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

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Abstract

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-deoxypentenolide **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-(α 1 $\rightarrow$ 2)-*L*-Gal-(β 1 $\rightarrow$ 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

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>.

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

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-deoxypentenoides (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 $\rightarrow$ 2)- β -L-Gal-(1 $\rightarrow$ 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.

SCHEME 1.

Synthesis of 4-Deoxypentenoside 4^a

^a Reagents and conditions: (a) *p*-MeOC₆H₄CH(OMe)₂, CSA, THF, 85 °C; (b) NaH, BnBr, DMF, rt; (c) 8:1:1 AcOH/THF/H₂O, 45 °C (60% over three steps); (d) NaOCl, TEMPO (5 mol %), satd aq NaHCO₃, CH₂Cl₂, 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-glucose²⁵ 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% yield³⁰, 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 O₂, 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 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.

SCHEME 2.

Synthesis of L-Glucal 1^a

^a PMP = *p*-methoxyphenyl. Reagents and conditions: (a) PhSH, BF₃·OEt₂, CH₂Cl₂, rt; (b) NaOMe, MeOH/CH₂Cl₂, 0 °C; (c) *p*-MeOC₆H₄CH(OMe)₂, CSA, THF, 85 °C; (d) NaH, BnBr, DMF, rt; (e) lithium naphthalenide, THF, -78 °C (47% over five steps); (f) DMDO, acetone/CH₂Cl₂, 0 °C; (g) Me₂(*i*-PrO)SiCH₂MgCl (3.5 equiv), CuI (0.5 equiv), THF, -10 °C; (h) H₂O₂, KOH, MeOH/THF, rt (66% over three steps); (i) Bu₂SnO, toluene, reflux then Bu₄NI, BnBr, reflux (94%); (j) AcOH, THF/H₂O, 45 °C (96%); (k) NaOCl, TEMPO (5 mol %), satd aq NaHCO₃, CH₂Cl₂, 0 °C; (l) DMFDNA, xylenes, 150 °C (60% over two steps).

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 dimethyl-dioxirane (DMDO) gave α-epoxyglycal **6**, followed by CuI-mediated

addition of $\text{Me}_2(i\text{-PrO})\text{SiCH}_2\text{MgCl}$ and Tamao–Kumada oxidation³⁵ 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 ($\text{Me}_2\text{PhSiCH}_2\text{MgCl}$) 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}

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 , $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, -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 periodinane³⁹ produced an unstable ketone, which was reduced immediately with NaBH_4 in 1:1 $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ 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-deoxypentenose **4** in hand, a variety of mirror-image oligosaccharides were now synthetically accessible.

SCHEME 4.Synthesis of L-Lactosamine Derivatives^a

^a Reagents and conditions: (a) DMDO, CH₂Cl₂/acetone, -55 °C; (b) EtSLi, THF, 0 °C; (c) Ac₂O, 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, CH₂Cl₂, 0 °C (73%); (e) I (collidine)₂ClO₄, PhSO₂NH₂, 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) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt (96%); (i) PMBOCH₂CH₂OH, MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 4A molecular sieves, CH₂Cl₂, 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 glycol⁴⁴ 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*-acetyl-L-lactosamine, 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*-acetyl-glucosamines, 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 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 -epoxyglycols, 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 $\text{BF}_3\cdot\text{Et}_2\text{O}$ produced acyclic dithioacetal **22b** instead.⁴⁹

SCHEME 6.

Synthesis of Mirror-Image Trisaccharide 1^a

^a Reagents and conditions: (a) DMDO, CH₂Cl₂/acetone, -55 °C; (b) AlMe₃, toluene, -78 °C; (c) NaH, BnBr, DMF, rt (74% over three steps); (d) BF₃·OEt₂ (1.1 equiv), EtSH (5.0 equiv), CH₂Cl₂, rt (1:2 α/β, 77%); (e) BF₃·OEt₂ (3.3 equiv), EtSH (5.0 equiv), CH₂Cl₂, 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, CH₂Cl₂, -78 °C to room temperature (5:1 α/β, 71%); (h) H₂, Pd(OH)₂/C, MeOH, rt (99%).

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-deoxypentenoides 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_2 Ph), 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 $\text{C}_{20}\text{H}_{23}\text{O}_4$ $[\text{M} + \text{H}]^+$ 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)- $\text{Me}_2\text{SiCH}_2\text{MgCl}$ (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 $\text{Na}_2\text{S}_2\text{O}_3$ (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 (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, CH-Ph), 4.63 (d, 1 H, $J = 11.7$ Hz, CH-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, $J_{\text{OH},2} = 2.7$ 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 $\text{C}_{22}\text{H}_{26}\text{O}_7$ $[\text{M}]^+$ 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*-Bu) $_2\text{SnO}$ (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%): $[\alpha]_D^{20} = -12.4$ ($c = 1$ in CHCl_3); ^1H 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, CH-Ph), 4.73 (d, 1 H, $J = 12.0$ Hz, CH-Ph), 4.37 (AB system, 2 H, $J_{\text{AB}} = 12.3$ 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, $\text{CH}_2\text{-Ph}$), 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 $[\text{M} + \text{H}]^+$. 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): $[\alpha]^{20}_{\text{D}} = +35.0$ ($c = 1$ in CHCl_3); ^1H 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; HRESIMS calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4$ $[\text{M}]^+$ 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 $\text{Na}_2\text{S}_2\text{O}_3$ (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: $[\alpha]^{20}_{\text{D}} = +42.0$ ($c = 1$ in CHCl_3); ^1H 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, CH-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, CH-Ph), 4.36 (AB system, 2 H, $J_{\text{AB}} = 12.0$ Hz, $\text{CH}_2\text{-Ph}$), 4.30 (AB system, 2 H, $J_{\text{AB}} = 12.0$ Hz, $\text{CH}_2\text{-Ph}$), 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 $\text{C}_{27}\text{H}_{28}\text{O}_4$ $[\text{M}]^+$ 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 CH₂Cl₂ (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 NaHCO₃ (15 mL) and EtOAc (80 mL), extracted, dried over Na₂SO₄, 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 NaHCO₃ (50 mL), diluted with CHCl₃ (80 mL), extracted, washed with brine (10 mL), dried with Na₂SO₄, 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): [α]_D²⁰ = +2.4 (*c* = 0.63 in CHCl₃); ¹H NMR (C₆D₆) 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, CH-Ph), 4.31–4.51 (m, 3 H, CH-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, CH₂S), 1.72 (s, 3 H, OAc), 1.11 (t, 3 H, *J* = 7.5 Hz, SCH₂-CH₃); ¹³C NMR (CDCl₃) 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 C₃₁H₃₇O₆S [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 CH₂Cl₂ (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 Et₃N (0.1 mL). EtOAc (50 mL) was added, and the mixture was filtered, diluted with satd aq NaHCO₃ (15 mL), extracted, dried with Na₂SO₄, and concentrated. Silica gel chromatography using a 9:1 to 4:1 hexanes–EtOAc gradient containing 0.1% of Et₃N gave a mixture of L-lactal **13** and L-glucal acceptor **10** as a colorless oil. Size-exclusion liquid chromatography (JAI LC-908, CHCl₃) afforded pure L-lactal **13** as a clear oil (67 mg, 73% yield), as well as recovered L-glucal acceptor **10** (15 mg): [α]_D²⁰ = -2.5 (*c* = 1 in CHCl₃); IR (thin film) 3030, 2868, 1750, 1649, 1496, 1367, 1232, 1075, 1027, 735, 697, 478; ¹H NMR (C₆D₆) 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, CH-Ph), 4.72 (m, 2 H, CH-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, 1H, *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); ¹³C NMR (CDCl₃) 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 C₄₉H₅₂O₁₀Na [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 $\text{I}(\text{sym-collidine})_2\text{ClO}_4$ (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 $\text{Na}_2\text{S}_2\text{O}_3$ (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%): $[\alpha]_D^{20} = +12.5$ ($c = 0.2$ in CHCl_3); $^1\text{H NMR}$ (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, $4\text{CH}_2\text{Ph}$), 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, $J_{\text{NH},2a} = 7.2$ Hz, NH), 4.03 (t, 1 H, $J_{2a,3a} = 7.8$ 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 $[\text{M} + \text{Na}]^+$.

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 $\text{I}(\text{sym-collidine})_2\text{ClO}_4$ (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 $\text{Na}_2\text{S}_2\text{O}_3$ (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%): $[\alpha]_D^{20} = +32.0$ ($c = 1$ in CHCl_3); IR (thin film) 2869, 1749, 1453, 1367, 1328, 1231, 1157, 1089, 735, 697; $^1\text{H NMR}$ (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, CH-Ph), 4.72 (d, 1 H, $J = 12.0$ Hz, CH-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); $^{13}\text{C NMR}$ (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 $[\text{M} + \text{Na}]^+$.

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 (CHCl₃, 20 mL) followed by silica gel chromatography using a 2:1 to 0:100 hexanes–EtOAc gradient afforded *N*-acetyl- β -lactosamine **18** as an oil (45 mg, 81%): $[\alpha]_D^{20} = +29.5$ ($c = 1.0$ in CHCl₃); ¹H NMR (CDCl₃) 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, CH-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, OCH₃), 2.01 (s, 3 H, Ac), 1.95 (s, 3 H, Ac); HR-ESIMS calcd for C₅₂H₅₉NO₁₂Na $[M + Na]^+$ 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 Et₃N (0.45 mL) in CH₂Cl₂ (2.0 mL) was treated with acetic anhydride (0.2 mL, 2.11 mmol) and stirred for 18 h at rt. Aqueous workup (CHCl₃, 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 glycol⁴³ (30 mg, 0.164 mmol) was azeotroped with toluene (3 $\times$ 10 mL) and dried under high vacuum. Molecular sieves (4A, 50 mg), di-*tert*-butyl-4-methylpyridine (40 mg, 0.192 mmol), and CH₂Cl₂ (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 μ L, 0.192 mmol). The reaction mixture was stirred at 0 °C for 18 h, warmed to rt for 30 min, treated with Et₃N (0.1 mL), and diluted with EtOAc (50 mL). The mixture was filtered, diluted with satd aq NaHCO₃ (15 mL), washed with H₂O (8 mL), dried with Na₂SO₄, and concentrated. Preparative TLC using 2:1 hexanes–EtOAc yielded compound **17** as a clear oil (39.5 mg, 68%): ¹H NMR (CDCl₃) 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, CH-Ph), 4.83 (AB system, 2 H, $J_{AB} = 11.7$ Hz, CH₂-Ph), 4.26–4.70 (m, 10 H), 3.80–3.95 (m, 5 H), 3.79 (s, 3 H, OCH₃), 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 (CHCl₃, 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; ¹H NMR (CDCl₃) 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, CH-Ph), 4.50–4.75 (m, 7 H, CH-Ph), 4.43 (d, 1 H, $J = 7.8$ Hz, Hb-1), 4.37 (s, 2 H, CH₂-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-CH₃), 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 CH₂Cl₂ (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 AlMe₃ (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 NH₄Cl (10 mL) at –78 °C, and allowed to reach

rt. The mixture was diluted with EtOAc (20 mL), extracted, dried over Na₂SO₄, 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 CHCl₃); ¹H NMR (C₆D₆) 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, 2CH₂-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, OCH₃), 2.26 (bs, 1 H, OH), 1.34 (d, 3 H, CH₃); ¹³C NMR (C₆D₆) 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 NH₄Cl (6 mL) and Et₂O (40 mL), extracted, and concentrated. Silica gel chromatography using a 19:1 to 9:1 hexanes–EtOAc gradient containing 0.1% of Et₃N yielded the perbenzylated methyl D-fucoside **21** (182 mg, 79%): $[\alpha]^{20}_D = +22.0$ ($c = 1.0$ in CHCl₃); IR (thin film): 2896, 1496, 1453, 1355, 1193, 1133, 1099, 1049, 734, 696; ¹H NMR (CDCl₃) δ 7.35–7.47 (m, 15 H, Ar-H), 5.08–4.71 (m, 7 H, H-1, 3CH₂-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, OCH₃), 1.19 (d, 3 H, CH₃); ¹³C NMR (CDCl₃) 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 C₂₇H₂₉O₄ [M – CH₃OH]⁺ 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 μ L, 0.22 mmol) in CH₂Cl₂ (1 mL) was treated at 0 °C with BF₃·OEt₂ (7 μ L, 0.048 mmol) and stirred for 1 h. Aqueous workup (CHCl₃, 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 ¹H NMR (CDCl₃) 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, 3CH₂Ph), 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, CH₂S), 1.28 (t, 3 H, $J = 7.5$ Hz, CH₃CH₂S), 1.14 (d, 3 H, CH₃). **Ethyl 2,3,4-tri-*O*-benzyl-1-thio- β -D-fucopyranose (major isomer):**⁵³ ¹H NMR (CDCl₃) δ 7.22–7.42 (m, Ar-H), 4.68–5.02 (m, 6 H, 3CH₂Ph), 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, CH₂S), 1.30 (t, 3 H, $J = 7.5$ Hz, CH₃CH₂S), 1.21 (d, 3 H, CH₃); HR-CIMS calcd for C₂₉H₃₅O₄S [M + H]⁺ 479.2256, found 479.2259.

Performing the above reaction with an excess of BF₃·OEt₂ (21 μ L, 0.132 mmol) yielded instead the corresponding acyclic dithioacetal **22b** (18 mg, 75%): $[\alpha]^{20}_D = -5.4$ ($c = 0.5$ in CHCl₃); ¹H NMR (CDCl₃) δ 7.27–7.36 (m, 15 H, Ar-H), 4.82 (m, 4H, 2CH₂-Ph), 4.75 (d, 1 H, $J = 11.7$ Hz, CH-Ph), 4.60 (d, 1H, $J = 11.7$ 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, SCH₂), 1.22 (m, 6 H, SCH₂CH₃, CH₃); ¹³C NMR (CDCl₃) 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 C₃₁H₄₀O₄S₂Na [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-glucopyranoside (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 (CHCl₃, 25 mL) afforded the glycosyl acceptor **23** as a clear wax (43 mg, 99%): $[\alpha]^{20}_D = +9.6$ ($c = 0.5$ in CHCl₃); ¹H NMR (CDCl₃) 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, CH₂-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 C₅₀H₅₈NO₁₁ [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 CH₂Cl₂ (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 CH₂Cl₂ (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 Et₃N (0.1 mL), diluted with CHCl₃ (15 mL), filtered, washed with CHCl₃ (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 CHCl₃:MeOH to yield major isomer **24** as a clear oil: $[\alpha]^{20}_D = +35.0$ ($c = 0.84$ in CHCl₃); ¹H NMR (CDCl₃) δ 7.14–7.39 (m, 40 H, ArH), 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, 8CH₂Ph), 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); ¹³C NMR (CDCl₃) 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 H₂ 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 CH₃OH); ¹H NMR (CD₃OD) 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, OCH₃), 1.98 (s, 3 H, NHC(=O)CH₃), 1.22 (d, 3 H, $J_{5c,6c} = 6.5$ Hz, CH₃); ¹³C NMR (CD₃OD) 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 C₂₁H₃₇NO₁₅Na [M + Na]⁺ 566.2061, found 566.2068.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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