JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

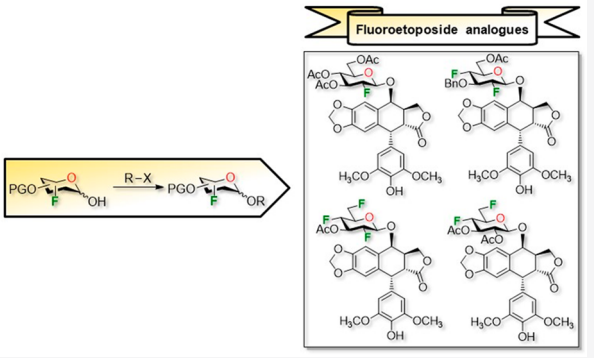
Polyfluoroglycoside Synthesis via Simple Alkylation of an Anomeric Hydroxyl Group: Access to Fluoroetoposide Analogues

Thomas Tremblay, Jacob St-Gelais, Maxime Houde, and Denis Giguère*

Cite This: J. Org. Chem. 2021, 86, 4812−4824 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: In this work, we have developed a new approach for the synthesis of fluoroglycoside analogues. This strategy used a simple alkylation protocol and allowed the installation of a simple aglyconic alkane with the β configuration. Moreover, the glycosylation of fluorinated glucoside analogues with 4′-demethylepipodophyllotoxin furnished novel fluoroetoposide analogues. In these cases, the α anomers were formed as major products with an *S* configuration at the C-4 of the aglycone.



Most of the carbohydrates found in nature do not occur in a free form but are present as *O*- or *N*-glycosidic compounds. Glycosylations play a central role in the study of glycobiology and many pathologies. Therefore, chemical syntheses toward complex glycoconjugates or glycomimetics are a major challenge for the rapid development of glycobiology and related sciences.[1]

In the last decades, tremendous advances in the field of chemical glycosylation reaction have been achieved.[2] Three general strategies are employed for the construction of oligosaccharides or related glycoside analogues (Figure 1a).[3] Method A involves an alkylation of glycosyl alkoxides **2** and is of little general use, as it is only useful for the preparation of glycosides of primary alcohols.[4] The second strategy (method B) is the most frequently employed method. It is extensively used for the preparation of oligosaccharides, and the anomeric selectivity is governed by suitably protected glycosyl donors **4** via an oxocarbenium ion **5**. Lastly, method C is a nucleophilic displacement of glycosyl halides **6** with aglyconic alkoxides. This practical methodology allows the preparation of *O*- or *S*-aryl glycosides; however, elimination leading to the corresponding glycal can occur as a side-reaction.[5]

Fluorinated carbohydrates are invaluable tools to study lectin−carbohydrate interactions.[6] The preparation of these stable probes is challenging; for that reason, only a limited number of complex fluorosugar analogues have been used in biological investigations to date.[7] Our group is interested in the chemistry, biology, and physical properties of polyfluorinated carbohydrate analogues.[8] In the course of our synthetic endeavors, we were faced with challenging glycosylation reactions when heavily fluorinated pyrans were used as glycosyl donors. Figure 1b shows two representative examples from our group of glycosylation reactions using polyfluorinated carbohydrates. Recently, we developed a glycosylation reaction involving microwave heating that allowed O-allylation presumably via an oxocarbenium ion (Method B).[8d] The reaction worked well on difluorinated glucose analogues but gave a low yield and selectivity with 2,3,4-trifluoroallose **8** as the starting substrate. In such a case, anomers **9** and **10** were isolated in 29% yield (38% yield, based on recovered starting material).[8b] This result can be explain by the low reactivity of the donor[9] originated by the destabilization of the positively charged oxocarbenium on the fluorinated pyran.[10] We also evaluated the reactivity of the glycosyl bromide **11** under various alkylation conditions (Method C).[8b] The α-allosyl bromide **11** was slowly generated in 76 h in an anomeric mixture (α/β = 3.3:1), and then under alkylating conditions, only a trace amount of volatile 2,3,4-trifluoroallal **13** was isolated arising from the elimination. It is important to point out that this alkylation reaction worked well on a trifluorinated galactoside analogue.[8c] This difference in reactivity can be explain by a shielding of the H-2 proton by an axial fluorine at C-4 of the galactoside analogue, thus reducing the formation of an elimination byproduct. Finally, we want to point out that the selective glycosylation reaction involving monofluorinated carbohydrates can proceed smoothly via an oxocarbenium ion

Received: November 29, 2020
Published: February 25, 2021

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

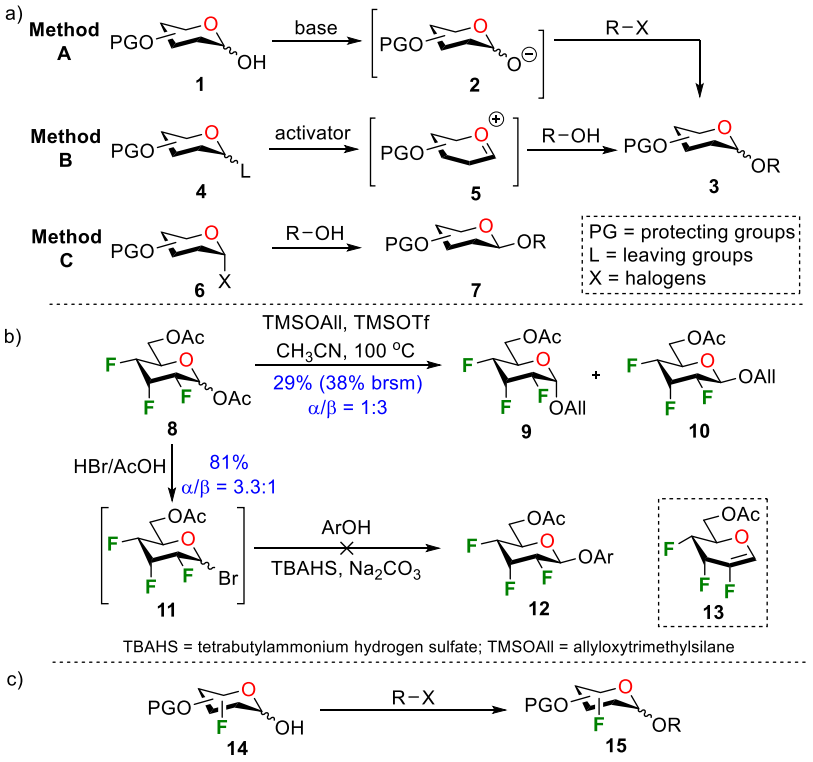
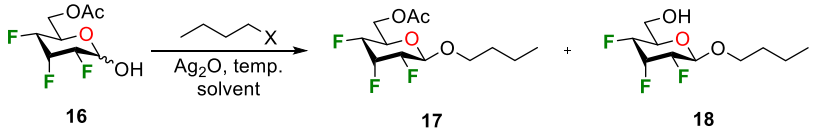


Figure 1. (a) General strategies for glycoside synthesis; (b) representative examples related to challenging glycosylation of polyfluorinated carbohydrates; (c) this work.

Table 1. Optimization of the Glycosylation Reaction Leading to Trifluoroallose Analogue 17



					yield (%)[a]	
entry	reagent (X)	solvent	temperature (°C)	conversion (%)[a]	**17**	**18**
1	Cl	toluene	100	87	0	0
2	Br	toluene	100	74	11	0
3	I	toluene	100	100	67	8
4	OTf	toluene	100	73	0	0
5	Cl	toluene	60	0	0	0
6	Br	toluene	60	0	0	0
7	I	toluene	60	100	85	7
8	OTf	toluene	60	0	0	0
9	I	toluene	40	34	31	3
10	I	toluene	80	100	76	12
11	I	acetonitrile	60	100	14	0
12	I	DMF	60	100	1	0
13	**I**	**dichloroethane**	**60**	**100**	**95**	**5**
14	I	chloroform	60	100	92	8
15	I	1,4-dioxane	60	72	70	2

[a]Conversions and yields were determined by ^{19}F NMR analysis of the crude mixture after workup. Conversion refers to consumption of the starting material.

(Method B) if the fluorine atom is located far from the reactive anomeric center[11] or if the C−F bond in 2-fluoropyranose analogues is used to control oxonium ion conformation.[12]

Interestingly, enzymatic approaches have been employed for glycosylations involving fluorinated carbohydrates.[13] This strategy was used for a wide range of monofluorinated sugars but remains challenging for polyfluorinated carbohydrates. Thus, a simple synthetic method must be developed to successfully generate heavily fluorinated glycomimetics or polyfluorinated oligosaccharides.

Based on previous results, we concluded that strategies B and C (Figure 1a) were not general for the glycosylation reactions of heavily fluorinated pyrans. Therefore, we wish to report on the exploration of method A (alkylation of the

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

anomeric hydroxyl group) for the glycosylation of fluorosugars (Figure 1c). We optimized the glycosylation reaction and generated a small set of polyfluoroglycoside analogues. Finally, we used 4′-demethylepipodophyllotoxin as a glycosyl acceptor and generated novel fluoroetoposide analogues.

As a proof of concept, we optimized the installation of an *O*-alkyl group on 6-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α/β-D-allopyranose **16** (Table 1). Our initial experiments involved the use of four electrophiles: chloro-, bromo-, and iodobutane as well as butyl triflate. We first used 2.75 equiv of the electrophile at 100 °C for 18 h with Ag_2O (3 equiv) in toluene (entries 1−4).[14] Good to excellent conversions were observed based on ^{19}F NMR analysis of the crude mixture after workup; however, only iodobutane furnished compound **17** in decent yield (entry 3). In order to increase the practicality of this method, we evaluated the same reaction conditions but at a lower temperature (entries 5−8, 60 °C). Iodobutane provided the best conversion, and trifluorinated glycoside **17** was generated in 85% yield, along with 7% of the unprotected analogue **18** (entry 7). Then, decreasing (entry 9) or increasing (entry 10) the temperature gave a lower conversion or yield. We finally evaluated various solvents (entries 11−15), and dichloroethane gave the highest yield and allowed formation of compound **17** in 95% yield (entry 13), along with 5% of unprotected side-product **18**.

With the glycosylation reaction successfully optimized, we evaluated various aglyconic electrophiles and polyfluorinated carbohydrates. Figure 2 shows the scope of the alkylation of anomeric hydroxyl groups leading to polyfluoroglycosides. First of all, in almost all cases, only the β anomer was formed as a major product. We propose that at high temperature, the equatorial kinetic product is preferred. The β-alkoxide is more nucleophilic due to a dipole−dipole repulsion between the glycosidic oxygen and the lone pairs on the ring oxygen.[4] Further experiments will be required to confirm this hypothesis. Alkyl fluorinated glycoside analogues **10**, **17**, and **19**−**21** were isolated in excellent yields. As such, this is a real improvement in terms of the yield for the isolation of compound **10** (91% as compared to 29% yield using a microwave heating glycosylation reaction).[8b] Correspondingly, 3-*O*-benzyl-2,4-dideoxy-2,4-difluoroglucopyranose was a suitable starting material for the anomeric alkylation reaction and led to fluoroglycoside **22** in 76% yield, along with the 1,6-bis-*O*-allylated product in 23% yield (not shown). Moreover, 4-pentynyl glycoside **23** was isolated in a 57% yield as a mixture of anomers (α/β = 1.3:1), and more hindered cyclohexyl **24** was isolated in a low 29% yield (75% yield, based on recovered starting material). Finally, 1,4-diiodobutane and methyl 16-iodohexadecanoate successfully produced fluorinated homodimer **25** in modest yield[15] and fluoroglycolipid **26** in good yield, respectively. It is important to point out that the more complex iodinated electrophile failed to produced their corresponding products: 6-deoxy-6-iodogalactose **27**, protected amino acids **28**, and cholesteryl iodide **29**.

Encouraged by the successful synthesis of various polyfluorinated glycoside analogues, we maintained our efforts toward the preparation of novel biologically active tools. Thus, screening of glycans to improved anticancer agents is a practical approach to understand the structure−function relationship of anticancer drugs and allowed a clear mode of action to be unveiled.[16] Accordingly, we explored the usefulness of the developed strategy for the preparation of novel fluorinated anticancer agents. Podophyllotoxin **30** is a natural product with interesting antitumor activity (Figure 3).[17] Because of its excessive toxicity, other analogues were developed. Etoposide (4′-demethylepipodophyllotoxin 4-(4,6-*O*-ethylidene)-β-D-glucopyranoside) is less toxic than podophyllotoxin and is used in chemotherapy for the treatment of

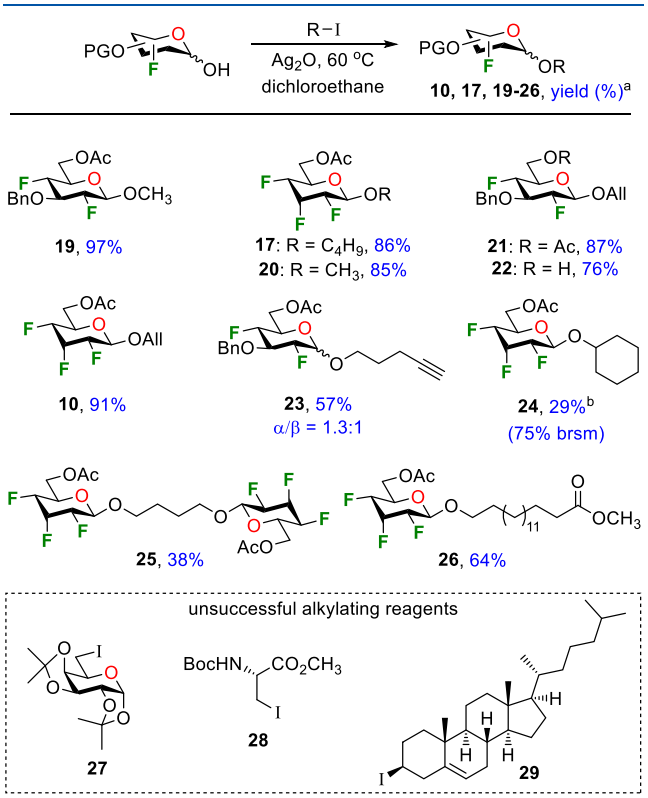


Figure 2. Scope of the alkylation of anomeric hydroxyl groups leading to polyfluoroglycosides **10**, **17**, and **19**−**26**. [a]Yields refer to isolated pure products after flash column chromatography. [b]The reaction mixture was stirred 72 h.

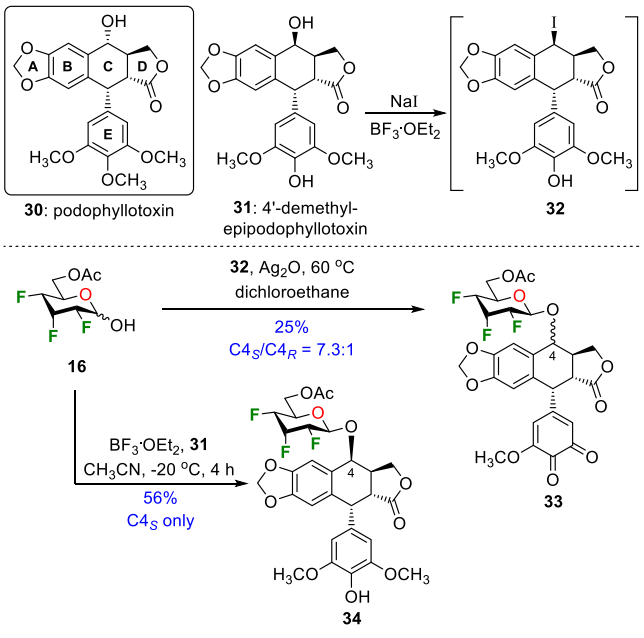


Figure 3. Synthesis of fluoroetoposide analogues **33** and **34**.

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

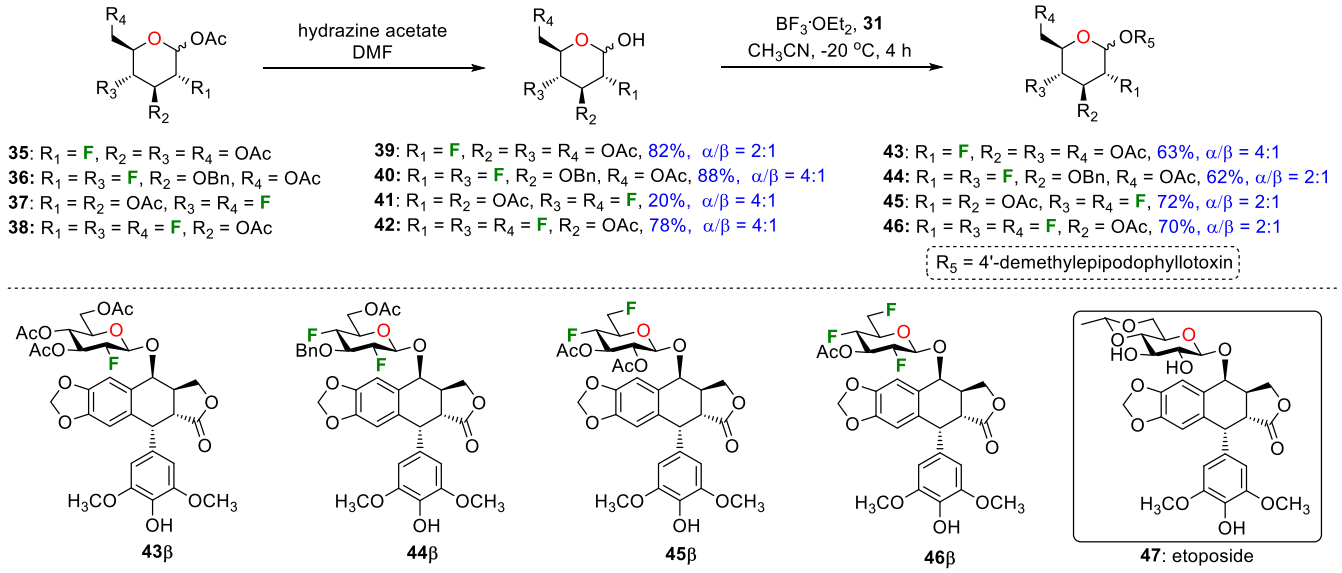


Figure 4. Synthesis of fluoroetoposide analogues **43**–**46**.

carcinomas and cancer.[18] Over the years, efforts were directed toward modification of epipodophyllotoxin glucosides in a search for a more water-soluble etoposide.[19] In view of this report, 2-deoxy-D-hexopyranoses seem to possess an interesting balance between hydrophilicity and lipophilicity.[20] Thus, treatment of compound **31** with $BF_3{\cdot}OEt_2$/sodium iodide furnished the iodinated intermediate **32**,[21] which was used directly in our glycosylation reaction. Under our optimized conditions, trifluorinated hexose analogue **16** was transformed into compound **33** as an inseparable diastereoisomeric mixture at C-4 (*S*/*R* = 7.3:1) in 25% yield. Moreover, only the product corresponding to the oxidation of the E ring was isolated leading to the 4′,5′-didemethoxy-4′,5′-dioxoepipodophyllotoxin aglycone. Interestingly, to the best of our knowledge, this is the first one-pot glycosylation/quinone preparation with 4′-demethylepipodophyllotoxin aglycone. The quinone metabolites contribute to strand breaks that trigger leukemic translocations[22] and is a useful intermediate for the synthesis of insecticidal[23] and antiviral[24] compounds. Although rather disappointing in terms of yield and diastereomeric ratio at C-4, we were compelled to change the nature of the electrophile for the glycosylation reaction. Consequently, we evaluated the possibility to use 4′-demethylepipodophyllotoxin **31** activated with a Lewis acid, as previously described.[25] This method should lead to a secondary benzylic carbocation that could be attacked by the anomeric hydroxyl group of fluorinated carbohydrates. To test this strategy, we subjected trifluorinated allose analogue **16** and compound **31** to $BF_3{\cdot}OEt_2$ in acetonitrile at −20 °C for 4 h. Delightedly, fluoroetoposide analogue **34** was formed in 56% yield as the only diastereoisomer at C-4 of the aglycone.

We then applied this strategy to protected glucose analogues previously described by our group bearing fluorine atoms at C-2 (**35**), C-2 and C-4 (**36**), C-4 and C-6 (**37**), and finally C-2, C-4, and C-6 (**38**) (Figure 4).[8e] Anomeric acetate removal using hydrazine acetate furnished the corresponding fluorohexose analogues **39**–**42**. Direct glycosylation with 4′-demethylepipodophyllotoxin **31** was achieved with $BF_3{\cdot}OEt_2$, resulting in the formation of fluoroglucosides **43**–**46** in good yields. In all cases, the α anomer was formed as the major isomer. The change in the stereochemical outcome of this reaction points to some mechanistic differences that will need further study in the future.[4] Also, anomeric hydroxyl groups attack the carbocation only from the top face due to the bulky aryl group at C-1 of the aglycone. This led to the formation of only one diastereoisomer at C-4 of the aglycone as determined using the NMR [for example: ^{1}H NMR (500 MHz): δ = 5.05 (d, $^3J_{H3-H4}$ = 3.2 Hz, H-4) for **46*β***]. In some cases, both fluoroglycoside anomers were separated using preparative high-performance liquid chromatography (both etoposide analogues with α and β configurations have been reported to have interesting biological activities).[19] Products **43*β*–46*β*** represent stable analogues of anticancer drug etoposide **47** (Figure 4, bottom).

In the present study, we use a simple and practical alkylation strategy for the preparation of polyfluoroglycoside analogues. The versatility of this method allowed rapid access to simple aglyconic alkanes from their corresponding iodoalkanes. Moreover, four complex fluoroetoposide analogues were prepared. Deprotections and biological evaluations of these potential anticancer agents will be reported in due course. Fluorine-containing carbohydrates allowed us to developed new tools to deepen investigations in biology.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Methylene chloride (CH_2Cl_2) and tetrahydrofuran (THF) were purified using a Vacuum Atmospheres Inc. Solvent Purification System. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality available and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and charring with a solution of 3 g of PhOH and 5 mL of H_2SO_4 in 100 mL of EtOH, followed by heating with a heatgun. SiliaFlash P60 40–63 μm (230–400 mesh) was used for flash column chromatography. Reactions that required heating were performed using an oil bath, unless otherwise stated. NMR spectra were recorded with an Agilent DD2 500 MHz spectrometer and calibrated using residual undeuterated solvent (chloroform-*d*: ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm) as an internal reference. Calibration of ^{19}F NMR was performed using hexafluor-

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

obenzene, which was measured at −162.29 ppm compared to the chemical shift of reference compound $CFCl_3$. Coupling constants (J) are reported in Hertz (Hz), and the following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad. Assignments of NMR signals were made by homonuclear (COSY) and heteronuclear (HSQC, HMBC, HOESY) two-dimensional correlation spectroscopy. Infrared spectra were recorded using an an Aminco Bowmen Adrid Zone infrared spectrometer with a NaCl crystal matrix. The absorptions are given in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were measured with an Agilent 6210 LC time of flight mass spectrometer in electrospray mode. Either protonated molecular ions $[M + nH]^{n+}$, sodium adducts $[M + Na]^+$, or ammonium adducts $[M + NH_4]^+$ were used for empirical formula confirmation. Optical rotations were measured with a JASCO DIP-360 digital polarimeter and are reported in units of 10^{-1} (deg cm^2 g^{-1}). High-pressure liquid chromatography (HPLC) experiments were performed on an Agilent 1260 Infinity II HPLC system coupled with a diode array UV/vis detector operated at 254 nm and an evaporating light scattering detector (ELSD). Chromatography analysis was performed with a SiliaChrom Plus C18 column (5 μm, 250 × 4.6 mm i.d.). Experiments were carried out at 25 °C, and the injection volume selected was 10 μL with a run time of 45 min each. Deionized (17.2 MΩ cm^{-1}) water and HPLC-grade acetonitrile and methanol were used for the preparation of eluents and samples. The elution was performed at a flow rate of 1 mL/min with a mobile phase composed of H_2O containing 0.1% TFA (A), CH_3CN (B), or MeOH (C). Semipreparative HPLC was carried out using a SiliaChrom Plus C18 column (5 μm, 250 × 10 mm i.d.).

General Procedure I: Selective Removal of the Anomeric Acetyl Group. To a solution of the polyacetylated carbohydrate (1.0 equiv) in anhydrous dimethylformamide (0.5 M) was added hydrazine acetate (1.5 equiv) at room temperature. The mixture was stirred until consumption of the starting material (~2−24 h), and then, water (5 mL) was added. The mixture was extracted with EtOAc (3 × 5 mL), and the combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes) to give the corresponding hemiacetal.

General Procedure II: Alkylation of the Anomeric Hydroxyl Group. To a stirred solution of the fluorinated carbohydrate (1.0 equiv) in 1,2-dichloroethane (0.1 M) was added an alkyl halide (2.75 equiv). Silver(I) oxide (3.0 equiv) was added, and the mixture was protected from light and stirred at 60 °C using an oil bath for 18 h. The mixture was then filtered on Celite and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes) to give the corresponding polyfluorinated glycoside.

General Procedure III: Synthesis of Fluorinated Etoposide Analogues. To a solution of the fluorinated carbohydrate (1.0 equiv) in anhydrous acetonitrile (0.15 M) was added 4′-demethylepipodophyllotoxin (2.0 equiv). Boron trifluoride (3.0 equiv) was added dropwise at −20 °C, and the mixture was stirred for 4 h at this temperature. The mixture was then diluted with CH_2Cl_2 (10 mL) and quenched with the addition of a saturated aqueous $NaHCO_3$ solution (5 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes) to give the corresponding fluorinated etoposide analogue. In some cases, anomers were separated by preparative HPLC.

6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α/β-D-allopyranose (16). This was synthesized using general procedure I starting from 1,6-di-*O*-acetyl-2,3,4-trideoxy-2,3,4-trifluoro-α/β-D-allopyranose.[8b] The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3 → 1:1) to give **16** as an anomeric mixture (α/β 1:6.3) as an amorphous white solid (37.1 mg, 0.1613 mmol, 81% yield). R_f = 0.59 (silica, EtOAc/hexanes 1:1); $[\alpha]_D^{25}$ = +7.5 (c 0.3, $CHCl_3$); IR (ATR, NaCl) ν 3436, 2959, 1738, 1727, 1244, 1029 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 5.41 (dtt, $^2J_{H3-F3}$ = 54.9 Hz, $^3J_{H3-F2}$ = $^3J_{H3-F4}$ = 8.8 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 2.4 Hz, 1H, H-3α), 5.40 (t, $^3J_{H1-H2}$ = $^3J_{H1-F2}$ = 3.9 Hz, 1H, H-1α), 5.32 (dtt, J = 54.4 Hz, $^3J_{H3-F2}$ = $^3J_{H3-F4}$ = 9.1 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 2.3 Hz, 1H, H-3β), 5.21 (dt, $^3J_{H1-H2}$ = 7.6 Hz, $^3J_{H1-F2}$ = $^4J_{H1-F3}$ = 1.5 Hz, 1H, H-1β), 4.60−4.42 (m, 2H, H-4α, H-5α), 4.51 (dddt, $^2J_{H4-F4}$ = 45.4 Hz, $^3J_{H4-F3}$ = 25.3 Hz, $^3J_{H4-H5}$ = 9.6 Hz, $^3J_{H4-H3}$ = $^4J_{H4-F2}$ = 1.9 Hz, 1H, H-4β), 4.47 (dt, $^2J_{H6a-H6b}$ = 12.2 Hz, $^3J_{H6a-H5}$ = 2.0 Hz, 1H, H-6aβ), 4.32−4.15 (m, 3H, H-2α, H-6aα, H-6bα), 4.24 (dddtd, $^2J_{H2-F2}$ = 46.3 Hz, $^3J_{H2-F3}$ = 26.6 Hz, $^3J_{H2-H1}$ = 7.8 Hz, $^3J_{H2-H3}$ = 2.2 Hz, $^4J_{H2-F4}$ = 1.8 Hz, $^4J_{H2-H4}$ = 0.6 Hz, 1H, H-2β), 4.21 (ddd, $^2J_{H6b-H6a}$ = 12.0 Hz, $^3J_{H6b-H5}$ = 5.1 Hz, $^4J_{H6b-F4}$ = 1.6 Hz, 1H, H-6bβ), 4.17 (ddt, $^3J_{H5-H4}$ = 9.8 Hz, $^3J_{H5-H6b}$ = 4.4 Hz, $^3J_{H5-H6a}$ = 2.4 Hz, $^3J_{H5-F4}$ = 1.5 Hz, 1H, H-5β), 2.11 (s, 6H, $COCH_3$-α, $COCH_3$-β); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d) δ 170.83 (s, 1C, $COCH_3$-β), 170.78 (s, 1C, $COCH_3$-α), 92.4 (dd, $^2J_{C1-F2}$ = 24.3 Hz, $^3J_{C1-F3}$ = 4.0 Hz, 1C, C-1β), 90.5 (dd, $^2J_{C1-F2}$ = 23.4 Hz, $^3J_{C1-F3}$ = 1.5 Hz, 1C, C-1α), 88.2 (dt, $^1J_{C3-F3}$ = 185.8 Hz, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 17.6 Hz, 1C, C-3α), 87.6 (ddd, $^1J_{C2-F2}$ = 196.4 Hz, $^2J_{C2-F3}$ = 16.6 Hz, $^3J_{C2-F4}$ = 5.2 Hz, C1, C-2β), 87.5 (dt, $^1J_{C3-F3}$ = 185.4 Hz, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 17.6 Hz, 1C, C-3β), 84.0 (ddd, $^1J_{C4-F4}$ = 193.4 Hz, $^2J_{C4-F3}$ = 17.4 Hz, $^3J_{C4-F2}$ = 5.1 Hz, 1C, C-4β), 83.7 (ddd, $^1J_{C2-F2}$ = 198.5 Hz, $^2J_{C2-F3}$ = 15.7 Hz, $^3J_{C2-F4}$ = 5.3 Hz, 1C, C-2α), 83.2 (ddd, $^1J_{C4-F4}$ = 194.2 Hz, $^2J_{C4-F3}$ = 17.0 Hz, $^3J_{C4-F2}$ = 4.8 Hz, 1C, C-4α), 69.3 (dd, $^2J_{C5-F4}$ = 24.7 Hz, $^3J_{C5-F3}$ = 3.6 Hz, 1C, C-5β), 62.7 (dd, $^2J_{C5-F4}$ = 23.5 Hz, $^3J_{C5-F3}$ = 3.6 Hz, 1C, C-5α), 62.3, (1C, C-6β), 62.0 (1C, C-6α), 20.9 (2C, $COCH_3$-β, $COCH_3$-α) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −200.82 (ddddt, $^2J_{F2-H2}$ = 46.5 Hz, $^3J_{F2-F3}$ = 12.3 Hz, $^3J_{F2-H3}$ = 8.9 Hz, $^4J_{F2-F4}$ = 4.5 Hz, $^3J_{F2-H1}$ = $^4J_{F2-H4}$ = 2.9 Hz, 1F, F-2α), −201.56 (dddd, $^2J_{F4-H4}$ = 44.3 Hz, $^3J_{F4-F3}$ = 12.9 Hz, $^3J_{F2-H3}$ = 8.6, $^4J_{F2-F4}$ = 4.5 Hz, $^3J_{F2-H1}$ = $^4J_{F2-H4}$ = 2.7 Hz, 1F, F-4α), −203.14 (ddddt, $^2J_{F2-H2}$ = 46.0 Hz, $^3J_{F2-F3}$ = 13.2 Hz, $^3J_{F2-H3}$ = 9.0 Hz, $^4J_{F2-F4}$ = 4.3 Hz, $^3J_{F2-H1}$ = $^4J_{F2-H4}$ = 1.9 Hz, F-2β), −203.99 (ddddt, $^2J_{F4-H4}$ = 45.3 Hz, $^3J_{F4-F3}$ = 14.8 Hz, $^3J_{F4-H3}$ = 9.1 Hz, $^4J_{F4-F2}$ = 4.1 Hz, $^3J_{F4-H5}$ = $^4J_{F4-F2}$ = 2.0 Hz, 1F, F-4β), −214.37 (dddt, $^2J_{F3-H3}$ = 54.9 Hz, $^3J_{F3-H2}$ = 29.1 Hz, $^3J_{F3-H4}$ = 25.8, $^3J_{F3-F2}$ = $^3J_{F3-F4}$ = 13.1 Hz, 1F, F-3α), −216.78 (dddt, $^2J_{F3-H3}$ = 54.6 Hz, $^2J_{F3-H2}$ = 28.2 Hz, $^2J_{F3-H4}$ = 25.5 Hz, $^3J_{F3-F2}$ = $^3J_{F3-F4}$ = 13.2 Hz, 1F, F-3β) ppm; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_8H_{11}F_3NaO_4$ 251.0502, found 251.0511.

Butyl 6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranoside (17) and Butyl 2,3,4-Trideoxy-2,3,4-trifluoro-β-D-allopyranoside (18). These were synthesized using general procedure II starting from **16**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3 → 2:3) to give **17** as a colorless oil (17.1 mg, 0.060 mmol, 86% yield) and byproduct **18** as an amorphous white solid (0.7 mg, 0.003 mmol, 4% yield). **17**: R_f = 0.69 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = −66.9 (c 0.1, $CHCl_3$); IR (ATR, NaCl) ν 2957, 2873, 2361, 2337, 1743, 1230, 1027 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 5.29 (dtt, $^2J_{H3-F3}$ = 54.5 Hz, $^3J_{H3-F2}$ = $^3J_{H3-F4}$ = 9.3 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 2.3 Hz, 1H, H-3), 4.85 (dt, $^3J_{H1-H2}$ = 7.8 Hz, $^3J_{H1-F2}$ = $^4J_{H1-F3}$ = 1.5 Hz, 1H, H-1), 4.50 (dddt, $^2J_{H4-F4}$ = 45.4 Hz, $^3J_{H4-F3}$ = 25.4 Hz, $^3J_{H4-H5}$ = 9.8 Hz, $^3J_{H4-H3}$ = $^4J_{H4-F2}$ = 1.8 Hz, 1H, H-4), 4.43 (ddd, $^2J_{H6a-H6b}$ = 12.2 Hz, $^3J_{H6a-H5}$ = 2.3 Hz, $^4J_{H6a-F4}$ = 1.6 Hz, 1H, H-6a), 4.25 (dddddd, $^2J_{H2-F2}$ = 46.0 Hz, $^3J_{H2-F3}$ = 26.5 Hz, $^3J_{H2-H1}$ = 7.8 Hz, $^3J_{H2-H3}$ = 2.2 Hz, $^4J_{H2-F4}$ = 1.6 Hz, $^4J_{H2-H4}$ = 0.5 Hz, 1H, H-2), 4.23 (ddd, $^2J_{H6b-H6a}$ = 12.2 Hz, $^3J_{H6b-H5}$ = 5.0 Hz, $^4J_{H6b-F4}$ = 1.5 Hz, 1H, H-6b), 4.10 (dddt, $^3J_{H5-H4}$ = 9.8 Hz, $^3J_{H5-H6b}$ = 4.9 Hz, $^3J_{H5-H6a}$ = 2.4 Hz, $^3J_{H5-F4}$ = 1.3 Hz, 1H, H-5), 3.90 (dt, J = 9.5, 6.6 Hz, 1H, $OCH^I_2CH_2CH_2CH_3$), 3.59 (dt, J = 9.5, 6.7 Hz, 1H, $OCH^{II}_2CH_2CH_2CH_3$), 2.10 (s, 3H, $COCH_3$), 1.65−1.58 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.43−1.35 (m, 2H, $OCH_2CH_2CH_2CH_3$), 0.92 (t, J = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-d) δ 170.7 (1C, $COCH_3$), 98.3 (dd, $^2J_{C1-F2}$ = 23.7 Hz, $^3J_{C1-F3}$ = 3.7 Hz, 1C, C-1), 87.7 (dt, $^1J_{C3-F3}$ = 185.0 Hz, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 17.5 Hz, 1C, C-3), 86.7 (ddd, $^1J_{C2-F2}$ = 196.4 Hz, $^2J_{C2-F3}$ = 16.8 Hz, $^3J_{C2-F4}$ = 5.2 Hz, 1C, C-2), 84.2 (ddd, $^1J_{C4-F4}$ = 193.9 Hz, $^2J_{C4-F3}$ = 17.4 Hz, $^3J_{C4-F2}$ = 5.0 Hz, 1C, C-4), 70.5 (1C, $OCH_2CH_2CH_2CH_3$), 68.9 (dd, $^2J_{C5-F4}$ = 24.4 Hz, $^3J_{C5-F3}$ = 3.3 Hz, 1C, C-5), 62.3 (1C, C-6), 31.6 (1C, $OCH_2CH_2CH_2CH_3$), 20.9 (1C, $COCH_3$), 19.1 (1C,

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

$OCH_2CH_2CH_2CH_3$), 13.9 (1C, $OCH_2CH_2CH_2CH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-*d*) δ −203.28 (ddddt, $^2J_{F2-H2}$ = 46.0 Hz, $^3J_{F2-F3}$ = 14.2 Hz, $^3J_{F2-H3}$ = 9.6 Hz, $^4J_{F2-F4}$ = 4.3 Hz, $^3J_{F2-H1}$ = $^4J_{F2-H4}$ = 1.7 Hz, 1F, F-2), −203.83 (dddq, $^2J_{F4-H4}$ = 45.7 Hz, $^3J_{F4-F3}$ = 13.8 Hz, $^3J_{F4-H3}$ = 9.4 Hz, $^4J_{F2-F4}$ = 3.9 Hz, $^3J_{F2-H1}$ = $^4J_{F2-H4}$ = 1.9 Hz, 1F, F-4), −216.55 (dtt, $^2J_{F3-H3}$ = 53.8 Hz, $^3J_{F3-H2}$ = $^3J_{F3-H4}$ = 26.6 Hz, $^3J_{F3-F2}$ = $^3J_{F3-F4}$ = 14.0 Hz, 1F, F3) ppm; HRMS (ESI) *m*/*z*: $[M + NH_4]^+$ calcd for $C_{12}H_{23}F_3NO_4$ 302.1574, found 302.1574. **18**: R_f = 0.15 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = −64.5 (*c* 0.3, $CHCl_3$); IR (ATR, NaCl) ν 3428, 2961, 2937, 1176, 1097, 1030 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 5.31 (dtt, $^2J_{H3-F3}$ = 54.7 Hz, $^3J_{H3-F2}$ = $^3J_{H3-F4}$ = 9.2 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 2.2 Hz, 1H, H-3), 4.89 (dt, $^3J_{H1-H2}$ = 7.8 Hz, $^3J_{H1-F2}$ = $^4J_{H1-F3}$ = 1.5 Hz, 1H, H-1), 4.59 (dddt, $^2J_{H4-F4}$ = 45.2 Hz, $^3J_{H4-F3}$ = 26.3 Hz, $^3J_{H4-H5}$ = 9.5 Hz, $^3J_{H4-H3}$ = $^4J_{H4-F2}$ = 1.9 Hz, 1H, H-4), 4.22 (dddt, $^2J_{H2-F2}$ = 45.9 Hz, $^3J_{H2-F3}$ = 26.4 Hz, $^3J_{H2-H1}$ = 7.7 Hz, $^3J_{H2-H3}$ = $^4J_{H2-F4}$ = 1.6 Hz, 1H, H-2), 3.99−3.91 (m, 2H, H-5, H-6a), 3.91 (dt, *J* = 9.5, 6.6 Hz, 1H, $OCH^I_2CH_2CH_2CH_3$), 3.78 (ddd, $^2J_{H6b-H6a}$ = 12.4 Hz, $^3J_{H6b-H5}$ = 3.6 Hz, $^4J_{H6b-F4}$ = 1.9 Hz, 1H, H-6b), 3.60 (dt, *J* = 9.5, 6.7 Hz, 1H, $OCH^{II}_2CH_2CH_2CH_3$), 2.11 (br, 1H, OH), 1.67−1.58 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.45−1.35 (m, 2H, $OCH_2CH_2CH_2CH_3$), 0.93 (t, *J* = 7.4 Hz, 3H, $OCH_2CH_2CH_2CH_3$) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 98.3 (dd, $^2J_{C1-F2}$ = 23.9 Hz, $^3J_{C1-F3}$ = 3.8 Hz, 1C, C-1), 87.9 (dt, $^1J_{C3-F3}$ = 184.3 Hz, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 17.4 Hz, 1C, C-3), 86.8 (ddd, $^1J_{C2-F2}$ = 195.9 Hz, $^2J_{C2-F3}$ = 16.8 Hz, $^3J_{C2-F4}$ = 5.6 Hz, 1C, C-2), 83.4 (ddd, $^1J_{C4-F4}$ = 192.1 Hz, $^2J_{C4-F3}$ = 17.5 Hz, $^3J_{C4-F2}$ = 5.2 Hz, 1C, C-4), 71.2 (dd, $^2J_{C5-F4}$ = 25.4 Hz, $^3J_{C5-F3}$ = 2.8 Hz, 1C, C-5), 70.6 (1C, $OCH_2CH_2CH_2CH_3$), 60.9 (1C, C-6), 31.7 (1C, $OCH_2CH_2CH_2CH_3$), 19.2 (1C, $OCH_2CH_2CH_2CH_3$), 13.9 (1C, $OCH_2CH_2CH_2CH_3$); ^{19}F NMR (470 MHz, chloroform-*d*) δ −203.28 (ddddt, $^2J_{F2-H2}$ = 45.9 Hz, $^3J_{F2-F3}$ = 13.0 Hz, $^3J_{F2-H3}$ = 9.1 Hz, $^4J_{F2-F4}$ = 3.9 Hz, $^3J_{F2-H1}$ = $^4J_{F2-H4}$ = 2.0 Hz, 1F, F-2), −204.51 (ddddp, $^2J_{F4-H4}$ = 45.1 Hz, $^3J_{F4-F3}$ = 11.4 Hz, $^3J_{F4-H3}$ = 9.1 Hz, $^4J_{F4-F2}$ = 3.9 Hz, $^4J_{F4-H2}$ = $^3J_{F4-H5}$ = $^4J_{F4-H6a}$ = $^4J_{F4-H6b}$ = 2.0 Hz, 1F, F-4), −216.32 (dttt, $^2J_{F3-H3}$ = 54.3 Hz, $^3J_{F3-H2}$ = $^3J_{F3-H4}$ = 26.5 Hz, $^3J_{F3-F2}$ = 14.7 Hz, $^3J_{F3-F4}$ = 13.5 Hz, $^4J_{F3-H1}$ = $^4J_{F3-H5}$ = 1.3 Hz, 1F, F-3) ppm; HRMS (ESI) *m*/*z*: $[M + NH_4]^+$ calcd for $C_{10}H_{21}F_3NO_3$ 260.1468, found 260.1464.

Methyl 6-*O*-Acetyl-3-*O*-benzyl-2,4-dideoxy-2,4-difluoro-β-D-glucopyranoside (19). This was synthesized using general procedure II starting from **40**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 2:3) to give **19** as a colorless oil (11.2 mg, 0.034 mmol, 97% yield). R_f = 0.26 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = −11.1 (*c* 0.6, $CHCl_3$); IR (ATR, NaCl) ν 2919, 2854, 2361, 1220, 1026, 733 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 7.41−7.29 (m, 5H, Ar), 4.82 (s, 2H, CH_2Ph), 4.48 (ddd, $^2J_{H4-F4}$ = 50.0 Hz, $^3J_{H4-H5}$ = 9.9 Hz, $^3J_{H4-H3}$ = 8.5 Hz, 1H, H-4), 4.43 (dd, $^3J_{H1-H2}$ = 7.7 Hz, $^3J_{H1-F2}$ = 2.9 Hz, 1H, H-1), 4.41 (dt, $^1J_{H6a-H6b}$ = 11.9 Hz, $^3J_{H6a-H5}$ = $^4J_{H6a-F4}$ = 2.2 Hz, 1H, H-6a), 4.29 (dt, $^2J_{H2-F2}$ = 50.2 Hz, $^3J_{H2-H3}$ = 8.6 Hz, $^3J_{H2-H1}$ = 7.7 Hz, 1H, H-2), 4.24 (ddd, $^1J_{H6b-H6a}$ = 12.4 Hz, $^3J_{H6b-H5}$ = 5.2 Hz, $^4J_{H6b-F4}$ = 1.7 Hz, 1H, H-6b), 3.82 (tt, $^3J_{H3-F4}$ = $^3J_{H3-F2}$ = 15.8 Hz, $^3J_{H3-H4}$ = $^3J_{H3-H2}$ = 8.5 Hz, 1H, H-3), 3.66 (ddt, $^3J_{H5-H4}$ = 10.1 Hz, $^3J_{H5-H6b}$ = 5.2 Hz, $^3J_{H5-F4}$ = $^3J_{H5-H6a}$ = 2.6 Hz, 1H, H-5), 3.57 (s, 3H, OCH_3), 2.10 (s, 3H, $COCH_3$) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 170.8 (1C, $COCH_3$), 137.5, 128.6, 128.2, 128.1 (6C, Ar), 101.5 (dd, $^2J_{C1-F2}$ = 23.2 Hz, $^4J_{C1-F4}$ = 1.3 Hz, 1C, C-1), 91.9 (dd, $^1J_{C2-F2}$ = 188.6 Hz, $^3J_{C2-F4}$ = 9.0 Hz, 1C, C-2), 89.1 (dd, $^1J_{C4-F4}$ = 185.9 Hz, $^3J_{C4-F2}$ = 9.0 Hz, 1C, C-4), 80.0 (t, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 18.6 Hz, 1C, C-3), 74.5 (t, $^4J_{CH2Ph-F2}$ = $^4J_{CH2Ph-F4}$ = 1.5 Hz, 1C, CH_2Ph), 71.3 (d, $^3J_{C5-F4}$ = 24.3 Hz, 1C, C-5), 62.2 (1C, C-6), 57.4 (1C, OCH_3), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-*d*) δ −197.65 (ddt, $^2J_{F2-H2}$ = 50.1 Hz, $^3J_{F2-F3}$ = 15.1 Hz, $^3J_{F2-H1}$ = $^4J_{F2-F4}$ = 2.8 Hz, 1F, F-2), −197.78 (ddt, $^2J_{F4-H4}$ = 50.1 Hz, $^3J_{F4-H3}$ = 15.5 Hz, $^3J_{F4-H6a}$ = $^3J_{F4-H6b}$ = 3.2 Hz, 1F, F-4) ppm; HRMS (ESI) *m*/*z*: $[M + NH_4]^+$ calcd for $C_{16}H_{24}F_2NO_5$ 348.1617, found 348.1623.

Methyl 6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranoside (20). This was synthesized using general procedure II starting from **16**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 2:3) to give **20** as a colorless oil (9.6 mg, 0.040 mmol, 85% yield). R_f = 0.24 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = −28.5 (*c* 0.2, $CHCl_3$); IR (ATR, NaCl) ν 2961, 2851, 2360, 1726, 1171, 1022 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 5.30 (dtt, $^2J_{H3-F3}$ = 54.4 Hz, $^3J_{H3-F2}$ = $^3J_{H3-F4}$ = 9.2 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 2.3 Hz, 1H, H-3), 4.79 (dt, $^3J_{H1-H2}$ = 7.8 Hz, $^3J_{H1-F2}$ = $^4J_{H1-F3}$ = 1.5 Hz, 1H, H-1), 4.52 (dddt, $^2J_{H4-F4}$ = 45.4 Hz, $^3J_{H4-F3}$ = 25.4 Hz, $^3J_{H4-H5}$ = 9.7 Hz, $^3J_{H4-H3}$ = $^4J_{H4-F2}$ = 2.0 Hz, 1H, H-4), 4.46 (dt, $^2J_{H6a-H6b}$ = 12.4 Hz, $^3J_{H6a-H5}$ = $^4J_{H6a-F4}$ = 2.0 Hz, 1H, H-6a), 4.251 (dddt, $^2J_{H2-F2}$ = 45.8 Hz, $^3J_{H2-F3}$ = 26.5 Hz, $^3J_{H2-H1}$ = 7.8 Hz, $^4J_{H2-F4}$ = $^3J_{H2-H3}$ = 2.1 Hz, 1H, H-2), 4.245 (ddd, $^2J_{H6b-H6a}$ = 12.3 Hz, $^3J_{H6b-H5}$ = 4.7 Hz, $^4J_{H6b-F4}$ = 1.6 Hz, 1H, H-6b), 4.14−4.09 (m, 1H, H-5), 3.59 (s, 3H, OCH_3), 2.11 (s, 3H, $COCH_3$) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 170.7 (1C, $COCH_3$), 99.3 (dd, $^2J_{C1-F2}$ = 23.8 Hz, $^3J_{C1-F3}$ = 3.8 Hz, 1C, C-1), 87.6 (dt, $^1J_{C3-F3}$ = 185.9 Hz, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 17.5 Hz, 1C, C-3), 86.7 (ddd, $^1J_{C2-F2}$ = 195.0 Hz, $^2J_{C2-F3}$ = 16.7 Hz, $^3J_{C2-F4}$ = 3.8 Hz, 1C, C-2), 84.1 (ddd, $^1J_{C4-F4}$ = 193.7 Hz, $^2J_{C4-F3}$ = 17.3 Hz, $^3J_{C4-F2}$ = 5.0 Hz, 1C, C-4), 69.0 (dd, $^2J_{C5-F4}$ = 24.4 Hz, $^3J_{C5-F3}$ = 3.6 Hz, 1C, C-5), 62.2 (1C, C-6), 57.6 (1C, OCH_3), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-*d*) δ −203.64 (ddddd, $^2J_{F2-H2}$ = 45.9 Hz, $^3J_{F2-F3}$ = 14.4 Hz, $^3J_{F2-H3}$ = 8.9 Hz, $^4J_{F2-F4}$ = 4.2 Hz, $^3J_{F2-H1}$ = 2.0 Hz, 1F, F-2), −203.94 (ddddp, $^2J_{F4-H4}$ = 45.4 Hz, $^3J_{F4-F3}$ = 14.9 Hz, $^3J_{F4-H3}$ = 9.7 Hz, $^4J_{F4-F2}$ = 4.3 Hz, $^4J_{F4-H2}$ = $^3J_{F4-H5}$ = $^4J_{F4-H6a}$ = $^4J_{F4-H6b}$ = 1.6 Hz, 1F, F-4), −216.58 (dttt, $^2J_{F3-H3}$ = 53.9 Hz, $^3J_{F3-H2}$ = $^3J_{F3-H4}$ = 26.1 Hz, $^3J_{F3-F2}$ = $^3J_{F3-F4}$ = 14.0 Hz, $^4J_{F3-H1}$ = $^4J_{F3-H5}$ = 1.5 Hz, 1F, F-3) ppm; HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_9H_{13}F_3NaO_4$ 265.0658, found 265.0667.

Allyl 6-*O*-Acetyl-3-*O*-benzyl-2,4-dideoxy-2,4-difluoro-β-D-glucopyranoside (21). This was synthesized using general procedure II starting from **40**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 2:3) to give **21** as a colorless oil (21.7 mg, 0.061 mmol, 87% yield). The spectroscopic data derived from compound **21** match those reported in the literature.[8d]

Allyl 3-*O*-Benzyl-2,4-dideoxy-2,4-difluoro-β-D-glucopyranoside (22) and Allyl 6-*O*-Allyl-3-*O*-benzyl-2,4-dideoxy-2,4-difluoro-β-D-glucopyranoside (22(6-OAll)). These were synthesized using general procedure II starting from 3-*O*-benzyl-2,4-dideoxy-2,4-difluoro-glucopyranose.[8d] The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3 → 2:3) to give **22** as an amorphous white solid (14.9 mg, 0.062 mmol, 76% yield) and byproduct **22(6-OAll)** as a colorless oil (6.9 mg, 0.014 mmol, 23% yield). **22**: R_f = 0.33 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = −24.3 (*c* 0.5, $CHCl_3$); IR (ATR, NaCl) ν 3452, 2930, 2880, 1367, 1087, 1041, 742 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 7.42−7.29 (m, 5H, Ar), 5.94 (dddd, *J* = 16.8, 10.8, 6.1, 5.7 Hz, 1H, OAll), 5.36 (dq, *J* = 17.2, 1.5 Hz, 1H, OAll), 5.26 (dq, *J* = 10.4, 1.2 Hz, 1H, OAll), 4.83 (s, 2H, CH_2Ph), 4.60 (dd, $^3J_{H1-H2}$ = 7.8 Hz, $^3J_{H1-F2}$ = 3.0 Hz, 1H, H-1), 4.53 (ddd, $^2J_{H4-F4}$ = 50.0 Hz, $^3J_{H4-H5}$ = 9.7 Hz, $^3J_{H4-H3}$ = 8.5 Hz, 1H, H-4), 4.38 (ddt, *J* = 12.8, 5.2, 1.5, 1.5 Hz, 1H, OAll), 4.32 (dt, $^2J_{H2-F2}$ = 50.1 Hz, $^3J_{H2-H3}$ = $^3J_{H2-H1}$ = 8.3 Hz, 1H, H-2), 4.20 (ddt, *J* = 13.0, 6.1, 1.3 Hz, 1H, OAll), 3.97−3.91 (m, 1H, H-6a), 3.84 (tt, $^3J_{H3-F4}$ = $^3J_{H3-F2}$ = 15.7 Hz, $^3J_{H3-H4}$ = $^3J_{H3-H2}$ = 8.6 Hz, 1H, H-3), 3.81−3.74 (m, 1H, H-6b), 3.52 (ddt, $^3J_{H5-H4}$ = 10.5 Hz, $^3J_{H5-H6b}$ = 5.4 Hz, $^3J_{H5-F4}$ = $^3J_{H5-H6a}$ = 2.9 Hz, 1H, H-5), 1.93 (s, 1H, OH) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 137.7 (1C, Ar), 133.4 (1C, OAll), 128.5, 128.1, 128.1 (5C, Ar), 118.3 (1C, OAll), 99.5 (dd, $^2J_{C1-F2}$ = 23.4 Hz, $^4J_{C1-F4}$ = 1.1 Hz, 1C, C-1), 91.9 (dd, $^1J_{C2-F2}$ = 188.7 Hz, $^3J_{C2-F4}$ = 9.4 Hz, 1C, C-2), 88.9 (dd, $^1J_{C4-F4}$ = 184.2 Hz, $^3J_{C4-F2}$ = 9.3 Hz, 1C, C-4), 80.2 (t, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 18.7 Hz, 1C, C-3), 74.4 (t, $^4J_{CH2Ph-F2}$ = $^4J_{CH2Ph-F4}$ = 1.5 Hz, 1C, CH_2Ph), 73.6 (d, $^3J_{C5-F4}$ = 24.8 Hz, 1C, C-5), 70.7 (1C, OAll), 61.4 (1C, C-6) ppm; ^{19}F NMR (470 MHz, chloroform-*d*) δ −197.62 (ddt, $^2J_{F2-H2}$ = 50.1 Hz, $^3J_{F2-H3}$ = 15.7 Hz, $^3J_{F2-H1}$ = $^4J_{F2-F4}$ = 2.9 Hz, 1F, F-2), −198.06 (ddt, $^2J_{F4-H4}$ = 49.9 Hz, $^3J_{F4-H3}$ = 16.2 Hz, $^3J_{F4-H5}$ = $^4J_{F4-F2}$ = 2.5 Hz, 1F, F-4) ppm; HRMS (ESI) *m*/*z*: $[M + NH_4]^+$ calcd for $C_{16}H_{24}F_2NO_4$ 332.1668, found 332.1671. **(22(6-OAll))**: R_f = 0.81 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = −20.1 (*c* 0.3, $CHCl_3$); IR (ATR, NaCl) ν 2922, 2858, 2362, 1059, 992, 928, 740 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*)

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

δ 7.41−7.28 (m, 5H, Ar), 5.91 (dtt, J = 16.9, 10.7, 10.6, 6.3, 5.5 Hz, 2H, OAll), 5.36−5.19 (m, 4H, OAll), 4.82 (s, 2H, CH_2Ph), 4.54 (dd, $^3J_{H1-H2}$ = 7.7 Hz, $^3J_{H1-F2}$ = 2.9 Hz, 1H, H-1), 4.49 (ddd, $^2J_{H4-F4}$ = 50.3 Hz, $^3J_{H4-H5}$ = 9.5 Hz, $^3J_{H4-H3}$ = 8.7 Hz, 1H, H-4), 4.39 (ddt, J = 12.9, 6.2, 1.3 Hz, 1H, OAll), 4.33 (dt, $^2J_{H2-F2}$ = 50.4 Hz, $^3J_{H2-H1}$ = $^3J_{H2-H3}$ = 8.2 Hz, 1H, H-2), 4.16 (ddt, J = 12.9, 6.3, 1.1 Hz, 1H, OAll), 4.10−4.02 (m, 2H, OAll), 3.80 (tt, $^3J_{H3-F4}$ = $^3J_{H3-F2}$ = 16.0 Hz, $^3J_{H3-H4}$ = $^3J_{H3-H2}$ = 8.3 Hz, 1H, H-3), 3.76 (dt, $^2J_{H6a-H6b}$ = 11.2 Hz, $^4J_{H6a-F4}$ = $^3J_{H6a-H5}$ = 2.3 Hz, 1H, H-6a), 3.63 (ddd, $^2J_{H6b-H6a}$ = 11.0 Hz, $^3J_{H6b-H5}$ = 5.3 Hz, $^4J_{H6b-F4}$ = 1.9 Hz, 1H, H-6b), 3.56 (ddd, $^3J_{H5-H4}$ = 9.9 Hz, $^3J_{H5-H6b}$ = 5.0, $^3J_{H5-F4}$ = $^3J_{H5-H6a}$ = 2.3 Hz, 1H, H-5) ppm; ^{13}C{^{1}H} NMR (126 MHz, chloroform-d) δ 137.7 (1C, Ar), 134.5, 133.5 (2C, OAll), 128.5, 128.1, 128.0 (5C, Ar), 118.2, 117.5 (2C, OAll), 99.4 (dd, $^2J_{C1-F2}$ = 22.9 Hz, $^4J_{C1-F4}$ = 0.8 Hz, 1C, C-1), 92.0 (dd, $^1J_{C2-F2}$ = 188.7 Hz, $^3J_{C2-F4}$ = 9.5 Hz, 1C, C-2), 89.2 (dd, $^1J_{C4-F4}$ = 185.0 Hz, $^3J_{C4-F2}$ = 9.1 Hz, 1C, C-4), 80.4 (t, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 18.6 Hz, 1C, C-3), 74.4 (t, $^4J_{CH2Ph-F2}$ = $^4J_{CH2Ph-F4}$ = 1.9 Hz, 1C, CH_2Ph), 73.3 (d, $^2J_{C5-F4}$ = 24.3 Hz, 1C, C-5), 72.8 (2C, OAll), 70.3 (2C, OAll), 68.2 (1C, C-6) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −197.20 (ddt, $^2J_{F2-H2}$ = 50.7 Hz, $^3J_{F2-H3}$ = 15.6 Hz, $^3J_{F2-H1}$ = $^4J_{F2-F4}$ = 2.8 Hz, 1F, F-2), −197.28 (ddt, $^2J_{F4-H4}$ = 51.0 Hz, $^3J_{F4-H3}$ = 15.5 Hz, $^3J_{F4-H5}$ = $^4J_{F4-F2}$ = 3.0 Hz, 1F, F-4) ppm; HRMS (ESI) m/z: [M + NH_4]$^+$ calcd for $C_{19}H_{28}F_2NO_4$ 372.1981, found 372.1985.

Allyl 6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranoside (10). This was synthesized using general procedure II starting from **16**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 2:3) to give **10** as a colorless oil (10.3 mg, 0.038 mmol, 91% yield). The spectroscopic data derived from compound **10** match those reported in the literature.[8b]

4-Pentyne 6-*O*-Acetyl-3-*O*-benzyl-2,4-dideoxy-2,4-difluoro-α/β-D-glucopyranoside (23). This was synthesized using general procedure II starting from **40**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 2:3) to give **23** (α/β = 1:1.3) as a colorless oil (7.8 mg, 0.020 mmol, 57% yield). R_f = 0.33 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = +16.5 (c 0.4, $CHCl_3$); IR (ATR, NaCl) ν 3297, 2919, 2854, 1744, 1368, 1236, 1030 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 7.41−7.28 (m, 10H, Ar-α/β), 5.01 (t, $^3J_{H1-H2}$ = $^3J_{H1-F2}$ = 3.5 Hz, 1H, H-1α), 4.82 (s, 4H, CH_2Ph-α/β), 4.51 (dd, $^3J_{H1-H2}$ = 7.8 Hz, $^3J_{H1-F2}$= 3.0 Hz, 1H, H-1β), 4.46 (ddd, $^2J_{H4-F4}$ = 50.0 Hz, $^3J_{H4-H5}$ = 9.7 Hz, $^3J_{H4-H3}$ = 8.7 Hz, 1H, H-4β), 4.45 (dt, $^2J_{H4-F4}$ = 49.9 Hz, $^3J_{H4-H5}$ = $^3J_{H4-H3}$ = 8.8 Hz, 1H, H-4α), 4.43 (ddd, $^2J_{H2-F2}$ = 50.3 Hz, $^3J_{H2-H3}$ = 9.3 Hz, $^3J_{H1-H2}$= 3.5 Hz, 1H, H-2α), 4.42−4.34 (m, 2H, H-6aα/β), 4.28 (dt, $^2J_{H2-F2}$ = 50.0 Hz, $^3J_{H2-H1}$ = $^3J_{H2-H3}$ = 8.0 Hz, 1H, H-2β), 4.27 (ddd, $^1J_{H6b-H6a}$ = 12.2 Hz, $^3J_{H6b-H5}$ = 4.8 Hz, $^4J_{H6b-F4}$ = 1.6 Hz, 1H, H-6bα), 4.23 (ddd, $^1J_{H6b-H6a}$ = 12.1 Hz, $^3J_{H6b-H5}$ = 5.2 Hz, $^4J_{H6b-F4}$ = 1.4 Hz, 1H, H-6bβ), 4.10 (ddt, $^3J_{H3-F4}$ = 15.5 Hz, $^3J_{H3-F2}$ = 12.7 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 8.9 Hz, 1H, H-3α), 4.03 (dtd, $^3J_{H5-H4}$ = 9.5 Hz, $^3J_{H5-H6b}$ = $^3J_{H5-F4}$ = 4.6 Hz, $^3J_{H5-H6a}$ = 2.3 Hz, 1H, H-5α), 3.98 (dt, J = 9.8, 5.9 Hz, 2H, CH^I_2CH$_2$CH$_2$CCHβ), 3.89 (ddd, J = 9.8, 7.3, 5.4 Hz, 1H, CH_2CH$_2$CH$_2$CCHα), 3.81 (tt, $^3J_{H3-F4}$ = $^3J_{H3-F2}$ = 15.7 Hz, $^3J_{H3-H4}$ = $^3J_{H3-H2}$ = 8.5 Hz, 1H, H-3β), 3.69 (ddd, J = 10.1, 7.1, 5.9 Hz, 1H, CH^{II}_2CH$_2$CH$_2$CCHβ), 3.65 (dddd, $^3J_{H5-H4}$ = 9.8 Hz, $^3J_{H5-H6b}$ = 5.3 Hz, $^3J_{H5-F4}$ = 2.5 Hz, $^3J_{H5-H6a}$ = 2.3 Hz, 1H, H-5β), 3.61 (dt, J = 9.9, 5.8 Hz, 1H, CH^{II}_2CH$_2$CH$_2$CCHα), 2.37−2.30 (m, 4H, CH$_2$CH$_2$CH$_2$CCHα/β), 1.96 (t, J = 2.7 Hz, 1H, CH$_2$CH$_2$CH$_2$CC$H\alpha$), 1.95 (t, J = 2.7 Hz, 1H, CH$_2$CH$_2$CH$_2$CC$H\beta$), 1.93−1.78 (m, 4H, CH$_2$CH$_2$CH$_2$CCHα/β) ppm; ^{13}C{^{1}H} NMR (126 MHz, chloroform-d) δ 170.77 (1C, $COCH_3$-β), 170.76 (1C, $COCH_3$-α), 138.0, 137.6, 128.6, 128.6, 128.2, 128.14, 128.06, 128.04 (10C, Ar-α/β), 100.8 (dd, $^2J_{C1-F2}$ = 23.4 Hz, $^4J_{C1-F4}$ = 1.6 Hz, 1C, C-1β), 96.3 (dd, $^2J_{C1-F2}$ = 20.5 Hz, $^4J_{C1-F4}$ = 1.4 Hz, 1C, C-1α), 91.9 (dd, $^1J_{C2-F2}$ = 188.8 Hz, $^3J_{C2-F4}$ = 9.4 Hz, 1C, C-2β), 89.6 (dd, $^1J_{C2-F2}$ = 193.6 Hz, $^3J_{C2-F4}$ = 9.0 Hz, 1C, C-2α), 89.2 (dd, $^1J_{C4-F4}$ = 186.2 Hz, $^3J_{C4-F2}$ = 9.0 Hz, C-4α), 89.1 (dd, $^1J_{C4-F4}$ = 185.9 Hz, $^3J_{C4-F2}$ = 8.5 Hz, 1C, C-4β), 83.7 (1C, CH$_2$CH$_2$CH$_2$CCHβ), 83.3 (1C, CH$_2$CH$_2$CH$_2$CCHα), 80.1 (t, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 18.7 Hz, 1C, C-3β), 77.9 (t, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 18.6 Hz, C-3α), 74.9 (t, $^4J_{CH2Ph-F2}$ = $^4J_{CH2Ph-F4}$ = 1.4 Hz, 1C, CH_2Ph-α), 74.5 (t, $^4J_{CH2Ph-F2}$ = $^4J_{CH2Ph-F4}$ = 1.6 Hz, 1C, CH_2Ph-β), 71.3 (d, $^3J_{C5-F4}$ = 24.1 Hz, 1C, C-5β), 68.9 (1C, CH$_2$CH$_2$CH$_2$CCH-β), 67.1 (d, $^3J_{C5-F4}$ = 24.2 Hz, 1C, C-5α), 67.0 (1C, CH$_2$CH$_2$CH$_2$CCHα), 62.3 (1C, C-6β), 62.2 (1C, C-6α), 28.6 (1C, CH$_2$CH$_2$CH$_2$CCH-β), 28.1 (1C, CH$_2$CH$_2$CH$_2$CCH-α), 20.92 (1C, $COCH_3$-β), 20.90 (1C, $COCH_3$-α), 15.3 (1C, CH$_2$CH$_2$CH$_2$CCH-α), 15.1 (1C, CH$_2$CH$_2$CH$_2$CCH-β) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −196.38 (ddt, $^2J_{F4-H4}$ = 50.5 Hz, $^3J_{F4-H3}$ = 15.5 Hz, $^3J_{F4-H5}$ = $^4J_{F4-H6a}$ = 2.9 Hz, 1F, F-4α), −197.39 (ddt, J = 50.1, 15.5, 2.6 Hz, 1F, F-β), −197.64 (ddt, J = 50.1, 16.0, 2.5 Hz, 1F, F-β), −200.66 (ddt, $^2J_{F2-H2}$ = 48.9 Hz, $^3J_{F2-H3}$ = 12.8 Hz, $^3J_{F2-H1}$ = $^4J_{F2-F4}$ = 2.0 Hz, 1F, F-2α) ppm; HRMS (ESI) m/z: [M + NH_4]$^+$ calcd for $C_{20}H_{28}F_2NO_5$ 400.1930, found 400.1936.

Cyclohexyl 6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranoside (24). This was synthesized using general procedure II starting from **16**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 2:3) to give **24** as a colorless oil (3.8 mg, 0.012 mmol, 29% yield, 75% yield based on the recovered starting material). R_f = 0.27 (silica, EtOAc/hexanes 1:9); $[\alpha]_D^{25}$ = −39.8 (c 0.2, $CHCl_3$); IR (ATR, NaCl) ν 2935, 2858, 1745, 1258, 1102, 1029 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 5.30 (dtt, $^2J_{H3-F3}$ = 54.6 Hz, $^3J_{H3-F2}$ = $^3J_{H3-F4}$ = 9.1 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 2.3 Hz, 1H, H-3), 4.96 (dt, $^3J_{H1-H2}$ = 7.7 Hz, $^3J_{H1-F2}$ = $^4J_{H1-F3}$ = 1.6 Hz, 1H, H-1), 4.49 (dddt, $^2J_{H4-F4}$ = 45.7 Hz, $^3J_{H4-F3}$ = 25.4 Hz, $^3J_{H4-H5}$ = 9.8 Hz, $^3J_{H4-H3}$ = $^4J_{H4-F2}$ = 2.0 Hz, 1H, H-4), 4.41 (dt, $^2J_{H6a-H6b}$ = 12.2 Hz, $^3J_{H6a-H5}$ = $^4J_{H6a-F4}$ = 2.0 Hz, 1H, H-6a), 4.246 (ddd, $^2J_{H6b-H6a}$ = 12.3 Hz, $^3J_{H6b-H5}$ = 5.1 Hz, $^4J_{H6b-F4}$ = 1.5 Hz, 1H, H-6b), 4.235 (dddt, $^2J_{H2-F2}$ = 45.7 Hz, $^3J_{H2-F3}$ = 26.7 Hz, $^3J_{H1-H2}$ = 7.9 Hz, $^4J_{H2-F4}$ = $^3J_{H2-H3}$ = 2.0 Hz, 1H, H-2), 4.13−4.07 (m, 1H, H-5), 3.69 (tt, J = 9.5, 3.9 Hz, 1H, CH), 2.10 (s, 3H, $COCH_3$), 1.95−1.88 (m, 2H, 2 × CH^I_2), 1.79−1.72 (m, 2H, 2 × CH^I_2), 1.59−1.50 (m, 1H, CH^I_2), 1.49−1.34 (m, 2H, 2 × CH^{II}_2), 1.34−1.17 (m, 3H, 3 × CH^{II}_2) ppm; ^{13}C{^{1}H} NMR (126 MHz, chloroform-d) δ 170.7 (1C, $COCH_3$), 96.6 (dd, $^2J_{C1-F2}$ = 23.9 Hz, $^3J_{C1-F3}$ = 3.5 Hz, 1C, C-1), 87.8 (dt, $^1J_{C3-F3}$ = 185.2 Hz, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 17.5 Hz, 1C, C-3), 86.6 (ddd, $^1J_{C2-F2}$ = 196.3 Hz, $^2J_{C2-F3}$ = 16.7 Hz, $^3J_{C2-F4}$ = 5.2 Hz, 1C, C-2), 84.3 (ddd, $^1J_{C4-F4}$ = 194.1 Hz, $^2J_{C4-F3}$ = 17.6 Hz, $^3J_{C4-F2}$ = 5.1 Hz, 1C, C-4), 78.8 (1C, CH), 68.9 (dd, $^2J_{C5-F4}$ = 24.1 Hz, $^3J_{C5-F3}$ = 3.5 Hz, 1C, C-5), 62.4 (1C, C-6), 33.5 (1C, CH_2), 31.9 (1C, CH_2), 25.6 (1C, CH_2), 24.1 (1C, CH_2), 23.9 (1C, CH_2), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −202.79 (ddddt, $^2J_{F2-H2}$ = 45.8 Hz, $^3J_{F2-F3}$ = 13.2 Hz, $^3J_{F2-H3}$ = 8.8 Hz, $^4J_{F2-F4}$ = 4.0 Hz, $^3J_{F2-H1}$ = $^4J_{F2-H4}$ = 2.1 Hz, 1F, F-2), −203.77 (ddddt, $^2J_{F4-H4}$ = 45.6 Hz, $^3J_{F4-F3}$ = 13.4 Hz, $^3J_{F4-H3}$ = 9.5 Hz, $^4J_{F4-F2}$ = 3.8 Hz, $^4J_{F4-H2}$ = $^3J_{F4-H5}$ = 1.4 Hz, 1F, F-4), −216.46 (dtt, $^2J_{F3-H3}$ = 54.3 Hz, $^3J_{F3-H2}$ = $^3J_{F3-H4}$ = 26.3 Hz, $^3J_{F3-F2}$ = $^3J_{F3-F4}$ = 12.6 Hz, 1F, F-3) ppm; HRMS (ESI) m/z: [M + NH_4]$^+$ calcd for $C_{14}H_{25}F_3NO_4^+$ 328.1730, found 328.1742.

1,4-Bis-*O*-(6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranosyl)-butane (25). This was synthesized using general procedure II starting from **16**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 2:3) to give **25** as a colorless oil (4.6 mg, 0.009 mmol, 38% yield). The spectroscopic data derived from compound **25** match those reported in the literature.[8b]

16-Methoxycarbonylhexanedecanyl 6-*O*-Acetyl-2,3,4-trideoxy-2,3,4-trifluoro-β-D-allopyranoside (26). This was synthesized using general procedure II starting from **16**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:9 → 3:7) to give **26** as a white amorphous solid (18.1 mg, 0.037 mmol, 64% yield). R_f = 0.36 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = −26.1 (c 0.5, $CHCl_3$); IR (ATR, NaCl) ν 2920, 2850, 1737, 1255, 1174, 1039, 720 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 5.29 (dtt, $^2J_{H3-F3}$ = 54.4 Hz, $^3J_{H3-F2}$ = $^3J_{H3-F4}$ = 9.2 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 2.3 Hz, 1H, H-3), 4.85 (dt, $^3J_{H1-H2}$ = 7.7 Hz, $^3J_{H1-F2}$ = $^4J_{H1-F3}$ = 1.5 Hz, 1H, H-1), 4.50 (dddt, $^2J_{H4-F4}$ = 45.4 Hz, $^3J_{H4-F3}$ = 25.5 Hz, $^3J_{H4-H5}$ = 9.8 Hz, $^3J_{H4-H3}$ = $^4J_{H4-F2}$ = 2.0 Hz, 1H, H-4), 4.43 (dt, $^2J_{H6a-H6b}$ = 12.1 Hz, $^3J_{H6a-H5}$ = 1.9 Hz, 1H, H-6a), 4.25 (dddt, $^2J_{H2-F2}$ = 46.1 Hz, $^3J_{H2-F3}$ = 26.4 Hz, $^3J_{H2-H1}$ = 7.8 Hz, $^4J_{H2-F4}$ =

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

$^{3}J_{H2-H3}$ = 2.0 Hz, 1H, H-2), 4.23 (ddd, $^{2}J_{H6b-H6a}$ = 12.3 Hz, $^{3}J_{H6b-H5}$ = 4.9 Hz, $^{4}J_{H6b-F4}$ = 1.5 Hz, 1H, H-6b), 4.13−4.07 (m, 1H, H-5), 3.89 (dt, J = 9.5, 6.7 Hz, 1H, CH^{I}_{2}), 3.66 (s, 3H, CO_2CH_3), 3.57 (dt, J = 9.5, 6.8 Hz, 1H, CH^{II}_{2}), 2.30 (t, J = 7.5 Hz, 2H, CH_2), 2.10 (s, 3H, $COCH_3$), 1.67−1.57 (m, 4H, 2 × CH_2), 1.38−1.22 (m, 22H, 11 × CH_2) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, chloroform-d) δ 174.5, 170.7 (2C, CO), 98.3 (dd, $^{2}J_{C1-F2}$ = 23.7 Hz, $^{3}J_{C1-F3}$ = 3.6 Hz, 1C, C-1), 87.7 (dt, $^{1}J_{C3-F3}$ = 184.8 Hz, $^{2}J_{C3-F2}$ = $^{2}J_{C3-F4}$ = 17.6 Hz, 1C, C-3), 86.7 (ddd, $^{1}J_{C2-F2}$ = 196.2 Hz, $^{2}J_{C2-F3}$ = 16.7 Hz, $^{3}J_{C2-F4}$ = 5.2 Hz, 1C, C-2), 84.2 (ddd, $^{1}J_{C4-F4}$ = 194.0 Hz, $^{2}J_{C4-F3}$ = 17.5 Hz, $^{3}J_{C4-F2}$ = 5.1 Hz, 1C, C-4), 70.9 (1C, CH_2), 68.9 (dd, $^{2}J_{C5-F4}$ = 24.3 Hz, $^{3}J_{C5-F3}$ = 3.6 Hz, 1C, C-5), 62.3 (1C, C-6), 51.6 (1C, CO_2CH_3), 34.3, 29.78, 29.77, 29.73, 29.72, 29.68, 29.64, 29.59, 29.5, 29.4, 29.3, 25.9, 25.1 (14C, 14 × CH_2), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −203.24 (ddddt, $^{2}J_{F2-H2}$ = 45.9 Hz, $^{3}J_{F2-F3}$ = 14.3 Hz, $^{3}J_{F2-H3}$ = 9.1 Hz, $^{4}J_{F2-F4}$ = 4.1 Hz, $^{3}J_{F2-H1}$ = $^{4}J_{F2-H4}$ = 1.6 Hz, 1F, F-2), −203.82 (dddqd, $^{2}J_{F4-H4}$ = 45.4 Hz, $^{3}J_{F4-F3}$ = 14.8 Hz, $^{3}J_{F4-H3}$ = 9.4 Hz, $^{4}J_{F4-F2}$ = 3.9 Hz, $^{4}J_{F4-H2}$ = $^{3}J_{F4-H5}$ = $^{4}J_{F4-H6a}$ = $^{4}J_{F4-H6b}$ = 1.7 Hz, 1F, F-4), −216.53 (dttt, $^{2}J_{F3-H3}$ = 54.1 Hz, $^{3}J_{F3-H2}$ = $^{3}J_{F3-H4}$ = 26.4 Hz, $^{3}J_{F3-F2}$ = $^{3}J_{F3-F4}$ = 14.0 Hz, $^{4}J_{F3-H1}$ = $^{4}J_{F3-H5}$ = 1.2 Hz, 1F, F-3) ppm; HRMS (ESI) m/z: $[M + NH_4]^+$ calcd for $C_{25}H_{47}F_3NO_6$ 514.3350, found 514.3350.

Compound (32). To a solution of 4′-demethylepipodophyllotoxin (1.0 equiv) in anhydrous acetonitrile (0.1 M) was added sodium iodide (2.0 equiv). The solution was cooled at 0 °C, and boron trifluoride (3.0 equiv) was added dropwise. The mixture was stirred for 15 min at this temperature. The mixture was then concentrated under reduced pressure and used for the next step without further purification.[21]

4-*O*-(6″-*O*-Acetyl-2″,3″,4″-trideoxy-2″,4″,6″-trifluoro-α/β-D-allopyranosyl)-5′-didemethoxy-3′,4′-dioxopodophyllotoxin (33). This was synthesized using general procedure II starting from **16** and crude iodine **32**.[21] The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:9 → 3:7) to give **33** as a reddish oil (7.1 mg, 0.012 mmol, 25% yield). R_f = 0.44 (silica, EtOAc/hexanes 2:1); IR (ATR, NaCl) ν 2923, 2851, 1777, 1484, 1233, 1032, 733 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 6.83 (s, 1H, Ar), 6.58 (s, 1H, Ar), 6.49 (s, 1H, Ar), 6.04 (d, J = 7.3, 1.2 Hz, 2H, CH_2 acetal), 5.42 (s, 1H, OH), 5.31 (dtt, $^{2}J_{H3''-F3''}$ = 54.3 Hz, $^{3}J_{H3''-F2''}$ = $^{3}J_{H3''-F4''}$ = 8.7 Hz, $^{3}J_{H3-H2}$ = $^{3}J_{H3-H4}$ = 2.2 Hz, 1H, H-3″), 5.16 (s, 1H, Ar), 4.96−4.94 (m, 2H, H-1″, H-4), 4.57 (dt, $^{2}J_{H6a''-H6b''}$ = 12.3 Hz, $^{3}J_{H6a''-H5''}$ = 2.0 Hz, 1H, H-6a″), 4.54−4.41 (m, 2H, H-11a, H-11b), 4.41 (dddt, $^{2}J_{H4''-F4''}$ = 45.8 Hz, $^{3}J_{H4''-F3''}$ = 26.2 Hz, $^{3}J_{H4''-H5''}$ = 9.9 Hz, $^{3}J_{H4''-H3''}$ = $^{4}J_{H4''-F2''}$ = 1.9 Hz, 1H, H-4″), 4.30 (d, $^{3}J_{H1-H2}$ = 6.0 Hz, 1H, H-1), 4.28 (dddt, $^{2}J_{H2''-F2''}$ = 46.1 Hz, $^{3}J_{H2''-F3''}$ = 26.0 Hz, $^{3}J_{H2''-H1''}$ = 8.7 Hz, $^{4}J_{H2''-F4''}$ = $^{3}J_{H2''-H3''}$ = 2.0 Hz, 1H, H-2″), 4.22 (ddt, $^{2}J_{H6''b-H6''a}$ = 12.3 Hz, $^{3}J_{H6''b-H5''}$ = 6.2 Hz, $^{4}J_{H6''b-F4''}$ = 1.5 Hz, 1H, H-6b″), 4.15−4.10 (m, 1H, H-5″), 3.85 (s, 3H, OCH_3), 3.50 (dd, $^{3}J_{H2-H3}$ = 14.1 Hz, $^{3}J_{H2-H1}$ = 5.9 Hz, 1H, H-2), 2.89 (dddd, $^{3}J_{H3-H2}$ = 14.7 Hz, $^{3}J_{H3-H11a}$ = 10.9 Hz, $^{3}J_{H3-H11b}$ = 7.7 Hz, $^{3}J_{H3-H4}$ = 3.0 Hz, 1H, H-3), 2.17 (s, 3H, $COCH_3$) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, chloroform-d) δ 178.4, 175.4, 174.5, 170.5 (4C, 4 × CO), 157.7, 151.9, 149.6, 148.3, 130.0, 127.0, 123.9, 113.4, 110.6, 109.8, (12C, Ar), 102.2 (1C, CH_2 acetal), 95.6 (dd, $^{2}J_{C1''-F2''}$ = 23.9 Hz, $^{3}J_{C1''-F3''}$ = 4.2 Hz, 1C, C-1″), 87.4 (dt, $^{1}J_{C3''-F3''}$ = 186.4 Hz, $^{2}J_{C3''-F2''}$ = $^{2}J_{C3''-F4''}$ = 18.2 Hz, 1C, C-3″), 86.5 (ddd, $^{1}J_{C2''-F2''}$ = 196.1 Hz, $^{2}J_{C2''-F3''}$ = 16.6 Hz, $^{3}J_{C2''-F4''}$ = 5.0 Hz, 1C, C-2″), 84.0 (ddd, $^{1}J_{C4''-F4''}$ = 194.2 Hz, $^{2}J_{C4''-F3''}$ = 18.6 Hz, $^{3}J_{C4''-F2''}$ = 6.4 Hz, 1C, C-4″), 72.6 (1C, C-4), 69.3 (dd, $^{2}J_{C5''-F4''}$ = 24.1 Hz, $^{3}J_{C5''-F3''}$ = 3.3 Hz, 1C, C-5″), 68.0 (1C, C-11), 62.2 (1C, C-6″), 56.4 (1C, OCH_3), 45.4 (1C, C-1), 40.1 (1C, C-2), 38.2 (1C, C-3), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −203.24 (dddt, $^{2}J_{F4''-H4''}$ = 45.5 Hz, $^{3}J_{F4''-F3''}$ = 14.1 Hz, $^{3}J_{F4''-H3''}$ = 9.0, $^{4}J_{F4''-F2''}$ = 3.6 Hz, $^{4}J_{F4''-H2''}$ = $^{3}J_{F4''-H5''}$ = 1.9 Hz, 1F, F-4″), −203.62 (ddddt, $^{2}J_{F2''-H2''}$ = 46.4 Hz, $^{3}J_{F2''-F3''}$ = 14.2 Hz, $^{3}J_{F2''-H3''}$ = 9.2 Hz, $^{4}J_{F2''-F4''}$ = 3.3 Hz, $^{3}J_{F2''-H1''}$ = $^{4}J_{F2''-H4''}$ = 1.6 Hz, 1F, F-2″), −216.33 (dtt, $^{2}J_{F3''-H3''}$ = 53.7 Hz, $^{3}J_{F3''-H2''}$ = $^{3}J_{F3''-H4''}$ = 26.6 Hz, $^{3}J_{F3''-F2''}$ = $^{3}J_{F3''-F4''}$ = 14.0 Hz, 1F, F-3″) ppm; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{26}F_3O_{11}$ 595.1427, $[M + H]^+$, found 595.1448.

4-*O*-(6″-*O*-Acetyl-2″,3″,4″-trideoxy-2″,3″,4″-trifluoro-β-D-allopyranosyl)-4′-demethylepipodophyllotoxin (34). This was synthesized using general procedure III starting from **16**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1 → 3:1) to give **34** as an amorphous white solid (20.8 mg, 0.0341 mmol, 56% yield). R_f = 0.42 (silica, EtOAc/hexanes 1:1); IR (ATR, NaCl) ν 3455, 2919, 1775, 1611, 1485, 1232, 1031 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H, Ar), 6.56 (s, 1H, Ar), 6.25 (s, 2H, Ar), 6.00 (dd, J = 9.9, 1.3 Hz, 2H, CH_2 dioxolane), 5.42 (s, 1H, OH), 5.32 (dtt, $^{2}J_{H3''-F3''}$ = 54.3 Hz, $^{3}J_{H3''-F2''}$ = $^{3}J_{H3''-F4''}$ = 8.7 Hz, $^{3}J_{H3''-H2''}$ = $^{3}J_{H3''-H4''}$ = 2.2 Hz, 1H, H-3″), 5.03−4.99 (m, 2H, H-1″, H-4), 4.61 (d, $^{3}J_{H1-H2}$ = 5.3 Hz, 1H, H-1), 4.58 (dt, $^{2}J_{H6a''-H6b''}$ = 12.3 Hz, $^{3}J_{H6a''-H5''}$ = $^{4}J_{H6a''-F4''}$ = 2.0 Hz, 1H, H-6a″), 4.48 (dddt, $^{2}J_{H4''-F4''}$ = 45.5 Hz, $^{3}J_{H4''-F3''}$ = 25.5 Hz, $^{3}J_{H4''-H5''}$ = 9.9 Hz, $^{3}J_{H4''-H3''}$ = $^{4}J_{H4''-F2''}$ = 1.8 Hz, 1H, H-4″), 4.40 (dd, $^{3}J_{H11a-H3}$ = 10.8 Hz, $^{2}J_{H11a-H11b}$ = 8.8 Hz, 1H, H-11a), 4.29 (dddt, $^{2}J_{H2''-F2''}$ = 46.0 Hz, $^{3}J_{H2''-F3''}$ = 26.6 Hz, $^{3}J_{H1''-H2''}$ = 8.0 Hz, $^{4}J_{H2''-F4''}$ = $^{3}J_{H2''-H3''}$ = 1.9 Hz, 1H, H-2″), 4.25 (t, $^{2}J_{H11b-H11a}$ = $^{3}J_{H11b-H3}$ = 8.2 Hz, 1H, H-11b), 4.20 (ddd, $^{2}J_{H6b''-H6a''}$ = 12.4 Hz, $^{3}J_{H6b''-H5''}$ = 5.6 Hz, $^{4}J_{H6b''-F4''}$ = 1.2 Hz, 1H, H-6b″), 4.14−4.09 (m, 1H, H5″), 3.31 (dd, $^{3}J_{H2-H3}$ = 14.0 Hz, $^{3}J_{H2-H1}$ = 5.4 Hz, 1H, H-2), 2.92 (dddd, $^{3}J_{H3-H2}$ = 13.9 Hz, $^{3}J_{H3-H11a}$ = 10.6 Hz, $^{3}J_{H3-H11b}$ = 7.7 Hz, $^{3}J_{H3-H4}$ = 2.9 Hz, 1H, H-3), 2.16 (s, 3H, $COCH_3$) ppm; $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 174.7, 170.4 (2C, 2 × CO), 149.0, 147.1, 146.4, 134.1, 133.5, 130.6, 126.8, 111.0, 109.2, 107.9 (12C, Ar), 101.7 (1C, CH_2 dioxolane), 95.8 (dd, $^{2}J_{C1''-F2''}$ = 23.7 Hz, $^{3}J_{C1''-F3''}$ = 3.5 Hz, 1C, C-1″), 87.4 (dt, $^{1}J_{C3''-F3''}$ = 186.1 Hz, $^{2}J_{C3''-F2''}$ = $^{2}J_{C3''-F4''}$ = 17.4 Hz, 1C, C-3″), 86.4 (ddd, $^{1}J_{C2''-F2''}$ = 197.6 Hz, $^{2}J_{C2''-F3''}$ = 16.6 Hz, $^{3}J_{C2''-F4''}$ = 5.6 Hz, 1C, C-2″), 83.9 (ddd, $^{1}J_{C4''-F4''}$ = 194.4 Hz, $^{2}J_{C4''-F3''}$ = 17.1 Hz, $^{3}J_{C4''-F2''}$ = 5.4 Hz, 1C, C-4″), 73.5 (1C, C-4), 69.0 (dd, $^{2}J_{C5''-F4''}$ = 24.6 Hz, $^{3}J_{C5''-F3''}$ = 3.5 Hz, 1C, C-5″), 67.5 (1C, C-11), 62.0 (1C, C-6″), 56.5 (2C, 2 × OCH_3), 43.7 (1C, C-1), 40.9 (1C, C-2), 37.6 (1C, C-3), 20.8 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ −203.02 (ddddt, $^{2}J_{F2''-H2''}$ = 45.6 Hz, $^{3}J_{F2''-F3''}$ = 13.7 Hz, $^{3}J_{F2''-H3''}$ = 8.5 Hz, $^{4}J_{F2''-F4''}$ = 3.5 Hz, $^{3}J_{F2''-H1''}$ = $^{4}J_{F2''-H4''}$ = 2.1 Hz, 1F, F-2″), −203.65 (ddddt, $^{2}J_{F4''-H4''}$ = 45.4 Hz, $^{3}J_{F4''-F3''}$ = 13.3 Hz, $^{3}J_{F4''-H3''}$ = 9.7 Hz, $^{4}J_{F4''-F2''}$ = 3.9 Hz, $^{4}J_{F4''-H2''}$ = $^{3}J_{F4''-H5''}$ = 1.9 Hz, 1F, F-4″), −216.35 (dtt, $^{2}J_{F3''-H3''}$ = 53.6 Hz, $^{3}J_{F3''-H2''}$ = $^{3}J_{F3''-H4''}$ = 26.6 Hz, $^{3}J_{F3''-F2''}$ = $^{3}J_{F3''-F4''}$ = 13.9 Hz, 1F, F-3″) ppm; HRMS (ESI) m/z: $[M + NH_4]^+$ calcd for $C_{29}H_{33}F_3NO_{11}$ 628.2000, found 628.2010.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-α/β-D-glucopyranose (35). To a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal[26] (205 mg, 0.75 mmol) in nitromethane/water (7.5 mL, 5:1) at 0 °C was added Selectfluor (400 mg, 1.13 mmol, 1.5 equiv). The mixture was stirred overnight, while the temperature was allowed to rise to room temperature. Then, the reaction mixture was heated under reflux using an oil bath for 1 h. The nitromethane was evaporated under reduced pressure. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), and the combined organic phases were washed with water (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was used for the next step without further purification. The crude oil was dissolved in pyridine (0.6 mL, 7.5 mmol, 10 equiv) at 0 °C, and Ac_2O (0.38 mL, 3.8 mmol, 5 equiv) was added. The mixture was stirred at room temperature for 2 h, and water (5 mL) and CH_2Cl_2 (10 mL) were added. The biphasic solution was stirred 30 min, and the phases were separated. The organic phase was washed with water (2 × 10 mL), a saturated aqueous $NaHCO_3$ solution (10 mL), and an aqueous 1 M HCl solution (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The mixture 2-deoxy-2-fluoromannose and 2-deoxy-2-fluoroglucose analogues were separated by flash column chromatography (silica gel, EtOAc/hexanes, 1:9 to 1:1) to give pure 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoroglucopyranose (79.2 mg, 0.225 mmol, 30% yield) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoromannopyranose (84.4 mg, 0.240 mmol, 32% yield). The spectroscopic data match those reported in the literature.[12]

1,6-Di-*O*-acetyl-3-*O*-benzyl-2,4-dideoxy-2,4-difluoro-α/β-D-glucopyranose (36). Compound **36** was made as previously

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

reported, and the spectroscopic data derived from compound **36** match those reported in the literature.[8d]

1,2,3-Tri-*O*-acetyl-4,6-dideoxy-4,6-difluoro-α/β-D-glucopyranose (37). To a stirred solution of 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-difluoro-allyl-α/β-D-glucopyranoside[8e] (90.8 mg, 0.2245 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was added a 1 M solution of boron trichloride (BCl_3) in CH_2Cl_2 (1.35 mL, 1.347 mmol, 6 equiv) dropwise, and the reaction was allowed to go back to room temperature. The mixture was stirred 2.5 h and quenched with water (6 mL). CH_2Cl_2 was removed under reduced pressure, and the resulting aqueous phase was stirred for 1 h. The remaining water was evaporated, and the crude oil was dissolved in pyridine (2 mL). Ac_2O (675 μL, 6.735 mmol, 30 equiv) was added at 0 °C, and the mixture was allowed to go back to room temperature for 16 h. Water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were successively washed with water (2 × 10 mL), a saturated aqueous $NaHCO_3$ solution (25 mL), and an aqueous 1 M HCl solution (25 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:9 to 3:7) to give **37** (α/β = 3.7:1) as a thick yellow oil (60 mg, 0.1939 mmol, 86% yield); R_f = 0.71 (silica, EtOAc/hexanes 1:1); $[\alpha]_D^{25}$ = +23.0 (*c* 1.0, $CHCl_3$); IR (ATR, NaCl) ν 2361, 1765, 1250, 1214, 1081, 1001, 879 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 6.32 (t, $^3J_{H1-H2}$ = $^5J_{H1-F4}$ = 3.3 Hz, 1H, H-1α), 5.74 (d, $^3J_{H1-H2}$ = 8.2 Hz, 1H, H-1β), 5.62 (ddd, $^3J_{H3-F4}$ = 13.7 Hz, $^3J_{H3-H2}$ = 10.3 Hz, $^3J_{H3-H4}$ = 8.8 Hz, 1H, H-3α), 5.40 (ddd, $^3J_{H3-F4}$ = 14.7 Hz, $^3J_{H3-H2}$ = 9.7 Hz, $^3J_{H3-H4}$ = 9.0 Hz, 1H, H-3β), 5.08 (ddd, $^3J_{H2-H3}$ = 9.7 Hz, $^3J_{H2-H1}$ = 8.2 Hz, $^4J_{H2-F4}$ = 0.6 Hz, 1H, H-2β), 5.03 (ddd, $^3J_{H2-H3}$ = 10.4 Hz, $^3J_{H2-H1}$ = 3.7 Hz, $^3J_{H2-F4}$ = 1.0 Hz, 1H, H-2α), 4.75−4.57 (m, 4H, H-6α/β), 4.64 (dt, $^2J_{H4-F4}$ = 49.9 Hz, $^3J_{H4-H5}$ = 10.0 Hz, $^3J_{H4-H3}$ = 9.5 Hz, 1H, H-4β), 4.61 (dd, $^2J_{H4-F4}$ = 50.3 Hz, $^3J_{H4-H5}$ = 10.1 Hz, $^3J_{H4-H3}$ = 9.1 Hz, 1H, H-4α), 4.08 (ddtd, $^3J_{H5-F6}$ = 26.5 Hz, $^3J_{H5-H4}$ = 9.5 Hz, $^3J_{H5-H6b}$ = 4.4 Hz, $^4J_{H5-H1}$ = 2.8 Hz, $^3J_{H5-H6a}$ = 2.2 Hz, 1H, H-5α), 3.81 (ddtd, $^3J_{H5-F6}$ = 25.5 Hz, $^3J_{H5-H4}$ = 10.0 Hz, $^3J_{H5-H6b}$ = $^3J_{H5-F4}$ = 3.1 Hz, $^3J_{H5-H6a}$ = 1.7 Hz, 1H, H-5β), 2.19 (s, 3H, $COCH_3$-α), 2.12 (s, 3H, $COCH_3$-α), 2.12 (s, 3H, $COCH_3$-β), 2.11 (s, 3H, $COCH_3$-β), 2.05 (s, 3H, $COCH_3$-β), 2.03 (s, 3H, $COCH_3$-α); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 170.08 (s, 1C, $COCH_3$-α), 170.05 (s, 1C, $COCH_3$-β), 169.8 (s, 3H, $COCH_3$-α), 169.5 (s, 1C, $COCH_3$-β), 169.1 (s, 1C, $COCH_3$-β), 168.9 (s, 1C, $COCH_3$-α), 91.7 (d, $^4J_{C1-F4}$ = 1.3 Hz, 1C, C-1β), 89.1 (d, $^2J_{C1-F4}$ = 1.1 Hz, 1C, C-1α), 85.5 (dd, $^1J_{C4-F4}$ = 187.3 Hz, $^3J_{C4-F6}$ = 7.8 Hz, 1C, C-4α), 85.2 (dd, $^1J_{C4-F4}$ = 187.8 Hz, $^3J_{C4-F6}$ = 7.8 Hz, 1C, C-4β), 80.3 (d, $^1J_{C6-F6}$ = 176.4 Hz, 1C, C-6α), 80.1 (d, $^1J_{C6-F6}$ = 176.6 Hz, 1C, C-6β), 73.1 (dd, $^2J_{C5-F4}$ = 24.5 Hz, $^2J_{C5-F6}$ = 18.7 Hz, 1C, C-5β), 72.7 (d, $^2J_{C3-F4}$ = 20.0 Hz, 1C, C-3β), 70.6 (dd, $^2J_{C5-F4}$ = 23.8 Hz, $^2J_{C5-F6}$ = 18.2 Hz, 1C, C-5α), 70.1 (d, $^3J_{C2-F4}$ = 7.9 Hz, 1C, C-2β), 69.7 (d, $^2J_{C3-F4}$ = 19.6 Hz, 1C, C-3α), 69.0 (d, $^3J_{C2-F4}$ = 8.4 Hz, 1C, C-2α), 21.0, 20.9, 20.8, 20.7, 20.6 (m, 6C, 3 × $COCH_3$-α/β); ^{19}F NMR (470 MHz, chloroform-*d*) δ −199.0 (ddq, $^2J_{F4-H4}$ = 50.2 Hz, $^3J_{F4-H3}$ = 13.0 Hz, $^3J_{F4-H5}$ = $^4J_{F5-H6}$ = 3.4 Hz, $^4J_{F4-H2}$ = 1.3 Hz, 1F, F-4α), −200.7 (ddt, $^2J_{F4-H4}$ = 50.1 Hz, $^3J_{F4-H3}$ = 14.8 Hz, $^3J_{F4-H5}$ = 2.7 Hz, $^4J_{F4-H2}$ = 0.8 Hz, 1F, F-4β), −236.7 (td, $^2J_{F6-H6a}$ = $^2J_{F6-H6b}$ = 47.2 Hz, $^3J_{F6-H5}$ = 25.4 Hz, 1F, F-6β), −236.9 (td, $^2J_{F6-H6a}$ = $^2J_{F6-H6b}$ = 47.3 Hz, $^3J_{F6-H5}$ = 26.5 Hz, 1F, F-6α); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{16}F_2NaO_7$ 333.0756, found 333.0747.

1,3-Di-*O*-acetyl-2,4,6-trideoxy-2,4,6-trifluoro-α/β-D-glucopyranose (38). To a stirred solution of 2,4,6-trideoxy-2,4,6-trifluoro-α/β-D-glucopyranose[8d] (31.9 mg, 0.1714 mmol) in pyridine (170 μL) at 0 °C was added Ac_2O (97 μL, 1.028 mmol, 6 equiv). The mixture was allowed to go back to room temperature and was stirred for 3 h. EtOAc (10 mL) was added, and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution (5 mL), an aqueous 1 M HCl solution (2 × 5 mL), water (5 mL), and brine (5 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:9 → 1:3) to give **38** (α/β = 1:14.3) as a colorless oil (25.8 mg, 0.0955 mmol, 56% yield). R_f = 0.55 (silica, EtOAc/hexanes 1:1); $[\alpha]_D^{25}$ = +9.6 (*c* 0.3, $CHCl_3$); IR (ATR, NaCl) ν 2361, 1765, 1250, 1214, 1081, 1001, 879 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 6.42 (t, *J* = 3.2 Hz, 1H, H-1α), 5.80 (dd, $^3J_{H1-H2}$ = 8.0 Hz, $^3J_{H1-F2}$ = 3.2 Hz, 1H, H-1β), 5.54 (tt, $^3J_{H3-F4}$ = $^3J_{H3-F2}$ = 14.5 Hz, $^3J_{H3-H4}$ = $^3J_{H3-H2}$ = 9.1 Hz, 1H, H-3), 4.69 (ddd, $^2J_{H6a-F6}$ = 47.2 Hz, $^2J_{H6a-H6b}$ = 10.8 Hz, $^3J_{H6a-H5}$ = 2.0 Hz, 1H, H-6a), 4.63 (ddt, $^2J_{H6b-F6}$ = 46.5 Hz, $^2J_{H6b-H6a}$ = 10.9 Hz, $^3J_{H6b-H5}$ = 3.1 Hz, $^4J_{H6b-F4}$ = 1.4 Hz, 1H, H-6b), 4.58 (dt, $^2J_{H4-F4}$ = 49.9 Hz, $^3J_{H4-H5}$ = 9.9 Hz, $^3J_{H4-H3}$ = 9.0 Hz, 1H, H-4), 4.39 (dt, $^2J_{H2-F2}$ = 50.5 Hz, $^3J_{H2-H3}$ = 9.1 Hz, $^3J_{H1-H2}$ = 7.8 Hz, 1H, H-2), 3.82 (dddt, $^3J_{H5-F6}$ = 25.9 Hz, $^3J_{H5-H4}$ = 10.0 Hz, $^3J_{H5-H6b}$ = 3.2 Hz, $^3J_{H5-H6a}$ = $^4J_{H5-F4}$ = 1.7 Hz, 1H, H-5), 2.19 (s, 3H, $COCH_3$), 2.18 (s, 3H, $COCH_3$); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 169.7, 168.9 (2C, 2 × $COCH_3$), 91.2 (dd, $^2J_{C1-F2}$ = 25.1 Hz, $^4J_{C1-F4}$ = 1.5 Hz, 1C, C-1), 88.0 (dd, $^1J_{C2-F2}$ = 193.8 Hz, $^3J_{C2-F4}$ = 8.7 Hz, 1C, C-2), 85.0 (dt, $^1J_{C4-F4}$ = 181.8 Hz, $^3J_{C6-F6}$ = $^3J_{C2-F2}$ = 8.2 Hz, 1C, C-4), 79.9 (d, $^1J_{C6-F6}$ = 176.7 Hz, 1C, C-6), 73.1 (dd, $^2J_{C5-F4}$ = 24.2 Hz, $^2J_{C5-F6}$ = 18.8 Hz, 1C, C-5), 72.3 (t, $^2J_{C3-F4}$ = $^2J_{C3-F2}$ = 20.2 Hz, 1C, C-3), 20.91, 20.88 (2C, 2 × $COCH_3$); ^{19}F NMR (470 MHz, chloroform-*d*) δ −200.2 (dd, *J* = 50.1, 14.4 Hz, 1F, F-α), −201.5 (dddt, $^2J_{F4-H4}$ = 49.9 Hz, $^3J_{F4-H3}$ = 14.4 Hz, $^4J_{F4-F2}$ = 2.1 Hz, $^3J_{F4-H5}$ = $^4J_{F4-H6b}$ = 1.5 Hz, 1F, F-4β), −201.8 (ddt, $^2J_{F2-H2}$ = 50.6 Hz, $^3J_{F2-H3}$ = 14.4 Hz, $^3J_{F2-H1}$ = 2.8 Hz, $^4J_{F2-F4}$ = 2.2 Hz, 1F, F-2β), −203.30 (dd, *J* = 48.5, 12.1 Hz, 1F, F-α), −237.07 (td, $^2J_{F6-H6a}$ = $^2J_{F6-H6b}$ = 47.1 Hz, $^3J_{F6-H5}$ = 25.8 Hz, 1F, F-6β), −237.30 (td, *J* = 47.1, 27.0 Hz, 1F. F-6α); HRMS (ESI) *m/z*: $[M + NH_4]^+$ calcd for $C_{10}H_{17}F_3NO_5$ 288.1053, found 288.1054.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α/β-D-glucopyranose (39). This was synthesized using general procedure I starting from **35**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:1) to give **39** (α/β = 2.3:1) as a colorless oil (36.1 mg, 0.117 mmol, 82% yield). The spectroscopic data derived from compound **39** match those reported in the literature.[12]

6-*O*-Acetyl-3-*O*-benzyl-2,4-dideoxy-2,4-difluoro-α/β-D-glucopyranose (40). This was synthesized using general procedure I starting from **36**.[8e] The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:1) to give **40** (α/β = 4:1) as a colorless oil (116.1 mg, 0.367 mmol, 88% yield). R_f = 0.44 (silica, EtOAc/hexanes 1:1); $[\alpha]_D^{25}$ = +60.7 (*c* 0.2, $CHCl_3$); IR (ATR, NaCl) ν 3426, 2954, 1744, 1727, 1370, 1239, 1039 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ: 7.44−7.28 (m, 10H, Ar-α/β), 5.41 (t, $^3J_{H1-H2}$ = $^3J_{H1-F2}$ = 3.5 Hz, 1H, H-1α), 4.82 (m, 5H, H-1β; CH_2Ph-α/β), 4.47 (dt, $^2J_{H4-F4}$ = 50.0 Hz, $^3J_{H4-H5}$ = 10.0 Hz, $^3J_{H4-H3}$ = 8.7 Hz, 1H, H-4β), 4.45 (ddd, $^2J_{H2-F2}$ = 48.6 Hz, $^3J_{H2-H3}$ = 9.1 Hz, $^3J_{H2-H1}$ = 3.5 Hz, 1H, H-2α), 4.44 (dt, $^2J_{H4-F4}$ = 49.9 Hz, $^3J_{H4-H5}$ = $^3J_{H4-H3}$ = 8.9 Hz, 1H, H-4α), 4.45−4.37 (m, 2H, H-6α/β), 4.26 (dt, $^2J_{H2-F2}$ = 50.7 Hz, $^3J_{H2-H1}$ = $^3J_{H2-H3}$ = 8.1 Hz, 1H, H-2β), 4.28−4.20 (m, 3H, H-5α; H-6α/β), 4.15 (ddt, $^3J_{H3-F4}$ = 15.3 Hz, $^3J_{H3-F2}$ = 12.9 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 8.8 Hz, 1H, H-3α), 3.83 (tt, $^3J_{H3-F4}$ = $^3J_{H3-F2}$ = 15.3 Hz, $^3J_{H3-H4}$ = $^3J_{H3-H2}$ = 8.6 Hz, 1H, H-3β), 3.77 (br, 1H, OH-β), 3.71 (ddt, $^3J_{H5-H4}$ = 10.3 Hz, $^3J_{H5-H6b}$ = 5.4 Hz, $^3J_{H5-H6a}$ = $^3J_{H5-F4}$ = 2.7 Hz, 1H, H-5β), 3.37 (br, 1H, OH-α), 2.10 (s, 6H, $COCH_3$-α/β); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 170.99 (s, 1C, $COCH_3$-α), 170.96 (s, 1C, $COCH_3$-β), 137.8, 137.4, 128.60, 128.57, 128.2, 128.11, 128.09 (10C, Ar-α/β), 94.7 (dd, $^2J_{C1-F2}$ = 23.8 Hz, $^4J_{C1-F4}$ = 1.2 Hz, 1C, C-1β), 93.0 (dd, $^1J_{C2-F2}$ = 188.9 Hz, $^3J_{C2-F4}$ = 9.4 Hz, 1C, C-2β), 90.8−88.2 (m, 1C, C-4β), 90.4 (dd, $^2J_{C1-F2}$ = 21.5 Hz, $^2J_{C1-F4}$ = 1.2 Hz, 1C, C-1α), 90.0 (dd, $^1J_{C2-F2}$ = 192.0 Hz, $^3J_{C2-F4}$ = 9.1 Hz, 1C, C-2α), 89.0 (dd, $^1J_{C4-F4}$ = 185.7 Hz, $^3J_{C4-F2}$ = 8.8 Hz, 1C, C-4α), 79.8 (t, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 18.7 Hz, 1C, C-3β), 77.3 (t, $^2J_{C3-F2}$ = $^2J_{C3-F4}$ = 18.3 Hz, 1C, C-3α), 74.9 (s, 1C, CH_2Ph-α), 74.6 (s, 1C, CH_2Ph-β), 71.6 (d, $^2J_{C5-F4}$ = 24.2 Hz, 1C, C-5β), 67.0 (d, $^2J_{C5-F4}$ = 24.0 Hz, 1C, C-5α), 62.34 (s, 1C, C-6β), 62.29 (s, 1C, C-6β), 20.92 (s, 1C, $COCH_3$-α), 20.91 (s, 1C, $COCH_3$-β); ^{19}F NMR (470 MHz, chloroform-*d*) δ −196.6 (ddq, $^2J_{F4-H4}$ = 51.4 Hz, $^3J_{F4-H3}$ = 15.5 Hz, 2.9 Hz, 1F, F-4α), −197.5 (ddt, *J* = 50.3 Hz, 15.1, 3.0 Hz, 1F, F-β), −197.7 (ddt, *J* = 50.3, 15.5, 2.5 Hz, 1F, F-β), −199.4 (ddd, $^2J_{F2-H2}$ = 48.9 Hz, $^3J_{F2-H3}$ = 12.9 Hz, $^3J_{F2-H1}$ = 2.1 Hz, 1F, F-2α); HRMS (ESI) *m/z*: $[M + NH_4]^+$ calcd for $C_{15}H_{22}F_2NO_5$ 334.1461, found 334.1457.

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

2,3-Di-*O*-acetyl-4,6-dideoxy-4,6-difluoro-α/β-D-glucopyranose (41). This was synthesized using general procedure I starting from **37**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:1) to give **41** (α/β = 4:1) as a colorless oil (7.0 mg, 0.0261 mmol, 20% yield). R_f = 0.46 (silica, EtOAc/hexanes 1:1); $[\alpha]_D^{25}$ = +20.5 (*c* 0.2, $CHCl_3$); IR (ATR, NaCl) ν 3451, 2963, 1755, 1735, 1231, 1033, 1014 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 5.68 (dt, $^3J_{H3-F4}$ = 14.1 Hz, $^3J_{H3-H4}$ = $^3J_{H3-H2}$ = 9.7 Hz, 1H, H-3), 5.47 (t, $^3J_{H1-H2}$ = $^4J_{H1-H5}$ = 3.4 Hz, 1H, H-1), 4.84 (ddd, $^3J_{H2-H3}$ = 10.3 Hz, $^3J_{H2-H1}$ = 3.6 Hz, $^4J_{H2-F4}$ = 0.9 Hz, 1H, H-2), 4.67 (dddd, $^2J_{H6b-F6}$ = 47.0 Hz, $^2J_{H6b-H6a}$ = 10.6 Hz, $^3J_{H6b-H5}$ = 3.4 Hz, $^4J_{H6b-F4}$ = 1.8 Hz, 1H, H-6b), 4.63 (ddt, $^2J_{H6a-F6}$ = 47.6 Hz, $^2J_{H6a-H6b}$ = 10.6 Hz, $^3J_{H6a-H5}$ = $^4J_{H6a-F4}$ = 1.7 Hz, 1H, H-6a), 4.53 (dt, $^2J_{H4-F4}$ = 50.5 Hz, $^3J_{H4-H5}$ = 10.1 Hz, $^3J_{H4-H3}$ = 9.0 Hz, 1H, H-4), 4.26 (dddd, $^3J_{H5-F6}$ = 26.7 Hz, $^3J_{H5-H4}$ = 9.8 Hz, $^3J_{H5-H6b}$ = $^4J_{H5-H1}$ = 3.8 Hz, $^3J_{H5-H6a}$ = 1.8 Hz, 1H, H-5), 3.03 (s, 1H, OH), 2.11 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 170.3, 170.1 (s, 2C, 2 × $COCH_3$), 90.4 (s, 1C, C-1), 86.0 (dd, $^1J_{C4-F4}$ = 187.2 Hz, $^3J_{C4-F6}$ = 7.7 Hz, 1C, C-4), 80.9 (d, $^1J_{C6-F6}$ = 175.0 Hz, 1C, C-6), 70.8 (d, $^3J_{C2-F4}$ = 7.7 Hz, 1C, C-2), 69.7 (d, $^2J_{C3-F4}$ = 19.8 Hz, 1C. C-3), 68.1 (dd, $^2J_{CS-F4}$ = 23.4, $^2J_{CS-F6}$ = 18.1 Hz, 1C, C-5), 20.9, 20.8 (s, 2C, 2 × $COCH_3$); ^{19}F NMR (470 MHz, chloroform-*d*) δ −198.4 (ddtd, $^2J_{F4-H4}$ = 50.4 Hz, $^3J_{F4-H3}$ = 14.4 Hz, $^2J_{F4-H4}$ = $^2J_{F4-H4}$ = 3.6 Hz, $^2J_{F4-H4}$ = 1.8 Hz, 1F, F-4α), − 200.6 (ddd, *J* = 50.4, 14.4, 2.9 Hz, 1F, F-4β), −235.6 (td, *J* = 47.0, 24.4 Hz, 1F, F-6β), −236.4 (td, $^2J_{F6-H6a}$ = $^2J_{F6-H6b}$ = 47.2 Hz, $^2J_{F6-H5}$ = 26.7 Hz, 1F, F-6α); HRMS (ESI) *m*/*z*: $[M + NH_4]^+$ calcd for $C_{10}H_{18}F_2NO_6$ 286.1097, found 286.1093.

3-*O*-Acetyl-2,4,6-trideoxy-2,4,6-trifluoro-α/β-D-glucopyranose (42). This was synthesized using general procedure I starting from **38**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:3 → 1:1) to give **42** (α/β = 3.6:1) as a colorless oil (17.1 mg, 0.0750 mmol, 78% yield). R_f = 0.21 (silica, EtOAc/hexanes 1:3); $[\alpha]_D^{25}$ = +89.5 (*c* 0.4, $CHCl_3$); IR (ATR, NaCl) ν 3453, 2963, 1754, 1737, 1232, 1058, 1033 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 5.74 (ddt, $^3J_{H3-F4}$ = 14.3 Hz, $^3J_{H3-F2}$ = 12.2 Hz, $^3J_{H3-H4}$ = $^3J_{H3-H2}$ = 9.3 Hz, 1H, H-3α), 5.48 (dd, $^3J_{H1-H2}$ = 3.7 Hz, $^3J_{H1-F2}$ = 2.2 Hz, 1H, H-1α), 5.48 (tt, $^3J_{H3-F4}$ = 14.8 Hz, $^3J_{H3-F2}$ = 13.9 Hz, $^3J_{H3-H2}$ = $^3J_{H3-H4}$ = 9.2 Hz, 1H, H-3β), 4.96 (dd, $^3J_{H1-H2}$ = 7.7 Hz, $^3J_{H1-F2}$ = 2.7 Hz, 1H, H-1β), 4.75−4.55 (m, 4H, H-6α/β), 4.57−4.42 (m, 1H, H-4β), 4.50 (dt,$^2J_{H4-F4}$ = 50.5 Hz, $^3J_{H4-H5}$ = $^3J_{H4-H3}$ = 9.5 Hz, 1H, H-4α), 4.43 (ddd, $^2J_{H2-F2}$ = 49.3 Hz, $^3J_{H2-H3}$ = 9.7 Hz, $^3J_{H2-H1}$ = 3.7 Hz, 1H, H-2α), 4.25 (ddtd, $^3J_{H5-F6}$ = 27.4 Hz, $^3J_{H5-H4}$ = 9.5 Hz, $^3J_{H5-H6b}$ = 4.1 Hz, $^3J_{H5-F4}$ = 3.1 Hz, $^3J_{H5-H6a}$ = 1.6 Hz, 1H, H-5α), 4.22 (ddd, $^2J_{H2-F2}$ = 50.5 Hz, $^3J_{H2-H3}$ = 9.2 Hz, $^3J_{H2-H1}$ = 7.7 Hz, 1H, H-2β), 3.77 (ddtd, $^3J_{H5-F6}$ = 24.1 Hz, $^3J_{H5-H4}$ = 9.9 Hz, $^3J_{H5-H6b}$ = 4.1 Hz, $^3J_{H5-F4}$ = 3.0 Hz, $^3J_{H5-H6a}$ = 1.6 Hz, 1H, H-5β), 3.56 (br, 1H, OH-α), 2.18 (s, 3H, $COCH_3$-β), 2.17 (s, 3H, $COCH_3$-α); $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 170.3 (s, 1C, $COCH_3$-α), 170.2 (s, 1C, $COCH_3$-β), 94.7 (dd, $^2J_{C1-F2}$ = 23.1 Hz, $^4J_{C1-F4}$ = 1.4 Hz, 1C, C-1β), 90.30 (dd, $^2J_{C1-F2}$ = 21.3 Hz, $^4J_{C1-F4}$ = 1.2 Hz, 1C, C-1α), 90.29 (dd, $^1J_{C2-F2}$ = 191.7 Hz, $^3J_{C2-F4}$ = 8.1 Hz, 1C, C-2β), 87.6 (dd, $^1J_{C2-F2}$ = 194.1 Hz, $^3J_{C2-F4}$ = 8.0 Hz, 1C, C-2α), 85.52 (dt, $^1J_{C4-F4}$ = 188.6 Hz, $^3J_{C4-F6}$ = $^3J_{C4-F2}$ = 7.8 Hz, 1C, C-4β), 85.47 (dt, $^1J_{C4-F4}$ = 188.2 Hz, $^3J_{C4-F6}$ = $^3J_{C4-F2}$ = 7.6 Hz, 1C, C-4α), 80.7 (d, $^1J_{C6-F6}$ = 174.9 Hz, 1C, C-6α), 80.6 (d, $^1J_{C6-F6}$ = 175.7 Hz, 1C, C-6β), 72.5 (dd, $^2J_{CS-F4}$ = 23.7 Hz, $^2J_{CS-F6}$ = 18.8 Hz, 1C, C-5β), 72.4 (t, $^2J_{C3-F4}$ = $^2J_{C3-F2}$ = 20.0 Hz, 1C, C-3β), 70.3 (t, $^2J_{C3-F4}$ = $^2J_{C3-F2}$ = 19.7 Hz, 1C, C-3α), 68.1 (dd, $^2J_{CS-F4}$ = 23.6 Hz, $^2J_{CS-F2}$ = 17.9 Hz, 1C, C-5α), 21.0 (s, 1C, $COCH_3$-α), 20.9 (s, 1C, $COCH_3$-β); ^{19}F NMR (470 MHz, chloroform-*d*) δ −199.5 (ddt, $^2J_{F4-H4}$ = 50.3 Hz, $^3J_{F4-H3}$ = 14.4 Hz, $^3J_{F4-H5}$ = 3.0 Hz, $^4J_{F4-F2}$ = 2.4 Hz, 1F, F-4α), −200.4 (ddt, $^2J_{F2-H2}$ = 50.6 Hz, $^3J_{F2-H3}$ = 14.0 Hz, $^3J_{F2-H1}$ = $^4J_{F2-F4}$ = 2.9 Hz, 1F, F-2β), −201.1 (ddt, $^2J_{F4-H4}$ = 50.3 Hz, $^3J_{F4-H3}$ = 14.9 Hz, $^3J_{F4-H5}$ = $^4J_{F4-F2}$ = 2.4 Hz, 1F, F-4β), −201.14 (ddd, $^2J_{F2-H2}$ = 49.2 Hz, $^3J_{F2-H3}$ = 12.1 Hz, $^3J_{F2-H1}$ = 2.0 Hz, 1F, F-2α), −235.4 (td, $^2J_{F6-H6a}$ = $^2J_{F6-H6b}$ = 47.0 Hz, $^3J_{F6-H5}$ = 24.1 Hz, 1F, F-6β), −236.9 (td, $^2J_{F6-H6a}$ = $^2J_{F6-H6b}$ = 47.2 Hz, $^2J_{F6-H5}$ = 27.5 Hz, 1F, F-6α); HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_8H_{11}F_3NaO_4$ 251.0516, found 251.0503.

4-*O*-(3″,4″,6″-Tetra-*O*-acetyl-2″-deoxy-2″-fluoro-α/β-D-glucopyranosyl)-4′-demethylepipodophyllotoxin (43). This was synthesized using general procedure III starting from **39**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1 → 3:1) to give **43** (α/β = 3.6:1) as an amorphous white solid (51.1 mg, 0.074 mmol, 63% yield). HPLC: isocratic elution of (60% MeOH/40% H_2O) for 45 min followed with 100% MeOH for 60 min. HPLC (MeOH/H_2O, 60:40): 19.344 min. **43α**: R_f = 0.31 (silica, EtOAc/hexanes 2:1); $[\alpha]_D^{25}$ = 7.0 (*c* 0.1, $CHCl_3$); IR (ATR, NaCl) ν 2921, 2363, 1777, 1744, 1485, 1233, 1035 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 6.95 (s, 1H, Ar), 6.56 (s, 1H, Ar), 6.26 (s, 2H, Ar), 6.00 (dd, *J* = 4.7, 1.0 Hz, 2H, CH_2 dioxolane), 5.43 (dt, $^3J_{H3''-F2''}$ = 11.7 Hz, $^3J_{H3''-H2''}$ = $^3J_{H3''-H4''}$ = 9.7 Hz, 1H, H-3″), 5.41 (s, 1H, OH), 5.25 (d, $^3J_{H1''-H2''}$ = 4.0 Hz, 1H, H-1″), 5.01 (t, $^3J_{H4''-H3''}$ = $^3J_{H4''-H5''}$ = 9.9 Hz, 1H, H-4″), 4.82 (d, $^3J_{H4-H3}$ = 3.0 Hz, 1H, H-4), 4.65 (d, $^3J_{H1-H2}$ = 5.4 Hz, 1H, H-1), 4.58 (ddd, $^2J_{H2''-F2''}$ = 49.5 Hz, $^3J_{H2''-H3''}$ = 9.8 Hz, $^3J_{H2''-H1''}$ = 4.0 Hz, 1H, H-2″), 4.40 (dd, $^3J_{H11a-H3}$ = 10.9 Hz, $^2J_{H11a-H11b}$ = 8.2 Hz, 1H, H-11a), 4.29 (t, $^3J_{H11b-H3}$ = $^2J_{H11b-H11a}$ = 7.9 Hz, 1H, H-11b), 4.23 (dd, $^2J_{H6b''-H6a''}$ = 12.5 Hz, $^3J_{H6b''-H5''}$ = 4.7 Hz, 1H, H-6b″), 4.05 (dd, $^2J_{H6a''-H6b''}$ = 12.5 Hz, $^3J_{H6a''-H5''}$ = 2.2 Hz, 1H, H-6a″), 3.88 (ddd, $^3J_{H5''-H4''}$ = 10.5 Hz, $^3J_{H5''-H6b''}$ = 4.7 Hz, $^3J_{H5''-H6a''}$ = 2.2 Hz, 1H, H-5″), 3.77 (s, 6H, 2 × OCH_3), 3.38 (dd, $^3J_{H2-H3}$ = 14.0 Hz, $^3J_{H2-H1}$ = 5.3 Hz, 1H, H-2), 2.90 (dddd, $^3J_{H3-H2}$ = 14.8 Hz, $^3J_{H3-H11a}$ = 10.5 Hz, $^3J_{H3-H11b}$ = 7.7 Hz, $^3J_{H3-H4}$ = 3.0 Hz, 1H, H-3), 2.16 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.00 (s, 3H, $COCH_3$) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 174.3, 170.6, 170.1, 169.5 (4C, 4 × CO), 148.8, 147.2, 146.4, 134.2, 133.1, 130.3, 128.2, 110.6, 109.5, 108.0 (12C, Ar), 101.7 (1C, CH_2 dioxolane), 97.8 (d, $^2J_{C1''-F2''}$ = 20.2 Hz, 1C, C-1″), 87.4 (d, $^1J_{C2''-F2''}$ = 195.2 Hz, 1C, C-2″), 77,1 (1C, C-4), 70.2 (d, $^2J_{C3''-F2''}$ = 19.1 Hz, 1C, C-3″), 68.1 (1C, C-5″), 68.0 (d, $^3J_{C4''-F2''}$ = 7.0 Hz, 1C, C-4″), 66.5 (1C, C-11), 61.5 (1C, C-6″), 56.5 (2C, 2 × OCH_3), 43.6 (1C, C-1), 40.8 (1C, C-2), 38.2 (1C, C-3), 20.74, 20.68, 20.6 (3C, 3 × $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-*d*) δ −197.62 (dd, $^2J_{F2''-H2''}$ = 49.5 Hz, $^3J_{F2''-H3''}$ = 11.8 Hz, 1F, F-2″) ppm; HRMS (ESI) *m*/*z*: $[M + NH_4]^+$ calcd for $C_{33}H_{39}FNO_{15}$ 708.2298, found 708.2291.

4-*O*-(6″-*O*-Acetyl-3″-*O*-benzyl-2″,4″-dideoxy-2″,4″-difluoro-α/β-D-glucopyranosyl)-4′-demethylepipodophyllotoxin (44). This was synthesized using general procedure III starting from **40**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1 → 3:1) to give **44** (α/β = 1.7:1) as an amorphous white solid (30.3 mg, 0.047 mmol, 62% yield). HPLC: isocratic elution of (80% MeOH/20% H_2O) for 45 min followed with 100% MeOH for 60 min. HPLC (MeOH/H_2O 80:20): **44α** = 10.915 min, **44β** = 9.435 min. **44α**: R_f = 0.51 (silica, EtOAc/hexanes 2:1); $[\alpha]_D^{25}$ = +5.4 (*c* 0.3, $CHCl_3$); IR (ATR, NaCl) ν 2923, 2361, 1777, 1743, 1484, 1234, 1035 cm^{-1}; ^1H NMR (500 MHz, chloroform-*d*) δ 7.39−7.28 (m, 5H, Ar), 6.98 (s, 1H, Ar), 6.54 (s, 1H, Ar), 6.26 (s, 2H, Ar), 6.00 (s, 2H, CH_2 dioxolane), 5.42 (s, 1H, OH), 5.16 (t, $^3J_{H1''-H2''}$ = $^3J_{H1''-F2''}$ = 3.4 Hz, 1H, H-1″), 4.80 (d, $^3J_{H4-H3}$ = 3.1 Hz, 1H, H-4), 4.79 (s, 2H, CH_2Ph), 4.64 (d, $^3J_{H1-H2}$ = 5.3 Hz, 1H, H-1), 4.48 (ddd, $^2J_{H2''-F2''}$ = 49.1 Hz, $^3J_{H2''-H3''}$ = 9.5 Hz, $^3J_{H2''-H1''}$ = 4.0 Hz, 1H, H-2″), 4.43 (dd, $^3J_{H11a-H3}$ = 11.0 Hz, $^2J_{H11a-H11b}$ = 8.5 Hz, 1H, H-11a), 4.41 (dt, $^2J_{H4''-F4''}$ = 50.2 Hz, $^3J_{H4''-H5''}$ = 9.2 Hz, $^3J_{H4''-H3''}$ = 7.9 Hz, 1H, H-4″), 4.33 (dd, $^2J_{H6a''-H6b''}$ = 10.7 Hz, $^3J_{H6a''-H5''}$ = $^4J_{H6a''-F4''}$ = 3.5 Hz, 1H, H-6a″), 4.31 (dd, $^2J_{H11b-H11a}$ = 8.1 Hz, $^3J_{H11b-H3}$ = 7.8 Hz, 1H, H-11b), 4.22 (dd, $^2J_{H6b''-H6a''}$ = 12.3 Hz, $^3J_{H6b''-H5''}$ = 5.1 Hz, $^4J_{H6b''-F4''}$ = 1.3 Hz, 1H, H-6b″), 4.00 (ddt, $^3J_{H3''-F4''}$ = 14.9 Hz, $^3J_{H3''-F2''}$ = 12.2 Hz, $^3J_{H3''-H2''}$ = 9.0 Hz, 1H, H-3″), 3.86 (dtd, $^3J_{H5''-H4''}$ = 9.8 Hz, $^3J_{H5''-H6b''}$ = 4.9 Hz, $^3J_{H6a''-H5''}$ = 2.2 Hz, 1H, H-5″), 3.77 (s, 6H, 2 × OCH_3), 3.31 (dd, $^3J_{H2-H3}$ = 14.0 Hz, $^3J_{H2-H1}$ = 5.3 Hz, 1H, H-2), 2.90 (dddd, $^3J_{H3-H2}$ = 13.8 Hz, $^3J_{H3-H11a}$ = 10.5 Hz, $^3J_{H3-H11b}$ = 7.7 Hz, $^3J_{H3-H4}$ = 2.8 Hz, 1H, H-3), 2.18 (s, 3H, $COCH_3$) ppm; $^{13}C\{^1H\}$ NMR (126 MHz, chloroform-*d*) δ 174.7, 170.8 (2C, 2 × CO), 148.9, 147.4, 146.6, 137.6, 134.3, 133.0, 130.5, 128.6, 128.5, 128.2, 128.2, 110.6, 109.8, 108.1 (18C, Ar), 101.8 (1C, CH_2

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

dioxolane), 98.1 (d, $^2J_{C1''\text{-}F2''}$ = 20.9 Hz, 1C, C-1″), 89.8 (dd, $^1J_{C2''\text{-}F2''}$ = 193.7 Hz, $^3J_{C2''-F4''}$ = 9.4 Hz, 1C, C-2″), 89.1 (dd, $^1J_{C4''\text{-}F4''}$ = 186.1 Hz, $^3J_{C4''-F2''}$ = 9.0 Hz, 1C, C-4″), 77.0 (1C, C-4) 77.2−76.8 (m, 1C, C-3″), 74.9 (1C, CH_2Ph), 67.9 (d, $^2J_{C5''-F4''}$ = 24.1 Hz, 1C, C-5″), 66.7 (d, J = 5.9 Hz, 1C, C-11), 62.1 (1C, C-6″), 56.6 (2C, 2 × OCH_3), 43.8 (1C, C-1), 41.1 (1C, C-2), 38.3 (1C, C-3), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −196.39 (dd, $^2J_{F4''-H4''}$ = 50.2 Hz, $^3J_{F4''-H3''}$ = 15.1 Hz, 1F, F-4″), −196.88 (dd, $^2J_{F2''-H2''}$ = 49.0 Hz, $^3J_{F4''-H3''}$ = 12.3 Hz, 1F, F-2″). HRMS (ESI) m/z: $[M + NH_4]^+$ calcd for $C_{36}H_{40}F_2NO_{12}^+$ 716.2513, found 716.2509. **44*β***: R_f = 0.60 (silica, EtOAc/hexanes 2:1); $[\alpha]_D^{25}$ = −89.1 (c 0.1, $CHCl_3$); IR (ATR, NaCl) ν 2923, 2360, 1777, 1745, 1485, 1237, 1032 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 7.38−7.29 (m, 5H, Ar), 6.86 (s, 1H, Ar), 6.58 (s, 1H, Ar), 6.25 (s, 2H, Ar), 6.00 (d, J = 8.6 Hz, 2H, CH_2 dioxolane), 5.41 (s, 1H, OH), 5.03 (d, 1H, $^3J_{H4-H3}$ = 1.9 Hz, H-4), 4.80 (s, 2H, CH_2Ph), 4.61 (d, $^3J_{H1-H2}$ = 5.4 Hz, 1H, H-1), 4.59−4.53 (m, 2H, H1″, H-6a″), 4.424 (dt, $^2J_{H4''-F4''}$ = 49.6 Hz, $^3J_{H4''-HS''}$ = $^3J_{H4''-H3''}$ = 9.3 Hz, 1H, H-4″), 4.415 (dd, $^3J_{H11a-H3}$ = 11.4 Hz, $^2J_{H11a-H11b}$ = 8.6 Hz, 1H, H-11a), 4.33 (ddd, $^2J_{H2''-F2''}$ = 50.1 Hz, $^3J_{H2''-H3''}$ = 9.0 Hz, $^3J_{H2''-H1''}$ = 5.0 Hz, 1H, H-2″), 4.26 (dd, $^2J_{H11b-H11a}$ = 8.1 Hz, $^3J_{H11b-H3}$ = 7.8 Hz, 1H, H-11b), 4.19 (dd, $^2J_{H6b''-H6a''}$ = 12.2 Hz, $^3J_{H6b''-HS''}$ = 6.3 Hz, 1H, H-6b″), 3.86−3.72 (m, 1H, H-3″), 3.77 (s, 6H, 2 × OCH_3), 3.67−3.61 (m, 1H, H-5″), 3.35 (dd, $^3J_{H2-H3}$ = 13.9 Hz, $^3J_{H2-H1}$ = 5.2 Hz, 1H, H-2), 2.92 (dddd, $^3J_{H3-H2}$ = 15.2 Hz, $^3J_{H3-H11a}$ = 10.6 Hz, $^3J_{H3-H11b}$ = 6.6 Hz, $^3J_{H3-H4}$ = 2.2 Hz, 1H, H-3), 2.17 (s, 3H, $COCH_3$) ppm; ^{13}C{^{1}H} NMR (126 MHz, chloroform-d) δ 174.9, 170.7 (2C, 2 × CO), 149.1, 147.1, 146.5, 137.4, 134.3, 134.0, 130.8, 128.6, 128.21, 128.17, 126.5, 111.4, 109.4, 108.1 (18C, Ar), 101.8 (1C, CH_2 dioxolane), 97.2 (d, $^2J_{C1''\text{-}F2''}$ = 23.5 Hz, 1C, C-1″), 91.9 (dd, $^1J_{C4''\text{-}F4''}$ = 188.0 Hz, $^3J_{C4''-F2''}$ = 8.3 Hz, 1C, C-4″), 89.1 (dd, $^1J_{C2''\text{-}F2''}$ = 186.6 Hz, $^3J_{C2''-F4''}$ = 9.0 Hz, 1C, C-2″), 79.8 (t, $^2J_{C3''-F2''}$=$^2J_{C3''-F4''}$ = 18.8 Hz, 1C, C-3″), 74.4 (1C, CH_2Ph), 72.7 (1C, C-4), 71.6 (d, $^2J_{C5''-F4''}$ = 24.3 Hz, 1C, C-5″), 67.5 (1C, C-11), 62.4 (1C, C-6″), 56.7 (2C, 2 × OCH_3), 43.9 (1C, C-1), 40.9 (1C, C-2), 37.7 (1C, C-3), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −197.00 (dd, $^2J_{F4''-H4''}$ = 49.6 Hz, $^3J_{F4''-H3''}$ = 15.7 Hz, F4″), −197.30 (dd, $^2J_{F2''-H2''}$ = 50.1 Hz, $^3J_{F4''-H3''}$ = 16.0 Hz, F2″) ppm; HRMS (ESI) m/z: $[M + NH_4]^+$ calcd for $C_{36}H_{40}F_2NO_{12}$ 716.2513, found 716.2503.

4-*O*-(2″,3″-Di-*O*-acetyl-4″,6″-dideoxy-4″,6″-difluoro-α/β-D-glucopyranosyl)-4′-demethylepipodophyllotoxin (45). This was synthesized using general procedure III starting from **41**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1 → 3:1) to give **45** (α/β = 2:1) as an amorphous white solid (12.0 mg, 0.0189 mmol, 72% yield). R_f = 0.55 (silica, EtOAc/hexanes 2:1); $[\alpha]_D^{25}$ = −15.4 (c 0.2, $CHCl_3$); IR (ATR, NaCl) ν 2920, 2361, 1757, 1485, 1233, 1116, 1035 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 6.92 (s, 1H, Ar-α), 6.79 (s, 1H, Ar-β), 6.56 (s, 1H, Ar-β), 6.54 (s, 1H, Ar-α), 6.245 (s, 2H, Ar-α), 6.241 (s, 2H, Ar-β), 6.00 (s, 2H, CH_2 dioxolane-β), 5.99 (s, 2H, CH_2 dioxolane-α), 5.51 (dt, $^3J_{H3''-F4''}$ = 13.6 Hz, $^3J_{H3''-H2''}$ = 10.2 Hz, $^3J_{H3''-H4''}$ = 9.1 Hz, 1H, H-3α″), 5.41 (s, 2H, OH-α, OH-β), 5.35 (dt, $^3J_{H3''-F4''}$ = 14.9 Hz, $^3J_{H3''-H2''}$ = $^3J_{H3''-H4''}$ = 9.2 Hz, 1H, H-3β″), 5.24 (t, $^3J_{H1''-H2''}$ = $^5J_{H1''-F4''}$ = 3.4 Hz, 1H, H-1α″), 4.95 (dd, $^3J_{H2''-H3''}$ = 10.7 Hz, $^3J_{H2''-H1''}$ = 3.6 Hz, 1H, H-2α″), 4.935 (dd, $^3J_{H2''-H3''}$ = 9.6 Hz, $^3J_{H2''-H1''}$ = 7.5 Hz, 1H, H-2β″), 4.934 (d, $^3J_{H4-H3}$ = 2.8 Hz, 1H, H-4β), 4.77 (d, $^3J_{H2''-H1''}$ = 7.9 Hz, 1H, H-1″β), 4.75 (d, $^3J_{H4-H3}$ = 2.9 Hz, 1H, H-4α), 4.71−4.51 (m, 4H, H-6aα″, H-6bα″, H-6aβ″, H-6bβ″), 4.66 (d, $^3J_{H1-H2}$ = 5.4 Hz, 1H, H-1α), 4.58 (d, $^3J_{H1-H2}$ = 5.0 Hz, 1H, H-1β), 4.51 (dt, $^2J_{H4''-F4''}$ = 50.5 Hz, $^3J_{H4''-HS''}$ = 9.9 Hz, $^3J_{H4''-H3''}$ = 9.3 Hz, 1H, H-4α″), 4.47 (dt, $^2J_{H4''-F4''}$ = 54.6 Hz, $^3J_{H4''-HS''}$ = 10.4 Hz, $^3J_{H4''-H3''}$ = 8.7 Hz, 1H, H-4β″), 4.43−4.24 (m, 4H, H-11aα, H-11bα, H-11aβ, H-11bβ), 3.82−3.69 (m, 2H, H-5α″, H-5β″), 3.77 (s, 6H, 2 × OCH_3-α), 3.76 (s, 6H, 2 × OCH_3-β), 3.44 (dd, $^3J_{H2-H3}$ = 14.1 Hz, $^3J_{H2-H1}$ = 5.4 Hz, 1H, H-2α), 3.14 (dd, $^3J_{H2-H3}$ = 14.1 Hz, $^3J_{H2-H1}$ = 5.3 Hz, 1H, H-2β), 2.96−2.85 (m, 2H, H-3α, H-3β), 2.10 (s, 3H, $COCH_3$-α), 2.089 (s, 3H, $COCH_3$-α), 2.085 (s, 3H, $COCH_3$-β), 1.88 (s, 3H, $COCH_3$-β) ppm; ^{13}C{^{1}H} NMR (126 MHz, chloroform-d) δ 174.8, 174.4, 170.1, 170.0, 169.9, 169.3 (6C, 3 × CO-α, 3 × CO-β), 149.0, 148.9, 147.2, 147.1, 146.6, 146.6, 134.3, 134.3, 133.4, 133.2, 130.5, 130.5, 128.3, 127.5, 111.1, 110.8, 109.8, 109.8, 109.1, 108.1, 108.0 (24C, Ar-α/β), 101.83 (1C, CH_2 dioxolane-α), 101.80 (1C, CH_2 dioxolane-β), 99.3 (d, $^4J_{C1''\text{-}F4''}$ = 1.5 Hz, 1C, C-1β″), 98.3 (d, $^4J_{C1''\text{-}F4''}$ = 1.1 Hz, 1C, C-1α″), 86.1 (dd, $^1J_{C4''\text{-}F4''}$ = 188.8 Hz, $^3J_{C4''\text{-}F6''}$ = 8.5 Hz, 1C, C-4β″), 84.6 (dd, $^1J_{C4''\text{-}F4''}$ = 186.4 Hz, $^3J_{C4''\text{-}F6''}$ = 8.0 Hz, 1C, C-4α″), 81.0 (d, $^1J_{C6''\text{-}F6''}$ = 174.4 Hz, 1C, C-6β″), 80.5 (d, $^1J_{C6''\text{-}F6''}$ = 175.9 Hz, 1C, C-6α″), 77.3 (1C, C-4α), 74.5 (1C, C-4β), 72.5 (dd, $^2J_{C5''\text{-}F4''}$ = 23.2 Hz, $^2J_{C5''\text{-}F6''}$ = 19.1 Hz, 1C, C-5β″), 72.2 (d, $^2J_{C3''\text{-}F4''}$ = 23.2 Hz, 1C, C-3β″), 71.1 (d, $^3J_{C2''\text{-}F4''}$ = 7.6 Hz, 1C, C-2β″), 70.4 (d, $^3J_{C2''\text{-}F4''}$ = 7.9 Hz, 1C, C-2α″), 69.6 (d, $^2J_{C3''\text{-}F4''}$ = 19.5 Hz, 1C, C-3α″), 68.9 (dd, $^2J_{C5''\text{-}F4''}$ = 24.2 Hz, $^2J_{C5''\text{-}F6''}$ = 18.3 Hz, C-5α″), 67.8 (1C, C-11β), 66.3 (1C, C-11α), 56.7 (2C, 2 × OCH_3-α), 56.6 (2C, 2 × OCH_3-β), 43.84 (1C, C-1β), 43.76 (1C, C-1α), 41.3 (1C, C-2β), 40.8 (1C, C-2α), 38.4 (1C, C-3α), 37.7 (1C, C-3β), 20.9, 20.80, 20.79, 20.5 (4C, 4 × $COCH_3$-α/β) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −198.15 (ddt, $^2J_{F4''-H4''}$ = 50.7 Hz, $^3J_{F4''-H3''}$ = 14.0 Hz, $^3J_{F4''-HS''}$ = 3.5 Hz, $^5J_{F4''-H1''}$ = 3.0 Hz, 1F, F-4α″), −199.93 (ddd, $^2J_{F4''-H4''}$ = 51.2 Hz, $^3J_{F4''-H3''}$ = 14.6 Hz, $^3J_{F4''-HS''}$ = 2.2 Hz, 1F, F-4β″), −233.7 (td, $^2J_{F6''-H6a''}$ = $^2J_{F6''-H6b''}$ = 47.0 Hz, $^3J_{F6''-HS''}$ = 21.4 Hz, 1F, F-6β″), −236.4 (td, $^2J_{F6''-H6a''}$ = $^2J_{F6''-H6b''}$ = 47.2 Hz, $^3J_{F6''-HS''}$ = 26.1 Hz, 1F, F-6α″); HRMS (ESI) m/z: $[M + NH_4]^+$ calcd for $C_{31}H_{36}F_2NO_{13}$ 668.2149, found 668.2117.

4-*O*-(3″-*O*-Acetyl-2″,4″,6″-trideoxy-2″,4″,6″-trifluoro-α/β-D-glucopyranosyl)-4′-demethylepipodophyllotoxin (46). This was synthesized using general procedure III starting from **42**. The resulting crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:1 → 3:1) to give **46** (α/β = 1.9:1) as an amorphous white solid (32.2 mg, 0.0527 mmol, 70% yield). HPLC: isocratic elution of (40% MeCN/60% H_2O) for 45 min followed with 100% MeCN for 60 min. HPLC (MeCN/H_2O 40:60): **46*α*** = 31.558 min; **46*β*** = 34.073 min. **46*α***: R_f = 0.53 (silica, EtOAc/hexanes 2:1); $[\alpha]_D^{25}$ = +46.7 (c 0.2, $CHCl_3$); IR (ATR, NaCl) ν 2941, 1765, 1611, 1484, 1229, 1112, 1030 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 6.90 (s, 1H, Ar), 6.55 (s, 1H, Ar), 6.26 (s, 2H, Ar), 5.99 (s, 2H, CH_2dioxolane), 5.59 (ddt, $^3J_{H3''-F4''}$ = 14.1 Hz, $^3J_{H3''-F2''}$ = 11.9 Hz, $^3J_{H3''-H4''}$ = $^3J_{H3''-H2''}$ = 9.5 Hz, 1H, H-3″), 5.41 (s, 1H, OH), 5.28 (t, $^3J_{H1''-H2''}$ = $^3J_{H1''-F2''}$ = 3.3 Hz, 1H, H-1″), 4.81 (d, $^3J_{H4-H3}$ = 2.9 Hz, 1H, H-4), 4.67−4.63 (m, 1H, H6a″, H-1), 4.57−4.54 (m, 1H, H-6b″), 4.48 (ddd, $^2J_{H2''-F2''}$ = 49.3 Hz, $^3J_{H2''-H3''}$ = 9.7 Hz, $^3J_{H1''-H2''}$ = 3.8 Hz, 1H, H-2″), 4.45 (dt, $^2J_{H4''-F4''}$ = 51.0 Hz, $^3J_{H4''-HS''}$ = 9.6 Hz, $^3J_{H4''-H3''}$ = 9.2 Hz, 1H, H-4″), 4.39 (dd, $^3J_{H11a-H3}$ = 10.6 Hz, $^2J_{H11a-H11b}$ = 8.5 Hz, 1H, H-11a), 4.29 (t, $^2J_{H11b-H11a}$ = $^3J_{H11b-H3}$ = 7.9 Hz, 1H, H-11b), 3.85−3.79 (m, 1H, H-5″), 3.77 (s, 6H, 2 × OCH_3), 3.38 (dd, $^3J_{H2-H3}$ = 14.1 Hz, $^3J_{H2-H1}$ = 5.3 Hz, 1H, H-2), 2.91 (dddd, $^3J_{H3-H2}$ = 14.9 Hz, $^3J_{H3-H11a}$ = 10.7 Hz, $^3J_{H3-H11b}$ = 7.1 Hz, $^3J_{H3-H4}$ = 3.0 Hz, 1H, H-3), 2.15 (s, 3H, $COCH_3$) ppm; ^{13}C{^{1}H} NMR (126 MHz, chloroform-d) δ 174.3, 169.7 (2C, 2 × CO), 148.8, 147.1, 146.4, 134.1, 133.1, 130.3, 128.1, 110.7, 109.4, 108.0 (12C, Ar), 101.7 (1C, CH_2dioxolane), 98.0 (d, $^2J_{C1''\text{-}F2''}$ = 20.0 Hz, 1C, C-1″), 87.1 (dd, $^1J_{C2''\text{-}F2''}$ = 195.9 Hz, $^3J_{C2''-F4''}$ = 8.8 Hz, 1C, C-2″), 85.5 (dd, $^1J_{C4''\text{-}F4''}$ = 188.2 Hz, $^3J_{C4''-F2''}$ = 7.1 Hz, 1C, C-4″), 80.2 (d, $^1J_{C6''\text{-}F6''}$ = 175.4 Hz, 1C, C-6″), 77.6 (1C, C-4), 69.8 (t, $^2J_{C3''-F2''}$ = $^2J_{C3''-F4''}$ = 19.7 Hz, 1C, C-3″), 68.7 (dd, $^2J_{C5''-F4''}$ = 23.9 Hz, $^2J_{C5''-F6''}$ = 18.3 Hz, 1C, C-5″), 66.4 (d, J = 5.0 Hz, C-11), 56.5 (2C, 2 × OCH_3), 43.6 (1C, C-1), 40.8 (1C, C-2), 38.1 (1C, C-3), 20.8 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-d) δ −198.85 (dd, $^2J_{F2''-H2''}$ = 49.3 Hz, $^2J_{F2''-H3''}$ = 11.8 Hz, 1F, F-2″), −199.35 (dd, $^2J_{F4''-H4''}$ = 50.5 Hz, $^3J_{F4''-H3''}$ = 14.2 Hz, 1F, F-4″), −236.52 (td, $^2J_{F6''-H6a''}$ = $^2J_{F6''-H6b''}$ = 47.1 Hz, $^3J_{F6''-HS''}$ = 26.3 Hz, 1F, F-6″) ppm; HRMS (ESI) m/z: $[M + NH_4]^+$ calcd for $C_{29}H_{33}F_3NO_{11}^+$ 628.2000, found 628.1984. **46*β***: R_f = 0.47 (silica, EtOAc/hexanes 2:1); $[\alpha]_D^{25}$ = −93.4 (c 0.2, $CHCl_3$); IR (ATR, NaCl) ν 2940, 1765, 1612, 1485, 1231, 1116, 1031 cm^{-1}; ^{1}H NMR (500 MHz, chloroform-d) δ 6.78 (s, 1H, Ar), 6.57 (s, 1H, Ar), 6.24 (s, 2H, Ar), 6.01 (dd, J = 10.3, 1.4 Hz, 2H, CH_2 dioxolane), 5.45 (tt, $^3J_{H3''-F4''}$ = $^3J_{H3''-F2''}$ = 14.5 Hz, $^3J_{H3''-H4''}$ = $^3J_{H3''-H2''}$ = 9.1 Hz, 1H, H-3″), 5.41 (s, 1H, OH), 5.05 (d, $^3J_{H4-H3}$ = 3.2 Hz, 1H, H-4), 4.78 (dd, $^3J_{H1''-H2''}$ = 7.7 Hz, $^3J_{H1''-F2''}$ = 2.6 Hz, 1H, H-1″), 4.74 (ddt, $^2J_{H6a''-F6''}$ = 47.5 Hz, $^2J_{H6a''-H6b''}$ = 10.6 Hz, $^3J_{H6a''-HS''}$ = $^4J_{H6a''-F4''}$ = 2.2

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824

Hz, 1H, H-6a″), 4.64 (dddd, $^{2}J_{H6b''-F6''}$ = 47.5 Hz, $^{2}J_{H6b''-H6a''}$ = 10.6 Hz, $^{3}J_{H6a''-HS''}$ = 4.9 Hz, $^{4}J_{H6a''-F4''}$ = 1.7 Hz, 1H, H-6b″), 4.61 (d, $^{3}J_{H1-H2}$ = 5.3 Hz, 1H, H-1), 4.44 (dt, $^{2}J_{H4''-F4''}$ = 50.5 Hz, $^{3}J_{H4''-HS''}$ = $^{3}J_{H4''-H3''}$ = 9.6 Hz, 1H, H-4″), 4.43 (dd, $^{3}J_{H11a-H3}$ = 10.7 Hz, $^{2}J_{H11a-H11b}$ = 8.8 Hz, 1H, H-11a), 4.29 (t, $^{2}J_{H11b-H11a}$ = $^{3}J_{H11b-H3}$ = 8.2 Hz, 1H, H-11b), 4.27 (ddd, $^{2}J_{H2''-F2''}$ = 50.4 Hz, $^{3}J_{H2''-H3''}$ = 9.2 Hz, $^{3}J_{H1''-H2''}$ = 7.6 Hz, 1H, H-2″), 3.765 (s, 6H, 2 × OCH_3), 3.762 (dddt, $^{3}J_{HS''-F6''}$ = 22.0 Hz, $^{3}J_{HS''-H4''}$ = 9.5 Hz, $^{3}J_{HS''-H6b''}$ = 4.5 Hz, $^{3}J_{HS''-F4''}$ = $^{3}J_{H4''-H6a''}$ = 2.4 Hz, 1H, H-5), 3.33 (dd, $^{3}J_{H2-H3}$ = 14.0 Hz, $^{3}J_{H2-H1}$ = 5.3 Hz, 1H, H-2), 2.94 (dddd, $^{3}J_{H3-H2}$ = 13.9 Hz, $^{3}J_{H3-H11a}$ = 10.8 Hz, $^{3}J_{H3-H11b}$ = 7.7 Hz, $^{3}J_{H3-H4}$ = 3.2 Hz, 1H, H-3), 2.16 (s, 3H, $COCH_3$). $^{13}C\{^{1}H\}$ NMR (126 MHz, chloroform-*d*) δ 174.8, 169.8 (2C, 2 × CO), 149.2, 147.2, 146.6, 134.2, 133.7, 130.7, 126.6, 111.3, 109.3, 108.0 (12C, Ar), 101.9 (1C, CH_2dioxolane), 97.6 (d, $^{2}J_{C1''-F2''}$ = 23.3 Hz, 1C, C-1″), 89.1 (dd, $^{1}J_{C2''-F2''}$ = 192.8 Hz, $^{3}J_{C2''-F4''}$ = 7.8 Hz, 1C, C-2″), 85.5 (dt, $^{1}J_{C4''-F4''}$ = 189.6 Hz, $^{3}J_{C4''-F2''}$ = $^{3}J_{C1''-F6''}$ = 8.2 Hz, 1C, C-4″), 80.7 (d, $^{1}J_{C6''-F6''}$ = 176.7 Hz, 1C, C-6″), 73.4 (1C, C-4), 72.4 (dd, $^{2}J_{C5''-F4''}$ = 23.4 Hz, $^{2}J_{C5''-F6''}$ = 18.9 Hz, 1C, C-5″), 72.3 (t, $^{2}J_{C3''-F2''}$ = $^{2}J_{C3''-F4''}$ = 20.1 Hz, 1C, C-3″), 67.6 (1C, C-11), 56.6 (2C, 2 × OCH_3), 43.9 (1C, C-1), 41.0 (1C, C-2), 37.7 (1C, C-3), 20.9 (1C, $COCH_3$) ppm; ^{19}F NMR (470 MHz, chloroform-*d*) δ − 200.07 (ddt, $^{2}J_{F2''-H2''}$ = 50.4 Hz, $^{2}J_{F2''-H3''}$ = 14.3 Hz, $^{3}J_{F2''-H1''}$ = $^{4}J_{F2''-F4''}$ = 2.8 Hz, 1F, F-2″), −200.60 (ddt, $^{2}J_{F4''-H4''}$ = 50.6 Hz, $^{3}J_{F4''-H3''}$ = 14.9 Hz, $^{3}J_{F4''-HS''}$ = $^{4}J_{F4''-F2''}$ = 2.6 Hz, 1F, F-4″), −234.01 (td, $^{2}J_{F6''-H6a''}$ = $^{2}J_{F6''-H6b''}$ = 46.9 Hz, $^{3}J_{F6''-HS''}$ = 21.9 Hz, 1F, F-6″) ppm; HRMS (ESI) *m*/*z*: $[M + NH_4]^+$ calcd for $C_{29}H_{33}F_3NO_{11}$ 628.2000, found 628.1979.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02841.

^{1}H, ^{13}C, ^{19}F, COSY, and HSQC NMR spectra for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Denis Giguère − *Département de Chimie, Université Laval, PROTEO, Québec City, QC, Canada G1 V 0A6;* orcid.org/0000-0003-2209-1428; Email: denis.giguere@chm.ulaval.ca

Authors

Thomas Tremblay − *Département de Chimie, Université Laval, PROTEO, Québec City, QC, Canada G1 V 0A6*

Jacob St-Gelais − *Département de Chimie, Université Laval, PROTEO, Québec City, QC, Canada G1 V 0A6*

Maxime Houde − *Département de Chimie, Université Laval, PROTEO, Québec City, QC, Canada G1 V 0A6*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02841

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) and Université Laval. T.T. thanks NSERC for a postgraduate fellowship, and J.St-G. thanks the Fonds de Recherche du Québec-Nature et Technologies (FRQNT) for a postgraduate fellowship. Finally, M.H. thanks PROTEO for an Undergraduate student research award.

■ REFERENCES

(1) Hevey, R. Strategies for the Development of Glycomimetic Drug Candidates. *Pharmaceuticals* **2019**, *12*, 55.

(2) Selected reviews: (a) Yao, H.; Vu, M. D.; Liu, X.-W. Recent advances in reagent-controlled stereoselective/stereospecific glycosylation. *Carbohydr. Res.* **2019**, *473*, 72−81. (b) Bohé, L.; Crich, D. A propos of glycosyl cations and the mechanism of chemical glycosylation; the current state of the art. *Carbohydr. Res.* **2015**, *403*, 48−59. (c) Das, R.; Mukhopadhyay, B. Chemical *O*-Glycosylations: An Overview. *ChemistryOpen* **2016**, *5*, 401−433. (d) Nielsen, M. M.; Pedersen, C. M. Catalytic Glycosylations in Oligosaccharide Synthesis. *Chem. Rev.* **2018**, *118*, 8285−8358.

(3) Crich, D. Mechanism of a Chemical Glycosylation Reaction. *Acc. Chem. Res.* **2010**, *43*, 1144−1153.

(4) (a) Schmidt, R. R.; Kinzy, W. Anomeric-oxygen activation for glycoside synthesis: The trichloroacetimidate method. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123. (b) Schmidt, R. R. New methods for the synthesis of glycosides and oligosaccharides − Are there alternatives to the Koenigs-Knorr method? *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235.

(5) Christensen, H. M.; Oscarson, S.; Jensen, H. H. Common side reactions of the glycosyl donor in chemical Glycosylation. *Carbohydr. Res.* **2015**, *408*, 51−98.

(6) (a) Williams, S. J.; Withers, S. G. Glycosyl fluorides in enzymatic reactions. *Carbohydr. Res.* **2000**, *327*, 27−46. (b) Allman, S. A.; Jensen, H. H.; Vijayakrishnan, B.; Garnett, J. A.; Leon, E.; Liu, Y.; Anthony, D. C.; Sibson, N. R.; Feizi, T.; Matthews, S.; Davis, B. G. Potent fluoro-oligosaccharide probes of adhesion in Toxoplasmosis. *ChemBioChem* **2009**, *10*, 2522−2529. (c) Zhu, J.-S.; McCormick, N. E.; Timmons, S. C.; Jakeman, D. L. Synthesis of α-Deoxymono and Difluorohexopyranosyl 1-Phosphates and Kinetic Evaluation with Thymidylyl- and Guanidylyltransferases. *J. Org. Chem.* **2016**, *81*, 8816−8825. (d) Street, I. P.; Armstrong, C. R.; Withers, S. G. Hydrogen bonding and specificity. Fluorodeoxy sugars as probes of hydrogen bonding in the glycogen phosphorylase-glucose complex. *Biochemistry* **1986**, *25*, 6021−6027.

(7) Linclau, B.; Arda, A.; Reichardt, N.-C.; Sollogoub, M.; Unione, L.; Vincent, S. P.; Jiménez-Barbero, J. Fluorinated carbohydrates as chemical probes for molecular recognition studies. Current status and perspectives. *Chem. Soc. Rev.* **2020**, *49*, 3863−3888.

(8) (a) Denavit, V.; Lainé, D.; St-Gelais, J.; Johnson, P. A.; Giguère, D. Chiron approach towards the stereoselective synthesis of polyfluorinated carbohydrates. *Nat. Commun.* **2018**, *9*, 4721. (b) Denavit, V.; St-Gelais, J.; Tremblay, T.; Giguère, D. Exploring the Chemistry of Non-sticky Sugars: Synthesis of Polyfluorinated Carbohydrate Analogues of D-Allopyranose. *Chem. - Eur. J.* **2019**, *25*, 9272−9279. (c) Denavit, V.; Lainé, D.; Bouzriba, C.; Shanina, E.; Gillon, É.; Fortin, S.; Rademacher, C.; Imberty, A.; Giguère, D. Stereoselective Synthesis of Fluorinated Galactopyranosides as Potential Molecular Probes for Galactophilic Proteins: Assessment of Monofluorogalactoside−LecA Interactions. *Chem. - Eur. J.* **2019**, *25*, 4478−4490. (d) St-Gelais, J.; Bouchard, M.; Denavit, V.; Giguère, D. Synthesis and Lipophilicity of Trifluorinated Analogues of Glucose. *J. Org. Chem.* **2019**, *84*, 8509−8522. (e) St-Gelais, J.; Côté, É.; Lainé, D.; Johnson, P. A.; Giguère, D. Addressing the structural complexity of fluorinated glucose analogues: Insight into lipophilicities and solvation effects. *Chem. - Eur. J.* **2020**, *26*, 13499−13506.

(9) van der Vorm, S.; Hansen, T.; van Hengst, J. M. A.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. Acceptor reactivity in glycosylation reactions. *Chem. Soc. Rev.* **2019**, *48*, 4688−4706.

(10) (a) Lainé, D.; Denavit, V.; Lessard, O.; Carrier, L.; Fecteau, C.-É.; Johnson, P. A.; Giguère, D. Fluorine effect in nucleophilic fluorination at C4 of 1,6-anhydro-2,3-dideoxy-β-D-hexopyranose. *Beilstein J. Org. Chem.* **2020**, *16*, 2880−2887. (b) Creary, X. Electronegatively substituted carbocations. *Chem. Rev.* **1991**, *91*, 1625−1678. (c) Jansen, M. P.; Koshy, K. M.; Mangru, N. N.; Tidwell, T. T. Solvolysis of 2-(trifluoromethyl)-2-propyl trifluoromethanesulfonate. Solvent, salt, and.beta.-deuterium isotope effects. Substituent effect of a strongly deactivating group and rate-limiting solvent-

assisted elimination. *J. Am. Chem. Soc.* **1981**, *103*, 3863−3867. (d) McCarter, J. D.; Adam, M. J.; Withers, S. G. Binding energy and catalysis. Fluorinated and deoxygenated glycosides as mechanistic probes of Escherichia coli (lacZ) β-galactosidase. *Biochem. J.* **1992**, *286*, 721−727.

(11) See for example: Kurfirt, M.; Cervenkova, C.; Dracinsky, M.; Müllerova, M.; Hamala, V.; Curinova, P.; Karban, J. Stereoselectivity in glycosylation with deoxofluorinated glucosazide and galactosazide thiodonors. *J. Org. Chem.* **2019**, *84*, 6405−6431.

(12) Bucher, B.; Gilmour, R. Fluorine-directed glycosylation. *Angew. Chem., Int. Ed.* **2010**, *49*, 8724−8728.

(13) Council, C. E.; Kilpin, K. J.; Gusthart, J. S.; Allman, S. A.; Linclau, B.; Lee, S. S. Enzymatic glycosylation involving fluorinated carbohydrates. *Org. Biomol. Chem.* **2020**, *18*, 3423−3451.

(14) Wang, L.; Hashidoko, Y.; Hashimoto, M. Cosolvent-promoted O-benzylation with silver(I) oxide: Synthesis of 1′-benzylated sucrose derivatives, mechanistic studies, and scope investigation. *J. Org. Chem.* **2016**, *81*, 4464−4474.

(15) Compound **25** was previously described in 3% global yield from compound **8** (see reference 8b).

(16) Recent examples: (a) Wander, D. P. A.; van der Zanden, S. Y.; van der Marel, G. A.; Overkleeft, H. S.; Neefjes, J.; Codée, J. D. C. Doxorubicin and aclarubicin: Shuffling anthracycline glycans for improved anticancer agents. *J. Med. Chem.* **2020**, *63*, 12814−12829. (b) Meng, X.; Lian, X.; Li, X.; Ya, Q.; Li, T.; Zhang, Y.; Yang, Y.; Zhang, Y. Synthesis of 2′-paclitaxel 2-deoxy-2-fluoro-glucopyranosyl carbonate for specific targeted delivery to cancer cells. *Carbohydr. Res.* **2020**, *493*, 108034.

(17) Canel, C.; Moraes, R. M.; Dayan, F. E.; Ferreira, D. Podophyllotoxin. *Phytochemistry* **2000**, *54*, 115−120.

(18) Belani, C. P.; Doyle, L. A.; Aisner, J. Etoposide: Current Status and Future Perspectives in the Management of Malignant Neoplasms. *Cancer Chemother. Pharmacol.* **1994**, *34*, S118−S126.

(19) (a) Cheng, J.; Zhao, W.; Yao, H.; Shen, Y.; Zhang, Y.; Li, Y.-Z.; Qi, Q.; Wongprasert, K.; Tang, Y.-J. Discovery of 4,6-*O*-Thenylidene-β-D-glucopyranoside-(2″-acetamido, 3″-acetyl-di-*S*-5-fluorobenzothizole/5-fluorobenzoxazole)-4′-demethylepipodophyllotoxin as Potential Less Toxic Antitumor Candidate Drugs by Reducing DNA Damage and Less Inhibition of PI3K. *J. Med. Chem.* **2020**, *63*, 2877−2893. (b) Zi, C.-T.; Yang, D.; Dong, F.-W.; Li, G.-T.; Li, Y.; Ding, Z.-T.; Zhou, J.; Jiang, Z.-H.; Hu, J.-M. Synthesis and antitumor activity of novel per-butyrylated glycosides of podophyllotoxin and its derivatives. *Bioorg. Med. Chem.* **2015**, *23*, 1437−1446. (c) Saito, H.; Yoshikawa, H.; Nishimura, Y.; Kondo, S.; Takeuchi, T.; Umezawa, H. Studies on Lignan Lactone Antitumor Agents. I. Synthesis of Aminoglycosidic Lignan Variants Related to Podophyllotoxin. *Chem. Pharm. Bull.* **1986**, *34*, 3733−3740. (d) Saito, H.; Yoshikawa, H.; Nishimura, Y.; Kondo, S.; Takeuchi, T.; Umezawa, H. Studies on Lignan Lactone Antitumor Agents. II. Synthesis of N-alkylamino- and 2,6-dideoxy-2-aminoglycosidic Lignan Variants Related to Podophyllotoxin. *Chem. Pharm. Bull.* **1986**, *34*, 3741−3746. (e) Hollis Showalter, H. D.; Winters, R. T.; Sercel, A. D.; Michel, A. Facile Synthesis of Thioglucose Analogs of the Anticancer Agent, Etoposide. *Tetrahedron Lett.* **1991**, *32*, 2849−2852. (f) Allevi, P.; Anastasia, M.; Ciuffreda, P. A Short and Simple Synthesis of the Thioglucose Analogs of the Antitumor Agent, Etoposide. *Tetrahedron Lett.* **1991**, *32*, 6927−6930. (g) Saito, H.; Nishimura, Y.; Kondo, S.; Umezawa, H. Synthesis of the All Four Possible Diastereoisomers of Etoposide and its Aminoglycosidic Analogues via Optical Resolution of (±)-Podophyllotoxin by Glycosidation with D- and L-sugars. *Chem. Lett.* **1987**, *16*, 799−802. (h) Allevi, P.; Anastasia, M.; Ciuffreda, P. The First Synthesis of the N-glucosyl Analogues of the Antitumor Agent, Etoposide. *Tetrahedron Lett.* **1993**, *34*, 7313−7316. (i) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Scala, A. A Simple Synthesis of C-Glucosides Related to the Antitumor Agent Etoposide. *J. Carbohydr. Chem.* **1993**, *12*, 209−222.

(20) Daley, L.; Guminski, Y.; Demerseman, P.; Kruczynski, A.; Étiévant, C.; Imbert, T.; Hill, B. T.; Monneret, C. Synthesis and Antitumor Activity of New Glycosides of Epipodophyllotoxin, Analogues of Etoposide, and NK 611. *J. Med. Chem.* **1998**, *41*, 4475−4485.

(21) Kamal, A.; Kumar, B. A.; Arifuddin, M. A one-pot, efficient and facile synthesis of 4β-arylaminopodophyllotoxins: synthesis of NPF and GL-331 as DNA topoisomerase II inhibitors. *Tetrahedron Lett.* **2003**, *44*, 8457−8459.

(22) Jacob, D. A.; Gibson, E. G.; Mercer, S. L.; Deweese, J. E. Etoposide catechol is an oxidizable topoisomerase II poison. *Chem. Res. Toxicol.* **2013**, *26*, 1156−1158.

(23) Wang, J.; Zhi, X.; Yu, X.; Xu, H. Synthesis and insecticidal activity of new deoxypodophyllotoxin-based phenazine analogues against Mythimna separata Walker. *J. Agric. Food Chem.* **2013**, *61*, 6336−6343.

(24) (a) Castro, M. A.; Miguel del Corral, J. M.; Gordaliza, M.; Gomez-Zurita, M. A.; de la Puente, M. L.; Betancur-Galvis, L. A.; Sierra, J.; San Feliciano, A. Synthesis, cytotoxicity and antiviral activity of podophyllotoxin analogues modified in E-ring. *Eur. J. Med. Chem.* **2003**, *38*, 899−911. (b) Saulnier, M. G.; Vyas, D. M.; Langley, D. R.; Doyle, T. W.; Rose, W. C.; Crosswell, A. R.; Long, B. H. E-Ring desoxy analogues of etoposide. *J. Med. Chem.* **1989**, *32*, 1418−1420.

(25) (a) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M.; Macdonald, P. A short and simple synthesis of the antitumor agent etoposide. *Tetrahedron Lett.* **1992**, *33*, 4831−4834. (b) Kuhn, M.; von Wartburg, A. Concerning a new glycoside preparation method. Synthesis of epidopodophyllotoxin-β-D-glucopyranoside. *Helv. Chim. Acta* **1968**, *51*, 1631−1641.

(26) Chen, H.; Xian, T.; Zhang, W.; Si, W.; Luo, X.; Zhang, B.; Zhang, M.; Wang, Z.; Zhang, J. An efficient method for the synthesis of pyranoid glycals. *Carbohydr. Res.* **2016**, *431*, 42−46.

https://dx.doi.org/10.1021/acs.joc.0c02841
J. Org. Chem. 2021, 86, 4812−4824