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Synthesis of 2-C-trifluoromethyl substituted D-ribose

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Abstract—A stereoselective three step synthesis of 2-C-trifluoromethyl D-ribose via McMurry pinacol cross coupling of 2,3-di-*O*-isopropylidene D-glyceraldehyde and methyl trifluoropyruvate is described. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Chemical and biological properties of target molecules can be modified by introduction of fluorine and fluoroalkyl groups into strategical positions.[1] In this context, a variety of monofluoro- and difluoro-substituted carbohydrates exhibiting interesting biological activities have been synthesized.[2] Routes to difluoroalkyl- and trifluoroalkyl-substituted carbohydrates have been reviewed recently.[3]

Chemically modified carbohydrates are substructures of nucleosides (e.g. AZT, ddC, ddI, d4T, 3TC) exhibiting anticancer, antiviral and anti-HIV activity. Likewise, C-2′-methyl-substituted adenosine and cytidine show antiviral properties. Among the possible modifications of the carbohydrate ring, the C-2 position of ribose is of special interest. Since it has been shown that C-2′-*O*-methyl oligoribonucleotides form a more stable duplex with RNA and exhibit an increased nuclease resistance compared to natural oligodeoxynucleotides.[4] Recently it was disclosed that C-2′-ethyl, C-2′-allyl and C-2′-styryl nucleosides have much lower affinity to RNA than natural oligonucleotides. However, they exhibit higher stability towards 3′-exonucleases.[5]

A methyl group placed at C-2 of a sugar moiety induces severe conformational changes. The rotation about the N-glycosidic bond is restricted, resulting in an increased nuclease resistance and consequently in an enhanced biological activity.[6]

Recently, we reported on a four step synthesis of C-2-trifluoromethyl DL-ribose and DL-arabinose.[7] We now disclose a preparative simple three step access to C-2-trifluoromethyl D-ribose starting from the readily available trifluoromethyl-containing building block methyl trifluoropyruvate.

2. Results and discussion

A modified McMurry protocol[8] provides an efficient access to 1,2-dihydroxy cycloalkanes from terminal dialdehydes. Preparatively even more flexible is the cross coupling of two different carbonyl compounds to give unsymmetrically substituted diols.[9] We adapted this strategy for a cross coupling of 2,3-di-*O*-isopropylidene D-glyceraldehyde (**1**)[10] and methyl trifluoropyruvate (**2**).[11] The coupling reagent was prepared from titanium(III)-chloride and activated zinc in DME. ^{19}F NMR data of the crude reaction product revealed the formation of only two new trifluoromethyl-containing compounds. Interestingly, the formation of the two diastereomeric dimethyl 2,3-bis(trifluoromethyl) tartrates (**5a**, **5b**), the result of the cross coupling of two methyl trifluoropyruvate molecules, was not observed. However, the cross coupling product **6**, the dimer of the protected D-glyceraldehyde **1**, was one of the by-products (Scheme 1).

The two new trifluoromethyl-containing compounds were separated and purified by flash chromatography. While the main product (50%) crystallized spontaneously, the second product (20%) needed weeks to crystallize. Based on the IR, NMR and mass spectra data, we ascribe both compounds the structures of diastereomeric acetone-protected methyl 2-trifluoromethyl aldonates (**3**, **4**).

The relative configuration of the main product **3** was established by X-ray structure analysis (Fig. 1). From previous

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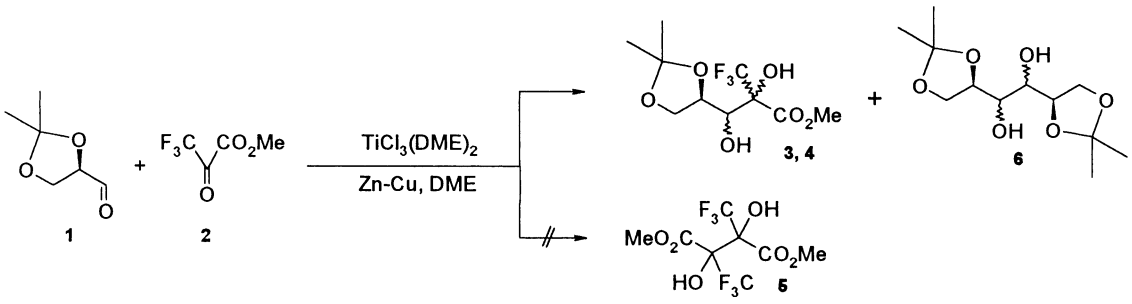


Scheme 1.

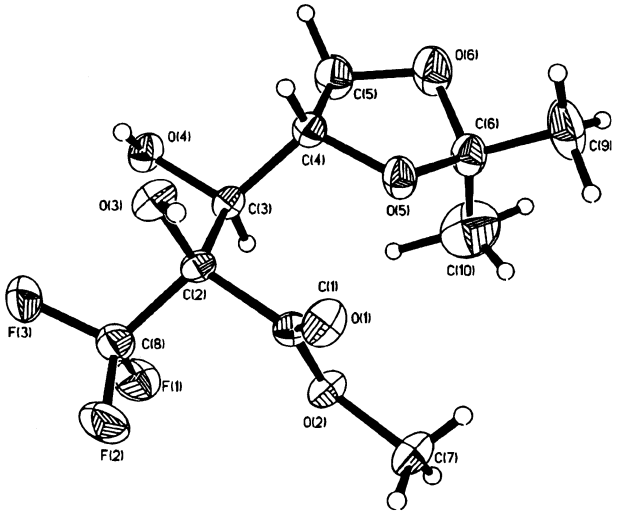
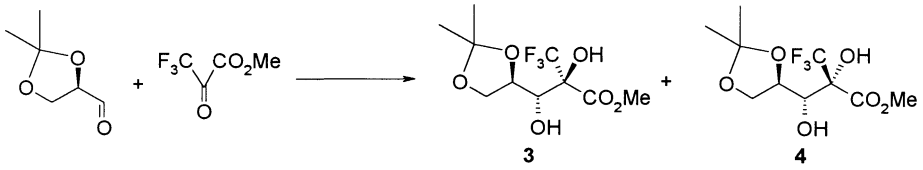


Figure 1. A molecule of **3** in the crystal.

D-ribonic ester and 2-C-trifluoromethyl D-arabinonic ester should be formed preferentially or exclusively (Scheme 2). The experimental findings are in agreement with this assumption (Scheme 3).

The standard protocol for deblocking of the diol moiety (1–2N HCl, THF) of **3** and **4** caused spontaneous decomposition. However, 2-trifluoromethyl D-ribonic ester **7** was obtained on treatment of **3** with diluted acetic acid (60%), which spontaneously ring closed to give the 2-C-trifluoromethyl D-ribolactone (**9**). The NMR data of **9** turned out to be very similar to those obtained for 2-C-methyl D-ribolactone. As expected, the ν-CO band of **9** absorbs at shorter wavelength (1788 cm^{-1}) than its methyl analogue (1750 cm^{-1}).[13]

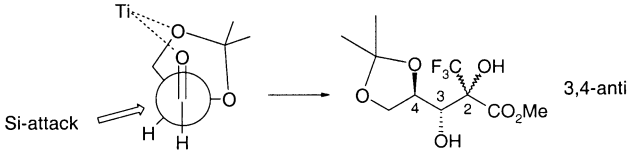
From the vicinal coupling constant $J_{H\text{-}3/H\text{-}4}$ information about the conformation of the five membered ring should be obtained. Characteristically, γ-lactones exist in a stable ^3E-conformation. When this conformation is adapted the



Scheme 2.

work it is known that low valent titanium species do not affect the configuration of glyceraldehyde. Furthermore, Mulzer et al. demonstrated that the carbonyl group of D-glyceraldehyde **1** is preferentially attacked from the *Si*-site by carbon nucleophiles to form stereoselectively a new C–C bond.[12]

Consequently, when we assume preservation of the configuration of the glyceraldehyde **1**, the C–C bond formation from the *Si*-site and additionally the maximum number of contacts of the oxygen-containing functions with the titanium species in the transition state, 2-C-trifluoromethyl

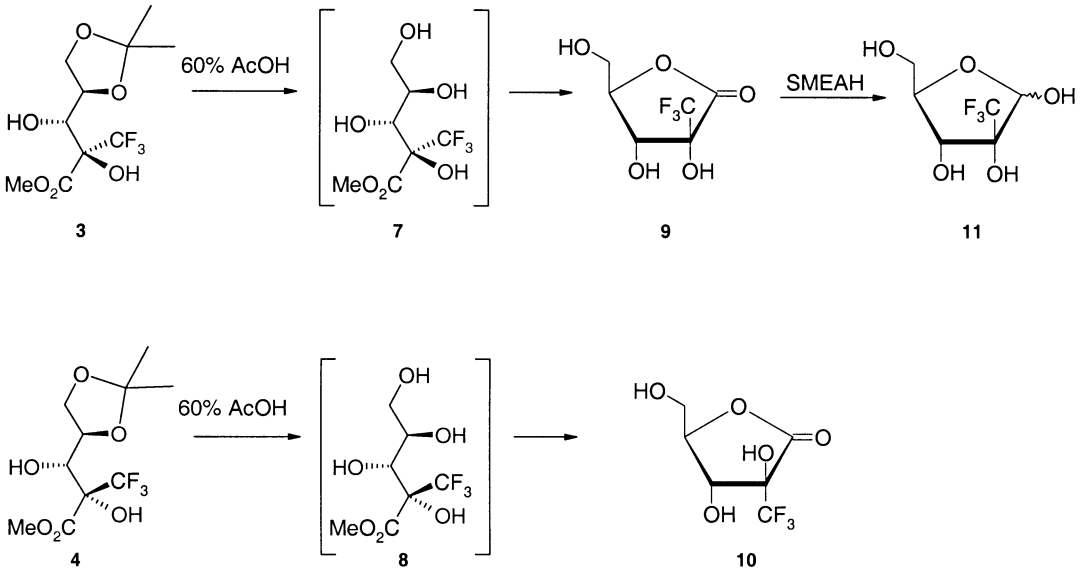


Scheme 3.

torsion angle between H-3 and H-4 should be close to 180° resulting in a coupling constant of ca. 10 Hz (electronical effects of the trifluoromethyl group are neglected). The data extracted from the spectra are in agreement with this assumption ($^3J_{H\text{-}3/H\text{-}4}$=8.2 Hz).

Purification of the second compound which, based on the argumentation given in Scheme 2, should have the structure of the acetone-protected 2-trifluoromethyl arabinonic ester **4**, turned out to be difficult and so far we did not obtain suitable crystals for X-ray analysis. It was deblocked to give the 2-trifluoromethyl arabinonic ester which again ring closed spontaneously to give a lactone (**4→8→10**). The NMR and the mass spectra data of the lactone are identical to those previously obtained for 2-trifluoromethyl DL-arabinolactone.[7] Therefore, we ascribe it the configuration depicted in formula **10** (Scheme 4).

Reduction of D-ribolactone **9** to give 2-C-trifluoromethyl D-ribose (**11**) was performed on treatment with Red-Al



Scheme 4.

(sodium bis (methoxyethoxy)-dihydroaluminate, SMEAH[14]). The spectra data of **11** are identical to those obtained previously for the racemate.[7] As expected, the anomeric and tautomeric equilibria observed for 2-C-trifluoromethyl D-ribose and 2-C-trifluoromethyl DL-ribose[7] are identical.

The stereoselective McMurry cross coupling of fluorinated with unfluorinated carbonyl compounds described in this paper offers a very versatile access to new chiral fluorine containing building blocks, which i.a. are useful tools for fluoro modification of natural products. On further applications of the McMurry pinacol cross coupling in fluorine chemistry we report elsewhere.

3. Experimental

3.1. General

Microanalyses were carried out with a Heraeus CHN-O Rapid apparatus. Melting points were determined on a Boëtius apparatus and are corrected. Mass spectra were obtained with a MASSLAB VG 12-250 instrument (EI, 70 eV). IR spectra were measured with a Genesis Series FTIR ATI Mattson spectrometer. NMR spectra were recorded on Varian GEMINI 200 (^{1}H 199.96; ^{13}C 50.29 MHz), GEMINI 2000 (^{1}H 200.04; ^{13}C 50.31 MHz) and GEMINI 300 (^{1}H 300.08; ^{13}C 75.46 MHz) instruments. Chemical shifts are reported in ppm relative to tetramethylsilane. For ^{19}F NMR spectra, external trifluoroacetic acid is used as reference. Optical rotations were measured with a Schmidt and Haensch POLARTRONIC-D polarimeter. A CCD diffractometer (AXS Bruker) was used for X-ray measurements (MoK_α radiation (0.71069 Å), room temperature).

All solvents were dried by standard methods. Reactions were carried out under dry argon.

3.1.1. 4,5-*O*-Isopropylidene-2-C-trifluoromethyl-D-ribonic- and D-arabinonic methylester (3,4). 13.6 mmol (2.10 g) titanium(III)-chloride were heated for 48 h under reflux in 30 ml of dry DME. After cooling to room temperature, 2.70 g of activated zinc powder was added and heated for 5 h under reflux. After cooling to room temperature, 13 mmol (2.03 g) methyl trifluoropyruvate (**2**) and 13 mmol (1.69 g) freshly distilled 2,3-di-*O*-isopropylidene D-glyceraldehyde (**1**)[10] in 10 ml DME were added slowly with a syringe. After 12 h stirring at room temperature, the mixture was poured into a solution of 15 g potassium carbonate in 75 ml water and stirred vigorously for 3 h. The solution was extracted with ethyl acetate. The combined organic phase was dried over sodium sulfate and evaporated. The resulting oil was purified by flash chromatography (eluent: THF). The oily product crystallizes within 1 week.

3.1.2. 4,5-*O*-Isopropylidene-2-C-trifluoromethyl-D-ribonic methylester (3). Yield 50% (1.87 g); colourless crystals; mp 114–115.5°C ($CHCl_3$); $[\alpha]_D^{24}$: −18.4 (c=1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.28 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$), 2.48 (d, 1H, OH-3, $^3J_{H3OH3}$=8.8 Hz), 3.86 (s, 3H, OCH_3), 4.07–4.17 (m, 4H, H-3,4,5), 4.23 (s, 1H, OH-2); ^{13}C NMR ($CDCl_3$): δ=24.5 (CH_3), 25.8 (CH_3), 53.6 (O–CH_3), 66.6 (C-5), 72.6 (C-3), 73.0 (C-4), 77.6 (q, C-2, $^2J_{CF}$=28.3 Hz), 109.7 ($C(Me)_2$), 122.6 (q, CF_3, $^1J_{CF}$=287.6 Hz), 167.9 (–CO_2–); ^{19}F NMR ($CDCl_3$): δ=4.04 (s, CF_3); IR (KBr): ν=3555 (OH), 2991 (CH_3), 1756 (C=O), 1159 (C–O–C) cm^{-1}; MS: *m/e* (%) 288 $M^{+\cdot}$ (<1), 273 $[M-CH_3]^+$ (22), 255 $[M-H_2O, CH_3]^+$ (14), 231 $[M-C_3H_5O]^+$ (7), 171 $C_5H_6F_3O_3^+$ (5), 153 $C_5H_4F_3O_2^+$ (10), 132 $C_6H_{12}O_3^+$ (10), 101 $C_5H_8O_2^+$ (58), 59 $C_3H_7O^+$(42), 44 CO_2^+ (100); Anal. calcd for $C_{10}H_{15}F_3O_6$: C 41.67, H 5.25; found: C 41.60, H 5.18.

3.1.3. Crystallographic data. Crystal system: monoclinic; space group: $P2_1$; a=6.0153(6) Å, b=10.9285(1) Å, c=9.9747(1) Å, α and γ=90.00°, β=101.416(2)°. V=642.75(1) Å^3; Z=2; density ρ_{calcd}=1.489 g m^{-3}; collected reflections 2946; unique reflections 2097; number of parameters 232; R_1=0.0353, wR_2=(0.1031) for [$I>2\sigma(I)$]. The

structure was solved by direct methods using the program SHELX-97. All hydrogen atoms were located.[15]

3.1.4. 4,5-*O*-Isopropylidene-2-C-trifluoromethyl-D-arabinonic methylester (4). Yield 21% (0.78 g); colourless crystals; mp 117–119°C (CCl_4). ^{1}H NMR ($CDCl_3$): δ=1.37 (s, 3H, $C(CH_3)_2$), 1.41 (s, 3H, $C(CH_3)_2$), 2.28 (d, 1H, OH-3, $^3J_{H3OH3}$=9 Hz), 3.95 (s, 3H, OCH_3), 4.10–4.14 (m, 4H, H-3,4,5), 4.44 (s, 1H, OH-2); ^{13}C NMR ($CDCl_3$): δ=25.7 (CH_3), 26.6 (CH_3), 54.9 (O–CH_3), 64.9 (C-5), 70.4 (C-3), 75.5 (C-4), 78.9 (q, C-2, $^2J_{CF}$=24.8 Hz), 110.6 ($C(Me)_2$), 123.5 (q, CF_3, $^1J_{CF}$=288.0 Hz), 169.4 (–CO_2–); ^{19}F NMR ($CDCl_3$): δ=3.53 (s, CF_3); IR (film): ν=2958 (CH_3), 1758 (C=O), 1456, 1378, 1305, 1251, 1158 (C–O–C) cm^{-1}; MS: *m/e* (%) 273 $[M-CH_3]^+$ (7), 255 $[M-H_2O, CH_3]^+$ (5), 231 $[M-C_3H_5O]^+$ (4), 171 $C_5H_6F_3O_3^+$ (4), 153 $C_5H_4F_3O_2^+$ (6), 132 $C_6H_{12}O_3^+$ (9), 102 $C_5H_9O_2^+$ (29), 59 $C_3H_7O^+$(60), 41 $C_3H_5^+$ (100), 28 $C_2H_4^+$ (20).

3.1.5. 2-C-Trifluoromethyl-D-ribolactone (9). 0.7 mmol (0.202 g) **3** was stirred in 10 ml 60% AcOH for 24 h. After evaporating the AcOH the product crystallized. Yield 90% (0.14 g). Colourless crystals; mp 123–124°C; $[\alpha]_D^{24}$: +83.3 (*c*=1.08, acetone); ^{1}H NMR (acetone-d_6): δ=3.78 (dd, 1H, H-5, ^2J=12.9 Hz, ^3J=2.9 Hz), 4.03 (dd, 1H, H-5, ^2J=12.9 Hz, ^3J=2 Hz), 4.34 (m, 1H, H-4), 4.4 (s, 1H, OH-5) 4.75 (d, 1H, H-3, ^3J=8.2 Hz), 5.72 (s, 1H, OH-3), 6.26 (s, 1H, OH-2); ^{13}C NMR (acetone-d_6): δ=60.2 (C-5), 68.5 (C-3), 76.3 (q, C-2, $^2J_{CF}$=30.9 Hz), 84.2 (C-4), 125.2 (q, CF_3, $^1J_{CF}$=283.4 Hz), 169.3 (q, C-1, $^3J_{CF}$=1.6 Hz); ^{19}F NMR (acetone-d_6): δ=−0.99 (s, CF_3); IR (KBr): ν=3499, 3426 (OH), 1788 (C=O), 1363, 1186, 1158, 1032 cm^{-1}; MS: *m/e* (%) 216 M^+ (<1), 142 $[M-CH_2O, CO]^+$ (8), 102 $C_4H_5O_3^+$ (21), 71 $C_4H_6O^+$ (24), 58 $C_3H_6O^+$ (54), 41 $C_3H_5^+$ (100); Anal. calcd for $C_6H_7F_3O_5$: C 33.34, H 3.26; found: C 33.19, H 3.15.

3.1.6. 2-C-Trifluoromethyl-D-arabinolactone (10). 0.35 mmol (0.101 g) **4** was stirred in 5 ml 60% AcOH for 24 h. After evaporating AcOH the product crystallized slowly. Yield 70% (0.06 g); colourless crystals; mp 170–172°C. ^{1}H NMR (acetone-d_6): δ=3.81 (dd, 1H, H-5, ^2J=12.8 Hz, ^3J=3.5 Hz), 4.04 (dd, 1H, H-5, ^2J=12.8 Hz, ^3J=2.5 Hz), 4.44 (m, 1H, H-4), 4.49 (s, 1H, OH-5), 4.74 (d, 1H, H-3, ^3J=8.2 Hz), 5.69 (s, 1H, OH-3), 6.46 (s, 1H, OH-2); ^{13}C NMR (acetone-d_6): δ=60.0 (C-5), 72.9 (C-3), 77.3 (q, C-2, $^2J_{CF}$=29 Hz), 83.2 (C-4), 123.2 (q, CF_3, $^1J_{CF}$=286.1 Hz), 169.7 (q, C-1, $^3J_{CF}$=1 Hz); ^{19}F NMR (acetone-d_6): δ=4.10 (s, CF_3); IR (KBr): ν=3500, 3419 (OH), 1795 (C=O), 1360, 1189, 1160, 1040 cm^{-1}; MS: *m/e* (%) 216 $M^{+\cdot}$ (<1), 198 $[M-H_2O]^+$ (1), 102 $C_4H_5O_3^+$ (15), 71 $C_4H_6O^+$ (12), 58 $C_3H_6O^+$ (44), 41 $C_3H_5^+$ (100).

3.1.7. 2-C-Trifluoromethyl-D-ribose (11). To a solution of 0.3 mmol (0.065 g) ribolactone **9** in 5 ml dry THF at 0°C, 1.65 mmol Red-Al (sodium bis(2-methoxyethoxy)-dihydroaluminate, SMEAH) in 2 ml toluene and 1.65 mmol ethanol was added slowly. The solution was stirred 48 h at 0°C. 1 ml 1N H_2SO_4 was added and the suspension was stirred for further 2 h. Then 20 ml ethyl acetate was added. The solution was neutralized with Na_2CO_3 and dried over Na_2SO_4. After evaporation, the crude product was purified by flash chromatography (eluent: ethyl acetate/methanol 2:1;R_f: 0.6). 60% (0.039 g); colourless crystals; mp 96–97°C; $[\alpha]_D^{24}$: −2.5 (*c*=0.33, H_2O), after 1 day: −17. IR (KBr): ν=2926, 1639, 1452, 1414, 1341, 1248, 1150, 1080 cm^{-1}; MS: *m/e* (%) 201 $[M-OH]^+$ (1), 187 $[M-CH_2OH]^+$ (19), 170 $[M-CH_2OH, OH]^+$ (17), 154 $[M-H_2O, HCO_2H]^+$ (9), 141 $[M-HCO_2H, CH_2OH]^+$ (100), 109 $C_3F_3O^+$ (88), 71 $C_3H_3O_2^+$ (59), 61 $C_2H_5O_2^+$ (41), 43 $C_2H_3O^+$ (41), 29 CHO^+ (53).

α-Ribofuranose: 65% in acetone-d_6; ^{1}H NMR (399.95 MHz): δ=3.67 (dd*, H-5, ^2J=12.3 Hz, ^3J=4.1 Hz), 3.85 (dd*, H-5, ^2J=12.3 Hz, ^3J=2.2 Hz), 3.91 (ddd, 1H, H-4, ^3J=8.4 Hz, ^3J=4.1, 2.2 Hz), 4.27 (d, 1H, H-3, ^3J=8.4 Hz), 5.44 (s, 1H, 1-H), (* integrals overlapping); ^{13}C NMR (100.58 MHz): δ=60.8 (C-5), 69.8 (C-3), 77.9 (q, C-2, $^2J_{CF}$=28.2 Hz), 81.7 (C-4), 95.6 (q, C-1, $^3J_{CF}$=1.9 Hz), 125.8 (q, CF_3, $^1J_{CF}$=283.4 Hz); ^{19}F NMR (282.33 MHz): δ=−2.01 (s, CF_3).

β-Ribofuranose: 21% in acetone-d_6; ^{1}H NMR (399.95 MHz): δ=3.73 (dd*, H-5, ^2J=12.4 Hz, $^3J_{45}$=2.8 Hz), 4.19 (dd*, H-5, ^2J=12.4 Hz, ^3J=1.1 Hz), 3.97–7.99 (m, 2H, H-3,4), 5.20 (s, 1H, 1-H); (* integrals overlapping); ^{13}C NMR (100.58 MHz): δ=63.0 (C-5), 70.5 (C-3), 80.7 (q, C-2, $^2J_{CF}$=27.1 Hz), 84.1 (C-4), 101.0 (C-1), 125.3 (q, CF_3, $^1J_{CF}$=283.4 Hz); ^{19}F NMR (282.33 MHz): δ=3.37 (s, CF_3).

α-Ribopyranose: 2% in acetone-d_6; ^{1}H NMR (399.95 MHz): signals could not be extracted because of low intensity; ^{13}C NMR (100.58 MHz): δ=59.0 (C-5), 124.1 (q, CF_3, $^1J_{CF}$=285.2 Hz), other signals could not be extracted because of low intensity; ^{19}F NMR (282.33 MHz): δ=−1.02 (s, CF_3).

β-Ribopyranose: 12% in acetone-d_6; ^{1}H NMR (399.95 MHz): δ=3.70 (dd*, H-5, ^2J=12 Hz, ^3J=2.8 Hz), 3.79 (dd*, H-5, ^2J=12 Hz, ^3J=2.9 Hz), 4.11 (d, 1H, H-3, ^3J=4.5 Hz), 4.99 (dd, 1H, H-4, ^3J=4.5 Hz, ^3J=2.8 Hz), 5.18 (s, 1H, 1-H), (* integrals overlapping); ^{13}C NMR (100.58 MHz): δ=61.9 (C-5), 64.5 (C-3), 76.7 (q, C-2, $^2J_{CF}$=28.1 Hz), 83.1 (C-4), 94.3 (C-1), 125.2 (q, CF_3, $^1J_{CF}$=285.7 Hz); ^{19}F NMR (282.33 MHz): δ=4.07 (s, CF_3).

4. Supplementary material

Further details on the structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number CCDC 156324.

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