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Note

The reaction of *O*-isopropylidene pentodialdo-1,4-furanoses with lithium diisopropylamide

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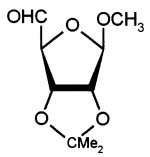
Abstract

Three *O*-isopropylidene group-protected pentose aldehydes (methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**1**), methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**2**), and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**3**)) were treated at −30 °C with lithium diisopropylamide (LDA) and the mixtures obtained were reduced with $LiAlH_4$. The products, obtained in moderate yields, proved that deacetonation occurred followed by aldol reactions between aldehydes **1**–**3** and acetone.

Keywords: *O*-Isopropylidene-pentodialdo-1,4-furanoses; Lithium diisopropylamide (LDA); Aldol reaction

When performing chain-elongation reactions on monosaccharide terminal aldehydes (protected pentodialdo-1,4-furanoses or hexodialdo-1,5-pyranoses) with alkoxymethylmagnesium chlorides, we often came across side products originating from aldehydes inverted at the α position [1–3]. The formation of these products was interpreted by assuming inversion of configuration at the α position of aldehydes due to the basicity of the medium resulting from an excess of Grignard reagent followed by the normal addition reaction.



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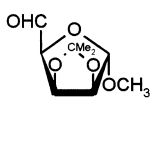

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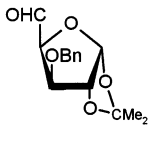

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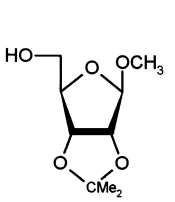
We decided to investigate whether pentose terminal aldehydes methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**1**), methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**2**), and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**3**) will undergo configuration inversion at C-4 in the presence of a strong base. To this end, solutions of aldehydes **1**–**3** in tetrahydrofuran were treated with lithium diisopropylamide (LDA, 4 molar excess) at −30 °C, the products were reduced in situ with $LiAlH_4$, and isolated. When aldehyde **1** was reacted



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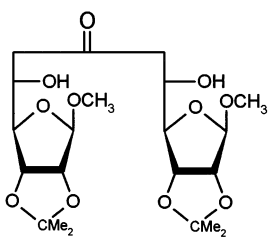

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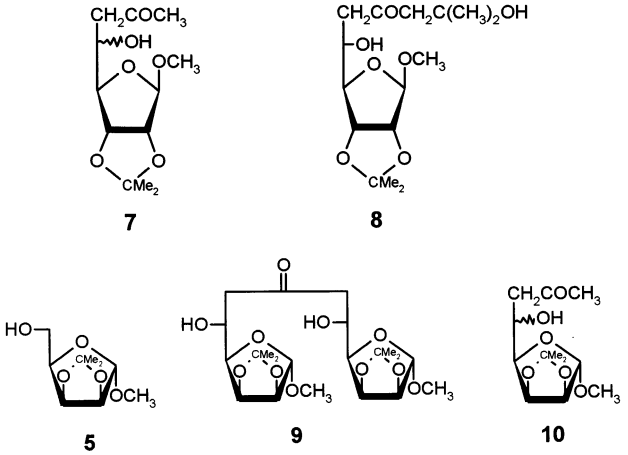


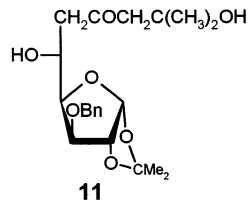
with LDA for 15 min, the only isolated product was methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**4**, 85.6%) as expected. Similarly, methyl 2,3-*O*-isopropylidene-α-D-lyxofuranoside (**5**, 79.1%) was obtained from compound **2**.

However, prolongation of the reaction time of aldehydes with the base to 1 h substantially changed the outcome of the reactions, and furanoside **4** was formed in 7.4% yield starting with compound **1** and two other products, **6** and **7**, were isolated. The structure of 1,3-di-*C*-(methyl 2,3-*O*-isopropylidene-α-L-*talo*-pentofuranos-5-yl)acetone was assigned to the major product **6** (19.6%) on the basis of analytical, spectral and synthetic (vide infra) data. The third product, **7** (7.1%), was identified as a 4:1 mixture of the α-L-talo and β-D-allo stereoisomers of methyl 6,8-dideoxy-2,3-*O*-isopropylidene-octofuranosid-7-ulose.

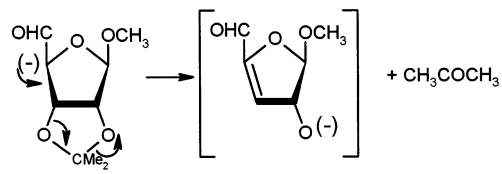
Formation of products **6** and **7** points to the deacetonation of the substrate and a follow-up aldol reaction between the aldehyde **1** and the liberated acetone. However, it must be added that we did not succeed in isolation of the deacetonated sugar products in this and other cases (vide infra).

In order to substantiate the structures of the acetone-derived products **6** and **7,** a solution of **1** was treated again at −30 °C with LDA (1 h), but this time acetone was added to the solution. When the molar ratio **1**:acetone was 1:2, product **6** was, in fact, obtained in 24.4% yield. Another product was also isolated and the structure of a substituted 'diacetone alcohol' **8** (24.4%) was assigned. When the ratio **1**:acetone was changed to 1:0.5, the yield of **6** dropped to 13.1% and that of **8** rose to 45%. The presence of **7** was not detected in either reaction mixture.

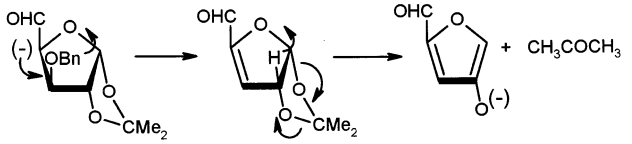
The results of the LDA treatment (−30 °C, 1 h, then $LiAlH_4$) of the aldehyde **2** were similar, i.e., 1,3-disubstituted acetone **9** was the main product (17.1%), accompanied by stereoisomeric octuloses **10** (11.8%) and the alcohol **5** (12%). The behaviour of the aldehyde **3** was different. From the reaction, a single product **11** (21%) was isolated to which the structure of substituted 'diacetone alcohol' was assigned on the basis of analytical and spectral data.



Deacetalation of monosaccharide benzylidene and isopropylidene derivatives under the influence of strong bases (BuLi or LDA) was extensively studied by Klemer et al. [4–7] (see also Ref. [8]) and interesting unsaturated or deoxy-keto sugar derivatives have been obtained. Incorporation of the base ligand (butyl group) to some of the products, but not of the released acetone, was observed. For the cleavage of acetone from aldehydes **1** and **2**, the elimination shown in **12** seems to be more plausible than Klemer's proposals [6]. Deacetonation of the aldehyde **3** can be interpreted as shown in **13**[1]. Furthermore, it seems that the deacetonated aldehydes are unstable and undergo further (self ?) condensations to polymeric materials. The results described here might be regarded as a caveat when performing reactions of isopropylidene acetal-containing sugar aldehydes in the presence of strong bases. On the other hand, the results did not prove the facile inversion of configuration at α



[1] We thank a Referee for this suggestion.



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position of pentodialdo-1,4-furanoses, at least when LDA was present as the base.

1. Experimental

General methods.—^{1}H NMR spectra were recorded with a Varian AC-200 (200 MHz) spectrometer using $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded in the DEPT mode. High-resolution mass spectra (HRMS) were measured in the FAB^+ ion mode with an AMD-604 mass spectrometer. IR spectra were recorded with a Perkin–Elmer 1640 FT-IR spectrometer. Optical rotations were measured with a Jasco DIP-360 automatic polarimeter at 24 ± 2 °C. Melting points were determined with a Kofler apparatus and are not corrected.

*Reaction of methyl 2,3-*O*-isopropylidene-β-*D*-ribo-pentodialdo-1,4-furanoside* (**1**) *with lithium diisopropylamide (LDA).*—To a stirred solution of LDA (6.9 mmol) in THF (15 mL) at −30 °C under an argon atmosphere, a solution of methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside (**1**) [9,10] (0.346 mg, 1.7 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at this temperature for 1 h, then $LiAlH_4$ (33 mg, 0.85 mmol) was added in one portion and stirring was continued for 15 min. The reaction was quenched with water (2 mL). The mixture was then filtered through Celite pad, the filtrate was dried (Na_2SO_4), concd under reduced pressure, and the crude product was chromatographed on Silica Gel with 3.5:1.5 then 1:1 hexane–EtOAc to give **4** (0.026 g, 7.4%), the mixture of stereoisomeric **7** (0.031 g, 7.1%, a 4:1 ratio of L:D isomers) and the main product **6** (0.155 g, 19.6%).

The reactions of methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**2**) [11] and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**3**) (obtained by the method used for **2** from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose) with LDA were carried out according to the same method.

*1,3-Di-*C*-(methyl 2,3-*O*-isopropylidene-α-*L*-talo-pentofuranos-5-yl)acetone* (**6**).—Yield 0.155 g (19.6%); white solid, mp 151–152 °C; $[\alpha]_D$ −34.6° (*c* 1.8, $CHCl_3$); IR ν_{max} (KBr): 3417, 2944, 1710, 1378, 1091, 868 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.96 (s, 1 H, H-1), 4.86 (d, 1 H, *J* 6.0 Hz, H-3), 4.48 (d, 1 H, *J* 6.0 Hz, H-2), 4.20–4.08 (m, 2 H, H-4, H-5), 3.40 (s, 3 H, OCH_3), 2.75–2.66 (m, 2 H, H-6a, H-6b), 1.47, 1.32 (2 s, 6 H, $(CH_3)_2C$). ^{13}C NMR ($CDCl_3$): δ 208.4 (CO), 112.3 ($(CH_3)_2C$), 109.9 (C-1), 90.1 (C-4), 85.5 (C-2), 80.4 (C-3), 68.5 (C-5), 55.7 (OCH_3), 46.6 (C-6), 26.3, 24.7 ($(CH_3)_2C$). HRMS (LSIMS): *m*/*z* 485.2003 $[M + Na]^+$. Calcd for $C_{21}H_{34}O_{11}Na$: 485.1999. Anal. Calcd for $C_{21}H_{34}O_{11}$: C, 54.54; H, 7.41. Found: C, 54.32; H, 7.58.

*Methyl 6,8-dideoxy-2,3-*O*-isopropylidene-α-*L*-talo- and -β-*D*-allo-octofuranosid-7-uloses* (**7a,b**).—Yield 0.031 g (7.1%): **7a** + **7b**; white foam; NMR data are taken from the spectra of a 4:1 mixture of L:D isomers. Configuration assignments are based on analogy of ^{1}H and ^{13}C NMR signals (H-1, C-1,2,3) with methyl 6-*O*-allyl-2,3-*O*-isopropylidene-β-D-*allo*- and -α-L-*talo*-furanosides [3].

7a: ^{1}H NMR ($CDCl_3$): δ 4.96 (s, 1 H, H-1), 4.88 (d, 1 H, *J* 5.6 Hz, H-3), 4.58 (d, 1 H, *J* 5.6 Hz, H-2), 4.18–4.08 (m, 2 H, H-4, H-5), 3.40 (s, 3 H, OCH_3), 2.72–2.64 (m, 2 H, H-6a, H-6b), 2.22 (s, 3 H, CH_3CO), 1.47, 1.32 (2 s, 6 H, $(CH_3)_2C$). ^{13}C NMR ($CDCl_3$): δ 207.5 (CO), 112.2 ($(CH_3)_2C$), 109.9 (C-1), 90.0 (C-4), 85.4 (C-2), 80.4 (C-3), 68.4 (C-5), 55.6 (OCH_3), 46.3 (C-6), 30.8 (CH_3CO), 26.3, 24.7 ($(CH_3)_2C$). IR ν_{max} (KBr): 3458, 2944, 1714, 1375, 1089, 867 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_6$ (260.28): C, 55.37; H, 7.74. Found: C, 55.36; H, 7.90.

7b: ^{1}H NMR ($CDCl_3$): δ 4.98 (s, 1 H, H-1), 4.82 (d, 1 H, *J* 5.5 Hz, H-3), 4.39 (d, 1 H, *J* 5.5 Hz, H-2), 4.12–4.01 (m, 2 H, H-4, H-5), 3.47 (s, 3 H, OCH_3), 2.75–2.67 (m, 2 H, H-6a, H-6b), 2.20 (s, 3 H, CH_3CO), 1.47, 1.32 (2 s, 6 H, $(CH_3)_2C$). ^{13}C NMR ($CDCl_3$): δ 206.6 (CO), 112.1 ($(CH_3)_2C$), 110.4 (C-1, 89.8 (C-4), 85.3 (C-2), 82.1 (C-3), 67.9 (C-5), 55.8 (OCH_3), 47.6 (C-6), 30.6 (CH_3CO), 26.3, 24.7 ($(CH_3)_2C$).

Methyl 6,8,10-trideoxy-2,3-O-isopropylidene-9-C-methyl-α-L-talo-decofuranosid-7-ulose (**8**).—Yield 39.5%; colourless oil (from the ^{13}C NMR spectrum of **8**, a minute admixture of the β-D-allo stereoisomer can be discerned (>1:8); we did not succeed in its isolation); $[\alpha]_D$ −33.6° (*c* 1.4 $CHCl_3$); IR ν_{max} (film): 3427, 2974, 1700, 1379, 1093, 869 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.96 (s, 1 H, H-1), 4.85 (d, 1 H, *J* 5.9 Hz, H-3), 4.58 (d, 1 H, *J* 5.9 Hz, H-2), 4.17–4.06 (m, 2 H, H-4, H-5), 3.70–3.51 (m, 2 H, CH_2), 3.41 (s, 3 H, OCH_3), 2.80–2.59 (m, 2 H, H-6a, H-6b), 1.47, 1.32 (2 s, 6 H, $(CH_3)_2C$), 1.28 (s, 6 H, $(CH_3)_2$–COH. ^{13}C NMR ($CDCl_3$): δ 211.2 (CO), 109.9 (C-1), 90.2, 85.5, 80.2 (C-2, C-3, C-4), 68.6 (C-5), 55.7 (OCH_3), 54.5 (CH_2), 46.9 (C-6), 29.4, 29.3 (CH_3)$_2$C–OH), 26.3, 24.7 ((CH_3)$_2$C). HRMS (LSIMS): *m*/*z* 341.1568 $[M+Na]^+$. Calcd for $C_{15}H_{26}O_7Na$: 341.1576.

1,3-Di-C-(methyl 2,3-O-isopropylidene-α-D-manno-pentofuranosid-5-yl)acetone (**9**).—Yield 0.086 (17.1%); white foam; $[\alpha]_D$ +49.3° (*c* 0.9, $CHCl_3$); IR ν_{max} (film): 3457, 2937, 1711, 1373, 1090, 863 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.87 (s, 1 H, H-1), 4.82 (dd, 1 H, *J* 5.9, 3.7 Hz, H-3), 4.58 (d, 1 H, *J* 5.9 Hz, H-2), 4.47 (m, 1 H, *J* 4.1, 8.3 Hz, H-5), 3.81 (dd, 1 H, *J* 3.7, 8.3 Hz, H-4), 3.30 (s, 3 H, OCH_3), 2.92 (dd, 1 H, *J* 4.1, 16.9 Hz, H-6a), 2.76 (dd, 1 H, *J* 8.3, 16.9 Hz, H-6b), 1.47, 1.32 (2 s, 6 H, $(CH_3)_2C$). ^{13}C NMR ($CDCl_3$): δ 207.5 (CO), 107.0 (C-1), 84.8, 81.2, 79.5 (C-2, C-3, C-4), 66.0 (C-5), 54.6 (OCH_3), 47.4 (C-6), 25.9, 24.6 ((CH_3)$_2$C). HRMS (LSIMS): *m*/*z* 485.2001$[M+Na]^+$. Calcd for $C_{21}H_{34}O_{11}Na$: 485.1999.

Methyl 6,8-dideoxy-2,3-O-isopropylidene-β-L-gulo- and -α-D-manno-octofuranosid-7-uloses (**10a,b**).—Yield 0.033 g (11.8%): **10a** + **10b**; colourless oil; (NMR data are taken from a 6:1 mixture of L:D isomers. Configuration assignments are based on analogy with methyl 6-*O*-alkyl-2,3-*O*-isopropylidene-β-L-*gulo*- and α-D-*manno*-furanosides [3]).

10a: ^1H NMR ($CDCl_3$): δ 4.96 (s, 1 H, H-1), 4.73 (dd, 1 H, *J* 5.9, 3.6 Hz, H-3), 4.58 (d, 1 H, *J* 5.9 Hz, H-2), 4.54–4.43 (m, 1 H, H-5), 3.86 (dd, 1 H, *J* 3.6, 5.5 Hz, H-4), 3.33 (s, 3 H, OCH_3), 3.38, 3.26 (ABq, 2 H, H-6a, H-6b), 2.23 (s, 3 H, CH_3CO), 1.47, 1.31 (2 s, 6 H, $(CH_3)_2C$). ^{13}C NMR ($CDCl_3$): δ 214.1 (CO), 106.7 (C-1), 85.2, 80.8, 80.2 (C-2, C-3, C-4), 66.8 (C-5), 54.7 (OCH_3), 46.5 (C-6), 30.9 (CH_3CO), 25.9, 24.5 ((CH_3)$_2$C). IR ν_{max} (film): 3487, 2938, 1715, 1374, 1091, 861 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_6$ (260.28): C, 55.37; H, 7.74. Found C, 55.21; H, 7.95.

10b: ^1H NMR ($CDCl_3$): δ 4.88 (s, 1 H, H-1), 4.82 (dd, 1 H, *J* 6.0, 3.8 Hz, H-3), 4.55 (d, 1 H, *J* 6.0 Hz, H-2), 4.42–4.36 (m, 1 H, H-5), 3.78 (dd, 1 H, *J* 3.8, 7.8 Hz, H-4), 3.34 (s, 3 H, OCH_3), 3.28, 3.22 (ABq, 2 H, H-6a, H-6b), 2.22 (s, 3 H, CH_3CO), 1.43, 1.26 (2 s, 6 H, $(CH_3)_2C$). ^{13}C NMR ($CDCl_3$): δ 212.4 (CO), 107.1 (C-1), 84.8, 81.1, 79.5 (C-2, C-3, C-4), 66.0 (C-5), 54.5 (OCH_3), 47.2 (C-6), 30.8 (CH_3CO), 25.9, 24.6 ((CH_3)$_2$C)

3-O-Benzyl-6,8,10-trideoxy-1,2-O-isopropylidene-9-C-methyl-α-D-gluco-decapyranosulos-7-ulose (**11**).—Yield 0.166 g (21%); colourless oil; (the gluco configuration of **11** was based on the close analogy of its ^{13}C NMR spectral data with other compounds of the same configuration [3]; $[\alpha]_D$ −29.0° (*c* 2.1, $CHCl_3$); IR ν_{max} (film): 3493, 2987, 2936, 1710, 1374, 1076, 887, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.91 (d, 1 H, *J* 3.8 Hz, H-1), 4.82, 4.64 (ABq, 2 H, CH_2Ph), 4.59 (d, 1 H, *J* 3.8 Hz, H-2), 4.44 (m, 1 H, H-5), 4.08 (d, 1 H, *J* 2.8 Hz, H-3), 4.01 (dd, 1 H, *J* 2.8, 8.6 Hz, H-4), 1.95 (dt, 1 H, *J* 2.3, 4.8, 13.9 Hz, H-6a), 1.83 (dd, 1 H, *J* 2.3, 13.9 Hz, H-6b), 1.54–1.38 (m, 2 H, CH_2), 1.31 (s, 6 H, $(CH_3)_2C$–OH), 1.47, 1.23 (2 s, 6 H, $(CH_3)_2C$). ^{13}C NMR ($CDCl_3$): δ 209.5 (CO), 104.9 (C-1), 82.9, 82.7, 80.8 (C-2, C-3, C-4), 72.7 (CH_2PH), 62.9 (CH), 62.8 (C-5), 45.1 (C-6), 41.2 (CH_2), 30.9, 29.3 ((CH_3)$_2$C–OH), 26.7, 26.2 ((CH_3)$_2$C). HRMS (LISIMS): *m*/*z* 417.1874 $[M+Na]^+$. Calcd for $C_{21}H_{30}O_7Na$: 417.1889. Anal. Calcd for $C_{21}H_{30}O_7$: C, 63.94; H, 7.67. Found: 63.95, H, 7.74.

Acknowledgements

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