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Note

A simple synthesis of L-gulose*

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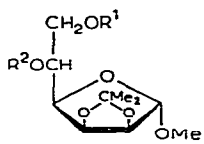
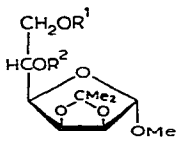
In continuation of studies[1] of glycosidation reactions in the presence of metal ions, the uncommon sugar gulose was needed. Although the D enantiomer is available by the methods of Meyer zu Reckendorf[2] and of Slessor and Tracey[3], and the L enantiomer may be prepared from 2,4-*O*-benzylidene-D-glucitol[4], we took this opportunity to develop a new synthesis, starting from D-mannose. A similar D-*manno* to L-*gulo* conversion has been described[5] recently for a nucleoside.

J. D. Stevens has described[6] reactions of D-glucose with acidified mixtures of acetone and methanol, and has also investigated reactions of various sugars with acidified mixtures of 2,2-dimethoxypropane, acetone, and methanol[7]. We found that treatment of D-mannose with the latter mixture gives a major product presumed to be methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (**1**), which on graded hydrolysis gives methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**2**), identified as its diacetate (**3**). Methanesulfonylation of **2** gives a bis(methanesulfonate) (**4**). Reaction



1 R^1, R^2 = Me_2C
2 R^1=R^2 = H
3 R^1=R^2 = MeCO
4 R^1=R^2 = $MeSO_2$



5 R^1 = R^2 = MeCO
6 R^1 = R^2 = H
7 R^1, R^2 = Me_2C

of **4** with sodium acetate in boiling *N*,*N*-dimethylformamide, followed by acetylation, gives methyl 5,6-di-*O*-acetyl-2,3-*O*-isopropylidene-β-L-gulofuranoside (**5**), which is converted by deacetylation into methyl 2,3-*O*-isopropylidene-β-L-gulofuranoside (**6**).

*Dedicated to Dr. Louis Long, Jr., in honor of his 70th birthday.

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Both **4** and **6** are highly crystalline, making purification easy; compound **6** is obtained in 50% yield from D-mannose.

The structures of **2**–**6** were deduced from the n.m.r. spectra of **3**–**5**, and by assuming that no rearrangement occurred during sulfonylation, acetylation, or deacetylation, all effected under basic conditions. The relevant n.m.r. data are shown in Table I.

TABLE I

N.M.R. DATA FOR COMPOUNDS **3**–**5**[a]

Compound	*Coupling constants (Hz)*						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
3	0	5.9	3.3	8.2	2.4	5.1	−12.3
4	0	5.9	3.4	7.6	2.3	4.3	−11.9
5	0	5.7	3.2	8.4	3.0	4.4	−12.6

Compound	*Chemical shifts (δ)*				
	H-5	*H-1 to H-4, H-6, H-6'*	*AcO or $MeSO_2O$*	*MeO*	*CMe_2*
3	5.28	3.9 to 4.9	2.05	3.30	1.30, 1.44
4	5.04	4.0 to 5.2	3.08, 3.12	3.30	1.32, 1.46
5	5.35	3.9 to 4.9	2.07	3.30	1.30, 1.46

[a]Determined on *ca.* 10% solutions in $CDCl_3$ with *ca.* 1% Me_4Si as internal standard, $\delta = 0.0$.

The spectra of **3** and **5** confirmed that each compound contains an isopropylidene group, two acetyl groups, one methoxyl group, and seven other protons. Each spectrum displayed a low-field octet (attributed to H-5) showing that O-5 was acetylated and thus not involved in ring formation, and hence both **3** and **5** must be furanosides. However, $J_{5,6}$ and $J_{5,6'}$ were quite different in the two spectra, reflecting the difference between **3** and **5** in their configuration at C-5. The spectrum of **4** also included an octet at low field, showing **4** to be a furanoside; but the values of $J_{5,6}$ and $J_{5,6'}$ for this compound do not coincide with the corresponding pair of values for either **3** or **5**. This probably reflects different favored conformations for the C-5–C-6 side-chain in compounds **3** and **4**. The values of $J_{1,2'}$, $J_{2,3'}$, and $J_{3,4}$ were closely similar in all three spectra, indicating that the furanose ring has the same configuration and conformation in each compound; the common value of $J_{1,2} \sim 0$ Hz indicates that H-1 and H-2 are trans in all three compounds.

Hydrolysis of **6**, under conditions similar to those used by Randall[8] for hydrolysis of **1**, was monitored by g.l.c., and conditions were found for preparation of methyl β-L-gulofuranoside in 64% yield from **6**. Hydrolysis of **6** for 2.5 h in boiling 10mM hydrochloric acid gave L-gulose in quantitative yield.

Treatment of L-gulose with acidified 2,2-dimethoxypropane–acetone–methanol gives methyl 2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranoside (**7**), which crystallizes well and is suitable for characterization of gulose. Isopropylidenation of **6** under very mild conditions also gives **7**.

EXPERIMENTAL

General. — Solutions were concentrated at <40° under diminished pressure. Hexane and light petroleum (b.p. 60–80°) were used interchangeably. G.l.c. was performed with a Perkin–Elmer 801 chromatograph programmed at 5° min^{-1} from 160 to 210°, with a column (1/16 in. × 3 ft) of 3% OV17 on Chromosorb W. T.l.c. was conducted with 0.25-mm layers of Silica Gel G (E. Merck, Darmstadt), with the irrigant indicated in parentheses.

Methyl 2,3-O-isopropylidene-5,6-di-O-methylsulfonyl-α-D-mannofuranoside (**4**). — A mixture of D-mannose (1 g), 2,2-dimethoxypropane (3.4 ml), acetone (3.3 ml), methanol (3.3 ml), and concentrated hydrochloric acid (32%, 0.1 ml) was boiled for 2 h under reflux. The solution was cooled, diluted with water (10 ml), and concentrated to ~10 ml at <30°. Methanol (10 ml) and concentrated hydrochloric acid (0.25 ml) were added and the solution was kept for 200 min at 23°. At this stage t.l.c. (1:1 hexane–ethyl acetate) showed that almost no **1** was left. Saturated aqueous sodium hydrogen carbonate (7.5 ml) was added; the solution was then concentrated to remove the methanol, and extracted with chloroform for 3 h. The extract was dried ($MgSO_4$) and concentrated to a syrup that was almost pure **2***. This syrup was stirred at <35° in pyridine (5 ml) whilst methanesulfonyl chloride (1.5 ml) was added, and then kept for 2 h at 20°. Excess acid chloride was decomposed by cautious addition of water at <50°, until 150 ml of water had been added. The product was filtered off, washed thoroughly with water, and dried to constant weight, giving **4** (1.67 g, 77%), m.p. 143–144°. Recrystallisation from ethanol (25 ml) gave pure **4** (1.64 g, 75%), m.p. 143.5–145°, $[\alpha]_D$ +32.6° (*c* 0.50, chloroform).

Anal. Calc. for $C_{12}H_{22}O_{10}S_2$: C, 36.9; H, 5.6; S, 16.4. Found: C, 36.9; H, 5.5; S, 16.4.

Methyl 2,3-O-isopropylidene-β-L-gulofuranoside (**6**). — A mixture of **4** (5.0 g), sodium acetate (5.0 g), and *N,N*-dimethylformamide (40 ml) was boiled for 6 h under reflux. Acetic anhydride (7.5 ml) was added, and boiling was continued for 1 h. The solution was cooled and the solvents were removed at 65°/30 torr with the aid of a short-path evaporation adaptor[9], and the residue was dried for 30 min at 95°/30 torr. The product was dissolved in methanol (6 ml), and after 5 min the solution was stirred rapidly whilst saturated aqueous sodium hydrogen carbonate (25 ml) and water (70 ml) were added successively, and the solution was extracted with hexane for 16 h.

*A sample of this compound was purified by elution from silica gel with 2:3 ethyl acetate–hexane, and then acetylated in the usual way with acetic anhydride–pyridine. The product (**3**) failed to crystallise (Randall reported[8] m.p. 54–55°) but appeared pure from its very well resolved n.m.r. spectrum.

The extract was dried ($MgSO_4$) and evaporated to dryness*. The residue was dissolved in 0.1M sodium methoxide in methanol (10 ml). The solution was kept for 5 h at 23°, and then neutralized with carbon dioxide and concentrated to dryness. The product was dissolved in ethyl acetate (30 ml) and passed successively through a mixture of charcoal (3 g) and Celite (3 g) and then silica gel (20 g) packed in the same 22-mm diameter column, which was eluted with ethyl acetate (150 ml). The eluate was concentrated to a syrup that crystallized. The product was dissolved in hot ethyl acetate (4 ml), hexane (12 ml) was added, and the solution was nucleated and cooled slowly to 3° affording **6** (1.94 g, 64.5%), m.p. 76.5–77° (unchanged on recrystallization), $[\alpha]_D$ +82.3° (*c* 1.17, methanol).

Anal. Calc. for $C_{10}H_{18}O_6$: C, 51.2; H, 7.6. Found: C, 51.5; H, 7.7.

Methyl 5,6-di-O-acetyl-2,3-O-isopropylidene-β-L-gulofuranoside (**5**). — Acetic anhydride (3 ml) containing **6** (1.0 g) and sodium acetate (0.3 g) was boiled for 1 min under reflux and then cooled to 25°. Ethanol (2 ml) was added and the solution was stirred for 30 min, and was then poured into rapidly stirred saturated aqueous sodium hydrogen carbonate (50 ml). When effervescence had ceased, the solution was extracted for 30 min with chloroform. The extract was dried ($MgSO_4$) and concentrated to a syrup (1.35 g, 98%) that crystallized on long storage at 3°; recrystallization from 1:1 ethanol–water (4 ml) gave pure **5**, m.p. 54–55°, $[\alpha]_D$ +58° (*c* 1.0, chloroform).

Methyl β-L-gulofuranoside. — A solution of **6** (1.0 g) in methanol (12 ml) and 0.033M hydrochloric acid (28 ml) was kept at 45°, and the hydrolysis was monitored by acetylation of samples and examination by g.l.c. After 3 days the solution was cooled and applied to a column (2.5 × 35 cm) of Dowex-1 (X2) ion-exchange resin (OH^-, 200–400 mesh). The column was eluted with water, and 10-ml fractions were collected and examined polarimetrically.

Fractions 10–13 had positive rotations and gave **6** (0.177 g, 18%).

Fractions 25–28 had negative rotations and gave a compound (0.013 g) tentatively identified as methyl α-L-gulofuranoside.

Fractions 42–59 had positive rotations and gave methyl β-L-gulofuranoside (0.53 g, 64%) having m.p. 101° (unchanged on recrystallization from propyl alcohol), $[\alpha]_D$ +108° (*c* 1.0, water); lit.[10] (for the D enantiomer), m.p. 101°, $[\alpha]_D$ −108° (H_2O). The product was compared with methyl β-D-gulofuranoside[10] by electrophoresis; in 0.2M calcium acetate both compounds showed identical small migration towards the cathode, and in 0.05M sodium tetraborate each showed an M_N value[11] of 0.68. In each case, detection was achieved by the chromium trioxide–potassium permanganate–sulfuric acid reagent[11].

L-*Gulose.* — A solution of **6** (0.5 g) in 0.01M hydrochloric acid (5 ml) was boiled under reflux for 150 min, and then cooled to 30°, Dowex-1 (X8) resin (HCO_3^-, 0.5 ml) was added and the mixture was aerated for 10 min. The resin was filtered off and

*We have found that processing of products from acetate-exchange reactions by acetylation and extraction into hexane gives a product much lighter in color than that obtained by the more usual extraction into chloroform.

washed with water (4 × 5 ml). The filtrate and washings were combined, concentrated to a syrup, and dried for 3 h at 40°/30 torr to give L-gulose (0.395 g, 100%), $[\alpha]_D$ +21.3° (*c* 4.58, water); lit.[4] $[\alpha]_D$ +20° (water). The product gave a phenylhydrazone having m.p. 143°; lit.[12] (for the D enantiomer), m.p. 143°. Acetylation and g.l.c. of the product showed a single peak, having a retention time similar to those of other acetylated hexoses; when the hydrolysis was allowed to proceed for 24 h, similar examination of the product showed a second major product, of much shorter retention time, probably 1,6-anhydro-β-L-gulose.

Methyl 2,3:5,6-di-O-isopropylidene-β-L-gulofuranoside (**7**). — *From* **6**. A solution of **6** (0.105 g) and *p*-toluenesulfonic acid monohydrate (1.5 mg) in 2,2-dimethoxypropane (2 ml) was stirred for 30 min at 23°. At this stage t.l.c. (1:1 ethyl acetate–hexane) showed a single product. Pyridine (0.05 ml) was added and the mixture was washed through silica gel (1.5 ml) with ethyl acetate–hexane (1:1, 15 ml). The eluate was concentrated to give **7** (0.12 g, 97%), m.p. 76–77°. Recrystallization from hexane (0.5 ml) gave **7** (0.063 g), having m.p. 76–77°, $[\alpha]_D$ +41.9° (*c* 1.13, chloroform). A sample of the D enantiomer of **7**, prepared[13] by Kuhn methylation of 2,3:5,6-di-*O*-isopropylidene-β-D-gulose (cf. ref. 8), had m.p. 75–76°, $[\alpha]_D$ −44.9° ($CHCl_3$).

Anal. Calc. for $C_{13}H_{22}O_6$: C, 56.9; H, 8.0. Found: C, 56.8; H, 8.1.

From L-gulose. A mixture of L-gulose (0.14 g), *p*-toluenesulfonic acid monohydrate (0.12 g), acetone (1 ml), 2,2-dimethoxypropane (1 ml), and methanol (1 ml) was boiled under reflux for 2 h and then cooled, and neutralized by addition of saturated aqueous sodium hydrogen carbonate (5 ml). The product was concentrated to dryness, and then kept for 15 min at 70°/30 torr. The residue was extracted with hexane (3 × 6 ml) and the extracts were combined and evaporated. The product was recrystallized from methanol (0.25 ml) to give **7** (0.05 g), m.p. 76–77° alone or mixed with the product from the preceding experiment.

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REFERENCES

1 S. J. Angyal and M. E. Evans, *Carbohyd. Res.*, 25 (1972) 43.
2 W. Meyer zu Reckendorf, *Methods Carbohyd. Chem.*, 6 (1972) 129; *Angew. Chem.*, 79 (1967) 151; *Angew. Chem. Intern. Ed. Engl.*, 6 (1972) 177; *Chem. Ber.*, 102 (1969) 1071.
3 K. N. Slessor and A. S. Tracey, *Can. J. Chem.*, 47 (1969) 3989.
4 R. L. Whistler and J. N. BeMiller, *Methods Carbohyd. Chem.*, 1 (1962) 137.
5 L. M. Lerner, *J. Org. Chem.*, 37 (1972) 470.
6 J. D. Stevens, *Carbohyd. Res.*, 21 (1972) 490.
7 J. D. Stevens, personal communication.
8 M. H. Randall, *Carbohyd. Res.*, 11 (1969) 173.
9 M. E. Evans, *Carbohyd. Res.*, 21 (1972) 473.

10 H. G. FLETCHER, JR., H. W. DIEHL, AND R. K. NESS, *J. Amer. Chem. Soc.*, 76 (1954) 3029.
11 J. L. FRAHN AND J. A. MILLS, *Aust. J. Chem.*, 12 (1959) 65.
12 H. S. ISBELL, *Methods Carbohyd. Chem.*, 1 (1962) 135.
13 S. J. ANGYAL, personal communication.