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Synthesis of 5-Fluoro *N*-Acetylglucosamine Glycosides and Pyrophosphates via Epoxide Fluoridolysis: Versatile Reagents for the Study of Glycoconjugate Biochemistry

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Abstract: Numerous carbohydrate-processing enzymes facilitate catalysis via stabilization of positive charges on or near the C-1, C-4, C-5, or C-6 positions. Substrate analogues differing only in the substitution of a fluorine for the axial C-5 hydrogen would possess reduced electron density at these positions and could be useful mechanistic probes of these enzymes. Introduction of this 5-fluoro substituent after radical halogenation was problematic because of the incompatibility of many protecting groups to the radical halogenation and the instability of the subsequent 5-fluoro hexosamines. Thus, to allow easy access to a wide variety of 5-fluoro glycosides and glycosyl phosphates, a versatile method for the introduction of the 5-fluoro group has been developed, the key step being the fluoridolysis of C-5, 6 epoxides. By use of this method, two fluorinated carbohydrates, uridine 5′-diphospho-5-fluoro-*N*-acetylglucosamine and octyl 5-fluoro-*N*-acetylglucosamine, have been synthesized. Initial biochemical investigations of these compounds show that 5-fluoro analogues are useful probes of transition-state charge development in several enzyme-catalyzed reactions.

Introduction

Carbohydrates are a functionally and structurally diverse class of biological macromolecules.[1] Enzymes that catalyze biosynthetic reactions to create this diversity include the following: Glycosyltransferases[2] assemble carbohydrate monomers into oligomers and polymers or glycosylate proteins.[3−5] Glycosidases[6−8] hydrolyze inter-saccharidic linkages. Dehydrogenases, dehydratases, and epimerases modify carbohydrate monomers.[9] While the reactions catalyzed by these enzymes are diverse, many of the chemical transformations during catalysis occur at the C-1, C-4, C-5, and C-6 positions (Figure 1).

Incorporation of a 5-fluoro group would provide a useful probe for many of these enzyme-catalyzed reactions (Table 1). For example, glycosyltransferases utilize nucleotide diphospho sugars such as uridine 5′-diphospho-*N*-acetylglucosamine (UDP-GlcNAc) as glycosyl donors. Evidence from crystal structures[10−15] and substrate analogues[16−18] points to formation of a glycosyl oxocarbenium ion during catalysis. Epimerization at C-2 (UDP-GlcNAc → UDP-*N*-acetylmannosamine) also involves formation of a transient oxocarbenium ion followed by reprotonation from the opposite face of the proposed glycal intermediate.[19] An electron-withdrawing 5-fluoro substituent would be expected

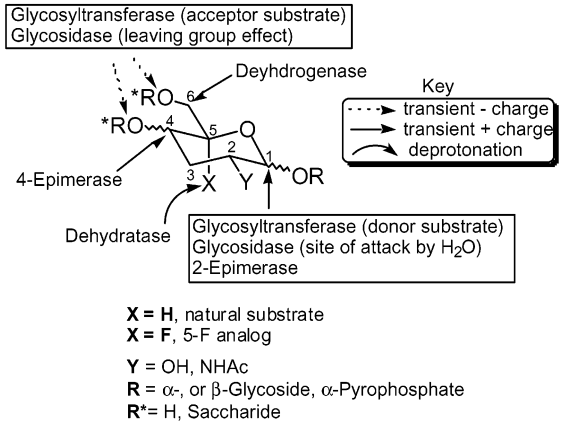

Figure 1. Sites of possible charge buildup during specified enzyme-catalyzed reactions.

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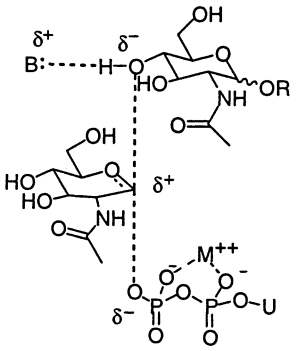
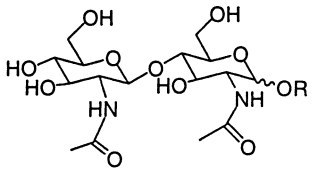
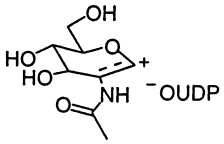
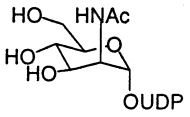
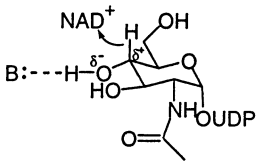
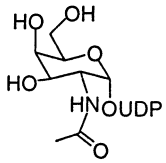
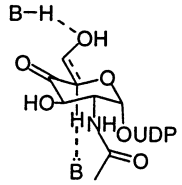
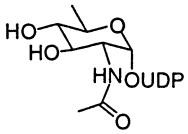
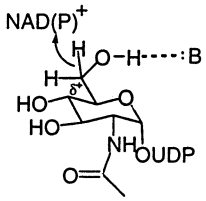
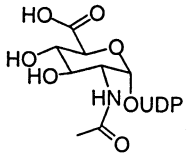
Table 1. UDP-GlcNAc Utilizing Enzymes That May Be Affected by 5-Fluoro Substrate Analogs

Enzyme utilizing UDP-GlcNAc as a substrate	Transition-state affected by fluorine at C-5	Product
Glycosyltransferases		
C-2 Epimerases		
C-4 Epimerases		
Dehydratases		
Dehydrogenases		

to destabilize the putative oxocarbenium ion in either case. This, in turn, should lead to slower turnover than in the natural substrate if these hypotheses are correct.

Epimerase-catalyzed reactions at C-4 proceed via a different mechanism that involves C-4 oxidation followed by reduction of the opposite face of the ketone.[9] Partial carbocationic character at C-4 is expected to develop along the reaction coordinate for these oxidation reactions, and the 5-fluoro substituent should, therefore, slow this reaction. Dehydratase-catalyzed reactions also involve oxidation at C-4 followed by elimination of water across the C-5,6 bond.[20] In addition to retarding the oxidation reaction, the 5-fluoro substituent would prevent the H-5 deprotonation step required for this elimination. C-6 dehydrogenases, which lead to the corresponding uronic acids, proceed via two oxidations (with a thiohemiacetal intermediate)[21] that should be affected in a similar manner.

Returning to the glycosyltransferases, glycosylation often involves the 4-OH or 6-OH groups of the glycosyl acceptor. A 5-fluoro analogue of the natural acceptor could be a useful mechanistic probe because the pK_a of each neighboring hydroxyl group and nucleophilicity of the conjugate base would be lowered by the presence of the electron-withdrawing fluorine atom.[22] Finally, glycosidases have been extensively studied using 5-fluoro glycosyl fluorides.[23] The affinity of these reagents could

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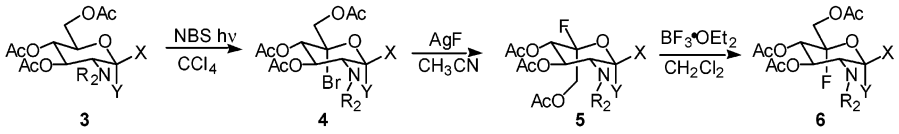
Table 2. Synthesis of 5-Fluoro Glucosamine Compounds Subsequent to Radical Halogenation

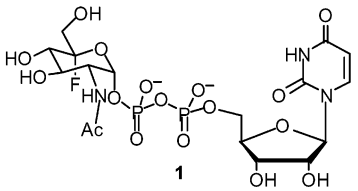


				% yield		
entry	R_2	X	Y	**3 → 4**	**4 → 5**	**5 → 6**
a	Ac_2	H	OAc	a	nd	nd
b	TCP	$OC_6H_4OMe(p)$	H	<5	nd	nd
c	TCP	OCH_2CCl_3	H	43	55	nd
d	TCP	H	OAc	52	56	25
e	TCP	OAc	H	35	43	nd
f	Pht	OAc	H	66	52	75

[a] Inseparable 5-Br and 1-Br regioisomers.

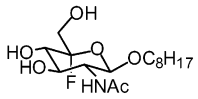
be improved by incorporation of the natural aglycon.[24] Alternatively, incorporation of a 5-fluoro substituent on the aglycon would be useful for investigating the effect of the leaving group pK_a in C-4 or C-6 linked oligosaccharides. With these multiple applications in mind, the synthesis of 5-fluoro GlcNAc derivatives **1** and **2** (Figure 2) has been investigated.

Glycosyltransferase Donor, Epimerase, Dehydrogenase and Dehydratase Substrate Analog



1

Glycosyltransferase Acceptor Substrate Analog



2

Figure 2. 5-Fluoro synthetic targets.

The wide variety of substrates for these diverse enzymes requires a flexible synthetic route for incorporation of the 5-fluoro substituent. Other than the synthesis of 5-fluoro glycosyl fluorides by Withers and co-workers,[23] no methods (flexible or otherwise) for introducing fluorine at C-5 have been developed. In prior syntheses, the key step was introduction of a 5-bromo moiety via radical halogenation.[25] Although this step allows introduction of the 5-fluoro group concisely, the types of substrates compatible with this reaction are limited, and the yields are usually only modest. In particular, C-1 electron-withdrawing groups are required to prevent competing bromination at that position. Common carbohydrate protecting groups containing a radical-stabilizing functionality such as benzyl or allyl groups are also incompatible. Furthermore, because of competing bromination at other C-5 positions, these reactions are typically limited to monosaccharides; only one 5-bromo disaccharide has been described.[26] Finally, the only application of this method to nitrogen-containing monosaccharides gave very low yields.[27] Thus, we sought to either circumvent these limitations or create a new and more versatile method to incorporate the 5-fluoro moiety. GlcNAc-based carbohydrates were selected as the first synthetic targets because working with amino sugars provides a rigorous test of any new methodology.

Results

Introduction of the 5-Fluoro Moiety after Radical Halogenation. Our initial work centered on improving the yields and the scope of the radical halogenation method. A series of *N*-substituted, tri-*O*-acetyl glucosamine derivatives, **3**, were synthesized as described in the literature (**3b,d−f**) or in the Experimental Section (**3a,c**). These substrates were then subjected to radical bromination, halide exchange (Br → F), and epimerization conditions. The results are summarized in Table 2.

It was initially observed that amide NH groups were incompatible with the *N*-bromosuccinimide (NBS) reaction, likely due to bromine transfer from NBS to the carbohydrate amide. Thus, imide protecting groups such as *N*,*N*-diacetyl (entry **a**), tetrachlorophthaloyl (TCP) (entries **b**−**e**), and phthaloyl (Pht) (entry **f**) were investigated. The *N*,*N*-diacetyl compound **4a** gave a mixture of 5-bromo and 1-bromo isomers during the NBS reaction. The tetrachlorophthaloyl protecting group was compatible with these reaction conditions, leading to the desired 5-bromo derivatives, **4**, but yields were consistently lower as compared to the phthaloyl series (compare **4e** and **4f**).

Since 5-fluoro glycosyl pyrophosphates (**1**) were desired, we decided to investigate alternative C-1 hydroxyl protecting groups that might survive the bromination and fluorination steps yet would be amenable to selective deprotection in the presence of *O*-acetyl protecting groups. For this purpose, the *p*-methoxyphenyl[28] and trichloroethyl[29] groups (entries **b** and **c**), prepared by BF_3·OEt_2-mediated glycosylation of the corresponding glycosyl acetates,[30,31] were chosen. Unfortunately, these protect-

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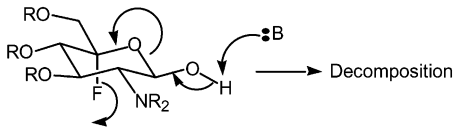


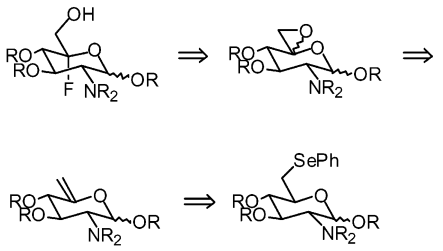
Figure 3. Rationale for instability of 5-fluoro reducing sugars.

ing groups proved unsatisfactory in the NBS reaction, leading to competing bromination at C-1. Thus the reaction seems limited to C-1 ester protecting groups.

The *N*-phthaloyl β-acetate (entry **f)** compound proved to be the best substrate for the series of reactions. Bromination proceeded in good yield; silver fluoride displacement yielded only the L-ido configured compound **5f**. The final inversion reaction was accomplished with $BF_3{\cdot}OEt_2$ in the presence of molecular sieves to prevent hydrolytic attack of the carbocationic intermediate. Unfortunately, deprotection of the 5-fluoro product **6f** gave only decomposition, likely due to a postulated ring opening resulting in a keto aldehyde (Figure 3) with concomitant loss of fluoride as observed by ^{19}F NMR.

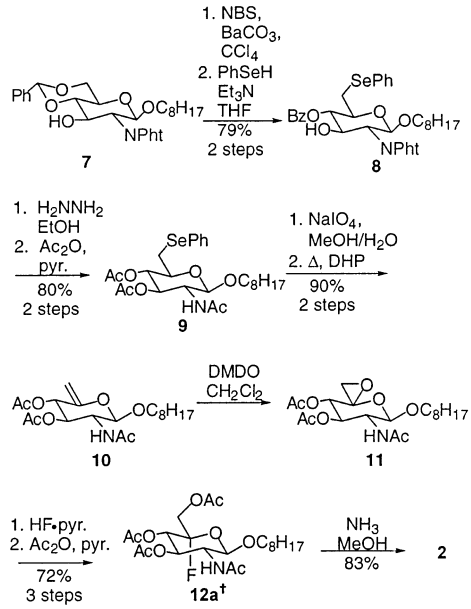
Synthesis of 5-Fluoro Glycosides via Epoxide Fluoridolysis. The demonstrated instability of these 5-fluoro hexosamines necessitated development of a new method to introduce the 5-fluoro group (Scheme 1). We envisioned that a C-5,6 epoxy group could be opened in the presence of fluoride, thus giving the desired 5-fluoro product. The C-5,6 epoxide could be prepared from a C-5,6 alkene which should be readily available from a C-6 selenide after oxidation and elimination.[32] The C-6 selenide should be inert to several transformations, allowing introduction of the fluorine late in the synthesis.[33−35]

Scheme 1. Retrosynthetic Analysis for Introduction of the 5-Fluoro Group



Synthesis of 5-F-GlcNAc Glycosides via Epoxide Fluoridolysis: Development of the Method. To explore the proposed new methodology, β-octyl 5-F-GlcNAc, **2**, was selected as the initial synthetic target. 4,6-Benzylidene glucosamine derivative **7**[36] served as the starting material (Scheme 2). NBS bromination gave the corresponding 6-bromo, 4-*O*-benzoyl compound, following which the selenide was introduced in high yield by nucleophilic displacement with PhSeH to give **8**. Cleavage of the base-labile protecting groups with ethanolic hydrazine at 80 °C followed by acetylation gave *N*-acetyl glycoside **9**. After one-pot oxidation (*m*-chloroperoxybenzoic acid (mCPBA)) and elimination (Et_3N, reflux)[32] failed, the desired alkene **10** was prepared by oxidation of **9** with $NaIO_4$ followed by thermal

Scheme 2. Synthesis of 5-F Octyl Glycoside **2**



†The C-5 epimer, **12b**, was also obtained in the crude reaction mixture. It could be separated from **12a** and was isolated in 10% yield.

selenoxide elimination in dihydropyran. Dihydropyran was used as the solvent to trap the postulated electrophilic selenium products,[37] thereby preventing electrophilic addition onto the electron-rich olefin of **10**. Surprisingly, epoxidation gave only one of the two possible diastereomeric epoxides, **11**. This epoxide was opened with HF·pyridine and acetylated. The desired D-gluco isomer **12a** was formed in excellent yield and was easily separable from a small amount of the C-5 epimer, **12b**. Deprotection of the acetates of **12a** with methanolic ammonia provided the desired octyl 5-fluoro GlcNAc **2** in good yield. The overall yield from **7** in the 10-step synthesis was 34%.

Synthesis of Glycosyl Phosphates via Epoxide Fluoridolysis. Inspired by this success, we now turned to the second challenge, namely, to introduce the 5-fluoro substituent into glycosyl phosphates. Because some methods for synthesizing glycosyl phosphates require a reducing sugar,[38] a functionality previously shown to be incompatible with the 5-fluoro substituent (Figure 3), introduction of the glycosyl phosphate prior to the fluorine atom would be advantageous. This presented a different problem, however, because the unstable GlcNAc phosphate triesters[39] would have to be carried through multiple steps as the fluorine was introduced. Thus, the *N*-trifluoroacetyl (TFA) group was utilized because of its ability to stabilize C-1 phosphotriesters.[40] With these constraints in mind, three routes to phosphate introduction were envisioned (Scheme 3). A reducing sugar could serve as a phosphorylation substrate either via the phosphite[41] (route A) or direct phosphorylation with tetrabenzylpyrophosphate (route B).[39] The oxazoline method[40,42] (route C) could also be utilized.

(32) Myers, A. G.; Gin, D. Y.; Rogers, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4697−4718.
(33) While this work was in progress, Murphy and co-workers (refs 34 and 35) described the synthesis of 5-ketohexoses via hydrolysis of a C-5,6 epoxy intermediate derived from appropriately protected 6-deoxyhex-5-enopyranosides.
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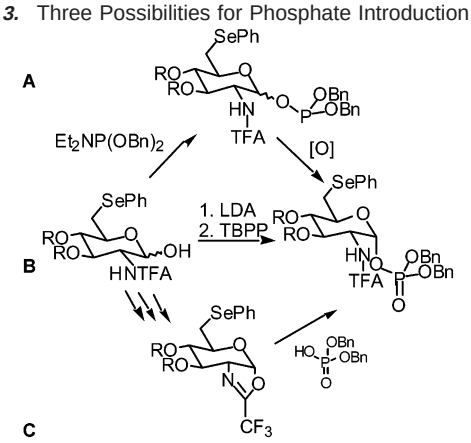
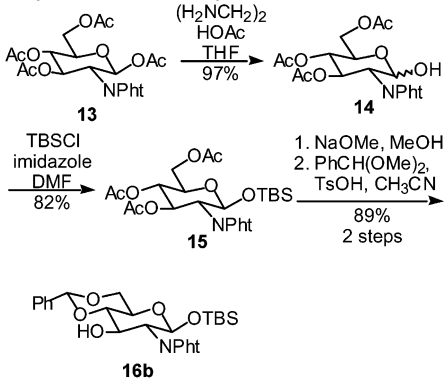
Scheme 3. Three Possibilities for Phosphate Introduction



Scheme 4. Synthesis of TBS Glycoside **16b**

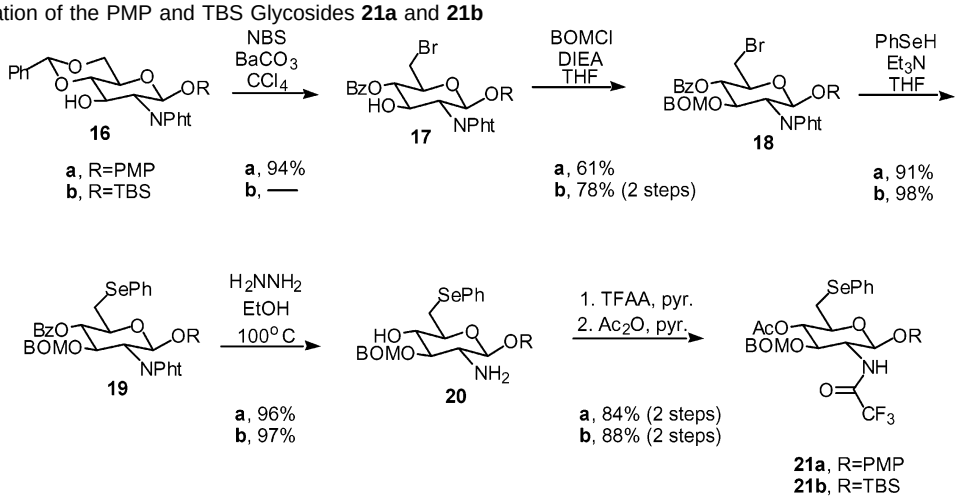


Two anomeric protecting groups that should be easily removed to allow introduction of the phosphate, the *p*-methoxyphenyl (PMP) and *tert*-butyldimethylsilyl (TBS), were investigated. PMP glycosides in particular are stable to a wide variety of conditions yet can be cleaved to give glycosyl bromides, thiophenyl glycosides, and reducing glycosides.[28] The PMP glycoside, **16a**, was prepared according to a literature procedure,[43] and the corresponding TBS glycoside, **16b**, was synthesized as shown in Scheme 4. Selective anomeric deacetylation of **13** proceeded smoothly using the method of Zhang and Kovac.[44] After silylation to give **15**, deprotection and benzylidenation gave 4,6-benzylidene **16b** in good yield.

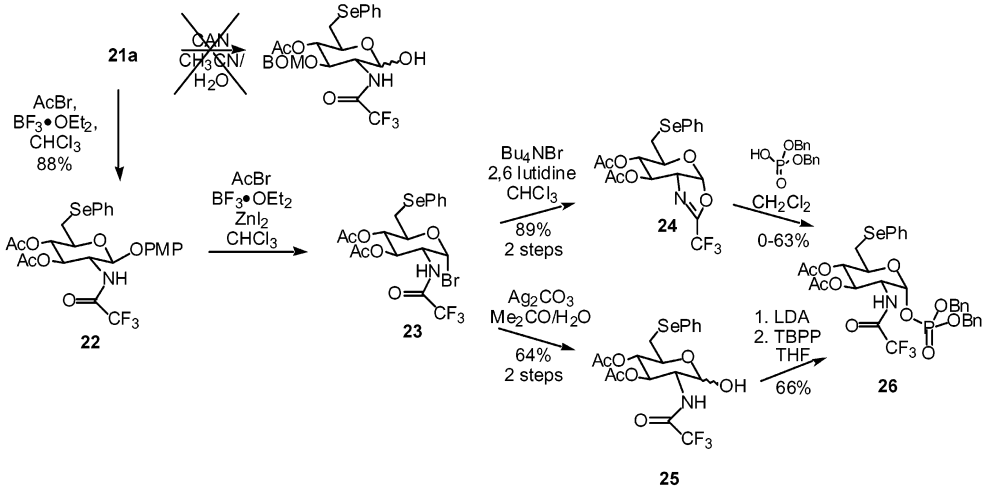
The selenide and *N*-TFA groups on both the PMP and TBS glycosides were then introduced (Scheme 5). Treatment with NBS gave the 6-bromo compounds, **17**. In the context of ultimately employing this new methodology in the synthesis of 5-F-GlcNAc-containing oligosaccharides, it was desirable to protect the 3-hydroxyl so that it could be selectively unmasked in the presence of the 4-*O*-benzoyl protecting group and vice versa. Therefore, the benzyloxymethyl (BOM) group was chosen for 3-hydroxyl protection. Benzyloxymethylation with BOMCl gave the selectively protected compounds **18** in good yield. With the PMP glycoside, the BnOH byproduct was difficult to remove, and the isolated yield of pure **18a** was therefore reduced. Formation of the C-6 selenide **19** proceeded in good yield for both glycosides. With the selenide in place, the TFA group could be introduced in three steps. First, cleavage of the phthaloyl and benzoate groups with hydrazine in EtOH gave **20** in excellent yield. Trifluoroacetylation with trifluoroacetic anhydride (TFAA) in pyridine followed by acetylation of the C-4 hydroxyl gave trifluoroacetamides **21** which contained the suitable protecting groups for C-1 phosphorylation.

Introduction of the C-1 Phosphate Starting from the PMP Glycoside. Attempted oxidative cleavage of the PMP group failed to give the reducing sugar, probably as a result of competing oxidation of the selenide. Thus an alternate route to the reducing sugar was developed (Scheme 6). Treatment of **21a** with AcBr and $BF_3{\cdot}OEt_2$[28] did not give the glycosyl bromide as expected. Instead, the BOM group was cleaved and acetylated to give **22**. Treatment of **22** with AcBr, $BF_3{\cdot}OEt_2$, and catalytic ZnI_2 gave glycosyl bromide **23**. The glycosyl phosphate could be introduced via two routes from this intermediate. Conversion of **23** to the trifluoromethyl oxazoline **24** using Bu_4NBr and 2,6-lutidine proceeded smoothly. Bu_4NBr was required to suppress glycal formation.[45] Unfortunately, phosphorolysis of the oxazoline to give **26**[40] was difficult to reproduce in good yield. The reaction was highly sensitive to the presence of water, and even when water was rigorously excluded, the extended reaction times required for larger scale reactions led to decomposition. As evidenced by thin-layer chromatography (TLC), the β-phosphate formed rapidly; decomposition occurred only during subsequent heating to obtain the desired α-glycosyl phosphate, **26**, as the thermodynamic product. Because this reaction proceeded smoothly on the corresponding 6-OAc compound,[40] the 6-seleno substituent likely decreased the thermal stability of this glycosyl phosphate, resulting in decomposition. An alternative route, however,

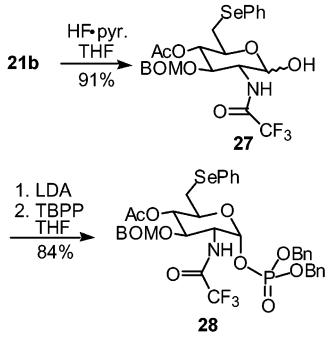
Scheme 5. Preparation of the PMP and TBS Glycosides **21a** and **21b**



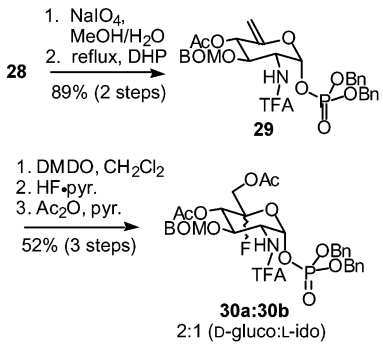
Scheme 6. Introduction of the Phosphate from the PMP Glycoside **21a**



Scheme 7. Introduction of the Phosphate from the TBS Glycoside **21b**



Scheme 8. Preparation of Protected 5-F Glucosamine Phosphate **30a**



proved to be more successful. Conversion of **23** to the reducing sugar **25** using Ag_2CO_3 in wet acetone followed by lithium alkoxide formation and phosphorylation with tetrabenzylpyrophosphate[39] gave glycosyl phosphate **26** in satisfactory yields. Compound **26** proved to be stable to chromatography.

Introduction of the C-1 Phosphate Starting from the TBS Glycoside. The deprotection of **21b** proceeded most easily using HF·pyridine in THF,[46] giving intermediate **27** as a mixture of α/β-isomers (10:1) (Scheme 7). Phosphitylation[41] gave a mixture of α/β-phosphites in a 3:2 ratio and was not pursued further. Phosphorylation using lithium diisopropylamide (LDA) and tetrabenzylpyrophosphate,[39] however, proceeded smoothly to give stable glycosyl phosphate **28** in the desired α-configuration and in high yield. During the reaction, the β-phosphotriester was also formed but was converted in situ to the 1,2-oxazoline, which was easily separated from **28** by flash chromatography. Comparing the number of steps, reaction conditions, and overall yields (Scheme 6 vs Scheme 7) the preferred method for synthesis of the desired *N*-TFA, 6-seleno glucosamine α-1-phosphate, is via the TBS glycoside, **21b**. This synthetic route offers the additional advantage of maintaining the differential protection at C-3 and C-4.

With **28** in hand, the main challenge remaining was the introduction of the 5-fluoro group (Scheme 8). The standard one-pot mCPBA oxidation/elimination method led only to decomposition during the selenoxide elimination, probably due to the basic conditions required to prevent electrophilic addition of the "PhSeOH" onto the alkene product.[37] Oxidation with an excess of dimethyldioxirane (DMDO) led to some overoxidation to the selenone. In contrast, oxidation of **28** with $NaIO_4$ followed by thermal selenoxide elimination in dihydropyran (see also Scheme 2) gave alkene **29** in good yield. Treatment of **29** with DMDO provided a 3:2 mixture of epoxides. Fluoridolysis with HF·pyridine followed by acetylation of the resulting fluorohydrins led to a mixture of separable 5-fluoro epimers, **30**, in good overall yield. The epimers could be partially separated by flash chromatography and completely separated by preparative high-performance liquid chromatography (HPLC). Thus, the newly developed fluorination strategy was useful for the preparation of glycosyl phosphates. To utilize this 5-fluoro glycosyl phosphate, **30a**, in the synthesis of **1**, deprotection of **30a** was required (Scheme 9). Hydrogenation of the BOM and benzyl groups gave free phosphate **31**. Deacetylation with methanolic ammonia proceeded smoothly to give an unstable amine that was immediately acetylated with Ac_2O/Et_3N to give the desired GlcNAc phosphate, **32**. Purification of **32** was difficult as a result of pH-dependent instability. Anion-exchange chromatography could, however, be performed at pH 4.5 to give **32** in good yield. UMP-morpholidate was treated with **32** and 1*H*-tetrazole[47] in pyridine, giving the desired sugar nucleotide **1** in moderate yield.

Biochemical Studies. Biochemical evaluation of compounds **1**, **2**, and **32** has focused on the enzyme-catalyzed reactions shown in Scheme 10.

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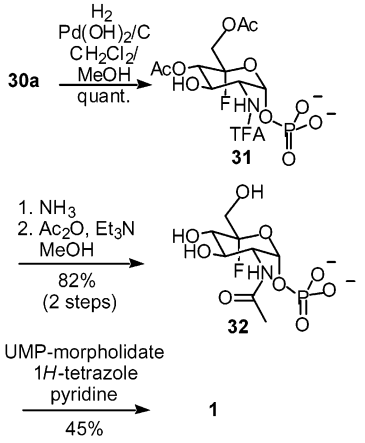
Scheme 9. Deprotection and Synthesis of UDP-5F-GlcNAc **1**



To investigate the effect of fluorine on hydride transfer at an adjacent carbon, the epimerization reaction catalyzed by UDP-GlcNAc 4-epimerase (reaction e) was studied. This enzyme, encoded by the WbgU gene from *Plesiomonas shigelloides* (P. Kowal and P. G. Wang, unpublished results), catalyzes the epimerization of UDP-GlcNAc to UDP-*N*-acetylgalactosamine (UDP-GalNAc) (Figure 4a). Under the reaction conditions described in Figure 4b, the electron-withdrawing fluorine at C-5 completely blocks the corresponding epimerization of UDP-5FGlcNAc (**1**). Inhibition of UDP-GlcNAc epimerization in the presence of **1** (Figure 4c) indicates that **1** binds to the enzyme. Thus, the strongly electron-withdrawing fluorine at C-5 markedly retards an epimerization reaction that, by analogy to UDP-galactose 4-epimerase,[9] is expected to involve sequential NADH-mediated oxidation and reduction at C-4 via a 4-keto intermediate. These preliminary results with **1** are in accord with the underlying hypothesis that a 5-fluoro substituent should destabilize developing positive charge associated with hydride transfer at C-4 (Table 1).

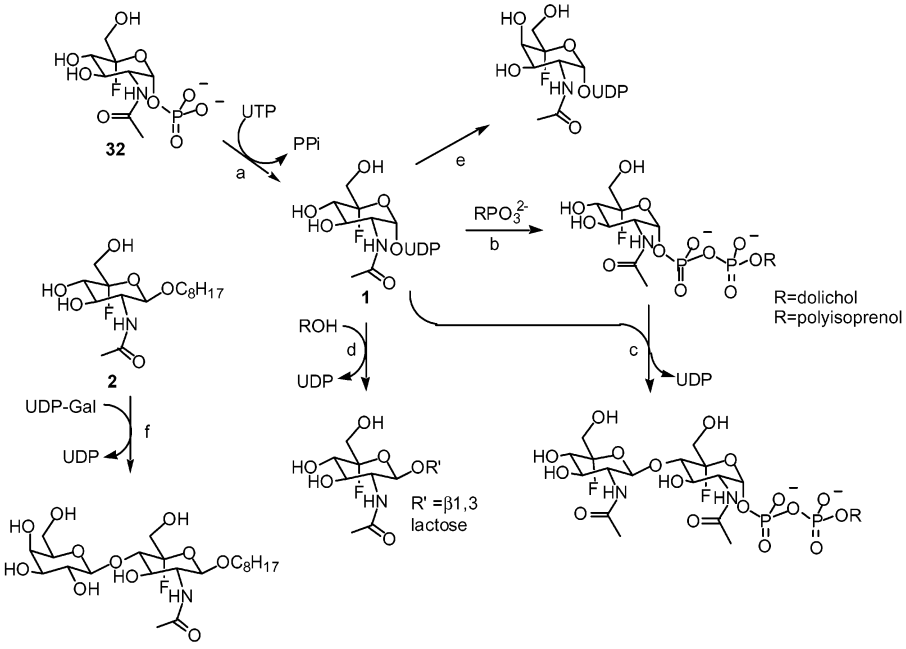
To assess the effect of a 5-fluoro substituent on the nucleophilicity of a hydroxyl group at C-4 or C-6, the ability of the 5-F-GlcNAc glycoside, **2**, to act as a glycosyltransferase acceptor was investigated. Thus, in the reaction catalyzed by β-1,4-galactosyltransferase (GalT, Scheme 10, reaction f), compound **2** shows an 8-fold reduction in k_{cat}/K_m when compared with GlcNAc β-octyl glycoside (Figure 5). Again, these results are in accord with the predicted effect of fluorine on the acidity of adjacent hydroxyl groups[22] and the resulting attenuated reactivity of compounds such as **2** in glycosyltransferase-catalyzed reactions (Table 1). Interestingly, the major effect of the 5-F substituent appears to be in K_m (ca. 6-fold increase) rather than k_{cat} (ca. 30% decrease). The magnitude of this k_{cat} effect is consistent with the small value of β_{nuc} calculated for an analogous system, the deglycosylation of the galactosyl enzyme intermediate in β-galactosidase.[48] A more complete investigation of the GalT reaction kinetics is currently in progress in our laboratory.

Preliminary results indicate that **32** is an alternate substrate for the phosphotransferase, glmU (Scheme 10, reaction a, data not shown), consistent with the expected minimal electronic effect of the fluorine on the nucleophilicity of the distal glycosyl phosphate. Similarly, compound **1** competes with UDP-GlcNAc in binding to *N*-acetyl glucosaminylphosphotransferase (reaction b, data not shown) as would be expected for an alternate substrate; however, turnover of compound **1** has not yet been evaluated. Biochemical studies of GlcNAc transferases (reactions c and d) are currently underway. Complete details of these biochemical investigations will be published in due course.

Discussion

Because of the ability of the 5-F group to effect large electronic changes with only small steric alterations, 5-F glycosides and phosphates can be useful reagents in enzymology (Table 1). Initial attempts to create a versatile strategy for the

Scheme 10. Initial Biochemical Evaluations of 5-FGlcNAc Derivatives (**1**, **2**, and **32**)[a]



[a] (a) UDP *N*-acetylglucosamine pyrophosphorylase, glmU, EC 2.7.7.23; (b) UDP-*N*-acetylglucosamine dolichyl/polyisoprenyl phosphate *N*-acetylglucosaminephosphotransferase, EC 2.7.8.15; (c) *N*-acetylglucosaminyldiphosphodolichol *N*-acetylglucosaminyltransferase, EC 2.4.1.141; (d) β-1,3-*N*-acetylglucosaminyltransferase, lgtA; (e) UDP-*N*-acetylglucosamine 4-epimerase EC 5.1.3.7; (f) β-1,4-galactosyltransferase from bovine milk, EC 2.4.1.38.

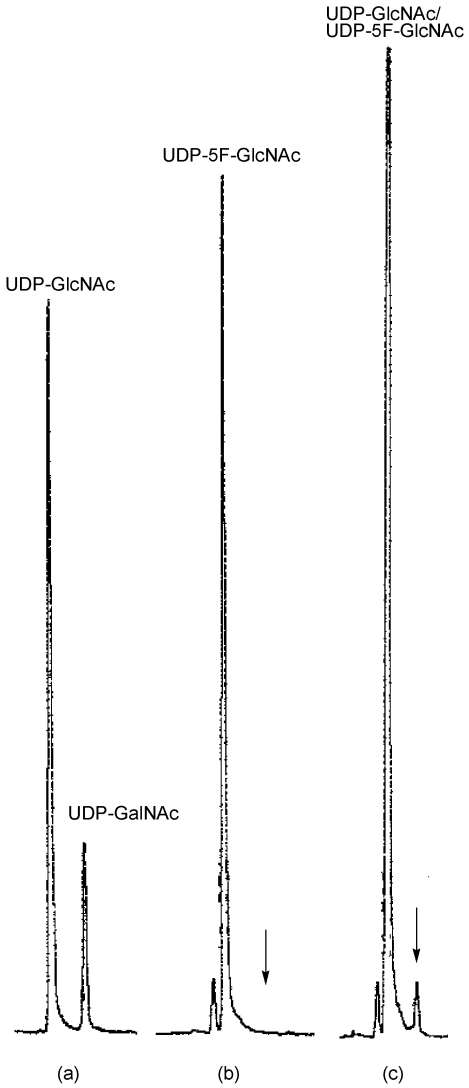
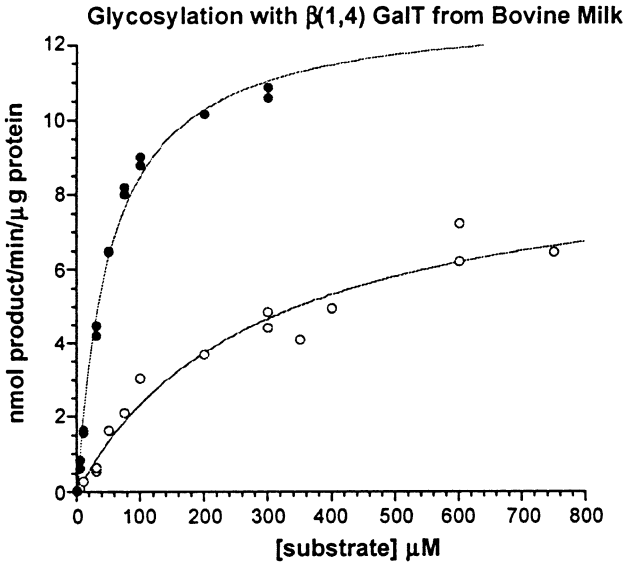


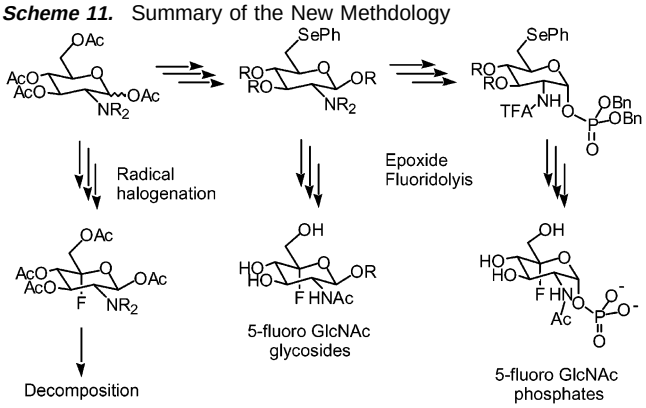
Figure 4. Comparison of capillary electrophoretic analysis of UDP-GlcNAc and UDP-5-F-GlcNAc, **1**, in the reactions catalyzed by UDP-GlcNAc 4-epimerase, WbgU. In addition to the substrate, each reaction mixture contained 20 mM Tris·HCl, pH = 8.5, 10 mM BME, and 150 ng of enzyme in a total volume of 40 μL. (a) Incubation of UDP-GlcNAc (200 μM) with epimerase (3 min). (b) Incubation of **1** (200 μM) with epimerase (3 min). The arrow shows the expected location of UDP-5-F-GalNAc. (c) Incubation of both **1** (200 μM) and UDP-GlcNAc (200 μM) with epimerase (3 min), clearly showing inhibition of epimerization of UDP-GlcNAc by **1**. The arrow shows the smaller UDP-GalNAc peak.



Substrate	Km (μM)	kcat (s^{-1})	kcat/Km (M^{-1} s^{-1})
octyl GlcNAc	52	9.1	1.8×10^5
octyl 5-F GlcNAc	295	6.5	2.2×10^4

Figure 5. Comparison of octyl 5-F-GlcNAc, **2** (open circles), and octyl GlcNAc (closed circles) in a Sep-Pak assay (ref 49) with β-1,4-galactosyltransferase from bovine milk (Sigma).

Scheme 11. Summary of the New Methdology



synthesis of these reagents via fluorination after radical halogenation failed, as a result of incompatibility of various protecting groups in the bromination reaction (Scheme 11). Deprotection of **6f**, derived from the best substrate for the halogenation and isomerization reactions, **3f**, led only to decomposition.

Epoxide fluoridolysis, on the other hand, is much more general, simply requiring the synthesis of a suitable C-6 seleno precursor. As long as the chosen protecting groups are stable to the oxidation conditions required for the two-step conversion of the selenide to an epoxide, the fluoridolysis should succeed on stable glycosides. A variety of protecting groups on the C-1 through C-4 oxygen or nitrogen groups can be utilized successfully. Even 5-fluoro glycosyl phosphate triesters can be prepared with this methodology provided a suitable C-2 electron-withdrawing protecting group (such as the *N*-TFA) is employed.

The fluorination step itself is accomplished under mild conditions (HF·pyridine) compatible with numerous functional groups. Fluorination favors the D-configured pyranoses, and selectivity is good to excellent. Configuration of the 5-F compounds can be readily determined by a comparison of ^{19}F chemical shift data and $J_{4,5}$ coupling constants from ^1H NMR spectral data. As shown in Table 3, ^{19}F ppm values for the D-gluco-configured compounds were consistently shifted upfield relative to the L-ido-configured compounds. In addition, the H-4−F-5 coupling constants for the L-ido compounds were typically severalfold less. This is reasonable because the trans-diaxial character of the D-gluco compounds places H-4 and F-5 at a 180° dihedral angle. These trends are in accord with a recent review of NMR spectral data for fluorinated carbohydrates.[50]

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Table 3. NMR Spectral Characteristics of D-Gluco and L-Ido Isomers

D-gluco			L-ido		
compound	^{19}F, ppm	$J_{4,5}$, Hz	compound	^{19}F, ppm	$J_{4,5}$, Hz
			5c	−30.06	4.8
			5e	−30.94	5.1
6d	−47.86	22.4	**5d**	−29.24	6.2
6f	−55.96	23.0	**5f**	−30.80	6.1
12a	−52.46	22.7	**12b**	−26.35	12.7
30a	−48.32	22.8	**30b**	−42.08	*a*
31	−47.28	22.8			
32	−54.57	*a*			
1	−54.11	*a*			
2	−61.64	*a*			

[a] H-4 was obscured by other protons, and the coupling constant could not be determined.

In addition to providing access to a new class of fluorinated carbohydrates, this research provides evidence that 5-F GlcNAc glycosides and phosphates are useful mechanistic probes for a wide variety of enzyme-catalyzed reactions (Figure 1 and Table 1). Preliminary results from several enzyme-mediated transformations (Scheme 10) illustrate the useful mechanistic data that can be gathered about transition state charge buildup using the 5-F GlcNAc derivatives, **1** and **2**. In conclusion, an efficient and versatile route for the synthesis of 5-fluoro glycosides and phosphates has been accomplished via epoxide fluoridolysis. These reagents show considerable promise for mechanistic studies of various carbohydrate-utilizing enzymes.

Experimental Section

General. All chemicals were purchased from Aldrich or Acros with the exception of BOM-Cl which was purchased from TCI America. Solvents were purified by distillation as follows: tetrahydrofuran (THF) from sodium benzophenone ketyl; MeOH, Et_3N, DMF, CH_2Cl_2, and pyridine from CaH_2; CCl_4 from $CaCl_2$. $CHCl_3$ was purified by passing through a column of activated Al_2O_3. Flash chromatography was carried out using 230−400 mesh Whatman SiO_2. TLC analyses were performed on SiO_2 60 F_{254} Whatman plates, and compounds were visualized with UV light, by staining with cerium molybdate followed by heating, or by phosphorus stain.[51,52] Preparative TLC utilized Whatman plates (250 μm). Cation exchange was performed on DOWEX 50WX8-100 (Aldrich). Anion exchange was performed with AG 1-X8 (Bio-Rad Laboratories) converted to the appropriate form prior to use. Size-exclusion chromatography was performed on Bio-Gel P-2, fine (Bio-Rad Laboratories). NMR spectra were recorded on Bruker AVANCE DRX-500 or DPX-300 spectrometers as indicated. ^{1}H NMR chemical shifts in $CDCl_3$ and MeOH are reported relative to tetramethylsilane at 0.00 ppm. Spectra obtained in D_2O are reported referenced to HOD at 4.79 ppm. ^{13}C NMR chemical shifts are reported relative to the center solvent peak, $CDCl_3$ (77.00), and CD_3OD (49.00). The number of attached protons (1, 2, or 3) is indicated and was determined by DEPT NMR. ^{19}F NMR chemical shifts are referenced to an external standard of TFA in $CDCl_3$. ^{31}P NMR chemical shifts are referenced to a capillary containing 0.85% H_3PO_4 in H_2O. Compounds **3b**,[31] **3d**,[53] **3e**,[31] **3f**,[54] **7**,[36] **13**,[54,55] and **16a**[43] and tetrabenzylpyrophosphate[56] were prepared as described.

***N,N*-Diacetyl-1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose (3a).** To a stirred solution of α-$(AcO)_4$GlcNAc (0.5 g, 1.28 mmol)[57] in dry THF in an atmosphere of N_2 was added diisopropylethylamine (1.38 mL, 7.94 mmol) and freshly distilled acetyl chloride (0.456 mL, 6.42 mmol). Within 5 min, a white solid began to precipitate. After stirring for 2.5 days at room temperature, the solid was filtered and the solvent was evaporated in vacuo, leaving a brown oil (1.1 g). The oil was dissolved in 40 mL of EtOAc and washed with saturated $NaHCO_3$ (3 × 40 mL), water (40 mL), and saturated NaCl (40 mL). The organic extract was evaporated, leaving a brown oil (670 mg) which was purified by flash chromatography (hexanes/EtOAc 3:2−2:3). The resulting yellow oil crystallized upon standing and was triturated with anhydrous ether, giving the title compound as white needles (229 mg, 42%). mp 111−113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (d, 1H, J = 3.3 Hz), 6.10 (dd, 1H, J = 9.0, 11.4 Hz), 5.10 (dd, 1H, J = 9.0, 10.0 Hz), 4.68 (dd, 1H, J = 3.3, 11.4 Hz), 4.35 (dd, 1H, J = 4.0, 12.4 Hz), 4.23 (m, 1H), 4.09 (dd, 1H, J = 1.9, 12.4 Hz), 2.35 (s, 6H), 2.11−1.98 (m, 12H). ^{13}C NMR (75 MHz, $CHCl_3$): δ 173.73, 170.55, 169.71, 169.51, 169.18, 90.60, 70.10, 69.42, 68.93, 61.41, 57.47, 26.64, 20.92, 20.67, 20.56. FAB-MS *m*/*z* (rel intensity): 454.2 ($[M + Na]^+$ 100.0), 394.1 (44.8), 372.1 (48.5), 330.1 (75.9), 176.0 (70.4), 136.1 (90.1). FAB-HRMS calcd for $C_{18}H_{25}NO_{11}Na$ $[M + Na]^+$, 454.1325; obsd, 454.1318.

2,2,2-Trichloroethyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranose (3c). A mixture of **3d** and **3e** (1:4) (250 mg, 0.41 mmol) and 2,2,2-trichloroethanol (47 μL, 0.49 mmol) were dissolved in dry CH_2Cl_2 (2.5 mL), and the solution was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (300 μL, 2.36 mmol) was added dropwise over 2 min, and the reaction was allowed to warm to room temperature after 1.25 h. After 24 h, the reaction was diluted with CH_2Cl_2 (10 mL), extracted with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL), dried over $MgSO_4$, filtered, and evaporated, leaving a dark brown oil (340 mg). The oil was purified by flash chromatography ($CHCl_3$/EtOAc 60:1−5:1), giving the title compound as a white solid (40%, 117 mg). mp 212−214 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (dd, 1H, J = 9.3, 10.7 Hz), 5.59 (d, 1H, J = 8.5 Hz), 5.23 (dd, 1H, J = 9.3, 10.3 Hz), 4.43 (dd, 1H, J = 8.4, 10.7 Hz), 4.38 (d, 1H, J = 12.1 Hz), 4.35 (dd, 1H, J = 4.4, 12.2 Hz), 4.20 (dd, 1H, J = 2.4, 12.2 Hz), 4.12 (d, 1H, J = 12.1 Hz), 3.89 (ddd, 1H, J = 2.4, 4.4, 10.3 Hz), 2.14 (s, 3H), 2.05 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.62, 170.40, 169.34, 140.67, 129.94, 126.84, 98.52, 95.82, 80.43, 72.08, 70.20, 68.37, 61.59, 55.02, 20.75, 20.57, 20.51. The TCP C=O peak was presumably broad and not observed. EIMS *m*/*z* (rel intensity): 703.0 ($[M]^+$, 0.6), 393.0 (11.8), 326.9 (17.1), 43.4 (100.00). EI-HRMS calcd for $C_{22}H_{18}NO_{10}Cl_7$ $[M]^+$, 700.8750; obsd, 700.8779.

2,2,2-Trichloroethyl 5-Bromo-3,4,6-tri-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranose (4c). *N*-Bromosuccinimide (130 mg, 0.73 mmol) and **3c** (117 mg, 0.17 mmol) were suspended in CCl_4 (10 mL). The mixture was illuminated with a 150 W flood lamp placed ca. 0.25 in. from the flask, and the reaction gradually turned bright orange. After 1.5 h, the mixture was cooled on ice, the white solid was filtered off, and the filtrate was washed with water, saturated $NaHCO_3$ (10 mL), and saturated NaCl (10 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo, leaving a yellow oil (184 mg) which was purified by flash chromatography (hexanes/EtOAc 4:1−2:1), giving the title compound as a colorless oil (56 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.10 (d, 1H, J = 8.5 Hz), 6.06 (dd, 1H, J = 9.3, 10.5 Hz), 5.35 (d, 1H, J = 9.3 Hz), 4.57−4.53 (m, 2H), 4.44 (d, 1H, J = 12.2 Hz), 4.39 (d, 1H, J = 12.0 Hz), 4.10 (dd, 1H, J = 12.1 Hz), 2.17 (s, 3H), 2.10 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.02, 169.81, 168.99, 162.05, 140.79, 130.04, 126.76, 98.89 (1), 95.38, 95.38, 80.82 (2), 69.02 (1), 68.91 (1), 65.75 (2), 54.03 (1), 20.65 (3), 20.52 (3), 20.40 (3).

2,2,2-Trichloroethyl 5-Fluoro-3,4,6-tri-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-α-L-idopyranose (5c). To a stirred solution of **4c**

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in dry CH_3CN (1.0 mL) under an Ar atmosphere was added AgF (18 mg, 0.142 mmol). The flask was immediately covered with foil and stirred. After 5 h, the suspension was filtered through SiO_2/Celite, washing with EtOAc (30 mL). The filtrate was evaporated and then purified on a plug of SiO_2, eluting with $CHCl_3$/EtOAc (20:1), giving the title compound as an oil (28 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (dd, 1H, J = 5.1, 8.0 Hz), 5.72 (dd, 1H, J = 3.5, 10.0 Hz), 5.37 (dd, 1H, J = 3.5, 4.8 Hz), 4.88 (ddd, 1H, J = 2.0, 8.0, 10.0 Hz), 4.48−4.24 (m, 3H), 4.16 (d, 1H, J = 12.0 Hz), 2.20 (s, 3H), 2.15 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.18, 169.88, 168.74, 162.84, 140.76, 129.99, 126.86, 110.76 (d, J = 226 Hz), 96.74, 95.75, 79.80, 70.14 (d, J = 44 Hz), 68.56, 62.24 (d, J = 29 Hz), 54.39 (d, J = 162 Hz), 20.66, 20.61, 20.58. ^{19}F NMR (282 MHz, $CDCl_3$): δ −30.06 (m). FAB-MS m/z (rel intensity): 743.9 ([M + Na]$^+$, 100.00). FAB-HRMS calcd for $C_{22}H_{17}NO_{10}FNaCl_7$, 741.8554; obsd, 741.8545.

5-Bromo-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-α-D-glucopyranose (4d). To a stirred solution of **3d** (0.359 g, 0.58 mmol) in dry CCl_4 (35 mL) was added *N*-bromosuccinimide (0.457 g, 2.57 mmol). The mixture was illuminated with a 150 W flood lamp placed ca. 0.25 in. from the flask, and the reaction gradually turned bright orange. After 7 h, the orange suspension was cooled, the white solid was filtered off, and the filtrate was washed with water (50 mL), saturated $NaHCO_3$ (50 mL) (a disappearance of the orange color was observed), and saturated NaCl (50 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo, leaving an off-white foam (423 mg) which was purified by flash chromatography (hexanes/EtOAc 2:1), giving the title compound as a white powder (209 mg, 52%). mp 175 °C dec. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (dd, 1H, J = 9.6, 11.4 Hz), 6.39 (d, 1H, J = 4.1 Hz), 5.21 (d, 1H, J = 9.6, Hz), 4.85 (dd, 1H, J = 4.1, 11.7 Hz), 4.52 (d, 1H, J = 12.2 Hz), 4.33 (d, 1H, J = 12.2 Hz), 2.16−1.91 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.75, 169.39, 169.02, 168.46, 161.96, 140.95, 130.28, 126.58, 93.46, 90.34 (1), 70.18 (1), 66.47 (2), 64.91 (1), 52.36 (1), 21.20 (3), 20.61 (3), 20.53 (3), 20.53 (3). FAB-MS m/z (rel intensity): [M + Na]$^+$ 715.8. FAB-HRMS calcd for $C_{22}H_{18}NO_{11}NaCl_4Br$ [M + Na]$^+$, 713.8715; obsd, 713.8720.

5-Fluoro-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-L-idopyranose (5d). To a stirred solution of **4d** (50 mg, 0.72 mmol) in freshly distilled CH_3CN under a N_2 atmosphere was added AgF (21 mg, 0.146 mmol). The flask was immediately covered with foil, and the reaction was stirred for 39 h. The black/brown suspension was filtered through SiO_2/Celite, washing with EtOAc (10 mL). The yellow filtrate was washed with saturated $NaHCO_3$ (6 mL), water (6 mL), and saturated NaCl (6 mL). After drying over $MgSO_4$, filtering, and evaporating, the resulting oil (39 mg) was purified by preparative TLC ($CHCl_3$/EtOAc 10:1), giving a white solid (25 mg, 56%). mp 157−159.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.33 (dd, 1H, J = 0.7, 3.4 Hz), 6.27 (ddd, 1H, J = 1.1, 2.7, 9.8 Hz), 5.39 (dd, 1H, J = 2.7, 6.2 Hz), 5.10 (dd, 1H, J = 3.4, 9.7 Hz), 4.49 (dd, 1H, J = 12.3, 22.1 Hz), 4.22 (dd, 1H, J = 12.5, 12.5 Hz), 2.19−2.03 (m, 12H). ^{13}C NMR (75 MHz, $CHCl_3$): δ 169.84, 169.60, 169.22, 168.59, 162.73, 140.81, 130.16, 126.66, 110.22 (d, J = 223 Hz), 88.28, 69.97 (d, J = 44 Hz), 66.11, 62.44 (d, J = 27 Hz), 60.36, 21.02, 20.95, 20.60, 20.56. ^{19}F NMR (282 MHz, $CDCl_3$): δ −29.24 (ddd, J = 20.3, 12.7, 6.2 Hz). FAB-MS m/z (rel intensity): 656.0 ([M + Na]$^+$, 6.5), 329.1 (28.6), 289.1 (17.0), 176.0 (100.0). FAB-HRMS calcd for $C_{22}H_{18}NO_{11}FNaCl_4$ [M + Na]$^+$, 656.9516; obsd, 656.9519**.**

5-Fluoro-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-α-D-glucopyranose (6d). To a 0 °C solution of **5d** (25 mg, 0.039 mmol) in CH_2Cl_2 (0.5 mL) in an NMR tube were added 3 Å molecular sieves and BF_3·OEt_2 (3.0 μL, 0.023 mmol). The reaction was monitored by ^{19}F NMR over 4 h. Gradual disappearance of the starting material peak at −30.13 ppm and appearance of a peak at −48.76 ppm were observed. A number of other smaller peaks at −70 to −80 ppm were also observed (along with BF_3·OEt_2). After 4 h, the reaction was worked up by diluting with EtOAc, filtering, and washing the filtrate with saturated $NaHCO_3$ (5 mL) and saturated NaCl (5 mL). The organic extract was dried over $MgSO_4$, filtered, and evaporated, leaving a yellow oil (15 mg) which was purified by preparative TLC ($CHCl_3$/EtOAc 10:1). The R_f 0.41 band was removed, and the product was extracted with 4% MeOH in CH_2Cl_2 and evaporated, leaving the product as a white solid (5 mg, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (dd, 1H, J = 9.7, 11.6 Hz), 6.31 (d, 1H, J = 3.7 Hz), 5.31 (dd, 1H, J = 9.7, 22.4 Hz), 4.83 (dd, 1H, J = 3.7, 11.6 Hz), 4.36 (dd, 1H, J = 5.5, 12.0 Hz), 4.03 (dd, 1H, J = 3.6, 12.0 Hz), 2.15 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.77, 169.74, 169.56, 168.75, 162.51, 140.95, 130.28, 126.57, 110.54 (d, J = 235 Hz), 89.71, 69.17 (d, J = 23 Hz), 63.52, 61.87 (d, J = 40 Hz), 52.47, 21.01, 20.60, 20.47, 20.47. ^{19}F NMR (282 MHz, $CDCl_3$, ^{1}H decoupled): δ −47.86. CI-MS (NH_3) m/z (rel intensity): 651.6 (M + NH_4^+, 100.00), 614.5 (38.59), 554.5 (31.53). CI-HRMS (NH_3) calcd for $C_{22}H_{22}N_2O_{11}FCl_4$ [M + NH_4]$^+$, 648.9961; obsd, 648.9977.

5-Bromo-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranose (4e). Compound **3e** (1.0 g, 1.63 mmol) and *N*-bromosuccinimide (1.27 g, 7.15 mmol) were suspended in dry CCl_4 (100 mL) in a flask flushed with Ar and fitted with a condenser and drying tube ($CaCl_2$). The mixture was illuminated with a 150 W flood lamp placed at a distance of 0.5 in. from the flask. Over the first 0.5 h, the reaction mixture became deep orange. After 9 h, the reaction was cooled on ice and filtered. The filtrate was washed with sat. $NaHCO_3$ (120 mL) and sat. NaCl (120 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo, leaving a white foam/oil (2.23 g). The oil was purified by flash chromatography, eluting with $CHCl_3$/EtOAc (400:1−12.5:1), giving the title compound as a foam (395 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, 1H, J = 9.1 Hz), 6.06 (dd, 1H, J = 9.3, 10.4 Hz), 5.35 (d, 1H, J = 9.3 Hz), 4.65 (d, 1H, J = 12.3 Hz), 4.57 (dd, 1H, J = 9.2, 10.3 Hz), 4.35 (d, 1H, J = 12.3 Hz), 2.16 (s, 3H), 2.13 (s, 3H), 2.05 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (75 MHz, $CHCl_3$): δ 170.13, 169.75, 169.01, 168.04, 162.54, 140.86, 130.23, 126.75, 94.75, 89.51 (1), 69.32 (1), 68.59 (1), 65.70 (2), 53.34 (1), 20.65 (3), 20.61 (3), 20.49 (3), 20.31 (3).

5-Fluoro-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-L-idopyranose (5e). Compound **4e** (396 mg, 0.57 mmol) was dissolved in dry CH_3CN (10 mL) under an Ar atmosphere (the solution remained slightly cloudy). AgF (146 mg, 1.15 mmol) was added, and the flask was immediately covered with foil. After 43 h, the reaction was filtered twice through a Celite/SiO_2 plug, eluting with 30:1 $CHCl_3$/EtOAc. The filtrate was extracted with sat. $NaHCO_3$, H_2O, and sat. NaCl. The organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was purified by flash chromatography (hexanes/EtOAc 3:1), giving the title compound as a light yellow film (155 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (dd, 1H, J = 8.2, 4.4 Hz), 5.69 (ddd, 1H, J = 3.5, 6.1, 9.6 Hz), 5.35 (dd, 1H, J = 3.5, 5.1 Hz), 4.51 (ddd, 1H, J = 2.3, 8.2, 9.6 Hz), 4.47−4.25 (m, 2H), 2.20 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.14, 169.70, 169.02, 168.93, 162.69, 140.85, 130.20, 126.77, 111.09 (d, J = 228 Hz), 88.29 (1), 70.17 (d, J = 45 Hz) (1), 68.59 (1), 62.17 (d, J = 28 Hz) (2), 52.44 (d, J = 3.0 Hz) (1), 20.86 (3), 20.63 (3), 20.53 (3), 20.49 (3). ^{19}F NMR (282 MHz, $CDCl_3$): δ −30.94 (m). FAB-MS m/z (rel intensity): 656.0 ([M + Na]$^+$, 37.8), 513.9 (100.0), 411.9 (54.7), 107.0 (100.0). FAB-HRMS calcd for $C_{22}H_{18}NO_{11}FNaCl_4$ [M + Na]$^+$, 653.9516; obsd, 653.9540.

5-Bromo-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (4f). Compound **3f** (300 mg, 0.628 mmol) and *N*-bromosuccinimide (492 mg, 2.76 mmol) were suspended in dry CCl_4 (30 mL). The mixture was illuminated with a 150 W flood lamp placed at a distance of 0.5 in. from the flask with a piece of filter paper positioned to reflect some of the incident light. The mixture gradually turned bright orange. After 3.5 h, the reaction was cooled on ice, and the insoluble succinimide was filtered and washed with cold CCl_4. The filtrate (~40 mL) was washed with sat. $NaHCO_3$ (40 mL), H_2O (40

mL), and sat. NaCl (40 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo, leaving a white oil (480 mg) which was purified by flash chromatography (hexanes/EtOAc 4:1−1:1), giving the title compound as a white solid (229 mg, 66%). mp 158 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (m, 2H), 7.72 (m, 2H), 6.94 (d, 1H, J = 9.2 Hz), 6.09 (dd, 1H, J = 9.4, 10.5 Hz), 5.27 (d, 1H, J = 9.4 Hz), 4.58 (d, 1H, J = 12.3 Hz), 4.51 (dd, 1H, J = 9.3, 10.5 Hz), 4.27 (d, 1H, J = 12.3 Hz), 2.07 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.74, 169.61, 169.13, 168.03, 167.14, 134.57 (1), 131.14, 123.85 (1), 95.16, 89.74 (1), 69.09 (1), 68.96 (1), 65.79 (2), 52.62 (1), 20.63 (3), 20.63 (3), 20.55 (3), 20.28 (3). FAB-MS m/z (rel intensity): 580.1 ([M + H]$^+$, 6.5), 289.1 (42.4), 106.1 (98.5), 89.0 (96.6), 77.0 (100.0). FAB-HRMS calcd for $C_{22}H_{22}NO_{11}NaBr$ [M + Na]$^+$, 578.0274; obsd, 578.0261.

5-Fluoro-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α-L-idopyranose (5f). Compound **4f** (1.56 g, 2.8 mmol) was dissolved in freshly distilled CH_3CN (20 mL) under a N_2 atmosphere. AgF (0.685 g, 5.5 mmol) was added, and the flask was immediately covered with foil. After 2.5 h, the reaction mixture was filtered through SiO_2/Celite and washed with EtOAc (∼80 mL). The filtrate was washed with sat. $NaHCO_3$ (100 mL), H_2O (100 mL), and sat. NaCl (100 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo, leaving a brown oil (1.33 g) which was purified by flash chromatography (hexanes/EtOAc 4:1−3:2), giving the title compound as a white solid (720 mg, 52%). mp 129 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (m, 2H), 7.71 (m, 2H), 6.72 (dd, 1H, J = 4.1, 8.3 Hz), 5.72 (dd, 1H, J = 3.9, 9.9 Hz), 5.27 (dd, 1H, J = 3.9, 6.1 Hz), 4.51 (ddd, 1H, J = 2.3, 8.3, 9.9 Hz), 4.38−4.20 (m, 2H), 2.10 (s, 3H), 2.05 (s, 3H), 1.97 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.67, 168.98, 168.87, 167.22, 134.49, 131.11, 123.74, 111.20 (d, J = 229 Hz), 88.57, 70.70 (d, J = 44.4 Hz), 68.53, 62.29 (d, J = 27.8 Hz), 51.29, 20.75, 20.54, 20.45, 20.36. On the basis of peak intensity, two of the acetate carbonyl carbons were indistinguishable. ^{19}F NMR (282 MHz, $CDCl_3$): δ −30.80 (m). FAB-MS m/z (rel intensity): 518.1 ([M + Na]$^+$, 29.0), 376.1 (15.9), 289.1 (45.7), 107.0 (100.0), 89.0 (94.1), 77.0 (96.5). FAB-HRMS calcd for $C_{22}H_{22}NO_{11}FNa$ [M + Na]$^+$, 518.1075; obsd, 518.1074.

5-Fluoro-1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (6f). Compound **5f** (200 mg, 0.40 mmol) was dissolved in freshly distilled CH_2Cl_2 (4 mL). Molecular sieves (4 Å) were added, and the solution was cooled to 0 °C. BF_3·OEt_2 (4 μL, 0.036 mmol) was added, and the flask was removed from the ice bath. The reaction was followed by ^{19}F NMR. After all of the starting material had been consumed (60 min), the solution was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ (10 mL), H_2O (10 mL), and sat. NaCl (10 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo, leaving an oil (230 mg) which was dissolved in $CHCl_3$ and purified by flash chromatography (hexanes/EtOAc 1:1), giving the title compound as an off-white foam (149 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (m, 2H), 7.79 (m, 2H), 6.94 (d, 1H, J = 9.1 Hz), 6.12 (dd, 1H, J = 9.7, 10.7 Hz), 5.40 (dd, 1H, J = 9.7, 23.0 Hz), 4.51 (dd, 1H, J = 9.1, 10.7 Hz), 4.45 (dd, 1H, J = 4.4, 12.0 Hz), 4.16 (dd, 1H, J = 4.0, 12.0 Hz), 2.18 (s, 3H), 2.14 (s, 3H), 1.97 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.64, 169.50, 169.32, 168.02, 167.03, 134.51, 130.97, 123.75, 109.49 (d, J = 230 Hz), 86.66 (d, J = 4.9 Hz), 68.37, 67.14, 61.54 (d, J = 37.7 Hz), 52.73, 20.52, 20.44, 20.32, 20.16. ^{19}F NMR (282 MHz, $CDCl_3$): δ −55.96 (ddd, J = 4.5, 4.5, 22.6 Hz). FAB-MS m/z (rel intensity): 518.1 (M + Na$^+$, 100.00), 476.3 (54.43), 436.3 (35.83), 376.2 (88.85), 274.2 (31.93), 272.2 (25.18), 254.2 (29.79), 226.2 (73.66), 214.2 (20.80). FAB-HRMS calcd for $C_{22}H_{22}N_2O_{11}FNa$ [M + Na]$^+$, 518.1075; obsd, 518.1098.

Octyl 4-*O*-Benzoyl-2,6-dideoxy-6-phenylseleno-2-phthalimido-β-D-glucopyranoside (8). *N*-Bromosuccinimide (433 mg, 2.43 mmol), barium carbonate (1.31 g, 6.63 mmol), and compound **7** (1.13 g, 2.21 mmol) were suspended in CCl_4 (56 mL) under an Ar atmosphere. The flask was fitted with a drying tube ($CaCl_2$), and the suspension was heated to reflux temperature. As the reaction progressed, the solution turned deep orange; the disappearance of color signified termination of the reaction. After 75 min, the colorless suspension was cooled and filtered. The solid was washed with $CHCl_3$ (85 mL), and the filtrate was evaporated, leaving a white powder (1.89 g) which was dissolved in $CHCl_3$ (60 mL) and washed with H_2O (3 × 100 mL) and sat. $NaCHO_3$ (60 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, leaving the 6-bromo, 4-*O*-benzoyl compound as a white powder sufficiently pure for further transformations (1.25 g, 96% crude recovery). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06−8.03 (m, 2H), 7.86−7.83 (m, 2H), 7.73−7.70 (m, 2H), 7.62−7.58 (m, 1H), 7.48−7.43 (m, 2H), 5.32 (d, 1H, J = 8.4 Hz), 5.15 (dd, 1H, J = 9.1, 9.7 Hz), 4.62 (dd, 1H, J = 9.1, 10.8 Hz), 4.31 (dd, 1H, J = 8.4, 10.8 Hz), 3.99 (ddd, 1H, J = 2.6, 7.4, 9.7 Hz), 3.88 (ddd, 1H, J = 6.3, 6.3, 9.8 Hz), 3.60 (dd, 1H, J = 2.6, 11.2 Hz), 3.55−3.45 (m, 2H), 1.49−1.38 (m, 2H), 1.25−1.00 (m, 10H), 0.84−0.80 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.26, 166.41, 134.14, 133.77, 131.59, 129.93, 128.84, 128.58, 123.46, 98.24, 75.39, 73.47, 70.29, 70.07, 57.16, 31.63, 31.40, 29.22, 29.10, 29.10, 25.77, 22.57, 14.03. In addition, ^{1}H and ^{13}C NMR spectra indicated the presence of succinimide as a contaminant.

To a stirred solution of crude product (1.25 g, 2.12 mmol) in freshly distilled THF (5.4 mL) under an Ar atmosphere were added phenylselenol (700 μL, 6.64 mmol) and triethylamine (1.87 mL, 13.3 mmol). A voluminous white precipitate formed, and freshly distilled THF (20 mL) was added to permit stirring. The yellow suspension was heated to reflux temperature. After 12 h, the brown suspension was diluted with CH_2Cl_2 (200 mL) and washed with sat. $NaHCO_3$ (200 mL). The aqueous layer was back-extracted with CH_2Cl_2 (100 mL), and the combined organic layers were washed with sat. NaCl (75 mL), dried over $MgSO_4$, filtered, and evaporated, leaving a yellow powder (2.13 g). The crude solid was purified by flash chromatography (hexanes/EtOAc 2:1), giving the title compound as a white powder (610 mg) together with mixed fractions which were further purified by flash chromatography (hexanes/EtOAc 9:4), giving an additional 495 mg of the title compound. Total yield: 1.11 g, 79% over two steps. mp 160−164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04−7.97 (m, 2H), 7.86−7.84 (m, 2H), 7.75−7.70 (m, 2H), 7.61−7.57 (m, 1H) 7.53−7.42 (m, 4H), 7.22−7.19 (m, 3H), 5.26 (d, 1H, J = 8.4 Hz), 5.12 (dd, 1H, J = 9.2, 9.7 Hz), 4.60−4.52 (m, 1H), 4.29 (dd, 1H, J = 8.4, 10.8 Hz), 3.98 (ddd, 1H, J = 3.4, 7.8, 9.7 Hz), 3.77 (ddd, 1H, J = 6.2, 6.2, 9.7 Hz), 3.42 (ddd, 1H, J = 6.6, 6.6, 9.6 Hz), 3.22−3.10 (m, 2H), 2.71 (d, 1H, J = 6.6 Hz), 1.43−1.42 (m, 2H), 1.19−1.01 (m, 10H), 0.82 (t, 3H, J = 7.0 Hz).^{13}C NMR (75 MHz, $CDCl_3$): δ 168.23, 166.65, 134.09, 133.67, 132.50, 131.67, 130.48, 129.91, 129.05, 128.96, 128.52, 126.95, 123.43, 98.18, 76.92, 74.00, 70.47, 69.84, 57.31, 31.66, 29.48, 29.24, 29.14, 29.14, 25.81, 22.59, 14.06. EIMS m/z (rel intensity): 665.2 (M$^+$, 3.3), 228.0 (15.1), 189.0 (10.9), 105.0 (100.0). EI-HRMS calcd for $C_{35}H_{39}NO_7Se$ [M]$^+$, 665.1891; obsd, 665.1897.

Octyl 3,4-Di-*O*-acetyl-2,6-dideoxy-2-acetamido-6-phenylseleno-β-D-glucopyranoside (9). To a suspension of **8** (50 mg, 0.078 mmol) in EtOH (1.8 mL) in a sealed tube was added hydrazine hydrate (200 μL, 4.1 mmol). The tube was placed under vacuum and sealed, and the suspension was heated to 80 °C. Upon heating, the suspension became clear, and as the reaction progressed, a white solid precipitated. After 15.5 h, the reaction mixture was cooled and evaporated under high vacuum, leaving a white solid (57 mg). Pyridine (0.50 mL) and acetic anhydride (0.50 mL, 5.2 mmol) were added. After 26 h, DMAP (8 mg, 0.065 mmol) was added. After 44 h, the reaction was diluted with CH_2Cl_2 (5 mL) and washed with cold HCl (1.0 M, 3 × 5 mL) and sat. $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, leaving an oil (105 mg) which was purified by preparative TLC (hexanes/EtOAc 1:2), giving the title compound as a white solid (35 mg, 80% over two steps). For larger scale reactions, the product could be purified by crystallization from EtOH/H_2O. In each case, similar yields were obtained. mp 116−121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.48 (m, 2H), 7.27−7.24 (m, 3H), 5.53

(d, J = 8.8 Hz), 5.26 (dd, 1H, J = 9.2, 10.6 Hz), 4.96 (dd, 1H, J = 9.2, 10.5 Hz), 4.62 (d, 1H, J = 8.3 Hz), 3.84 (ddd, 1H, J = 8.3, 8.8, 10.5 Hz), 3.78−3.69 (m, 2H), 3.42 (ddd, 1H, J = 6.9, 6.9, 9.6 Hz), 3.06−3.03 (m, 2H), 2.03 (s, 3H), 2.01 (s, 3H), 1.94 (s, 3H), 1.54−1.52 (m, 2H), 1.26 (m, 10H), 0.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.92, 170.09, 169.63, 132.44 (1), 130.42, 129.04 (1), 126.98 (1), 100.51 (1), 73.68 (1), 72.60 (1), 72.30 (1), 69.77 (2), 54.93 (1), 31.78 (2), 29.37 (2), 29.27 (2), 29.25 (2), 29.17 (2), 25.84 (2), 23.30 (3), 22.62 (2), 20.73 (3), 20.71 (3), 14.08 (3). FAB-MS m/z (rel intensity): 580.2 ([M + Na]$^+$, 72.8), 558.2 (53.2) 428.1 (100.00). FAB-HRMS calcd for $C_{26}H_{39}NO_7NaSe$ [M + Na]$^+$, 580.1789; obsd, 580.1785.

Octyl 3,4-Di-*O*-acetyl-2,6-dideoxy-5,6-didehydro-2-acetamido-β-D-glucopyranoside (10). To a stirred suspension of **9** (195 mg, 0.350 mmol) in MeOH/H_2O (6:1, 10 mL) at room temperature were added $NaHCO_3$ (32 mg, 0.385 mmol) and $NaIO_4$ (97 mg, 0.455 mmol). As the reaction progressed, a white precipitate formed. After 30 min, the MeOH was evaporated and the resulting aqueous suspension was partitioned between H_2O (75 mL) and CH_2Cl_2 (75 mL). The aqueous layer was re-extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and evaporated, leaving the diastereomeric selenoxides (3:1 ratio) as a white powder (193 mg, 96%) which was used directly in the following step without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76−7.71 (m, 2H), 7.58−7.53 (m), 5.37−5.34 (m), 5.06−4.98 (m), 4.83 (d, J = 8.5 Hz), 4.60 (d, J = 8.4 Hz), 4.26−4.12 (m), 3.98−3.90 (m), 3.66−3.55 (m), 3.30 (ddd), 3.16−3.02 (m), 2.06 (s), 2.04 (s), 2.03 (s), 2.02 (s), 1.98 (s), 1.82 (s), 1.63−1.61 (m), 1.25 (m), 0.88−0.83 (m).

A stirred cloudy suspension of the diastereomeric selenoxides (193 mg, 0.337 mmol) in dry dihydropyran (6.5 mL) was heated to reflux temperature. After 40 min, the yellow solution was cooled and diluted with CH_2Cl_2 (65 mL). This solution was washed with H_2O (150 mL), sat. $NaHCO_3$ (65 mL), and sat. NaCl (65 mL). The organic extracts were dried over Na_2SO_4, filtered, and evaporated. The resulting yellow residue (500 mg) was purified by flash chromatography (hexanes/EtOAc 2:3), giving the title compound as a white solid (126 mg, 90% over two steps). mp 133−136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (d, 1H, J = 8.8 Hz), 5.63 (d, 1H, J = 7.4 Hz), 4.96 (dd, 1H, J = 6.0, 7.4 Hz), 4.76−4.75 (m, 2H), 4.55 (dd, 1H, J = 1.3, 1.3 Hz), 4.22 (ddd, 1H, J = 4.0, 6.0, 8.8 Hz), 3.81 (ddd, 1H, J = 6.6, 6.6, 9.4 Hz), 3.42 (ddd, 1H, J = 6.4, 6.4, 9.4 Hz), 2.13 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H), 1.60−1.56 (m, 2H), 1.36−1.26 (m, 10H), 0.88 (t, 3H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.30, 169.69, 168.97, 150.70, 101.12 (1), 96.52 (2), 71.37 (1), 69.03 (2), 68.61 (1), 52.50 (1), 31.70 (2), 29.26 (2), 29.18 (2), 29.13 (2), 25.84 (2), 23.09 (3), 22.53 (2), 20.73 (3), 20.68 (3), 13.99 (3). CI-MS (NH_3) m/z (rel intensity): 400.3 ([M + H]$^+$, 100.00), 340.3 (22.94), 270.2 (11.42), 139.1 (11.79). CI-HRMS (NH_3) calcd for $C_{20}H_{34}NO_7$ [M + H]$^+$, 400.2335; obsd, 400.2329.

Octyl 5-Fluoro-3,4,6-tri-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucopyranoside (12a). To a stirred 0 °C solution of **10** (202 mg, 0.506 mmol) in freshly distilled CH_2Cl_2 (3.5 mL) was added excess dimethyldioxirane in acetone (7.0 mL). After 4.5 h, the solvent was evaporated, leaving **11** as a white powder (212 mg, 95%). The product contained only one of the two possible diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73 (d, 1H, J = 9.5 Hz), 5.63 (d, 1H, J = 9.6 Hz), 5.28 (dd, 1H, J = 9.6, 9.6 Hz), 4.77 (d, 1H, J = 7.9 Hz), 4.33 (ddd, 1H, J = 7.9, 9.5, 9.6 Hz), 3.77 (ddd, 1H, J = 6.4, 6.4, 9.6 Hz), 3.42 (ddd, 1H, J = 6.6, 6.6, 9.6 Hz), 3.06 (d, 1H, J = 4.0 Hz), 2.73 (d, 1H, J = 4.0 Hz), 2.06 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.55−1.52 (m, 2H), 1.26 (m, 10H), 0.87 (t, 3H, J = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.79, 169.83, 169.54, 99.87 (1), 79.41, 70.75 (1), 70.03 (2), 66.59 (1), 53.43 (1), 49.54 (2), 31.77 (2), 29.31 (2), 29.23 (2), 25.78 (2), 23.23 (3), 22.61 (2), 20.65 (3), 20.49 (3), 14.05 (3). On the basis of peak intensity, two carbons of the octyl side chain (~29 ppm) were indistinguishable.

To a stirred −78 °C solution of the epoxide **11** (212 mg, 0.510 mmol) (previously dried under vacuum for 45 min) in CH_2Cl_2 (7 mL) under an atmosphere of Ar was added dropwise HF·pyridine (150 μL). After 0.5 h, the solution was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (30 mL) and sat. $NaHCO_3$ (30 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated, leaving a white powder (223 mg). The white powder was dissolved in pyridine (1.5 mL), and acetic anhydride (1.5 mL, 15.8 mmol) was added. After 2 h, the reaction was diluted with CH_2Cl_2 (30 mL) and washed with sat. $NaHCO_3$ (3 × 30 mL) and sat. NaCl (30 mL). The organic layer was dried over Na_2SO_4, filtered through a plug of SiO_2, and evaporated, leaving a white powder (230 mg). The white powder was purified by flash chromatography (hexanes/EtOAc 1:2), giving the title compound as a white powder (174 mg, 72%) along with 25 mg (10%) of the C-5 epimer.

(a) D-Gluco Isomer, 12a (Major Product). mp 136−138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.61 (d, J = 9.4 Hz), 5.38 (dd, 1H, J = 9.7, 22.7 Hz), 5.32 (ddd, 1H, J = 9.6, 9.7 Hz), 4.94 (d, 1H, J = 7.9 Hz), 4.33 (dd, 1H, J = 6.9, 11.8 Hz), 4.27 (ddd, 1H, J = 7.9, 9.4, 9.6 Hz), 4.02 (dd, 1H, J = 4.9, 11.8 Hz), 3.86 (ddd, 1H, J = 6.4, 6.4, 9.5 Hz), 3.49 (ddd, 1H, J = 6.8, 6.8, 9.5 Hz), 2.10 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.96 (s, 3H), 1.58−1.57 (m, 2H), 1.30−1.26 (m, 10H), 0.88 (t, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.87, 169.90, 169.82, 169.25, 109.64 (d, J = 228 Hz), 98.54 (d, J = 4 Hz), 70.21, 69.62, 68.36 (d, J = 25 Hz), 62.09 (d, J = 39 Hz), 53.25, 31.77, 29.28, 29.24, 25.79, 23.21, 22.62, 20.62, 20.58, 20.46, 14.06. On the basis of peak intensity, two carbons of the octyl side chain (~29 ppm) were indistinguishable. ^{19}F NMR (282 MHz $CDCl_3$): δ −52.46 (ddd, J = 5.1, 5.1, 21.7 Hz). FAB-MS m/z (rel intensity): 500.0 ([M + Na]$^+$, 100.0), 478.1 (26.2), 458.1 (56.6), 180.0 (64.9), 175.9 (74.9). FAB-HRMS calcd for $C_{22}H_{36}NO_9FNa$ [M + Na]$^+$, 500.2272; obsd, 500.2274.

(b) L-Ido Isomer, 12b (Minor Product). mp 94−96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.09 (d, J = 8.4 Hz), 5.80 (dd, 1H, J = 8.4, 12.7 Hz), 5.07 (dd, 1H, J = 5.5, 8.4 Hz), 4.91 (dd, 1H, J = 1.3, 2.3 Hz), 4.54 (dd, 1H, J = 11.9, 12.1 Hz), 4.30 (m, 1H), 4.10 (dd, 1H, J = 10.4, 11.8 Hz), 3.86 (ddd, 1H, J = 6.8, 6.8, 9.2 Hz), 3.46 (ddd, 1H, J = 6.5, 6.5, 9.2 Hz), 2.16 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.60−1.58 (m, 2H), 1.27−1.25 (m, 10H), 0.88 (t, 3H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.49, 170.08, 169.69, 168.59, 110.03 (d, J = 226 Hz), 101.39 (1), 71.07 (d, J = 7 Hz, 1), 70.12 (d, J = 37 Hz, 1), 69.23 (2), 63.46 (d, J = 39 Hz, 2), 53.94 (1), 31.79 (2), 29.27 (2), 29.18 (2), 29.18 (2), 25.85 (2), 23.18 (3), 22.62 (2), 20.74 (3), 20.74 (3), 20.56 (3), 14.07 (3). ^{19}F NMR (282 MHz $CDCl_3$): δ −26.35 (ddd, J = 12.1, 12.1, 12.1 Hz). FAB-MS m/z (rel intensity): 500.0 ([M + Na]$^+$, 88.4), 478.3 (100.00), 458.3 (39.9), 180.1 (37.6), 176.0 (74.3). FAB-HRMS calcd for $C_{22}H_{36}NO_9FNa$ [M + Na]$^+$, 500.2272; obsd, 500.2281

Octyl 5-Fluoro-2-deoxy-2-acetamido-β-D-glucopyranoside (2). NH_3 was bubbled through a stirred methanolic (2.0 mL) solution of **12a** (50 mg, 0.105 mmol) cooled to ca. −10 °C. After 10 min, the flask was sealed and allowed to warm to ambient temperature. After 70 min, the solvent and NH_3 were removed with a stream of nitrogen. The resulting white solid (41 mg) was purified by flash chromatography (EtOAc/MeOH 5:1), giving the title compound as a white powder (30 mg, 83%). mp 95−96 °C. ^{1}H NMR (500 MHz, CD_3OD): δ 4.82 (m, H-1), 3.86 (ddd, 1H, J = 6.1, 6.1, 9.6 Hz), 3.79−3.76 (m, 3H), 3.65 (m, 1H), 3.63 (dd, 1H, J = 4.6, 11.8 Hz), 3.46 (ddd, 1H, J = 6.7, 6.7, 9.5 Hz), 1.98 (s, 3H) 1.55−1.54 (m, 2H), 1.36−1.29 (m, 10H), 0.90 (t, 3H, J = 6.2 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 173.58, 113.57 (d, J = 224 Hz), 99.94 (d, J = 4 Hz) (1), 72.09 (d, J = 26 Hz) (1), 71.60 (1), 70.92 (2), 63.11 (d, J = 34 Hz) (2), 56.72 (1), 33.01 (2), 30.57 (2), 30.47 (2), 27.08 (2), 23.73 (2), 22.96 (3), 14.43 (3). On the basis of peak intensity, two carbons (~30 ppm) were indistinguishable. ^{19}F NMR (282 MHz CD_3OD): δ −61.64 (m). CI-MS (NH_3) m/z (rel intensity): 352.2 ([M + H]$^+$, 3.18), 332.2 (64.40), 314.4 (26.06), 272.2

(18.89), 242.2 (68.23), 202.1 (100.00), 184.1 (30.47), 102.01 (46.05). CI-HRMS (NH_3) calcd for $C_{16}H_{31}NO_6F$ $[M + H]^+$, 352.2135; obsd, 352.2127.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (14). Under an atmosphere of Ar, ethylenediamine (840 μL, 12.6 mmol) and acetic acid (840 μL, 14.7 mmol) were added to THF (250 mL). To this suspension was added **13** (5.00 g, 10.4 mmol). After 6 h, the suspension was diluted with water (100 mL) and was extracted with CH_2Cl_2 (1.0 L). The organic layer was washed with 0.1 M HCl (1.0 L), sat. $NaHCO_3$ (1.0 L), and sat. NaCl (1.0 L). The organic layer was dried over $MgSO_4$, filtered, and evaporated, leaving a white solid which was purified through a short column of SiO_2 eluting with (hexanes/EtOAc 1:1), giving the product as a white powder (4.41 g, 97%), α/β 10:1. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88−7.86 (m, 2H), 7.76−7.73 (m, 2H), 5.87 (dd, 1H, J = 9.1, 10.8 Hz), 5.64 (dd, 1H, J = 7.3, 8.3 Hz), 5.18 (dd, 1H, J = 9.1, 10.1 Hz), 4.36−4.18 (m, 3H), 3.94 (ddd, 1H, J = 2.2, 4.7, 10.1 Hz), 3.16 (d, 1H, J = 7.3 Hz), 2.13 (s, 3H), 2.05 (s, 3H), 1.88 (s, 3H). The literature provides ^{1}H NMR spectral data for this compound but only for the carbohydrate protons.[58]

***tert*-Butyldimethylsilyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (15).** To a stirred 0 °C solution of **14** (846 mg, 1.94 mmol) in dry dimethylformamide (DMF) (4 mL) was added imidazole (264 mg, 3.89 mmol). After stirring for 10 min, TBDMSCl (381 mg, 2.53 mmol) was added. The solution was gradually warmed to room temperature (RT) over 2 h. After 45 h, sat. $NaHCO_3$ (0.5 mL) was added to the light yellow solution. Following stirring for 10 min, most of the solvent was removed in vacuo. The resulting oily solid was equilibrated between $CHCl_3$ (20 mL) and sat. $NaHCO_3$ (200 mL). The organic layer was drained and the aqueous layer was extracted with $CHCl_3$ (2 × 100 mL). The combined organic layers were washed with sat. NaCl (200 mL), dried over $MgSO_4$, filtered, and evaporated, leaving an oil (1.1 g) which was purified by flash chromatography (hexanes/EtOAc 1:1), giving the title compound as a white powder, 881 mg (82%). mp 139−140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88−7.84 (m, 2H), 7.76−7.73 (m, 2H), 5.85 (dd, 1H, J = 9.0, 10.8 Hz), 5.56 (d, 1H, J = 8.0 Hz), 5.13 (dd, 1H, J = 9.0, 10.1 Hz), 4.30−4.24 (m, 2H), 4.16 (dd, 1H, J = 2.4, 12.0 Hz), 3.89 (ddd, 1H, J = 2.4, 4.8, 10.1 Hz), 2.10 (s, 3H), 2.04 (s, 3H), 1.87 (s, 3H), 0.69 (s, 9H), 0.06 (s, 3H), −0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.66, 170.17, 169.57, 167.91 (broad), 134.26 (1), 131.34, 123.46 (1), 93.16 (1), 71.80 (1), 70.26 (1), 69.47 (1), 62.42 (2), 56.68 (1), 25.25 (3), 20.73 (3), 20.65 (3), 20.51 (3), 17.51, −4.38 (3), −5.58 (3).

***tert*-Butyldimethylsilyl 4,6-*O*-Benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (16b).** To a stirred solution of **15** (3.67 g, 6.68 mmol) in dry MeOH (30 mL) under an atmosphere of Ar was added 1.0 M NaOMe (625 μL, 0.625 mmol, prepared by adding Na (23 mg) to MeOH (1.0 mL) under Ar). After stirring at RT for 2.5 h, DOWEX 50WX8-100 (H^+ form) (945 mg) was added, and the suspension was stirred gently for 105 min. The resin was removed by filtration, and the filtrate was evaporated and then coevaporated with pentane, leaving a white powder (2.96 g). The powder was suspended in dry CH_3CN (58 mL) under an Ar atmosphere, and benzaldehyde dimethyl acetal (1.6 mL, 11.6 mmol) and $TsOH \cdot H_2O$ (13 mg, 0.068 mmol) were added. After 11 h, the pink solution was placed under a gentle vacuum. After 13.5 h total reaction time, K_2CO_3 (378 mg, 2.73 mmol) was added and the mixture was stirred for 0.5 h. The mixture was filtered and evaporated, leaving a white solid/oil (4.24 g) which was purified by flash chromatography (hexanes/EtOAc 3:1), giving the title compound as a white foam (3.03 g, 89% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84−7.80 (m, 2H), 7.72−7.67 (m, 2H), 7.52−4.47 (m, 2H), 7.39−7.35 (m, 3H), 5.56 (s, 1H), 5.45 (d, 1H, J = 8.0 Hz), 4.64 (ddd, 1H, J = 3.4, 8.5, 11.0 Hz), 4.32 (dd, 1H, J = 3.4, 9.8 Hz), 4.19 (dd, 1H, J = 8.0, 10.7 Hz), 3.86−3.79 (m, 1H), 3.63−3.56 (m, 2H), 2.77 (d, 1H, J = 3.6 Hz), 0.69 (s, 9H), 0.04 (m, 3H), −0.09 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.16, 136.98, 134.07 (1), 131.53, 129.28 (1), 128.32 (1), 126.30 (1), 123.29 (1), 101.87 (1), 93.83 (1), 82.28 (1), 68.65 (2), 68.22 (1), 66.14 (1), 58.68 (1), 25.20 (3), 17.43, −4.32 (3), −5.66 (3). FAB-MS m/z (rel intensity): 534.3 ($[M + Na]^+$, 35.4), 454.2 (63.5), 380.1 (66.0), 274.1 (32.8), 256.0 (37.7), 246.0 (42.8), 136.0 (100.00), 105.0 (90.9). FAB-HRMS calcd for $C_{27}H_{33}NO_7NaSi$ $[M + Na]^+$, 534.1924; obsd, 534.1946.

***p*-Methoxyphenyl 4-*O*-Benzoyl-2,6-dideoxy-6-bromo-2-phthalimido-β-D-glucopyranose (17a).** Compound **16a** (4.09 g, 8.12 mmol), NBS (1.59 g, 8.94 mmol), and $BaCO_3$ (4.81 g, 24.36 mmol) were suspended in dry CCl_4 (200 mL) in a flask fitted with a reflux condenser and drying tube ($CaCl_2$). The colorless suspension was heated to reflux temperature and turned orange after ∼2 min. After 50 min, additional NBS (60 mg, 0.34 mmol) was added. After 60 min total reaction time, the reaction mixture was cooled on ice and filtered. The solid was washed with $CHCl_3$, and the filtrate was evaporated, leaving a solid (25 g). The solid was dissolved in $CHCl_3$ (400 mL), and the resulting solution was washed with H_2O (3 × 400 mL) and sat. NaCl (400 mL). The organic layer was evaporated in vacuo, giving a white solid (7.69 g) which was purified by flash chromatography (EtOAc/toluene 1:4.5), giving the title compound as a white powder (4.43 g, 94%). mp 237−240 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07−8.03 (m, 2H), 7.87−7.83 (m, 2H), 7.76−7.70 (m, 2H), 7.64−7.59 (m, 1H), 7.49−7.44 (m, 2H), 7.28−7.13 (m, 2H), 6.98−6.90 (m, 2H), 6.79−6.71 (m, 2H), 5.80 (d, J = 8.3 Hz, H-1), 5.21 (dd, 1H, J = 8.9, 10.0 Hz), 4.71 (ddd, 1H, J = 6.9, 8.9, 10.7 Hz), 4.57 (dd, 1H, J = 8.3, 10.7 Hz), 4.10 (ddd, 1H, J = 2.5, 7.6, 10.0 Hz), 3.73 (s, 3H), 3.62 (dd, 1H, J = 2.5, 11.2 Hz), 4.18 (dd, 1H, J = 7.6, 11.2 Hz), 2.81 (d, 1H, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.17, 166.43, 155.60, 150.67, 134.29 (1), 133.90 (1), 131.53, 129.96 (1), 128.70, 128.64 (1), 123.63 (1), 118.73 (1), 114.43 (1), 97.57 (1), 75.20 (1), 73.92 (1), 70.25 (1), 56.98 (1), 55.58 (3), 31.08 (2). FAB-MS m/z (rel intensity): 606.1 ($[M + Na]^+$, 6.8), 329.2 (100.00). FAB-HRMS m/z calcd for $C_{28}H_{24}NO_8NaBr$ $[M + Na]^+$, 604.0582; obsd, 604.0610.

***p*-Methoxyphenyl 4-*O*-Benzoyl-3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-6-bromo-2-phthalimido-β-D-glucopyranoside (18a).** To a stirred solution of **17a** (4.43 g, 7.61 mmol) in THF (45 mL) under Ar in a flask fitted with a reflux condenser and drying tube were added benzyl chloromethyl ether (4.5 mL, 32.7 mmol) and diisopropylethylamine (6.2 mL, 36 mmol). The resulting light yellow solution was heated to reflux temperature. After 27 h, the reaction was cooled and diluted with CH_2Cl_2 (400 mL). This solution was washed with sat. $NaHCO_3$ (400 mL). The aqueous layer was back-extracted with CH_2Cl_2 (400 mL). The organic layers were each washed with sat. NaCl (400 mL) and were dried over $MgSO_4$, filtered, and evaporated, leaving a brown oil. The oil was purified by flash chromatography ($CHCl_3$/EtOAc 40:1), giving the product contaminated with BnOH (4.37 g). To remove the BnOH, the mixture was repeatedly crystallized from hexanes, giving white needles (3.03 g). The mother liquor of the final crystallization was concentrated in vacuo and the resulting residue triturated with cold 95% EtOH, giving additional product as a white powder (184 mg). Total yield: 3.21 g, 61%. A small sample was recrystallized from hexanes, giving colorless needles. mp 121−122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08−8.02 (m, 2H), 7.74 (broad m, 2H), 7.62−7.57 (m, 3H), 7.47−7.43 (m, 2H), 7.12−7.06 (m, 3H), 6.93−6.90 (m, 2H), 6.82−6.81 (m, 2H), 6.76−6.73 (m, 2H), 5.75 (d, 1H, J = 8.5 Hz), 5.36 (dd, 1H, J = 8.9, 9.9 Hz), 4.85 (dd, 1H, J = 8.9, 10.6 Hz), 4.65 (d, 1H, J = 7.2 Hz), 4.65 (dd, 1H, J = 8.5, 10.6 Hz), 4.55 (d, 1H, J = 7.2 Hz), 4.11−4.02 (m, 3H), 3.72 (s, 3H), 3.69 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$): δ 165.16, 155.24, 150.75, 136.87, 134.12 (1), 133.74 (1), 131.36, 129.81 (1), 128.75, 128.66 (1), 128.05 (1), 127.21 (1), 126.86 (1), 123.41 (1), 118.47 (1), 114.41 (1), 97.67 (1), 96.18 (2), 77.35 (1), 74.54 (1), 73.21 (1), 69.67 (2), 55.63 (1), 55.55 (3), 43.51 (2). The N-Pht C═O peak was presumably very broad and not observed. CI-MS m/z (rel intensity): 721.4 ($[M + NH_4]^+$, 74.08), 675.5 (100.00),

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414.2 (51.87), 396.2 (36.95), 274.1 (48.29), 240.2 (54.87), 124.1 (30.11), 121.1 (65.34), 105.1 (66.23), 91.1 (52.98). CI-HRMS calcd for $C_{36}H_{36}N_2O_9Br$ $[M + Na]^+$, 719.1604; obsd, 719.1636.

***p*-Methoxyphenyl 4-*O*-Benzoyl-3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-6-phenylseleno-2-phthalimido-*β*-D-glucopyranoside (19a).** To a stirred solution of **18a** (0.775 g, 1.1 mmol) in THF (8.0 mL) under an Ar atmosphere in a flask fitted with a reflux condenser and drying tube were added phenylselenol (0.35 mL, 3.3 mmol) and triethylamine (0.928 mL, 6.6 mmol). The solution was heated to reflux temperature. After ~5 min, a white precipitate began to appear, and the reflux was maintained for 24 h. The suspension was then cooled and equilibrated between sat. $NaHCO_3$ (70 mL) and CH_2Cl_2 (70 mL). The aqueous layer was back-extracted with CH_2Cl_2 (70 mL), and the organic layers were combined and washed with sat. NaCl, dried over $MgSO_4$, filtered, and evaporated, leaving a yellow oil (1.51 g). The oil was purified by flash chromatography (hexanes/EtOAc 2:1), giving the title compound as a white foam (780 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01−7.98 (m, 2H), 7.72 (broad m, 2H), 7.64−7.55 (m, 3H), 7.46−7.41 (m, 4H), 7.18−7.13 (m, 3H), 7.09−7.04 (m, 3H), 6.93−6.90 (m, 2H), 6.81−6.79 (m, 2H), 6.75−6.71 (m, 2H), 5.73 (d, 1H, J = 8.3 Hz), 5.39 (dd, 1H, J = 9.1, 9.2 Hz), 4.81 (dd, 1H, J = 9.1, 10.5 Hz), 4.65 (dd, 1H, J = 8.3, 10.6 Hz), 4.62 (d, 1H, J = 7.2 Hz), 4.53 (d, 1H J = 7.2 Hz), 4.06−3.96 (m, 3H), 3.71 (s, 3H), 3.13 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.53, 165.20, 155.42, 150.74, 136.91, 134.06 (1), 133.59 (1), 132.39 (1), 131.37, 130.21, 129.77 (1), 129.06 (1), 128.97, 128.59 (1), 128.02 (1), 127.16 (1), 126.96 (1), 126.82 (1), 123.40 (1), 118.55 (1), 114.34 (1), 97.67 (1), 96.09 (2), 77.31 (1), 75.19 (1), 74.17 (1), 69.60 (2), 55.76 (1), 55.56 (3), 29.02 (2).

***p*-Methoxyphenyl 3-*O*-[(Benzyloxy)methyl]-2,6-dideoxy-6-phenylseleno-2-amino-*β*-D-glucopyranoside (20a).** To a suspension of **19a** (1.71 mg, 2.20 mmol) in EtOH (40 mL) in a glass tube was added hydrazine hydrate (5.0 mL, 160 mmol). The suspension was placed under a gentle vacuum, and the tube was sealed. The suspension was heated, and the temperature was maintained between 95 and 110 °C. Upon heating, the suspension gradually became clear. After 17 h, the reaction was cooled and the solution was equilibrated between EtOAc (400 mL) and water (400 mL). The EtOAc layer was washed with sat. $NaHCO_3$ (400 mL) and sat. NaCl (400 mL). After drying over Na_2SO_4, the organic layer was filtered and evaporated, leaving an oil which was purified by flash chromatography (EtOAc). The product eluted as a colorless oil (1.15 g, 96.0%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53−7.48 (m, 2H), 7.37−7.32 (m, 5H), 7.22−7.19 (m, 3H), 7.09−7.07 (m, 2H), 6.85−6.79 (m, 2H), 5.01 (d, 1H, J = 7.2 Hz), 4.82 (d, 1H, J = 7.3 Hz), 4.81 (d, 1H, J = 11.7 Hz), 4.67 (d, 1H, J = 7.3 Hz), 4.61 (d, 1H, J = 11.7 Hz), 3.76 (s, 3H), 3.57−3.42 (m, 3H), 3.27 (dd, 1H, J = 9.6, 9.6 Hz), 3.15−3.06 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.25, 151.19, 136.20, 132.02 (1), 130.77, 128.97 (1), 128.62 (1), 128.25 (1), 128.05 (1), 126.57 (1), 118.36 (1), 114.39 (1), 102.86 (1), 96.46 (2), 89.08 (1), 75.61 (1), 72.60 (1), 70.54 (2), 55.86 (1), 55.56 (3), 29.66 (2). CI-MS (NH_3) m/z (rel intensity): 546.1 ($M + H^+$, 100.00), 422.0 (63.46), 390.1 (29.64), 284.2 (25.48), 124.0 (42.45), 110.0 (38.96), 108.1 (44.40), 91.0 (36.17). CI-HRMS (NH_3) m/z calcd for $C_{27}H_{32}NO_6Se$ $[M + H]^+$, 546.1395; obsd, 546.1398.

***p*-Methoxyphenyl 4-*O*-Acetyl-3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-6-phenylseleno-2-trifluoroacetamido-*β*-D-glucopyranoside (21a).** To a stirred solution of **20a** (1.12 g, 2.06 mmol) in pyridine (11 mL) at 0 °C was added trifluoroacetic anhydride (1.45 mL, 10.3 mmol). After 30 min, the solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. $NaHCO_3$ (200 mL), 0.1 M HCl (2 × 180 mL), sat. $NaHCO_3$ (150 mL), and sat. NaCl (150 mL). The organic layer was stirred over SiO_2 (10 g) overnight. The suspension was filtered, and the filtrate was evaporated, leaving *p*-methoxyphenyl 3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-6-phenylseleno-2-trifluoroacetamido-*β*-D-glucopyranoside contaminated with a small amount of pyridine (1.36 g, 103%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53−7.49 (m, 2H), 7.38−7.32 (m, 5H), 7.23−7.19 (m, 3H), 7.00−6.96 (m, 2H), 6.82−6.77 (m, 2H), 6.71 (broad d, 1H, J = 6.6 Hz), 5.11 (d, 1H, J = 7.9 Hz), 4.92 (d, 1H, J = 7.2 Hz), 4.76 (d, 1H, J = 11.8 Hz), 4.70 (d, 1H, J = 7.2 Hz), 4.57 (d, 1H, J = 11.7 Hz), 4.39 (s, 1H), 3.90−3.85 (m, 2H), 3.75 (s, 3H), 3.62 (ddd, 1H, J = 2.4, 8.5, 9.1 Hz), 3.51−3.45 (m, 2H), 3.09 (dd, 1H, J = 8.5, 13.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.48 (q, J = 37 Hz), 155.64, 150.96, 136.08, 132.12 (1), 130.52, 129.07 (1), 128.67 (1), 128.34 (1), 128.06 (1), 126.76 (1), 118.73 (1), 115.56 (q, J = 288 Hz), 114.54 (1), 99.18 (1), 96.04 (2), 83.54 (1), 75.48 (1), 73.32 (1), 70.63 (2), 56.44 (1), 55.59 (3), 29.38 (2).

To the crude *N*-TFA compound (1.36 g, 2.12 mmol) in pyridine (7 mL) was added Ac_2O (7.0 mL, 74 mmol). The reaction was allowed to stir at ambient temperature overnight. The solution was diluted with EtOAc and washed with an equal volume of sat. $NaHCO_3$ (3×), sat. $CuSO_4$, and sat. NaCl. The organic layer was dried over $MgSO_4$, filtered, and evaporated, leaving an off-white solid which was purified on a plug of SiO_2, giving the title compound as a white powder (1.18 g, 84% over two steps). mp 171−174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49−7.46 (m, 2H), 7.36−7.21 (m, 8H), 7.00−6.97 (m, 2H), 6.92 (broad d, 1H, J = 7.7 Hz), 6.82−6.76 (m, 2H), 5.21 (d, 1H, J = 8.2 Hz), 5.03 (dd, 1H, J = 9.0, 9.6 Hz), 4.72 (s, 2H), 4.55 (s, 2H), 4.18 (dd, 1H, J = 9.0, 10.3 Hz), 3.91 (ddd, J = 7.7, 8.1, 10.2 Hz), 3.75 (s, 3H), 3.71 (ddd, 1H, J = 4.4, 7.8, 9.6 Hz), 3.10−3.01 (m, 2H), 1.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.84, 157.56 (q, J = 37 Hz), 155.71, 150.97, 136.89, 132.59, 130.13, 129.13, 128.44, 127.90, 127.77, 127.15, 118.85, 115.55 (q, J = 288 Hz), 114.52, 99.42, 95.32, 77.35, 73.94, 73.93, 69.91, 56.85, 55.56, 29.11, 20.87. FAB-MS m/z (rel intensity): 706.1 ($[M + Na]^+$, 8.7), 560.1 (9.3), 91.0 (100.00). FAB-HRMS calcd for $C_{31}H_{32}NO_8F_3NaSe$ $[M + Na]^+$, 706.1143; obsd, 706.1147.

***tert*-Butyldimethylsilyl 4-*O*-Benzoyl-3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-6-bromo-2-phthalimido-*β*-D-glucopyranoside (18b).** *N*-Bromosuccinimide (1.16 g, 6.52 mmol), barium carbonate (3.50 g, 17.7 mmol), and **16b** (3.01 g, 5.87 mmol) were suspended in dry CCl_4 (110 mL) under an Ar atmosphere. The suspension was heated to reflux temperature. As the reaction progressed, the solution turned deep orange; the disappearance of color signified completion of the reaction. After 1 h, the colorless suspension was cooled and filtered. The solid was washed with $CHCl_3$, and the filtrate was evaporated, leaving a white powder which was dissolved in $CHCl_3$ (300 mL) and washed with H_2O (3 × 100 mL) and sat. $NaCHO_3$ (100 mL). The solvent was dried over $MgSO_4$, filtered, and evaporated, leaving **17b** as a white powder sufficiently pure for further transformations, 3.40 g (98% crude recovery). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08−8.04 (m, 2H), 7.85−7.81 (m, 2H), 7.73−7.69 (m, 2H), 7.62−7.57 (m, 1H), 7.48−7.43 (m, 2H), 5.53 (d, 1H, J = 8.0 Hz), 5.14 (dd, 1H, J = 9.0, 10.2 Hz), 4.70 (dd, 1H, J = 9.0, 10.9 Hz), 4.29 (dd, 1H, J = 8.0, 10.9 Hz), 4.01 (ddd, 1H, J = 2.5, 8.0, 10.2 Hz), 3.56 (dd, 1H, J = 2.5, 11.2 Hz), 3.48 (dd, 1H, J = 8.0, 11.2 Hz), 0.71 (s, 9H), 0.15 (m, 3H), 0.01 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.35, 166.35, 134.16 (1), 133.73 (1), 131.45, 129.89 (1), 128.82, 128.55 (1), 123.34 (1), 93.35 (1), 75.45 (1), 73.91 (1), 69.74 (1), 59.18 (1), 31.22 (2), 25.27 (3), 17.44, −4.12 (3), −5.72 (3).

To a stirred solution of crude **17b** (3.40 g, 5.74 mmol) in freshly distilled THF (50 mL) under Ar were added DIEA (5.5 mL, 31.5 mmol) and benzyl chloromethyl ether (3.89 mL, 28.0 mmol). The solution was heated to reflux temperature. After 27.5 h, the reaction was cooled and diluted with CH_2Cl_2 (500 mL). This solution was washed with sat. $NaCHO_3$ (500 mL). After back-extracting the aqueous layer with CH_2Cl_2 (500 mL), the organic extracts were combined and washed with sat. NaCl (500 mL), dried over $MgSO_4$, filtered, and evaporated. The resulting brown oil was purified by flash chromatography (hexanes/EtOAc 6:1−5:1), giving pure product as a white foam (2.61 g) along with product contaminated with BOMCl (1.85 g). The contaminated product was purified a second time by flash chromatography (hexanes/EtOAc 6:1−5:1), giving the product as a foam (630 mg). Total yield: 3.24 g (78% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05−

8.03 (m, 2H), 7.74 (broad m, 2H), 7.67−7.57 (m, 3H), 7.48−7.44 (m, 2H), 7.13−7.04 (m, 3H), 6.84−6.82 (m, 2H), 5.51 (d, 1H, J = 8.1 Hz), 5.28 (dd, 1H, J = 8.9, 10.4 Hz), 4.82 (dd, 1H, J = 8.9, 10.7 Hz), 4.67 (d, 1H, J = 7.2 Hz), 4.55 (d, 1H, J = 7.2 Hz), 4.36 (dd, 1H, J = 8.1, 10.7 Hz), 4.09 (s, 2H), 3.94 (ddd, 1H, J = 4.6, 6.8, 10.4 Hz), 3.65−3.47 (m, 2H), 0.74 (s, 9H), 0.17 (m, 3H), 0.01 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.71, 165.25, 136.95, 134.00 (1), 133.65 (1), 131.40, 129.78 (1), 128.88, 128.62 (1), 128.00 (1), 127.14 (1), 126.85 (1), 123.08 (1), 96.03 (2), 93.48 (1), 77.08 (1), 74.42 (1), 74.34 (1), 69.55 (1), 57.92 (1), 31.10 (2), 25.26 (3), 17.43, −4.02 (3), −5.77 (3). FAB-MS m/z (rel intensity): 734.2 ([M + Na]$^+$, 6.0), 176.0 (43.0), 105.0 (100.0), 91.0 (70.8). FAB-HRMS calcd for $C_{35}H_{40}NO_8NaSeBr$ [M + Na]$^+$, 732.1604; obsd, 732.1622.

***tert*-Butyldimethylsilyl 4-*O*-Benzoyl-3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-6-phenylseleno-2-phthalimido-β-D-glucopyranoside (19b).** To a stirred solution of **18b** (3.23 g, 4.54 mmol) in freshly distilled THF (30 mL) under an Ar atmosphere were added phenylselenol (1.4 mL, 14 mmol) and triethylamine (3.8 mL, 27.2 mmol). The yellow suspension was heated to reflux temperature. After 4.5 days, the reaction was diluted with CH_2Cl_2 (300 mL) and washed with sat. $NaHCO_3$ (300 mL) and sat. NaCl (75 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated. Purification by flash chromatography (hexanes/EtOAc 5:1) gave the title compound as a white powder (3.50 g, 98%). mp 131.5−132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02−7.99 (m, 2H), 7.73 (broad m, 2H), 7.65−7.60 (m, 3H), 7.46−7.41 (m, 4H), 7.20−7.18 (m, 3H), 7.08−7.06 (m, 3H), 6.82−6.80 (m, 2H), 5.50 (d, 1H, J = 8.1 Hz), 5.32 (dd, 1H, J = 8.9, 9.4 Hz), 4.78 (dd, 1H, J = 8.9, 10.7 Hz), 4.62 (d, 1H, J = 7.2 Hz), 4.53 (d, 1H, J = 7.2 Hz), 4.38 (dd, 1H, J = 8.1, 10.7 Hz), 4.08 (s, 2H), 3.94 (ddd, 1H, J = 2.9, 9.4, 9.4 Hz), 3.20−3.06 (m, 2H), 0.71 (s, 9H), 0.14 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.64 (broad d), 165.23, 136.96, 133.93 (1), 133.45 (1), 133.45 (1), 132.07 (1), 131.37, 130.51, 129.69 (1), 129.08, 129.02 (1), 128.50 (1), 127.93 (1), 127.05 (1), 126.77 (1), 123.07 (broad d) (1), 95.93 (2), 93.49 (1), 77.08 (1), 75.60 (1), 73.93 (1), 69.47 (2), 57.93 (1), 29.16 (2), 25.22 (3), 17.36, −4.12 (3), −5.82 (3). FAB-MS m/z (rel intensity): 810.3 ([M + Na]$^+$, 87.6), 758.3 (64.2), 730.2 (100.0), 680.2 (25.7), 656.1 (29.5). FAB-HRMS calcd for $C_{41}H_{45}NO_8$-NaSiSe [M + Na]$^+$, 810.1977; obsd, 810.2005.

***tert*-Butyldimethylsilyl 3-*O*-[(Benzyloxy)methyl]-2,6-dideoxy-6-phenylseleno-2-amino-β-D-glucopyranoside (20b).** To a suspension of **19b** (3.50 g, 4.44 mmol) in EtOH (3.2 mL) in a glass tube was added hydrazine hydrate (2.0 mL, 416 mmol). The tube was placed under vacuum and sealed, and the suspension was heated to 100 °C. Upon heating, the suspension gradually became clear. After 15 h, the reaction was cooled and the solution was equilibrated between EtOAc (900 mL) and water (900 mL). The EtOAc layer was washed with sat. $NaHCO_3$ (900 mL) and sat. NaCl (900 mL). After drying over $MgSO_4$, the organic layer was filtered and evaporated, leaving an oil which was purified by flash chromatography using EtOAc as the eluant. The title compound eluted as a colorless oil (2.38 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55−7.48 (m, 2H), 7.38−7.29 (m, 5H), 7.25−7.16 (m, 3H), 4.97 (d, 1H, J = 7.1 Hz), 4.79 (d, 1H, J = 7.1 Hz), 4.78 (d, 1H, J = 11.8 Hz), 4.59 (d, 1H, J = 11.8 Hz), 4.47 (d, 1H, J = 7.6 Hz), 3.53−3.37 (m, 3H), 3.20 (dd, 1H, J = 9.5, 9.5 Hz), 3.10 (dd, 1H, J = 8.9, 12.8 Hz), 2.83 (m, 1H), 0.92, (s, 9H), 0.18 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.26, 131.84 (1), 131.16, 128.90 (1), 127.55 (1), 128.14 (1), 127.97 (1), 126.37 (1), 98.49 (1), 96.37 (2), 89.06 (1), 75.48 (1), 72.97 (1), 70.37 (2), 57.70 (1), 29.94 (2), 25.73 (3), 17.88, −3.89 (3), −5.42 (3). CI-MS (NH_3) m/z (rel intensity): 554.4 (M + H$^+$, 100.00), 398.4 (22.71), 242.3 (10.81). CI-HRMS (NH_3) calcd for $C_{26}H_{40}NO_5SiSe$ [M + H]$^+$, 554.1841; obsd, 554.1826.

***tert*-Butyldimethylsilyl 4-*O*-Acetyl-3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-6-phenylseleno-2-trifluoroacetamido-β-D-glucopyranoside (21b).** To a stirred 0 °C solution of **20b** (2.38 g, 4.29 mmol) in pyridine (30 mL) under an atmosphere of Ar was added dropwise trifluoroacetic anhydride (3.1 mL, 22.0 mmol). After 45 min, the solution was diluted with CH_2Cl_2 (300 mL) and washed with sat. $NaHCO_3$ (300 mL), 0.1 M HCl (2 × 300 mL), $NaHCO_3$ (300 mL), and sat. NaCl (300 mL). The organic extracts were dried over $MgSO_4$ and filtered, and the filtrate was stirred overnight with SiO_2 (50 g). After filtering the suspension, the filtrate was evaporated, leaving the title compound contaminated with pyridine. To remove the pyridine, the oil was dissolved in CH_2Cl_2 (300 mL) and washed with sat. $CuSO_4$ (2 × 300 mL), H_2O (300 mL), and sat. NaCl (300 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated, leaving the 2-*N*-TFA derivative as a white powder sufficiently pure for further transformations (2.54 g, 91%). mp 106−109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50−7.47 (m, 2H), 7.35−7.15 (m, 8H), 6.85 (broad d, 1H), 4.89 (d, 1H, J = 7.2 Hz), 4.88 (d, 1H, J = 7.4 Hz), 4.73 (d, 1H, J = 11.8 Hz), 4.67 (d, 1H, J = 7.2 Hz), 4.53 (d, 1H, J = 11.8 Hz), 4.31 (s, 1H), 3.73−3.65 (m, 2H), 3.54 (ddd, 1H, J = 2.3, 8.6, 9.0 Hz), 3.45−3.41 (m, 2H), 3.08 (dd, 1H, J = 8.6, 12.6 Hz), 0.87 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.50 (q, J = 37 Hz), 136.20, 131.84 (1), 130.97, 129.01 (1), 128.59 (1), 128.21 (1), 127.97 (1), 126.53 (1), 115.68 (q, J = 288 Hz), 95.06 (2), 94.89 (1), 83.87 (1), 75.33 (1), 73.54 (1), 70.52 (2), 58.11 (1), 29.64 (2), 25.41 (3), 17.66, −4.04 (3), −5.69 (3).

To this crude product (1.50 g, 0.52 mmol) in pyridine (7.5 mL) was added Ac_2O (7.5 mL, 79.5 mmol). After 18 h, the solution was diluted with CH_2Cl_2 (80 mL) and washed with sat. $CuSO_4$ (2 × 150 mL), H_2O (150 mL), sat. $NaHCO_3$ (2 × 150 mL), and sat. NaCl (150 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, leaving the title compound as an off-white powder (1.55 g, 97%). mp 161−162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49−7.43 (m, 2H), 7.38−7.21 (m, 8H), 6.90 (broad d, 1H, J = 8.2 Hz), 4.98−4.92 (m, 2H), 4.70 (s, 2H), 4.54 (s, 2H), 4.08 (dd, J = 9.2, 10.4 Hz), 3.74−3.61 (m, 2H), 3.09−2.94 (m, 2H), 1.96 (s, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.93, 157.35 (q, J = 38 Hz), 137.00, 132.24 (1), 130.55, 129.09 (1), 128.39 (1), 127.81 (1), 127.72 (1), 126.93 (1), 115.61 (q, J = 288 Hz), 95.20 (2), 94.89 (1), 77.42 (1), 74.50 (1), 73.74 (1), 69.75 (2), 58.81 (1), 29.20 (2), 25.38 (3), 20.89 (3), 17.63, −4.10 (3), −5.76 (3). FAB-MS m/z (rel intensity): 714.0 ([M + Na]$^+$, 8.0), 662.0 (2.2), 90.9 (100.0). EI-HRMS calcd for $C_{26}H_{31}NO_7F_3SiSe$ [M − C_4H_9]$^+$, 634.0987; obsd, 634.0956.

***p*-Methoxyphenyl 3,4-Di-*O*-acetyl-2,6-dideoxy-6-phenylseleno-2-trifluoroacetamido-β-D-glucopyranoside (22).** To a stirred 0 °C solution of **21a** (1.17 g, 1.71 mmol) in dry $CHCl_3$ (24 mL) under an atmosphere of Ar was added AcBr (250 μL, 3.38 mmol) and BF_3·OEt_2 (21 μL, 0.17 mmol). After 2 h, additional BF_3·OEt_2 (84 μL, 0.66 mmol) was added. After a further 30 min, additional AcBr (250 μL, 3.38 mmol) was added. After 7 h total reaction time, the solution was diluted with CH_2Cl_2 (200 mL) and washed with sat. $NaHCO_3$ (200 mL), H_2O (200 mL), and sat. NaCl (200 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated, leaving an off-white powder (1.49 g). The powder was purified by flash chromatography (hexanes/EtOAc 2:1), giving the title compound as a white powder (920 mg, 88%). mp 194−195 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.47 (m, 2H), 7.37−7.23 (m, 3H), 7.00−6.95 (m, 2H), 6.83−6.78 (m, 2H), 6.54 (broad d, 1H, J = 8.9 Hz), 5.28 (dd, 1H, J = 9.4, 10.4 Hz), 5.08 (dd, 1H, J = 8.7, 9.4 Hz), 4.99 (d, 1H, J = 8.3 Hz), 4.26 (ddd, 1H, J = 8.3, 8.9, 9.4 Hz), 3.83−3.76 (m, 4H), 3.11−3.01 (m, 2H), 2.05 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.39, 169.54, 157.46 (q, J = 37 Hz), 155.84, 150.89, 132.51 (1), 130.01, 129.20 (1), 127.27 (1), 118.85 (1), 115.56 (q, J = 288 Hz), 114.52 (1), 100.20 (1), 74.02 (1), 72.12 (1), 71.60 (1), 55.61 (3), 54.76 (1), 28.85 (2), 20.62 (3), 20.42 (3). FAB-MS m/z (rel intensity): 628.0 ([M + Na]$^+$, 13.5) 482.0 (27.0), 329.1 (23.5), 176.0 (81.5), 124.1 (100.00). FAB-HRMS calcd for $C_{25}H_{26}NO_8F_3NaSe$ [M + Na]$^+$, 628.0673; obsd, 628.0685.

3,4-Di-*O*-acetyl-2,6-dideoxy-6-phenylseleno-2-trifluoroacetamido-β-D-glucopyranosyl bromide (23). To a stirred 0 °C solution of **22** (100 mg, 0.165 mmol) in dry $CHCl_3$ (2.0 mL) under an atmosphere of

Ar was added dropwise AcBr (77 μL, 1.04 mmol) and BF_3·OEt_2 (33 μL, 0.265 mmol), followed by ZnI_2 (5 mg, 0.016 mmol). The reaction was gradually warmed to RT. After 11.5 h, the reaction mixture was warmed to 40 °C. After 16.5 h total reaction time, the reaction was diluted with CH_2Cl_2 (20 mL) and washed with sat. $NaHCO_3$ (containing 6 crystals of $Na_2S_2O_3$) (20 mL), H_2O (20 mL), and sat. NaCl (20 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated, leaving a brown oil (114 mg) which contained product contaminated with *p*-methoxyphenyl acetate. The oil was used in the subsequent reactions without prior purification.

2-Trifluoromethyl-(3,4-di-*O*-acetyl-1,2,6-trideoxy-6-phenylseleno-α-D-glycopyrano)[2,1-d]-2-oxazoline (24). To a stirred solution of crude **23** (115 mg) in dry CH_3CN (2 mL) under an atmosphere of Ar was added Bu_4NBr (53 mg, 0.165 mmol) and 2,6-lutidine (29 μL, 0.249 mmol). After 20 min, the reaction was diluted with CH_2Cl_2 (20 mL) and washed with pH = 7 K_2PO_4 buffer (20 mL), H_2O (20 mL), and sat. NaCl (20 mL). The organic extracts were dried with Na_2SO_4, filtered, and evaporated, leaving a brown oil (168 mg). The oil was purified by flash chromatography (hexanes/EtOAc/Et_3N 3:1:0.04), giving the product as a light brown oil (70 mg, 89% over two steps). ^{1}H NMR (300 MHz, C_6D_6): δ 7.43−7.39 (m, 2H), 6.95−6.86 (m, 3H), 5.44 (dd, 1H, *J* = 1.5, 2.1 Hz), 5.43 (d, 1H *J* = 7.6 Hz), 5.10 (ddd, 1H, *J* = 1.5, 2.1, 8.2 Hz), 3.68 (ddd, 1H, *J* = 3.9, 6.8, 8.2 Hz), 3.58 (ddd, 1H, *J* = 2.1, 2.1, 7.6 Hz), 2.95 (dd, 1H, *J* = 3.9, 13.0 Hz), 2.81 (dd, 1H, *J* = 6.8, 13.0 Hz), 1.57 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.45, 169.05, 133.37, 129.20, 128.15, 127.51, 102.25, 71.13, 69.90, 68.84, 63.86, 30.83, 20.85, 20.73. The sample was too dilute to observe the oxazoline CF_3 and N=C peaks. ^{19}F NMR (282 MHz, $CDCl_3$, machine standard): δ 5.85.

3,4-Di-*O*-acetyl-2,6-dideoxy-6-phenylseleno-2-trifluoroacetamido-β-D-glucopyranose (25). To a stirred solution of crude glycosyl bromide **23** (49 mg, 0.079 mmol) in acetone/H_2O 2:1 (3.6 mL) was added Ag_2CO_3 (44 mg, 0.16 mmol). The flask was immediately covered with foil. After 45 min, the reaction was filtered through Celite which was washed with EtOAc. The filtrate was washed with sat. $NaHCO_3$ (30 mL) and sat. NaCl (30 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, leaving a residue (42 mg) which was purified by preparative TLC (hexanes/EtOAc 2:1), giving the product as a powder (25 mg, 64% over two steps) (α/β 8:1). ^{1}H NMR (α-anomer) (300 MHz, $CDCl_3$): δ 7.52−7.49 (m, 2H), 7.27−7.25 (m, 3H), 6.69 (d, 1H, *J* = 9.5 Hz), 5.35−5.28 (m, 2H), 5.06 (dd, 1H, *J* = 9.7, 9.7 Hz), 4.44−4.22 (m, 2H), 3.38 (d, 1H, *J* = 2.1 Hz), 3.06 (dd, 1H, *J* = 3.5, 12.9 Hz), 2.99 (dd, 1H, *J* = 8.0, 12.9 Hz), 2.01 (s, 6H).

3,4-Di-*O*-acetyl-2,6-dideoxy-6-phenylseleno-2-trifluoroacetamido-α-D-glucopyranosyl 1-Dibenzyl Phosphate (26). To a stirred −78 °C solution of **25** (25 mg, 0.050 mmol) in freshly distilled THF (1.25 mL) was added 0.49 M LDA in hexanes (143 μL). After 15 min, a −78 °C solution of tetrabenzylpyrophosphate (33 mg, 0.063 mmol) in freshly distilled THF (750 μL) was added. After a further 20 min, the yellow solution was warmed to 0 °C. Seventy minutes later, the suspension was diluted with CH_2Cl_2 (20 mL) and washed with sat. $NaHCO_3$ (2 × 20 mL) and sat. NaCl (20 mL). The CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and evaporated, leaving an oil which was purified by preparative TLC (hexanes/EtOAc 2:1), giving the product as an oil (25 mg, 66%). ^{1}H NMR (300 MHz, C_6D_6): δ 8.95 (d, 1H, *J* = 8.7 Hz), 7.57−7.54 (m, 2H), 7.35−7.03 (m, 13H), 5.72 (dd, 1H, *J* = 9.4, 10.8 Hz), 5.68 (dd, 1H, *J* = 3.4, 7.1 Hz), 5.36 (dd, 1H, *J* = 9.4, 10.0 Hz), 5.20 (d, 2H, *J* = 8.3 Hz), 5.06−5.02 (m, 2H), 4.66 (dddd, 1H, *J* = 2.6, 3.4, 8.7, 10.8 Hz), 4.58 (ddd, 1H, *J* = 3.2, 6.9, 10.0 Hz), 3.23 (dd, 1H, *J* = 3.2, 13.2 Hz), 2.98 (dd, 1H, *J* = 6.9, 13.2 Hz), 1.78 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ 170.74, 168.93, 158.00 (q, *J* = 38 Hz), 136.09 (d, *J* = 6.9 Hz), 135.62 (d, *J* = 6.3 Hz), 133.24, 131.29, 129.33, 128.85, 128.78, 128.64, 127.27, 116.65 (q, *J* = 288 Hz), 95.45 (d, *J* = 6.3 Hz), 72.02, 71.42, 70.18−70.11 (m, 2C), 52.94 (d, *J* = 7.2 Hz), 29.83, 20.16, 20.04. Several expected ^{13}C peaks were obscured by the solvent peak. ^{31}P NMR (121 MHz, $CDCl_3$): δ −2.47 (m). EIMS *m*/*z* (rel intensity): 759.3 ($[M]^+$, 0.88), 481.1 (20.03), 264.1 (10.95), 222.1 (19.01), 157.0 (11.37), 91.1 (50.17), 43.0 (100.00). EI-HRMS calcd for $C_{32}H_{33}NO_{10}F_3PSe$ $[M]^+$, 759.0959; obsd, 759.0925.

4-*O*-Acetyl-3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-6-phenylseleno-2-trifluoroacetamido-β-D-glucopyranoside (27). To a stirred 0 °C solution of **21b** (202 mg, 0.292 mmol) and pyridine (1.1 mL) in freshly distilled THF (4.5 mL) was added dropwise HF·pyridine (400 μL). After 2.75 h, the reaction was removed from the ice bath and allowed to warm to RT. After 6.5 h total reaction time, the reaction was diluted with CH_2Cl_2 (80 mL), and the organic layer was washed with sat. $NaHCO_3$ (80 mL) and sat. NaCl (80 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, leaving a yellow oil (230 mg) which was purified by flash chromatography (hexanes/EtOAc 2:1), giving the desired product as a white powder (153 mg), 91% (α/β 10:1). mp 165−166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) (α anomer): δ 7.52−7.47 (m, 2H), 7.38−7.23 (m, 8H), 7.17 (broad d, 1H, *J* = 7.1 Hz), 5.47 (dd, 1H, *J* = 3.0, 3.4 Hz), 4.99 (dd, 1H, *J* = 9.0, 9.8 Hz), 4.74 (d, 1H, *J* = 6.6 Hz), 4.67 (d, 1H, *J* = 6.6 Hz), 4.59 (d, 1H, *J* = 12.3 Hz), 4.54 (d, 1H, *J* = 12.3 Hz), 4.17 (ddd, 1H, *J* = 5.9, 5.9, 9.8 Hz), 4.11 (ddd, 1H, *J* = 3.0, 7.1, 10.6 Hz), 3.98 (dd, 1H, *J* = 9.0, 10.3 Hz) 3.57 (d, 1H, *J* = 3.4 Hz), 3.03−2.99 (m, 2H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.68, 157.32 (q, *J* = 37 Hz), 136.61, 132.75, 130.24, 129.10, 128.53, 128.05, 127.80, 127.18, 119.46 (q, *J* = 288 Hz), 95.54, 90.39, 74.00, 69.87, 69.65, 53.63, 29.30, 20.86. One carbon was obscured by the $CDCl_3$ solvent peak. EIMS *m*/*z* (rel intensity): 577.1 ($[M]^+$, 7.2), 120.1 (18.5), 91.1 (100.00), 43.4 (43.0). EI-HRMS calcd for $C_{24}H_{26}NO_7F_3Se$ $[M]^+$, 577.0827; obsd, 577.0837.

4-*O*-Acetyl-3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-6-phenylseleno-2-trifluoroacetamido-α-D-glucopyranosyl 1-Dibenzyl Phosphate (28). To a stirred −78 °C solution of **27** (1.09 g, 1.89 mmol) in freshly distilled THF (57 mL) was added dropwise freshly prepared LDA (0.49 M in THF/hexanes, 5.4 mL). After 15 min, a −78 °C solution of tetrabenzylpyrophosphate (1.27 g, 2.36 mmol) in freshly distilled THF (27 mL) was added. The solution was stirred for 20 min at −78 °C and was then warmed to 0 °C via an ice bath. After an additional 2 h, the solution was diluted with CH_2Cl_2 (800 mL) and was washed with sat. $NaHCO_3$ (2 × 800 mL) and sat. NaCl (800 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated, leaving a colorless oil which was purified by flash chromatography (hexanes/EtOAc 2:1), giving the title compound as a low-melting solid (1.33 g, 84%). In a separate fraction, a small amount of the 1,2-oxazoline was obtained. mp 59−62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46−7.44 (m, 2H), 7.37−7.19 (m, 19H), 5.92 (dd, 1H, *J* = 3.0, 6.5 Hz), 5.07−5.00 (m, 5H), 4.72 (d, 1H, *J* = 6.4 Hz), 4.60 (d, 1H, *J* = 6.4 Hz), 4.57 (d, 1H, *J* = 12.4 Hz), 4.52 (d, 1H, *J* = 12.4 Hz), 4.16−4.08 (m, 2H), 3.84 (dd, 1H, *J* = 9.3, 10.5 Hz), 3.00−2.91 (m, 2H), 1.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.39, 157.54 (q, *J* = 38 Hz), 136.45, 135.26 (d, *J* = 6.5 Hz), 135.09 (d, *J* = 6.2 Hz), 132.72, 130.34, 129.12, 128.77, 128.74, 128.62, 128.62, 128.57, 128.30, 128.15, 128.08, 127.85, 127.17, 115.77 (q, *J* = 288 Hz), 95.48, 94.57 (d, *J* = 6.4 Hz), 76.00, 73.01, 71.71, 69.99 (d, *J* = 5.7 Hz), 69.88 (d, *J* = 5.7 Hz), 69.85, 53.46 (d, *J* = 7.4 Hz), 29.67, 20.78. ^{31}P NMR (121 MHz, $CDCl_3$): δ −2.57 (m). FAB-MS *m*/*z* (rel intensity): 860.0 ($[M + Na]^+$, 59.46), 837.0 ($[M]^+$, 21.15), 560.0 (100.00), 530.0 (30.39), 482.0 (18.60), 460.1 (25.54). FAB-HRMS calcd for $C_{38}H_{39}NO_{10}F_3PSe$ $[M]^+$, 837.1429; obsd, 837.1429.

4-*O*-Acetyl-3-*O*-[(benzyloxy)methyl]-2,6-dideoxy-5,6-didehydro-2-trifluoroacetamido-α-D-glucopyranosyl 1-Dibenzyl Phosphate (29). To a stirred RT suspension of **28** (670 mg, 0.816 mmol) in MeOH/H_2O (6:1, 175 mL) were added $NaHCO_3$ (75 mg, 0.90 mmol) and $NaIO_4$ (261 mg, 1.22 mmol). As the reaction progressed, a white precipitate formed. After 1.5 h, the suspension was filtered and washed with CH_2Cl_2. The organic portion of the filtrate was evaporated, and the resulting aqueous suspension was partitioned between H_2O (135 mL) and CH_2Cl_2 (135 mL). The aqueous layer was washed with CH_2Cl_2 (2 × 70 mL). The organic layers were combined, dried over Na_2SO_4, filtered,

and evaporated, leaving the product selenoxides (2:1 ratio) as a white powder (690 mg), 101%. ^{1}H NMR (only nonoverlapping assigned peaks) (300 MHz, $CDCl_3$): δ 7.77−7.73 (m, 2H, SePh), 7.68−7.65 (m, 2H, SePh), 5.98 (dd, J = 3.1, 6.5 Hz), 5.89 (dd, J = 3.1, 6.3 Hz).

A stirred clear, colorless suspension of the selenoxides (690 mg) in freshly distilled dihydropyran (30 mL) was heated to reflux temperature. Upon heating, the residual solid dissolved. After 4.75 h, the yellow solution was cooled and diluted with CH_2Cl_2 (200 mL). This solution was washed with H_2O (200 mL), sat. $NaHCO_3$ (200 mL), and sat. NaCl (200 mL). The organic extracts were dried over Na_2SO_4, filtered, and evaporated, leaving a yellow oil (900 mg) which was purified by flash chromatography (hexanes/EtOAc 2:1), giving the title compound as a white solid (480 mg, 89% over two steps). mp 97−98 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (broad d, 1H, J = 6.9 Hz), 7.37−7.26 (m, 15H), 5.94 (dd, 1H, J = 3.0, 6.8 Hz), 5.42 (dd, 1H, J = 1.8, 1.8, 8.8 Hz), 5.04 (m, 4H), 4.78−4.77 (m, 2H), 4.69 (d, 1H, J = 6.5 Hz), 4.58 (d, 1H, J = 12.4 Hz), 4.55 (d, 1H, J = 12.4 Hz), 4.55 (dd, 1H, J = 1.8, 2.0 Hz), 4.28 (dddd, 1H, J = 2.6, 3.0, 6.9, 9.8 Hz), 3.94 (dd, 1H, J = 8.8, 9.8 Hz), 2.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.93, 157.51 (q, J = 38 Hz), 149.73, 136.49, 135.79 (d, J = 6.7 Hz), 135.04 (d, J = 6.2 Hz), 128.77 (1), 128.75 (1), 128.61 (1), 128.54 (1), 128.08 (1), 128.03 (1), 127.94 (1), 127.79 (1), 115.50 (q, J = 288 Hz), 99.25 (2), 95.29 (2), 94.14 (1, d, J = 5.9 Hz), 75.20 (1), 70.39 (1), 60.96−60.85 (2, m, 2C), 52.94 (1, d, J = 7.9 Hz), 20.64 (3). ^{31}P NMR (121 MHz, $CDCl_3$): δ −2.86 (m). FAB-MS m/z (rel intensity): 702.2 ([M + Na]$^+$, 11.3), 176.0 (53.1), 91.0 (100.0). FAB-HRMS calcd for $C_{32}H_{33}NO_{10}F_3NaP$ [M + Na]$^+$, 702.1692; obsd, 702.1688.

4,6-Di-*O*-acetyl-5-fluoro-3-*O*-[(benzyloxy)methyl]-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl 1-Dibenzyl Phosphate (30a). To a solution of **29** (410 mg, 0.622 mmol) in freshly distilled CH_2Cl_2 (9 mL) was added excess dimethyldioxirane (20 mL in acetone). After 14.5 h, an additional aliquot of dimethyldioxirane (freshly prepared, 3.0 mL in acetone) was added. After 17.5 h total reaction time, the colorless solution was dried over Na_2SO_4, filtered, and evaporated, leaving a white foam/oil (417 mg). ^{1}H NMR (C_6D_6) confirmed the presence of diastereomeric epoxides (1.5:1 ratio). The product was transferred to a Schlenk tube and was placed under vacuum for 30 min. The flask was purged with Ar (3×), and the residue was dissolved in freshly distilled CH_2Cl_2 (6.5 mL). The solution was cooled to −78 °C, and HF·pyridine (150 μL) was added. After 3.5 h, HF·pyridine (50 μL) was added. After 4.5 h total reaction time, HF·pyridine (50 μL) was added. After 17 h, a final aliquot of HF·pyridine (150 μL) was added. Since no further reaction was observed, the reaction was quenched with Et_3N until pH = 7 (2.75 mL). The solution was warmed to ambient temperature, diluted with CH_2Cl_2 (40 mL), and extracted with H_2O (40 mL) and sat. $NaHCO_3$ (40 mL). The organic layer was dried over Na_2SO_4 and filtered, and the filtrate along with heptane (10 mL) was evaporated, leaving an oil (610 mg). The oil was dissolved in pyridine (2 mL), and Ac_2O (1.5 mL, 21 mmol) was added. After stirring for 1 h, the solution was partially evaporated and then diluted with CH_2Cl_2 (30 mL) and washed with sat. $NaHCO_3$ (3 × 30 mL) and sat. NaCl (30 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, leaving a green/yellow oil (472 mg). The oil was purified by flash chromatography (CH_2Cl_2/MeOH 200:1−100:1), giving mixed fractions (310 mg). The mixed fractions were further purified by preparative HPLC (Dynamax normal phase column 40% EtOAc in hexanes), giving the D-gluco title compound (125 mg, 30%) as a colorless oil along with the L-ido configured compound (59 mg 19%) as a colorless oil, as well as the 3-OAc D-gluco compound (11 mg 2.5%) as a colorless oil. Total of the 5-fluoro products: 195 mg, 52%.

(a) D-Gluco Isomer, 30a (Major Product). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.26 (m, 16H), 6.04 (dd, 1H, J = 3.2, 7.6 Hz), 5.42 (dd, 1H, J = 9.3, 22.8 Hz), 5.12−4.99 (m, 5H), 4.76 (d, 1H, J = 6.3 Hz), 4.66 (d, 1H, J = 6.3 Hz), 4.57 (m, 2H), 4.30−4.17 (m, 2H), 3.92 (dd, 1H, J = 4.3, 12.0 Hz), 2.07 (s, 3H), 2.06 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$): δ 169.66, 169.17, 157.63 (q, J = 38 Hz), 136.40, 135.17 (d, J = 7.1 Hz), 135.02 (d, J = 7.2 Hz), 128.68 (1), 128.56 (1), 128.56 (1), 128.53 (1), 128.09 (1), 127.94 (1), 127.86 (1), 127.76 (1), 115.47 (q, J = 288 Hz), 110.79 (d, J = 233 Hz), 95.65 (2), 94.04 (d, J = 6.4 Hz) (1), 71.97 (1), 69.93 (2), 69.78 (2, d, J = 5.3 Hz), 69.74 (2, d, J = 5.4 Hz), 69.34 (1, d, J = 23 Hz), 62.02 (2, d, J = 39 Hz), 52.84 (1, d, J = 7.6 Hz), 20.46 (3), 20.42 (3). ^{19}F NMR (282 MHz, $CDCl_3$): δ 0.12, −48.32 (ddd, J = 5.6, 5.6, 22.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ −3.40 (ddddd, J = 7.0 Hz) FAB-MS m/z (rel intensity): 780.3 ([M + Na]$^+$, 100.00), 758.4 ([M + H]$^+$, 31.60). FAB-HRMS calcd for $C_{34}H_{36}NO_{12}F_4NaP$ [M + Na]$^+$, 780.1809; obsd, 780.1834.

(b) L-Ido Isomer, 30b (Minor Product). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.35 (m, 15H), 6.90 (d, 1H, J = 8.8 Hz), 6.04 (dd, 1H, J = 1.0, 7.6 Hz), 5.22 (m, 1H), 5.09−5.01 (m, 4H), 4.90 (d, 1H, J = 7.2 Hz), 4.83 (d, 1H, J = 7.2 Hz), 4.69−4.58 (m, 2H), 4.50−4.37 (m, 2H), 4.01−3.92 (m, 2H), 2.03 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.68, 167.79, 156.84 (q, J = 38 Hz), 136.80, 135.10 (d, J = 6.9 Hz), 134.98 (d, J = 7.1 Hz), 128.81, 128.76, 128.62, 128.46, 128.02, 127.95, 127.90, 111.41 (d, J = 230 Hz), 94.30, 90.92 (dd, J = 3.5, 4.5 Hz), 72.54, 70.03 (d, J = 7.7 Hz), 69.95 (d, J = 7.8 Hz), 64.59 (d, J = 43 Hz), 64.76 (d, J = 23 Hz), 49.05 (d, J = 7.0 Hz), 20.37, 20.28. Several carbons overlapped in the aromatic region. Also, the sample was too dilute to observe the CF_3.^{19}F NMR (282 MHz, $CDCl_3$): δ 0.10, −42.08 (s, broad). ^{31}P NMR (121 MHz, $CDCl_3$): δ −3.15 (ddddd, J = 8.4 Hz). FAB-MS m/z (rel intensity): 780.2 ([M + Na]$^+$, 100.00), 758.2 ([M + H]$^+$, 49.05), 650.2 (13.98). FAB-HRMS calcd for $C_{34}H_{36}NO_{12}F_4NaP$ [M + H]$^+$, 780.1809; obsd, 780.1838.

Triethylammonium 4,6-Di-*O*-acetyl-5-fluoro-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl Phosphate (31). Compound **30a** (41 mg, 0.054 mmol) was dissolved in 3:1 CH_2Cl_2/MeOH (3.0 mL). Pd(OH)$_2$/C (15 mg) was added, and the reaction was fitted with a balloon containing H_2. After 4.5 h, Et_3N (15.8 μL, 0.114 mmol) was added and the reaction was filtered through Celite, washing with MeOH. The filtrate was concentrated in vacuo to give the title compound as a light yellow oil (34 mg, 100%). NMR showed 1.7 equiv Et_3N. ^{1}H NMR (300 MHz, CD_3OD): δ 5.69 (dd, 1H, J = 2.1, 8.4 Hz), 5.43 (dd, 1H, J = 8.0, 22.8 Hz), 4.30−4.24 (m, 2H), 4.19 (dd, 1H, J = 5.5, 11.7 Hz), 4.01 (dd, 1H, J = 5.4, 11.7 Hz), 3.12 (q, 12H, J = 7.2 Hz), 2.11 (s, 3H), 2.06 (s, 3H), 1.28 (t, 18H, J = 7.2 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 171.67, 171.60, 159.70 (q, J = 37 Hz), 111.49 (d, J = 232 Hz), 94.94 (d, J = 5.2 Hz), 72.93 (d, J = 24 Hz), 66.10, 63.50 (d, J = 41 Hz), 55.81 (d, J = 6.4 Hz), 47.26, 20.68, 20.55, 9.32. The sample was too dilute to observe the CF_3 carbon. ^{19}F NMR (282 MHz, CD_3OD): δ 0.67 (s), −47.28 (ddd, J = 5.6, 5.6, 22.6 Hz). ^{31}P NMR (121 MHz, CD_3OD): δ 0.57 (d, J = 8.2 Hz). FAB-MS m/z (rel intensity): 456.0 (M$^-$, 96.0), 199.0 (100.0).

Pyridinium 5-Fluoro-2-deoxy-2-acetamido-α-D-glucopyranosyl Phosphate (32). NH_3 was bubbled through a stirred −10 °C solution of **31** (34 mg, 0.054 mmol) in MeOH. The flask was sealed, and the reaction was allowed to warm to room temperature. After 1.75 h, the solvent was evaporated, giving a white powder which was dissolved in MeOH (2 mL). Acetic anhydride (100 μL, 1.07 mmol) and triethylamine (38 μL, 0.27 mmol) were added. Additional aliquots of Ac_2O (550 μL total) were added to push the reaction to completion. After 25 h, the solvent was evaporated. The resulting mixture was dissolved in MeOH and slowly added to Ac_2O (500 μL). After 2 h, the reaction was evaporated, dissolved in MeOH (4 mL), and treated for 0.5 h with NH_3 in a sealed tube. The solvent was evaporated, and the residue was dissolved in MeOH (4 mL) and treated with DOWEX 50WX8 (H$^+$ form) (100 mg) for 0.5 h. The resin was removed by filtration, and Et_3N (20 μL) was added to the filtrate. The filtrate was evaporated, leaving a brown oil (51 mg). The oil was dissolved in MeOH and purified by anion exchange chromatography (BioRad AG 1 × 8 resin, AcO$^-$ form) by washing with first H_2O (30 mL) and then 0.5 M aqueous pyridine/AcOH, pH = 4.5 (30 mL). The buffered wash was collected as one fraction and lyophilized, giving the title compound as a light brown hygroscopic solid (17 mg, 82% over two steps). ^{1}H

NMR (300 MHz, D_2O): δ 8.75 (m, 2H), 8.60 (m, 1H), 8.05 (m, 2H), 5.49 (dd, 1H, J = 3.0, 8.3 Hz), 4.08−3.98 (m, 2H), 3.73−3.63 (m, 3H), 2.01 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD): δ 173.98, 145.45, 144.71, 127.68, 114.33 (d, J = 231 Hz), 95.53 (d, J = 4.4 Hz), 72.12 (d, J = 25 Hz), 67.69, 63.18 (d, J = 36 Hz), 54.86 (d, J = 5.1 Hz), 22.69. ^{19}F NMR (282 MHz, D_2O): δ −54.57 (ddd, J = 4.5, 7.9, 23.2 Hz). ^{31}P NMR (121 MHz, D_2O): δ −1.47 (broad m). FAB-MS m/z (rel intensity): 318.1 (M^-, 100.00), 96.9 (71.93), 78.9 (69.08). A trace amount of the *N*-TFA O-deacetylated precursor of **32** was observed as indicated by a peak at 372.

Pyridinium 5-Fluoro-2-deoxy-2-acetamido-α-D-glucopyranosyl Uridine 5′-Diphosphate (1). UMP-morpholidate (8.0 mg, 0.012 mmol) and **32** (3.0 mg, 0.0078 mmol) were dissolved in dry pyridine (1.0 mL). The resulting solution was evaporated under high vacuum, and the flask was purged with Ar. This was repeated two times, and the flask was placed under high vacuum for 1.5 h. The resulting foam was dissolved in dry pyridine (500 μL), and 1*H*-tetrazole (1.6 mg, 0.024 mmol) was added. The reaction was stirred under an Ar atmosphere for 4 days. H_2O (1.0 mL) was added, and the solution was evaporated. The resulting oil was dissolved in 50 mM pyridine/AcOH buffer (pH = 4.5) and was purified via size exclusion chromatography (Biogel P-2, 1.5 cm × 67 cm), eluting with 50 mM pyridine/AcOH, pH = 4.5. Fractions (100 drops) containing the desired product as detected by TLC (3:1 CH_3CN/H_2O) were collected and lyophilized, giving the title compound as a white powder (monopyridinium salt) (2.5 mg, 45%). ^{1}H NMR (500 MHz, D_2O): δ 8.63 (m, 1H), 8.35 (m, 0.5H), 7.84−7.83 (m, 2H), 5.87−5.86 (m, 2H), 5.50 (dd, 1H, J = 3.4, 8.0 Hz), 4.26−4.25 (m, 2H), 4.16−4.03 (m, 4H), 3.95 (dd, 1H, J = 9.8, 9.8 Hz), 3.68−3.60 (m, 3H), 1.97 (s, 3H). ^{19}F NMR (282 MHz, D_2O): δ −54.11 (m). ^{31}P NMR (121 MHz, D_2O): δ −11.05 (broad m), −12.92 (broad m). FAB-MS m/z (rel intensity): 624.2 ([M]$^-$, 100.0).

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Supporting Information Available: ^{1}H spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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