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TARTRALDEHYDES II[1]. SYNTHESIS OF D- AND L-DIGINOSE AND D- AND L-SARMENTOSE

Pál Herczegh*, Imre Kovács, Ferenc J. Sztaricskai*

Research Group for Antibiotics, Hungarian Academy of Sciences,
H-4010 Debrecen, P.O. Box 70., Hungary

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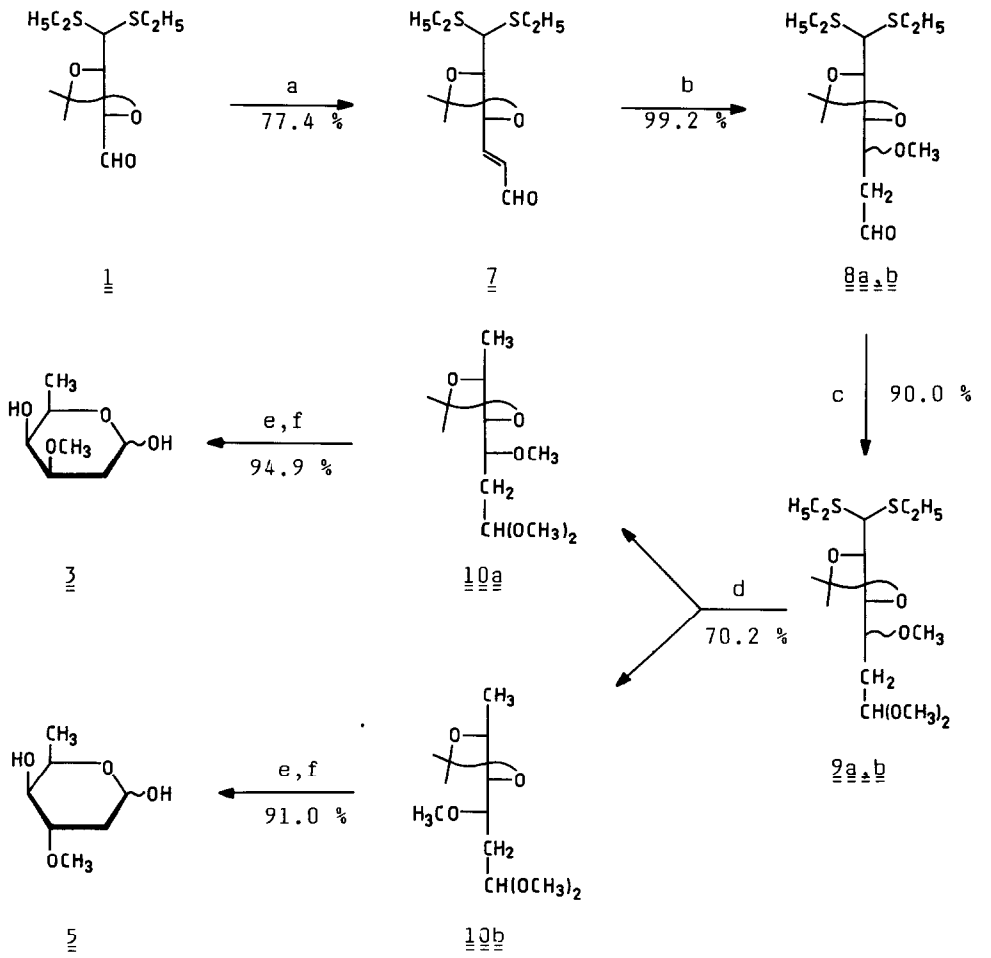
Abstract: The title compounds have been synthesized from tartraldehyde mercaptals in six steps.

Recently we reported on the synthesis of isopropylidene-D- and L--tartraldehyde diethyl dithioacetals **1** and **2**[1]. These dichiral, four-carbon synthetic building blocks served as starting compounds for the preparation of some biologically important aminodeoxy sugars.

In this paper we describe a new application of the (2S,3S) and the (2R,3R) isomers **1** and **2**, respectively. 3-O-Methyl ethers of 2,6-dideoxy hexoses have been found in several natural products[2]. D- and L-Diginose (**3** and **4**), having lyxo configurations, are constituents of cardiac glycosides [3,4], and the latter is the sugar component of the antibiotic arugomycin[5]. D-Sarmentose **5**, the D-xylo isomer can also be found in cardiac glycosides[6]. Only a few syntheses are known for **3**[4], **4**[7] and **5**[6,8]. Tartraldehyde derivatives **1** and **2** offer a short synthetic route to D- and L-diginose, as well as to D- and L-sarmentose.

Conjugate addition of methoxide anion to the double bond of **7**, obtained[1] from **1**, gave rise to a diastereomeric mixture of **8a,b** (Scheme 1). A slight diastereoselection was observed since the ratio of the arabino and xylo isomers was 9:5 by ^{1}H-NMR spectroscopic investigation. In order to protect the formyl group the **8a,b** mixture was treated with methanol and 2,2-dimethoxypropane using acid catalyst to give **9a,b**. Reductive desulfurization of the latter compound, using Raney-nickel resulted in **10a** and **10b** which were separated by column chromatography. The acetal type protective groups of **10a** and **10b** were removed upon methanolysis and subsequent hydrolysis since direct hydrolysis gave lower yields. In this way D-digi-

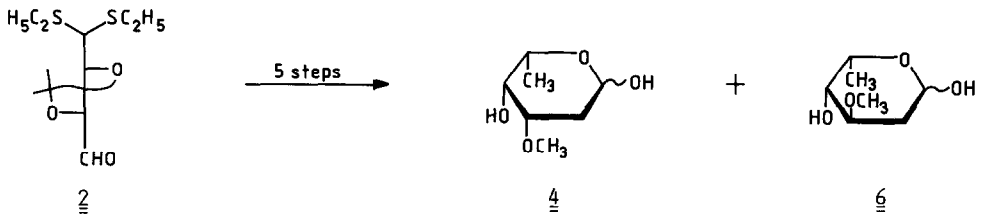


SCHEME 1

(a) $Ph_3PCHCHO$/PhH, reflux, 1 h,
(b) NaOMe (cat)/MeOH, rt, 10 h,
(c) MeOH, TsOH (cat)/DMP, rt, 1 h,
(d) Ra-Ni/EtOH, reflux, 5 h,
(e) H_2SO_4/MeOH, rt, 1 h,
(f) H_2SO_4/H_2O, 60 °C, 1 h,

nose 3 and D-sarmentose 5 were obtained in 29.6 % and 15.8 % overall yiel respectively, from 1. The ^{1}H-NMR spectra of 3 and 5 showed that these com pounds are present (in aqueous solutions) as anomeric mixtures of the py- ranoside and furanoside forms.

By means of similar transformations L-digınose 4 and L-sarmentose 6 (an unnatural ısomer) were synthesized from 2 (Scheme 2).



2 4 6

SCHEME 2

EXPERIMENTAL

General methods: Organic extracts were dried with anhydrous magnesium sulphate. Solutions were concentrated at 40 °C (bath) at ca 17 mmHg. Adsorption chromatography was carried out using Kieselgel 60. For TLC, precoated aluminiumbacked plates (Kieselgel 60 F_{254}, Merck) were used. Melting points were determined on a Kofler melting point apparatus and were uncorrected. IR spectra (KBr discs) were recorded on a Perkin-Elmer 283 B spectrophotometer. Mass spectrometry was performed using a VG-7035 GC/MS/DS instrument (70 eV). NMR spectra were obtained by using a Bruker WP-200 SY spectrometer. Specific rotations were measured at room temperature on a Perkin-Elmer 141 MC polarimeter.

2,3-O-Isopropylidene-D-threo-tetrodialdose 1,1-diethyl dithioacetal 1

Lead(IV)acetate (17.30 g, 39.0 mmol) was added to a well stirred solution of 2,3-O-isopropylidene-D-arabinose diethyl mercaptal[9] in dry benzene (300 ml). After 10 minutes the reaction mixture was filtered through a Celite pad, washed with benzene (2x100 ml). The benzene solution was washed with saturated aqueous $NaHCO_3$ (2x180 ml). The combined aqueous phase was reextracted with benzene (2x100 ml). The organic layers were washed with $NaHCO_3$ solution (50 ml) again. The dried benzene extracts were evaporated to give crude 1 as a light yellow syrup (9.30 g, 99.0 %), which was utilized for the next step without further purification. 1 was characterized in the form of its p-nitro-phenylhydrazone: m.p. 110-1 °C. $[\alpha]_D$-8.3 (c 1.32, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ1.17-1.36 (m, 6H, $CH_2\underline{CH_3}$), 1.46 and 1.55 (2s, 6H, $C(\underline{CH_3})_2$), 2.64-2.92 (m, 4H, $SC\underline{H_2}$), 3.97 (d, 1H, H-1), 4.44 (dd, 1H, H-2),

4.79 (dd, 1H, H-3), 7.00-7.13 and 8.12-8.24 (m, 4H, ArCH), 7.19 (dd, 1H, H-4), 8.05 (br, 1H, NH) ppm. Anal. Calcd for $C_{17}H_{25}N_3O_4S_2$: N, 10.52. Found: N, 10.58.

2,3-O-Isopropylidene-L-threo-tetrodialdose 1,1-diethyl dithioacetal 2

A dry benzene (290 ml) solution of 2,3-O-isopropylidene-D-glucose diethyl mercaptal[10] (9.00 g, 27.6 mmol) was treated with lead(IV)acetate (26.87 g, 60.6 mmol). The reaction and the work up were carried out as in preparation of 1 affording 2 (7.12 g, 97.7 %) as a yellow syrup. p-Nitro-phenylhydrazone of 2: m.p. 109-10 °C. $[\alpha]_D$ +8.4 (c 1.30, $CHCl_3$). Anal. Calcd for $C_{17}H_{25}N_3O_4S_2$: N, 10.52. Found: N, 10.67.

2 can also be prepared starting from 2,3-O-isopropylidene-L-arabinose-diethyl dithioacetal[9] following the same procedure as described for 1.

4,5-Dideoxy-2,3-O-isopropylidene-D-threo-hex-4E-eno-dialdose 1,1-diethyl dithioacetal 7

A solution of 1 (5.89 g, 22.3 mmol) and formylmethylenetriphenyl-phosphorane[11] (7.12 g, 23.4 mmol) in dry benzene (170 ml) was heated at reflux for 50-60 minutes. Evaporation of the reaction mixture in vacuum afforded a residue which was chromatographed with hexanes-EtOAc (10:1) mixture as eluent, to give 7 (5.01 g, 77.4 %) as an oil: $[\alpha]_D$ +36.1 (c 1.94, $CHCl_3$). IR: 1695 cm^{-1} (CHO). MS m/e: 290 (M^+). ^{1}H-NMR ($CDCl_3$): δ1.20-1.35 (2t, 6H, CH_2CH_3), 1.43 and 1.52 (2s, 6H, $C(CH_3)_2$), 2.65-2.87 (m, 4H, SCH_2), 3.97 (d, 1H, H-1), 4.10 (dd, 1H, H-2), 4.79 (m, 1H, H-3), 6.45 (ddd, 1H, $J_{4,5}$= 15 Hz, $J_{5,6}$= 7.5 Hz, $J_{3,5}$= 1.5 Hz, H-5), 6.96 (dd, 1H, $J_{4,5}$= 15 Hz, $J_{3,4}$= 4,5 Hz, H-4), 9.63 (d, 1H, $J_{5,6}$= 7.5 Hz, CHO) ppm. Anal. Calcd for $C_{13}H_{22}O_3S_2$: C, 53.76, H, 7.64. Found: C, 53.50, H, 7.51.

5-Deoxy-2,3-O-isopropylidene-4-O-methyl-D-arabino and L-xylo-hexodialdose 1,1-diethyl dithioacetal 8a,b

A solution of 7 (3.55 g, 12.2 mmol) and a catalytic amount of sodium methoxide (3.3 mg, 0.06 mmol) in dry methanol (72 ml) was kept overnight at room temperature. Addition of some drops of water, evaporation of methanol, dissolution of the residue in dichloromethane, and washing the solution with saturated $NaHCO_3$ afforded, after evaporation of the solvent, 8a,b (3.91 g, 99.2 %) as an oil. The ratio of the D-arabino and L-xylo isomers was 9 to 5. ^{1}H-NMR ($CDCl_3$): δ1.20-1.35 (m, 6H, CH_2CH_3), 1.35-1.50 (each 2s, 6H, $C(CH_3)_2$), 2.62-2.83 (m, 6H, SCH_2 and H-5), 3.42 and 3.45 (each s, 3H, OCH_3), 3.8-4.4 (m, 4H, H-1, H-2, H-3, H-4), 9.84-9.89 (q, 1H, CHO) ppm. Anal. Calcd for $C_{14}H_{26}O_4S_2$: S, 19.88. Found: S, 19.53.

5-Deoxy-2,3-O-izopropylidene-4-O-methyl-D-arabino- and L-xylo-hexodialdose 1,1-diethyl dithioacetal 6,6-dimethyl acetal 9a,b

To a stirred solution of 8a,b (3.80 g, 11.8 mmol) in 2,2-dimethoxypropane (17.0 ml) dry methanol (2.00 ml) and a catalytic amount of p-toluene-

sulfonic acid monohydrate was added. After 1 hour the reaction mixture was partitioned between dichloromethane (100 ml) and saturated $NaHCO_3$ solution (15 ml). The organic layer was concentrated and the residue was purified by chromatography using hexanes-acetone (15:1) mixture as eluent to give 9a,b (3.90 g, 90.0 %). ^{1}H-NMR ($CDCl_3$): δ1.21-1.33 (m, 6H, $CH_2\underline{CH_3}$), 1.38-1.49 (each 2s, 6H, $C(\underline{CH_3})_2$), 1.85-1.95 (m, 2H, H-5), 2.65-2.85 (m, 4H, $S\underline{CH_2}$), 3.35 and 3.36 (each s, 6H, $CH(O\underline{CH_3})_2$), 3.43 and 3.45 (each s, 3H, $O\underline{CH_3}$), 3.5-4.7 (m, 5H, H-1, H-2, H-3, H-4, H-6) ppm. Anal. Calcd for $C_{16}H_{32}S_2O_5$: C, 52.14, H, 8.75. Found: C, 51.81, H, 8.56.

2,6-Dideoxy-4,5-O-isopropylidene-3-O-methyl-D-lyxo-hexose dimethyl acetal 10a and 2,6-dideoxy-4,5-O-isopropylidene-3-O-methyl-D-xylo-hexose dimethyl acetal 10b

To a solution of 9a,b (3.83 g) in ethanol (190 ml) Raney-nickel (57.5 g) was added and the mixture was refluxed for 5 hours. After filtration through a Celite pad and efficient washing, the filtrate was evaporated in vacuum and the two diastereoisomers were separated using column chromatography, eluting with hexanes-Et_2O-EtOAc (30:3:1) to yield pure 10a (1.16 g, 45.1 %) and 10b (0.65 g, 25.1 %) as oils. Compound 10a had $[\alpha]_D$ +12.2 (c 0.66, $CHCl_3$) ^{1}H-NMR ($CDCl_3$): δ1.33 (d, 3H, H-6), 1.39 and 1.40 (2s, 6H, $C(\underline{CH_3})_2$), 1.76--1.87 (m, 2H, H-2), 3.35 (s, 6H, $CH(O\underline{CH_3})_2$), 3.44 (s, 3H, $O\underline{CH_3}$), 3.2-4.7 (m, 4H, H-1, H-3, H-4, H-5) ppm. Anal. Calcd for $C_{12}H_{24}O_5$: C, 58.04, H, 9.74, Found: C, 57.92, H. 9.76. 10b: $[\alpha]_D$ -9.2 (c 0.62, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.32 (d, 3H, H-6), 1.40 and 1.41 (2s, 6H, $C(\underline{CH_3})_2$), 1.73-1.89 (m, 2H, H-2), 3.36 (s, 6H, $CH(O\underline{CH_3})_2$), 3.46 (s, 3H, $O\underline{CH_3}$), 3.3-4.7 (m, 4H, H-1, H-3, H-4, H-5) ppm. Anal. Calcd for $C_{12}H_{24}O_5$: C, 58.04, H, 9.74. Found: C, 57.95, H, 9.68.

2,6-Dideoxy-3-O-methyl-D-lyxo-hexose (D-Diginose) 3

10a (510 mg) was dissolved in 0.05 M methanolic H_2SO_4 (14.5 ml). After an hour water (15 ml) was added to the solution and methanol was removed with several additions and reevaporations of water leaving 10-15 ml of opalesque solution. After being stirred for an hour at 60 ^oC the mixture was neutralized by the addition of a strongly basic anion-exchange resin (DOWEX-1, OH^- form) which, after 30 minutes stirring, was removed by filtration and thorough washing with methanol. The filtrate was evaporated and the residue was purified by chromatography using CH_2Cl_2-MeOH (9:1) mixture as eluent to give 3 (316 mg, 94.9 %): m.p. 84-6 ^oC. $[\alpha]_D$ +70.1 $\rightarrow$ +55.8 (equilibrium, c 1.00, H_2O), lit[4].: $[\alpha]_D^{18}$ +56.2 (c 0.68, H_2O), lit[7].: $[\alpha]_D^{19}$ -60 (c 0.7, H_2O) (for L-Diginose). ^{1}H-NMR (D_2O) (mixture): δ1.1-1.3 (m, 3H, H-6), 1.4-2.2 (m, 2H, H-2), 3.4 (s, 3H, $O\underline{CH_3}$). Anal. Calcd for $C_7H_{14}O_4$: C, 51.84, H, 8.70. Found: C, 52.10, H, 8.33.

2,6-Dideoxy-3-O-methyl-D-xylo-hexose (D-Sarmentose) 5

Starting from 10b, 5 was prepared as described for 3, yield 91.0 %. m.p. 62-4 °C. $[\alpha]_D$ +5.6 ⟶ +14.4 (equilibrium, c 0.88, H_2O), lit[6].: $[\alpha]_D^{23}$ +16.6 (c 2.01, H_2O). ^{1}H-NMR (D_2O) (mixture): δ1.05-1.15 (m, 3H, H-6), 1.45--2.25 (m, 2H, H-2), 3.4 (s, 3H, OCH_3). Anal. Calcd for $C_7H_{14}O_4$: C, 51.84, H, 8.70. Found: C, 52.28, H, 8.42.

All of the compounds in the synthesis of L-diginose 4 and L-sarmentose 6, starting from 2, gave satisfactory spectroscopic evidence and elemental analysis.

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