Carbohydrate Research, 241 (1993) 295–299
Elsevier Science Publishers B.V., Amsterdam

Note

An improved synthesis of 4-deoxy-4-fluoro-D-galactopyranosyl derivatives

Kevin Koch and Robert J. Chambers

Central Research Division, Pfizer, Inc., Groton, CT 06340 (USA)

(Received April 3rd, 1992; accepted with revision August 3rd 1992)

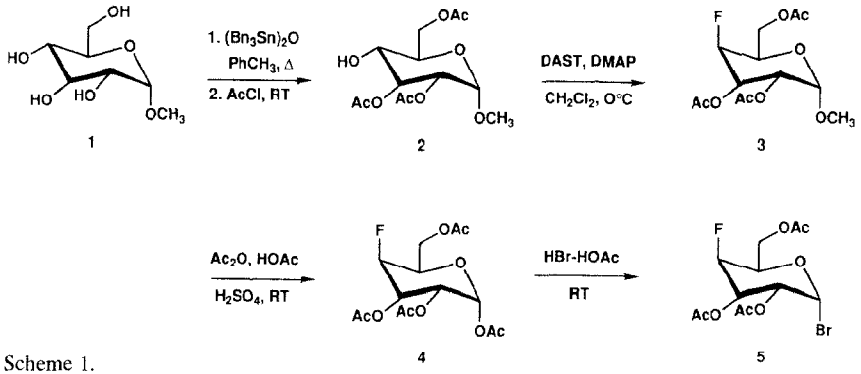
The function of carbohydrates in biological systems has been the topic of intensive study. Most recently, glycoprotein recognition has been reported to be essential in cellular trafficking[1], viral infectivity[2], cancer metastasis[3], and immunological regulation[4]. Given these important roles and the potential for novel therapeutic intervention[5] in a number of disease states, the modulation of glycoprotein synthesis/degradation or the antagonism of lectin binding sites has become an expanding area of research.

Fluorinated carbohydrates are valuable tools for the study of mammalian cell metabolism, transport, enzyme specificity and mechanism, as well as potential therapeutic agents in their own right[6]. Substitution of carbohydrate hydroxyl groups with fluorine atoms provides analogues which are sterically similar and polarized. Fluorine substitution also stabilizes glycosidic linkages to cleavage by electronically destabilizing the developing positive charge in oxonium intermediates during glycoside hydrolysis[7].

Our studies involving glycosidase inhibitors[8] required the synthesis of suitably protected 4-deoxy-4-fluoro-D-galactopyranose derivatives as glycosyl donors. A survey of the literature revealed two procedures for the preparation of these analogues; however, each of them involved elaborate protection–deprotection protocols[9]. Furthermore, no synthesis of a preferred glycosyl donor, 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α-D-galactopyranosyl bromide had been published.

A number of workers have reported successful regioselective acylations and alkylations of polyols involving stannylation methodology[10]. In one paper[11], stannylation of methyl α-D-glucopyranoside, followed by benzoylation with excess benzoyl chloride, afforded methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside as the major product, with the tribenzoylated adduct as a contaminant. We believed that the use of a sterically unencumbered acylating agent such as acetyl chloride would

Correspondence to: Dr. K. Koch, Central Research Division, Pfizer, Inc., Groton, CT 06340, USA.



Scheme 1.

afford the tri-*O*-acetyl derivative as the major product. This structure would provide an intermediate amenable to the subsequent introduction of fluorine with inversion at the C-4 position.

Stannylation of methyl α-D-glucopyranoside (**1**) in the presence of two equiv of bis(tributyltin)oxide, with the removal of water using a Dean–Stark trap, afforded the intermediate stannyl ether, which was treated without purification with four equiv of acetyl chloride. The mixture was stirred overnight at ambient temperature to give after purification a 40% yield of the triacetate **2** (Scheme 1). Methyl α-D-glucopyranoside and methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside were obtained as readily separable byproducts.

The use of diethylaminosulfur trifluoride (DAST) has seen widespread use for the introduction of fluorine into organic molecules, including carbohydrates[12]. Treatment of **2** with two equiv of DAST in the presence of DMAP gave, after chromatography, a 39% yield of methyl 2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro-α-D-galactopyranoside (**3**), as a single stereoisomer resulting from complete inversion of the C-4 hydroxyl group. This compound had been previously prepared via a four-step route[9].

Acetolysis of **3** using standard conditions[13] [100:100:1 (v/v) Ac_2O–AcOH–H_2SO_4] gave a 92% yield of the tetraacetate **4** as a 5:1 $\alpha:\beta$ mixture of anomers. Polyacetylated carbohydrates are important intermediates for the preparation of glycosyl halides. Glycosyl halides continue to be valuable as glycosyl donors in the synthesis of both simple glycosides as well as more complex oligosaccharides[14]. Treatment of **4** with HBr–AcOH gave, after chromatography, the glycosyl bromide **5** as a homogeneous oil in 94% yield. This compound was stable on storage under nitrogen at 0°C for at least one week.

In conclusion, we have described an improved preparation of 4-deoxy-4-fluoro-D-galactopyranose derivatives by taking advantage of the regioselective acylation of methyl α-D-glucopyranoside via a stannyl ether intermediate. In addition, the first synthesis of the glycosyl donor **5** has been accomplished in 23% overall yield in

four steps. The use of **5** in the preparation of novel glycosidase inhibitors will be reported in future papers.

EXPERIMENTAL

General methods.—^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AC 300 spectrometer indirectly referenced to Me_4Si from $CDCl_3$. Mass spectra were recorded on a Kratos Concept spectrometer. Infrared spectra were recorded on a Perkin–Elmer 283B spectrophotometer. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. Elemental analyses were performed on a Perkin–Elmer 2400 CHN analyzer. All substrates and reagents were obtained from Aldrich Chemical Company and were used as received.

Methyl 2,3,6-tri-O-acetyl-α-D-glucopyranoside (**2**).—A mixture of methyl α-D-glucopyranoside (3.0 g, 0.015 mol) and bis(tributyltin)oxide (17 mL, 20.1 g, 0.034 mol) in dry toluene (60 mL) was refluxed for 4 h with azeotropic removal of water. The reaction mixture was cooled to ambient temperature, then acetyl chloride (4 mL, 4.7 g, 0.06 mol) was added, and the mixture was stirred for 18 h. The reaction mixture was diluted with ether (400 mL), then washed with 5% HCl (40 mL), 5% $NaHCO_3$ (40 mL), brine (40 mL), dried ($MgSO_4$), and concentrated in vacuo to give an oil. Flash chromatography on silica gel eluting with 40:60 EtOAc–hexanes afforded **2** (1.92 g, 40%): $[\alpha]_D$ +102.7° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3500, 1716 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.27 (dd, 1 H, $J_{2,3}$ 9.3, $J_{3,4}$ 8.6 Hz, H-3), 4.87 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.81 (dd, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 10.1 Hz, H-2), 4.41 (dd, 1 H, $J_{5,6a}$ 4.5, $J_{6a,6b}$ 12.1 Hz, H-6a), 4.28 (dd, 1 H, $J_{5,6b}$ 2.2, $J_{6a,6b}$ 12.1 Hz, H-6b), 3.80 (m, 1 H, H-5), 3.55 (m, 1 H, H-4), 3.37 (s, 3H, OCH_3), 3.23 (m, 1 H, O*H*), 2.09 (s, 3 H, OCOCH_3), 2.06 (s, 3 H, OCOCH_3), and 2.05 (s, 3 H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5 (O*C*OCH$_3$), 170.3 (O*C*OCH$_3$), 96.8 (C-1), 72.8 (C-4), 70.7 (C-5), 69.6 (C-3), 69.2 (C-2), 62.9 (C-6), 55.3 (OCH$_3$), 20.9 (OCO*C*H$_3$), 20.8 (OCO*C*H$_3$), and 20.7 (OCO*C*H$_3$); FABMS *m/z* (%): 321 (M + 1)$^+$ (46), 289 (100). Anal. Calcd for $C_{13}H_{20}O_9$: C, 48.75; H, 6.29. Found: C, 48.35; H, 6.29.

Methyl 2,3,6-tri-O-acetyl-4-deoxy-4-fluoro-α-D-galactopyranoside (**3**).—To a stirred solution of **2** (1.78 g, 5.56 mmol) and 4-dimethylaminopyridine (DMAP, 1.49 g, 12.23 mmol) in dry CH_2Cl_2 (20 mL) at 0°C was added dimethylaminosulfur trifluoride (DAST, 1.54 mL, 1.88 g, 11.67 mmol). The reaction mixture was allowed to warm to ambient temperature over 18 h, then cooled to 0°C and quenched with MeOH (5 mL). The mixture was diluted with ether (400 mL) and washed with 5% HCl (40 mL), 5% $NaHCO_3$ (40 mL), dried ($MgSO_4$) and concentrated in vacuo to yield an oil. Flash chromatography on silica gel, eluting with 30:70 EtOAc–hexanes afforded **3** (695 mg, 39%): mp 86–88°C (ether–hexanes), (lit.[9] mp 91–92°C); $[\alpha]_D$ +155.7° (*c* 0.6, $CHCl_3$); lit.[9] $[\alpha]_D$ +150° (*c* 1.2, $CHCl_3$); IR (KBr): 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.22 (ddd, 1 H, $J_{3,4}$ 2.6, $J_{2,3}$ 10.9, $J_{F,3}$ 25.3 Hz, H-3), 5.18 (m, 1 H, H-2), 4.97 (m, 1 H, H-1), 4.89 (dd, 1 H, $J_{4,5}$ 1.4, $J_{F,4}$ 49.6 Hz, H-4), 4.25 (m, 2 H, H-6), 4.03 (dt, 1 H, $J_{5,6}$ 6.5, $J_{F,5}$ 28.8 Hz, H-5), 3.38 (s, 3 H, OCH_3),

2.08 (s, 3 H, OCOCH_3), 2.06 (s, 3 H, OCOCH_3), and 2.05 (s, 3 H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4 (O*C*OCH$_3$), 170.2 (O*C*OCH$_3$), 170.1 (O*C*OCH$_3$), 97.1 (C-1), 86.9 ($J_{F,4}$ 184.6 Hz, C-4), 68.2 (C-5), 67.9 (C-2), 66.5 ($J_{F,3}$ 18.1 Hz, C-3), 61.8 (C-6), 55.5 (O*C*H$_3$), 20.7 (OCO*C*H$_3$), and 20.6 (OCO*C*H$_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −220; FABMS *m/z* (%): 323 $(M+1)^+$ (8), 291 (100). Anal. Calcd for $C_{13}H_{19}FO_8$: C, 48.45; H, 5.94. Found: C, 48.64; H, 5.73.

*1,2,3,6-Tetra-*O*-acetyl-4-deoxy-4-fluoro-α-*D*-galactopyranoside* (**4**).—A mixture of **3** (520 mg, 1.61 mmol) in acetic anhydride (5 mL) and galcial acetic acid (5 mL) containing H_2SO_4 (98%, 5 drops) was stirred for 18 h at ambient temperature. The mixture was diluted with ether (400 mL) and washed with 5% $NaHCO_3$ (40 mL), brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo to give an oil. Flash chromatography on silica gel eluting with 35:65 EtOAc–hexanes yielded **4** (518) $[\alpha]_D$ +85.6° (*c*, 0.5, $CHCl_3$); IR ($CHCl_3$); 1749 cm^{-1}; ^{1}H NMR (300 MHz. $CDCl_3$): δ 6.36 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1α) 5.67 (d, 1 H, $J_{1,2}$ 9.0 Hz, H-1β), 5.31 (m, 2 H, H-2,3), 4.94 (dd, 1 H, $J_{4,5}$ 2.3, $J_{F,4}$ 50.1 Hz, H-4), 4.22 (m, 3 H, H-5) 2.13 (s, 3 H, OCOCH_3), 2.11 (s, 3 H, OCOCH_3), 2.06 (s, 3 H, OCOCH_3), and 2.00 (s, 3 H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (O*C*OCH$_3$), 169.6 (O*C*OCH$_3$), 168.8 (O*C*OCH$_3$), 89.6 (C-1), 86.4 ($J_{F,4}$ 186.2 Hz, C-4), 69.0 ($J_{F,5}$ 18.2 Hz, C-5), 67.9 ($J_{F,3}$ 17.4 Hz), 66.1 (C-2), 61.0 (C-6), 20.8 (OCO*C*H$_3$), 20.7 (OCO*C*H$_3$), 20.6 (OCO*C*H$_3$), 20.5 (OCO*C*H$_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −220; FABMS *m/z* (%): 291 (100). Anal Calcd for $C_{14}H_{19}FO_9$: C, 48.00; H, 5.47. Found: C, 48.06; H, 5.50.

*2,3,6-Tri-*O*-acetyl-4-deoxy-4-fluoro-α-*D*-galactopyranosyl bromide* (**5**).—A mixture of **4** (350 mg, 0.10 mmol) in a solution of 33% HBr–HOAc (5 mL) was stirred for 3 h at ambient temperature. The mixture was concentrated in vacuo to give an oil. Flash chromatography on silica gel eluting with 30:70 EtOAc–hexanes afforded **5** (347 mg, 94%): $[\alpha]_D$ +214.3° (*c*, 0.5, $CHCl_3$); IR ($CHCl_3$): 1743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 5.32 (ddd, $J_{3,4}$ 2.6, $J_{2,3}$ 10.7, $J_{F,3}$ 26.5 Hz, H-3), 5.07 (m, 1 H, H-2), 5.00 (dd, 1 H, $J_{4,5}$ 2.6, $J_{F,4}$ 47.5 Hz, H-4), 4.29 (m, 3 H, H-5,6a,6b), 2.13 (s, 3 H, OCOCH_3), 2.10 (s, 3 H, OCOCH_3), and 2.08 (s, 3 H, OCOCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (O*C*OCH$_3$), 170.1 (O*C*OCH$_3$), 169.8 (O*C*OCH$_3$), 87.8 (C-1), 85.8 ($J_{F,4}$ 185.6 Hz, C-4), 71.3 ($J_{F,5}$ 18.1 Hz), 68.5 ($J_{F,3}$ 17.1 Hz, H-3), 67.5 (C-2), 60.9 (C-6), 20.7 (OCO*C*H$_3$), and 20.6 (OCO*C*H$_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ −216; FABMS *m/z* (%): 371 (M^+, 10), 291 (40), 249 (50), 231 (100). Anal. Calcd for $C_{12}H_{16}BrFO_7$: C, 38.83; H, 4.31. Found: C, 38.85; H, 4.48.

REFERENCES

1 J.C. Paulson, *Trends Biol. Sci.*, 14 (1989) 272–275; M.L. Phillips, E. Nudelman, F.C.A. Gaeta, M. Perez, A.K. Singhal, S. Hakomori, and J.C. Paulson, *Science*, 250 (1990) 1130–1131.

2 D.A. Leigh, *J. Antimicrob. Chemother.*, 22 (1988) 269–721. R. Huang, E. Dietsch, O. Lockhoff, M. Schiler, and W. Reutter, *FEBS Lett.*, 291 (1991) 199–202.

3 G. Poste and L. Weiss (Eds.), *Fundamental Aspects of Metastasis*, North Holland Publishing Co., Amsterdam, 1976; M.J. Humphries, K. Matsamoto, S.L. White, and K. Olden, *Cancer Res.*, 46 (1986) 5215–5221; T. Feizi, *Nature (London)*, 314 (1985) 53–57.
4 N. Sharon and H. Lis, *Science*, 246 (1989) 227–233.
5 K.A. Karlsson, *Trends Pharmacol. Sci.*, 12 (1991) 265–275.
6 N.F. Taylor, *ACS Symp. Ser.*, 374 (1988).
7 S.G. Withers, D.J. Maclennan, and I.P. Street, *Carbohydr. Res.*, 154 (1986) 127–143.
8 E. Truscheit, W. Frommer, B. Junge, L. Miller, D.D. Schmidt, and N. Wingerder, *Angew. Chem. Int. Ed. Engl.*, 20 (1981) 744–761; H.D. Elbein, *Annu. Rev. Biochem.*, 56 (1987) 497–534.
9 D. Marcus and J. Westwood, *Carbohydr. Res.*, 17 (1971) 269–274; P.J. Card and G.S. Reddy, *J. Org. Chem.*, 48 (1983) 4734–4743.
10 S. David and S. Hanessian, *Tetrahedron*, 41 (1985) 643–663.
11 T. Ogawa and M. Matsui, *Tetrahedron*, 37 (1981) 2363–2369.
12 W.J. Middleton, *J. Org. Chem.*, 40 (1975) 574–578; M. Hudlicky, *Org. React.*, 35 (1988) 531–535. P.J. Card, *J. Carbohydr. Chem.*, 4 (1985) 451–487.
13 R.D. Guthrie and J.F. McCarthy, *Adv. Carbohydr. Chem.*, 22 (1967) 11–23.
14 H. Paulsen, *Angew. Chem. Int. Ed. Engl.*, 21 (1982) 155–173; H. Paulsen, *Chem. Soc. Rev.*, 13 (1984) 15–45.