*Carbohydrate Research*, 67 (1978) 257–262


**Note**

# A convenient synthesis of methyl 2,3-anhydro-α-D-ribofuranoside

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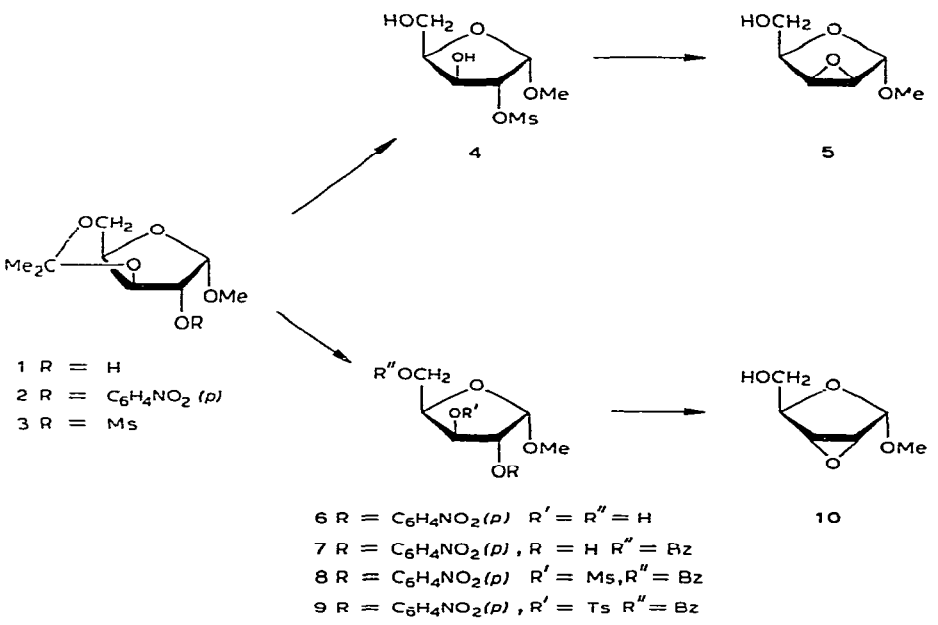
(Received August 15th, 1977 accepted for publication, October 8th 1977)

The 2,3-anhydropentofuranosides can undergo a large variety of reactions through nucleophilic scission of the epoxide ring, as has been reviewed[1,2] For syntheses of azido and diazido analogues of methyl α-D-arabinofuranoside[3], we required substantial amounts of both pure methyl 2,3-anhydro-α-D-lyxofuranoside (**5**) and pure methyl 2,3-anhydro-α-D-ribofuranoside (**10**) Whereas crystalline **5** is conveniently obtained by the procedure of Baker *et al*[4], the method of Baker and




assoc [5] for the synthesis of **10** seemed less suitable as it involves a Fischer glycosylation late in the reaction sequence and thus furnishes both the α and β anomers Although these can be separated by vacuum distillation, some cross-contamination is difficult to avoid, as **10** has not been obtained in crystalline form so far Moreover, we had no use

for the β anomer of **10** Therefore, an alternative synthesis of **10**, which is based on methyl 3,5-*O*-isopropylidene-α-D-xylofuranoside (**1**), an intermediate also required for the synthesis[4] of **5**, was devised Finally, in repeating the synthesis of **5** according to Baker *et al* [4], we succeeded in crystallizing two of the intermediates (**3** and **4**) previously reported[4] as gums This allowed raising the yield of pure **5** from 76% to 94% (based on **1**)

Baker *et al* [4] separated the common intermediate **1** from its anomer by fractional distillation In our hands, t l c analysis revealed the presence of a considerable proportion of β anomer in the fraction containing **1** Hence, **1** was purified by column chromatography on silica gel Anomerically pure **1** (by t l c and n m r analysis) was converted, in quantitative yield, into the *p*-nitrobenzoate **2**, which thus far has resisted all attempts at crystallization Removal of the isopropylidene group with 67% acetic acid gave the crystalline 2-*p*-nitrobenzoate **6** in 97% yield In all subsequent preparations, **6** was obtained in crystalline form without chromatographic purification of crude **1** Selective monobenzoylation of **6** gave an 81% yield of the crystalline 5-benzoate-2-*p*-nitrobenzoate **7**, which was converted into crystalline methyl 5-*O*-benzoyl-3-*O*-methylsulfonyl-2-*O*-*p*-nitrobenzoyl-α-D-xylofuranoside (**8**) in quantitative yield Tosylation of **7** gave a product inferior to that obtained by mesylation, requiring 4 days to achieve completion and to give a 67% yield of crystalline, but not pure 3-*O*-tosyl derivative **9** Treatment of either **8** or **9** with excess sodium methylate in methanol gave the desired highly pure methyl 2,3-anhydro-α-D-ribofuranoside (**10**) in quantitative yield Distillation of **10** did not improve its purity, but caused loss of material

The present synthesis of **10** offers several advantages over the previously published procedure[5] The yield over five stages (based on **1**) is 79%, the yield based on D-xylose is ~31% as compared to[5] ~16% The product consists of only one anomer of high anomeric purity Three out of four intermediates are crystalline whereby purification and scale-up are facilitated When repeating the original synthesis of the *lyxo*-epoxide **5** according to Baker *et al* [4], we obtained crystalline methyl 2-*O*-methylsulfonyl-α-D-xylofuranoside (**4**), which Baker *et al* [4] had not isolated Reisopropylidenation of **4** and preparative t l c gave crystalline **3**, previously described as a gum[4] By use of the crystalline intermediates **3** and **4**, we were able to raise the yield of pure **5** from the original 76% to 94% (based on **1**)

## EXPERIMENTAL

*General* — Melting points were determined with a Kofler hot-stage and are uncorrected Optical rotations were determined with a Perkin–Elmer 141 polarimeter Elemental analyses were performed by Dr J Zak, Mikroanalytisches Laboratorium am Institut fur Physikalische Chemie, Universitat Wien N m r spectra were recorded with a Varian HA-100 instrument, tetramethylsilane being the internal standard, chemical shifts are reported in p p m (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), or m (complex multiplet), coupling constants are

first-order. Thin-layer chromatography (t.l.c.) was performed on Merck precoated plates (5 × 10 cm, layer thickness 0.25 mm, Silica Gel 60 $F_{254}$) and preparative t.l.c. on Merck PLC plates of Silica Gel 60 $F_{254}$, (layer thickness 2 mm, 20 × 20 cm).

*Methyl 3,5-O-isopropylidene-α-D-xylofuranoside* (**1**) — This compound was prepared in 39% yield according to the procedure of Baker *et al.*[4], b.p. $_{0.2\,mtorr}$ 69–75° (lit.[4] b.p. $_{0.1\,torr}$ 85–88°), $[\alpha]_D^{20}$ +43.3° (*c* 2.0, water) {lit.[4] $[\alpha]_D^{24}$ +17.6° (*c* 2.0, water)}. A sample was purified by column chromatography [40-fold excess (w/w) of Merck Silica Gel 60, 5:1 (v/v) benzene–ethyl acetate], $[\alpha]_D^{20}$ +92.6° (*c* 0.51, chloroform), n.m.r. (chloroform-*d*) $\delta$ 2.97 (d, 1 H, $J_{OH\,H\text{-}2}$ ~2 Hz, OH-2), 3.57 (s, 3 H, $OCH_3$), 3.80–4.40 (m, 5 H, H-2, H-3, H-4, H-5, H-5'), and 5.23 (d, 1 H, $J_{1,2}$ ~2 Hz, H-1).

*Anal.* Calc. for $C_9H_{16}O_5$: C, 52.9; H, 7.9. Found: C, 53.2; H, 8.1.

*Methyl 3,5-O-isopropylidene-2-O-p-nitrobenzoyl-α-D-xylofuranoside* (**2**) — A solution of **1** (30 g) in dry pyridine (100 ml) was treated dropwise with a solution of *p*-nitrobenzoyl chloride (30 g) in dry pyridine (300 ml) at 0° with magnetic stirring. The mixture was stirred at room temperature overnight. Water (10 ml) was added, pyridine was removed by evaporation, and the residue was dissolved in chloroform (200 ml). The solution was washed with water, 3M sodium hydrogensulfate and sodium hydrogencarbonate solutions (200 ml each), dried (magnesium sulfate), and evaporated, leaving **2** (55.8 g, 105%) as a thick, yellow syrup still containing some solvent and traces of impurities (t.l.c., 10:1, v/v, benzene–ethyl acetate). A sample was purified by preparative t.l.c. in the same solvent system, $[\alpha]_D^{20}$ +118° (*c* 0.4, chloroform), $\lambda_{max}^{EtOH}$ 258 nm (ε 12 200). n.m.r. (chloroform-*d*) $\delta$ 3.40 (s, 3 H, $OCH_3$), 3.97 (d of d, 1 H, $J_{5,4}$ ~2.5 Hz, $J_{5,5'}$ ~10 Hz, H-5), 4.10 (d of d, 1 H, $J_{5',4}$ ~2.5 Hz, $J_{5',5}$ ~10 Hz, H-5'), 4.23 (d of t, 1 H, $J_{4,3}$ ~2 Hz, $J_{4,5,5'}$ ~2.5 Hz, H-4), 4.58 (d of d, 1 H, $J_{3,2}$ ~1 Hz, $J_{3,4}$ ~2 Hz, H-3), 5.28 (d of d, 1 H, $J_{2,1}$ ~2 Hz, $J_{2,3}$ ~1 Hz, H-2), and 5.40 (d, 1 H, $J_{1,2}$ ~2 Hz, H-1).

*Anal.* Calc. for $C_{16}H_{19}NO_8$: C, 54.4, H, 5.4, N, 4.0. Found: C, 53.3, H, 5.3, N, 3.8.

*Methyl 2-O-p-nitrobenzoyl-α-D-xylofuranoside* (**6**) — Compound **2** (55.8 g) was mixed with acetic acid (100 ml) and water (50 ml), and the mixture was stirred at 50° until no more starting material was observed by t.l.c. (5:1, v/v, benzene–ethyl acetate, 2 h). The solvent was evaporated, the remaining syrup dried by three additions and evaporations of toluene, dissolved in ethanol, and evaporated, whereby it crystallized. Recrystallization from benzene–pentane gave colorless needles (44.6 g, 97%), m.p. 109–111°, $[\alpha]_D^{20}$ +144° (*c* 0.37, chloroform), $\lambda_{max}^{EtOH}$ 278 nm (ε 13 700). n.m.r. (chloroform-*d*) $\delta$ 2.80 (t, 1 H, $J_{OH\text{-}5\,H\text{-}5,5'}$ ~3 Hz, OH-5), 3.40 (s, 3 H, $CH_3O$), 3.73 (d, 1 H, $J_{OH\text{-}3\,H\text{-}3}$ ~4 Hz, OH-3), 3.99 (m, 2 H, H-5,5'), 4.33 (d of t, 1 H, $J_{3,2}$ ~3 Hz, $J_{3\,OH\text{-}3}$ ~4 Hz, $J_{3,4}$ ~4 Hz, H-3), 5.10 (d of d, 1 H, $J_{2,1}$ ~2 Hz, $J_{2,3}$ ~3 Hz, H-2), and 5.28 (d, 1 H, $J_{1,2}$ ~2 Hz, H-1).

*Anal.* Calc. for $C_{13}H_{15}NO_8$: C, 49.8, H, 4.8, N, 4.5. Found: C, 49.8, H, 4.7, N, 4.4.

*Methyl 5-O-benzoyl-2-O-p-nitrobenzoyl-α-D-xylofuranoside* (**7**) — Compound **6** (41.2 g) in dry pyridine (150 ml) was treated dropwise at 0° with a solution of benzoyl

chloride (13.2 ml) in dry pyridine (50 ml), after the addition, the reaction was monitored by t.l.c. (5:1, v/v, benzene–ethyl acetate). A maximum amount of 5-monobenzoate **7** was formed after ~2 h, after which time the reaction mixture was treated with water (1 ml) and evaporated to a syrup. This was taken up in chloroform (200 ml), and the solution was washed successively with water, 3M sodium hydrogensulfate, and saturated sodium hydrogencarbonate (~200 ml each), dried (magnesium sulfate), and evaporated. The residue was dissolved in dry benzene (~50 ml) and pentane was added to slight turbidity, whereupon **7** crystallized as needles (45 g, 81%), m.p. 124–127°, $[\alpha]_D^{20}$ +70.1° (*c* 0.39, chloroform) (from ethyl acetate–pentane). **4** crystallized as prisms, m.p. 95–96°) $\lambda_{max}^{EtOH}$ 261 nm (ε 12 600). n.m.r. (chloroform-*d*) δ 3.20 (broad s, 1 H, OH-3), 3.42 (s, 3 H, $OCH_3$), 4.40–4.95 (m, 4 H, H-3, H-4, H-5,5'), 5.24 (d of d, 1 H, $J_{2,1}$ ~2 Hz, $J_{2,3}$ ~2 Hz, H-2), and 5.32 (d, 1 H, $J_{1,2}$ ~2 Hz, H-1).

*Anal.* Calc. for $C_{20}H_{19}NO_9$: C, 57.6; H, 4.6; N, 3.4. Found: C, 57.8; H, 4.6; N, 3.3.

*Methyl 5-O-benzoyl-3-O-methylsulfonyl-2-O-p-nitrobenzoyl-α-D-xylofuranoside* (**8**). — Compound **7** (8.4 g) was dissolved in pyridine (50 ml) and treated with methanesulfonyl chloride (1.8 ml) according to standard procedure. The crude, solid **8** was crystallized from 2-propanol to give needles (9.97 g, 100%, m.p. 126–130°) after two recrystallizations, m.p. 128–129°, $[\alpha]_D^{20}$ +127° (*c* 0.61, chloroform), $\lambda_{max}^{EtOH}$ 257 (ε 13 300) and 231 nm (ε 15 800). n.m.r. (chloroform-*d*) δ 3.04 (s, 3 H, Ms), 3.36 (s, 3 H, $OCH_3$), 4.40–4.80 (m, 3 H, H-4, H-5,5'), 5.20–5.45 (m, 2 H, H-1, H-2), and 5.66 (t, 1 H, $J_{3,2} = J_{3,4}$ ~3 Hz, H-3).

*Anal.* Calc. for $C_{21}H_{21}NO_{11}S$: C, 50.9; H, 4.2; N, 2.8; S, 6.5. Found: C, 50.8; H, 4.2; N, 2.8; S, 6.9.

*Methyl 5-O-benzoyl-2-O-p-nitrobenzoyl-3-O-p-tolylsulfonyl-α-D-xylofuranoside* (**9**). — To **7** (34.6 g) in dry pyridine (100 ml) was added dropwise with stirring at 0° a solution of *p*-toluenesulfonyl chloride (21.5 g) in dry pyridine (100 ml). After stirring had been continued at room temperature for 48 h, more *p*-toluenesulfonyl chloride (8 g) in pyridine (40 ml) was added and stirring continued for a total of 72 h. At this time no further change was detectable by t.l.c. (10:1, v/v, benzene–ethyl acetate), and the reaction mixture was poured onto crushed ice (~1.5 l) with efficient stirring and addition of seed crystals of **9**. The light-tan solid that separated was filtered off, washed extensively with water, dried in a vacuum desiccator (calcium chloride), and crystallized from benzene–2-propanol as plates (32.6 g, 69%), m.p. 145–151°, $[\alpha]_D^{20}$ +126° (*c* 0.49, chloroform). $\lambda_{max}^{EtOH}$ 258 (ε 14 500) and 226 nm (ε 28 400). n.m.r. (chloroform-*d*) δ 2.30 (s, 3 H, $CH_3$-Ph), 3.36 (s, 3 H, $OCH_3$), 4.38–4.78 (m, 3 H, H-4, H-5,5'), and 5.12–5.62 (m, 3 H, H-1, H-2, H-3).

*Anal.* Calc. for $C_{27}H_{25}NO_{11}S$: C, 56.6; H, 4.5; N, 2.4; S, 5.7. Found: C, 56.6; H, 4.5; N, 2.4; S, 5.7.

*Methyl 2,3-anhydro-α-D-ribofuranoside* (**10**). — Compound **8** (9.02 g), dissolved in warm (40°) 1:1 (v/v) benzene–methanol (100 ml), was treated with a solution of sodium (0.4 g) in dry methanol (50 ml) until the starting material ($R_f$ of **8** 0.86

$R_F$ of **10** ~0 5) was no longer visible by t l c (3 h, 5 5 1, v/v, benzene–butanone–ethanol) The mixture was evaporated, and the residue was dissolved in water (100 ml) and extracted with benzene (2 × 50 ml) The aqueous phase, which contained all of the product, was evaporated to half its original volume and was extracted for 48 h with dichloromethane in a liquid–liquid extractor Evaporation of the organic solvent, followed by drying to constant weight in a desiccator (Drierite), gave pure **10** as a colorless syrup (2 68 g, 100%), $[\alpha]_D^{20}$ +21 6° (*c* 2 31, water) lit [5] $[\alpha]_D^{29}$ +13 1° (*c* 2 29, water), n m r (chloroform-*d*) $\delta$ 2 61 (t, 1 H, $J_{OH\text{-}5\ H\text{-}5\ 5}$ ~3 Hz, OH-5), 3 49 (s 3 H, $OCH_3$), 3 60–3 80 (m, 4 H, H-2, H-3, H-5,5′), 4 31 (t, 1 H, $J_{4\ 5\ 5}$ ~2 Hz, H-4), and 5 19 (s, 1 H, H-1)

*Methyl 3,5-O-isopropylidene-2-O-methylsulfonyl-α-D-xylofuranoside* (**3**) — This compound was prepared by the procedure of Baker *et al* [4] in quantitative yield It had previously been reported[4] as a gum, $[\alpha]_D^{24}$ +65 7° (*c* 1 3, methanol) Crystalline **3** was obtained by isopropylidenation of twice-recrystallized **4**, employing the reaction conditions described by Baker *et al* [4] m p 85–86° (from ether–pentane), $[\alpha]_D^{20}$ +96 5° (*c* 1 chloroform) n m r (chloroform-*d*) $\delta$ 3 12 (s, 3 H, Ms) 3 52 (s, 3 H, $OCH_3$) 3 86 (d of d 1 H, $J_{5\ 4}$ ~2 Hz, $J_{5\ 5}$ ~6 Hz, H-5), 4 05 (d of d, 1 H, $J_{5\ 4}$ ~2 Hz, $J_{5\ 5}$ ~6 Hz H-5′), 4 20 (q 1 H, $J_{4\ 3} = J_{4\ 5\ 5}$ ~2 Hz, H-4), 4 46 (d of d, 1 H, $J_{3\ 2}$ ~1 Hz $J_{3\ 4}$ ~2 Hz H-3), 4 97 (d of d 1 H, $J_{2\ 3}$ ~1 Hz, $J_{2\ 1}$ ~2 Hz, H-2), and 5 26 (d 1 H, $J_{1\ 2}$ ~2 Hz, H-1)

*Anal* Calc for $C_{10}H_{18}O_7S$ C, 42 6 H, 6 4 S 11 4 Found C 42 5, H, 6 3, S 11 0

*Methyl 2-O-methylsulfonyl-α-D-xylofuranoside* (**4**) — This compound was obtained by the procedure of Baker *et al* [4] but it crystallized in our hands (yield, 94%) as large prisms, m p 110–111° (from ethanol–toluene) $[\alpha]_D^{20}$ +3 04° (*c* 0 47, water) n m r (chloroform-*d*–dimethyl sulfoxide-$d_6$) $\delta$ 3 15 (s, 3 H Ms) 3 40 (s, 3 H $OCH_3$) 3 67 (t, 2 H $J_{5\ 4} \simeq J_{5\ OH\text{-}5}$ ~2 Hz H-5 5′) 4 09 (d of t, 1 H, $J_{4\ 3}$ ~3 Hz, $J_{4\ 5}$ ~2 Hz, H-4) 4 46 (q 1 H $J_{3\ 2} \simeq J_{3\ 4} \simeq J_{3\ OH\text{-}3}$ ~3 Hz, H-3 superimposed d 1 H, temp dep $J_{OH\text{-}5\ 5\ 5}$ ~2 Hz, OH-5) 4 81 (d of d 1 H, $J_{2\ 1}$ ~3 Hz $J_{2\ 3}$ ~3 Hz, H-2) 5 02 (d, 1 H, $J_{OH\text{-}3\ 3}$ ~3 Hz, OH-3), and 5 51 (d, 1 H, $J_{1\ 2}$ ~3 Hz, H-1)

*Anal* Calc for $C_5H_{14}O_7S$ C 34 7 H 5 8 S, 13 2 Found C, 34 8 H 5 7 S 12 9

*Methyl 2,3-anhydro-α-D-lyxofuranoside* (**5**) — This compound was obtained in quantitative yield from **4** by the procedure of Baker *et al* [4] m p 78–80° (lit [4] m p 80–82°), $[\alpha]_D^{20}$ +65 7° (*c* 0 42, water) {lit [4] $[\alpha]_D^{26}$ +67° (*c* 2, water)} n m r (chloroform-*d*) $\delta$ 2 60 (t, 1 H, temp dep , $J_{OH\text{-}5\ 5\ 5}$ ~3 Hz OH-5), 3 45 (s 3 H $OCH_3$), 3 67 and 3 78 (2 d, 2 H, $J_{2\ 3}$ ~2 Hz, H-2, H-3) 3 86 (t, 2 H, $J_{5\ 4} \simeq J_{5\ OH\text{-}5}$ ~3 Hz, H-5 5′) 4 15 (t, 1 H, $J_{4\ 5}$ ~3 Hz, H-4), and 4 99 (s, 1 H, H-1)

ACKNOWLEDGMENTS

We are indebted to Dr G Schulz and Mrs E Ott for recording the n m r measurements

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