Synthesis of Trifluoromethyl Analogue of L-Fucose and 6-Deoxy-D-altrose

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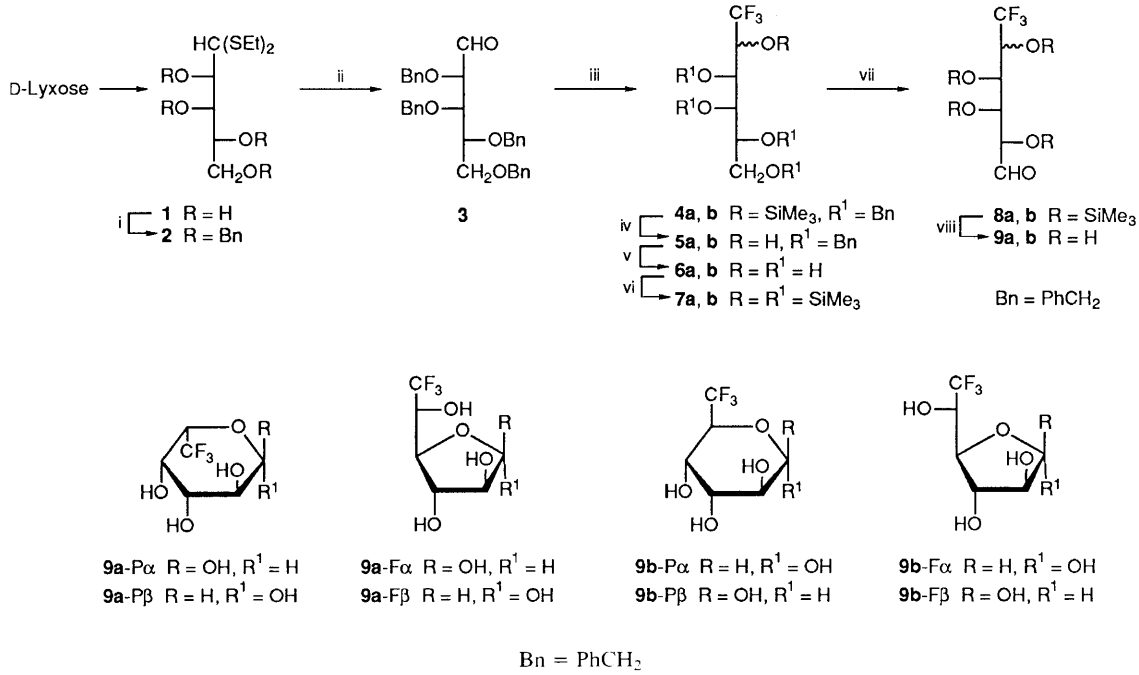
Trifluoromethylation of the acyclic derivative of D-lyxose, **3**, with trifluoromethyltrimethylsilane in the presence of tetrabutylammonium fluoride yielded a mixture of trifluoromethyl adducts, **5a** and **b**, which was converted to 6,6,6-trifluoro-L-fucose **9a** and 6-deoxy-6,6,6-trifluoro-D-altrose **9b** *via* selective oxidation of the primary hydroxy group involving treatment of the trimethylsiloxy derivatives, **7a** and **b**, with Collins reagent.

Cell surface carbohydrates are currently of much interest due to increasing evidence that points out their important role in cellular interaction and the onset of cancer.[1] We have recently shown that Le^x–Le^x (Le^x: Galβ1→4[Fucα1→3]GlcNAcβ1→R) interaction could be the basic mechanism for cell–cell recognition in preimplantation embryos and in embryonal carcinoma cells.[2] Understanding the chemical basis of this carbohydrate–carbohydrate interaction[3] requires a variety of structural analogues of Le^x. Since the hydrophobic region of the molecule seems to play an important role in the interaction,[4] replacement of the methyl group in the fucose residue with the more hydrophobic trifluoromethyl group[5] would provide an artificial inhibitor for the Le^x–Le^x interaction. Molecular mechanics calculations using SYBYL (Tripos Associates, St. Louis, MO) indicate that such replacement should not cause marked changes in the Le^x–Le^x interaction energy (van der Waals and electrostatic energy).[6] For this reason we have synthesized 6,6,6-trifluoro-L-fucose **8** from D-lyxose, together with 6-deoxy-6,6,6-trifluoro-D-altrose **9**. The main feature of the synthesis includes the application of a nucleophilic trifluoromethylation reaction using trifluoromethyltrimethylsilane (TMS–CF_3)[7] to an acyclic sugar aldehyde. This is the first example for trifluoromethyl analogues of 6-deoxysugars.[8]

The acyclic derivative of D-lyxose, 3,† was prepared from the known diethyl dithioacetal derivative,[9] **1**, in an overall yield of 89% by sequential perbenzylation with benzyl bromide in the presence of sodium hydride (**1** → **2**) and dethioacetalization with mercury(II) chloride and calcium carbonate (**2** → **3**). Trifluoromethylation using TMS–CF_3 was then carried out with **3** in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF), according to the conditions reported by Prakash *et al.*,[7] yielding a mixture of trifluoromethylated siloxy adducts, **4a** and **b**. Subsequent hydrolysis with HCl (1 mol dm^{-3}) gave a *ca.* 1 : 1 mixture of trifluoromethylated alcohols, **5a** and **b**, in a 79% overall yield from **3**. Column chromatography on silica gel (7 : 1 hexane–acetone) resulted in a moderate separation of **5a** (R_f 0.26) and **5b** (R_f 0.21). **5a**: $[\alpha]_D$ −22.3° (*c* 3.8, $CHCl_3$); **5b**: $[\alpha]_D$ −15.2° (*c* 3.7, $CHCl_3$). Since the separation of these alcohols was found to be troublesome, the mixture of **5a** and **b** was used for further reactions.

After catalytic hydrogenation with palladium hydroxide, the resulting alcohols, **6a** and **b**, were subjected to Schick

† All new compounds exhibited satisfactory spectral and high-resolution mass data.



Scheme 1 *Reagents and conditions*: i, BnBr, NaH, dimethylformamide (DMF), room temp., 3 h; ii, $HgCl_2$, $CdCO_3$, acetone–H_2O, room temp., 20 h; iii, TMS–CF_3, TBAF, tetrahydrofuran (THF), 0 °C → room temp., 2 h; iv, HCl (1 mol dm^{-3}), room temp., 4 h; v, palladium hydroxide on carbon, H_2 (1 atm), room temp., 5 h; vi, Me_3SiCl, $Me_3SiNHSiMe_3$, pyridine, room temp., 3 h; vii, CrO_3–pyridine, CH_2Cl_2, 0 °C → room temp., 1 h; viii, MeOH–H_2O, reflux, 3 h

Table 1 ^{1}H NMR data[a] for **9a** and **9b**

δ,[b] Multiplicity[c] (*J*/Hz)

	1-H	2-H	3-H	4-H	5-H
9a-Pα	5.32, d (3.5)	3.79, dd (10.5, 3.5)	3.84, dd (10.5, 3.0)	4.23, d (3.0)	4.51, q (7.0)
-Pβ	4.65, d (8.0)	3.50, dd (10.0, 8.0)	3.63, dd (10.0, 3.5)	4.18, d (3.5)	4.10–4.25[d]
-Fα	5.26, d (5.0)	4.06, dd (8.0, 5.0)	—[e]	—[e]	4.10–4.25[d]
-Fβ	5.20, d (3.5)	3.97, dd (4.0, 3.5)	—[e]	—[e]	4.10–4.25[d]
9b-Pα	5.03, d (3.0)	3.82, dd (5.5, 3.0)	3.93–3.96[d]	4.11, dd (7.5, 3.5)	4.49–4.41[d]
-Pβ	5.16, d (1.0)	3.81, dd (4.0, 1.0)	4.02–4.07[d]	—[e]	—[e]
-Fα	5.25, d (2.0)	4.00, t (2.0)	4.18–4.21[d]	4.02–4.05[d]	4.14–4.25[d]
-Fβ	5.28, d (4.5)	4.05, dd (6.0, 4.5)	4.29, t (6.0)	3.94, dd (7.5, 6.0)	4.14–4.25[d]

[a] 500 MHz; D_2O at 35 °C; after 24 h. [b] In ppm downfield from sodium 3-(trimethylsilyl)propionate. [c] d = doublet, dd = doublet of doublets, t = triplet, q = quartet. [d] The peaks were overlapping and the assignments thus remained obscure. [e] Not resolved.

oxidation[10] in order to convert the primary hydroxy group into the aldehyde. The reaction sequence (**6a, b** → **7a, b** → **8a, b**) was basically the same as reported for the conversion of L-fucitol to L-fucose.[11] Thus, pertrimethylsilylation, yielding **7a** and **b**, followed by oxidation with Collins reagent (CrO_3–pyridine complex) afforded a mixture of trimethylsiloxy aldehydes, **8a** and **b**. Desilylation with aqueous methanol under reflux for 3 h,[12] and subsequent column chromatography on silica gel (20 : 1 : 0.1 EtOAc–EtOH–H_2O) furnished the trifluoromethyl analogue of L-fucose **9a** (R_f 0.36) and of 6-deoxy-D-altrose **9b** (R_f 0.51) in 38 and 36% overall yields, respectively, from the mixture of **7a** and **b**. **9a**: m.p. 122–123 °C; $[\alpha]_D$ −36.5° (*c* 2.5, H_2O, after 24 h); ^{19}F NMR (CD_3OD, $CFCl_3$) δ −103.11 (d, *J* 7.0 Hz), −103.23 (d, *J* 8.5 Hz), −106.39 (d, *J* 8.5 Hz) and −106.42 (d, *J* 7.0 Hz); high resolution MS 201.0363 ($C_6H_8F_3O_4$[M−OH]$^+$, calc. 201.0375); **9b**: syrup; $[\alpha]_D$ −1.3° (*c* 2.5, H_2O, after 24 h); ^{19}F NMR (CD_3OD, $CFCl_3$) δ −103.16 (d, *J* 9.0 Hz), −103.37 (d, *J* 6.5 Hz), −105.29 (d, *J* 6.5 Hz) and −105.06 (d, *J* 9.0 Hz); high resolution MS 201.0365 ($C_6H_8F_3O_4$ [M−OH]$^+$, calc. 201.0375).

The ^{1}H NMR spectra of **9a** and **b** revealed an equilibrium mixture composed of two pyranoses (P α, β) and two furanoses (F α, β) (Table 1). The proportions of each form were found to be 29 : 43 : 11 : 17 (**9a**-Pα : **9a**-Pβ : **9a**-Fβ) and 14 : 20 : 33 : 33 (**9b**-Pα : **9b**-Pβ : **9b**-Fα : **9b**-Fβ). The ratios for L-fucose and D-altrose were reported to be 28 : 67 : 5 (Pα : Pβ : Fα + Fβ)[13] and 30 : 41 : 18 : 11 (Pα : Pβ : Fα : Fβ),[14] respectively. It is worth noting that replacement of the methyl group with the trifluoromethyl group increases the furanose content, particularly for **9b** which exists mainly in the furanose form. The spectrum of crystalline **9a** soon after dissolution showed a similar composition as at equilibrium, probably due to its rapid mutarotation.

The synthesis of Le^x analogues possessing **9a** in place of L-fucose is currently in progress.

We are grateful to Professors G. K. S. Prakash and G. A. Olah (Donald P. and Katherine B. Locker Hydrocarbon

Research Institute, University of Southern California) for providing us with the experimental detail for the preparation of TMS–CF_3. This work was supported by funds from The Biomembrane Institute.

Received, 29th January 1991; Com. 1/00425E

References

1 For reviews, see: S. Hakomori, *Annu. Rev. Biochem.*, 1981, **50**, 733; S. Hakomori, *Adv. Cancer Res.*, 1989, **52**, 257; B. K. Brandley, S. J. Swiedler and P. W. Robbins, *Cell*, 1990, **63**, 861; H. J. Gabius and S. Gabius, *Naturwissenschaften*, 1990, **77**, 505.
2 I. Eggens, B. A. Fenderson, T. Toyokuni and S. Hakomori, *Biochem. Biophys. Res. Commun.*, 1989, **158**, 913; I. Eggens, B. Fenderson, T. Toyokuni, B. Dean, M. Stroud and S. Hakomori, *J. Biol. Chem.*, 1989, **264**, 9476.
3 The carbohydrate–carbohydrate interaction is also suggested to be the basis for the species-specific sorting of reaggregating sponge cells: G. N. Misevic, J. Finne and M. M. Burger, *J. Biol. Chem.*, 1987, **262**, 5870.
4 N. Kojima and S. Hakomori, *J. Biol. Chem.*, 1989, **264**, 20159.
5 N. Ishikawa, *Kagaku no Ryoiki*, 1981, **35**, 45; Y. Yano, K. Tanaka, Y. Doi and M. Janado, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2963.
6 R. Habermann, personal communication, 1989.
7 G. K. S. Prakash, R. Krishnamurti and G. A. Olah, *J. Am. Chem. Soc.*, 1989, **111**, 393.
8 Synthesis of 6-monofluoro-L-fucose has been reported: J. R. Sufrin, R. J. Bernacki, M. J. Morin and W. Korytnyk, *J. Med. Chem.*, 1980, **23**, 143; for a review of fluorinated carbohydrates, see: *Fluorinated Carbohydrates. Chemical and Biochemical Aspects*, ed. N. F. Taylor, American Chemical Society, Washington, DC, 1988.
9 M. L. Wolfrom and F. B. Moody, *J. Am. Chem. Soc.*, 1940, **62**, 3465.
10 R. Mahrwald, F. Theil, H. Schick, S. Schwarz, H.-J. Palme and G. Weber, *J. Prakt. Chem.*, 1986, **328**, 777.
11 H. Kristen, Ch. Vogel, F. Wrubel, R. Mahrwald and H. Schick, *J. Carbohydr. Chem.*, 1988, **7**, 277.
12 D. T. Hurst and A. G. McInnes, *Can. J. Chem.*, 1965, **43**, 2004.
13 S. J. Angyal and V. A. Pickles, *Aust. J. Chem.*, 1972, **25**, 1695.
14 S. J. Angyal and V. A. Pickles, *Aust. J. Chem.*, 1972, **25**, 1711.