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β-ELIMINATION IN ALDONOLACTONES. SYNTHESIS OF 2-DEOXY-D-*lyxo*-HEXOSE AND 2-DEOXY-D-*arabino*-HEXOSE

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ABSTRACT

Benzoylation of D-*glycero*-L-*manno*-heptono-1,4-lactone (**1**) with benzoyl chloride and pyridine for 2 h afforded crystalline penta-*O*-benzoyl-D-*glycero*-L-*manno*-heptono-1,4-lactone (**2**), but a large excess of reagent during 8 h also led to 2,5,6,7-tetra-*O*- benzoyl-3-deoxy-D-*lyxo*-hept-2-enono-1,4-lactone (**3**). Catalytic hydrogenation of **3** was stereoselective and gave 2,5,6,7-tetra-*O*-benzoyl-3-deoxy-D-*galacto*-heptono-1,4-lactone (**4**). Debenzoylation of **4** followed by oxidative decarboxylation with ceric sulfate in aqueous sulfuric acid gave 2-deoxy-D-*lyxo*-hexose (**5**). Application of the same reaction to 3-deoxy-D-*gluco*-heptono-1,4-lactone afforded 2-deoxy-D-*arabino*-hexose (**6**).

INTRODUCTION

In previous papers, we have described the synthesis of benzoylated 3-deoxy-aldonolactones, *via* β-elimination reactions, followed by stereoselective, catalytic hydrogenation, for D-galactono-1,4-lactone[1], D-*glycero*-D-*gulo*-heptono-1,4-lactone[2], and for D-glucono-[3] and L-rhamnono-[4] 1,5-lactones.

The simplicity of this pathway suggested its application for the synthesis of deoxy sugars. Thus, we have recently reported a convenient synthesis of 3,6-dideoxy-L-*arabino*-hexose (ascarylose) in four steps from L-rhamnono-1,5-lactone[4].

2-Deoxy sugars may be obtained by degradation of the 3-deoxy-lactones, and we have reported the preparation of 2-deoxy-D-*erythro*-pentose by oxidative decarboxylation of 3-deoxy-D-*arabino*-hexono-1,4-lactone with ceric sulfate[5]. We have recently established the general applicability of this reagent for synthesis of aldoses, when the aldonolactone is oxidized under nitrogen[6,7].

In this paper, we report the synthesis of 2-deoxy-D-*lyxo*-hexose (**5**) and 2-deoxy-D-*arabino*-hexose (**6**) from 3-deoxy-D-*galacto*-heptono-1,4-lactone and 3-deoxy-D-*gluco*-heptono-1,4-lactone, respectively, as prepared *via* elimination reactions.

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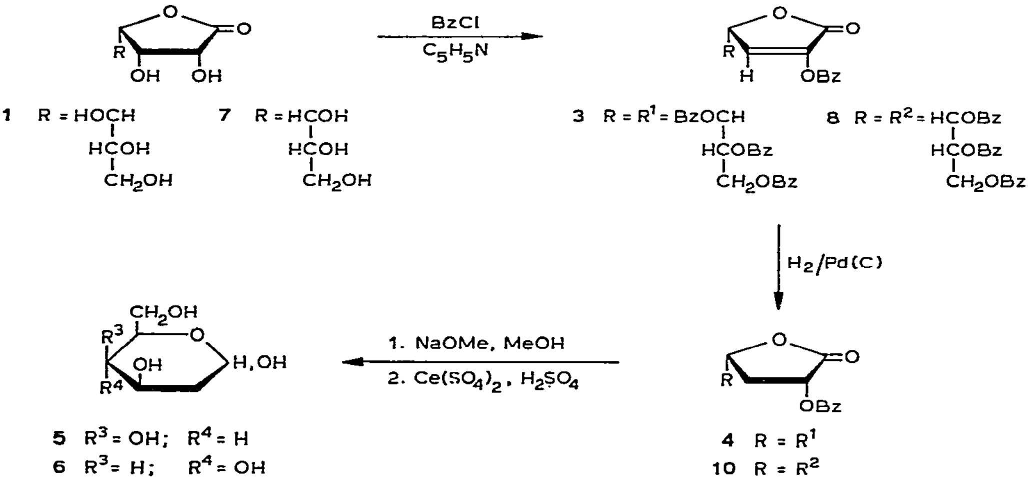
RESULTS AND DISCUSSION

D-*glycero*-L-*manno*-Heptono-1,4-lactone (**1**) was benzoylated with a slight excess of benzoyl chloride and pyridine for 2 h at room temperature to give crystalline 2,3,5,6,7-penta-*O*-benzoyl-D-*glycero*-L-*manno*-heptono-1,4-lactone (**2**) in 70% yield. The i.r. spectrum of **2** showed a carbonyl band at 1810 cm^{-1}, characteristic of a 1,4-lactone.



Benzoylation with a fourfold excess of benzoyl chloride and pyridine for 8 h at room temperature afforded the saturated benzoate **2**, together with 2,5,6,7-tetra-*O*-benzoyl-3-deoxy-D-*lyxo*-hept-2-enono-1,4-lactone (**3**). Two minor products, having higher mobility in t.l.c., may correspond to di- and tri-unsaturated lactones, by analogy with the known behavior of D-*glycero*-D-*gulo*-heptono-1,4-lactone[8] (**7**). The enonolactone **3** was obtained by column chromatography as a syrup, but in only 1.7% yield. The shift in the lactone carbonyl absorption in the infrared with respect to the saturated lactone **2**, together with the ^{1}H-n.m.r. data, support the structure assigned.

Catalytic hydrogenation of **3** proceeded stereoselectively and gave crystalline 2,5,6,7-tetra-*O*-benzoyl-3-deoxy-D-*galacto*-heptono-1,4-lactone (**4**, 95%). Similar behavior was observed on hydrogenation of 2,5,6,7-tetra-*O*-benzoyl-3-deoxy-D-*arabino*-hept-2-enono-1,4-lactone[2] (**8**).

Compound **4** was ammonolyzed to give crystalline 3-deoxy-D-*galacto*-heptonamide (**9**). The configuration at C-2 was in accord with Hudson's amide rule[9].

2-Deoxy-D-*lyxo*-hexose (**5**) was obtained crystalline in 90% yield by oxidative decarboxylation of the 3-deoxy-D-*galacto*-heptonolactone with Ce(IV) sulfate in aqueous sulfuric acid.

Synthesis of **4** could be simplified by hydrogenating the crude product of benzoylation of D-*glycero*-L-*manno*-heptono-1,4-lactone (**1**). This manipulation avoids separation of the 2-enonolactone **3** by column chromatography, and improves the total yield of **4**.

2,5,6,7-Tetra-*O*-benzoÿl-3-deoxy-D-*arabino*-hept-2-enono-1,4-lactone (**8**) has been previously obtained[2] in 24% yield by direct benzoylation of D-*glycero*-D-*gulo*-heptono-1,4-lactone (**7**) for 16 h. From the mother liquors, the di- and tri-unsaturated products, namely, 3-benzoyloxy-5-(2,3-dibenzoyloxypropylidene)-(5*H*)-furan-2-one and 3-benzoyloxy-5-(2-benzoyloxyallylidene)-(5*H*)-furan-2-one[8] were isolated.

In an attempt to improve the yield of **8**, the reaction was monitored by t.l.c. The maximum yield in the 2-enono-lactone **8** was observed after 8 h. Longer periods favored multiple elimination.

The β-elimination reaction that affords the 2-enonolactone determines the total yield in the synthesis of 2-deoxy sugars, as the subsequent steps are almost quantitative.

Catalytic hydrogenation of 2,5,6,7-tetra-*O*-benzoyl-3-deoxy-D-*arabino*-hept-2-enono-1,4-lactone (**8**) afforded[2] 2,5,6,7-tetra-*O*-benzoyl-3-deoxy-D-*gluco*-heptono-1,4-lactone (**10**). Debenzoylation of **10** with sodium methoxide gave a syrup that could not be induced to crystallize. Its elementary analysis was in accord with formulation as a 3-deoxyheptonolactone. The i.r. spectrum showed a strong absorption at 1815 cm^{-1} corresponding to a 1,4-lactone and weak absorption at 1740 cm^{-1}, which may indicate a small proportion of the 1,5-lactone in equilibrium with the former. The mixture of isomeric lactones was oxidized with a 1:2 molar proportion of cerium(IV) sulfate in aqueous sulfuric acid for 7 h at room temperature. The presence of a 3-deoxy group in the aldonolactone prevents further oxidation, making work under nitrogen unnecessary[6].

After neutralization and deionization of the mixture, crystalline 2-deoxy-D-*arabino*-hexose (**6**) was obtained in 94% yield.

This report further illustrates the utility of the β-elimination reaction in aldonolactones, coupled with the ceric sulphate degradation method, for the synthesis of biologically important 2-deoxy sugars.

EXPERIMENTAL

General. — Melting points were determined with a Kofler apparatus and are uncorrected. Evaporations were performed *in vacuo*. Specific rotations were recorded with a Perkin–Elmer 141 polarimeter. Infrared spectra were recorded with a Perkin–Elmer Infracord 421 B spectrophotometer. ^{1}H-N.m.r. spectra were determined in chloroform-*d* with tetramethylsilane as reference, by using a Varian A-60 spectrometer. T.l.c. was performed on Silica Gel G (Merck) with *A*, 19:1 benzene–ethyl acetate, or *B*, 49:1 benzene–ethyl acetate as the mobile phase; detection was effected with iodine vapor. Paper chromatography was conducted by the descending method on Whatman No. 1 paper with the following solvent systems: *C*, 5:2:2 1-butanol–ethanol–water, and *D*, 6:4:3 1-butanol–pyridine–water. Detection was effected with:

(*a*) silver nitrate–sodium hydroxide[10], (*b*) *p*-anisidine hydrochloride[11], and (*c*) hydroxylamine–ferric chloride[12].

*2,3,5,6,7-Penta-O-benzoyl-*D-glycero-L-manno*-heptono-1,4-lactone* (**2**). — D-*glycero*-L-*manno*-Heptono-1,4-lactone (**1**, 0.5 g) was suspended in anhydrous pyridine (2.5 mL) and benzoyl chloride (2.3 mL) was added with external cooling. The mixture was shaken for 2 h at room temperature and then poured with stirring into ice–water. The gum that separated was washed several times with ice–water by decantation until it solidified. The dry product (yield 1.2 g, 70%) crystallized upon addition of ether and was homogeneous in t.l.c. (R_F 0.50, solvent *A*). It was recrystallized from 1:2 benzene–cyclohexane; m.p. 78–80°, $[\alpha]_D^{20}$ +55.9° (*c* 1.3, acetone); ν_{max}^{Nujol} 1810 (1,4-lactone) and 1720 cm^{-1} (benzoate C=O),

Anal. Calc. for $C_{42}H_{32}O_{12}$: C, 69.23; H, 4.39. Found: C, 69.53; H, 4.54.

*2,5,6,7-Tetra-O-benzoyl-3-deoxy-*D-lyxo*-hept-2-enono-1,4-lactone* (**3**). — To a suspension of **1** (2 g) in anhydrous pyridine (40 mL) benzoyl chloride (20 mL) was added with external cooling. After being shaken for 8 h at room temperature, the mixture was poured into ice–water and extracted with dichloromethane (3 × 100 mL). The organic layer was washed successively with saturated, aqueous sodium hydrogencarbonate and water, dried over magnesium sulfate, and evaporated to a syrup. Benzoic acid was then removed by sublimation at 70°, 0.1 mmHg. T.l.c. of the residue showed four spots, having R_F 0.16, 0.70, 0.85, and 0.90, respectively (solvent *B*). The mixture was separated by column chromatography on silica gel (Davison), using benzene with increasing concentrations of ethyl acetate as eluent. The two faster-moving compounds were eluted admixture with benzoic anhydride. 2,5,6,7-Tetra-*O*-benzoyl-3-deoxy-D-*lyxo*-hept-2-enono-1,4-lactone (**3**) was obtained as a syrup (yield 0.1 g, 1.7%) which could not be induced to crystallize. It was homogeneous in t.l.c. (R_F 0.70, solvent *B*); $[\alpha]_D^{25}$ −68° (*c* 0.6, dichloromethane); ν_{max}^{Nujol} 1800 (α,β-unsaturated 1,4-lactone), 1770 (vinyl benzoate C=O), 1735 (benzoate C=O), and 1650 cm^{-1} (C=C, conj); ^{1}H-n.m.r. data: δ 8.3–7.3 (m, 21 H, 4 BzO and H-3), 6.05 (m, 2 H, H-5 and H-6), 5.65 (m, H-4), and 5.1–4.6 (m, 2 H, H-7 and H-7′).

Anal. Calc. for $C_{35}H_{26}O_{10}$: C, 69.30; H, 4.20. Found: C, 69.34; H, 4.54.

*2,5,6,7-Tetra-O-benzoyl-3-deoxy-*D-galacto*-heptono-1,4-lactone* (**4**). — A solution of **3** (0.107 g) in ethyl acetate (50 mL) was hydrogenated over 10% palladium-on-charcoal in an ice–water bath at atmospheric pressure, with monitoring by t.l.c. The catalyst was filtered off and the solution evaporated to a chromatographically homogeneous syrup that crystallized upon addition of ethanol (95 mg, 95%). Following recrystallization, it had m.p. 133–135°, $[\alpha]_D^{25}$ −3.7° (*c* 0.6, acetone); R_F 0.16 (solvent *B*); ν_{max}^{Nujol} 1810 (1,4-lactone) and 1720 cm^{-1} (benzoate C=O), ^{1}H-n.m.r. data: δ 8.0–7.2 (m, 20 H, 4 BzO), 6.3–5.55 (m, 3 H, H-2, H-5 and H-6), 5.25–4.55 (m, 3 H, H-4, H-7 and H-7′), and 2.9–2.1 (m, 2 H, H-3, and H-3′).

Anal. Calc. for $C_{35}H_{28}O_{10}$: C, 69.08; H, 4.62. Found: C, 69.16; H, 4.90.

Hydrogenation could also be conducted directly on the benzoylation mixture prior to sublimation of the benzoic anhydride and separation of a polymeric product by precipitation with ethyl ether. Compound **4** crystallized in 6.4% yield (from **1**).

*Debenzoylation of 2,5,6,7-tetra-O-benzoyl-3-deoxy-*D-galacto*-heptono-1,4-lactone* (**4**). — Compound **4** (0.215 g) was dissolved in 8 mL of methanol and 0.2 M sodium methoxide (5 mL) was added. After 2 h at room temperature, the solution was neutralized with Dowex-50 (H^+), and evaporated to a syrup. Paper chromatography (solvent *D*, reagents *a* and *c*) showed only one spot (R_F 0.60).

The lactone thus obtained (33 mg) was dissolved in water (1.5 mL) and 0.4M potassium hydroxide (0.15 mL) was added. The solution was kept for 10 min at room temperature and then heated for 1 h at 80°. After cooling to room temperature, 0.5M sulfuric acid (0.05 mL) was added and the resulting solution was diluted to 3.71 mL. Optical rotations were measured at different times and the value for 3-deoxy-D-*galacto*-heptonic acid was obtained by extrapolation to $t = 0$; $[\alpha]_D^{25}$ +3.0° (*c* 0.9, water); $[M]_D^{25}$ +6.30°.

*3-Deoxy-*D-galacto*-heptonamide* (**9**). — 2,5,6,7-Tetra-*O*-benzoyl-3-deoxy-D-*galacto*-heptono-1,4-lactone (**4**, 200 mg) was treated with saturated methanolic ammonia (40 mL) and shaken at room temperature. After 24 h, the solution was evaporated to a syrup, which was extracted with benzene to remove methyl benzoate, and the residue was crystallized from 2-propanol (yield 25 mg, 36%). Upon recrystallization from the same solvent, compound **9** showed m.p. 171–172°, $[\alpha]_D^{25}$ +46° (*c* 0.9, water); $[M]_D^{25}$ +96°; ν_{max}^{Nujol} 3250 (OH), 3100 (NH_2), 1650 and 1580 cm^{-1} (amide C=O).

Anal. Calc. for $C_7H_{15}NO_6$: C, 40.20; H, 7.23; N, 6.68. Found: C, 40.36; H, 7.39; N, 6.23.

*2-Deoxy-*D-lyxo*-hexose* (**5**). — The syrup obtained by debenzoylation of compound **4** (60 mg) with sodium methoxide was treated with 1.62 mL of 0.192M Ce(IV) sulfate in M sulfuric acid for 3 h at 37°. The mixture was made neutral with barium carbonate, filtered, and deionized by successive passage through Dowex-50 (H^+) (2 × 30 cm) and De Acidite G (—NEt_2) (2 × 30 cm) resins. The eluate was evaporated to a syrup. 2-Deoxy-D-*lyxo*-hexose (**5**) was obtained crystalline in 90% yield. Recrystallized from methanol, it had m.p. and mixed m.p. 108–110°, $[\alpha]_D^{25}$ +33° (*c* 1.0, water) [lit.[13] m.p. 110°, $[\alpha]_D^{25}$ +33.6° (*c* 1.19, water).

*2,5,6,7-Tetra-O-benzoyl-3-deoxy-*D*-arabino-hept-2-enono-1,4-lactone* (**8**). — Compound **8** was synthesized by benzoylation of D-*glycero*-D-*gulo*-heptono-1,4-lactone (**7**, 2 g) with an excess of benzoyl chloride and pyridine as already described by Litter and Lederkremer[2]. The reaction time was shortened to 8 h in order to obtain a higher yield of the enono-lactone **8**, which crystallized from ether in 50% yield.

*2,5,6,7-Tetra-O-benzoyl-3-deoxy-*D-gluco*-heptono-1,4-lactone* (**10**). — Compound **8** was hydrogenated over 5% paladium-on-charcoal as already described[2].

*2-Deoxy-*D*-arabino-hexose* (**6**). — 2,5,6,7-Tetra-*O*-benzoyl-3-deoxy-D-*gluco*-heptono-1,4-lactone (**10**, 0.920 g) was debenzoylated with 0.2M sodium methoxide (7 mL) in abs. methanol (8.6 mL) for 2 h at room temperature. The solution was made neutral with Dowex-50 (H^+) resin and evaporated to a syrup that was dissolved in water and extracted with ether (3 × 5 mL) to remove methyl benzoate. The aqueous layer was evaporated, 1,4-dioxane was added, and the resulting solution was heated for 1 h at 80° to lactonize the product. 3-Deoxy-D-*gluco*-heptono-lactone was obtained as a syrup (0.3 g) that showed by paper chromatography (solvent *C*) only one spot (R_F 0.86, reagents *a* and *c*); $[\alpha]_D^{25}$ $-13.0°$ (0.7, water); ν_{max}^{Nujol} 1815 (1,4-lactone) and 1740 cm^{-1} (1,5-lactone).

Anal. Calc. for $C_7H_{12}O_6$: C, 43.75; H, 6.25. Found: C, 43.45; H, 5.99.

3-Deoxy-D-*gluco*-heptono-lactone (0.150 g) was oxidized with 8.12 mL of 0.19M Ce(IV) sulfate in M sulfuric acid for 7 h at 37°. The mixture was made neutral with barium carbonate, filtered, and the filtrate deionized by successive passage through Dowex-50 (H^+) and De Acidite G ($-NEt_2$) resins. The eluate was evaporated to a syrup that crystallized from abs. ethanol (yield 120 mg, 94%). Paper chromatography showed only one spot, having the same mobility as that of an authentic sample of 2-deoxy-D-*arabino*-hexose (R_F 0.48, solvent *D*, reagents *a* and *b*); m.p. and mixed m.p. 142–144°, $[\alpha]_D^{25}$ +41° (*c* 1.0, water); [lit.[14] m.p. 142°, $[\alpha]_D^{25}$ +42° (water)].

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