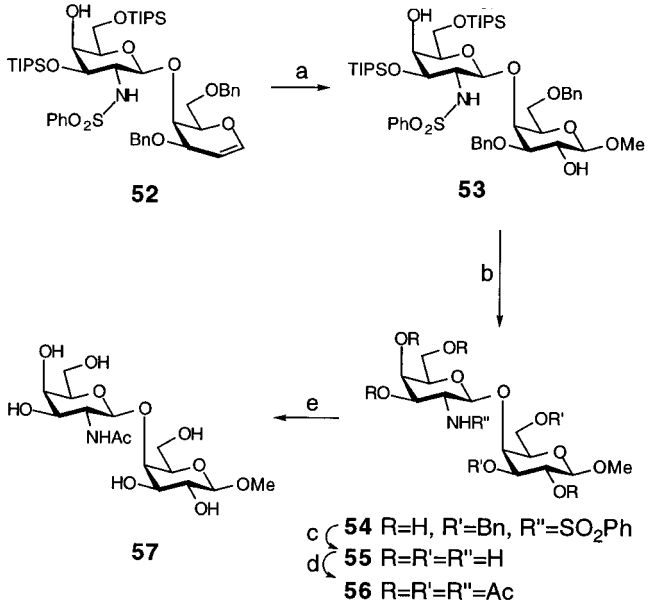
species. It seems probable, on stereoelectronic grounds, that a species of the type **61** would be discharged by axial attack of a glycosyl acceptor.

In these terms it follows that any structural feature of the molecule which tends to favor a confomer of the type **58** would be likely to lead to β-glycoside formation. In such a structure, participation from the ring oxygen to expel an equatorial anomeric group, *en route* to an onium species, would appear to be stereoelectronically attenuated. By contrast, conformers related to **62**[19] in which the pyranose oxygen is well disposed to participate in expulsion of an axial C_1 leaving group might favor onium ion formation, resulting in weakening the β-selectivity. Given such a framework of analysis, there remains a need to explain why the distribution among these modalities is affected to such a significant extent by the state of the C_4 β-oxygen.

In studying the infrared spectra of several of the compounds in this series, we observed some suggestive phenomena. The spectra of the donor thioglycosides **13** and **49**, their precursor glycals **11** and **43**, and their derived coupling products **21** and **52** exhibited weak and sharp bands in the OH stretching region,[20]

(19) Conformer **58** could well be more stable than **62**. However, if overall glycosidation through the latter is faster, glycosidation via **58**, which lacks participation from the pyranose oxygen, formation of α-product will be competitive or even dominant.

Scheme 9[a]



[a] Reagents: (a) dimethyldioxirane, 4 Å MS, CH_2Cl_2, 0 °C; MeOH, 64% (+17% of isomer); (b) TBAF, THF, 0 °C; (c) Na, NH_3, THF, −78 to −33 °C; NH_4Cl; (d) Ac_2O, pyridine, DMAP, 82% (three steps); (e) NaOMe, MeOH, 44%.

generally attributable to intramolecular hydrogen bonding. For example compounds **11**, **13**, **21**, **43**, **49**, and **52** contain such absorbances at 3569, 3537, 3534, 3558, 3570, and 3569 cm^{-1}, respectively. By contrast, the compounds that have hydroxyl groups in other placements exhibit broad absorption patterns in the region characteristic of intermolecular hydrogen bonding.

In addition to the observations arising from these experiments, NMR measurements presented supporting data strongly suggesting the pyranose ring oxygen to be the intramolecular hydrogen-bonding acceptor sites for the C_4-free hydroxyl in the galactose-derived pyranoses.[21] For instance, in the proton NMR spectrum of 3,6-di-*O*-TIPS-D-galactal (**43**), the free hydroxyl hydrogen appears as a triplet and shows two cross peaks corresponding to H4 and H5 in its COSY spectrum. Since compound **43** contains a secondary alcohol, only the "virtual" bond between the C_4 axial hydroxyl and the pyranose ring oxygen through strong hydrogen bonding explains the triplet in the proton NMR spectrum and two cross peaks for the hydroxyl hydrogen in the COSY spectrum. A similar pattern of cross peaks for the C_4 hydroxyl proton arising from *J*-coupling to H4 and H5 is observed throughout the thioglycosides (**13** and **49**), precursor glycals (**11** and **43**), and azaglycosidation products (**21** and **53**).

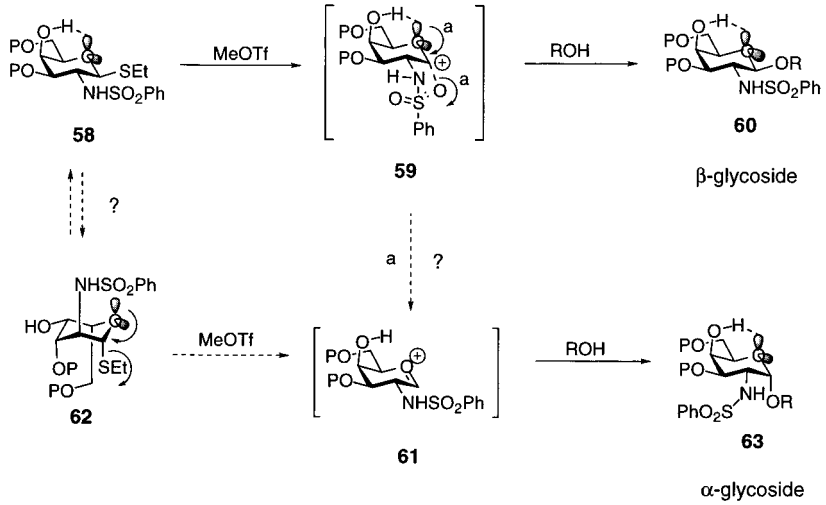
Intramolecular hydrogen bonding between axial hydroxyl groups and ring oxygens in six-membered rings has previously been reported. Wilson[22] demonstrated through microwave spectroscopy that 1,3-dioxan-5-ol exists in a chair conformation with the hydroxyl group occupying axial position with an intramolecular hydrogen bond of the O−H- - -O type (Scheme 11).

(20) Silverstein, R. M.; Bassler, G. C.; Morill, T. C. *Spectroscopic identification of organic compounds*; John Wiley & Sons: New York, 1991; pp 96, 101.

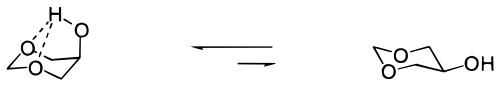
(21) Intramolecular hydrogen bonding between C_4 axial amido nitrogen and the pyranose ring oxygen has been suggested by ab initio calculation after submission of this manuscript. See: Miljković, M.; Yeagley, D.; Deslongchamps, P.; Dong, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604.

(22) Alonso, J. L.; Wilson, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 1248−1251.

Scheme 10



Scheme 11



As discussed earlier, the competition between neighboring group participation by C_2 sulfonamide versus onium ion formation could well be governing the stereocontrol in the 1β-(thioethyl)-2α-sulfonamidoglycosylation reaction. Given those terms, and given the arguments presented above, the preferred β-galactosidation in the case of the C_4-free hydroxyl can be explained. An intramolecular hydrogen bond between this hydroxyl and the pyranosidal oxygen would help to (i) stabilize the chair conformation in which the sulfonamide groups are equatorial and (ii) destabilize onium ion contributions (see structure type **61**) which favor α-glycoside formation as discussed above in Scheme 10.

This type of argument, suggesting the possibility of exploiting subtle changes in resident functions to influence glycosyl donor conformations, thereby controlling the stereochemical outcome of glycosidation, has broad implications and ramifications. Ongoing studies are directed to the further exploration of this theme as well as to the evaluation of the central biological concept of using carbohydrates as decoys for bacterial invasion.

Experimental Procedures[23]

Synthesis of Disaccharide Glycal 10. 3,4-*O*-Cyclic carbonate-6-*O*-TIPS-D-galactal (**8**) (1.00 g, 3.04 mmol) was azeotropically dried using benzene before being dissolved in dry CH_2Cl_2 (5 mL) under nitrogen. The solution was cooled to 0 °C, treated with dimethyldioxirane (73 mL, ~3.65 mmol), and stirred for 40 min, at which time TLC analysis indicated no trace of starting material. The solvent was evaporated by a stream of dry argon to give the epoxide **9**, which was dried *in vacuo* for 1 h. To the epoxide **9**, under nitrogen, was added via cannula a solution of 6-*O*-TIPS-D-galactal (**7**) (1.38 g, 4.57 mmol) in dry THF (10 mL). The resulting solution was cooled to −78 °C, and $ZnCl_2$ (5.0 mL, 1.0 M in ether) was added. The mixture was maintained at −78 °C for 2 h and then allowed to slowly warm to room temperature and stirred for additional 12 h. The reaction was quenched using saturated $NaHCO_3$ solution (50 mL) and partioned between water (50 mL) and EtOAc (3 × 100 mL). The collected organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography using 3:1 hexane/EtOAc gave **10** (1.53 g, 78%) as a white foam: $[\alpha]^{23}_D$ −36.4° (*c* 1.24, $CHCl_3$); FTIR (neat) 3451, 2943, 2866, 1799, 1647, 1464, 1383, 1238, 1163, 1114, 1070, 1031, 882, 786, 685, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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), 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; HRMS (FAB) calcd for $C_{31}H_{58}O_{10}Si_2Na$ (M + Na^+) 669.3466, found 669.3491.

Synthesis of Disaccharide Glycal 11. To a solution of the glycal **10** (665 mg, 1.03 mmol) and imidazole (420 mg, 6.16 mmol) in anhydrous DMF (7.0 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (465 mg, 3.08 mmol). The mixture was slowly warmed to rt and stirred overnight. It was diluted with EtOAc and poured into water (50 mL) and extracted with 3:1 hexane/EtOAc (3 × 50 mL). Combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography using 20:1−10:1 hexane/EtOAc afforded **11** (782 mg, quant.) as a white foam: $[\alpha]^{23}_D$ −39.2° (*c* 1.10, $CHCl_3$); FTIR (neat) 3569, 2943, 2866, 1819, 1809, 1651, 1464, 1384, 1367, 1240, 1142, 1114, 1071, 1034, 882, 838, 782, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.36 (1H, dd, J = 6.3, 1.5 Hz, H1), 4.89 (1H, dd, J = 7.8, 1.5 Hz, H4′), 4.72 (1H, d, J = 5.0 Hz, H1′), 4.63−4.59 (2H, m, H2, H3′), 4.42 (1H, m, H3), 4.09 (1H, br s, H4), 4.00 (1H, dd, J = 8.8, 6.4 Hz), 3.96 (1H, dt, J = 1.5, 6.9 Hz, H5′), 3.88−3.81 (5H, m), 2.76 (1H, d, J = 1.8 Hz, OH), 1.11−1.02 (42H, m), 0.87 (9H, s), 0.12 (3H, s), 0.10 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.25, 145.26, 99.69, 77.58, 76.99, 73.71, 72.60, 71.15, 70.84, 63.45, 61.63, 61.48, 25.49, 17.81, 11.77, 11.71, −4.77, −5.10; HRMS (FAB) calcd for $C_{37}H_{72}O_{10}Si_3Na$ (M + Na^+) 738.4331, found 738.4336.

Synthesis of Ethanethiosulfonamide 13. To a stirred mixture of the glycal **11** (480 mg, 0.630 mmol), benzenesulfonamide (297 mg, 1.89 mmol), and freshly activated powdered 4 Å MS (500 mg) in dry

(23) **General Experimental Procedures**: All commercial materials were used without further purification unless otherwise noted. The following solvents were distilled under positive pressure of dry argon immediately before use: THF and ether from sodium−benzophenone ketyl and CH_2Cl_2 from CaH_2. All the reactions were performed under argon atmosphere. NMR (^1H, ^{13}C) spectra were recorded on Bruker AMX-400 MHz, Bruker Advanced DMX-500 MHz, and Varian VXR-400 MHz referenced to $CDCl_3$ (^1H NMR, δ 7.26; ^{13}C NMR, δ 77.00), CD_3OD (^1H NMR, δ 4.78; ^{13}C NMR, δ 49.05), DMSO-d_6 (^1H NMR, δ 2.49; ^{13}C NMR, δ 39.7), and D_2O (^1H NMR, δ 4.63) peaks unless otherwise stated. Assignment of each peak (NH or OH peak) in ^1H NMR is based on D_2O exchange experiments. Also, decoupling experiment, Hetcor, J-res, magnitude COSY, selective COSY, and/or ROESY experiments. LB = 0.1 Hz was used before Fourier transformation for all of the 125 MHz ^{13}C NMR. IR spectra were recorded with a Perkin-Elmer Paragon 1000 FTIR spectrometer, and optical rotations were measured with a Jasco DIP-370 or DIP-1000 digital polarimeter using a 10 cm path length cell. Low- and high-resolution mass spectral analyses were performed with a JEOL JMS-DX-303HF mass spectrometer. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Flash column chromatography was performed using the indicated solvent on E. Merck silica gel 60 (40−63 mm) or Sigma H-Type silica gel (10−40 mm) for normal phase and EM Science LiChroprep RP-18 (15−25 mm) for reverse phase.

CH_2Cl_2 (6 mL) at 0 °C was added I(*sym*-coll)$_2ClO_4$ (1.18 g, 2.52 mmol). The resulting mixture was stirred for 30 min in the dark at 0 °C and treated with $Na_2S_2O_3$ solution (6 mL). The filtrate was washed with $Na_2S_2O_3$ solution and $CuSO_4$ solution, dried over $MgSO_4$, and concentrated *in vacuo*. The bulk of the benzenesulfonamide was precipitated by dissolving the crude product in a minimum amount of 7:1 hexane/EtOAc solution (8 mL). The crude product (520 mg) was subjected to the next reaction without further purification.

To a solution of ethanethiol (184 μL, 2.49 mmol) in anhydrous DMF (2.5 mL) at −40 °C were added LHMDS (995 μL, 1.0 M in THF) and a solution of iodosulfonamide **12** (520 mg, crude) in DMF (2.5 mL). The reaction was stirred for 1 h at −40 °C, slowly warmed to −10 °C for 1 h, poured into ice, neutralized with NH_4Cl solution (50 mL), and extracted with 2:1 hexane/EtOAc solution (3 × 50 mL). Combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography using 10:1−7:1 hexane/EtOAc gave **13** (259 mg, 42%) as a white foam: $[\alpha]^{23}_D$ −43.6° (*c* 1.78, $CHCl_3$); FTIR (neat) 3537, 3263, 2943, 2866, 2360, 1794, 1456, 1332, 1256, 1162, 1112, 1084, 1031, 882, 838, 784, 686, 592 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93−7.48 (5H, m), 5.39 (1H, s, H4′), 5.09 (1H, d, J = 9.1 Hz, H1′), 4.67 (1H, d, J = 8.8 Hz, H2′), 4.52 (1H, d, J = 6.3 Hz, NH), 4.48 (1H, s, H3′), 4.31 (1H, d, J = 10.2 Hz, H1), 4.25 (1H, dd, J = 9.0, 5.4 Hz), 4.09 (1H, s, H4), 3.92 (1H, dd, J = 9.6, 7.2 Hz), 3.85 (1H, dd, J = 9.6, 5.4 Hz), 3.81−3.74 (3H, m), 3.53 (1H, dt, J = 6.5, 9.9 Hz, H2), 3.47 (1H, t, J = 6.3 Hz), 2.90 (1H, s, OH), 2.40 (1H, dq, J = 12.4, 7.4 Hz), 2.20 (1H, dq, J = 12.4, 7.4 Hz), 1.12−1.05 (42H, m), 0.90 (9H, s), 0.24 (3H, s), 0.19 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.66, 139.93, 132.79, 128.83, 127.96, 100.89, 83.50, 81.70, 79.46, 73.75, 72.84, 68.90, 68.11, 61.82, 61.77, 55.00, 25.58, 23.59, 17.92, 17.89, 17.71, 14.39, 11.87, 11.86, −4.67, −5.23; HRMS (FAB) calcd for $C_{45}H_{83}O_{12}NS_2Si_3Na$ (M + Na^+) 1000.4560, found 1000.4580.

Synthesis of a GM$_1$ Tetrasaccharide Glycal 21. A mixture of thioglycoside **13** (124 mg, 0.127 mmol) and lactal **20** (96 mg, 0.127 mmol) was azeotroped three times with anhydrous benzene and placed under high vacuum overnight. Freshly activated 4 Å MS (1.10 g) was added to the mixture, and that was taken up in dry CH_2Cl_2 (1.0 mL) and dry ether (2.0 mL), stirred for 5 min at rt, and cooled to 0 °C. After the mixture was stirred for 5 min at 0 °C, MeOTf (72 μL, 0.64 mmol) was added dropwise. The reaction was stirred for 9 h at 0 °C, and then Et_3N (230 μL) was added. The reaction mixture was filtered through a Celite pad and concentrated. Purification by flash column chromatography using 9:1−6:1−4:1 hexane/EtOAc afforded **21** (152 mg, 71%) as a white foam accompanied by α-isomer **22** (12 mg, 6%): $[\alpha]^{23}_D$ −19.6° (*c* 1.12, $CHCl_3$); FTIR (neat) 3534, 3268, 3027, 2941, 2866, 1792, 1651, 1457, 1366, 1331, 1247, 1164, 1084, 1031, 885, 747, 702, 600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (2H, d, J = 7.5 Hz), 7.41−7.21 (28H, m), 6.53 (1H, d, J = 6.2 Hz), 5.55 (1H, d, J = 4.2 Hz), 5.16 (1H, s), 5.07 (1H, d, J = 9.1 Hz), 4.97−4.93 (3H, m), 4.79 (1H, d, J = 10.6 Hz), 4.67−4.63 (2H, m), 4.58−4.47 (5H, m), 4.43 (1H, d, J = 7.2 Hz), 4.39−4.24 (5H, m), 4.15 (1H, t, J = 3.6 Hz), 4.09 (1H, t, J = 3.8 Hz), 3.96−3.93 (2H, m), 3.89−3.83 (2H, m), 3.79−3.75 (2H, m), 3.66 (1H, dd, J = 10.6, 4.1 Hz), 3.58 (1H, dd, J = 9.1, 5.0 Hz), 3.53−3.44 (3H, m), 3.38−3.28 (3H, m), 3.23 (1H, dd, J = 7.2, 5.6 Hz), 3.17 (1H, dd, J = 9.9, 2.3 Hz), 3.01 (1H, d, J = 2.3 Hz), 1.13−1.03 (42H, m), 0.93 (9H, s), 0.29 (3H, s), 0.20 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.96, 144.72, 138.45, 138.22, 138.12, 138.05, 137.21, 132.66, 129.16, 128.75, 128.47, 128.41, 128.37, 128.34, 128.28, 128.09, 127.74, 127.69, 127.66, 127.58, 127.50, 127.48, 127.41, 102.79, 102.72, 101.01, 99.29, 81.62, 81.12, 79.74, 75.85, 75.70, 75.30, 75.26, 74.72, 73.57, 73.29, 73.24, 73.16, 73.06, 72.76, 70.91, 69.65, 69.25, 68.71, 67.82, 67.77, 65.58, 61.96, 60.90, 55.92, 25.61, 17.93, 17.90, 17.69, 11.89, 11.84, −4.50, −5.30 (three unresolved aromatic resonances); HRMS (FAB) calcd for $C_{90}H_{127}O_{21}NSSi_3Na$ (M + Na^+) 1696.7830, found 1696.7860.

Synthesis of the Tetrasaccharide 25. To a stirred mixture of the glycal **21** (57 mg, 0.034 mmol) and freshly activated powdered 4 Å MS (60 mg) in anhydrous CH_2Cl_2 (3.0 mL) at 0 °C was added dimethyldioxirane (822 μL, 0.05 M in acetone). After 30 min, the reaction was contcentrated with a stream of argon and further dried under vacuum for 10 min. A solution of the azido alcohol **24**[14] (183 mg, 0.34 mmol) in dry THF (1.0 mL) was added to it, and then the resulting mixture was cooled to −60 °C. Anhydrous zinc chloride was added (41 μL, 1.0 M in ether), and the resultant solution was slowly warmed to rt as the dry ice melted and stirred overnight. The reaction mixture was poured into ice water (5 mL), neutralized with $NaHCO_3$ solution (5 mL), and extracted with 2:1 hexane/EtOAc (3 × 10 mL). Collected extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography using 9:1−7:1−6:1−4:1 hexane/EtOAc provided **25** (43 mg, 60%) accompanied by isomer **26** (4 mg, 6%): $[\alpha]^{24}_D$ −14.1° (*c* 1.12, $CHCl_3$); FTIR (neat) 3542, 3238, 2927, 2112, 1797, 1455, 1365, 1323, 1165, 1085, 877, 735, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 7.8 Hz), 7.38−7.15 (33H, m), 5.99 (1H, d, J = 2.9 Hz), 5.76 (1H, dt, J = 15.4, 6.7 Hz), 5.42 (1H, dd, J = 15.4, 8.6 Hz), 5.09−4.92 (4H, m), 4.82 (1H, d. J = 10.7 Hz), 4.68−4.52 (5H, m), 4.38−4.18 (7H, m), 4.01−3.91 (5H, m), 3.86−3.82 (2H, m), 3.79−3.74 (2H, m), 3.71−3.66 (3H, m), 3.62−3.55 (2H, m), 3.53−3.43 (4H, m), 3.39 (1H, dd, J = 9.3, 2.9 Hz), 3.34 (1H, dt, J = 7.4, 3.1 Hz), 3.28−3.21 (4H, m), 2.92 (1H, br s), 2.43 (1H, br s), 2.09 (2H, app q, J = 6.5 Hz), 1.43−1.25 (22H, m), 1.12−1.02 (42H, m), 0.91 (9H, s), 0.88 (3H, t, J = 6.8 Hz), 0.25 (3H, s), 0.16 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.72, 138.58, 138.50, 138.32, 138.25, 138.20, 138.11, 137.91, 137.18, 132.61, 129.06, 128.71, 128.59, 128.36, 128.33, 128.32, 128.28, 128.22, 128.12, 128.01, 127.78, 127.74, 127.64, 127.55, 127.52, 127.46, 127.33, 127.28, 125.83, 103.36, 102.79, 101.65, 82.93, 82.60, 81.63, 80.28, 79.36, 76.43, 75.63, 75.53, 75.28, 74.59, 74.31, 73.52, 73.40, 73.24, 73.06, 72.69, 69.97, 68.80, 68.69, 68.68, 67.99, 67.69, 65.52, 64.17, 61.76, 60.80, 56.20, 32.37, 31.90, 29.68, 29.67, 29.66, 29.64, 29.63, 29.45, 29.34, 29.19, 29.02, 25.59, 22.67, 17.93, 17.91, 17.89, 17.67, 14.10, 11.90, 11.84, −4.49, −5.31 (four unresolved carbons); HRMS (FAB) calcd for $C_{115}H_{168}O_{24}N_4SSi_3Na$ (M + Na^+) 2128.0970, found 2128.0930.

Synthesis of the Tetrasaccharide 27. A flask containing the azide **25** (79 mg, 0.038 mmol), palmitic anhydride (38 mg, 0.076 mmol), and Lindlar's catalyst (160 mg) was evacuated and vented to a hydrogen atmosphere twice. Ethyl acetate (3.0 mL) was added, and the mixture was stirred under hydrogen atmosphere for 12 h. The reaction was filtered through a short pad of silica gel, concentrated, and flash chromatographed using 4:1−3:1 hexane/EtOAc to afford **27** (78 mg, 89%): $[\alpha]^{27}_D$ +17.4° (*c* 1.06, $CHCl_3$); FTIR (neat) 3538, 3296, 2926, 2855, 1798, 1634, 1455, 1364, 1330, 1125, 1169, 1085, 888, 737, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 7.5 Hz), 7.55−7.16 (33H, m), 6.08 (1H, d, J = 8.8 Hz), 5.99 (1H, d, J = 3.3 Hz), 5.70 (1H, dt, J = 15.4, 6.8 Hz), 5.37 (1H, dd, J = 15.4, 8.4 Hz), 5.10−5.07 (2H, m), 4.97 (2H, AB, J = 11.1 Hz, $\Delta\nu$ = 41.8 Hz, OCH_2Ar), 4.96 (1H, d, J = 11.2 Hz), 4.78 (2H, AB, J = 10.8 Hz, $\Delta\nu$ = 33.8 Hz, OCH_2Ar), 4.65−4.51 (5H, m), 4.35−4.17 (7H, m), 4.00−3.96 (2H, m), 3.93 (1H, t, J = 9.2 Hz), 3.88−3.72 (6H, m), 3.66 (1H, d, J = 9.8 Hz), 3.62−3.57 (2H, m), 3.55−3.41 (4H, m), 3.37−3.32 (2H, m), 3.29−3.21 (4H, m), 2.93 (1H, br s), 2.15−2.04 (4H, m), 1.40−1.25 (48H, m), 1.16−1.03 (42H, m), 0.92 (9H, s), 0.89 (6H, t, J = 6.9 Hz), 0.26 (3H, s), 0.18 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.25, 155.72, 138.60, 138.53, 138.46, 138.33, 138.20, 137.91, 137.18, 137.14, 132.59, 129.05, 128.71, 128.57, 128.35, 128.31, 128.28, 128.22, 128.14, 128.00, 127.79, 127.75, 127.72, 127.57, 127.53, 127.48, 127.46, 127.31, 127.29, 126.80, 104.26, 103.35, 102.76, 101.63, 82.90, 82.76, 81.64, 80.27, 79.67, 76.55, 76.42, 75.51, 75.36, 75.25, 74.54, 74.32, 73.52, 73.36, 73.35, 73.22, 73.05, 72.69, 70.16, 69.67, 68.79, 68.66, 68.13, 67.67, 65.52, 61.77, 60.78, 56.19, 52.31, 36.96, 32.30, 31.91, 29.69, 29.67, 29.65, 29.54, 29.50, 29.43, 29.34, 29.33, 29.26, 29.22, 25.73, 25.59, 22.67, 17.93, 17.90, 17.89, 17.67, 14.10, 11.90, 11.83, −4.49, −5.32 (13 unresolved carbons); HRMS (FAB) calcd for $C_{131}H_{200}O_{25}N_2SSi_3Na$ (M + Na^+) 2340.3370, found 2340.3410.

Synthesis of Asialo GM$_1$ (1a). A solution of **27** (88 mg, 0.038 mmol) in THF (380 μL) was treated with glacial AcOH (44 μL) and TBAF (1.1 mL, 1.0 M in THF) and stirred for 12 h at rt. The reaction was poured into ice cold $NaHCO_3$ solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated, and flash chromatographed using 10:10:1 hexane/EtOAc/MeOH to afford **28** (59 mg, 82%).

To liquid ammonia (∼7 mL) at −78 °C were added Na (∼100 mg) and a solution of **28** (59 mg, 0.031 mmol) in anhydrous THF (0.7 mL).

The resulting dark blue solution was allowed to reflux for 30 min and cooled to −78 °C again. MeOH (3.0 mL) was added to it, and the solution was stirred overnight at rt. The reaction was neutralized by adding Dowex 58×8-200 ion-exchange resin (∼2.5 g), filtered through a sintered glass funnel, and concentrated to be put under vacuum for 1 h. It was dissolved in anhydrous pyridine (∼1.5 mL) and cooled to 0 °C, and acetic anyhydride (0.5 mL) was added to it. The resultant solution was stirred overnight at rt. The resultant material was poured into water (15 mL) and extracted with EtOAc (3 × 15 mL). Collected extracts were washed with saturated $CuSO_4$ solution, dried over $MgSO_4$, and concentrated. Flash column chromatography using 20:10:1−30:15:2 hexane/EtOAc/MeOH provided **29** (42 mg, 75% for two steps).

A solution of **29** (39 mg, 0.022 mmol) in anhydrous MeOH (0.8 mL) was treated with NaOMe (6 mg, 0.11 mmol) and stirred overnight at rt. The reaction was neutralized with Dowex 50 × 8−200 (∼50 mg), filtered, and concentrated. Flash column chromatography on RP-18 silica gel using 15%−10%−5% water in MeOH provided asialo GM$_1$ (**1a**) (24 mg, 89%). TLC with 2:1:1 *n*-BuOH/EtOH/H_2O: $R_f = 0.56$; $[\alpha]^{24}_D$ −1.45° (*c* 0.25, 1:1 $CHCl_3$/MeOH); FTIR (neat) 3390, 2918, 2850, 2358, 1652, 1634, 1068 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (2H, d, J = 7.6 Hz), 5.51 (1H, dt, J = 15.2, 6.6 Hz), 5.33 (1H, dd, J = 15.3, 7.0 Hz), 5.27 (1H, br s), 5.14 (1H, br s), 4.87 (2H, br s), 4.78 (1H, br s), 4.61−4.37 (7H, m), 4.54 (1H, d, J = 8.3 Hz, anomeric H), 4.20 (1H, d, J = 7.4 Hz, anomeric H), 4.19 (1H, d, J = 7.6 Hz, anomeric H), 4.14 (1H, d, J = 7.7 Hz, anomeric H), 3.99−3.96 (2H, m), 3.85−3.73 (7H, m), 3.64−3.59 (4H, m), 3.50−3.19 (5H, m), 3.02 (1H, t, J = 8.1 Hz), 2.00 (2H, t, J = 7.3 Hz), 1.91 (2H, bum), 1.81 (3H, s), 1.44−1.22 (48H, m), 0.84 (6H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.72, 170.65, 131.37, 104.42, 103.72, 103.45, 102.51, 80.78, 79.62, 76.37, 75.28, 75.22, 74.75, 74.39, 74.32, 73.17. 72.97, 70.73, 70.62, 69.14, 68.04, 67.25, 60.51, 60.42, 60.31, 60.30, 59.92, 52.88, 51.67, 40.05, 39.84, 39.64, 39.43, 39.22, 39.01, 38.80, 35.54, 31.71, 31.24, 29.09, 29.04, 28.99, 28.97, 28.73, 28.71, 28.66, 25.34, 23.24, 22.04, 13.86 (10 unresolved carbons); HRMS (FAB) calcd for $C_{60}H_{110}O_{23}N_2Na$ (M + Na^+) 1249.7400, found 1249.7420.

Synthesis of Asialo GM$_1$ Tetrasaccharide Glycal 33 and Its Isomer 34. A mixture of thioglycoside **32** (60 mg, 0.057 mmol) and the lactal **20** (44 mg, 0.057 mmol) was azeotroped three times with anhydrous benzene and placed under high vacuum overnight. Freshly activated 4 Å MS (520 mg) was added to the mixture and the material was taken up in anhydrous THP (1.5 mL), stirred for 5 min at rt, and cooled to 0 °C. After the mixture was stirred for 5 min at 0 °C, MeOTf (32 μL, 0.29 mmol) was added dropwise. The reaction was stirred for 8 h at 0 °C and then Et_3N (100 μL) was added. The reaction mixture was filtered through a Celite pad and concentrated. Purification by flash column chromatography using 25:1−15:1−7:1 benzene/EtOAc provided separation between products from acceptor left. Further purification by HPLC using 15% EtOAc in hexane (UV 260 nm) afforded **34** (39 mg, 39%) and **33** (4 mg, 4%).

For **33**: $[\alpha]^{18}_D$ −26.56° (*c* 3.37, $CHCl_3$); FTIR (neat) 3258, 3032, 2942, 2866, 1814, 1732, 1649, 1497, 1462, 1360, 1248, 1211, 1163, 1098, 1028, 911, 883., 793, 735, 697, 597, 458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (2H, d, J = 7.6 Hz), 7.47−7.21 (38H, m), 6.56 (1H, d, J = 6.2 Hz), 5.59 (1H, d, J = 5.0 Hz), 5.15 (1H, app s), 5.11 (1H, d, J = 11.4 Hz), 5.01−4.92 (3H, m), 4.88 (1H, dd, J = 8.5, 1.4 Hz), 4.83 (1H, dd, J = 8.5, 2.6 Hz), 4.75 (2h, app t, J-10.5 Hz), 4.62−4.51 (4H, m), 4.45 (1H, d, J = 7.3 Hz), 4.41−4.34 (3H, m), 4.32 (1H, d, J = 8.3 Hz), 4.26 (1H, d, J = 3.0 Hz), 4.19−4.15 (2H, m), 4.08 (1H, app t, J = 6.9 Hz), 3.97−3.88 (3H, m), 3.85 (1H, d, J = 3.0 Hz), 3.79 (1H, dd, J = 9.3, 8.2 Hz), 3.69 (1H, dd, J = 10.6, 4.1 Hz), 3.63−3.58 (2H, m), 3.54 (1H, dd, J = 8.5, 4.2 Hz), 3.50−3.36 (4H, m), 3.30−3.27 (2H, m), 1.19−1.12 (21H, m), 1.03 (21H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.89, 144.66, 139.66, 139.11, 138.48, 138.41, 138.19, 138.01, 137.85, 137.32, 132.54, 129.07, 128.70, 128.58, 128.40, 128.31, 128.26, 128.22, 127.88, 127.87, 127.84, 127.76, 127.70, 127.69, 127.56, 127.45, 127.35, 126.94, 104.20, 102.95, 102.81, 99.38, 82.96, 81.08, 79.63, 76.00, 75.97, 75.77, 75.40, 75.20, 74.68, 74.56, 73.46, 73.31, 73.22, 73.16, 73.11, 73.10, 72.62, 71.09, 70.58, 69.74, 69.18, 67.76, 61.19, 56.25, 17.94, 17.92, 11.87, 11.80 (eight unresolved resonances); HRMS (FAB) calcd for $C_{98}H_{125}O_{21}NSSi_2Na$ (M + Na^+) 1762.7900, found 1762.7900.

For **34**: $[\alpha]^{18}_D$ +27.69° (c 1.52, $CHCl_3$); FTIR (neat) 3506, 3200, 3032, 2942, 2866, 1813, 1651, 1497, 1454, 1367, 1337, 1247, 1211, 1164, 1097, 1038, 999, 910, 823., 792, 734, 697, 592, 458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, J = 7.3 Hz), 7.77−7.21 (38H, m), 6.49 (1H, dd, J = 7.0, 0.9 Hz), 6.20 (1H, d, J = 9.0 Hz), 5.07 (1H, app s), 5.03 (1H, d, J = 3.5 Hz), 4.92−4.68 (8H, m), 4.62−4.57 (3H, m), 4.54 (1H, d, J = 7.6 Hz), 4.14 (1H, app s), 4.08 (1H, d, J = 2.6 Hz), 3.96 (1H, dd, J = 11.0, 2.1 Hz), 3.93−3.80 (5H, m), 3.68−3.60 (3H, m), 3.39 (1H, t, J = 6.8 Hz), 3.33 (1H, dd, J = 9.8, 2.7 Hz), 3.10 (1H, dd, J = 3.1, 1.1 Hz), 1.14−1.00 (21H, m), 0.95−0.92 (21H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.75, 145.48, 141.49, 139.48, 138.34, 138.26, 137.92, 137.89, 137.06, 132.32, 129.01, 128.63, 128.43, 128.37, 128.32, 128.26, 128.15, 127.93, 127.98, 127.77, 127.74, 127.69, 127.64, 127.60, 127.58, 127.56, 127.49, 126.94, 104.65, 103.17, 100.91, 99.64, 80.30, 79.63, 78.84, 76.19, 76.09, 75.06, 74.60, 74.40, 74.08, 73.55, 73.43, 73.21, 73.18, 73.02, 72.60, 72.26, 72.13, 71.88, 71.63, 70.46, 68.41, 67.61, 67.40, 61.16, 60.43, 59.96, 17.98, 17.95, 17.93, 17.88, 11.84, 11.78 (five unresolved aromatic resonances); HRMS (FAB) calcd for $C_{98}H_{125}O_{21}NSSi_2Na$ (M + Na^+) 1762.7900, found 1762.7930.

Synthesis of the Tetrasaccharides 35 and 39. The tetrasaccharide glycal **33** (122 mg, 0.0699 mmol) in dry CH_2Cl_2 (0.7 mL) at 0 °C was treated with dimethyldioxirane (1.7 mL, ∼0.0839 mmol) and stirred at 0 °C for 30 min, after which time the mixture was concentrated by passing a stream of argon over the solution and put under vacuum for 1 h. The resulting epoxide was dissolved in dry THF (0.5 mL) and anhydrous MeOH (0.7 mL), cooled to −78 °C, and treated with $ZnCl_2$ (84 μL, 1.0 M in ether). The mixture was slowly warmed to rt and stirred overnight. After dilution with EtOAc, the solution was poured into ice, neutralized with $NaHCO_3$ solution (20 mL), and extracted with 2:1 hexane/EtOAc solution (3 × 20 mL). The extracts were dried over $MgSO_4$, concentrated, and subjected to flash chromatography using 3:1−2:1 hexane/EtOAc to yield the methyl glycoside **35** (54 mg, 43%): $[\alpha]^{20}_D$ −11.6° (*c* 0.62, $CHCl_3$); FTIR (neat) 3460, 3225, 3030, 2941, 2865, 1812, 1497, 1453, 1363, 1209, 1162, 1095, 1063, 1028, 882, 752, 696, 593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (2H, m), 7.42−7.13 (37H, m), 6.97 (1H, t, J = 7.3 Hz), 6.01 (1H, d, J = 4.2 Hz), 5.07−4.82 (7H, m), 5.03 (1H, d, J = 3.5 Hz), 4.76 (1H, dd, J = 8.6, 3.0 Hz), 4.68−4.51 (5H, m), 4.40−4.14 (6H, m), 4.03−3.82 (9H, m), 3.76−3.55 (5H, m), 3.56 (3H, s), 3.53−3.46 (4H, m), 3.42 (1H, dd, J = 9.5, 3.2 Hz), 3.38−3.30 (2H, m), 3.27−3.21 (2H, m), 2.47 (1H, d, J = 1.3 Hz), 1.19−1.07 (21H, m), 1.03−0.99 (21H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.86, 139.65, 138.99, 138.72, 138.50, 138.26, 138.02, 137.74, 137.39, 132.28, 128.90, 128.68, 128.66, 128.50, 128.46, 128.34, 128.28, 128.27, 128.23, 128.18, 127.65, 127.92, 127.79, 127.76, 127.74, 127.72, 127.59, 127.55, 127.48, 127.34, 127.19, 126.86, 104.57, 103.68, 103.56, 102.81, 83.82, 82.62, 81.56, 80.27, 76.25, 75.92, 75.52, 75.26, 74.80, 74.68, 74.35, 73.57, 73.42, 73.25, 73.22, 73.12, 73.10, 73.07, 72.63, 70.68, 68.51, 68.05, 61.05, 60.90, 56.97, 56.50, 17.98, 17.97, 17.94, 11.90, 11.82 (three unresolved carbon resonances); HRMS (FAB) calcd for $C_{99}H_{129}O_{23}NSSi_2Na$ (M + Na^+) 1810.8110, found 1810.8100.

Compound **39** was prepared in a fashion identical to that for **34**. For **39**: $[\alpha]^{21}_D$ +18.4° (*c* 1.19, $CHCl_3$); FTIR (neat) 3449, 3194, 3064, 2944, 2866, 1810, 1607, 1496, 1463, 1368, 1335, 1266, 1210, 1088, 919, 883, 791, 748, 695, 664, 580 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (2H, d, J = 7.7 Hz), 7.44 (1H, t, J = 7.5 Hz), 7.38 (2H, t, J = 7.2 Hz), 7.35−7.18 (35H, m), 6.08 (1H, d, J = 8.6 Hz), 4.99 (1H, d, J = 3.3 Hz), 4.93−4.87 (3H, m), 4.82−4.78 (3H, m), 4.72−4.62 (5H, m), 4.51−4.41(6H, m), 4.31 (1H, d, J = 12.1 Hz), 4.18−4.13 (3H, m), 4.09 (1H, br s), 4.00 (1H, d, J = 2.3 Hz), 3.96−3.92 (2H, m), 3.88−3.75 (5H, m), 3.72 (1H, t, J = 8.9 Hz), 3.66−3.62 (2H, m), 3.59−3.47 (4H, m), 3.53 (3H, s), 3.39−3.35 (2H, m), 3.26 (1H, app t, J = 7.0 Hz), 3.22 (1H, dd, J = 9.9, 2.5 Hz), 2.30 (1H, d, J = 1.1 Hz), 1.10−1.04(21H, m), 0.95 (21H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.71, 141.24, 139.39, 138.78, 138.36, 138.17, 137.90, 137.72, 137.12, 132.38, 129.06, 128.58, 128.47, 128.41, 128.31, 128.25, 128.20, 128.08, 128.01, 127.95, 127.82, 127.76, 127.71, 127.69, 127.59, 127.53, 127.50, 127.46, 127.40, 127.34, 127.00, 126.92, 104.46, 103.44, 102.94, 100.08, 81.86, 80.91, 79.47, 79.41, 76.18, 75.95, 75.34, 75.26, 75.25, 75.06,

74.63, 74.60, 73.50, 73.25, 73.12, 72.98, 72.81, 72.77, 72.49, 71.91, 71.73, 70.63, 68.11, 67.15, 61.20, 60.54, 56.97, 54.31, 18.03, 17.96, 17.92, 17.87, 11.83, 1179; HRMS (FAB) calcd for $C_{99}H_{129}O_{23}NSSi_2$-Na (M + Na^+) 1810.8110, found 1810.8110.

Asialo GM_1 Methyl Glycosides 38 and 42. A solution of peracetylated β-methyl glycoside of asialo GM_1 **37** (18 mg, 0.015 mmol) in anhydrous MeOH (0.6 mL) was treated with NaOMe (3.6 mg) and stirred overnight at rt. After diluted with MeOH, the reaction was neutralized with Dowex 50×8-200 (∼50 mg), filtered, and concentrated. Flash column chromatography on LiChroprep RP-18 (from Merck) using 40%−10% water in MeOH and subsequent size-exclusion chromatography on Lipophilic Sephadex LH-20 (from Sigma) using MeOH afforded **38** (11 mg, 99%) For **3**: $[\alpha]^{19}_D$ −12.8° (*c* 0.71, MeOH); FTIR (neat) 3356, 2891, 1636, 1559, 1375, 1312, 1234, 1156, 1116, 1051, 891, 763, 668 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.65 (1H, d, J = 8.4 Hz), 4.41 (1H, d, J = 7.6 Hz), 4.40 (1H, d, J = 8.0 Hz), 4.37 (1H, d, J = 8.1 Hz), 4.12 (1H, d, J = 2.6 Hz), 4.06 (1H, d, J = 2.1 Hz), 4.00−3.93 (2H, m), 3.86−3.83 (2H, m), 3.77−3.67 (7H, m), 3.64−3.47 (5H, m), 3.53 (3H, s, OMe), 3.37 (1H, dd, J = 9.7, 7.8 Hz), 3.25 (1H, t, J = 8.4 Hz), 2.00 (3H, s, NAc); ^{13}C NMR (100 MHz, CD_3OD) δ 174.83, 106.67, 105.30, 105.24, 104.20, 82.09, 81.05, 77.72, 77.64, 76.82, 76.53, 76.46, 76.32, 76.17, 74.75, 74.55, 72.57, 70.36, 70.30, 69.81, 69.73, 62.72, 61.91, 61.65, 57.37, 53.53, 23.52; HRMS (FAB) calcd for $C_{27}H_{47}O_{21}NNa$ (M + Na^+) 744.2538, found 744.2548.

Compound **42** was prepared in an identical fashion from **41**.

For **42**: $[\alpha]^{19}_D$ +67.6° (*c* 0.62, MeOH); FTIR (neat) 3366, 2931, 1636, 1558, 1376, 1322, 1224, 1116, 1045, 886, 704, 633 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.69 (1H, d, J = 3.5 Hz), 4.31 (2H, m), 4.26 (1H, t, J = 6.4 Hz), 4.22 (1H, d, J = 8.1 Hz), 4.17 (1H, dd, J = 11.4, 3.9 Hz), 4.10 (1H, s), 3.88 (1H, d, J = 10.4 Hz), 3.83−3.80 (2H, m), 3.71 (1H, br s), 3.64 (1H, dd, J = 12.7, 4.5 Hz), 3.58−3.40 (9H, m), 3.38 (3H, s), 3.33 (1H, t, J = 8.8 Hz), 3.15 (1H, d, J = 1.7 Hz), 3.12 (1H, t, J = 8.3 Hz), 1.87 (3H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 173.12, 105.40, 104.39, 104.24, 99.37, 79.89, 77.93, 77.07, 76.14, 75.75, 75.51, 75.45, 73.88, 73.77, 73.56, 71.52, 71.44, 70.86, 69.27, 68.92, 61.57, 60.92, 60.34, 56.30, 49.43, 21.84 (one unresolved carbon); HRMS (FAB) calcd for $C_{27}H_{47}O_{21}NNa$ (M + Na^+) 744.2538, found 744.2537.

Synthesis of Sulfonamidothioglycoside 49. A solution of **48** (827 mg, 1.15 mmol) in dry ether (23 mL) at −15 °C was treated with LAH (1.15 mL, 1.0 M in ether). TLC analysis showed incomplete consumption of **48** after 2 h, and more LAH (0.5 mL) was added. Additional LAH (0.25 mL) was added to complete the reaction, and it caused formation of byproduct. Reaction was diluted with EtOAc (50 mL) and stirred vigorously with half-saturated Rochelle salt solution (50 mL) until it showed clear separation between two layers. Aqueous layer was extracted with EtOAc (2 × 50 mL). The collected organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography using benzene−50:1 benzene/EtOAc afforded **49** (608 mg, 78%): $[\alpha]^{22}_D$ −20.5° (*c* 5.86, $CHCl_3$); FTIR (neat) 3570, 3288, 2942, 2866, 1720, 1462, 1382, 1327, 1259, 1159, 1108, 1015, 884, 798, 686, 594 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86−7.41 (5H, m), 4.51 (1H, d, J = 7.9 Hz, NH), 4.28 (1H, d, J = 10.2 Hz, H1), 4.05 (1H, d, J = 2.7 Hz, H4), 3.94 (1H, dd, J = 9.4, 3.0 Hz, H3), 3.80 (1H, dd, J = 9.6, 5.3 Hz, H6), 3.64 (1H, td, J = 9.7, 8.1 Hz, H2), 3.44 (1H, dd, J = 6.8, 6.0 Hz, H5), 2.44−2.33 (3H, m, OH, SCH_2), 1.18−0.98 (45H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.92, 132.15, 128.45, 127.36, 84.28, 78.21, 75.64, 68.48, 61.68, 57.05, 23.96, 18.21, 18.15, 17.81, 17.78, 14.16, 12.86, 11.78; HRMS (FAB) calcd for $C_{32}H_{61}O_6NS_2Si_2K$ (M + K^+) 714.3116, found 714.3085.

Synthesis of Disaccharide Glycal 51. Reaction between thioglycoside **48** (100 mg, 0.139 mmol) and galactal **50** (46 mg, 0.139 mmol) according to the procedure used in preparation of **21** followed by flash column chromatography using 10:1−9:1−5:1 hexane/EtOAc gave **51** (70 mg, 51%) accompied by α-isomer (22 mg, 16%): $[\alpha]^{21}_D$ −53.01° (*c* 1.05, $CHCl_3$); FTIR (neat) 3025, 2923, 1942, 1870, 1802, 1746, 1668, 1601, 1493, 1372, 1181, 1154, 1069, 1028, 965, 907, 842, 757, 700, 620, 541 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90−7.87 (2H, m), 7.49−7.26 (13H, m), 6.14 (1H, dd, J = 6.4, 1.7 Hz), 5.58 (1H, dd, J = 5.2 Hz), 5.40 (1H, d, J = 1.9 Hz), 4.68 (1H, dt, J = 6.4, 1.8 Hz), 4.62 (2H, AB, J = 11.8 Hz, $\Delta\nu$ = 113 Hz, OCH_2Ar), 4.50 (2H, s, OCH_2Ar), 4.23 (1H, m), 4.00−3.97 (2H, m), 3.73 (1H, dd, J = 9.7, 2.7 Hz), 3.61−3.57 (4H, m), 3.44−3.38 (2H, m), 2.10 (3H, s, CH_3-CO), 1.09−1.06 (21H, m), 1.00 (21H, app d, J = 0.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.56, 144.78, 140.48, 138.10, 137.15, 131.95, 128.73, 128.40, 128.33, 128.25, 128.15, 127.76, 127.59, 127.38, 102.42, 98.49, 75.36, 74.65, 74.02, 73.20, 71.64, 71.46, 71.35, 70.21, 69.03, 61.06, 57.77, 20.91, 18.34, 18.30, 17.85, 17.83, 12.95, 11.76; HRMS (FAB) calcd for $C_{52}H_{79}O_{11}NSSi_2K$ (M + K^+) 1020.4550, found 1020.4570.

Synthesis of Disaccharide Glycal 52. A stirred mixture of thioglycoside **49** (98 mg, 0.15 mmol), galactal **50** (48 mg, 0.15 mmol), and freshly activated powdered 4 Å MS (730 mg) in dry CH_2Cl_2 (1.0 mL) and dry ether (2.0 mL) at 0 °C was treated with MeOTf (82 μL, 0.73 mmol). The reaction was stirred for 8 h at 0 °C, filtered through a pad of Celite after addition of Et_3N (260 μL), and concentrated. Flash column chromatography using 25:1−15:1 benzene/EtOAc provided **52** (92 mg, 67%) accompanied by its α-anomer (8.4 mg, 6.2%): $[\alpha]^{21}_D$ −51.7° (*c* 2.09, $CHCl_3$); FTIR (neat) 3569. 3264, 2942, 2866, 1648, 1454, 1341, 1236, 1212, 1161, 1110, 1058, 995, 882, 807, 752, 684, 594, 561, 459 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87−7.23 (15H, m), 6.10 (1H, dd, J = 6.3, 0.98 Hz, H1), 5.71 (1H, d, J = 4.7 Hz, NH), 4.67 (1H, app d, J = 6.3 Hz, H2), 4.59 (2H, AB, J = 11.5 Hz, $\Delta\nu$ = 164 Hz, CH_2Ar), 4.45 (2H, s, CH_2Ar), 4.36 (1H, d, J = 8.4 Hz, H1′), 4.22 (1H, app s), 3.95−3.91 (4H, m), 3.63−3.59 (2H, m, H6′, H3′), 3.56 (1H, dd, J = 9.9, 5.7 Hz), 3.49 (1H, dd, J = 9.9, 6.4 Hz), 3.34 (1H, dd, J = 8.2, 4.8 Hz, H5′), 3.29 (1H, td, J = 8.8, 4.8 Hz, H2′), 2.45 (1H, app s, OH), 1.20−0.98 (42H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.92, 139.98, 137.99, 136.96, 132.03, 128.74, 128.50, 128.33, 128.32, 128.31, 128.23, 127.61, 127.48, 102.55, 98.44, 75.65, 75.40, 74.96, 73.19, 71.88, 71.44, 71.33, 68.98, 68.05, 60.76, 57.21, 18.30, 18.26, 17.85, 17.82, 13.02, 11.75; HRMS (FAB) calcd for $C_{50}H_{77}O_{10}NSSi_2Na$ (M + Na^+) 962.4704, found 962.4722.

***β*-Methyl Glycoside of GalNAcβ1-4Gal (57).** A stirred mixture of **52** (42 mg, 0.044 mmol) and flame-dried powdered 4 Å MS (50 mg) in dry CH_2Cl_2 (0.1 mL) at 0 °C was treated with dimethyldioxirane (0.6 mL, ∼0.044 mmol). After 15 min, the reaction mixture was concentrated with a stream of argon. The residue was further dried under vacuum and then dissolved in anhydrous MeOH (1.0 mL) and dry THF (1.0 mL). The mixture was stirred overnight. The product was filtered through a pad of Celite, concentrated, and subjected to flash column chromatography using 30% EtOAc in hexane to give methyl glycosides **53** and its isomer (combined weights 36 mg, 81%, α/β ∼3.7:1): ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 7.2 Hz), 7.44−7.28 (14H, m), 4.98 (1H, d, J = 6.4 Hz), 4.78 (2H, AB, J = 11.3 Hz, $\Delta\nu$ = 174 Hz), 4.53 (2H, AB, J = 12.0 Hz, $\Delta\nu$ = 17.7 Hz), 4.36 (1H, d, J = 8.3 Hz), 4.03 (1H, d, J = 7.7 Hz), 3.99−3.94 (3H, m), 3.71−3.66 (2H, m), 3.58−3.43 (5H, m), 3.55 (3H, s), 3.34 (1H, t, J = 8.2 Hz), 3.26 (1H, dd, J = 8.4, 5.2 Hz), 2.51 (1H, s), 2.27 (1H, d, J = 1.6 Hz), 1.04−0.98 (42H, m).

The methyl glycosides (36 mg, 0.036 mmol) were dissolved in THF (0.36 mL), cooled to 0 °C, and treated with TBAF (144 μL, 1.0 M in THF). The resulting solution was warmed to rt and stirred overnight. The reaction was only completed after addition of more TBAF (432 μL, 1.0 M in THF) and further stirring for 48 h. $NaHCO_3$ (48 mg, 0.58 mmol) was added. The mixture was filtered through Celite, concentrated, and purified by flash column chromatography using 10:10:1 hexane/EtOAc/MeOH to yield desilylated methyl glycosides **54** and its isomer (24 mg, quantitative): ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (2H, d, J = 7.2 Hz), 7.48 (1H, t, J = 7.2 Hz), 7.42 (2H, t, J = 7.2 Hz), 7.33−7.20 (10H, m), 4.76 (2H, AB, J = 11.5 Hz, $\Delta\nu$ = 130 Hz), 4.43 (2H, AB, J = 16.8 Hz, $\Delta\nu$ = 19.8 Hz), 4.20 (1H, d, J = 8.1 Hz), 4.00 (1H, d, J = 7.6 Hz), 3.79 (1H, d, J = 3.0 Hz), 3.73−3.67 (2H, m), 3.59 (1H, dd, J = 11.6, 4.9 Hz), 3.46−3.27 (6H, m), 3.45 (3H, s), 3.19−3.16 (6H, m).

A 10 mL flask, fitted with a dry ice condenser, was charged with anhydrous ammonia (∼5 mL) and Na (∼50 mg). The above-described desilylated methyl glycoside mixture (24 mg, 0.036 mmol) in dry THF (0.7 mL) was added at −78 °C. The resulting dark blue solution was allowed to reflux for 30 min, cooled to −78 °C, and NH_4Cl (119 mg) was added. The ammonia was allowed to evaporate and the THF was removed by passing a stream of argon over the solution and the residue

was further concentrated under vacuum for 1 h. The material was dissolved in anhydrous pyridine (1.5 mL) and treated with Ac_2O (0.5 mL) and catalytic DMAP. The solution was stirred for 12 h and then the contents were poured into water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography using EtOAc afforded peracetylated methyl glycoside of GalNAcβ1-4Gal (19 mg, 82% overall, β/α 3.7:1).

For β-anomer **56**: $[\alpha]^{20}_D$ −18.7° (*c* 0.66, $CHCl_3$); FTIR (neat) 1748, 1370, 1229, 1047 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (1H, dd, J = 11.3, 3.4 Hz, H3′), 5.70 (1H, d, J = 6.9 Hz, NH), 5.38 (1H, d, J = 3.2 Hz, H4′), 5.25 (1H, dd, J = 10.4, 7.9 Hz, H2), 5.13 (1H, d, J = 8.2 Hz, H1′), 4.94 (1H, dd, J = 10.5, 2.7 Hz, H3), 4.37 (1H, d, J = 7.9 Hz, H1), 4.31 (1H, dd, J = 11.8, 5.5 Hz, H6), 4.28 (1H, dd, J = 11.8, 6.5 Hz, H6), 4.13 (1H, d, J = 2.5 Hz, H4), 4.05 (2H, app d, J = 6.6 Hz, 2H6′) 3.91 (1H, t, J = 6.6 Hz, H5′), 3.74 (1H, t, J = 6.0 Hz, H5), 3.51 (3H, s, OMe), 3.35 (1H, dt, J = 11.2, 7.6 Hz, H2′), 2.13 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 2.07(3H, s, CH_3CO), 2.04 (3H, s, CH_3CO), 2.03 (3H, s, CH_3CO), 1.99 (3H, s, CH_3CO), 1.98 (3H, s, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.28, 170.88, 170.54, 170.44, 170.11, 169.72, 169.59, 101.82, 98.86, 73.19, 72.87, 72.07, 70.37, 69.05, 67.97, 66.94, 63.07, 61.44, 57.00, 53.60, 23.45, 20.81, 20.75, 20.65, 20.64, 20.61, 20.60; HRMS (FAB) calcd for $C_{27}H_{39}O_{17}NNa$ (M + Na^+) 672.2115, found 672.2134.

A solution of **56** (13 mg, 0.020 mmol) in anhydrous MeOH (0.8 mL) was treated with NaOMe (4.4 mg, 0.082 mmol) and stirred overnight. After diluted with MeOH, the reaction was neutralized with Dowex 50×8−200 (∼50 mg, Aldrich), filtered, and concentrated. Flash chromatography on RP-18 silica gel using 40%−10% water in MeOH provided **57** (4 mg, 44%): $[\alpha]^{28}_D$ −12.1° (*c* 0.18, MeOH); FTIR (MeOH film) 3338, 1643, 1056 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 4.52 (1H, d, J = 8.5 Hz), 4.00 (1H, d, J = 7.7 Hz), 3.90 (1H, d, J = 2.1 Hz), 3.77 (1H, dd, J = 11.2, 7.7 Hz), 3.75 (1H, t, J = 9.5 Hz), 3.69 (1H, dd, J = 11.2, 8.1 Hz, H3), 3.64 (1H, d, J = 2.7 Hz), 3.58 (1H, dd, J = 11.2, 4.2 Hz, H6), 3.52−3.48 (2H, m), 3.46 (1H, dd, J = 10.5, 3.3 Hz), 3.41−3.39 (2H, m), 3.37 (3H, s, OMe), 3.31 (1H, dd, J = 9.7, 7.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 175.18, 105.88, 104.33, 78.31, 76.94, 75.57, 74.89, 74.70, 72.64, 69.56, 62.67, 61.37, 57.20, 55.53, 23.02; HRMS (FAB) calcd for $C_{15}H_{27}O_{11}NNa$ (M + Na^+) 420.1482, found 420.1490.

Acknowledgment. This research was supported by the National Institutes of Health (Grant Nos. AI 16943 and HL25848). O.K. gratefully acknowledges the Kanagawa Academy of Science and Technology for a graduate fellowship. We thank Dr. G. Sukenick of MSKCC and Drs. V. and B. Parmakovich of Columbia University for mass spectral measurements.

Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for **45** and **47**, ^{1}H NMR spectra and LRMS for **17**, **31**, and **36**, and spectral data (^{1}H NMR, ^{13}C NMR, FTIR, and HRMS) for compounds **14**, **16**, **18**−**20**, **30**, **32**, **37**, **41**, **43**, **44**, **46**, **48**, and **50** (14 pages). See any current masthead page for ordering and Internet access instructions.

JA9724957