Preliminary communication

Base-catalyzed isomerization of keto sugars. Synthesis of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hexopyranosid-4-ulose and its conversion into derivatives of 4-amino-4,6-dideoxy-D-allose

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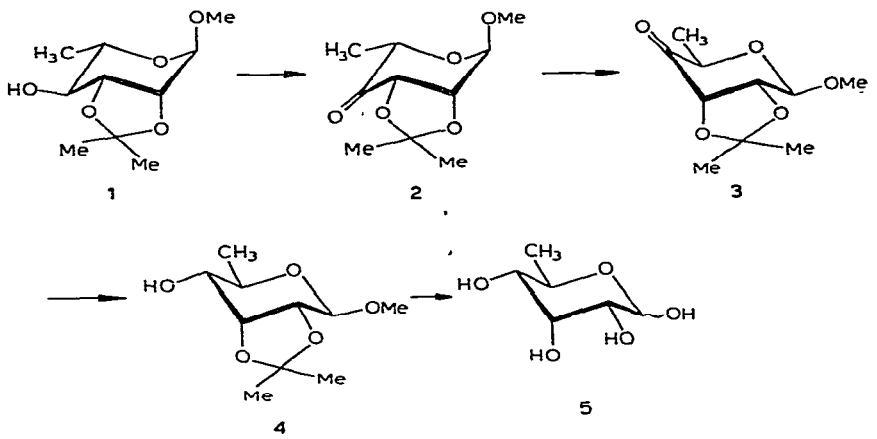
Keto sugars are gaining importance in carbohydrate chemistry, both as biological precursors[1–4] and as synthetic intermediates[5,6]. We now report the conversion of an L-hexos-4-ulose (2) into a D-keto sugar (3) by base-catalyzed inversion at C-5. Further, the new ketone 3 was used for synthesis of derivatives of 4-amino-4,6-dideoxyallose, one of the 4-amino-4,6-dideoxyhexoses of potential biological activity[7].

Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose[8,9] (2) was prepared by oxidation of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (1) as described previously[6]. When a solution of 2 in 80% aqueous pyridine was heated at 100°, a small proportion of a new product was formed, as shown by g.l.c.★. Further examination of this reaction showed that equilibrium was reached after 2.5 h and the mixture contained 82% of 2 and 18% of the new compound, subsequently shown to be methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hexopyranosid-4-ulose (3).

Keto sugars 2 and 3 were separated on a F and M Model 775 preparative gas chromatograph by using a column ¾ in. × 8 ft packed with 3% ethylene glycol succinate on Chromosorb W. Compound 3 was crystallized from pentane, m.p. 40–42° $[\alpha]_D^{26}$ +36.2° (*c* 0.34, $CHCl_3$), and the elemental analysis ($C_{10}H_{16}O_5$) indicated it to be isomeric with 2. The o.r.d. curve of 3 exhibited a positive Cotton effect with a peak at 325 nm and a trough at 290 nm, whereas the starting ketone showed a negative Cotton effect having a trough at 330 nm and a peak at 290 nm. The i.r. spectrum of 3 had absorptions at 1730 (C=O) and 1375 cm^{-1} (*gem*-dimethyl) and the n.m.r. spectrum was consistent with the structure 3.

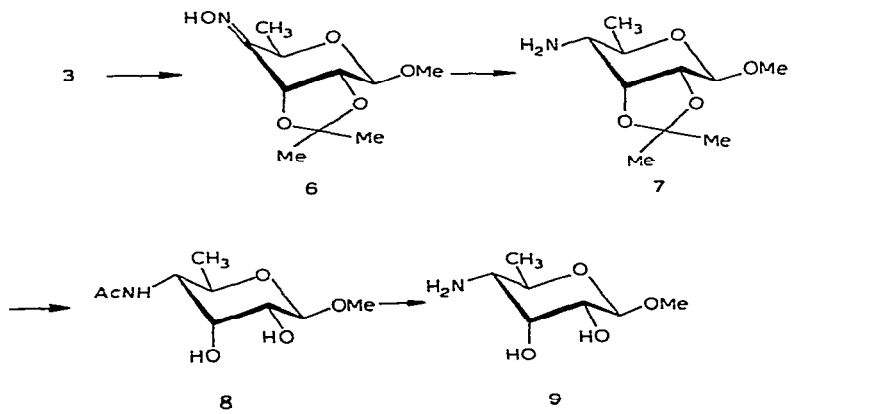
Reduction of 3 with sodium borohydride in methanol gave methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (4) as a colorless liquid in 90% yield, $[\alpha]_D^{26}$ −50° (*c* 0.45, $CHCl_3$). Examination of the crude reduction product by g.l.c. on three different columns indicated that it consisted of at least 95% of one material. The stereoselectivity of this reaction is due to the attack by the hydride ion from the less-hindered side of the carbonyl group and is in accordance with previous findings[6]. Hydrolysis of 4 with hot 0.5 M sulfuric acid provided 6-deoxy-D-allose[10] (5, 60%), m.p. 143–144.5°, $[\alpha]_D^{26}$ −4.2° (*c* 1, H_2O)

★G.l.c. analyses were performed on a F and M Model 810 instrument equipped with a ¼ in. × 3 ft 6% ethylene glycol succinate column operated at 130°.



identical with an authentic sample. This reaction sequence of reduction and hydrolysis provides unequivocal proof for the structure of **3** and also establishes that inversion took place only at C-5. The fact that no change occurred at C-3 was not totally unexpected, as 2,3-*cis* stereochemistry is favored for the isopropylidene group, as observed in related base-catalyzed isomerizations[11].

Treatment of **3** with hydroxylamine hydrochloride in a mixture of pyridine and ethanol at room temperature gave the oxime **6** as a mixture of *syn* and *anti* isomers. The mixture was separated by p.t.l.c. on silica gel to yield 62% of the major isomer, m.p. 133–134.5° $[\alpha]_D^{26}$ +42.5° (*c* 0.63, $CHCl_3$), anal. $C_{10}H_{17}NO_5$, and 16% of the minor isomer as a gum, $[\alpha]_D^{26}$ +9.14° (*c* 0.72, $CHCl_3$), anal. $C_{10}H_{17}NO_5$. Reduction of **6** (mixture or either of the pure isomers) with lithium aluminum hydride in tetrahydrofuran at room temperature gave methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-β-D-allopyranoside (**7**) in 86% yield as a colorless liquid, isolated and characterized as the crystalline hydrogen *p*-toluenesulfonate, m.p. 191–193° $[\alpha]_D^{26}$ −28.5° (*c* 0.67, $CHCl_3$), anal. $C_{17}H_{27}NO_7S$. G.l.c. indicated that the crude amine was at least 95% of one material, showing that the reduction of the oxime proceeded, as with the ketone analog **3**, by attack of the hydride ion almost exclusively from the less-hindered side[6].



Acetylation of 7 with acetic anhydride and pyridine, followed by hydrolysis with 50 mM hydrochloric acid gave methyl 4-acetamido-4,6-dideoxy-β-D-allopyranoside (8, 52%), m.p. 224–225°, $[\alpha]_D^{26}$ +3.55° (*c* 0.4, H_2O), anal. $C_9H_{17}NO_5$. Hydrolysis of 8 with a 9% solution of barium hydroxide in water under refluxing conditions provided methyl 4-amino-4,6-dideoxy-β-D-allopyranoside (9) in 56% yield, m.p. 174–176°, $[\alpha]_D^{26}$ −50.6° (*c* 0.75, CH_3OH), pKa 7.20, anal. $C_7H_{15}NO_4$. The D-*erythro* stereochemistry at C-4 and C-5 of 9 was confirmed by the degradation of 8 to D-allothreoninol according to a method described previously[12].

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