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Synthesis of Selected Le^Y and KH-1 Analogues: A Medicinal Chemistry Approach to Vaccine Optimization

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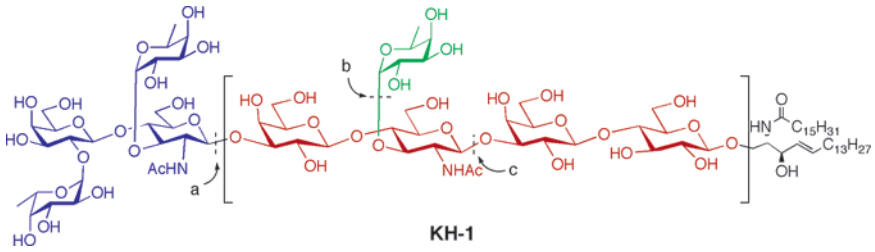

KH-1

As part of our ongoing anticancer vaccine program, we recently found that antibodies generated in response to the KH-1−KLH construct recognized not only KH-1 antigen but also the Lewis Y (Le^y) antigen as well, with antibody titer levels much higher than those observed after immunization with individual Le^y−KLH vaccine constructs. In an attempt to explore the structure-antigenic relationship of these carbohydrate epitopes, several analogues of both KH-1 and Le^y were synthesized. A convergent synthetic approach to the analogues was designed on the basis of well-established glycal methodology, employing a minimum number of building blocks to generate competent antigens with high stereoselectivity and reasonable yield.

Introduction

Lewis Y (Le^y) and KH-1 are carbohydrate tumor-associated antigens that are often overexpressed on the surfaces of breast and prostate cancer cells as membrane glycolipids.[1] Like many other carbohydrate epitopes, these antigens are of potential interest in the search for an effective anticancer vaccine. Although research in the field of tumor immunology was initiated about 100 years ago through the pioneering work of Coley[2] and Ehrlich,[3] active and passive cancer immunotherapies still await full development. The challenge is that the cancer host immune system, unlike the case in other invasive diseases, is unable to develop effective endogenous immunity. Tumor cells are seemingly able to evade immune surveillance. Recent advances in the cellular and molecular immunology of the complex interactions between the immune system and tumor cells lead to a better understanding of these phenomena. Several mechanisms have been advanced to explain these differences, including the development of tumor variants lacking certain tumor antigens,[4] loss of MHC expression,[5] downregulation of the

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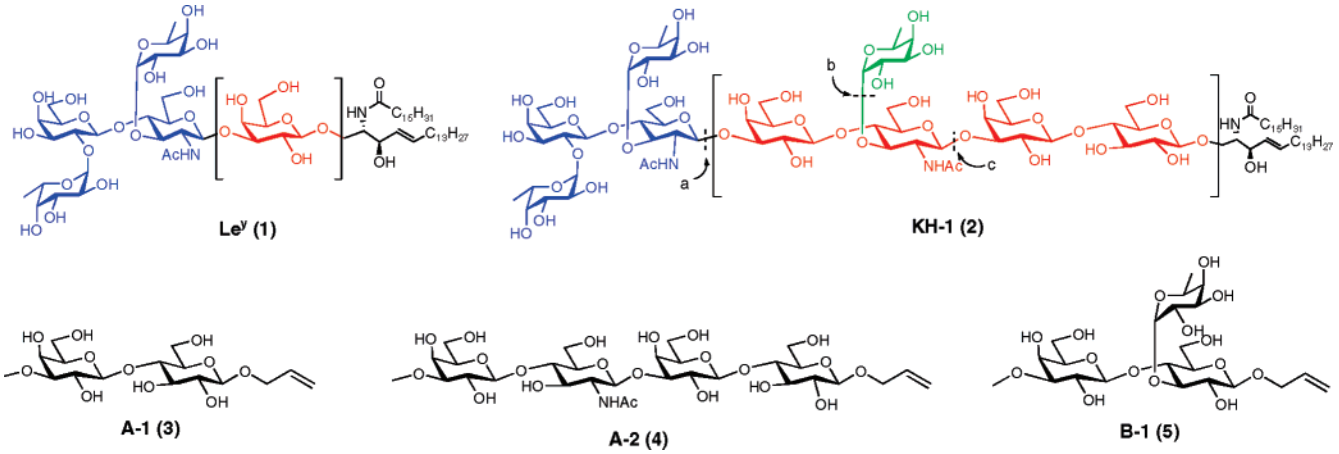

FIGURE 1. Structures of Le^y, KH-1, and proposed analogues.

antigen-processing mechanism,[6] and expression of inhibitory molecules, such as TGF-β, which may promote escape from immune surveillance.[7] However, despite increasing amounts of information developed from recent studies, the problem is still far from being fully understood. For instance, the observation, in rare cases, of spontaneous regression of human tumors remains unexplained. A particularly problematic observation is that in many cancer types there are no chemically defined "tumor-specific" structures[8] that cleanly differentiate tumor immunity from immunity in other diseases, especially in the case of carbohydrate antigens. Extensive studies with monoclonal antibodies have detected many carbohydrate tumor-associated antigens.[8] However, most of them are self-antigens, i.e., antigens present in normal cells or tissue, but overexpressed at the tumor cell surface. In some instances, the antigens, although present on the tumor cell surface and absent in progenitor cells, are expressed in other normal tissues (e.g., di- or trimeric Le^x, and sialyl Le^a in gastrointestinal cancer). Due to altered glycosylation patterns during the oncogenic transformation, the antigens are accumulated as precursors with incomplete or truncated structures, neoglycolipids (di- or trimeric Le^x, trifucosyl Le^y, sialyl Le^a), or branched structures.[9]

Le^y pentasaccharide (**1**) and KH-1 (**2**) are membrane glycolipids that are expressed as ceramides. Both antigens contain (Fuc1−2)Gal1−4(Fuc1−3)GlcNAc, a core motif known as Le^y tetrasaccharide (Figure 1, in blue). In Le^y pentasaccharide (**1**), the core structure is extended with a Gal unit through a 1−3 glycosidic bond. In KH-1 (**2**), the tetrasaccharide core structure is attached to 3Gal1−4(Fuc1−3)GlcNAc1−3Gal1−4Glc, known as Le^x pentasaccharide. Le^y, KH-1, and other carbohydrate tumor associated antigens, such as Globo H, GM2 and MUC1, have been extensively studied as potential candidates for anticancer vaccines. Most of the carbohydrate-based antigens are, as a practical matter, not available by isolation. Their presence is inferred from degradative studies. Total syntheses of these epitopes had to be developed to overcome this problem.[10−14]

Recent preclinical[15] and clinical trials[16] with mixtures of individual KLH-conjugates and multivalent KLH-conjugate vaccines with the same antigens revealed the strong immunogenic properties of KH-1. Antibodies generated in response to immunization with KH-1−KLH constructs recognized not only KH-1 antigen but Le^y as well, and their antibody titers were found to be much higher than those of Le^y antibodies generated after immunization with individual Le^y−KLH vaccine constructs. The superiority of KH-1 relative to Le^y as an antigen is not surprising. Thus, compounds that are endogenously expressed at high levels, such as Le^y, are typically less effective as antigens than are those which are naturally present in only low levels, such as KH-1. Having established the potency of KH-1 as an antigen to induce Le^y antibodies, we hoped to design and execute the syntheses of a series of truncated analogues, each containing the crucial Le^y tetrasaccharide fragment in the context of a more elaborate construct, which is not normally encountered. In designing routes to fully syn-

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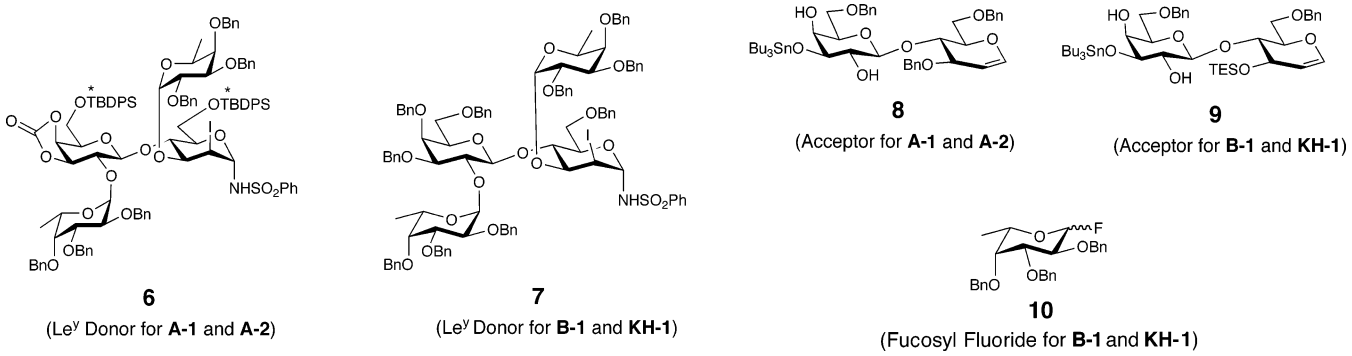
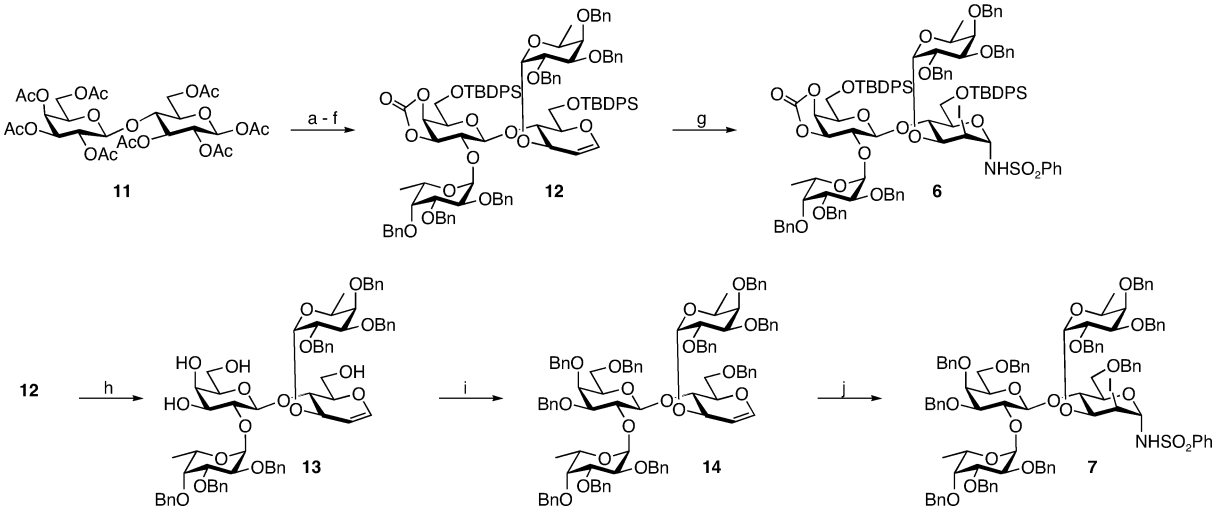


FIGURE 2. Proposed building blocks.

SCHEME 1. Synthesis of Le^y Core Donors 6 and 7[a]



[a] Key: (a) 30% HBr/HOAc; (b) Zn/HOAc, two steps, 78%; (c) 4 M NH_3/MeOH, 98%; (d) TBDPSCl, imidazole, −10 °C, DMF, 84%; (e) CDI, imidazole, THF, 58%; (f) **10**, $Sn(OTf)_2$, 4 Å mol. sieves, 2,6-di-*tert*-butyl-4-methylpyridine, toluene, THF 60%; (g) $PHSO_2NH_2$, $I(sym\text{-}coll)_2ClO_4$, 4 Å mol. sieves, CH_2Cl_2, 83%; (h) 1 M TBAF/THF, 89%; (i) BnBr, NaH, TBAI, DMF, 88%; (j) $PHSO_2NH_2$, $I(sym\text{-}coll)_2ClO_4$, 4 Å mol. sieves, CH_2Cl_2, 87%.

thetic carbohydrate-based antigens, we are in a unique position of being able to apply hard won capabilities in oligosaccharide assembly, to bring to bear the mindset of medicinal chemistry in optimizing antigen design.

Results and Discussion

As a part of this program, we developed an approach (vide infra) to the synthesis of Le^y and KH-1 analogues, which might clarify the structure−antigenic relationship of key carbohydrate epitopes. The concise preparation of complex oligosaccharides in the laboratory still remains a significant challenge for synthetic organic chemists. The demands of regio- and stereoselectivity in glycosylation reactions often lead to lengthy synthetic schemes and extensive protecting group manipulations. Here we have tried to take advantage of the existing synthetic methods for the preparation of Le^y pentasaccharide (**1**) and KH-1 nonasaccharide (**2**), and to design a convergent synthetic approach to analogues based on well-established glycal methodology,[10] using a minimum number of building blocks with high stereoselectivity and reasonable glycosylation reaction yields. The main consideration in the selection of analogues (Figure 1) was that of including compounds with more rigid conformations, of the type likely to enhance immunogenicity.[8]

Since KH-1 contains within it the Le^y tetrasaccharide motif (Figure 1, shown in blue), this substructure was considered "conserved". As the "variable" part of the molecules (shown in red) we chose different oligosaccharide linkers, attached to the core tetrasaccharide structure through a β-1,3-glycosidic bond: lactose (A-1, **3**); a tetrasaccharide consisting of acetyl lactosamine attached to lactose (A-2, **4**); and α-fucosylated lactose (B-1, **5**). In addition, we planned to synthesize KH-1 (**2**). The presence of both fucose and acetylaminosugars in oligosaccharides are known to impart structural rigidity to the molecular framework.[8]

Our synthetic strategy was to prepare a number of common synthetic "building blocks" that could be combined, as needed, to fashion the core target structures. Following examination of the most complex target structure, KH-1 (**2**), three disconnection points present themselves. First, the conserved Le^y tetrasaccharide could serve as a donor in an azaglycosylation reaction (disconnection *a*). Second, the α-fucosyl fragment (shown in green), required for the KH-1 and B-1 syntheses, could be introduced through formation of an α-(1−3) glycosidic bond at a differentiated hydroxyl group (disconnection *b*). Finally, the tetrasaccharide, required for the KH-1 and A-2 syntheses, could be assembled by a second

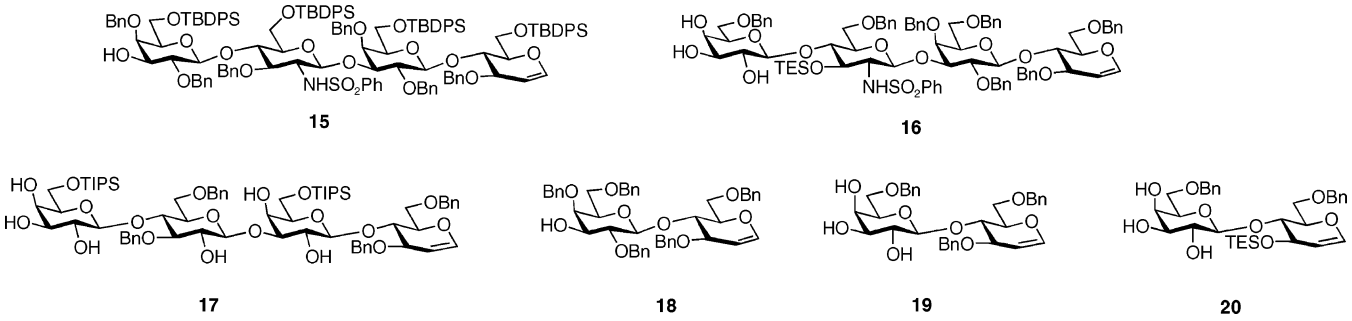
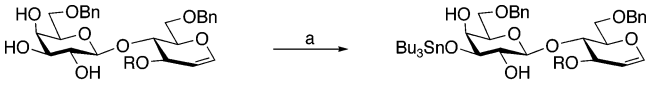


FIGURE 3. Screening of acceptors.

SCHEME 2. Preparation of the Acceptor Fragments[a]



[a] Key: (a) $(Bu_3Sn)_2O$, C_6H_6.

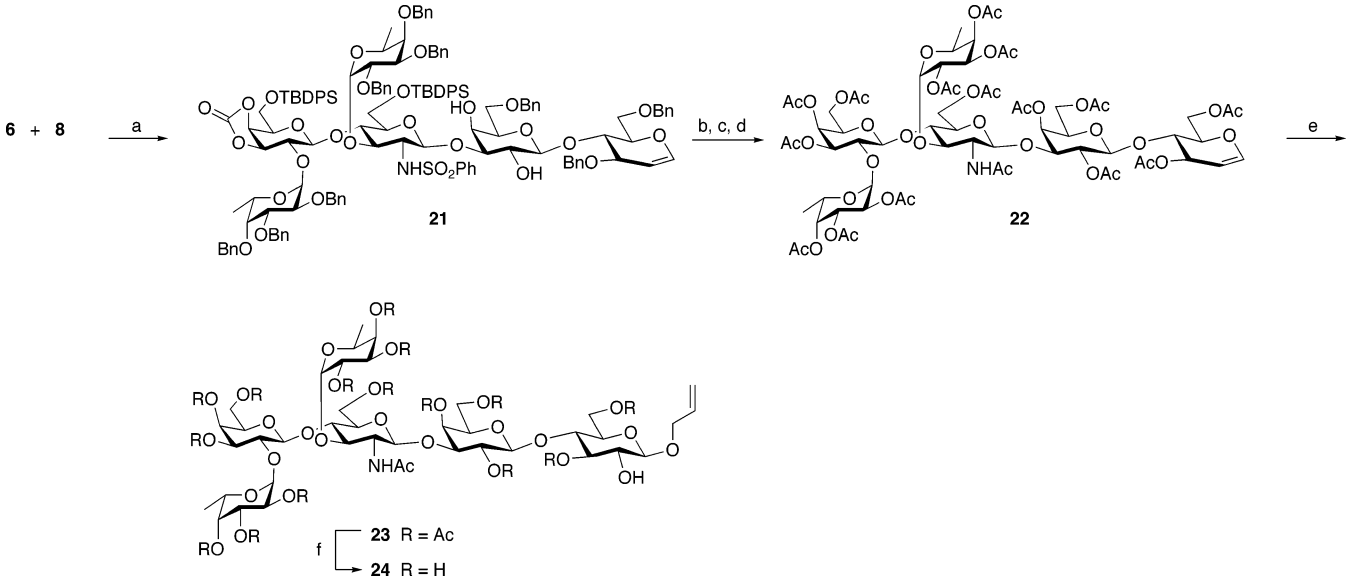
azaglycosylation reaction with a disaccharide acceptor (disconnection *c*). In this manner, the synthesis of each analogue might be achieved in a convergent fashion through the assembly of several readily synthesizable, suitably protected building blocks.

One factor influencing the selection of protecting groups was the need to install the α-fucosyl fragment in the course of the KH-1 and B-1 syntheses. The disaccharide component used in these cases would have to incorporate a differentially protected alcohol that would be unmasked prior to fucosylation. We planned to employ the commonly used TES protecting group (cf. **9**) to achieve this end. In addition, since fucosylation would occur at a late stage, the Le^y core donor must be appropriately protected so as to be stable to TES deprotection conditions. In this case, Le^y donor **7** might be preferable to the known donor **6**. With these considerations in mind, we identified five common building blocks which, when suitably combined, should allow for efficient access to our four target molecules (Figure 2).

The synthesis of **6** from **11** has previously been described (Scheme 1).[10,12] Perbenzylated core donor **7** was prepared from intermediate **12** in three steps through simultaneous silyl and carbonate deprotection, followed by benzylation of the resulting tetraol and, finally, iodosulfonamidation.

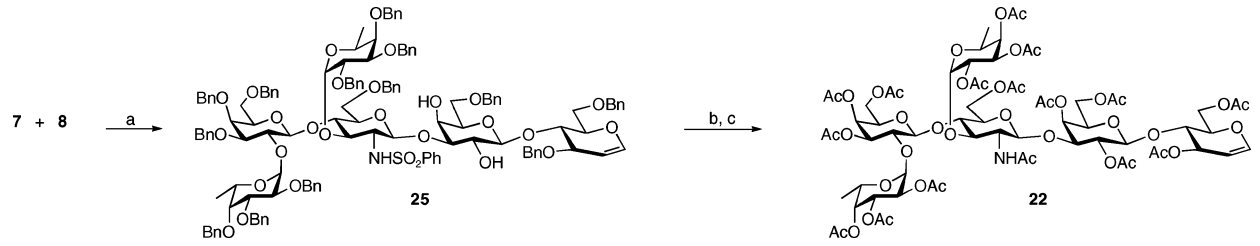
With the goal of achieving maximum convergency in the synthesis of the tetrasaccharide-containing analogues (A-2 and KH-1), we explored the possibility of coupling the Le^y core donors, **6** and **7**, with tetrasaccharide acceptors. Unfortunately, when subjected to azaglycosylation conditions, a sampling of preassembled tetrasaccharides containing a variety of permutations of resident protecting groups (Figure 3, **15** to **17**) failed to efficiently couple with either **6** or **7** (yields ~10%). The coupling of disaccharide **18** was similarly low-yielding. However, the coupling of disaccharides **19** and **20** with the Le^y core donors did proceed in somewhat better yields (28% to 46%) and with high stereoselectivity. Hence, the idea of coupling preassembled tetrasaccharide moieties with **6** and **7** in the construction of A-2 and KH-1 was abandoned

SCHEME 3. Synthesis of A-1[a]



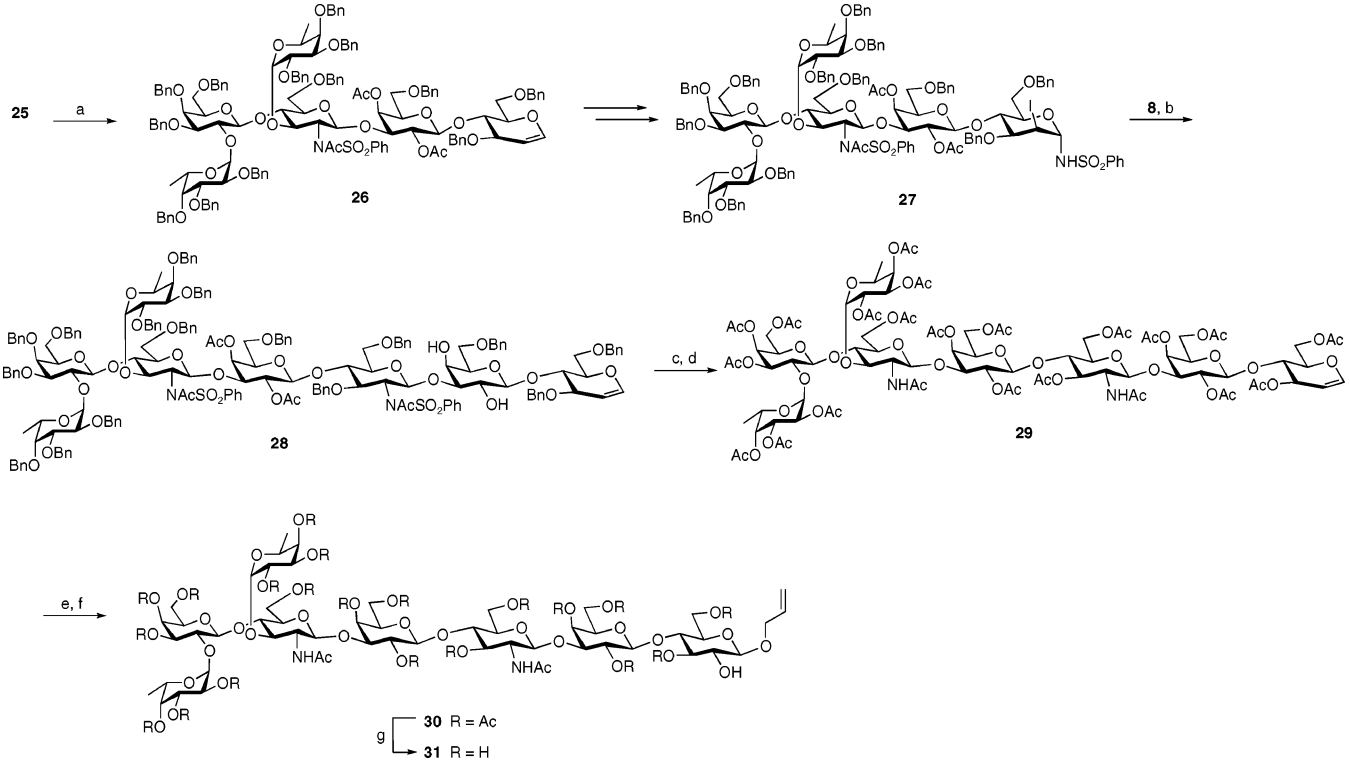
[a] Key: (a) $AgBF_4$, THF, 4 Å mol. sieves, 28%; (b) 1 M TBAF/THF; (c) Na/NH_3, THF; (d) Ac_2O, TEA, DMAP, THF/DMF, 44% for three steps; (e) DMDO, CH_2Cl_2, then allyl alcohol, 88% for two steps; (f) MeONa/MeOH, 90%.

SCHEME 4. Alternate Synthesis of 22 (en Route to A-1)[a]



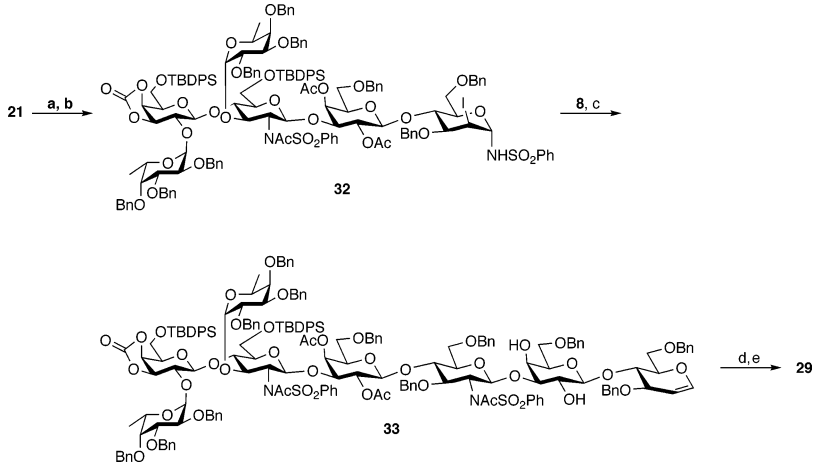
[a] Key: (a) $AgBF_4$, THF, 4 Å mol. sieves, 42%; (b) Na/NH_3, THF; (c) Ac_2O, TEA, DMAP, THF/DMF, 81% for two steps.

SCHEME 5. Synthesis of A-2[a]



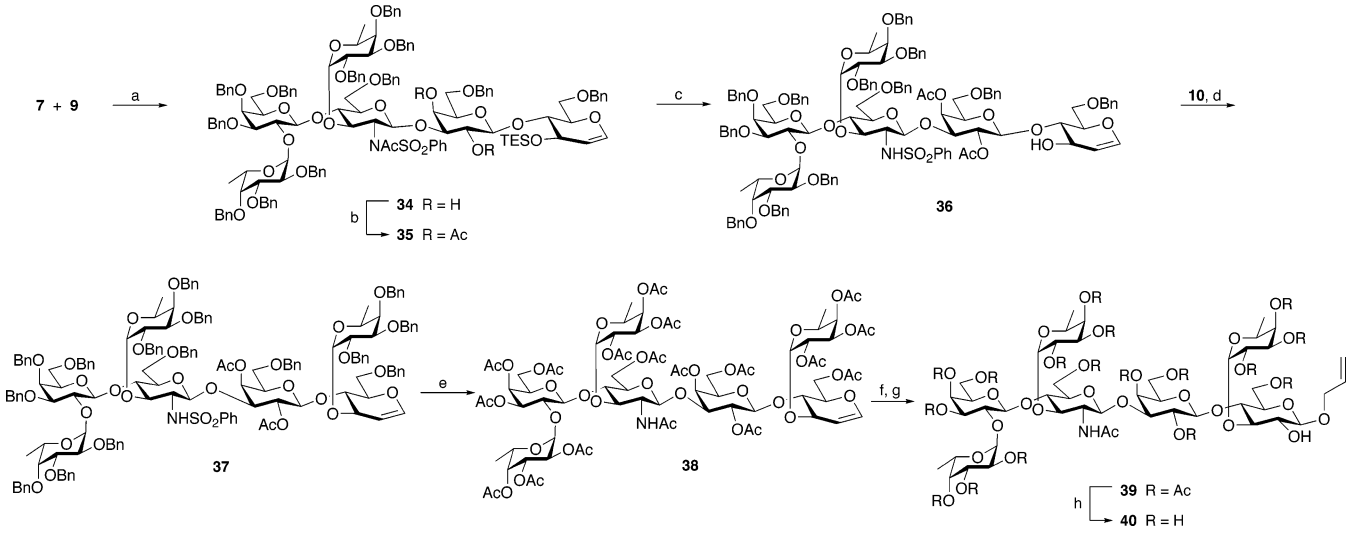
[a] Key: (a) Ac_2O, TEA, DMAP, CH_2Cl_2, 77%; (b) $AgBF_4$, THF, 4 Å mol. sieves, 65%; (c) Na/NH_3; (d) Ac_2O, TEA, DMAP, THF/DMF, 80%; (e) DMDO, CH_2Cl_2; (f) allyl alcohol, 90% for two steps; (g) MeONa/MeOH, 89%.

SCHEME 6. Alternate Synthesis of 29 (en Route to A-2)[a]



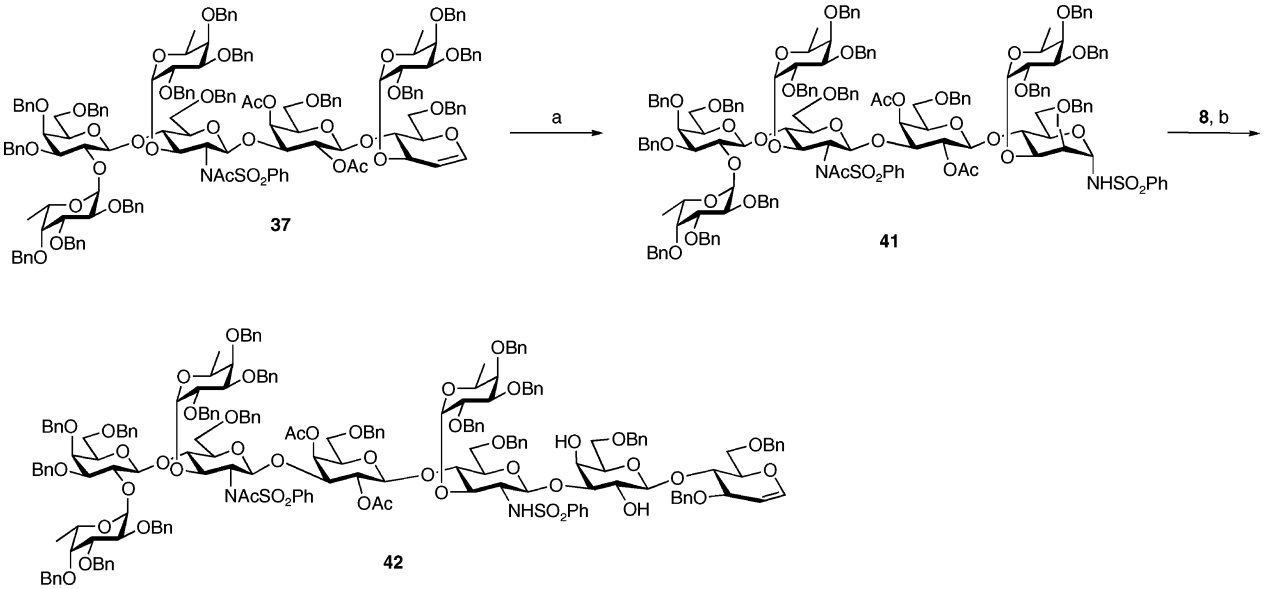
[a] Key: (a) Ac_2O, TEA, DMAP, CH_2Cl_2; (b) $C_6H_5SO_2NH_2$, $I(sym\text{-}coll)_2ClO_4$, CH_2Cl_2, 56% for two steps; (c) $AgBF_4$, THF, 4 Å mol. sieves, 52%; (d) 1 M TBAF/THF; (e) Na/NH_3, then Ac_2O, TEA, DMAP, THF/DMF, 60% for two steps.

SCHEME 7. Synthesis of B-1[a]



[a] Key: (a) $AgBF_4$, THF, 4 Å mol. sieves, 46%; (b) Ac_2O, TEA, DMAP, CH_2Cl_2, 80%; (c) 1 M TBAF/THF: CH_3COOH (1:1), 97%; (d) di-*tert*-butyl pyridine, $Sn(OTf)_2$, THF, 48%; (e) Na/NH_3, then Ac_2O, TEA, DMAP, THF/DMF, 67%; (f) DMDO, CH_2Cl_2; (g) allyl alcohol, 92% for two steps; (h) MeONa/MeOH, 90%.

SCHEME 8. KH-1 Synthesis[a]



[a] Key: (a) $C_6H_5SO_2NH_2$, $I(sym\text{-}coll)_2ClO_4$, CH_2Cl_2, (b) $AgBF_4$, THF, 4 Å mol. sieves, 32% for two steps.

in favor of stepwise addition of disaccharide lactal acceptors to the core structures.

The disaccharide acceptor fragments (**8** and **9**) were prepared through the conversion of the known disaccharides **19** and **20** to their corresponding tributylstannyl ethers (Scheme 2).

With the donor and acceptor fragments in hand, we set out to assemble our target molecules. We well recognized that the azaglycosylation steps would be critical to the syntheses, and an optimized protocol was used in all cases. The coupling of the stannylated acceptors and the donors was carried out in an acceptor-to-donor ratio of 3 to 3.5:1 in the presence of silver tetrafluoroborate at −70 °C. Following slow warming to room temperature, the reaction was allowed to proceed for 3 days at rt. As discussed below, we found the yield of the coupling step to be highly dependent on the nature of the protecting groups on the Le^y core donor fragment.

In the event, the synthesis of A-1 commenced with the coupling of donor **6** and acceptor **8**. This reaction proceeded in only 28% yield to afford **21**, which was subsequently converted to hexasaccharide **24** through a series of straightforward manipulations (Scheme 3). By contrast, the coupling of the same acceptor with the perbenzylated donor (**7**) gave rise to hexasaccharide **25** in 42% yield (Scheme 4). The latter was readily converted to the acetylated hexasaccharide **22**.

Interestingly, the impact of the nature of the seemingly remote Le^y tetrasaccharide protecting group pattern was also pertinent to the success of the coupling reactions, as evidenced in the elaboration of the A-1 framework to produce A-2. Thus, hexasaccharide **25**, which incorpo-

rated the perbenzylated Le^y core, was converted to **27**. The latter was subjected to azaglycosylation with acceptor **8** to afford **28** in 65% yield. The latter was readily converted to **31** (Scheme 5). By comparison, the analogous coupling of intermediate **32** with the same acceptor gave rise to **33**, albeit in only 52% yield (Scheme 6). The latter was transformed to the acetylated intermediate, **29**. Although far from the glycosylation donor site, it is evident that the presence of the deactivating silyl and carbonate groups of the Le^y tetrasaccharide decreases the efficiency of the glycosylation reaction.

It is also of note that the yields of the second set of glycosylations (65% for **27** → **28** and 52% for **32** → **33**) were markedly improved over the first (42% for **7** → **25** and 28% for **6** → **21**). This difference can perhaps be attributed to steric effects, with the reaction efficiency increasing when the anomeric center is further removed from the hindered tetrasaccharide core structure.

The synthesis of the B-1 analogue commenced with the coupling of **7** and **9** to afford **34**. The latter was advanced to provide **36** in two steps (Scheme 7). The latter was treated with β-tribenzylfucosyl fluoride (**10**) in the presence of di-*tert*-butyl pyridine to generate **37** through the formation of an α-(1−3) glycosidic bond at the free hydroxyl group. This reaction proceeded in 50% yield and with apparently complete α-selectivity. The remaining steps to **40** were accomplished through a series of well-established protocols.

The synthesis of KH-1 was completed by converting intermediate **37** from the B-1 synthetic route to the corresponding β-2-iodo-α-1-sulfonamide **41**. The latter was coupled with acceptor **8** to afford nonasaccharide **42** in 32% overall yield from **37** (Scheme 8).

Conclusion

In summary, KH-1 and three analogues have been prepared with high stereoselectivity and in reasonable yields using five common building blocks. Conjugation of these analogues to carrier protein by previously applied sequences has been accomplished and immunological tests are currently being completed. Clearly, the advent of the general notion of glycal assembly,[10] and the development of a menu of reactions directed to glycal linkages, enables the assembly of large oligosaccharide arrays on a scale and in a time frame that would not have been anticipated earlier. Possibilities for developing fully synthetic vaccines for the selective targeting of certain tumors are now being pursued.

Experimental Procedures

General Methods. NMR (^{1}H, ^{13}C) spectra were recorded on an AMX-400 MHz or a DRX-500 MHz spectrometer. Chemical shifts are reported in ppm, referenced to TMS (^{1}H NMR and ^{13}C NMR 0.00), $CDCl_3$ (^{13}C NMR, 77.0), unless otherwise stated. Coupling constants (*J*) (H, H) are given in Hz. Signal splitting patterns are designated as singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet and overlapping signals (m), and broad signals (br). IR spectra were recorded on an FTIR spectrometer and absorption bands presented in cm^{-1}. Optical rotations were measured with a digital polarimeter using a 10 and 5 cm path length cell at rt (23 °C). Low-resolution mass spectral analyses were performed using electrospray ionization with a single quad analyzer. High-resolution mass spectra were acquired using electrospray ionization with a time-of-flight analyzer.

Most of the reactions with air- or moisture-sensitive reagents and reaction products were performed under argon or nitrogen atmosphere. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), and toluene were obtained from a dry solvent system (activated alumina columns, positive pressure of argon). All other dry solvents were purchased in Sure/Seal bottles (Aldrich). Triethylamine was distilled from CaH_2 prior to use. All chemicals were high-quality reagents and used without further purification.

Synthesis of Le^{Y}Tetrasaccharide Glycal 14. Le^Y tetrasaccharide glycal **12** (4 g, 2.44 mmol) was dissolved in THF (20 mL). TBAF/THF (1 M, 30 mL) was added, and the reaction mixture was stirred at room temperature for 24 h to complete disappearance of the starting material. The reaction mixture was concentrated and the residue chromatographed (EtOAc/Hexanes 2:1) to give 2.45 g (89%) of the corresponding tetraole **13** as a white solid. Deprotected glycal tetraol and a few crystals of TBAI were taken up in DMF (25 mL) and cooled to 0 °C. NaH (1.2 g 60% dispersion in mineral oil, 30.05 mmol, 14 equiv) was added in portions, followed by BnBr (3.57 mL, 30.05 mmol, 14 equiv). The reaction mixture was allowed to reach room temperature and stirred to disappearance of the starting tetraole. The reaction mixture was poured into ice−water (250 mL) and extracted with EtOAc (3 × 250 mL). The combined organics were washed with water (2 × 300 mL) and brine (1 × 200 mL), dried over $MgSO_4$, and concentrated. The residue was chromatographed (FC, 30% EtOAc/hexanes) to give 2.82 g (88%) of **14** as a white solid: $[\alpha]^{23}_D = -61.6$ (*c* 1, $CHCl_3$); IR (thin film) 3425, 3060, 3025, 2919, 2860, 1954, 1878, 1813, 1725, 1649, 1606, 1580, 1496, 1455, 1361, 1261, 1208, 1072, 1026, 912, 836, 735, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.02 (m, 50 H), 6.33 (d, J = 6.2 Hz, 1 H), 5.69 (d, J = 3.7 Hz, 1H), 4.91−3.26 (m, 42 H), 1.09 (d, J = 6.4 Hz, 3 H), 1.02 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 144.96, 139.58, 139.53, 139.31, 139.21, 139.18, 139.09, 139.01, 138.89, 138.68, 138.42, 138.16, 129.05, 128.96, 128.94, 128.85, 128.78, 128.71, 128.70, 128.65, 128.58, 128.50, 128.44, 128.40, 128, 36, 128.34, 128.31, 128.24, 128.17, 128.04, 127.97, 127.94, 127.93, 127.89, 127.86, 127.81, 127.78, 127.76, 127.70, 127.64, 127.57, 127.45, 126.60, 126.50, anomeric carbons (100.91, 99.52, 97.84, 95.06), 84.65, 80.16, 79.93, 79.60, 78.74, 78.28, 78.13, 77.74, 77.49, 77.41, 77.24, 76.33, 75.98, 75.49, 75.30, 75.14, 73.88, 73.62, 73.45, 73.23, 73.12, 73.02, 72.90, 72.83, 72.76, 72.68, 72.20, 71.89, 71.52, 71.32, 69.53, 68.34, 68.30, 66.89, 66.86, 17.01, 16.73; MS (ESI) 1523 [M + Na$^+$]; HRMS (FAB) calcd for $C_{94}H_{100}O_{17}Na$ 1523.6857, found 1523.6876.

Synthesis of Iodo Sulfonamide 7. A mixture of tetrasaccharide glycal **14** (939 mg, 0.625 mmol) and benzenesulfonamide (295 mg, 1.875 mmol) was azeotroped with benzene (3 × 20 mL) and then dried under high vacuum for 3 h. Freshly activated 4 Å powdered molecular sieves (900 mg) were added, and the mixture was dissolved in CH_2Cl_2 (12 mL). The resulting solution was cooled to 0 °C, and iodonium di-*sym*-collidine perchlorate was added in one portion. The reaction was stirred for 40 min at 0 °C, quenched with saturated aqueous sodium thiosulfate (6 mL), diluted with ethyl acetate, and filtered through a pad of Celite. The filtrate was washed with saturated aqueous sodium thiosulfate, saturated aqueous copper sulfate, and saturated brine. The organics were dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by FC (12−25% EtOAc/hexanes) afforded 975 mg (87%) of **7** as a white foam: $[\alpha] = -73.9$ (*c* 1, $CHCl_3$); IR (thin film) 3260, 3031, 2868, 1951, 1878, 1811, 1729, 1603, 1490, 1449, 1360, 1220, 107, 915, 768, 692; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 7.67 Hz, 2H), 7.33−7.09 (m, 55 H), 5.67 (d, J = 3.70, 1 H), 5.51 (bs, 1 H), 4.91 (s, 1 H), 4.89 (s, 1 H), 4.73−3.24 (m, 43 H), 1.07 (d, J = 6.32, 3 H), 0.99 (d, J = 6.28, 3 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 141.16, 139.39, 139.30, 139.19, 139.11, 139.03, 138.83, 138.67, 138.34, 138.31, 133.13, 129.232, 129.01, 128.80, 128.76, 128.67, 128.59, 128.55, 128.51, 128.42, 128.36, 128.20, 128.15, 128.10, 128.02, 127.96, 127.87, 127.81, 127.75, 127.66, 127.50, 127.42, 126.62, 126.50, ano-

meric carbons (100.54, 98.42, 98.08, 96.40), 84.42, 79.96, 79.89, 79.06, 78.34, 78.10, 76.46, 75.83, 75.35, 75.22, 75.14, 74.01, 73.78, 73.72, 73.43, 73.18, 73.04, 72.95, 72.84, 72.76, 72.67, 71.67, 67.72, 67.55, 66.74, 17.32, 17.14, 16.97, 16.77, 16.65; MS (ESI) 1807.6 [M + Na^+].

Le^y Hexasaccharide Glycal 21. To a solution of compound **19** (552 mg, 0.954 mmol) in dry benzene (200 mL) was added bis(tributyltin) oxide (0.55 equiv, 0.524 mmol, 0.267 mL), and the resulting solution was refluxed overnight with removal of water with a Dean−Stark trap. The resulting solution of tin ether **8** was concentrated *in vacuo*, and the residue was diluted with THF (9 mL) and added to a mixture of azeotropically dried (3 × 10 mL of benzene) iodosulfonamide **6** (612 mg, 0.3179 mmol) and freshly activated 4 Å molecular sieves (600 mg). The resulting suspension was cooled to −70 °C, and a solution of $AgBF_4$ (134 mg) in THF (3 mL) was added to it via cannula. The reaction mixture was stirred for 2 days with exclusion of light while slowly being allowed to reach room temperature. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (5 mL), diluted with EtOAc (60 mL), and filtered through a pad of Celite. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 30 mL) and brine (1 × 30 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated and the crude product purified by FC (20−30% EtOAc/hexane) to give 224 mg (28%) of **21** as a white foam: [α] = −43.2 (*c* 1, $CHCl_3$); IR (thin film) 3498, 3242, 3063, 2935, 2845, 1814, 1642, 1456, 1347, 1162, 1104, 1050, 820, 743, 698; ^1H NMR ($CDCl_3$) δ 7.60−7.00 (m, 70H), 6.63 (d, *J* = 3.0 Hz, 1H), 6.42 (d, *J* = 6.1 Hz, 1H), 5.14 (d, *J* = 3.5 Hz, 1H), 4.98−3.42 (m, 54), 3.01 (bs, 1H), 2.74 (bs, 1H), 1.04−0.90 (m, 21H), 0.83(d, *J* = 6.4, 3H); ^{13}C (500 MHz, $CDCl_3$) δ 153.42, 144.49, 141.91, 138.55, 138.52, 135.74, 135.56, 135.45, 135.16, 132.29, 130.00, 128.63, 128.59, 128.51, 128.45, 128.36, 128.34, 128.29, 128.21, 128.17, 127.91, 127.86, 127.83, 127.77, 127.72, 1276.67, 127.59, 127.57, 127.42, 127.42, 126.75, anomeric carbons (102.71, 101.81, 100.42, 100.29, 98.32, 97.72), 79.03, 78.57, 78.06, 77.55, 76.29, 74.90, 74.73, 74.64, 74.50, 74.45, 74.23, 73.68, 73.58, 73.48, 72.74, 72.07, 71.81, 70.80, 70.73, 69.20, 68.61, 68.09, 67.51, 61.55, 61.14, 27.94, 27.85, 27.77, 27.11, 26.86, 26.81, 26.64, 19.37, 19.20, 18.87, 17.53, 16.69, 16.44, 16.26, 16.20, 13.62; LRMS (ESI) calcd for $C_{138}H_{153}NO_{29}SSi_2Na$ 2398.9684, found 2398.9 [M + Na^+].

Peracetate Le^y Hexasaccharide Glycal 22. To a solution of hexasaccharide **21** (260 mg, 0.11 mmol) in THF (4 mL) was added 1 M TBAF/THF (0.95 mL, 0.95 mmol), and the resulting solution was stirred for 10 h at room temperature. The reaction mixture was concentrated and purified by FC (5%MeOH/$CHCl_3$). The resulted white solid was dissolved in THF (3 mL) and added via cannula to a solution of sodium (300 mg, 13.04 mmol) in liquid ammonia (18 mL) under Ar at −78 °C and stirred for 40 min. The reaction mixture was quenched with MeOH (6 mL), stirred for 15 min, and concentrated with a stream of dry Ar. MeOH (10 mL) was added, followed by NH_4Cl (698 mg, 13.04 mmol), and the solution stirred for 15−20 min and then concentrated again to dryness. The crude product was suspended in a mixture of THF (5 mL), DMF (2 mL), and TEA (1.5 mL). To this were added Ac_2O (1.64 mL, 17.82 mmol) and a catalytic amount of DMAP, the mixture was stirred at room temperature for 10 h and then poured into ice−water (40 mL) and extracted with EtOAc (3 × 70 mL). The organics were washed with saturated aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by FC (65% EtOAc/CH_2Cl_2) afforded 76 mg (44% overall from the three steps) of **22** as a white solid: [α] = −55 (*c* 1, $CHCl_3$); IR (thin film) 3394, 2974, 2963, 2904, 2834, 1752, 1723, 1685, 1461, 1374, 1263, 1129, 1076, 1030, 960, 907; ^1H NMR ($CDCl_3$) δ 6.40 (D, *J* = 6.1 Hz, 1H), 5.45 (d, *J* = 7.11, 1H), 5.38−5.29 (m, 7H), 5.28 (d, *J* = 3.9, 1H), 5.09 (dd, *J* = 6.9, *J* = 3.1, 1H), 5.07−4.95 (m, 8H), 4.85 (dd, *J* = 6.11, *J* = 3.3, 1H), 4.62 (m, 2H), 4.60−4.45 (m, 4H), 4.25−3.76 (m, 12H), 3.42 (d, *J* = 9.9 Hz, 1H), 2.18−1.96 (m, 45H), 1.91 (s, 3H), 1.21 (d, *J* = 6.54 Hz, 3H), 1.18 (d, *J* = 6.53 Hz, 3H); LRMS (ESI) 1618.6 [M + Na^+]; HRMS (FAB) calcd for $C_{68}H_{93}NO_{42}Na$ 1618.5069, found 1618.5073.

Alternative Synthesis of Peracetate Le^y Hexasaccharide Glycal 22: (a) Synthesis of Perbenzylated Le^y Hexasaccharide Glycal 25. To a solution of compound **19** (378 mg, 0.0654 mmol) in dry benzene (150 mL) was added bis-(tributyltin) oxide (0.359 mmol, 0.183 mL), and the solution was refluxed overnight with removal of water with a Dean−Stark trap. The resulting tin ether **8** was concentrated *in vacuo*, diluted with THF (5 mL), and added to a mixture of azeotropically dried (3 × 10 mL of benzene) iodosulfonamide **7** (388 mg, 0.218 mmol) and freshly activated 4 Å molecular sieves (500 mg). The suspension was cooled to −70 °C, and a solution of $AgBF_4$ (138 mg) in THF (2.5 mL) was added to it via cannula. The reaction mixture was stirred for 2 days with exclusion of light while slowly being allowed to reach room temperature. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (4 mL), diluted with EtOAc (50 mL), and filtered through a pad of Celite. The filtrate was washed with saturated aqueous solution of $NaHCO_3$ (3 × 30 mL) and brine (1 × 30 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated and the crude product purified by FC (20−30% EtOAc/hexanes) to give 204 mg (42%) of **25** as white foam: [α] = −60.2 (*c* 1, $CHCl_3$); IR (thin film) 3496, 3280, 3075, 3020, 2870, 1957, 1871, 1808, 1723, 1643, 1580, 1501, 1455, 1358, 1313, 1250, 1210, 1153, 1096, 1022, 914, 732; ^1H NMR ($CDCl_3$) δ 7.65−7.15 (m, 65H), 6.39 (d, *J* = 6.07 Hz, 1H), 5.81 (d, *J* = 6.58 Hz, 1H), 5.68 (d, *J* = 3.74 Hz, 1H), 5.03−4.52 (m, 24H), 4.40−4.34 (m, 8H), 4.32−4.20 (m, 6H), 4.14−4.09 (q, 4H), 4.03−3.26 (m, 26H), 2.82 (bs, 1H), 0.95−0.90 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 144.59, 140.86, 138.97, 138.83, 138.76, 138.65, 138.51, 13840, 138.22, 138.12, 137.91, 137.80, 137.63, 137.56, 137.44, 132. 43, 129.22, 129.12, 128.92, 128.88, 128.64, 128.56, 128.51, 128.44, 128.42, 128.40, 128.34, 128.30, 128.24, 128.16, 128.12, 128.07, 128.03, 127.97, 127.87, 127.75, 127.71, 127.63, 127.61, 127.59, 127.51, 127.47, 127.40, 127.37, 127.33, 127.24, 127.20, 126.93, 126.85, 126.26, 126.13, 125.63, 124.06, anomeric carbons (102.89, 101.63, 100.47, 100.34, 98.59, 97.55), 84.11, 84.05, 80.61, 80.11, 80.01, 79.85, 79.72, 79.39, 78.05, 77.78, 77.65, 77.27, 77.02, 76.76, 76.61, 76.22, 75.69, 75.60, 75.39, 75.11, 74.91, 74.83, 74.79, 74.36, 74.09, 73.73, 73.58, 73.46, 73.42, 73.36, 73.27, 73.24, 72.99, 72.80, 72.64, 72.58, 72.39, 72.24, 71.75, 71.26, 71.07, 70.76, 70.61, 70.42, 69.42, 69.04, 68.21, 67.89, 67.84, 67.15, 66.96, 66.88, 66.78, 60.39, 27.84, 26.85, 22.91, 21.06, 17.52, 16.68, 16.60, 16.39, 16.25, 14.20, 13.61, 8.25, 4.14; LRMS (ESI) 2256.9; HRMS (FAB) calcd for $C_{133}H_{143}O_{28}NSNa$ 2256.9414, found 2256.9421 [M + Na^+]. **(b) Le^y Hexasaccharide Glycal Peracetate 22 .** Le^y glycal **25** (120 mg, 0.0537 mmol) was dissolved in THF (3 mL) and added via cannula to a solution of sodium (150 mg, 6.52 mmol) in liquid ammonia (10 mL) under Ar at −78 °C and stirred for 40 min. The reaction mixture was quenched with MeOH (3 mL), stirred for 15 min and concentrated with a stream of dry Ar. MeOH (5 mL) was added, followed by NH_4Cl (349 mg, 6.52 mmol), and the solution stirred for 15−20 min and then concentrated again to dryness. The crude product was suspended in a mixture of THF (1 mL), DMF (0.5 mL), and TEA (1 mL). To this were added Ac_2O (0.82 mL, 8.91 mmol) and a catalytic amount of DMAP, and the mixture was stirred at room temperature for 10 h, poured into ice−water (40 mL), and extracted with EtOAc (3 × 70 mL). The organics were washed with saturated aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$, filtered, and concentrated. The purification of the crude product by FC (65% EtOAc/CH_2Cl_2) afforded 69 mg (81%) of **22**.

Allyl Glycoside of Le^y Hexasaccharide Peracetate 23. A mixture of Le^y hexasaccharide glycal **22** (32 mg, 0.019 mmol), dried azeotropically with benzene (3 × 5 mL) and under high vacuum for 2 h, and freshly activated 4 Å powdered molecular sieves (50 mg) was suspended in CH_2Cl_2 (1 mL) and cooled to 0 °C, and DMDO (0.70 mL 0.1 M solution in Me_2CO) was added. The reaction mixture was stirred at 0 °C for 1 h, the

solvent was evaporated, and the residue was taken up in allyl alcohol (6 mL). This mixture was stirred at room temperature for 48 h, the solvent was evaporated, and the product was purified by FC (60% EtOAc/CH_2Cl_2) affording 30 mg (88%) of **23** as a white solid: [α] = −51 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.84 (d, 1H, *J* = 6.9), 5.28−4.89 (m, 19 H), 4.55 (d, *J* = 7.9 Hz, 1H), 4.37−3.34 (m, 23), 2.81 (bs, 1H), 2.10−1.85 (m, 48H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.35, 169.89, 169.74, 169.62, 169.52, 169.42, 169.37, 169.33, 169.25, 169.18, 169.00, 168.79, 168.52, 168.50, 132.38, 117.37, anomeric protons (100.40, 99.66, 99.40, 97.96, 95.24, 94.66), 75.33, 74.58, 73.53, 72.89, 72.29, 71.96, 71.78, 71.57, 71.54, 70.38, 70.13, 69.89, 69.77, 69.44, 68.40, 67.64, 66.84, 66.69, 66.46, 65.82, 64.10, 62.95, 61.10, 60.46, 59.42, 58.96, 58.66, 28.67, 28.30, 28.20, 22.49, 21.67, 20.09, 19.99, 19.93, 19.90, 19.81, 19.76, 19.71, 19.68, 19.65, 19.60, 14.89, 14.52,; LRMS (ESI) 1692 [M + Na^+]; HRMS calcd for $C_{71}H_{99}NO_{44}Na$ 1692.5437, found 1692.5440.

Allyl Glycoside of Le^y Hexasaccharide 24. A solution of hexasaccharide **23** (26 mg, 0.0154 mmol) in MeOH (1 mL) was treated with NaOMe/MeOH (5%, 0.283 mL). After 12 h, the mixture was neutralized with Dowex 50-X8, filtered, and concentrated. Purification of the residue with RP-18 reversed-phase silica gel (5% MeOH/H_2O) gave 14 mg (90%) of **24** as a white solid: [α] = −41.1 (*c* 0.9, MeOH); IR (thin film) 3359, 2974, 2893, 1723, 1665, 1630, 1578, 1467, 1368, 1315, 1070, 1024; ^{1}H NMR (D_2O) δ 5.99 (m, 1H), 5.39 (d, *J* = 17.3 Hz, 1H, CH=CH_2), 5.30−5.28 (m, 2H), 5.12 (d, *J* = 3.9, 1H), 4.89−4.78 (multiple protons), 4.72 (d, *J* = 8.2, 1H), 4.54−4.43 (m, 5H), 4.26−4.14 (m, 4H), 4.01−3.56 (m, 35H), 3.46 (bs, 1H), 3.35−3.32 (m, 1H), 2.03 (s, 3H), 1.24 (d, *J* = 6.6, 3H), 1.18 (d, *J* = 6.7, 3H); ^{13}C NMR (D_2O) δ 188.49, 135.92, 121.44, 105.58, 105.15, 103.68, 102.87, 102.09, 101.26, 84.66, 80.99, 79.04, 77.51, 77.42, 77.07, 75.45, 74.60, 74.36, 73.34, 72.66, 72.39, 71.83, 71.41, 70.94, 70.36, 69.59, 64.13, 63.57, 62.74, 62.43, 60.00, 33.78, 24.94, 18.12, 14.43; LRMS (ESI) 1062.4 [M + Na^+]; HRMS (FAB) calcd for $C_{41}H_{69}NO_{29}Na$ 1062.3851, found 1062.3854.

Acetylated Hexasaccharide 26. To a solution of Le^Y hexasaccharide **25** (160 mg, 0.0716 mmol), a catalytic amount of DMAP, and TEA (0.132 mL, 1 mmol) in CH_2Cl_2 (3 mL) was added Ac_2O (0.095 mL, 1.0 mmol). The reaction mixture was stirred for 24 h. EtOAc (100 mL) was added and the solution washed with saturated aqueous $NaHCO_3$ (3 × 60 mL), dried over $MgSO_4$, filtered, concentrated, and purified by FC (25% EtOAc/hexane) to afford 131 mg (77%) of **26** as a white solid: [α] = −35.70 (*c* 1, $CHCl_3$); IR (thin film) 3315, 2870, 1748, 1716, 1600, 1450, 1350, 1220, 1120, 1102, 909, 728; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.12 (m, 70H), 6.38 (d, *J* = 6.1 Hz, 1H), 5.67 (d, *J* = 3.2 Hz, 1H), 5.40m, 2H), 5.17 (m, 1H), 4.92(d, 2H), 4.82, 4.66 (m, 9H), 4.53−4.28 (m, 22H0, 4.15−3.94 (m, 8H), 3.84−3.61 (m, 13H), 3.53−3.21 (m, 5H), 2.00 (s, 3H), 1.96 (s, 6H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.71, 170.34, 170.30, 144.50, 139.72, 138.79, 138.71, 138.68, 138.04, 137.85, 137.83, 137.76, 137.14, 133.84, 130.38, 129.33, 129.22, 128.63, 128.51, 128.46, 128.43, 128.40, 128.36, 128.33, 128.21, 128.15, 128.07, 128.02, 127.94, 127.88, 127.76, 127.64, 127.58, 127.38, 127.05, 126.94, 126.87, 126.00, anomeric protons (101.72, 100.16, 99.63, 99.44, 98.00, 96.65), 83.98, 79.86, 78.98, 78.29, 75.73, 75.55, 74.96, 74.34, 74.11, 73.85, 73.81, 73.70, 73.70, 73.67, 73.51, 73.37, 73.31, 72.65, 72.57, 72.38, 72.20, 72.12, 70.12, 69.42, 67.97, 67.05, 66.97, 66.81, 24.59, 22.64, 21.00, 20.93, 16.26, 14.12; LRMS (ESI) calcd for $C_{139}H_{149}O_{31}NSNa$ 2382.9731, found 2381.6 [M + Na^+].

Le^Y Octasaccharide Glycal 28. A mixture of Le^Y hexasaccharide **26** (129 mg, 0.055 mmol) and benzenesulfonamide (26 mg, 0.16 mmol) was azeotropically dried with benzene (3 × 4 mL) under high vacuum for 2 h. To the dried mixture was added freshly activated 4 Å molecular sieves (130 mg) under Ar, followed by CH_2Cl_2 (4 mL). The resulting suspension was cooled to 0 °C, and I (sym-coll)$_2ClO_4$ (90 mg, 0.191 mmol) was added under Ar. The reaction mixture was stirred at 0 °C for 40 min, quenched with saturated aqueous $Na_2S_2O_3$ (3 mL), diluted with EtOAc (60 mL), and then filtered through Celite. The filtrate was washed with saturated aqueous $Na_2S_2O_3$ (2 × 30 mL), saturated aqueous $CuSO_4$ (2 × 30 mL), and brine (1 × 30 mL), and the organics were dried over $MgSO_4$, filtered, and concentrated. The residue was taken up in 30% EtOAc/hexanes and passed through a short SiO_2 column to give 108 mg **27** (75%). This was azeotroped with benzene (3 × 3 mL), kept under high vacuum for 3 h, and used without further purification. Freshly activated 4 Å molecular sieves (110 mg) were added to it under Ar, followed by a solution of tin ether of **8** (prepared from 83 mg of **19** and 0.042 mL of $(Bu_3Sn)_2O$ as described for **21**). The resulting suspension was cooled to −70 °C and $AgBF_4$ (28 mg, 0.143 mmol) in THF (1 mL) added via cannula. The reaction mixture was stirred with exclusion of light, allowed to warm slowly over about 5 h to room temperature, and stirred for 3 days. EtOAc was added, and the mixture was filtered through Celite. The filtrates were diluted additionally with EtOAc and washed with saturated aqueous solution of $NaHCO_3$ (3 × 30 mL) and brine (1 × 30 mL). The organics were dried over $MgSO_4$, filtered, concentrated, and chromatographed (FC 30−40% EtOAc/hexanes) to give 82 mg of **28** (65% for this step and 50% overall for the two steps): [α] = −18.5 (*c* 0.87, $CHCl_3$); IR (thin film) 3483, 3319, 3048, 2872, 1742, 1702, 1642, 1578, 1454, 1366, 1308, 1237, 1166, 1096, 1061, 1020, 908, 802, 732, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10(d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 6.1 Hz, 2H), 7.46−7.09 (m, 80 H), 7.02 (d, 7.4 Hz, 2H), 6.92 (d, *J* = 7.5 Hz, 2H), 6.39 (d, *J* = 6.1 Hz, 1H), 5.67 (d, *J* = 3.6 Hz, 1H), 5.41−5.37 (m, 2H), 5.13−5.03 (m, 2H), 4.82−3.21 (m, 82H), 2.00 (s, 6H), 1.89 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.36, 170.08, 167.78, 144.66, 140.56, 139.78, 138.94, 138.81, 138.73, 138.71, 138.67, 138.60, 138.50, 138.25, 138.13, 138.07, 137.82, 133.88, 132.51, 130.45, 129.07, 128.90, 128.83, 128.76, 128.65, 128.61, 128.56, 128.46, 128.40, 128.35, 128.32, 128.16, 128.10, 128.05, 128.01, 127.98, 127.94, 127.91, 127.84, 127.82, 127.79, 127.76, 127.71, 127.64, 127.60, 127.48, 127.43, 127.38, 127.34, 127.31, 127.13, 127.10, 127.00, 126.92, 126.85, 126.05, anomeric protons (103.02, 102.38, 101.98, 100.56, 100.52, 99.72, 98.06, 96.60), 84.01, 82.17, 80.12, 79.89, 79.12, 79.08, 78.84, 78.33, 78.25, 77.23, 76.78, 75.64, 75.61, 75.39, 74.98, 74.69, 74.59, 74.34, 74.14, 73.98, 73.88, 73.73, 73.60, 73.55, 73.43, 73.40, 72.78, 72.62, 72.45, 72.35, 72.29, 71.58, 70.99, 70.95, 70.28, 69.35, 68.99, 68.48, 68.31, 68.18, 68.03, 67.70, 67.11, 66.98, 66.87, 57.95, 55.13, 38.76, 31.95, 30.39, 29.72, 29.39, 28.95, 24.63, 23.77, 23.01, 22.72, 21.07, 20.80, 16.62, 16.29, 14.15, 14.08, 10.99; LRMS calcd for $C_{178}H_{192}O_{42}N_2S_2Na$ 3116.2287, found 3116 [M + Na^+].

Le^Y Octasaccharide Glycal Peracetate 29. A solution of Le^Y octasaccharide glycal **28** (72 mg, 0.018 mmol) in THF (1 mL) was added via cannula to a solution of sodium (280 mg, 12.17 mmol) in liquid ammonia (10 mL) under Ar at −78 °C and stirred for 40 min. The reaction mixture was quenched with MeOH (5 mL), stirred for 15 min, and concentrated with a stream of dry Ar. MeOH (10 mL) was added, followed by NH_4Cl (651 mg, 12.18 mmol), and the solution stirred for 15−20 min and then concentrated again to dryness. The crude product was suspended in a mixture of THF (1.5 mL), DMF (1 mL), and TEA (0.4 mL). To this were added Ac_2O (0.4 mL, 1.48 mmol) and a catalytic amount of DMAP, and the reaction mixture was stirred at room temperature for 10 h. The reaction mixture was poured into ice−water (40 mL) and extracted with EtOAc (3 × 70 mL). The organics were washed with saturated aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$, filtered, and concentrated. The purification of the crude product by FC (85% EtOAc/CH_2Cl_2) afforded 32 mg (80%) of **29** as a white solid: [α] = −46.2 (*c* 1, $CHCl_3$); IR (thin film) 3372, 2971, 1746, 1673, 1534, 1434, 1373, 1223, 1156, 1123, 1067, 1034, 945; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (d, *J* = 6.1 Hz, 1H), 5.58 (d, *J* = 7.0 Hz, 1H), 5.43 (d, 1H), 5.36−5.31 (m, 7H), 5.25−5.12 (m, 3H), 5.10−4.95 (m, 9H), 4.83−4.82 (m, 2H), 4.74 (d, *J* = 6.9 Hz,

1H), 4.62 (d, J = 7.8 Hz, 1H), 4.50 (d, J = 7.6 Hz, 1H), 4.45 (q, 2H), 4.43−4.35 (m, 3H), 4.29−4.25 (m, 2H), 4.21−3.75 (m, 17H), 3.51−3.41 (m, 2H), 2.1 (s, 3H), 2.15−2.14 (m, 12H), 2.13−2.11 (m, 15H), 2.10−2.04 (m, 18H), 2.01−1.98 (m, 12 H), 1.91 (s, 3H), 1.89 (s, 3H), 1.21 (d, 6.5 Hz, 3H), 1.18 (d, 6.5 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.52, 171.30, 170.93, 170.75, 170.68, 170.64, 170.61, 170.54, 170.49, 170.44, 170.34, 170.25, 170.23, 170.21, 170.11, 169.97, 169.84, 169.81, 169.46, 169.22, 145.34, anomeric carbons (100.90, 100.70, 100.41, 100.27, 98.98 (two carbons), 96.22, 95.68), 75.26, 74.26, 74.16, 73.88, 73.32, 73.01, 72.69, 72.46, 71.39, 71.20, 71.09, 71.02, 70.87, 70.80, 68.77, 68.72, 67.85, 67.69, 67.50, 66.85, 65.09, 63.99, 61.93, 61.65, 61.32, 29.70, 29.66, 29.36, 27.16, 23.50, 23.19, 23.09, 22.69, 21.09, 20.96, 20.94, 20.91, 20.87, 20.82, 20.78, 20.74, 20.69, 20.67, 20.62, 20.60, 15.91, 15.53, 14.20, 14.13, 1.029; LRMS (ESI) 2194.8; HRMS (FAB) calcd for $C_{92}H_{126}O_{57}N_2Na$ 2193.6919, found 2193.6989 [M + Na^+].

Alternative synthesis of Le^Y Octasaccharide Glycal Peracetate 29: (a) Synthesis of Le^Y Octasaccharide Glycal 33. To a solution of Le^Y hexasaccharide **21** (156 mg, 0.066 mmol), a catalytic amount of DMAP, and TEA (0.090 mL, 0.722 mmol) in CH_2Cl_2 (2 mL) was added Ac_2O (0.070 mL, 0.722 mmol), and the mixture was stirred for 24 h. EtOAc (60 mL) was added and the solution washed with cold saturated aqueous $NaHCO_3$ (3 × 40 mL), dried over $MgSO_4$, filtered, concentrated, and passed through a short column of silica gel (25% EtOAc/hexanes) to give 118 mg (72%) of acetylated **21**: LRMS (ESI) calcd for $C_{144}H_{159}NO_{32}SSi_2Na$ 2525.0001, found 2525.9 [M + Na^+]. A mixture of the product and benzenesulfonamide (20 mg, 0.126 mmol) was dried azeotropically with benzene (3 × 4 mL) under high vacuum for 2 h. Freshly activated 4 Å molecular sieves (100 mg) were added to the mixture under Ar, followed by CH_2Cl_2 (2 mL). The resulting suspension was cooled to 0 °C and I(sym-coll)$_2$$ClO_4$ (69 mg, 0.0.146 mmol) added under Ar. The reaction mixture was stirred at 0 °C for 40 min and quenched with saturated aqueous $Na_2S_2O_3$ (2 mL), diluted with EtOAc (60 mL), and then filtered through Celite. The filtrate was washed with saturated aqueous $Na_2S_2O_3$ (2 × 20 mL), saturated aqueous $CuSO_4$ (2 × 20 mL), and brine (1 × 20 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The residue was taken up in 30%EtOAc/hexanes and passed through a short SiO_2 column. The collected iodosulfonamide **32** (101 mg, 77%) was dried azeotropically with benzene (3 × 3 mL) and under high vacuum for 3 h and used without further purification. Freshly activated 4 Å molecular sieves (80 mg) were added to it under Ar, followed by a solution of **8** in THF (prepared from 70 mg of **19** and 0.035 mL of $(Bu_3Sn)_2O$ as described for **21**). The resulting suspension was cooled to −70 °C and $AgBF_4$ (22 mg, 0.112 mmol) in THF (1 mL) added via cannula. The reaction mixture was stirred with exclusion of light, allowed to warm slowly to room temperature over about 5 h, and then stirred for 3 days. EtOAc was added, and the mixture was filtered through Celite. The filtrates were diluted additionally with EtOAc and washed with a saturated aqueous solution of $NaHCO_3$ (3 × 30 mL) and brine (1 × 30 mL). The organics were dried over $MgSO_4$, filtered, and concentrated, and the residue was chromatographed (FC 30−40% EtOAc/hexanes) to give 62 mg (52%, 30% overall for the three steps) of **33** as a white foam: [α] = −45.6 (c 1, $CHCl_3$); IR (thin film) 3485, 3305, 3029, 2929, 2858, 1835, 1821, 1754, 1694, 1495, 1453, 1360, 1214, 1159, 1103, 1050, 1028, 739, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 7.5 Hz, 2H), 7.81 (d, J = 7.2 Hz, 2H), 7.54−6.90 (m, 86 H), 6.39 (d, J = 6.0 Hz, 1H), 5.52 (d, J = 4.1 Hz, 1H), 5.38 (s, 1H), 5.19 (m, 1H), 5.00−3.22 (m, 80H), 2.12 (s, 3H), 1.94 (s, 3H), 1.76 (s, 3H), 1.19 (d, J = 6.3 Hz), 1.12 (s, 9H), 1.00 (s, 9H), 0.90 (d, J = 6.4 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.98, 168.97, 168.75, 153.36, 144.52, 140.28, 139.70, 138.92, 138.80, 138.71, 138.60, 138.54, 138.47, 138.44, 138.02, 137.90, 137.72, 137.57, 137.54, 136.09, 135.98, 135.46, 135.39, 135.33, 135.28, 133.97, 133.70, 132.47, 132.30, 132.25, 131.91, 130.20, 130.12, 130.06, 130.00, 129.88, 129.80, 129.20, 128.85, 128.82, 128.68, 128.53, 128.50, 128.48, 128.44, 128.41, 128.35, 128.24, 128.20, 128.13, 128.06, 128.01, 127.95, 127.91, 127.82, 127.71, 127.60, 127.56, 127.51, 127.49, 127.46, 127.40, 127.36, 127.31, 127.22, 126.99, 126.85, anomeric carbons (103.65, 100.12, 99.73, 99.17, 98.15, 98.10, 96.88, 95.14), 78.65, 78.29, 78.17, 77.95, 77.66, 77.54, 76.26, 76.22, 75.28, 75.15, 75.05, 74.88, 74.70, 74.60, 74.09, 74.04, 73.82, 73.74, 73.71, 73.65, 73.61, 73.54, 73.28, 72.60, 72.26, 72.11, 71.80, 70.66, 70.38, 70.02, 69.84, 69.39, 68.12, 68.01, 67.19, 66.23, 65.74, 64.09, 60.87, 57.13, 78.65, 78.29, 78.17, 77.95, 77.66, 77.54, 76.26, 76.22, 75.28, 75.15, 75.05, 74.88, 74.70, 74.60, 74.09, 74.04, 73.82, 73.74, 73.71, 73.65, 73.61, 73.54, 73.28, 72.60, 72.26, 72.11, 71.80, 70.66, 70.38, 70.02, 69.84, 69.39, 68.12, 68.01, 67.19, 66.23, 65.74, 64.09, 60.87, 57.13, 29.71, 26.86, 26.77, 26.75, 26.66, 26.05, 20.64, 20.62, 19.34, 19.13, 16.61, 16.50, 16.42, 1.03; LRMS (ESI) calcd for $C_{183}H_{202}N_2O_{43}S_2Si_2Na_2$ 3281.2455, found 3281.4 [M + 2Na^{2+}]. **(b) Le^Y Octasaccharide Glycal Peracetate 29.** To a solution of Le^Y octasaccharide glycal **33** (62 mg, 0.019 mmol) dissolved in THF (3 mL) was added 1 M TBAF/THF (0.230 mL, 0.230 mmol). The reaction mixture was stirred for 24 h at room temperature and then concentrated and chromatographed (FC, 5%MeOH/$CHCl_3$). The white solid residue was taken up in THF (3 mL) and added via cannula to a solution of sodium (61 mg, 2.65 mmol) in liquid ammonia (8 mL) under Ar at −78 °C. The reaction mixture was stirred for 40 min, quenched with MeOH (3 mL), stirred for 15 min, and concentrated with a stream of dry Ar. MeOH (5 mL) was added, followed by NH_4Cl (141 mg, 2.65 mmol), and the mixture stirred for 15−20 min and then concentrated again to dryness. The crude product was suspended in a mixture of THF (1.0 mL), DMF (0.3 mL), and TEA (0.6 mL). To this were added Ac_2O (0.395 mL, 4.18 mmol) and a catalytic amount of DMAP. The mixture was stirred at room temperature for 10 h and then poured into ice−water (15 mL) and extracted with EtOAc (3 × 60 mL). The organics were washed with saturated aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by FC (65% EtOAc/CH_2Cl_2) afforded 25 mg (60% overall yield) of **29**.

Allyl Glycoside of Le^y Octasaccharide Peracetate 30. A mixture of Le^y octasaccharide glycal **29** (32 mg, 0.0147 mmol, azeotropically dried with benzene (3 × 5 mL) and under high vacuum for 2 h) and freshly activated 4 Å powdered molecular sieves (50 mg) was suspended in CH_2Cl_2 (1 mL) under Ar and cooled to 0 °C. DMDO (220 mL 0.12 M solution in Me_2CO) was then added. The reaction mixture was stirred at 0 °C for 1 h, the solvent was evaporated, and the residue was taken up in allyl alcohol (5 mL). The reaction mixture was stirred at room temperature for 48 h, the solvent was evaporated, and the product was purified by FC (40−70% EtOAc/CH_2Cl_2) to afford 30 mg (90%) of **30** as a white solid: [α] = −17.3 (c 1, CH_2Cl_2); IR (thin film) 3486, 3377, 3087, 2961, 2873, 1748, 1683, 1539, 1430, 1372, 1228, 1066, 976, 944; ^{1}H NMR ($CDCl_3$) δ 5.90 (m, 1H), 5.53 (d, J = 7.08 Hz, 1H), 5.45 (d, J = 8.3 Hz, 1H), 5.36−4.96 (m, 20 H), 4.84 (d, J = 2.00 Hz, 1H), 4.81 (m, 1H), 4.69 (d, J = 7.8 Hz, 1H), 4.62 (d, J = 7.9 Hz, 1H), 4.50−4.49 (m, 2H), 4.45−4.34 (m, 5H), 4.28 (q, 2H), 4.08−3.75 (m, 15H), 3.73 (dd, J = 9.8 Hz, J = 3.6 Hz, 2H), 3.69−3.41 (m, 6H), 2.84 (bs, 1H), 2.15−1.89 (m, 66H), 1.21 (d, J = 6.5 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.39, 171.21, 170.96, 170.78, 170.73, 170.66, 170.62, 170.54, 170.48, 170.37, 170.28, 170.24, 170.15, 169.88, 169.84, 169.77, 169.61, 169.51, 169.00, 133.41, 133.29, 128.33, 118.43, 118.13, anomeric carbons (101.46, 100.90, 100.43, 100.24, 99.04, 98.39, 96.23, 95.70), 79.06, 75.25, 73.89, 73.35, 73.01, 72.83, 72.72, 72.61, 72.48, 71.42, 71.19, 71.07, 70.91, 70.82, 70.52, 69.42, 68.70, 67.87, 67.72, 67.53, 66.88, 65.11, 64.02, 61.64, 61.36, 60.48, 60.43, 55.07, 41.84, 31.94, 30.07, 29.72, 29.38, 27.21, 23.91, 23.51, 23.22, 23.10, 22.71, 21.11, 21.08, 21.01, 20.96, 20.94, 20.88, 20.84, 20.80, 20.75, 20.73, 20.69, 20.64, 19.84, 15.93, 15.55, 14, 22, 14.15; LRMS (ESI) calcd for $C_{95}H_{132}N_2O_{59}Na$ 2267.7287, found 2266.6 [M + Na^+].

Allyl Glycoside of Le^y Octasaccharide 31. To a solution of octasaccharide **30** (28 mg, 0.0124 mmol) in MeOH (0.5 mL) was added NaOMe/MeOH (5%, 0.294 mL). After 12 h, the mixture was neutralized with Dowex 50-X8, filtered, and concentrated. Purification of the residue with RP-18 reversed-phase silica gel (5% MeOH/H_2O) gave 15.8 mg (89%) of **31** as a white solid: [α] = −34.32 (*c* 0.88, MeOH); IR (thin film) 3369, 2933, 2848, 1643, 1558, 1473, 1377, 1318, 1249, 1074; ^{1}H NMR (D_2O) δ 5.98 (m, 1H), 5.39 (d, *J* = 17.3 Hz, 1H, CH=CH$_2$), 5.37 (s, 1H), 5.28 (d, *J* = 2.7 Hz, 1H), 5.12 (d, *J* = 3.9, 1H), 4.92 (bs, 1H), 4.88 (d, *J* = 7.8 Hz, 1H), 4.84−4.82 (m, 2H), 4.71 (*J* = 8.1, 2H), 4.53−4.38 (m, 5H), 4.23 (m, 2H), 4.15 (bs, 2H), 4.10−3.31 (m, 59H), 2.04 (s, 3H−Ac), 2.03 (s, 3H−Ac), 1.70 (bs, 1H), 1.28 (d, *J* = 6.7, 3H), 1.24 (d, *J* = 6.6, 3H); ^{13}C NMR (D_2O) δ 175.24, 175.07, 161.14, 133.61, 133.55, 119.10, 118.83, anomeric carbons (103.30, 103.23, 103.10, 102.85, 101.38, 100.57, 99.79, 98.96), 82.38, 78.66, 78.48, 76.73, 75.71, 75.22, 75.12, 74.98, 74.77, 73.91, 73.39, 73.15, 72.53, 72.30, 72.06, 71.03, 70.36, 70.09, 69.53, 69.11, 68.64, 68.08, 67.28, 67.15, 62.31, 61.83, 61.29, 60.41, 60.28, 60.12, 56.46, 55.51, 49.21, 48.91, 48.73, 48.56, 48.39, 48.21, 48.04, 47.87, 22.62, 22.52, 15.81; LRMS (ESI) 1421.1 [M + Na$^+$] HRMS (FAB) calcd for $C_{55}H_{92}N_2O_{39}Na$ 1427.5174, found 1427.5181 [M + Na$^+$].

Le^Y Hexasaccharide Glycal 34. To a solution of compound **20** (419 mg, 0.69 mmol) in dry benzene (200 mL) was added bis(tributyltin) oxide (0.55 equiv, 0.359 mmol, 0.183 mL). The solution was refluxed overnight with removal of water with a Dean−Stark trap. The resulting tin ether **9** was concentrated in vacuo, diluted with THF (5 mL), and added to a mixture of azeotropically dried (3 × 10 mL of benzene) iodosulfonamide **7** (235 mg, 0.132 mmol) and freshly activated 4 Å molecular sieves (300 mg). The resulting suspension was cooled to −70 °C, and a solution of $AgBF_4$ (85 mg) in THF (0.5 mL) was added to it via cannula. The reaction mixture was stirred for 48 h with exclusion of light while slowly being allowed to reach room temperature and then quenched with saturated aqueous $NaHCO_3$ (1 mL), diluted with EtOAc (50 mL), and filtered through a pad of Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ (3 × 25 mL) and brine (1 × 25 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated and the residue purified by FC (20−30% EtOAc/hexanes) to give 136 mg (46%) of **34** as a white foam: IR (thin film) 3488, 3282, 3067, 3029, 2952, 2868, 2247, 1951, 1874, 1809, 1729, 1648, 1606, 1495, 1449, 1361, 1315; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.37−7.05 (m, 63H), 6.35 (d, *J* = 6.2 Hz, 1H), 5.87 (d, *J* = 6.6 Hz, 1H), 5.68 (d, *J* = 3.6 Hz, 1H), 5.08 (d, *J* = 2.2 Hz, 1H), 4.92 (d, *J* = 11.4 Hz, 1H), 4.82 (d, *J* = 6.3 Hz, 2H), 4.79−4.55 (m, 12H), 4.52 (d, *J* = 4.6 Hz, 2H), 4.46 (s, 2H), 4.42−4.19 (m, 11H), 4.12 (q, *J* = 8.2 Hz, 1H), 4.05 (dd, *J* = 6.3 Hz, *J* = 3.7 Hz, 1H), 4.01−3.35 (m, 26H), 3.26 (bs, 1H), 3.19 (bs, 1H), 2.93 (bs, 1H), 1.24 (d, *J* = 6.5 Hz, 3H, −CH$_3$), 0.90 (m, 12H), 0.58 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 143.26, 140.86, 138.83, 138.77, 138.19, 138.13, 138.03, 137.81, 137.68, 128.51, 128.45, 128.42, 128.39, 128.37, 128.33, 128.29, 128.16, 128.12, 128.09, 128.03, 127.84, 127.72, 127.63, 127.49, 127.45, 127.36, 127.22, 126.28, anomeric carbons (102.70, 102.35, 101.66, 100.44, 98.58, 97.50), 84.10, 79.86, 79.72, 78.07, 77.77, 76.13, 76.01, 75.62, 75.08, 74.92, 74.82, 73.66, 73.50, 73.41, 73.28, 73.24, 73.01, 72.96, 72.64, 72.57, 72.45, 71.01, 68.67, 68.13, 67.76, 65.88, 60.39, 27.84, 26.84, 17.52, 16.66, 16.38, 14.20, 13.60, 6.88, 4.90; LRMS (ESI) 2281[M + Na$^+$] HRMS (FAB) calcd for $C_{132}H_{151}NO_{28}$-SSiNa, 2280.9809 found 2280.9812 [M + Na$^+$].

Acetylated Hexasaccharide 35. To a solution of Le^Y hexasaccharide **34** (256 mg, 0.113 mmol), a catalytic amount of DMAP, and TEA (0.108 mL) in CH_2Cl_2 (4 mL) was added Ac_2O (0.107 mL, 1.13 mmol), and the mixture was stirred for 24 h. EtOAc (60 mL) was added and the solution washed with saturated aqueous $NaHCO_3$ (3 × 30 mL), dried over $MgSO_4$, filtered, concentrated, and purified by FC (25% EtOAc/hexanes) to afford 217 mg (80%) of **35** as a white solid: [α] = −68.8 (*c* 1, $CHCl_3$); IR (thin film) 2948, 2868, 1746, 1706, 1646, 1497, 1452, 1367, 1237, 1222, 1166, 1097, 1068, 990, 913, 843, 804, 739; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.2 Hz, 2H), 7.56−6.94 (m, 63H), 6.30 (d, *J* = 6.1 Hz, 1H), 5.67 (d, *J* = 3.5 Hz, 1H), 5.44 (d, *J* = 2.8 Hz, 1H), 5.39 (d, *J* = 8.0 Hz, 1H), 5.14 (t, *J* = 8.4 Hz, 1H), 4.92 (d, *J* = 11.2 Hz, 1H), 4.76−4.70 (m, 8H), 4.65 (d, *J* = 6.3 Hz, 1H), 4.60 (s, 1H), 4.57−4.30 (m, 19H), 4.18−4.11 (m, 3H), 4.07 (dd, *J* = 10.2, *J* = 3.7 Hz, 1H), 4.03−3.61 (m, 17H), 3.54 (m, 1H), 3.47 (m, 2H), 3.37 (q, *J* = 8.9 Hz, *J* = 4.7 Hz, 1H), 3.22 (s, 1H), 1.97 (m, 9H), 1.36 (d, *J* = 6.3 Hz, 3H, CH$_3$), 1.18 (d, *J* = 6.2 Hz, 3H, CH$_3$), 0.91 (t, *J* = 7.9 Hz, 9H, −Si−CH$_2$CH$_3$), 0.55 (q, *J* = 7.8 Hz, 6H, −Si−CH$_2$CH$_3$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.73, 170.31, 170.25, 143.11, 139.75, 139.08, 138.81, 138.69, 138.62, 138.54, 138.08, 138.04, 137.92, 137.87, 137.78, 133.81, 130.38, 128.61, 128.54, 128.45, 128.40, 128.37, 128.34, 128.17, 128.09, 128.06, 128.03, 127.96, 127.92, 127.85, 127.75, 127.70, 127.62, 127.51, 127.43, 127.40, 127.33, 127.10, 127.06, 126.98, 126.92, 126.01, anomeric carbons (102.11 101.68, 100.05, 99.65, 98.03, 96.68), 83.99, 79.88, 79.18, 78.98, 78.29, 75.57, 75.35, 75.15, 74.98, 74.37, 74.13, 73.86, 73.75, 73.44, 73.38, 73.29, 72.61, 72.39, 72.21, 71.57, 69.77, 69.21, 67.97, 67.11, 66.99, 64.65, 24.58, 20.99, 20.90, 16.58, 16.29, 6.86, 4.85; LRMS (ESI) 2407 [M + Na$^+$] HRMS (FAB) calcd for $C_{138}H_{157}O_{31}NSSiNa$, 2407.0126, found 2407.0127 [M + Na$^+$].

Le^Y Hexasaccharide Glycal 36. To a solution of **35** (208 mg, 0.0871 mmol) in THF (5 mL) was added a solution of 1 M TBAF/THF and CH_3COOH (1:1, 0.348 mmol, 4 equiv). The resulting solution was stirred at room temperature for 15 h, diluted with EtOAc (60 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 30 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by FC (1:1 EtOAc/hexanes) to give 192 mg (97%) of **36** as a white foam: [α] = −21.8 (*c* 1, $CHCl_3$); IR (thin film) 3377, 2931, 2860, 1742, 1466, 1396, 1366, 1266, 1049, 1008, 949, 861, 793, 723; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7 Hz, 2H), 7.50−7.03 (multiple protons, Bn, Ph), 6.34 (d, *J* = 6.0 Hz, 1H), 5.68 (d, *J* = 2.7 Hz, 1H), 5.41 (d, *J* = 8.0 Hz, 1H), 5.31 (d, *J* = 3.5 Hz, 1H), 5.21 (d, m, 1H), 4.92 (d, *J* = 9.6 Hz, 1H), 4.81−4.64 (m, 11 H), 4.62 (d, *J* = 11.3 Hz, 2H), 4.55−4.28 (m, 20 H), 4.15−3.98 (m, 4H), 3.94 (d, *J* = 1.6 Hz, 1H), 3.90−3.70 (m, 12 H), 3.64 (dd, *J* = 6.1 Hz, *J* = 3.3 Hz, 1H), 3.55 (dd, *J* = 10.2 Hz, *J* = 2.8 Hz, 1H), 3.44 (dd, *J* = 9.6 Hz, *J* = 2.5 Hz, 1H), 3.40−3.22 (m, 5H), 2.02 (s, 3H), 1.95 (s, 6H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.66, 170.64, 170.38, 143.76, 139.70, 138.77, 138.68, 138.39, 138.23, 137.73, 137.28, 130.31, 128.63, 128.52, 128.47, 128.42, 128.39, 128.37, 128.33, 128.16, 128.08, 128.06, 128.03, 128.01, 127.95, 127.89, 127.61, 127.58, 127. 33, 127.31, 126.94, 125.99, anomeric carbons (103.18, 101.87, 101.66, 99.69, 97.97, 96.69), 83.98, 80.64, 79.87, 78.98, 78.25, 76.76, 76.02, 75.55, 74.87, 74.39, 74.35, 74.17, 73.74, 73.65, 73.64, 73.58, 73.38, 73.22, 72.52, 72.40, 72.35, 72.16, 71.56, 68.34, 66.92, 66.84, 53.26, 29.70, 24.51, 21.02, 20.85, 16.56, 16.26, 14.22, 14.03; LRMS (ESI) 2292.9[M + Na$^+$] HRMS (FAB) calcd for $C_{132}H_{143}O_{31}NSNa$ 2292.9261818, found 2292.9232[M + Na$^+$].

Le^Y Heptasaccharide Glycal 37. A mixture of Le^Y hexasaccharide glycal **36** (192 mg, 0.0845 mmol) and β-fluoroucose **10** (148 mg, 0.338 mmol, 4 equiv) was dried azeotropically with benzene (3 × 3 mL) and under high vacuum for 2 h. Freshly activated 4 Å molecular sieves (300 mg) were added to the mixture under Ar, followed by toluene (5 mL). The suspension was cooled to 0 °C, and 2,6-di-*tert*-butyl pyridine (0.190 mL, 0.85 mmol, 10 equiv) was added, followed by a solution of Sn(OTf)$_2$ (71 mg, 0.169 mmol, 2 equiv) in THF (0.55 mL). The suspension was allowed to warm slowly to room temperature, stirred for 48 h, and then quenched with Et_3N (1 mL), diluted with EtOAc (60 mL), and washed with saturated aqueous $NaHCO_3$ and brine. The organics were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by FC (15−25% EtOAc/hexane to afford 109 mg (48%) of **37** as white foam: [α] = −78 (*c* 0.7, $CHCl_3$); IR (thin film) 3360, 3027,

2871, 1957, 1879, 1816, 1749, 1702, 1650, 1577, 1452, 1362, 1301, 1223, 1156, 1098, 1020, 739, 690; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J = 7.5 Hz, 2H), 7.53−7.10 (multiple protons, Bn, Ph), 7.01 (m, 2H), 6.94 (d, J = 6.8 Hz, 2H), 6.41 (d, J = 6.1 Hz, 1H), 5.67 (d, J = 4.6 Hz, 1H), 5.45−5.37 (m, 2H), 5, 19−4.90 (m, 3H), 4.87 (d, J = 4.4 Hz, 1H), 4.82−4.44 (m, 26H), 4.41−3.44 (m, 35H), 3.40 (d, J = 2.8 Hz, 1H), 3.36 (d, J = 10.5 Hz, 1H), 3.26−3.21 (m, 2H), 2.02 −1.83 (m, 9H), 1.35 (d, J = 6.1 Hz, 3H), 1.18 (d, J = 6.1, 1.05 (d, J = 6.4 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.73, 170.22, 144.86, 139.75, 138.79, 138.69, 138.62, 138.06, 137.78, 130.40, 128.63, 128.54, 128.40, 128.25, 128.19, 128.15, 128.10, 128.05, 127.96, 127.91, 127.73, 127.61, 127.54, 127.48, 127.43, 127.39, 127.07, 126.97, 126.87, 126.02, anomeric carbons (101.77, 101.67, 99.90, 99.61, 98.04, 96.67, 94.14), 83.99, 79.87, 78.29, 75.58, 75.37, 74.99, 74.47, 74.37, 74.22, 74.13, 73.79, 73.59, 73.40, 73.15, 73.08, 72.56, 72.38, 72.23, 71.58, 70.90, 67.81, 67.74, 66.99, 66.85, 29.72, 24.60, 20.98, 20.87, 16.66, 16.58, 16.30; LRMS (ESI) calcd for $C_{159}H_{171}O_{35}NSNa$ 2709.1249, found 2708.6 [M + Na^+].

Le^y Heptasaccharide Glycal Peracetate 38. A solution of heptasaccharide **37** (51 mg, 0.0188 mmol) in THF (1.5 mL) was added via cannula to a solution of sodium (72 mg, 3.13 mmol) in liquid ammonia (10 mL) under Ar at −78 °C. The reaction mixture was stirred for 40 min, quenched with MeOH (2 mL), stirred for 15 min, and concentrated with a stream of dry Ar. MeOH (5 mL) was added to the residue, followed by NH_4Cl (168 mg, 3.13 mmol), and the resulting solution was stirred for 80 min and then concentrated to dryness. The crude product was suspended in a mixture of THF (1.5 mL), DMF (0.5 mL), and TEA (0.6 mL). To this were added Ac_2O (0.32 mL, 3.4 mmol) and a catalytic amount of DMAP, and the reaction mixture was stirred at room temperature for 10 h and then poured into ice−water (10 mL) and extracted with EtOAc (3 × 50 mL). The organics were washed with saturated aqueous $NaHCO_3$ and H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by FC (65% EtOAc/CH_2Cl_2) afforded 23 mg (67%) of **38** as a white solid: [α] = −27.3 (*c* 0.7, CH_2Cl_2); IR (thin film) 3365, 2954, 1742, 1678, 1537, 1443, 1372, 1231, 1137, 1072, 967, 912, 737, 696; ^{1}H NMR ($CDCl_3$) δ 6.30 (d, J = 6.2 Hz, 1H), 5.38−5.26 (m, 6H), 5.21 (d, J = 4.1 Hz, 1H), 5.18 (d, J = 3.4 Hz, 1H), 5.15 (m, 1H), 5.10(dd, J = 11 Hz, J = 3.1 Hz, 1H), 5.06−4.87 (m, 8H), 4.68 (q, J = 6.2 Hz, J = 3.3 Hz, 1H), 4.61 (d, J = 7.9 Hz, 1H)), 4.55−4.41 (m, 4H), 4.36 (d, J = 6.6 Hz, 1H), 4.30 (t, J = 9 Hz, 1H), 4.25−3.97 (m, 9H), 3.88−3.69 (m, 6H), 3.37 (d, J = 9.8 Hz, 1H), 2.86 (bs, 1H), 2.12−1.83 (m, 54 H), 1.14 (d, J = 6.5 Hz, 3H), 1.11 (d, J = 6. Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.16, 169.92, 169.73, 169.68, 169.64, 169.56, 169.42, 169.25, 169.17, 168.98, 168.85, 168.78, 168.67, 143.77, anomeric carbons (99.42, 99.00, 98.11, 96.78, 95.25, 94.65, 91.49), 75.15, 73.64, 72.97, 72.31, 71.97, 71.55, 71.30, 70.49, 70.39, 70.26, 69.91, 69.81, 69.52, 67.67, 67.11, 67.07, 66.87, 66.70, 66.49, 65.86, 64.09, 63.54, 62.97, 60.44, 60.20, 59.48, 28.68, 22.44, 20.12, 19.96, 19.91, 19.77, 19.75, 19.72, 19.69, 19.65, 19.60, 14.90, 14.54; LRMS (ESI) 1848.5 [M + Na^+]; HRMS (FAB) calcd for $C_{78}H_{107}NO_{48}Na$ 1848.5859, found 1848.5867.

Allyl Glycoside of Le^y Heptasaccharide Peracetate 39. A mixture of Le^y heptasaccharide glycal **38** (23 mg, 0.0125 mmol, dried azeotropically with benzene (3 × 5 mL) and under high vacuum for 2 h) and freshly activated 4 Å powdered molecular sieves (30 mg) was suspended in CH_2Cl_2 (1 mL) and cooled to 0 °C. DMDO (0.6 mL, 0.11 M solution in Me_2CO) was then added. The reaction mixture was stirred at 0 °C for 1 h, the solvent was evaporated, and the residue was taken up in allyl alcohol (5 mL). This mixture was stirred at room temperature for 48 h, the solvent was evaporated, and the product was purified by FC (60% EtOAc/CH_2Cl_2) to afford 23 mg (92%) **39** as a white solid: [α] = −30.5 (*c* 1, CH_2Cl_2); IR (thin film) 3375, 2999, 1749, 1664, 1531, 1428, 1367, 1222, 1071, 1035, 974, 944, 732; ^{1}H NMR ($CDCl_3$) δ 5.90 (m, 1H, CH=CH_2), 5.63 (d, J = 3.7 Hz, 1H), 5.41 (d, J = 3.5 Hz, 2H), 5.35−5.22 (m, 9H), 5.16 (dd, J = 10.6 Hz, 1H),5.12 (ds, J = 3.5 Hz, 1H), 5.07−4.95 (m, 8H), 4.67 (d, J = 11.0 Hz, 1H), 4.62 (d, J = 7.9 Hz, 1H), 4.57 (d, J = 8.1 Hz, 1H), 4.51 (q, 2H), 4.42 (d, J = 7.6 Hz, 1H), 4.40 (d, J = 8.2 Hz, 1H), 4.35−4.30 (m, 3H), 4.26 (d, J = 7.8 Hz, 1H), 4.10 (q, J = 11.5 Hz, J = 3.8 Hz, 1H), 4.08−3.69 (m, 11H), 3.46 (m, 3H), 2.92(bs, 1H), 2.19−1.89 (m, 54H), 1.22 (d, J = 6.6 Hz, 6H), 1.18 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.56, 171.34, 171.27, 171.16, 171.05, 170.90, 170.83, 170.79, 170.76, 170.65, 170.59, 170.38, 170.20, 170.16, 169.81, 133.75, 119.06, anomeric carbons (101.74, 101.01, 100.85, 99.39, 96.69, 96.38, 96.08), 78.11, 76.76, 75.69, 74.35, 73.90, 73.76, 73.38, 73.05, 72.01, 71.82, 71.68, 71.37, 71.22, 71.11, 70.98, 69.01, 68.61, 68.55, 68.32, 68.12, 67.88, 67.21, 65.54, 64.38, 61.27, 60.87, 30.09, 23.86, 21.52, 21.38, 21.35, 21.29, 21.26, 21.18, 21.14, 21.08, 21.0116.32, 15.98; LRMS (ESI) 1922.8 [M + Na^+]; HRMS calcd for $C_{81}H_{113}NO_{50}Na$ 1922.6226, found 1922.6227.

Allyl Glycoside of Le^y Heptasaccharide 40. To a solution of hexasaccharide **39** (23 mg, 0.0121 mmol) in MeOH (0.5 mL) was added NaOMe (5%, 0.235 mL). After 12 h, the mixture was neutralized with Dowex 50-x8, filtered, and concentrated. Purification of the residue with RP-18 reversed-phase silica gel (5% MeOH/H_2O) gave 12.9 mg (90%) of **40** as a white solid: [α] = −31 (*c* 0.23, MeOH); IR (thin film) 3411, 2975, 2891, 1585, 1416, 1355, 1077, 1022, 768; ^{1}H NMR (D_2O) δ 5.86 (m, 1H, CH=CH_2), 5.34 (d, J = 3.9 Hz, 1H), 5.24 (dd, J = 17.2 Hz, J = 1.7, 1H), 5.07 (d, J = 3.3, 2H), 5.06 (d, J = 1.7 Hz, 1H), 4.7 (d, J = 3.9 Hz, 1H), 4.59 (d, 8.3 Hz, 1H), 4.42 (m, 1H), 4.32 (d, J = 7.8 Hz, 1H), 4.22 (d, J = 7.9 Hz, 1H), 4.11−3.25 (multiple protons), 1.9 (s, 3H), 1.15 (m, 6H), 1.06 (d, J = 6.6 Hz, 3H); LRMS (ESI) 1208.4 [M + Na^+]; HRMS (FAB) calcd for $C_{47}H_{79}NO_{33}Na$ 1208.4431, found 1208.4433.

Le^y Nonasaccharide Glycal 42. A mixture of Le^y heptasaccharide **37** (59 mg, 0.022 mmol) and benzenesulfonamide (10 mg, 0.065 mmol) was dried azeotropically with benzene (3 × 3 mL) and under high vacuum for 2 h. Freshly activated 4 Å molecular sieves (60 mg) were added to the mixture under Ar, followed by CH_2Cl_2 (1 mL). The resulting suspension was cooled to 0 °C, and I (sym-coll)$_2ClO_4$ (36 mg, 0.077 mmol) was added under Ar. The reaction mixture was stirred at 0 °C for 40 min, quenched with saturated aqueous $Na_2S_2O_3$ (1 mL), diluted with EtOAc (20 mL), and then filtered through Celite. The filtrate was washed with saturated aqueous $Na_2S_2O_3$ (2 × 10 mL), saturated aqueous $CuSO_4$ (2 × 10 mL), and brine (1 × 10 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The residue was taken up in 30% EtOAc/hexanes and passed through a short SiO_2 column. The collected iodosulfonamide **41** was dried (azeotropically with benzene and under high vacuum for 3 h) and used without further purification. Freshly activated 4 Å molecular sieves (40 mg) were added to **41** under Ar, followed by solution of tin ether of **8** (prepared from 35 mg of **19** and 0.018 mL of $(Bu_3Sn)_2O$ (0.018 mL) as described for **21**). The suspension was cooled to −70 °C and $AgBF_4$ (10 mg) in THF (1 mL) added via cannula. The reaction mixture was stirred with exclusion of light, allowed to warm slowly during about 5 h, and then stirred at room temperature for 3 days. EtOAc was added, and the mixture was filtered through Celite. The filtrates were diluted additionally with EtOAc and washed with saturated aqueous solution of $NaHCO_3$ (3 × 30 mL) and brine (1 × 30 mL). The organics were dried over $MgSO_4$, filtered, concentrated, and chromatographed (FC 27−50% EtOAc/hexanes) to give 34 mg of **42** (32% overall yield for the two steps): [α] = −25.7 (*c* 1, CH_2Cl_2); IR (thin film) 3477, 3335, 3050, 2931, 2860, 1741, 1706, 1445, 1362, 1225, 1166, 1101, 1053, 733; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10(d, J = 7.7 Hz, 2H), 7.80 (d, J = 7.5 Hz, 1H), 7.55−6.92 (m, 98H), 6.40 (d, J = 6.0 Hz, 1H), 5.67 (d, J = 3.7 Hz, 1H), 5.42−5.39 (m, 2H), 5.21−5.15 (m, 1H), 4.94−3.21 (m, 90H), 2.03 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.18 (d, J = 6.1 Hz, 3H), 0.90 (s, J = 6.4 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 172.74, 171.01, 170.45, 144.58 (anomeric olefinic), 139.71, 138.84, 138.69, 138.54, 138.43, 137.82, 137.76, 133.94, 132.40, 130.38, 128.88, 128.63,

128.55, 128.48, 128.45, 128.40, 128.36, 128.32, 128.26, 128.22, 128.11, 128.07, 127.97, 127.92, 127.87, 127.75, 127.69, 127.65, 127.61, 127.57, 127.52, 127.43, 127.36, 127.28, 127.14, 127.00, 126.97, 126.88, 126.44, 126.02, 109.20, anomeric carbons (103.29, 102.84, 101.69, 100.50, 100.30, 99.61, 98.03, 96.69, 96.13), 83.93, 79.87, 78.97, 78.33, 75.60, 75.41, 74.98, 74.67, 74.40, 74.15, 74.11, 73.82, 73.49, 73.39, 72.65, 72.43, 72.28, 71.63, 70.90, 70.74, 69.06, 67.69, 67.11, 66.86, 55.34, 53.74, 48.11, 46.47, 44.53, 29.71, 24.57, 21.07, 20.95, 16.57, 16.28, 14.15, 11.47; LRMS calcd for $C_{198}H_{214}O_{46}N_2S_2$·2Na 3465.3703, found 3465.4 [M + 2Na^{2+}].

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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