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Facile synthesis of 4-deoxy-4-fluoro-α-D-talopyranoside, 4-deoxy-4-fluoro-α-D-idopyranoside and 2,4-dideoxy-2,4-difluoro-α-D-talopyranoside

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Fluorinated carbohydrates

Dedicated to Professor Alain Tressaud, recipient of the 2011 ACS Award for Creative Work in Fluorine Chemistry.

ABSTRACT

The title compounds were prepared by two independent syntheses using inexpensive commercially available starting materials. 4-Deoxy-4-fluoro-α-D-talopyranoside served as a precursor to 4-deoxy-4-fluoro-α-D-idopyranoside, allowing for inversion of configuration at C-3 *via* a three-step protocol. The synthesis of 2,4-dideoxy-2,4-difluoro-α-D-talopyranoside is based on two nucleophilic fluorination events at C-2 then at C-4 using TBAF·3H$_2$O and TBAF·4*t*BuOH as a fluoride source. All compounds are prepared as pure stereoisomers and are therefore suitable probes for OH···F H-bonding studies by ^{1}H NMR spectroscopy.

1. Introduction

Fluorine substitution has become a widespread and important strategy in drug and new material development. It is therefore of paramount importance to enhance continuously our understanding of how the physical properties of a molecule are changed upon fluorination [1]. The effect of fluorine substitution on size, lipophilicity and conformation has been well studied and documented [2]. The C–F and C–OH groups are commonly recognized as so-called bioisosteric motifs but present some fundamental differences. The alcohol group can function as both hydrogen donor and acceptor whereas a fluorine substituent can only act as hydrogen acceptor [1,3,4]. ^{1}H NMR spectroscopy is a powerful tool to detect intramolecular O–H···F H-bonds by scalar couplings between F and OH (^{h1}J(F,OH)) in apolar solvents [5–7]. In polar solvents such as DMSO, weak intramolecular OH···F H-bonding is superseded by intermolecular H-bonds with the solvent, a phenomenon diagnosed by the disappearance of ^{h1}J(F,OH) couplings. For these NMR studies, various molecular probes were designed and synthesized, including a range of fluorinated monosaccharides, some of them conformationally rigidified. These compounds are well suited for such studies because 1,3-diaxial and 1,2-*cis* fluoroalcohols are ideal motifs for the investigation of intramolecular OH···F H-bonding [5]. Careful ^{1}H NMR studies were already conducted on a series of fluorinated saccharide analogs (Fig. 1). To further investigate intramolecular H-bonds in solution we selected 4-deoxy-4-fluoro-α-D-talopyranoside **1**, 4-deoxy-4-fluoro-α-D-idopyranoside **2** and 2,4-dideoxy-2,4-difluoro-α-D-talopyranoside **3** as next targets. Protection groups at HO-6 favour the solubility in apolar solvents, but should have a negligible influence upon the intramolecular H-bonding. Probes **1** and **2** should allow us to study possible subtleties arising from a change of configuration at C-3 and probe **3** is unique in the sense that it features two fluorine substituents (Fig. 1).

As part of our research program aimed at discovering novel methods for efficient fluorination [8], we became interested in facilitating access to fluorinated carbohydrate analogs [9] and embarked on the synthesis of compounds **1**, **2** and **3**. Fluorinated carbohydrates are accessible by fluorination, the manipulation of

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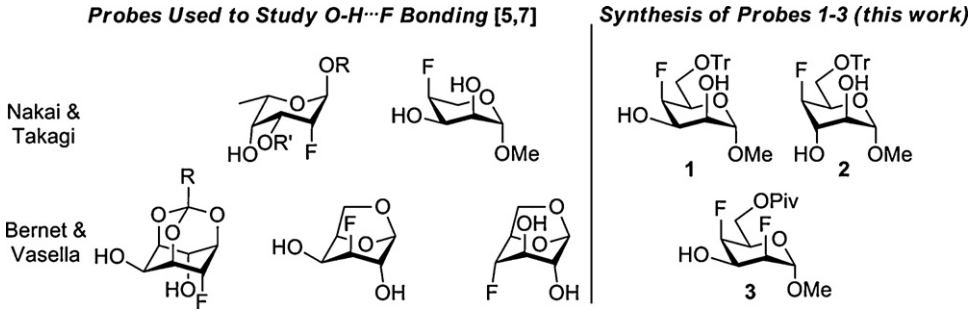


Fig. 1. 1,3-Diaxial and 1,2-*cis* fluoro alcohols ideal for the investigation of OH···F H-bonds.

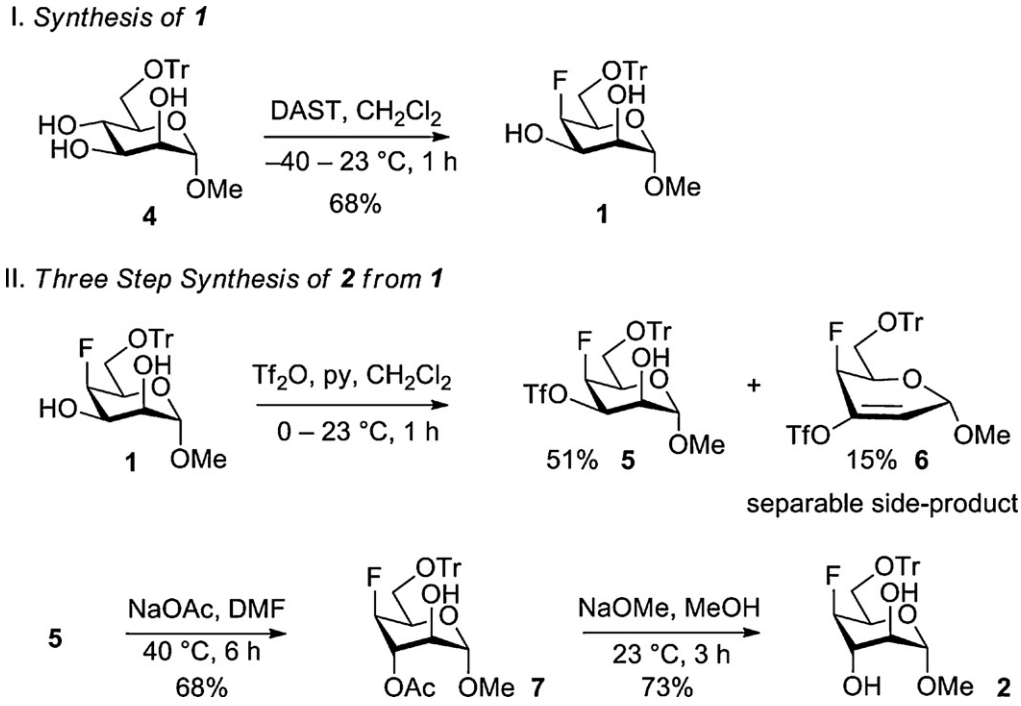
fluorinated building blocks or a combination of both strategies with extensive use of protecting group chemistry. Fluorination is typically performed by nucleophilic substitution of a leaving group or the opening of an epoxide with fluoride, by the displacement of a hydroxy group with diethylaminosulfur trifluoride (DAST) or by electrophilic fluorination of a glycal [10,11]. Herein, we present multistep synthetic routes to **1**–**3** all based on a key displacement reaction using nucleophilic fluorinating reagents.

2. Results and discussion

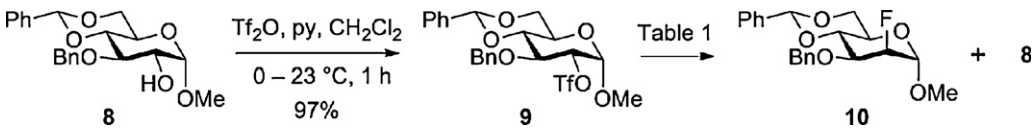
2.1. 4-Deoxy-4-fluoro-α-D-talopyranoside 1 and 4-deoxy-4-fluoro-α-D-idopyranoside 2

To increase synthetic efficiency, we opted for a retrosynthetic approach letting us use the readily accessible 4-deoxy-4-fluoro-α-D-talopyranoside **1** as a starting material to prepare 4-deoxy-4-fluoro-α-D-idopyranoside **2**. Indeed, these two compounds only differ by their configuration at C-3. The fluorination of the 6-*O*-trityl-α-D-glucopyranoside **4** in the presence of an excess of DAST has been reported by Card and Reddy, affording the 4-deoxy-4-fluoro-α-D-talopyranoside **1** in 40% isolated yield (Scheme 1) [12]. This fluorination occurs under mild conditions (−40 °C to 25 °C) and proceeds with remarkable selectivity. The high degree of selectivity can be explained by an intramolecular delivery of fluoride from the DAST-activated axial secondary hydroxy group at C-2 in an S_N2 fashion to the equatorial DAST-activated alcohol functionality at C-4. Pleasingly, we could reproduce this reaction and increase the yield of **4** significantly from 40 to 68% by shortening the reaction time from 2 h to 1 h.

With 4-deoxy-4-fluoro-α-D-talopyranoside **1** in hand, we investigated the possibility to invert the configuration at C-3 to access 4-deoxy-4-fluoro-α-D-idopyranoside **2**, being well aware that this substitution may be complicated due to the presence of the adjacent axial methoxy group. Relying on the favourable reactivity of the most accessible equatorial OH group (C-3) with respect to the axial OH group (C-2), we expected selective trifluoromethanesulfonylation at the C-3 OH. The reaction of **1** with 1 equiv. of trifluoromethanesulfonic anhydride in CH_2Cl_2/pyridine indeed gave 51% of the desired monotriflate **5** as the major product, along with 15% of the enol triflate **6**. This easily separable side-product is resulting from a facile anti-periplanar elimination of trifluoromethanesulfonic acid from the ditrifluoromethanesulfonylated product. Upon treatment with sodium acetate in DMF at 40 °C, triflate **5** was transformed to the 3-*O*-acetyl-α-D-idopyranoside **7** in 68% yield. Subsequently, deacetylation with sodium methoxide in methanol led to the desired diol **2** in 73% yield. In DMSO-d_6, the trityloxymethyl and the solvated hydroxyl groups of



Scheme 1.



Scheme 2.

the idopyranosides **2** and **7** prefer to adopt a pseudoequatorial position leading to a $^{O}S_2$ conformation [13] as evidenced by the vicinal coupling constants $J(1,2) \approx J(3,4) \approx J(4,5) = 3.0–4.7$ Hz and by a large $J(2,3)$ value (**2**: 9.1, **7**: 8.3 Hz). The configuration at C-3 is confirmed by a decrease of ^{3}J(3,F) from 28.2 Hz for **6** to 20.8–22.1 Hz for **2** and **7** (torsion angle changing from 180° to −30°), whereas ^{3}J(5,F) does not change (30.1–31.0 Hz; torsion angle changing from 180° to −155°) [14].

2.2. 2,4-Dideoxy-2,4-difluoro-α-D-talopyranoside 3

Fluorine substitution at C-2 to access 2-deoxy-2-fluoro-α-D-mannopyranosides is a challenging operation. Nucleophilic fluorination using DAST suffers from the formation of several side-products emerging from competitive pathways such as rearrangement and ring contraction [15]. Electrophilic fluorination of D-glucal with Selectfluor or *N*-fluorobenzenesulfonimide afforded 2-deoxy-2-fluoromannose as the minor product, 2-deoxy-2-fluoroglucose being formed predominantly [11]. 2-Deoxy-2-fluoro-β-D-mannopyranosides are easily accessible in high yields (circa 80%) from 2-*O*-trifluoromethanesulfonyl-β-D-glucopyranosides upon treatment with tetrabutylammonium fluoride trihydrate (TBAF·3H$_2$O) [16]. In contrast, when similar reaction conditions are applied to 2-*O*-trifluoromethanesulfonyl-α-D-glucopyranoside, 2-deoxy-2-fluoro-α-D-mannopyranoside is obtained in much lower chemical yield (30–35%) [16]. With these considerations in mind, we opted to prepare the novel 2,4-dideoxy-2,4-difluoro-α-D-talopyranoside **3** by sequential fluorination at C-2 then at C-4 building on two literature precedents. Firstly, the synthesis of the key monofluorinated intermediate is known; however, since the fluorination as described is inefficient (30–35% yield), it will be necessary to improve this particular step. Secondly, a C-4 trifluoromethanesulfonylation–fluorination sequence of a selectively protected α-D-glucopyranoside has been reported in the literature [17] allowing us to focus our efforts on the validation of this chemistry to a 2-deoxy-2-fluoro-α-D-mannopyranoside.

Our study began with the synthesis of **9** from **8** following a known protocol and the subsequent fluorination of **9** to access **10** in synthetically useful yields (Table 1).

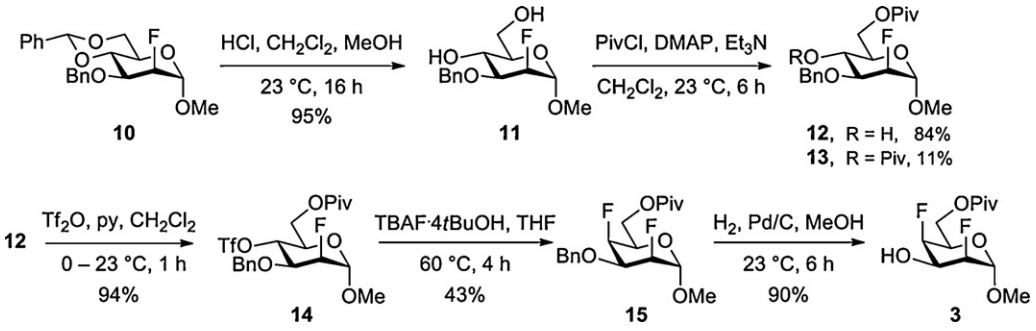
The fluorination of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-trifluoromethanesulfonyl-α-D-glucopyranoside **9** is typically hampered by incomplete conversion and/or the cleavage of the sulfonyl ester leading to the recovery of alcohol **8** (Scheme 2 and Table 1). The introduction of the fluorine substituent at C-2 was first attempted with 2 equiv. of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)/pyridine [18] in CH_2Cl_2/MeCN. No reaction occurred after 24 h at 40 °C. Heating the reaction mixture at 85 °C for 48 h gave the fluorinated product **10** in 19% yield with 56% recovered starting material **9** (Table 1, Entry 1). When the reaction was performed at 50 °C using a larger excess of the expensive TASF reagent, **10** was isolated with an improved chemical yield of 39% (Entry 2). The complete disappearance of **9** was observed with 15 equiv. of 1 M TBAF in THF at room temperature but under these conditions **10** was isolated in low yield (16%) (Entry 3); at 50 °C, the yield dropped further to 10%. With 8 equiv. of TBAF·3H$_2$O in MeCN, the desulfonylated side-product **8** was formed as the major compound (95%) (Entry 4). The use of freshly prepared TBAF·4*t*-tBuOH [19] in dry THF led to significant improvements (Entries 5–7). Complete conversion of **9** occurred when using 20 equiv. of TBAF·4*t*BuOH at 50 °C or with 10 equiv. at 65 °C (Entries 6 and 7; 55–56% of **10** and 43–44% of **8**). In the presence of 4 Å molecular sieves, the yield of both **10** and **8** dropped dramatically (Entry 8). For this reagent, THF was found to be the best solvent (Entries 9 and 10). The highest isolated chemical yield, was obtained using TBAF·4*t*BuOH generated *in situ* by heating TBAF·3H$_2$O in *t*BuOH [20] to 60 °C for 72 h and in the presence of triflate **9**; under these conditions, the desired 2-deoxy-2-fluoromannopyranoside **10** was isolated in a satisfactory yield of 77% (Entry 11); performing the reaction at higher temperature or in *t*BuOH/THF 1:1 proved detrimental (Entries 12 and 13).

Several methods for the regioselective reduction of 4,6-*O*-benzylidene acetals to 6-*O*-benzyl ethers have been described [21], but proved unsatisfactory when applied to **10** (Scheme 3).

Table 1
Optimization of the fluorination at C-2 of triflate **9**. Conditions: 252 mg (0.5 mmol) of **9**, 1 M concentration of TASF and TBAF·3H$_2$O, 0.5 M concentration of TBAF·4*t*BuOH.

Entry	Reagent (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield[a] (%) of **10** (**9**, **8**)
1	TASF/pyridine (2)	CH_2Cl_2/CH_3CN	85	48	19 (56, –[b])
2	TASF/pyridine (5)	CH_2Cl_2/CH_3CN	50	16	39 (59, –[b])
3	1 M TBAF (15)	THF	23	16	16 (0, –[b])
4	TBAF·3H$_2$O (8)	CH_3CN	90	2.5	5 (0, 95)
5	TBAF·4*t*BuOH (15)	THF	50	16	45 (4, 40)
6	TBAF·4*t*BuOH (20)	THF	50	16	55 (0, 43)
7	TBAF·4*t*BuOH (10)	THF	65	16	56 (0, 44)
8	TBAF·4*t*BuOH (10)[c]	THF	65	16	29 (0, 4)
9	TBAF·4*t*BuOH (10)	*t*BuOH/THF 1:1	60	16	29 (13, 2)
10	TBAF·4*t*BuOH (10)	DMF	120	16	37 (0, 31)
11	**TBAF·3H$_2$O (10)**	***t*BuOH**	**60**	**72**	**77 (0, –[b])**
12	TBAF·3H$_2$O (10)	*t*BuOH	100	8	55 (4, 33)
13	TBAF·3H$_2$O (10)	*t*BuOH/THF 1:1	60	16	50 (0, 19)

[a] Isolated yield.
[b] Not isolated.
[c] In the presence of mol. sieves 4 Å.



Scheme 3.

Alternatively, alcohol **12** is accessible by hydrolysis of the benzylidene acetal and selective protection of the primary hydroxyl group. A series of readily available acids, including camphorsulfonic acid, *para*-toluenesulfonic acid, trifluoroacetic acid and hydrochloric acid delivered diol **11** with the best chemical yield (95%) obtained using concentrated hydrochloric acid in a mixture of methanol and CH_2Cl_2. Pivaloylation of **11** gave the desired monopivaloate **12** and the dipivaloate **13** in 84% and 11% yield, respectively. The absence of the axial hydroxy functionality at C-2 did not allow for DAST-mediated intramolecular fluorination at C-4 [12]; we indeed found that 2-deoxy-2-fluoro-α-D-mannopyranoside **12** is inert in the presence of DAST even at 40 °C. The alcohol **12** was therefore activated as triflate **14** in 94% yield using standard condition (trifluoromethanesulfonic anhydride in CH_2Cl_2/pyridine). Fluorination of **14** with TBAF·4*t*BuOH in THF at 60 °C successfully delivered the 2,4-dideoxy-2,4-difluoro-α-D-talopyranoside **15** in 43% yield in 4 h, along with starting material **14** (13%), desulfonylated **12** (8%) and a range of unidentified decomposition products. Hydrogenolysis of **15** gave the desired alcohol **3** in 90% yield.

Careful ^{1}H NMR analysis indicated that the difluorides **15** and **3** are adopting a $^4C_1$ conformation as diagnosed by the small vicinal J(1,2), J(2,3), J(3,4), and J(4,5) couplings (≤2.5 Hz). The similar large ^3J(3,F-2), ^3J(3,F-4), and ^3J(5,F-4) values of 29.0–32.2 Hz and the ^{1F}J(F-2,F-4) coupling of 25 Hz [22] are all consistent with the *talo*-configuration.

3. Conclusions

The easily accessible 4-deoxy-4-fluoro-α-D-talopyranoside **1** was transformed in 3 steps and 25% overall yield to the 4-deoxy-4-fluoro-α-D-idopyranoside **2** by inversion of configuration at C-3. The fluorination of the 2-*O*-triflyl-α-D-glucopyranoside **9** was optimized from ~35% to 77% using TBAF·3H$_2$O in *t*BuOH at 60 °C. The resulting 2-fluoro-α-D-mannopyranoside **10** was successfully converted to 2,4-dideoxy-2,4-difluoro-α-D-talopyranoside **3** (5 steps and 29% overall yield). A detailed study on the conformation of these compounds in different solvents and of their ability to engage in intramolecular OH···F H-bonding is ongoing and will be reported in due course.

4. Experimental

4.1. General

All reactions requiring anhydrous conditions were conducted in dried apparatus under an inert atmosphere of argon or nitrogen. Solvents were dried and purified before use according to standard procedures. All reactions were monitored by TLC using Merck Kiesegel 60 F254 plates. Visualizations of the reaction components were achieved using UV fluorescence (254 nm) and $KMnO_4$ stain. Column chromatography was carried out over Merck silica gel C60 (40–60 μm) or using a Biotage SP4 automated chromatography system using commercially available Biotage® SNAP cartriges KP-sil. All ^{1}H NMR spectra (for organofluoro compounds, both with and without fluorine decoupling) were recorded in deuterated solvents using Bruker DPX400, AV400 and AV500 spectrometers. ^{13}C NMR spectra were recorded in deuterated solvents using Bruker DPX400, AV400 and AV500 spectrometers with a carbon-13 cryoprobe. ^{19}F NMR spectra (both with and without proton decoupling) were recorded on Bruker AV400 and AV500 spectrometers. ^{1}H and ^{13}C NMR data are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). ^{19}F NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Coupling constants (J) are reported in units of Hertz (Hz). The following abbreviations are used to describe multiplicities, s = singlet, d = doublet, t = triplet, q = quartet, br. = broad m = multiplet. Low and high resolution mass spectra were recorded on Bruker MicroTof spectrometer using positive or negative electrospray ionization (ESI+/ESI−). IR spectra were recorded as thin films on NaCl plates, neat or in solution in $CHCl_3$ or CH_2Cl_2 on a Bruker Tensor 27 FTIR spectrometer. Absorptions are measured in wavenumbers (cm^{-1}) and only peaks of interest are reported.

4.2. Methyl 4-deoxy-4-fluoro-6-O-trityl-α-D-mannopyranoside 1 [12]

DAST (6.1 mL, 46 mmol) was added to a solution of methyl 6-*O*-triphenylmethyl-α-D-mannopyranoside **4** [12] (5.0 g, 11 mmol) in CH_2Cl_2 (46 mL) at −40 °C. The mixture was stirred for 1 h at room temperature, cooled to −20 °C, diluted with MeOH (46 mL) and stirred for 15 min at room temperature. After the addition of solid $NaHCO_3$, the mixture was filtered through a celite pad. Evaporation *in vacuo* and purification by column chromatography on silica gel (gradient hexane/EtOAc 25:75 → 15:85) afforded fluoride **1** (3.4 g, 68%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.43–7.39 (6 H, m, 6 arom. H), 7.37–7.32 (6 H, m, 6 arom. H), 7.30–7.24 (3 H, m, 3 arom. H), 4.95 (1 H, d, J = 7.8 Hz, HO-3), 4.64 (1 H, s, H-1), 4.50 (1 H, br. d, ^2J(H,F) = 50.0 Hz, H-4), 4.45 (1 H, br. d, J = 4.8 Hz, HO-2), 3.78 (1 H, dt, ^3J(H,F) = 31.5, J = 6.2 Hz, H-5), 3.59 (1 H, dddd, ^3J(H,F) = 33.0, $J \approx$ 7.6, 4.0, 3.4 Hz, H-3), 3.56–3.52 (1 H, m, H-2), 3.32 (3 H, s, OMe), 3.22 (1 H, dd, J = 9.3, 7.0 Hz, H$_A$-6), 3.12 (1 H, dd, J = 9.3, 5.6 Hz, H$_B$-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (3 C of Tr), 128.6, 127.9, 127.2 (15 CH of Tr), 101.4 (C-1), 90.9 (d, ^1J(C,F) = 178 Hz, C-4), 87.0 (*C*Ph$_3$), 70.2 (C-2), 68.1 (d, ^2J(C,F) = 18 Hz, C-5), 67.9 (d, ^2J(C,F) = 17 Hz, C-3), 61.9 (d, ^3J(C,F) = 5 Hz, C-6), 55.3 (OMe); ^{19}F NMR (376 MHz, DMSO-d$_6$) δ −214.9 (dt, J = 50, 32 Hz); ESI MS 461.2 (100%, [M+Na]$^+$).

4.3. Trifluoromethanesulfonylation of diol 1

Tf_2O (0.42 mL, 2.5 mmol) was added to a solution of diol **1** (1.1 g, 2.5 mmol) in CH_2Cl_2 (13 mL) and pyridine (4 mL) at 0 °C. The

mixture was stirred for 1 h at room temperature. Evaporation *in vacuo* and purification by column chromatography on silica gel (gradient hexane/EtOAc 85:15 → 75:25) afforded triflate **5** [16] (0.90 g, 51%) and enol triflate **6** (0.20 g, 15%).

4.3.1. Data for methyl 4-deoxy-4-fluoro-3-O-trifluoromethanesulfonyl-6-O-trityl-α-D-mannopyranoside 5

White solid. mp 84 °C; $[\alpha]_D^{25}$ = +29.3 (*c* = 0.45, $CHCl_3$); IR ($CHCl_3$) (ν, cm^{-1}): 3444 (O-H), 2941 (C-H); ^1H NMR (400 MHz, DMSO-d_6) δ 7.43–7.39 (6 H, m, 6 arom. H), 7.38–7.33 (6 H, m, 6 arom. H), 7.30–7.25 (3 H, m, 3 arom. H), 5.68 (1 H, br. s, HO-2), 5.15 (1 H, dt, ^3J(H,F) = 28.2, *J* = 3.2 Hz, H-3), 4.96 (1 H, br. d, ^2J(H,F) = 51.2 Hz, H-4), 4.75 (1 H, br. s, H-1), 4.05 (1 H, ddd, ^3J(H,F) = 30.1, *J* = 7.1, 5.3 Hz, H-5), 3.88 (1 H, t, *J* ≈ 1.7 Hz, H-2), 3.36 (3 H, s, OMe), 3.25 (1 H, dd, *J* = 9.5, 6.8 Hz, H_A-6), 3.16 (1 H, dd, *J* = 9.5, 5.1 Hz, H_B-6); ^{13}C NMR (101 MHz, C_6D_6) δ 144.1 (3 C of Tr), 128.2, 128.0, 127.7 (15 CH of Tr), 119.9 (q, ^1J(C,F) = 320 Hz, CF_3), 101.7 (C-1), 88.6 (d, ^1J(C,F) = 187 Hz, C-4), 87.4 (*C*Ph_3), 81.2 (d, ^2J(C,F) = 15 Hz, C-3), 69.0 (C-2), 68.7 (d, ^2J(C,F) = 18 Hz, C-5), 62.5 (d, ^3J(C,F) = 5 Hz, C-6), 54.8 (OMe); ^{19}F NMR (376 MHz, DMSO-d_6) δ −74.6 (3F, s, CF_3), −214.1 (1F, dt, *J* = 51, 29 Hz, F-4); ESI HR-MS (positive mode) *m*/*z* 593.1225 ($[M+Na]^+$, calculated for $C_{27}H_{26}F_4NaO_7S^+$: 593.1228).

4.3.2. Data for methyl 2,4-dideoxy-4-fluoro-3-O-trifluoromethanesulfonyl-6-O-trityl-α-D-threo-hex-2-enopyranoside 6

White solid. mp decomp. 110 °C; IR (CH_2Cl_2) (ν, cm^{-1}): 3060, 2939 (C-H), 1688 (C=C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.43 (6 H, m, 6 arom. H), 7.35–7.30 (6 H, m, 6 arom. H), 7.29–7.24 (3 H, m, 3 arom. H), 6.15 (1 H, t, *J* = ^4J(H,F) = 3.1 Hz, H-2), 5.20 (1 H, t, *J* = ^5J(H,F) = 3.2 Hz, H-1), 4.76 (1 H, dd, ^2J(H,F) = 49.9, *J* = 1.9 Hz, H-4), 4.18 (1 H, br. ddd, ^3J(H,F) = 29.2, *J* = 6.6, 6.3 Hz, H-5), 3.55 (1 H, ddd, *J* = 9.9, 6.6, ^4J(H,F) = 1.4 Hz, H_A-6), 3.49 (3 H, s, OMe), 3.40 (1 H, dd, *J* = 9.9, 6.0 Hz, H_B-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.8 (d, ^2J(C,F) = 19 Hz, C-3), 143.6 (3 C of Tr), 128.6, 127.9, 127.2 (15 CH of Tr), 118.4 (q, ^1J(C,F) = 320 Hz, CF_3), 121.3 (d, ^3J(C,F) = 7 Hz, C-2), 94.8 (d, ^4J(C,F) = 1 Hz, C-1), 87.1 (*C*Ph_3), 81.7 (d, ^1J(C,F) = 186 Hz, C-4), 69.7 (d, ^2J(C,F) = 19 Hz, C-5), 61.6 (d, ^3J(C,F) = 7 Hz, C-6), 56.2 (OMe); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.4 (3 F, d, ^1FJ(F,F) = 4 Hz, CF_3), −199.3 (1 F, ddq, *J* = 50, 29, ^1F*J*(F,F) = 4 Hz, 4-F); ESI HR-MS (positive mode) *m*/*z* 725.0723 ($[M+Na]^+$, calculated for $C_{27}H_{24}F_4NaO_6S$: 725.07209).

4.4. Methyl 3-O-acetyl-4-deoxy-4-fluoro-6-O-trityl-α-D-idopyranoside 7

A solution of triflate **5** (0.46 g, 0.8 mmol) in DMF (2 mL) was treated with NaOAc (0.33 g, 4.0 mmol) and stirred at 40 °C for 6 h. Evaporation *in vacuo* and purification by column chromatography on silica gel (gradient hexane/EtOAc 80:20 → 50:50) afforded acetate **7** (0.26 g, 68%). mp 84 °C; $[\alpha]_D^{25}$ = +24.4 (*c* = 0.425, $CHCl_3$); IR (CH_2Cl_2) (ν, cm^{-1}): 3469 (O–H), 3058, 2938 (C–H), 1745 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ 7.43–7.39 (6 H, m, 6 arom. H), 7.37–7.32 (6 H, m, 6 arom. H), 7.30–7.25 (3 H, m, 3 arom. H), 5.62 (1 H, d, *J* = 5.6 Hz, OH), 4.95 (1 H, ddd, ^3J(H,F) = 20.8, *J* = 8.3, 4.7 Hz, H-3), 4.65 (1 H, ddd, ^2J(H,F) = 49.9, *J* = 4.7, 3.1 Hz, H-4), 4.57 (1 H, d, *J* = 4.3 Hz, H-1), 4.12 (1 H, ddt, ^2J(H,F) = 30.9, *J* = 7.2, 3.5 Hz, H-5), 3.48 (1 H, dt, *J* ≈ 8.3, 4.9 Hz, H-2), 3.41 (3 H, s, OMe), 3.24 (1 H, br. dd, *J* = 9.7, 7.3, ^4J(H,F) < 1.5 Hz, H_A-6), 3.07 (1 H, dd, *J* = 9.9, 3.8 Hz, H_B-6), 2.04 (3 H, s, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (C=O), 143.7 (3 C of Tr), 128.6, 127.9, 127.1 (15 CH of Tr), 101.5 (C-1), 87.5 (d, ^1J(C,F) = 179 Hz, C-4), 87.1 (*C*Ph_3), 69.0 (d, ^2J(C,F) = 27 Hz, C-3), 67.0 (C-2), 66.0 (d, ^2J(C,F) = 18 Hz, C-5), 62.1 (d, ^3J(C,F) = 6 Hz, C-6), 55.6 (OMe), 20.9 (*Me*C=O); ^{19}F NMR (376 MHz, DMSO-d_6) δ −195.0 (ddd, *J* = 50, 31, 21 Hz); ESI HR-MS (positive mode) *m*/*z* 503.1829 ($[M+Na]^+$, calculated for $C_{28}H_{29}FNaO_6^+$: 503.1840).

4.5. Methyl 4-deoxy-4-fluoro-6-O-trityl-α-D-idopyranoside 2

A solution of acetate **7** (50 mg, 0.10 mmol) in MeOH (2 mL) was treated with NaOMe (5.4 mg, 0.10 mmol), stirred at room temperature for 3 h, treated with Dowex gel 50W-X8 (H^+ form), and filtered. Evaporation *in vacuo* and purification by column chromatography on silica gel (hexane/EtOAc 50:50) afforded diol **2** (32 mg, 73%). $[\alpha]_D^{25}$ = +5.6 (*c* = 0.18, $CHCl_3$); IR (CH_2Cl_2) (ν, cm^{-1}): 3429 (O–H), 3059, 3033, 2937 (C–H); ^1H NMR (400 MHz, DMSO-d_6) δ 7.43–7.40 (6 H, m, 6 arom. H), 7.38–7.33 (6 H, m, 6 arom. H), 7.30–7.28 (3 H, m, 3 arom. H), 5.29 (2 H, d, *J* = 5.0 Hz, 2 OH), 4.48 (1 H, d, *J* = 4.2 Hz, H-1), 4.44 (1 H, ddd, ^2J(H,F) = 50.0, *J* = 4.5, 3.0 Hz, H-4), 4.11 (1 H, ddt, ^3J(H,F) = 31.0, *J* ≈ 7.2, 3.6 Hz, H-5), 3.57 (1 H, ddt, ^3J(H,F) = 22.1, *J* = 9.1, 4.7 Hz, H-3), 3.40 (3 H, s, OMe), 3.32–3.29 (1 H, m, H-2), 3.20 (1 H, br. dd, *J* = 9.3, 7.1, ^4J(H,F) < 1.5 Hz, H_A-6), 3.06 (1 H, dd, *J* = 9.6, 4.4 Hz, H_B-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (3 C of Tr), 128.6, 127.9, 127.2 (15 CH of Tr), 101.7 (C-1), 89.1 (d, ^1J(C,F) = 180 Hz, C-4), 87.0 (*C*Ph_3), 67.4 (d, ^2J(C,F) = 23 Hz, C-3), 67.3 (C-2), 64.9 (d, ^2J(C,F) = 18 Hz, C-5), 62.2 (d, ^3J(C,F) = 6 Hz, C-6), 55.7 (OMe); ^{19}F NMR (376 MHz, $CDCl_3$) δ −193.8 (ddd, *J* = 53, 31, 22 Hz); ESI HR-MS (positive mode) *m*/*z* 461.1727 ($[M+Na]^+$, calculated for $C_{26}H_{27}FNaO_5^+$: 461.1735).

4.6. Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-trifluoromethanesulfonyl-α-D-glucopyranoside 9 [16]

A solution of α-D-glucopyranoside **8** [16] (2.5 g, 6.7 mmol) in CH_2Cl_2 (37 mL) and pyridine (10 mL) was cooled to −15 °C, treated with Tf_2O (3.8 g, 13 mmol), stirred for 15 min at −15 °C and for 1 h at room temperature, and evaporated *in vacuo*. A solution of the residue in $CHCl_3$ (15 mL) was washed with water (10 mL), dried over $MgSO_4$, and filtered. Evaporation *in vacuo* and purification by column chromatography on silica gel (hexane/EtOAc 67:33) delivered triflate **9** (3.3 g, 97%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.28 (10 H, m, 10 arom. H), 5.58 (1 H, s, *CH*Ph), 4.98 (1 H, d, *J* = 3.4 Hz, H-1), 4.86 and 4.78 (2 H, 2 d, *J* = 10.9 Hz, CH_2Ph), 4.76 (1 H, dd, *J* = 9.5, 3.8 Hz, H-2), 4.33 (1 H, dd, *J* = 10.2, 4.6 Hz, H_{eq}-6), 4.14 (1 H, t, *J* = 9.4 Hz, H-3), 3.90 (1 H, td, *J* = 9.9, 4.6 Hz, H-5), 3.77 (1 H, t, *J* = 10.3 Hz, H_{ax}-6), 3.71 (1 H, t, *J* = 9.4 Hz, H-4), 3.49 (3 H, s, OMe); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 136.9 (2 C of Ph), 129.2, 128.3, 128.3, 128.3, 127.9, 126.0 (10 CH of Ph), 120.0 (q, ^1J(C,F) = 321 Hz, CF_3), 101.5 (*C*HPh), 97.6 (C-1), 83.6 (C-2), 82.0 (C-4), 75.3 (CH_2Ph), 75.0 (C-3), 68.7 (C-6), 62.2 (C-5), 55.8 (OMe); ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.8 (s); ESI MS 527.1 (100%, $[M+Na]^+$).

4.7. Methyl 3-O-benzyl-4-6-O-benzylidene-2-deoxy-2-fluoro-α-D-mannopyranoside 10 [16]

A solution of triflate **9** (0.26 g, 0.50 mmol) in *t*BuOH (5 mL) was treated TBAF·$3H_2O$ (1.6 g, 5.0 mmol), stirred at 60 °C for 72 h, cooled to room temperature, diluted with Et_2O (25 mL), washed with 1 M aqueous HCl (2 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (15 mL), dried over $MgSO_4$, and filtered. Evaporation *in vacuo* and purification by column chromatography on silica gel (gradient hexane/EtOAc 88:12 → 67:33) afforded fluoride **10** (0.14 g, 77%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.25 (10 H, m, 10 arom. H), 5.65 (1 H, s, *CH*Ph), 4.91–4.84 (2 H, m, CH_APh, H-1), 4.76 (1 H, dt, ^2J(H,F) = 48.8, *J* = 2.0 Hz, H-2), 4.76 (1 H, d, *J* = 12.2 Hz, CH_BPh), 4.30 (1 H, dd, *J* = 9.2, 3.5 Hz, H_{eq}-6), 4.13 (1 H, t, *J* = 9.0 Hz, H-4), 3.94 (1 H, ddd, ^3J(H,F) = 27.6, *J* = 9.9, 2.3 Hz, H-3), 3.90–3.79 (2 H, m, H-5,

H_{ax}-6), 3.40 (3 H, s, OMe); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 137.4 (2 C of Ph), 129.0, 128.4, 128.2, 127.8, 127.7, 126.1 (10 CH of Ph), 101.7 (*C*HPh), 99.3 (d, ^2J(C,F) = 31 Hz, C-1), 88.2 (d, ^1J(C,F) = 178 Hz, C-2), 78.7 (C-4), 74.1 (d, ^2J(C,F) = 17 Hz, C-3), 73.0 (*C*H_2Ph), 68.7 (C-6), 63.7 (C-5), 55.2 (OMe); ^{19}F NMR (376 MHz, $CDCl_3$) δ −203.8 (ddd, J = 49, 28, 8 Hz); ESI MS 392.2 (25%, $[M+NH_4]^+$), 397.1 (100%, $[M+Na]^+$).

4.8. Methyl 3-O-benzyl-2-deoxy-2-fluoro-α-D-mannopyranoside 11

A solution of benzylidene acetal **10** (1.2 g, 3.2 mmol) in MeOH/CH_2Cl_2 1:1 (20 mL) was treated with conc. HCl (3 mL), stirred for 16 h at room temperature, diluted with CH_2Cl_2 (100 mL), and washed with saturated $NaHCO_3$ solution (100 mL). The organic phase was dried over $MgSO_4$ and filtered. Evaporation *in vacuo* and purification by column chromatography on silica gel (gradient hexane/EtOAc 50:50 → 25:75) afforded diol **11** (0.87 g, 95%) as a colourless oil. $[\alpha]_D^{25}$ = +25.6 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2) (ν, cm^{-1}): 3416 (O–H), 3060, 2931 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.27 (5 H, m, 5 arom. H), 4.86 (1 H, dd, ^3J(H,F) = 7.1, J = 1.3 Hz, H-1), 4.74 (1 H, d, J = 11.6 Hz, CH_APh), 4.68 (1 H, dt, ^2J(H,F) = 50.0, $J \approx$ 2.1 Hz, H-2), 4.63 (1 H, d, J = 11.6 Hz, CH_BPh), 3.96 (1 H, t, J = 9.7 Hz, H-4), 3.85 (1 H, dd, J = 11.7, 3.4 Hz, H_A-6), 3.82 (1 H, dd, J = 11.7, 4.0 Hz, H_B-6), 3.68 (1 H, ddd, ^3J(H,F) = 29.6, J = 9.4, 2.6 Hz, H-3), 3.60 (1 H, ddd, J = 9.4, 4.0, 3.4 Hz, H-5), 3.36 (3 H, s, OMe), 2.97 (2 H, br. s, 2 OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (C of Ph), 128.5, 128.0, 127.9 (5 CH of Ph), 98.6 (d, ^2J(C,F) = 29 Hz, C-1), 86.0 (d, ^1J(C,F) = 177 Hz, C-2), 78.0 (d, ^2J(C,F) = 17 Hz, C-3), 72.1 (C-5), 71.9 (*C*H_2Ph), 66.6 (C-4), 62.1 (C-6), 55.1 (OMe); ^{19}F NMR (376 MHz, $CDCl_3$) δ −205.5 (ddd, J = 50, 30, 7 Hz); ESI HR-MS (positive mode) m/z 309.1109 ($[M+Na]^+$, calculated for $C_{14}H_{19}FNaO_5^+$: 309.1109).

4.9. Pivaloylation of 11

4-(Dimethylamino)pyridine (33 mg, 0.27 mmol) and pivaloyl chloride (140 μl, 1.1 mmol) were added to a solution of diol **11** (0.31 g, 1.1 mmol) and Et_3N (0.20 mL, 2.7 mmol) in CH_2Cl_2 (11 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C, warmed to room temperature, stirred for 6 h, and washed with saturated aqueous $NaHCO_3$ solution (5 mL). The organic phase was washed with brine (5 mL), dried over $MgSO_4$, and filtered. Evaporation *in vacuo* and column chromatography on silica gel (gradient hexane/EtOAc 88:12 → 17:83) afforded the monopivaloate **12** (0.34 g, 84%) and the dipivaloate **13** (53 mg, 11%).

4.9.1. Data for methyl 3-O-benzyl-2-deoxy-2-fluoro-6-O-pivaloyl-α-D-mannopyranoside 12

Colourless oil. $[\alpha]_D^{24}$ = +32.3 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2) (ν, cm^{-1}): 3500 (O–H), 2931 (C–H), 1725 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (5 H, m, 5 arom. H), 4.86 (1 H, br. d, ^3J(H,F) = 7.2 Hz, H-1), 4.77 (1 H, d, J = 11.6 Hz, CH_APh), 4.71 (1 H, dt, ^2J(H,F) = 49.6, $J \approx$ 2.0 Hz, H-2), 4.64 (1 H, d, J = 11.6. Hz, CH_BPh), 4.38 (2 H, d, J = 3.2 Hz, 2 H-6), 3.83 (1 H, t, J = 9.4 Hz, H-4), 3.79–3.73 (1 H, m, H-5), 3.69 (1 H, ddd, ^3J(H,F) = 29.2, J = 9.3, 2.0 Hz, H-3), 3.39 (3 H, s, OMe), 2.71 (1 H, br. s, OH), 1.23 (9 H, s, CMe_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9 (C=O), 137.6 (C of Ph), 128.6, 128.1, 127.9 (5 CH of Ph), 98.5 (d, ^2J(C,F) = 29 Hz, C-1), 85.8 (d, ^1J(C,F) = 179 Hz, C-2), 77.8 (d, ^2J(C,F) = 17 Hz, C-3), 72.0 (*C*H_2Ph), 70.7 (C-5), 66.4 (C-4), 63.0 (C-6), 55.0 (OMe), 38.9 (*C*Me_3), 27.2 (C*Me*$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −205.2 (ddd, J = 50, 29, 7 Hz); ESI HR-MS (positive mode) m/z 393.1683 ($[M+Na]^+$, calculated for $C_{19}H_{27}FNaO_6^+$: 393.1684).

4.9.2. Data for methyl 3-O-benzyl-2-deoxy-2-fluoro-4,6-di-O-pivaloyl-α-D-mannopyranoside 13

Colourless oil. $[\alpha]_D^{25}$ = +44.8 (c = 1.0, $CHCl_3$); IR (CH_2Cl_2) (ν, cm^{-1}): 2972 (C–H), 1736 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (5 H, m, 5 arom. H), 5.34 (1 H, t, J = 9.7 Hz, H-4), 4.87 (1 H, br. d, ^3J(H,F) = 6.7 Hz, H-1), 4.70 (1 H, br. d, ^2J(H,F) = 48.5 Hz, H-2), 4.66 and 4.59 (2 H, 2 d, J = 12.2 Hz, CH_2Ph), 4.23 (1 H, br. d, J = 12.2 Hz, H_A-6), 4.07 (1 H, dd, J = 12.2, 5.7 Hz, H_B-6), 3.94–3.74 (2 H, m, H-3, H-5), 3.39 (3 H, s, OMe), 1.23 (9 H, s, CMe_3), 1.19 (9 H, s, CMe_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 176.8 (2 C=O), 137.6 (C of Ph), 128.4, 127.8, 127.5 (5 CH of Ph), 98.4 (d, ^2J(C,F) = 29 Hz, C-1), 86.1 (d, ^1J(C,F) = 179 Hz, C-2), 75.8 (d, ^2J(C,F) = 17 Hz, C-3), 71.9 (*C*H_2Ph), 69.2 (C-5), 66.7 (C-4), 62.3 (C-6), 55.2 (OMe), 38.8, 38.8 (2 *C*Me_3), 27.1, 27.1 (2 C*Me*$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ −205.2 (ddd, J = 50, 29, 7 Hz); ESI HR-MS (positive mode) m/z 477.2261 ($[M+Na]^+$, calculated for $C_{24}H_{35}FNaO_7^+$: 477.2259).

4.10. Methyl 3-O-benzyl-2-deoxy-2-fluoro-6-O-pivaloyl-4-O-trifluoromethanesulfonyl-α-D-mannopyranoside 14

A solution of pivaloate **12** (0.53 g, 1.4 mmol) in CH_2Cl_2 (7 mL) and pyridine (2 mL) was cooled to −15 °C, treated with Tf_2O (0.48 mL, 2.9 mmol), stirred for 15 min at −15 °C and for 1 h at room temperature, and evaporated *in vacuo*. A solution of the residue in $CHCl_3$ (10 mL) was washed with water (10 mL), dried over $MgSO_4$, and filtered. Evaporation *in vacuo* and purification by column chromatography on silica gel (hexane/EtOAc 75:25) afforded the triflate **14** (0.67 g, 94%) as a white solid. mp 90 °C (decomp.), $[\alpha]_D^{25}$ = +61.0 (c = 0.5, $CHCl_3$); IR (CH_2Cl_2) (ν, cm^{-1}): 3031, 2965, 2937 (C–H), 1735 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.29 (5 H, m, 5 arom. H), 5.19 (1 H, t, J = 9.9 Hz, H-4), 4.84 (1 H, dd, ^3J(H,F) = 6.6, J = 1.4 Hz, H-1), 4.75 and 4.64 (2 H, 2 d, J = 11.7 Hz, CH_2Ph), 4.63 (1 H, dt, ^2J(H,F) = 49.0, $J \approx$ 1.9 Hz, H-2), 4.54 (1 H, dd, J = 12.6, 1.7 Hz, H_A-6), 4.10 (1 H, dd, J = 12.6, 3.7 Hz, H_B-6), 4.06–4.01 (1 H, m, H-5), 3.94 (1 H, ddd, ^3J(H,F) = 27.7, J = 9.7, 2.3 Hz, H-3), 3.39 (3 H, s, OMe), 1.23 (9 H, s, CMe_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 77.9 (C=O), 136.6 (C of Ph), 128.5, 128.2, 128.1 (5 CH of Ph), 118.3 (q, ^1J(C,F) = 318 Hz, CF_3), 98.1 (d, ^2J(C,F) = 28 Hz, C-1), 85.6 (d, ^1J(C,F) = 181 Hz, C-2), 79.5 (C-4), 75.0 (d, ^2J(C,F) = 17 Hz, C-3), 72.4 (*C*H_2Ph), 67.8 (C-5), 61.1 (C-6), 55.6 (OMe), 38.9 (*C*Me_3), 27.0 (C*Me*$_3$); ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.6 (3 F, s, CF_3), −205.7 (1 F, ddd, J = 49, 28, 7 Hz, F-2); ESI HR-MS (positive mode) m/z 525.1178 ($[M+Na]^+$, calculated for $C_{20}H_{26}F_4NaO_8S^+$: 525.1177).

4.11. Methyl 3-O-benzyl-2,4-dideoxy-2,4-difluoro-6-O-pivaloyl-α-D-talopyranoside 15

TBAF·4*t*BuOH (1.1 g, 2.0 mmol) was added to a solution of triflate **14** (0.10 g, 0.20 mmol) in THF (4 mL) at room temperature. The solution was stirred at 60 °C for 4 h, cooled to room temperature, diluted with Et_2O (10 mL), washed with water (10 mL), dried over $MgSO_4$, and filtered. Evaporation *in vacuo* and purification by column chromatography on silica gel (gradient hexane/EtOAc 92:8 → 66:34) gave difluoride **15** (32 mg, 43%) as colourless oil and desulfonylated **12** (6 mg, 8%). Starting material could be recovered (13 mg, 10%) amongst other fluorinated products that were not identified. $[\alpha]_D^{25}$ = +18.8 (c = 0.48, $CHCl_3$); IR ($CHCl_3$) (ν, cm^{-1}): 2967, 2922 (C–H), 1722 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.29 (5 H, m, 5 arom. H), 4.98 (1 H, br. d, J = 8.2 Hz, H-1), 4.77 (1 H, d, J = 12.0 Hz, CH_APh), 4.73 (1 H, br. d, ^2J(H,F) = 48.7 Hz, H-4), 4.72 (1 H, d, J = 12.0 Hz, CH_BPh), 4.66 (1 H, br. d, ^2J(H,F) = 47.5 Hz, H-2), 4.38–4.30 (2 H, m, 2 H-6), 3.91 (1 H, dt, ^3J(H,F) = 29.0, J = 6.1 Hz, H-5), 3.64 (1 H, tt, ^3J(H,F) = 31.2, J = 2.5 Hz, H-3), 3.39 (3 H, s, OMe), 1.21 (9 H, s, CMe_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1 (C=O), 137.0 (C of Ph), 128.6, 128.2, 127.9 (5 CH of Ph), 98.7 (d, ^2J(C,F) = 31 Hz, C-1), 85.4 (d, ^1J(C,F) = 191 Hz, C-4 or C-2), 84.9 (d, ^1J(C,F) = 183 Hz, C-2 or C-4), 70.9 (t, ^2J(C,F) = 17 Hz, C-3), 70.8 (*C*H_2Ph), 67.6 (d, ^2J(C,F) = 18 Hz, C-5), 62.6 (d, ^3J(C,F) = 7 Hz, C-6), 55.3 (OMe), 38.7 (*C*Me_3), 27.1 (C*Me*$_3$); ^{19}F NMR (376 MHz, $CDCl_3$): δ −203.9 (1 F, dddd, J = 48, 32, ^{1F}J(F,F) = 25, J = 8 Hz, F-2),

−217.0 (1 F, dtd, J = 51, 29, ^{1F}J(F,F) = 25 Hz, F-4); ESI HR-MS (positive mode) m/z 395.1637 ([M+Na]$^+$, calculated for $C_{19}H_{26}F_2NaO_5^+$: 395.1637).

4.12. Methyl 2,4-dideoxy-2,4-difluoro-6-O-pivaloyl-α-D-talopyranoside 3

A vial containing a suspension of difluoride **15** (5.7 mg, 0.016 mmol) and Pd/C (2 mg, 0.016 mmol) in MeOH (0.2 mL) was evacuated and flushed with H_2 (3×). The suspension was stirred for 6 h under an atmospheric H_2 pressure at room temperature and then filtered through a celite pad. Evaporation *in vacuo* gave difluoroalcohol **3** (3.9 mg, 90%) as colourless oil. $[\alpha]_D^{25}$ = +9.8 (c = 0.19, $CHCl_3$); IR ($CHCl_3$) (ν, cm^{-1}): 1717 (C=O); ^{1}H NMR (400 MHz, CD_3OD) δ 4.95 (1 H, br. d, ^3J(H,F) = 8.8 Hz, H-1), 4.69 (1 H, br. d, ^2J(H,F) = 50.6 Hz, H-4), 4.52 (1 H, br. d, ^2J(H,F) = 49.0 Hz, H-2), 4.33 (1 H, dd, J = 11.3, 7.7 Hz, H_A-6), 4.26 (1 H, dd, J = 11.3, 4.7 Hz, H_B-6), 4.07 (1 H, ddd, ^3J(H,F) = 30.0, J = 7.3, 5.0 Hz, H-5), 3.85 (1 H, tt, ^3J(H,F) = 32.2, J = 3.0 Hz, H-3), 3.44 (3 H, s, OMe), 1.29 (9 H, s, CMe_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1 (C=O), 98.5 (d, ^2J(C,F) = 28 Hz, C-1), 87.6 (d, ^1J(C,F) = 184 Hz, C-4 or C-2), 87.3 (d, ^1J(C,F) = 177 Hz, C-2 or C-4), 67.0 (d, ^2J(C,F) = 18 Hz, C-5), 65.0 (t, ^2J(C,F) = 18 Hz, C-3), 62.4 (d, ^3J(C,F) = 7 Hz, C-6), 55.4 (OMe), 38.8 (CMe_3), 29.7 (CMe_3); ^{19}F {H} NMR (470 MHz, $CDCl_3$): δ −207.0 (1 F, d, ^{1F}J(F,F) = 25 Hz, F-2), −217 (1 F, d, ^{1F}J(F,F) = 25 Hz, F-4); ESI HR-MS (positive mode) m/z 305.1170 ([M+Na]$^+$, calculated for $C_{12}H_{20}F_2NaO_5^+$: 305.1171).

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