JOC Article

Mirror-Image Carbohydrates: Synthesis of the Unnatural Enantiomer of a Blood Group Trisaccharide

Fabien P. Boulineau and Alexander Wei*

Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084

alexwei@purdue.edu

Received December 6, 2003

Methyl D-glucoside and D-glucose pentaacetate are transformed, respectively, into methyl α-*O*-glucuronide **3** and hydroxymethyl *β*-*C*-glucuronide **9**, which undergo decarboxylative elimination efficiently to produce 4-deoxypentenoside **4** and L-glucal **10**. These unsaturated pyranosides provide an expeditious entry into mirror-image oligosaccharides, as demonstrated in the synthesis of the unnatural enantiomer of the H-type II blood group determinant trisaccharide (D-Fuc-(α1→2)-L-Gal-(*β*1→4)-L-GlcNAc-*β*-OMe). This work illustrates that D-glucose, a common starting material in the synthesis of naturally occurring carbohydrates, can also be used to prepare their mirror-image analogues.

Introduction

The role of chirality at the chemistry−biology interface is a topic of enormous fascination and importance.[1−3] Organic structures have an intrinsic capacity for chiral discrimination, but the relationships between molecular stereochemistry and biological function are not always predictable. While it is often assumed that biomolecular recognition processes are stereospecific, there are many notable exceptions. A well-known example in which chiral specificity is completely absent is the mammalian taste bud receptor, which recognizes D-sugars and L-sugars with equal avidity.[4] The biological activities of various natural products versus that of their antipodes also provide numerous instances in which activity is not exclusively determined by molecular chirality.[5−10] Indeed, there are cases in which signaling can be modulated by varying the enantiomeric excess of the pheromone,[11] and there is at least one example in which the potency of the unnatural enantiomer is superior to that of the natural product itself.[12] It is therefore apparent that enantiospecificity, while important in very many situations, is not a universal trait of biomolecular recognition.

A dichotomy in this paradigm is that the building blocks of the three main classes of biopolymers—peptides, nucleic acids, and carbohydrates—are essentially homochiral. The basic set of amino acids which comprise most proteins share the same α-carbon stereochemistry commonly referred to as the L configuration, whereas nucleotides and most pyranosidic polysaccharides are derived from carbohydrates having a D configuration, as defined by the chiral center most remote from the reducing end.[13] To further probe this fundamental aspect of biomolecular chirality, a number of research groups have engaged in the synthesis and evaluation of mirror-image biopolymers. Proteins and polypeptides comprised solely of D-amino acids have been synthesized and shown to be intriguing compounds in mirror-image receptor binding, as these are likely to resist enzymatic degradation.[14−17] A similar line of thinking has been applied to nucleic acids: oligomers composed of nucleotides derived from 2-deoxy-L-ribofuranose have been synthesized and successfully assembled into mirror-image DNA duplexes,[18] and efforts toward mirror-image RNA oligonucleotides are being pursued.[19]

(1) Prelog, V. *Science* **1976**, *193*, 17.
(2) Joyce, G. F.; Visser, G. M.; van Boeckel, C. A. A.; van Boom, J. H.; Orgel, L. E.; van Westrenen, J. *Nature* **1984**, *310*, 602.
(3) Takats, Z.; Nanita, S. C.; Cooks, R. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 3521.
(4) Shallenberger, R. S.; Acree, T. E.; Lee, C. Y. *Nature* **1969**, *221*, 555.
(5) Kelly, R. C.; Gebhard, I.; Wicnienski, N.; Aristoff, P. A.; Johnson, P. D.; Martin, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 6837.
(6) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796.
(7) Mickus, D. E.; Levitt, D. G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 359.
(8) Boger, D. L.; Johnson, D. S.; Yun, W. *J. Am. Chem. Soc.* **1994**, *116*, 1635.
(9) Boger, D. L.; Hüter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839.
(10) Gargiulo, D.; Musser, S. S.; Yang, L.; Fukuyama, T.; Tomasz, M. *J. Am. Chem. Soc.* **1995**, *117*, 9388.
(11) Mori, K. *Eur. J. Org. Chem.* **1998**, *1479*, 9 and references therein.
(12) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515.
(13) McNaught, A. D. *Pur. Appl. Chem.* **1996**, *68*, 1919.
(14) (a) Milton, R. C. D.; Milton, S. C. F.; Kent, S. B. H. *Science* **1992**, *256*, 1445. (b) Chalifour, R. J.; McLaughlin, R. W.; Lavoie, L.; Morissette, C.; Tremblay, N.; Boule, M.; Sarazin, P.; Stea, D.; Lacombe, D.; P., T.; Gervais, F. *J. Biol. Chem.* **2003**, *278*, 34874.
(15) Dooley, C. T.; Chung, N. N.; Wilkes, B. C.; Schiller, P. W.; Bidlack, J. M.; Pasternak, G. W.; Houghten, R. A. *Science* **1994**, *266*, 2019.
(16) Schumacher, T. N. M.; Mayr, L. M.; Minor, D. L. J.; Milhollen, M. A.; Burgess, M. W.; Kim, P. S. *Science* **1996**, *271*, 1854.
(17) Kozlov, I. A.; Mao, S.; Xu, Y.; Huang, X.; Lee, L.; Sears, P. S.; Gao, C.; Coyle, A. R.; Janda, K. D.; Wong, C.-H. *ChemBioChem* **2001**, *2*, 741.
(18) (a) Urata, H.; Shinohara, K.; Ogura, E.; Ueda, Y.; Akagi, M. *J. Am. Chem. Soc.* **1991**, *113*, 8174. (b) Urata, H.; Ueda, Y.; Usami, Y.; Akagi, M. *J. Am. Chem. Soc.* **1993**, *115*, 7135.
(19) Akagi, M.; Omae, D.; Tamura, Y.; Ueda, T.; Kumashiro, T.; Urata, H. *Chem. Pharm. Bull.* **2002**, *50*, 866.

10.1021/jo035789l CCC: $27.50
Published on Web 04/09/2004

In comparison, oligosaccharides and glycoconjugates based on mirror-image pyranosides have received less attention. This is partly due to the synthetic challenge and high cost of using L-pyranosides as synthetic precursors but also to the knowledge base still being developed for the various biological roles of carbohydrates. Mirror-image carbohydrates may be useful for addressing the significance of molecular chirality in glycobiology, particularly in situations where the biomolecular interactions are not well defined, such as carbohydrate−carbohydrate interactions.[20] In addition, it is worth noting that compounds containing L-sugars often have biological activities of medicinal or agricultural value which are superior to that of their D-sugar analogues.[21−23] This suggests that mirror-image oligosaccharides and glycoconjugates may present untapped opportunities for the discovery and development of compounds with potent biological activity.

The synthesis of mirror-image carbohydrates requires a general but expeditious route to L-pyranosides and other rare sugars. To address this, we have developed methodologies based on the degradation of D-glucuronic acid (GlcA) derivatives to unsaturated pyranosides, in which the C4 and C5 substituents have been removed.[24] For example, α- and *β*-*O*-GlcA derivatives can be transformed in good yields into 4-deoxypentenosides (4-DPs) by decarboxylative elimination, a method originally described by Žemlička and co-workers.[25] We have recently demonstrated that the same approach can also be applied to *β*-*C*-GlcA intermediates to obtain L-glycals.[26] These dihydropyrans can be epoxidized and reacted with nucleophiles with high levels of stereocontrol and provide a novel entry into L-sugars and mirror-image oligosaccharides.

In this paper, we describe an efficient synthesis of trisaccharide **1**, the unnatural enantiomer of the H-type II blood group determinant (see Figure 1).[27] The H-type II trisaccharide is characterized by an *N*-acetyllactosamine unit which is α-fucosylated at the C2 position of the galactosyl moiety. The synthesis of mirror-image trisaccharide **1** (α-D-Fuc(1→2)-*β*-L-Gal-(1→4)-*β*-L-GlcNAc-OMe) is achieved by constructing the D-fucosyl and *N*-acetyl-L-lactosaminyl units from 4-DP and L-glycal derivatives, respectively, both of which are ultimately derived from D-glucose.

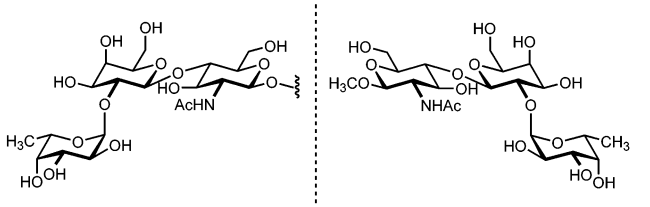
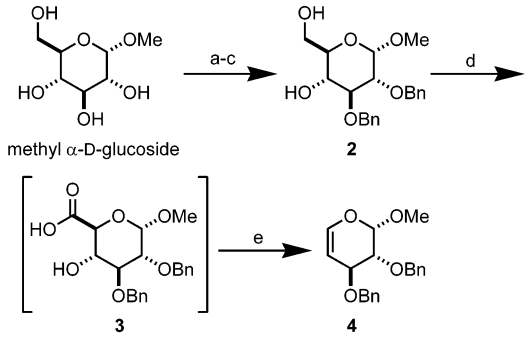


FIGURE 1. H-type II blood group determinant and its unnatural enantiomer **1**.

SCHEME 1. Synthesis of 4-Deoxypentenoside 4[a]



[a] Reagents and conditions: (a) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, THF, 85 °C; (b) NaH, BnBr, DMF, rt; (c) 8:1:1 AcOH/THF/H_2O, 45 °C (60% over three steps); (d) NaOCl, TEMPO (5 mol %), satd aq $NaHCO_3$, CH_2Cl_2, 0 °C; (e) DMFDNA, toluene, 120 °C (70% over two steps).

Results and Discussion

Synthesis of 4-Deoxypentenosides and L-Glycals. Given the successful application of D-glycals as building blocks in organic chemistry and oligosaccharide synthesis,[28] we considered that other chiral dihydropyrans could be similarly useful as synthons for exploring uncharted areas of structural or chiral space. In particular, 4-DPs (4,5-unsaturated pentopyranosides) were attractive because of their structural resemblance to glycals. Such derivatives have been prepared by the degradation of common pyranosides such as D-glucose[25] and D-xylose,[29] but to the best of our knowledge no synthetic applications of 4-DPs had been reported prior to our work.

We elected to synthesize 4-DP derivative **4** from D-glucose, based on the route described by Žemlička and co-workers (see Scheme 1).[25] 2,3-Di-*O*-benzyl glucoside **2** was prepared in multigram quantities from methyl α-D-glucoside in three steps and 60% yield[30], then oxidized to GlcA derivative **3** and refluxed in toluene with *N*,*N*-dimethylformamide dineopentyl acetal (DMFDNA), a reagent developed by Eschenmoser for the decarboxylative elimination of *β*-hydroxy acids.[31] In their original protocol, Žemlička and co-workers oxidized 4,6-diol **2** with Pt/C and O_2, followed by treatment with DMFDNA in DMF at 40 °C; however, in our hands this sequence did not produce high yields. Replacing the first step with a

(20) (a) Rojo, J.; Morales, J. C.; Penadés, S. In *Host−Guest Chemistry*; Penadés, S., Ed.; Topics in Currrent Chemistry Vol. 218; Springer: Berlin, 2002; p 45. (b) Burger, M. M.; Spillmann, D. *J. Cell. Biochem.* **1996**, *61*, 562.

(21) Berkowitz, D. B.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 4518.

(22) Anzeveno, P. B.; Green, F. R., III. In *Synthesis and Chemistry of Agrochemicals VI*; Baker, D. R., Fenyes, J. G., Lahm, G. P., Selby, T. P., Stevenson, T. M., Eds.; ACS Symposium Series 800; American Chemical Society: Washington, DC, 2002; p 262.

(23) Flekhter, O. B.; Baltina, L. A.; Tolstikov, G. A. *J. Nat. Prod.* **2000**, *63*, 992.

(24) Boulineau, F. P.; Wei, A. *Org. Lett.* **2002**, *4*, 2281.

(25) Philips, K. D.; Zemlicka, J.; Horwitz, J. P. *Carbohydr. Res.* **1973**, *30*, 281.

(26) Boulineau, F. P.; Wei, A. *Org. Lett.* **2004**, *6*, 119.

(27) Examples of blood group determinant syntheses: (a) Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4063. (b) Jacquinet, J.-C.; Sinay, P. *Tetrahedron Lett.* **1976**, *32*, 1693. (c) Petrakova, E.; Spohr, U.; Lemieux, R. U. *Can. J. Chem.* **1992**, *70*, 233. (d) Danishefsky, S. J.; Behar, V.; Randolph, J. T.; Lloyd, K. O. *J. Am. Chem. Soc.* **1995**, *117*, 5701. (e) Routenberg, K.; Andrade, R. B.; Seeberger, P. H. *J. Org. Chem.* **2001**, *66*, 8165.

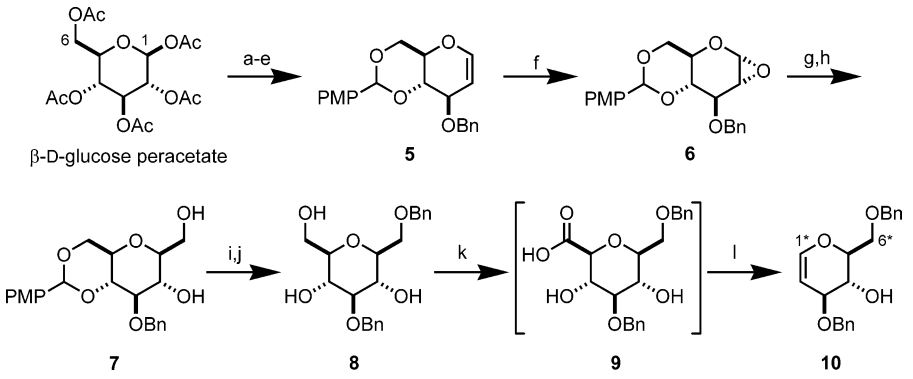
(28) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

(29) Ferrier, R. J.; Tyler, P. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2767.

(30) Bakó, P.; Bajor, Z.; László, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3651.

(31) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.

SCHEME 2. Synthesis of L-Glucal 1[a]



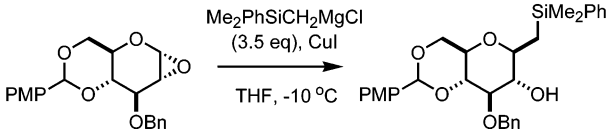
[a] PMP = *p*-methoxyphenyl. Reagents and conditions: (a) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt; (b) NaOMe, MeOH/CH_2Cl_2, 0 °C; (c) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, THF, 85 °C; (d) NaH, BnBr, DMF, rt; (e) lithium naphthalenide, THF, −78 °C (47% over five steps); (f) DMDO, acetone/CH_2Cl_2, 0 °C; (g) $Me_2(i\text{-PrO})SiCH_2MgCl$ (3.5 equiv), CuI (0.5 equiv), THF, −10 °C; (h) H_2O_2, KOH, MeOH/THF, rt (66% over three steps); (i) Bu_2SnO, toluene, reflux then Bu_4NI, BnBr, reflux (94%); (j) AcOH, THF/H_2O, 45 °C (96%); (k) NaOCl, TEMPO (5 mol %), satd aq $NaHCO_3$, CH_2Cl_2, 0 °C; (l) DMFDNA, xylenes, 150 °C (60% over two steps).

hypochlorite oxidation catalyzed by tetramethyl-1-piperidine oxide (TEMPO)[32] and raising the temperature of the decarboxylative elimination afforded compound **4** from diol **2** in 70% yield.

The decarboxylative elimination approach was then applied toward the synthesis of L-glucal **10** from the corresponding *β-C*-glycoside intermediate (see Scheme 2).[26] D-Glucal **5** was obtained on a multigram scale from commercially available *β*-D-glucose pentaacetate in five steps and 47% overall yield, using the procedure reported by Sinaÿ and co-workers.[33,34] Treatment with dimethyldioxirane (DMDO) gave α-epoxyglycal **6**, followed by CuI-mediated addition of $Me_2(i\text{-PrO})SiCH_2MgCl$ and Tamao−Kumada oxidation[35] to afford hydroxymethyl *β-C*-glycoside **7** in three steps and 66% overall yield from **5**. A brief survey of reaction conditions with a similar α-silyl Grignard reagent ($Me_2PhSiCH_2MgCl$) demonstrated the importance of CuI for efficient addition: whereas high yields were observed with 0.5 equiv of CuI, the yields decreased with 0.1 equiv and the absence of CuI did not provide any conversion at all (see Table 1).

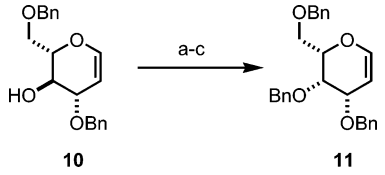
Regioselective benzylation and deacetalization transformed unsymmetrically protected *meso C*-glycoside **7** into triol **8** in 90% yield, which was converted into *β-C*-GlcA **9** by TEMPO oxidation (see Scheme 2). Decarboxylative elimination using DMFDNA in refluxing xylenes yielded 3*,6*-*O*-dibenzyl-L-glucal **10** in 60% yield.[36] Higher temperatures were needed for efficient decarboxylative elimination of the *β-C*-glucuronide, indicative of a greater activation barrier imposed by the anomeric alkyl substituent.[26] This strongly suggests that decarboxylative elimination proceeds by an E2 mechanism, in which the intermediate glucuronides must adopt $^1C_4$ or twist-boat conformations with *trans*-diaxial C4 and C5 substituents, rather than by the concerted fragmentation of a cyclic orthoamide intermediate.[32,37,38]

TABLE 1. CuI-Mediated Additions of α-Silyl Grignard Reagents to Epoxyglycal 6



entry	equiv of CuI	yield (%)
1	0.5	80
2	0.1	66
3	0	0

SCHEME 3. Synthesis of L-Galactal 11[a]



[a] Reagents and conditions: (a) Dess−Martin periodinane, $NaHCO_3$, 4A molecular sieves, CH_2Cl_2, rt; (b) $NaBH_4$, CH_3OH/CH_2Cl_2, −5 °C; (c) NaH, BnBr, DMF, rt (80% over three steps).

L-Galactal was obtained in a straightforward manner from L-glucal **10** by epimerization of C4* (see Scheme 3). Oxidation using the Dess−Martin periodinane[39] produced an unstable ketone, which was reduced immediately with $NaBH_4$ in 1:1 CH_3OH/CH_2Cl_2 to afford 3*,6*-*O*-dibenzyl-L-galactal (L-*galacto*/L-*gluco* > 30:1); benzylation yielded tri-*O*-benzyl-L-galactal **11** in high overall yields. With L-glucal **10**, L-galactal **11**, and 4-deoxypentenoside **4** in hand, a variety of mirror-image oligosaccharides were now synthetically accessible.

(32) (a) Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, *19*, 1545. (b) Davis, N. J.; Flitsch, S. L. *Tetrahedron Lett.* **1993**, *34*, 1181.

(33) Fernandez-Mayoralas, A.; Marra, A.; Trumtel, M.; Veyrières, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *188*, 81.

(34) This process is highly scalable, as no column chromatography is required for this sequence. See the Supporting Information for details.

(35) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120.

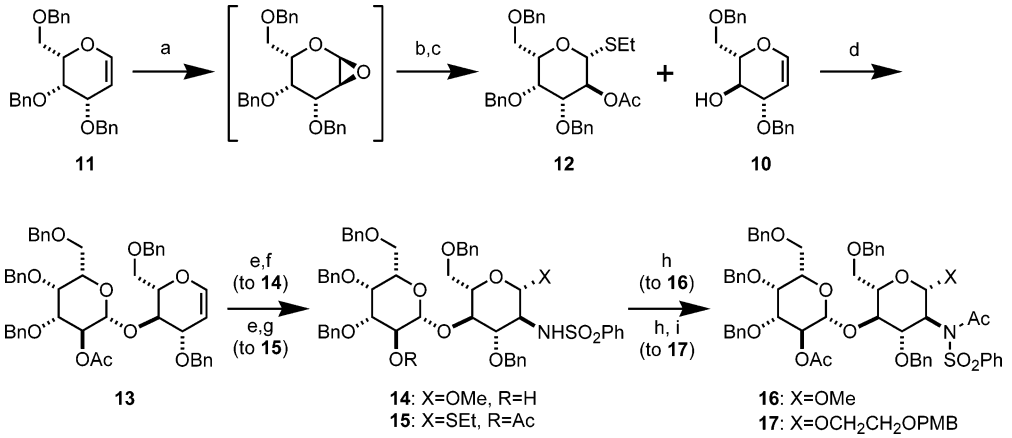
(36) To maintain a consistent nomenclature, the carbons of L-glycals and derivatives thereof have been numbered 1* through 6*.

(37) Mulzer, J.; Brüntrup, G. *Chem. Ber.* **1982**, *115*, 2057.

(38) In addition to the E2 pathway, it is possible that fragmentation may proceed by intramolecular S_N2 displacement of the activated C4 hydroxyl to form an intermediate *β*-lactone, prior to thermal decarboxylation. However, no direct evidence of such intermediates has been observed.

(39) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

SCHEME 4. Synthesis of L-Lactosamine Derivatives[a]



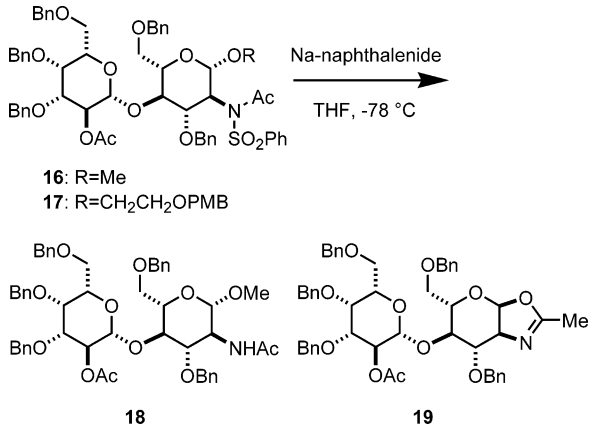
[a] Reagents and conditions: (a) DMDO, CH_2Cl_2/acetone, −55 °C; (b) EtSLi, THF, 0 °C; (c) Ac_2O, pyridine, rt (69% over three steps); (d) donor **12** (1.0 equiv), acceptor **10** (1.5 equiv), MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 4A molecular sieves, CH_2Cl_2, 0 °C (73%); (e) $I(collidine)_2ClO_4$, $PhSO_2NH_2$, 4A molecular sieves, 0 °C; (f) NaOMe, MeOH, rt (84% over two steps); (g) LiHMDS, EtSH, DMF, −40 °C to rt (72% over two steps); (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (96%); (i) $PMBOCH_2CH_2OH$, MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 4A molecular sieves, CH_2Cl_2, 0 °C (68%).

Synthesis of Mirror-Image Carbohydrates. We chose to couple L-galactal with L-glucal to produce L-lactal, a precursor for *N*-acetyl-L-lactosamine and L-lactose (see Scheme 4). The natural enantiomers of both disaccharides are common to the blood group oligosaccharides; in the latter case, a β-lactosyl spacer separates the carbohydrate antigen from the cell-surface anchor.[40] Tribenzyl-L-galactal **11** was treated with anhydrous DMDO to yield the corresponding α-epoxide and then reacted with EtSLi and acetylated to produce thioethyl β-L-galactoside donor **12** in 69% yield. It is worth noting that all traces of acid must be assiduously removed to avoid the competitive formation of the 1,2-*cis*-isopropylidene acetal.[41] L-Galactosyl donor **12** was coupled with 1.5 equiv of L-glucal **10** using the activation conditions described by Danishefsky and co-workers to furnish protected L-lactal **13** in 73% yield.[42]

N-Phenylsulfonyl-L-lactosamine derivatives **14** and **15** were obtained using the sulfonamidoglycosylation protocol developed by Griffith and Danishefsky.[43] Treatment of L-lactal **13** with iodonium dicollidine perchlorate and subsequent reaction with sodium methoxide yielded methyl *N*-phenylsulfonyl-β-L-lactosaminoside **14**, whereas quenching with lithium ethanethiolate afforded the thioethyl β-glycoside **15**. Acetylation of **14** yielded *N*-acetyl-*N*-phenylsulfonyl derivative **16**; an L-lactosaminoside with an extended glycosyl linkage was also prepared by coupling thioglycoside **15** with PMB-protected ethylene glycol[44] after *N*-acetylation to afford **17** as a single stereoisomer. Coupling this linker to **15** without prior *N*-acetylation resulted in a lower yield and a 4:1 β/α ratio of stereoisomers.

The reductive cleavage of the acetylated *N*-phenylsulfonamido groups was expected to yield the corresponding acetamides under relatively mild conditions.[45] This was indeed observed in the case of methyl glycoside **16**, which was transformed cleanly into *N*-acetyl-L-lactosaminoside **18** in 81% yield using sodium naphthalenide (see Scheme 5). However, reductive cleavage of glycol-linked disaccharide **17** did not result in the desired *N*-acetyllactosamine, but instead produced oxazoline **19** in 94% yield plus recovery of the PMB-protected ethylene glycol linker. One possible explanation for this unexpected observation may be attributed to the chelating properties of the ethylene glycol linker: coordination of the sodium counterion could promote nucleophilic attack on the anomeric carbon by the acetamido oxygen. This provides an interesting alternative to 1,2-oxazolines from *N*-acetylglucosamines, which are more typically obtained from their corresponding α-glycosyl halides.[46]

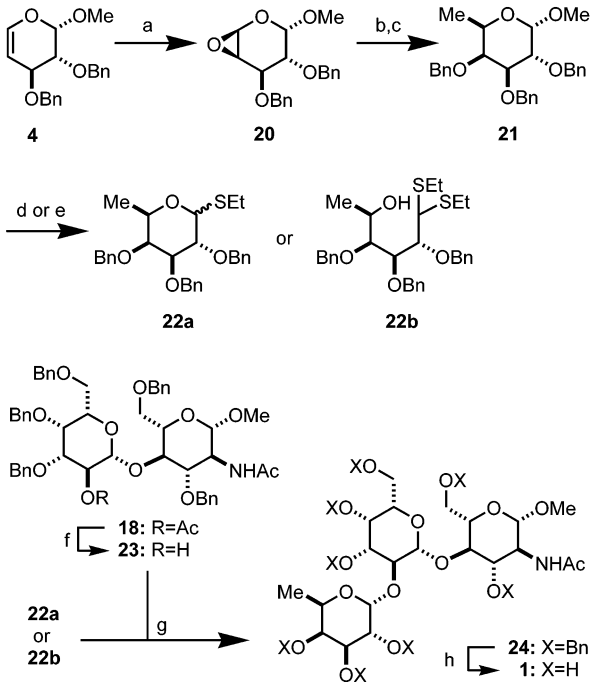
SCHEME 5. Reductive Cleavage of *N*-acetylsulfonamides



The rare sugar D-fucose was synthesized from 4-DP derivative **4**.[47] Stereoselective epoxidation using DMDO

(40) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **2001**, *57*, 207.
(41) Lohman, G. J. S.; Seeberger, P. H. *J. Org. Chem.* **2003**, *68*, 7541.
(42) Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064.
(43) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811.
(44) Huang, H.; Wong, C.-H. *J. Org. Chem.* **1995**, *60*, 3100.
(45) Danishefsky, S. J.; Hu, S.; Cirillo, P. F.; Eckhardt, M.; Seeberger, P. H. *Chem. Eur. J.* **1997**, *3*, 1617.
(46) Shoda, S.-I.; Izumi, R.; Suenaga, M.; Saito, K.; Fujita, M. *Chem. Lett.* **2002**, *2*, 150.
(47) D-Fucose has also been synthesized by C6 deoxygenation of D-galactose: Roush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2227.

SCHEME 6. Synthesis of Mirror-Image Trisaccharide 1[a]



[a] Reagents and conditions: (a) DMDO, CH_2Cl_2/acetone, −55 °C; (b) $AlMe_3$, toluene, −78 °C; (c) NaH, BnBr, DMF, rt (74% over three steps); (d) $BF_3{\cdot}OEt_2$ (1.1 equiv), EtSH (5.0 equiv), CH_2Cl_2, rt (1:2 α/β, 77%); (e) $BF_3{\cdot}OEt_2$ (3.3 equiv), EtSH (5.0 equiv), CH_2Cl_2, rt (75%); (f) NaOMe, MeOH, 45 °C (99%); (g) D-fucosyl donor (2.5 equiv), acceptor **23** (1.0 equiv), DMTST, 2,6-di-*tert*-butyl-4-methylpyridine, 4A molecular sieves, CH_2Cl_2, −78 °C to room temperature (5:1 α/β, 71%); (h) H_2, $Pd(OH)_2$/C, MeOH, rt (99%).

at low temperatures afforded epoxypyranoside **20** in a 10:1 β/α ratio, which was treated with trimethylaluminum in toluene at −78 °C and protected as a C4 benzyl ether to yield D-fucoside **21** in three steps and 74% isolated yield from **4** (see Scheme 6). The stereocontrolled methylation of the 4,5-β-epoxypyranoside is analogous to the syn addition of trialkylaluminum compounds to α-epoxyglycals, which is considered to proceed via an oxocarbenium ion to produce α-*C*-glycosides in good yields.[48] Methyl α-D-fucoside **21** was then converted into thioethyl D-fucoside **22a** in 77% yield as a mixture of diastereoisomers. This reaction was found to be sensitive to reagent stoichiometry; using 2 or more equiv of ethanethiol and $BF_3{\cdot}Et_2O$ produced acyclic dithioacetal **22b** instead.[49]

Methyl *N*-acetyl-β-L-lactosaminoside **18** was deacetylated at O2′ to yield glycosyl acceptor **23** (see Scheme 6). Attempts to couple this with glycosyl donor **22a** using MeOTf (cf. Scheme 4) did not produce any trisaccharide, even after long reaction times at room temperature. However, activation by dimethyl(methylthio)sulfonium triflate (DMTST)[50] afforded trisaccharide **24** as the major product in 59% isolated yield (α/β = 5:1). It is worth mentioning that coupling disaccharide acceptor **23** with acyclic dithioacetal **22b** produced identical results, presumably via in situ regeneration of fucopyranoside **22a**. Last, global debenzylation afforded mirror-image trisaccharide **1**, whose optical activity was opposite that of the naturally occurring enantiomer.[51]

In summary, we have demonstrated an efficient and straightforward synthesis of the unnatural enantiomer of a blood group antigen using 4-deoxypentenosides and L-glycals, derived from readily available D-glucose derivatives. An important benefit provided by this approach is the generation of L-pyranosides in differentially protected forms; a similar synthesis starting from unprotected L-hexoses would be far less practical and efficient. This synthetic methodology can be extended to a diverse range of oligosaccharide structures for investigating the role of chirality in carbohydrate recognition and biological function.

Experimental Section

Methyl 2,3-Di-*O*-benzyl-4-deoxy-β-L-*threo*-pent-4-enopyranoside (4-Deoxypentenoside) (4). A solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **2** (0.993 g, 2.652 mmol) in CH_2Cl_2 was stirred at 0 °C and treated with TEMPO (20 mg, 0.132 mmol), followed by satd aq $NaHCO_3$ (10 mL) and the dropwise addition of commercial bleach (∼0.7 M, 9 mL). After 45 min, aqueous 1.0 M HCl was added (30 mL), and the mixture was stirred for an additional 5 min. EtOAc (150 mL) was added, and the mixture was separated, dried over Na_2SO_4, and concentrated. The resulting yellow oil was evaporated four times with toluene (30 mL) under reduced pressure and kept under high vacuum for 24 h to afford methyl 2,3-di-*O*-benzyl-α-D-glucuronic acid **3**. The crude oil was dissolved in toluene (10 mL) and treated with *N*,*N*-dimethylformamide dineopentyl acetal (4.0 mL, 14.33 mmol). The resulting mixture was stirred and heated to 120 °C for 1 h under argon, cooled to 40 °C, and evaporated to a brown oil. Silica gel chromatography using a 5:95 to 10:90 EtOAc−hexanes gradient containing 0.1% of Et_3N yielded 4-deoxypentenoside **4** as a clear oil (0.607 g, 70% over two steps): $[\alpha]_D$ +148 (c = 1, $CHCl_3$); ^1H NMR (C_6D_6, 300 MHz) δ 7.31−7.05 (m, 10 H, Ar−H), 6.12 (dd, 1 H, $J_{3,5}$ = 1.2 Hz, $J_{4,5}$ = 6.0 Hz, H-5), 4.83 (dd, 1 H, $J_{3,4}$ = 3.0 Hz, H-4), 4.81 (d, 1 H, $J_{1,2}$ = 2.4 Hz, H-1), 4.62 (s, 2 H, CH_2-Ph), 4.45 (s, 2 H, CH_2Ph), 4.32 (ddd, 1 H, $J_{2,3}$ = 6.0 Hz, H-3), 3.85 (dd, 1 H, H-2), 3.20 (s, 3 H, OCH_3); ^{13}C NMR (C_6D_6, 125 MHz) δ 144.22, 141.28, 141.18, 128.57, 128.55, 127.87, 127.81, 127.59, 127.52, 97.45, 95.16, 68.60, 64.20, 63.81, 61.36, 44.18; HR-ESIMS calcd for $C_{20}H_{23}O_4$ $[M + H]^+$ 327.1596, found 327.1598.

Hydroxymethyl (3-*O*-Benzyl-4,6-*O*-*p*-methoxybenzylidene)-β-*C*-glucopyranoside (7). D-Glucal **5** (2.98 g, 8.41 mmol) was dissolved in CH_2Cl_2 (8 mL) and treated with freshly prepared DMDO (140 mL, 0.1 M in acetone) at 0 °C for 30 min. The resulting epoxide was concentrated to dryness, dissolved in anhydrous THF (35 mL), and treated with (*i*-PrO)-Me_2SiCH_2MgCl (30 mL, 1.0 M in THF) and CuI (800 mg, 4.2 mmol) at −10 °C for 20 min under an argon atmosphere. After aqueous workup and extraction with Et_2O (150 mL), the crude oil was dissolved in 1:1 THF/CH_3OH (120 mL) and treated with 15% aqueous KOH (90 mL), followed by the slow addition of 30% aqueous H_2O_2 (90 mL) at 0 °C. The reaction mixture was stirred at rt for 18 h, carefully quenched with saturated aqueous $Na_2S_2O_3$ (60 mL), and extracted with Et_2O (150 mL). Diol **7** was recrystallized from 25% EtOAc in hexanes to afford a white crystalline solid (2.25 g, 66% yield over 3 steps): mp 147 °C; $[\alpha]_D$ −13.3 (c = 1 in $CHCl_3$); ^1H NMR (C_6D_6) δ 7.53

(48) Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707.
(49) Lehmann, J.; Petry, S.; Scheuring, M.; Schmidt-Schuchardt, M. *Carbohydr. Res.* **1994**, *264*, 199.
(50) Wacowich-Sgarbi, S. A.; Bundle, D. R. *J. Org. Chem.* **1999**, *64*, 9080.
(51) The specific rotation of **1** ($[\alpha]^{20}_D$ = +101.3; c = 0.37, MeOH) is opposite in sign but nearly equal in magnitude to that reported for the natural enantiomer ($[\alpha]^{20}_D$ = −94.3; c = 0.9, H_2O): Cromer, R.; Spohr, U.; Khare, D. P.; LePendu, J.; Lemieux, R. U. *Can. J. Chem.* **1992**, *70*, 1511.

(m, 2H, Ar-H), 7.26 (m, 2 H, Ar-H), 7.09 (m, 3 H, Ar-H), 6.82 (m, 2 H, Ar-H), 5.29 (s, 1 H, CH-acetal), 5.02 (d, 1 H, $J = 11.7$ Hz, C*H*-Ph), 4.63 (d, 1 H, $J = 11.7$ Hz, C*H*-Ph), 4.10 (dd, 1 H, $J_{5,6} = 5.1$ Hz, $J_{6a,6b} = 10.2$ Hz, H-6a), 3.64−3.80 (m, 3 H), 3.55 (dt, 1 H, $J_{OH,2} = 2.7$ Hz, $J_{1,2} = J_{2,3}$ 9.3 Hz, H-2), 3.36−3.46 (m, 2 H), 3.26 (s, 3 H, OMe), 3.14−3.23 (m, 2 H), 2.07 (d, 1 H, $J =$ 2.7 Hz, OH), 1.52 (t, 1 H, $J = 5.7$ Hz, OH); ^{13}C NMR ($CDCl_3$) δ 160.01, 138.28, 129.73, 128.54, 128.03, 127.93, 127.26, 113.59, 101.15, 82.09, 81.93, 79.77, 74.56, 70.55, 70.41, 68.68, 62.60, 55.26; HR-EIMS calcd for $C_{22}H_{26}O_7$ $[M]^+$ 402.1679, found 402.1684.

3*,6*-Di-*O*-benzyl-L-glucal (10).[36] Diol **7** (2.25 g, 5.59 mmol) was refluxed in toluene (110 mL) with $(n\text{-Bu})_2$SnO (1.95 g, 7.83 mmol) for 2 h, with azeotropic distillation of water using a Dean−Stark apparatus. TBAI (2.50 g, 6.76 mmol), Et_3N (35 μL, 0.27 mmol), and BnBr (2.32 mL, 19.5 mmol) were successively added, and the reaction mixture was refluxed for an additional 18 h before being concentrated and passed through a silica gel plug (hexanes/EtOAc) to afford the primary benzyl ether as a wax (2.58 g, 94%): $[\alpha]^{20}_D = -12.4$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.53 (m, 2H, Ar-H), 7.34 (m, 2 H, Ar-H), 7.28 (m, 2 H, Ar-H), 7.07−7.18 (m, 6 H, Ar-H), 6.82 (m, 2 H, Ar-H), 5.29 (s, 1 H, CH-acetal), 5.05 (d, 1 H, $J = 12.0$ Hz, C*H*-Ph), 4.73 (d, 1 H, $J = 12.0$ Hz, C*H*-Ph), 4.37 (AB system, 2 H, $J_{AB} = 12.3$ Hz, CH_2−Ph), 4.19 (dd, 1 H, $J_{5,6a} = 4.8$ Hz, $J_{6a,6b} =$ 10.5 Hz, H-6), 3.76 (t, 1 H, $J_{1,2} = J_{2,3}$ 9.0 Hz, H-2), 3.68 (d, 2 H, CH_2-Ph), 3.22−3.58 (m, 8 H), 2.54 (bs, 1 H, OH); ^{13}C NMR (C_6D_6) δ 160.47, 139.42, 138.82, 130.86, 128.59, 128.55, 128.16, 127.86, 127.80, 127.78, 127.73, 127.68, 113.77, 101.45, 82.69, 82.20, 79.71, 74.52, 73.65, 71.40, 70.88, 70.44, 68.99, 54.73. CIMS *m*/*z* 493 $[M + H]^+$. The partially benzylated intermediate was redissolved in 8:1:1 AcOH/THF/H_2O (60 mL) and stirred at 45 °C for 2 h, concentrated, and purified by silica gel chromatography (hexanes/EtOAc) to afford triol **8** as a colorless oil (1.89 g, 96%), which was used without further purification.

Triol **8** (1.89 g, 5.04 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated with TEMPO (39 mg, 0.25 mmol), saturated aqueous $NaHCO_3$ (50 mL), and NaOCl (28 mL, 0.7 m in H_2O) at 0 °C for 30 min. The reaction mixture was diluted with satd aq NH_4Cl until pH = 5 and then thoroughly extracted with EtOAc (3 × 75 mL) and concentrated to yield *C*-glucuronide **9** as a clear oil. This was dissolved in degassed xylenes (50 mL) and *N*,*N*-dimethylformamide dineopentyl acetal (7 mL, 25.0 mmol) and heated to 70 °C for 15 min and then to 150 °C for 45 min under an argon atmosphere. The crude mixture was concentrated and purified by gradient silica gel chromatography (hexanes/EtOAc) to afford 3*,6*-di-*O*-benzyl-L-glucal **10** as a colorless oil (0.99 g, 58% yield over three steps): $[\alpha]^{20}_D =$ +35.0 ($c = 1$ in $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.06−7.30 (m, 10 H, Ar-H), 6.19 (dd, 1 H, $J_{1,3} = 1.2$ Hz, $J_{1,2} = 6.0$ Hz, H-1*), 4.66 (dd, 1 H, $J_{2,3} = 2.1$ Hz, H-2*), 4.06 (dd, 1 H, $J = 6.6$, 9.0 Hz, H-4*), 3.97 (m, 1 H, H-3*), 3.86 (m, 1 H, H-5*), 3.70 (dd, $J_{5,6a} = 4.8$ Hz, $J_{6a,6b} = 10.8$ Hz, H-6a*), 3.65 (dd, $J_{5,6b} = 3.6$ Hz, $J_{6a,6b} = 10.5$ Hz, H-6b*), 2.22 (bs, 1 H, OH); ^{13}C NMR (C_6D_6) δ 144.61, 139.38, 138.69, 128.55, 128.53, 127.81, 127.76, 127.72, 127.65, 100.37, 77.28, 76.49, 73.27, 70.54, 69.34, 69.03; HR-ESIMS calcd for $C_{20}H_{22}O_4$ $[M]^+$ 326.1518, found 326.1520.

3*,4*,6*-Tri-*O*-benzyl-L-galactal (11). A solution of 3*,6*-di-*O*-benzyl-L-glucal **10** (121 mg, 0.370 mmol), 4A molecular sieves (80 mg), and $NaHCO_3$ (180 mg) in dry CH_2Cl_2 (4.5 mL) was stirred at rt under argon atmosphere and treated with Dess−Martin periodinane (280 mg, 0.660 mmol). The mixture was vigorously stirred under complete disappearance of the starting material (1 h), filtered, and rinsed with CH_2Cl_2 (2 × 3 mL). The filtrate was quickly diluted with CH_3OH (11 mL), cooled to −5 °C, and treated with $NaBH_4$ (52 mg, 1.374 mmol, added in three portions). After 1.5 h, the reaction was diluted with acetone (5 mL), satd aq $Na_2S_2O_3$ (15 mL), satd aq NH_4Cl (15 mL), and $CHCl_3$ (80 mL). The mixture was extracted, dried with Na_2SO_4, and concentrated. Silica gel chromatography using a 9:1 to 4:1 hexanes−EtOAc gradient containing 0.1% of Et_3N yielded 3*,6*-di-*O*-benzyl-L-galactal as a colorless oil (102 mg, 84%, 30:1 l-*galacto*/l-*gluco*).

A solution of di-*O*-benzyl-L-galactal (102 mg, 0.312 mmol) in dry DMF (5 mL) was treated at −5 °C with NaH (60% in mineral oil, 75 mg, 1.875 mmol), stirred for 5 min under argon, and then treated with BnBr (0.11 mL, 0.937 mmol). After being stirred for 1.5 h at rt, the reaction mixture was diluted at 0 °C with satd aq NH_4Cl (6 mL) and Et_2O (40 mL), extracted, and concentrated. Silica gel chromatography using a 19:1 to 9:1 hexanes−EtOAc gradient containing 0.1% of Et_3N yielded L-galactal **11** as a colorless oil: $[\alpha]^{20}_D = +42.0$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.06−7.30 (m, 15 H, Ar−H), 6.25 (dd, 1 H, $J_{1,3} = 1.5$ Hz, $J_{1,2} = 6.3$ Hz, H-1*), 4.78 (d, 1 H, $J = 11.7$ Hz, C*H*-Ph), 4.72 (ddd, 1 H, $J_{1,4} = 1.5$ Hz, $J_{2,3} = 3.0$ Hz, H-2*), 4.45 (d, 1 H, $J = 11.7$ Hz, C*H*-Ph), 4.36 (AB system, 2 H, $J_{AB} = 12.0$ Hz,CH_2-Ph), 4.30 (AB system, 2 H, $J_{AB} = 12.0$ Hz, CH_2-Ph), 4.24 (m, 1 H, H-3*), 3.81−3.91 (m, 4 H, H-4*,5*,6a*,6b*); ^{13}C NMR (C_6D_6) δ 144.23, 139.22, 138.93, 128.49, 128.42, 128.39, 127.99, 127.86, 127.60, 127.57, 127.49, 100.11, 76.02, 73.33, 73.29, 72.19, 71.28, 70.94, 68.73; HR-ESIMS calcd for $C_{27}H_{28}O_4$ $[M]^+$ 416.1988, found 416.1996.

Ethyl 2*-*O*-Acetyl-3*,4*,6*-tri-*O*-benzyl-1-thio-β-L-galactopyranoside (12). A solution of l-galactal **11** in CH_2Cl_2 (1 mL, 0.17 m solution) was added dropwise to a solution of DMDO (5 mL, 0.1 m in acetone) at −55 °C under argon and stirred for 3 h. The reaction mixture was warmed to rt, concentrated, and dried under high vacuum. The highly acid-sensitive α-epoxy-L-galactal was used without further purification.

A stirring solution of EtSH (0.5 mL, 6.75 mmol) in dry THF (4 mL) at 0 °C was treated with *n*-BuLi (0.1 mL, 2.6 M in hexanes) under an argon atmosphere. The resulting mixture was treated with α-epoxy-L-galactal (0.168 mmol, in 4 mL of THF) at 0 °C and stirred for 18 h. The reaction was diluted with satd aq $NaHCO_3$ (15 mL) and EtOAc (80 mL), extracted, dried over Na_2SO_4, and concentrated. Silica gel chromatography using a 9:1 to 4:1 hexanes−EtOAc gradient yielded the corresponding thioethyl β-L-galactoside as a colorless oil.

The galactoside C2* alcohol was dissolved in dry pyridine (4 mL) and treated with acetic anhydride (2 mL). After being stirred at rt for 18 h, the reaction was quenched at 0 °C with satd aq $NaHCO_3$ (50 mL), diluted with $CHCl_3$ (80 mL), extracted, washed with brine (10 mL), dried with Na_2SO_4, and azeotroped with dry toluene (15 mL) under high vacuum to afford 2*-*O*-acetyl-L-galactoside **12** as a colorless oil (63 mg, 69% over three steps): $[\alpha]^{20}_D = +2.4$ ($c = 0.63$ in $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.06−7.30 (m, 15 H, Ar-H), 5.39 (dd, 1 H, $J =$ 9.0, 9.9 Hz, H-2*), 4.62−4.75 (m, 3 H, C*H*-Ph), 4.31−4.51 (m, 3 H, C*H*-Ph), 4.21 (d, 1 H, $J = 9.9$ Hz, H-1*), 3.54−3.66 (m, 4 H, H-3*,4*,6a*,6b*), 3.29 (dt, 1 H, $J = 2.7$, 9.3 Hz, H-5*), 2.66 (m, 2 H, CH_2S), 1.72 (s, 3 H, OAc), 1.11 (t, 3 H, $J = 7.5$ Hz, SCH_2-CH_3); ^{13}C NMR ($CDCl_3$) δ 169.95, 138.91, 138.31, 138.13, 128.74, 128.72, 128.48, 128.28, 128.24, 128.14, 128.04, 127.77, 127.74, 83.96, 81.78, 77.77, 74.71, 73.85, 73.22, 72.25, 69.95, 68.83, 23.85, 21.37, 15.13; HR−CIMS calcd for $C_{31}H_{37}O_6S$ $[M + H]^+$ 537.2311, found 537.2318.

Protected L-Lactal (13). A mixture of thioethyl-L-galactosyl donor **12** (63 mg, 0.117 mmol) and L-glucal acceptor **10** (53 mg, 0.162 mmol) were azeotroped with toluene (3 × 10 mg) and dried under high vacuum. 4A molecular sieves (200 mg), di-*tert*-butyl-4-methylpyridine (96 mg, 0.468 mmol), and CH_2Cl_2 (2 mL) were added under an argon atmosphere. The suspension was stirred at rt for 30 min, cooled to 0 °C, and treated dropwise with MeOTf (53 μL, 0.468 mmol). The reaction mixture was stirred at 0 °C for 18 h, warmed to rt for 30 min, and then treated with Et_3N (0.1 mL). EtOAc (50 mL) was added, and the mixture was filtered, diluted with satd aq $NaHCO_3$ (15 mL), extracted, dried with Na_2SO_4, and concentrated. Silica gel chromatography using a 9:1 to 4:1 hexanes−EtOAc gradient containing 0.1% of Et_3N gave a mixture of L-lactal **13** and L-glucal acceptor **10** as a colorless oil. Size-exclusion liquid chromatography (JAI LC-908, $CHCl_3$)

afforded pure L-lactal **13** as a clear oil (67 mg, 73% yield), as well as recovered L-glucal acceptor **10** (15 mg): $[\alpha]^{20}_D = -2.5$ ($c = 1$ in $CHCl_3$); IR (thin film) 3030, 2868, 1750, 1649, 1496, 1367, 1232, 1075, 1027, 735, 697, 478; ^{1}H NMR (C_6D_6) δ 7.40−7.05 (m, 25 H, ArH), 6.24 (dd, 1 H, $J_{1,3} = 0.9$ Hz, $J_{1,2} = 6.3$ Hz, H-1a), 5.85 (dd, 1 H, $J = 8.1$, 10.5 Hz, H-2b), 4.92 (d, 1 H, $J = 11.4$ Hz, C*H*-Ph), 4.72 (m, 2 H, C*H*-Ph, H-2a), 4.60−4.15 (m, 11 H), 4.09 (m, 1 H), 3.92 (dd, 1 H, $J = 4.5$, 10.8 Hz), 3.81 (d, 1 H, $J = 2.4$ Hz), 3.70 (m, 2 H), 3.49 (dd, 1 H, $J = 5.4$, 9.0 Hz), 3.36 (dd, 1 H, $J = 7.2$, 6.0 Hz), 3.25 (dd, 1 H, $J = 2.7$, 10.2 Hz), 1.80 (s, 3 H, OAc); ^{13}C NMR ($CDCl_3$) δ 169.39, 144.32, 138.69, 138.44, 138.04, 137.90, 137.73, 128.36, 128.34, 128.29, 128.17, 128.11, 127.87, 127.76, 127.69, 127.67, 127.57, 127.45, 127.36, 127.31, 127.25, 100.30, 99.81, 80.17, 75.83, 74.43, 73.80, 73.53, 73.46, 73.44, 73.34, 72.36, 71.75, 71.51, 70.48, 68.28, 68.02, 20.92; HR-ESIMS calcd for $C_{49}H_{52}O_{10}Na$ [M + Na]$^+$ 823.3458, found 823.3457.

Methyl 3,6-Di-*O*-benzyl-4-*O*-(3,4,6-tri-*O*-benzyl-β-L-galactopyranosyl)-2-deoxy-2-phenylsulfonamido-β-L-glucopyranoside (14). A suspension of L-lactal **13** (62 mg, 0.077 mmol), benzenesulfonamide (49 mg, 0.309 mmol), and 4A molecular sieves (60 mg) in CH_2Cl_2 (4 mL) at 0 °C was treated with I(*sym*-collidine)$_2ClO_4$ (145 mg, 0.309 mmol) under an argon atmosphere. After 30 min, the mixture was filtered, rinsed with Et_2O (40 mL), washed with satd aq $Na_2S_2O_3$ (20 mL), satd aq $CuSO_4$ (10 mL), and brine (20 mL), dried with Na_2SO_4, and concentrated. Silica gel chromatography using a 9:1 to 4:1 hexanes−EtOAc gradient afforded the corresponding 2-iodo-1-phenylsulfonamide as an oil (76 mg, 90%). The resulting iodosulfonamide (76 mg, 0.070 mmol) was treated with a 0.3 M solution of NaOMe in MeOH (3 mL) at rt under argon and stirred for 18 h. The mixture was treated with satd aq NH_4Cl (20 mL) and $CHCl_3$ (60 mL), extracted, dried over Na_2SO_4, and concentrated to give **14** as clear oil (63 mg, 95%): $[\alpha]^{20}_D = +12.5$ ($c = 0.2$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2 H, Ar−H), 7.21−7.47 (m, 28 H, Ar-H), 4.94 (d, 1 H, $J_{1a,2a} = 6.9$ Hz, H-1a), 4.48−4.89 (m, 8 H, 4CH_2Ph), 4.43 (d, 1 H, $J_{1b,2b} = 7.8$ Hz, H-1b), 4.32 (AB system, 2 H, $J_{AB} = 11.7$ Hz, CH_2Ph), 4.05 (d, 1 H, $J_{NH,2a} = 7.2$ Hz, NH), 4.03 (t, 1 H, $J_{2a,3a} = J_{3a,4a} = 7.8$ Hz, H-3a), 3.90 (m, 3 H, H-2b,4b,5b), 3.70 (dd, 1 H, $J = 3.0$, 10.8 Hz, H-6b), 3.60 (t, 1 H, $J_{4a,5a} = 8.1$ Hz, H-4a), 3.34−3.58 (m, 6 H), 3.29 (dd, 1 H, $J_{3b,4b} = 2.7$ Hz, $J_{2b,3b} = 9.6$ Hz), 2.97 (s, 3 H, OCH_3); ESIMS *m*/*z* 968 [M + Na]$^+$.

Ethyl 4-*O*-(2-Acetyl-3,4,6-tri-*O*-benzyl-β-L-galactopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-2-phenylsulfonamido-1-thio-β-L-glucopyranoside (15). A suspension of L-lactal **13** (62 mg, 0.077 mmol), benzenesulfonamide (49 mg, 0.309 mmol), and 4A molecular sieves (60 mg) in CH_2Cl_2 (4 mL) at 0 °C was treated with I(*sym*-collidine)$_2ClO_4$ (145 mg, 0.309 mmol) under an argon atmosphere. After 30 min, the mixture was filtered, rinsed with Et_2O (40 mL), washed with satd aq $Na_2S_2O_3$ (20 mL), satd aq $CuSO_4$ (10 mL), and brine (20 mL), dried with Na_2SO_4, and concentrated. Silica gel chromatography using a 9:1 to 4:1 hexanes−EtOAc gradient afforded the 2-iodo-1-phenylsulfonamide as an oil (76 mg, 90%).

LiHMDS (0.95 M in THF) was added to a stirred solution of EtSH (0.15 mL, 2.02 mmol) in DMF (2 mL) at −40 °C, followed by the dropwise addition of the iodosulfonamide (2 mL, 0.032 mM in DMF). The reaction mixture was stirred at −40 °C for 1 h and then at room temperature for 3 h, diluted with satd aq NH_4Cl (10 mL) and Et_2O (80 mL), extracted, dried over Na_2SO_4, and concentrated. Silica gel chromatography using a 9:1 to 4:1 hexanes−EtOAc gradient afforded disaccharide **15** as a white solid (52.7 mg, 80%): $[\alpha]^{20}_D = +32.0$ ($c = 1$ in $CHCl_3$); IR (thin film) 2869, 1749, 1453, 1367, 1328, 1231, 1157, 1089, 735, 697; ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2 H, SO_2Ph), 7.25−7.45 (m, 28 H, Ar-H), 5.34 (m, 2 H, NH, H-2), 4.98 (d, 1 H, *J* 11.7 Hz, C*H*-Ph), 4.72 (d, 1 H, $J = 12.0$ Hz, C*H*-Ph), 4.37−4.63 (m, 10 H), 4.00 (m, 2 H), 3.43−3.76 (m, 9 H), 2.56 (m, 2 H, SCH_2), 2.04 (s, 3 H, OAc), 1.19 (t, 3 H, $J = 7.5$ Hz, SCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 170.03, 141.79, 138.54, 138.18, 138.10, 138.03, 137.96, 132.22, 128.67, 128.54, 128.49, 128.44, 128.32, 128.21, 128.13, 128.05, 127.94, 127.81, 127.78, 127.65, 127.43, 127.36, 100.32, 83.55, 79.91, 79.58, 74.91, 74.79, 73.67, 73.58, 73.45, 72.81, 72.67, 71.99, 69.42, 67.98, 56.54, 24.92, 21.10, 14.75; ESIMS *m*/*z* 1040 [M + Na]$^+$.

Methyl 2-Acetamido-4-*O*-(2-acetyl-3,4,6-tri-*O*-benzyl-β-L-galactopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-β-L-glucopyranose (18). A solution of *N*-phenylsulfonamide **14** (63 mg, 0.066 mmol), DMAP (2 mg), and Et_3N (0.45 mL) in CH_2Cl_2 (2.0 mL) was treated with acetic anhydride (0.2 mL, 2.11 mmol) and stirred for 18 h at rt. Aqueous workup ($CHCl_3$, 20 mL) followed by silica gel chromatography using 4:1 hexanes−EtOAc afforded *N*-acetylsulfonamide **16** as an oil (64 mg, 95%). Compound **16** was azeotroped twice with toluene, dissolved in THF (2 mL) at −78 °C under an argon atmosphere, and treated dropwise with a freshly prepared solution of sodium naphthalenide (1.5 mL, 0.23 M in THF) until a green color persisted. Aqueous workup ($CHCl_3$, 20 mL) followed by silica gel chromatography using a 2:1 to 0:100 hexanes−EtOAc gradient afforded *N*-acetyl-L-lactosamine **18** as an oil (45 mg, 81%): $[\alpha]^{20}_D = +29.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.22−7.33 (m, 25 H, Ar-H), 6.15 (d, 1 H, $J = 9.0$ Hz, NH), 5.29 (dd, 1 H, $J = 7.8$, 9.9 Hz, Hb-2), 4.91 (d, 1 H, $J = 11.7$ Hz, C*H*-Ph), 4.32−4.68 (m, 11 H), 3.92−4.03 (m, 3 H), 3.70−3.82 (m, 4 H), 3.42−3.59 (m, 4 H), 3.41 (s, 3 H, OCH_3), 2.01 (s, 3 H, Ac), 1.95 (s, 3 H, Ac); HR-ESIMS calcd for $C_{52}H_{59}NO_{12}Na$ [M + Na]$^+$ 912.3935, found 912.3941.

2-Amino-4-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-L-galactopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-1-*O*,2-*N*-(ethan-1-yl-1-ylidene)-α-L-glucopyranoside (19). A solution of *N*-phenylsulfonamide **15** (52 mg, 0.051 mmol), DMAP (2 mg), and Et_3N (0.45 mL) in CH_2Cl_2 (2.0 mL) was treated with acetic anhydride (0.2 mL, 2.11 mmol) and stirred for 18 h at rt. Aqueous workup ($CHCl_3$, 20 mL) followed by silica gel chromatography using 4:1 hexanes−EtOAc afforded the *N*-acetylsulfonamide as an oil (51.4 mg, 95%). A mixture of the resulting *N*-acetylsulfonamide donor (51.4 mg, 0.048 mmol) and PMB-protected ethylene glycol[43] (30 mg, 0.164 mmol) was azeotroped with toluene (3 × 10 mL) and dried under high vacuum. Molecular sieves (4A, 50 mg), di-*tert*-butyl-4-methylpyridine (40 mg, 0.192 mmol), and CH_2Cl_2 (1 mL) were added under an argon atmosphere. The suspension was stirred at rt for 30 min, cooled to 0 °C, and treated dropwise with MeOTf (22 μL, 0.192 mmol). The reaction mixture was stirred at 0 °C for 18 h, warmed to rt for 30 min, treated with Et_3N (0.1 mL), and diluted with EtOAc (50 mL). The mixture was filtered, diluted with satd aq $NaHCO_3$ (15 mL), washed with H_2O (8 mL), dried with Na_2SO_4, and concentrated. Preparative TLC using 2:1 hexanes−EtOAc yielded compound **17** as a clear oil (39.5 mg, 68%): ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2 H, Ar-H), 7.18−7.48 (m, 30 H, Ar-H), 6.86 (m, 2 H, Ar-H), 5.39 (d, 1 H, $J = 5.7$ Hz, Ha-1), 5.32 (dd, 1 H, $J = 8.1$, 10.2 Hz, Hb-2), 4.96 (d, 1 H, $J = 12.0$ Hz, C*H*-Ph), 4.83 (AB system, 2 H, $J_{AB} = 11.7$ Hz, CH_2-Ph), 4.26−4.70 (m, 10 H), 3.80−3.95 (m, 5 H), 3.79 (s, 3 H, OCH_3), 3.33−3.72 (m, 10 H), 1.97 (s, 3 H, Ac), 1.86 (s, 3 H, Ac).

A solution of *N*-acetylsulfonamide **17** (39.5 mg, 0.033 mmol) in THF (3 mL) at −78 °C was treated dropwise with a freshly prepared solution of sodium naphthalenide (1.0 mL, 0.23 M in THF) under an argon atmosphere until the green color persisted. Aqueous workup ($CHCl_3$, 20 mL) followed by silica gel chromatography using a 2:1 to 0:100 hexanes−EtOAc gradient afforded the oxazoline derivative **19** as a crude oil (27 mg, 94%): IR (thin film) 2866, 1750, 1671, 1513, 1496, 1454, 1367, 1235, 1071, 736, 698; ^{1}H NMR ($CDCl_3$) δ 7.24−7.42 (m, 25 H, Ar-H), 6.01 (d, 1 H, $J = 7.5$ Hz, Ha-1), 5.35 (dd, 1 H, J =7.8, 9.9 Hz, Hb-2), 4.97 (d, 1 H, J =12.0 Hz, C*H*-Ph), 4.50−4.75 (m, 7 H, C*H*-Ph), 4.43 (d, 1 H, J =7.8 Hz, Hb-1), 4.37 (s, 2 H, CH_2-Ph), 4.27 (t, J =2.1 Hz, Hb-3), 4.20 (m, 1 H, Ha-2), 3.97 (m, 2 H, Hb-4, Ha-3), 3.41−3.68 (m, 7 H, Ha-4,5,-6a,6b, Hb-5,6a,6b), 2.07 (d, 3 H, J 1.8 Hz, N=C-CH_3), 1.94 (s, 3 H, OAc); ESIMS *m*/*z* 880 [M + Na]$^+$.

Methyl 2,3,4-Tri-*O*-benzyl-α-D-fucoside (21). A solution of 4-deoxypentenoside **4** (0.433 g, 1.326 mmol) in CH_2Cl_2 (2 mL) was stirred at −55 °C and treated with a freshly prepared solution of DMDO (27 mL, 0.1 M in acetone). The resulting mixture was stirred at −55 °C under argon for 2 days and then warmed to 0 °C over a period of 4 h. The mixture was concentrated to an oil to afford the β-epoxypyranoside **20** as a 10:1 β/α mixture (0.452 g, 99%). The crude epoxide was evaporated with toluene (10 mL) under reduced pressure, kept under high vacuum for 24 h, and then used without further purification.

A solution of the epoxide (15 mg, 0.044 mmol) in anhydrous toluene (1.5 mL) was treated with $AlMe_3$ (0.1 mL, 2.0 M in hexanes) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 15 min, quenched with satd aq NH_4Cl (10 mL) at −78 °C, and allowed to reach rt. The mixture was diluted with EtOAc (20 mL), extracted, dried over Na_2SO_4, and concentrated. Silica gel chromatography using a 4:1 hexanes−EtOAc gradient afforded methyl 2,3-di-*O*-benzyl-α-D-fucoside as a clear oil (15 mg, 95%): $[\alpha]^{20}_D = +48$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.05−7.39 (m, 10 H, Ar-H), 4.70 (d, 1 H, $J_{1,2} = 3.3$ Hz, H-1), 4.43−4.60 (m, 4 H, 2CH_2-Ph), 3.94 (dd, 1 H, $J_{2,3} = 9.6$ Hz, H-2), 3.86 (dd, 1 H, $J_{3,4} = 3.0$ Hz, H-3), 3.64 (dq, 1 H, $J_{4,5} = 1.8$ Hz, $J_{5,6} = 6.6$ Hz, H-5), 3.53 (dd, 1 H, H-4), 3.13 (s, 3 H, OCH_3), 2.26 (bs, 1 H, OH), 1.34 (d, 3 H, CH_3); ^{13}C NMR (C_6D_6) δ 139.52, 139.06, 128.57, 128.53, 128.51, 128.00, 127.87, 127.79, 127.58, 98.79, 78.00, 76.78, 72.91, 72.60, 70.50, 65.63, 54.92, 16.53.

A solution of methyl 2,3-di-*O*-benzyl-α-D-fucoside (185 mg, 0.516 mmol) in anhydrous DMF (6 mL) was treated with NaH (60% in mineral oil, 103 mg, 2.58 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 5 min, treated with BnBr (0.185 mL, 1.55 mmol), and warmed to rt. After being stirred for 1 h, the reaction was diluted at 0 °C with satd aq NH_4Cl (6 mL) and Et_2O (40 mL), extracted, and concentrated. Silica gel chromatography using a 19:1 to 9:1 hexanes−EtOAc gradient containing 0.1% of Et_3N yielded the perbenzylated methyl D-fucoside **21** (182 mg, 79%): $[\alpha]^{20}_D = +22.0$ ($c = 1.0$ in $CHCl_3$); IR (thin film): 2896, 1496, 1453, 1355, 1193, 1133, 1099, 1049, 734, 696; ^{1}H NMR ($CDCl_3$) δ 7.35−7.47 (m, 15 H, Ar-H), 5.08−4.71 (m, 7 H, H-1, 3CH_2-Ph), 4.12 (dd, 1 H, $J_{1,2} = 3.6$ Hz, $J_{2,3} = 9.9$ Hz, H-2), 4.01 (dd, $J_{3,4} = 3.3$ Hz, H-3), 3.91 (q, 1 H, $J_{5,6} = 6.6$ Hz, H-5), 3.71 (m, 1 H, H-4), 3.43 (s, 3 H, OCH_3), 1.19 (d, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.86, 138.53, 138.47, 128.32, 128.27, 128.21, 128.08, 127.99, 127.55, 127.46, 127.38, 98.71, 79.31, 77.75, 76.23, 74.71, 73.37, 73.26, 65.97, 55.18, 16.50; HR-CIMS calcd for $C_{27}H_{29}O_4$ [M − CH_3OH]$^+$ 417.2066, found 417.2071.

Ethyl 2,3,4-Tri-*O*-benzyl-1-thio-D-fucopyranose (22a). A solution of D-fucoside **21** (20 mg, 0.044 mmol) and EtSH (15 μL, 0.22 mmol) in CH_2Cl_2 (1 mL) was treated at 0 °C with $BF_3{\cdot}OEt_2$ (7 μL, 0.048 mmol) and stirred for 1 h. Aqueous workup ($CHCl_3$, 25 mL) and preparative TLC using 4:1 hexanes−EtOAc yielded thioglycoside **22a** as a separable 2:1 mixture of anomers (16 mg, 77%). **Ethyl 2,3,4-tri-*O*-benzyl-1-thio-α-D-fucopyranose (minor isomer):**[52] ^{1}H NMR ($CDCl_3$) δ 7.22−7.42 (m, 15 H, Ar-H), 5.47 (d, 1 H, $J_{1,2} = 5.4$ Hz, H-1), 5.01−5.64 (m, 6 H, 3CH_2Ph), 4.29 (dd, 1 H, $J_{2,3} = 10.0$ Hz, H-2), 4.20 (q, 1 H, $J_{5,6} = 6.0$ Hz, H-5), 3.79 (dd, 1 H, $J_{3,4} = 1.8$ Hz, H-3), 3.64 (m, 1 H, H-4), 2.55 (m, 2 H, CH_2S), 1.28 (t, 3 H, $J = 7.5$ Hz, CH_3CH$_2$S), 1.14 (d, 3 H, CH_3). **Ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-fucopyranose (major isomer):**[53] ^{1}H NMR ($CDCl_3$) δ 7.22−7.42 (m, Ar-H), 4.68−5.02 (m, 6 H, 3CH_2Ph), 4.40 (d, 1 H, $J_{1,2} = 9.6$ Hz, H-1), 3.83 (t, 1 H, $J_{2,3} = 9.3$ Hz, H-2), 3.61 (m, 1 H, H-4), 3.56 (dd, 1 H, $J_{3,4} = 1.8$ Hz, H-3), 3.49 (q, 1 H, $J = 6.0$ Hz, H-5), 2.73 (m, 2 H, CH_2S), 1.30 (t, 3 H, $J = 7.5$ Hz, CH_3CH$_2$S), 1.21 (d, 3 H, CH_3); HR-CIMS calcd for $C_{29}H_{35}O_4S$ [M + H]$^+$ 479.2256, found 479.2259.

Performing the above reaction with an excess of $BF_3{\cdot}OEt_2$ (21 μL, 0.132 mmol) yielded instead the corresponding acyclic dithioacetal **22b** (18 mg, 75%): $[\alpha]^{20}_D = -5.4$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.27−7.36 (m, 15 H, Ar-H), 4.82 (m, 4 H, 2CH_2-Ph), 4.75 (d, 1 H, $J = 11.7$ Hz, CH-Ph), 4.60 (d, 1 H, $J = 11.7$ Hz, CH-Ph), 4.29 (dd, 1 H, $J = 4.5$, 6.0 Hz, H-3), 4.03 (m, 1 H, H-5), 3.96 (m, 2 H, H-1,2), 4.48 (dd, 1 H, $J = 3.0$, 4.5 Hz, H-4), 2.68 (m, 2 H, SCH_2), 1.22 (m, 6 H, SCH_2CH_3, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.40, 138.06, 137.85, 128.28, 128.13, 128.00, 127.96, 127.73, 127.68, 127.62, 127.39, 82.68, 81.78, 80.93, 75.07, 74.48, 73.22, 67.08, 53.63, 25.24, 25.10, 19.83, 14.30; HR-ESIMS calcd for $C_{31}H_{40}O_4S_2Na$ [M + Na]$^+$ 563.2266, found 563.2258.

Methyl 2-Acetamido-4-*O*-(3,4,6-tri-*O*-benzyl-β-L-galactopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-β-L-glucopyranose (23). Acetate **18** (45 mg, 0.050 mmol) was diluted in a 0.3 M solution of NaOMe in MeOH and stirred for 18 h at 45 °C. Aqueous workup ($CHCl_3$, 25 mL) afforded the glycosyl acceptor **23** as a clear wax (43 mg, 99%): $[\alpha]^{20}_D = +9.6$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.23−7.36 (m, 25 H, Ar-H), 5.74 (d, 1 H, $J = 7.8$ Hz, NH), 4.89 (d, 1 H, $J = 11.7$ Hz, CH-Ph), 4.87 (d, 1 H, $J = 11.7$ Hz, CH-Ph), 4.53−4.74 (m, 8 H), 4.48 (d, 1 H, $J = 7.5$ Hz, Ha-1), 4.32 (AB system, 2 H, $J_{AB} = 12.0$ Hz, CH_2−Ph), 3.89−4.04 (m, 6 H), 3.81 (dd, 1 H, $J = 2.7$ Hz, 11.1 Hz), 3.30−3.63 (m, 10 H), 3.01 (bs, 1 H, OH), 1.85 (s, 3 H, NAc); HR-ESIMS calcd for $C_{50}H_{58}NO_{11}$ [M + H]$^+$ 848.4010, found 848.4007.

Methyl 2-Acetamido-2-deoxy-3,6-di-*O*-benzyl-4-*O*-[3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4-tri-*O*-benzyl-α-D-fucopyranosyl)-β-L-galactopyranosyl]-β-L-glucopyranoside (24). A mixture of L-glycosyl acceptor **23** (9.5 mg, 0.0106 mmol) and D-fucosyl donor **22** (13 mg, 0.027 mmol) was azeotroped three times with toluene (15 mL) and then dissolved in anhydrous CH_2Cl_2 (0.5 mL). The solution was added dropwise to a stirring mixture of dimethyl(methylthio)sulfonium triflate (DMTST)[54] (11 mg, 0.042 mmol), di-*tert*-butyl-4-methylpyridine (DTBMP) (13 mg, 0.063 mmol), and 4A molecular sieves (15 mg) in dry CH_2Cl_2 (0.5 mL) at −78 °C under argon. The reaction mixture was stirred and slowly warmed to room temperature over a period of 14 h. The mixture was treated with Et_3N (0.1 mL), diluted with $CHCl_3$ (15 mL), filtered, washed with $CHCl_3$ (10 mL), and concentrated to afford the desired trisaccharide as a 5:1 mixture of diastereomers (10 mg, 71%). The mixture was further separated by preparative TLC using 96:4 $CHCl_3$:MeOH to yield major isomer **24** as a clear oil: $[\alpha]^{20}_D = +35.0$ ($c = 0.84$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.14−7.39 (m, 40 H, Ar-H), 5.86 (d, 1 H, $J = 7.8$ Hz, NH), 5.79 (d, 1 H, $J_{1c,2c} = 3.6$ Hz, H-1c), 4.39−5.04 (m, 19 H, H-1,1b,5c 8CH_2Ph), 4.27 (dd, 1 H, $J_{1b,2b} = 7.8$ Hz, $J_{2b,3b} = 9.3$ Hz, H-2b), 4.11 (dd, 1 H, $J_{2c,3c} = 9.6$ Hz, H-2c), 3.80−4.07 (m, 6 H), 3.68 (dd, 1 H, $J_{3b,4b} = 1.8$ Hz, H-3b), 3.49−3.64 (m, 8 H), 1.94 (s, 3 H, Ac), 1.31 (d, 3 H, $J_{5c,6c} = 6.3$ Hz, H-6c); ^{13}C NMR ($CDCl_3$) δ 170.24, 138.87, 138.77, 138.63, 138.54, 138.46, 138.22, 138.01, 137.85, 128.44, 128.36, 128.27, 128.15, 128.00, 127.91, 127.81, 127.72, 127.51, 127.46, 127.39, 127.34, 127.28, 127.23, 126.19, 101.31, 100.83, 97.38, 84.01, 79.28, 77.95, 76.55, 76.06, 75.64 (2), 74.82, 74.60, 74.01, 73.54, 73.34, 73.02 (2), 72.65, 72.41, 72.21, 70.98, 68.84, 68.12, 66.43, 56.61, 55.07; ESIMS *m*/*z* 1286 [M + Na]$^+$.

Methyl 2-Acetamido-2-deoxy-4-*O*-[2-*O*-(α-D-fucopyranosyl)-β-L-galactopyranosyl]-β-L-glucopyranoside (1). A solution of trisaccharide **24** (14 mg, 0.011 mmol) in EtOAc (5 mL) was treated with activated charcoal (10 mg), stirred for 15 min at rt, passed through a short column of silica gel with EtOAc (60 mL), and concentrated to dryness. Trisaccharide **24** was dissolved in MeOH (3.5 mL) with $Pd(OH)_2$ (30 mg, ∼20% Pd) and stirred under an H_2 atmosphere for 18 h at rt. The mixture was then filtered over a pad of Celite, rinsed with MeOH (20 mL), and concentrated to afford trisaccharide **1** as a wax (6 mg, 99%): $[\alpha]^{20}_D = +101.3$ ($c = 0.37$ in CH_3OH); ^{1}H

(52) Murphy, P. V.; Hubbard, R. E.; Manallack, D. T.; Wills, R. E.; Montana, J. G.; Taylor, R. J. K. *Bioorg. Med. Chem.* **1998**, *6*, 2421.
(53) Zhang, Z. Y.; Magnusson, G. *Carbohydr. Res.* **1994**, *262*, 79.
(54) Ravenscroft, M.; Roberts, R. M. G.; Tillett, J. G. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1569.

NMR (CD_3OD) δ 4.50 (bd, 1 H, H-1c), 4.32 (d, 1 H, $J_{1b,2b} = 8.5$ Hz, H-1), 4.19 (d, 1 H, $J_{1a,2a} = 6.6$ Hz, H-1a), 3.36−3.56 (m, 16 H), 3.47 (s, 3 H, OCH_3), 1.98 (s, 3 H, $NHCOCH_3$), 1.22 (d, 3 H, $J_{5c,6c} = 6.5$ Hz, CH_3); ^{13}C NMR (CD_3OD) δ 176.35, 103.83, 102.69, 101.97, 79.09, 78.28, 77.21, 77.09, 75.41, 74.42, 73.71, 71.81, 70.85, 68.44, 62.77, 61.69, 57.24, 56.67, 23.06, 16.89; HR-ESIMS calcd for $C_{21}H_{37}NO_{15}Na$ $[M + Na]^+$ 566.2061, found 566.2068.

Acknowledgment. We gratefully acknowledge financial support from the American Cancer Society (CDD-106244), the American Heart Association (30399Z), and the National Institutes of Health (EB-001777-01).

Supporting Information Available: Full experimental details and characterization of intermediates leading to D-glucal **5** and ^1H NMR spectra of selected intermediates leading to mirror-image trisaccharide **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035789L