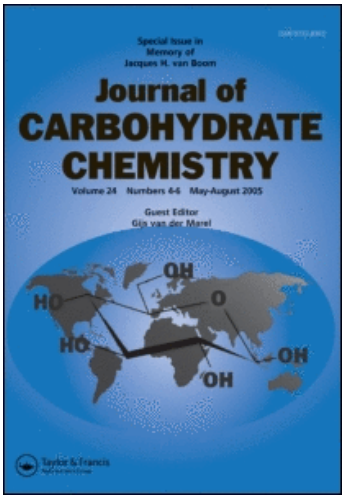

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SYNTHESIS OF 3-DEOXY-3-*C*-TRIFLUOROMETHYL-D-RIBOSE FROM D-XYLOSE OR D-GLUCOSE

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ABSTRACT

The synthesis of 3-deoxy-1,2-*O*-isopropylidene-3-*C*-trifluoromethyl-α-D-ribofuranose is described. After a first approach from a commercial D-xylose derivative which was limited by an incomplete stereoselectivity, the synthesis of the title compound was performed from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose by a reaction sequence where key steps: trifluoromethylation with CF_3SiMe_3 and radical deoxygenation are highly stereoselective.

INTRODUCTION

The need for new antiviral agents has led to growing interest in the synthesis of modified nucleosides. Fluoro substituted derivatives are attractive compounds, with the fluorine incorporated either into the base or sugar moiety. The latter derivatives are most often encountered. Mono and difluoro sugars have been widely studied,[1] and recently several papers have reported the syntheses of trifluoromethyl substituted sugars.[2] A very recent publication of the synthesis of 3'-*C*-trifluoromethyl ribonucleosides[3] prompted us to report our results about two approaches to the synthesis of 3-deoxy-3-*C*-trifluoromethyl-D-ribose derivatives from D-xylose and D-glucose, respectively.

RESULTS AND DISCUSSION

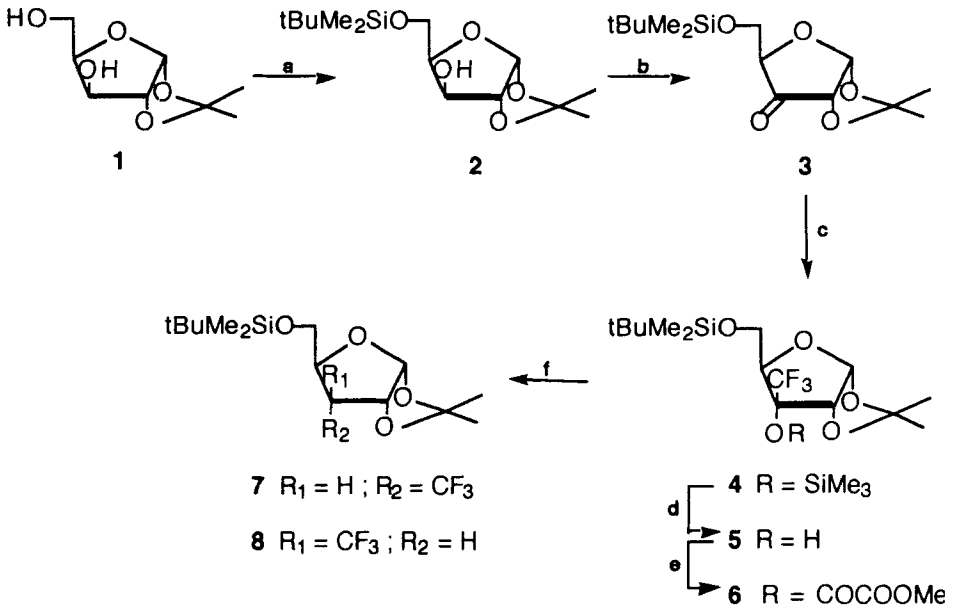
The key reactions in the sequence were a nucleophilic trifluoromethylation of a 3-oxo-furanose derivative followed by a radical deoxygenation. The success of such a strategy depended on the stereoselectivity of the process. Trifluoromethylation was carried out using trifluoromethyltrimethylsilane (TFMTMS), a very convenient reagent.[4] However, owing to its tedious preparation,[4] or its high commercial cost, it is important to limit the number of steps after the trifluoromethylation.

Hence, we began the synthesis with the commercially avalaible D-xylose derivative **1**, 1,2-*O*-isopropylidene-α-D-xylofuranose (Scheme 1). Selective protection[5] of the 5-hydroxyl group as a silyl ether gave compound **2**. Protection as a silyl ether rather than an ester would avoid side reactions with TFMTMS. Compound **2** was oxidized using pyridinium dichromate (PDC) by a standard procedure[6] to give the 3-oxo-pentofuranose derivative **3**. Treatment of **3** with TFMTMS under catalytic fluoride activation led to the bis-silylated 3-*C*-trifluoromethyl-D-ribose derivative **4** which, when in methanol solution, was easily and specifically desilylated at the 3-position by addition of a catalytic amount of sodium. The stereochemistry of **4** was based on the well known β-face preference of addition on an sp^2 C-3 for this type of compound.[3,7,8]

Deoxygenation at C-3 was attempted via reduction of the methyloxalate ester **6**, an excellent method for deoxygenation of tertiary alcohols.[9] Compound **6** was easily obtained by treating **5** with methyl oxalyl chloride and pyridine. It was then dissolved in toluene and reduced with tributyltin hydride (TBTH) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN). Two drawbacks appeared at this stage of the synthesis: (i) the deoxygenation was difficult to complete and starting alcohol **5** was recovered beside the expected deoxygenated product; (ii) the hydrogen transfer step was not completely stereoselective and a mixture of nonseparable D-ribo and D-xylo derivatives **7** and **8** was obtained in a ratio **7**/**8** = 93/7. This result is to be compared with similar high stereoselectivity observed at the 2 position of an analogous compound.[8]

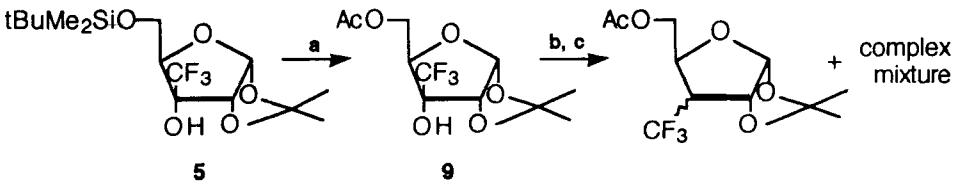
The configuration at C-3 for **7** and **8** was confirmed from their ^1H and ^{19}F NMR spectra: in the major stereoisomer **7** the coupling constant $J_{2,3} = 4.7$ Hz is representative of a *cis* relation between the corresponding hydrogens.[10] This configuration was corroborated by comparison of the chemical shifts of the CF_3 group of the two epimers: $\delta_F(\mathbf{7}) > \delta_F(\mathbf{8})$ which is in agreement with δ(cis) > δ(trans) observed for a series of sugar derivatives with vicinal CF_3 and oxygen atom.[11]

We attempted to improve the yield and the stereoselectivity of this deoxygenation by changing the bulky TBDMS group for an acetyl group.[12] Compound **5** was converted to



(a) 1.1 equiv Et_3N, DMAP cat., 1.1 equiv TBDMSCl, CH_2Cl_2, rt, 3 h; (b) 1.5 equiv PDC, molecular sieve powder 3 A, 1.6 equiv AcOH, CH_2Cl_2, rt; (c) 1.1 equiv CF_3SiMe_3, THF, TBAF cat., rt; (d) 0.1 equiv Na, MeOH, rt, 1 h; (e) 3 equiv pyridine, 2 equiv ClCOCOOMe, CH_2Cl_2, rt, 1 h; (f) 2 equiv Bu_3SnH, 0.5 equiv AIBN, toluene, 100 °C, 1 h.

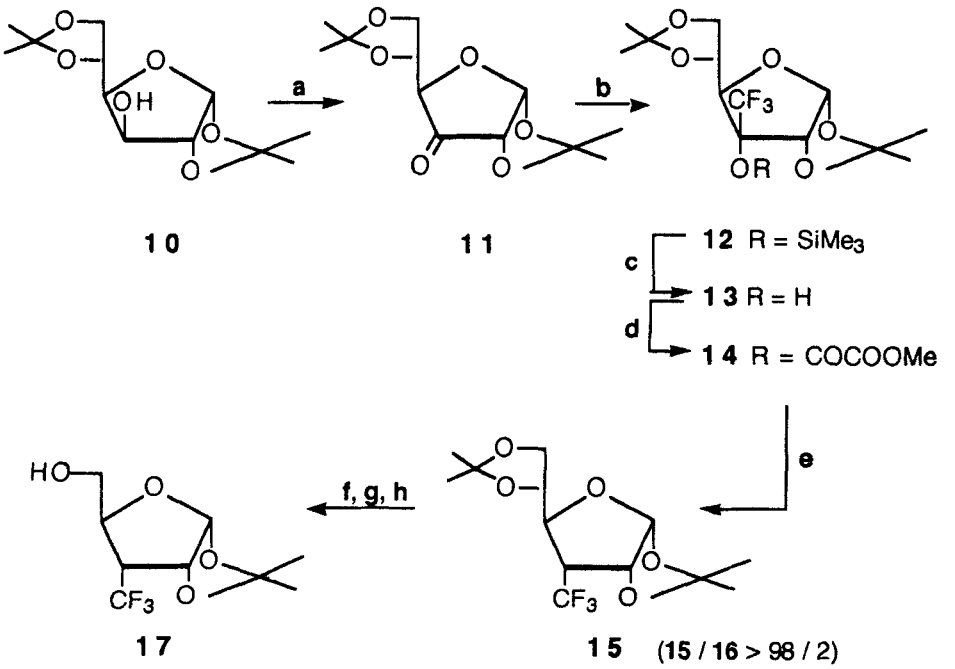
Scheme 1



(a) 1 equiv TBAF, 0.5 equiv DMAP, 1.2 equiv Ac_2O, CH_2Cl_2, rt, 1 h 30'; (b) 3 equiv pyridine, 2 equiv ClCOCOOMe, CH_2Cl_2, rt, 1 h; (c) 2 equiv Bu_3SnH, 0.5 equiv AIBN, toluene, 100 °C, 1 h.

Scheme 2

the corresponding 5-*O*-acetyl derivative **9** (Scheme 2) by desilylation with tetrabutylammonium fluoride (TBAF) and subsequent *in situ* acetylation by acetic anhydride. However, deoxygenation of the corresponding oxalate gave a complex mixture (**5**, the two epimeric deoxygenated products and tin derivatives) which was not further



(a) 1.5 equiv PDC, molecular sieve powder 3 A, 1.6 equiv AcOH, CH_2Cl_2, rt; (b) 1.1 equiv CF_3SiMe_3, THF, TBAF cat., rt; (c) 1 equiv TBAF, MeOH, rt, 1 h; (d) 3 equiv pyridine, 2 equiv ClCOCOOMe, CH_2Cl_2, rt, 1 h; (e) 2 equiv Bu_3SnH, 0.5 equiv AIBN, toluene, 100 °C, 1 h; (f) H_2SO_4 0.8%, methanol-dioxane, 35 °C, 72 h; (g) 1 equiv $NaIO_4$, H_2O, rt, 1 h 30'; (h) 1 equiv $NaBH_4$, H_2O-MeOH, 0 °C, 2 h.

Scheme 3

resolved. Therefore the reaction sequence **1**→**7** suffered several drawbacks justifying another approach.

Although it will necessarily require further steps to reach the pentose series, we have examined the reaction sequence starting from the readily available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, **10**. After oxidation of **10** (Scheme 3) leading to the 3-oxo derivative **11**, trifluoromethylation with TFMTMS under the same conditions as above gave the 1,2:5,6-di-*O*-isopropylidene-3-*C*-trifluoromethyl-3-*O*-trimethylsilyl-α-D-allofuranose **12** in a virtually quantitative yield and with complete stereoselectivity. Compound **12** was submitted as above to deoxygenation. Conversion to methyl oxalate **14** was a clean reaction and crude **14** was directly treated with TBTH. Good results were obtained both from the yield (73%) and stereoselectivity points of view. Only traces of β-CF_3 epimer **16** could be detected in a saturated ^{19}F NMR spectrum, showing a highly selective hydrogen transfer from the β-face of the planar radical intermediate. We have to

mention that anhydrous conditions are a crucial requirement for the transformation **13→15** (as well as for **5→7**) owing to the fairly easy hydrolysis of the oxalate ester, the electrophilicity of which is enhanced by the CF_3 group.

Thus the key sequence trifluoromethylation-deoxygenation works much better in the allose series than in the ribose series. It remained to cleave the C-5-C-6 bond to have access to 3-deoxy-3-*C*-trifluoromethyl-D-ribose. Classical reactions, selective hydrolysis of the 5,6 ketal, periodic oxidation and $NaBH_4$ reduction,[13] led to the crystallized expected compound **17** with a satisfactory overall yield (68%).

CONCLUSION

Comparison of the two pathways led to the conclusion that in spite of the greater number of steps, the preparation of 3-deoxy-3-*C*-trifluoromethyl-D-ribose (protected) from D-glucose is the more efficient strategy due to increased yield and the high stereoselective trifluoromethylation-deoxygenation sequence. We have now in hand the pure compound for further transformation into corresponding nucleosides and/or deoxynucleosides.

EXPERIMENTAL

General methods. All reactions were performed under a constant flow of dry argon. Toluene was dried with CaH_2 and then distilled directly before use. Commercial dichloromethane (Fluka puriss) was used without further purification. Tetrahydrofuran was distilled directly before use from sodium / benzophenone. Merck silica gel F_{254} (0.2 mm) was used for TLC plates, detection being carried out by spraying with an alcoholic solution of phosphomolybdic acid, followed by heating. Flash column chromatography was performed on silica gel Merck Art 9385 Kieselgel 60 (0.04-0.063). Melting points were determined with a Buchi apparatus. IR spectra were recorded with an IR^{TM} plus MIDAC spectrophotometer and are expressed in cm^{-1}. NMR spectra were recorded in $CDCl_3$ on a Brücker AC 250 spectrometer (250 MHz for ^1H, 62.5 MHz for ^{13}C and 235.36 MHz for ^{19}F). Chemical shifts are expressed in parts per million from TMS (^1H and ^{13}C) or $CFCl_3$ as internal reference. Coupling constants are in Hz and splitting pattern abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Optical rotations were determined with a Perkin-Elmer Model 241 polarimeter. Elemental analyses were performed with a Perkin-Elmer CHN 2400 apparatus. Mass spectra were recorded on a Jeol D 30 spectrometer, at 70 eV.

1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-α-D-xylofuranose (2) To a solution of 1,2-*O*-isopropylidene-α-D-xylofuranose **1** (5 g, 26.3 mmol), Et_3N (4 mL,

28.6 mmol) and DMAP (0.3 g, 2.6 mmol) in CH_2Cl_2 (100 mL) was added *tert*-butyldimethylsilyl chloride (4.3 g, 28.6 mmol). The mixture was stirred for 3 h at room temperature and then washed with a saturated $NaHCO_3$ solution (25 mL) and water (2 x 20 mL). The organic layer was dried over Na_2SO_4 and, after filtration, the solvent was removed *in vacuo*. The residue was distilled under reduced pressure to give an oil (6.46 g, 81%): $bp_{0.3}$ 120-122 °C; $[\alpha]^{17}_D$ -5.5° (*c* 0.63, $CHCl_3$); IR (KBr) 3462, 2936, 2487, 1078, 1014, 839; SM (70 eV): 289 (8), 247 (17), 189 (34), 171 (37), 129 (37), 117 (97), 75 (100); ^1H NMR ($CDCl_3$) δ 0.14 (s, 6H, $Si(CH_3)_2$), 0.92 (s, 9H, $(CH_3)_3$), 1.34 and 1.51 (2 x (s, 3H, CH_3)), 4.14 (m, 3H, H-4, H-5, H-5'), 4.32 (m, 2H, OH, H-3), 4.53 (d, 1H, $J_{2,1}$ = 3.4 Hz, H-2), 5.98 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ -5.7 and -5.6 (2 x $SiCH_3$), 18.0 (Cq TBDMS), 25.6 (*tert*-butyl), 26.1 and 26.7 (2 x CH_3), 62.2 (C-5), 76.8 (C-4), 78.3 (C-3), 85.5 (C-2), 104.9 (C-1), 111.4 (Cq isopropylidene).

Anal. Calcd for $C_{14}H_{28}O_5Si$ (304.46): C, 55.26; H, 9.21. Found: C, 55.20; H, 9.13.

1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-α-D-*erythro*-pentofuranos-3-ulose (3). According to the general procedure[6] of oxidation employing PDC and after standard work up and purification by distillation, compound **3** was obtained as an oil (4.41 g, 89%): $bp_{0.4}$ 120-121 °C; $[\alpha]^{16}_D$ +132.3° (*c* 0.85, $CHCl_3$); IR (KBr) 2936, 2860, 1780, 1253, 1114, 839; SM (70 eV) 303 (M+1, 7), 287 (26), 245 (33), 129 (70), 117 (100), 75 (85), 59 (63); ^1H NMR ($CDCl_3$) δ 0.01 and 0.04 (2 x (s, 3H, $SiCH_3$)), 0.85 (s, 9H, $(CH_3)_3$), 1.41 and 1.43 (2 x (s, 3H, CH_3)), 3.80 (dd, 1H, $J_{5,5'}$ = 11.0 Hz, $J_{5,4}$ = 2.0 Hz, H-5), 3.86 (dd, 1H, $J_{5',5}$ = 11.0 Hz, $J_{5',4}$ = 1.5 Hz, H-5'), 4.25 (d, 1H, $J_{2,1}$ = 4.6 Hz, H-2), 4.34 (m, 1H, H-4), 6.11 (d, 1H, $J_{1,2}$ = 4.6 Hz, H-1); ^{13}C NMR ($CDCl_3$) -5.7 and -5.6 (2 x $SiCH_3$), 18.1 (Cq TBDMS), 25.7 (*tert*-butyl), 27.1 and 27.6 (2 x CH_3), 63.9 (C-5), 77.1 (C-4), 81.7 (C-2), 103.7 (C-1), 114.0 (Cq isopropylidene), 210.7 (CO).

Anal. Calcd for $C_{14}H_{26}O_5Si$ (302.45): C, 55.63; H, 8.60. Found: C, 55.82; H, 8.79.

General procedure for the nucleophilic trifluoromethylation. The 3-oxo hydrate was dehydrated by azeotropic distillation from a solution in toluene before use. To a stirred solution of the nonhydrated keto compound (1 mmol) in anhydrous THF (5 mL) was added trifluoromethyltrimethylsilane (TFMTMS, 1.1 mmol) and a catalytic amount of tetra-*n*-butylammonium fluoride (20 mg for 10 mmol) at room temperature. When the reaction was completed, the mixture was washed with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O (2 x 10 mL) and the organic layer dried with magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography.

1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-3-*C*-trifluoromethyl-α-D-ribofuranose (5). The general procedure for trifluoromethylation was followed

from compound **3**. To the crude product **4**, in methanol solution, was added a catalytic amount (0.1 equiv) of metallic Na at 0 °C. The reaction was completed within 1 h, the reaction mixture was treated with a saturated NH_4Cl solution and the aqueous layer was extracted with Et_2O. The combined organic layer was dried over Na_2SO_4. After purification by flash chromatography (petroleum ether/AcOEt 97/3), compound **5** was obtained as an oil (3.73 g, 86%): $[\alpha]^{22}D$ +21.8° (*c* 0.88, $CHCl_3$); IR (KBr) 3373, 2936, 1479, 1165, 1028, 839; SM (70 eV) 372 ($M^{+\circ}$, trace), 357 (7), 257 (25), 117 (98), 101 (31), 89 (64), 73 (81), 59 (100); ^1H NMR ($CDCl_3$) δ -0.56 (s, 6H, $Si(CH_3)_2$), 0.25 (s, 9H, $(CH_3)_3$), 0.76 and 0.96 (2 x (s, 3H, CH_3)), 2.68 (s, 1H, OH), 3.16-3.35 (m, 2H, H-5, H-5'), 3.48 (m, 1H, H-4), 3.93 (d, 1H, $J_{2,1}$ = 4.2 Hz, H-2), 5.27 (d, 1H, $J_{1,2}$ = 4.2 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ -5.6 and -5.4 (2 x $SiCH_3$), 18.3 (Cq TBDMS), 25.8 (*tert*-butyl), 26.4 and 26.9 (2 x CH_3), 60.9 (C-5), 78.9 (C-4), 79.2 (q, $^2J_{C,F}$ = 29.5 Hz, C-3), 83.5 (C-2), 104.4 (C-1), 113.8 (Cq isopropylidene), 124.3 (q, $J_{C,F}$ = 284.0 Hz, CF_3); ^{19}F NMR δ -76.47 (s, 3F, CF_3).

Anal. Calcd for $C_{15}H_{27}O_5F_3Si$ (372.46): C, 48.38; H, 7.25. Found: C, 48.20; H, 7.30.

3-Deoxy-1,2-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilyl-3-*C*-trifluoromethyl-α-D-ribofuranose (7) and D-xylofuranose (8). To a solution of compound **5** (0.39 g, 1 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.24 mL, 3 mmol) was added dropwise, under argon, methyl oxalyl chloride (0.18 mL, 2 mmol). The reaction mixture was stirred for 1 h at room temperature. The reaction was then poured into a saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic layer was dried under Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the residue was dried under high vacuum to give crude compound **6**. Without further purification, the residue was dissolved in anhydrous toluene (4 mL) and a solution of 2-2'-azobisisobutyronitrile (AIBN, 34 mg, 0.2 mmol) and Bu_3SnH (0.53 mL, 2 mmol) in anhydrous toluene was added at room temperature. The mixture was then heated to reflux under an argon atmosphere. When the reaction was completed (1 h), the solvent was removed under reduced pressure. The residue was separated by flash chromatography to give compounds **7** and **8** (petroleum ether/AcOEt 99/1) as a mixture of diastereoisomers (0.197 g, 53%, 93/7 by ^{19}F NMR), and starting material **5** (45%).

7: IR (Film) 2936, 2860, 1265, 1128, 1028, 839; SM (70 eV) 356 ($M^{+\circ}$, 5), 341 (51), 163 (65), 131 (30), 117 (100); ^1H NMR ($CDCl_3$) δ 0.06 and 0.07 (2 x (s, 3H, $SiCH_3$)), 0.88 (s, 9H, $(CH_3)_3$), 1.35 and 1.54 (2 x (s, 3H, CH_3)), 3.01 (ddq, 1H, $J_{3,F}$ = 7.4 Hz, $J_{3,2}$ = 4.7 Hz, $J_{3,4}$ = 4.2 Hz, H-3), 3.70 (dd, 1H, $J_{5,5'}$ = 11.8 Hz, $J_{5,4}$ = 2.3 Hz, H-5), 3.97 (dd, 1H, $J_{5',5}$ = 11.8 Hz, $J_{5',4}$ = 1.9 Hz, H'-5), 4.37 (ddd, 1H, $J_{4,3}$ = 4.2 Hz, $J_{4,5}$ = 2.3 Hz, $J_{4,5'}$ = 1.9 Hz, H-4), 4.86 (dd, 1H, $J_{2,3}$ = 4.7 Hz, $J_{2,1}$ = 3.6 Hz, H-2), 5.83 (d,

1H, $J_{1,2}$ = 3.6 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ -5.6 and -5.3 (2 x $SiCH_3$), 18.3 (Cq TBDMS), 25.8 (*tert*-butyl), 26.5 and 26.6 (2 x CH_3), 46.6 (q, $^2J_{C,F}$ = 27.5 Hz, C-3), 61.4 (C-5), 78.2 (C-4), 79.5 (C-2), 104.9 (C-1), 113.2 (Cq isopropylidene), 124.6 (q, $J_{C,F}$ = 278.0 Hz, CF_3); ^{19}F NMR δ -62.71 (d, 3F, $J_{F,H}$ = 7.4 Hz, CF_3).

8: ^{19}F NMR δ -65.40 (d, 3F, $J_{F,H}$ = 11.0 Hz, CF_3).

Anal. Calcd for $C_{15}H_{27}O_4F_3Si$ (356.46): C, 50.56; H, 7.58. Found: C, 50.95; H, 7.66.

1,2:5,6-Di-*O*-isopropylidene-3-*C*-trifluoromethyl-α-D-allofuranose (13) The general procedure for trifluoromethylation was applied from 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose **11**.[6] To the crude **12** dissolved in methanol was added 1 equivalent of TBAF at rt for desilylation. The reaction was completed within 1 h, the solvent was evaporated and the residue purified by flash chromatography (petroleum ether/AcOEt 80/20) to give **13** as a white solid (88%): mp 76 °C; $[\alpha]^{20}_D$+23.0° (*c* 1.8, $CHCl_3$); IR (KBr) 3374, 2986, 1215, 1153, 1014, 877; SM (70 eV) 313 (100), 195 (22), 131 (30), 101 (96), 69 (39), 59 (68); ^1H NMR ($CDCl_3$) δ 1.36, 1.39, 1.45 and 1.61 (4 x (s, 3H, CH_3)), 3.31 (s, 1H, OH), 3.94 (dd, 1H, $J_{6,6'}$ = 8.8 Hz, $J_{6,5}$ = 5.3 Hz H-6), 4.00 (d, 1H, $J_{4,3}$ = 2.3 Hz, H-4), 4.11 (dd, 1H, $J_{6',6}$ = 8.8 Hz and $J_{6',5}$ = 6,1 Hz, H-6'), 4.34 (m, 1H, H-5), 4.60 (d, 1H, $J_{2,1}$ = 3.8 Hz, H-2), 5.83 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 26.1 and 26.8 (2 x 2 CH_3), 67.2 (C-6), 72.8 (C-5), 79.1 (C-2), 80.1 (q, $^2J_{C,F}$= 28.0 Hz, C-3), 81.4 (C-4), 104.0 (C-1), 109.8 (Cq isopropylidene), 113.8 (Cq isopropylidene), 124.2 (q, $^2J_{C,F}$ = 285.0 Hz, CF_3); ^{19}F NMR δ -76.25 (s, 3F, CF_3).

Anal. Calcd for $C_{13}H_{19}O_6F_3$ (328.28): C, 47.56; H, 5.79. Found: C, 47.44; H, 5.54.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-trifluoromethyl-α-D-allofuranose (15) and D-glucofuranose (16). To a solution of compound **13** (1 g, 3 mmol) in CH_2Cl_2 (15 mL) and pyridine (0.73 mL, 9 mmol) was added dropwise, under argon, methyl oxalyl chloride (0.55 mL, 6 mmol). The reaction mixture was stirred for 1 h at room temperature. Then, the reaction was poured into a saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the residue was dried under high vacuum to give crude compound **14**. Without further purification, **14** was dissolved in anhydrous toluene (7 mL) and a solution of AIBN (246 mg, 1.5 mmol) and Bu_3SnH (1.61 mL, 6 mmol) in anhydrous toluene was added at room temperature. The mixture was then heated to 100 °C under an argon atmosphere. When the reaction was completed (1 h), the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/AcOEt 95/5), to give compound **15** (0.69 g, 73%) containing a trace of **16** (**15/16** > 98/2 by ^{19}F NMR).

15: IR (Film) 2990, 2941, 1386, 1024; SM (70 eV) 313 (M+1, 20), 312 ($M^{+\bullet}$, 17), 297 (100), 211 (76), 179 (99), 153 (55), 122 (67); ^1H NMR ($CDCl_3$) δ 1.35, 1.43, 1.56 and 1.72 (4 x (s, 3H, CH_3)), 2.68 (ddq, 1H, $J_{3,4}$ = 9.3 Hz, $J_{3,F}$ = 7.6 Hz, $J_{3,2}$ = 5.0 Hz, H-3), 3.91 (dd, 1H, $J_{6,6'}$ = 8.4 Hz, $J_{6,5}$ = 5.8 Hz, H-6), 4.07 (dd, 1H, $J_{6',6}$ = 8.4 Hz, $J_{6',5}$ = 6.8 Hz, H-6'), 4.21 (m, 1H, H-5), 4.37 (dd, 1H, $J_{4,3}$ = 9.3 Hz, $J_{4,5}$ = 5.0 Hz, H-4), 4.85 (dd, 1H, $J_{2,3}$ = 5.0 Hz, $J_{2,1}$ = 3.7 Hz, H-2), 5.83 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 25.1 (2 x CH_3), 26.2 and 26.6 (2 x CH_3), 50.3 (q, $^2J_{C,F}$ = 27.5 Hz, C-3), 65.7 (C-6), 76.1 (C-5), 77.0 (C-4), 79.8 (C-2), 104.5 (C-1), 110.0 (Cq isopropylidene), 113.6 (Cq isopropylidene), 124.2 (q, $^2J_{C,F}$ = 278.0 Hz, CF_3); ^{19}F NMR: δ -61.02 (d, 3F, $J_{F,H}$ = 7.6 Hz, CF_3).

16: ^{19}F NMR: -65.05 (d, 3F, $J_{F,H}$ = 10.0 Hz, CF_3).

Anal. Calcd for $C_{13}H_{19}O_5F_3$ (312.28): C, 49.99; H, 6.13. Found: C, 50.28; H, 6.07.

3-Deoxy-1,2-*O*-isopropylidene-3-*C*-trifluoromethyl-α-D-ribofuranose (17). To the mixture **15-16** (6.6 g, 21.1 mmol) dissolved in a mixture of methanol-dioxane (50/50, v/v, 76 mL) was added an aqueous solution 0.8% (v/v) of sulfuric acid (13.2 mL). The reaction was warmed to 35 °C and the reaction followed by TLC. After 24 h, 2 mL of the sulfuric acid solution was added. After stirring for 72 h at 35 °C, a saturated aqueous solution of $NaHCO_3$ was added (15 mL) and the solution was concentrated under reduced pressure. The residue was then poured in 75 mL of water and extracted with CH_2Cl_2 (2 x 100 mL). The organic layer was dried under Na_2SO_4 and the solvent removed *in vacuo* to give a syrup (4.92 g, 85%). The periodic oxidation followed by $NaBH_4$ reduction was carried out according to the reported procedure.[12] Compound **17** was obtained as a white solid which was recrystallized in petroleum ether (3.5 g, 68% overall): mp 80 °C; $[\alpha]^{17}_D$ +33.0° (*c* 0.8, $CHCl_3$); IR (KBr) 3501, 2986, 2936, 1379, 1128, 1014; SM (70 eV) 242 ($M^{+\bullet}$, 3), 227 (81), 212 (51), 153 (27), 105 (21), 83 (66), 59 (100); ^1H NMR ($CDCl_3$) δ 1.36 and 1.56 (2 x (s, 3H, CH_3)), 1.94 (dd, 1H, $J_{OH,5}$ = 8.8 Hz, $J_{OH,5'}$ = 4.2 Hz, OH), 2.95 (ddq, 1H, $J_{3,4}$ = 10.3 Hz, $J_{3,F}$ = 8.8 Hz, $J_{3,2}$ = 4.9 Hz, H-3), 3.66 (ddd, 1H, $J_{5,5'}$ = 12.5 Hz, $J_{5,OH}$ = 8.8 Hz, $J_{5,4}$ = 2.7 Hz, H-5), 4.01 (m, 1H, H-5'), 4.42 (ddd, 1H, $J_{4,3}$ = 10.3 Hz, $J_{4,5}$ = 2.7 Hz, $J_{4,5'}$ = 1.5 Hz, H-4), 4.87 (dd, 1H, $J_{2,3}$ = 4.9 Hz, $J_{2,1}$ = 3.8 Hz, H-2), 5.87 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 26.3 and 26.4 (2 x CH_3), 46.6 (q, $^2J_{C,F}$ = 27.6 Hz, C-3), 60.6 (C-5), 77.0 (C-4), 79.2 (C-2), 104.7 (C-1), 113.3 (Cq isopropylidene), 124.2 (q, $^2J_{F,F}$ = 278.0 Hz, CF_3); ^{19}F NMR δ -62.58 (d, 3F, $J_{F,H}$ = 8.8 Hz, CF_3).

Anal. Calcd for $C_9H_{13}O_4F_3$ (242.19): C, 44.63; H, 5.41. Found: C, 44.70; H, 5.25.

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