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Trifluoromethylation of Sugar 1,4-Lactones : Synthesis of 5-Deoxy-5,5,5-Trifluoro-D and L-Ribose and Lyxose Derivatives

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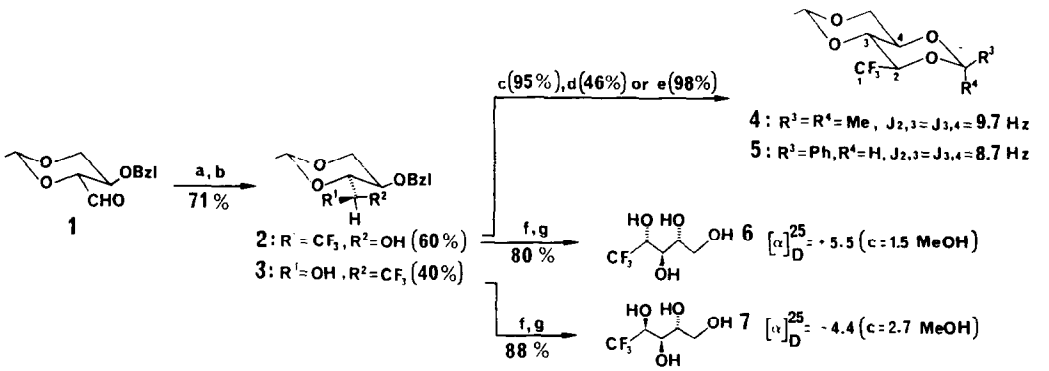
Key words : 5-deoxy-5,5,5-trifluoro-D and L-riboses ; 5-deoxy-5,5,5-trifluoro-D and L-lyxoses ; trifluoromethylation ; selective reduction of 2-ketoses.

Abstract : The four 5-deoxy-5,5,5-trifluoro-D and L-ribo and -lyxo furanoses were synthesized from lactones using CF_3SiMe_3 in 5 or 6 steps and 30-40 % overall yield. The key step was a stereoselective reduction of 1,1,1-trifluoro-2-ketoses with $LiAlH_4$ or $NaBH_4$ at an anomeric centre.

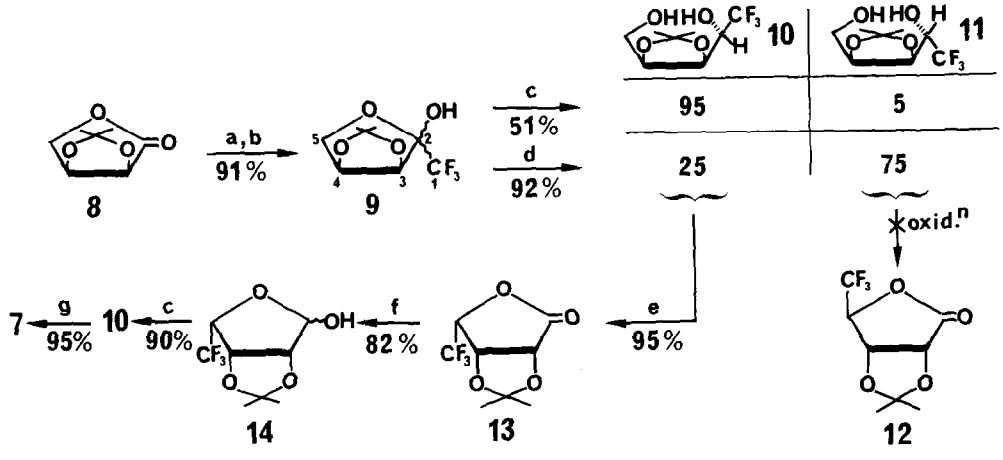
Many publications have appeared concerning mono or difluorinated carbohydrates mainly due to their potential biological activities.[1] Nevertheless, except for some CF_3 branched sugars, only three syntheses of 6-deoxy-6,6,6-trifluorohexoses have been published.[2,3,4] Replacement of the methyl group of L-fucose by the more hydrophobic trifluoromethyl one could be interesting because hydrophobic region of some polysaccharides having a L-fucose residue seems to play an important role in recognition phenomena.[2] The trifluoromethyl group could also modify the cyclization equilibria between pyranose and furanose. Furthermore, the increase of the inductive effect of an electron withdrawing substituent attached to the C-6 carbon of a 2-methoxytetrahydropyran decreases the rate of hydrolysis (for example in a ratio of 200 to 1 when CH_2OH is replaced by CO_2Et).[5] The CF_3 and CO_2Et groups having a σ value of -0.42 and +0.34 respectively for the inductive substituent constants,[6] it can be expected that 6-deoxy-6,6,6-trifluoro-hexopyranosides or 5-deoxy-5,5,5-trifluoropentopyranosides will be more stable than the corresponding uronates toward the hydrolysis ; therefore the lifetime of compounds having a biological interest such as L-daunosaminide or 5'-deoxyadenosine could be increased when the CH_3 group is replaced by a CF_3 one and their biological properties could thus be improved. Among the three methods employed to introduce the CF_3 group, the first one[2] seems the most interesting : CF_3SiMe_3[7] (donor of CF_3^-, reactive towards aldehydes, ketones and some lactones[7b,8]) was used to transform an acyclic pentose suitably protected in the desired hexose. The second paper[3] refers to a method using a slow addition of gazeous trifluoromethyl iodide to a mixture of zinc and chiral aldehyde under the irradiation of ultra-sound. The third one[4] involves the reduction of a trifluoromethylketone followed with an enzymatic resolution of the corresponding acetate. Nevertheless, no 5-deoxy-5,5,5-trifluoropentose has ever been described and none of the two chemical syntheses[2,3] gave a good diastereoselection ; furthermore, for 5-deoxy-5,5,5-trifluoropentofuranoses (unlike the hexopyranoses), ^1H n.m.r. coupling constants cannot prove the configuration at the C-4 of the two diastereoisomers and it is necessary to use another method.



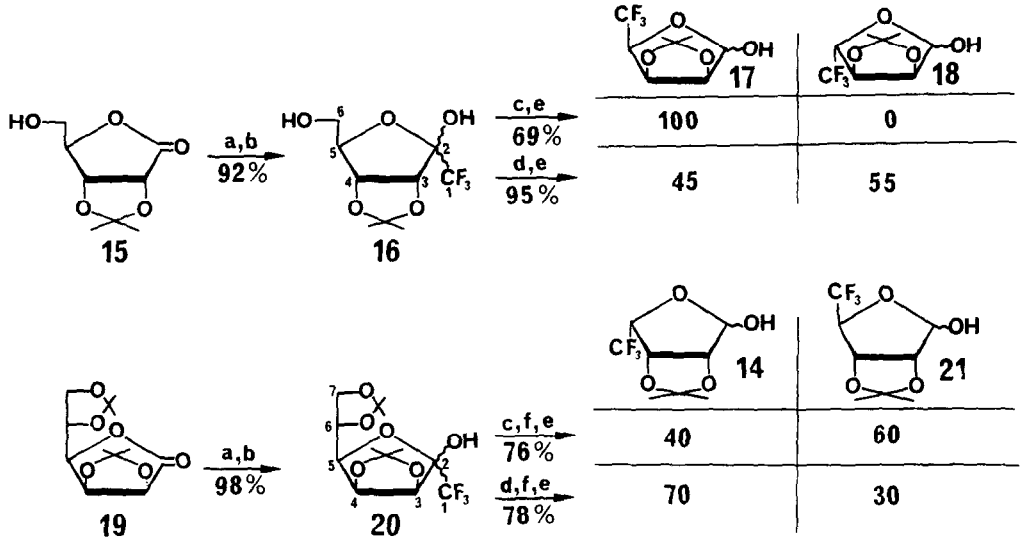
Scheme 1.- (a) 1.1 eq. CF_3SiMe_3, THF, -10°C, then TEAF catal. 5 min ; (b) EtOH, HCl 2N, R.T., 5 min ; (c) H_2, Pd/C 10 %, EtOH/AcOH : 10/1, R.T., 2 h ; (d) 5 eq. $PhCH(OMe)_2$, CSA 5 %, toluene (Dean-Stark), 30 min ; (e) 2 eq. $(MeO)_2CMe_2$, CSA 10 %, acetone, 60°C, 30 min ; (f) EtOH/HCl 2N : 2/1, 85°C, 6 h ; (g) H_2, Pd/C 10 %, EtOH 95 %, 2 h 30.

Our purpose was to find convenient ways to 5-deoxy-5,5,5-trifluoropentoses and particularly D-ribose owing to its expected biological importance with an approach to the diastereoselectivity control. Starting material was first a D-erythrose derivative **1** (obtained from D-glucose[9] in five steps and 40 % yield) ; stereoselectivity was poor in spite of the cyclic structure more strained than the literature example.[2] The main product **2** resulting from the trifluoromethylation of compound **1** was isolated by flash chromatography then debenzylated and converted into two bicyclic derivatives **4** and **5** the n.m.r. spectra of which, proved that H-2, H-3 and H-4 were axial protons. The compound **2** was consequently a 1-deoxy-1,1,1-trifluoro-D-ribitol derivative ; the structural assignments of 1,2-dioxolanes[10a] and hydroxyaminoacids[10b] have been made using a closely related way. It is noteworthy that no bicyclic derivative could be formed starting from **3** : molecular models show a great steric hindrance during the cyclization step leading to the axially oriented trifluoromethyl group (recent work[11] pointed out that trifluoromethyl group has the same bulkiness than a cyclohexyl group). Compounds **2** and **3**, the structure of which was therefore proved, led to tetrols **6** and **7**, respectively. Because of the lack of selectivity for the trifluoromethylation, CF_3 group was introduced on the lactone **8**[12] to give the hemiketal **9** as a mixture of α and β isomers in equilibrium, the reduction of which led to the diols **10** and **11** with a selectivity depending on the reducing agent (scheme 2). However, if the synthetic pathway : oxidation of **10** to **13**, then reduction led to the L-lyxose derivative **14** (reduction of **14** with $LiAlH_4$ gave **10** back which proved that no loss of stereochemical integrity has occured at the C-4 centre of **10** during the oxidation step ; **10** was then hydrolyzed to **7** for structural determination), oxidation of **11** (expected to lead to D-ribo derivative **12**) failed whatever the oxidating agent we used (PDC, Moffat or Swern oxidation, perruthenate procedure, CrO_3 oxidation of persilylated derivative, NaOCl/TEMPO). These unsuccessful results are close tho those related by Mandala[14] in syntheses of analogous linear carbohydrate or by Kanger *et al.*[15] during benzylation depending on the stereochemistry of the other end of the chain. So we tried to generate the aldehyde by periodate cleavage of a vicinal diol ; the scheme 3 shows the two performed examples starting from derivatives of commercially available D-ribono-1,4-lactone and L-gulono-1,4-lactone[16]. The two or three steps (reduction, 6,7-O-isopropylidene cleavage for **20**, oxidation) were made in one-pot and the two isomers (D-lyxo **17** and L-ribo **18** or L-lyxo **14** and D-ribo **21**) were easily separated by flash chromatography. Results of the reductions (schemes 2 and 3) show different selectivities depending not only on the reducing agent but also on the substitution at C-5 or C-6.

The same pathway is on course starting from D-lyxono-1,4 lactone (obtained from D-galactose[19]) to compare the selectivity of reduction with the observed one for **16**. Isopropylidene deprotection of **14**, **17**, **18** and **21** led in good yields (75-85 %) to the four wanted 5,5,5-trifluoro-5-deoxy-pentofuranoses respectively : L-lyxo $[\alpha]_D^{30}$ = +18, D-lyxo $[\alpha]_D^{30}$ = -18, L-ribo $[\alpha]_D^{30}$ = +8, D-ribo $[\alpha]_D^{30}$ = -7 (c=1.3, MeOH).



Scheme 2.- (a) 1.1 eq. CF_3SiMe_3, THF, R.T., then TEAF catal. 15 min ; (b) 1 eq. TEAF, THF, R.T., 15 min ; (c) 6 eq. $LiAlH_4$, THF, R.T., 12 h ; (d) 1.5 eq. $NaBH_4$, H_2O, R.T., then contin. extract. ; (e) 2 eq. PDC, CH_2Cl_2, R.T., 25 min ; (f) 1 eq. DIBAL, toluene, -78°C → R.T. ; (g) HCl catal., THF, 65°C, 1 h.



Scheme 3.- (a) 2.1 eq. CF_3SiMe_3, THF, R.T., 10 min, then TEAF catal. 15 min ; (b) 2 eq. TEAF, THF, R.T., 15 min ; (c) 6 eq. $LiAlH_4$, Et_2O, R.T., 12 h ; (d) 8 eq. $NaBH_4$, H_2O, R.T., 48 h ; (e) 3 eq. $NaIO_4$, H_2O, R.T., 1 h ; (f) $AcOH/H_2O$: 7/1, R.T., 16 h.

This work is, to our knowledge, the first example of 5-deoxypentoses trifluoromethylated analogues.[20] Studies on threitol derivatives are under way to obtain D (or L)-arabinose and L (or D)-xylose analogues.

References and Notes

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20. All new compounds were purified and gave satisfactory ^{1}H, ^{13}C, ^{19}F n.m.r. spectra and elemental analyses. For example, ^{13}C n.m.r. : **14**α or **17**α (α/β : 9/1) 123.0 ($J_{C,F}$=279, C5) ; 114.3 (Cq) ; 101.5 (C1) ; 84.9 (C2) ; 78.6 ($J_{C,F}$=0.6, C3) ; 77.6 ($J_{C,F}$=32.4, C4) ; 25.6 and 24.7 (CH_3). **14**β or **17**β 122.6 ($J_{C,F}$=279, C5) ; 115.0 (Cq) ; 97.6 (C1) ; 78.2 (C2) ; 74.1 ($J_{C,F}$=33, C4) ; 67.0 (C3) ; 25.5 and 24.9 (CH_3). **18**α or **21**α (α/β : 2/1) 123.9 ($J_{C,F}$=283, C5) ; 114.4 (Cq) ; 99.0 ($J_{C,F}$=1.6, C1) ; 79.5 ($J_{C,F}$=2, C3) ; 78.9 ($J_{C,F}$=31.3, C4) ; 78.3 (C2) ; 26.0 and 24.7 (CH_3). **18**β or **21**β 123.6 ($J_{C,F}$=282, C5) ; 113.6 (Cq) ; 104.2 (C1) ; 85.7 (C2) ; 84.9 ($J_{C,F}$=32.1, C4) ; 80.1 ($J_{C,F}$=2.1, C3) ; 26.6 and 24.9 (CH_3).These data are in accordance with those reported by Ohrui *et al.* [21] : C3 and C4 occur at higher field when C5 and dioxolan ring are in *cis* relationship (**14** and **17**).
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