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Total stereo- and enantio-selective synthesis of 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentose and its ethyl furanosides

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ABSTRACT

A total stereo- and enantio-selective synthesis of 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentose and its ethyl furanosides is described. The key reaction of the synthesis is formation of the 3-*C*-methylene function by catalytic isomerisation of an epoxy alcohol, obtained by silylation of 3-methyl-2-butenal, followed by condensation of the silyl ether with triethyl orthoformate, reduction of the aldehydo group, and Sharpless asymmetric epoxidation of the allylic alcohol. The overall yield is 17% from commercially available 3-methyl-2-butenal as the starting compound.

INTRODUCTION

Monosaccharides, which contain exocyclic double bonds are valuable compounds for use as starting materials in the synthesis of branched and functionally substituted carbohydrates[1,2]. It is well known, for example, that various 3′-substituted nucleosides show antiretroviral activity[3,4]. Thus, 2-deoxypentoses with an exocyclic double bond at the C-3 position might be very interesting as precursors of 3-*C*-methylene derivatives of nucleosides. We have found no communications dealing with synthesis of such deoxy 3-*C*-methylene-modified sugars.

RESULTS AND DISCUSSION

We have developed the method of total stereo- and enantio-selective synthesis of 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentose (**9**) and its ethyl furanosides **7** and **8** as shown in Scheme 1.

Condensation of 3-methyl-1-trimethylsilyloxy-1,3-butadiene (**2**, which was obtained in 72% yield by silylation of 3-methyl-2-butenal (**1**) with chlorotrimethylsilane according to a well-known method[5] with triethyl orthoformate in presence of $ZnCl_2$[6]) gave 5,5-diethoxy-3-methyl-2-pentenal (**3**) in 60% yield. Compound **3** was shown to be a 75:25 mixture of (*E*)-5,5-diethoxy-3-methyl-2-pentenal (**3a**) and (*Z*)-5,5-diethoxy-3-

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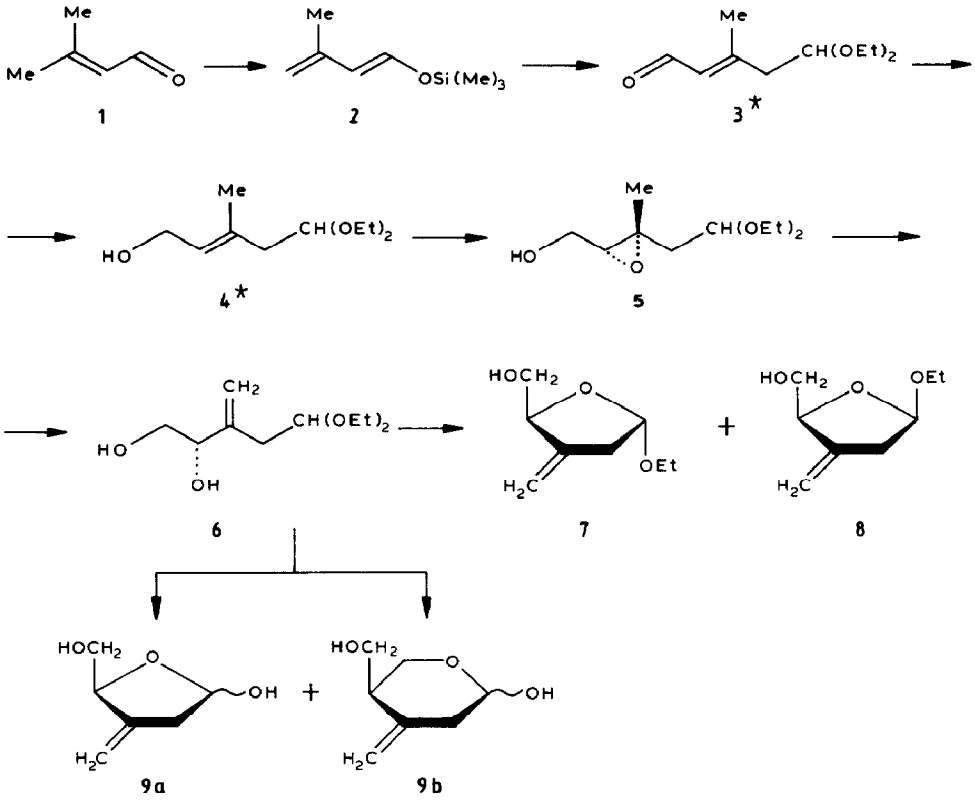

*Only the *(E)* –isomers of compounds 3 and 4 are represented.

Scheme 1.

methyl-2-pentenal (**3b**), respectively, as determined by ^{1}H-n.m.r. spectroscopy. The mixture was reduced by Red-Al® [sodium bis(2-methoxyethoxy)aluminum hydride] and again gave a 75:25 mixture off (*E*)- and (*Z*)-5,5-diethoxy-3-methyl-2-penten-1-ol (**4a** and **4b**, respectively) in 81% yield.

Since our goal was to obtain carbohydrates of the D-configuration, bis(2-propyl) D(−)-tartrate was used in the reaction as dictated by the Sharpless enantioselectivity rule[7,8].

As it is known that asymmetric epoxidation of an *E* double bond of allylic alcohols goes much faster than that for the *Z* double bond[7], the mixture was subjected to the Sharpless asymmetric epoxidation[9] without preliminary separation. Analysis of the reaction mixture by n.m.r. spectroscopy showed that the ratio of epoxides obtained from *E* and *Z* isomers was 98:2, respectively. Column chromatography of the reaction mixture gave (2*R*,3*R*)-2,3-epoxy-5,5-diethoxy-3-methylpentanol (**5**) in 90% yield, if only the *E* alcohol **4a** is taken into consideration. An e.e. of 95% for compound **5** was determined by ^{1}H-n.m.r. spectroscopy of the Mosher ester derivative[10].

TABLE I

^{1}H-N.m.r. data (δ, p.p.m.) for compounds **5–8**[a]

Compound	*H-1*	*H-2*	*H-2'*	*H-4*	*H-5*	*H-5'*	CH_3	$=CH_2$
5[b]	4.61	1.63	1.89	2.90	3.55	3.68	1.26	—
6	4.63	2.31	2.38	4.12	3.42	3.57	—	4.99 5.14
7	5.15	2.41	2.67	4.41	3.53	3.62	—	4.98
8	5.12	2.47	2.76	4.49	3.57	3.57	—	5.01

Coupling constants (Hz)

Compound	$J_{1,2}$	$J_{1,2'}$	$J_{2,2'}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
5	6.2	5.0	14.0	6.1	4.7	11.9
6	5.6	5.6	14.8	7.0	4.0	11.2
7	1.2	5.2	16.0	4.0	5.3	11.4
8	0.7	5.6	16.5	5.5	5.5	—

[a] In acetone-d_6. [b] Numbering of the H-atoms corresponds to the numbering of the sugar H-atoms in compounds **6–8**.

(2*R*,3*R*)-2,3-Epoxy-5,5-diethoxy-3-methylpentanol (**5**) was used as the starting compound for the preparation of 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentose (**9**). We managed to synthesize the acyclic acetal **6** in 87% yield by refluxing epoxy alcohol **5** in benzene in the presence of a catalytic amount of titanium(IV) 2-propoxide for 3 h. Then cyclization of **6** in ethanol in presence of trace amount of HCl gave the α and β anomers of ethyl 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentofuranosides (**7** and **8**) in a 7:3 ratio as determined by n.m.r. spectroscopy (Tables I and II).

As we intended to use these glycosides in a nucleoside synthesis, it was necessary to develop a selective method of synthesis for **7** and **8**. We researched in detail the effect of acyclic acetal concentration, HCl concentration, temperature, and process duration on the ratio of pyranosides:furanosides. From these studies we have managed to establish a set of conditions for the near-exclusive formation of furanosides **7** and **8**. (The α and β anomers of ethyl 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentopyranosides in the mixture was determined to be $<0.5\%$ from the ^{13}C-n.m.r. spectral data.)

Column chromatographic separation of **7** and **8** resulted in the isolation of ethyl 2,3-dideoxy-3-*C*-methylene-α-D-*glycero*-pentofuranoside (**7**) in 62% yield and ethyl 2,3-dideoxy-3-*C*-methylene-β-D-*glycero*-pentofuranoside (**8**) in 22% yield.

Hydrolysis of the acyclic acetal **6** in presence of QU-2 (H^+) ion-exchange resin gave 2,3-dideoxy-3-*C*-methylene-D-*glycero*-pentose (**9a, 9b**) as a mixture of furanose (**9a**) and pyranose (**9b**) forms (Table II) in 84% yield (overall yield, 17%, in six steps).

TABLE II

^{13}C-N.m.r. data (δ, p.p.m.) for compounds **5–9**[a]

Compound	*Anomer*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-3'*	OC_2H_5
5[b]	—	101.30	43.59	58.30	63.84	61.45	17.70	61.25 61.93 15.58
6	—	103.25	37.38	146.06	75.57	66.24	113.35	61.86 61.59 15.51
7	α-D-furanoside (70%)	103.15	40.63	148.48	81.13	65.62	105.67	62.64 15.42
8	β-D-furanoside (30%)	103.46	40.73	147.95	82.84	67.00	106.24	62.94 15.31
9a	α-D-furanose (12%)	97.14	41.42	148.24	80.90	65.54	106.13	—
	β-D-furanose (12%)	97.75	41.93	147.65	82.43	65.77	106.59	—
9b	α-D-pyranose (38%)	93.82	41.11	145.86	69.52	69.11	108.47	—
	β-D-pyranose (38%)	96.14	40.07	145.34	69.35	67.19	109.15	—

[a] In acetone-d_6. [b] Numbering of the C-atoms corresponds to the C-atom numbering in compounds **6–9**.

EXPERIMENTAL

General methods. — N.m.r. spectra were recorded with either a Bruker CXP 200 (200 MHz, ^{1}H; 50 MHz, ^{13}C) or AM 360 (360 MHz ^{1}H; 90 MHz, ^{13}C) instrument for solutions in acetone-d_6. Optical rotations were determined with a Perkin–Elmer model 141 spectropolarimeter. T.l.c. was conducted on Silufol UV_{254} (Kavalier, Czechoslovakia) in 1:10 methanol–chloroform with detection by heating. Column chromatography was conducted on Silica Gel 60 (E. Merck).

3-Methyl-1-trimethylsilyloxy-1,3-butadiene (**2**). — To a suspension of anhydrous sodium iodide (180 g, 1.20 mol) in dry acetonitrile (300 mL) were added triethylamine (112 g, 1.11 mol), 3-methyl-2-butenal (**1**) (84.0 g, 1.00 mol), and pentane (400 mL) at room temperature, followed by the dropwise addition of chlorotrimethylsilane (109 g, 1.00 mol) at 35–38°. The mixture was stirred for 4 h at 40–45°, the resulting solid was filtered and washed with pentane (400 mL), and the solvent was evaporated at room temperature. Distillation of the residue gave **2** (112 g, 72%): b.p. 56–60°/35 torr; n_D^{20} 1.4496.

Anal. Calc. for $C_8H_{16}OSi$: C, 61.48; H, 10.32; Si, 17.97. Found: C, 61.59; H, 10.24; Si, 17.68.

5,5-Diethoxy-3-methyl-2-pentenal (**3**). — To a mixture of triethyl orthoformate (104 g, 703 mmol) and a 15% solution of $ZnCl_2$ in ethyl acetate was added **2** (109 g, 699 mmol), dropwise with stirring at room temperature. After 1 h at room temperature, saturated aq. $NaHCO_3$ (600 mL) was added. The resulting precipitate was filtered and washed with ether (600 mL). The aqueous phase was separated, the organic phase was washed with saturated aq. $NaHCO_3$ (200 mL), dried (K_2CO_3), and concentrated. Distillation of the residue gave **3** (78.0 g, 60%): b.p. 68–70°/3 torr; n_D^{20} 1.4590; ^{13}C-n.m.r. data for E-isomer **3a**: δ 191.12 (*C*HO), 159.71 (C-3), 129.85 (C-2), 101.74 (C-5), 61.75 (Et), 45.13 (C-4), 18.13 (CH_3), 15.46 (Et); for *Z*-isomer **3b**: 191.20 (*C*HO), 159.04 (C-3), 130.27 (C-2), 62.61 (Et), 38.00 (C-4), 26.17 (CH_3), 15.56 (Et).

Anal. Calc. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.72; H, 9.89.

5,5-Diethoxy-3-methyl-2-penten-1-ol (**4**). — Red-Al® (200 mL of a 30% solution in toluene, Aldrich) was added dropwise with stirring at 0° to a solution of **3** (50.0 g, 268 mmol) in ether (50 mL), and the mixture was stirred for 1 h at 0–5°. Saturated aq. NH_4Cl was then added dropwise at 0–5°, and the mixture was stirred for 30 min at 10–15°. The solid which precipitated was filtered and washed with ether (300 mL). The organic phase was separated, dried (K_2CO_3), and concentrated. Distillation of the residue gave **4** (41.0 g, 81%): b.p. 93–96°/0.5 torr; n_D^{20} 1.4550; ^{13}C-n.m.r. data for *E*-isomer **4a**: δ 133.44 (C-3), 128.45 (C-2), 102.76 (C-5), 61.32 (Et), 58.96 (C-1), 44.31 (C-4), 16.90 (CH_3), 15.54 (Et); for *Z*-isomer **4b**: 134.25 (C-3), 128.51 (C-2), 102.61 (C-5), 62.11 (Et), 58.69 (C-1), 37.45 (C-4), 21.62 (CH_3), 15.60 (Et).

Anal. Calc. for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.71; H, 10.75.

(2R,3R)-5,5-Diethoxy-2,3-epoxy-3-methylpentanol (**5**). — A mixture of powdered, activated 4A molecular sieves (5 g) and CH_2Cl_2 (300 mL) was cooled to −20°. Bis-(2-propyl) D(−)-tartrate (3.51 g, 15.0 mmol), titanium(IV) 2-propoxide (2.84 g,

10.0 mmol), and *tert*-butyl hydroperoxide (45.5 mL, 4.4M in CH_2Cl_2) were added sequentially at −20°, and the resulting mixture was stirred for 30 min. A solution of **4** (18.8 g, 100 mmol) in CH_2Cl_2 (20 mL) was then added dropwise, and stirring was maintained for 8 h at −20°. At the end of this time, a 10% aq. solution of NaOH saturated with sodium chloride (8 mL) was added at −20°, and anhydrous $MgSO_4$ (8 g) with Celite (1 g) were added at +10°. The mixture was stirred for 15 min and was then allowed to stand for an additional 1 h. The resulting suspension was filtered through a Celite pad, and the solid was washed with ether (3 × 50 mL) and filtered, and the washings were combined, dried ($MgSO_4$), and evaporated. Column chromatography (hexane–ether, gradient elution) of the residue on silica gel gave **5** (13.7 g, 67%): R_F 0.36; n_D^{20} 1.4465; $[\alpha]_D$ +19° (*c* 3.5, methanol). For ^{1}H- and ^{13}C-n.m.r. data, see Table I and II, respectively.

Anal. Calc. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.76; H, 9.88.

2,3-Dideoxy-3-C-methylene-D-glycero-*pentose diethyl acetal* (**6**). — To a solution of **5** (2.04 g, 10.0 mmol) in benzene (80 mL) at 20° was added titanium(IV) 2-propoxide (1.42 g, 5.00 mmol). The mixture was refluxed for 3 h, then cooled to room temperature. Ether (30 mL) and saturated aq. $NaHCO_3$ (2 mL) were added and stirred for 30 min. The suspension was filtered through Celite pad, the solid was washed with ether (3 × 10 mL), and the solvent was evaporated. Column chromatography (20:1 chloroform–methanol) of the residue on silica gel gave **6** (1.78 g, 87%) as a syrup: R_F 0.27; $[\alpha]_D$ +12° (*c* 2.2, methanol). For ^{1}H- and ^{13}C-n.m.r. data, see Tables I and II, respectively.

Anal. Calc. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.83; H, 9.85.

*Ethyl 2,3-dideoxy-3-*C*-methylene-α-*D*-glycero-pentofuranoside* (**7**) *and ethyl 2,3-dideoxy-3-*C*-methylene-β-*D*-glycero-pentofuranoside* (**8**). — To a solution of **6** (1.75 g, 8.58 mmol) in dry ethanol (230 mL) was added a 10% solution of HCl in ethanol (0.22 mL) at room temperature. The mixture was stirred for 30 min, then K_2CO_3 (0.1 g) was added, and the mixture was stirred for an additional 1 h. The solid was filtered and washed with dry ether (3 × 10 mL), and the solvent was evaporated. Column chromatography (chloroform) of the residue on silica gel gave **7** (0.84 g, 62%) as a syrup: R_F 0.42; $[\alpha]_D$ +218° (*c* 2.0, methanol). Then eluted compound **8** (0.30 g, 22%) also as a syrup: R_F 0.49, $[\alpha]_D$ −89° (*c* 1.9, methanol). For ^{1}H- and ^{13}C-n.m.r. data, see Tables I and II, respectively.

Anal. Calc. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found for **7**: C, 60.70; H, 8.91; found for **8**: C, 60.78; H, 8.96.

*2,3-Dideoxy-3-*C*-methylene*-D-glycero-*pentose* (**9a, 9b**). — To a solution of **6** (2.04 g, 10.0 mmol) in water (40 mL) was added QU-2 (H^+) ion-exchange resin (0.4 g), and the mixture was stirred for 3 h at room temperature. The resin was then filtered and washed with water (2 × 5 mL), and to the filtrate was added $BaCO_3$ (0.6 g). The mixture was stirred for 30 min, the solid was filtered, the water was evaporated, and compound **9** was obtained (1.09 g, 84%) as a syrup: R_F 0.17; $[\alpha]_D$ +4° (*c* 2.0, H_2O). For ^{1}H- and ^{13}C-n.m.r. data, see Tables I and II, respectively.

Anal. Calc. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.33; H, 7.70.

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