Carbohydrate Research, 36 (1974) 392–397

Note

A new preparation of some 6-deoxyhexoses

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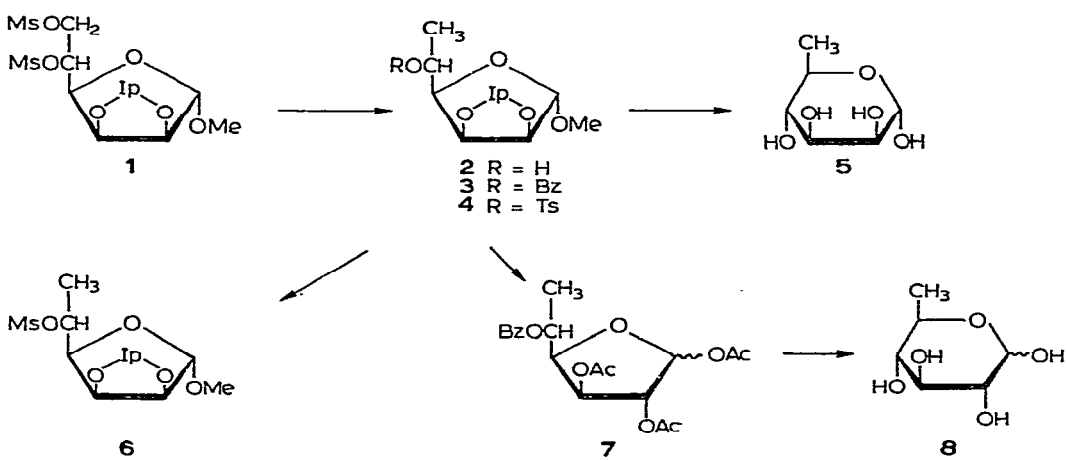
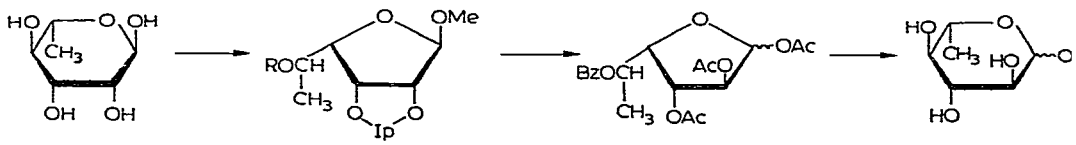
(Received February 4th, 1974; accepted May 17th, 1974)

The epimerization at C-2 during acetolysis of sugar derivatives that contain furanose rings and contiguous hydroxyl groups, the ring hydroxyl groups being in the cis configuration[1], is a specific example of a transformation of sugars by inversion of configuration at one or more carbon atoms[2]. Although a number of papers have been published describing this reaction with sugars such as D-mannose[1,3], D-gulose[3], D-allose[4], D-*glycero*-D-*gulo*-heptose[3], D-ribose[3,5], and D-lyxose[5], and attempts have been made to describe a plausible mechanism[1,3], only two attempts appear to have been made to utilize this reaction in a large-scale synthesis[6,7]. In both of these cases, 1,5-di-*O*-acetyl-6-deoxy-2,3-*O*-isopropylidene-L-mannofuranose was the starting substance leading to a synthesis of 6-deoxy-L-glucose. Based on this reaction, a new, rapid, and simple synthesis of 6-deoxy-D-mannose (D-rhamnose), 6-deoxy-D-glucose (D-quinovose), 6-deoxy-L-glucose (L-quinovose), and some of their hexofuranosyl intermediates is described.

The reaction sequence leading to 6-deoxy-D-mannose (**5**) and 6-deoxy-D-glucose (**8**) starts from methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-



α-D-mannofuranoside (**1**), synthesized by the method recently reported by Evans and Parrish[8]. This preparation, starting from D-mannose, was scaled up many times and could be completely accomplished in two days with only minor modifications. Treatment of **1** with sodium borohydride in dimethyl sulfoxide at 85°, a procedure developed by Weidmann *et al.*[9], gave a very high yield of methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methylsulfonyl-α-D-mannofuranoside (**6**). However, the methylsulfonyl group in this case could not be removed under mild conditions with sodium amalgam. Since it was clear that a stronger reagent would be necessary to cleave the sulfonyl group and it was advantageous to achieve the preparation of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranoside (**2**) in one step instead of two, **1** was treated directly with lithium aluminum hydride in a 2:1 ether–benzene mixture. Compound **2** was obtained as an oil and showed an i.r. spectrum similar to that of the L-form (**10**) of this compound, prepared directly from 6-deoxy-L-mannose (L-rhamnose) (**9**) under the conditions described by Evans and Parrish for D-mannose[8]. Further proof of the identity of **2** was obtained by treatment with methylsulfonyl chloride, which yielded **6** again, and by preparation of the 5-*p*-toluenesulfonate (**4**). The latter compound was identical with its enantiomer **12**, a compound described many years ago by Levene and Compton[10]. Acid treatment of **2** afforded 6-deoxy-D-mannose (**5**) and constitutes an excellent and simple method of preparation of this sugar.



Benzoylation of **2** yielded crystalline methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranoside (**3**), which was treated with a solution of 10:1 acetic acid–acetic anhydride containing 5% sulfuric acid. The syrupy product, presumably the acetate **7**, was treated with methanolic sodium methoxide to obtain 6-deoxy-D-glucose (**8**). In a similar manner, the enantiomeric compound, 6-deoxy-L-glucose (**14**) was prepared from compound **9** in an improved synthesis over that reported earlier[6,11].

EXPERIMENTAL

General. — Melting points were determined with a Kofler hot-stage and correspond to corrected values. Infrared spectra were recorded with a Perkin–Elmer Model 21 spectrophotometer and optical rotations were determined with a Rudolph polarimeter. Evaporations were performed *in vacuo* in a rotary evaporator at a bath temperature of 40–45°. All moist organic solutions were dried with anhydrous

magnesium sulfate. Elementary analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

*Methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methylsulfonyl-α-*D*-mannofuranoside* (**1**). — The procedure reported by Evans and Parrish[8] was scaled up fifty times and performed essentially as described with only minor modifications. Because of the low solubility of **1** in ethanol, it was crystallized from methanol more easily and advantageously as needles, m.p. 147–148°, $[\alpha]_D^{25}$ +33.5° (*c* 1.39, chloroform). The ethanol-crystallized material had a slightly lower melting point, 143.5–145°, $[\alpha]_D^{24}$ +33.8° (*c* 1.49, chloroform); lit.[8]: m.p. 143.5–145°, $[\alpha]_D$ +32.6° (*c* 0.50, chloroform). From 50 g of D-mannose was obtained 61 g of **1** (56% yield).

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*D*-mannofuranoside* (**2**). — A well-stirred mixture containing **1** (6.99 g), ethyl ether (240 ml), benzene (120 ml), and lithium aluminum hydride (4.8 g) was gently heated at reflux for 3 days. The mixture was chilled in ice, and water (5 ml) was cautiously added, followed by 15% aqueous sodium hydroxide solution (15 ml), and more water (5 ml). The white, granular precipitate was removed by filtration and washed well with ethyl ether. The filtrate was evaporated to a syrup, which was dissolved in chloroform (75 ml), washed with water (75 ml), and dried. Evaporation afforded a clear oil (3.79 g, 97%), the i.r. spectrum of which closely resembled that of the L-form (**9**) prepared from L-rhamnose.

*6-Deoxy-*D*-mannose* (**5**). — A mixture containing methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranoside (**2**, 5 g) and 0.5M sulfuric acid solution was heated at reflux for 2 h. The solution was neutralized with barium carbonate, heated on a steam bath for several min, and filtered through a Celite pad. The solution was evaporated to a small volume, filtered again, decolorized with Norit A, and passed through a small column (10 cm × 1.8 cm) of MB-3 resin. The eluate was evaporated to give a clear, colorless syrup, which was dissolved in 95% ethanol and seeded with an authentic sample. The yield was 2.72 g (65%) in three crops, m.p. 76–86°, $[\alpha]_D^{27}$ −7.6° (*c* 4.04, water, equil.); lit.: m.p. 75–86° (Ref. 12); 75–93°, $[\alpha]_D^{25}$ −6.1° (*c* 1.4, water, equil.) (Ref. 13). The i.r. spectrum of **5** was identical to that of an authentic sample and of 6-deoxy-L-mannose (Pfanstiehl).

*Methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-methylsulfonyl-α-*D*-mannofuranoside* (**6**). — *A*. A mixture of compound **1** (11.7 g), sodium borohydride (4.56 g), and dimethyl sulfoxide (85 ml) was heated for 24 h at 80–85° (*cf.* Ref. 9). The mixture was cooled to room temperature and poured into a vigorously stirred solution of 1% aqueous acetic acid (300 ml). Crystallization of the product occurred during the stirring procedure, which was continued for 1.5 h. Recrystallization was effected by dropwise addition of water to a methanol solution until turbidity, whereupon scratching of the inner wall of the flask with a glass rod caused immediate crystallization as needles. A small amount of additional product was isolated by extraction of the original filtrate with chloroform, washing of the chloroform solution several times with water, and evaporation and crystallization in the manner just described. The total yield was 7.7 g (87%), m.p. 65°, $[\alpha]_D^{25}$ +28.1° (*c* 1.4, chloroform); i.r.:

ν_{max}^{KBr} 1378 (*gem*-dimethyl), 1358, 1179 (sulfonyl), 1162, 1120, 1096, 1076, and 1050 cm^{-1} (C–O–C, dioxolane ring).

Anal. Calc. for $C_{11}H_{20}O_7S$: C, 44.58; H, 6.80; S, 10.82. Found: C, 44.67; H, 6.81; S, 10.75.

B. Compound **2** (0.5 g) was dissolved in dry pyridine (3 ml) and chilled in an ice bath. Methylsulfonyl chloride (0.65 ml) was added, and after 2 h at room temperature, the mixture was chilled again and the excess methylsulfonyl chloride decomposed with water. After 1 h, water (25 ml) was added and the mixture was extracted with chloroform (3 × 25 ml). The combined chloroform extracts were washed with saturated sodium hydrogen carbonate (3 × 30 ml) and dried. The chloroform was evaporated, and traces of pyridine were removed by addition and evaporation of toluene. Crystallization from methanol–water afforded 578 mg (85%) of needles, m.p. 61–64°. Recrystallization gave 417 mg, m.p. 64–65°, identical to the product described in *A*, as shown by mixed m.p. and i.r. spectrum.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-*D*-mannofuranoside* (**4**). — Compound **2** (1.3 g) was treated with *p*-toluenesulfonyl chloride (3.2 g) in dry pyridine (5.5 ml) for 20 h. Water (0.5 ml) was added to the chilled mixture, and after 0.5 h, the mixture was poured into a vigorously stirred mixture of ice and saturated sodium hydrogen carbonate (40 ml). Crystallization occurred, and after 0.5 h the crystals were filtered off and washed well with water. Recrystallization from methanol gave 1.38 g (62%) of **6** in three crops, m.p. 84–85°, $[\alpha]_D^{25}$ +14.1° (*c* 3.19, methanol). These data and the i.r. spectrum are in agreement with those of the L form **12**, except for the sign of the optical rotation.

Anal. Calc. for $C_{17}H_{24}O_7S$: C, 54.80; H, 6.45; S, 8.60. Found: C, 54.82; H, 6.31; S, 8.66.

*Methyl 5-*O*-benzoyl-2,3-*O*-6-deoxy-isopropylidene-α-*D*-mannofuranoside* (**3**). — To a chilled solution of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannofuranoside (**2**, 6 g) in pyridine (50 ml) was added, dropwise, benzoyl chloride (5 ml). The mixture was stirred for 1 h in an ice bath, then kept for 45 h at room temperature. The mixture was poured into a stirred mixture of ice and saturated sodium hydrogen carbonate (350 ml). Crystallization occurred and, after 1 h of stirring, the product was isolated by filtration and washed well with water (yield 8.22 g, 93%), m.p. 72–75°; the product was satisfactory for further reactions. For analytical purposes, a sample (400 mg) was recrystallized from methanol–water to yield needles (267 mg), m.p. 75–76°; $[\alpha]_D^{27}$ +19.9° (*c* 1.41, methanol); i.r.: ν_{max}^{KBr} 1709 (benzoate C=O), 1601 (phenyl C=C), 1376 (*gem*-dimethyl, doublet), 1262 (benzoate C–O–C), 1162, 1124, 1107, 1082, 1049 (sugar C–O–C, dioxolane ring), and 713 cm^{-1} (monosubstituted phenyl).

Anal. Calc. for $C_{17}H_{22}O_6$: C, 63.33; H, 6.88. Found: C, 63.34; H, 6.78.

*6-Deoxy-*D*-glucose* (**8**). — The crude product **3** was dissolved in a mixture of acetic acid (220 ml), acetic anhydride (22 ml), and conc. sulfuric acid (12 ml). After 48 h at room temperature, the mixture was poured onto ice (500 g) and this was stirred until the ice melted. The product was extracted with chloroform (3 × 100 ml), and the chloroform solution was stirred while saturated sodium hydrogen carbonate

(200 ml) was cautiously added. Additional solid sodium hydrogen carbonate was added portionwise until neutralization, and the chloroform layer was separated, washed with water (2 × 100 ml), and dried. Evaporation afforded a clear, colorless syrup (**7**, 6.1 g, 64%). This was dissolved in methanol (112 ml), M sodium methoxide (12.5 ml) was added, and the mixture was kept for 3 h at room temperature. Bio-Rad AG 50-X8 (H^+) resin was added and, after 1 h of stirring, the resin was removed by filtration and the methanol evaporated. Water was added and evaporated four times to remove azeotropically methyl benzoate. The syrup was dried by several additions and evaporations of absolute ethanol, and the residue was crystallized from acetone in two crops (1.45 g, 57% from **7**), m.p. 142–144°; $[\alpha]_D^{27}$ +31.0° (*c* 1.67, water, equil.); lit.: m.p. 146°, $[\alpha]_D^{28}$ +30° (*c* 1.5, water, equil.)[14]; m.p. 135–145°, $[\alpha]_D^{20}$ +30.8° (water)[15]; i.r. spectrum identical to that of the L form (**14**).

*Methyl 6-deoxy-2,3-*O*-isopropylidene-α-*L*-mannofuranoside* (**10**). — 6-Deoxy-L-mannose (5 g) was added to a mixture of acetone (17 ml), 2,2-dimethoxypropane (19 ml), methanol (17 ml), and conc. hydrochloric acid (0.5 ml). After being heated at reflux for 2 h, the mixture was cooled, water (50 ml) was added, and the volume was reduced to ~50 ml by evaporation. The aqueous solution was extracted with chloroform (4 × 50 ml), and the chloroform solution was dried and evaporated to yield 5 g of a yellow oil, suitable for use in the next steps.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-p-tolylsulfonyl-α-*L*-mannofuranoside* (**12**) (cf. *Ref. 10*). — A mixture of **9** (21.2 g) in dry pyridine (43 ml) was chilled in an ice bath and *p*-toluenesulfonyl chloride (34 g) was added. After being stirred for 17 h at room temperature, the mixture was chilled again and water (5 ml) was added. A solid mass formed which was transferred to a beaker containing a mixture of ice (200 g) and saturated sodium hydrogen carbonate (350 ml). This mixture was stirred for 1.5 h, and the solid was filtered off and washed well with water. Recrystallization from methanol gave 29.5 g (81%) in several crops, m.p. 84–85°, $[\alpha]_D^{25}$ −14.8° (*c* 3.22, methanol); lit.[10]: m.p. 82–83°, $[\alpha]_D^{26}$ −13.6° (*c* 3.168, methanol).

Anal. Calc. for $C_{17}H_{24}O_7S$: C, 54.80; H, 6.45; S, 8.60. Found: C, 54.85; H, 6.34; S, 8.53.

*Methyl 5-*O*-benzoyl-6-deoxy-2,3-*O*-isopropylidene-α-*L*-mannofuranoside* (**11**). — Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannofuranoside (**9**, 17.6 g) was treated with benzoyl chloride (15 ml) in pyridine (150 ml) as described for the D form (**3**). When the mixture was poured into ice–saturated sodium hydrogen carbonate (1400 ml), a yield of 24.9 g (96%) of crystals was obtained. A sample (900 mg) of this was twice recrystallized from methanol–water to afford needles (324 mg), m.p. 74–75°, $[\alpha]_D^{27}$ −18.9° (*c* 1.43, methanol); i.r. spectrum identical to that of the D form (**3**).

Anal. Calc. for $C_{17}H_{22}O_6$: C, 63.33; H, 6.88. Found: C, 63.36; H, 6.83.

6-Deoxy-L-glucose (**14**). — Compound **11** (24 g) was treated with a mixture of acetic acid (660 ml), acetic anhydride (66 ml), and conc. sulfuric acid (36 ml) and the resulting product was processed as described for the D form. The acetate **13** (20.4 g) was similarly treated with sodium methoxide solution to remove the blocking groups, and the syrup obtained was crystallized from acetone in three crops (3.53 g, 42%

from **13**), m.p. 142–145°; $[\alpha]_D^{25}$ −30.2° (*c* 1.53, water, equil.); lit.[16]: m.p. 142–144°, $[\alpha]_D^{20}$ −29.9° (*c* 2, water, equil.). The compound was identical to the sample of 6-deoxy-L-glucose prepared previously[6], as shown by mixed melting point and identical i.r. spectra. Paper chromatography (Whatman No. 1) of the mother liquor with 8:2:1 ethyl acetate–pyridine–water (a system known to separate 6-deoxy-L-mannose from 6-deoxy-L-glucose[11]) showed that some 6-deoxy-L-mannose was still present. From this mother liquor, 625 mg of crystalline 6-deoxy-L-mannose was recovered.

Phenylosazones of **5**, **8**, *and* **14**. — The phenylosazones of the 6-deoxy sugars were prepared as previously described[11]. The melting points were: 181–183° (**3**); 181–183.5° (**8**); and 180–182° (**14**). The sample prepared earlier[11] from 6-deoxy-L-mannose had m.p. 178–180°. The i.r. spectra of all these compounds were identical.

ACKNOWLEDGMENTS

This work was supported by a grant (CA-13802) from the National Cancer Institute, National Institutes of Health, United States Public Health Service. The author is grateful to Dr. George A. Barber of Ohio State University for seed crystals of 6-deoxy-D-mannose.

REFERENCES

1 P. JERKEMAN, *Acta Chem. Scand.*, 17 (1963) 2769–2771.
2 L. GOODMAN, *Advan. Carbohyd. Chem.*, 22 (1967) 109–175.
3 W. SOWA, *Can. J. Chem.*, 49 (1971) 3292–3298.
4 W. SOWA, *Can. J. Chem.*, 50 (1972) 1092–1094.
5 G. J. F. CHITTENDEN, *Carbohyd. Res.*, 22 (1972) 491–493.
6 L. M. LERNER, *J. Org. Chem.*, 37 (1972) 4386–4391.
7 P. J. BOON, A. W. SCHWARTZ, AND G. J. F. CHITTENDEN, *Carbohyd. Res.*, 30 (1973) 179–182.
8 M. E. EVANS AND F. W. PARRISH, *Carbohyd. Res.*, 28 (1973) 359–364.
9 H. WEIDMANN, N. WOLF, AND W. TEMPE, *Carbohyd. Res.*, 24 (1972) 184–187.
10 P. A. LEVENE AND J. COMPTON, *J. Amer. Chem. Soc.*, 57 (1935) 2306–2310.
11 L. M. LERNER, *J. Org. Chem.*, 38 (1973) 3704–3709.
12 G. A. BARBER, *Biochemistry*, 8 (1969) 3692–3695.
13 W. W. ZORBACH AND C. O. TIO, *J. Org. Chem.*, 26 (1960) 3543–3545.
14 M. E. EVANS AND F. W. PARRISH, *Methods Carbohyd. Chem.*, 6 (1972) 177–179.
15 K. FREUDENBERG AND K. RASCHIG, *Ber.*, 62 (1923) 373–383.
16 E. ZISSIS, N. K. RICHTMYER, AND C. S. HUDSON, *J. Amer. Chem. Soc.*, 73 (1951) 4714–4716.