Carbohydrate Research, 242 (1993) 291–295
Elsevier Science Publishers B.V., Amsterdam

Note

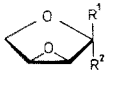
Synthesis of methyl 2,3-anhydro-α- and -β-L-erythrofuranoside

Jiří Jarý and Ivan Raich

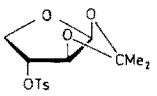
Department of Chemistry of Natural Compounds, Institute of Chemical Technology, 166 28 Prague 6 (Czechoslovakia)

(Received April 22nd, 1992; accepted October 1st, 1992)

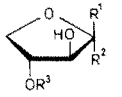
For synthetic and stereochemical studies in the methyl tetroside series, we needed methyl 2,3-anhydro-α-L-erythrofuranoside (**1**) and methyl 2,3-anhydro-β-L-erythrofuranoside (**2**) (or the corresponding D enantiomers). Only the racemic epoxides **1** and **2** have been prepared by Gagnieu et al.[1], using epoxidation of 2-methoxy-2,5-dihydrofuran with peroxybenzimidic acid. We now report on new syntheses of the optically active oxiranes **1** and **2**, starting either from 1,2-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-β-D-threofuranose (**3**) or methyl α-D-threofuranoside (**4**) and its β anomer **5**.



1 R^1 = OMe, R^2 = H
2 R^1 = H, R^2 = OMe



3



4 R^1 = H, R^2 = OMe, R^3 = H
5 R^1 = OMe, R^2 = H, R^3 = H
6 R^1 = H, R^2 = OMe, R^3 = Ts
7 R^1 = OMe, R^2 = H, R^3 = Ts

Methanolysis of the 3-*O*-*p*-toluenesulfonyl derivative **3** (the sign of the specific rotation of **3** was incorrect in our previous paper[2]) in the presence of a strongly acidic ion-exchange resin for 30 h gave a mixture containing methyl 3-*O*-*p*-toluenesulfonyl-α-D-threofuranoside (**6**) and its β anomer **7** in 72% yield (ratio 1.3 : 1) in addition to unreacted starting material **3**. Prolonged treatment of **3** could not be used to increase the yield of **6** and **7** due to the concomitant solvolysis of the *p*-toluenesulfonyl group in the methyl threofuranosides **6** and **7**. The configuration at the anomeric centre was assigned to the new methyl glycosides on the basis of ^{1}H NMR spectra. The larger $J_{1,2}$ coupling of **7** (4.5 Hz) indicates, in a furanose series, the 1,2-*cis* arrangement[3–5], i.e., the β-D configuration, whilst the $J_{1,2}$ coupling of 1.2 Hz clearly designates the α anomer **6**. IR spectra also support this assignment. The stretching vibration of the hydroxyl group of **7** provides in the spectrum a sharp band at ν_{max} 3560 cm^{-1} corresponding to a strong hydrogen bond to O-1. The measured value is almost the same as for the corresponding

intramolecular hydrogen bond $O_{(2)}$–H $\cdots$ $O_{(1)}$ of the diol **5** (ν_{max} 3562 cm^{-1}, ref 6), but considerably lower than for an analogous 3-*O*-methyl derivative (ν_{max} 3574 cm^{-1}, ref 6), probably as a consequence of a slightly different conformation in the 3-methyl ether. However, in the case of the α anomer **6**, where such a hydrogen bond is impossible, a band with two maxima at ν_{max} 3621 and 3579 cm^{-1} occurs, the first corresponding to a weaker hydrogen-bonded OH group, presumably to O-4; the origin of the second maximum is not clear. However, we assume that it is probably due to a hydrogen bond to one of the oxygen atoms of the SO_2 group.

The *p*-toluenesulfonyl compounds **6** and **7** gave, with 1.5 equivalents of sodium methoxide in methanol, the optically active oxiranes **2** and **1** in 76 and 91% yield, respectively, the ^1H NMR and IR spectra of which were identical with the data published for racemic **2** and **1** (ref 1).

Alternatively, epoxides **1** and **2** were synthesized directly from methyl threofuranosides **5** and **4**, respectively, using the Mitsunobu procedure[7]. α-D-Threoside **4** gave, with 2 equivalents of diethyl azodicarboxylate–triphenylphosphine in dichloromethane, the β-L-*erythro* epoxide **2** exclusively in 73% yield, while methyl glycoside **5** yielded, under the same conditions, 65% of a 17:1 mixture of epoxide **1** and the D enantiomer of **2**. The minor component was not isolated, but it had the same retention time and mass spectrum as **2** according to the GLC–MS analysis of the product.

Epoxide synthesis via the Mitsunobu reaction has been widely utilized in carbohydrate furanoses[8,9], particularly in sucrose[10–12] and nucleoside chemistry[13,14]. Its stereoselectivity, however, has not been fully clarified, especially in derivatives lacking a free primary hydroxyl group.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler block and are uncorrected. NMR data (^1H and ^{13}C) were obtained with a Bruker AM-400 spectrometer operated at 400 MHz for ^1H and 100 MHz for ^{13}C. Chemical shifts are reported relative to internal Me_4Si. Reactions were monitored by TLC on Silica Gel G acc. to Stahl (Merck, Darmstadt; 25 × 75 mm plates; layer thickness, 0.2–0.3 mm), with detection by charring with H_2SO_4. The following solvent systems (v/v) were used: (*A*) 10:1 benzene–acetone and (*B*) 3:2 hexane–EtOAc. Column chromatography was performed on silica gel (Lachema, Brno) 100–250 μm. Optical rotations were measured on an Opton photoelectric polarimeter at 20°C. IR spectra were recorded for CCl_4 solutions with a Perkin–Elmer 325 apparatus at ambient temperature. Combined GLC–MS was performed with a Jeol DX 303 GC-MS apparatus, using a capillary column (40 m × 0.32 mm i.d.) coated with SPB, the temperature programme 40 → 120°C at 4°C/min, and an ionization potential of 70 eV. Solvents were evaporated at < 30°C under diminished pressure. Light petroleum refers to the fraction with bp 45–60°C.

Methyl 3-O-p-toluenesulfonyl-α-D-threofuranoside (**6**) *and methyl 3-O-p-toluenesulfonyl-β-D-threofuranoside* (**7**). — To a stirred solution of compound **3** {2.80 g, 8.9 mmol, mp 50–51°C; $[\alpha]_D$ −22° (*c* 1.0, $CHCl_3$); ref 2} in MeOH (45 mL) was added Amberlite IR-120 (H^+) ion-exchange resin (9 mL), and the mixture was boiled for 30 h. The resin was filtered off and the filtrate was evaporated. The residue was chromatographed on a silica gel column (200 g) with 30:1 benzene–acetone, to give **3** (0.13 g); crystalline **7** (0.80 g, 33% based on **3** consumed), R_f 0.46 (solvent *A*); and syrupy **6** (1.04 g, 42%), R_f 0.35 (*A*). Compound **7**, after repeated recrystallization, had mp 69–70°C (benzene–light petroleum); $[\alpha]_D$ −145° (*c* 1.6, $CHCl_3$); ν_{max} 3560 (OH), 1596, 1185, 1173, and 870 cm^{-1} (Ts). ^1H NMR data ($CDCl_3$): **7**, δ 7.82 and 7.36 (m, 4 H, Ar-H), 4.91 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 4.76 (m, 1 H, H-3), 4.23 (m, 1 H, H-2), 4.08 (dd, 1 H, $J_{3,4R}$ 5.8, $J_{4R,4S}$ −10.8 Hz, H-4*R*) *, 3.85 (dd, 1 H, $J_{3,4S}$ 2.9 Hz, H-4*S*), 3.44 (s, 3 H, OCH_3), 2.72 (b, 1 H, OH), 2.46 (s, 3 H, CH_3). *Anal.* Calcd for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59; S, 11.12. Found: C, 49.72; H, 5.50; S, 11.41.

Compound **6** had $[\alpha]_D$ +89° (*c* 1.4, $CHCl_3$); ν_{max} 3621, 3579 (OH), 1597, 1187, 1175, and 893 cm^{-1} (Ts). ^1H NMR data ($CDCl_3$): **6**, δ 7.81, 7.38 (m, 4 H, Ar-H), 4.81 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 4.69 (m, 1 H, $J_{2,3}$ 2.5, $J_{3,4R}$ 7.0, $J_{3,4S}$ 6.1 Hz, H-3), 4.29 (ddd, 1 H, $J_{2,4R}$ 0.6 Hz, H-2), 4.17 (ddd, 1 H, $J_{4R,4S}$ −10.1 Hz, H-4*R*), 3.86 (dd, 1 H, H-4*S*), 3.36 (s, 3 H, OCH_3), 2.47 (s, 3 H, CH_3). *Anal.* Calcd for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59; S, 11.12. Found: C, 50.46; H, 5.52; S, 10.76.

Methyl 2,3-anhydro-β-L-erythrofuranoside (**2**). — (*a*) To a cooled solution of tosylate **6** (3.79 g, 13.2 mmol) in MeOH (90 mL) was added 40 mL of methanolic 0.5 M NaOMe (20.0 mmol), and the mixture was kept at 0°C. After the reaction was complete, the solution was saturated with CO_2 and MeOH was then evaporated off. The residue was extracted with ether, and the combined extracts were filtered and evaporated to give **2** (1.16 g, 76%), R_f 0.76 (solvent *B*), which was distilled at 135°C (bath)/3.34 kPa; $[\alpha]_D$ +167° (*c* 1.9, $CHCl_3$); lit.[1] bp 90°C/3.34 kPa; ν_{max} 2860, 860, and 815 cm^{-1}. ^1H NMR data ($CDCl_3$): δ 4.94 (s, 1 H, H-1), 3.99 (d, 1 H, $J_{4R,4S}$ −10.4 Hz, H-4*S*), 3.80 (d, 1 H, H-4*R*), 3.77 (d, 1 H, $J_{2,3}$ 2.9 Hz, H-2), 3.66 (d, 1 H, H-3), 3.41 (s, 3 H, OCH_3). ^{13}C NMR data (C_6D_6): δ 103.12 (C-1), 66.64 (C-4), 56.79 (C-2), 55.58 (OCH_3), 53.84 (C-3). Mass spectrum: *m/z* 116 (0.5%, M^+), 115 (0.5), 85 (16), 61 (100), 59 (14), 57 (7), 56 (16), 55 (27), 45 (6), 43 (4), 42 (5), 37 (3).

(*b*) Triphenylphosphine (1.17 g, 4.5 mmol) was added to a stirred solution of diol **4** {0.30 g, 2.2 mmol; bp 96°C/27 Pa; $[\alpha]_D$ +102° (*c* 0.5, H_2O), ref 15} in CH_2Cl_2 (5 mL) and the resulting mixture was heated to reflux under Ar. A solution of diethyl azodicarboxylate (0.7 mL, 4.5 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise and boiling was continued for 45 min. After addition of water (0.05 mL), the cooled mixture was evaporated and hot diethyl ether (3 mL) was

* Designation of the C-4 protons according to Serianni and Barker[5].

added to the residue. The mixture was kept overnight at −15°C, crystals of triphenylphosphine oxide were then filtered off, and the filtrate was evaporated to dryness. Neither TLC (solvent *B*) nor GLC–MS of the crude product (under the conditions stated above, **2** had t_R 914 s) revealed the presence of the second oxirane. The residue was chromatographed on silica gel (20 g) by elution first with 2:1 CH_2Cl_2–light petroleum (100 mL) and then with CH_2Cl_2 (200 mL). The latter solvent afforded epoxide **2** which was distilled at 135°C (bath)/3.34 kPa to give pure **2** (0.19 g, 73%), the specific rotation and ^1H NMR spectrum of which were identical to those obtained for **2** in (*a*). *Anal.* Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.65; H, 7.12.

Methyl 2,3-anhydro-α-L-erythrofuranoside (**1**).—(*a*) Compound **7** (1.07 g, 3.7 mmol) and NaOMe (5.6 mmol) were treated according to the previous procedure to give **1** (0.39 g, 91%); R_f 0.56 (solvent B); bp 105°C (bath)/3.34 kPa; $[\alpha]_D$ −55° (*c* 3.0, $CHCl_3$); lit.[1] bp 64°C/3.34 kPa; ν_{max} 2860, 860, and 815 cm^{-1}. NMR data ($CDCl_3$): ^1H, δ 5.02 (s, 1 H, H-1), 4.19 (d, 1 H, $J_{4R,4S}$ −10.8 Hz, H-4*S*), 3.78 (dd, 1 H, $J_{3,4R}$ 0.6 Hz, H-4*R*), 3.72 (m, 2 H, H-2,3), 3.52 (s, 3 H, OCH_3); ^{13}C, δ 102.64 (C-1), 66.99 (C-4), 56.84 (OCH_3), 55.74 (C-2), 54.76 (C-3). Mass spectrum: *m/z* 116 (0.5%, M^+), 115 (1), 85 (12), 61 (100), 59 (10), 57 (6), 56 (17), 55 (35), 45 (5), 43 (5), 42 (7), 37 (2).

(*b*) *Methyl β-D-threofuranoside* (**5**; 0.45 g, 3.3 mmol; bp 87–95°C/27 Pa; $[\alpha]_D$ −185° (*c* 0.5, H_2O), ref 15) was treated with triphenylphosphine (1.76 g, 6.8 mmol) and diethyl azodicarboxylate (1.1 mL, 6.8 mmol) as described above for α-threoside **4**. Two oxirane derivatives in a 17:1 ratio were identified in the crude product, using GLC–MS, with t_R 1120 and 912 s, respectively. Column chromatography (conditions as above for **2**) afforded traces of the D enantiomer of **2**, followed by **1** which was further distilled at 105°C (bath)/3.34 kPa to give pure **1** (0.16 g, 61%), the physical properties of which were identical to those of **1** obtained in (*a*). *Anal.* Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.73; H, 6.82.

REFERENCES

1 C.H. Gagnieu and A.V. Grouiller, *J. Chem. Soc., Perkin Trans. 1*, (1982) 1009–1011.
2 J. Jarý, M. Masojídková, I. Kozák, M. Marek, and J. Staněk, Jr., *Collect. Czech. Chem. Commun.*, 45 (1980) 3378–3391.
3 B. Capon and D. Thacker, *Proc. Chem. Soc.*, (1964) 369.
4 J. Jarý and M. Marek, *Collect. Czech. Chem. Commun.*, 45 (1980) 3571–3582.
5 A.S. Serianni and R. Barker, *J. Org. Chem.*, 49 (1984) 3292–3300.
6 J. Jarý and M. Marek, *Collect. Czech. Chem. Commun.*, 46 (1981) 3289–3293.
7 O. Mitsunobu, *Synthesis*, (1981) 1–28.
8 R.D. Guthrie, I.D. Jenkins, R. Yamasaki, B.W. Skelton, and A.H. White, *J. Chem. Soc., Perkin Trans. 1*, (1981) 2328–2334.
9 M.G. Martin, B. Ganem, and J.R. Rasmussen, *Carbohydr. Res.*, 123 (1983) 332–334.
10 R.D. Guthrie, I.D. Jenkins, S. Thang, and R. Yamasaki, *Carbohydr. Res.*, 121 (1983) 109–117.
11 K. Čapek, T. Vydra, M. Ranný, and P. Sedmera, *Collect. Czech. Chem. Commun.*, 50 (1985) 2191–2200.

12 R. Khan, M.R. Jenner, M. Lindseth, K.S. Mufti, and G. Patel, *Carbohydr. Res.*, 162 (1987) 199–207.
13 R. Mengel and M. Bartke, *Angew. Chem.*, 90 (1978) 725.
14 Y.C.J. Chen, F. Hansske, K.D. Janda, and M.J. Robins, *J. Org. Chem.*, 56 (1991) 3410–3413.
15 J.M. Baxter and A.S. Perlin, *Can. J. Chem.*, 38 (1960) 2217–2225.