Electrophilic Fluorination−Nucleophilic Addition Reaction Mediated by Selectfluor: Mechanistic Studies and New Applications

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The electrophilic fluorination−nucleophilic addition reaction with Selectfluor-type reagents upon glycals has been studied and optimized. This reaction leads to selective fluorination at the 2-position with concomitant nucleophilic addition to the anomeric center. To understand the stereochemical outcome of this process, a mechanistic study has led to the discovery that, in the fucose series, Selectfluor adds specifically in a *syn* manner, yielding a 1-[TEDA-CH_2Cl]-2-fluoro saccharide that anomerizes slowly to a more stable intermediate. The anomeric α/β distribution was studied as a function of reactants and conditions, and it was found that a judicious choice of protective group strategy can improve the stereoselectivity of both fluorination and nucleophilic addition. Furthermore, a hypersensitive radical probe was used to probe the reaction, and no product characteristic of a radical process was isolated, suggesting that no single electron transfer occurs during the attack of the glycal on Selectfluor. The importance of solvent effect, Selectfluor counterion, and stepwise procedure has also been discussed. This study has brought an important improvement of yields and a broader range of allowed nucleophiles such as secondary alcohols of carbohydrates, amino acids, phosphates, or phosphonates. This optimized process was further applied to the modification of important bioactive molecules, including the synthesis of fluorinated daunomycin and oleandrin analogues and the oxidation of thioglycosides to the corresponding sulfoxides.

Introduction

Fluorinated carbohydrates have received great attention recently as evidenced by an abundance of literature concerning the synthesis,[1−5] biological activity, and structure[6,7] of fluorocarbohydrates, particularly 2-deoxy-2-fluoro glycosides. Their intriguing biological activities include antiviral therapeutics,[8−11] cancer imaging diagnosis,[12−14] and antitumor applications.[15] Enzymologically, these molecules have been used to probe the mechanism and specificity of individual glycosyltransferases[16,17] and glycosidases,[18,19] as they can modify the activity of substrates and stabilize the glycosidic linkage against hydrolysis.[3] Though methods are available for the synthesis of 2-deoxy-2-fluoro glycosides, they are often too tedious to be of practical use. Recent procedures involve the use of molecular fluorine[20,21] or solid xenon difluoride[22−24] in reaction with glycals. Hydrolysis of the resulting 1,2-difluoro saccharide is followed by bromination and substitution with a nucleophile at the anomeric position.[5,17,25] All of these procedures require the activation of the 2-deoxy-2-fluoro sugar for glycosylation, which is a very difficult process because the inductive effect posed by the 2-fluoro group greatly suppresses the anomeric reactivity in glycosylation reactions. The poor overall yield of these reactions prompted us to develop a more direct approach to the synthesis of fluorinated glycosides.

Recently, we reported the first synthesis of fluorinated carbohydrates via reaction of glycals with 1-chloromethyl-

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(17) Murray, B. W.; Wittmann, V.; Burkart, M. D.; Hung, S.-C.; Wong, C.-H. *Biochemistry* **1997**, *36*, 823.
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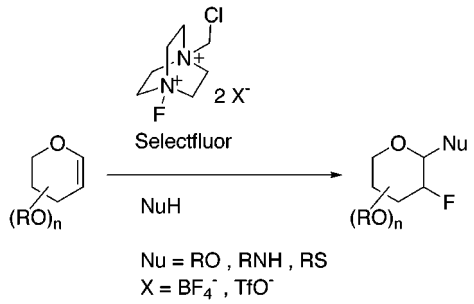
Table 1. Reaction of Diacetylfucal (2) with Selectfluor (1.2 equiv) and Benzyl Alcohol to Yield 3,4-Diacetyl-2-deoxy-2-fluoro-1-benzyl-fucose 3

entry	method	nucleophile equiv (BnOH)	solvent	method	temperature step 1	temperature step 2	α/β ratio	yield (%)
1	BF_4	excess	CH_3CN	nonstepwise	25	25	0/100	71
2	BF_4	excess	CH_3NO_2	nonstepwise	25	25	26/74	72
3	BF_4	3	CH_3NO_2	stepwise	25	25	50/50	2.4
4	BF_4	3	CH_3NO_2	stepwise	25	90	17/83	26
5	OTf	3	CH_3NO_2	stepwise	25	90	50/50	72
6	OTf	3	CH_3NO_2	nonstepwise	25	90	50/50	75
7	OTf	3	CH_3NO_2	stepwise	25	25	40/60	7
8	OTf	3	CH_3NO_2	nonstepwise	25	25	40/60	6

Scheme 1



4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate),[1] or Selectfluor[26] (Scheme 1), which has been demonstrated to be a reagent for mild fluorination.[27,28] We have demonstrated that Selectfluor reacts regioselectively with glycals to give specific fluorination at the 2-position with a concomitant functionalization at the anomeric position in one pot. It also converts the anomeric hydroxyl group to the fluorine group in the presence of dimethyl sulfide and acts as an activator of thioglycosides in glycosylation reactions. Promise of this new reagent has encouraged us to investigate the reaction mechanism and to optimize procedures for practical synthesis.

Here we report the mechanisitic study of this reaction and its application to the practical synthesis of 2-deoxy-2-fluoro glycosides, including fluoro disaccharides, fluoroglycosyl phosphates, fluorinated natural product glycosides, and the synthesis of glycosyl sulfoxides from thioglycosides.

Results and Discussion

Improvement of the Reaction between Glycal and Selectfluor. In our experience, we have found three parameters that are crucial to improving the yields and the use of a greater range of nucleophiles: solvent, reaction sequence, and reactant counterion. Combination of each optimal parameter gives an optimized reaction procedure.

Solvent Effect. In the fluorination−nucleophilic addition reaction, DMF may be used as solvent when the desired nucleophile is water. Acetonitrile may be used when other nucleophiles are present in excess.[1] Acetonitrile appears to influence the anomeric stereoselectivity in a manner similar to the situation in conventional glycosylation, favoring products with β configuration.[29] A reaction which gives exclusively the β product in acetonitrile yields an anomeric ratio of 1:3 (α/β) in nitromethane (Table 1, entries 1−2). When the nucleophile is added in stoichiometric amounts with acetonitrile as solvent (Scheme 2), acetonitrile participates in the reaction with attack at the anomeric position, and consequent addition of the nucleophile at the nitrile carbon gives the fluorinated disaccharide **1**. To avoid this undesirable reaction, nitromethane is used as the solvent because it dissolves the charged Selectfluor salts and remains inert during the reaction. Although a base or proton sponge is necessary with reactions in acetonitrile, reactions in nitromethane require no additional reagents to deprotonate the nucleophile. In a general manner, we observed that the rates of the fluorination−nucleophilic addition reaction are optimal in nitromethane.

Stepwise versus One-Step Reaction. When a stoichiometric quantity of nucleophile is used, markedly improved yields may be obtained through a two-step and one-pot reaction procedure: an initial reaction of the glycal with Selectfluor, followed by addition of the nucleophile to the mixture with heating. For most glycals, the first step must be performed at room temperature. Increased temperature for the second step improves yields with all nucleophiles (Table 1, entries 4−6) and effects anomeric configuration. Mechanistic studies concerning anomeric stereoselectivity are discussed below. The stepwise procedure allows the formation of a reactive intermediate comprised of the 1-[TEDA-CH_2Cl]-2-deoxy-2-fluoro saccharide **4**, similar to the galactose derivative described by Albert et al.[2] When the glycal has reacted completely with Selectfluor, the nucleophile is added, and heat may be applied. This new technique allows a wider scope of possible nucleophiles that can be chosen independent of their reactivity with Selectfluor. Although alcohols may be used in either the stepwise or one-step procedure as a result of their poor reactivity with Selectfluor, other reactive nucleophiles, such as phenols, amines, phosphates or thiols, benefit from a stepwise protocol. This new condition greatly expands the possible functionality to be introduced at the anomeric position.

Selectfluor Counterion. Using the triflate counterion of Selectfluor (F-TEDA-CH_2Cl 2OTf or Selecfluor triflate)[28,30] instead of the more commonly available tetrafluoroborate salt (F-TEDA-CH_2Cl $2BF_4$) gives fewer side products and improves yields dramatically.[31] The tetrafluoroborate salt gives the corresponding 1,2-difluoro saccharide as a major side product, presumably as a result of the nucleophilic addition of fluoride from the tetrafluoroborate counterion. We reasoned that a triflate

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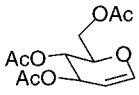
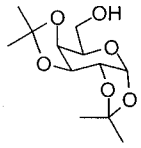
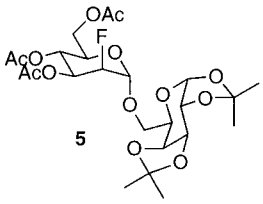
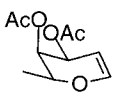
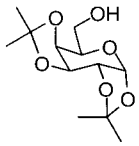
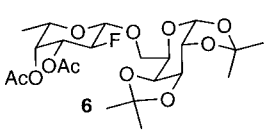
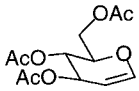
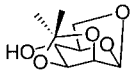
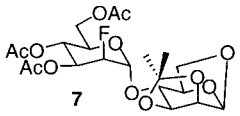
(30) Resil Chemical Co., Ltd., PO Box 113, Manchester M20, U.K.
(31) The term "Selectfluor" relates to the family of compounds with the general formula 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane (Its bis(triflate) form will be noted, in this paper, F-TEDA·2OTf or Selectfluor bistriflate form).

Scheme 2

Table 2

Entry	Glycal	Nucleophile	Product	Yield from Selectfluor Salt $2BF_4^-$	Yield from Selectfluor Salt $2OTf^-$
9			 **5**	29	75[a]
10			 **6**	40[b]	80[c]
11			 **7**	33	67[d]

a. α/β and C-F ax/eq ratios are detailed in Table 4, entry 19 **b**. this experiment is described in our first publication[1] **c**. α/β = 43/57 **d**. α/β and C-F ax/eq ratios are detailed in Table 4, entry 18.

counterion would avoid this unwanted side product and display greater solubility in nitromethane. Table 2 summarizes the importance of the triflate counterion to the fluorination−nucleophilic addition reaction. In all cases, Selectfluor triflate provides greater yields than the tetrafluoroborate salt. Entries 4 and 5 in Table 1 also demonstrate the synthetic benefit of the triflate reagent in producing higher yields. These data implicate the aforementioned side reaction of the tetrafluoroborate salt responsible for consumption of the α anomer in entry 4. A previous comparison of the triflate vs tetrafluoroborate salts for the electrophilic fluorination of aromatic rings showed little difference in reactivity and product outcome.[32] The dramatic effects seen in the fluorination−nucleophilic addition reaction illustrate the special nature of glycal chemistry.

Mechanism and Stereoselection. The fluorination−nucleophilic addition reaction may be mechanistically separated into the two stages of the stepwise procedure. The first step is reaction of the glycal with Selectfluor to form the 1-[TEDA-CH_2Cl]-2-deoxy-2-fluoro sugar intermediate. The second step is the reaction of this intermediate with the nucleophile. Our goal is to understand the mechanism of each step independently.

Selectfluor Attack: *syn*-Addition, Fluorine Stereocontrol, and Anomeric Selectivity. We have followed the first step via ^{19}F and ^{1}H NMR in CD_3NO_2 to determine the mechanism of Selectfluor attack, the structure of the intermediate, and the nature of nucleophilic addition (Figure 1). The reaction with diacetyl fucal **2** and Selectfluor triflate was chosen because it gave exclusively equatorially fluorinated products and no 1,2-difluoro side products. After 15 min of reaction, two peaks are found by ^{19}F NMR (Figure 1a). The octet corresponds to the $^4C_1$ (ring-flipped chair) form of the reactive intermediate, α-1-[TEDA-CH_2Cl]-2-deoxy-2-fluoro sugar intermediate **4** (Scheme 3).[2] ^{1}H NMR revealed the nature of the quartet as 2-fluoro diacetylfucal **8**, a side product resulting from elimination of the reactive intermediate. It should be noted that this elimination occurs only when intermediate **4** is in the $^1C_4$ conformation because of the *trans*-diaxial relationship of the leaving [TEDA-CH_2Cl] moiety and the H-2. In the spectrum from 3 h of reaction (Figure 1b,g), the glycal **2** was completely consumed (demonstrated by ^{1}H NMR), yielding only intermediate **4** and the side product of elimination (compound **8**).[33] Therefore, Selectfluor attacks the glycal in a pure *syn*-addition manner.

After 3 h, a second intermediate, **10**, began to form from **4**. Isolation and characterization of **10** showed it to

(32) Banks, R. E.; Besheesh, M. K. *J. Fluorine Chem.* **1996**, *76*, 161.

(33) In the NMR experiment, the other side reaction is the hydrolysis of the intermediates, whose structure has been assigned in our previous article. In the procedure described in the experimental part, this side reaction was prevented by the use of molecular sieves.

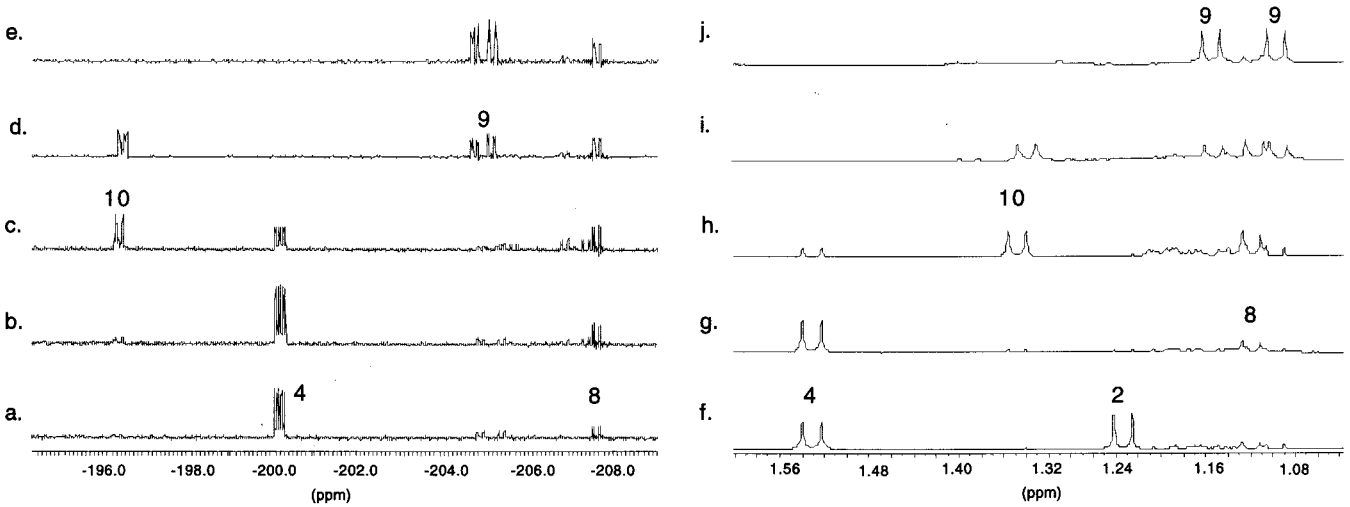
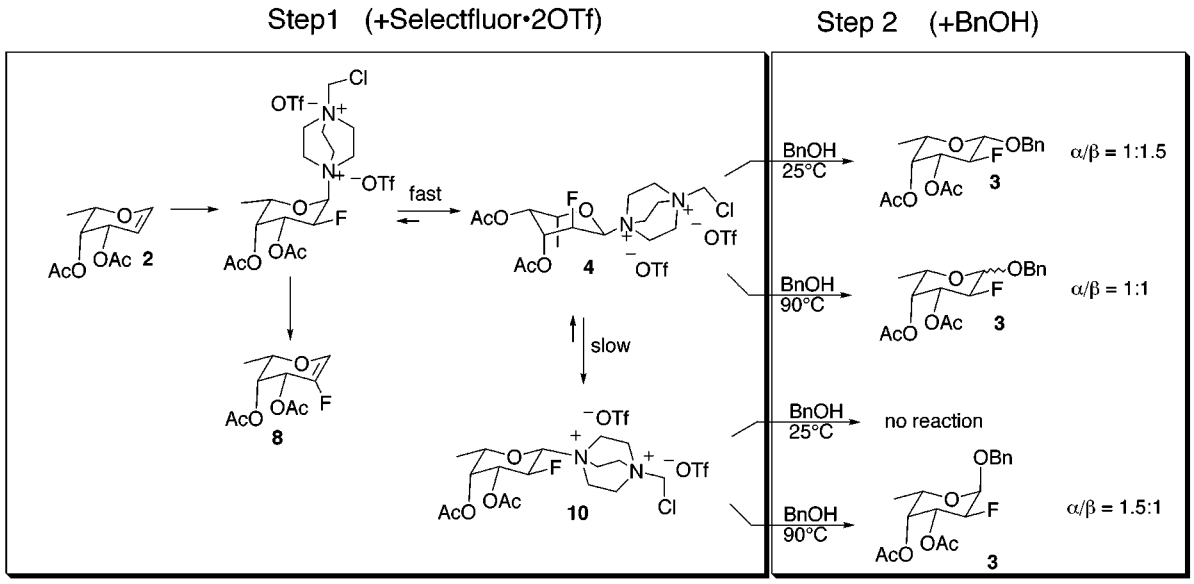


Figure 1. Time course of reaction with diacetylfucal and 1.1 equiv Selectfluor triflate in CD_3NO_2 by ^{19}F NMR (a−e) and ^1H NMR (f−j); a and f, 15 min after addition; b and g, 3 h after addition; c and h, 24 h after addition; d and i, 24 h after addition of excess H_2O at rt; e and j, after 1 h at 75 °C.

Scheme 3



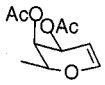
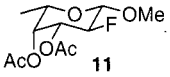
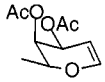
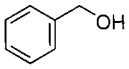
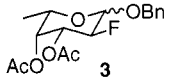
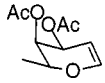
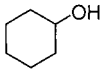
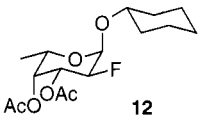
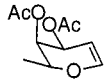
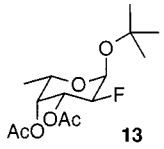
be the epimerization product of **4**, in the $^1C_4$ (non-ring flipped chair) conformation of the β-1-[TEDA-CH_2Cl]-2-deoxy-2-fluoro intermediate. It could be assumed that an anomeric triflate intermediate is involved in this process, though it is considered unstable at room temperature.[34] However this NMR experiment does not show any new species that could be assigned as a glycosyl triflate. After 24 h (Figure 1c,h), the amount of **10** continued to increase as **4** decreased in concentration, and **8** did not increase in concentration (which remained the same as at 15 min). In a separate experiment, conversion of **4** to **10** reached 95% after 72 h. When excess water was added, intermediate **4** was converted completely to the hydrolyzed form (Figure 1d,i). Only a small percentage of **10** was hydrolyzed after 24 h of exposure to water at room temperature. Heating the mixture to 75° for 30 min resulted in a complete hydrolysis of **10** (Figure 1e,j). These results indicate that the *syn*-adduct **4** slowly epimerizes to the thermodynamically more stable form **10**. The difference in hydrolysis rates may be explained by the relative stability of each intermediate. Hence, the stereochemistry of the carbon−fluorine bond is determined prior to and independent of nucleophilic addition.

At this point, the mechanism of the second step of the fluorination−nucleophilic addition reaction may be understood. Whether the nucleophile adds with pure inversion of stereochemistry (S_N2-type mechanism) or an intermediate oxonium species is involved (S_N1-type mechanism) must be understood for directed, stereocontrolled addition of complex nucleophiles.

The first experiment to identify the mechanism of nucleophilic attack is to determine the effect of steric hindrance on product distribution. We reasoned that if the reaction occurs via a pure S_N2 mechanism, the α/β anomeric ratio would remain unchanged when varying the steric bulk of the nucleophile. Table 3, entry 12, with methanol providing the least steric bulk, gives a product α/β anomeric ratio of 40:60. Benzyl alcohol (entry 13) yields 50:50, and cyclohexanol (entry 14) gives 55:45. *tert*-Butyl alcohol (entry 15), the most bulky, gives a 70:30

(34) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435.

Table 3

Entry	Glycal	Nucleophile	Product	Yield (%)	F – eq/ax	α / β
12		MeOH	 **11**	67	100	40/60
13			 **3**	75	100	50/50
14			 **12**	42	100	55/45
15			 **13**	48	100	70/30

Experimental conditions : selectfluor triflate (1.2 eq.) and glycal **2** are stirred 6h in nitromethane, then the nucleophile is added (2 eq., except for entry 15 : 10 eq.) and the mixture is heated at 90 °C during 2 hours.

α/β ratio. These results, conducted under exactly the same conditions, demonstrate that increasing steric hindrance of the nucleophile favors an α-selectivity of the process, indicating that the mechanism of nucleophilic attack is not a pure S_N2 process.

The second experiment to identify the mechanism of the second step involved addition of benzyl alcohol to **4** and **10** separately (Scheme 3). When benzyl alcohol is added to a sample of **4** in CD_3NO_2 and heated to 100° for 15 min, the resultant product proved to be a 1:1 α/β anomeric mixture. The same procedure conducted with **10** yielded a 3:2 α/β anomeric ratio. This demonstrates that both intermediates do not share the same transition state, otherwise the α/β ratio would have been the same from both epimers. These results can be explained by a pure S_N1 mechanism, with the assumption that both intermediates (**4** and **10**) follow independent pathways, yielding disparate α/β ratios. Alternatively, the results may be caused by a competition between S_N1 and S_N2 mechanisms.

Hence, general rules of anomeric selectivity can be proposed. Allowing the initial *syn*-adduct (**4**) to epimerize to the thermodynamically more stable intermediate (**10**) will lead to a higher α-selectivity of the product. Also, steric bulk of the nucleophile plays a direct role in the outcome of product anomeric selectivity, with greater bulk favoring higher α-selectivity.

Another factor that may be utilized to control anomeric stereoselectivity is the influence of protecting groups upon attack of the nucleophile. We reasoned that, in a manner similar to the steric effect of nucleophiles, one can select hindered protecting groups for the glycal to favor α products. Figure 2 shows how bulky protecting groups may be used to favor α products formation. This principle is well demonstrated in the syntheses of fluorinated daunomycinone glycosides **14**−**16** (Scheme 6) below. As the protecting group size increases on the fucal starting material, from acetyl to benzoyl to pivaloyl, α-selectivity increases consequently.

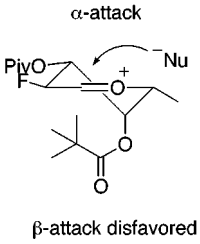


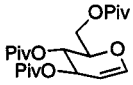
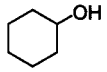
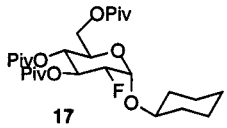
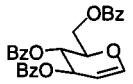
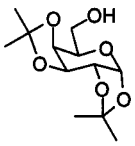
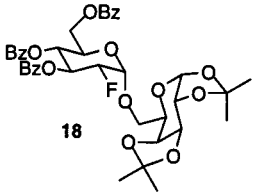
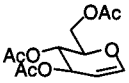
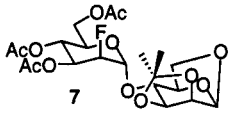
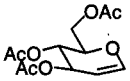
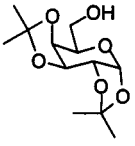
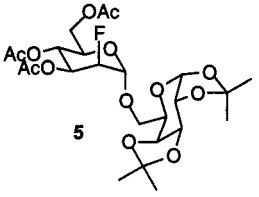
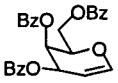
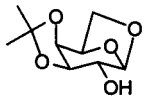
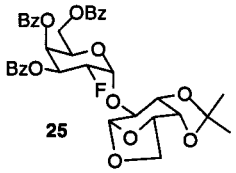
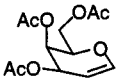
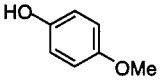
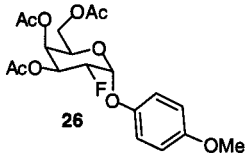
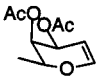
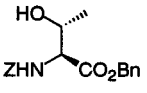
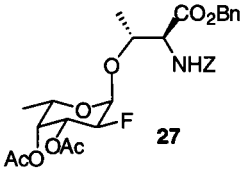
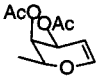
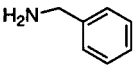
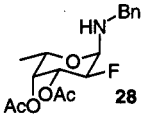
Figure 2. Oxonium intermediate involved in a S_N1-type mechanism.

Fluorination Stereoselectivity. Knowing that the mechanism of Selectfluor attack upon the glycal in the first step occurs via a *syn*-addition, we proposed to utilize glycal protecting groups to direct fluorination stereoselectivity. In the galactose and fucose series, the protecting group at the 4-position directs the stereoselectivity of the fluorine addition, yielding exclusively equatorially fluorinated products even with acetate-protected hydroxyls.[35] As triacetylglucal typically yields a 40:60 equatorial/axial ratio, favoring manno- over gluco- forms,[1] larger protecting groups should therefore lead to a larger proportion of gluco- product. Table 4, entries 16−18, demonstrates this principle. With glucal protected as the acetyl, benzoyl, and pivaloyl forms, the products possess fluorine equatorial/axial ratios of 45:55, 75:25, and 90:10, respectively. The C−F selectivity has been simply reversed through modifying the protecting group strategy. It should be noted that purification of equatorial/axial fluorinated epimers can be extremely difficult. Therefore, improving the stereoselectivity of fluorination is an essential improvement to fluoroglycoside synthesis.

In the synthesis of fluorinated oleandrigenin glycoside **19** (Scheme 6), pivaloyl protecting groups are used on the L-rhamnal starting material for the purpose of directing

(35) A correction to our previous publication:[1] in Table 1 entry 4, the C−F selectivity should be 100% in favor of the equatorial position in the galactal series.

Table 4

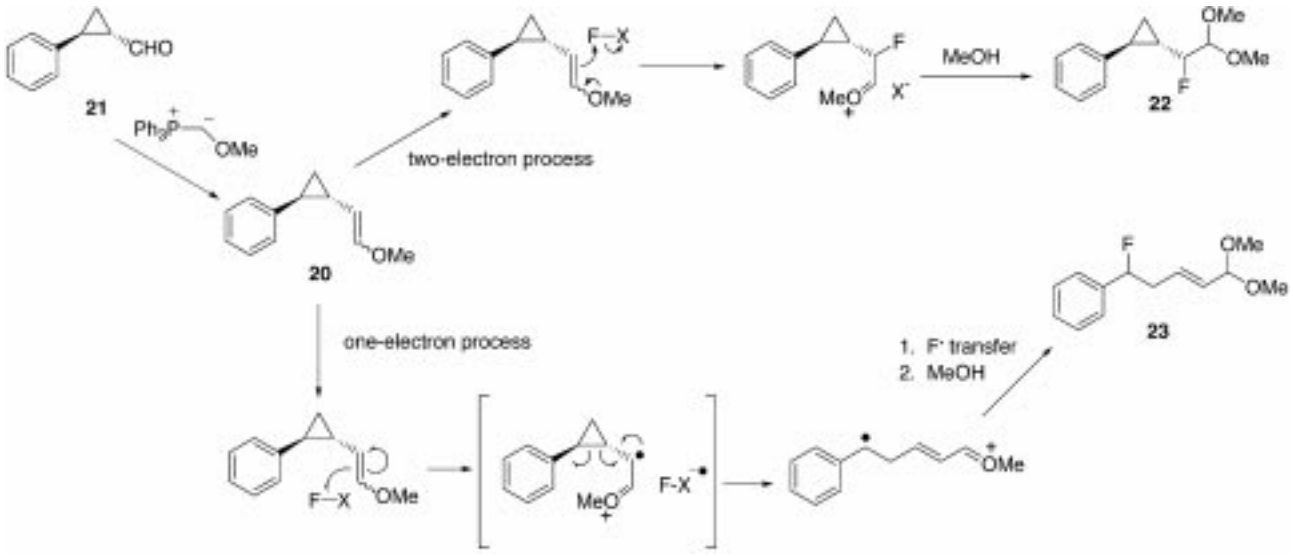
Entry	Glycal	Nucleophile	Product	Yield (%)	F – eq/ax	α / β
16			 **17**	63	90 /10	63/37 100/0
17			 **18**	68	75 / 25	61/39 100/0
18			 **7**	67	45 / 55	100/0 100/0
19			 **5**	75	33 / 67	20/80 100/0
20			 **25**	65	100/0	79/21
21			 **26**	60	100/0	60/40
22			 **27**	55	100/0	67/33
23			 **28**	53	100/0	80/20

both the C−F and the anomeric stereochemistry. We found that the fluorine equatorial/axial ratio of the product was 60:40, favoring the expected equatorial fluorination. Unlike results for fucal or galactal, this experiment shows the steric influence of both 6- and 3-positions on the stereoselectivity of fluorination when compared to the case of tripivaloyl glucal above (entry 16, Table 4).

Single-Electron vs Two-Electron Transfer Mechanism. Given our finding that Selectfluor reacts with the glycal in a *syn*-addition fashion, it must be emphasized that this is only a stereochemical observation. The true mechanism of the first step is uncertain.[36] Different mechanisms have been proposed for reactions involving N−F fluorinating reagents. Several mechanistic studies have been conducted, mainly for the fluorination reaction of carbanionic species.[37,38] Reaction mechanisms can be extremely sensitive to experimental conditions; for instance, reaction with a given radical probe may provide different results in two different solvents, demonstrating that the mechanism could not be the same in different conditions.[39] More recently, Ramsden et al. showed that

(36) Differding, E.; Bersier, P. M. *Tetrahedron* **1992**, *48*, 1595.
(37) Differding, E.; Wehrli, M. *Tetrahedron Lett.* **1991**, *32*, 3819.
(38) Differding, E.; Ruegg, G. *Tetrahedron Lett.* **1991**, *32*, 3815.
(39) Ashby, E. C.; Pham, T. N. *Tetrahedron Lett.* **1987**, *28*, 3197.

Scheme 4



reactions involving xenon difluoride could adopt different pathways depending on the basicity of the solvent used and the nature of the reaction vessel.[40] Because the glycal reaction with Selectfluor is very sensitive to solvent variation and obviously very different to the fluorination reaction of carbanions, we decided to investigate its mechanism.

The mechanistic study was begun by probing the reaction with three radical scavengers: 2,6-di-*tert*-butyl-4-methylphenol (BHT), 2,2,6,6-tetramethylpiperidinooxy (TEMPO), and *p*-quinone. To Selectfluor and triacetyl glucal were added 2 equiv of scavenger and excess methanol as nucleophile. No inhibition was seen with *p*-quinone, and methyl-2-deoxy-2-fluoroglucoside was isolated. BHT elicited slow reactivity with Selectfluor and decreased yield by 50%. TEMPO inhibited the reaction completely, and all of the starting material was recovered. In a separate experiment without glycal, TEMPO reacted independently with Selectfluor. The reactivity of TEMPO with Selectfluor points to a homolytic cleavage of the N−F bond, although no monosaccharide products that would implicate a single-electron transfer (SET) or another radical mechanism were isolated from any of these experiments.

Several recent mechanistic studies have attempted to determine the mechanism of N−F fluorinating reagents.[36−38,41−43] These studies based on kinetics, electrochemistry, or radical trapping inspired our synthesis of more sensitive molecules based on the hypersensitive radical probes containing a phenyl-cyclopropyl moiety.[44,45] Radicals formed on these molecules trigger the opening of a cyclopropyl ring at a rate of 10^{11} sec^{-1}.[44,45] We reasoned that if a SET occurs during the reaction between Selectfluor and a glycal the radical cation formed would rearrange into a noncyclic olefin.

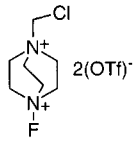
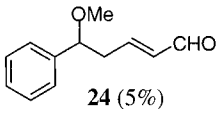
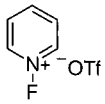
The synthesis of **20** was accomplished through a Wittig reaction of the aldehyde **21**[45] and methoxymethyl triphenylphosphonium chloride (Scheme 4). The methyl vinyl ether **20** was combined with Selectfluor triflate in the optimized conditions for fluorosugar synthesis, with methanol serving as nucleophile. As shown in Scheme 4, if the process proceeds via a heterolytic N−F cleavage, the cyclopropyl moiety will remain intact, yielding the α-fluoro acetal **22**. If a radical intermediate is involved in this process it should rearrange and give compounds such as **23**. The mechanism suggested by Umemoto et al.[43] involves a SET and subsequent F• transfer. We found that the expected fluorinated dimethoxy acetal **22** was obtained in a 45% yield with no rearrangement occurring despite complete consumption of **20**. With this probe in hand, we compared other fluorinating reagents using the same reaction to identify SET mechanisms (Table 5). With the *N*-fluoro diphenylsulfonimide (entry 25), the expected fluorinated acetal **22** was isolated with a 40% yield along with the rearranged α,*β*-unsaturated aldehyde **24** (compound already described by Mukaiyama et al.[46]), suggesting the possible existence of SET (Scheme 5). To explain the formation of compound **24**, we propose two distinct pathways, both involving SET as the first step. The two possible radical cations could undergo either a cationic or radical rearrangement. Then, F• transfer would occur followed by attack of methanol. The aldehyde is possibly formed during the workup or purification through hydrolysis of the resulting dimethoxy acetal or *gem*-fluoro methoxy compound. If **25** is formed by the radical pathway, the process involves a nucleophilic substitution of the benzylic fluoride by methanol catalyzed by the acidic diphenylsulfonamide proton.

The reaction with xenon difluoride (entry 27) provided several products containing olefins and ring-opened compounds, as seen by crude NMR. These data corroborate the recent finding that xenon difluoride can give rise to a radical process.[40] *N*-Fluoro pyridinium gave no reaction under its optimal conditions.

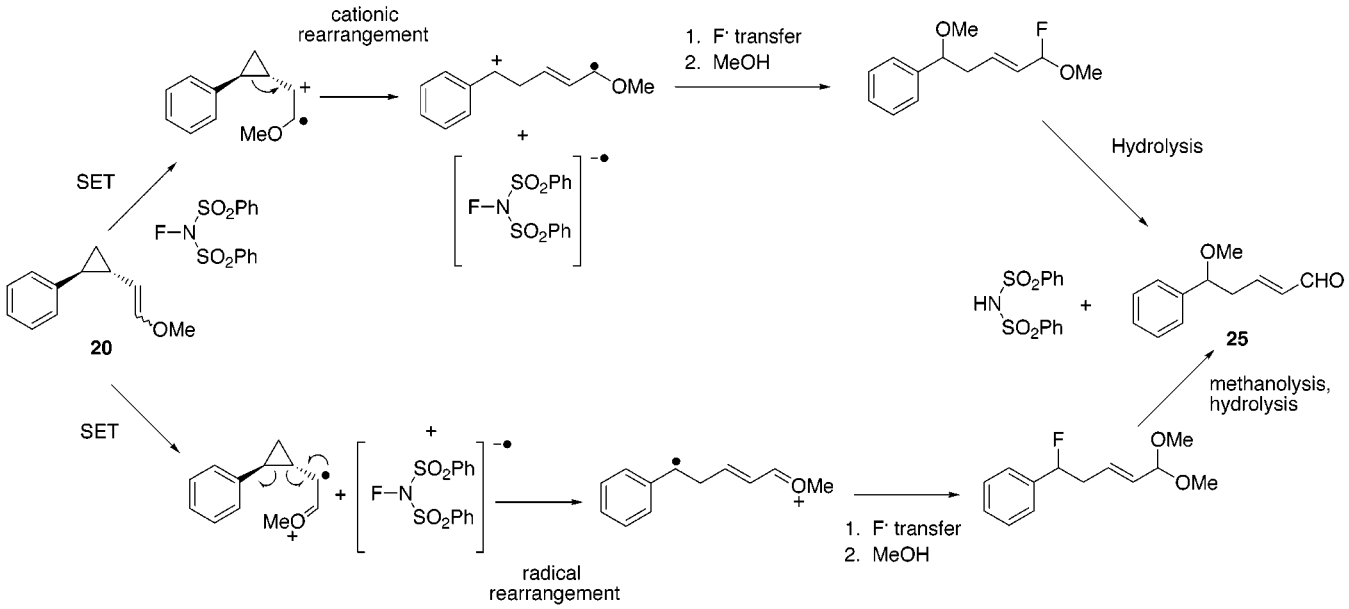
These mechanistic experiments conclude that Selectfluor proceeds via a two-electron mechanism in reaction with vinyl ethers, which may be extrapolated to reaction

(40) Ramsden, C. A.; Smith, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 6842.
(41) Zupan, M.; Skulj, P.; Stavber, S. *Chem. Lett.* **1998**, 641.
(42) DesMarteau, D. D.; Xu, Z.-Q.; Witz, M. *J. Org. Chem.* **1992**, *57*, 629.
(43) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.
(44) Newcomb, M.; Manek, B. *J. Am. Chem. Soc.* **1990**, *112*, 9663.
(45) Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6497.
(46) Ishida, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1161.

Table 5

Entry	Fluorinating reagent	Nucleophile	Product (Yield)	Mechanism type
24		MeOH	**22** (45%)	Two-electron
25	$(PhSO_2)NF$	MeOH	**22** (40%) +  **24** (5%)	one-electron
26		MeOH	No Reaction	Not determined
27	XeF_2	No nucleophile	Various Olefins; Cyclopropyl dissappearance	one-electron

Scheme 5. Putative Mechanism for Formation of Aldehyde 25

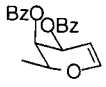
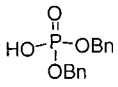
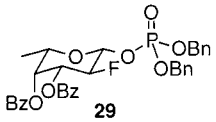
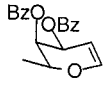
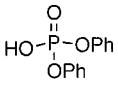
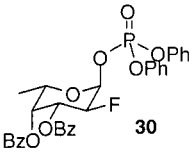
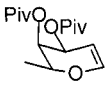
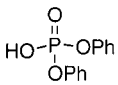
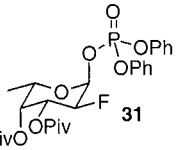
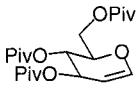
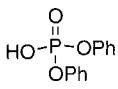
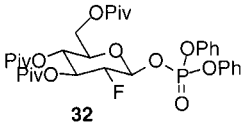
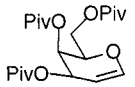
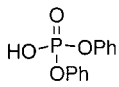
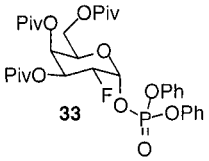
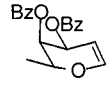
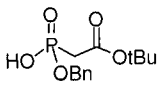
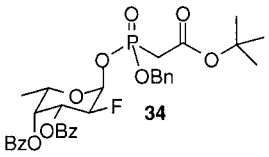


with glycals. Although these findings support previous conclusions,[41] these are the first examples of using a hypersensitive vinyligous ether radical probe to study fluorination, and they are of particular importance to the use of Selectfluor in glycal chemistry.

Synthesis of Important Fluorinated Glycosides. 2′-Deoxy-2′-fluorodisaccharides and 2-Deoxy-2-fluoro Glycosides. Given the improved reaction conditions, Selectfluor salt, and mechanistic knowledge described above, we began with the synthesis of several glycosides. Table 4 outlines 2′-deoxy-2′-fluorodisaccharides (entries 17−19) that can be made via Selectfluor triflate in good yields. Recent publications reporting the synthesis of fluorinated disaccharides required the synthesis of 1,2-difluoride from the glycal (69%),[23] formation of the 1-bromo-2-fluoride (99%),[25] and final coupling with a monosaccharide (41%),[5] giving an overall yield of 28% over three steps. By the use of Selectfluor, the reaction is conducted in one pot with a higher overall yield. In entry 17, the benzoyl protection of glucal gives the expected gluco-stereoselectivity as well as α anomeric selection. A very favorable yield is found in entry 18 even with an extremely bulky nucleophile. We believe that the severe steric hindrance of the nucleophile leads to α anomeric specificity. Increasing the size of nucleophile also increases α-selectivity as shown in entry 20. 2′-Deoxy-2′-fluorodisaccharides have been shown to be specific, mechanism-based inhibitors of glycosidases.[5]

Amino acids (entry 22), phenols (entry 21), and amines (entry 23) also serve as good nucleophiles, which must be utilized in the stepwise procedure. These reactions provide a new direction to the synthesis of new fluori-

Table 6

Entry	Glycal	Nucleophile	Product	Yield (%)	F – eq/ax	α / β
28			 **29**	54	100/0	40/60
29			 **30**	44	100/0	100/0
30			 **31**	38	100/0	100/0
31			 **32**	71	90 / 10	45/55 / 100/0
32			 **33**	70	100/0	70/30
33			 **34**	36	100/0	100/0

nated glycosides, including fluorinated glycopeptides, fluorinated nucleotides, and chromophore-labeled fluoroglycosides.

Fluoro-phosphorylation. One-pot synthesis of 2-deoxy-2-fluoro phosphate saccharides has been a goal of our Selectfluor chemistry, as they can be used for the synthesis of glycosyltransfer enzyme inhibitors. As mentioned above, nonstepwise procedures result in no desirable product formation, presumably through decomposition of Selectfluor by phosphate acidity. From these experiments, several conclusions may be drawn concerning the synthesis of fluoroglycosyl phosphates. First, the reaction is very sensitive to the choice of glycal protection. Protection with acetate gave the lowest yields (never exceeding 15% of impure material), whereas benzoyl and pivaloyl protection gave much better results (Table 6, entries 29 and 30).[47] Additionally, we found that the nature of phosphate protection can significantly modify the yield and anomeric distribution of the phosphorylation in the fucose series (entries 28 and 29). When diphenyl phosphate is used as a nucleophile, the reaction is α-specific, whereas a *β*-selectivity is observed when using dibenzyl phosphate. This trend may be due to in situ decomposition of the *β* products under the reaction conditions (90−100 °C), as phosphates in the *β*-L-fucose series generally must be stored at low temperature and have the propensity to anomerize.[47−49] It had also been noticed that *β*-fucosyl phosphates are more stable when the sugar is protected by benzoyl groups rather than acetates.[47]

Attempts to use deprotonated phosphates (triethylammonium and pyridinium salts) to enhance the nucleophilicity failed completely, yielding no expected fluoroglycosyl phosphates. The utility of this fluoro-phosphorylation technique is obvious when compared with standard methods that require at least three steps and give lower overall yields.[17] Reaction of diphenyl phosphoric acid with tripivaloyl glucal (Table 6, entry 31) and galactal (entry 32) gave both α and *β* anomers with favorable yields. In keeping with the C−F stereoselectivity described above in the gluco series, protection with pivaloates gave the expected 90:10 equatorial/axial ratio. It should be noted that the *β* phosphate is the major product of the gluco form, whereas the galacto form favors the α phosphate.

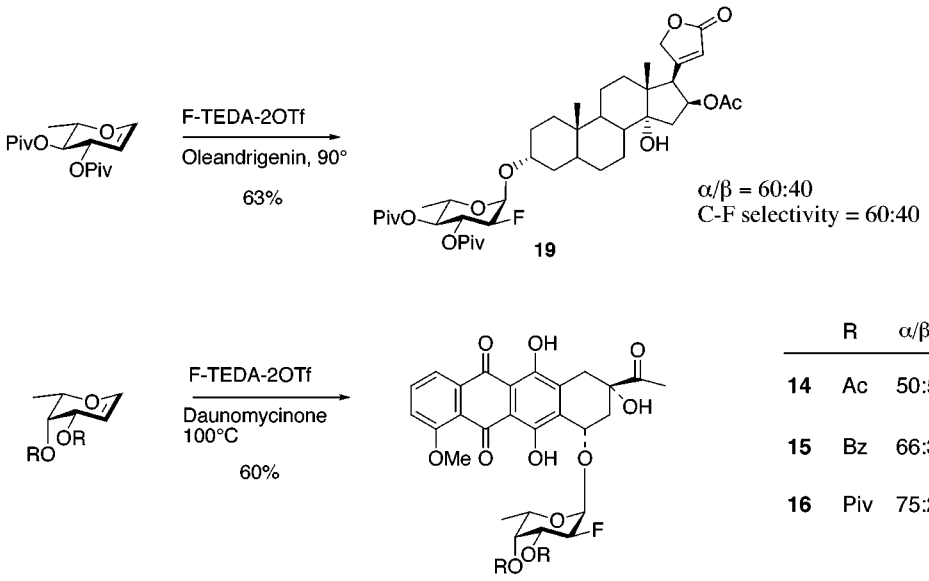
In an attempt to extend this reaction to other phosphorus-based nucleophiles, phosphites were reacted with the intermediates, but the products decomposed during

(47) Adelhorst, K.; Whitesides, G. *Carbohydr. Res.* **1993**, *249*, 69.

(48) Sim, M. M.; Kondo, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 2260.

(49) Gokhale, U. B.; Hindsgaul, O.; Palcic, M. M. *Can. J. Chem.* **1990**, *68*, 1063.

Scheme 6



	R	α/β
14	Ac	50:50
15	Bz	66:34
16	Piv	75:25

the course of the reaction. Results were more favorable with phosphonate addition, giving the expected product **34** in 36% yield with exclusive α-selectivity. This result compares favorably with standard phosphonate glycoside syntheses in which direct phosphonylation obtain produces from 25% to 50% in harsher conditions (170 °C under vacuum).[50]

Application to Known Bioactive Molecules: Cardiac Glycosides and Anthracycline Glycosides. To demonstrate the synthetic utility of the electrophilic fluorination−nucleophilic addition reaction, two biologically active natural product glycosides were chosen for the synthesis of fluorinated analogues. The following two-step procedure is a useful method of modifying natural product glycosides through fluorination. The carbohydrate is first hydrolyzed, and a glycal is used for the fluoroglycosylation of the aglycone. Fluorinated analogues of the natural product improve hydrolysis resistance and may display modified biological activity.

We began with oleandrin, a cardiac glycoside from the leaves of *Nerium oleander* that is a member of the digitalis class of cardiotonics. Hydrolysis of oleandrigeninin in boiling methanol and 1 N H_2SO_4 gives the aglycon, oleandrigenin, and the monosaccharide oleandrose. Oleandral, or 3-*O*-methyl-L-rhamnal, may be easily synthesized from the parent monosaccharide or by other methods.[51,52] For the purposes of this experiment, the commercially available L-rhamnal is used, first combined with Selectfluor triflate for 3 h at room temperature, followed by oleandrigenin and heat to reflux for 1 h (Scheme 6). Product **19** was isolated in 63% yield. The C−F stereoselectivity was 60:40 eq/ax and is rationalized by the steric hindrance of the pivaloyl protecting group. It should be noted that whereas a 60:40 α/*β* mixture is obtained when the fluorine is equatorial, only the natural α-configuration of oleandrin is observed for the product with axial fluorine, thus giving an overall 75:25 α/*β* ratio. This observation seems to be general for all reactions involving glucal-type starting materials; products with manno configuration at the 2-position consistently exhibit pure α-configuration (see also Table 4, entries 16 to 19).

The anthracycline antibiotic daunorubicin (daunomycin) is a commonly used chemotherapeutic agent that displays some undesirable side effects including high cardiotoxicity.[53] With inspiration from the glycal oxidative coupling techniques of Danishefsky to make hybrid anthracyclines,[54] we chose to synthesize the fluorinated analogue of daunorubicin by the fluorination−nucleophilic addition reaction. Several fluorinated analogues in this family have been previously described.[15] Daunorubicin was hydrolyzed in methanol/aqueous HCl to yield daunomycinone and daunosamine. We chose to substitute the natural daunosamine with 2-deoxy-2-fluoro fucal to demonstrate the viability of the one-pot reaction to bioactive molecules. To study the glycal protecting group participation in the fluorination−nucleophilic addition reaction, we investigated acetylated, benzoylated, and pivaloylated fucal as glycosyl donors. Protected fucal and Selectfluor triflate were allowed to react at room temperature for 4 h, followed by addition of daunomycinone and heat to reflux for 1 h. Products **14**−**16** were isolated in 60% yield. Daunomycinone serves as an important example of nucleophile reactivity in the fluorination−nucleophilic addition reaction. With four unprotected hydroxyls, only the secondary hydroxyl at C-7 attacks the reactive intermediate. Protecting group strategy plays an important role in product outcome. The bulky pivaloyl protecting groups on the glycal served to direct the anomeric ratio to 3:1 α/*β*. The benzoyl fucal gave a 2:1 anomeric ratio, and the acetyl derivative yielded 3:1. As the natural α-configuration is desired, the pivaloylated starting material should serve as a future route to fluorinated analogues of adriamycin and other glycosylated anthracyclines.

Oxidation of Thioglycoside to Sulfoxide. The electrophilic nature of Selectfluor was then used to fluorinate thioglycosides for use as activated glycosylation reagents[1] or as precursors to sulfoxides (Scheme 7).[34,55−58] The

(50) Vaghefi, M. M.; Bernacki, R. J.; Hennen, W. J.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1391.
(51) Tolman, R. L.; Peterson, L. H. *Carbohydr. Res.* **1989**, *189*, 113.
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(55) Kahne, D.; Walker, S.; Cheng, Y.; van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

Scheme 7. Proposed Mechanism for Activation of Thioglycoside using Selectfluor

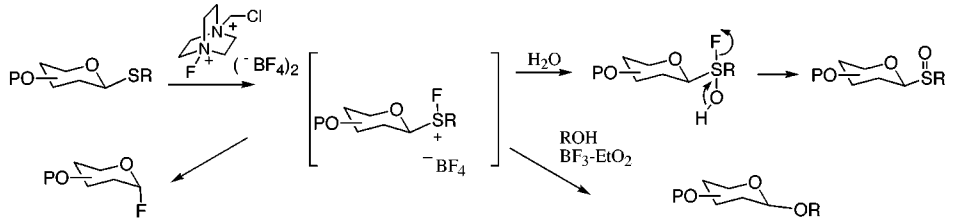
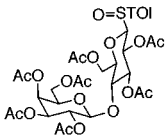
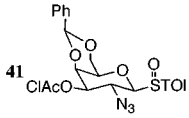
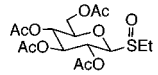
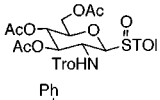
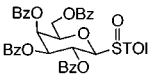
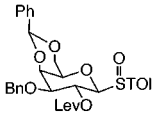
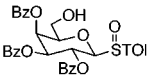
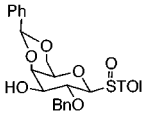
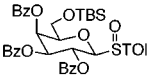
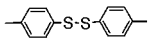
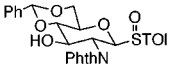
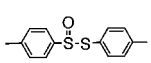


Table 7. Oxidation of Thioglycosides by Selectfluor to the Corresponding Sulfoxide

	product	Yield		product	Yield
35		99%	**41**		99%
36		99%	**42**		99%
37		99%	**43**		99%
38		99%	**44**		99%
39		95%	**45**		98%
40		99%	**46**		95%

available methods for the oxidation of thioglycosides to sulfoxides are based on *m*-chloroperoxybenzoic acid (MCPBA) at low temperature (−78 C)[55,56] or H_2O_2−AcOH.[59] The first method may cause overoxidation, requires low temperature, and is not trivial in product purification. The second method is relatively inexpensive but less efficient when dealing with less reactive thioglycosides. We have found that Selectfluor in CH_3CN-H_2O (20:1) can quantitatively oxidize thioglycosides to the corresponding sulfonyl glycosides in minutes, and no purification is needed (Scheme 7). The reaction may proceed through the fluoro-sulfonium cation,[1] which reacts with water to give the sulfoxide.

As shown in Table 7, thioglycosides with different protecting groups and with about 10^4-fold reactivity difference[60] can be oxidized quantitatively by Selectfluor. When a silyl ether (TBS) protected thioglycoside was used as substrate, the HF released from the reaction also cleaved the TBS group. To solve this problem, a weak base (5 equiv of $NaHCO_3$) was added, and the reaction was carried out in a higher concentration of water, CH_3CN-H_2O (10:1), to neutralize the HF. This modified system is also applied to the synthesis of the more reactive compound **44** to avoid the decomposition of the product.

The advantages of this method are short reaction time, quantitative conversion, and easy workup. The product generated from the reagent is not soluble in CH_2Cl_2 and can be easily washed away by water. After evaporation of the solvent, the diastereomeric mixture was obtained in quantitative yield, and the purity was confirmed by NMR. We also performed this reaction with thioglycosides bearing a hydroxyl group (**38**, **40**, and **44**). Interestingly, when we treated *p*-methylthiophenol with 0.5 equiv of Selectfluor in CH_3CN-H_2O, the disulfide **45** (Table 6) was the only product. Use of 1.5 equiv of Selectfluor gave the monosulfoxide **46**.

In conclusion, we have conducted a mechanistic study upon the electrophilic fluorination−nucleophilic addition reaction of glycals mediated by Selectfluor, which brings new insights into the nature of the intermediates involved, the factors affecting the stereochemistry of both fluorination and nucleophilic addition, and the electrophilic character of this reaction. These results allowed us to explore a broader range of nucleophiles, giving fluorinated disaccharides, glycopeptides, glycosyl phosphates, or phosphonates and fluorinated analogues of biologically relevant glycosylated compounds, directly from glycals, in a one-pot procedure. Additionally, we found that Selectfluor is a very efficient reagent for the oxidation of thioglycosides to the corresponding sulfoxides.

Experimental Section

General Procedure for the Fluorination−Nucleophilic Addition Reaction. To a mixture of glycals (100−200 mg scale, 1 equiv) and 4 Å dry molecular sieves (200 mg) in dry nitromethane (4 mL) was added F-TEDA·2OTf (1.1 equiv). After 6 h of stirring room temperature under argon, a solution of the nucleophile (1.1 equiv) in nitromethane (1 mL) is added quickly, and the solution is stirred at 100 °C for 1 h. The mixture is poured onto 100 mL of dichloromethane, filtered through Celite, and concentrated. The resulting mixture is then chromatographed.

Compound 1. Ethanimidic Acid, *N*-(2-Fluoro-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl)-1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosyl Ester. To a mixture of tri-*O*-acetyl-galactal (209 mg, 0.77 mmol), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (100 mg, 0.38 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (158 mg, 0.77 mmol), and 4 Å molecular sieves (200 mg) in dry acetonitrile (3 mL) was added F-TEDA·2BF_4 (272 mg, 0.77 mmol). The mixture was stirred for 18 h at room temperature under argon. To the reaction mixture was added dichloromethane (25 mL). The resulting solution was filtered, concentrated, and purified by silica gel chromatography (hexanes/ethyl acetate, 2:1) to give the title compound (74.8 mg, 0.13 mmol, in a 54% yield based on recovered starting material (38%)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (d, $J_{1-2} = 5.0$ Hz, 1H), 5.52 (dd, $J_{1'-2'} = 3.1$ Hz, $J_{1'-F} = 2.1$ Hz, 1H), 5.40−5.31 (m, 2H), 4.91 (ddd, $J_{2'-F} = 51.1$ Hz,

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$J_{2'-3'}$ = 10.1 Hz, $J_{2'-1'}$ = 3.1 Hz, 1H), 4.70 (t, J = 6.7 Hz, 1H), 4.64 (dd, J = 7.9, 2.4 Hz, 1H), 4.36−4.28 (m, 3H), 4.19−4.03 (m, 4H), 2.15 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.42, 170.08, 169.92, 164.55, 109.48, 108.60, 96.27, 86.7 (d, J = 187.4 Hz), 83.33 (d, J = 22.0 Hz), 71.08, 70.60, 70.50, 69.04 (d, J = 7.6 Hz), 68.77 (d, J = 18.6 Hz), 66.77, 65.91, 64.26, 61.65, 25.99, 25.92, 24.89, 24.41, 20.70, 20.65, 20.57, 16.21; ^{19}F NMR (376 MHz, $CDCl_3$) δ −202.40 (dd, J = 51.1, 10.6 Hz); HRMS (M + Cs^+) calcd for $C_{26}H_{38}FNO_{13}Cs$ 724.1382, found 724.1402.

Compound 5-*gluco*α. 2-Deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-glucosyl-(1-6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 2:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.55 (dt, $J_{3'-2'}$ = 9.6 Hz $J_{3'-F}$ = 12.6 Hz $J_{3'-4'}$ = 9.6 Hz, 1H), 5.48 (d, J_{1-2} = 5.0 Hz, 1H), 5.11 (d, $J_{1'-2'}$ = 3.8 Hz, 1H), 5.01 (t, $J_{3'-4'}$ = $J_{5'-4'}$ = 9.6 Hz, 1H), 4.59 (dd, J_{3-2} = 7.9 Hz J_{3-4} = 2.4 Hz, 1H), 4.48 (ddd, $J_{1'-2'}$ = 3.9 Hz $J_{3'-2'}$ = 9.6 Hz $J_{2'-F}$ = 49.3 Hz, 1H), 4.28 (m, 2H), 4.15 (ddd, $J_{5'-4'}$ = 10.2 Hz $J_{6'A-5'}$ = 2.1 Hz $J_{6'B-5'}$ = 4.0 Hz, 1H), 4.07 (m, 2H), 4.00 (dt, J_{5-6} = 7.9 Hz J_{5-4} = 2.4 Hz, 1H), 3.81 (AB part of an ABX system, J_{5-6A} = J_{5-6B} = 6.2 Hz J_{AB} = 10.5 Hz, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.55 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.1, 169.7, 109.3, 108.7, 96.5 (d, J_{C-F} = 25.0 Hz), 96.2, 87.3 (d, J_{C-F} = 200.0 Hz), 70.8 (d, J = 20.8 Hz), 70.7, 70.6, 70.5, 68.1, 67.9 (d, J_{C-F} = 7.5 Hz), 67.2, 66.6, 61.7, 26.1, 25.9, 24.9, 24.3, 20.7, 20.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −197.85 (dd, J_{2-F} = 49.3 Hz, J_{3-F} = 12.6 Hz); HRMS (M + Na^+) calcd for $C_{24}H_{35}FO_{13}$ 573.1959, found 573.1980.

Compound 5-*manno*α. 2-Deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-mannosyl-(1-6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.0 (d, J_{1-2} = 5.0 Hz, 1H), 5.32 (t, $J_{3'-4'}$ = $J_{5'-4'}$ = 10.1 Hz, 1H), 5.25 (ddd, $J_{3'-2'}$ = 2.5 Hz $J_{3'-F}$ = 28.3 Hz $J_{3'-4'}$ = 10.1 Hz, 1H), 5.06 (dd, $J_{1'-F}$ = 7.1 Hz $J_{1'-2'}$ = 1.6 Hz, 1H), 4.78 (dt, $J_{1'-2'}$ = $J_{3'-2'}$ = 2.0 Hz $J_{2'-F}$ = 49.7 Hz, 1H), 4.63 (dd, J_{3-2} = 2.4 Hz J_{3-4} = 7.9 Hz, 1H), 4.34 (dd, J_{3-2} = 2.4 Hz J_{1-2} = 5.0 Hz, 1H), 4.29 (dd, $J_{6'a-5'}$ = 4.7 Hz $J_{6'a-6'b}$ = 12.5 Hz, 1H), 4.22 (dd, J_{3-4} = 7.9 Hz J_{5-4} = 1.8 Hz, 1H), 4.11 (m, 2H), 3.97 (dt, J_{5-6a} = J_{5-6b} = 4.7 Hz J_{5-4} = 1.8 Hz, 1H), 3.80 (AB part of ABX, J_{5-6a} = J_{5-6b} = 4.7 Hz J_{6a-6b}= 10.4 Hz, 2H), 2.11 (s, 3H.), 2.10 (s, 3H), 2.05 (s, 3H), 1.56 (s, 3H), 1.44 (s, 3H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.78, 170.16, 169.52, 109.46, 108.72, 97.19 (d, J_{C-F} = 29.0 Hz), 96.24, 86.84 (d, J_{C-F} = 178.0 Hz), 70.86, 70.59, 70.46, 69.98 (d, J = 16.7 Hz), 68.55, 67.06, 66.09, 65.64, 61.99, 26.06, 25.93, 24.89, 24.47, 20.76, 20.66; ^{19}F NMR (376 MHz, $CDCl_3$) δ −200.85 (dd, J_{2-F} = 49.7 Hz, J_{3-F} = 28.3 Hz); HRMS (M + Na^+) calcd for $C_{24}H_{35}FO_{13}$ 573.1959, found 573.1942.

Compound 7-*gluco*α. 3′,4′,6′-Tri-*O*-acetyl-2′-deoxy-2′-fluoro-α-D-glucopyranosyl-(1′-4)-1,6-anhydro-2,3-*O*-isopropylidene-*β*-D-mannopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 2:1. The isolated products were an inseparable mixture of the α-gluco glycoside **7-*gluco*α** and the α-manno glycoside **7-*manno*α** in a ratio of 45:55.^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (dt, $J_{3'-F}$ = 11.8 Hz, $J_{3'-2'}$ = 9.6 Hz, $J_{3'-4'}$ = 9.6 Hz, 1H), 5.37−5.21 (m, 2H), 5.02 (t, $J_{4'-3'}$ = 9.6 Hz, $J_{4'-5'}$ = 9.6 Hz, 1H), 4.76 (dd, J = 6.3, 1.3 Hz, 1H), 4.52 (ddd, $J_{2'-F}$ = 49.2 Hz, $J_{2'-3'}$ = 9.6 Hz, $J_{2'-1'}$ = 3.9 Hz, 1H), 4.33−4.17 (m, 4H), 4.12 (dd, J_{2-3} = 6.3 Hz, J_{2-1} = 3.2 Hz, 1H), 3.99 (dd, J_{3-2} = 7.1 Hz, J_{3-4} = 1.1 Hz, 1H), 3.93 (s, 1H), 3.75 (t, J_{5-6} = 7.1 Hz, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.54 (s, 3H), 1.33 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −196.60 (dd, J_{F-2H} = 49.7 Hz, J_{F-3H} = 11.6 Hz); HRMS (M + Cs^+) calcd for $C_{21}H_{29}FO_{12}Cs$ 625.0697, found 625.0715.

Compound 7-*manno*α. 3′,4′,6′-Tri-*O*-acetyl-2′-deoxy-2′-fluoro-α-D-mannopyranosyl-(1′-4)-1,6-anhydro-2,3-*O*-isopropylidene-*β*-D-mannopyranose. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37−5.21 (m, 4H), 4.82 (dd, J = 6.3, 1.2 Hz, 1H), 4.80 (dt, $J_{2'-F}$ = 49.6 Hz, $J_{2'-1'}$ = 2.1 Hz, $J_{2'-3'}$ = 2.1 Hz, 1H), 4.27−4.17 (m, 4H), 4.09 (dd, J = 6.4, 3.0 Hz, 1H), 3.98 (dd, J = 7.4, 1.1 Hz, 1H), 3.95 (s, 1H,), 3.75 (t, J_{5-6} = 7.1 Hz, 1H), 2.11 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 1.54 (s, 3H), 1.33 (s,-3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −199.63 (dd, J_{F-2H} = 49.6 Hz, J_{F-3H} = 27.9 Hz); HRMS (M + Cs^+) calcd for $C_{21}H_{29}FO_{12}Cs$ 625.0697, found 625.0715.

Compound 10. 1-Chloromethyl-4-*N*-(2-deoxy-2-fluoro-3,4-di-*O*-acetyl-*β*-1-L-fucopyranosyl)-1,4-diazoniabicyclo-[2.2.2]octane Bistriflate. To a mixture of diacetyl fucal (50 mg scale, 1 equiv) and 4 Å dry molecular sieves (200 mg) in dry nitromethane (8 mL) was added F-TEDA·2OTf (1.1 equiv). After 2 days of stirring at room temperature under argon, 10 mL of AcOEt was added, and the mixture was filtered. The resulting filtrate was poured onto a mixture of AcOEt/hexane 1:1 (100 mL). After removal of the supernatant, the resulting white solid was washed once with 3 mL of chloroform and dried. ^{1}H NMR (600 MHz, CD_3NO_2) δ 5.50 (AB system, J_{AB} = 10.0 Hz, CH_2Cl), 5.47−5.38 (m, 3H 3-H and 1-H), 5.37 (dd, J_{4-F} = 2.3 Hz J_{3-4} = 2.9 Hz, 1H), 4.51−4.25 (m, partially hidden by the solvent and CH_2N), 2.17 (s, 3H), 2.07 (s, 3H), 1.33 (d, J_{5-6} = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, CD_3NO_2) δ 172.03, 171.43, 122.15 (q, J_{C-F} = 318.0 Hz, TfO^-), 95.64 (d, J_{C-F} = 23.0 Hz), 85.51 (d, J_{C-F} = 186.3 Hz), 15.64 (CH_2Cl); 72.52 (d, J = 19.5 Hz), 70.84 (d, J = 8.5 Hz), 70.59, 52.96, 51.99, 51.92, 20.62, 20.39, 15.82; ^{19}F NMR (376 MHz, CD_3NO_2) δ −109.6837 (s, TfO^-), −196.65 (dd, J_{2-F} = 55.9 Hz, J_{3-F} = 12.7 Hz); HRMS (M + Na^+) calcd for $C_{17}H_{28}O_5FClN_2$ 393.1593, found 393.1589.

Compound 11*β*. 2-Deoxy-2-fluoro-3,4-di-*O*-acetyl-α-1-methyl-L-fucopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (ddd, J_{4-5} = 0.8 Hz J_{4-F} = 2.7 Hz J_{3-4} = 3.8 Hz, 1H), 5.11 (ddd, J_{3-4} = 3.8 Hz, J_{F-3} = 13.5 Hz, J_{3-2} = 9.7 Hz, 1H), 4.49 (ddd, J_{1-2} = 7.6 Hz J_{3-2} = 9.7 Hz J_{2-F} = 53.5 Hz, 1H), 4.48 (dd, J_{1-2} = 7.6 Hz J_{1-F} = 2.2 Hz, 1H), 3.84 (qd, J_{5-6} = 6.3 Hz J_{5-4} = 0.8 Hz, 1H), 3.61 (s, 3H), 2.16 (s, 3H), 2.06 (s, 3H), 1.24 (d, J_{5-6} = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.48, 170.07, 101.49 (d, J_{C-F} = 23.1 Hz), 88.05 (d, J_{C-F} = 184.9 Hz), 71.45 (d, J = 17.3 Hz), 70.80 (d, J = 8.7 Hz), 69.08, 57.21, 20.61, 20.55, 15.84; ^{19}F NMR (376 MHz, $CDCl_3$) δ −204.08 (dd, J_{2-F} = 53.3 Hz, J_{3-F} = 15.2 Hz); HRMS (M+H^+) calcd for $C_{11}H_{17}O_6F$ 265.1087, found 265.1085.

Compound 12α. 2-Deoxy-2-fluoro-3,4-di-*O*-acetyl-α-1-(cyclohexyl)-L-fucopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (td, J_{3-2} = 9.3 Hz J_{3-F} = 9.3 Hz J_{3-4} = 3.5 Hz, 1H), 5.32 (td, J_{3-4} = 3.5 Hz, J_{F-4} = 3.5 Hz J_{5-4} = 1.0 Hz, 1H), 5.17 (d, J_{1-2} = 4.0 Hz), 5.27 (ddd, J_{1-2} = 4.0 Hz J_{3-2} = 9.3 Hz J_{2-F} = 50.5 Hz, 1H), 4.27 (qd, J_{5-6} = 7.1 Hz J_{5-4} = 1.0 Hz, 1H), 3.61 (h, J = 3.8 Hz, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 1.87 (m, 2H), 1.76 (m, 2H), 1.33 (m, 6H), 1.12 (d, J_{5-6} = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.48, 170.13, 94.86 (d, J_{C-F} = 19.2 Hz), 85.26 (d, J_{C-F} = 189.6 Hz), 76.71, 71.87 (d, J = 7.6 Hz), 68.77 (d, J = 18.0 Hz), 64.45, 33.27, 31.44, 25.50, 23.98, 23.68, 20.73, 20.60, 15.67; HRMS (M + Na^+) $C_{16}H_{25}O_6F_1$ calcd for 355.1533, found 355.1529.

Compound 12*β*. 2-Deoxy-2-fluoro-3,4-di-*O*-acetyl-*β*-1-(cyclohexyl)-L-fucopyranose. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (td, J_{3-4} = 3.5 Hz, J_{F-4} = 3.5 Hz J_{5-4} = 1.1 Hz, 1H), 5.09 (ddd, J_{3-2} = 9.4 Hz J_{3-F} = 16.7 Hz J_{3-4} = 3.5 Hz, 1H), 4.63 (dd, J_{1-2} = 7.8 Hz J_{1-F} = 3.8 Hz, 1H), 5.27 (ddd, J_{1-2} = 7.8 Hz J_{3-2} = 9.4 Hz J_{2-F} = 51.3 Hz, 1H), 3.81 (qd, J_{5-6} = 6.5 Hz J_{5-4} = 1.1 Hz, 1H), 3.61 (m, 1H), 2.15 (s, 3H), 2.05 (s, 3H), 1.95 (m, 2H), 1.76 (m, 2H), 1.36 (m, 6H), 1.21 (d, J_{5-6} = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.59, 170.14, 94.83 (d, J_{C-F} = 21.8 Hz), 88.00 (d, J_{C-F} = 184.8 Hz), 78.08, 71.69 (d, J = 19.0 Hz), 70.95 (d, J = 7.6 Hz), 64.46 (5), 33.40, 31.65, 25.49, 24.06, 23.83, 20.67, 20.64, 16.04; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 203.42 (dd, J_{2-F} = 53.3 Hz, J_{3-F} = 15.3 Hz); HRMS (M + Na^+) calcd for $C_{16}H_{25}O_6F$ 355.1533, found 355.1710.

Compound 13α. 2-Deoxy-2-fluoro-3,4-di-*O*-acetyl-α-1-*tert*-butyl-L-fucopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (td, J_{3-2} = 10.2 Hz J_{3-F} = 10.2 Hz J_{3-4} = 3.5 Hz, 1H), 5.32 (td, J_{3-4} = 3.5 Hz, J_{F-4} = 3.5 Hz, J_{5-4} = 2.2 Hz, 1H), 5.30 (d, J_{1-2} = 4.0 Hz), 4.71 (ddd, J_{1-2} = 4.0 Hz J_{3-2} = 10.2 Hz J_{2-F} = 51.0 Hz, 1H), 4.27 (qd, J_{5-6} = 7.0 Hz J_{5-4} = 2.2 Hz, 1H), 2.16 (s, 3H), 2.04 (s, 3H), 1.27 (s,

9H), 1.10 (d, J_{5-6} = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.50, 170.18, 90.95 (d, J_{C-F} = 19.9 Hz), 85.06 (d, J_{C-F} = 188.6 Hz), 75.75, 71.96 (d, J = 7.6 Hz), 68.95 (d, J = 18.0 Hz), 63.99, 28.41, 20.75, 20.59, 15.69; ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.42 (dd, J_{2-F} = 50.8 Hz, J_{3-F} = 7.6 Hz); HRMS (MH^+) calcd for $C_{14}H_{23}O_6F$ 307.1557, found 307.1554.

Compound 13*β*. 2-Deoxy-2-fluoro-3,4-di-*O*-acetyl-α-1-*tert*-butyl-L-fucopyranose. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (ddd, J_{4-5} = 1.1 Hz J_{4-F} = 2.5 Hz J_{3-4} = 3.5 Hz, 1H), 5.12 (ddd, J_{3-4} = 3.5 Hz, J_{F-3} = 13.2 Hz, J_{3-2} = 9.7 Hz, 1H), 4.68 (dd, J_{1-2} = 7.6 Hz J_{1-F} = 3.8 Hz), 4.58 (ddd, J_{1-2} = 7.6 Hz J_{3-2} = 9.7 Hz J_{2-F} = 51.3 Hz, 1H), 3.81 (qd, J_{5-6} = 6.5 Hz J_{5-4} = 1.1 Hz, 1H), 2.15 (s, 3H), 2.06 (s, 3H), 1.30 (s, 9H), 1.20 (d, J_{5-6} = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.60, 170.15, 95.17 (d, J_{C-F} = 22.8 Hz), 87.90 (d, J_{C-F} = 183.9 Hz), 75.66, 71.76 (d, J = 18.0 Hz), 71.00 (d, J = 7.6 Hz), 68.89, 28.47, 20.67, 20.64, 16.19; ^{19}F NMR (376 MHz, $CDCl_3$) δ −202.91 (dd, J_{2-F} = 50.8 Hz, J_{3-F} = 12.7 Hz); HRMS (MH^+) calcd for $C_{14}H_{23}O_6F$ 307.1557, found 307.1554.

Compound 16. 7-*O*-(2-Deoxy-2-fluoro-3,4-*O*-dipivaloyl-α-L-fucopyranosyl)-daunomycinone. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.01 (s, 1H, 6-OH), 13.27 (s, 1H, 11-OH), 8.04 (d, J_{1-2} = 8.1 Hz, 1H), 7.78 (t, J_{1-2} = 8.1 Hz, 1H), 7.78 (d, J_{3-2}= 8.1 Hz, 1H), 5.74 (d, 1H), 5.44 (dd, J_{7-8ax} = 3.7 Hz, J_{7-8eq}= 5.9 Hz, 1H, 7-H), 5.38 (t, $J_{4'-3'}$ = 2.9 Hz, 1H), 5.23 (dt, $J_{3'-4'}$ = 2.9 Hz, $J_{3'-2'}$ = 10.3 Hz, 1H), 4.74 (ddd, $J_{2'-1'}$ = 4.1 Hz, $J_{2'-3'}$ = 10.3 Hz, $J_{2'-F}$ = 49.9 Hz, 1H), 4.41 (m, 1H), 4.20 (s, 1H, 9-OH), 4.08 (s, 3H, 4-OMe), 3.27 (dd, J = 1.5 Hz, J_{ax-eq} = 19.1 Hz, 1H, 10 ax-H), 3.01 (d, J_{ax-eq} = 19.1 Hz, 1H, 10 eq- H), 2.42 (s, 3H, 9-COMe), 2.33 (dd, J = 3.7 Hz, J_{ax-eq} = 15.0 Hz, 1H, 8 eq-H), 2.21 (d, J_{ax-eq} = 15.0 Hz, 1H, 8 ax-H), 1.28 (s, 9H, tBu), 1.18 (d, $J_{5'-6'}$ = 6.6, 3H), 1.12 (s, 9H, tBu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.2 (CO-13), 187.1 (5-C), 186.8 (12-C), 177.3 (CO−Pv), 177.2 (CO−Pv), 161.0 (4), 156.3, 155.7 (11), 135.7 (2-C), 135.6 (12a−C), 134.7 (10a−C), 133.1 (6a−C), 121.0 (4a−C), 119.8, 118.4 (3-C), 111.63 (5a−C), 111.56 (11a−C), 98.4 ($J_{1'-F}$ = 9.5 Hz), 85.1 ($J_{2'-F}$ = 192.6 Hz), 76.5 (9-C), 71.2 ($J_{3'-F}$ = 7.6 Hz), 69.3 (7-C), 68.4, ($J_{4'-F}$ = 18.1 Hz), 66.0 (5′-C), 56.7 (4-OMe), 35.5 (8), 33.8 (10), 29.7 (Pv), 27.3 (Pv), 26.9 (Pv), 24.9, (14), 15.8 (6′-C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −205.7 (dd, J = 9.9, 49.7 Hz); HRMS (M + Cs^+) calcd for $C_{37}H_{43}FNO_{13}Cs$ 847.1742, found 847.1773.

Compound 17α. 2-Deoxy-2-fluoro-3,4,6-tri-*O*-pivaloyl-α-1-(cyclohexyl)-D-glucopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 3:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (td, J_{3-2} = 9.7 Hz J_{3-F} = 11.9 Hz J_{3-4} = 9.7 Hz, 1H), 5.18 (d, J_{1-2} = 3.8 Hz, 1H), 5.02 (t, J_{3-4} = 9.7 Hz, J_{5-4} = 10.0 Hz, 1H), 4.44 (ddd, J_{1-2} = 3.8 Hz J_{3-2} = 9.7 Hz J_{2-F} = 49.9 Hz, 1H), 4.17−4.03 (m, 3H), 3.61 (m, 1H), 1.89 (m, 2H), 1.76 (m, 2H), 1.36 (m, 6H), 1.22 (s, 9H), 1.17 (s, 9H), 1.16 (s, 9H).

Compound 17*β*. 2-Deoxy-2-fluoro-3,4,6-tri-*O*-pivaloyl-*β*-1-(cyclohexyl)-D-glucopyranose. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.35 (td, J_{3-2} = 9.2 Hz J_{3-F} = 14.0 Hz J_{3-4} = 9.2 Hz, 1H), 5.01 (t, J_{3-4} = 9.2 Hz, J_{5-4} = 10.0 Hz, 1H), 4.68 (dd, J_{1-2} = 7.9 Hz J_{1--F} = 2.6 Hz, 1H), 4.25 (ddd, J_{1-2} = 7.9 Hz J_{3-2} = 9.2 Hz J_{2-F} = 50.8 Hz, 1H), 4.11 (AB part of ABX, J_{A-B} = 12.2 Hz J_{A-X} = 1.7 Hz J_{B-X} = 7.0 Hz, 2H), 3.73 (ddd, J_{5-4} = 10.0 Hz J_{A-X} = 1.7 Hz J_{B-X} = 7.0 Hz, 1H), 3.67 (m, 1H), 1.90 (m, 2H), 1.76 (m, 2H), 1.53−1.23 (m, 6H), 1.21 (s, 9H), 1.17 (s, 9H), 1.16 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.03, 177.30, 176.65, 98.72 (d, J_{C-F} = 22.0 Hz), 89.87 (d, J_{C-F} = 189.0 Hz), 72.49 (d, J = 19.8 Hz), 72.18, 67.85 (d, J = 6.6 Hz), 62.26, 38.78, 33.40, 31.64, 27.07, 27.03, 26.98, 25.46, 23.91, 23.76; ^{19}F NMR (376 MHz, $CDCl_3$) δ −196.37 (dd, J_{2-F} = 48.2 Hz, J_{3-F} = 12.7 Hz); HRMS (MH^+) calcd for $C_{27}H_{45}O_8F$ 517.3177, found 517.3161.

Compound 18-*gluco*α. 3′,4′,6′-Tri-*O*-benzoyl-2′-deoxy-2′-fluoro-α-D-glucopyranosyl-(1′-6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 4:1. The title compound was isolated as an inseparable mixture of the α-gluco glycoside **18-*gluco*α** and the α-manno glycoside **18-*manno*α** in a ratio of 2:1. The *β*-gluco glycoside **18-*glucoβ*** was isolated to purity. **18-*gluco*α**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−7.92 (m, 6H), 7.56−7.39 (m, 9H), 6.07 (dt, $J_{3'-F}$ = 11.4 Hz, $J_{3'-2'}$ = 9.6 Hz, $J_{3'-4'}$ = 9.6 Hz, 1H), 5.60 (t, $J_{4'-3'}$ = 9.7 Hz, $J_{4'-5'}$ = 9.7 Hz, 1H), 5.54 (d, J_{1-2} = 4.8 Hz, 1H), 5.27 (d, $J_{1'-2'}$ = 3.8 Hz, 1H), 4.74 (ddd, $J_{2'-F}$ = 49.5, $J_{2'-3'}$ = 9.6 Hz, $J_{2'-1'}$ = 3.8 Hz, 1H), 4.65−3.92 (m, 9H), 1.63 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −197.38 (dd, $J_{F-2'}$ = 51.1 Hz, $J_{F-3'}$ = 10.6 Hz); HRMS (M + Cs^+) calcd for $C_{39}H_{41}FO_{13}Cs$ 869.1586, found 869.1611.

Compound 18-*glucoβ*. 3′,4′,6′-Tri-*O*-benzoyl-2′-deoxy-2′-fluoro-*β*-D-glucopyranosyl-(1′-6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.88 (m, 6H), 7.56−7.32 (m, 9H), 5.84 (dt, $J_{3'-F}$ = 14.0 Hz, $J_{3'-2'}$ = 9.2 Hz, $J_{3'-4'}$ = 9.2 Hz, 1H), 5.58 (t, $J_{4'-3'}$ = 9.2 Hz, $J_{4'-5'}$ = 9.2 Hz, 1H), 5.54 (d, J_{1-2} = 5.0 Hz, 1H), 4.98 (dd, $J_{1'-2'}$ = 7.6 Hz, $J_{1'-F}$ = 2.8 Hz, 1H), 4.62−4.57 (m, 2H), 4.58 (ddd, $J_{2'-F}$ = 50.5 Hz, $J_{2'-3'}$ = 9.2 Hz, $J_{2'-1'}$ = 7.6 Hz, 1H), 4.45 (dd, $J_{6b'-6a'}$ = 12.1 Hz, $J_{6b'-5'}$ = 5.5 Hz, 1H), 4.31 (dd, J_{1-2} = 5.0 Hz, J_{2-3} = 2.4 Hz, 1H), 4.22 (dd, J_{4-3} = 7.9 Hz, J_{4-5} = 1.5 Hz, 1H), 4.15−4.03 (m, 3H), 3.95−3.90 (m, 1H), 1.55 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.03, 165.54, 165.18, 133.46, 133.32, 133.06, 129.80, 129.68, 128.39, 128.33, 128.30, 109.36, 108.75, 100.46 (d, $J_{1'C-F}$ = 23.2 Hz), 96.22, 89.55 (d, $J_{2'C-F}$ = 191.7 Hz), 73.07 (d, $J_{3'C-F}$ = 20.3 Hz), 71.92, 71.17, 70.57, 7034, 69.27 (d, $J_{4'C-F}$ = 7.2 Hz), 68.80, 67.68, 63.06, 25.96, 25.89, 24.92, 24.34; ^{19}F NMR (376 MHz, $CDCl_3$) δ −195.28 (dd, $J_{F-2'H}$ = 50.5 Hz, $J_{F-3'H}$ = 14.0 Hz); HRMS (M + Cs^+) calcd for $C_{39}H_{41}FO_{13}Cs$ 869.1586, found 869.1554.

Compound 18-*manno*α. 3′,4′,6′-Tri-*O*-benzoyl-2′-deoxy-2′-fluoro-α-D-mannopyranosyl-(1′-6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−7.92 (m, 6H), 7.56−7.39 (m, 9H), 5.96 (t, $J_{4'-3'}$ = 10.1 Hz, $J_{4'-5'}$ = 10.1 Hz, 1H), 5.70 (ddd, $J_{3'-F}$ = 28.5, $J_{3'-4'}$ = 10.1 Hz, $J_{3'-2'}$ = 2.6 Hz, 1H), 5.55 (d, J_{1-2} = 4.3 Hz, 1H), 5.19 (dd, $J_{1'-F}$ = 7.0 Hz, $J_{1'-2'}$ = 1.8 Hz, 1H), 5.03 (dt, $J_{2'-F}$ = 49.9, $J_{2'-3'}$ = 2.2 Hz, $J_{2'-1'}$ = 2.2 Hz, 1H), 4.65−3.96 (m, 7H), 4.26 (dd, J_{4-3} = 7.9 Hz, J_{4-5} = 1.9 Hz, 1H), 3.86 (dd, J_{6b-6a} = 10.4 Hz, J_{6b-5} = 5.9 Hz, 1H), 1.60 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −201.14 (ddd, $J_{F-2'H}$ = 49.6 Hz, $J_{F-3'H}$ = 28.3 Hz, $J_{F-1'H}$ = 6.2 Hz); HRMS (M + Cs^+) calcd for $C_{39}H_{41}FO_{13}Cs$ 869.1586, found 869.1611.

Compound 19. (3*β*,5*β*,14*β*,16*β*,17*β*)-3-[2-Deoxy-2-fluoro-3,4-di-*O*-pivaloyl-α-L-rhamnosyl]-16-acetoxy-14-hydroxy-card-20(22)-enolide (XX) (3-[2-Deoxy-2-fluoro-3,4-di-*O*-pivaloyl-α-L-rhamnopyranosyl]-oleandrigenin). Silica gel chromatography (9:1 dichloromethane/ethyl acetate) yields product (33.6 mg, 65%) as a fluffy white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H, 21-H), 5.49 (dt, J = 9.4 Hz J = 2.4 Hz, 1H, 16-H), 5.32 (dt, $J_{3'-4'}$ = $J_{2'-3'}$ = 9.2 Hz J_{F-3} = 14.3 Hz, 1H), 4.95 (ABX, J_{AB} = 9.2 Hz J_{AX} = J_{BX} = 1.6 Hz, 2H, 21-H), 4.84 (dd, $J_{3'-4'}$ = $J_{5'-4'}$ = 9.2 Hz, 1H), 4.60 (dd, $J_{1'-2'}$ = 7.8 Hz $J_{F-1'}$ = 2.7 Hz, 1H), 4.28 (ddd, $J_{1'-2'}$ = 7.8 Hz $J_{2'-3'}$ = 9.2 Hz $J_{2'-F}$ = 50.8 Hz, 1H), 4.06 (s, 1H, 14-O*H*), 3.59 (m, 1H), 3.20 (d, J = 8.6 Hz, 1H, 17-H), 2.74 (dd, J = 9.7 Hz J = 15.7 Hz, 3H, 15a-H).

Compound 20. (*trans*-Phenyl-cyclopropyl)-methoxy-ethene. A suspension of triphenyl[(methoxy)-methyl]phosphonium chloride (2.78 g, 8.11 mmol) in 10 mL of anhydrous THF at −78 °C was treated dropwise with a solution of *n*-BuLi (4.7 mL, 1.6 M in hexane, 7.52 mmol). The reaction mixture was stirred for 5 min at −78 °C, the cooling bath was removed, and the mixture was stirred and allow to warm until it reached 0 °C. The mixture was recooled to −78 °C, and the aldehyde **21** (1.1 g, 7.53 mmol) in 10 mL of THF was added dropwise. The reaction mixture was stirred 1 h at −78 °C and then 12 h at room temperature before it was quenched by the addition of phosphate buffer (pH = 7.1). The mixture was extracted 3 times with EtOAc, and the combined organic phase was dried over $MgSO_4$ and concentrated in vacuo. Chromatography on silica gel (AcOEt/hexane/Et_3N, 4:95:1) afforded **20** (0.88 g, 5.06 mmol, 67% yield) as a mixture of E and Z olefin isomers in a 3/2 ratio. Some fractions of pure E isomer have been collected that allowed the interpretation of the NMR spectra of the mixture. **Pure E**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, J = 7.7 Hz, $2H_m$), 7.13 (dd, J = 7.3 Hz J = 9.2 Hz, $1H_p$), 7.05 (d, J

= 8.1 Hz, 2H$_o$), 6.42 (d, J_{trans} = 12.4 Hz, 1H, 1), 4.62 (dd, J_{trans} = 12.4 Hz, J = 7.7 Hz, 1H, 4), 3.50 (s, 3H), 1.78 (ddd, J = 4.8 Hz J = 4.4 Hz J = 9.2 Hz, 1H, 4), 1.54 (m, 1H, 3), 1.11 (td, J = 5.1 Hz J = 5.1 Hz J_{B-X} = 5.8 Hz, 1H, 5), 0.99 (td, J = 5.1 Hz J = 5.1 Hz J = 9.2 Hz, 1H, 5); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.24, 142.81, 128.26, 125.48, 125.38, 105.40, 56.06 (OMe), 24.74 (4), 22.30 (3), 16.38 (5). **Mixture E/Z 3/2:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.00 (m, 5H), 6.42 (d, J_{trans} = 12.4 Hz, 0.6H, 1$_E$), 5.93 (d, J_{cis} = 6.2 Hz, 0.4H, 1$_Z$), 4.62 (dd, J_{trans} = 12.4 Hz, J = 7.7 Hz, 0.6H, 2$_E$), 4.03 (dd, J_{cis} = 6.2 Hz J = 9.2 Hz, 0.4H, 2$_Z$), 3.58 (s, 1.2H, OMe$_Z$), 3.50 (s, 1.8H, OMe$_E$), 1.98 (m, 0.4H, 3$_Z$), 1.84 (ddd, J = 4.8 Hz J = 4.4 Hz J = 9.2 Hz, 0.4H, 4$_Z$), 1.78 (ddd, J = 4.8 Hz J = 4.4 Hz J = 9.2 Hz, 0.6H, 4$_E$), 1.54 (m, 0.6H, 3$_E$), 1.18 (td, J = 5.1 Hz J = 5.1 Hz J = 9.2 Hz, 0.4H, 5$_Z$), 1.11 (td, J = 5.1 Hz J = 5.1 Hz J = 9.2 Hz, 0.6H, 5E), 0.99 (m, 1H, 5); ^{13}C NMR (150 MHz, $CDCl_3$) 147.24 (1E), 146.22 (1Z), 142.81, 128.26, 128.18, 125.55, 125.48, 125.38, 109.31 (2Z), 105.40 (2E), 59.64 (OMeZ), 56.06 (OMeE), 24.97 (4Z), 24.74 (4E), 22.30 (3E), 19.85 (3Z), 17.36 (5Z), 16.38 (5E).

Compound 22. 2-(*trans*-2-Phenyl-cyclopropyl)-2-fluoro-ethanal dimethylacetal. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 9:1; 2 diastereoisomers, ratio 6/4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.00 (m, 5H), 4.44 (dd, J = 5.1 Hz J = 2.7 Hz, 0.4H), 4.42 (dd, J = 5.7 Hz, J = 2.7 Hz, 0.6H), 4.11 (ddd, J = 5.7 Hz J = 7.3 Hz J = 47.8 Hz, 0.6H), 4.09 (ddd, J = 5.2 Hz J = 7.6 Hz J = 47.5 Hz, 0.4H), 3.48 (d, J = 2.4 Hz, 1.2H), 3.46 (d, J = 4.0 Hz, 1.8H), 2.04 (m, 1H), 1.44 (m, 1H), 1.14 (td, J = 5.1 Hz J = 5.1 Hz J = 9.2 Hz, 0.4H), 1.11 (m, 1.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.73, 141.61, 128.40, 128.35, 126.22, 125.89, 125.82, 104.56 (d, J = 26 Hz), 104.45 (d, J = 27 Hz), 94.26 (d, J = 176 Hz), 93.80 (d, J = 175 Hz), 55.36 (d, J = 117 Hz), 55.07 (d, J = 126 Hz), 22.26 (d, J = 23 Hz, 4), 22.02 (d, J = 23 Hz, 4), 20.36 (d, J = 10 Hz), 19.92 (d, J = 2.9 Hz), 12.49 (d, J = 8.7 Hz), 11.81 (d, J = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −187.41 (dd), −189.22 (dd).

Compound 25α. 3′,4′,6′-Tri-*O*-benzoyl-2′-deoxy-2′-fluoro-α-D-galactopyranosyl-(1′-2)-1,6-anhydro-3,4-*O*-isopropylidene-*β*-D-galactose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 3:1. The title compound was isolated as an inseparable mixture of the α-gluco glycoside **25-*gluco*α** and the α-manno glycoside **25-*manno*α** in a ratio of 4:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−7.98 (m, 4H), 7.88−7.84 (m, 2H), 7.65−7.30 (m, 9H), 6.03 (t, $J_{4'-F}$ = 2.4 Hz, $J_{4'-3'}$ = 2.4 Hz, 1H), 5.85 (td, $J_{3'-F}$ = 10.3 Hz, $J_{3'-2'}$ = 10.3 Hz, $J_{3'-4'}$ = 3.4 Hz, 1H), 5.49 (s, 1H), 5.46 (d, $J_{1'-2'}$ = 3.8 Hz, 1H), 5.12 (ddd, $J_{2'-F}$ = 49.9 Hz, $J_{2'-3'}$ = 10.3 Hz, $J_{2'-1'}$ = 3.8 Hz, 1H), 4.66 (t, J = 6.8 Hz, 1H), 4.57−4.49 (m, 3H), 4.36 (dd, $J_{6b'-6a'}$ = 11.4 Hz, $J_{6b'-5'}$ = 5.5 Hz, 1H), 4.35 (d, J = 8.0 Hz, 1H), 4.11 (d, J = 7.6 Hz, 1H), 3.98 (s, 1H), 3.60 (dd, J = 7.4, 5.2 Hz, 1H), 1.47 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.02, 165.48, 165.27, 133.67, 133.29, 133.24, 129.81, 129.74, 128.63, 128.39, 128.27, 108.72, 99.01, 96.57 (d, $J_{1'C-F}$ = 20.9 Hz), 85.29 (d, $J_{2'C-F}$ = 192.1 Hz), 77.17, 74.56, 71.97, 69.38 (d, $J_{4'C-F}$ = 7.4 Hz), 69.13, 68.66 (d, $J_{3'C-F}$ = 18.6 Hz), 67.90, 63.08, 62.35, 25.69, 24.15; ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.66 (dd, $J_{F-2'H}$ = 49.9 Hz, $J_{F-3'H}$ = 10.1 Hz); HRMS (M + Cs^+) calcd for $C_{36}H_{35}FO_{12}Cs$ 811.1167, found 811.1196.

Compound 26. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-1-α-(4-methoxyphenyl)-D-galactose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 3:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07−7.02 (m, 2H), 6.87−6.82 (m, 2H), 5.64−5.58 (m, 2H) 5.56 (td, J = 3.4 Hz, J = 3.4 Hz, J = 1.0 Hz, 1H), 4.90 (ddd, J = 49.6 Hz, J = 10.2 Hz, J = 3.8 Hz, 1H), 4.43 (td, J = 6.7 Hz, J = 1.0 Hz, 1H), 4.11 (d, J = 6.7 Hz, 2H), 3.78 (s, 3H), 2.16 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.31, 169.99, 155.56, 150.30, 118.33, 114.60, 96.20 (d, J_{1C-F} = 21.0 Hz), 84.89 (d, J_{2C-F} = 192.6 Hz), 68.47 (d, J_{4C-F} = 7.5 Hz), 68.15 (d, J_{3C-F} = 18.9 Hz), 67.12, 61.35, 55.61, 20.65, 20.59, 20.55; ^{19}F NMR (376 MHz, $CDCl_3$) δ −204.39 (dd, J_{F-2H} = 49.6 Hz, J_{F-3H} = 9.7 Hz); HRMS (M + Na^+) calcd for $C_{19}H_{23}FO_9Na$ 437.1224, found 437.1209.

Compound 26*β*. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-*β*-1-(4-methoxyphenyl)-D-galactose. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06−7.02 (m, 2H), 6.86−6.82 (m, 2H), 5.48−4.46 (m, 1H), 5.18 (ddd, J_{3-F} = 13.3 Hz, J_{3-2} = 9.8 Hz, J_{3-4} = 3.6 Hz, 1H), 5.01 (dd, J_{1-2} = 7.7 Hz, J_{1-F} = 3.9 Hz, 1H), 4.75 (ddd, J_{2-F} = 51.2 Hz, J_{2-3} = 9.8 Hz, J_{2-1} = 7.7 Hz, 1H), 4.23 (dd, J_{6a-6b} = 11.3 Hz, J_{6a-5} = 6.7 Hz, 1H), 4.14 (dd, J_{6b-6a} = 11.3 Hz, J_{6b-5} = 6.7 Hz, 1H), 4.02 (td, J_{5-6} = 6.7 Hz, J_{5-4} = 1.0 Hz, 1H), 3.79 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.33, 170.06, 169.99, 155.89, 150.71, 119.03, 114.52, 100.39 (d, J_{1C-F} = 23.7 Hz), 87.50 (d, J_{2C-F} = 187.9 Hz), 71.01 (d, J_{3C-F} = 18.9 Hz), 70.86, 67.46 (d, J_{4C-F} = 8.3 Hz), 61.11, 55.62, 20.65, 20.61, 20.57; ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.00 (dd, J_{F-2H} = 51.2 Hz, J_{F-3H} = 13.3 Hz); HRMS (M + Na^+) calcd for $C_{19}H_{23}FO_9Na$ 437.1224, found 437.1209.

Compound 27α. L-Threonine, *N*-[(phenylmethoxy)-carbonyl]-*O*-(3,4-di-*O*-acetyl-2-deoxy-2-fluoro-α-L-fucopyranosyl)-, Phenylmethyl Ester. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 3:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.33 (m, 10H), 5.52 (d, J = 9.7 Hz, 1H), 5.23−5.16 (m, 3H), 5.14 (s, 2H,), 5.11 (td, J_{4-F} = 3.5 Hz, J_{4-3} = 3.5 Hz, J_{4-5} = 1.1 Hz, 1H), 5.08 (d, J_{1-2} = 4.0 Hz, 1H), 4.69 (ddd, J_{2-F} = 50.1 Hz, J_{2-3} = 10.3 Hz, J_{2-1} = 4.0 Hz, 1H), 4.52 (dd, J = 9.7, 2.2 Hz, 1H), 4.41 (qd, J = 6.3, 2.2 Hz, 1H), 3.79 (qd, J_{5-6} = 6.5 Hz, J_{5-4} = 1.1 Hz, 1H), 2.13 (s, 3H), 2.03 (s, 3H), 1.26 (d, J = 6.3 Hz, 3H), 0.92 (d, J_{6-5} = 6.5 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.28, 170.23, 169.84, 156.66, 136.02, 134.99, 128.77, 128.62, 128.53, 128.51, 128.20, 128.13, 94.06 (d, J_{1C-F} = 20.4 Hz), 84.81 (d, J_{2C-F} = 190.7 Hz), 73.52, 71.37 (d, J_{4C-F} = 7.5 Hz), 68.33 (d, J_{3C-F} = 18.6 Hz), 67.61, 67.28, 65.14, 58.73, 20.67, 20.53, 15.70, 15.51; ^{19}F NMR (376 MHz, $CDCl_3$) δ −205.10 (dd, J_{F-2H} = 50.1 Hz, J_{F-3H} = 9.7 Hz); HRMS (M + Cs^+) calcd for $C_{29}H_{34}FNO_{10}Cs$ 708.1221, found 708.1204.

Compound 27*β*. L-Threonine, *N*-[(phenylmethoxy)carbonyl]-*O*-(3,4-di-*O*-acetyl-2-deoxy-2-fluoro-*β*-L-fucopyranosyl)-, Phenylmethyl Ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.30 (m, 10H), 5.54 (d, J = 9.7 Hz, 1H), 5.22−5.09 (m, 5H), 4.92 (ddd, J_{3-F} = 13.4 Hz, J_{3-2} = 9.7 Hz, J_{3-4} = 3.6 Hz, 1H), 4.46−4.24 (m, 4H), 3.56 (qd, J_{5-6} = 6.4 Hz, J_{5-4} = 0.8 Hz, 1H), 2.13 (s, 3H), 2.04 (s, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.15 (d, J_{6-5} = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.45, 169.98, 169.83, 156.70, 136.15, 135.16, 128.79, 128.65, 128.58, 128.50, 128.13, 127.97, 101.39 (d, J_{1C-F} = 22.5 Hz), 87.64 (d, J_{2C-F} = 186.9 Hz), 77.95, 71.21 (d, J_{3C-F} = 18.3 Hz), 70.56 (d, J_{4C-F} = 8.4 Hz), 69.09, 67.50, 67.12, 58.69, 20.61, 20.58, 18.81, 15.89; ^{19}F NMR (376 MHz, CDCl3) δ −203.29 (dd, J_{F-2H} = 53.6 Hz, J_{F-3H} = 13.3 Hz); HRMS (M + Cs^+) calcd for $C_{29}H_{34}FNO_{10}Cs$ 708.1221, found 708.1204.

Compound 28. *N*-Benzyl-2-deoxy-2-fluoro-3,4-di-*O*-acetyl-α-L-fucopyranosylamine. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 1:3. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H, Ph), 5.29 (m, 1H), 5.09 (m, 1H), 4.89 (dt, J_{2-1} = 9.0 Hz, J_{2-F} = 51.5 Hz, 1H), 4.18 (dd, J_{1-2} = 9.0 Hz, J_{1-F} = 2.3 Hz, 1H), 4.13 (d, J = 13.5 Hz, 1H), 3.96 (d, J = 13.5 Hz, 1H), 2.16 (s, 3H), 2.05 (s, 3H), 1.20 (d, J = 6.5 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −199.8 (dd, J = 15.3, 50.9 Hz); HRMS (M + H^+) calcd for $C_{17}H_{23}FNO_5$ 340.1560, found 340.1570.

Compound 29*β*. 2-Deoxy-2-fluoro-3,4-di-*O*-benzoyl-*β*-1-(dibenzylphosphoryl)-L-fucopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 4:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, J = 7.5 Hz, 2H), 7.87 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.55−7.25 (m, 15H), 5.69 (broad t, J_{3-4} = J_{F-4} = 2.6 Hz, 1H), 5.52 (m, 2H), 5.14 (m, 4H), 4.90 (ddd, J = 7.9 Hz J = 10.1 Hz J_{2-F} = 51.7 Hz, 1H), 4.12 (q, J_{5-6} = 7.0 Hz, 1H), 1.29 (d, J_{5-6} = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.60, 165.35, 133.60−120.05, 96.45 (dd, J_{C-P} = 4.4 Hz J_{C-F} = 22.0 Hz), 88.30 (dd, J_{C-P} = 8.8 Hz J_{C-F} = 189.0 Hz), 71.57 (d, J = 19.8 Hz), 71.12 (d, J = 8.8 Hz), 70.72, 69.64 (d, J_{C-P} = 4.4 Hz), 69.58 (d, J_{C-P} = 4.4 Hz), 15.96; ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.55 (dd, J_{2-F} = 53.4 Hz, J_{3-F} = 12.7 Hz); ^{31}P NMR (161 MHz, $CDCl_3$)

δ −2.14 (s); HRMS (MH^+) calcd for $C_{34}H_{32}O_9PF$ 635.1846, found 635.1824.

Compound 29α. ^1H NMR (600 MHz, $CDCl_3$) δ 8.01 (dd, J = 8.3 Hz J = 1.3 Hz, 2H), 7.87 (dd, J = 8.3 Hz J = 1.3 Hz, 2H), 7.61 (tt, J = 7.4 Hz J = 1.3 Hz, 1H), 7.55−7.25 (m, 15H), 6.13 (dd, J_{1-P} = 6.1 Hz J_{1-2} = 3.5 Hz, 1H), 5.75 (td, J_{3-2} = 10.5 Hz J_{3-F} = 10.5 Hz J_{3-4} = 3.5 Hz, 1H), 5.68 (td, J_{3-4} = J_{F-4} = 3.5 Hz, J_{5-4} = 0.9 Hz, 1H), 5.15 (m, 4.5H overlapping half of the 2-H signal), 5.06 (td, J_{1-2} = 3.1 Hz J_{3-2} = 10.5 Hz J_{2-P} = 3.1 Hz, 0.5H), 4.31 (q, J_{5-6} = 6.5 Hz, 1H), 1.11 (d, J_{5-6} = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.59, 165.43, 133.6−127.9, 94.82 (dd, J_{C-P} = 4.4 Hz J_{C-F} = 19.8 Hz), 85.11 (dd, J_{C-P} = 8.8 Hz J_{C-F} = 191.2 Hz), 71.79 (d, J = 6.6 Hz), 69.71 (d, J_{C-P} = 4.4 Hz), 69.57 (d, J_{C-P} = 4.4 Hz), 68.69 (d, J = 17.6 Hz), 67.25, 15.68; ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.55 (dd, J_{2-F} = 48.3 Hz, J_{3-F} = 10.2 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −1.81 (s); HRMS (MH^+) calcd for $C_{34}H_{32}O_9PF$ 635.1846, found 635.1824.

Compound 30. 2-Deoxy-2-fluoro-3,4-di-*O*-benzoyl-α-1-(diphenylphosphoryl)-L-fucopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 4:1. ^1H NMR (600 MHz, $CDCl_3$) δ 8.10−7.10 (m, 20H), 6.29 (dd, J = 6.1 Hz J = 3.5 Hz, 1H), 5.77 (td, J = 10.6 Hz J = 10.6 Hz J = 3.5 Hz, 1H), 5.71 (dd, J = 3.5 Hz, J = 2.6 Hz, 1H), 5.12 (dddd, J = 3.5 Hz J = 10.6 Hz J = 3.5 Hz J = 49.1 Hz, 1H), 4.32 (q, J = 10.2 Hz, 1H), 1.08 (d, J = 10.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.54, 165.41, 150.36 (d, J = 7.7 Hz), 150.26 (d, J = 7.7 Hz, C_{Ar}), 133.60−120.05, 95.89 (dd, J_{C-P} = 5.5 Hz J_{C-F} = 22.0 Hz), 84.90 (dd, J_{C-P} = 7.7 Hz J_{C-F} = 192.3 Hz), 71.54 (d, J = 6.6 Hz), 68.64 (d, J = 17.6 Hz), 67.63, 15.58; ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.53 (dd, J_{2-F} = 49.2 Hz, J_{3-F} = 14.1 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −12.54 (s); HRMS (M + Cs^+) calcd for $C_{32}H_{28}O_9PF$ 739.0509, found 739.0488.

Compound 31. 2-Deoxy-2-fluoro-3,4-di-*O*-pivaloyl-α-1-(diphenylphosphoryl)-L-fucopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 4:1. ^1H NMR (600 MHz, $CDCl_3$) δ 7.40−7.15 (m, 20H), 6.16 (dd, J_{1-P} = 5.9 Hz J_{1-2} = 3.5 Hz, 1H), 5.41 (td, J_{3-2} = 10.5 Hz J_{3-F} = 10.5 Hz J_{3-4} = 3.5 Hz, 1H), 5.30 (t, J_{3-4} = 3.5 Hz, J_{F-4} = 3.5 Hz, 1H), 4.82 (dddd, J_{1-2} = 3.5 Hz J_{3-2} = 10.5 Hz J_{2-P} = 3.5 Hz J_{2-F} = 49.4 Hz, 1H), 4.14 (q, J_{5-6} = 6.5 Hz, 1H), 1.25 (s, 9H), 1.18 (s, 9H), 0.95 (d, J_{5-6} = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.24, 177.09, 129.9−120.0, 95.80 (dd, J_{C-P} = 5.8 Hz J_{C-F} = 21.7 Hz), 84.75 (dd, J_{C-P} = 7.2 Hz J_{C-F} = 192.1 Hz), 70.51 (d, J = 7.2 Hz), 67.97 (d, J = 18.8 Hz), 67.67, 39.07, 38.81, 27.18, 26.97, 15.37; ^{19}F NMR (376 MHz, $CDCl_3$) δ −204.67 (dd, J_{2-F} = 48.2 Hz, J_{3-F} = 7.6 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −7.66 (s); HRMS (M + Cs^+) calcd for $C_{28}H_{36}O_9PF$ 699.1135, found 699.1155.

Compound 32-*manno*α. 2-Deoxy-2-fluoro-3,4,6-tri-*O*-pivaloyl-α-1-(diphenylphosphoryl)-D-mannopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 4:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.24 (m, 10H), 6.02 (ddd, J_{1-P} = 5.4 Hz J_{1-F} = 5.4 Hz J_{1-2} = 2.2 Hz, 1H), 5.53 (t, J_{3-4} = 10.0 Hz, J_{5-4} = 10.0 Hz, 1H), 5.25 (ddd, J_{3-2} = 2.4 Hz J_{3-F} = 27.6 Hz J_{3-4} = 10.0 Hz, 1H), 4.73 (ddd, J_{1-2} = 2.2 Hz J_{3-2} = 2.4 Hz J_{2-F} = 48.9 Hz, 1H), 4.02−3.96 (m, 3H, 5), 1.20 (s, 9H), 1.19 (s, 9H), 1.16 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.99, 177.46, 177.12, 130−120, 95.58 (dd, J_{C-P} = 5.5 Hz J_{C-F} = 31.9 Hz), 71.09, 68.86 (d, J = 16.5 Hz), 63.70, 60.70, 38.90, 27.02, 27.00; ^{19}F NMR (376 MHz, $CDCl_3$) δ −200.78 (ddd, J_{2-F} = 48.3 Hz, J_{3-F} = 27.9 Hz J_{1-F} = 5.1 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −6.89 (s); HRMS (M + Cs^+) calcd for $C_{33}H_{44}O_{11}PF$ 799.1660 found, 799.1690.

Compound 32-*gluco*α. 2-Deoxy-2-fluoro-3,4,6-tri-*O*-pivaloyl-α-1-(diphenylphosphoryl)-D-glucopyranose. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.19 (m, 10H), 6.14 (dd, J_{1-F} = 6.5 Hz J_{1-2} = 3.5 Hz, 1H), 5.59 (td, J_{3-2} = 9.7 Hz J_{3-F} = 11.4 Hz J_{3-4} = 10.0 Hz, 1H), 5.14 (t, J_{3-4} = 10.0 Hz, J_{5-4} = 10.0 Hz, 1H), 4.73 (ddt, J_{1-2} = 3.5 Hz J_{3-2} = 9.7 Hz J_{2-F} = 48.6 Hz J_{2-P} = 3.5 Hz, 1H), 3.91−3.85 (m, 3H), 1.19 (s, 9H), 1.17 (s, 9H), 1.14 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.86, 177.09, 176.20, 130−120, 94.79 (dd, J_{C-P} = 5.5 Hz J_{C-F} = 22.0 Hz), 86.90 (dd, J_{C-P} = 7.7 Hz J_{C-F} = 150.6 Hz), 69.97, 69.46 (d, J = 18.7 Hz), 65.96 (d, J_{C-F} = 6.6 Hz), 60.59, 38.83, 38.73, 27.02, 26.98; ^{31}P NMR (161 MHz, $CDCl_3$) δ −12.71 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −197.83 (dd, J_{2-F} = 48.2 Hz, J_{3-F} = 12.7 Hz); HRMS (M + Cs^+) calcd for $C_{33}H_{44}O_{11}PF$ 799.1660 found, 799.1690.

Compound 32-*glucoβ*. 2-Deoxy-2-fluoro-3,4,6-tri-*O*-pivaloyl-*β*-1-(diphenylphosphoryl)-D-glucopyranose. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.19 (m, 10H), 5.52 (td, J = 7.6 Hz J = 7.6 Hz J = 3.0 Hz, 1H), 5.37 (td, J = 9.0 Hz J = 13.8 Hz J = 10.0 Hz, 1H), 5.11 (t, J = 10.0 Hz, J = 10.0 Hz, 1H), 4.73 (ddd, J = 7.6 Hz J = 9.0 Hz J = 50.8 Hz, 1H), 4.08 (d, J = 3.5 Hz, 2H), 4.85 (td, J = 10.0 Hz J = 3.5 Hz, 3H), 1.18 (s, 9H), 1.16 (s, 9H), 1.13 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.86, 176.99, 176.39, 150.25 (d, J_{C-P} = 7.7 Hz, phenyl), 150.05 (d, J_{C-P} = 7.7 Hz, phenyl), 130−120, 96.56 (dd, J_{C-P} = 4.4 Hz J_{C-F} = 19.8 Hz), 89.48 (dd, J_{C-P} = 9.9 Hz J_{C-F} = 192.3 Hz), 73.16, 73.71 (d, J = 19.8 Hz), 66.56 (d, J_{C-F} = 7.2 Hz), 61.09, 38.81, 38.78, 38.76, 27.02, 26.97; ^{19}F NMR (376 MHz, $CDCl_3$) δ −197.33 (dd, J_{2-F} = 50.8 Hz, J_{3-F} = 12.7 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −13.23 (s); HRMS (M + Cs^+) calcd for $C_{33}H_{44}O_{11}PF$ 799.1660, found 799.1692.

Compound 33α. 2-Deoxy-2-fluoro-3,4,6-tri-*O*-pivaloyl-α-1-(diphenylphosphoryl)-D-galactopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 4:1. ^1H NMR (600 MHz, $CDCl_3$) δ 7.40−7.17 (m, 10H), 6.20 (dd, J_{1-P} = 6.5 Hz J_{1-2} = 3.5 Hz, 1H), 5.50 (td, J_{3-4} = 3.5 Hz, J_{F-4} = 3.5 Hz, J_{5-4} = 1.3 Hz, 1H), 5.45 (td, J_{3-2} = 10.2 Hz J_{3-F} = 10.2 Hz J_{3-4} = 3.5 Hz, 1H), 4.82 (ddt, J_{1-2} = 3.5 Hz J_{3-2} = 10.2 Hz J_{2-F} = 49.4 Hz J_{2-P} = 3.5 Hz, 1H), 4.25 (dd, J_{5-6A} = 8.4 Hz J_{5-6B} = 6.2 Hz, 1H), 3.84 (AB part of ABX, J_{A-B} = 11.1 Hz J_{A-X} = 8.4 Hz J_{B-X} = 6.2 Hz, 2H), 1.22 (s, 9H), 1.19 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.54, 177.12, 176.40, 130−120, 94.45 (dd, J_{C-P} = 5.5 Hz J_{C-F} = 22.0 Hz), 86.90 (dd, J_{C-P} = 7.8 Hz J_{C-F} = 192.3 Hz), 68.93, 67.46 (d, J = 18.7 Hz), 67.20 (d, J_{C-F} = 7.7 Hz), 60.11, 39.02, 38.84, 38.61, 27.10, 26.98; ^{19}F NMR (376 MHz, $CDCl_3$) δ −204.09 (dd, J_{2-F} = 48.3 Hz, J_{3-F} = 7.6 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −7.57 (s); HRMS (M + Cs^+) calcd for $C_{33}H_{44}O_{11}PF$ 799.1660, found: 799.1688.

Compound 33*β*. 2-Deoxy-2-fluoro-3,4,6-tri-*O*-pivaloyl-*β*-1-(diphenylphosphoryl)-D-galactopyranose. ^1H NMR (600 MHz, $CDCl_3$) δ 7.40−7.17 (m, 10H), 5.50 (td, J_{1-P} = 7.6 Hz J_{1-F} = 3.8 Hz J_{1-2} = 7.6 Hz, 1H), 5.50 (t, J_{3-4} = 2.7 Hz, J_{F-4} = 2.7 Hz, 1H), 5.45 (ddd, J_{3-2} = 10.2 Hz J_{3-F} = 13.2 Hz J_{3-4} = 2.7 Hz, 1H), 4.60 (ddd, J_{1-2} = 7.6 Hz J_{3-2} = 10.2 Hz J_{2-F} = 51.6 Hz, 1H), 4.10 (dd, J_{5-6A} = 6.2 Hz J_{5-6B} = 7.6 Hz, 1H), 3.96 (AB part of ABX, J_{A-B} = 11.1 Hz J_{A-X} = 6.2 Hz J_{B-X} = 7.6 Hz, 2H), 1.25 (s, 9H), 1.18 (s, 9H), 1.15 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.74, 177.03, 176.46, 130−120, 96.98 (dd, J_{C-P} = 4.4 Hz J_{C-F} = 24.2 Hz), 87.98 (dd, J_{C-P} = 8.8 Hz J_{C-F} = 189.0 Hz), 72.06, 70.60 (d, J = 17.6 Hz), 66.78 (d, J_{C-F} = 8.8 Hz), 60.34, 39.04, 38.84, 38.68, 27.10, 27.01, 26.97; ^{19}F NMR (376 MHz, $CDCl_3$) δ −204.24 (dd, J_{2-F} = 50.8 Hz, J_{3-F} = 10.2 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ −13.17 (s).

Compound 34. 2-Deoxy-2-fluoro-3,4-di-*O*-benzoyl-α-1-(benzyl-(*t*-butylacetyl-phosphonyl))-L-fucopyranose. The general procedure was applied. Chromatographic conditions, hexane/AcOEt, 3:1, 2 diastereoisomers. ^1H NMR (600 MHz, $CDCl_3$) δ 8.10−7.10 (m, 15H), 6.29 (dd, J_{1-P} = 6.1 Hz J_{1-2} = 3.5 Hz, 1H), 5.77 (td, J_{3-2} = 10.6 Hz J_{3-F} = 10.6 Hz J_{3-4} = 3.5 Hz, 1H), 5.71 (dd, J_{3-4} = 3.5 Hz, J_{F-4} = 2.6 Hz, 1H), 5.12 (dddd, J_{1-2} = 3.5 Hz J_{3-2} = 10.6 Hz J_{2-P} = 3.5 Hz J_{2-F} = 49.1 Hz, 1H), 4.32 (q, J_{5-6} = 10.2 Hz, 1H), 1.08 (d, J_{5-6} = 10.2 Hz, 3H); ^{13}C NMR (150 MHz, D_2O) δ 165.54, 165.41, 150.36 (d, J = 7.7 Hz), 150.26 (d, J = 7.7 Hz), 133.60−120.05, 95.89 (dd, J_{C-P} = 5.5 Hz J_{C-F} = 22.0 Hz), 84.90 (dd, J_{C-P} = 7.7 Hz J_{C-F} = 192.3 Hz), 71.54 (d, J = 6.6 Hz), 68.64 (d, J = 17.6 Hz), 67.63, 15.58; ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.32 (s); −203.49 (s); ^{31}P NMR (161 MHz, $CDCl_3$) δ 22.42 (s), 22.20 (s); HRMS (M + Cs^+) calcd for $C_{33}H_{36}O_{10}PF$ 775.1084, found 775.1104.

General Procedure for the Oxidation of Thioglycosides. To a stirred solution of thioglycoside (0.2 mmol) in CH_3CN-H_2O (2 mL, 20:1 or 10:1; with or without $NaHCO_3$) was added a solution of F-TEDA·$2BF_4$ (0.24 mmol) in CH_3CN-H_2O. After a stirring time of 20 min, the mixture was concentrated

and redissolved in a mixture of CH_2Cl_2 and 10% aqueous $NaHCO_3$ (1:1, 50 mL). The organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated. The crude products were checked by ^1H NMR and HRMS. All starting thioglycosides are prepared by the methods described in the previous paper.[60]

Compound 35. *p*-Methylphenyl 2,3,6-Tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-1-sulfinyl-*β*-D-glucopyranoside. ^1H NMR (400 MHz, $CDCl_3$), for one diastereomer, δ 5.08 (dd, 1H, J = 7.8 and 10.4 Hz), 4.95 (dd, 1H, J = 3.0 and 10.4 Hz), 4.39 (d, 1H, J = 9.5 Hz); for the other, 5.074 (dd, 1H, J = 7.8 and 10.4 Hz), 4.94 (dd, 1H, J = 3.0 and 10.4 Hz), 4.14 (d, 1H, J = 9.5 Hz); the ratio = 1:1, HRMS for $C_{33}H_{42}O_{18}SCs$ (M + Cs^+) calcd 891.1146, found 891.1166.

Compound 36. Ethyl 2,3,4,6-tetra-*O*-acetyl-1-sulfinyl-*β*-D-galactopyranoside. ^1H NMR (500 MHz, $CDCl_3$), for one diastereomer, δ 5.67 (t, 1H, J = 10 Hz), 5.20 (dd, 2H, J = 3.5 and 10.0 Hz), 2.18 (s, 3H); for the other, 5.24 (t, 1H, J = 10 Hz), 5.16 (dd, 1H, J = 3.5 and 10.0 Hz), 2.17 (s, 3H); the ratio = 1:1, HRMS for $C_{15}H_{22}O_{10}SCs$ (M + Cs^+) calcd 417.0831, found 417.084.

Compound 37. *p*-Methylphenyl 2,3,4,6-Tetra-*O*-benzoyl-1-sulfinyl-*β*-D-galactopyranoside. ^1H NMR (500 MHz, $CDCl_3$), for one diastereomer, δ 6.13(t, 1H, J = 10 Hz), 5.85 (d, 1H, J = 3.0 Hz), 4.65 (d, 1H, J = 10.0 Hz), 2.31 (s, 3H); for the other, 5.82 (d, 1H, J = 3.0 Hz), 5.13 (d, 1H, J = 10 Hz), 2.37 (s, 3H); the ratio = 3:1, HRMS for $C_{34}H_{30}O_9SCs$ (M + Cs^+) calcd 747.0465, found 747.0485.

Compound 38. *p*-Methylphenyl 2,3,4-Tri-*O*-benzoyl-1-sulfinyl-*β*-D-galactopyranoside. ^1H NMR (500 MHz, $CDCl_3$), for one diastereomer, δ 6.13(t, 1H, J = 10 Hz), 5.85 (d, 1H, J = 3.0 Hz), 4.65 (d, 1H, J = 10.0 Hz), 2.31 (s, 3H); for the other, 5.82 (d, 1H, J = 3.0 Hz), 5.13 (d, 1H, J = 10 Hz), 2.37 (s, 3H); the ratio = 3:1, HRMS for $C_{34}H_{30}O_9SCs$ (M + Cs^+) calcd 747.0465, found 747.0485.

Compound 39. *p*-Methylphenyl 2,3,4-Tri-*O*-benzoyl-6-*O*-*t*-butyldimethylsilyl-1-sulfinyl-*β*-D-galactopyranoside. ^1H NMR (400 MHz, $CDCl_3$), for one diastereomer, δ 5.99 (t, 1H, J = 10 Hz), 5.93 (d, 1H, J = 3.0 Hz), 4.65 (d, 1H, J = 10.0 Hz), 2.36 (s, 3H); for the other, 5.89 (d, 1H, J = 3.0 Hz), 5.72 (t, 1H, J = 10 Hz), 4.93 (d, 1H, J = 10.0 Hz), 2.42 (s, 3H); the ratio = 3:1, HRMS for $C_{40}H_{44}O_9SSiCs$ (M + Cs^+) calcd 861.1530, found 861.1550.

Compound 40. *p*-Methylphenyl 4,6-*O*-Benzylidine-2-deoxy-2-phthalimido-1-sulfinyl-*β*-D-glucopyranoside. ^1H NMR (500 MHz, $CDCl_3$), for one diastereomer, δ 5.56 (s, 1H), 5.40 (d, 1H, J = 10.0 Hz), 4.78 (t, 1H, J = 10 Hz), 2.04 (s, 3H); for the other, 5.55 (s, 1H), 5.23 (d, 1H, J = 10.0 Hz), 4.64 (t, 1H, J = 10 Hz), 2.67 (s, 3H); the ratio = 3:1, HRMS for $C_{28}H_{25}NO_7SCs$ (M + Cs^+) calcd 652.0406, found 652.0426.

Compound 41. *p*-Methylphenyl 2-Azido-4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-dexoy-1-sulfinyl-*β*-D-galactopyranoside. ^1H NMR (500 MHz, $CDCl_3$), for one diastereomer, δ 5.45 (s, 1H), 3.50 (d, 1H, J = 1.0 Hz), 2.39 (s, 3H); for the other, 5.40 (s, 1H), 3.61 (d, 1H, J = 1.0 Hz), 2.44 (s, 3H); the ratio = 4:5, HRMS for $C_{28}H_{22}ClN_7O_6SNa$ (M + Na^+) calcd 514.0816, found 514.0823.

Compound 42. *p*-Methylphenyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxylcarbonylamino)-1-sulfinyl-*β*-D-glucopyranoside. ^1H NMR (400 MHz, $CDCl_3$), for one diastereomer, δ 6.48 (d, 1H, J = 7.3 Hz), 5.66 (t, 1H, J = 9.6 Hz), 5.02 (t, 1H, J = 9.8 Hz); for the other, 5.98 (d, 1H, J = 7.3 Hz), 5.41 (t, 1H, J = 9.6 Hz), 4.90 (t, 1H, J = 9.8 Hz); the ratio = 1:2, HRMS for $C_{28}H_{26}NO_{10}Cl_3SCs$ (M + Cs^+) calcd 733.9397, found 733.9371.

Compound 43. *p*-Methylphenyl 3-*O*-Benzyl-4,6-*O*-benzylidine-2-*O*-levulinyl-1-sulfinyl-*β*-D-galactopyranoside. ^1H NMR (400 MHz, $CDCl_3$), for one diastereomer, δ 4.06 (d, 1H, J = 3.2 Hz), 3.94 (dd, 1H, J = 1.6 and 12.5 Hz), 3.67 (dd, 1H, J = 3.3 and 9.5 Hz), 2.33 (s, 3H); for the other, δ 4.03 (d, 1H, J = 3.2 Hz), 3.85 (dd, 1H, J = 1.6 and 12.5 Hz), 3.62 (dd, 1H, J = 3.3 and 9.5 Hz), 2.38 (s, 3H); the ratio = 1:2, HRMS for $C_{28}H_{26}NO_{10}Cl_3SCs$ (M + Cs^+) calcd 733.9397, found 733.9371.

Compound 44. *p*-Methylphenyl 2-*O*-Benzyl-4,6-*O*-benzylidine-1-sulfinyl-*β*-D-galactopyranoside. ^1H NMR (500 MHz, $CDCl_3$), for one diastereomer, δ 5.38 (s, 1H), 4.46 (t, 1H, J = 9.5 Hz), 4.19 (d, 1H, J = 9.5 Hz), 4.07 (d, 1H, J = 3.0 Hz), 3.32 (d, 1H, J = 0.5 Hz), 2.42 (s, 1H); for the other, 5.27 (s, 1H), 4.19 (d, 1H, J = 9.5 Hz), 3.95 (d, 1H, J = 3.0 Hz), 3.44 (d, 1H, J = 0.5 Hz), 2.37 (s, 1H); the ratio = 3:1, HRMS for $C_{27}H_{28}O_6SNa$ (M + Na^+) calcd 503.1504, found 503.1516.

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