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Syntheses of methyl (4,6-dideoxy-α-L-*lyxo*-hexopyranosyl)-(1 → 3)- and (4-deoxy-4-fluoro-α-L-rhamnopyranosyl)-(1 → 3)-2-acetamido-2-deoxy-α-D-glucopyranosides, analogs of the mycobacterial arabinogalactan linkage disaccharide

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Abstract

We have made thioglycoside donors for the 4,6-dideoxy-L-*lyxo*-hexopyranosyl ('4-deoxy-L-rhamnosyl') and 4-deoxy-4-fluoro-L-rhamnosyl monosaccharide residues. The preparation of the deoxyfluororhamnose was not straightforward, and revealed some unexpected behavior of the diethylaminosulfur trifluoride (DAST) reagent. The new glycosyl donors were used to synthesize two analogs of the mycobacterial arabinogalactan linkage disaccharide →4)-α-L-Rha-(1 → 3)-α-D-GlcNAc. These analogs are prototypes for a family of potential inhibitors of the enzymes involved in the early stages of cell-wall construction in mycobacteria.

Keywords: Mycobacteria; Arabinogalactan; Deoxy sugars; Fluoro sugars; Diethylaminosulfur trifluoride (DAST); Thioglycosides

1. Introduction

Mycobacteria cause tuberculosis and leprosy, as well as a host of serious infections in immunosuppressed people. Although many people in the industrialized nations have come to consider tuberculosis as a disease of the past, it again poses a major threat. An estimated 1.7 billion people carry *M. tuberculosis*, leading to 8–10 million new cases of disease and 3 million deaths annually. Antibiotic-resistant and highly pathogenic strains of *M. tuberculosis* have been appearing, prompting renewed interest in anti-mycobacterial drug development.

Mycobacteria are Gram-positive bacteria resistant to many antibiotics, due to their unique, carbohydrate-rich cell wall structure [1]. A key feature of the cell-wall is an underlying cross-linked peptidoglycan layer supporting a superstructure of arabinogalactan (AG) [2,3]. The AG may be visualized as a tree whose trunk is a linear chain of D-galactofuranosyl residues, while its branches are formed from D-arabinofuranosyl units. Each branch ends in a hexa-arabinoside esterified at its termini by long-chain mycolic acids, forming a waxy outer layer.

In 1990, Brennan and co-workers revealed that the root of the AG tree is a disaccharide

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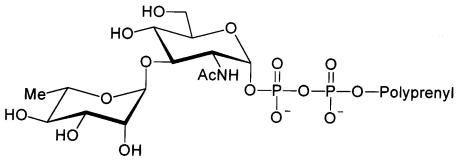
phosphate, →4)-α-L-Rha-(1→3)-D-GlcNAc-(1→P)- [4], anchoring a mycolyl-AG assembly to the 6-position of each of about 10–12% of the muramic acid residues in the peptidoglycan layer [1]. A subsequent study [5] suggested that the biosynthesis of the mycobacterial cell wall begins with the synthesis of the linkage disaccharide on a polyprenyl pyrophosphate carrier to form **1**.



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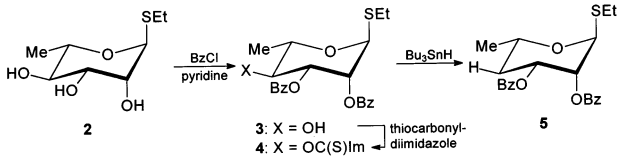
The galactan chain is then built up from its 4′-position. Once it is complete, the mycolyl-AG-linker structure is finally joined to the peptidoglycan. Although several authors have pointed out that the linkage disaccharide is an attractive target for rational anti-mycobacterial drug design [4,6], there has been remarkably little work in this direction reported in the literature to date.

We are developing inhibitors for the (currently unknown) galactofuranosyl transferase(s) that build the AG onto the 4′-position of the L-rhamnose in **1**. Among the sterically conservative modifications of the 4′ hydroxyl that might yield inhibitors, we chose to begin by preparing 4′-deoxy- and 4′-deoxy-4′-fluoro- versions of the linkage disaccharide. This required the synthesis of suitable glycosyl donors for the modified rhamnose residues, which have not been reported in the literature. In this paper, we describe the synthesis of these donors and the preparation and characterization of two prototypical modified linkage disaccharides as their methyl glycosides.

2. Results and discussion

4,6-Dideoxy D- and L-*lyxo*-hexopyranosyl compounds have been prepared several times [7–10], but no glycosyl donors for either enantiomer of this residue have been reported. We extended earlier reports to prepare a thioglycoside derivative (Scheme 1). Thus, ethyl 1-thio-α-L-rhamnoside (**2**) [11]

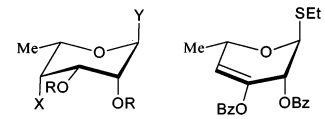


2 **3**: X = OH; **4**: X = OC(S)Im (thiocarbonyldiimidazole) **5**

Scheme 1.

was selectively acylated using the method described by Ando et al. for the corresponding methyl thioglycoside [12], giving the 2,3-di-*O*-benzoyl derivative **3** (72%). Deoxygenation of **3** by treatment of thiocarbonylimidazolide **4** with tributyltin hydride in boiling toluene cleanly afforded the thioglycoside donor **5** in 81% overall yield.

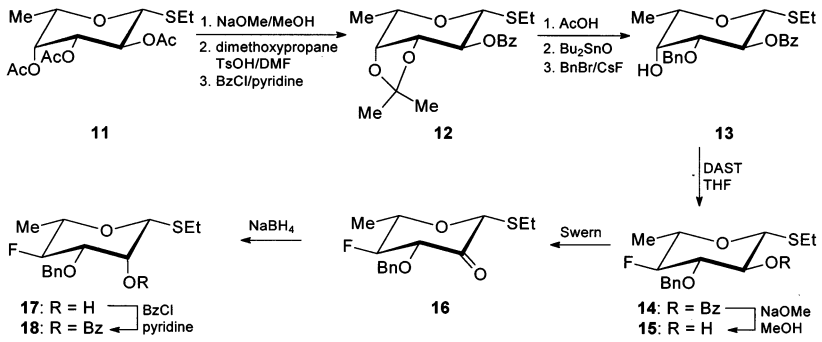
The synthesis of a 4-deoxy-4-fluoro-L-rhamnosyl donor proved to be much more challenging.



	R	X	Y
6	Me_2C	OH	OMe
7	Me_2C	OTf	OMe
8	Bz	OH	SEt
9	Bz	OTf	SEt

10

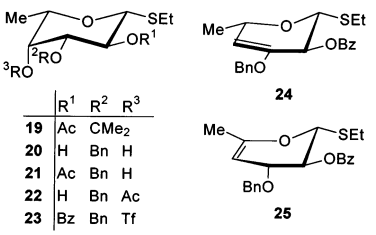
Model studies were carried out on 2,3-*O*-isopropylidene (**6**) [13] and 2,3-di-*O*-benzoyl-6-deoxy-α-L-talopyranosides (**8**, obtained in low yield by Swern oxidation/borohydride reduction of **3**). NMR analysis of the products showed that reaction of the free 4-OH groups of **6** or **8** with diethylaminosulfur trifluoride (DAST) in dichloromethane led to complex mixtures. Morpholinosulfur trifluoride (morpho-DAST) reacted sluggishly with **8**, producing a low yield of epimeric morpholine adducts at the 4-position. Attempts to displace the 4-*O*-triflate from **7** [14] using KF/18-crown-6/DMF likewise gave a mixture whose NMR spectrum showed no evidence of fluorine incorporation, while treatment of **9** with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) [15] led only to a product whose NMR spectra suggested structure **10**. These negative results are perhaps not surprising, given the known difficulty of nucleophilic displacements at C-4 in monosaccharides having an axial substituent at C-2 [16], although more potent nucleophiles than F^- have been successful in other cases [14,17].



Scheme 2.

Since the axial C-2 substituent of the L-talosides was evidently a problem, we turned to a route from L-fucose, whose C-2 hydroxyl is equatorial. There are precedents for the DAST fluorination of methyl 2,3-di-*O*-benzoyl-1-thio-β-L-fucopyranoside [12] and 1,2,3-tri-*O*-benzoyl-α-L-fucopyranose [18]. This approach required inverting the C-2 stereochemistry after introducing the C-4 fluorine substituent, and to do this we needed a thiofucoside in which the 2- and 3-positions were orthogonally protected. A convenient approach was suggested by the work of van Boom and co-workers [19]. Thus, ethyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside (**11**) [20] was deprotected under Zemplén conditions, and the resulting triol was immediately converted to its 3,4-*O*-isopropylidene derivative. After quenching the reaction with Et_3N, the solvents were evaporated, and the crude residue was dissolved in pyridine and treated with benzoyl chloride. The reaction was worked up at this stage to give 86% of crystalline ethyl 2-*O*-benzoyl-3,4-*O*-isopropylidene-1-thio-β-L-fucopyranoside (**12**), after chromatography. We also made the 2-*O*-acetyl derivative **19** (71%) by a variation of this route, using acetic anhydride in place of benzoyl chloride at the last step (Scheme 2).

The *O*-isopropylidene derivative **12** was deprotected in 80% acetic acid at 50 °C. After evaporating the solvents in vacuo, the residual 2-*O*-benzoyl-3,4-diol was dried and treated with dibutyltin oxide in boiling toluene, with azeotropic removal of water. Evaporation of the solvents afforded the crude 3,4-*O*-stannylene acetal, which was then selectively benzylated at O-3. The benzylation occurred quite rapidly, but it was generally convenient to leave the reaction overnight. This three-step, one-pot sequence provided a 95% yield of **13** after chromatography. In contrast, when acetate **19** was subjected to this sequence, we observed that the conditions of stannylene acetal formation promoted migration and cleavage of the acetate group, leading to **20** (45%) and a chromatographically inseparable 1.7:1.0 mixture of **21** and **22** (11%), which were identified by NMR spectroscopy.



	R^1	R^2	R^3
19	Ac	CMe_2	
20	H	Bn	H
21	Ac	Bn	H
22	H	Bn	Ac
23	Bz	Bn	Tf

Replacing the axial 4-OH group of **13** with an equatorial fluorine in good yield was not straightforward. We examined the reactions of the 4-*O*-triflate **23** with TASF in dichloromethane or with anhydrous tetrabutylammonium fluoride (TBAF) in *N*,*N*-dimethylformamide at 40 °C. In both cases a 37% yield of the desired fluoride **14** was isolated, but the use of TASF also led to about 10% of **24**, while TBAF formed 7% of **24** and 6% of **25** (identified by their ^1H and ^{13}C NMR spectra). The significant proportions of elimination products obtained were particularly troublesome, because in all chromatography systems we tested **25** ran very slightly faster than **14**, while **24** ran slightly slower. As a consequence, we found it impossible to completely separate **14** from **24** by column chromatography. The reactions of **23** with TBAF in *N*,*N*-dimethylformamide or acetonitrile at room temperature did not proceed to comple-

tion even after 2 days, and high proportions of **24** and **25** were also formed.

Ando et al. had obtained methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-4-fluoro-1-thio-β-L-glucopyranoside in 45% yield from the reaction of the corresponding fucoside with DAST in dichloromethane [12]. When similar conditions were applied to **13**, we obtained 32–35% of **14**, accompanied by smaller proportions of **24** and **25** than we had observed in the reactions of **23**. Considerable effort was expended to try to enhance this yield, by varying the reagent (DAST, morpho-DAST) and the number of equivalents used, the concentration (0.05 M, 0.15 M, neat) and the solvent (dichloromethane, tetrahydrofuran, toluene), the temperature (− 30 °C, 0 °C, room temperature, 40 °C, 80 °C), the presence of additives (DMAP, TASF), the type of reaction vessel (Pyrex, Teflon-FEP), and the reaction time (up to 5 days).

In the course of these experiments we made several salient observations. The alcohol **13** disappeared from the TLC almost immediately after the addition of DAST, with the formation of a UV-active baseline spot. Product **14** appeared very early, but the amount did not increase if the reaction time was extended beyond a few hours. Reactions in dichloromethane or toluene formed a precipitate within a few minutes of adding DAST to **13**. The yield of **14** was significantly lower at 0 °C, while no reaction was observed below this temperature. Elimination and decomposition were enhanced at temperatures above ambient. Most significantly, if the reactions were quenched with water, methanol or aqueous sodium bicarbonate, the mass recoveries were very low, while quenching a reaction conducted in tetrahydrofuran with 1 N aqueous sodium hydroxide led to the reappearance of the alcohol **13**. This was our most efficient reaction, giving **14** in 44% yield after chromatography, along with 42% of recovered **13**.

This suggested to us that the intermediate diethylaminosulfur difluoride ester that formed during the reaction of **13** with DAST was highly polar and unusually unreactive either to displacement or hydrolysis. The baseline TLC spot and the precipitates we observed were presumably this 'activated' intermediate. Mange and Middleton have suggested [21] that displacement of the activated intermediate by fluoride occurs concurrently with or very soon after its formation, while the fluoride ion and the intermediate are still together within the solvent cage. In our case, it would appear that because the displacement by fluoride is sluggish, the nucleophile is able to diffuse away. In solvents of low polarity, extending the reaction time had little effect because the intermediate precipitated. In more polar solvents where the intermediate remained in solution, the fluoride nucleophile may have been more solvated, thus attenuating its nucleophilicity.

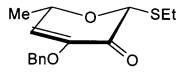
This is not the first time that an unreactive intermediate has been observed in the DAST reaction of a carbohydrate, but most commonly this situation arises when nucleophilic attack is sterically hindered [22]. It is unlikely that steric effects were important in our case, as the nucleophile was approaching from the equatorial direction. A similar situation was reported by Yang et al. [23], who treated a *myo*-inositol derivative with DAST in dichloromethane, and recovered intact starting material despite the formation of the expected sulfur ester intermediate.

The high polarity and poor solubility of our putative intermediate was unexpected, and it seemed possible that the thioglycoside group might be involved in some way. Ando et al. reported essentially the same low yield from DAST treatment of their thiofucoside [12], whereas Lindhorst and Thiem obtained a 76% yield of fluorine-containing products from a very similar reaction of an O-benzoylated fucose [18]. In order to see whether there was some interaction between the reagent and the thioglycoside in **13**, we attempted to observe the intermediate in tetrahydrofuran-d_8 solution by ^{19}F and ^{1}H NMR spectrometry. Spectra obtained at or below − 30 °C showed only signals due to DAST and **13**, while at 0 °C or above, product **14** was seen. No NMR signals attributable to an intermediate could be detected. The exact reasons for the sluggish reaction of DAST with our fucoside remain obscure.

Since the polar intermediate did not degrade during the reaction and could be hydrolyzed back to **13** by 1 N aqueous sodium hydroxide, we recycled the reaction to obtain a high overall conversion of **13** to **14**. Thus, reaction with 1.5 equivalents of DAST at room temperature in tetrahydrofuran gave about 40% conversion after 2 h, as judged by ^{1}H NMR analysis of the crude product. We carried out this treatment sequentially three more times, maintaining the concentrations of unreacted substrate and of reagent essentially constant at each cycle. This process, while admittedly unwieldy, gave an 80% yield of **14** (based on the amount of **13** submitted to the first reaction cycle) as an oil contaminated with only a small amount of the more polar elimination product **24**. This oily product was pure enough to be used directly in the next step, but it could be crystallized to obtain pure material if so desired.

The removal of the 2-*O*-benzoyl group from **14** under typical Zemplén conditions was remarkably sluggish, requiring 90 h and 3 equivalents of sodium methoxide to proceed to completion at room temperature. A molecular mechanics-derived structure suggested that the flanking equatorial 3-*O*-benzyl and 1-*S*-ethyl groups of **14** were hindering access to the 2-position ester group. However, in boiling methanolic sodium methoxide, the reaction proceeded smoothly in only 1.5 h to form **15** (97%).

Our approach to a 4-fluoro-L-rhamnoside from an L-fucose derivative required us to invert the stereochemistry of the 2-position of **15**. In principle, this could be done by an S_N2 process, but Baer et al. observed that analogous 2-triflates undergo ring contraction when subjected to even mild nucleophilic displacement conditions [24]. We therefore used an oxidation–reduction sequence. The steric constraints around the 2-OH group caused some difficulties here also. Neither pyridinium dichromate–acetic anhydride–3 Å molecular sieves [25,26] nor tetrapropylammonium perruthenate–*N*-methylmorpholine *N*-oxide [27] oxidized **15**, even under forcing conditions. Treatment of **15** with acetic anhydride and dimethyl sulfoxide afforded predominantly the α,β-unsaturated ketone **26**, as did Pfitzner–Moffatt conditions.



26

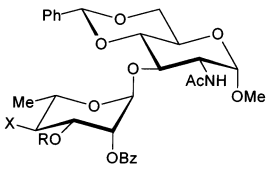
The 2-ulose product **16** is evidently very prone to elimination of the 4-fluoride, despite the fact that this process is formally an axial/equatorial 1,2-*syn* elimination. Perlin and coworkers noted this type of elimination many years ago, arising from dimethyl sulfoxide–SO_3·pyridine oxidations of D-glucosides [28].

We found that Swern oxidation of **15** was a good method to obtain the 2-ulose **16**, although the conditions for the base-promoted step of the reaction had to be carefully controlled. The usual procedure of employing an excess of triethylamine led to a complex product mixture that included **26** as well as ring-opened products. When a stoichiometric amount of triethylamine was added gradually to the reaction mixture at −78 °C, followed by warming to room temperature over 45 min, **16** was obtained accompanied by little or no elimination or degradation. NMR analysis of the crude products obtained from several repetitions of this reaction typically revealed about 7% of unreacted **15**. Chromatographic purification of **16** was impossible because it streaked on silica gel, presumably due to equilibration between the ketone and its hydrate.

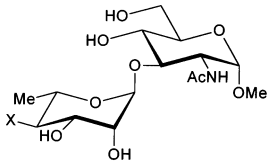
The ketone **16** was immediately reduced with sodium borohydride in 1:1 2-propanol–dichloromethane at 0 °C, affording a 55:18 mixture of **17** and **15**, from which pure **17** was obtained by careful chromatography (54%; 63% correcting for recovered **15**). Allowing for the 7% of **15** present in the ketone, the selectivity of this reduction was about 5:1. This was disappointing, because Lichtenthaler and Schneider-Adams reported 20–50:1 D-*manno*:D-*gluco* selectivities in several analogous sodium borohydride reductions of 2-uloses [29]. Nevertheless, the reaction provided a reasonable yield of the desired L-*rhamno* configuration, and the isomer could be resubmitted to the oxidation–reduction procedure. Benzoylation of the 2-OH group of **17** gave the desired 4-deoxy-4-fluoro-L-rhamnosyl donor **18** (99%).

Glycosidations of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside [30] with donors **5** and **18** were performed in

dichloromethane in the presence of *N*-iodosuccinimide and triflic acid to afford the α-linked disaccharides **27** (82%) and **28** (55%) as single anomers. The disarming effect of the 4-fluoride in **18** was clearly evident in both the yields and the rates of these reactions; the reaction of **5** was complete in 15 min, whereas that of **18** required 50 min to consume the donor. The anomeric configurations of the newly formed glycosidic bonds were assigned as α on the basis of the $^1J_{C,H}$ of approximately 171 Hz [31] observed in both **27** and **28**.



27: X = H, R = Bz
28: X = F, R = Bn



29: X = H
30: X = F

Deprotection of the disaccharides required two steps in each case, and we found that the order in which the reactions were performed was crucial. Thus, treatment of **27** with 80% acetic acid at 70 °C for 1.5 h cleanly hydrolyzed the benzylidene acetal. Subsequent methoxide-promoted removal of the benzoate groups afforded the unprotected disaccharide **29** in 95% yield. On the other hand, if the benzoates were removed first, subsequent acid-catalyzed hydrolysis of the acetal was extremely sluggish, and after 8 h of heating several byproducts were evident by thin-layer chromatography (TLC) analysis. To deprotect **28**, it was necessary first to remove the 2′-benzoate, and subsequently to cleave both the acetal and the benzyl ether by atmospheric pressure hydrogenolysis in methanol over 10% palladium-on-charcoal. The hydrogenolysis of the benzyl ether occurred within 3 h, but removal of the benzylidene acetal was rather slow, requiring a further 20 h. Nevertheless, an 81% yield of **30** was easily obtained after chromatography. In contrast, we could not induce hydrogenolysis of **28** to occur, even under a hydrogen pressure of 3 atm.

The disaccharides **29** and **30** are prototypes of potential inhibitors of mycobacterial AG biosynthesis. We are now extending the chemistry described in this paper to disaccharides having aglycons that better mimic the phospholipid moiety of **1**. The syntheses of these materials and their biological activities will be reported in future publications. We also anticipate that the new glycosyl donors **5** and **18** will be useful to other workers exploring inhibitors of the synthesis of various bacterial polysaccharides containing linkages to the 4-position of L-rhamnose.

3. Experimental

General methods.—Reagents were obtained from Aldrich Chemical Co. and were used as received except as noted. Benzyl bromide was passed through a plug of alumina immediately before use. Dimethyl sulfoxide and *N*,*N*-dimethylformamide (DMF) were dried over 3 Å molecular sieves [32]. Triethylamine and pyridine were dried by distillation from CaH_2. *N*-Iodosuccinimide was recrystallized from dioxane–CCl_4. Tetrahydrofuran (THF), CH_2Cl_2 and MeOH were dried according to literature methods [33] before use; other solvents were used as received. All reactions requiring dry conditions were performed under a positive pressure of dry nitrogen or argon, in glassware dried at 120 °C for at least 18 h. Organic layers from extractions were dried using $MgSO_4$ before concentration. 'Chromatography' refers to the use of the flash procedure on Silica Gel 60 (230–400 mesh E. Merck).

NMR spectra were acquired on Bruker AM 300 or AMX 500 instruments at 300 K (except as noted) in the deuterated solvents indicated, at 300.133 or 500.138 MHz for ^1H, at 75.469 or 125.773 MHz for ^{13}C, and at 282.467 MHz for ^{19}F. For ^1H or ^{13}C spectra, the residual signals of the solvents were used as internal chemical shift standards, except for spectra acquired in D_2O. In these cases, external referencing to TSP was employed. The ^{19}F spectra were externally referenced to C_6F_6 and are reported in ppm relative to $CFCl_3$ at 0.00 ppm. All signal assignments given were confirmed by analysis of *J*-couplings, COSY, DEPT and/or ^{13}C–^1H HSQC experiments. In ambiguous cases, coupling constants and chemical shifts were verified by iterative simulations using the computer program XSIM, written by Dr K. Marat.

Positive-ion mass spectra were obtained using 70-eV electron-impact ionization (EIMS, HRMS) on a VG ZAB 7070E instrument, or by electrospray ionization (ESIMS) on a Micromass Quattro LC instrument at a cone voltage of 20 V. Optical rotations were measured at ambient temperature using a Rudolph Research Autopol III polarimeter in the indicated solvents. Elemental analyses were performed by Chemisar Laboratories, Guelph, Ont.

Ethyl 2,3-di-O-*benzoyl-1-thio-α*-L-*rhamnopyranoside* (**3**).—Following a procedure of Ando et al. [12], rhamnoside **2** [11] (1.00 g, 4.8 mmol) was dissolved in dry pyridine (3.5 mL) and CH_2Cl_2 (7 mL). The solution was cooled to −40 °C, and a solution of benzoyl chloride (1.22 mL, 10.5 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 20 min. The mixture was stirred for 30 additional min, and then MeOH (5 mL) was added. The cooling bath was then removed. When the mixture reached room temperature, the solvents were evaporated, and the residue was redissolved in CH_2Cl_2 (75 mL). The solution was washed with 1.2 N HCl (3 × 15 mL), water (3 × 15 mL) and brine (15 mL). The dried organic layer was evaporated, and the residual oil was chromatographed (4:1 hexanes–EtOAc) to afford 538 mg of the tribenzoate and 1.45 g (72.5%) of **3**, as a viscous oil: ^{1}H NMR ($CDCl_3$): δ 1.34 (tr, 3 H, J 7.4 Hz), 1.46 (d, 3 H, $J_{5,6}$ 6.1 Hz, H-6), 2.61–2.80 (m, 2 H), 3.97 (dd, 1 H, $J_{4,5}$ 9.4, $J_{3,4}$ 9.8 Hz, H-4), 4.26 (dq, 1 H, H-5), 5.41 (d, 1 H, $J_{1,2}$ 1.4 Hz, H-1), 5.48 (dd, 1 H, $J_{2,3}$ 3.4 Hz, H-3), 5.69 (dd, 1 H, H-2), 7.33 (m, 2 H), 7.45–7.53 (m, 3 H), 7.61 (m, 1 H), 7.90 (m, 2 H), 8.08 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 14.94, 17.64, 25.55, 69.34, 72.31, 72.74, 73.53, 82.08 ($^1J_{C,H}$ 166.7 Hz), 128.41, 128.57, 129.28, 129.67, 129.86, 133.42, 133.48, 165.46, 166.74; Anal. Calcd for $C_{22}H_{24}O_6S$: C, 63.44; H, 5.81. Found: C, 63.41; H, 5.87.

Ethyl 2,3-di-O-*benzoyl-4,6-dideoxy-1-thio-α*-L-lyxo-*hexopyranoside* (**5**).—Rhamnoside **3** (967 mg, 2.32 mmol) and thiocarbonyldiimidazole (1.30 g, 7.3 mmol) were boiled in dry toluene (50 mL) for 18 h. After cooling, the supernatant was decanted from an insoluble oily material and evaporated. The residue was redissolved in a small amount of toluene and applied to a plug of silica gel (approximately 50 g) in a fritted funnel. The plug was eluted with 4:1 hexanes–EtOAc to yield the thiocarbonylimidazolide **4**, 1.16 g (95%).

Tributyltin hydride (1 mL, 3.71 mmol) was dissolved in dry toluene (30 mL). The mixture was boiled, and a solution of **4** in toluene (11 mL) was added dropwise over 30 min. Heating was continued for 1 h, after which time the reaction was cooled and the solvent was evaporated. The residue was dissolved in MeCN (100 mL), and the solution was washed with hexanes (3 × 25 mL). Evaporation of the MeCN layer afforded a crude oil that was purified by chromatography (9:1 hexanes–EtOAc) to yield 758 mg (86%) of oily **5**: $[\alpha]_D$ −35.2° (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.34 (tr, 3 H, J 7.4 Hz), 1.34 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6), 1.97–2.15 (m, 2 H, H-4$_{ax}$, H-4$_{eq}$), 2.60–2.80 (m, 2 H), 4.45 (m, 1 H, H-5), 5.48 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 5.51–5.58 (m, 2 H, H-2, H-3), 7.33 (m, 2 H), 7.45–7.52 (m, 3 H), 7.61 (m, 1 H), 7.89 (m, 2 H), 8.12 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 15.07, 21.17, 25.59, 34.30, 64.90, 68.40, 70.42, 82.87, 128.32, 128.51, 129.66, 129.84, 130.02, 133.06, 133.29, 165.43, 165.69; Anal. Calcd for $C_{22}H_{24}O_5S$: C, 65.98; H, 6.04; S, 8.01. Found: C, 66.06; H, 6.25; S, 7.89.

Ethyl 2-O-*benzoyl-3,4*-O-*isopropylidene-1-thio-β*-L-*fucopyranoside* (**12**).—A solution of **11** [20] (3.00 g, 8.97 mmol) in dry MeOH (30 mL) was treated with sodium (20 mg). After stirring for 45 min, Amberlite IR-120 (H^+) was added. The neutralized mixture was then filtered and evaporated, removing the last traces of methanol using a vacuum pump.

The resulting syrup was dissolved in dry DMF (15 mL). To this solution was added 2,2-dimethoxypropane (15 mL) and p-toluenesulfonic acid hydrate (50.5 mg, 0.265 mmol), and the mixture was allowed to stir for 2.5 h. Triethylamine (2.5 mL) was added, after which the solvents were evaporated on the vacuum pump.

The residue was dissolved in dry pyridine (7.5 mL), and the solution was cooled to 0 °C. Benzoyl chloride (1.6 mL, 13.8 mmol) was added dropwise, and the reaction was stirred overnight, gradually warming to room tem-

perature. An excess of MeOH was added, after which the solvents were evaporated. The residue was dissolved in ether (100 mL), and the solution was washed with 25-mL portions of cold water, cold 1.2 N HCl, and satd aq $NaHCO_3$. The ether layer was dried and evaporated. The residue was purified by chromatography (6:1 hexanes–EtOAc) to yield **12**, 2.71 g, (85.7%) as white crystals: mp 94–95 °C; $[\alpha]_D$ −48.1° (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.23 (tr, 3 H, *J* 7.4 Hz), 1.36 (s, 3 H), 1.45 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6), 1.62 (s, 3 H), 2.59–2.84 (m, 2 H), 3.94 (dq, 1 H, $J_{4,5}$ 2.0 Hz, H-5), 4.12 (dd, 1 H, $J_{3,4}$ 5.3 Hz, H-4), 4.30 (dd, 1 H, $J_{2,3}$ 7.3 Hz, H-3), 4.48 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 5.26 (dd, 1 H, H-2), 7.42 (m, 2 H), 7.54 (m, 1 H), 8.05 (m 2 H); ^{13}C NMR ($CDCl_3$): δ 14.74, 16.85, 23.83, 26.37, 27.86, 72.09, 72.74, 76.49, 77.29, 82.36, 110.09, 128.21, 129.79, 129.87, 132.97, 165.39; Anal. Calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86; S, 9.10. Found: C, 61.61; H, 7.17; S, 9.08.

*Ethyl 2-*O*-benzoyl-3-*O*-benzyl-1-thio-β-*L*-fucopyranoside* (**13**).—Compound **12** (1.50 g, 4.26 mmol) was stirred for 3.5 h in 80% AcOH (25 mL) at 50 °C. The solvent was evaporated, after which dry toluene (3 × 20 mL) was added and evaporated from the residue. Dibutyltin oxide (1.17 g, 4.70 mmol) and dry toluene (50 mL) were then added, and the mixture was boiled for 2 h, with azeotropic removal of water in a Dean–Stark trap. The cooled solution was then evaporated.

The residue was dissolved in dry DMF (15 mL). Anhydrous CsF (1.28 g, 8.49 mmol) was added, followed by benzyl bromide (0.63 mL, 5.3 mmol), and the mixture was stirred overnight at 40 °C. The solvents were evaporated, and the residue was dissolved in ether (100 mL). The solution was washed with water (3 × 20 mL), dried, and evaporated. Chromatography (3:1 hexanes–EtOAc) afforded **13** (1.63 g, 95%) as a thick oil that crystallized on scratching and standing: mp 97–98 °C; $[\alpha]_D$ −13.6° (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.20 (tr, 3 H, *J* 7.4 Hz), 1.41 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6), 2.52 (br s, 1 H, O*H*), 2.64–2.83 (m, 2 H), 3.62–3.69 (m, 2 H, H-3, H-5), 3.91 (br s, 1 H, H-4), 4.46 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1), 4.55 (d, 1 H, *J* 12.3 Hz), 4.67 (d, 1 H, *J* 12.3 Hz), 5.50 (dd, 1 H, $J_{2,3}$ 9.3 Hz, H-2), 7.16–7.18 (m, 5 H), 7.46 (m, 2 H), 7.59 (m 1 H), 8.02 (m 2 H); ^{13}C NMR ($CDCl_3$): δ 14.82, 16.82, 23.51, 69.13, 69.51, 71.40, 74.62, 79.66, 83.11, 127.85, 127.99, 128.38, 128.46, 129.88, 130.05, 133.10, 137.21, 165.49; Anal. Calcd for $C_{22}H_{26}O_5S$: C, 65.65; H, 6.51; S, 7.97. Found: C, 65.32; H, 6.75; S, 7.71.

*Ethyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-dideoxy-4-fluoro-1-thio-β-*L*-glucopyranoside* (**14**).—The reaction of **13** (2.00 g, 4.97 mmol) with DAST in dry THF was performed in four cycles. In each cycle, the substrate was dissolved in THF and stirred, while DAST was added dropwise at rt. Stirring was continued for 2 h. The reaction mixture was then transferred dropwise into a mixture of 1 N aq NaOH (50 mL) and ether (100 mL), and vigorously stirred for 10–15 min, after which the phases were separated. The ether layer was washed with water (2 × 25 mL), 1.2 N HCl (25 mL), and satd aq $NaHCO_3$ (25 mL). The organic extract was then dried and evaporated, and the residual oil was dried in vacuo. The extent of conversion was estimated by ^1H NMR spectroscopy. The amounts of reagent and solvent used were calculated to provide roughly constant reactant concentrations, assuming 40% conversion at each cycle. These are summarized in Table 1.

After the fourth cycle, the crude oil was chromatographed (gradient elution from 5% → 30% EtOAc–hexanes) to provide **14** (1.62 g, 80%) as a pale yellow oil contaminated by a small amount of elimination product **24**. After standing for several days, the oil solidified. A pure sample of **14** recrystallized as long needles from petroleum ether (bp 30–60 °C): mp 59–60 °C; $[\alpha]_D$ −14.1° (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.23 (tr, 3 H, *J* 7.5 Hz), 1.42 (dd, 3 H, $J_{6,F}$ 1.3, $J_{5,6}$ 6.2 Hz, H-6), 2.62–2.79 (m, 2 H), 3.59 (ddd, 1 H, $J_{5,F}$ 3.0, $J_{4,5}$ 9.1 Hz, H-5), 3.83 (ddd, 1 H, $J_{3,F}$

Table 1
Reaction of ethyl 2-*O*-benzoyl-3-*O*-benzyl-1-thio-β-L-fucopyranoside (**13**) with DAST

Cycle	THF (mL)	DAST [μL (mmol)]
1	20	990 (7.5)
2	12	600 (4.5)
3	7	360 (2.7)
4	5	220 (1.7)

14.4, $J_{3,4}$ 8.9, $J_{2,3}$ 9.2 Hz, H-3), 4.29 (ddd, 1 H, $J_{4,F}$ 50.1 Hz, H-4), 4.53 (d, 1 H, $J_{1,2}$ 9.8 Hz, H-1), 4.67 (d, 1 H, J 11.5 Hz), 4.78 (d 1 H, J 11.5 Hz), 5.26 (dd, 1 H, H-2), 7.12–7.19 (m, 5 H), 7.46 (m, 2 H), 7.60 (m, 1 H), 8.01 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 14.76, 17.53, 23.91, 71.58 (d, $J_{C,F}$ 9.4 Hz), 73.90 (d, $J_{C,F}$ 20.0 Hz), 74.07, 80.51 (d, $J_{C,F}$ 17.7 Hz), 83.24, 95.15 (d, $J_{C,F}$ 184.3 Hz), 127.62, 127.95, 128.17, 128.26, 128.33, 128.41, 129.70, 129.84, 133.15, 137.48, 165.04; ^{19}F NMR ($CDCl_3$): δ −197.10 (dddq, $J_{6,F}$ 1.3, $J_{5,F}$ 3.0, $J_{3,F}$ 14.4, $J_{4,F}$ 50.1 Hz); EIMS: m/z 343 $[M-SEt]^+$, 235, 176, 149, 105, 91, 77; HRMS on m/z 343 fragment: Calcd for $[C_{20}H_{20}FO_4]^+$: 343.1345. Found: 343.1347; Anal. Calcd for $C_{22}H_{25}FO_4S$: C, 65.33; H, 6.23; F, 4.70. Found: C, 64.97; H, 6.53; F, 4.89.

*Ethyl 3-*O*-benzyl-4,6-dideoxy-4-fluoro-1-thio-β-*L*-glucopyranoside* (**15**).—A solution of **14** (550 mg, 1.36 mmol) in dry MeOH (25 mL) was treated with sodium (100 mg, 4.35 mmol). The reaction was gently boiled under reflux for 1.5 h. Amberlite IR-120 (H^+) was added to the cooled solution to neutralize the base, after which the mixture was filtered and evaporated to dryness. The resulting yellow oil was chromatographed (6:1 hexanes–EtOAc) to afford 397 mg (97%) of crystalline **15**: mp: 35.5–37 °C; $[\alpha]_D$ +43.9° (c 0.82 $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.31 (tr, 3 H, J 7.4 Hz), 1.37 (dd, 3 H, $J_{6,F}$ 1.4, $J_{5,6}$ 6.1 Hz, H-6), 2.44 (m, 1 H, O*H*), 2.65–2.81 (m, 2 H), 3.47–3.63 (m, 3 H, H-2, H-3, H-5), 4.16 (ddd, 1 H, J 8.5, J 9.4, $J_{4,F}$ 50.1 Hz, H-4), 4.34 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), 4.81 (d, 1 H, J 11.5 Hz), 4.90 (d, 1 H, J 11.5 Hz), 7.30–7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$): δ 15.14, 17.49, 24.29, 72.52 (d, $J_{C,F}$ 9.1 Hz), 73.76 (d, $J_{C,F}$ 23.7 Hz), 74.42 (d, $J_{C,F}$ 1.9 Hz), 82.81 (d, $J_{C,F}$ 17.2 Hz), 85.45, 94.55 (d, $J_{C,F}$ 183.9 Hz), 127.74, 127.89, 128.34, 138.02; ^{19}F NMR ($CDCl_3$): δ −193.54 (app dd, J_{app} 13.3, J_{app} 50.2 Hz); Anal. Calcd for $C_{15}H_{21}FO_3S$: C, 59.98; H, 7.05. Found: C, 59.66; H, 7.17.

*Ethyl 3-*O*-benzyl-4-deoxy-4-fluoro-1-thio-β-L-rhamnopyranoside* (**17**).—Oxalyl chloride (225 μL, 2.58 mmol) was added dropwise to a cold (−78 °C) solution of Me_2SO (185 μL, 2.60 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 15 min, and then a solution of **15** (600 mg, 2.00 mmol) in CH_2Cl_2 (2.5 mL + a 2.5 mL rinse) was added dropwise over 10 min. After stirring the reaction at −78 °C for a further 30 min, Et_3N (615 μL, 4.40 mmol) was added over 3 min. The cloudy mixture was kept at −78 °C for 15 min, and then the cold bath was removed. The reaction mixture reached rt over 45 min, after which time it was diluted with ether (50 mL) and washed with water (2 × 10 mL) and brine (10 mL). The dried solution was evaporated to afford a yellow oily residue (608 mg). The product was identified by NMR spectroscopy as a mixture of unreacted **15** (approximately 7%) and ethyl 3-*O*-benzyl-4-deoxy-4-fluoro-1-thio-β-L-*arabino*-hex-2-ulopyranoside (**16**): ^{1}H NMR ($CDCl_3$): δ 1.30 (tr, 3 H, J 7.5 Hz), 1.46 (dd, 3 H, $J_{6,F}$ 1.4, $J_{5,6}$ 6.2 Hz, H-6), 2.71 (app q, 2 H, J_{app} 7.5 Hz), 3.83 (ddq, 1 H, $J_{5,F}$ 2.8, $J_{4,5}$ 9.2 Hz, H-5), 4.17 (dd, 1 H, $J_{3,4}$ 8.9, $J_{3,F}$ 17.0 Hz, H-3), 4.36 (ddd, 1 H, $J_{4,F}$ 50.5 Hz, H-4), 4.71 (d, 1 H, J 11.8 Hz), 4.96 (d, 1 H, J 11.8 Hz), 5.04 (d, 1 H, $J_{1,F}$ 0.4 Hz, H-1), 7.30–7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$); δ 14.75, 17.57, 23.80, 73.35, 74.21 (d, $J_{C,F}$ 23.9 Hz), 83.44 (d, $J_{C,F}$ 18.5 Hz), 86.19, 95.04 (d, $J_{C,F}$ 192.4 Hz), 127.91, 128.00, 128.40, 136.85, 196.25 (d, $J_{C,F}$ 8.0 Hz).

The crude ketone **16** was dissolved in 1:1 CH_2Cl_2–2-PrOH (5 mL), and the solution was cooled in an ice bath. Finely powdered $NaBH_4$ (115 mg, 3.05 mmol) was added gradually, and the mixture was stirred while warming slowly to rt. After 4.5 h, TLC analysis indicated complete conversion to a mixture of two products. The reaction mixture was cooled on ice and quenched by dropwise addition of 15% AcOH until all effervescence ceased. Ether (50 mL) was then added, and the solution was washed with water (5 mL) and satd aq $NaHCO_3$ (5 mL). The dried solution was evaporated to provide a clear oil. High-performance liquid chromatography (HPLC) analysis (Waters μ-Porasil 3.9 × 300 mm column, linear gradient elution from 0.1 to 0.5% 2-PrOH–hexanes at 1.00 mL min^{-1}, UV detection at 254 nm) showed a 55:18 ratio of major products, along with several byproducts. Careful flash chromatography of the

mixture (gradient elution, 10→20% EtOAc–hexanes) afforded **15** (79 mg, 13%) and **17** (326 mg, 54%), which crystallized on standing: mp: 78–79.2 °C; $[\alpha]_D$ +57.3° (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.30 (tr, 3 H, *J* 7.5 Hz), 1.39 (dd, 3 H, $J_{6,F}$ 1.0, $J_{5,6}$ 6.1 Hz, H-6), 2.57 (br s, O*H*), 2.73 (app q, 2 H, J_{app} 7.4 Hz), 3.44 (ddq, 1 H, $J_{5,F}$ 2.5, $J_{4,5}$ 9.2 Hz, H-5), 3.57 (ddd, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 9.0, $J_{3,F}$ 13.9 Hz, H-3), 4.11 (m, 1 H, H-2), 4.46 (ddd, 1 H, $J_{4,F}$ 50.7 Hz, H-4), 4.55 (br s, 1 H, H-1), 4.70 (d, 1 H, *J* 11.9 Hz), 4.80 (d, 1 H, *J* 11.9 Hz), 7.31–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$): δ 14.96, 17.45, 25.47, 71.09 (d, $J_{C,F}$ 9.4 Hz), 72.18, 74.03 (d, $J_{C,F}$ 24.5 Hz), 79.06 (d, $J_{C,F}$ 15.1 Hz), 83.25, 93.02 (d, $J_{C,F}$ 180.7 Hz), 127.80, 128.02, 128.50, 137.35; Anal. Calcd for $C_{15}H_{21}FO_3S$: C, 59.98; H, 7.05. Found: C, 59.70; H, 7.20.

*Ethyl 2-*O*-benzoyl-3-*O*-benzyl-4-deoxy-4-fluoro-1-thio-β-*L*-rhamnopyranoside* (**18**).—A mixture of **17** (200 mg, 0.67 mmol), dry pyridine (2.5 mL) and DMAP (8 mg, 0.07 mmol) was treated with benzoyl chloride (230 μL, 1.98 mmol). The reaction was stirred for 2.5 h at rt. It was then cooled on a water bath, while cold water (2.5 mL) was added dropwise. The mixture was stirred for 1 h more, and then diluted with ether (30 mL). The phases were separated, and the organic layer was washed with 1.2 N HCl (4 × 5 mL) and satd aq Na_2CO_3 (5 mL). Drying and evaporation (finishing on a vacuum pump to remove all traces of solvent) provided 270 mg (99%) of **18** as a pure oil: $[\alpha]_D$ +141.1° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.28 (tr, 3 H, *J* 7.4 Hz), 1.48 (dd, 3 H, $J_{6,F}$ 1.3, $J_{5,6}$ 6.1 Hz, H-6), 2.65–2.82 (m, 2 H), 3.56 (ddq, 1 H, $J_{5,F}$ 3.2, $J_{4,5}$ 9.2 Hz, H-5), 3.75 (ddd, 1 H, $J_{2,3}$ 3.7, $J_{3,4}$ 9.2, $J_{3,F}$ 12.9 Hz, H-3), 4.47 (ddd, 1 H, $J_{4,F}$ 50.5 Hz, H-4), 4.62 (d, 1 H, *J* 12.2 Hz), 4.76 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1), 4.81 (d, 1 H, *J* 12.2 Hz), 5.88 (ddd, 1 H, $J_{2,F}$ 2.7 Hz, H-2), 7.28–7.33 (m, 5 H), 7.45 (m, 2 H), 7.57 (m, 1 H), 8.10 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 14.83, 17.79, 25.64, 71.20 (d, $J_{C,F}$ 9.2 Hz), 71.47, 74.40 (d, $J_{C,F}$ 24.0 Hz), 77.72 (d, $J_{C,F}$ 18.2 Hz), 82.40, 92.29 (d, $J_{C,F}$ 182.1 Hz), 127.74, 128.33, 129.48, 130.03, 133.18, 137.38, 165.72; Anal. Calcd for $C_{22}H_{25}FO_4S$: C, 65.33; H, 6.23. Found: C, 65.60; H, 6.67.

*Methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-α-*L*-lyxo-hexopyranosyl-(1→3)-2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-*D*-glucopyranoside* (**27**).—Thioglycoside **5** (200 mg, 0.50 mmol), methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside [30] (194 mg, 0.60 mmol) and powdered, freshly activated 4 Å molecular sieves (500 mg) were placed in a dry two-necked flask fitted with a septum, a three-way gas inlet valve and a magnetic stirring bar and left overnight at 0.1 torr. The flask was then flushed with argon, dry CH_2Cl_2 (4.0 mL) was added, and the mixture was vigorously stirred for 1 h. Recrystallized *N*-iodosuccinimide (146 mg, 0.65 mmol) was added, followed by TfOH (5.8 μL, 0.065 mmol). TLC analysis indicated complete consumption of the donor after 15 min. The mixture was filtered through Celite into 50% satd aq $Na_2S_2O_3$ (5 mL) in a separatory funnel. The filter cake was washed with several portions of CH_2Cl_2 (45 mL total), which were also added to the separatory funnel. The mixture was shaken until all color was discharged, and the phases were separated. The organic layer was washed with satd aq $NaHCO_3$ (5 mL), water (5 mL) and brine (5 mL), then dried and concentrated. Chromatography of the solid residue (3:1 CH_2Cl_2–EtOAc) afforded **27** (272 mg, 82%) as white crystals: mp 230–231 °C; $[\alpha]_D$ +32.0° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.76 (d, 3 H, $J_{5',6'}$ 6.2 Hz, H-6′), 1.78–1.98 (m, 2 H, H-4′, H-4a′), 2.17 (s, 3 H) 3.40 (s, 3 H), 3.69 (dd, 1 H, $J_{4,5}$ 8.6, $J_{3,4}$ 9.8 Hz, H-4), 3.76–3.90 (m, 2 H, H-5′, H-6), 3.95 (dd, 1 H, $J_{2,3}$ 10.0 Hz, H-3), 4.18–4.32 (m, 2 H, H-5, H-6a), 4.47 (ddd, 1 H, $J_{1,2}$ 3.7, $J_{NH,2}$ 10.0 Hz, H-2), 4.66 (d, 1 H, H-1), 5.17–5.20 (m, 2 H, H-1′, H-2′), 5.54 (ddd, 1 H, $J_{2',3'}$ 3.0, $J_{4',3'}$ 5.1, $J_{4a',3'}$ 11.8 Hz, H-3′), 5.57 (s, 1 H), 5.77 (d, 1 H, N*H*), 7.30–7.37 (m, 5 H), 7.43–7.53 (m, 5 H), 7.59 (m, 1 H), 7.89 (m, 2 H), 8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 20.35, 23.51, 33.71, 53.15, 55.17, 63.11, 64.25, 67.76, 68.97, 69.40, 76.06, 80.32, 99.08 ($^1J_{C,H}$ 171.6 Hz), 99.43 ($^1J_{C,H}$ 170.2 Hz), 102.15, 126.42, 128.13, 128.21, 128.40, 129.09, 129.56, 129.67, 129.94, 130.00, 132.91, 133.14, 137.22, 165.40, 165.62, 170.57; Anal. Calcd for $C_{36}H_{39}NO_{11}$: C, 65.35; H, 5.94; N, 2.12. Found: C, 65.68; H, 6.21, N, 2.09.

Methyl 2-O-benzoyl-3-O-benzyl-4-deoxy-4-fluoro-α-L-rhamnopyranosyl-(1→3)-2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (**28**).—Using the procedure described above for the synthesis of **27**, the coupling of fluororhamnose **18** (128 mg, 0.32 mmol) and methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside [30] (123 mg, 0.38 mmol) in CH_2Cl_2 (2.5 mL) was effected in the presence of 4 Å molecular sieve powder (350 mg), recrystallized *N*-iodosuccinimide (92 mg, 0.41 mmol) and TfOH (3.6 μL, 0.041 mmol). TLC analysis indicated complete consumption of the donor after 50 min. Workup and chromatography (3:2 EtOAc–hexanes) afforded disaccharide **28** (116 mg, 55%) as an amorphous solid: $[\alpha]_D$ +53.0° (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.80 (dd, 3 H, $J_{6',F}$ 1.2, $J_{5',6'}$ 6.1 Hz, H-6′), 2.16 (s, 3 H), 3.40 (s, 3 H), 3.65 (dd, 1 H, $J_{3,4}$ 9.3, $J_{4,5}$ 9.3 Hz, H-4), 3.77 (dd, 1 H, $J_{6,6a}$ 9.9, $J_{5,6}$ 10.3 Hz, H-6), 3.81–3.84 (m, 1 H, H-5), 3.88 (dd, 1 H, $J_{2,3}$ 10.1 Hz, H-3), 4.02–4.08 (m, 2 H, H-3′, H-5′), 4.30 (dd, 1 H, $J_{5,6a}$ 4.4 Hz, H-6a), 4.41 (ddd, 1 H, $J_{3',4'}$ 9.5, $J_{4',5'}$ 9.5, $J_{4',F}$ 51.4 Hz, H-4′), 4.45 (ddd, 1 H, $J_{1,2}$ 3.8, $J_{NH,2}$ 10.0 Hz, H-2), 4.64 (d, 1 H, *J* 11.9 Hz), 4.65 (d, 1 H, H-1), 4.68 (d, 1 H, *J* 11.9 Hz), 4.98 (dd, 1 H, $J_{1',2'}$ 2.0, $J_{1',F}$ 2.8 Hz, H-1′), 5.33 (ddd, 1 H, $J_{2',3'}$ 3.2, $J_{2',F}$ 3.2 Hz, H-2′), 5.55 (s, 1 H), 5.72 (d, 1 H, N*H*), 7.19–7.57 (m, 13 H), 7.98 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 16.74 (C-6′), 23.59 (C(O)*C*H$_3$), 53.14 (C-2), 55.26 (O*C*H$_3$), 63.18 (C-5), 66.09 (d, $J_{C,F}$ 25.0 Hz, C-5′), 68.99 (C-6), 70.92 (d, $J_{C,F}$ 9.1 Hz, C-2′), 71.74 (O*C*H$_2$Ar), 74.99 (d, $J_{C,F}$ 18.3 Hz, C-3′), 77.15 (C-3), 80.17 (C-4), 92.88 (d, $J_{C,F}$ 179.9 Hz, C-4′), 98.67 ($^1J_{C,H}$ 171.0 Hz, C-1′), 99.49 ($^1J_{C,H}$ 171.3 Hz, C-1), 102.13 (O*C*O), 126.40, 127.54, 127.63, 128.28, 128.30, 128.43, 129.25, 129.75, 129.83, 133.28, 137.13, 138.03, 165.67 (ester *C*=O), 170.63 (amide *C*=O); Anal. Calcd for $C_{36}H_{40}FNO_{10}$: C, 64.95; H, 6.06; N, 2.10. Found: C, 64.82; H, 6.01; N, 2.01.

Methyl 4,6-dideoxy-α-L-lyxo-hexopyranosyl-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (**29**).—Protected disaccharide **27** (150 mg, 0.227 mmol) was suspended in 80% AcOH (10 mL), and the mixture was heated at 70 °C for 1.5 h. The resulting clear solution was then cooled and evaporated. The residue was re-evaporated from toluene (3 × 5 mL) and then dried on the vacuum pump. Methanol (5 mL) was added, followed by sodium (approximately 4 mg, 0.17 mmol). The reaction was complete after 4 h of stirring at rt. Amberlite IR-120 (H^+) was added to neutralize the base, and the mixture was filtered and concentrated. Chromatography of the residue (4:1 $CHCl_3$–MeOH) afforded the unprotected disaccharide **29** (78.8 mg, 95%) as a white crystalline solid: mp 255–256 °C; $[\alpha]_D$ +11.2° (*c* 0.47, water); ^{1}H NMR (310 K, D_2O): δ 1.16 (d, 3 H, $J_{5',6'}$ 6.2 Hz, H-6′), 1.56 (ddd, 1 H, $J_{4'ax,4'eq}$ 11.7, $J_{4'ax,5'}$ 11.7, $J_{4'ax,3'}$ 12.0 Hz, H-4′ax), 1.71 (m, 1 H, H-4′eq), 2.05 (s, 3 H, C(O)C*H*$_3$), 3.40 (s, 3 H, OC*H*$_3$), 3.51 (dd, 1 H, $J_{3,4}$ 8.9, $J_{4,5}$ 10.1 Hz, H-4), 3.60 (m, 1 H, H-2′), 3.69 (ddd, 1 H, $J_{5,6a}$ 2.3, $J_{5,6}$ 5.4 Hz, H-5), 3.72 (dd, 1 H, $J_{2,3}$ 10.4 Hz, H-3), 3.78 (dd, 1 H, $J_{6,6a}$ 12.2 Hz, H-6), 3.88 (dd, 1 H, H-6a), 3.98 (ddd 1 H, $J_{2',3'}$ 3.0, $J_{3',4'eq}$ 4.8 Hz, H-3′), 4.04 (dd, 1 H, $J_{1,2}$ 3.6 Hz, H-2), 4.21 (ddq, 1 H, $J_{4'eq,5'}$ 2.2 Hz, H-5′), 4.71 (d, 1 H, H-1), 4.89 (d, 1 H, $J_{1',2'}$ 1.9 Hz, H-1′); ^{13}C NMR (310 K, D_2O): δ 20.62 (C-6′), 22.66 (C(O)*C*H$_3$), 35.15 (C-4′), 53.82 (C-2), 55.90 (O*C*H$_3$), 61.38 (C-6), 65.85 (C-3′), 66.38 (C-5′), 69.18 (C-2′), 69.32 (C-4), 72.64 (C-5), 80.15 (C-3), 99.01 ($^1J_{C,H}$ 171.8 Hz, C-1), 102.76 ($^1J_{C,H}$ 168.4 Hz, C-1′), 174.86 (*C*=O); ESIMS *m/z* 388.25 $[M+Na]^+$, 366.21 $[M+H]^+$, 236.00 $[GlcNAcOCH_3+H]^+$; Anal. Calcd for $C_{15}H_{27}NO_9$: C, 49.31; H, 7.45; N, 3.83. Found: C, 49.19; H, 7.60; N, 3.72.

Methyl 4-deoxy-4-fluoro-α-L-rhamnopyranosyl-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (**30**).—Protected disaccharide **28** (114 mg, 0.17 mmol) was dissolved in dry MeOH (5 mL) and treated with sodium (2.5 mg, 0.11 mmol). The mixture was stirred for 16 h, then neutralized with Amberlite IR-120 (H^+) and filtered into a fresh flask containing a magnetic stirring bar. The resin was washed with an additional 5 mL of MeOH, and the washings were also added to the flask. Pd/C catalyst (10%; 20 mg) was added to this solution (Caution! Extreme fire hazard!), the flask was fitted with a three-way stopcock, and evacuated on a water aspirator. A balloon containing hydrogen was attached to the stopcock and the flask was charged with the gas. The reaction was vigorously stirred for 23 h, at which point TLC indicated complete re-

moval of all protecting groups. The mixture was filtered through Celite and evaporated. Chromatography of the residue on a short column (gradient elution from 15 → 30% MeOH–$CHCl_3$) afforded **30** (53.3 mg, 81%). The product could be recrystallized from MeCN: mp 253 °C (dec.); $[\alpha]_D$ + 16.0° (*c* 0.50, water); ^{1}H NMR (D_2O, 310 K): δ 1.27 (dd, 3 H, $J_{6',F}$ 1.2, $J_{5',6'}$ 6.2 Hz, H-6′), 2.05 (s, 3 H, C(O)CH_3), 3.40 (s, 3 H, OCH_3), 3.54 (dd, 1 H, $J_{3,4}$ 8.9, $J_{4,5}$ 10.1 Hz, H-4), 3.69 (ddd, 1 H, $J_{5,6a}$ 2.3, $J_{5,6}$ 5.4 Hz, H-5), 3.75 (dd, 1 H, $J_{2,3}$ 10.4 Hz, H-3), 3.78 (dd, 1 H, $J_{6,6a}$ 12.2 Hz, H-6), 3.82 (ddd, 1 H, $J_{2',F}$ 1.8, $J_{1',2'}$ 3.0, $J_{2',3'}$ 3.5 Hz, H-2′), 3.88 (dd, 1 H, H-6a), 3.99 (ddd, 1 H, $J_{3',4'}$ 9.3, $J_{3',F}$ 14.5 Hz, H-3′), 4.05 (dd, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 10.4 Hz, H-2), 4.18 (ddq, 1 H, $J_{5',F}$ 4.8, $J_{4',5'}$ 9.6 Hz, H-5′), 4.31 (ddd, 1 H, $J_{4',F}$ 51.5 Hz, H-4′), 4.71 (d, 1 H, H-1), 4.85 (dd, 1 H, $J_{1',F}$ 2.0 Hz, H-1′); ^{13}C NMR (D_2O): δ 16.85 (C-6′), 22.68 (C(O)CH$_3$), 53.88 (C-2), 55.92 (OCH$_3$), 61.37 (C-6), 67.01 (d, $J_{C,F}$ 24.9 Hz, C-5′), 69.20 (C-4), 69.52 (d, $J_{C,F}$ 17.6 Hz, C-3′), 72.11 (d, $J_{C,F}$ 9.3 Hz, C-2′), 72.72 (C-5), 80.36 (C-3), 94.14 (d, $J_{C,F}$ 175.0 Hz, C-4′), 99.00 ($^1J_{C,H}$ 171.9 Hz, C-1), 101.81 ($^1J_{C,H}$ 170.0 Hz, C-1′), 174.89 (*C*=O); ^{19}F NMR (D_2O, 300 K): δ −204.18 (m); ESIMS *m*/*z* 406.17 [M + Na]$^+$, 384.26 [M + H]$^+$, 236.18 [GlcNAcO-CH_3 + H]$^+$; Anal. Calcd for $C_{15}H_{26}FNO_9 \cdot H_2O$: C, 44.89; H, 7.03; N, 3.49. Found: C, 44.83, H, 7.01; N, 3.39.

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