Synthesis of Homochiral 2-*C*-Trifluoromethyl D-and L-Ribose *via* Trifluoromethylation of Pentopyranosid-2-uloses

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Received August 1 2002

Dedicated to Prof. Rüdiger Mews on the occasion of his 60th birthday.

Efficient syntheses of 2-*C*-trifluoromethyl D- and L-ribose and some *O*-glycosides *via* trifluoromethylation of D- and L-3,4-*O*-isopropylidene-β-*erythro*-pentopyranosid-2-ulose with Ruppert's reagent are described.

J. Heterocyclic Chem., **40**, 329 (2002).

Introduction.

Chemically modified carbohydrates, especially pentoses, are substructures of nucleosides, like AZT, ddC, ddI, d4T, 3TC, exhibiting antiviral, anticancer and anti-HIV activities [1]. Among the possible modifications of the carbohydrate ring (Figure 1), substitution reactions at C-2 are highly attractive targets, since it has been demonstrated that already the incorporation of a methyl group into C-2 position of a sugar moiety induces severe conformational changes. Among other effects, rotation about the *N*-glycosidic bond is restricted, resulting in an improved nuclease resistance and consequently in an enhanced biological activity [2].

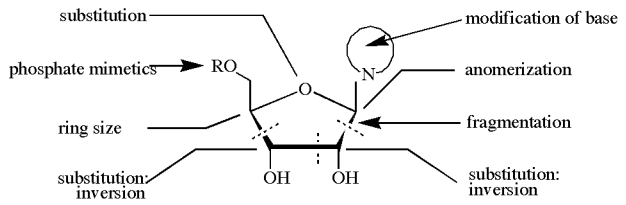


Figure 1. General strategies for carbohydrate modification.

When a perfluoroalkyl group is attached to C-2 of a carbohydrate, reactions at C-1 *via* cationic intermediates are much more difficult to achieve [3]. Consequently, glycosides derived from thus modified carbohydrates should exhibit improved chemical and enzymatic stability.

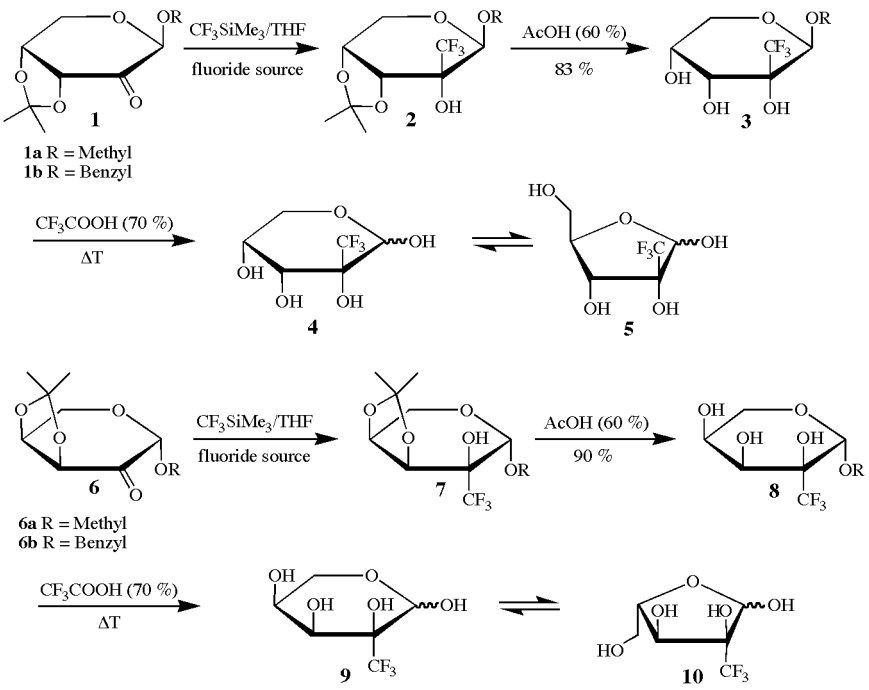
Fluoroalkyl groups placed in strategic positions of bioactive molecules may improve lipophilicity increasing *in vivo* absorption, enhancing permeability through certain body barriers [4,5]. Furthermore, they are suitable nmr probes for monitoring transport and metabolism of drugs by ^{19}F nmr spectroscopy *in vitro* and *in vivo*. Therefore, the development of new routes to homochiral trifluoromethyl and perfluoroalkyl substituted carbohydrates, especially pentoses, is of current interest to bioorganic and medicinal chemists [6,7].

Results and Discussion.

A report on the first synthesis of 2'-*C*-β-trifluoromethyl pyrimidine ribonucleosides [8] prompts us to disclose our results. Recently, we reported on a synthesis of 2-C-trifluoromethyl DL-ribose and DL-arabinose and of homochiral 2-*C*-trifluoromethyl D-ribose [9] starting from methyl trifluoropyruvate. We now describe efficient methodology for the stereoselective transfer of a trifluoromethyl group to a carbonyl moiety in a late step of the synthesis, applying Ruppert's reagent [10]. As substrates we used methyl and benzyl D- and L-3,4-*O*-isopropylidene-β-*erythro*-pentopyranosid-2-ulose (**1**,**6**), readily available on oxidation from acetone protected D- and L-arabopyranosides [11] with pyridinium dichromate (PDC) [12] or Dess-Martin reagent (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-on) [13]. From nmr experiments (APT, HETCOR, DEPT, ^{1}H, ^{1}H-COSY) β-configuration of O-glycosides (**1,6**) was established.

When **1a** was treated with trifluoromethyl trimethylsilane [14] in the presence of a fluoride source [tetrabutylammonium fluoride (TBAF) or tetrabutylammonium difluorotriphenyl-stannate] **2a** (R = CH_3) was obtained as colorless crystals, while in the case of **1b** → **2b** (R = Bn) even after column chromatography we were not able to get a crystalline product. ^{19}F nmr spectroscopy of crude **2** revealed that only one diastereomer was formed. Because of the concave geometry of **1** the carbonyl group should be attacked preferentially from the Si-site to give 2-*C*-tri-

Scheme 1



Synthesis of 2-*C*-trifluoromethyl-D-ribose (**5**) and L-ribose (**10**).

fluoromethyl-3,4-*O*-isopropylidene-β-D-*erythro*-ribopyranosides (**2a,2b**) and from the Re-site in the case of **6** to give the enantiomers **7**. Pentacoordinated silicium species are the intermediates of the nucleophilic trifluoromethylation reaction [15]. They add to the carbonyl moiety to give *O*-silylated *tert*-alcohols, which are deblocked on treatment with diluted acid or tetrabutylammonium fluoride (TBAF) [16].

Satisfactory yields were obtained only, when the catalyst was dried prior to use. We found that tetrabutylammonium difluorotriphenylstannate [14] is superior to TBAF hydrate when methylene chloride is used as solvent.

The application of Ruppert's reagent for trifluoromethylation reactions in carbohydrate chemistry restricts the arsenal of protection groups, since O-acyl groups are of no use, because Ruppert's reagent reacts readily with an ester carbonyl moiety [17].

Deblocking of the acetonide protecting group to give the homochiral *O*-glycosides **3a,b** was achieved on treatment with aqueous acetic acid (v/v = 3:2). On recrystallization of **3a** from tetrahydrofuran/hexane we obtained suitable crystals to perform a X-ray structure analysis [18] to establish the pyranose structure and to elucidate the relative configuration at C-2. Since the configuration at C-3 and C-4 is known, the absolute configuration of C-2 can be determined unequivocally as 2-*C*-trifluoromethyl-β-D-ribopyranoside **3a**, C-(1) exhibiting R-configuration, as expected for steric reasons.

Deblocking of the glycosidic OH function can be achieved on heating compounds **3a**,**b** under reflux with diluted trifluoroacetic acid (v/v = 7:3) in excellent yields (85-90%). A freshly prepared solution of the unprotected compound in D_6-acetone after column chromatography (eluent: ethyl acetate/methanol) and recrystallization reveals that only a single compound is present. Based on the ^1H and ^{13}C nmr data we ascribe this compound the structure of a 2-*C*-trifluoromethyl-α-furanose **5**. In water solution mutarotation [19] can be observed: For a freshly prepared solution of **5** in water (c = 0.33) an optical rotation of $[\alpha]_D$ = -2.5° was recorded, which changed to $[\alpha]_D$ = -17.0° after 24 hours.

Starting the above discussed reaction sequence from 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosid-2-ulose **6** [11] the corresponding compounds of the L-series **7** - **10** become readily avaiable. The spectroscopic data of compounds **2** - **5** and **7** - **10** are identical, only the optical rotation values are opposite. The optical rotation value of a freshly prepared solution of **10** (c = 0.52, H_2O) changed from $[\alpha]_D$ = + 1.0° to $[\alpha]_D$ = + 15.3° during 24 hours.

To study the fluorine effect we compared some physical data of compounds **2** - **5** and **7** - **10** with methyl substituted analogues **11** - **13**. Surprisingly, we could not find complete nmr data of 2-*C*-methylribopyranosides in the literature. Therefore, we synthesized the protected benzyl-2-*C*-methylribopyranoside derivative **11**, which was transformed into the benzyl-2-*C*-ribopyranoside **12** on

treatment with diluted acid. Relevant ^1H and ^{13}C nmr data are summarized in Table 1.

Scheme 2

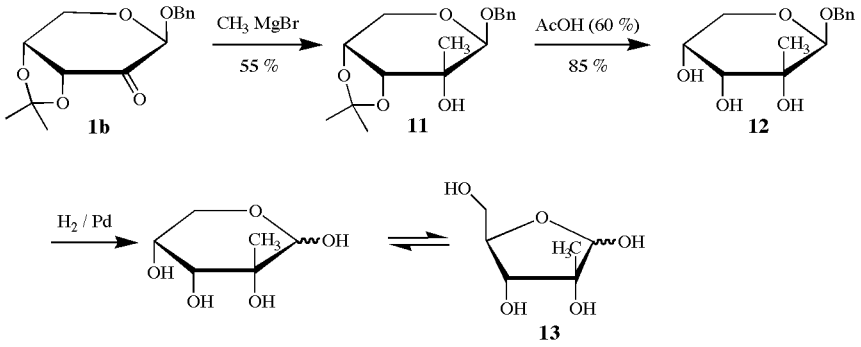


Table 1

^1H and ^{13}C NMR Data of 2-*C*-Trifluoromethyl- and 2-*C*-Methylribopyranosides (acetone-d_6)

	C-1	C-2	C-3	C-4	C-5	H-1	H-3	H-4	H-5a	H-5b
3a	101.4	77.5	65.8	70.3	63.4	4.68	3.69	3.98	3.90	3.73
3b	99.7	76.5	64.7	70.4	63.8	4.23	4.10	4.10	4.01	3.79
12	102.0	72.6	73.8	66.8	63.9	4.56	3.69	4.02	3.75	3.55

Table 3

Relative Amounts of Tautomeric Forms for Differently Substituted Riboses at Equilibrium in D_2O^* at 40 °C, and Acetone-d_6^{**} at Room Temperature.

ribose	α-furanose	β-furanose	α-pyranose	β-pyranose	
2-C-H*	6	18	20	56	[19,23]
2-C-CH_3**	35	22	28	15	
2-C-CF_3**	65	21	2	12	
2-C-C_3F_7**	69	17	<1	14	[24]

Table 2

Mps and Optical Rotation Values of Methyl- and benzylribopyranosides

methyl-2-C-trifluoromethyl-β-D-ribopyranoside (**3a**)	methyl-2-C-methyl-β-D-ribofuranoside [20]	methyl-β-D-ribopyranoside [21]
mp 180.5 - 182 °C $[\alpha]_D$ - 130.9° (c = 1.1, acetone)	109 °C -82° (c = 0.5, EtOH) [21]	80 - 81 °C - 142.0° (c = 0.2, $CHCl_3$)
benzyl-2-C-trifluoromethyl-β-D-ribopyranoside (**3b**)	benzyl-2-C-methyl-β-D-ribopyranoside (**12**)	benzyl-β-D-ribo-pyranoside [22]
mp 184.5 - 186 °C $[\alpha]_D$ - 147° (c = 1, acetone)	109 - 110.5 °C - 120.0° (c = 1, acetone)	105 - 106 °C - 116° (c = 1.3, H_2O)

Remarkable are the significantly higher melting points of the 2-*C*-trifluoromethyl substituted ribopyranosides **3a** and **3b** in comparison to the 2-*C*-methyl and 2-C-H analogues.

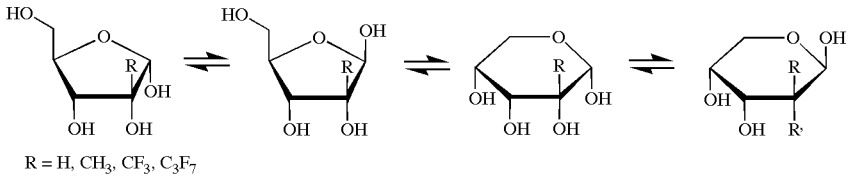
The relative amounts of tautomeric forms at equilibrium very much depend upon the size of the substituents at C-2. With increasing size of the substituents at C-2 the ratio of α-furanose increases, where the anomeric OH group is placed *trans* in respect to the bulky trifluoromethyl group. In contrast, in the pyranose series β-pyranose dominates, where the anomeric OH-function is *cis* positioned with respect to the sterically demanding trifluoromethyl group, occupying the favorable axial position (anomeric effect).

Alcohols with a trifluoromethyl group in β-position exhibit lower pK_a-values than unfluorinated analogues. A pK_a value of 12.4 is described for 2,2,2-trifluoroethanol [25] (C_2H_5OH: 15.9); a pK_a value of 13.86 (± 0.02) measured for **2a** [18] was found in the expected region. This result explains convincingly the unsuccessful fluorodehydroxylation experiments of **2** with DAST [26].

We carried out a series of reactions of 2-*C*-trifluoromethyl *O*-glycosides with trimethylsilylbromide [27], BCl_3 [28] and NBS [29]. Substitution products at C-1 and at C-2 were not obtained, as a consequence of the destabilization of cationic and radical intermediates at C-1 as well as at C-2 caused by the trifluoromethyl group [4].

In summary, we demonstrated that Ruppert's reagent is useful for CF_3-group transfer to carbonyl compounds. However, the synthetic potential of the new 2-*C*-trifluoromethyl subsituted *O*-glycosides as glycosyl-donors seems to be limited.

Scheme 3



Tautomeric forms of **5** and **10** at equilibrium in acetone-d_6 at room temperature.

EXPERIMENTAL

General.

Microanalyses were carried out with a Heraeus CHN-O Rapid apparatus. Melting points were determined on a Boetius apparatus. 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 199.98; ^{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 POLARONIC-D polarimeter. Thin-layer chromatography was performed on Merck (Darmstadt, Germany) Kieselgel 60F_{254} precoated plates. All solvents were dried by standard methods. Reactions are carried out under dry argon.

Trifluoromethylation of 3,4-*O*-Isopropylidene-β-D-ribopyranosides with Trifluoromethyl trimethylsilane (**1** → **2**).

General Procedure.

Method A: 10.0 mmol pentopyranosid-2-ulose (**1** or **6**) were dissolved in 20 ml dry THF and stirred under argon at 0 °C with 1.70 g (12 mmol = 2 ml) trifluoromethyl trimethylsilane, which was added *via* syringe. The reaction was started on addition of 0.5 ml of a TBAF solution in dry THF. After stirring the reaction mixture at 0 °C for 1 hour, the mixture was warmed up to room temperature, and stirred for another 4 hours (reaction followed by TLC). After evaporation of the solvent *in vacuo*, the residue was dissolved in 20 ml of methylene chloride. The organic phase was washed carefully with water (3 x 10 ml). Afterwards the organic phase was dried with $MgSO_4$, then the solvent was distilled off under reduced pressure. The residue was purified by column chromatography (eluent: ethyl acetate).

Method B: Procedure see method A. However, dry methylene chloride was used as solvent and tetrabutylammonium difluorotriphenylstannate as catalyst. After completion of the reaction (reaction followed by TLC), the solvent was distilled off *in vacuo*, the residue was redissolved in methanol and stirred 6 hours with 2.59 g (10.0 mmol) TBAF. After the reaction mixture was evaporated to dryness, the residue was purified by column chromatography (eluent: ethyl acetate).

(-)-Methyl 3,4-*O*-Isopropylidene-2-*C*-trifluoromethyl-β-D-ribopyranoside (**2a**).

Methyl-3,4-*O*-isopropylidene-2-*C*-trifluoromethyl-β-D-*erythro*-ribopyranosid-2-ulose **1a** 2.04 g (10.0 mmol) was treated with 1.70 g (12 mmol = 2 ml) trifluoromethyl trimethylsilane. R_f value: 0.71 (eluent: ethyl acetate); Yield: 1.05 g (39%) **2a** (method A), 1.75 g (64%) (method B), mp 95 - 96.5 °C, colorless crystals; $[\alpha]_D$ = - 137.5° (c = 1.76, $CHCl_3$); pK_s-value: 13.86 ± 0.02 (v/v = 3:1, dioxane/water; pK_w = 16.74; ir (Nujol): 2940, 2854, 1460, 1190 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.40 (s, 3H), 1.59 (s, 3H), 3.28 (s, 1H, C(2)-OH), 3.42 (s, 3H), 3.98 (dd, 1H, J = 13.3 Hz, J = 3.2 Hz), 4.08 (d, 1H, J = 13.3 Hz), 4.29 (dd, 1H, J = 6.4 Hz, J = 3.2 Hz), 4.49 (d, 1H, J = 6.4 Hz), 4.79 ppm (s, 1H); ^{13}C nmr ($CDCl_3$): δ 25.1, 26.4, 56.5, 58.2, 68.9 (q, J = 1.9 Hz), 70.3 (q, J = 26.6 Hz), 70.8, 98.9 (q, J = 1.9 Hz), 110.0, 124.9 ppm (q, J = 286.1 Hz); ^{19}F nmr ($CDCl_3$): δ 0.15 ppm (s, CF_3); ms (EI) m/z = 257 $[M - CH_3]^+$ (25), 241 $[M - OCH_3]^+$ (6), 215 $[M - C_3H_5O]^+$ (23), 182 $[M - CH_3OH, CH_3COCH_3]^+$ (19), 154 $[C_7H_6O_4]^+$ (7), 142 $[C_6H_6O_4]^+$ (10), 137 $[C_7H_5O_3]^+$ (19), 100 $[C_5H_8O_2]^+$ (11), 85 $[C_4H_5O_2]^+$ (19), 59 $[C_3H_7O]^+$ (58), 43 $[C_3H_7]^+$ (100).

Anal. Calcd. for $C_{10}H_{15}F_3O_5$ (272.23): C, 44.12; H, 5.55. Found: C, 44.25; H, 5.81.

(-)-Benzyl-3,4-*O*-Isopropylidene-2-*C*-trifluoromethyl-β-D-ribopyranoside (**2b**).

Benzyl-3,4-*O*-isopropylidene-2-*C*-trifluoromethyl-β-D-*erythro*-pentopyranosid-2-ulose (**1b**) 2.80 g (10.0 mmol) were treated with 1.70 g (12 mmol = 2 ml) trifluoromethyl trimethylsilane in 20 ml dry THF. R_f value: 0.70 (eluent: ethyl acetate); Yield: 1.38 g (40%) **2b** (method A), 2.25 g (65%) (method B), colorless oil; $[\alpha]_D$ = -127.7° (c = 0.81, $CHCl_3$); ir (Nujol) ν 2930, 1459, 1380, 1189 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.36 (s, 3H), 1.60 (s, 3H), 3.36 (s, 1H, C(2)-OH), 4.05 (dd, 1H, J = 13.6, J = 3.2 Hz), 4.13 (dd, 1H, J = 13.6 Hz, J = 1.4 Hz), 4.30 (dd, 1H, J = 6.5 Hz, J = 2.2 Hz), 4.51 (d, 1H, J = 11.6 Hz), 4.56 (d, 1H, J = 6.5 Hz), 4.74 (d, 1H, J = 11.6 Hz), 5.01 (s, 1H), 7.26 - 7.35 ppm (m, 5H); ^{13}C nmr ($CDCl_3$): δ 25.2, 26.5, 58.7, 69.0 (q, J = 1.9 Hz), 70.5 (q, J = 26.4), 70.7, 70.8, 97.0 (q, J = 1.7 Hz), 110.1, 125.0 (q, J = 286.2 Hz), 128.4, 128.7, 129.0, 136.6 ppm; ^{19}F nmr ($CDCl_3$): δ 0.57 ppm (s, CF_3); ms m/z = 348 $[M]^+$ (< 1), 333 $[M - CH_3]^+$ (4), 257 $[M - Bn]^+$ (5), 199 $[M - Bn, - CH_3COCH_3]^+$ (11), 153 $[C_8H_9O_3]^+$ (5), 97 $[C_5H_5O_2]^+$ (32), 91 $[C_7H_7]^+$ (100), 59 $[C_3H_7O]^+$ (17), 41 $[C_3H_5]^+$ (25).

Anal. Calcd. for $C_{16}H_{19}F_3O_5$ (348.33): C, 55.17; H, 5.50. Found: C, 55.35; H, 5.39.

(+) Methyl-3,4-*O*-Isopropylidene-2-*C*-trifluoromethyl-β-L-ribopyranoside (**7a**).

Methyl-3,4-*O*-isopropylidene-2-C-trifluoromethyl-β-L-*erythro*-pentopyranosid-2-ulose (**6a**) 2.04 g (10.0 mmol) were treated with 1.70 g (12 mmol = 2 ml) trifluoromethyl trimethylsilane in 20 ml dry THF. R_f value: 0.71 (eluent: ethyl acetate); Yield: 1.08 g (40%) **7a** (method A), 1.89 g (70%) (method B), mp

95 - 96.5 °C, colorless crystals; $[\alpha]_D$ = + 139.1° (c = 1.1, $CHCl_3$); ir (KBr) ν 3510, 2998, 1387, 1192, 1161 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.34 (s, 3H), 1.53 (s, 3H), 3.25 (s, 1H, C(2)-OH), 3.36 (s, 3H), 3.94 (dd, 1H, J = 13.6 Hz, J = 3.2 Hz), 4.04 (dd, 1H, J = 13.6 Hz, J = 0.8 Hz), 4.23 (dd, 1H, J = 6.4 Hz, J = 3.2 Hz), 4.43 (d, 1H, J = 6.4 Hz), 4.72 ppm (s, 1H); ^{13}C nmr ($CDCl_3$): δ 25.1, 26.4, 56.5, 58.2, 68.9 (q, J = 1.9 Hz), 70.3 (q, J = 26.3 Hz), 70.8, 98.9 (q, J = 1.9 Hz), 110.0, 124.0 ppm (q, J = 286.5 Hz); ^{19}F NMR ($CDCl_3$) δ 0.14 ppm (s, 3F); ms m/z = 272 $[M]^+$ (< 1), 257 $[M - CH_3]^+$ (17), 182 $[M - CH_3OH - CH_3COCH_3]^+$ (13), 143 $[C_6H_7O_4]^+$ (7), 137 $[C_7H_5O_3]^+$ (22), 100 $[C_5H_8O_2]^+$ (9), 85 $[C_4H_5O_2]^+$ (29), 59 $[C_3H_7O]^+$ (38), 42 $[C_3H_6]^+$ (100).

Anal. Calcd. for $C_{10}H_{15}F_3O_5$ (272.23): C, 44.12; H, 5.55. Found: C, 44.07; H, 5.43.

(+)-Benzyl-3,4-*O*-Isopropylidene-2-trifluoromethyl-β-L-ribopyranoside (**7b**).

Benzyl-3,4-*O*-isoproyplidene-β-L-*erythro*-pentopyranosid-2-ulose (**6b**) 2.80 g (10.0 mmol) was trifluoromethylated according to method A. R_f value: 0.7 (eluent: ethyl acetate); Yield: 1.42 g (41%) **7b** colorless oil; $[\alpha]_D$ = +129.8° (c = 0.9, $CHCl_3$); ir (Nujol) ν 2924, 1460, 1382 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.40 (s, 3H), 1.60 (s, 3H), 3.32 (s, 1H, C(2)-OH), 4.05 (dd, 1H, J = 13.6 Hz, J = 3.2 Hz), 4.13 (dd, 1H, J = 13.6 Hz, J = 1.4 Hz), 4.30 (dd, 1H, J = 6.5 Hz, J = 2.2 Hz), 4.51 (d, 1H, J = 11.6 Hz), 4.56 (d, 1H, J = 6.5 Hz), 4.74 (d, 1H, J = 11.6 Hz), 5.01 (s, 1H), 7.26 - 7.35 ppm (m, 5 H); ^{13}C nmr ($CDCl_3$): δ 25.1, 26.4, 58.6, 69.0 (q, J = 1.9 Hz), 70.4 (q, = 26.3 Hz), 70.7, 70.8, 97.0 (q, J = 1.5 Hz), 110.1, 125.0 (q, J = 286.5 Hz), 128.4, 128.7, 129.0, 136.6 ppm; ^{19}F nmr ($CDCl_3$): δ 0.56 ppm (s, 3F); ms m/z = 348 $[M]^+$ (< 1), 333 $[M - CH_3]^+$ (4), 257 $[M - Bn]^+$ (7), 199 $[M- Bn, - CH_3COCH_3]^+$ (12), 153 $[C_8H_9O_3]^+$ (6), 97 $[C_5H_5O_2]^+$ (32), 91 $[C_7H_7]^+$ (100), 59 $[C_3H_7O]^+$ (18), 42 $[C_3H_6]^+$ (40).

Anal. Calcd. for $C_{16}H_{19}F_3O_5$ (348.33): C, 55.17; H, 5.50. Found: C, 55.05; H, 5.41.

Synthesis of *O*-Glycosides (**2** → **3**).

General Procedure.

3,4-*O*-Isopropylidene-2-C-trifluoromethylribopyranoside (**2**) 10.0 mmol were dissolved in 10 ml aqueous acetic acid (v/v = 3:2, CH_3CO_2H/H_2O) and stirred at room temperature for 24 hours. After evaporation of the solvents *in vacuo* compounds **3** were obtained as colorless crystals. The *O*-glycosides are analytically pure after recrystallization from THF/hexanes.

(-)-Methyl-2-*C*-trifluoromethyl-β-D-ribopyranoside (**3a**).

Methyl-3,4-*O*-isopropylidene-2-C-trifluoromethyl-β-D-ribopyranoside (**2a**) 1.36 g (5.0 mmol) were treated with 10 ml aqueous acetic acid according to the general protocol. Yield: 1.10 g (95%) **3a**, mp 180.5 - 182 °C, colorless crystals; $[\alpha]_D$ = - 130.9° (c = 1.1, acetone); ir (KBr) ν 3344, 1342, 1307, 1267, 1200, 1146 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.38 (s, 3H), 3.73 (dd, 1H, J = 12.8 Hz, J = 1.6 Hz), 3.90 (d, 1H, J = 12.8 Hz), 3.98 (m, 1H), 4.02 (d, J = 3.4 Hz), 4.18 (d, 1H, C(3)-OH, J = 9.4 Hz), 4.68 (s, 1H), 4.94 (s, 1H, C(4)-OH, J = 5.2 Hz), 5.31 ppm (s, 1H, C(2)-OH); ^{13}C nmr (acetone-d_6): δ 56.4, 64.6, 65.8, 71.5, 77.5 (q, J = 25.0 Hz), 101.5 (q, J = 2.7 Hz), 126.2 ppm (q, J = 285.7 Hz); ^{19}F nmr (acetone-d_6): δ 3.97 ppm (s, 3F); ms m/z = 232 $[M]^+$ (2), 215 $[M - OH]^+$ (12), 201 $[M - OCH_3]^+$ (7), 183 $[M - OCH_3, - H_2O]^+$ (5), 171 $[M - OCH_3, - CH_2O]^+$ (4), 155 $[M - OCH_3, - CH_2O_2]^+$ (9), 142 $[C_4H_5F_3O_2]^+$ (15), 128 $[C_3H_3F_3O_2]^+$ (16), 85 $[C_4H_5O_2]^+$ (26), 61 $[C_2H_5O_2]^+$ (100), 41 $[C_3H_5]^+$ (51).

Anal. Calcd. for $C_7H_{11}F_3O_5$ (232.16): C, 36.22; H, 4.78. Found: C, 36.53; H, 4.79.

(-)-Benzyl-2-*C*-trifluoromethyl-β-D-ribopyranoside (**3b**).

Benzyl-3,4-*O*-isopropylidene-2-*C*-trifluoromethyl-β-D-ribopyranoside (**2b**) 1.74 g (5.0 mmol) were deblocked on reaction with aqueous acetic acid according to the general procedure. Yield: 1.46 g (95%) **3b**, mp 184.5 - 186 °C, colorless crystals; $[\alpha]_D$ = - 147° (c = 1, acetone); ir (KBr): ν 3341, 1268, 1206, 1185, 1141 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.79 (dd, 1H, J = 12.6 Hz, J = 2.0 Hz), 4.01 (d, 1H, J = 12.6 Hz), 4.10 (m, 1H), 4.10 (dd, 1H, J = 9.2 Hz, J = 3.4 Hz), 4.23 (d, 1H, C(3)-OH, J = 9.2 Hz), 4.56 (d, 1H, J = 11.8 Hz), 4.77 (d, 1H, J = 11.8 Hz), 4.93 (s, 1H), 4.98 (d, 1H, C-(4)-OH, J = 4.8 Hz), 5.37 (s, 1H, C(2)-OH), 7.30 - 7.40 ppm (m, 5H); ^{13}C nmr (acetone-d_6): δ 63.8, 64.7, 69.9, 70.4, 76.5 (q, J = 25.9 Hz), 99.7 (q, J = 2.3 Hz), 125.1 (q, J = 285.7 Hz), 128.2, 128.3, 128.8, 137.8 ppm; ^{19}F nmr (acetone-d_6) δ 4.31 ppm (s, 3F); ms m/z = 308 $[M]^+$ (< 1), 217 $[M - Bn]^+$ (3), 201 $[M - OBn]^+$ (9), 171 $[M - OBn, - CH_2O]^+$ (12), 107 $[BnO]^+$ (10), 91 $[C_7H_7]^+$ (100).

Anal. Calcd. for $C_{13}H_{15}F_3O_5$ (308.26): C, 50.65; H, 4.90. Found: C, 50.49, H, 4.79.

(+)-Methyl-2-*C*-trifluoromethyl-β-L-ribopyranoside (**8a**).

Methyl-3,4-*O*-isopropylidene-2-*C*-trifluoromethyl-β-L-ribopyranoside (**7a**) 1.36 g (5.0 mmol) were treated with aqueous acetic acid according to the general protocol. Yield: 1.04 g (90%) **8a**, mp 180.5 - 182 °C, colorless crystals; $[\alpha]_D$ = + 129.5 ° (c = 1.04, acetone); ir (KBr). ν 3343, 2933, 1452, 1266, 1201, 1146 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.38 (s, 3H), 3.73 (dd, 1H, J = 12.6 Hz, J = 1.8 Hz), 3.91 (d, 1H, J = 12.6 Hz), 3.97 (m, 1H), 4.02 (d, 1H, J = 3.4 Hz), 4.18 (d, 1H, C(3)-OH, J = 9.2 Hz), 4.68 (m, 1H), 4.94 (d, 1H, C(4)-OH, J = 4.9 Hz), 5.31 ppm (s, 1H, C(2)-OH); ^{13}C nmr (acetone-d_6) δ 55.2, 63.4, 64.7, 70.3, 76.4 (q, J = 25.9 Hz), 101.4 (q, J = 2.2 Hz), 125.0 ppm (q, J = 285.3 Hz); ^{19}F nmr (acetone-d_6): δ 3.97 ppm (s, 3F); ms m/z = 217 $[M - CH_3]^+$ (2), 215 $[M - OH]^+$ (49), 201 $[M - OCH_3]^+$ (1), 173 $[M - OCH_3, - CO]^+$ (2), 157 $[M - CH_3O, - CO_2]^+$ (11), 143 $[C_4H_6F_3O_2]^+$ (6), 114 $[C_5H_6O_3]^+$ (5), 98 $[C_5H_6O_2]^+$ (28), 85 $[C_4H_5O_2]^+$ (16), 69 $[CF_3]^+$ (34), 58 $[C_3H_6O]^+$ (35), 41 $[C_3H_5]^+$ (100).

Anal. Calcd. for $C_7H_{11}F_3O_5$ (232.16): C, 36.22; H, 4.78. Found: C, 36.49; H, 4.94.

(+)-Benzyl-2-*C*-trifluoromethyl-β-L-ribopyranoside (**8b**).

Benzyl-3,4-*O*-isopropylidene-2-*C*-trifluoromethyl-β-L-ribopyranoside (**7b**) 1.74 g (5.0 mmol) were treated with 10 ml aqueous acetic acid according to the general protocol. Yield: 1.46 g (95%) **8b**, mp 184.5 - 186 °C, colorless crystals; $[\alpha]_D$ = + 138.7° (c = 1.24, acetone); ir (KBr) ν 3341, 1268, 1204, 1185, 1113 cm^{-1}; ^1H nmr (acetone-d_6): δ 3.79 (dd, 1H, J = 12.7 Hz, J = 2.2 Hz), 4.01 (d, 1H, J = 12.7 Hz), 4.04 (1H, m), 4.10 (dd, 1H, J = 9.2 Hz, J = 3.2 Hz), 4.20 (d, 1H, C-(3)-OH, J = 9.2 Hz), 4.56 (d, 1H, J = 11.8 Hz), 4.77 (d, 1H, J = 11.8 Hz), 4.93 (s, 1H), 4.96 (s, 1H, C(4)-OH), 5.34 (s, 1H, C(2)-OH), 7.32 - 7.39 ppm (m, 5H); ^{13}C nmr (acetone-d_6): δ 63.8, 64.7, 69.9, 70.5, 76.5 (q, J = 25.9 Hz), 99.7, 125.1 (q, J = 285.7 Hz), 128.2, 128.3, 128.8, 137.8 ppm; ^{19}F nmr (acetone-d_6): δ 4.31 ppm (s, 3F); ms m/z = 308 $[M]^+$ (< 1), 231 $[M - C_6H_5]^+$ (< 1), 217 $[M - Bn]^+$ (1), 201 $[M - OBn]^+$(5),

171 [M - OBn, - CH_2O]$^+$ (6), 141 [$C_4H_4F_3O_2$]$^+$ (2), 107 [BnO]$^+$ (5), [C_7H_7]$^+$ (100)

Anal. Calcd. for $C_{13}H_{15}F_3O_5$ (308.26): C, 50.65; H, 4.90. Found: C, 50.58; H, 4.81.

(-) 2-*C*-Trifluoromethyl-D-ribose (**5**).

Compound **3a** 0.46 g (0.2 mmol), or 0.62 g (0.2 mmol) **3b** were heated in 10 ml of a CF_3CO_2H/H_2O mixture (v/v 7:3) under reflux until compound **3** was completely consumed (TLC analysis). Then the solvent was evaporated *in vacuo* and the remaining oil was purified by column chromatography (eluent: ethyl acetate/methanol, 2:1).Yield: 0.40 g (90%) **5**, mp 96 - 97 °C, colorless crystals; $[\alpha]_D$ = -2.5° (c = 0.33, H_2O), after 1 day $[\alpha]_D$ = -17°; for further data see [9b].

(+)-2-*C*-Trifluoromethyl-L-ribose (**10**).

Compound **8a** 0.46 g (0.2 mmol) or 0.62 g (0.2 mmol) **8b** were heated in 10 ml of CF_3CO_2H/H_2O mixture (v/v = 7:3) under reflux until compound **8** was completely consumed (TLC analysis). Then the solvent was evaporated *in vacuo* and the remaining oil was purified by column chromatography (eluent: ethyl acetate/methanol, 2:1). Yield: 0.38 g (85 %) **10**, mp 96 - 97 °C, colorless crystals; $[\alpha]_D$ = + 1.0° (c = 0.52, H_2O), after 1 day $[\alpha]_D$ = + 15.3°.

Synthesis of 2-Methyl-D-ribose.

(-)-Benzyl-3,4-*O*-isopropylidene-2-*C*-methyl-β-D-ribopyranoside (**11**).

To a solution of 2.80 g (10.0 mmol) benzyl-3,4-*O*-isopropylidene-β-D-*erythro*-pentopyranosid-2-ulose (**1b**) in 10 ml dry diethyl ether at -78 °C, 10 mmol methyl magnesiumbromide (3 *M* in ether) were slowly added *via* syringe. The reaction mixture was slowly warmed up to -10 °C and quenched with a saturated solution of NH_4Cl. After extraction with diethyl ether, the organic phase was dried with $MgSO_4$. Then the solvent was distilled off under reduced pressure and the remaining product was purified by column chromatography (eluent: methylene chloride, R_f value: 0.6). Yield: 1.62 g (55%) **11**, colorless oil; $[\alpha]_D$ = - 125.2 ° (c = 1.2, $CHCl_3$); ir (Nujol) ν 2984, 1455, 1375, 1161 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.30 (s, 3H), 1.31 (s, 3H), 1.46 (s, 3H), 3.13 (s, 1H, C(2)-OH), 3.58 (dd, 1H, J = 12.2 Hz, J = 2.3 Hz), 4.08 (dd, 1H, J-= 12.2 Hz, J = 2.9 Hz), 4.18 (d, 1H, J = 7.0 Hz), 4.27 (dt, 1H, J = 7.0 Hz, J = 2.3 Hz, J = 2.9 Hz), 4.57 (d, 1H, J = 11.9 Hz), 4.60 (s, 1H), 4.84 (d, 1H, J = 11.9 Hz), 7.27 - 7.33 ppm (m, 5H); ^{13}C nmr ($CDCl_3$) δ 24.8, 25.5, 26.5, 63.5, 69.9, 70.0, 73.2, 77.8, 98.6, 110.1, 128.3, 128.5, 128.9, 138.1 ppm; ms m/z = 279 [M - CH_3]$^+$ (4), 203 [M - Bn]$^+$ (2), 170 [M - BnO, - OH]$^+$ (2), 157 [$C_6H_5O_5$]$^+$ (25), 145 [M - Bn, - CH_3COCH_3]$^+$ (8), 99 [$C_5H_7O_2$]$^+$ (36), 91 [C_7H_7]$^+$ (100), 59 [C_3H_7O]$^+$ (38), 43 [C_3H_7]$^+$ (82).

Anal. Calcd. for $C_{16}H_{22}O_5$ (294.35): C, 65.32; H, 7.54. Found: C, 65.25; H, 7.71.

(-)-Benzyl-2-C-methyl-β-D-ribopyranoside (**12**).

Compound **11** 0.59 g (0.2 mmol) were stirred with 5 ml aqueous acetic acid (v/v = 3:2) at room temperature for 48 hours. After evaporation of the solvent under reduced pressure the remaining solid was recrystallized from THF/hexane. Yield: 0.43 g (85%) **12**, mp 109 - 110.5 °C, colorless crystals; $[\alpha]_D$ = - 120.0° (c = 1.0, acetone); ir (KBr) ν 2933, 2920, 1456, 1306, 1148, 1029 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 1.25 (s, 3H), 3.55 (dd, 1H, J = 11.4 Hz, J = 7.2 Hz), 3.69 (s, 3H), 3.75 (d. 1H, J = 11.4 Hz, J = 4.0 Hz), 4.02 (dd, 1H, J = 7.2 Hz, J = 4.0 Hz), 4.54 (d, 1H, J = 12.2 Hz), 4.56 (s, 1H), 4.78 (d, 1H, J = 12.0 Hz), 7.30 - 7.38 ppm (m, 5H); ^{13}C nmr (acetone-d_6): δ 21.3, 63.9, 66.8, 70.2, 72.6, 73.8, 102.0, 128.0, 128.3, 128.8, 138.7 ppm; ms m/z = 223 [M - CH_3O]$^+$ (1), 177 [M - C_6H_5]$^+$ (2), 159 [M - C_6H_5, - H_2O]$^+$ (1), 145 [M - Bn, - H_2O]$^+$ (149), 130 [M - OBn, - OH]$^+$ (3), 117 [M - OBn, - CH_2O]$^+$ (28), 91 [C_7H_7]$^+$ (100), 43 [C_3H_7]$^+$ (59).

Anal. Calcd. for $C_{13}H_{18}O_5$ (254.29): C, 61.40; N, 7.14. Found: C, 61.17; N, 6.97.

(-)-2-*C*-Methyl-D-ribose (**13**).

Method A: A solution of 0.26 g (0.1 mmol) **12** in 5 ml of dry methanol was stirred for 24 hours in an atmosphere of hydrogen in the presence of a Pd-catalyst (10% on char coal). After filtration of the catalyst and evaporation of the solvent *in vacuo*, **13** was obtained as pure compound.

Method B: 0.26 g (0.1 mmol) **12** were heated with 10 ml diluted sulfuric acid (5%) under reflux. After cooling to room temperature, the mixture was neutralized with NH_4OH and evaporated to dryness. The residue was dissolved in methanol and filtered off. After evaporation of the solvent compound **13** was analytically pure. Yield: 0.15 g (90%) method A, 0.14 g (87%) method B, mp 93 - 94 °C, colorless crystals; lit. mp 93-95 °C [29]; $[\alpha]_D$ = - 3.0 ° (c = 0.41, H_2O), after 1 day $[\alpha]_D$ = - 15.0°.

Acknowledgements.

The authors thank the European Community (Training - Mobility - Research: Contract no. ERBFMRXCT 970120: “Fluorine a Unique Tool for Engineering Chemical Properties”) and the Funds of the Chemical Industry for financial support.

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