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# Improved Synthesis of 6-Deoxy-1,2-O-isopropylidene-β-*L*-talofuranose and 6-Deoxy-1,2-O-isopropylidene-β-*L*-idofuranose

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**Summary.** The key step in the preparation of 6-deoxy-1,2-O-isopropylidene-β-*L*-talofuranose (**7**) and 6-deoxy-1,2-O-isopropylidene-β-*L*-idofuranose (**13**) is the selective exchange of the 6-O-mesyl rest of 3-O-acetyl-5,6-O-dimesyl-1,2-O-isopropylidene-α-*D*-allofuranose (**4**) and 3-O-acetyl-5,6-O-dimesyl-1,2-O-isopropylidene-α-*D*-glucofuranose (**10**) by acetate group (potassium acetate/18-crown-6).

**Keywords.** 6-Deoxy-1,2-O-isopropylidene-β-*L*-idofuranose; 6-Deoxy-1,2-O-isopropylidene-β-*L*-talofuranose.

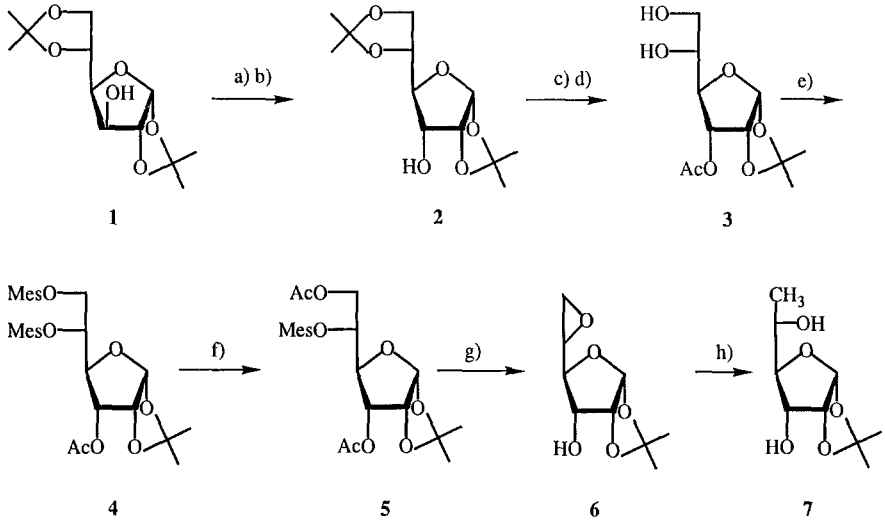
**Ein neuartiger und präparativ nützlicher Zugang zu 6-Desoxy-1,2-O-isopropyliden-β-*L*-talofuranose und 6-Desoxy-1,2-O-isopropyliden-β-*L*-idofuranose**

**Zusammenfassung.** Schlüsselschritt bei der Herstellung von 6-Desoxy-1,2-O-isopropyliden-β-*L*-talofuranose (**7**) und 6-Desoxy-1,2-O-isopropyliden-β-*L*-idofuranose (**13**) ist der selektive Austausch der primären Mesyl-Gruppe in 3-O-Acetyl-5,6-O-dimesyl-1,2-O-isopropyliden-α-*D*-allofuranose (**4**) und 3-O-Acetyl-5,6-O-dimesyl-1,2-O-isopropyliden-α-*D*-glucofuranose (**10**) durch den Acetat-Rest in Gegenwart von Kaliumacetat/Kronen-Ether.

In a previous paper we have reported the synthesis of epimeric 6-deoxy-1,2-O-isopropylidene-α-*D*-allofuranose (**14**) and 6-deoxy-1,2-O-isopropylidene-β-*L*-talofuranose (**7**) [1]. The procedure described for **7** is suffering from tedious chromatographic operations.

**14** and **7** could be transformed into 6-deoxy-1,2-O-diacetyl-3,5-O-(tetraisopropyl-disiloxane-1,3-diyl)-β-*D*-allofuranose [1], 6-deoxy-1,2-O-diacetyl-3,5-O-dibenzoyl-β-*D*-allofuranose [2], and the anomeric mixture of 6-deoxy-1,2-O-diacetyl-3,5-O-dibenzoyl-*L*-talofuranose [3] by selective acetolysis of the 1,2-O-isopropylidene protecting group.

These sugar derivatives are most suited for the silyl-Hilbert-Johnson method [4]. This one-pot procedure [5] is a simple and high yield strategy to generate new nucleoside analogues, which correspond for instance to the 5′-C-methyl-derivatives of biological active nucleoside analogs [6–7]. The derivatives of 6-deoxy-*D*-allofuranose and 6-deoxy-*L*-talofuranose [8–10] have recently caught special interest. The success of such a protocol is limited to the availability of the sugar derivatives.

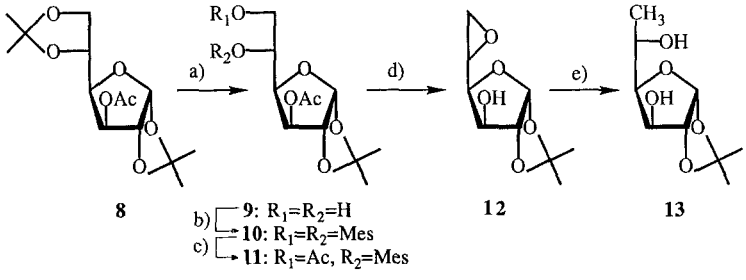



**Scheme 1.** a) $RuO_4/KIO_4$; b) $NaBH_4$; c) *Ac*$_2$O, pyridine; d) *Ac*OH : $H_2O$ = 4 : 1, 16 h; e) *Mes*Cl, pyridine, 4°C, 16 h; f) KO*Ac*, 18-crown-6, $CH_3CN$; g) $NaOCH_3$, $CH_2Cl_2$; h) $LiAlH_4$, *THF*

We now present a new strategy to the title compounds starting from the easily available 1,2 : 5,6-O-diisopropylidene-α-*D*-glucofuranose (**1**). The synthesis of **7** and **13** can be carried out without chromatographic separations and can be performed as large-scale preparation. The overall yield from **3** to **7** is also improved from ca. 20% to ca. 51% compared to the procedure described in ref. [1].

1,2 : 5,6-O-diisopropylidene-α-*D*-glucofuranose (**1**) [1, 11] was converted into 3-O-acetyl-1,2-O-isopropylidene-α-*D*-allofuranose (**2**) [1, 12] as presented in Scheme 1. It was then mesylated to give crystalline 3-O-acetyl-5,6-O-dimesyl-1,2-O-isopropylidene-α-*D*-allofuranose (**4**). Compound **4** was selectively transformed to 3,6-O-diacetyl-5-O-mesyl-1,2-O-isopropylidene-α-*D*-allofuranose (**5**) by potassium acetate in the presence of crown-ether [13–14]. Zemplén-saponification afforded the 5,6-anhydro-compound **6**, which has *L*-talose configuration. Opening of the oxirane of **6** with $LiAlH_4$ gives the crystalline 6-deoxy-1,2-O-isopropylidene-β-*L*-talofuranose (**7**).

Applying the strategy described above to 3-O-acetyl-1,2-O-isopropylidene-α-*D*-glucofuranose (**8**) [15] opens an attractive way to 6-deoxy-1,2-O-isopropylidene-β-*L*-idofuranose (**13**) (Scheme 2).




**Scheme 2.** a) *Ac*OH : $H_2O$ = 4 : 1, 16 h; b) *Mes*Cl, pyridine, 4°C, 16 h; c) KO*Ac*, 18-crown-6, $CH_3CN$; d) $NaOCH_3$, $CH_2Cl_2$; e) $LiAlH_4$, *THF*

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## Experimental Part

Melting points were determined on a Kofler apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker WM 250 spectrometer operating at 250 MHz for $^1$H and 62.9 MHz for $^{13}$C. Chemical shifts are expressed in ppm downfield from *TMS*. If not indicated otherwise, $CDCl_3$ was used as solvent. Precoated Merck silica gel F 254 plates were used for TLC, and the spots were examined with UV light and by spraying with a solution of 2% $Ce(NO_3)_4$ in 2 *N* $H_2SO_4$ followed by heating at 200°C. Flash chromatography [16] was performed with 230–400 mesh silica gel from E. Merck. Abbreviations used are *EA* (ethylacetate) and *PE* (petroleum ether).

Infrared spectra were recorded with a Perkin-Elmer 377 spectrophotometer. Mass spectra were recorded on a Varian CH-7 apparatus (70 eV). The source of the anhydrous solvents was as follows: pyridine and acetonitrile were refluxed over $CaH_2$ and distilled; dichloromethane was refluxed on phosphorus pentoxide and distilled; tetrahydrofuran (*THF*) was obtained after reflux with potassium – benzophenone.

*3-O-Acetyl-3,5-O-dimesyl-1,2-O-isopropylidene-α-D-allofuranose* (**4**)

3-O-acetyl-1,2-O-isopropylidene-α-*D*-allofuranose (**3**) (5.04 g, 19.2 mmol) [1] was dissolved in pyridine (50 ml). Mesyl chloride (3.72 ml, 48.0 mmol) was added dropwise at 0°C. After 14 h at 4°C the reaction mixture was poured into cold water, extracted with $CH_2Cl_2$, washed with 3% HCl-solution, dried with $Na_2SO_4$, evaporated and crystallized from *EA/PE*. Yield: 93%, m.p. 96–98°C, $R_f = 0.75$ (*EE*: $CHCl_3$ = 2 : 1). $^1$H NMR (250 MHz, *TMS*, δ): 1.35 and 1.55 (s, 3 H, isopropylidene-$CH_3$), 2.15 (s, 3 H, $OCOCH_3$), 3.10 and 3.17 (s, 3 H, $SO_3CH_3$), 4.34 (m, 2 H, 4-H, 6-Ha), 4.53 [dd, 1 H, *J* (6 a, 6 b) = 12.0 Hz, *J* (6 b, 5) = 4.0 Hz, 6-Hb], 4.88 (m, 2 H, 2-H, 3-H), 5.01 (m, 1 H, 5-H), 5.81 [d, 1 H, *J* (1, 2) = 4.0 Hz, 1-H]. $C_{13}H_{22}O_{11}S_2$ (418.4). Calc. C 37.32, H 5.30, S 15.32; found C 37.58, H 5.35, S 15.50.

*3,6-O-Diacetyl-1,2-O-isopropylidene-5-O-mesyl-α-D-allofuranose* (**5**)

Compound **4** (5.73 g, 13.7 mmol) was dissolved in acetonitrile (100 ml). Dry potassium acetate (15.6 g, 159 mmol) and 18-crown-6 (0.32 g, 1.2 mmol) were added. The mixture was stirred and heated under reflux. After TLC showed complete disappearance of starting material (20 h) the mixture was cooled and filtered. The remaining solid was washed several times with $CH_2Cl_2$. The combined organic phases were concentrated, dissolved in $CH_2Cl_2$, and washed with water, dried with $Na_2SO_4$ and evaporated. Although TLC is indicating a second spot ($R_f = 0.68$, *EA* : *PE* = 1 : 1) repeated crystallisation from *EA*/diisopropyl ether gave 2.72 g (52%) **5**. The remaining material was chromatographied (*EA* : *PE* = 3 : 1) to give 1.20 g. Total yield: 75%, m.p. 60–62°C, $R_f = 0.57$ (*EA* : *PE* = 1 : 1). $^1$H NMR (250 MHz, *TMS*, δ): 1.31 and 1.52 (s, 3 H, isopropylidene-$CH_3$), 2.08 and 2.12 (s, 3 H, $OCOCH_3$), 3.04 (s, 3 H, $SO_3CH_3$), 4.09 [dd, 1 H, *J* (6 a, 6 b) = 12.5 Hz, *J* (6 a, 5) = 8.1 Hz, 6-Ha], 4.29 [dd, 1, *J* (4, 5) = 4.0 Hz, *J* (4, 3) = 8.5 Hz, 4-H], 4.43 [dd, 1 H, *J* (6 b, 5) = 3.4 Hz, 6-Hb], 4.79–4.88 (m, 2, 2-H, 3-H), 5.00 (ddd, 1, 5-H), 5.78 [d, 1, *J* (1, 2) = 3.4 Hz, 1-H]. $C_{14}H_{22}O_{10}S$ (382.4). Calc. C 43.97, H 5.80, S 8.39; found C 44.01, H 5.93, S 8.40.

*5,6-Anhydro-1,2-O-isopropylidene-β-L-talofuranose* (**6**)

Compound **5** (5.00 g, 13.1 mmol) was dissolved in dichloromethane (100 ml). Then 28.8 ml of 0.5 *M* solution of $NaOCH_3$ in methanol was added. After 10 min TLC (*PE* : *EA* = 1 : 1) showed complete

disappearance of starting material ($R_f = 0.45$) and one product ($R_f = 0.07$), 5-O-mesyl-1,2-O-isopropylidene-α-*D*-allofuranose (**6a**). When the mixture was reacted for a further 3 h **6** ($R_f = 0.24$) was formed with concurrent loss of **6a**. Then $CO_2$ was added. After removing of the solvent the residue was partitioned between water and *EA*. The organic phase was dried with $Na_2SO_4$ and evaporated to give pure **6**, yield: 83%, m.p. 62–64°C (*EA/PE*), $R_f = 0.24$ (*PE : EA* = 1 : 1). $^1$H NMR (250 MHz, *TMS*, δ): 1.37 and 1.56 (s, 3 H, isopropylidene-$CH_3$), 2.48 [d, 1, *J* (OH, 3) = 8.0 Hz, 3-OH, $D_2O$ exchangeable], 2.87 (m, 2, 6-Ha, 6-Hb), 3.18 [dt, 1, *J* (5, 6) = 3.6 Hz, 5-H], 3.70 [dd, 1, *J* (3, 4) = 8.4 Hz, *J* (4, 5) = 4.0 Hz, 4-H], 4.00 (m, after $D_2O$-exchange dd, 3-H), 4.59 [dd, 1, *J* (2, 3) = 6.0 Hz, 2-H], 5.81 [d, 1, *J* (1, 2) = 4.0 Hz, 1-H]. $C_9H_{14}O_5$ (202.2). Calc. C 53.46, H 6.98; found C 53.64, H 7.11.

*5-O-Mesyl-1,2-O-isopropylidene-α-D-allofuranose* (**6a**)

Colorless oil, $R_f = 0.07$ (*PE : EE* = 1 : 1). $^1$H NMR (250 MHz, *TMS*, δ): 1.38 and 1.50 (s, 3 H, isopropylidene-$CH_3$), 2.66 (br s, 2 H, 3-OH, 6-OH, $D_2O$ exchangeable), 3.10 (s, 3 H, $SO_3CH_3$), 3.90–4.25 [m, 4 H, *J* (6a, 6b) = 13.0 Hz, *J* (6a, 5) = 4.0 Hz, *J* (3, 4) = 9.6 Hz, 3-H, 4-H, 6-Ha, 6-Hb], 4.73 [dd, 1 H, *J* (2, 3) = 5.0 Hz, 2-H], 4.87 [dt, 1 H, *J* (5, 6) = *J* (5, 4) = 4.0 Hz, 5-H], 5.80 [d, 1, *J* (1, 2) = 4.0 Hz, 1-H]. $C_{10}H_{18}O_8S$ (298.3). Calc. C 40.26, H 6.08, S 10.75; found: C 40.62, H 6.38, S 10.93.

*6-Deoxy-1,2-O-isopropylidene-β-L-talofuranose* (**7**)

Reduction of **6** with $LiAlH_4$ gave compound **7**, yield 88%, m.p. 93–94°C (lit. m.p. [1], 94°C).

*3-O-Acetyl-1,2-O-isopropylidene-3,5-O-dimesyl-α-D-glucofuranose* (**10**)

Compound **10** was prepared in the same manner as described for compound **4**, with 3-O-acetyl-1,2-O-isopropylidene-α-*D*-glucofuranose (**9**) as starting material. Yield: 91%, m.p. 165–167°C (*EA/PE*), $R_f = 0.54$ (*EA : PE* = 1 : 1). $^1$H NMR (250 MHz, *TMS*, δ): 1.30 and 1.51 (s, 3 H, isopropylidene-$CH_3$), 2.12 (s, 3 H, $OCOCH_3$), 3.09 and 3.11 (s, 3 H, $SO_3CH_3$), 4.41–4.54 (m, 2 H, 4-H, 6-Ha), 4.54 [d, 1 H, *J* (1, 2) = 3.5 Hz, 2-H], 4.71 [dd, 1, *J* (6a, 6b) = 11.9 Hz, *J* (6b, 5) = 2.1 Hz, 6-Hb], 5.11 [ddd, 1 H, *J* (5, 6a) = 4.8 Hz, *J* (5, 4) = 8.0 Hz, 5-H], 5.32 [d, 1 H, *J* (3, 4) = 2.0 Hz, 3-H], 5.92 (d, 1 H, 1-H). $C_{13}H_{22}O_{11}S_2$ (418.4). Calc. C 37.32, H 5.30, S 15.32; found C 37.48, H 5.37, S 15.62.

*3,6-O-Diacetyl-1,2-O-isopropylidene-5-O-mesyl-α-D-glucofuranose* (**11**)

This compound was prepared analogously to compound **5**, with **10** as starting material. The desired product was obtained exclusively. Yield 83%, m.p. 108–110°C, lit. [14] m.p. 110–111°C, $R_f = 0.70$ (*EA : PE* = 1 : 1). $^1$H NMR (250 MHz, *TMS*, δ): 1.31 and 1.52 (s, 3 H, isopropylidene-$CH_3$), 2.12 and 2.13 (s, 3 H, $OCOCH_3$), 3.05 (s, 3 H, $SO_3CH_3$), 4.24 [dd, 1 H, *J* (6a, 6b) = 12.5 Hz, *J* (6a, 5) = 6.5 Hz, 6-Ha], 4.41 [dd, 1 H, *J* (5, 4) = 9.0 Hz, *J* (3, 4) = 3.0 Hz, 4-H], 4.53 [d, 1 H, *J* (1, 2) = 3.5 Hz, 2-H], 4.78 [dd, 1 H, *J* (6b, 5) = 2.1 Hz, 6-Hb], 5.11 (ddd, 1 H, 5-H), 5.31 (d, 1 H, 3-H), 5.91 (d, 1 H, 1-H). $C_{14}H_{22}O_{10}S$ (382.4). Calc. C 43.97, H 5.80, S 8.39; found C 44.17, H 5.89, S 8.53.

*5,6-Anhydro-1,2-O-isopropylidene-β-L-idofuranose* (**12**)

Applying the same procedure described above to **11** gave compound **12**. Yield 80%, m.p. 72–74°C (*EA/PE*), lit. m.p. [17] 73–75°C, $R_f = 0.81$ (*EA : PE* = 3 : 1). $^1$H NMR (250 MHz, *TMS*, δ): 1.32 and 1.48 (s, 3 H, isopropylidene-$CH_3$), 2.82 [dd, 1 H, *J* (6a, 6b) = 4.8 Hz, *J* (6a, 5) = 4.8 Hz, 6-Ha], 2.90 [dd, 1 H, *J* (6b, 5) = 2.9 Hz, 6-Hb], 2.92 [d, 1, *J* (3, OH) = 5.0 Hz, 3-OH, $D_2O$ exchangeable], 4.24 [t, 1 H, *J* (5, 4) = 3.4 Hz, *J* (4, 3) = 3.4 Hz, 4-H], 4.37 (dd, 1, 3-H), 4.54 [d, 1, *J* (2, 1) = 4.0 Hz, 2-H], 5.92 (d, 1 H, 1-H). $C_9H_{14}O_5S_2$ (202.2). Calc. C 53.46, H 6.98; found C 53.67, H 7.13.

*6-Deoxy-1,2-O-isopropylidene-β-L-idofuranose* (**13**)

Reduction of **12** with $LiAlH_4$ gave **13** (80%), m.p. 86–89°C (*EA/PE*), lit. [17] m.p. 88–89°C, $R_f = 0.66$ (*EA : PE* = 3 : 1). $^1H$ NMR (400 MHz, *TMS*, δ): 1.32 and 1.49 (s, 3 H, isopropylidene-$CH_3$), 1.37 [d, 3 H, *J* ($CH_3$, 5) = 6.4 Hz, $CH_3$], 2.45 [d, 1 H, *J* (5, OH) = 8.0 Hz, 5-OH, $D_2O$ exchangeable], 3.98 [t, 1 H, *J* (4, 5) = *J* (3, 4) = 3.0 Hz, 4-H], 4.04 [d, 1 H, *J* (3, OH) = 4.0 Hz, 3-OH, $D_2O$ exchangeable], 4.21 (m, 1 H, 5-H), 4.26 [dd, 1 H, 3-H, after $D_2O$ exchange d], 4.52 [d, 1 H, *J* (1, 2) = 4.0 Hz, 2-H], 5.95 (d, 1, 1-H). $C_9H_{16}O_5$ (204.2). Calc. C 52.93, H 7.90; found C 53.19, H 7.99.

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