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A New Method for the Selective Introduction of Difluoromethyl and Trifluoromethyl Groups into Sugar Moieties

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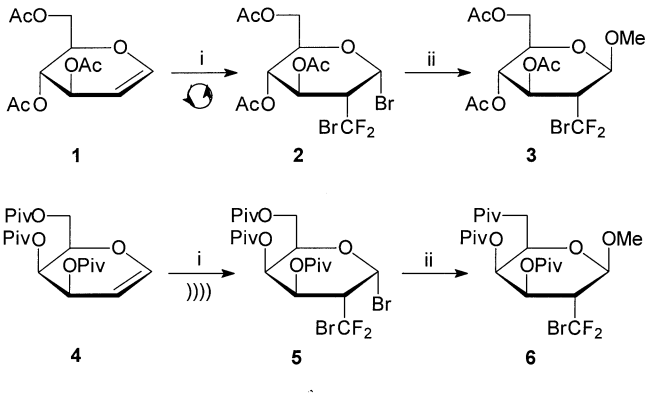
We have studied the fluoroalkylation of the glucal **1** and the galactal **4** with dibromodifluoromethane via the 2-*C*-bromodifluoromethyl-substituted glycosyl bromides **2** and **5**, respectively, followed by glycosylation to the methyl ß-D-glycosides **3** and **6**. The bromodifluoromethyl groups in the 2 position of the compounds **3** and **6** were converted into difluoromethyl and trifluoromethyl groups, respectively, giving the fluorinated monosaccharides **7**−**10**.

Interest in the fluorinated analogues of natural substances is increasing continuously[2][3] because the introduction of fluorine or fluoroalkyl groups may significantly modify the chemical, physical and biological properties of such substances. Carbohydrates containing trifluoromethyl or difluoromethyl groups may be regarded as very useful tools, e.g. for in vivo ^{19}F-NMR spectroscopy or for other biomedical purposes. Some perfluoroalkyl-substituted amphiphiles show interesting surface activity behaviour and transport properties[4][5]. 2-*C*-difluoromethyl- and 2-*C*-trifluoromethyl-substituted carbohydrate moieties of physiologically interesting glycosides may be attractive, because the strong electron-withdrawing group in the 2 position also stabilises the neighbouring anomeric centre. Only four reports have so far been published which describe the syntheses of 2-*C*- and 3-*C*-trifluoromethyl-substituted sugars[6][7][8][9]. In all cases, the choice of effective methods suitable for a selective introduction of difluoromethyl or trifluoromethyl groups[10] into natural substances is small. One of the most convenient procedures known, the addition of fluoroalkyl halides to olefins in the presence of dithionite[11], has found application in carbohydrate chemistry[12][13]. We have tried to reproduce additions of fluoroalkyl iodides (C_4−C_8) to 3,4,6-tri-*O*-acetyl-D-glucal (**1**) described by W.-Y. Huang, Y. Xie[12]; however, we observed only low conversions. In a second paper W.-Y. Huang et al.[14] reported the fluoroalkylation of aliphatic olefins with dibromodifluoromethane supported by dithionite. We found that this reaction can also be applied in carbohydrate chemistry using glycals as substrates. However, it is not yet certain whether such reactions are radical processes, as was assumed by W.-Y. Huang et al.[14], because equivalents of sodium dithionite are necessary to achieve a high conversion.

Scheme 1



Piv = Pivaloyl; i = CF_2Br_2 / $Na_2S_2O_4$ / $NaHCO_3$ (MeCN / H_2O), 0°C – r.t.; ii = MeOH / Ag_2CO_3, r.t.

We investigated the addition of dibromodifluoromethane to the glucal **1** and the galactal **4** in acetonitrile/water (5:3 v/v) stimulated by sodium dithionite (Scheme 1). Under these conditions the 3,4,6-tri-*O*-acetyl-D-glucal (**1**) generates the 3,4,6-tri-*O*-acetyl-2-bromodifluoromethyl-2-deoxy-α-D-glucopyranosyl bromide (**2**) as the major product. This compound is relatively unstable and its identification was therefore based only on the evaluation of the NMR spectra of the crude product. The latter was converted into the methyl β-D-glucoside **3** by adding to a methanolic suspension of silver carbonate (Scheme 1). After column chromatographic purification the compound **3** (overall yield of 45−52% relative to the glucal **1**) was still slightly contaminated by some by-product. After recrystallisation from methanol/water the pure glucoside **3** was obtained. The analogous synthesis of the corresponding D-galactose de-

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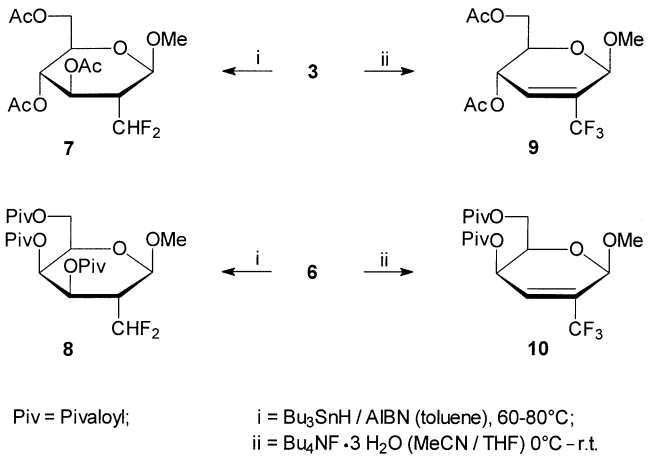
rivative from 3,4,6-tri-*O*-acetyl-D-galactal cannot be recommended because the purification of the desired product (syrup) is very difficult[15]. Such problems do not occur when 3,4,6-tri-*O*-pivaloyl-D-galactal (**4**) is used instead of the acetyl derivative, because the pivaloyl protecting groups obviously improve the ability to crystallize. The lower solubility of the pivaloyl derivative **4** in the acetonitrile/water system was counteracted by increasing the acetonitrile/water ratio to 7:3 v/v. The rate of the reaction of dibromodifluoromethane with the galactal **4** generating the galactosyl bromide **5** was lower than that with the acetylated derivative, although only very small amounts of by-products were observed. This is due to an increased stability of the starting material **4** as well as of the resulting glycosyl bromide **5** compared to the acetylated glucose derivatives **1** and **2**. In a further experiment we investigated the possibility of reducing the reaction time of the alkylation reaction by sonication using an ultrasonic cleaning bath. It was found that the reaction is effectively accelerated by ultrasound. The starting material **4** was completely converted after 1.5 hours at 8−10°C and the yield of **5** was virtually the same as under stirring (Scheme 2). In contrast, the sonochemical alkylation of the 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with dibromodifluoromethane gave a reduced yield of **2** and the corresponding reaction of 3,4,6-tri-*O*-pivaloyl-D-glucal was less selective[15].

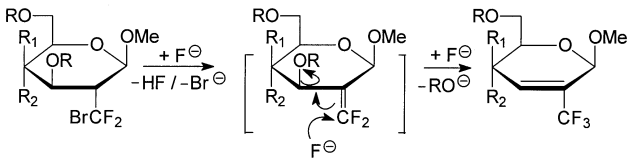
By analogy to the glucosyl bromide **2**, the galactosyl bromide **5** was converted into the methyl 2-bromodifluoromethyl-2-deoxy-3,4,6-tri-*O*-pivaloyl-β-D-galactopyranoside (**6**) by reaction with methanol in the presence of silver carbonate (Scheme 1). The crystalline product **6** was isolated in pure form after recrystallisation of the crude product from methanol with a yield of 61%.

Scheme 2



Compounds such as **3** and **6** are not only attractive building blocks (e.g. for C−C linking) but they should also be suitable precursors for syntheses of 2-deoxy-2-difluoromethyl or 2-deoxy-2-trifluoromethyl derivatives of sugars. Therefore, we studied the reactivity of the bromodifluoromethyl groups of glycosides **3** and **6** for the replacement of the bromine atom by hydrogen and fluorine, respectively. The hydrogen for bromide exchange proceeded successfully by treatment of the glycosides **3** and **6** with tributylstannane in toluene. The resulting 2-deoxy-2-difluoromethyl derivatives **7** and **8** were obtained in yields of > 80% (Scheme 2). The introduction of the third fluorine atom was achieved by treatment of the compounds **3** or **6** with an excess of tetrabutylammonium fluoride trishydrate (TBAF·3H_2O) in acetonitrile (Scheme 2). C. Wakselman et al.[16] have described a similar halogen exchange on 2-halodifluoromethyl-cyclohexanones using TBAF·3H_2O. We isolated the methyl 4,6-di-*O*-acyl-2,3-dideoxy-2-trifluoromethyl-β-D-hex-2-enopyranosides **9** and **10** in good yields (≈ 75%). However, it is noticeable that the rate and the yield of this fluorination reaction depend very strongly on the quality of the TBAF hydrate used.

Scheme 3



The pathway for the formation of the trifluoromethyl derivatives **9** and **10** from **3** and **6**, respectively, may be described as shown in Scheme 3. The relatively strong basic fluoride ion of TBAF supports the elimination of HBr by deprotonation of the 2 position. Subsequently, addition of a fluoride ion occurs to the exocyclic difluoromethylene group with simultaneous abstraction of the acylate function in the 3 position and formation of the double bond. The pseudoglycals **9** and **10** are interesting fluorinated "building blocks", e.g. for syntheses of bioactive substances via cycloadditions.

The structures of the compounds **3** and **6** were confirmed by X-ray analysis; Figure 1 shows the molecular structure of the acetylated compound **3** (for detailed solution data see Table 1). Moreover, the compounds **3**, and **6**−**10** are supported by their ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra. The small 1-H/2-H coupling constants of the intermediates **2** ($J \approx 3.3$ Hz) and **5** ($J \approx 3.1$ Hz) indicate an α-D-*gluco* and α-D-*galacto* configuration for the glycosyl bromides. The relatively large 1-H/2-H coupling constants of the compounds **3** ($J \approx 6.7$ Hz), **6** ($J \approx 7.8$ Hz), **7** ($J \approx 8.5$ Hz), and **8** ($J \approx 8.9$ Hz) correspond to ß-D-*gluco*- and ß-D-*galacto*-configured sugars, i.e. the fluorine-containing groups in the 2 position are equatorially arranged. As expected, the replacement of the bromine (compounds **3** and **6**) by hydrogen (compounds **7** and **8**) causes significant changes in the chemical shifts of the fluorine atoms, of the homonuclear F/F coupling constants and of the heteronuclear 2-H/F coupling constants.

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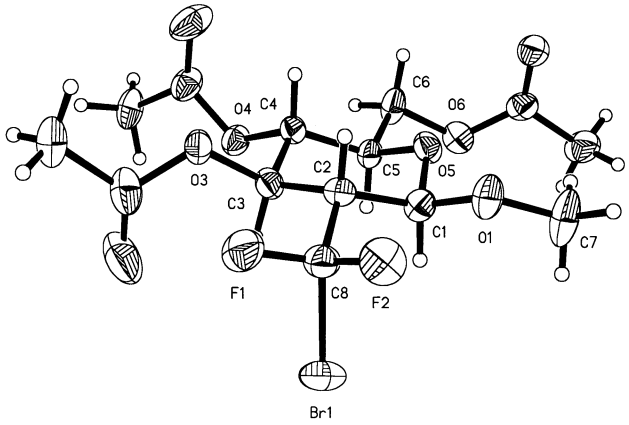
Figure 1. Molecular structure of **3** with 30% probability of the thermal ellipsoids



Selected bond lengths [Å], angles [°], and torsion angles [°]: Br1−C8 1.943(8), F1−C8 1.338(9), F2−C8 1.346(10), O5−C1 1.402(9), O5−C5 1.433(9), C1−C2 1.523(10), C2−C8 1.528(11), C2−C3 1.539(11), C3−C4 1.530(10), C4−C5 1.530(10), C5−C6 1.485(11), F1−C8−F2 105.5(7), F1−C8−Br1 106.6(5), F2−C8−Br1 106.1(5), C1−C2−C8−F1 −177.7(7), C3−C2−C8−F1 −51.1(9), C1−C2−C8−F2 63.7(9), C3−C2−C8−F2 −169.7(6)

Experimental Section

General: Column chromatography: Silica Gel 60 (63−200 μm, Merck). − Thin-layer chromatography (TLC): Silica Gel foils 60 F_{254} (Merck). − Sonication: Ultrasonic bath Sonorex RK 102 H (Bandelin), 35 kHz, 2 × 120 W. − NMR spectra: Bruker AC 250 and ARX 300 equipment, ^{1}H NMR and ^{13}C{^{1}H} NMR referred to TMS, ^{19}F{^{1}H} NMR, referred to $CFCl_3$. − Melting points: Polarizing microscope Leitz (Laborlux 12 Pol) equipped with a hot stage (Mettler FP 90). − Chemicals: TBAF trishydrate 1.1 M solution in THF (Aldrich), tributylstannane (Fluka), AIBN (Fluka), and CBr_2F_2 (Fluka).

For the crystals of **3** and **6** rotational photos were taken and eleven reflections chosen for the centering routine in order to find reasonable reduced cells with which to start. The data collection was done in routine ω-scan; the structures were solved by direct methods (Siemens SHELXTL, **1990**, Siemens Analytical X-ray Inst. Inc.) and refined by the full-matrix least-squares method of Siemens SHELXTL, Ver. 5.03. All non-hydrogen atoms were refined anisotropically. Attempts using empirical absorption correction calculations did not lead to improved final results. The hydrogen positions were refined using the riding model. For **6** the refinement was influenced by disorder phenomena in two pivaloyl groups. Best results were obtained with a ratio of 88 to 12% for the different positions. However, the split positions had to be calculated using distance restraints. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (depository number CCDC-100873). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +(1223)336033, e-mail: teched@chemcrys.cam.ac.uk].

Methyl 3,4,6-tri-O-acetyl-2-bromodifluoromethyl-2-deoxy-β-D-glucopyranoside (**3**): To a vigorously stirred solution of 3,4,6-tri-O-acetyl-D-glucal (**1**)[17] (0.54 g 2.0 mmol), $Na_2S_2O_4$ (0.63 g, 3.2 mmol) and $NaHCO_3$ (0.6 g, 7.2 mmol) in CH_3CN (5 ml)/water (3 ml) placed in an argon-flushed Schlenk flask CF_2Br_2 (1.3 g, 6.0 mmol) was added at 0°C. Under stirring the mixture was allowed slowly to warm up to room temperature during 2 hours and the procedure was continued for further 4 hours. Subsequently, diethyl ether (40 ml) was added and the mixture was washed with saturated NaCl solution (20 ml) and water. The separated ether phase was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. After drying under reduced pressure (temp. below 40°C) the syrupy residue (crude product **2**) was dissolved in 15 ml of dry methanol followed by addition of 0.5 g of drierite. The mixture was stirred for 1 h. During this time 0.45 g (1.6 mmol) of Ag_2CO_3 were added in small portions. After filtration of the solution the solvent was removed and the residue purified by column chromatography (R_f = 0.22, eluent: heptane/ethyl acetate = 7/3) giving the bromodifluoromethyl derivative **3** which still contained small amounts of impurities. The pure compound **3** was obtained after recrystallisation from methanol containing some water in a yield of 0.39 g (45%); m. p. 91−92°C. $[\alpha]_D^{20}$ = +23.73 (c = 1.13, $CHCl_3$). − ^{1}H NMR (250.1 MHz, $CDCl_3$): 5.48 (ddd, $^3J_{3\text{-H},4\text{-H}} \approx$ 8.9 Hz, $^3J_{3\text{-H},2\text{-H}} \approx$ 9.7 Hz, $^4J_{3\text{-H,F}} \approx$ 1.2 Hz, 1 H, 3-H), 5.12 (dd, $^3J_{3\text{-H},4\text{-H}} \approx$ 8.9 Hz, $^3J_{4\text{-H},5\text{-H}} \approx$ 10.1 Hz, 1 H, 4-H), 4.65 (d, $^3J_{1\text{-H},2\text{-H}} \approx$ 6.7 Hz, 1 H, 1-H), 4.27 (dd, $^3J_{5\text{-H},6a\text{-H}} \approx$ 5.1 Hz, $^2J_{6a\text{-H},6b\text{-H}} \approx$ 12.3 Hz, 1 H, 6a-H), 4.11 (dd, $^3J_{5\text{-H},6b\text{-H}} \approx$ 2.7 Hz, $^2J_{6a\text{-H},6b\text{-H}} \approx$ 12.3 Hz, 1 H, 6b-H), 3.77 (ddd, $^3J_{4\text{-H},5\text{-H}} \approx$ 10.1 Hz, $^3J_{5\text{-H},6a\text{-H}} \approx$ 5.1 Hz, $^3J_{5\text{-H},6b\text{-H}} \approx$ 2.7 Hz, 1 H, 5-H), 3.53 (s, 3 H, OMe), 2.65 (m[18], $^3J_{2\text{-H,Fa,b}} \approx$ 6.1 Hz, 8.4 Hz, 1 H, 2-H), 2.07, 2.01, 2.00 (all s, 9 H, 3 OAc). − ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 170.6, 169.7, 169.5 (all s, 3 CO), 121.4 (dd, $^1J_{\text{C,Fa,b}} \approx$ 310.0 Hz, 312.1 Hz, CF_2Br), 101.5 (d, $^3J_{\text{C-1,F}} \approx$ 5.7 Hz, C-1), 71.7 (s, C-5), 69.1 (d, $^3J_{\text{C-3,F}} \approx$ 3.7 Hz, C-3), 68.6 (d, $^4J_{\text{C-4,F}} \approx$ 2.0 Hz, C-4), 62.3 (s, C-6), 57.1 (s, OMe), 55.8 (dd, $^2J_{\text{C-2,Fa,b}} \approx$ 19.1 Hz, 16.2 Hz, C-2), 20.7, 20.6, 20.6 (all s, 3 MeCO). − ^{19}F{^{1}H} NMR (235.4 MHz, $CDCl_3$): −39.8 (d, $^2J_{\text{Fa,Fb}} \approx$ 169.0 Hz, Fa), −43.8 (d, $^2J_{\text{Fa,Fb}} \approx$ 169.0 Hz, Fb) (Note: which heteronuclear coupling constants belong to Fa and which to Fb was not determined); $C_{14}H_{19}BrF_2O_8$ (433.2) calcd. C 38.82 H 4.42 Br 18.45; found: C 38.79 H 4.36 Br 18.25.

Methyl 3,4,6-Tri-O-pivaloyl-2-bromodifluoromethyl-2-deoxy-β-D-galactopyranoside (**6**): To a solution of 3,4,6-tri-O-pivaloyl-D-galactal (**4**)[19] (1.0 g 2.5 mmol), $Na_2S_2O_4$ (0.63 g, 3.2 mmol) and $NaHCO_3$ (0.6 g, 7.2 mmol) in CH_3CN (7 ml)/water (3 ml) placed in an argon-flushed Schlenk flask CF_2Br_2 (2.0 g, 9.5 mmol) was added at 0°C. The mixture was then sonicated in an ultrasonic bath for 1.5 hours at 8−10°C (bath temperature). The work-up procedure for the intermediate (galactosyl bromide **5**) and the following glycosylation were carried out as described for compound **3**. After column chromatographic separation (R_f = 0.22, eluent: heptane/ethyl acetate = 15/1) compound **6** was recrystallised from methanol. Yield: 0.85 g (61%). m. p. 141−142°C. $[\alpha]_D^{20}$ = +11.11 (c = 1.08, $CHCl_3$). − ^{1}H NMR (250.1 MHz, $CDCl_3$): 5.30−5.39 (m, 2 H, 3-H, 4-H), 4.61 (d, $^3J_{1\text{-H},2\text{-H}} \approx$ 7.3 Hz, 1 H, 1-H), 3.96−4.22 (m, 3 H, 5-H, 6a-H, 6b-H), 3.53 (s, 3 H, OMe), 2.67 (ddt, $^3J_{2\text{-H},1\text{-H}} \approx$ 7.3 Hz, $^3J_{2\text{-H,Fa,b,3-H}} \approx$ 6.6 Hz, 6.6 Hz, 10.5 Hz, 1 H, 2-H), 1.23, 1.17, 1.12 (all s, 27 H, 3 OPiv). − ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 177.9, 176.7, 176.7 (all s, 3 CO), 121.4 (dd, $^1J_{\text{C,Fa,b}} \approx$ 310.5 Hz, 312.3 Hz, CF_2Br), 101.8 (d, $^3J_{\text{C-1,F}} \approx$ 6.4 Hz, C-1), 71.1 (s, C-5), 68.9 (d, $^3J_{\text{C-3,F}} \approx$ 4.1 Hz, C-3), 65.0 (s, C-4), 61.4 (s, C-6), 57.1 (s, OMe), 51.6 (dd, $^2J_{\text{C-2,Fa,b}} \approx$ 18.5 Hz, 16.2 Hz, C-2), 39.1, 38.7, 38.7 (all s, 3 quarternary pivaloyl C), 27.1, 27.1, 26.9 (all s, 9 pivaloyl CH_3). − ^{19}F{^{1}H} NMR (235.4 MHz, $CDCl_3$): −36.9 (d, $^2J_{\text{Fa,Fb}} \approx$ 170.0 Hz, Fa), −38.2 (d, $^2J_{\text{Fa,Fb}} \approx$ 170.0 Hz, Fb) (Note: which heteronuclear coupling constants belong to Fa and which to Fb was not determined); $C_{23}H_{37}BrF_2O_8$ (559.5) calcd. C 49.38 H 6.67 Br 14.28; found: C 49.35 H 6.65 Br 14.52.

Methyl 3,4,6-Tri-O-acyl-2-deoxy-2-difluoromethyl-β-D-hexopyranosides **7** or **8**: To a solution of the compounds **3** (0.43 g, 1.0

mmol) or **6** (0.56 g, 1.0 mmol) in 5 ml of dry toluene tributylstannane (0.38 g, 1.3 mmol) and of AIBN (2−5 mg) were added under an inert-gas atmosphere. The mixture was stirred for 2 h at 70°C. Subsequently, the solution was diluted with 50 ml of diethyl ether, washed with 10 ml of an aqueous solution of KF and with water. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography.

7: R_f = 0.17; eluent: heptane/ethyl acetate = 7/3; yield: 0.29 g (81%), m. p. 54−56°C (methanol), $[\alpha]_D^{20}$ = +2.34 (*c* = 1.37, $CHCl_3$). − ^{1}H NMR (250.1 MHz, $CDCl_3$): 5.96 (ddd, $^2J_{H,Fa,b} \approx$ 54.5 Hz, 55.6 Hz, $^3J_{H,2\text{-}H} \approx$ 1.3 Hz, 1 H, CF_2H), 5.48 (dd, $^3J_{3\text{-}H,4\text{-}H} \approx$ 9.2 Hz, $^3J_{3\text{-}H,2\text{-}H} \approx$ 10.9 Hz, 1 H, 3-H), 5.02 (m, 1 H, 4-H), 4.38 (d, $^3J_{1\text{-}H,2\text{-}H} \approx$ 8.5 Hz, 1 H, 1-H), 4.29 (dd, $^3J_{5\text{-}H,6a\text{-}H} \approx$ 4.8 Hz, $^2J_{6a\text{-}H,6b\text{-}H} \approx$ 12.3 Hz, 1 H, 6a-H), 4.11 (dd, $^3J_{5\text{-}H,6b\text{-}H} \approx$ 2.5 Hz, $^2J_{6a\text{-}H,6b\text{-}H} \approx$ 12.3 Hz, 1 H, 6b-H), 3.64 (ddd, $^3J_{5\text{-}H,6a\text{-}H} \approx$ 4.8 Hz, $^3J_{5\text{-}H,6b\text{-}H} \approx$ 2.5 Hz, $^3J_{4\text{-}H,5\text{-}H} \approx$ 10.1 Hz, 1 H, 5-H), 3.52 (s, 3 H, OMe), 2.37 (m[18], $^3J_{2\text{-}H,Fa,b} \approx$ 8.5 Hz, 22.4 Hz, 1 H, 2-H), 2.07, 2.01, 2.00 (all s, 9 H, 3 OAc). − ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 170.6, 169.7, 169.7 (all s, 3 CO), 114.5 (dd, $^1J_{C,Fa,b} \approx$ 245.4 Hz, 243.3 Hz, CF_2H), 99.9 (dd, $^3J_{C\text{-}1,Fa,b} \approx$ 8.6 Hz, 2.5 Hz, C-1), 71.7 (s, C-5), 69.2 (s, C-4), 67.4 (dd, $^3J_{C\text{-}3,Fa,b} \approx$ 4.8 Hz, 0.8 Hz, C-3), 62.1 (s, C-6), 57.1 (s, OMe), 48.9 (dd, $^2J_{C\text{-}2,Fa,b} \approx$ 19.2 Hz, 17.4 Hz, C-2), 20.7, 20.6, 20.5 (all s, 3 MeCO). − ^{19}F{^{1}H} NMR (235.4 MHz, $CDCl_3$): −124.7 (d, $^2J_{Fa,Fb} \approx$ 290.0 Hz, Fa), −126.9 (d, $^2J_{Fa,Fb} \approx$ 290.0 Hz, Fb) (Note: which heteronuclear coupling constants belong to Fa and which to Fb was not determined); $C_{14}H_{20}F_2O_8$ (354.3) calcd. C 47.46 H 5.69; found: C 47.66 H 5.59.

8: R_f = 0.15, eluent: heptane/ethyl acetate = 15/1; yield: 0.41 g (85%), m. p. 122−124°C (methanol), $[\alpha]_D^{20}$ = +9.17 (*c* = 1.09, $CHCl_3$). − ^{1}H NMR (250.1 MHz, $CDCl_3$): 6.02 (ddd, $^2J_{H,Fa,b} \approx$ 54.6 Hz, 55.8 Hz, $^3J_{H,2\text{-}H} \approx$ 1.2 Hz, 1 H, CF_2H), 5.27−5.36 (m, 2 H, 3-H, 4-H), 4.39 (d, broaden peaks, $^3J_{1\text{-}H,2\text{-}H} \approx$ 8.9, 1 H, 1-H), 4.17 (dd, $^3J_{5\text{-}H,6a\text{-}H} \approx$ 6.8 Hz, $^2J_{6a\text{-}H,6b\text{-}H} \approx$ 11.0 Hz, 1 H, 6a-H), 4.00 (dd, $^2J_{6a\text{-}H,6b\text{-}H} \approx$ 11.0 Hz, $^3J_{5\text{-}H,6b\text{-}H} \approx$ 6.6 Hz, 1 H, 6b-H), 3.88 (ddd, $^3J_{4\text{-}H,5\text{-}H} \approx$ 1.2 Hz, $^3J_{5\text{-}H,6a\text{-}H} \approx$ 6.8 Hz, $^3J_{5\text{-}H,6b\text{-}H} \approx$ 6.6 Hz, 1 H, 5-H), 3.52 (s, 3 H, OMe), 2.36−2.58 (m, 1 H, 2-H), 1.24, 1.17, 1.13 (all s, 27 H, 3 OPiv). − ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 177.8, 176.8, 176.8 (all s, 3 CO), 115.0 (dd, $^1J_{C,Fa,b} \approx$ 245.9 Hz, 242.2 Hz, CF_2H), 100.2 (dd, $^3J_{C\text{-}1,Fa,b} \approx$ 9.7 Hz, 1.0 Hz, C-1), 71.1 (s, C-5), 66.6 (d, $^3J_{C\text{-}3,F} \approx$ 6.4 Hz, C-3), 65.1 (s, C-4), 61.4 (s, C-6), 57.0 (s, OMe), 45.0 (dd, $^2J_{C\text{-}2,Fa,b} \approx$ 18.7 Hz, 18.0 Hz, C-2), 39.0, 38.7, 38.7 (all s, 3 Me_3C), 27.2, 27.0, 26.9 (all s, 9 CH_3). − ^{19}F{^{1}H} NMR (235.4 MHz, $CDCl_3$): −121.1 (d, $^2J_{Fa,Fb} \approx$ 292.0 Hz, Fa), −128.0 (d, $^2J_{Fa,Fb} \approx$ 292.0 Hz, Fb) (Note: which heteronuclear coupling constants belong to Fa and which to Fb was not determined); $C_{23}H_{38}F_2O_8$ (480.6) calcd. C 57.49 H 7.97; found: C 57.47 H 7.88.

Methyl 4,6-Di-O-acyl-2,3-dideoxy-2-trifluoromethyl-β-D-hex-2-enopyranosides **9 or 10**: To a stirred solution of 0.5 mmol of compound **3** or **6** in 3 ml of CH_3CN 0.5 ml of a 1.1 M solution of TBAF in THF were added at 0°C. After warming to room temperature a further equivalent of the TBAF solution was added and the mixture was stirred for 1−4 hours (TLC control). Subsequently, the solution was diluted with 40 ml of diethyl ether, washed with 5 ml of an aqueous solution of $CaCl_2$ and with water. The organic phase was separated, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography.

9: R_f = 0.3; eluent: heptane/ethyl acetate = 7/3; yield: 0.12 g (77%), syrup, $[\alpha]_D^{20}$ = +82.08 (*c* = 1.2, $CHCl_3$). − ^{1}H NMR (300.1 MHz, $CDCl_3$) (verified by simulation): 6.51 (dddq, $^3J_{3\text{-}H,4\text{-}H} \approx$ 3.9 Hz, $^4J_{3\text{-}H,F} \approx$ 1.4 Hz, $^4J_{3\text{-}H,1\text{-}H} \approx$ 1.2 Hz, $^4J_{3\text{-}H,5\text{-}H} \approx$ 0.5 Hz, 1 H, 3-H), 5.26 (dddq, $^3J_{4\text{-}H,5\text{-}H} \approx$ 4.3 Hz, $^5J_{4\text{-}H,1\text{-}H} \approx$ 1.1 Hz, $^5J_{4\text{-}H,F} \approx$ 1.9 Hz, 1 H, 4-H), 5.16 (ddq, $^4J_{1\text{-}H,F} \approx$ 0.6 Hz, $^4J_{1\text{-}H,3\text{-}H} \approx$ 1.2 Hz, $^5J_{1\text{-}H,4\text{-}H} \approx$ 1.1 Hz, 1 H, 1-H), 4.22−4.26 (m, 2 H, 6a-H, 6b-H), 4.07 (dddd, $^4J_{3\text{-}H,5\text{-}H} \approx$ 0.5 Hz, $^3J_{4\text{-}H,5\text{-}H} \approx$ 4.3 Hz, $^3J_{5\text{-}H,6a\text{-}H} \approx$ 6.2 Hz, $^3J_{5\text{-}H,6b\text{-}H} \approx$ 5.6 Hz, 1 H, 5-H), 3.48 (s, 3 H, OMe), 2.08 (s, 3 H, OAc), 2.06 (s, 3 H, OAc). − ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 170.5, 169.9 (both s, 2 CO), 131.4 (q, $^2J_{C\text{-}2,F} \approx$ 30.9 Hz, C-2), 129.5 (q, $^3J_{C\text{-}3,F} \approx$ 5.4 Hz, C-3), 121.7 (q, $^1J_{C,F} \approx$ 273.4 Hz, CF_3), 93.8 (q, $^3J_{C\text{-}1,F} \approx$ 1.4 Hz, C-1), 72.5 (s, C-5), 63.0 (s, C-4), 62.9 (s, C-6), 56.0 (s, OMe), 20.7, 20.7 (both s, 2 MeCO). − ^{19}F{^{1}H} NMR (235.4 MHz, $CDCl_3$): −65.7 (s, CF_3); $C_{12}H_{15}F_3O_6$ (312.2) calcd. C 46.16 H 4.84; found: C 46.28 H 4.88.

10: R_f = 0.25, eluent: heptane/ethyl acetate = 17/1; yield: 0.14 g (73%), syrup, $[\alpha]_D^{20}$ = −48.14 (*c* = 1.45, $CHCl_3$). − ^{1}H NMR (250.1 MHz, $CDCl_3$): 6.60−6.65 (m[18], $^3J_{3\text{-}H,4\text{-}H} \approx$ 5.0 Hz, 1 H, 3-H), 5.19−5.26 (m, 2 H, 4-H,1-H), 4.32 (dd, $^3J_{5\text{-}H,6a\text{-}H} \approx$ 7.5 Hz, $^2J_{6a\text{-}H,6b\text{-}H} \approx$ 11.3 Hz, 1 H, 6a-H), 4.21 (dd, $^3J_{5\text{-}H,6b\text{-}H} \approx$ 5.9 Hz, $^2J_{6b\text{-}H,6a\text{-}H} \approx$ 11.3 Hz, 1 H, 6b-H), 4.09 (ddd, $^3J_{4\text{-}H,5\text{-}H} \approx$ 3.5 Hz, $^3J_{5\text{-}H,6a\text{-}H} \approx$ 7.5 Hz, $^3J_{5\text{-}H,6b\text{-}H} \approx$ 5.9 Hz, 1 H, 5-H), 3.52 (s, 3 H, OMe), 1.21,1.18 (both s, 18 H, 2 OPiv). − ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$): 178.0, 177.4 (both s, 2 CO), 133.0 (q, $^2J_{C\text{-}2,F} \approx$ 30.4 Hz, C-2), 130.3 (q, $^3J_{C\text{-}3,F} \approx$ 5.3 Hz, C-3), 121.9 (q, $^1J_{C,F} \approx$ 273.3 Hz, CF_3), 95.7 (q, $^3J_{C\text{-}1,F} \approx$ 1.3 Hz, C-1), 70.6 (s, C-5), 62.3 (s, C-4), 61.7 (s, C-6), 55.8 (s, OMe), 39.0, 38.8 (both s, 2 Me_3C), 27.1, 27.0 (both s, 6 CH_3). − ^{19}F{^{1}H}-NMR (235.4 MHz, $CDCl_3$): −65.4 (s, CF_3); $C_{18}H_{27}F_3O_6$ (396.4) calcd. C 54.54 H 6.87; found: C 54.80 H 6.86.

Table 1. Crystal and structure solution data for compounds **3** and **6**

	3	**6**
Formula	$C_{14}H_{19}BrF_2O_8$	$C_{23}H_{37}BrF_2O_8$
M [g mol^{-1}]	433.20	559.44
a [Å])	10.789(2)	10.832(2)
b [Å]	7.481(1)	9.900(1)
c [Å]	11.562(2)	13.155(3)
α [°]	90	90
β [°]	98.44(1)	95.51(2)
γ [°]	90	90
V [Å^3]	923.1(3)	1404.2(4)
ρ calcd. [g cm^{-1}]	1.559	1.323
Z	2	2
Crystal system	monoclinic	monoclinic
Space group (No. I.T.)	$P2_1$ (4)	$P2_1$ (4)
F(000) e	440	584
μ (Mo-K_α) [mm^{-1}]	2.283	1.517
Radiation	λ = 0.71073 Å (Mo-K_α), graphite monochromator	
Diffractometer	Siemens P4	
Crystal size [mm]	0.2 × 0.22 × 0.4	0.4 × 0.4 × 0.76
Temperature [°C]	20	−60
Data collection mode	ω-scan	
Scan range (2Θ) [°]	3.56/44	3.78/44
hkl range	−11/11, −8/8, −12/12	−11/11, −10/10, −14/12
Measured reflections	2572	3742
Unique reflections	2238	3338
Observed reflections	1719	2793
$I \geq$	2σ(*I*)	
Refined param.	226	333
*R*1 for observed	0.0518	0.0581
*R*1 for all	0.0774	0.0749
*wR*2 for all	0.1403	0.1742
Flack x param.	0.01(2)	−0.03(2)
Goodness of Fit	1.036	1.016
Δρ (max/min) [e/Å^3]	0.244/−0.350	0.381/−0.572

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