Carbohydrate Research, 118 (1983) 286–291
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Knoevenagel–Doebner condensations with 2,4-*O*-ethylidene-D-erythrose and -threose

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(Received July 12th, 1982; accepted for publication, February 14th, 1983)

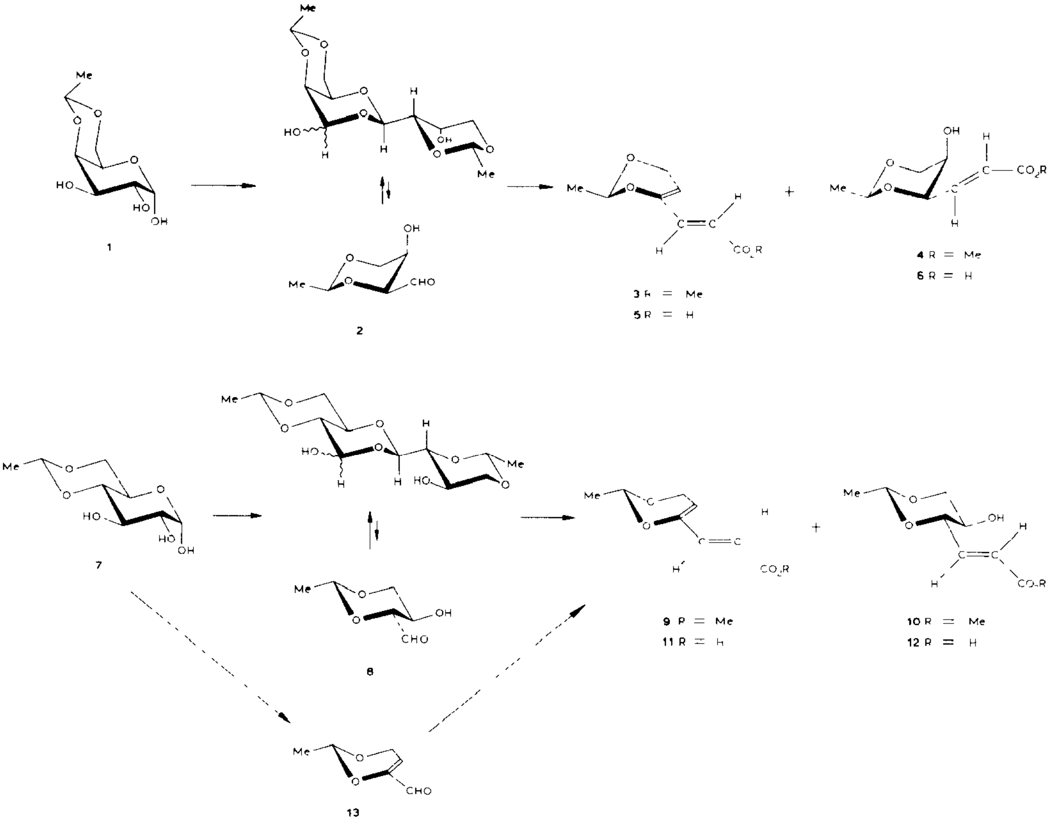
The Knoevenagel–Doebner reaction of aldehydo sugars with monomethyl malonate and malonic acid yields α,β-unsaturated derivatives, corresponding to a dehydration–decarboxylation process, as previously described for 2,3-*O*-isopropylidene-D-glyceraldehyde[1]. These unsaturated derivatives are useful for the synthesis of polyhydroxyalkylheterocycles[2] that are structurally closely related to *C*-nucleosides.

Condensation of 2,4-*O*-(*S*)-ethylidene-D-threose (**2**) and 2,4-*O*-(*R*)-ethylidene-D-erythrose (**8**) severally with monomethyl malonate and malonic acid gave the α,β-unsaturated esters methyl (*E*)-2,3-dideoxy-4,6-*O*-(*S*)-ethylidene-D-*threo*-hex-2-enonate (**4**) and methyl (*E*)-2,3-dideoxy-4,6-*O*-(*R*)-ethylidene-D-*erythro*-hex-2-enonate (**10**), and the acids (*E*)-2,3-dideoxy-4,6-*O*-(*S*)-ethylidene-D-*threo*-hex-2-enonic acid (**6**) and (*E*)-2,3-dideoxy-4,6-*O*-(*R*)-ethylidene-D-*erythro*-hex-2-enonic acid (**12**), by a decarboxylation–dehydration process. However, owing to the presence of one free hydroxyl group in each of the starting sugars, the enantiomeric pairs, methyl (2*E*,4*Z*)-4,6-*O*-(*S*)-ethylidene-4,6-dihydroxyhexa-2,4-dienoate (**3**) and methyl (2*E*,4*Z*)-4,6-*O*-(*R*)-ethylidene-4,6-dihydroxyhexa-2,4-dienoate (**9**), and (2*E*,4*Z*)-4,6-*O*-(*S*)-ethylidene-4,6-dihydroxyhexa-2,4-dienoic (**5**) and (2*E*,4*Z*)-4,6-*O*-(*R*)-ethylidene-4,6-dihydroxyhexa-2,4-dienoic acid (**11**) were also isolated, resulting from a double dehydration.

The yield of the doubly unsaturated compounds was higher for the threose derivatives than for erythrose derivatives, probably because of the more favourable dehydration process in the threose derivatives, where H-2 and HO-3 are *trans*-diaxial. The above condensations gave good yields, in spite of the fact that the tetrose derivatives did not have a free aldehyde group but were present as dimeric cyclic-acetals. A small increase in the reaction temperature up to 60–70° resulted in a satisfactory reaction-velocity. Compound **2**, in a dimeric form without a free aldehyde group, was obtained from 4,6-*O*-(*S*)-ethylidene-D-galactose (**1**), as previously reported[3,4].

The condensation of **2** severally with monomethyl malonate and malonic acid

0008-6215/83/$ 03.00



yielded the esters **3** (45%) and **4** (30%), and the acids **5** (51.5%) and **6** (24%), respectively. Similarly, condensation of **8**, prepared[5] as a dimeric cyclic-acetal[6–8] from 4,6-*O*-(*R*)-ethylidene-D-glucose (**7**), reacted severally with monomethyl malonate and malonic acid, to yield the esters **9** (4%, only traces in some experiments) and **10** (72.7%), and the acids **11** (16%) and **12** (40%), respectively. Compound **9** was also obtained by condensation of (*Z*)-2,4-*O*-(*R*)-ethylidene-2,4-dihydroxybut-2-enal (**13**) (prepared by oxidation of **7** with lead tetra-acetate in dry benzene) with monomethyl malonate under similar conditions, and **12** by saponification of **10**.

In the various condensation products, the configuration of the double bond conjugated with the carbonyl group was *trans*, as shown (Table I) by the high value (15–16 Hz) of the coupling constant for the vinylic hydrogens.

The base-catalysed epimerisation at C-4, reported in similar Knoevenagel reactions[9,10], prompted confirmation of the C-4 assignments in **4**, **6**, **10**, and **12**. The weaker basic character of reagent and solvent in the Wittig reaction than in the Knoevenagel reaction has been reported[10,11] as a convenient assay for these assignment studies, and we obtained a product identical with **4** by the Wittig reaction of **2** and (methoxycarbonylmethylene)triphenylphosphorane, which confirms the configuration assigned.

TABLE I

^{1}H-N M R DATA

Chemical shifts (δ scale)

Compound	*H-2*	*H-3*	*H-4*	*H-5*	*H-6,6'*	*Ethylidene*		*OMe*	*OH*	*COOH*
						CH	*CH_3*			
3^a	5.95 d	6.70 d	—	5.10 t	4.22 d	4.82 q	1.40 d	3.60 s	—	—
4^b	6.05 dd	6.80 dd	4.50 m	← 4.05–3.87 3.60–3.46	m →	4.75 q	1.40 d	3.70 s	2.75 s	—
5^b	6.18 d	7.03 d	—	5.35 t	4.30 d	5.03 q	1.50 d	—	—	9.70 bs
6^b	6.02 dd	6.85 dd	4.35 m	← 4.10–3.90 3.70–3.50	m →	4.75 q	1.45 d	—	← 6.60–6.40 bs →	
9^a	5.95 d	6.70 d	—	5.10 t	4.22 d	4.82 q	1.40 d	3.60 s	—	—
10^a	5.95 dd	6.89 dd	← 4.30–3.10 m →			4.57 q	1.27 d	3.65 s	4.30–3.10	—
11^b	6.13 d	7.03 d	—	5.35 t	4.30 d	5.03 q	1.50 d			8.40 bs
12^b	6.14 dd	7.16 dd	←	4.5–3.80 3.65–3.30	m →	4.73 q	1.35 d		← 6.50–6.30 bs →	

^{a}CCl$_4$. ^{b}CDCl$_3$

J values (Hz)

Compound	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{5,6}=J_{5,6'}$	$J_{ethylidene}$
3	15	—	—	3	5
4	16	2	3.5	—	5
5	15.5	—	—	4	5
6	15	3	4	—	5
9	15	—	—	3	5
10	16	2	4	—	5
11	15.5	—	—	4	5
12	15.5	1.5	4	—	5

EXPERIMENTAL

General methods. — Melting points were uncorrected. T.l.c. was performed on silica gel GF_{254} (Merck) with hexane–ethyl acetate mixtures: *A*, 1:1; *B*, 1:2; and *C*, 1:4; and detection by charring with sulphuric acid or by u.v. absorption. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, Merck). I.r. spectra (KBr discs) were recorded with a Beckmann Aculab IV spectrometer, and u.v. spectra, for solutions in methanol, with a Beckmann DB-GT spectrometer. ^{1}H-N.m.r. spectra (CCl_4 or $CDCl_3$, internal Me_4Si) were recorded with a Perkin–Elmer R-24B spectrometer, and mass spectra with a Hewlett–Packard 5930 A spectrometer. Optical rotations were measured with a Perkin–Elmer 141 polarimeter.

Knoevenagel–Doebner condensation of tetrose derivatives with monomethyl malonate and malonic acid. — Monomethyl malonate or malonic acid (0.1 mol) and piperidine (0.3 mL) were added to a solution of the tetrose derivative (0.1 mol) in pyridine (40–60 mL). The mixture was stirred at 60–70° for 3–7 h, and the reaction was monitored by t.l.c. The mixture was then concentrated *in vacuo*, and the residue was distilled or subjected to column chromatography (solvent *A* for esters, solvent *B* for acids).

*Condensation of 2,4-*O*-(*S*)-ethylidene-*D*-threose* (**2**) *with monomethyl malonate.* — After reaction for 7 h, the following products were obtained.

Methyl (2*E*,4*Z*)-4,6-*O*-(*S*)-ethylidene-4,6-dihydroxyhexa-2,4-dienoate (**3**, 45%), m.p. 77–79°, $[\alpha]_D^{20}$ −149° (*c* 1, chloroform), R_F 0.90 (solvent *A*); λ_{max} 270 nm (ε 15,400); ν_{max} 1730–1720 (C=O), 1645 and 1615 (C=C), and 960 cm^{-1} (*trans* -CH=CH-). Mass spectrum: *m/z* 184 (M^{+}), 169, 153, 141, 140, 125, and 113 (100%).

Anal. Calc. for $C_9H_{12}O_4$: C, 58.68; H, 6.56. Found: C, 58.42; H, 6.53.

Methyl (*E*)-2,3-dideoxy-4,6-*O*-(*S*)-ethylidene-D-*threo*-hex-2-enonate (**4**, 30%), m.p. 78–80°, $[\alpha]_D^{20}$ −87° (*c* 1, chloroform), R_F 0.44 (solvent *A*); λ_{max} 208 nm (ε 27,000); ν_{max} 3500 (OH), 1750 (C=O), 1670 (C=C), and 950 cm^{-1} (*trans* -CH=CH-). Mass spectrum: *m/z* 202 (M^{+}), 187, 171, 159, 158, 141, and 115 (100%).

Anal. Calc. for $C_9H_{14}O_5$: C, 53.45; H, 6.97. Found: C, 53.44; H, 7.14.

*Condensation of 2,4-*O*-(*S*)-ethylidene-*D*-threose* (**2**) *with malonic acid.* — After reaction for 3 h, the following products were obtained.

(2*E*,4*Z*)-4,6-*O*-(*S*)-Ethylidene-4,6-dihydroxyhexa-2,4-dienoic acid (**5**, 51.5%), m.p. 133–135° (from chloroform), $[\alpha]_D^{20}$ −115° (*c* 1, chloroform), R_F 0.44 (solvent *A*) and 0.73 (solvent *B*); λ_{max} 270 nm (ε 18,300); ν_{max} 3100–2550 (COOH), 1710–1680 (C=O), 1640 and 1620 (C=C), and 970 cm^{-1} (*trans* -CH=CH-). Mass spectrum: *m/z* 171 (M + 1), 170 (M^{+}), 153, 126, 125, and 109 (100%).

Anal. Calc. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.24; H, 6.16.

(*E*)-2,3-Dideoxy-4,6-*O*-(*S*)-ethylidene-D-*threo*-hex-2-enonic acid (**6**, 24%), m.p. 127–128° (from chloroform), $[\alpha]_D^{20}$ −77° (*c* 1, chloroform), R_F 0.11 (solvent *A*) and 0.22 (solvent *B*); λ_{max} 220 nm (ε 3,400); ν_{max} 3600–3100 (COOH, OH), 1710 (C=O), 1680–1660 (C=C), and 970 cm^{-1} (*trans* -CH=CH-).

Anal. Calc. for $C_8H_{12}O_4$: C, 51.08; H, 6.43. Found: C, 51.20; H, 6.40.

*Condensation of 2,4-O-(R)-ethylidene-*D*-erythrose* (**8**) *with monomethyl malonate.* — After reaction for 7 h, the following products were obtained.

Methyl (2*E*,4*Z*)-4,6-*O*-(*R*)-ethylidene-4,6-dihydroxyhexa-2,4-dienoate (**9**, 4%), colourless liquid, b.p. 108–110°/1 mmHg, which solidified at room temperature; $[\alpha]_D^{20}$ +150° (*c* 1, chloroform); R_F 0.90 (solvent *A*). λ_{max} 270 nm (ε 15,600); ν_{max} 1730–1720 (C=O), 1645 and 1615 (C=C), and 960 cm^{-1} (*trans* -CH=CH-).

Methyl (*E*)-2,3-dideoxy-4,6-*O*-(*R*)-ethylidene-D-*erythro*-hex-2-enonate (**10**, 72.7%), colourless liquid, b.p. 130–135°/1 mmHg; m.p. 68–69° (from hexane); $[\alpha]_D^{20}$ −58° (*c* 1, water); R_F 0.55 (solvent *A*); λ_{max} 220 nm (ε 6,500); ν_{max} 3600–3400 (OH), 1710 (C=O), 1650 (C=C), and 940 cm^{-1} (*trans* -CH=CH-).

A mixture of **10** (625 mg, 0.03 mol) and 0.16M NaOH (4 mL) was stored at 100° for 30 min, acidified to pH 4–5 with aqueous 10% HCl, and then extracted with ether (3 × 50 mL). The combined extracts were dried and concentrated, and the residue was dried *in vacuo* and then recrystallised from chloroform, to give **12** (470 mg, 81.5%) (see below).

*Condensation of 2,4-O-(R)-ethylidene-*D*-erythrose* (**8**) *with malonic acid.* — After reaction for 3 h, the following products were obtained.

(2*E*,4*Z*)-4,6-O-(*R*)-Ethylidene-4,6-dihydroxyhexa-2,4-dienoic acid (**11**, 16%), m.p. 133–135° (from chloroform), $[\alpha]_D^{20}$ +120° (*c* 1, chloroform), R_F 0.70 (solvent *B*); λ_{max} 276 nm (ε 18,800), ν_{max} 3100–2550 (COOH), 1710–1680 (C=O), 1640 and 1620 (C=C), and 970 cm^{-1} (*trans* -CH=CH-).

(*E*)-2,3-dideoxy-4,6-*O*-(*R*)-ethylidene-D-*erythro*-hex-2-enonic acid (**12**, 40%), m.p. 93–95° (from chloroform), $[\alpha]_D^{20}$ −55° (*c* 1, chloroform), R_F 0.6 (solvent *C*); λ_{max} 216 nm (ε 6,550); ν_{max} 3500–2600 (COOH, OH), 1710 (C=O), 1670 (C=C), and 980 cm^{-1} (*trans* -CH=CH-).

(Z)-2,4-O-(R)-*Ethylidene-2,4-dihydroxybut-2-enal* (**13**). — A suspension of 4,6-*O*-(*R*)-ethylidene D-glucose (**7**; 10 g, 48 mmol) and lead tetra-acetate (35 g, 105 mmol) in benzene (400 mL) was stirred for 40 min, and then filtered, neutralised with anhydrous K_2CO_3, and concentrated. The residue was distilled at 80°/0.5 mmHg to give a product (2 g) that was subjected to column chromatography (hexane–ethyl acetate, 1:3) to give **13** as colourless liquid, $[\alpha]_D^{20}$ −4° (*c* 1, chloroform), R_F 0.75 (solvent *A*), λ_{max} 250 nm (ε 760); ν_{max} 2810 (CHO), 1750–1690 (C=O), and 1645 cm^{-1} (C=C). ^{1}H-N.m.r. ($CDCl_3$): δ 8.9 (s, 1 H, CHO), 5.9 (t, 1 H, *J* 3 Hz, H-3), 4.9 (q, 1 H, *J* 5 Hz, CHMe), 4.4 (d, 2 H, *J* 3 Hz, H-4), and 1.5 (d, 3 H, *J* 5 Hz, CHMe).

The reaction of **13** with monomethyl malonate at room temperature for 12 h gave **9** (30%).

*Reaction of 2,4-O-(S)-ethylidene-*D*-threose* (**2**) *with (methoxycarbonylmethylene)triphenylphosphorane.* — To a stirred solution of **2** (2 g, 13.6 mmol) in dry benzene (25 mL) at room temperature was added a solution of (methoxycarbonylmethylene)triphenylphosphorane in dry benzene (25 mL). After 2 h, t.l.c. indicated that the reaction was complete. The benzene was evaporated under reduced pressure and the residue was subjected to column chromatography (hexane–ethyl acetate, 2:1), to afford methyl (*Z*)-2,3-dideoxy-4,6-*O*-(*S*)-ethylidene-D-*threo*-hex-2-enonate (1.6 g, 42%), m.p. 41–42° (from hexane), $[\alpha]_D^{20}$ −94° (*c* 1, chloroform), R_F 0.55 (solvent *A*); ν_{max} 3480 (OH), 1720 (C=O), and 1655 cm^{-1} (C=C). ^{1}H-N.m.r. ($CDCl_3$): δ 6.19 (dd, 1 H, *J* 11 and 7 Hz, H-3), 5.77 (dd, 1 H, *J* 11 and 1.5 Hz, H-2), 5.30–5.05 (m, 1 H, H-4), 4.72 (q, 1 H, *J* 5 Hz, CHMe), 4.05–3.50 (m, 3 H, H-5,6,6′), 3.63 (s, 3 H, OMe), 2.60 (bs, 1 H, OH), and 1.3 (d, 2 H, *J* 5 Hz, CHMe).

Anal. Calc. for $C_9H_{14}O_5$: C, 53.45; H, 6.97. Found: C, 53.51: H, 7.02.

Eluted second was a white solid (1 g, 36%) having physical and spectroscopic characteristics identical with those of **4**.

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