TRIFLUOROMETHYLATION OF CHIRAL ALDEHYDE AND SYNTHESIS OF 6-DEOXY-6,6,6-TRIFLUOROHEXOSES

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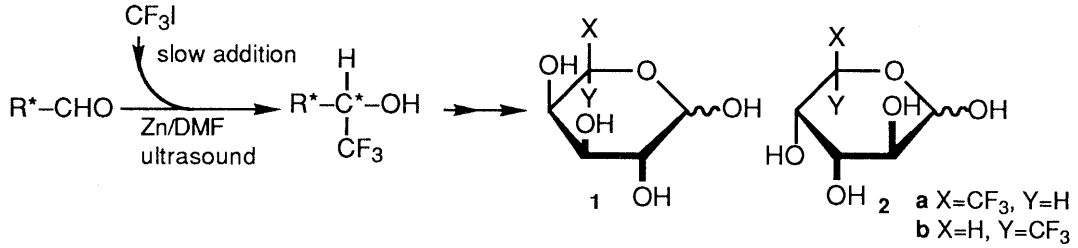
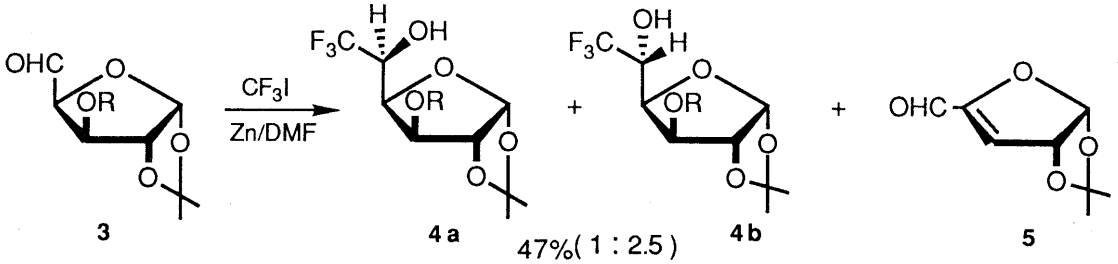
Trifluoromethylation of chiral aldehyde derived from sugar was efficiently carried out by a modification of the reported procedure. The preparation of 6,6,6-trifluoro-L-daunosamine was also achieved by using (2*S*,3*R*)-4,4,4-trifluorobutane-1,2,3-triol derivative.

KEYWORDS trifluoromethylation; ultrasound; slow addition; 6-deoxy-6,6,6-trifluorohexose; 6,6,6-trifluoro-L-daunosamine

Sugar derivatives containing the trifluoromethyl group are considered to be attractive molecules not only for important building blocks in the preparation of optically active fluoro molecules but also for assessment of expected biological activity. Many kinds of the monofluoro- and difluorosugar analogues have been studied to assess the biological activity of sugar analogues and/or glycosyl compounds.[1] The preparations of optically active trifluoromethylated carbinols have been developed extensively in recent years,[2] but elaboration on producing enantiomerically pure trifluoromethylated carbinols in a simple and effective manner remains a task for the synthesis of 6-deoxy-6,6,6-trifluorohexose derivatives.[3] We describe herein the trifluoromethylation of a chiral aldehyde and the synthesis of 6-deoxy-6,6,6-trifluorohexose derivatives involving 6,6,6-trifluoro-L-daunosamine.

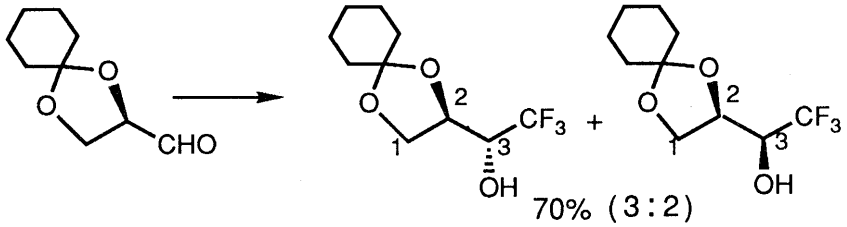


Trifluoromethylation was carried out efficiently by introducing trifluoromethyl iodide slowly (0.5 ml/0.5 h) to a mixture of zinc and aldehyde in dimethylformamide (DMF) under the irradiation of ultrasound. This simple modification of the original procedure[4] by the slow addition of trifluoromethyl iodide is indispensable, because none of the desirable products can be obtained by the original procedure. For example, the aldehyde **3**[5] was trifluoromethylated in 47% yield to give a separable mixture of diastereoisomers (**4a** and **4b**) in a 1 : 2.5 ratio and the α,β-unsaturated aldehyde **5** (20%) (Chart 1). Trifluoromethylation of 2,3-*O*-cyclohexylidene-D-glyceraldehyde also gave a mixture of 2*R*,3*R*- and 2*R*,3*S*-isomers (**6a** and **6b**, 70 % yield, ratio 3 : 2).



47%(1 : 2.5)

R=Bn $[\alpha]_D^{23}$ −37.6° (c=1.00, $CHCl_3$) $[\alpha]_D^{23}$ −31.0° (c=0.74, $CHCl_3$)



6a (2*R*, 3*R*) $[\alpha]_D^{23}$ 13.2° (c=0.65, $CHCl_3$)
6b (2*R*, 3*S*) $[\alpha]_D^{23}$ −14.8° (c=0.74, $CHCl_3$)

Chart 1

The absolute configuration of the newly formed chiral center of **4a** was determined to be the *S*-configuration by X-ray analysis of the corresponding p-nitrobenzoate of **4a**[6]. The structures of **6a** and **6b** were determined by converting these compounds to the methyl ether **7a, b** followed by comparison of the spectral data and rotational values ($[\alpha]_D$) with those of compound **7a** (2*S*, 3*S*) derived from **4a** (Chart 2). Under the same trifluoromethylation conditions, other aldehydes[7] derived from sugars also gave a mixture of diasetereoisomeric products, and the absolute configuration of each diastereoisomer was unambiguously determined in the same way as in Chart 2.

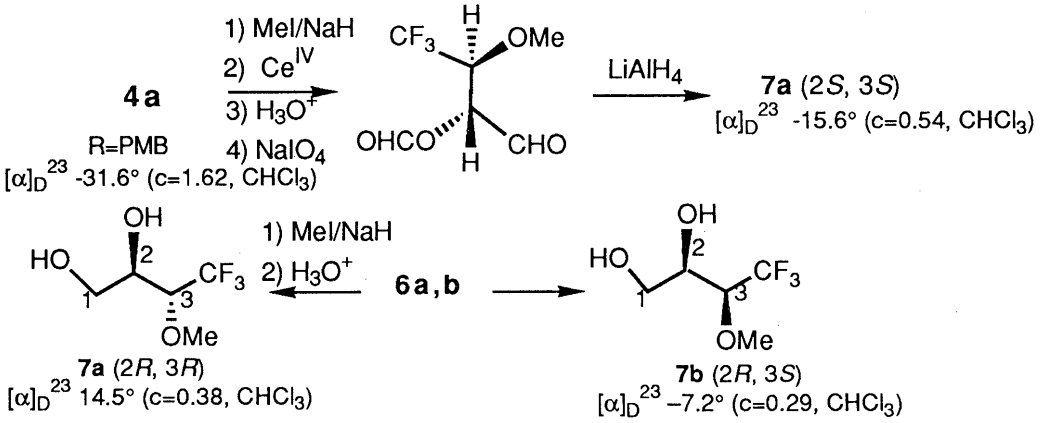


Chart 2

As one synthetic application of trifluoromethylated polyols, the preparation of 6,6,6-trifluoro-L-daunosamine (**8**),[8] which is the sugar moiety of anthracycline antibiotics, was carried out from **6b** (2*S*, 3*R*) obtained from 2,3-*O*-cyclohexylidene-L-glyceraldehyde (Chart 3). In the synthesis of **8**, the two points (oxidation of **9** and allylation of imine **10**) deserve comment. i) In the workup of the oxidation of primary alcohol **9** to aldehyde by Swern oxidation, termination of the reaction by adding the reaction mixture to ice-H_2O at 0°C to avoid the epimerization was necessary. ii) The allylation of **10** with allylmagnesium bromide yielded olefin (**11**) with low *syn*-selectivity (*syn*/*anti* = 3/2) due to α-chelation control.[9]

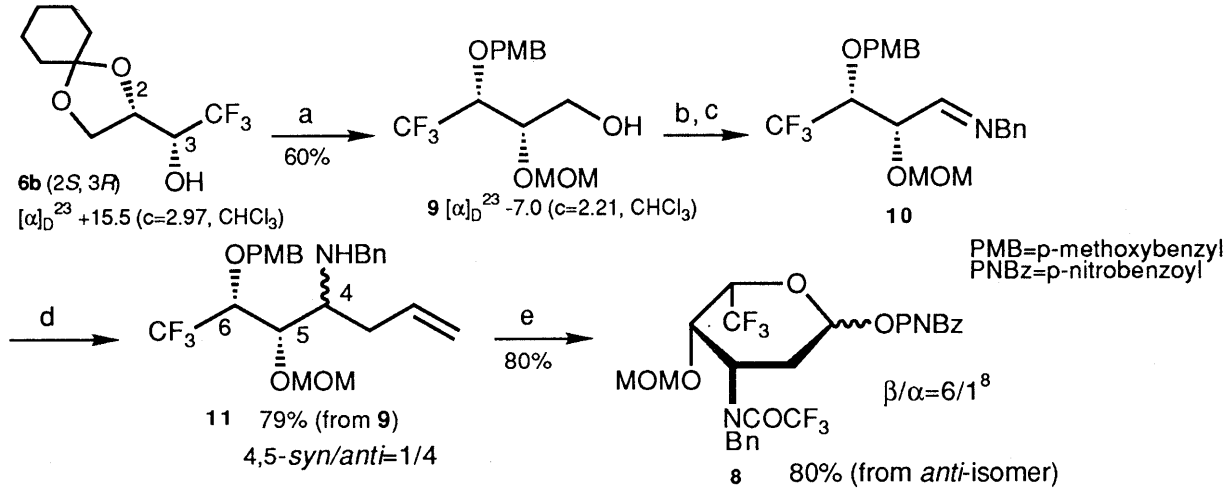


Chart 3. Reagents and Conditions: a; i PMBCl/NaH, ii H_3O^+ iii PivCl/Py, iv $CH_2(OMe)_2/P_2O_5$ v $LiAlH_4$ b; Swern Oxid. c; $BnNH_2$ d; allyl-$B(OiPr)_2$ e; i TFAA/ Et_3N/DMAP, ii DDQ/CH_2Cl_2–H_2O, iii O_3 iv Me_2S, v PNBzCl/Py

Although the biological assay of 6-deoxy-6,6,6-trifluorohexoses (**1a**, **1b**, **2a** and **2b**),[10] prepared by the present procedure, showed no significant inhibitory activity toward L1210 leukemia cells,[11] we believe that these 6-deoxy-6,6,6-trifluorohexoses are considered to play an important role in specifying the function of a sugar moiety such as the L-fucose involved in cell-surface oligosaccharides.

ACKNOWLEDGEMENT We wish to express our appreaciation to Dr. Akihiro Yoshimoto at Mercian Corporation for conducting the *in vitro* assay of the synthesized 6-deoxy-6,6,6-trifluorosugars.

ADDED IN PROOF (Aug. 14, 1991) Since submission of this manuscript, preparations of 6,6,6-trifluorohexoses which are the same analogues prepared by us has appeared. R. C. Bansal, B. Dean, S. Hakomori and T. Toyokuni, *J. Chem. Soc., Chem. Commun.*, **1991**, 796.

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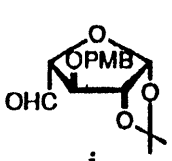
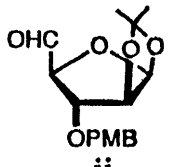
6) X-ray crystal data of p-nitrobenzoate of **4a**: $C_{23}H_{22}NO_8F_3$, M=497.422, orthorhombic, $P2_12_12_1$, a=10.953(1) Å, b=27.711(2) Å, c=7.875(1) Å, V=2390.2 Å^3, Dc=1.382 g/cm^3, Z=4, Cu Kα (λ=1.54178 Å). The structure was solved by direct methods and refined by a block-diagonal least squares method to R=0.054 for 1702 observed reflections [Fo>3σ(Fo)].

7) Aldehydes (**i** , **ii**) were also trifluoromethylated in 51~55% yields.



i



ii

8) Care should be taken in regard to the α–, β–definition for L–sugar derivatives. Spectral data of β-anomer of **8**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ring protons); 5.99 (1H, dd, J=2.2 and 9.8Hz, 1-H), 4.66 (1H, ddd, J=2.0, 3.7 and 13.7Hz, 3-H), 4.47 (1H, d, J=2.0, 4-H), 4.08 (1H, q, J_{H-F}=6.1Hz, 5-H), 2.41 (1H, ddd, J=3.7, 12.3 and 13.7Hz, 2-H_{ax}), 1.74 (1H, ddd, 2.2, 3.7 and 12.3Hz, 2-H_{eq}). ^{19}F-NMR ($CDCl_3$) ppm (higher field from external benzotrifluoride signal was expressed as negative); -6.1 (s) and -10.6 (d, J=6.1Hz), 1:1 ratio. $[\alpha]_D^{23}$ -14.5° (c=0.77, $CHCl_3$). α-Anomer of **8**; 6.51 (1H, dd, 1.5 and 2.3Hz, 1-H), 4.92 (1H, ddd, 2.5, 4.0 and 13.7Hz, 3-H), 4.55 (1H, d, J=2.5Hz, 4-H), 4.35 (1H, q, J_{H-F}=6.4Hz, 5-H), 2.54 (1H, ddd, J=2.3, 13.7 and 13.8Hz, 2-H_{ax}), 1.62 (1H, ddd, J=1.5, 4.0 and 13.8Hz, 2-H_{eq}). ^{19}F-NMR ($CDCl_3$) ppm; -6.1 (s) and -11.1 (d, J=6.4Hz), 1:1 ratio. $[\alpha]_D^{23}$ -158.1° (c=0.23, $CHCl_3$).

9) Addition reaction of the allylic compound to imines: a) Y. Yamamoto, T. Komatsu and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 814 (1985); b) Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu and W. Ito, *J. Am. Chem. Soc.*, **108**, 7778 (1986).

10) 6-Deoxy-6,6,6-trifluoro-D-galactose **1a**, mp 125–126°C, $[\alpha]_D^{23}$ 35.2° (c=0.20, H_2O); 6-deoxy-6,6,6-trifluoro-L-altrose **1b**, oil $[\alpha]_D^{23}$-7.0° (c=0.40, H_2O), 6-deoxy-6,6,6-trifluoro-D-altrose **2a**, oil $[\alpha]_D^{23}$ 8.5° (c=0.30, H_2O), 6,6,6-trifluoro-L-fucose **2b**, mp 121–124°C, $[\alpha]_D^{23}$-33.0° (c=0.70, H_2O).

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