A Synthesis of 2,6-Dideoxy-2-fluoro-L-glycopyranose from D-Fructose: Synthesis of 1,3,4-Tri-*O*-acetyl-2,6-dideoxy-2-fluoro-L-talopyranose

Yasushi Takagi, Geun-Jho Lim, Tsutomu Tsuchiya* and Sumio Umezawa
Institute of Bioorganic Chemistry, 1614 Ida, Nakahara-ku, Kawasaki 211, Japan

2,6-Dideoxy-2-fluoro-α-L-talopyranose has been prepared as its triacetate from inexpensive D-fructose by head-to-tail inversion.

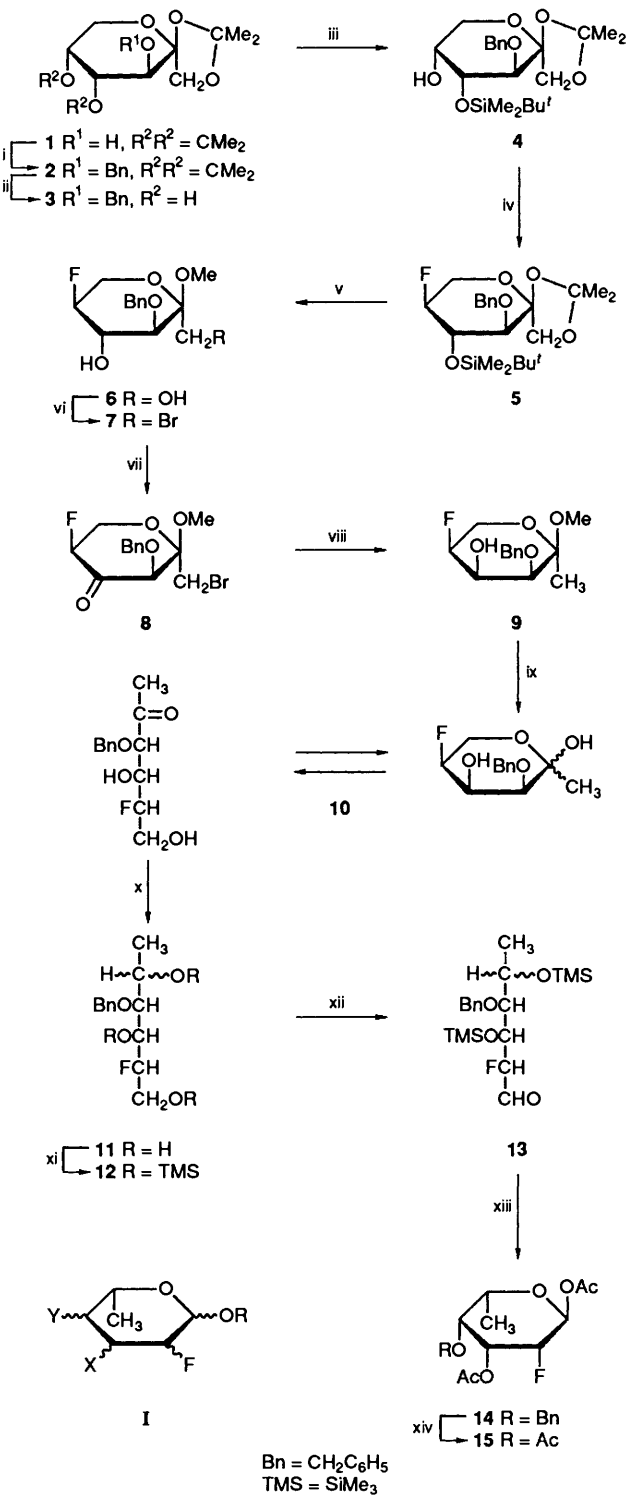
D-Fructose, a keto sugar, is one of the cheapest sugars together with D-glucose and sucrose, but in contrast to the last two sugars, has been rarely used[1] as a starting material for syntheses. Recently we reported the synthesis of 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)adriamycinone[2] and its derivatives, compounds which have low toxicity but are effective antileukemic agents.[3] However the synthesis of the sugar portion, 2,6-dideoxy-2-fluoro-L-talopyranose (as its triacetate), of these required expensive L-fucose as the starting material, a problem which hindered the scale-up of this promising drug. Recently 2,6-dideoxy-2-fluoro-L-taloside was prepared by Deal and Horton[4] from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-glucose, and in our laboratory[5] from L-rhamnal. Generally, introduction of a fluorine at C-2′ in doxorubicin-type antibiotics strengthens the glycosidic bond, stabilizes the drugs and reduces the toxicity. Several 2′-fluorodaunosamine derivatives[3b,6] were thus synthesized. In terms of orientation of the fluorine, however, only the 2′*R* configuration (L-*talo* and L-*manno*[5]) gave active compounds.[3a] Related deoxyfluoro sugars were reported[7] to show weak antitumour activity against murine L1210 leukemia *in vivo*,[7] but our fluoro sugar has not yet been tested. This paper describes the synthesis of 1,3,4-tri-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranose **15** from D-fructose with the aim of finding a low-cost synthesis as well as exploring the utility of D-fructose in synthesis.

The synthetic procedure was based on head-to-tail inversion of D-fructose in which C-2 is reduced and C-6 oxidized. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranose[8] **1**, readily prepared, from D-fructose was benzylated[9] to give **2**† {$[\alpha]_D^{23}$ −90 ($CHCl_3$);‡ no data reported[9]}. Selective deisopropylidenation[9] {to give **3**; m.p. 99–101 °C; $[\alpha]_D^{23}$ −115 ($CHCl_3$) (lit.,[9] m.p. 96–97 °C; $[\alpha]_D$ +113.2 ($CHCl_3$); the sign of the value should be reversed)} followed by silylation gave selectively the 4-*O*-silyl derivative **4** {$[\alpha]_D^{23}$ −80 ($CHCl_3$), 59%}. Fluorination of **4** with diethylaminosulfur trifluoride (DAST) gave 3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-5-deoxy-5-fluoro-1,2-*O*-isopropylidene-α-L-sorbopyranose **5** {62%, m.p. 40–40.5 °C; $[\alpha]_D^{23}$ −31 ($CHCl_3$)}. The mother structure, 5-deoxy-5-fluoro-1,2-*O*-isopropylidene-α-L-sorbopyranose was reported[10] to be formed (11%) by treatment of 3,4-anhydro-1,2-*O*-isopropylidene-β-D-tagatopyranose with KHF_2 *via* oxirane-ring migration followed by fluorinative ring-opening. Treatment of **5** in acidic methanol gave the methyl α-L-sorbopyranoside **6** {m.p. 98–98.5 °C; $[\alpha]_D^{22}$ −37 ($CHCl_3$), 80%}; the structure was confirmed by NMR spectroscopy: ^{1}H NMR for 5-H, dddd, $J_{4,5}$ 8.5, $J_{5,6ax}$ 10.5, $J_{5,6eq}$ 6, and $J_{5,F}$ 50.5 Hz; ^{19}F NMR for 5-F, ddd, $J_{4,F}$ 15.5, $J_{6ax,F}$ 4.5, and $J_{6eq,F}$ ~ 0 Hz. Selective bromine-substitution of the primary 1-OH of **6** with CBr_4–Ph_3P (ref. 11) gave the 1-bromo derivative **7** {56%, $[\alpha]_D^{22}$ −28 ($CHCl_3$)}. Inversion of the 4-OH of **7** was performed by oxidation at C-4 with dimethyl sulfoxide (DMSO) (to give **8**, 88%) followed by reduction with lithium aluminium hydride (LAH); this reductive debromination at C-1 gave **9** {80%, m.p. 66.5–67 °C; $[\alpha]_D^{23}$ +24 ($CHCl_3$)}; the methyl group in **9** becomes the 5-Me of the final product. The disposition of the methyl was confirmed by observation of NOE (3.8%) between the methyl and 3-H. Hydrolysis of **9** with aq. 80% AcOH gave **10** (87%) as an equilibrium mixture of two pyranoids and an acyclic keto form (confirmed by the ^{1}H and ^{19}F NMR spectroscopy). Reduction of **10** with lithium borohydride§ at 0 °C gave a diastereoisomeric mixture of **11** (89%) in the ratio of 2*S*:2*R* = 3.5:1 (based on ^{19}F NMR). Selective oxidation[12] of the primary hydroxy group of **11** was performed by Collins oxidation of the per-*O*-trimethylsilyl derivative **12** to give **13**. Subsequent acid-catalysed desilylation and acetylation gave, after chromatographic separation (SiO_2; EtOAc–hexane 1:3), 1,3-di-*O*-acetyl-4-*O*-benzyl-2,6-dideoxy-2-fluoro-α-L-talopyranose **14** {m.p. 100.5–101 °C; $[\alpha]_D^{21}$ −90 ($CHCl_3$)} in 36% overall yield, together with the 5-epimer (D-*allo*, 8%). Finally, catalytic debenzylation and reacetylation of **14** gave 1,3,4-tri-*O*-acetyl-2,6-dideoxy-2-fluoro-α-L-talopyranose **15** (89%) ready for condensation with aglycon, identical, in every respect, with the specimen reported.[2] It should be stressed that in this synthesis the reduction of **10** preferentially gave the desired 2*S* compound over the 2*R* compound. It is likely that the chiral compounds obtained in this synthesis will prove useful for the preparation of further compounds of specified chirality and, through analogous routes, compounds formulated as **I** (X and Y being an optional substituent, respectively). These would constitute potentially useful intermediates for fluorine-containing drugs, prepared from inexpensive D-fructose.

† Satisfactory analytical and spectroscopic data have been obtained for all new compounds except for **12** and **13** reported.
‡ $[\alpha]_D$ Values are recorded in 10^{-1} deg cm^2 g^{-1}.
§ Use of other reductants resulted in poor 2*S* selectivity; for example, sodium borohydride in tetrahydrofuran gave 81% of products with 2*S*:2*R* = 2.7:1; sodium borohydride–lithium chloride–ethanol, 85% (1.3:1); potassium borohydride–tetrahydrofuran, 95% (1.8:1); LAH-1,2-dimethoxyethane (DME), 48% (1.4:1; 18% of **10** was recovered); diisobutylaluminium hydride–DME, 30% (1:2.6; 39% of **10** was recovered); and K-Selectride or L-Selectride gave a complex mixture.

References

1 A. Vasella, in *Modern Synthetic Methods*, ed. R. Scheffold, Otto Salle Verlag, Frankfurt am Main, 1980, vol. 2, p. 233.
2 (*a*) T. Tsuchiya, Y. Takagi, K. Ok, S. Umezawa, T. Takeuchi, N. Wako and H. Umezawa, *J. Antibiot.*, 1986, **39**, 731; (*b*) K. Ok, Y. Takagi, T. Tsuchiya, S. Umezawa and H. Umezawa, *Carbohydr. Res.*, 1987, **169**, 69.
3 (*a*) T. Tsuchiya, Y. Takagi, S. Umezawa, T. Takeuchi, K. Komuro, C. Nosaka, H. Umezawa, S. Fukatsu and T. Yoneta, *J. Antibiot.*, 1988, **41**, 988; (*b*) Y. Takagi, H. Park, T. Tsuchiya, S. Umezawa, T. Takeuchi, K. Komuro and C. Nosaka, *J. Antibiot.*, 1989, **42**, 1315.
4 S. T. Deal and D. Horton, *Abstr. Pap. Am. Chem. Soc. Meet.*, 200 (1990), CARB-38.
5 T. Miyake, K. Takimura, Y. Takagi, T. Tsuchiya, S. Umezawa and T. Takeuchi, *58th Natl. Meet., Chem. Soc. Japan, Abstr. Pap.*, vol. II, 41L16 (1989).



Scheme 1 *Reagents and conditions:* i, BnBr, NaH, *N,N*-dimethylformamide, 1 h, room temp.; ii, aq. 80% AcOH, 15 h, room temp.; iii, Bu^{t}Me$_2$SiCl, pyridine, 15 h, 80 °C; iv, DAST, benzene–pyridine (18:1), 5 h, 60 °C; v, Dowex 50W (H^+), MeOH, 18 h, room temp.; vi, CBr_4, Ph_3P, pyridine, 8 h, 100 °C; vii, DMSO, dicyclohexylcarbodiimide, pyridinium trifluoroacetate, benzene, 3 h, room temp.; viii, LAH, tetrahydrofuran, 5 h, −78 °C ⟶ room temp.; ix, aq. 80% AcOH, 4 h, 50 °C; x, $LiBH_4$, tetrahydrofuran, 1 h, 0 °C; xi, TMSCl, 4-dimethylaminopyridine, pyridine, 15 h, room temp.; xii, CrO_3–pyridine, CH_2Cl_2, 1 h, 0 °C; xiii, 0.08 mol dm^{-3} H_2SO_4/1,4-dioxane–H_2O (5.5:1), 1 h, 70 °C; Ac_2O, pyridine, 15 h, room temp.; xiv, H_2, Pd black, 1,4-dioxane–AcOH–H_2O (10:1:1), 1.5 h, room temp.; Ac_2O, pyridine, 15 h, room temp.

6 M. K. Gurjar, V. J. Patil, J. S. Yadav and A. V. R. Rao, *Carbohydr. Res.*, 1984, **135**, 174; L. H. B. Baptistella, A. J. Marsaioli, J. D. S. Filho, G. G. Oliveira, A. B. Oliveira, A. Dessinges, S. Castillon, A. Olesker, T. T. Thang and G. Lukacs, *Carbohydr. Res.*, 1985, **140**, 51; H. H. Baer and A. Jaworska-Sobiesiak, *Carbohydr. Res.*, 1985, **140**, 201; S. Castillon, A. Dessinges, R. Faghih, G. Lukacs, A. Olesker and T. T. Thang, *J. Org. Chem.*, 1985, **50**, 4913; D. Picq and D. Anker, *J. Carbohydr. Chem.*, 1985, **4**, 113; H. H. Baer and L. Siemsen, *Can. J. Chem.*, 1988, **66**, 187; H. H. Baer, F. H. Mateo and L. Siemsen, *Carbohydr. Res.*, 1990, **195**, 225.
7 M. Sharma, R. J. Bernacki and W. Korytnyk, in *Fluorinated Carbohydrates*, ed. N. F. Taylor, ACS Symposium series 374, American Chemical Society, Washington, DC, 1988, p. 191.
8 R. F. Brady, Jr., *Carbohydr. Res.*, 1970, **15**, 35.
9 H. Steinlin, L. Camarda and A. Vasella, *Helv. Chim. Acta*, 1979, **62**, 378.
10 G. V. Rao, L. Que, Jr., L. D. Hall and T. P. Fondy, *Carbohydr. Res.*, 1975, **40**, 311.
11 A. K. M. Anisuzzaman and R. L. Whistler, *Carbohydr. Res.*, 1978, **61**, 511.
12 R. Mahrwald, F. Theil, H. Schick, S. Schwarz, H-J. Palme and G. Weber, *J. Prakt. Chem.*, 1986, **328**, 777.

Paper 2/00330I
Received 21*st January* 1992
Accepted 21*st January* 1992