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2-*C*-Trifluoromethyl Substituted Pentoses

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Dedicated to Professor Wolfgang Steglich on the occasion of his 65th birthday

Abstract

The synthesis of racemic 2-*C*-trifluoromethyl ribose and racemic 2-*C*-trifluoromethyl arabinose is described. The four step reaction sequence includes diastereoselective enol ether addition to methyl trifluoropyruvate, diastereoselective dihydroxylation of the CC double bond with potassium osmate, lactonization, and finally SMEAH reduction to give the lactol. 2-*C*-Trifluoromethyl pentoses exhibit unexpected anomeric and tautomeric stabilities.

Keywords: Fluoro Compounds, Trifluoropyruvate, 2-C-Trifluoromethyl Ribose, 2-C-Trifluoromethyl Arabinose

Introduction

Sugars assume functions in living organisms going far beyond their role as the main source of energy. They constitute the backbone of ribonucleic acid and control molecular recognition processes at the outer surface of cellular membranes [1]. I.a. they play a major role in cancer metastasis and in development of infections. Chemically modified carbohydrates are substructures of nucleosides (e.g. AZT, ddC, ddI, d4T, 3TC) exhibiting anticancer and antiviral – including anti-HIV – activity [2]. Furthermore, 2'-*C*-methyl substituted adenosine and cytidine show antiviral properties [3]. A methyl group placed at C-2 of the sugar moiety induces severe conformational restrictions particularly at the *N*-glycoside bond and improves nuclease resistance, resulting in an enhanced biological activity. Similar findings were reported for protein kinase C inhibitor 2-*C*'-methyl sangivamycin [4].

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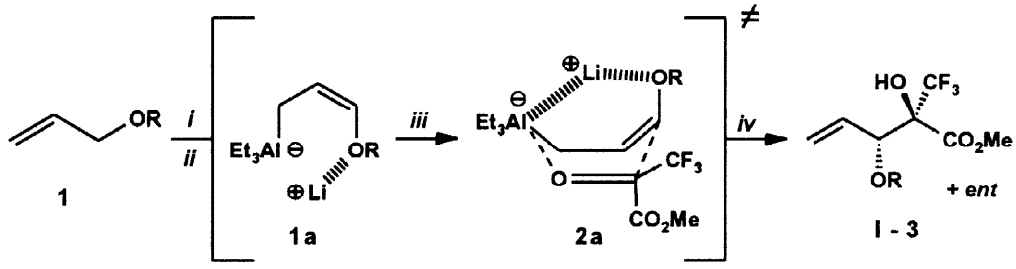
The presence of the sterically demanding trifluoromethyl group in strategical positions of bioactive compounds often causes reduced metabolism, enhanced bioavailability and increased lipophilicity [5]. Reactions at C-1 of carbohydrates via cationic intermediates are much more difficult to achieve when a trifluoromethyl group is attached to C-2 [6]. Glycosides and nucleosides derived from those modified carbohydrates should exhibit improved chemical and enzymatic stability. Furthermore, strong electron withdrawing substituents at C-2'-position of nucleosides increase binding affinity of RNA/DNA hybrides [7]. Therefore, glycosides and nucleosides derived from non-natural carbohydrates, especially from 2-*C*-trifluoromethyl substituted pentoses are of current interest [8].

Herein we report on the synthesis of racemic 2-*C*-trifluoromethyl ribose and racemic 2-*C*-trifluoromethyl arabinose [9] from the readily available trifluoromethyl containing building block methyl trifluoropyruvate [10].

Results and discussion

The keto function of trifluoropyruvate is highly electrophilic because of the adjacent trifluoromethyl and carboxylate groups. Therefore, nucleophiles add regioselectively to the keto function. Reaction of methyl trifluoropyruvate (TFBE) **2** and complex **1a** already provides the complete five carbon atom skeleton of pentose with a trifluoromethyl group in position 2.

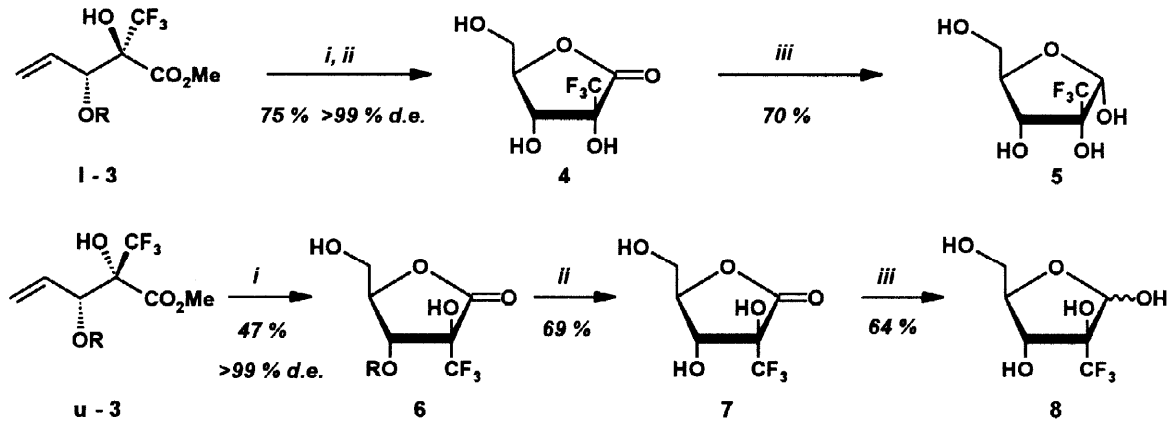


In the first step of the reaction sequence allyl *tert*-butyl ether **1** is deprotonated by *sec*-butyl lithium and then transmetallated with triethyl aluminium at -100 °C. The resulting chelate **1a** is stabilized by attractive intramolecular Coulomb interactions. Similar structures have already been described [11]. On addition of methyl trifluoropyruvate **2** we propose the formation

of a bicyclic transition state **2a** with the steric more demanding trifluoromethyl group in an equatorial position. After acidic work-up, product **3** can be isolated in excellent chemical yield. The diastereomeric mixture is separable by flash chromatography. Due to the above proposed mechanism compound **l-3** should be favoured.

At this stage the relative configuration of both diastereomers can not be determined unequivocally. Therefore, **l-3** and **u-3** were dihydroxylated in separate experiments. Unfortunately, neither catalytic dihydroxylation nor Sharpless epoxidation were successful. This may be due to the steric hindrance and the strong electron withdrawing effect of the trifluoromethyl group in the homoallyic position. Only with equimolar amounts of potassium osmate and prolonged reaction times the CC-double bond can be difunctionalized to yield the crystalline lactones **4** and **6** after ring closure, respectively. X-ray structure analysis of **4** [12] and **6** [9a] reveals that the major diastereomer of **3** is **l-3**. This result is in agreement with our expectations.

Dihydroxylation of **l-3** and acidic work-up provides compound **4** in good chemical yield and excellent diastereomeric excess. Lactone **7** is synthesized by deprotection of **6**. As can be seen from the yields for the reactions **l-3** → **4** and **u-3** → **6** → **7** the one-pot procedure for lactonization is superior. The final step of the reaction sequence, the reduction of the lactones **4** and **7** to yield the lactols **5** and **8**, respectively, is achieved with SMEAH [9a, 13].



i $K_2[OsO_2(OH)_4]$, *ii* HCl / MeOH, *iii* SMEAH / EtOH, *R* = tert - butyl

The carbohydrates **5** and **8** exhibit unexpected tautomeric and anomeric stabilities. In contrast to natural ribose, were the furanose form is less stable compared to the pyranose form [14], in the presence of a trifluoromethyl group at C-2, the furanose dominates in solution. 2-C-Trifluoromethyl ribose crystallizes to give exclusively α-furanose **5**, while 2-C-trifluoromethyl

arabinose **8** is only obtained as an oily mixture of both anomers. Table 1 shows the equilibrium ratio furanose/pyranose of **5** and **8** in D_2O after 2 months compared to natural occurring ribose and arabinose [15].

Table 1. Furanose/pyranose ratio (%) of 2-C-trifluoromethyl ribose **5** and 2-C-trifluoromethyl arabinose **8** compared to natural ocurring ribose and arabinose:

	5	ribose	**8**	arabinose
α-furanose	*74*	*7*	*19*	*3*
β-furanose	*18*	*14*	*41*	*2*
α-pyranose	*1*	*21*	*9*	*60*
β-pyranose	*7*	*58*	*31*	*35*

The equilibrium ratios for **5** and **8** are taken from integrals of the ^{19}F NMR spectra. The data obtained correspond to results taken from ^{13}C NMR spectra by a method suggested by Breitmaier *et al.* [16] (see also [9a,e]).

Experimental

General Methods

Microanalyses were carried out with a Heraeus CHN apparatus EA 415/0 (Monar System) and a Foss-Heraeus CHN-O-S-Rapid-apparatus. Melting points are determined on a Büchi SMP-20 apparatus (Tottoli) and are uncorrected. Mass spectra were obtained with Varian MAT CH5 (EI, 70eV) and Masslab VG-12-250 (EI, 14 eV or 70 eV) instruments. IR spectra were measured with Perkin-Elmer 157G, Perkin-Elmer 257, Carl Zeiss Jena Specord M80 and Unicom ATI Mattson instruments. NMR spectra were recorded on Bruker AM 360, AC 250, AC 200 and Varian Gemini 200, Gemini 2000, Gemini 300 instruments. Chemical shifts are reported in ppm relative to tetramethylsilane. For ^{19}F NMR spectra external trifluoroacetic acid is used as reference. All solvents were dried by standard methods. Reactions were carried out under dry argon.

Methyl 3-tert-Butoxy-2-hydroxy-2-trifluoromethyl-4-pentenoate **(3)**

To a solution of allyl *tert*-butyl ether **1** (17.6 ml, 120 mmol, 1.25 eq) in 300 ml THF at -100 °C TMEDA (16.5 ml, 110 mmol, 1.15 eq) and *sec*-butyl lithium (110 mmol, 1.15 eq) are added. After stirring 45 min triethyl aluminium (110 mmol, 1.15 eq) is added and stirred for additional 45 min. Then methyl trifluoropyruvate **2** (11.0 ml, 96.0 mmol, 1.00 eq) is added. The reaction mixture is stirred for 4 h and then quenched with an ice cold mixture of 2N HCl and MeOH. After warming up to r.t. the aqueous layer is extracted thrice with diethyl ether. The combined

organic layer was concentrated, dissolved in $CHCl_3$ and washed with saturated $NaHCO_3$ solution, 1N HCl and brine. The organic layer is dried over $MgSO_4$ and evaporated. Yield: 24.4 g **3**, 94 %, 94 % d.e. The diastereomers are separated by flash chromatography (silicagel, eluent: ethyl acetate/hexane 1:5).

Like-isomer (***l*-3**): $R_f = 0.29$. ^1H NMR ($CDCl_3$, 360.14 MHz): δ = 1.22 (s, 9H, $C(CH_3)_3$), 3.83 (s, 3H, CH_3), 4.56 (d, J = 7.9 Hz, 1H, 3-H), 5.23 (d, J = 10.3 Hz, 1H, 5-H), 5.26 (d, J = 17.5 Hz, 1H, 5-H), 5.85 (m, 1H, 4-H). ^{13}C {^1H} NMR ($CDCl_3$, 90.56 MHz): δ = 28.61 ($C(CH_3)_3$), 53.47 (CH_3), 73.57 (C-3), 76.47 ($OC(CH_3)_3$), 81.13 (q, J = 27.6 Hz, C-2), 119.04 (C-5), 123.60 (q, J = 287.1 Hz, CF_3), 136.06 (C-4), 167.51 (C-1). ^{19}F NMR ($CDCl_3$, 338.84 MHz): δ = 4.38 (s, CF_3).

Unlike-isomer (***u*-3**). R_f = 0.35. ^1H NMR ($CDCl_3$, 360.14 MHz): δ = 1.15 (s, 9H, $C(CH_3)_3$), 3.89 (s, 3H, CH_3), 4.56 (d, J = 8.1 Hz, 1H, 3-H), 5.33 (d, J= 10.6 Hz, 1H, 5-H), 5.37 (d, J = 17.8 Hz, 1H, 5-H), 5.95 (m, 1H, 4-H). ^{13}C {^1H} NMR ($CDCl_3$, 90.56 MHz): δ = 28.69 ($C(CH_3)_3$), 53.63 (CH_3), 74.01 (C-3), 75.94 ($OC(CH_3)_3$), 81.59 (q, J = 27.6 Hz, C-2), 119.55 (C-5), 122.29 (q, J = 285.6 Hz, CF_3), 135.35 (C-4), 168.88 (C-1). ^{19}F NMR ($CDCl_3$, 235.35 MHz): δ = 4.79 (s, CF_3).

Diastereomeric mixture (**3**) : Bp. 85 °C / 14 torr (kugelrohr). MS (EI, 70 eV): m/z = 255 (1.9), 197 (3.8), 113 (16), 69 (22), 59 (96), 57 (100), 41 (68), 39 (20). IR (film): ν_{max} = 3495, 2980, 1750 cm^{-1}. Anal. Calcd. for $C_{11}H_{17}F_3O_4$: C 48.89, H 6.34. Found: C 49.17, H 6.62.

2-C-Trifluoromethyl-4-DL-ribolactone (**4**)

***l*-3** (1.67 g, 6.17 mmol) is dissolved in 30 ml H_2O and 30 ml *tert*-butanol. 1 eq potassium osmate(VI) dihydrate, 3 eq potash, 3 eq potassium ferricyanide, 2 eq pyridine and 1 eq methane sulfonamide are added and stirred vigorously for 14 days. Then sodium sulphite (12 g) and 62 ml of H_2O are added. The reaction mixture is stirred for 24 h. Then diethyl ether and conc. HCl are added. The aqueous layer is extracted thrice with diethyl ether. The combined organic layer is washed twice with saturated $NaHCO_3$ solution and twice with brine and evaporated after drying over $MgSO_4$. The resulting oil is purified by flash chromatography (silicagel, eluent: ethyl acetate/hexane 1:2). Recrystallization is achieved from CH_2Cl_2 and yields colourless crystals (1.00 g, 75 %, > 99 % d.e.).

Mp. 124 °C. ^1H NMR ([D_6]DMSO, 300.08 MHz): δ = 3.58 (ddd, J = 13.1, 5.7, 3.7 Hz, 1H, 5-H), 3.81 (ddd, J = 13.1, 4.6, 2.0 Hz, 1H, 5-H), 4.26 (ddd, J = 8.2, 3.7, 2.0 Hz, 1H, 4-H), 4.39 (dd, J = 8.2, 7.4 Hz, 1H, 3-H), 5.19 (m, 1H, 5-OH), 6.21 (d, J = 7.4 Hz, 1H, 3-OH), 7.54 (s, 1H, 2-OH). ^{13}C {^1H} NMR ([D_6]DMSO, 75.46 MHz): δ = 57.83 (C-5), 66.70 (C-3), 74.48 (q, J = 29.8 Hz, C-2), 82.48 (C-4), 123.43 (q, J = 284.3 Hz, CF_3), 168.53 (C-1). ^{19}F NMR ([D_6]DMSO, 282.33 MHz): δ = 0.60 (s, CF_3). MS (EI, 70 eV): m/z = 216 (3.6), 142 (68), 141 (100), 129 (14), 128 (19), 122 (10), 109 (40), 69 (20), 61 (14). IR (KBr): ν_{max}= 3510-2900, 1790 cm^{-1}. Anal. Calcd. for $C_6H_7F_3O_5$: C 33.35, H 3.27. Found: C 33.49, H 3.38.

3-O-tert-Butyl-2-C-trifluoromethyl-4-DL-arabinolactone **(6)**

***u*-3** (662 mg, 2.45 mmol) is reacted as described for ***l*-3**. The workup is performed without using HCl. Recrystallization from $CHCl_3$/heptane gives colourless crystals (313 mg **6**, 47 %, > 99 % d.e.).

Mp. 141 °C. ^{1}H NMR ([D_6]DMSO, 200.13 MHz): δ = 1.17 (s, 9H, $C(CH_3)_3$), 3.53 (ddd, *J* = 13.4, 5.4, 2.3 Hz, 1H, 5-H), 3.78 (ddd, *J* = 13.4, 5.4, 2.3 Hz, 1H, 5-H), 4.20 (m, 1H, 4-H), 4.56 (m, 1H, 3-H), 5.30 (dd, *J* = 5.4, 5.4 Hz, 1H, 5-OH), 7.65 (s, 1H, 2-OH). ^{13}C {^{1}H} NMR ([D_6]DMSO, 90.56 MHz): δ = 27.83 ($C(CH_3)_3$), 57.30 (C-5), 72.85 (C-3), 75.42 ($OC(CH_3)_3$), 76.70 (q, *J* = 27.0 Hz, C-2), 81.76 (C-4), 122.72 (q, *J* = 287.0 Hz, CF_3), 169.76 (C-1). ^{19}F NMR ($CDCl_3$, 235.35 MHz): δ = 3.55 (s, CF_3). MS (EI, 70 eV): m/z = 257 (50), 216 (88), 57 (100). IR (KBr): ν_{max} = 3470, 3200, 2990, 1785 cm^{-1}. Anal. Calcd. for $C_{10}H_{15}F_3O_5$: C 44.12, H 5.55. Found: C 43.83, H 5.63.

2-C-Trifluoromethyl-4-DL-arabinolactone **(7)**

6 (205 mg, 753 μmol) is dissolved in 30 ml MeOH and 5 ml 1N HCl and stirred for 24 h. Then the emulsion is evaporated. The resulting oil is dissolved in H_2O and lyophilized. Yield: 112 mg **7**, 69 %, > 99 % d.e; white crystals.

Mp. 172 °C. ^{1}H NMR ([D_6]acetone, 300.08 MHz): δ = 3.83 (ddd, *J* = 12.8, 6.2, 3.6 Hz, 1H, 5-H), 4.05 (ddd, *J* = 12.8, 5.2, 2.6 Hz, 1H, 5-H), 4.44 (m, 1H, 4-H), 4.50 (dd, *J* = 6.2, 5.2 Hz, 1H, 5-OH), 4.73 (m, 1H, 3-H), 5.60 (d, *J* = 5.7 Hz, 1H, 3-OH), 6.54 (s, 1H, 2-OH). ^{13}C {^{1}H} NMR ([D_6]acetone, 50.31 MHz): δ = 59.51 (C-5), 73.98 (C-3), 77.79 (q, *J* = 28.1 Hz, C-2), 83.46 (C-4), 123.62 (q, *J* = 286.2 Hz, CF_3), 170.02 (C-1). ^{19}F NMR ([D_6]acetone, 188.21 MHz): δ = 4.03 (s, CF_3). MS (EI, 70 eV): m/z = 216 (13), 198 (2), 141 (100), 109 (33), 69 (3). IR (KBr): ν_{max} = 3530, 3350, 3100, 2880, 1795 cm^{-1}. Anal. Calcd. for $C_6H_7F_3O_5$: C 33.35, H 3.27. Found: C 33.19, H 3.28.

2-C-Trifluoromethyl-DL-ribose **(5)**

4 (875 mg, 4.05 mmol) is dissolved in 80 ml THF and cooled to 0 °C. Then a cold mixture of 5.5 eq SMEAH, 22 ml toluene and 5.5 eq ethanol is added. This solution is stirred for 41 h at 0 °C. The reaction mixture is quenched with 100 ml 1N H_2SO_4 and stirred 2 h. The resulting suspension is added to a mixture of 440 g Na_2SO_4 and 600 ml ethyl acetate and stirred additional 1 h. Then the organic layer is evaporated. The resulting oil is purified by flash chromatography (silicagel, eluent: ethyl acetate/$CHCl_3$ /methanol/acetic acid 7:4:1:0.1), dissolved in 50 ml H_2O and lyophilized. Yield: 618 mg **5** (70 %), colourless crystals.

Anomeric mixture: Mp. 94 °C. MS (EI, 14 eV): m/z = 218 (3), 201 (100), 141 (59), 109 (35), 69 (8). IR (KBr): ν_{max} = 3430, 2950 cm^{-1}. Anal. Calcd. for $C_6H_9F_3O_5$: C 33.04, H 4.16. Found: C 33.13, H 4.41.

α-Ribofuranose in D_2O after 64 d: 74 % (^{19}F NMR analysis). ^{1}H NMR (D_2O, 300.08 MHz): δ = 3.76 (dd, *J* = 12.8, 4.5 Hz, 5-H), 3.94 (dd, *J* = 12.8, 2.4 Hz, 5-H), 4.10 (m, 4-H),

4.34 (d, J = 9.1 Hz, 1H, 3-H), 5.61 (s, 1H, 1-H). ^{13}C {^1H} NMR (D_2O, 75.46 MHz): δ = 59.83 (C-5), 69.05 (C-3), 77.80 (q, J = 27.9 Hz, C-2), 80.32 (C-4), 95.34 (C-1), 124.80 (q, J = 283.9 Hz, CF_3). ^{19}F NMR (D_2O, 282.33 MHz): δ = -2.24 (s, CF_3).

β-Ribofuranose in D_2O after 64 d: 18 % (^{19}F NMR analysis). ^1H NMR (D_2O, 300.08 MHz): δ = 4.54 (d, J = 8.0 Hz, 3-H), 5.34 (s, 1-H) [17]. ^{13}C NMR (D_2O, 75.46 MHz): δ = 61.79 (C-5), 69.32 (C-3), 79.92 (q, J = 27.4 Hz, C-2), 81.46 (C-4), 100.03 (C-1), 124.15 (q, J = 282.9 Hz, CF_3). ^{19}F NMR (D_2O, 282.33 MHz): δ = 2.96 (s, CF_3).

α-Ribopyranose in D_2O after 64 d: 1 % (^{19}F NMR analysis). ^1H NMR (D_2O, 300.08 MHz): [16]. ^{13}C NMR (D_2O, 75.46 MHz): δ = 92.73 (C-1) [17]. ^{19}F NMR (D_2O, 282.33 MHz): δ = 3.75 (s, CF_3).

β-Ribopyranose in D_2O after 64 d: 7 % (^{19}F NMR analysis). ^1H NMR (D_2O, 300.08 MHz): [17]. ^{13}C NMR (D_2O, 75.46 MHz): δ = 93.22 (C-1) [17]. ^{19}F NMR (D_2O, 282.33 MHz): δ = 3.41 (s, CF_3).

2-C-Trifluoromethyl-DL-arabinose **(8)**

7 (64 mg, 296 μmol) is reacted as described above. Yield: 41 mg **8** (64 %), colourless oil.

Anomeric mixture: MS (EI, 14 eV): m/z = 218 (4), 201 (100), 171 (17), 141 (60), 69 (2). IR (KBr): ν_{max} = 3400, 2960, cm^{-1}. Anal. Calcd. for $C_6H_9F_3O_5$: C 33.04, H 4.16. Found: C 32.99, H 3.78.

α-Arabinofuranose in D_2O after 70 d: 19 % (^{19}F NMR analysis). ^1H NMR (D_2O, 300.08 MHz): δ = 5.44 (s, 1-H) [17]. ^{13}C {^1H} NMR (D_2O, 75.46 MHz): δ = 63.61 (C-5), 76.31 (C-3), 77.49 (q, J = 28.5 Hz, C-2), 82.86 (C-4), 100.51 (C-1), 124.54 (q, J = 286.7 Hz, CF_3). ^{19}F NMR (D_2O, 282.33 MHz): δ = 3.46 (s, CF_3).

β-Arabinofuranose in D_2O after 70 d: 41 % (^{19}F NMR analysis). ^1H NMR (D_2O, 300.08 MHz): δ = 5.55 (s, 1-H) [17]. ^{13}C {^1H}NMR (D_2O, 75.46 MHz): δ = 61.82 (C-5), 76.11 (C-3), 80.10 (q, J = 26.2 Hz, C-2), 81.49 (C-4), 95.61 (C-1), 124.33 (q, J = 284.9 Hz, CF_3). ^{19}F NMR (D_2O, 282.33 MHz): δ = 2.72 (s, CF_3).

α-Arabinopyranose in D_2O after 70 d: 9 % (^{19}F NMR analysis). ^1H NMR (D_2O, 300.08 MHz): δ = 5.14 (s, 1-H) [17]. ^{13}C {^1H} NMR (D_2O, 75.46 MHz): δ = 62.55 (C-5), 68.37 (C-4), 71.35 (C-3), 91.45 (C-1) [17]. ^{19}F NMR (D_2O, 282.33 MHz): δ = 6.32 (s, CF_3).

β-Arabinopyranose in D_2O after 70 d: 31 % (^{19}F NMR analysis). ^1H NMR (D_2O, 300.08 MHz): δ = 5.26 (s, 1-H) [17]. ^{13}C {^1H} NMR (D_2O, 75.46 MHz): δ = 63.22 (C-5), 69.52 (C-4), 73.35 (C-3), 74.85 (q, J = 24.4 Hz, C-2), 90.91 (C-1), 122.47 (q, J = 286.1 Hz, CF_3). ^{19}F NMR (D_2O, 282.33 MHz): δ = 3.21 (s, CF_3).

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