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Synthesis of 3-deoxy-3,3-difluoro-D-ribohexose from *gem*-difluorohomoallyl alcohol

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Abstract

A novel synthetic route to 3-deoxy-3,3-difluoro-D-ribohexose **1** has been developed. Dihydroxidation of *gem*-difluorohomoallyl alcohol followed by several steps of protection and deprotection gave key intermediate **9**. Oxidation of 1,5-diol **9** with 2 equiv. trichloroisocyanuric acid and catalytic TEMPO gave lactone **10**. Reduction of **10** with DIBAL-H followed by deprotections afforded the target molecule **1**.

Keywords: Fluorosugars; *Gem*-Difluoromethylenated compounds; Building block

1. Introduction

The interest of fluorinated analogues of natural substances is increasing continuously, because the incorporation of fluorine atom(s) or fluoroalkyl groups may greatly modify the chemical properties and biological activities of those molecules [1]. Among these fluorinated analogues of natural products, fluorinated carbohydrates (fluorosugars) have recently attracted more and more attentions from organic chemists and pharmaceutists [2]. Fluorosugars can retain much of the reactivity of natural saccharides while lacking the ability to enter into critical hydrogen bonding interactions with nucleic acids or proteins. Although monofluorinated [3] and trifluoromethylated sugars [4] have been well studied, only a few *gem*-difluoromethylenated sugars have been reported, which is probably due to the shortcomings of existing synthetic methods. 2-Deoxy-2,2-difluorinated sugars were obtained either by electrophilic fluorination of 2-fluoroglycals [5] and by reaction of carbonyl groups with DAST [6]. The difluorination at the 4-keto- and 3-keto-groups with DAST for synthesis of the corresponding 4-deoxy-4,4-difluorinated [7] and 3-deoxy-4,4-difluorinated [8] sugars have been described. The difluorinations of keto groups of carbohydrates have been well-documented complications arising from neighbouring group participation, group migration and elimination reactions [9]. Therefore, the development of efficient and practical route to *gem*-difluorinated sugars was anticipated. Percy and co-workers have reported the synthesis of 4-deoxy-4,4-difluoroglycosides from *gem*-difluoromethylene-containing building block using ring-closing metathesis as the key step [10]. Recently, our group has developed a practical route to *gem*-difluorinated homoallyl alcohol **2**. Staring from *gem*-difluoromethylene-containing building block **2**, several *gem*-difluorinated sugars such as 3-deoxy-3,3-difluoro-D-arabinofuranose **A** [11], 3-deoxy-3,3-difluoro-L-ribofuranose **B** [12], *gem*-difluorinated thiofuranose **C** [13] and *gem*-difluorinated azasugars **D–F** [14] were synthesized (Scheme 1). Herein, we wish to describe preparation of 3-deoxy-3,3-difluoro-D-ribohexose **1** from *gem*-difluorohomoallyl alcohol **2**.

2. Results and discussion

The building block *gem*-difluorohomoallyl alcohol **2** was prepared by the coupling of *gem*-difluoroallylindium, in situ generated from 3-bromo-3,3-difluoropropene **4** and indium in DMF, with 1-(*R*)-glyceraldehyde acetonide **3** [11] (Scheme 2). Compound **2** can be made on a 50 g scale in our group. The ratio

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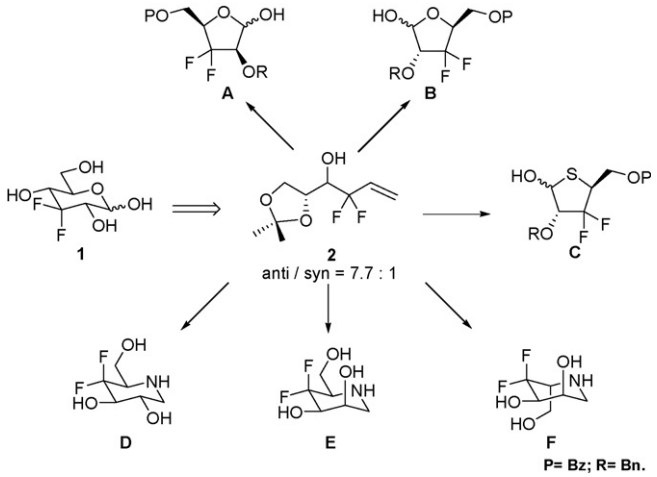
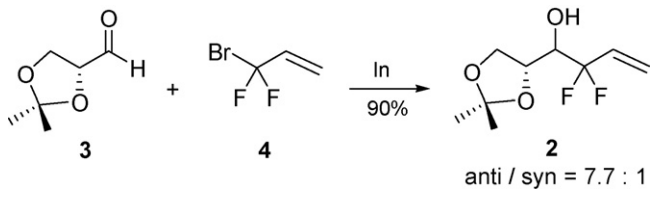


Scheme 1.

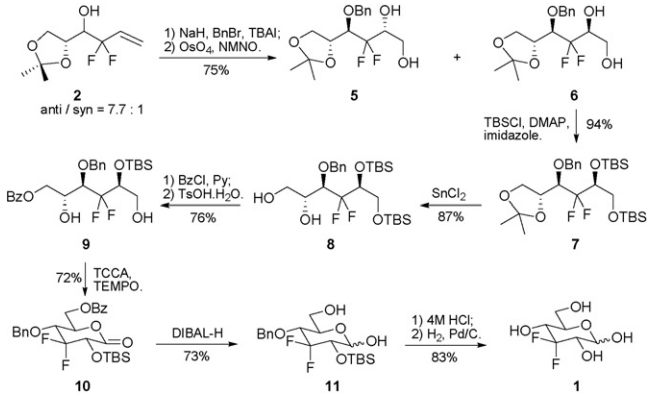
of *anti*/*syn* compound **2** is 7.7:1 determined by ^{19}F NMR. The difluoromethylene group of *anti*-**2** appeared at a higher field than that of *syn*-**2**. Notably, the *anti*-**2** isomer is our desired compound.

With *gem*-difluorohomoallyl alcohol **2** in hand, 3-deoxy-3,3-difluoro-D-ribohexose **1** was synthesized in a straightforward fashion (Scheme 3). Utilizing the kinetic resolution method and optimized reaction condition, benzylation of the *gem*-difluorohomoallyl alcohol **2** was easily accomplished by treatment with sodium hydride (0.8 equiv.) and catalytic TBAI, followed by benzyl bromide. The desired single *anti*-isomer was afforded in 78% yield. Then, the Os-catalyzed dihydroxylation of the resulting benzyl ether gave the mixture of diol compounds **5** and **6** in 95% yield and in 1:1 ratio, which could be easily separated by column chromatography. The two hydroxyl groups of diol **6** were protected to the *tert*-butyldimethylsilyl ether form and the desired compound **7** was provided in 94% yield. Deprotection of the acetonide moiety was achieved in a chemoselective manner by using $SnCl_2$ as the promoter to give diol **8** in 87% yield [15]. The beneficial effect of $SnCl_2$ was cleavage of the acetonide moiety without interference with the TBDMS and benzyl groups, which were easily cleaved under Lewis acids such as BCl_3. Selective benzoylation of the primary hydroxyl group of diol **8** followed by selective removal of the primary TBS group gave 1,5-diol **9** in 76% yield.

Recently, Giacomelli and co-workers described the chemoselective oxidation of primary alcohol to aldehyde without no overoxidation to carboxylic acids at room temperature using trichloroisocyanuric acid in the presence



Scheme 2.



Scheme 3.

of catalytic TEMPO [16]. We were interested in extending Giacomelli's reaction condition to compound **9**. It was expected that the primary hydroxyl group of **9** was oxidized to aldehyde followed by the subsequent cyclization to give the desired lactol. Initially, when compound **9** was oxidized with 1.0 equiv. of trichloroisocyanuric acid in the presence of catalytic TEMPO in CH_2Cl_2, the byproduct lactone **10** was formed even the oxidation was carried out at −5 °C. This result showed that compound **9** was overoxidized under Giacomelli's reaction condition. To obtain the single lactone **10**, the oxidation of **9** with 2.0 equiv. of trichloroisocyanuric acid and catalytic TEMPO was carried out. We were pleased to find that the single product **10** was isolated in 72% yield. Treatment of lactone **10** with DIBAL-H allowed efficient reduction of the lactone as well as removal of the benzoyl group to give 4-*O*-benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3,3-difluoro-D-ribohexose **11** in 73% yield as a 4:1 mixture of anomers determined by ^{19}F NMR. Finally, compound **11** was deprotected by treatment with 4 M HCl and followed by hydrogenation in the presence of Pd/C to furnish the target molecule 3-deoxy-3,3-difluoro-D-ribohexose **1** in 83% yield as a 4:1 mixture of anomers.

In summary, a novel *gem*-difluorinated sugar 3-deoxy-3,3-difluoro-D-ribohexose **1** has been synthesized from *gem*-difluoromethylene-containing building block **2**. The method was divergent and stereocontrolled and could be easily expanded to synthesize other similar *gem*-difluorinated sugars.

3. Experimental

3.1. General

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Reactions requiring anhydrous conditions were performed in vacuum flame-dried glassware under nitrogen atmosphere. NMR spectra were recorded on either 300 MHz (^1H NMR), 75 MHz (^{13}C NMR) or 282 MHz (^{19}F NMR, $FCCl_3$ as outside standard and low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz.

3.2. (2R,4R,5R)-4-O-Benzyl-3,3-difluoro-5,6-O-isopylidenehexane-1,2,4,5,6-pentol (**5**) and (2S,4R,5R)-4-O-benzyl-3,3-difluoro-5,6-O-isopylidenehexane-1,2,4,5,6-pentol (**6**)

To a suspension of NaH (60% in oil, 0.277 g, 6.94 mmol) and Bu_4NI (0.325 g, 0.85 mmol) in anhydrous THF (36 mL) was added a solution of compound **2** (1.803 g, 8.55 mmol) in anhydrous THF (18 mL) slowly at 0 °C. After the mixture was stirred for 20 min at 0 °C. The reaction mixture was stirred at room temperature for 30 min. Then the reaction mixture was cooled to 0 °C and treated with BnBr (1.08 mL, 9.10 mmol) in anhydrous THF (11 mL) and stirred at room temperature overnight. Water was added and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 10:1) to give 2.002 g (78.5% yield) of benzyl protected product (*anti*/*syn* = 21.8/1) as a clear oil and 0.353 g of recovered compounds **2** (*anti*/*syn* = 1.8/1, 19.6% recovery). Then to a solution of the benzyl ether (2.002 g, 6.71 mmol) in acetone (40 mL) was added NMNO (1.723 g, 12.75 mmol), followed by addition of water (8 mL) at room temperature with stirring. Then a catalytic amount of OsO_4 (5–10 mol%) solution in water (4% solution) was added. After the reaction mixture was stirred at room temperature for 48 h. The reaction was quenched with saturated $NaHSO_3$ solution. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with 1N HCl, then saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 1:1) to give 1.052 g (37.5% yield from compound **2**) of compound **5** as a white solid and 1.048 g (37.5% yield from compound **2**) of compound **6** as a white solid. Compound **5**: solid, mp 82–83 °C; $[\alpha]_D^{20} = +12.4°$ (*c* 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.35 (m, 5H), 4.93 (d, J = 10.8 Hz, 1H), 4.80 (d, J = 10.8 Hz, 1H), 4.49–4.45 (m, 1H), 4.28 (ddd, J = 22.6 Hz, 5.7 Hz, 2.5 Hz, 1H), 4.10–3.99 (m, 3H), 3.81 (s, 2H), 1.46 (s, 3H), 1.32 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −119.4 (dd, J = 265.6 Hz, 25.9 Hz), −121.3 (dd, J = 265.6 Hz, 21.0 Hz, 19.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.37, 128.57, 128.15, 128.08, 122.04, 108.49, 75.78 (dd, J_{C-F} = 28.6 Hz, 23.1 Hz), 75.66, 74.47, 69.53 (dd, J_{C-F} = 31.3 Hz, 23.6 Hz), 64.62 (d, J_{C-F} = 6.0 Hz), 60.27 (t, J_{C-F} = 3.6 Hz), 26.20, 24.99; MS *m*/*z* 317 (1), 101 (46), 91 (100); IR (thin film) υ_{max} 3341, 1500, 1455, 1230 cm^{-1}; Anal. Calcd for $C_{16}H_{22}O_5F_2$: C, 57.82; H, 6.67. Found: C, 57.74; H, 6.66. Compound **6**: solid, mp 46–48 °C; $[\alpha]_D^{20} = +22.9°$ (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5H), 4.82 (d, J = 11.1 Hz, 1H), 4.78 (d, J = 11.1 Hz, 1H), 4.38 (q, J = 6.0 Hz, 1H), 4.12–4.09 (m, 2H), 4.04–3.96 (m, 2H), 3.80 (d, J = 5.4 Hz, 2H), 2.97 (br, 2H), 1.45 (s, 3H), 1.37 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.7 (dt, J = 268.3 Hz, 8.7 Hz), −120.6 (dt, J = 268.3 Hz, 16.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.08, 128.54, 128.20, 121.79 (dd, J_{C-F} = 252.9 Hz, 248.9 Hz), 109.36, 77.52 (dd, J_{C-F} = 47.8 Hz, 23.6 Hz), 75.68, 74.26, 71.36 (dd, J_{C-F} = 28.8 Hz, 24.0 Hz), 65.73, 60.76, 26.23, 24.92; MS *m*/*z* 317 (1), 101 (41), 91 (100); IR (thin film) υ_{max} 3423, 1499, 1456 cm^{-1}; Anal. Calcd for $C_{16}H_{22}O_5F_2$: C, 57.82; H, 6.67. Found: C, 57.71; H, 6.57.

3.3. (2S,4R,5R)-4-O-Benzyl-1,2-O-bis-(tert-butyldimethylsilyl)-3,3-difluoro-5,6-O-isopylidenehexane-1,2,4,5,6-pentol (**7**)

To a solution of **6** (853 mg, 2.70 mmol) and DMAP (660 mg, 5.40 mmol) in DMF (1.4 mL) at 0 °C was added imidazole (919 mg, 13.50 mmol), followed by TBDMSCl (2034 mg, 13.50 mmol). Then, the mixture was warmed to room temperature and stirred over night. EtOAc (100 mL) was added and the resulting mixture was washed with brine (3× 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 50:1) to afford **7** (1423 mg, 94%) as a clear oil: $[\alpha]_D^{25} = +5.3$ (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.30 (m, 5H), 4.97 (d, J = 10.5 Hz, 1H), 4.72 (d, J = 11.1 Hz, 1H), 4.53–4.48 (m, 1H), 4.33 (ddd, J = 22.5 Hz, 6.3 Hz, 2.1 Hz, 1H), 4.12 (t, J = 8.1 Hz, 1H), 4.06–3.95 (m, 2H), 3.76 (dt, J = 11.4 Hz, 2.4 Hz, 1H), 3.63–3.57 (m, 1H), 1.43, 1.39 (2s, 6H), 0.94, 0.84 (2s, 18H), 0.14, 0.12, −0.03, −0.04 (4s, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −108.6 (dt, J = 264.8, 15.2 Hz, 1F), −118.8 (dd, J = 263.7, 23.1 Hz, 1F); MS (ESI) *m*/*z* 561.2 (M + H$^+$), 578.2 (M + NH_4^+); IR (thin film) υ_{max} 2957, 2860, 1473, 1381, 1257, 1137, 1058, 836 cm^{-1}; Anal. Calcd for $C_{28}H_{50}F_2O_5Si_2$: C, 60.02; H, 8.99. Found: C, 60.02; H, 8.98.

3.4. (2S,4R,5R)-4-O-Benzyl-1,2-O-bis-(tert-butyldimethylsilyl)-3,3-difluorohexane-1,2,4,5,6-pentol (**8**)

A mixture of compound **7** (1380 mg, 2.46 mmol) and tin(II) chloride (1242 mg, 4.92 mmol) were in anhydrous CH_2Cl_2 was stirred at room temperature for 0.5 h. The reaction was monitored by TLC with hexanes/EtOAc (4/1). The undissolved tin chloride was removed by filtration, and the filtrate was neutralized with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4. After the solvent was removed, the residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 3:1) to give **7** (1114 mg, 87%) as a clear oil: $[\alpha]_D^{25} = +10.5$ (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.30 (m, 5H), 4.82 (d, J = 10.5 Hz, 1H), 4.72 (d, J = 10.8 Hz, 1H), 4.01–3.93 (m, 3H), 3.82–3.71 (m, 4H), 2.87 (br, 2H), 0.93, 0.90 (2s, 18H), 0.16, 0.15 (2s, 6H), 0.06 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −112.5 (dt, J = 268.2, 9.3 Hz, 1F), −114.3 (dt, J = 265.6, 14.4 Hz, 1F); MS (ESI) *m*/*z* 521.1 (M + H$^+$), 543.0 (M + Na$^+$); IR (thin film) υ_{max} 3301, 2931, 2859, 1473, 1256, 1139, 1051, 838 cm^{-1}; Anal. Calcd for $C_{28}H_{50}F_2O_5Si_2$: C, 57.71; H, 8.91. Found: C, 57.87; H, 8.75.

3.5. (2S,4R,5R)-4-O-Benzyl-6-O-benzoyl-2-O-(tert-butyldimethylsilyl)-3,3-difluorohexane-1,2,4,5,6-pentol (**9**)

To a solution of compound **8** (1040 mg, 2.00 mmol) in anhydrous CH_2Cl_2 (10 mL) and pyridine (5 mL) was slowly added a solution of BzCl (0.22 mL, 2 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C. After the mixture was stirred at the same temperature for 2 h, MeOH (2 mL) was added and the mixture was stirred for 30 min. Then water was added to quench the reaction. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with 1N HCl, saturated aqueous $NaHCO_3$ and brine. After the resultant solution was dried over anhydrous Na_2SO_4 and filtered, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 12:1) to give 1.142 g product with the primary hydroxyl protected by benzoyl group. This compound then was dissolved in MeOH (30 mL), cooled to 0 °C and *p*-TsOH (348 mg, 1.83 mmol) was added. The reaction was stirred at 0 °C for 2 h and then partitioned between EtOAc (60 mL) and saturated aqueous $NaHCO_3$ and saturated aqueous NaCl (15 mL each). The aqueous layer was separated and washed with EtOAc (30 mL each). The organic layers were combined and washed with saturated aqueous NaCl (30 mL). The organic extracts were then dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by silica gel column chromatography (petroleum ether:ethyl acetate = 3:1) afforded **9** (541 mg) as a clear oil: $[\alpha]_D^{27}$ = +36.7 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.5 Hz, 2H), 7.40 (t, J = 7.2 Hz, 1H), 7.28 (d, J = 7.5 Hz, 2H), 7.18–7.12 (m, 5H), 4.68 (d, J = 11.1 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H), 4.50–3.35 (m, 2H), 4.20–4.15 (m, 1H), 4.05–3.91 (m, 2H), 3.67 (dd, J = 12.0 Hz, 3.6 Hz, 1H), 3.59 (dd, J = 11.7 Hz, 5.4 Hz, 1H), 2.44 (br, 2H), 0.77 (s, 9H), 0.00, −0.01 (2s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −113.0 (dd, J = 27.3, 13.8 Hz, 2F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.9, 136.9, 133.1, 129.7, 128.5, 128.4, 128.2, 128.1, 122.0 (t, J_{C-F} = 251.1 Hz), 78.5 (t, J_{C-F} = 23.5 Hz), 75.6, 74.5 (t, J_{C-F} = 27.2 Hz), 69.5 (t, J_{C-F} = 2.7 Hz), 66.3 (t, J_{C-F} = 2.6 Hz), 62.5 (t, J_{C-F} = 4.3 Hz), 25.7, 18.1, −4.8, −5.0; MS (ESI) *m*/*z* 511.2 (M + H^+), 533.2 (M + Na^+); IR (thin film) υ_{max} 3462, 2935, 2859, 1723, 1457, 1278, 1126, 838 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{36}F_2O_6SiNa$ 533.2141, found 533.2145.

3.6. (2S,4R,5R)-4-Benzyloxy-6-benzoyloxy-2-(tert-butyldimethylsilyloxy)-3,3-difluorotetrahydropyran-2-one (**10**)

2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO) (0.4 mg, 0.025 mmol) was added at 0 °C to a solution of compound **9** (615 mg, 1.21 mmol) and trichloroisocyanuric acid (TCCA) (562 mg, 2.42 mmol) in methylene chloride (20 mL). The reaction mixture was stirred for 15 min at room temperature and then filtered. The solvent was removed in vacuo and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 6:1) to afford **10** (440 mg, 72%) as a clear oil: $[\alpha]_D^{25}$ = +100.0 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.40 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 2H), 7.15–6.97 (m, 5H), 4.78 (d, J = 11.1 Hz, 1H), 4.49–4.38 (m, 3H), 4.31 (dd, J = 12.3 Hz, 3.3 Hz, 1H), 4.16 (dd, J = 17.4 Hz, 4.8 Hz, 1H), 3.88–3.78 (m, 3H), 0.77 (s, 9H), 0.03, 0.00 (2s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.5 (dt, J = 246.5 Hz, 5.9 Hz, 1F), −118.7 (dd, J = 246.2 Hz, 13.5 Hz, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (dd, J_{C-F} = 8.1 Hz, 2.4 Hz), 165.6, 135.8, 133.4, 129.7, 129.2, 128.6, 128.4, 117.9 (dd, J_{C-F} = 257.2 Hz, 249.8 Hz), 75.3 (dd, J_{C-F} = 6.0 Hz, 1.9 Hz), 75.0 (d, J_{C-F} = 3.1 Hz), 71.8 (dd, J_{C-F} = 23.5 Hz, 19.3 Hz), 71.4 (dd, J_{C-F} = 21.1 Hz, 16.5 Hz), 61.8, 25.4, 18.3, −4.9, −5.6; MS (ESI) *m*/*z* 507.2 (M + H^+), 524.3 (M + NH_4^+); IR (thin film) υ_{max} 2931, 2860, 1778, 1727, 1454, 1267, 1168, 841 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{32}F_2O_6$-SiNa 529.1828, found 529.1831.

3.7. 4-O-Benzyl-2-O-(tert-butyldimethylsilyl)-3-deoxy-3,3-difluoro-D-ribohexose (**11**)

To a solution of **10** (360 mg, 0.71 mmol) in anhydrous CH_2Cl_2 (15 mL) was added a 1 M solution of DIBALH in cyclohexane (3.0 mL, 3.0 mmol) dropwise at −78 °C. The reaction mixture was stirred at this temperature for 1 h. MeOH (10 mL) was added dropwise, and the mixture was allowed to warm to rt. The resultant suspension was filtered through Celite, and the filter was washed with MeOH (3× 20 mL). The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 2:1) to afford **11** (210 mg, 73%) as a clear oil: $[\alpha]_D^{26}$ = +47.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ, major 7.35–7.30 (m, 5H), 4.92 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 7.5 Hz, 1H), 4.64 (d, J = 11.7 Hz, 1H), 3.87–3.49 (m, 6H), 1.77 (s, 2H), 0.93 (s, 9H), 0.15 (s, 6H), minor 7.35–7.30 (m, 5H), 5.14 (s, 1H), 4.75–4.64 (m, 2H), 3.87–3.49 (m, 6H), 1.77 (s, 2H), 0.93 (s, 9H), 0.15 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ, major −111.8 (d, J = 243.9 Hz, 1F), −132.3 (dt, J = 243.1 Hz, 18.6 Hz, 1F), minor −108.9 (d, J = 245.9 Hz, 1F), −127.1 (dt, J = 247.0 Hz, 19.5 Hz, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ, major 136.9, 128.5, 128.3, 128.2, 120.1 (t, J_{C-F} = 251.3 Hz), 95.7 (d, J_{C-F} = 9.8 Hz), 74.8 (t, J_{C-F} = 3.2 Hz), 74.4 (t, J_{C-F} = 18.5 Hz), 74.1 (t, J_{C-F} = 18.5 Hz), 73.5 (d, J_{C-F} = 7.5 Hz), 61.4, 25.6, 18.3, −4.6, −5.1 (d, J_{C-F} = 1.7 Hz), minor 137.0, 128.5, 128.3, 128.2, 120.1 (t, J_{C-F} = 251.3 Hz), 92.6 (d, J_{C-F} = 8.0 Hz), 74.9 (t, J_{C-F} = 3.9 Hz), 73.5 (t, J_{C-F} = 18.4 Hz), 74.4 (dd, J_{C-F} = 19.1 Hz, 17.7 Hz), 69.1 (d, J_{C-F} = 6.8 Hz), 61.1, 25.5, 18.1, −5.0 (d, J_{C-F} = 2.0 Hz), −5.2; MS (ESI) *m*/*z* 422.2 (M + NH_4^+), 427.2 (M + Na^+); IR (thin film) υ_{max} 3400, 2931, 1706, 1473, 1362, 1249, 1099, 840 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{30}F_2O_5SiNa$ 427.1723, found 427.1723.

3.8. 3-Deoxy-3,3-difluoro-D-ribohexose (**1**)

To a solution of **11** (96 mg, 0.24 mmol) in THF (6 mL) was added 4 M HCl (4 mL). The reaction mixture was stirred at room temperature for 4 h. Then the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (ethyl acetate:MeOH = 10:1) to afford 62 mg product. A suspension of Pd/C (62 mg) and the above product

in MeOH (10 mL) was stirred under a hydrogen atmosphere over night. Filtration and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 5:1) to give **1** (54 mg, 83%) as an oil: $[\alpha]_D^{22}$ = +28.2 (*c* 0.50, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ, major 4.62 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 3.85 (dt, J = 12.0 Hz, 1.8 Hz, 1H), 3.78–3.62 (m, 3H), 3.47–3.36 (m, 1H), minor 5.20 (t, J = 4.8 Hz, 1H), 3.94 (dt, J = 10.2 Hz, 3.3 Hz, 1H), 3.78–3.62 (m, 1H), 3.47–3.36 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ, major −118.2 (dt, J = 242.2 Hz, 4.5 Hz, 1F), −137.3 (dd, J = 242.5 Hz, 20.9 Hz, 1F), minor −115.0 (ddd, J = 239.7 Hz, 10.2 Hz, 4.8 Hz, 1F), −132.3 (dt, J = 240.8 Hz, 19.2 Hz, 1F); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ, major 121.0 (dd, J_{C-F} = 250.7 Hz, 243.5 Hz), 96.8 (d, J_{C-F} = 9.7 Hz), 76.1 (d, J_{C-F} = 7.0 Hz), 74.1 (t, J_{C-F} = 19.3 Hz), 69.1 (t, J_{C-F} = 20.2 Hz), 62.1 (d, J_{C-F} = 1.7 Hz), minor 120.9 (dd, J_{C-F} = 249.0 Hz, 247.6 Hz), 93.3 (dd, J_{C-F} = 9.2 Hz, 2.0 Hz), 71.1 (d, J_{C-F} = 6.8 Hz), 70.5 (t, J_{C-F} = 19.6 Hz), 68.7 (t, J_{C-F} = 19.9 Hz), 61.9 (d, J_{C-F} = 1.1 Hz); MS (ESI) *m*/*z* 218.2 ($M + NH_4^+$), 223.2 ($M + Na^+$); IR (thin film) υ_{max} 3476, 2942, 1636, 1418, 1340, 1233, 1156, 847 cm^{-1}; HRMS (ESI) calcd for $C_6H_{10}F_2O_5Na$ 223.0388, found 223.0386.

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