Application of the Glycal Assembly Method to the Concise Synthesis of Neoglycoconjugates of Le^y and Le^b Blood Group Determinants and of H-Type I and H-Type II Oligosaccharides

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Abstract: The power of the glycal assembly strategy for reaching Lewis and H-type blood group determinants is demonstrated herein. Three key elements form the basis of the method. Thus, α-epoxides derived from galactal cyclic carbonate **13** are produced stereospecifically and are highly effective β-galactosyl donors. Also, 6-monoprotected glucals can be regiospecifically glycosylated at the C_3 hydroxyl (see **23** + **13** → **24**). Moreover, glycosylation via a glycal epoxide produces a unique C_2 hydroxyl in the product which can be exploited as the acceptor site for branching (see formation of **26**).

Introduction

Included among cell surface glycoconjugates are carbohydrate antigens of the A, B, H, and Lewis families. As they occur in nature, such carbohydrate arrays may serve a variety of functions such as control of growth and differentiation, cell−cell adhesion, and immune response in inflammatory processes.[1,2] Furthermore, the overexpression of novel carbohydrate patterns in cell surface bound glycoconjugate form can serve to mark the onset of a variety of carcinomas.[3] This phenomenon prompted consideration of the use of glycoconjugates to stimulate antibody production[4] against tumor associated structures.[5] It is also recognized that the docking of viral and bacterial pathogens is often initiated through binding of cell surface carbohydrates.[6] Thus, it might prove possible to inhibit such attachment through synthetic neoglycoconjugates which incorporate the determinant factor. Such a strategy could provide a therapy against pathogenic invasion. However, for all such applications, it would first be necessary to gain smooth access, through synthesis, to such complex systems.

Structurally the blood group determinants fall into two basic categories known as type I and type II. Type I is characterized by a backbone comprised of a galactose 1−3β linked to *N*-acetylglucosamine while type II contains, instead, a 1−4β linkage between the same building blocks (*cf.* *N*-acetyllactosamine). The position and extent of α-fucosylation of these backbone structures gives rise to the Lewis-type and H-type specificities (Figure 1). Thus, monofucosylation at the C_4-hydroxyl of the *N*-acetylglucosamine (type I series) constitutes the Le^a type, whereas fucosylation of the C_3-hydroxyl of this sugar (type II series) constitutes the Le^x determinant. Additional fucosylation of Le^a and Le^x types at the $C_{2'}$-hydroxyl of the galactose sector specifies the Le^b and Le^y types, respectively. The Le^y determinant was of particular interest to us due to the expression of such structures in human colonic and liver adenocarcinomas.[7] Also, the Le^b pattern has been implicated as the attachment site of the bacteria *Helicobacter pylori* in the human gastric epithelium.[6a]

Presence of an α-monofucosyl branch, solely at the $C_{2'}$-hydroxyl in the galactose moiety in the backbone, constitutes the H-type specifity (types I and II). Further permutation of the H-types by substitution of α-linked galactose or α-linked *N*-acetylgalactosamine at its $C_{3'}$-hydroxyl group provides the

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(1) (a) Phillips, M. L.; Nudelman, E.; Gaeta, F. C. A.; Perez, M.; Singhal, A.K.; Hakomori, S.; Paulson, J. C. *Science* **1990**, *250*, 1130. (b) Polley, M. J.; Phillips, M. L.; Wagner, E.; Nudelman, E.; Singhal, A. K.; Hakomori, S.; Paulson. J. C. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 6224. (c) Borman, S. *Chem. Eng. News* **1993**, *June 28*, 27. (d) Lasky, L. A. *Science* **1992**, *258*, 964. (e) Miller, D. J.; Macek, M. B.; Schur, B. D. *Nature* **1992**, *357*, 589. (f) Schulze, I. T.; Manger, I. D. *Glycoconjugate J.* **1992**, *9*, 63.

(2) (a) Taki, T; Hirabayashi, Y.; Ishikawa, H.; Kon, S.; Tanaka, Y.; Matsumoto, M. *J. Biol. Chem.* **1986**, *261*, 3075. (b) Hirabayashi, Y.; Hyogo, A.; Nakao, T.; Tsuchiya, K.; Suzuki, Y.; Matsumoto, M.; Kon, K.; Ando, S. *Ibid.* **1990**, *265*, 8144. (c) Hindsgaul, O.; Norberg, T.; Le Pendu, J.; Lemieux, R. U. *Carbohydr. Res.* **1982**, *109*, 109 and references cited therein. (d) Spohr, U.; Lemieux, R. U. *Ibid.* **1988**, *174*, 211.

(3) (a) Lloyd, K. O. *Am. J. Clin. Pathol.* **1987**, *87*, 129. (b) Lloyd, K. O. *Cancer Biol.* **1991**, *2*, 421.

(4) For pioneering work in this area see: (a) Goebel, W. F.; Avery, O. T. *J. Exp. Med.* **1929**, *50*, 521. (b) Avery, O. T; Goebel, W. F. *J. Exp. Med.* **1929**, *50*, 533. For significant advances in synthesis of carbohydrate antigens and molecular recogntition studies with antibodies see: (c) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V. James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056. (d) Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4063. (e) Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069. (f) Lemieux, R. U.; Bundle, D. R.; Baker, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 4076. (g) Spohr, U.; Morishima, N.; Hindsgaul, O.; Lemieux, R. U. *Can. J. Chem.* **1985**, *63*, 2659. (h) Lemieux, R. U.; Venot, A. P.; Spohr, U.; Bird, P.; Mandal, G.; Morishima, N.; Hindsgaul, O.; Bundle, D. R. *Can. J. Chem.* **1985**, *63*, 2664.

(5) (a) Dennis, J. *Oxford Glycosystems Glyconews Second*; 1992. (b) Lloyd, K. O. in *Specific Immunotherapy of Cancer with Vaccines*; New York Academy of Sciences: New York, 1993; pp 50−58 and references therein.

(6) (a) Boren, T.; Falk, P.; Roth, K. A.; Larson, G.; Normark, S. *Science* **1993**, *262*, 1892. (b) Falk, P.; Boren, T.; Normark, S. *Methods Enzymol.* **1994**, *236*, 353 and references cited therein.

(7) (a) Kaizu, T.; Levery, S. B.; Nudelman, E.; Stenkamp, R. E.; Hakomori, S. *J. Biol. Chem.* **1986**, *261*, 11254. (b) Levery, S. B.; Nudelman, E.; Anderson, N. H.; Hakomori, S. *Carbohydr. Res.* **1986**, *151*, 311. (c) Hakomori, S.; Nudelman, E.; Levery, S. B.; Kannagi, R. *J. Biol. Chem.* **1984**, *259*, 4672. (d) Fukushi, Y.; Hakomori, S.; Nudelman, E.; Cochran, N. *Ibid.* **1984**, *259*, 4681. (e) Fukushi, Y.; Nudelman, E.; Levery, S. B.; Hakomori, S.; Rauvala, H. *Ibid.* **1984**, *259*, 10511. (f) Sakamoto, J.; Furukawas, K.; Cardon-Dardo, C.; Lin, B. W. T.; Rettig, W. J.; Oettgen, H. F.; Old, L. J. and Lloyd, K. O. Cancer Res. **1986**, *46*, 1553.

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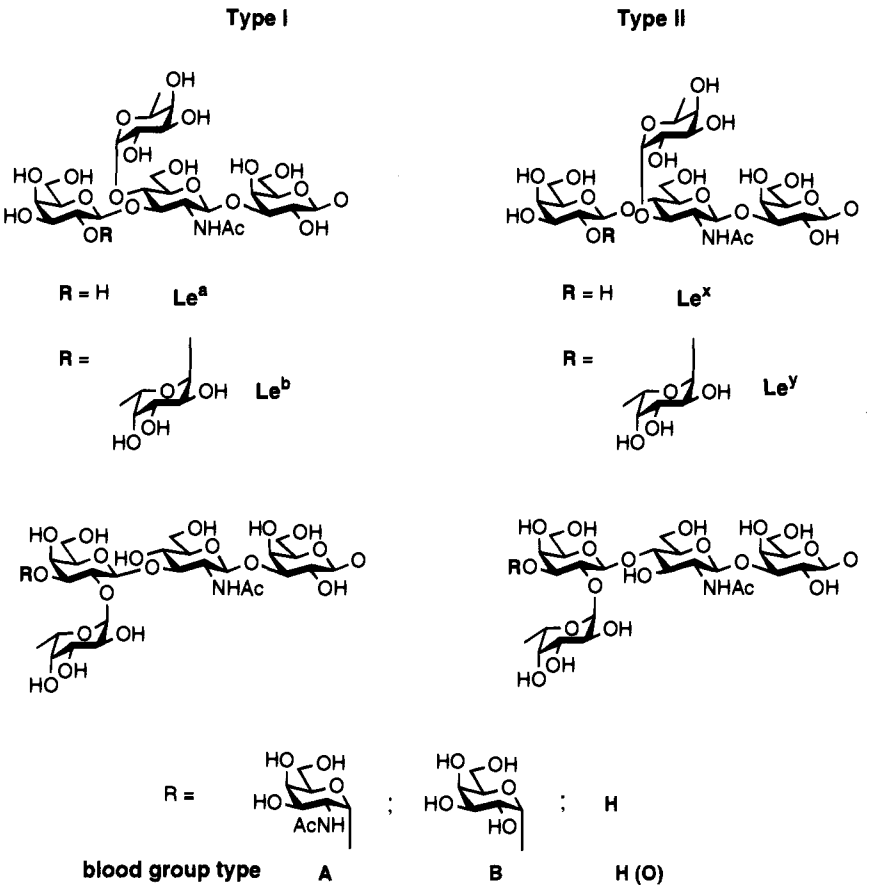


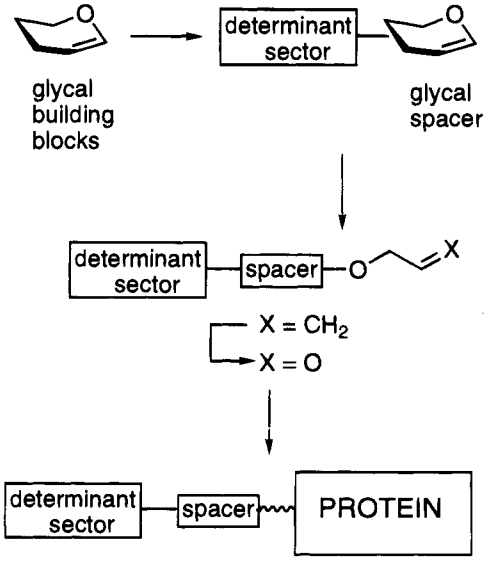
Figure 1.

molecular basis of the familiar serological blood group classifications A, B, and O.[8]

Several issues merit consideration in contemplating the synthesis of such blood group oligosaccharides and their neoglycoconjugates (vide infra). For purposes of synthetic economy it would be helpful to gain relief from the sorts of protecting group manipulations which have come to dominate traditional syntheses of complex branched carbohydrates. Another issue involves fashioning a determinant linked to a protein carrier. It is only in the context of such conjugates that the determinants are able to galvanize B-cell responses and complement fixation. In crafting such constructs, it is well to incorporate appropriate spacer units between the carbohydrate determinant and the carrier.[9] Although the current insights regarding optimal spacer–carrier combinations are far from precise, the central goal is that molecular recognition of the determinant sector not be compromised in its conjugation to biocarrier.

We demonstrate herein the use of the glycal assembly method to obtain glycals of the Le^y, Le^b, and H-type I and II specificities. The conjugation strategy we elected relies on the protocol of Bernstein and Hall[10] which calls for reductive coupling of a glycolaldehyde glycoside with the intended carrier, presumably at the ϵ-amino residues of exposed lysines. The interfacing of the glycal assembly logic with this conjugation strategy led us to the paradigm shown in Scheme 1.

Scheme 1. Strategy for Glycal Assembly of a Determinant–Spacer–Linker–Carrier Construct



Discussion of Results

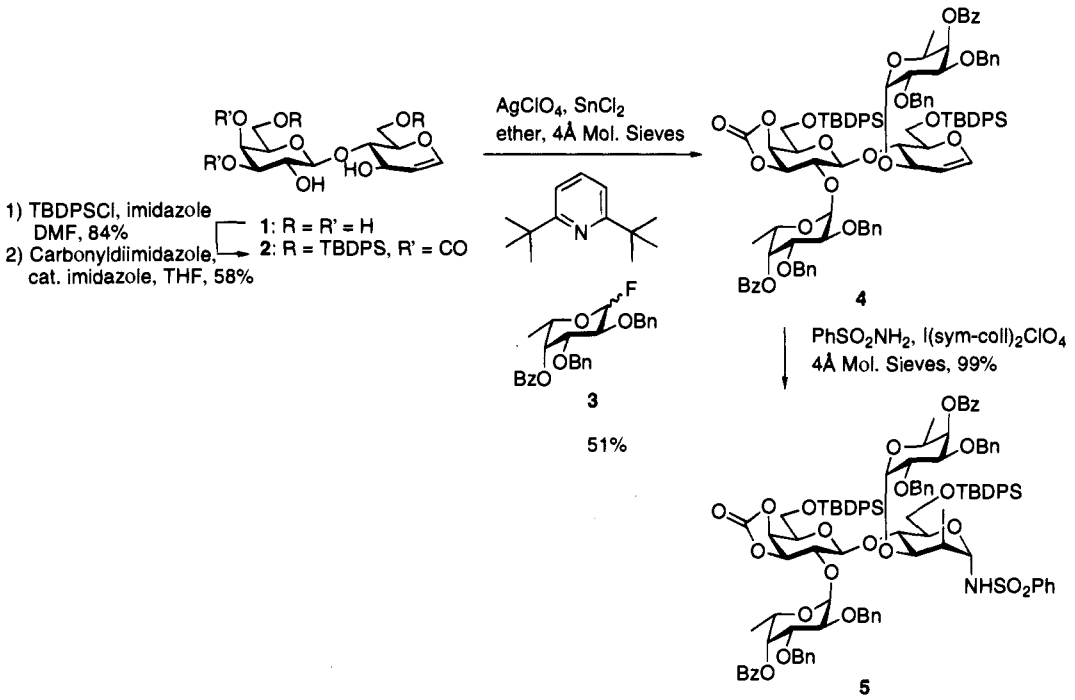
We describe the synthesis of the blood group determinants in order of ascending complexity. We therefore begin discussion with the Le^y system which could be constructed from a properly protected lactose derivative. In moving toward the H-type II system, the need to deal with the issue of regioselectivity in monofucosylation required fashioning a lactal derivative with appropriate protection already installed at the

(8) Lowe, J. B. *The Molecular Basis of Blood Diseases*; Stamatoyannopoulos, et al. Ed.; W. B. Saunders Co.: Philadelphia, PA, 1994; p 293.

(9) (a) Stroud, M. R.; Levery, S. B.; Martensson, S.; Salyan, M. E. K.; Clausen, H.; Hakomori, S.-I. *Biochemistry*, **1994**, *33*, 10672. (b) Yuen, C.-T.; Bezouska, K.; O'Brien, J.; Stoll, M.; Lemoine, R.; Lubineau, A.; Kiso, M.; Hasegawa, A.; Bockovich, N. J.; Nicolaou, K. C.; Feizi, T. *J. Biochem.* **1994**, *269*, 1595. (c) Stroud, M. R.; Levery, S. B.; Nudelman, E. D.; Salyan, M. E. K.; Towell, J. A.; Roberts, C. E.; Watanabe, M.; Hakomori, S.-I. *J. Biol. Chem.* **1991**, *266*, 8439.

(10) (a) Bernstein, M. A.; Hall, L. D. *Carbohydr. Res.* **1980**, *78*, C1. (b) Lemieux, R. U. *Chem. Soc. Rev.* **1978**, *7*, 423. (c) Lemieux, R. U.; Bundle, D. R.; Baker, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 4076 and references therein.

Scheme 2



C_3-hydroxyl of the glucal sector. In synthesizing the type I systems, the 1,3 linkage between galactose and glucal had to be made by chemical synthesis. As will be seen, this objective could be easily achieved, since the C_3-hydroxyl of a 6-monoprotected glucal is a much more reactive acceptor center than is the C_4-hydroxyl. Difucosylation at C_4 and C_2' allowed entry to the Le^b blood group system. Finally, construction of the H-type I system relied not only on the regioselective formation of the 1,3 backbone, but also on regioselective fucosylation in the galactose region.

Synthesis of a Le^y Pentasaccharide.[11a-f] A pentasaccharide containing the Le^y specificity was prepared as shown in Schemes 2 and 3. In the synthesis of this determinant, we could take advantage of the *N*-acetyllactosamine backbone in the target. Lactal[12] **1** presented itself as a potentially attractive starting material, if a concise way could be realized to identify the C_3- and $C_{2'}$-hydroxyls. Fortunately this was readily accomplished.

Readily available lactal was silylated at the two primary sites. Following these silylations, the 3'- and 4'-hydroxyls were engaged as cyclic carbonate, **2**. Thus was the exposure of the pertinent hydroxyl groups easily achieved. In the event, difucosylation of **2** utilizing fluoro sugar **3**[13] as the donor[14] was accomplished, thereby providing access to the Le^y series as glycal **4**. The double bond was activated for azaglycosylation by our previously developed iodo sulfonamidation protocol[15ab] to afford **5**.

Use of the iodo sulfonamide to glycosylate the tin ether of galactal **6**[15a] in the presence of silver tetrafluoroborate led to glycal **7** as shown in Scheme 3. Deprotection followed by peracetylation afforded peracetyl glycal **8**. Reaction of **8** with dimethyldioxirane,[16] followed by opening of the epoxide with allyl alcohol, followed by deacetylation with catayltic methoxide, led to pentasaccharide **9**.

The stage was now set for conjugation of the Le^y determinant to a protein carrier. In the event **9** was ozonolyzed in MeOH at −78 °C. Workup with dimethyl sulfide afforded masked aldehyde **10** which was reductively attached to its BSA-protein carrier as shown in Scheme 4. The reductive amination protocol described by Bernstein and Hall[10] was adapted to the case at hand. Thus, treatment of **10** with BSA in pH 8 phosphate buffer and excess sodium cyanoborohydride led to conjugate **11** which was purified by exhaustive dialysis. TFA analysis[17] showed the expected sugar composition: 2 parts galactose, 2 parts fucose, and 1 part glucosamine. Carbohydrate:protein analyses showed the substitution of an average of 15 Le^y moieties per carrier molecule.[17] This conjugate was recognized by an antibody to the Le^y blood group.

Synthesis of an H-Type II Tetrasaccharide.[18] Synthesis of a tetrasaccharide glycal having H-type II specificity proceeded as shown in Scheme 5. D-Galactal derivative **12**[19] was epoxidized using 3,3-dimethyldioxirane to provide 1,2-anhydro derivative **13**, which reacted with D-glucal derivative **14** in the presence of zinc chloride, thereby affording disaccharide glycal **15** in 81% yield. This glycosylation event produced a free hydroxyl group at 2' which was fucosylated using α-L-fucosyl fluoride donor **16**.[13] Coupling was mediated by the action of stannous triflate.[20a-c] The fucosylation, when conducted in the

(11) For previous syntheses of Lewis Y see: (a) Jacquinet, J. C.; Sinay, P. *J. Org. Chem.* **1977**, *42*, 720. (b) Nilsson, S.; Lohn, H.; Norberg, T. *Glycoconjugate J.* **1989**, *6*, 21. (c) Schmidt, R. R.; Topfer, A. *Tetrahedron Lett.* **1991**, *32*, 3353. (d) Kinzy, W.; Low, A. *Carbohydr. Res.* **1993**, *245*, 193. (e) Hindsgaul, O.; Norberg, T; Le Pendu, J.; Lemieux, R. U. *Carbohydr. Res.* **1982**, *109*, 109. (f) Windmuller, R; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *35*, 7927.

(12) Haworth, W. N.; Hirst, E. L.; Plant, M. M. T.; Reynolds, R. J. W. *J. Chem. Soc.* **1930**, 2644.

(13) Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koseki, K.; Oriyama, T.; Griffith, D. A.; Wong, C.-H.; Dumas, D. P. *J. Am. Chem. Soc.* **1992**, *114*, 8329.

(14) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431.

(15) (a) Danishefsky, S. J.; Koseki, K.; Griffith, D. A.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Oriyama, T. *J. Am. Chem. Soc.* **1992**, *114*, 8331. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811.

(16) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

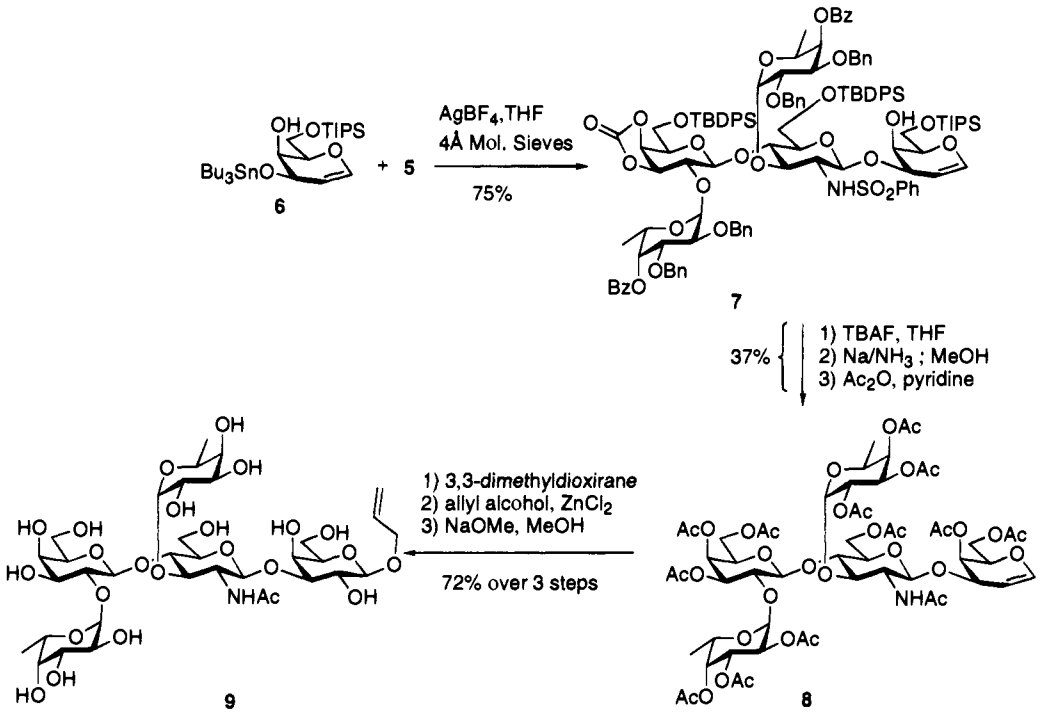
(17) For sugar analysis protocols see: (a) Lloyd, K. O.; Savage, A. *Glyconjugate J.* **1991**, *8* 493. (b) Hardy, M. R.; Townsend, R. R. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3289. For protein analysis see: (c) Bradford, M. M. *Anal. Biochem.* **1976**, *72*, 248. A full report on the immunochemistry of the Le^b, Le^y, and H type blood group substance conjugates will be disclosed elsewhere.

(18) For previous synthesis of an H type II target see: Petrakova, E; Spohr, U.; Lemieux, R. U. *Can. J. Chem.* **1992**, *70*, 233.

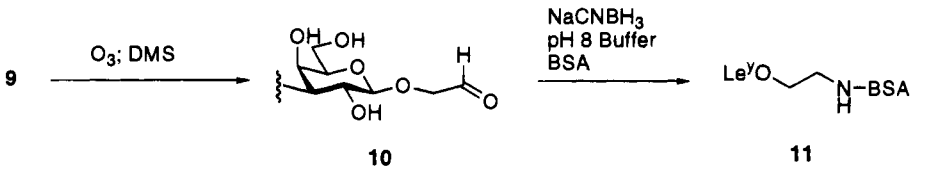
(19) Gervay, J.; Peterson, J. M.; Oriyama, T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 5465.

(20) Lubineau, A.; Malleron, A. *Tetrahedron Lett.* **1985**, *26*, 1713. (b) Lubineau, A.; Le Gallic, J.; Malleron, A. *Tetrahedron Lett.* **1987**, *28*, 5041. (c) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 6221.

Scheme 3



Scheme 4



presence of 2,6-di-*tert*-butylpyridine to maintain the stability of the acid-sensitive glycal moiety, proceeded in 67% yield.

The advantages of the glycal assemby logic are well demonstrated through this chemistry. Thus, the projected $C_{2'}$-hydroxyl acceptor of the galactose sector in **15** (see asterisk) has been uniquely identified as a consequence of the very reaction which constructs the functionalized lactose backbone. This obviates the need for selective hydroxyl functionalization in a lactal derivative such as **2**.

Trisaccharide glycal **17** containing the H-type II backbone was converted to iodo sulfonamide derivative **18** upon reaction with iodonium di-*sym*-collidine perchlorate and benzenesulfonamide. Compound **18** was coupled with D-galactal derivative **6** in the presence of silver tetrafluoroborate to give **19** in 77% yield. Compound **19** was desilylated to give **20**, which was converted to **21** by reduction with sodium in liquid ammonia. Peracetylation of **21** gave **22** in 60% overall yield from **19**. Tetrasaccharide glycal **22** is a peracetate of the H-type II blood group system. It, too, is equipped with a galactose spacer and with the implements necessary for conjugation to a suitable carrier.

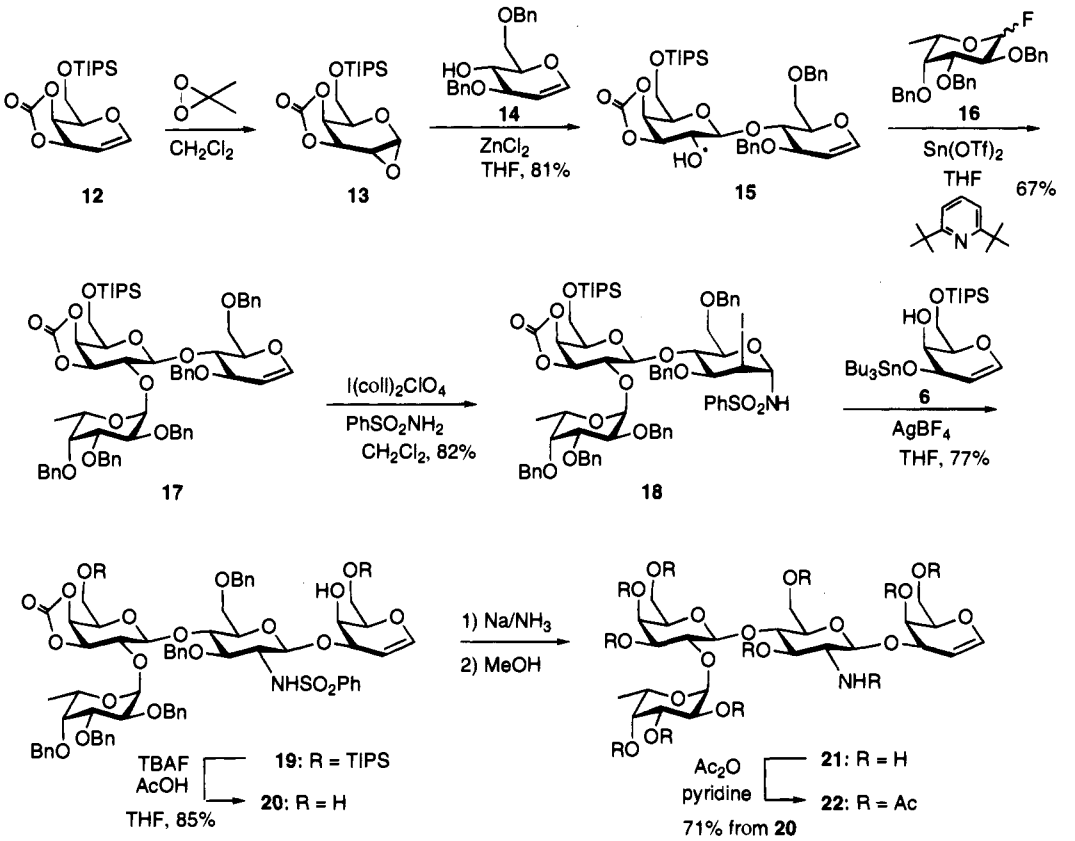
Synthesis of a Le^b Hexasaccharide.[21] The Le^b system was assembled as shown in Scheme 6. D-Glucal derivative **23** was regioselectively galactosylated at the 3 position using **13** and zinc chloride, thereby giving **24** in 94% yield. The selectivity of this kind of reaction was demonstrated earlier during our studies of the fucosylation of 6-silylated glucals in the SLe^x series.[13] Preparation of diacetate derivative **25** confirmed the regioselectivity of galactosylation. ^{1}H NMR analysis of **25** showed a signal at δ 5.14 (t apparent, 1 H, J = 4.2 Hz) corresponding to H_4 of glucal. Bisfucosylation of **24** proceeded smoothly using **16**, thereby giving tetrasaccharide glycal **26** in 70−86% yield. The conciseness provided by this version of glycal assembly should also be underscored. It takes advantage of a previously discovered high preference for glycosylation agents to "donate" from C_3 relative to C_4 of a 6-monoprotected glucal such as **23**. Furthermore it benefits from the defined exposure of the $C_{2'}$-hydroxyl which follows directly the glycal epoxide glycosylation method.

Compound **26** was converted to iodo sulfonamide **27**, which coupled with D-lactal derivative **28** to give hexasaccharide glycal **29** in 57% yield (Scheme 6). This remarkable regioselective glycosylation of acceptor **28** by selective activation of a single hydroxyl of a tetrol as a tin ether had been demonstrated previously in our syntheses of sialyl Lewis^x congeners.[15a] Desilylation of **29** gave **30**, which was converted to **31** by final deprotection with sodium−ammonia. Peracetylation of **31** provided **32** in a 51% overall yield from **29**.

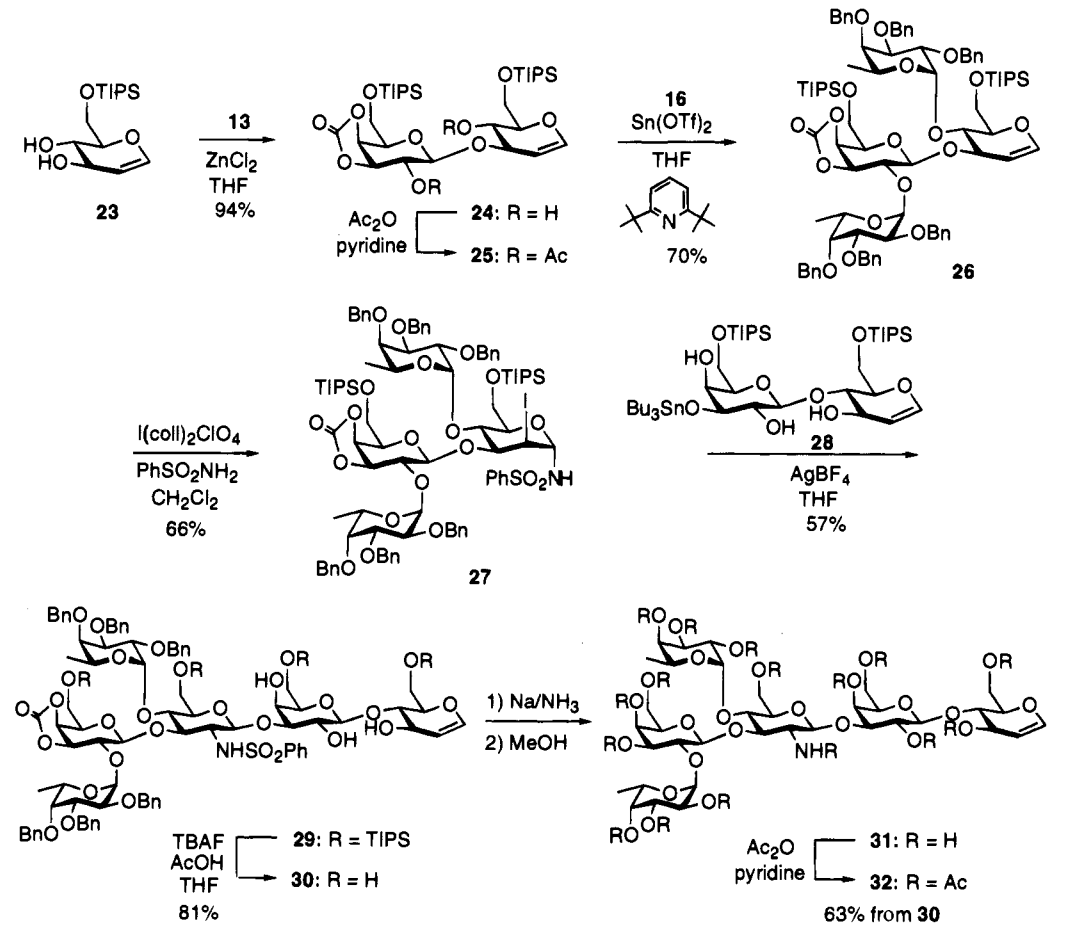
We next proceeded to introduce the linker for conjugation of the Le^b determinant to the biocarrier as shown in Scheme 7. Glycal **32** was epoxidized using 3,3-dimethyldioxirane, and the epoxide was stirred in allyl alcohol to provide the allyl glycoside. Surprisingly, deacetylation gave a 3:2 mixture of **33** and **34**, presumably resulting from alcoholysis of a mixture of epoxides obtained during dioxirane oxidation (Scheme 7). The virtually complete loss of stereoselectivity in this particular epoxidation is unprecedented in our work. It could reflect a unique molecular folding of the oligomeric glycal in a fashion which hinders the α-face. It stands in sharp contrast to the highly steroselective α-epoxidation of compound **8**. A detailed investigation of the preferred conformational disposition of **32**

(21) For previous syntheses of Lewis B type targets see: (a) Rana, S. S.; Barlow, J. J.; Matta, K. L. *Carbohydr. Res.* **1981**, *96*, 231. (b) Spohr, U.; Lemieux, R. U. *Carbohydr. Res.* **1988**, *174*, 211.

Scheme 5

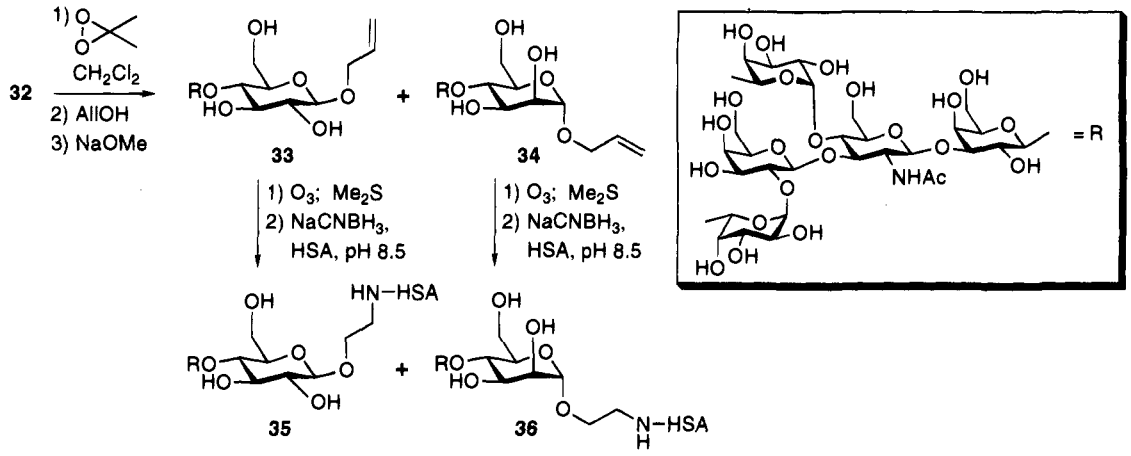


Scheme 6

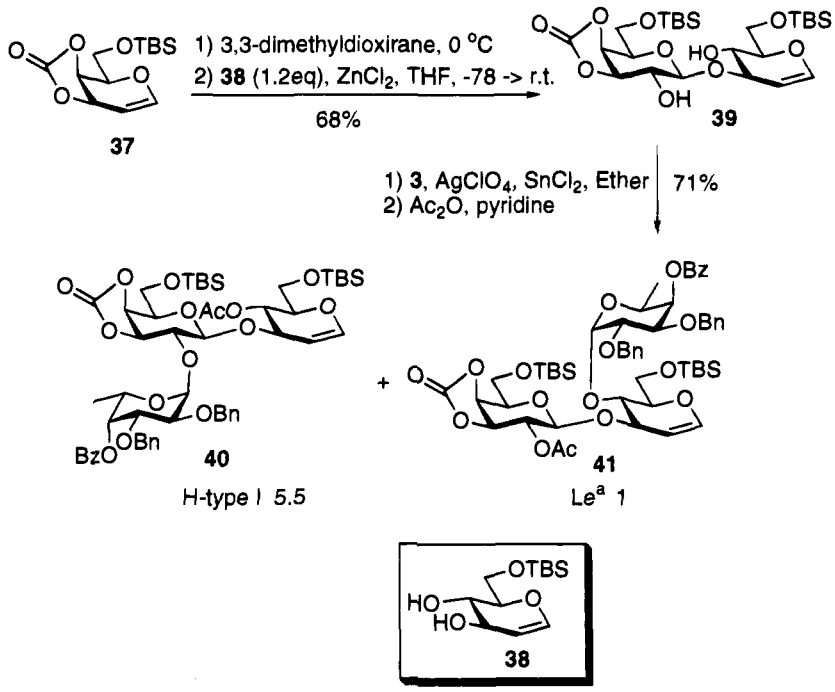


is planned. This mixture of glycosides was easily separable by RP-18 silica gel chromatography, and each isomer (both **33** and **34**) was ozonized to give the corresponding aldehyde. Each aldehyde was stirred at 37 °C with HSA and sodium cyanoboro-

Scheme 7



Scheme 8



hydride in pH 8.5 phosphate buffer,[10] thereby obtaining glycoconjugates **35** and **36** by reductive amination, presumably with the lysine units of the protein.

TFA analysis[17] of the glycoconjugates obtained indicated that a hexasaccharide:protein ratio on the order of 20–30 had been achieved. The carbohydrate composition of each neoglycoprotein conjugate was also confirmed by TFA analysis. Thus, the carbohydrate composition of **35** was found to be 2 parts galactose, 2 parts fucose, 1 part glucosamine, and 1 part glucose. The composition of **36** was determined to be 2 parts galactose, 2 parts fucose, 1 part glucosamine, and 1 part mannose. Furthermore, conjugate **35** was recognized by an antibody to the Le^b blood group.

Synthesis of an H-Type I Trisaccharide.[22] We identified as our goal a glycal of the type **40**. This goal compound was assembled from simple glycal building blocks as shown in Scheme 8. Thus, galactal carbonate **37** was epoxidized with 3,3-dimethyldioxirane. The immediate product reacted with 6-monoprotected glucal **38** in the presence of $ZnCl_2$ to afford **39**. Disaccharide **39** was treated with fluoro sugar **3**. Acetylation of this product led to a 71% yield of a 5.5:1 mixture of the H-type I **40** glycal and the Le^a glycal **41**, respectively. These glycals were easily separated by silica gel chromatography.

In summary, the solution based glycal assembly method has been shown to be eminently suitable for construction of the complex Lewis (b and y) and H-type (I and II) blood group determinants. These latter systems would appear to be attractive prospects for elaboration to the full human A and B types.

Experimental Section

General Methods. Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR or Perkin Elmer 1420 ratio recording infrared spectrophotometer. ^1H NMR spectra were obtained on a Bruker AMX 400 (400 MHz) or Varian 400 (400 MHz) and are reported in parts per million (δ) relative to either tetramethylsilane (0.00 ppm) or $CHCl_3$ (7.24 ppm) for spectra run in $CDCl_3$, acetone-d_6 (2.04 ppm), or CD_3OD (3.35 ppm). Coupling constants (J) are reported in hertz. ^{13}C NMR spectra were obtained on a Varian 300 (300 MHz) or at 100 MHz and are reported in δ relative to $CDCl_3$ (77.00 ppm), CD_3OD (49.05 ppm), or acetone-d_6 (20.83 ppm) as an internal reference. High-resolution mass spectra were recorded on a JOEL JMS-DX-303 HF mass spectrometer. Optical rotations were recorded on a Jasco DIP-370 polarimeter using a 1 dm cell at the reported temperatures and concentrations.

(22) For previous syntheses of H type I see: (a) Derevitskaya, V. A.; Novikova, O. S.; Evstigneev, A. Y.; Kochetkov, N. K. *Izv. Akad. Nauk. USSR, Ser. Khim* **1978**, *2*, 450. (b) Hatanaka, K.; Ito, Y.; Maruyama, A.; Watanabe, Y.; Akaike, T. *Macromolecules* **1993**, *26*, 1483.

Chemicals used were reagent grade and used as supplied except where noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under N_2. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under N_2. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm) and E. Merck HPTLC RP-18 WF_{254}s plates (0.20 mm). Compounds were visualized by dipping the plates in a cerium sulfate−ammonium molybdate solution followed by heating. Liquid column chromatography was performed using forced flow of 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.

Synthesis of Lactal Carbonate 2. To 2.11 g (6.84 mmol) of lactal **1** was added 2.80 g (41 mmol) of imidazole and 25 mL of dry DMF. The solution was cooled to −10 °C and 3.56 mL (13.7 mmol) of *tert*-butyldiphenylsilyl chloride was added dropwise over 15 min. The reaction was allowed to warm gradually to room temperature. After stirring 8 h the reaction was diluted with 200 mL of EtOAc and washed three times with 100 mL of water and once with saturated brine. The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was run through a plug of silica gel with 50% EtOAc/hexanes and concentrated to give 4.50 g (84%) of a white foam. This was taken up in 125 mL of dry THF, and a few crystals of imidazole were added. The solution was cooled to 0 °C, and 938 mg (5.79 mmol) of carbonyldiimidazole was added. After 2 h most of the starting material was consumed as judged by thin layer chromatography. The reaction was concentrated and chromatographed on silica gel (40% EtOAc/hexanes) to afford 910 mg (20%) of recovered starting material and 2.72 g (58%) of **2** as a white foam. $[\alpha]^{23}_D = -8.7°$ (*c* 1.35, $CHCl_3$); IR (thin film) 3450, 2900, 2830, 1785, 1632, 1415, 1225, 1145, 1100, 810, 730, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.69 (m, 8 H), 7.51−7.43 (m, 12 H), 6.38 (d, 1H, *J* = 5.9 Hz), 4.83 (d, 1H, *J* = 7.2 Hz), 7.75 (dd, 1H, *J* = 2.0, 6.1), 4.72 (d, 1H, *J* = 6.91 Hz), 4.64 (t apparent, 1H, *J* = 5.5 Hz), 4.40 (d, 1H), 4.08−3.86 (m, 7H), 3.69−3.68 (br, 2H), 2.80 (d, 1H, *J* = 3.6 Hz), 1.13 (s, 9H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$) 153.68, 143.99, 135.86, 135.77, 135.50, 135.40, 133.80, 132.65, 132.50, 132.35, 130.00, 129.84, 128.24, 128.17, 127.86, 127.76, 127.64, 101.98, 101.46, 79.68, 77.88, 77.40, 76.98, 76.61, 76.55, 74.13, 72.17, 71.39, 68.10, 62.43, 61.88, 26.86, 26.77, 19.34, 19.12; HRMS (FAB) calcd for $C_{45}H_{54}O_{10}Si_2Na$ 833.3153, found *m/z* 833.3157 (M + Na).

Synthesis of Le^y Glycal 4. To 2.00 g (2.47 mmol) of lactal carbonate **2** was added 4.44 g (9.86 mmol) of fucosyl fluoride **3**. The mixture was azeotroped five times with benzene and placed under high vacuum for 2 h. Under an argon atmosphere 2.77 mL (12. 33 mmol) of di-*tert*-butylpyridine and 16 mL of dry ether were added to the mixture of **2** and **3**. A 2.0 g amount of freshly activated 4 Å molecular sieves was added and the mixture stirred 1 h at room temperature. In an argon glove bag, 2.34 g (12.33 mmol) of stannous chloride ($SnCl_2$) and 2.56 g (12.33 mmol) of silver perchlorate ($AgClO_4$) were added. The flask was equipped with a reflux condensor and the reaction brought to reflux for 72 h. The reaction was quecnched with 5 mL of saturated bicarbonate and filtered through a pad of celite. The filtrate was diluted with 50 mL of ethyl acetate and washed twice with saturated sodium bicarbonate, twice with saturated copper sulfate, and twice with saturated brine. The organics were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography in 20% ethyl acetate/hexanes afforded 2.10 g (51%) of a white foam **4**: $[\alpha]_D$ −78.9° (*c*. 555, $CHCl_3$); IR (thin film) 3040, 3000, 2905, 2860, 2830, 1820, 1800, 1710,1635, 1585, 1570, 1480, 1460, 1440, 1415, 1370, 1350, 1300,1260, 1205, 1145,1100,950, 735, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.12 Hz, 2H), 8.00 (d, *J* = 8.26 Hz, 2H) 7.66 (m, 4H), 7.59 (d, *J* = 6.74 Hz, 4H), 7.56 (t, *J* = 7.27 Hz, 1H), 7.30−7.50 (m, 22H) 7.16−7.26 (m, 10H) 7.09 (m, 2H), 6.99 (t, *J* = 7.59 Hz, 2H) 6.89 (t, *J* = 7.97 Hz, 1H), 6.43 (d, *J* = 6.08 Hz, 1H), 5.46 (bs, 1H), 5.38 (bs, 1H), 5.35 (d, *J* = 3.42 Hz, 1H), 4.89 (d, *J* = 11.35 Hz, 1H), 4.75−4.80 (m, 4H), 4.72 (d, *J* = 5.88 Hz, 2H), 4.69 (d, *J* = 4.27 Hz, 2H), 4.36−4.55 (m, 5H), 4.28 (q, *J* = 6.51 Hz, 1H), 4.17 (bd, *J* = 5.46 Hz, 1H), 3.90−4.00 (m, 6H), 3.85 (d, *J* = 2.99 Hz, 1H), 3.82 (d, *J* = 2.89 Hz, 1H), 3.56−3.78 (m, 4H), 1.07 (m, 24H); ^{13}C NMR δ 166.24, 165.78, 153.26, 145.01, 138.47, 138.31, 138.22, 137.82, 135.85, 135.72, 135.36, 133.84, 133.17, 132.82, 132.72, 132.48, 131.92, 130.31, 130.20, 130.03, 129.93, 129.84, 129.57, 128.54, 128.47, 128.30, 128.12, 128.03, 127.97, 127.92, 127.83, 127.69, 127.53, 127.46, 127.28, 99.13, 97.88, 97.74, 97.33, 96.39, 79.70, 77.47, 77.31, 77.06, 76.92, 76.63, 75.89, 75.25, 75.09, 74.82, 74.66, 74.19, 74.00, 73.90, 73.53, 71.81, 71.70, 71.59, 71.42, 71.19, 70.99, 65.60, 65.13, 61.06, 26.82, 26.76, 19.39, 19.22, 16.16, 16.06; HRMS (FAB) calcd for $C_{99}H_{106}O_{20}Si_2Na$ 1694.6740 found *m/z* 1694.6787 (M + Na).

Synthesis of Iodo Sulfonamide 5. To 400 mg (0.239 mmol) of tetrasacharide glycal **4** (azeotroped 3× with 15 mL of benzene) was added 113 mg (0.718 mmol) of benzenesulfonamide and 400 mg of freshly activated 4 Å powdered molecular sieves. This was taken up in 2.7mL of methylene chloride and cooled to 0 °C. The solution was stirred for 30 min at 0 °C, and then 392 mg (0.837 mmol) of iodonium di-*sym*-collidine perchlorate was added in one portion. The reaction was stirred for 30 min and then quenched at 0 °C with 3 mL of saturated sodium thiosulfate. The reaction mixture was diluted with ethyl acetate and filtered through a Celite pad into a separatory funnel. The filtrate was washed once with saturated sodium thiosulfate, once with saturated copper sulfate, and once with saturated brine. The organics were dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (32% EtOAc/hexanes) afforded 468 mg (99%) of a white foam **5**: $[\alpha]^{23}_D = -95.8°$ (*c* 0.58, $CHCl_3$); IR (thin film) 2910, 2835, 1800, 1710, 1440, 1425, 1350, 1260, 1150, 1100, 1040, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 2H, *J* = 7.1 Hz), 8.02 (d, 2H, *J* = 6.99 Hz), 7.75 (d, 2H, *J* = 7.49 Hz), 7.67−7.09 (m, 49H), 5.93 (bs, 1H), 5.61 (bs, 1H), 5.46 (bs, 1H), 5.43 (bs, 1H), 5.06−4.54 (m, 10H), 4.47 (bd, 1H, *J* = 10.3 Hz), 4.36−4.30 (m, 2H), 4.18 (bs, 2H), 3.98−3.70 (m, 11H), 3.40−3.28 (bs, 2H), 1.10 (s, 9H), 1.05 (s, 9H), 1.02 (d, 3H, *J* = 6.4 Hz),. 98 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 165.67, 165.53, 153.68, 140.81, 138.07, 137.76, 137.68, 137.37, 135.34, 135.08, 135.02, 134.90, 133.03, 132.77, 132.49, 132.43, 132.23, 131.92, 129.70, 129.60, 129.39, 128.36, 128.23, 128.11, 128.04, 127.90, 127.80, 127.64, 127.54, 127.45, 127.30, 127.21, 127.05, 126.87, 126.67, 98.95, 98.68, 83.27, 77.00, 76.78, 76.58, 76.15, 75.95, 75.83, 75.70, 74.64, 73.71, 73.11, 72.86, 72.49, 71.37, 71.28, 70.78, 70.45, 69.97, 69.92, 65.55, 65.30, 61.57, 26.49, 18.86, 18.81, 15.87, 15.78; HRMS (FAB) calcd for $C_{105}H_{112}NO_{22}ISi_2Na$ 1977.5900, found *m/z* 1977.6037 (M + Na).

Synthesis of Le^y Pentasaccharide Glycal 7. A 230 mg (0.12 mmol) sample of iodo sulfonamide **5** was azeotroped five times with dry benzene and placed under high vacuum for 2 h. Added 15 equiv of tin ether **6** (generated by azeotropic removal of water overnight with a Dean−Stark trap equipped with freshly activated 4 Å molecular sieves from 561 mg (1.80 mmol) of 6-TIPS-galactal and 673 μL (1.32 mmol) bis(tributyltin) oxide in 80 mL of benzene) to **5** with 2.4 mL of THF. To this solution, stirring under an argon atmosphere, was added 200 mg of freshly activated 4 Å powdered molecular sieves. Stirring was continued for 1 h at room temperature. The solution was cooled to −78 °C and then a solution of 187 mg (0.96 mmol) of silver tetrafluoroborate in 2.4 mL of THF was added via cannula. The reaction was allowed to warm to room temperature over 15 h, during which time the reaction had turned bright yellow. The reaction was then quenched with 2 mL of saturated sodium bicarbonate. The reaction mixture was filtered through a pad of Celite into a separatory funnel. The Celite pad was washed thoroughly with ethyl acetate. The organics were washed twice with saturated sodium bicarbonate and twice with saturated brine. The organics were dried over $MgSO_4$ and then filtered. Concentration followed by column chromatography in 25% ethyl acetate/hexanes gave 193 mg (75%) of a white foam **7**: $[\alpha]_D$ −126.4° (*c* 0.505, $CHCl_3$); IR (thin film) 3500, 3040, 3000, 2905, 2840, 1820, 1800, 1705, 1635, 1590, 1440, 1410, 1255, 1195, 1100, 1080, 1035, 815, 730, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (t apparent, 4H), 7.65−7.08 (m, 46H), 6.90 (t, *J* = 7.65 Hz, 3H), 6.76 (d, *J* = 6.91 Hz, 2H), 6.12 (d, *J* = 6.59 Hz, 1H), 5.50 (bs, 1H), 5.45 (bs, 1H), 5.28 (t apparent, 2H), 4.91−3.03 (m, 36H), 2.82 (bs, 1H) 1.09 (m, 45H); ^{13}C NMR ($CDCl_3$) δ 166.21, 165.97, 153.22, 144.57, 142.49, 138.27, 138.20, 137.71, 137.60, 136.03, 135.90, 135.58, 135.43, 135.36, 135.25, 135.06, 133.81, 133.16, 132.81, 132.61, 132.14, 132.00, 130.20, 130.05, 129.84, 129.68, 129.39, 128.99, 128.78, 128.66, 128.43, 128.30, 128.21, 128.12, 128.01, 127.88, 127.68, 127.51, 127.43, 127.28, 126.52, 100.63, 100.03, 97.99, 97.88, 97.46, 80.57, 79.55, 77.38, 77.29, 77.16, 76.96, 76.54, 76.40, 76.32, 75.94, 75.25, 75.00, 74.84, 74.59, 74.43, 73.72, 72.83, 72.49, 71.74, 71.19, 71.03, 70.91, 70.82, 65.93, 65.44, 64.86, 63.88, 63.17, 61.18, 61.00, 59.35, 26.78, 26.68, 19.22, 17.92, 16.09,

11.93; HRMS (FAB) calcd for $C_{120}H_{141}NO_{26}SSi_3Na$ 2150.8668, found *m/z* 2150.8765 (M + Na).

Synthesis of Peracetate Le^y Pentasaccharide Glycal 8. A 480 mg (0.225 mmol) sample of pentasaccharide glycal **7** was taken up in 200 μL of THF and 52 μL (0.902 mmol) of glacial acetic acid. A 1.35 mL amount of TBAF (1 M in THF, 1.35 mmol) was added at room temperature. After stirring 8 h, **7** was completely consumed and a new product appeared as judged by TLC. The reaction mixture was concentrated and chromatographed in 8% MeOH/$CHCl_3$. The resulting white solid was taken up in THF and added to a solution of 15 mL of about 5:1 NH_3/THF to which a large excess of solid sodium metal had been added. The dark blue solution was allowed to reflux at −33 °C for 20 min. The reaction was quenched with 5 mL of MeOH and stirred overnight. The reaction mixture was partially concentrated and then cooled to 0 °C. The reaction mixture was then carefully acidified to pH 8 with Dowex 50-X200 ion exchange resin. The reaction was filtered and concentrated. The crude solids were taken up in 3 mL of pyridine and 3 mL of acetic anhydride and allowed to stir overnight. Purification by silica gel chromatography (30% acetone/benzene) gave 110 mg (37%) of a white solid **8**: $[\alpha]_D$ −121.3° (*c* 0.635, $CHCl_3$); IR (thin film) 2930, 1735, 1362, 1224, 1060, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, 1H, *J* = 6.3 Hz), 5.70 (d, 1H, *J* = 7.2 Hz), 5.30−5.26 (m, 6H), 5.13 (dd, 1H, *J* = 3.1, 11.0 Hz), 5.05 (dd, 1H, *J* = 3.2, 11.1 Hz), 5.00−4.92 (m, 4H), 4.88 (d, 1H, *J* = 6.6 Hz), 4.79 (dd, 1H, *J* = 3.4, 6.1 Hz), 4.53−4.28 (m, 7H), 4.22−4.08 (m, 4H), 3.83−3.69 (m, 3H), 3.51 (br dd, 1H, *J* = 3.7, 9.5 Hz), 2.17 (s, 3H), 2.14 (bs, 6H), 2.13 (bs, 6H), 2.11 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H) 2.00 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.91 (s, 3H), 1.17 (d, 3H, *J* = 6.4 Hz), 1.14 (d, 3H, *J* = 6.5 Hz); HRMS (FAB) calcd for $C_{56}H_{77}NO_{34}Na$ 1330.4220, found *m/z* 1330.4168 (M + Na).

Synthesis of Allyl Glycoside of Le^y Pentasaccharide 9. To 110 mg (84 μmol) of peracetate glycal **8** was added 100 μL of dry methylene chloride. The solution was cooled to 0 °C and 1.44 mL of 3,3-dimethyldioxirane solution (0.07 M in acetone, 100 μmol) was added. Stirring continued for 20 min at 0 °C, and then the reaction was concentrated in vacuo. The white solid was taken up in 1 mL of allyl alcohol and then cooled to −78 °C. A 100 μL volume of $ZnCl_2$ solution was added and the reaction was allowed to warm to room temperature overnight. The reaction was diluted with ethyl acetate and washed twice with saturated sodium bicarbonate and once with saturated brine. The organics were dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel chromatography (35% acetone/benzene) gave a white solid which was immediately deacetylated. A 1 mL volume of MeOH and then a few drops of 2.5% NaOMe in MeOH (Aldrich 25%, 1 mL diluted to 10 mL with MeOH) were added, and the mixture was stirred overnight. The reaction was cooled to 0 °C and acidified to pH 7 with Dowex 50-X200 ion exchange resin. The reaction was filtered and concentrated. Purification with RP-18 reverse phase silica gel (10% MeOH/H_2O) afforded 55 mg (72%) of a white solid **9**: $[\alpha]_D$ −72.7° (*c* 0.1 MeOH); IR (thin film) 3350, 2940, 2900, 2830, 1650, 1550, 1365, 1300, 1155, 1070. 1030; ^{1}H NMR (400 MHz, CD_3OD) δ 5.95 (m, 1H), 5.32 (d, *J* = 17.3 Hz, 1H), 5.19−5.14 (m, 2H), 5.04 (d, *J* = 3.8 Hz, 1H), 4.68 (d, *J* = 8.3 Hz, 2H), 4.51 (d, *J* = 5.7 Hz, 1H), 4.36 (dd, 1H, *J* = 5.2, Hz), 4.25 (d, 1H, 7.7 Hz), 4.19−4.10 (m, 2H), 4.04 (d, 1H, *J* = 2.2 Hz), 3.96−3.33 (m, 34H), 1.96 (s, 3H), 1.23 (m, 6H); ^{13}C NMR (CD_3OD) δ 174.59, 135.83, 117.36, 103.98, 103.93, 102.18, 102.08, 100.31, 83.87, 79.40, 77.26, 76.71, 76.24, 75.32, 74.22, 73.68, 71.88, 71.56, 71.22, 70.97, 70.77, 70.16, 69.94, 69.84, 68.24, 67.61, 62.78, 62.39, 61.22, 57.65, 23.14, 16.85, 16.79; HRMS (FAB) calcd for $C_{35}H_{56}NO_{24}Na$ 900.3325, found *m/z* 900.3310 (M + Na).

Synthesis of Le^y-BSA Neoglycoconjugate 11. A 3.2 mg (3.6 μmol) amount of allyl glycoside **9** was taken up in 2 mL of MeOH and cooled to −78 °C. Ozone was bubbled through the solution until it appeared to be faintly blue (<2 min). The reaction was stirred for an additional 2−3 min, and then the excess ozone was purged with a vigorous flow of argon until the blue color dissipated. About 2 mL of dimethyl sulfide was added. The reaction was gradually warmed to room temperature over about 4 h and then was stirred an additional 4 h. The reaction was concentrated in vacuo and placed under high vacuum for 1 h. To the crude aldehyde was added 1 mg (0.015 μmol) of bovine serum albumin (BSA, Sigma Diagnostics Protein Standard) and 200 μL of pH 8 sodium phosphate buffer. A 1 mg (14.4 μmol) amount of sodium cyanoborohydride was then added. The solution was stirred slowly for 3 days after which time it was placed in dialysis tubing (Spectra Por, MWCO 12,400). Exhaustive dialysis against distilled water, followed by lyophilization gave 1.2 mg of a fluffy white cotton **11**. TFA analysis of **11** indicated the Le^y pentasaccharide:protein ratio to be about 15:1. Carbohydrate composition was also determined with a composition of 2 parts fucose, 2 parts galactose, and 1 part glucosamine. Conjugate **11** was recognized by Anti-Le^y (S193).

Synthesis of 3,6-Dibenzyl Glucal 14. A 5.0 g sample of glucal (34.2 mmol) and 18.3 mL of tributyltin oxide (1.05 mol equiv) in 150 mL of dry benzene were refluxed for 20 h with a Dean−Stark trap. The reaction was cooled below boiling temperature and treated with 14 mL of benzyl bromide and 25.0 g of tetrabutylammonium bromide. The mixture was refluxed for 24 h. The reaction was cooled and concentrated and the residue dissolved in water (200 mL) and extracted twice with 100 mL of ethyl acetate. The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. Careful chromatography on silica gel with 15−20% EtOAc in hexanes gave 6.58 g (59%) of product **14**: $[\alpha]^{23}_D$ = −25.0° ($CHCl_3$, *c* = 5.7); 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 (dd, 1H, *J* = 6.1, 1.4 Hz), 4.82 (dd, 1H, *J* = 6.2, 2.3 Hz), 4.67 (d, 1H, *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 (d, 1H, *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 (CI) calcd for $C_{20}H_{26}NO_4$ 344.1862, found *m/z* 344.1841 (M + NH_4).

Synthesis of Disaccharide Glycal 15. A 1.00 g (3.04 mmol) sample of D-galactal derivative **12** was azeotropically dried using benzene before being dissolved in 20 mL of dry CH_2Cl_2 under N_2. The solution was cooled to 0 °C, and 50 mL (4.5 mmol) of 3,3-dimethyldioxirane solution was added with stirring. The solution was stirred at 0 °C for 40 min, at which time TLC (1:1 EtOAc:hexanes) indicated no trace of **12**. The solvents were evaporated using a dry N_2 stream to give **13**, which was dried in vacuo. To the flask containing **13** under N_2 was added, via cannula, a solution of 1.60 g (4.90 mmol) of **14**, which had been azeotropically dried using benzene, in 10 mL of dry THF. The stirred solution was cooled to −78 °C and 5.0 mL of 1.0 M $ZnCl_2$ in Et_2O was added. The mixture was maintained at −78 °C for 2 h and then allowed to slowly warm to room temperature and stirred an additional 10 h. The reaction mixture was quenched using 50 mL of saturated aqueous sodium bicarbonate and partitioned between 50 mL of water and 100 mL of ethyl acetate. The aqueous layer was extracted twice with 100 mL of ethyl acetate. The combined organic layers were dried over $MgSO_4$ and the crude product was purified by column chromatography on silica gel (1:3 EtOAc:hexanes). Compound **15** was obtained as a colorless glass (1.65 g, 81%): $[\alpha]^{22}_D$ = −12.5 ° (*c* 2.4, CH_2Cl_2); FTIR (thin film) 3442, 2942, 2865, 1805, 1649, 1454, 1240, 1163, 1099, 1071, 1043, 882, 777, 738, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.26 (m, 10 H), 6.39 (d, 1 H, *J* = 6.1 Hz), 4.85 (dd, 1 H, *J* = 2.6 Hz, *J* = 6.1 Hz), 4.76 (dd, 1 H, *J* = 1.9 Hz, *J* = 7.1 Hz), 4.68 (d, 1 H, *J* = 12.0 Hz), 4.67 (d, 1 H, *J* = 7.2 Hz), 4.64 (d, 1 H, *J* = 13 Hz), 4.60 (d, 1 H, *J* = 11.5 Hz), 4.56 (d, 1 H, *J* = 12.6 Hz), 4.55 (d, 1 H, *J* = 6.3 Hz), 4.25 (m, 1 H, *J* = 6.0 Hz), 4.19 (dd, 1 H, *J* = 6.2 Hz, *J* = 8.3 Hz), 4.04−3.84 (m, 4 H), 3.75−3.66 (m, 3 H), 3.61 (t apparent, 1 H, *J* = 6.8 Hz, $H_{2'}$), 1.10−1.00 (m, 21 H); ^{13}C NMR ($CDCl_3$) δ 154.07, 144.68, 138.17, 137.28, 128.47, 128.36, 128.05, 127.99, 127.63, 127.42, 101.18, 100.25, 78.50, 76.22, 75.30, 74.53, 74.33, 73.83, 72.52, 72.46, 70.62, 68.04, 61.35, 17.85, 17.82, 11.75; HRMS (FAB) calcd for $C_{36}H_{51}O_{10}Si$ 671.3252 found *m/z* 671.3272 (M+H)

Synthesis of H-Type II Glycal 17. A mixture 600 mg (0.89 mmol) of **15** and 1.00 g (2.29 mmol) **16** was azeotropically dried using benzene and placed under N_2. This mixture was dissolved in 20 mL of dry THF and 2.5 mL (11.1 mmol) of di-*tert*-butylpyridine, and the resulting solution was added via cannula to a flask containing 1.15 g (2.80 mmol) stannous triflate and powdered 4 Å molecular sieves (2.0 g) at 0 °C under N_2. The mixture was stirred at 0 °C for 4 h and then partitioned between 200 mL of saturated sodium bicarbonate and 100 mL of ethyl acetate. The aqueous layer was extracted twice more with 100 mL of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated, and the crude product was purified by column chromatography on silica gel (1:4 EtOAc:hexanes). Compound **17** was obtained as a colorless glass (0.66 g, 67%): $[\alpha]^{22}_D$ = −76.5 ° (*c* 1.9,

CH_2Cl_2); FTIR (thin film) 2940, 2865, 1816, 1650, 1454, 1366, 1245, 1168, 1100, 1050, 883, 736, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.22 (m, 25 H), 6.32 (d, 1 H, J = 6.2 Hz), 5.02 (d, 1 H, J = 3.6 Hz), 4.96 (d, 1 H, J = 11.6 Hz), 4.86–4.78 (m, 4 H), 4.77–4.72 (m, 2 H), 4.67–4.61 (m, 2 H), 4.60–4.56 (m, 3 H), 4.53 (d, 1 H, J = 12.0 Hz), 4.45 (d, 1 H, J = 12.0 Hz), 4.12–4.03 (m, 3 H), 4.02 (m, 1 H), 3.95 (m, 1 H, J = 6.4 Hz), 3.87–3.77 (m, 5 H), 3.71 (m, 1 H, J = 5.4 Hz), 3.64–3.58 (m, 2 H), 1.09–1.00 (m, 24 H); ^{13}C NMR ($CDCl_3$) δ 153.74, 144.25, 138.65, 138.49, 138.44, 138.39, 137.95, 128.46, 128.37, 128.34, 128.20, 128.19, 128.17, 127.88, 127.85, 127.73, 127.60, 127.55, 127.43, 127.34, 99.83, 98.64, 97.43, 78.92, 77.46, 76.43, 76.21, 75.46, 74.78, 73.88, 73.80, 73.64, 73.39, 73.03, 72.88, 72.52, 71.42, 70.50, 67.77, 67.16, 61.53, 17.87, 17.84, 16.53, 11.76; HRMS (FAB) calcd for $C_{63}H_{78}O_{14}SiNa$ 1109.5060, found *m/z* 1109.5069 (M + Na).

Synthesis of Iodo Sulfonamide 18. To a flask containing 300 mg (0.272 mmol) of **17**, which had been azeotropically dried using benzene, was added 65 mg (0.414 mmol) of benzenesulfonamide and powdered 4 Å molecular sieves (0.5 g). The mixture was suspended in 3 mL of dry CH_2Cl_2 at 0 °C under N_2, and a solution of iodonium di-*sym*-collidine perchlorate (freshly prepared from 250 mg of silver di-*sym*-collidine perchlorate and 140 mg of iodine) in 2 mL of dry CH_2Cl_2 was added. The mixture was stirred at 0 °C for 40 min, at which time TLC (1:2 EtOAc:hexanes) indicated a mixture of **17** and **18**. This mixture was filtered through celite and washed with 50 mL of Et_2O. The rinsings were washed twice with 20 mL of saturated aqueous $Na_2S_2O_3$, twice with 20 mL of saturated aqueous $CuSO_4$, and twice with 20 mL of brine. The organic layer was dried over $MgSO_4$, and the crude product was chromatographed on silica gel (1:4 EtOAc:hexanes) to give **17** (110 mg) and **18** (195 mg, 82% based upon recovered **17**): $[\alpha]^{22}_D$ = +2.4 ° (*c* 1.2, CH_2Cl_2); FTIR (thin film) 3406, 2921, 2852, 1801, 1647, 1454, 1371, 1242, 1165, 1071, 741, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 1 H, J = 7.4 Hz), 7.46–7.22 (m, 28 H), 5.85 (d, 1 H, J = 9.7 Hz), 5.38 (dd, 1 H, J = 8.2 Hz, J = 9.4 Hz), 4.97 (d, 1 H, J = 11.5 Hz), 4.92–4.87 (m, 2 H), 4.84 (d, 1 H, J = 11.8 Hz), 4.82–4.77 (m, 2 H), 4.72 (d, 1 H, J = 11.7 Hz), 4.67–4.56 (m, 5 H), 4.43 (d, 1 H, J = 11.9 Hz), 4.39 (dd, 1 H, J = 3.1 Hz, J = 8.1 Hz), 4.33 (d, 1 H, J = 11.9 Hz), 4.03 (dd, 1 H, J = 3.7 Hz, J = 10.2 Hz), 3.94 (t apparent, 1 H, J = 7.2 Hz), 3.87–3.77 (m, 5 H), 3.75 (dd, 1 H, J = 2.7 Hz, J = 10.2 Hz), 3.70 (t apparent, 1 H, J = 2.2 Hz), 3.65 (m, 1 H, J = 4.6 Hz), 3.62 (d, 1 H, J = 2 Hz), 3.41 (dd, 1 H, J = 5.2 Hz, J = 10.4 Hz), 3.27 (dd, 1 H, J = 5.8 Hz, J = 10.3 Hz), 1.15–1.01 (m, 24 H); ^{13}C NMR ($CDCl_3$) δ 154.31, 141.28, 138.46, 138.33, 138.28, 137.96, 137.27, 132.38, 128.63, 128.60, 128.42, 128.32, 128.30, 128.25, 128.17, 128.06, 127.93, 127.69, 127.63, 127.61, 127.32, 99.27, 99.00, 81.12, 79.04, 76.17, 75.17, 74.90, 74.18, 73.98, 73.31, 73.28, 73.10, 73.01, 72.62, 72.17, 69.70, 67.72, 67.58, 61.90, 17.98, 17.95, 16.63, 11.81; HRMS (FAB) calcd for $C_{69}H_{84}NO_{16}SSiINa$ 1392.4220, found *m/z* 1392.4208 (M + Na).

Synthesis of H-Type II Tetrasaccharide Glycal 19. To a mixture of 185 mg (0.133 mmol) of **18** and 4 Å molecular sieves (300 mg) under N_2 was added a solution of **6** (1.06 mmol) in 2 mL of dry THF. The mixture was stirred and cooled to −78 °C, and a solution of 200 mg (1.03 mmol) of silver tetrafluoroborate in 0.5 mL of dry THF was added via cannula. The reaction mixture, which was shielded from light, was allowed to slowly warm to room temperature over about 4 h and then stirred for an additional 30 h. The mixture was partitioned between saturated aqueous NH_4Cl (10 mL) and 10 mL of ethyl acetate. The aqueous layer was extracted twice with 10 mL of ethyl acetate, and the organic layers were combined and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel (1:3 EtOAc:hexanes) to give **19** as a colorless glass (160 mg, 77%): $[\alpha]^{22}_D$ = −65.4° (*c* 1.0, CH_2Cl_2); FTIR (thin film) 3512, 3285, 2941, 2865, 1836, 1811, 1650, 1454, 1360, 1328, 1239, 1160, 1099, 1051, 883, 789, 734, 689; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.85 (d, 1 H, J = 7.2 Hz), 7.48–7.22 (m, 28 H), 6.71 (d, 1 H, J = 8.5 Hz), 6.22 (d, 1 H, J = 6.3 Hz), 5.18 (d, 1 H, J = 3.6 Hz), 5.00–4.91 (m, 3 H), 4.90–4.85 (m, 2 H), 4.84–4.74 (m, 4 H), 4.68–4.61 (m, 4 H), 4.49 (d, 1 H, J = 12.1 Hz), 4.35 (m, 1 H, J = 2.0 Hz), 4.18 (m, 1 H, J = 1.9 Hz, J = 4.5 Hz), 4.12 (m, 1 H), 4.08–3.94 (m, 4 H), 3.94–3.80 (m, 6 H), 3.80–3.76 (m, 2 H), 3.75–3.49 (m, 5 H), 3.27 (bs, 1 H, OH), 1.16 (d, 3 H, J = 6.5 Hz, CH_3), 1.21–1.00 (m, 42 H); ^{13}C NMR (acetone-d_6) δ 145.49, 136.07, 135.13, 131.10, 131.03, 130.91, 130.84, 130.34, 123.62, 120.51, 120.17, 120.07, 119.90, 119.73, 119.66, 119.56, 119.43, 119.26, 119.13, 119.06, 118.76, 118.52, 94.99, 92.78, 92.03, 90.81, 88.59, 72.85, 70.70, 69.74, 69.49, 69.04, 68.64, 68.44, 67.92, 66.68, 66.49, 64.17, 63.62, 60.00, 58.94, 56.60, 55.34, 54.27, 54.14, 53.17, 51.22, 9.36, 9.33, 9.28, 8.03, 3.62, 3.53; HRMS (FAB) calcd for $C_{84}H_{113}NO_{20}SSi_2Na$ 1566.7010, found *m/z* 1566.7004 (M + Na).

Synthesis of Peracetate of H-Type II Tetrasaccharide Glycal 22. To a solution of 140 mg (90 μL) **19** in 3 mL of THF at 0 °C was added 0.25 mL of 1.0 M AcOH in THF, followed by 0.50 mL of 1.0 M TBAF in THF. The mixture was stirred for 3 h at room temperature. The solvents were removed by evaporation, and the crude product was purified by column chromatography on silica gel (EtOAc) to give **20** (95 mg, 85%). Compound **20** (60 mg, 48 μmol) in 0.5 mL of dry THF was added via cannula to a solution of Na (~30 mg) in 10 mL of NH_3 at −78 °C. The bright blue solution was stirred at reflux for 15 min and then quenched with 2 mL of dry MeOH. The NH_3 was boiled off, and the pH was adjusted to 9 using Dowex 50 × 8 [H^+] resin. The resin was filtered off and rinsed with MeOH, and the solution was concentrated in vacuo to give crude **21** as a colorless glass. This material was dissolved in 2 mL of anhydrous pyridine under N_2, and 0.5 mL of Ac_2O was added. The mixture was stirred at room temperature for 12 h, the solvents were removed in vacuo, and the crude product was purified by column chromatography on silica gel (4:1 EtOAc:hexanes). Compound **22** was obtained as a colorless solid (36 mg, 71% from **20**): $[\alpha]^{23}_D$ = −51.1° (*c* 1.8, CH_2Cl_2); FTIR (thin film) 2966, 2935, 1747, 1538, 1436, 1371, 1229, 1065, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, 1 H, J = 6.2 Hz), 5.65 (d, 1 H, J = 8.9 Hz), 5.35 (d, 1 H, J = 3.8 Hz), 5.33 (m, 1 H), 5.29 (d, 1 H, J = 2.6 Hz), 5.27 (d, 1 H, J = 3.1 Hz), 5.17–5.09 (m, 2 H), 4.97–4.90 (m, 2 H), 4.81 (dd, 1 H, J = 3 Hz, J = 6.1 Hz), 4.75 (d, 1 H, J = 8.0 Hz), 4.52 (m, 1 H), 4.48 (dd, 1 H, J = 12.0 Hz), 4.44–4.06 (m, 8 H), 3.88–3.77 (m, 4 H), 3.61 (m, 1 H), 2.18–1.97 (m, 3 H), 1.18 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 170.80, 170.77, 170.72, 170.67, 170.62, 170.34, 170.21, 170.09, 170.01, 169.99, 169.65, 144.92, 100.22, 98.83, 98.58, 95.55, 74.48, 73.38, 73.13, 73.06, 71.48, 71.01, 70.68, 67.97, 67.42, 67.18, 67.05, 65.94, 64.83, 62.35, 62.22, 60.88, 60.37, 54.21, 23.23, 22.15, 20.85, 20.82, 20.79, 20.76, 20.65, 20.61, 20.57, 15.51; HRMS (FAB) calcd for $C_{46}H_{63}NO_{28}Na$ 1100.3434, found *m/z* 1100.3436 (M+Na).

Synthesis of Disaccharide Glycal 24. A 1.00 g (3.04 mmol) sample of D-galactal derivative **12** was azeotropically dried with benzene and placed under N_2 before being dissolved in 20 mL of dry CH_2Cl_2. The solution was cooled to 0 °C, and 45 mL of 3,3-dimethyldioxirane solution (~4.1 mmol) was added. The stirred soluton was maintained at 0 °C for 40 min at which time TLC (1:1 EtOAc:hexanes) showed no trace of **12**. The solvents were evaporated using a dry N_2 stream, and **13** was dried in vacuo. To the flask containing **13** under N_2 was added, via cannula, a solution of 1.59 g (5.26 mmol) of **23** in 20 mL of dry THF. The stirred solution was cooled to −78 °C, and 6.0 mL of 1.0 M $ZnCl_2$ in Et_2O was added. The stirred mixture was maintained at −78 °C for 2 h, and then allowed to slowly warm to room temperature and stirred an additional 10 h. The reaction mixture was partitioned between 100 mL of saturated aqueous $NaHCO_3$ and 100 mL of ethyl acetate. The aqueous layer was washed two more times with 100 mL of ethyl acetate, and the combined organic layers were dried over $MgSO_4$. After filtering and concentration in vacuo the crude product was purified by silica gel chromatography (1:4 EtOAc:hexanes) to give **24** as a colorless glass (1.86 g, 94%): $[\alpha]^{23}_D$ = −9.8° (*c* 1.0, CH_2Cl_2); FTIR (thin film) 3473, 2943, 2867, 1796, 1652, 1464, 1384, 1242, 1151, 1096, 1068, 1032, 882, 813, 777, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (dd, 1 H, J = 1.3 Hz, J = 6.0 Hz), 4.80 (d, 1 H, J = 7.3 Hz), 4.72 (t apparent, 1 H, J = 6.7 Hz), 4.68 (dd, 1 H, J = 2.0 Hz, J = 6.1 Hz), 4.53 (d, 1 H, J = 7.5 Hz), 4.30 (m, 1 H, J = 2.0 Hz, J = 4.7 Hz), 4.09 (m, 1 H), 4.00–3.93 (m, 5 H), 3.84–3.77 (m, 3 H), 3.21 (bs, 1 H, OH), 1.18–1.02 (m, 42 H); ^{13}C NMR ($CDCl_3$) δ 154.08, 145.50, 100.28, 99.35, 79.36, 78.46, 77.93, 74.54, 72.96, 71.25, 68.46, 63.48, 61.87, 17.85, 17.83, 11.88, 11.75; HRMS (FAB) calcd for $C_{31}H_{58}O_{10}Si_2Na$ 647.3647, found *m/z* 647.3648 (M+H).

Synthesis of Diacetate 25. Compound **24** was acetylated in anhydrous pyridine using acetic anhydride to give **25** as a colorless glass: $[\alpha]^{23}_D$ = −14.0° (*c* 1.2, CH_2Cl_2); FTIR (thin film) 2942, 2866, 1814, 1752, 1646, 1464, 1370, 1228, 1118, 1100, 1065, 1054, 882, 786, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, 1 H, J = 6.3 Hz), 5.14 (t apparent, 1 H, J = 4.2 Hz), 5.00 (d, 1 H, J = 4.0 Hz), 4.94 (t

apparent, 1 H, J = 8.5 Hz), 4.93 (t apparent, 1 H, J = 3.9 Hz), 4.83 (m, 1 H, J = 4.4 Hz, J = 5.9 Hz), 4.76 (dd, 1 H, J = 3.4 Hz, J = 8.3 Hz), 4.21 (m, 1 H, J = 3.8 Hz), 4.17 (t apparent, 1 H, J = 3.7 Hz), 3.93 (s, 3 H), 3.91 (dd, 1 H, J = 7.5 Hz, J = 11.4 Hz), 3.81 (dd, 1 H, J = 3.0 Hz, J = 11.5 Hz), 2.14 (s, 3 H), 2.07 (s, 3 H), 1.15−1.02 (m, 42 H); ^{13}C NMR ($CDCl_3$) δ 169.49, 168.72, 153.47, 145.83, 96.31, 95.51, 77.83, 72.25, 72.53, 71.01, 69.32, 69.17, 68.23, 61.83, 61.60, 20.95, 20.75, 17.90, 11.94, 11.84; HRMS (FAB) calcd for $C_{35}H_{62}O_{12}Si_2Na$ 753.3666, found m/z 753.3656 (M+Na).

Synthesis of Le^b Glycal 26. To a flask containing 1.10 g (1.70 mmol) of **24**, which had been azeotropically dried using benzene, was added 2.83 g (6.79 mmol) of stannous triflate. This mixture was placed under N_2 and cooled to 0 °C, and a solution of 2.90 g (6.64 mmol) of fucosyl fluoride **16** in 35 mL of dry THF and di-*tert*-butylpyridine (6.0 mL, 26.7 mmol) was added via cannula. The mixture was allowed to warm to room temperature and was stirred for 8 h. The reaction mixture was partitioned between 300 mL of saturated aqueous $NaHCO_3$ and 200 mL of ethyl acetate. The aqueous layer was washed twice with 200 mL of ethyl acetate, and the combined organic layers were dried over $MgSO_4$. The drying agent was filtered off, and the solvents were removed in vacuo to give a thick syrup, which was filtered through a plug of silica gel using EtOAc to remove the tin salts. The crude product was purified by column chromatography on silica gel (1:9 EtOAc:hexanes) to give **26** as a colorless glass (1.76 g, 70%): $[\alpha]^{23}_D$ = −110.0° (c 1.0, CH_2Cl_2); FTIR (thin film) 2939, 2865, 1817, 1646, 1454, 1361, 1244, 1164, 1102, 1051, 883, 735, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.21 (m, 30 H), 6.19 (d, 1 H, J = 6.3 Hz), 5.24 (d, 1 H, J = 3.4 Hz), 5.12 (d, 1 H, J = 3.7 Hz), 5.01−4.91 (m, 3 H), 4.89−4.82 (m, 4 H), 4.79−4.63 (m, 8 H), 4.61 (d, 1 H, J = 7.1 Hz), 4.58 (dd, 1 H, J = 2.4 Hz, J = 6.2 Hz), 4.50−4.42 (m, 2 H), 4.20−4.06 (m, 4 H), 4.03−3.94 (m, 3 H), 3.94−3.86 (m, 3 H), 3.86−3.79 (m, 2 H), 3.74 (m, 1 H), 3.58 (d, 1 H, J = 1 Hz), 1.18 (d, 3 H, J = 6.4 Hz), 1.10 (d, 3 H, J = 6.6 Hz, CH_3), 1.10−1.00 (m, 42 H); ^{13}C NMR ($CDCl_3$) δ 153.49, 145.16, 138.75, 138.68, 138.57, 138.51, 138.40, 138.20, 128.46, 128.34, 128.26, 128.22, 128.18, 128.14, 128.10, 127.97, 127.88, 127.52, 127.42, 127.36, 127.33, 127.27, 127.19, 97.63, 97.41, 97.20, 97.16, 93.93, 80.26, 78.97, 78.90, 78.39, 77.79, 77.62, 76.12, 75.93, 75.10, 74.61, 74.00, 73.93, 73.71, 72.91, 72.34, 71.87, 70.15, 67.21, 66.37, 61.22, 60.87, 17.98, 17.91, 17.86, 17.82, 16.60, 16.33, 11.96, 11.76; HRMS (FAB) calcd for $C_{85}H_{114}O_{18}Si_2Na$ 1501.7430, found m/z 1501.7427 (M+Na).

Synthesis of Iodo Sulfonamide 27. To a flask containing 1.00 g (0.68 mmol) of **26**, which had been azeotropically dried using benzene, and 0.16 g (1.02 mmol) of benzenesulfonamide under N_2 was added 2 mL of dry CH_2Cl_2. The stirred mixture was cooled to 0 °C and a solution of iodonium di-*sym*-collidine perchlorate (freshly prepared from 0.60 g of silver di-*sym*-collidine perchlorate and 0.33 g of iodine) was added. The mixture was stirred at 0 °C for 30 min, and the mixture was diluted with 50 mL of ether and washed twice with saturated aqueous $Na_2S_2O_3$, twice with saturated aqueous $CuSO_4$, and once with brine. The organic layer was dried over $MgSO_4$, and the crude product was purified by column chromatography on silica gel (1:4 EtOAc:hexanes) to give **27** as a colorless glass (0.79 g, 66%): $[\alpha]^{23}_D$ = −85.7° (c 1.0, CH_2Cl_2); FTIR (thin film) 3264, 2942, 2866, 1838, 1820, 1496, 1454, 1346, 1263, 1207, 1162, 1103, 1048, 957, 911, 883, 734, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2 H, J = 8.1 Hz), 7.51 (t, 1 H, J = 7.1 Hz), 7.44−7.21 (m, 32 H), 5.81 (d, 1 H, J = 9.9 Hz), 5.28 (m, 1 H), 5.19 (d, 1 H, J = 2.7 Hz), 5.03 (d, 1 H, J = 11.8 Hz), 4.93 (d, 1 H, J = 11.5 Hz), 4.89 (d, 1 H, J = 11.8 Hz), 4.874.82 (m, 2 H), 4.81 (s, 2 H), 4.79−4.65 (m, 5 H), 4.62 (d, 1 H, J = 12.0 Hz), 4.59 (d, 1 H, J = 7.7 Hz), 4.32−4.17 (m, 3 H), 4.17−4.10 (m, 2 H), 3.98 (dd, 1 H, J = 3.5 Hz, J = 9.9 Hz), 3.91−3.80 (m, 6 H), 3.75−3.69 (m, 2 H), 3.51−3.42 (m, 3 H), 1.21 (d, 3 H, J = 6.3 Hz), 1.09 (d, 3 H, J = 6.6 Hz), 1.10−0.95 (m, 42 H); ^{13}C NMR ($CDCl_3$) δ 153.10, 141.04, 138.94, 138.51, 138.45, 138.33, 132.64, 128.72, 128.44, 128.42, 128.39, 128.29, 128.25, 128.12, 128.00, 127.97, 127.54, 127.50, 127.45, 127.39, 127.35, 127.14, 97.86, 96.19, 79.26, 78.00, 77.86, 75.93, 75.07, 74.90, 74.83, 74.31, 74.05, 73.75, 73.20, 72.60, 72.41, 72.15, 67.61, 66.93, 61.07, 60.64, 17.92, 17.87, 17.84, 17.78, 16.73, 16.32, 12.04, 11.74; HRMS (FAB) calcd for $^{12}C_{90}{}^{13}CH_{120}INO_{20}SSi_2Na$ 1785.6639, found m/z 1785.6634 (M + Na).

Synthesis of Le^b Hexasaccharide Glycal 29. To a flask containing 450 mg (0.26 mmol) of **27** and 4 Å molecular sieves (1.5 g) was added, via cannula, a solution of 1.24 g (2.00 mmol) of **28** in 5 mL of dry THF. The mixture was placed under N_2 and cooled to −78 °C, and a solution of 0.40 g (2.05 mmol) of silver tetrafluoroborate in 1.0 mL of dry THF was added via cannula. The stirred mixture was allowed to slowly warm to room temperature over 2 h. The reaction was allowed to stir an additional 8 hous at room temperature. The mixture was warmed to 45 °C and stirred for an additional 12 h until TLC (1:2 EtOAc:hexanes) indicated no trace of **27**. The reaction mixture was partitioned between 20 mL of saturated aqueous NH_4Cl and 20 mL of EtOAc. The aqueous layer was washed twice with 20 mL of ethyl acetate, and the combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel (1:3 EtOAc:hexanes) to give **29** as a colorless glass (330 mg, 57%): $[\alpha]^{23}_D$ = −33.8° (c 2.0, CH_2Cl_2); FTIR (thin film) 3492, 2941, 2866, 1836, 1820, 1650, 1496, 1462, 1347, 1246, 1155, 1095, 1049, 882, 735, 692; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.17 (d, 2 H, J = 7.3 Hz), 7.50−7.20 (m, 33 H), 6.52 (d, 1 H, J = 10.5 Hz), 6.30 (dd, 1 H, J = 6.0 Hz), 5.35−5.32 (m, 2 H), 5.25 (d, 1 H, J = 7.9 Hz), 5.15 (m, 2 H), 4.99−4.92 (m, 3 H), 4.86−4.52 (m, 14 H), 4.45 (dd, 1 H, J = 7.91 Hz, J = 2.4 Hz), 4.32−4.23 (m, 3 H), 4.22 (dd, 1 H), 4.17 (d, 1 H, J = 10.1 Hz), 4.08−3.84 (m, 18 H), 3.79−3.73 (m, 2 H), 3.66 (m, 1 H), 3.55 (dd, 1 H, J = 6 Hz), 3.50 (dd, 1 H, J = 9.7 Hz), 1.33 (d, 3 H, J = 6.5 Hz), 1.31 (d, 3 H, J = 6.4 Hz), 1.20−0.98 (m, 84 H); ^{13}C NMR (acetone-d_6) δ 145.66, 132.72, 131.48, 131.45, 131.28, 131.16, 130.77, 130.48, 121.31, 120.11, 119.86, 119.78, 119.25, 95.63, 94.70, 91.37, 89.64, 89.31, 86.52, 73.38, 72.24, 71.00, 70.71, 70.37, 69.80, 69.59, 69.06, 68.23, 67.92, 67.38, 67.10, 66.49, 65.67, 65.33, 64.60, 64.34, 64.03, 63.45, 63.30, 59.46, 58.83, 58.37, 54.45, 53.32, 49.86, 19.67, 18.42, 9.55, 9.48, 9.45, 9.31, 9.23, 3.82, 3.70, 3.64; HRMS (FAB) calcd for $^{12}C_{120}{}^{13}CH_{179}NNaO_{29}SSi_4$ 2278.1292, found m/z 2278.1296 (M + Na).

Synthesis of Peracetate of Le^b Hexasaccharide Glycal 32. To a solution of 325 mg (0.144 mmol) of **29** in 2 mL of THF at 0 °C was added 1.0 mL of 1.0 M AcOH in THF and 2.0 mL of 1.0 M TBAF in THF. The mixture was allowed to warm to room temperature and stirred for 36 h. The solvents were evaporated, and the crude product was chromatographed on silica gel (2:1 EtOAc:hexanes) to provide **30** (190 mg, 81%). A solution of 180 mg (0.110 mmol) of **30** in 0.5 mL of THF was added via cannula to a solution of Na (~50 mg) in NH_3 (~30 mL) at −78 °C. The bright blue solution was stirred at reflux for 20 min, and 5 mL of MeOH was added. Ammonia was removed by evaporation and the pH was adjusted to 9 using Dowex 50 × 8 [H^+] resin. The resin was filtered off and washed with MeOH, and the solvent was removed in vacuo to give **31** as a crude product. This material was dissolved in 2 mL of anhydrous pyridine under N_2, and 1 mL of Ac_2O was added. The mixture was stirred at room temperature for 12 h, solvents were removed in vacuo, and the crude product was purified by silica gel chromatography (EtOAc) to give **32** as a colorless glass (110 mg, 63% from **30**): $[\alpha]^{23}_D$ = −41.0° (c 0.8, CH_2Cl_2); FTIR (thin film) 2927, 1748, 1686, 1434, 1372, 1225, 1164, 1132, 1047; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, 1 H, J = 6.1 Hz), 5.59 (dd, 1 H, J = 3.6 Hz, J = 10.8 Hz), 5.40 (t apparent, 1 H, J = 4.3 Hz), 5.37−5.33 (m, 2 H), 5.32 (t apparent, 1 H, J = 2.9 Hz), 5.26 (d, 1 H, J = 3.2 Hz), 5.20 (d, 1 H, J = 4.3 Hz), 5.18 (dd, 1 H, J = 3.1 Hz, J = 11.3 Hz), 5.10−5.03 (m, 2 H), 5.03−4.97 (m, 3 H), 4.83 (dd, 1 H, J = 3.4 Hz, J = 6.1 Hz), 4.77 (d, 1 H, J = 8.0 Hz), 4.73 (d, 1 H, J = 3.3 Hz), 4.61 (d, 1 H, J = 7.9 Hz), 4.57−4.44 (m, 3 H), 4.41 (dd, 1 H, J = 2.5 Hz, J = 11.7 Hz), 4.29−4.09 (m, 7 H), 4.02−3.96 (m, 2 H), 3.87 (t apparent, 1 H, J = 7.0 Hz), 3.84−3.63 (m, 7 H), 2.31 (s, 3 H), 2.19−2.03 (m, 33 H), 2.03−1.95 (m, 12 H), 1.26 (d, 3 H, J = 6.4 Hz), 1.18 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 172.31, 170.74, 170.62, 170.45, 170.35, 170.18, 170.00, 169.95, 169.83, 145.44, 101.21, 101.04, 100.79, 99.91, 96.99, 96.75, 74.59, 74.12, 73.48, 73.36, 73.12, 71.99, 71.58, 71.13, 70.75, 70.16, 69.92, 68.99, 68.61, 67.89, 67.25, 66.68, 64.83, 61.77, 60.51, 60.39, 60.28, 53.01, 22.67, 21.13, 21.07, 20.80, 20.71, 20.60, 20.54, 15.77, 15.32; HRMS (FAB) calcd for $C_{68}H_{93}NNaO_{42}$ 1618.5100, found m/z 1618.5104 (M + Na).

Synthesis of Allyl Glycoside of Le^b Hexasaccharide 33. A 54 mg (34 μmol) sample of compound **32** was azeotropically dried with benzene and dissolved in 1 mL of dry CH_2Cl_2 under N_2. The solution was cooled to −10 °C, and 3,3-dimethyldioxirane solution (1.0 mL, ~0.1 mmol) was added. The mixture was stirred at −10 °C for 30 min at which time TLC (EtOAc) showed no trace of **32**. Solvents

were evaporated using a dry N_2 stream, and the residue was dried in vacuo. This material was dissolved in 1 mL of dry allyl alcohol (distilled from Mg) under N_2 and stirred at room temperature for 12 h. Allyl alcohol was removed by evaporation with a dry N_2 stream, the residue was placed under N_2 and dissolved in 1 mL of anhydrous MeOH, and 10 mg of NaOMe was added. The mixture was stirred at room temperature for 12 h, at which time TLC (RP-18, H_2O) showed that two products were obtained. Solvents were evaporated, and the products were separated by column chromatography on C-18 reverse-phase silica gel (H_2O). Compound **34** (see supplementary material) [10 mg; $R_f = 0.44$; $[\alpha]^{23}_D = +11.2°$ (*c* 0.50, MeOH)] was separated from **33** (16 mg): $[\alpha]^{23}_D = -8.7°$ (*c* 0.78, MeOH); FTIR (thin film) 3377, 2924, 1653, 1383, 1032; ^{1}H NMR (400 MHz, CD_3OD) δ 6.00 (m, 1 H, $J = 5.6$ Hz), 5.37 (dd, 1 H, $J = 1.6$ Hz, $J = 7.3$ Hz), 5.20 (dd, 1 H, $J = 1.6$ Hz, $J = 9.5$ Hz), 5.18 (d, 1 H, $J = 3.9$ Hz), 5.10 (d, 1 H, $J = 3.8$ Hz), 4.64 (d, 1 H, $J = 6.9$ Hz), 4.45 (d, 1 H, $J = 7.4$ Hz), 4.43−4.33 (m, 2 H), 4.27 (dd, 1 H, $J = 9.3$ Hz, $J = 10.6$ Hz), 4.23−4.11 (m, 2 H), 4.02−3.29 (m, 31 H), 2.06 (s, 3 H), 1.31 (d, 3 H, $J = 6.6$ Hz), 1.29 (d, 3 H, $J = 6.6$ Hz); ^{13}C NMR (CD_3OD) δ 173.20, 135.73, 117.51, 105.13, 103.30, 102.49, 101.62, 99.63, 96.86, 80.79, 80.67, 78.44, 76.67, 76.49, 75.89, 74.80, 74.59, 73.94, 73.61, 73.40, 71.55, 71.38, 71.16, 70.96, 70.42, 70.26, 70.14, 67.77, 67.30, 67.21, 62.79, 62.34, 61.99, 55.54, 22.97, 16.65; HRMS (FAB) calcd for $C_{41}H_{69}NNaO_{29}$ 1062.3853, found *m/z* 1062.3837 (M + Na).

Synthesis of Le^b-HSA Neoglycoprotein 35. A solution of 16 mg (15 μmol) of allyl glycoside **33** in 3 mL of MeOH at −78 °C was bubbled with O_3 until the solution became pale blue. The solution was stirred at −78 °C for 3 min and then bubbled with N_2 until the solution was colorless. Methyl sulfide (0.5 mL) was added, and the mixture was stirred at −78 °C for 2 h. Solvents were removed in vacuo, and the residue was dissolved in 1 mL of 0.2 M sodium phosphate buffer (pH 8.5) and added to an eppendorf containing HSA (8 mg, 0.12 μmol). To the resulting solution was added 8 mg (0.13 mmol) of $NaCNBH_3$, and the mixture was incubated at 37 °C for 72 h. Dialysis (15 000 MWCO), followed by lyophilization, provided **35** as a colorless powder. TFA analysis of **35** indicated the Le^b hexasaccharide:protein ratio to be ~25:1. The carbohydrate was determined to be composed of 2 parts fucose, 1 part glucosamine, 2 parts galactose, and 1 part glucose.

Synthesis of Neoglycoprotein 36. Allyl glycoside **34** (10 mg) was ozonized as described for the synthesis of **35**, and the resulting aldehyde was reacted with HSA (5 mg) in the presence of $NaCNBH_3$ (5 mg) to give **36**. TFA analysis of **36** indicated a hexasaccharide:protein ratio of ~25:1, with a carbohydrate composition of 2 parts fucose, 1 part glucosamine, 2 parts galactose, and 1 part mannose.

Synthesis of Disaccharide Glycal 39. To 514 mg (1.80 mmol) of galactal carbonate **37** was added 1.8 mL of methylene chloride. The solution was cooled to 0 °C, and then 30 mL of 3,3-dimethyldioxirane solution (0.07 M, 2.16 mmol in acetone) was added. The reaction was stirred for 30 min and then evaporated in vacuo. A solution of 515 mg (1.98 mmol) of glucal **38** in 4.0 mL of THF was then added to the crude epoxide. The reaction mixture was cooled to −78 °C, and 2.16 mL of $ZnCl_2$ (1.0 M in Et_2O, 2.16 mmol) solution was added. The reaction was allowed to warm to room temperature overnight. The reaction was diluted with EtOAc and then washed twice with saturated sodium bicarbonate and once with saturated brine. The organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel chromatography (30−35% EtOAc/hexane) afforded 690 mg (68%) of **39** as a white solid: $[\alpha]^{23}_D = -6.2°$ (*c*. 785, $CHCl_3$); IR (thin film) 3445, 2945, 2920, 2875, 2850, 1795, 1645, 1455, 1380, 1305, 1250, 1100, 835, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (dd, 1H, $J = 1.6$, 6.0 Hz), 4.77 (d, 1H, $J = 7.2$ Hz), 4.72 (t apparent, 1H, $J = 6.7$ Hz), 4.67 (dd, 1H, $J = 2.1$, 6.0 Hz), 4.50 (d, 1H, $J = 7.7$ Hz), 4.27 (bd, 1H, $J = 6.5$ Hz), 4.05 (d, 1H, $J = 1.9$ Hz), 4.02 (dd, 1H, $J = 2.7$, 11.3 Hz), 3.95−3.78 (m, 7H), 2.95 (d, 1H, $J = 3.0$ Hz), 0.99 (s, 9H), 0.92 (s, 9H), 0.12 (s, 6H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.13, 145.28, 100.45, 99.39, 80.53, 78.50, 78.10, 74.50, 72.44, 71.14, 67.54, 62.52, 61.65, 25.81, 25.76, 18.29, 18.17; HRMS (FAB) calcd for $C_{25}H_{47}O_{10}Si_2$ 563.2708, found *m/z* 563.2731 (M + H).

Synthesis of H-Type I Glycal 40. A mixture of 53 mg (93 μmol) of disaccharide **39** and 50 mg (112 μmol) of fluoro sugar **3** was azeotroped three times with 5 mL of benzene and placed under high vacuum overnight. A 77 mg amount of freshly activated 4 Å powdered molecular sieves were added to this and taken up in 0.5 mL of ether. A 105 μL (466 μmol) volume of 2,6-di-*tert*-butylpyridine was added and the mixture stirred for 1 h at room temperature. A 97 mg (466 μmol) amount of silver perchlorate and 88 mg (466 μmol) of stannous chloride were added in an argon glove box. The reaction was equipped with a reflux condenser and refluxed 48 h under argon. The reaction was quenched by addition of saturated sodium bicarbonate solution. The mixture was diluted with EtOAc and passed through a plug of celite into a separatory funnel. The organics were washed twice with saturated sodium bicarbonate and once with saturated brine. The organics were dried over $MgSO_4$, filtered, and concentrated. The residue was taken up in 2 mL of pyridine and 2 mL of acetic anhydride and stirred for 3 h. The reaction was concentrated and purifed by silica gel chromatography (20−30% EtOAc/hexanes) to afford 11 mg (11%) **41** (see supplementary material) and 58 mg (60%) **40** as a clear glass: $[\alpha]^{23}_D = -82.6°$ (*c* 1.26, $CHCl_3$); IR (thin film) 2945, 2920, 2875, 2850, 1810, 1771, 1733, 1717, 1652, 1576, 1558, 1497, 1436, 1362, 1270, 1099, 1051, 838, 780; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 2H, $J = 7.0$ Hz), 7.56 (t apparent, 1H, $J = 7.4$ Hz), 7.43 (t apparent, 2H, $J = 7.7$ Hz), 7.32−7.21 (m, 10H), 6.37 (d, 1H, $J = 6.6$ Hz), 5.58 (d, 1H, $J = 1.8$ Hz), 5.21 (app t, 1H, $J = 4.7$ Hz), 5.13 (d, 1H, $J = 3.2$ Hz), 4.80 (dd, 1H, $J = 3.0$, 11.5 Hz), 4.75 (bs, 1H), 4.70 (d, 1H, $J = 6.2$ Hz), 4.66−4.62 (m, 2H), 4.56 (d, 1H, $J = 11.6$ Hz), 4.31 (q, 1H, $J = 6.6$ Hz), 4.09−4.07 (m, 2H), 3.94−3.91 (m, 2H), 3.84−3.74 (m, 6H), 2.04 (s, 3H), 1.12 (d, 3H, $J = 6.5$ Hz), 0.87 (s, 9H), 0.85 (s, 9H), 0.07 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 174.79, 171.48, 158.95, 150.70, 143.36, 143.33, 138.43, 135.17, 133.78, 133.71, 133.55, 133.35, 133.24, 133.09, 132.82, 103.92, 102.93, 102.59, 83.10, 82.74, 82.61, 82.30, 81.98, 81.29, 80.26, 80.22, 79.27, 79.21, 77.32, 77.00, 76.71, 76.47, 73.63, 70.98, 66.68, 66.45, 34.97, 31.13, 31.07, 26.28, 23.57, 23.48, 21.41, −0.02, −0.04, −0.20, −0.26; HRMS (FAB) calcd for $C_{54}H_{74}O_{16}Si_2Na$ 1057.4410, found *m/z* 1057.4426 (M + Na).

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Supplementary Material Available: ^{1}H spectra for compounds **2**, **4**, **5**, **7−9**, **15**, **17−19**, **22**, **24**, **26**, **27**, **29**, **32−34**, and **39−41** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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