Synthesis of a Potent Antagonist of E-Selectin

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A synthesis of an antagonist of E-selectin previously reported by a group at Novartis Pharma in Basel is described. An important feature involves the formation of an ether linkage based on a Rh^{II}-catalyzed reaction. Stereocontrolled glycosylations rely on the anomeric activation of 2-pyridylthio carbonate as leaving group for the attachment of β-D-galactopyranosyl and α-L-fucopyranosyl units on a common 1,5-anhydro D-glucitol scaffold.

Introduction

The recruitment and extravasation of leukocytes from the blood stream to the locus of inflammation in tissues is an essential immune-modulated process leading to beneficial effects and healing.[1] However, excessive recruitment and influx of leukocytes at the site of injury may result in adverse reactions that can be manifested in reperfusion injuries, stroke, rheumatoid arthritis, asthma, diabetes, and other acute or chronic health problems.[2] The phenomenological and molecular basis for initiating the physiological events associated with the over-recruitment of leukocytes are reasonably well understood.[3] Endothelial cells lining the inner walls of blood vessels express adhesion molecules called E- and P-selectin when activated or induced. The sialyl Lewis^x tetrasaccharide expressed on the surface of glycoproteins of leukocytes are common epitopes recognized by the selectins.[4] In a cascade of events, leukocytes are recognized by these physiological ligands through specific interactions with pharmacophoric groups on the sialyl Lewis^x epitope. A rolling process of leukocytes on the endothelial cells at the inner blood vessels ensues, leading to excessive recruitment at the site of tissue inflammation. What follows is extravasation into the affected sites with beneficial or adverse effects.

Extensive studies on the design and synthesis of molecules that mimic sialyl Lewis^x have been reported in an effort to develop antagonists to the natural receptors such as E-selectin.[5] Numerous carbohydrate-type[6] and related structures consisting of hybrid molecules[7] have been reported, with binding affinities in the low micromolar level.[8] A common design element has capitalized on the nature of the known pharmacophores involved in the recognition between sialyl Lewis^x and E-selectin. Thus, the 3,4-hydroxyl groups of L-fucosyl and the 6-hydroxyl group of D-galactosyl units are essential for

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binding to a calcium ion.[9] The carboxylic acid group is involved in the formation of a salt bridge with an arginine residue in the receptor. Extensive studies involving molecular modeling,[10] NMR,[11] and X-ray crystallography[12] have delineated the importance of attaining an optimal bioactive conformation for efficient binding to E-selectin. Within the group of carbohydrate-type pseudosaccharide antagonists, the incorporation of an α-L-fucosyl and a β-D-galactosyl unit that strategically mimic their counterparts in sialyl Lewis^x appears to be essential for good binding. The GlcNAc moiety can be replaced by simple carboxylic[13,14] or heterocyclic units.[7a] Perhaps the most revealing modification was the replacement of the *N*-acetylneuraminyl portion in sialyl Lewis^x with an *S*-cyclohexyl-2-propionic acid group attached as an α-ether linkage to the C-4 position of D-gal.[15,16] A series of related analogues and their binding affinities expressed as IC_{50} values is shown in Figure 1. Starting with sialyl Lewis^x **1** at IC_{50} = 1000 μM, it is clear that considerable flexibility exists with regard to the GlcNAc portion provided the replacement motif is cyclic. The need for a hydrophobic unit associated with the *N*-acetylneuraminyl portion is evident in comparing glycolic acid and α-substituted variants. The most active analogue is represented by structure **2**,[16] which is represented in two perspective drawings. This structure was arrived at by refinements in the GlcNAc mimetic portion by replacing it with an 1,5-anhydro-2-deoxy-D-*xylo*-hexitol unit,[17] to which were glycosidically linked β-D-gal and α-L-fucosyl units at C-3 and C-4, respectively. The importance of

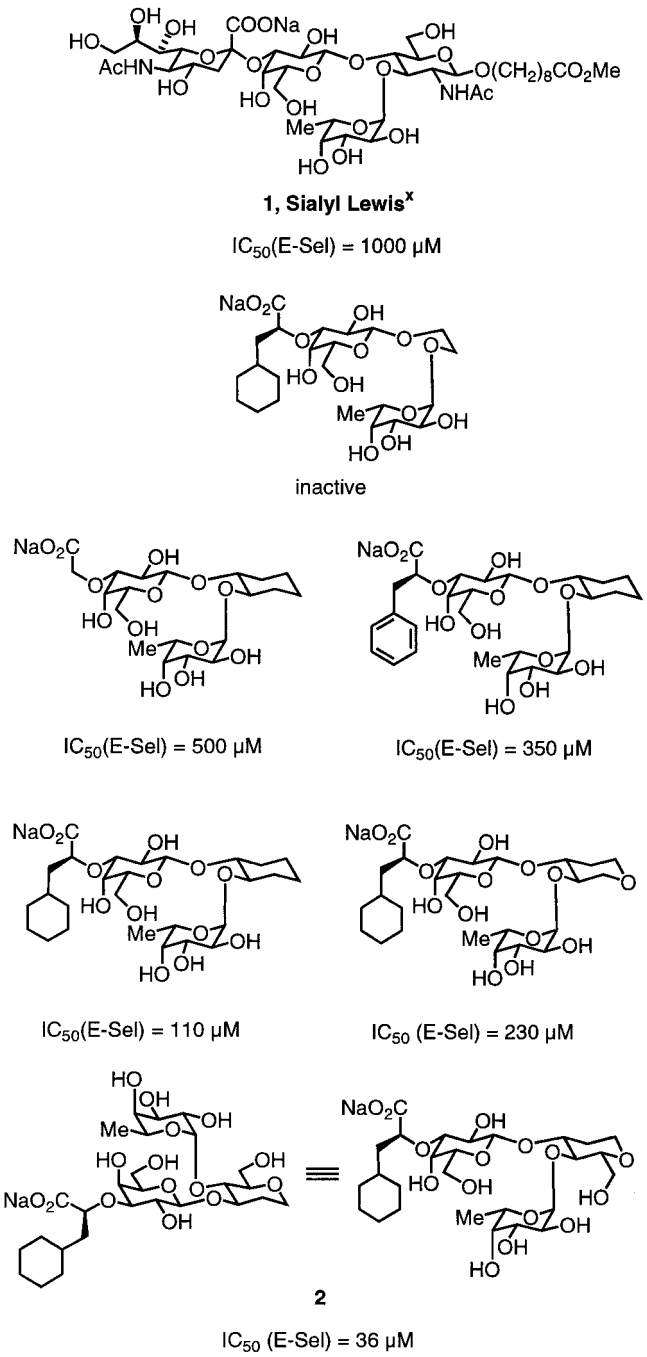

Figure 1. Some E-selectin carbohydrate-based antagonists (refs 16 and 18).

preorganization of the bioactive conformation of **2**, as well as multivalency was recently confirmed.[16]

The synthesis and biological evaluation of **2** and related analogues was reported by Thoma and co-workers[18] at Novartis Pharma in Basel, jointly with Patton and Magnani of Glycotech. Their synthesis strategy as illustrated in Figure 2 relies on glycosylations with D-gal[19] and α-L-fucosyl[20] thioglycosides. The crucial α-glycolate ether linkage was achieved by treatment of the 3,4-

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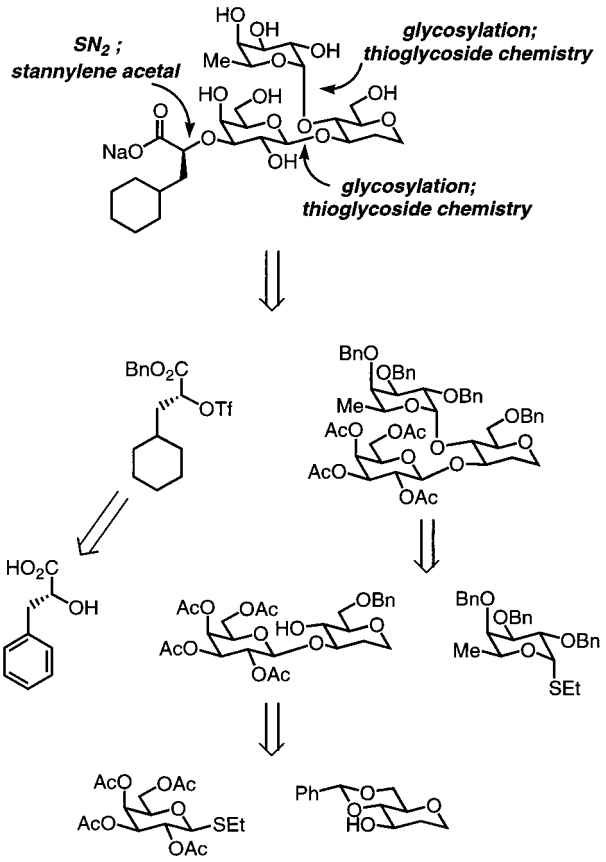

Figure 2. Novartis Pharma disconnection of antagonist 2 (ref 18).

stannylidene acetal derived from the D-gal unit with the triflate ester prepared from methyl 3-cyclohexyl-2*R*-hydroxy propionate.[21] This regioselective activation of vicinal diols via organotin derivatives in S_N2-type etherifications is well-known.[22] Further elaboration afforded the intended target **2**, which proved to be approximately 30 times more active than sialyl Lewis^x in a static cell-free E-selectin binding assay.

Our interest in the synthesis of **2** was motivated by a number of considerations and challenges. Foremost among these was the need to explore methodology that did not utilize thioglycosides[23] or other relatively labile activating groups[24] as glycosyl donors. Another factor was to avoid organotin chemistry late in the synthesis, to render a potential scale-up of the process practical.[25] We considered these issues as a good opportunity to apply recently developed glycosylation methods that rely on the remote activation concept[26] utilizing shelf-stable and often crystalline glycosyl donors. The exploration of alternative methods for ether formation, not relying on tin-mediated activation of hydroxyl groups was another challenge.

Figure 3 shows critical disconnections starting with **2**, where glycoside formation relies on a stereocontrolled α-L-fucosylation and β-D-galactosylation reactions with a common 2-thiopyridyl carbonate (TOPCAT) leaving group.[27] Etherification would involve a Rh^{II}-catalyzed carbene insertion reaction,[28] followed by a Horner−Wadsworth−Emmons extension and catalytic hydrogenation.

The readily available preferentially protected trimethylsilylethyl β-D-galactopyranoside **3**[29] was treated with methyl diazo(dimethoxyphosphoryl)acetate[30] under Rh^{II} catalysis[31] to afford the 3-*O*-α-phosphonoacetate **5** as a mixture of epimers in 72% yield (Scheme 1). Olefination with cyclohexane carboxyaldehyde in the presence of DBU and lithium chloride[32] afforded **6** as a major isomer in a 9:1 mixture in 97% yield as evidenced by NOE studies. Hydrogenation with 20% palladium hydroxide on carbon[33] (Pearlman's catalyst, Degussa), followed by treatment with benzaldehyde dimethylacetal in the presence of fluoroboric acid[34] led to a single isomer **7**. Benzoylation afforded a crystalline product **8**, suitable for single-crystal X-ray analysis as shown in the ORTEP drawing in Scheme 1. Thus, the correct stereochemistry at the α-cyclohexyl glycolate carbon atom was secured.

Scheme 2 shows the conversion of **8** into the required activated glycosyl donor **11**. In preliminary studies, several conditions normally utilized to cleave silyl glycosides such as TBAF/AcOH, TBAF/THF, or CsF/DMF, with or without 18-crown-6, resulted in recovery of starting material, even when heated (i.e., CsF/DMF, MeCN, or THF). Cleavage was successfully achieved with TFA in CH_2Cl_2 at 0 °C within 20 min, which also led to the hydrolysis of the benzylidene acetal. Subsequent steps involved acetal formation to **10** and esterification[27] with di(*S*-2-pyridyl) thiocarbonate[35] at the anomeric center to give the glycosyl donor **11** as a pale yellow solid in excellent yield.

The acceptor disaccharide unit was prepared form the readily available 1,5-anhydro-D-*xylo*-hexitol derivative **13**[17] (Scheme 3). Benzylation afforded **14**, which was subjected to reductive cleavage[36] of the 4,6-*O*-benzylidene acetal to afford the 6-*O*-benzyl derivative **15**. Glycosylation with L-fucosyl 2-thiopyridyl carbonate donor **16** proceeded in nearly quantitative yield to give the desired α-L-fucosylated disaccharide **17**. Subsequent debenzoylation gave the desired acceptor **18**.

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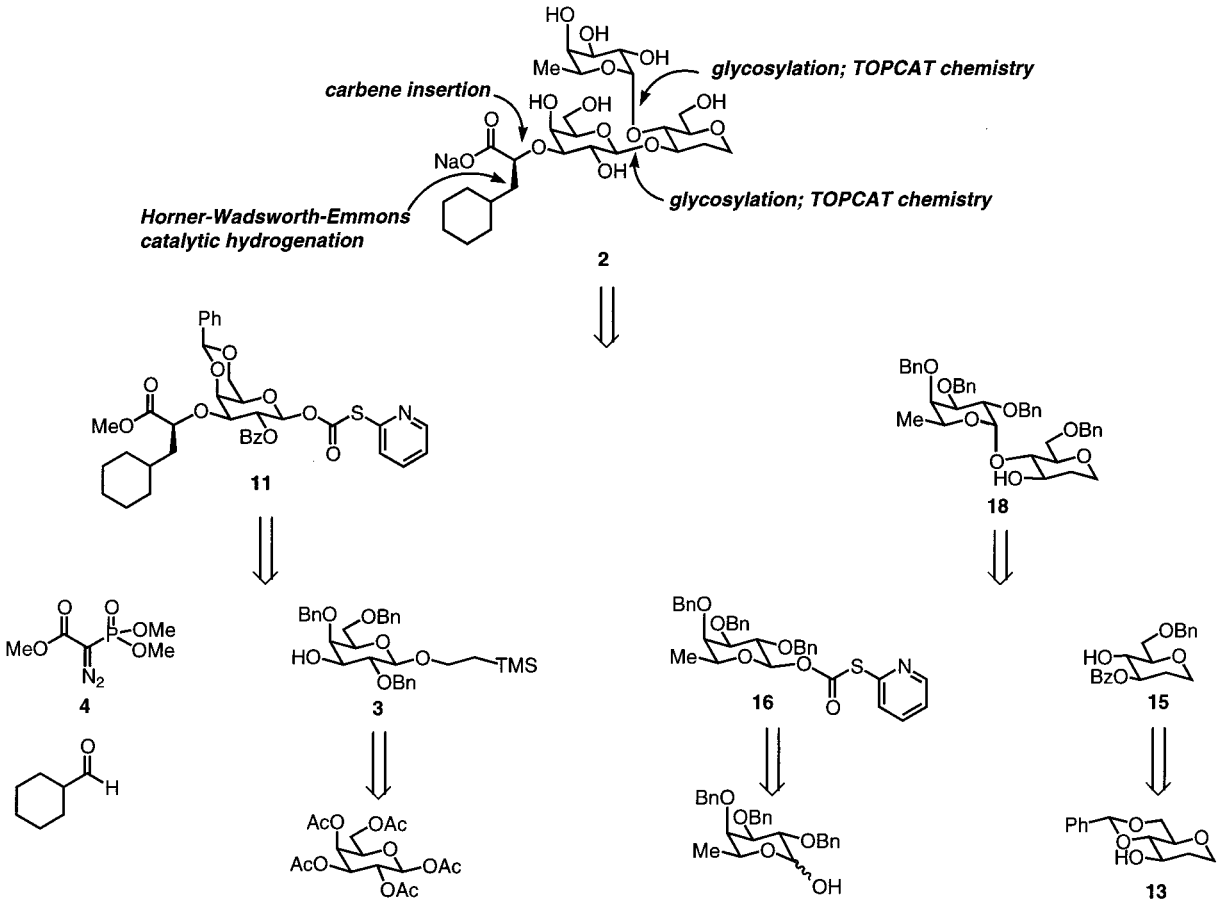

Figure 3. Disconnective analysis.

The β-D-galactosylation reaction required careful experimentation no doubt due to the hindered nature of the hydroxyl group in **18**. Under previously successful conditions using silver triflate[37] as promoter in the presence of 4 Å molecular sieves, and tetramethylurea[37a,b] as an acid scavenger, only low yields of the expected trisaccharide **19** were obtained. Eventually, it was found that pretreatment of the acceptor **18** with sodium hydride, followed by addition of silver triflate, and finally adding the donor **11** led to the target trisaccharide **19** in ~50% yield (Scheme 4). Cleavage of the methyl ester afforded the corresponding carboxylic acid **20** in quantitative yield. Debenzoylation required refluxing in methanol in the presence of sodium methoxide affording the penultimate precursor **21** in excellent yield. Removal of the benzyl ethers utilizing Pearlman's catalyst[33] under 60 psi of hydrogen in a mixture of aqueous dioxane containing acetic acid, followed by conversion to the sodium salt, afforded the target inhibitor **2** in quantitative yield.

We have described a new and practical synthesis of the potent carbohydrate-based E-selectin inhibitor **2**, utilizing a strategy that avoids thioglycosides as glycosyl donors and organotin activation late in the synthesis. The combined yields of α-L-fucosylation and β-D-galactosylation reactions utilizing thioethyl anomeric activation in the Novartis synthesis was 73%.[18] Coincidentally the yields of two glycosylations utilizing the 2-thiopyridyl carbonate group in the synthesis described herein was also 73%. The critical etherification reaction in our synthesis relied on the generation of a vinyl ether and a highly stereoselective catalytic hydrogenation proceeding in a combined yield of ~90%. Overall, the synthesis of **2** is convergent, high yielding in many steps, with the added advantage of a crystalline advanced intermediate, thus adding an element of practicality.

Experimental Section

Solvents were distilled under a positive pressure of dry nitrogen before use and dried by standard methods; THF and ether, from Na/benzophenone; and CH_2Cl_2, from CaH_2. All commercially available reagents were used without further purification. All reactions were performed under nitrogen atmosphere. NMR (^{1}H, ^{13}C) spectra were recorded on AMX-300 and ARX-400 spectrometers. The term [(−)] in ^{13}C data refers to the sign of the corresponding peak in the DEPT 135 NMR experiment. Low- and high-resolution mass spectra were recorded on Finningan MAT 900, VG Micromass, Ael-MS902, or Kratos MS-50 spectrometers using fast atom bombardment (FAB) or electrospray techniques. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ precoated silica gel plates. Visualization was done by ultraviolet light and/or by staining with ceric ammonium molybdate. Flash column chromatography[38] was performed using (40−60 μM) silica gel at increased pressure.

Methyl Diazo(dimethoxyphosphoryl)acetate (4).[30] To a suspension of *t*-BuOK (dried overnight under vacuum over

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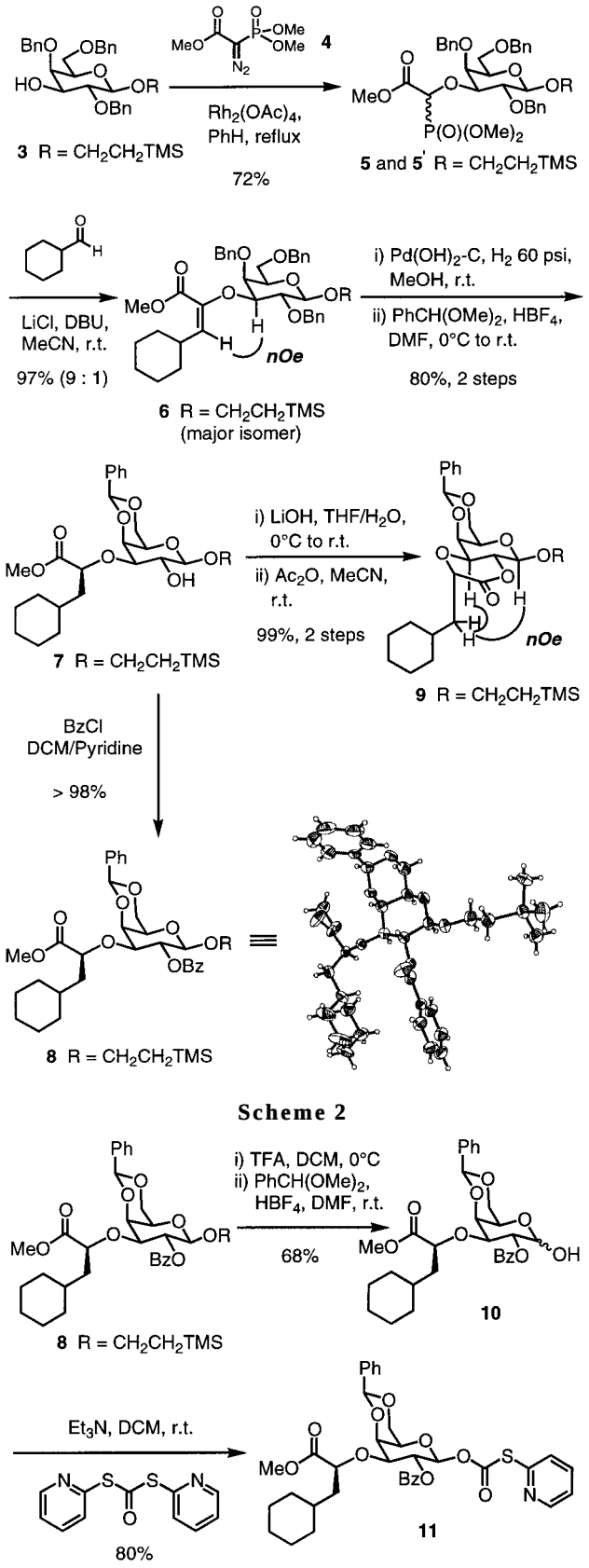
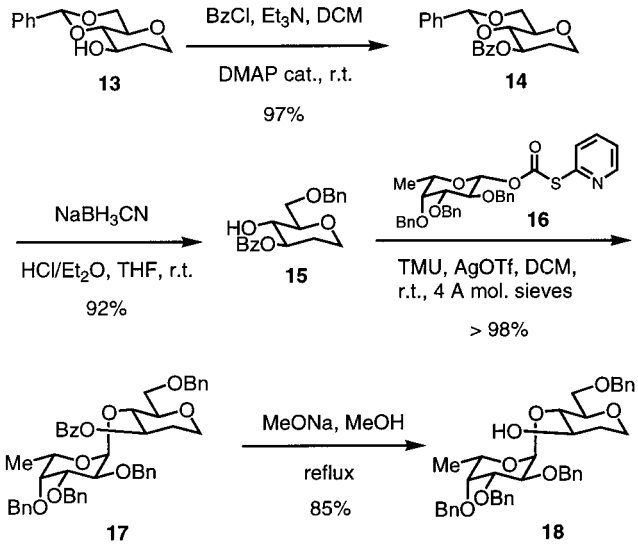
Scheme 1



Scheme 2

P_2O_5) (5.17 g, 46.2 mmol) in toluene (200 mL) cooled at 0 °C was added dropwise a solution of methyl (dimethoxyphosphoryl)acetate (7.00 g, 38.5 mmol) in toluene (20 mL) while maintaining the temperature below 5 °C. The viscous mixture was stirred for 1 h, and a solution of naphthalenesulfonyl azide[30] (9.05 g, 38.8 mmol) in toluene (20 mL) was added

Scheme 3

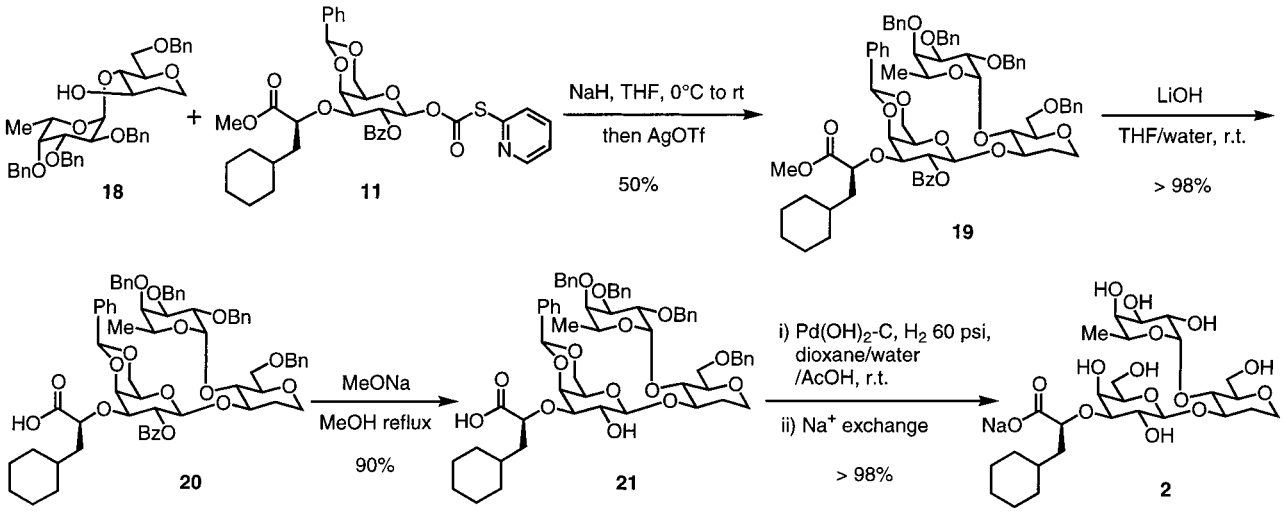


dropwise at 5 °C. After further stirring for 2 h, the mixture was filtered and concentrated, and the residue was purified by flash chromatography on neutral alumina, eluting with benzene/hexanes 1:1 to give **4** (3.9 g, 54%): bp 110 °C/10 mmHg (lit.[30] bp 65−69 °C/0.002 Torr); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84 (d, 3H, CO_2CH_3), 3.81 (d, 6H, $P(OCH_3)_2$, $^3J_{H-P}$ = 3.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5 (d, CO, $^2J_{C-P}$ = 12.5 Hz), 128.4 (d, CN_2, $^1J_{C-P}$ = 81 Hz), 53.7 (d, $P(OCH_3)_2$, $^2J_{C-P}$ = 6 Hz), 52.5 (s, OCH_3); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 13.8; IR (film, cm^{-1}) 2134, 1711, 1288, 1029; HR-FABMS calcd for $C_5H_9O_5N_2PNa$ *m/z* 231.01468, found 231.01465.

2-(Trimethylsilyl)ethyl *O*-2,4,6-Tri-*O*-benzyl-3-*O*-[(*E*)-1-(methoxycarbonyl)-2-cyclohexylethylen-1-oxy]-β-D-galactopyranoside (6). A mixture of 2-(trimethylsilyl)ethyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside[29] **3** (4.67 g, 8.48 mmol), methyl diazo(dimethoxyphosphoryl)acetate **4** (3.53 g, 2 equiv), and rhodium(II) acetate dimer (150 mg, 2 mol %/**4**) in benzene (280 mL) was refluxed for 5 h. After filtration on Celite and concentration, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 35:65, to give a 1:1 diastereomeric mixture of phosphonates **5** and **5′** (4.43 g, 71.5%): HR-FABMS calcd for $C_{37}H_{51}O_{11}PSiNa$ *m/z* 753.28360, found 753.28296.

A solution of the above mixture (2.80 g, 3.82 mmol), lithium chloride (dried under vacuum over P_2O_5 before use) (195 mg, 1.2 equiv), and DBU (distilled under reduced pressure over CaH_2 before use) (630 μL, 1.1 equiv) dissolved in acetonitrile (38 mL) was stirred at rt for 30 min, and then cyclohexane carboxaldehyde (510 μL, 1.1 equiv) was added dropwise at 0 °C and the mixture stirred at this temperature for 15 min (formation of a yellow precipitate). The resulting mixture was concentrated, redissolved in dichloromethane (50 mL), and washed with saturated aqueous ammonium chloride (40 mL) and 1 M aqueous hydrogen chloride (20 mL). The organic phase was dried (sodium sulfate) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 1:9, to give a 9:1 inseparable mixture of isomers (2.65 g, 97%). Data for the major isomer **6**: $[\alpha]_D$ −13.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 7.41−7.28 (m, 15H, ArH), 5.51 (d, 1H, $H_{vinylic}$, J = 9.9 Hz), 4.98 (d, 1H, PhC*H*H−, J = 11.7 Hz), 4.93 (d, 1H, PhC*H*H−, J = 10.8 Hz), 4.73 (d, 1H, PhCH*H*−, J = 10.8 Hz), 4.64 (d, 1H, PhCH*H*−, J = 11.7 Hz), 4.46 and 4.41 (AB, 2H, PhCH_2−, J = 11.7 Hz), 4.41 (d, 1H, H-1, $J_{1,2}$ = 7.6 Hz), 4.08−4.00 (m, 2H, H-4 and −OC*H*HCH$_2$TMS), 3.97 (dd, 1H, H-3, $J_{3,2}$ = 9.7 Hz, $J_{3,4}$ = 2.9 Hz), 3.86 (dd, 1H, H-2), 3.75 (s, 3H, OCH_3), 3.63−3.55 (m, 4H, H-5, H-6, H-6A and −OCH*H*CH$_2$-TMS), 2.84 (m, 1H, −CH−), 1.71−1.68 (m, 6H, −CH_2−), 1.36−0.98 (2m, 6H, −CH_2− and −CH_2TMS), 0.03 (s, 9H, −Si$(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164 (CO), 143.8, 138.9 (2C) and 138.1 (ArC), 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8,

Scheme 4



127.6 and 127.4 (ArCH), 103.5 (C-1), 82.7, 80.0, 73.8, 73.4 (C-2 to C-5), 75.0, 74.6, 73.5 [(−), $PhCH_2$−], 69.0 and 67.6 [(−), C-6 and −O*C*H_2CH_2TMS], 51.7 (−OCH_3), 36.0 (−CH−), 33.7, 33.5, 26.0, 25.9 (2C) [(−), −CH_2−], 18.6 [(−), −*C*H_2TMS], −1.3 [−Si-$(CH_3)_3$]; IR (film, cm^{-1}) 2926, 2852, 1724, 1249, 1216, 1102, 1076; HR-FABMS calcd for $C_{42}H_{56}O_8SiNa$ *m*/*z* 739.36422, found 739.36364.

2-(Trimethylsilyl)ethyl *O*-4,6-*O*-Benzylidene-3-*O*-[(S)-1-(methoxycarbonyl)-2-cyclohexylethyloxy]-β-D-galactopyranoside (7). To a solution of **6** and its inseparable isomer (1.07 g, 1.49 mmol) dissolved in methanol (21 mL) was added palladium hydroxide on carbon (Degussa, 107 mg). The resulting mixture was hydrogenated under 60 psi at rt for 2 h. After filtration on Celite and concentration, the residue was dissolved in DMF (15 mL) and cooled with an ice bath, and then benzaldehyde dimethyl acetal (268 μL, 1.2 equiv) and tetrafluoroboric acid (54% in ether, 246 μL, 1.2 equiv) were added.[34] The mixture was stirred under nitrogen atmosphere overnight at rt, and then triethylamine (270 μL, 1.3 equiv) was added and the solvent evaporated. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 2:8 to give **7** (640 mg, 80%) as clear syrup: $[\alpha]_D$ −18.1 (*c* 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 7.51 (d, 2H, ArH, *J* = 7.1 Hz), 7.34−7.30 (m, 3H, ArH), 5.53 (s, 1H, PhC*H*(O)(O)−), 4.50 (dd, 1H, −OC*H*CO_2-Me, *J* = 9.4, 3.6 Hz), 4.34 (fd, 1H, H-4, $J_{4,3}$ = 3.5 Hz), 4.30 (d, 1H, H-6, $J_{6,6A}$ = 12.4 Hz), 4.26 (d, 1H, H-1, $J_{1,2}$ = 7.8 Hz), 4.07 (d, 1H, H-6A), 4.05 (m, 1H, −OC*H*HCH_2TMS), 3.95 (dd, 1H, H-2, $J_{2,3}$ = 9.6 Hz), 3.62 (s, 3H, OCH_3), 3.55 (m, 1H, −OCH*H*CH_2TMS), 3.48 (dd, 1H, H-3), 3.39 (brs, 1H, H-5), 2.50 (brs, 1H, −OH), 1.90−1.50 (3m, 9H, −CH_2− and −CH−), 1.30−0.80 (m, 6H, −CH_2− and −CH_2TMS), 0.00 (s, 9H, −Si-$(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.7 (CO), 138,0 (ArC), 128.9, 128.0 (2C) and 126.6 (2C) (ArCH), 102.7 and 101.0 (Ph*C*H(O)(O)- and C-1), 79.4, 77.0, 74.9, 70.8 and 66.6 (C-2 to C-5 and −O*C*HCO$_2$Me), 69.3 and 67.4 [(−), C-6 and −O*C*H_2CH_2-TMS], 51.9 (−OCH_3), 40.8, 33.9, 32.6, 26.6, 26.4 and 26.3 [(−), −CH_2−], 33.9 (−CH−), 18.3 [(−), −*C*H_2TMS], −1.2 [−Si-$(CH_3)_3$]; IR (film, cm^{-1}) 2923, 1741, 1249, 1113, 1051; HR-FABMS calcd for $C_{28}H_{44}O_8SiNa$ *m*/*z* 559.27032, found 559.27057.

Lactone Derivative of 2-(Trimethylsilyl)ethyl *O*-4,6-*O*-Benzylidene-3-*O*-[(*S*)-1-(methoxycarbonyl)-2-cyclohexylethyloxy]-β-D-galactopyranoside (9). To a cooled solution of **7** (112 mg, 208.1 μmol) in THF (21 mL) was added at 0 °C lithium hydroxide (17.5 mg, 2 equiv) dissolved in water (2 mL). The mixture was stirred overnight at 7 °C (cold chamber) and neutralized with Amberlite IR-120 (H^+). After filtration and concentration, the residue was dissolved in a mixture of acetic anhydride (1.2 mL) and acetonitrile (4.6 mL)[39] and stirred at rt for 12 h. After concentration, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 2:8, to give **9** (104 mg, 99%) as a syrup: $[\alpha]_D$ −37 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 7.50 (d, 2H, ArH, *J* = 7.1 Hz), 7.35 (m, 3H, ArH), 5.59 (s, 1H, PhC*H*(O)(O)−), 4.66 (dd, 1H, H-2, $J_{2,3}$ = 10.1 Hz, $J_{2,1}$ = 7.7 Hz), 4.58 (m, 1H, −OC*H*CO_2Me), 4.57 (d, 1H, H-1), 4.37 (fdd, 1H, H-6, $J_{6,6A}$ = 12.5 Hz, $J_{6,5}$ = 1.3 Hz), 4.33 (fd, 1H, H-4, $J_{4,3}$ = 3.1 Hz), 4.11 (fdd, 1H, H-6A, $J_{6A,5}$ = 1.3 Hz), 4.10 (m, 1H, −OC*H*HCH_2TMS), 3.78 (dd, 1H, H-3), 3.63 (m, 1H, −OCH*H*CH_2TMS), 3.53 (brs, 1H, H-5), 1.88−1.50 (m, 9H, −CH_2− and −CH−), 1.30−0.80 (m, 6H, −CH_2− and −CH_2-TMS), 0.03 (s, 9H, −Si$(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2 (CO), 137,5 (ArC), 129.3, 128.4 (2C) and 126.5 (2C) (ArCH), 101.2 and 100.0 (Ph*C*H(O)(O)− and C-1), 74.5, 74.1, 72.3, 71.4 and 66.8 (C-2 to C-5 and −O*C*HCO$_2$Me), 69.3 and 67.7 [(−), C-6 and −O*C*H_2CH_2TMS], 38.6, 34.1, 32.1, 26.6, 26.4 and 26.1 [(−), −CH_2−], 33.7 (−CH−), 18.2 [(−), −*C*H_2TMS], −1.2 [-Si$(CH_3)_3$]; IR (film, cm^{-1}) 2925, 2853, 1756, 1251, 1049; HR-FABMS calcd for $C_{27}H_{40}O_7SiNa$ *m*/*z* 527.24410, found 527.24440.

2-(Trimethylsilyl)ethyl *O*-2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-[(*S*)-1-(methoxycarbonyl)-2-cyclohexylethyloxy]-β-D-galactopyranoside (8). To a cold solution of **7** (300 mg, 559 μmol) in dichloromethane (5.6 mL) and pyridine (1.1 mL) were added benzoyl chloride (325 μL, 5 equiv) and a catalytic amount of DMAP at 0 °C. The mixture was stirred at rt overnight. The excess of benzoyl chloride was quenched with MeOH and the mixture concentrated under vacuum. The crude product was redissolved in dichloromethane (25 mL), washed with aqueous saturated ammonium chloride (20 mL) and water (20 mL), and dried (sodium sulfate). After concentration, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 3:7, to give **8** (359 mg, 100%) as a white solid. White needle-shaped crystals were obtained by recrystallization from a mixture of hexanes/ethyl acetate: mp 160 °C; $[\alpha]_D$ +10 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 8.08 (d, 2H, ArH, *J* = 7.1 Hz), 7.60−7.30 (3m, 8H, ArH), 5.61 (dd, 1H, H-2, $J_{2,3}$ = 10.0 Hz, $J_{2,1}$ = 8.0 Hz), 5.58 (s, 1H, PhC*H*(O)(O)−), 4.60 (d, 1H, H-1), 4.46 (fd, 1H, H-4, $J_{4,3}$ = 3.5 Hz), 4.35 (fdd, 1H, H-6, $J_{6,6A}$ = 12.3 Hz, $J_{6,5}$ = 1.5 Hz), 4.13 (m, 1H, −OC*H*CO_2Me), 4.11 (fdd, 1H, H-6A, $J_{6A,5}$ = 1.5 Hz), 4.00 (m, 1H, −OC*H*HCH_2TMS), 3.76 (dd, 1H, H-3), 3.58 (s, 3H, OCH_3), 3.54 (m, 1H, −OCH*H*CH_2-TMS), 3.48 (brs, 1H, H-5), 1.57 (m, 1H, −C*H*HCHCO$_2$Me−), 1.50−1.20 (m, 7H, −CH_2− and −CH*H*CHCO$_2$Me−), 0.95−0.75 (m, 5H, −CH_2−, −CH− and −CH_2TMS), 0.71−0.55 (m, 2H, −CH_2−), 0.08 (s, 9H, −Si$(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.3 (*C*O_2Me), 165.0 (Ph*C*O), 138.0 and 130.4 (ArC), 133.1, 130.0 (2C), 129.0, 128.5 (2C), 128.2 (2C) and 126.7 (2C) (ArCH), 101.2 and 100.9 (Ph*C*H(O)(O)− and C-1), 79.0, 78.3, 75.2, 71.9 and 66.9 (C-2 to C-5 and −O*C*HCO$_2$Me), 69.2 and 66.8 [(−),

(39) (a) Zou, W.; Jennings, H. J. *J. Carbohydr. Chem.* **1996**, *15*, 257. (b) Severn, W. B.; Richards, C. *J. Am. Chem. Soc.* **1993**, *115*, 1114.

C-6 and −O*C*H$_2$CH$_2$TMS], 52.0 (−O*C*H$_3$), 41.0, 33.8, 32.6, 26.4, 25.9 and 25.7 [(−), −*C*H$_2$−], 33.3 (−*C*H−), 18.0 [(−), −*C*H$_2$-TMS], −1.3 [−Si(*C*H$_3$)$_3$]; IR (film, cm^{-1}) 2924, 1731, 1267, 1096; HR-FABMS calcd for $C_{35}H_{48}O_9SiNa$ *m/z* 663.29653, found 663.29590.

2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-[(*S*)-1-(methoxycarbonyl)-2-cyclohexylethyloxy]-α-D-galactopyranose (10). A solution of **8** (200 mg, 312 μmol) in dichloromethane (1.5 mL) and TFA (3.0 mL) was stirred at 0 °C for 30 min, concentrated, and codistilled twice with toluene. The crude product was dissolved in DMF (3.1 mL) cooled in an ice bath, and then benzaldehyde dimethyl acetal (56 μL, 1.2 equiv) and tetrafluoroboric acid (54% in ether, 47 μL, 1.1 equiv) were added. The mixture was stirred under nitrogen atmosphere for 6 h at rt, triethylamine (52 μL, 1.2 equiv) was added, and the solvent was evaporated. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 1:1, to give a 4:1 α/β inseparable mixture of isomers (115 mg, 68%) as a clear syrup. Data for the major α isomer **10**: ^{1}H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 8.08 (d, 2H, ArH, J = 7.3 Hz), 7.59−7.55 (m, 3H, ArH), 7.48−7.32 (2m, 5H, ArH), 5.67 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 5.58 (s, 1H, PhC*H*(O)(O)−), 5.54 (dd, 1H, H-2, $J_{2,3}$ = 10.4 Hz), 4.53 (fd, 1H, H-4, $J_{4,3}$ = 3.2 Hz), 4.31 (dd, 1H, −OC*H*CO$_2$Me, J = 9.1, 4.0 Hz), 4.23 (d, 1H, H-6, $J_{6,6A}$ = 12.5 Hz), 4.12 (dd, 1H, H-3), 4.06 (d, 1H, H-6A), 3.94 (brs, 1H, H-5), 3.64 (s, 3H, OCH_3), 1.62−1.27 (m, 8H, −CH_2− and −C*HH*CHCO$_2$Me−), 1.00−0.60 (m, 5H, −CH_2−, −CH−); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5 (*C*O$_2$Me), 166.0 (Ph*C*O), 137.9, 133.4, 129.9, 129.6 (2C), 129.0, 128.6 (2C), 128.2 (2C) and 126.5 (2C) (ArCH and ArC), 100.9 (Ph*C*H(O)(O)−), 91.2 (C-1), 78.4, 75.7, 74.2, 71.8, 69.4 and 62.9 (C-2 to C-6 and −O*C*HCO$_2$Me), 52.1 (−O*C*H$_3$), 41.0, 33.8, 33.7, 32.8, 26.4, 26.1 and 25.8 (−CH_2− and −CH−); HR-FABMS calcd for $C_{30}H_{36}O_9Na$ *m/z* 563.22570, found 563.22667.

2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-[(*S*)-1-(methoxycarbonyl)-2-cyclohexylethyloxy]-β-D-galactopyranosyl 2-Thiopyridyl Carbonate (11). A mixture of **10** and its β isomer (99.3 mg, 183.7 μmol), di(*S*-2-pyridyl) thiocarbonate (137 mg, 3 equiv), and triethylamine (77 μL, 3 equiv) in dichloromethane (1.84 mL) was stirred at rt for 24 h. Concentration and purification by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 1:1, gave **11** (100 mg, 80%) as a yellow powder: [α]$_D$ +17.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 8.52 (m, 1H, PyH), 8.07 (d, 2H, ArH, J = 7.1 Hz), 7.70−7.30 (4m, 10H, ArH), 7.25 (m, 1H, PyH), 5.87 (d, 1H, H-1, $J_{1,2}$ = 8.3 Hz), 5.80 (dd, 1H, H-2, $J_{2,3}$ = 9.8 Hz), 5.61 (s, 1H, PhC*H*(O)(O)−), 4.56 (fd, 1H, H-4, $J_{4,3}$ = 3.2 Hz), 4.37 (dfd, 1H, H-6, $J_{6,6A}$ = 12.5 Hz, $J_{6,5}$ = 1.3 Hz), 4.15 (m, 1H, −OC*H*CO$_2$Me), 4.12 (dfd, 1H, H-6A, $J_{6A,5}$ = 1.3 Hz), 3.81 (dd, 1H, H-3), 3.65 (brs, 1H, H-5), 3.63 (s, 3H, OCH_3), 1.59 (m, 1H, −C*H*HCHCO$_2$Me−), 1.50−1.20 (m, 7H, −CH_2− and −CH*H*CHCO$_2$Me−), 1.00−0.58 (2m, 5H, −CH_2−, −CH−); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0 (*C*O$_2$Me), 168.6 (−O*C*(O)S−), 164.7 (Ph*C*O), 151.2 (PyC), 150.6 (PyCH), 137.9, 137.7, 133.8, 130.3, 130.0, 129.7, 129.3, 128.9, 128.5, 126.8 and 124.0 (PhCH PyCH and PhC), 101.4 and 95.2 (Ph*C*H(O)(O)− and C-1), 79.0, 78.9, 74.9, 70.5 and 68.2 (C-2 to C-5 and −O*C*HCO$_2$Me), 68.9 [(−), C-6], 52.3 (−O*C*H$_3$), 41.1, 34.0, 32.9, 26.6, 26.2 and 25.9 [(−), −CH_2−], 33.6 (−CH−); IR (film, cm^{-1}) 2924, 1736, 1264, 1112, 1062; HR-FABMS calcd for $C_{35}H_{39}O_8NSNa$ *m/z* 656.22940, found 656.22971.

3-*O*-Benzoyl-4,6-*O*-benzylidene-1,2-dideoxy-D-glucopyranose (14). To a cold (5 °C) solution of 4,6-*O*-benzylidene-1,2-dideoxy-D-glucopyranoside[17] **13** (1.0 g, 4.24 mmol) in dichloromethane (47 mL) were added triethylamine (1.77 mL, 3 equiv), a catalytic amount of DMAP, and benzoyl chloride (1.0 mL, 2 equiv). The mixture was stirred at rt for 2 h, poured into a separatory funnel, washed with water and brine, dried (sodium sulfate), and filtered. After concentration, the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 1:9, to give **14** (1.40 g, 97%) as a clear syrup: [α]$_D$ −135.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 8.08 (d, 2H, ArH, J = 7.0 Hz), 7.57−7.33 (3m, 8H, ArH), 5.63 (s, 1H, PhC*H*(O)(O)−), 5.36 (ddd, 1H, H-3, $J_{3,2ax}$ = 10.9 Hz, $J_{3,4}$ = 9.5 Hz, $J_{3,2eq}$ = 5.3 Hz), 4.36 (dd, 1H, H-6, $J_{6,6A}$ = 10.4 Hz, $J_{6,5}$ = 4.9 Hz), 4.06 (ddfd, 1H, H-1eq, $J_{1eq,1ax}$ = 12.0 Hz, $J_{1eq,2ax}$ = 5.2 Hz, $J_{1eq,2eq}$ = 1.5 Hz), 3.86 (t, 1H, H-4), 3.81 (t, 1H, H-6A), 3.71 (td, 1H, H-1ax, $J_{1ax,2ax}$ = 12.0 Hz,, $J_{1ax,2eq}$ = 1.5 Hz), 3.54 (td, 1H, H-5, $J_{5,4}$ = $J_{5,6A}$ = 10.0 Hz), 2.35 (ddt, 1H, H-2eq, $J_{2eq,2ax}$ = 13.0 Hz), 1.95 (tdd, 1H, H-2ax); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 165.8 (CO), 137.1 and 130.0 (ArC), 132.9, 129.6 (2C), 128.8, 128.2 (2C), 128.0 (2C) and 126.0 (2C) (ArCH), 101.4 (Ph*C*H(O)(O)−), 80.4, 71.8 and 71.5 (C-3 to C-5), 68.8 and 65.9 [(−), C-6 and C-1], 31.5 [(−), C-2]; IR (film, cm^{-1}) 2866, 1719, 1452, 1315, 1270, 1133, 1103, 1014; HR-FABMS calcd for $C_{20}H_{20}O_5Na$ *m/z* 363.12084, found 363.12088.

3-*O*-Benzoyl-6-*O*-benzyl-1,2-dideoxy-D-glucopyranose (15). Hydrogen chloride in diethyl ether was added at rt to **14** (1.31 g, 3.84 mmol) and sodium cyanoborohydride[36] (966 mg, 4 equiv) in THF (87 mL) containing 4 Å molecular sieves until the evolution of gas ceased. The mixture was filtered through a Celite pad, diluted with dichloromethane (200 mL), and washed with water and saturated aqueous hydrogen carbonate. The organic layer was dried (sodium sulfate) and concentrated, and the resulting syrup was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 3:7, to give **15** (1.21 g, 92%) as a clear syrup: [α]$_D$ −28.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 8.06 (d, 2H, ArH, J = 7.0 Hz), 7.57−7.29 (3m, 8H, ArH), 5.08 (ddd, 1H, H-3, $J_{3,2ax}$ = 11.4 Hz, $J_{3,4}$ = 9.0 Hz, $J_{3,2eq}$ = 5.2 Hz), 4.61 (AB, 2H, PhCH_2−, J = 12.0 Hz), 4.05 (ddfd, 1H, H-1eq, $J_{1eq,1ax}$ = 12.0 Hz, $J_{1eq,2ax}$ = 4.9 Hz, $J_{1eq,2eq}$ = 1.5 Hz), 3.78−3.73 (m, 3H, H-4, H-6 and H-6A), 3.55 (td, 1H, H-1ax, $J_{1ax,2ax}$ = 12.0 Hz, $J_{1ax,2eq}$ = 2.0 Hz), 3.45 (dt, 1H, H-5, $J_{5,4}$ = 9.4 Hz, $J_{5,6}$ = $J_{5,6A}$ = 4.0 Hz), 2.14 (ddt, 1H, H-2eq, $J_{2eq,2ax}$ = 12.0 Hz), 1.86 (tdd, 1H, H-2ax); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7 (CO), 137.7 and 129.7 (ArC), 133.1, 129.6 (2C), 128.2 (3C), 127.7 (2C) and 127.6 (2C) (ArCH), 79.0, 76.0 and 70.9 (C-3 to C-5), 73.6, 70.1 and 65.3 [(−), Ph*C*H$_2$−, C-6 and C-1], 30.8 [(−), C-2]; IR (film, cm^{-1}) 3471, 2862, 1718, 1452, 1317, 1273, 1122, 1092, 1071, 1027; HR-FABMS calcd for $C_{20}H_{22}O_5Na$ *m/z* 365.13649, found 365.13638.

Di(*S*-2-pyridyl) Thiocarbonate. To a cold solution (0 °C) of 2-mercaptopyridine (8.89 g, 80 mmol) and triphosgene (3.95 g, 13.3 mmol) in dichloromethane (400 mL) was added dropwise triethylamine (12 mL, 86 mmol); the mixture was stirred at this temperature for 30 min and then at rt for 1 h. The mixture was concentrated, treated with cold saturated aqueous bicarbonate, and extracted with 400 mL of ethyl acetate. After being washed with water and brine, the organic layer was dried (sodium sulfate), filtered, and concentrated to give the product as a yellow solid that was dried in vacuo overnight. Pale yellow needle-shaped crystals were obtained by recrystallization from 2-propanol (8.32 g, 84%): mp 44 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (ddd, 2H, J = 4.8, 1.9, 0.8 Hz), 7.69 (td, 2H, J = 7.9, 1.9 Hz), 7.63 (dt, 2H, J = 7.9, 1.1 Hz), 7.26 (ddd, 2H, J = 7.3, 4.8, 1.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.6 (CO), 150.6 (PyC), 150.5, 137.5, 130.5 and 124.2 (PyCH); IR (film, cm^{-1}) 3047, 1712, 1656, 1572, 1562, 1449, 1421, 1282, 1152, 1113, 1083, 1045; HR-FABMS calcd for $C_{11}H_9ON_2S_2$ *m/z* 249.01563, found 249.01553.

2,3,4-Tri-*O*-benzyl-β-L-fucopyranosyl 2-Thiopyridyl Carbonate (16). A mixture of 2,3,4-tri-*O*-benzyl-L-fucopyranose[40] (714 mg, 1.65 mmol), di(*S*-2-pyridyl) thiocarbonate (1.22 g, 3 equiv), and triethylamine (690 μL, 3 equiv) in dichloromethane (16.5 mL) was stirred at rt for 24 h. Concentration and purification by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 3:7, gave **16** (840 mg, 89%) as a yellow powder: [α]$_D$ −9.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 8.60 (d, 1H, PyH, J = 5.0 Hz), 7.72 (m, 2H, ArH), 7.41−7.25 (m, 16H, ArH), 5.66 (d, 1H, H-1, $J_{1,2}$ = 8.0 Hz), 5.00 (d, 1H, PhC*H*H−, J = 11.6 Hz), 4.80 (s, 2H, PhCH_2−), 4.78 (AB, 2H, PhCH_2−, J = 11.9 Hz), 4.72 (d, 1H, PhCH*H*−, J = 11.6 Hz), 4.00 (t, 1H, H-2, $J_{2,3}$ = 8.0 Hz), 3.68−3.58 (m, 3H, H-3, H-4 and H-5), 1.22 (d, 3H, −CH_3, $J_{Me,5}$ = 6.4

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Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.7 (CO), 151.4 (PyC), 149.9, 137.1, 129.1, 128.3, 128.2, 128.1, 127.6, 127.4 and 123.4 (PhCH and PyCH), 138.1, 138.0, 137.9 (PhC), 96.9 (C-1), 82.3, 77.5, 75.7 and 71.6 (C-2 to C-5), 75.2, 74.6 and 73.0 [(−), Ph*C*H$_2$−], 16.5 (−CH$_3$); IR (film, cm^{-1}) 2874, 1736, 1573, 1497, 1454, 1422, 1102, 1062, 1021; HR-FABMS calcd for $C_{32}H_{33}O_4$NSNa *m*/*z* 550.20280, found 550.20292.

(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-*O*-(1 → 4)-3-*O*-benzoyl-6-*O*-benzyl-1,2-dideoxy-D-glucopyranose (17). A mixture of **15** (343 mg, 1.00 mmol), **16** (800 mg, 1.4 equiv), 1,1,3,3-tetramethylurea (170 μL, 1.4 equiv), and activated 4 Å molecular sieves in dichloromethane (38.5 mL) was stirred overnight at rt and then cooled at 0 °C. Silver triflate (2.32 g, 9 equiv) was added to the reaction mixture, and the stirring was continued 24 h at rt in the dark. The suspension was treated with a few drops of pyridine, filtered through Celite, and concentrated. Purification by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 2:8, gave **17** (758 mg, > 98%) as a syrup: $[\alpha]_D$ −48.6 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 8.08 (d, 2H, ArH, J = 7.0 Hz), 7.65−7.20 (3m, 23H, ArH), 5.30 (ddd, 1H, H-3, $J_{3,2ax}$ = 11.0 Hz, $J_{3,4}$ = 9.0 Hz, $J_{3,2eq}$ = 5.5 Hz), 5.07 (d, 1H, H-1′, $J_{1',2'}$ = 3.5 Hz), 4.92 (d, 1H, PhC*H*H−, J = 11.5 Hz), 4.84 (d, 1H, PhC*H*H−, J = 11.6 Hz), 4.74 (AB, 2H, PhC*H*$_2$−, J = 11.7 Hz), 4.62 (d, 1H, PhCH*H*−, J = 11.6 Hz), 4.58 (d, 1H, PhCH*H*−, J = 11.5 Hz), 4.46 (s, 2H, PhC*H*$_2$−), 4.06 (dd, 1H, H-1eq, $J_{1eq,1ax}$ = 11.6 Hz, $J_{1eq,2ax}$ = 4.0 Hz, $J_{1eq,2eq}$ = 0 Hz), 4.00 (dd, 1H, H-2′, $J_{2',3'}$ = 10.3 Hz), 3.95−3.84 (m, 5H, H-4, H-6, H-6A, H-3′ and H-5′), 3.60−3.51 (m, 3H, H-1ax, H-5 and H-4′), 2.20 (brdd, 1H, H-2eq, $J_{2eq,2ax}$ = 11.0 Hz), 1.86 (brq, 1H, H-2ax, $J_{2ax,1ax}$ = 11 Hz), 0.78 (d, 3H, −CH$_3$, $J_{Me,5'}$ = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.2 (CO), 138.9, 138.7 (2C), 138.4 and 130.5 (ArC), 133.1, 129.9, 128.4,128.3, 128.2, 128.0, 127.8, 127.7, 127.6 and 127.5 (ArCH), 99.4 (C-1′), 79.9, 79.5, 77.8, 76.6, 76.5, 74.6 and 67.2 (C-3 to C-5 and C-2′ to C-5′), 75.0, 74.2, 73.5, 72.9, 69.6, and 65.4 [(−), Ph*C*H$_2$−, C-6 and C-1], 31.6 [(−), C-2], 16.4 (−CH$_3$); IR (film, cm^{-1}) 3031, 2864, 1717, 1454, 1273, 1099, 1069, 1047, 1028; HR-FABMS calcd for $C_{47}H_{50}O_9$Na *m*/*z* 781.33525, found 781.33512.

(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-*O*-(1 → 4)-6-*O*-benzyl-1,2-dideoxy-D-glucopyranose (18). To a solution of **17** (758 mg, 1.00 mmol) in methanol (5 mL) was added 2 mL (1.0 equiv) of a freshly prepared methanol solution of sodium methoxide (0.5 M). The solution was stirred at 45 °C for 2 h and neutralized with Amberlite IR-120 (H^+). After filtration and concentration, the resulting syrup was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 3:7, to give **18** (514 mg, 85%) as a white powder: $[\alpha]_D$ −24.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 7.45−7.20 (m, 20H, ArH), 5.04 (d, 1H, PhC*H*H−, J = 11.4 Hz), 5.00 (d, 1H, H-1′, $J_{1',2'}$ = 3.8 Hz), 4.88 (d, 1H, PhC*H*H−, J = 11.9 Hz), 4.81 (d, 1H, PhC*H*H−, J = 11.9 Hz), 4.78 (d, 1H, PhCH*H*−, J = 12.1 Hz), 4.70 (d, 1H, PhCH*H*−, J = 11.4 Hz), 4.68 (d, 1H, PhCH*H*−, J = 11.7 Hz), 4.62 (brs, 1H, −OH), 4.42 (AB, 2H, PhC*H*$_2$−, J = 12.3 Hz), 4.15−4.07 (m, 2H, H-2′ and H-5′), 4.04 (dd, 1H, H-1eq, $J_{1eq,1ax}$ = 11.5 Hz, $J_{1eq,2ax}$ = 4.0 Hz), 3.99 (dd, 1H, H-6, $J_{6,6A}$ = 10.5 Hz, $J_{6,5}$ = 1.6 Hz), 3.93 (dd, 1H, H-3′, $J_{3',2'}$ = 10.2 Hz, $J_{3',4'}$ = 2.6 Hz), 3.74 (fd, 1H, H-4′), 3.73 (dd, 1H, H-6A, $J_{6A,5}$ = 6.3 Hz), 3.63 (m, 1H, H-3), 3.50−3.40 (m, 2H, H-1ax and H-5), 3.28 (t, 1H, H-4, $J_{4,3}$ = $J_{4,5}$ = 8.6 Hz), 2.03 (brdd, 1H, H-2eq, $J_{2eq,2ax}$ = 11.0 Hz, $J_{2eq,3}$ = 4.0 Hz), 1.73 (brq, 1H, H-2ax, $J_{2ax,1ax}$ = $J_{2ax,3}$ = 11 Hz, $J_{2ax,1eq}$ = 4 Hz), 1.22 (d, 3H, −CH$_3$, $J_{Me,5'}$ = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.7, 138.6, 138.4 (2C) (ArC), 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 127.5 and 127.4 (ArCH), 99.7 (C-1′), 84.0, 79.0, 78.3, 77.4, 76.0, 71.9 and 68.0 (C-3 to C-5 and C-2′ to C-5′), 75.0, 73.8, 73.3, 73.2, 70.1, and 65.7 [(−), Ph*C*H$_2$−, C-6 and C-1], 32.8 [(−), C-2], 16.8 (−CH$_3$); HR-FABMS calcd for $C_{40}H_{46}O_8$Na *m*/*z* 677.30904, found 677.30865.

(2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-[(*S*)-1-(methoxycarbonyl)-2-cyclohexyl-ethyloxy]-β-D-galactopyranosyl)-*O*-(1 → 3)-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-*O*-(1 → 4)]-6-*O*-benzyl-1,2-dideoxy-D-glucopyranose (19). To a cold solution of **18** (96 mg, 146.8 μmol) in THF (14.7 mL) was added sodium hydride (9 mg, 1.5 equiv), and the mixture was stirred at 0 °C for 30 min. Silver triflate (42 mg, 1.1 equiv) was added, the mixture stirred in the dark 15 min, **11** (66.3 mg, 0.7 equiv) and 4 Å molecular sieves were then added, and the mixture was allowed to warm to rt in the dark overnight. The mixture was filtered through Celite, concentrated, redissolved in dichloromethane (20 mL), and washed with saturated aqueous ammonium cloride (10 mL) and brine (10 mL). The organic phase was dried (sodium sulfate), concentrated, and purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes 6:4 gave **19** (55.3 mg, 48%) as a syrup: $[\alpha]_D$ −31.0 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, assigned by COSY45) δ 8.07 (dfd, 2H, ArH, J = 8.3, 1.2 Hz), 7.68 (d, 2H, ArH, J = 7.0 Hz), 7.58 (t, 1H, ArH, J = 7.0 Hz), 7.46 (t, 2H, ArH, J = 7.0 Hz), 7.40−7.10 (m, 23H, ArH), 5.67 (s, 1H, PhC*H*(O)(O)−), 5.62 (t, 1H, H-2′, $J_{2',1'}$ = $J_{2',3'}$ = 8.8 Hz), 4.91 (q, 1H, H-5″, $J_{5'',Me}$ = 6.4 Hz), 4.85 (d, 1H, H-1″, $J_{1'',2''}$ = 3.3 Hz), 4.75 (d, 1H, PhC*H*H−, J = 11.7 Hz), 4.66 (d, 1H, PhC*H*H−, J = 11.5 Hz), 4.65 (d, 1H, H-1′, $J_{1',2'}$ = 7.0 Hz), 4.57 (d, 1H, PhCH*H*-, J = 11.5 Hz), 4.55 (d, 1H, PhCH*H*−, J = 11.7 Hz), 4.49 (fd, 1H, H-4′, $J_{4',3'}$ = 2.9 Hz), 4.34 (s, 2H, PhC-*H*$_2$−), 4.33 (d, 1H, H-6′, $J_{6',6A'}$ = 12.6 Hz), 4.22 (d, 1H, PhC*H*H−, J = 11.3 Hz), 4.18−4.13 (m, 2H, −OC*H*CO$_2$Me and H-6A′), 3.97−3.88 (m, 2H, H-2″ and H-3″), 3.86−3.56 (m, 10H, H-1eq, H-3, H-4, H-3′, H-6, H-6A, PhCH*H*− and −OCH$_3$), 3.46 (s,1H, H-5′), 3.31−3.24 (m, 3H, H-1ax, H-5 and H-4″), 1.83 (brdd, 1H, H-2eq, $J_{2eq,2ax}$ = 12.0 Hz, $J_{2eq,3}$ = 5.0 Hz), 1.67 (m, 1H, −C*H*HCHCO$_2$Me−), 1.52−1.27 (m, 8H, H-2ax, −CH$_2$− and −CH*H*CHCO$_2$Me−), 1.26 (d, 3H, −CH$_3$), 0.96−0.71 (m, 5H, −CH$_2$− and −CH−); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.3 (*C*O$_2$Me), 164.8 (Ph*C*O), 140, 139.6, 138.9, 138.3 and 130.1 (ArC), 133.3, 129.9, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.0 and 126.2 (ArCH and ArC), 99.8, 99.3 and 97.6 (Ph*C*H(O)(O)−, C-1′ and C-1″), 80.4, 80.1, 78.9 (2C), 78.5, 78.3, 75.6, 75.1, 72.5, 71.6, 66.7 and 65.8 (C-3 to C-5, C-2′ to C-5′, C-2″ to C-5″ and −O*C*HCO$_2$Me), 75.0, 74.7, 73.4, 71.3, 69.4, 68.4 and 66.6 [(−), Ph*C*H$_2$−, C-1, C-6 and C-6′], 52.1 (−OCH$_3$), 41.0, 33.9, 32.6, 31.4, 26.4, 26.0 and 25.7 [(−), −CH$_2$− and C-2], 33.4 (−CH−), 16.3 (−CH$_3$); HR-FABMS calcd for $C_{70}H_{80}O_{16}$Na *m*/*z* 1199.53440, found 1199.53391.

(2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-[(*S*)-1-(oxycarbonyl)-2-cyclohexylethyloxy]-β-D-galactopyranosyl)-*O*-(1 → 3)-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-*O*-(1 → 4)]-6-*O*-benzyl-1,2-dideoxy-D-glucopyranose (20). To a cooled solution (0 °C) of **19** (94.2 mg, 80.06 μmol) in THF (8 mL) was added lithium hydroxide (3.7 mg, 1.1 equiv) dissolved in water (470 μL). The mixture was stirred at rt for 48 h and neutralized with Amberlite IR-120 (H^+). After filtration and concentration, the residue was purified by flash chromatography on silica gel, eluting with dichloromethane/methanol 14:1, to give **20** (93 mg, >98%) as a gum: $[\alpha]_D$ −86.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz) δ ppm 8.16 (d, 2H, ArH, J = 8.0 Hz), 7.74 (d, 2H, ArH, J = 7.7 Hz), 7.65 (t, 1H, ArH, J = 7.0 Hz), 7.53 (t, 2H, ArH, J = 7.0 Hz), 7.40−7.19 (m, 23H, ArH), 5.75 (s, 1H, PhC*H*(O)(O)−), 5.61 (t, 1H, H-2′, $J_{2',1'}$ = $J_{2',3'}$ = 9.0 Hz), 5.06 (q, 1H, H-5″, $J_{5'',Me}$ = 6.4 Hz), 4.83 (d, 1H, H-1″, $J_{1'',2''}$ = 3.8 Hz), 4.79 (d, 1H, H-1′, $J_{1',2'}$ = 8.0 Hz), 4.72 (d, 1H, J = 11.9 Hz), 4.67 (d, 1H, J = 11.4 Hz), 4.61 (d, 1H, J = 11.6 Hz), 4.59 (brs, 1H, H-4′), 4.42 (t, 2H, J = 11.4 Hz), 4.27−4.18 (m, 5H), 3.96−3.91 (m, 2H), 3.79−3.73 (m, 4H), 3.66−3.49 (m, 5H), 3.40 (brs, 1H), 3.20 (brd, 1H, J = 9 Hz), 2.00 (brdd, 1H, H-2eq, $J_{2eq,2ax}$ = 12.0 Hz, $J_{2eq,3}$ = 4.0 Hz), 1.70−0.80 (2m, 14H, H-2ax, −CH$_2$− and −CH−), 1.26 (d, 3H, −CH$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.9 (*C*O$_2$H), 166.7 (Ph*C*O), 139.9, 139.6, 139.0, 138.3 (2C) and 129.9 (ArC), 134.0, 130.3, 129.2, 128.9, 128.6, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, and 126.3 (ArCH), 100.1, 99.3 and 97.7 (Ph*C*H(O)(O)-, C-1′ and C-1″), 80.9, 80.7, 80.4, 79.0 (2C), 75.9, 75.8, 74.1, 72.7, 71.1, 66.8 and 66.7 (C-3 to C-5, C-2′ to C-5′, C-2″ to C-5″ and −O*C*HCO$_2$H), 75.4, 74.9, 73.6, 71.7, 69.5, 68.6 and 66.0 [(−), Ph*C*H$_2$−, C-1, C-6 and C-6′], 41.7, 33.5, 31.8, 30.1, 26.7, 26.2 and 26.1 [(−), −CH$_2$− and C-2], 34.0 (−CH−), 16.7 (−CH$_3$); IR (film, cm^{-1}) 2924, 1732, 1603, 1452, 1365, 1268, 1097, 1057; HR-FABMS calcd for $C_{69}H_{78}O_{16}$-Na *m*/*z* 1185.51880, found 1185.52240.

(4,6-*O*-Benzylidene-3-*O*-[(*S*)-1-(oxycarbonyl)-2-cyclohexylethyloxy]-β-D-galactopyranosyl)-*O*-(1 → 3)-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-*O*-(1 → 4)]-6-*O*-benzyl-1,2-dideoxy-D-glucopyranose (21). To a solution of **20** (44.1 mg, 37.93 μmol) in methanol (5.4 mL) was added 1.52 mL (20 equiv) of a freshly prepared methanol solution of sodium methoxide (0.5 M). The solution was refluxed for 2 h and neutralized with Amberlite IR-120 (H^+). After filtration and concentration, the resulting syrup was purified by flash chromatography on silica gel, eluting with dichloromethane/methanol 12:1, to give **21** (36 mg, 90%) as a gum: $[\alpha]_D$ −107.2 (*c* 0.18, CH_3OH); ^1H NMR (CD_3OD, 400 MHz, assigned by COSY45) δ 7.66 (d, 2H, ArH, *J* = 7.4 Hz), 7.40−7.10 (m, 23H, ArH), 5.68 (s, 1H, PhC*H*(O)(O)−), 5.01 (q, 1H, H-5″, $J_{5'',Me}$ = 6.4 Hz), 4.89 (d, 1H, H-1″, $J_{1'',2''}$ = 3.8 Hz), 4.72−4.67 (m, 3H, −OC*H*CO_2Me and 2 PhC*H*H−), 4.58 (d, 1H, PhCH*H*−, *J* = 11.9 Hz), 4.47 (d, 1H, PhC*H*H-, *J* = 11.8 Hz), 4.45 (d, 1H, PhCH*H*−, *J* = 11.4 Hz), 4.42 (d, 1H, H-4′, $J_{4',3'}$ = 3.3 Hz), 4.36 (d, 1H, H-1′, $J_{1',2'}$ = 7.7 Hz), 4.22−4.15 (m, 3H, H-6′, H-6A′ and PhC*H*H−), 3.95−3.78 (m, 6H, H-1eq, H-3, H-6, H-2′, H-2″ and H-3″), 3.68 (t, 1H, H-4, $J_{4,3}$ = $J_{4,5}$ = 9.4 Hz), 3.60−3.47 (m, 4H, H-6A, H-3′, H-5′ and PhCH*H*−), 3.39 (brt, 1H, H-1ax, $J_{1ax,2ax}$ = $J_{1ax,1eq}$ = 9.0 Hz), 3.31 (1H, H-4″), 3.24 (m, 1H, H-5), 2.10 (brdd, 1H, H-2eq, $J_{2eq,2ax}$ = 12.0 Hz, $J_{2eq,3}$ = 5.0 Hz), 2.00 (brd, 1H, *J* = 11.0 Hz), 1.90−1.55 (m,6H), 1.45−1.20 (m,5H) and 1.03−0.94 (m, 2H) (−CH_2−, H-2ax and −CH−), 1.09 (d, 3H, −CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 178.3 (CO), 140.5, 140.4, 140.2, 139.7 and 139.3 (ArC), 129.6, 129.4, 129.3, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.2 and 127.2 (ArCH), 102.1, 100.8 and 98.7 (Ph*C*H(O)(O)−, C-1′ and C-1″), 81.3, 80.4, 80.0 (2C), 78.5, 78.4, 76.9, 76.6, 74.6, 72.0, 67.9 and 67.7 (C-3 to C-5, C-2′ to C-5′, C-2″ to C-5″ and −O*C*HCO_2H), 76.3, 75.4, 74.4, 72.4, 70.7, 69.5 and 66.8 [(−), Ph*C*H_2−, C-1, C-6 and C-6′], 41.9, 35.1, 33.8, 32.5, 27.7, 27.6 and 27.4 [(−), −CH_2− and C-2], 35.4 (−CH−), 16.8 (−CH_3); HR-FABMS calcd for $C_{62}H_{73}O_{15}$ *m*/*z* 1057.49500, found 1057.49130.

(3-*O*-[(*S*)-1-(Oxycarbonyl)-2-cyclohexylethyloxy]-β-D-galactopyranosyl)-*O*-(1 → 3)-[α-L-fucopyranosyl-*O*-(1 → 4)]-1,2-dideoxy-D-glucopyranose Sodium Salt (2). To a solution of **21** (25 mg, 23.6 μmol) dissolved in a mixture of dioxane (5.50 mL) and water (2.40 mL) was added 20% palladium hydroxide on carbon (Degussa, 18.0 mg) and acetic acid (24 μL, 18 equiv). The resulting mixture was hydrogenated under 60 psi at rt for 40 h. After filtration on Celite and concentration, the product was passed through an ion-exchange resin column (Dowex in the sodium form); the solution afforded after rinsing the column with water and lyophilizing the eluate pure **2** as a sodium salt (14.4 mg, >98%) as a white powder: $[\alpha]_D$ −49.0 (*c* 1.06, H_2O); ^1H NMR (D_2O CH_3OD as external standard δ = 3.35 ppm, 400 MHz, assigned by COSY45) δ 4.97 (d, 1H, H-1″, $J_{1'',2''}$ = 3.9 Hz), 4.77 (q, 1H, H-5″), 4.52 (d, 1H, H-1′, $J_{1',2'}$ = 7.9 Hz), 4.10−3.92 (m, 3H, H-3, H-1eq and-OC*H*CO_2Me), 3.92 (fd, 1H, H-4′, $J_{4',3'}$ = 3.0 Hz), 3.90−3.85 (m, 3H, H-6, H-6A and H-3″), 3.82 (fd, 1H, H-4″, $J_{4'',3''}$ = 3.0 Hz), 3.78 (dd, 1H, H-2″, $J_{2'',3''}$ = 10.5 Hz), 3.74 (brd, 2H, H-6′ and H-6A′, *J* = 6 Hz), 3.64 (t, 1H, H-2′, $J_{2',3'}$ = 8.0 Hz), 3.62 (t, 1H, H-5′, $J_{5',6'}$ = $J_{5',6A'}$ = 6.0 Hz), 3.59 (t, 1H, H-4, $J_{4,3}$ = $J_{4,5}$ = 9.0 Hz), 3.50 (brt, 1H, H-1ax, $J_{1ax,2ax}$ = $J_{1ax,1eq}$ = 11.5 Hz), 3.42−3.39 (m, 2H, H-5 and H-3′), 2.23 (brdd, 1H, H-2eq, $J_{2eq,2ax}$ = 12.0 Hz, $J_{2eq,3}$ = 4.0 Hz), 1.80 (m, 1H), 1.75−1.50 (m, 8H), 1.35−1.10 (m, 6H) and 1.00−0.85 (m, 2H) (−CH_2−, H-2ax and −CH−), 1.21 (d, 3H, −CH_3, $J_{Me,5''}$ = 6.5 Hz); ^{13}C NMR (D_2O, CH_3OD as external standard δ = 49.6 ppm, 100 MHz) δ 183.1 (CO), 99.4 and 99.0 (C-1′ and C-1″), 83.1, 80.4, 79.6, 76.0, 75.0, 74.6, 72.2, 70.1, 69.6, 68.3, 67.2 and 66.6 (C-3 to C-5, C-2′ to C-5′, C-2″ to C-5″ and −O*C*HCO_2H), 65.5, 61.9 and 60.3 [(−), C-1, C-6 and C-6′], 41.5, 33.9, 32.2, 30.6, 26.5, 26.3, and 26.0 [(−), −CH_2− and C-2], 33.6 (−CH-), 15.9 (−CH_3); IR (KBr, cm^{-1}) 3430, 2925, 1599, 1400, 1079; HR-FABMS calcd for $C_{27}H_{46}O_{15}Na$ *m*/*z* 633.27344, found 633.27160.

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Supporting Information Available: Copies of selected ^1H and ^{13}C spectra and X-ray structure determination data. This material is available free of charge via the Internet at http://pubs.acs.org.

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