Carbohydrate Research, 103 (1982) 158–164
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

The Knoevenagel–Doebner reaction in the synthesis of branched-chain sugar derivatives*

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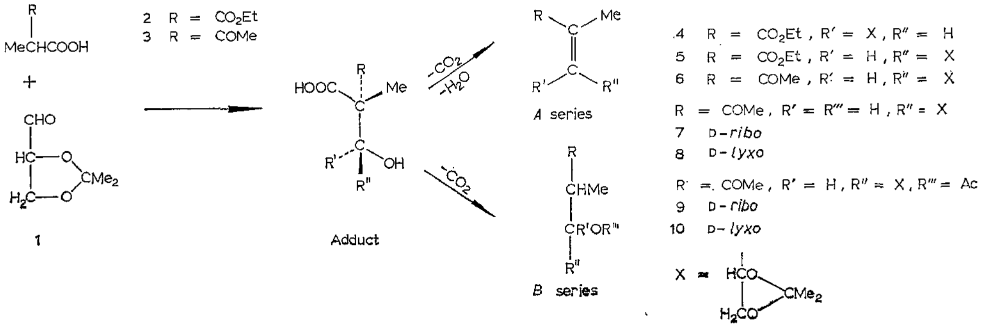
(Received July 27th, 1981; accepted for publication, October 9th, 1981)

The Knoevenagel–Doebner reaction between aldehydo sugars and β-dicarbonyl compounds is an excellent method for the extension of sugar chains. Thus, heptoses have been synthesised[2] by reduction of the corresponding heptonic acids, obtained from the reaction of 2,3:4,5-di-*O*-isopropylidene-L-arabinose with malonic acid and subsequent hydroxylation of the resulting, unsaturated compound. Hexuloses and deoxyhexuloses have been synthesised[3–5] by the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**) with various β-keto acids, and we have now extended this method to the synthesis of C-2 and C-3 branched sugar derivatives, by the reaction of **1** with monoethyl methylmalonate (**2**) and α-methylacetoacetic acid (**3**).

The Knoevenagel–Doebner type condensation between **1** and either **2** or **3** can produce two series of compounds[3–5] involving an addition reaction followed by *A* dehydration–decarboxylation or *B* decarboxylation (Scheme 1). The ratio of these products varies with the reaction conditions and the structure of the β-dicarbonyl compounds.



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*Branched-chain Sugars, Part II. For Part I, see ref. 1.

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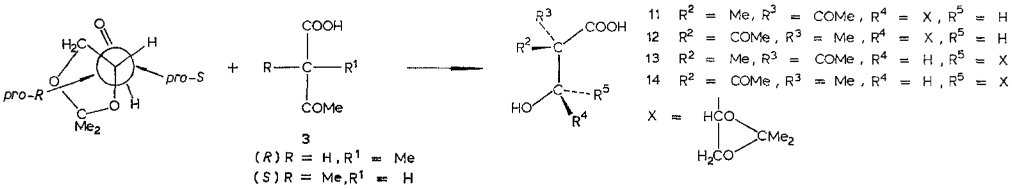
The reactions of **1** with **2** and **3** were performed in pyridine or toluene in the presence of piperidine or diethylamine. Thus, **1** and **2** gave **4***A* and **5***A*, whereas **1** and **3** gave **6***A*, **7***B*, and **8***B*. For the latter reaction, **6** was the major product in pyridine–piperidine, whereas **7** and **8** preponderated in toluene–diethylamine. These findings accord with previous results[3-5] for the reactions of **1** with monoethyl malonate, cyanoacetic acid, acetoacetic acid, and γ-methoxyacetoacetic acid, and reflect the more ready decarboxylation of β-keto acids than of β-dicarboxylic acids.

The reaction of **1** and **2** yielded the *cis* and *trans* forms (**4** and **5**, respectively) of ethyl 2,3-dideoxy-4,5-*O*-isopropylidene-2-*C*-methyl-D-*glycero*-pent-2-enonate, which were separated by column chromatography. The configurations at the double bond in **4** and **5** were indicated by ^{1}H-n.m.r. data. The H-3 and H-4 signals for **4** appeared at δ 6.07 and 5.26, and for **5** at δ 6.70 and 4.87. The ester carbonyl group deshields H-4 in the *cis* isomer, and H-3 in the *trans* isomer. These results accord with those found[6] for other α,β-unsaturated esters. Compound **4** had λ_{max} 227 nm (ε 4850) and **5** had λ_{max} 228 nm (ε 5410), which accord with reported[7] differences observed for *cis* and *trans* isomers.

Compound **6** was identified as *trans*-1,3,4-trideoxy-5,6-*O*-isopropylidene-3-*C*-methyl-D-*glycero*-hex-3-enulose. It had λ_{max} 230 nm (ε 11830), which is close to the absorption reported[3,4] for this kind of α,β-unsaturated ketone. The ^{1}H-n.m.r. signal at δ 6.38, assigned to H-4, indicated the deshielding effect of the carbonyl group on H-4. The structure of **6** was confirmed by its synthesis from **5** by hydrolysis followed by reaction with methyl-lithium.

Four stereoisomeric 1,3-dideoxy-5,6-*O*-isopropylidene-3-*C*-methylhexuloses might be expected from the reaction of **1** with **3**, since two new chiral centres are created. Only two products (**7** and **8**) could be isolated by column chromatography. The isomer of higher mobility (**7**) had $[\alpha]_D$ +22°, and that (**8**) of lower mobility had $[\alpha]_D$ −15°. The absolute configurations at C-4 in **7** and **8** were established by the Horeau method[8] for secondary chiral alcohols, consisting of a partial resolution of a molar excess of racemic α-phenylbutyric anhydride by formation of the corresponding ester, followed by hydrolysis of the excess of anhydride, and measurement of the optical rotation of the isolated acid. Thus, **7** and **8** gave a levorotatory and dextrorotatory acid, respectively, indicating a 4*S* and 4*R* configuration for such compounds, according to Horeau's rule[8]. The configurations at C-3 in **7** and **8** were indicated to be *R* and *S*, respectively, by the ^{1}H-n.m.r. data for the 4-acetates (**9**) and (**10**). The spectrum of **9** showed a triplet at δ 5.19 that was assigned to H-4 ($J_{3,4}$ = $J_{4,5}$ = 6.0 Hz). The *J* values indicate a *trans* disposition of H-3,4,5 in the most favourable conformation and therefore the D-*ribo* configuration. The spectrum of **10** showed a signal for H-4 at δ 5.22 as a double doublet ($J_{3,4}$ 4.5, $J_{4,5}$ 6.75 Hz), which must therefore have the D-*lyxo* configuration. A consideration of the mechanism of the condensation between **1** and **3** supports the proposed configurations. Four adducts (**11**–**14**) can be formed (Scheme 2). Adducts **11** and **14** arise by addition of (*S*)-**3** and (*R*)-**3** to the *pro-S* face of the carbonyl group, whereas adducts **12** and **13** would be formed by addition to the *pro-R* face. Adducts **11** and **14** would give **6***A* by elimination–decarboxylation (*trans* configuration), whereas **12** and **13** would produce the *cis* isomer. On the other hand, adducts **11**–**14** would yield, by decarboxylation, the *B* series of compounds with the D-*arabino*, D-*xylo*, D-*ribo*, and D-*lyxo* configurations, respectively. The fact that only one compound of the *A* series, which had the *trans* configuration, was isolated indicates that **11** and **14** probably lead to **6**, whereas **12** and **13** account for the formation of **7** and **8**, respectively. This situation also explains the stereoselectivity of the reaction of **1** with **3**, where the D-*ribo* compound (**7**) was obtained in a yield higher than that of the D-*lyxo* compound (**8**), in accord with Cram's rule[9] for this kind of addition reaction.



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(*R*) R = H, R^1 = Me
(*S*) R = Me, R^1 = H

11 R^2 = Me, R^3 = COMe, R^4 = X, R^5 = H
12 R^2 = COMe, R^3 = Me, R^4 = X, R^5 = H
13 R^2 = Me, R^3 = COMe, R^4 = H, R^5 = X
14 R^2 = COMe, R^3 = Me, R^4 = H, R^5 = X

EXPERIMENTAL

General. — Solvents were dried over Na_2SO_4 and evaporated under diminished pressure at <50°. T.l.c. was performed with Silica Gel G (Merck), using *A*, 3:2 ether–hexane; and *B*, 1:2 ether–hexane; and detection by charring with sulfuric acid. Column chromatography was performed with Silica Gel (Merck, 7734). I.r. spectra were recorded with a Perkin–Elmer Infracord spectrometer, u.v. spectra with a Perkin–Elmer 124 spectrometer, and ^{1}H-n.m.r. spectra (60 MHz, internal Me_4Si) with a Perkin–Elmer R-20B spectrometer (Table I). Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. Microanalyses were performed in a Carlo-Erba elemental analyzer Model 1106.

*Reaction of 2,3-O-isopropylidene-*D*-glyceraldehyde* (**1**) *with monoethyl methylmalonate* (**2**). — To a solution of the monopotassium salt of ethyl methylmalonate[10] (66 g, 0.36 mol) in water (50 mL) at −10° was added conc. hydrochloric acid (31 mL) at −10°. The mixture was extracted with ether (5 × 100 mL), the extracts were dried and concentrated, and the residue was distilled, to give monoethyl methylmalonate (**2**; 50 g, 96%), b.p. 77°/0.1 mmHg; lit.[11] b.p. 83.5°/0.2 mmHg.

(*a*) To a solution of **2**[11] (14 g, 0.1 mol) in pyridine (30 mL) at −10° was added a solution of **1**[13] (13 g, 0.1 mol) in pyridine (30 mL) and piperidine (1 mL) at −10°. The mixture was kept at ~5° for 4 days. T.l.c. then showed that **1** and **2** had disappeared and that only one product [R_F 0.50 (solvent *A*)] was present. Solvent and catalyst were evaporated and the residue was fractionally distilled at 0.5 mmHg, to give *A* (1.76 g), b.p. 94°; *B* (7.05 g), b.p. 94–120°; and *C* (9.32 g), b.p. 120°. T.l.c. of *A*–*C* revealed two products with R_F 0.42 and 0.22 (solvent *B*), in different ratios. The fractions were combined and subjected to column chromatography (ether–hexane mixtures 1:5→2:3). The fractions that contained the compound of higher

TABLE I

N.M.R. SPECTRAL DATA (60 MHz)

Compound	*Solvent*	*Chemical shift (δ scale, J in Hz)*										
		H-1	*H-3* ($J_{3,4}$) ($J_{3,Me}$)	*H-4* ($J_{4,5}$) ($J_{4,Me}$)	*H-5* ($J_{5,5'}$)	*H-5'* ($J_{4,5'}$)	*H-6* ($J_{5,6}$)	*H-6'* ($J_{5,6'}$) ($J_{6,6'}$)	*Me-2*	*Me-3* ($J_{3,Me}$)	*Me-CO*	*Me_2C*	*OH*
4	$CDCl_3$		6.07dq (6.75) (1.50)	5.26q (6.75)	4.30dd (8.25)	3.57dd (6.75)			1.95d			1.38s 1.43s	
5	$CDCl_3$		6.70dq (8.25) (1.50)	4.87q (6.75)	4.17dd (8.25)	3.67dd (8.25)			1.90d			1.42s 1.46s	
6	$CDCl_3$	2.28s		6.38dq (6.75) (1.20)	4.80q		4.08dd (6.00)	3.50dd (8.25) (8.25)		1.65d		1.31s 1.36s	
7	CCl_4	2.15s	2.75dq			← 3.50–4.30 →				1.14d (7.50)		1.25s 1.30s	3.55
8	CCl_4	2.15s	2.80dq			← 3.20–4.20 →				1.10d (7.50)		1.27s 1.30s	3.40
9	$CDCl_3$	2.17s	2.85dq (6.00)	5.19t (6.00)		← 3.55–4.35 →				1.13d (6.75)	2.01s	1.27s 1.32s	
10	$CDCl_3$	2.20s	2.93dq (4.50)	5.22dd (6.75)		← 3.55–4.30 →				1.08d (6.75)	2.01s	1.02s 1.12s	

mobility were combined and concentrated, to give ethyl *cis*-2,3-dideoxy-4,5-*O*-isopropylidene-2-*C*-methyl-D-*glycero*-pent-2-enonate (**4**; 2.7 g, 13%) as a mobile oil, $[\alpha]_D$ +7.5° (*c* 2.3, chloroform); λ_{max}^{MeOH} 228 nm (ε 4850); ν_{max}^{film} 1715 (C=O), 1650 (C=C), 1375 (C-H), 1250 (C-O-C), 1150, 1060, and 850 cm^{-1} (O-C-O).

Anal. Calc. for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 61.84; H, 8.74.

Concentration of the fractions which contained the compound with R_F 0.22 gave ethyl *trans*-2,3-dideoxy-4,5-*O*-isopropylidene-2-*C*-methyl-D-*glycero*-pent-2-enonate (**5**; 13.0 g, 61%), $[\alpha]_D$ +3° (*c* 2.1, chloroform); λ_{max}^{MeOH} 227 nm (ε 5410); ν_{max}^{film} 1715 (C=O), 1650 (C=C), 1375 (C-H), 1250 (C-O-C), 1150, 1060, and 850 cm^{-1} (O-C-O).

Anal. Found: C, 62.14; H, 8.64.

(*b*) To a solution of **2** (6 g, 0.04 mol) in toluene (15 mL) at −10° was added a solution of **1** (5.2 g, 0.04 mol) in toluene (15 mL) and diethylamine (1 mL) at −10°. The mixture was kept at 5° for 2 days. T.l.c. then showed the presence of the above compounds. Solvent and catalyst were evaporated and the residue was fractionally distilled at 0.1 mmHg, to give *A* (3.21 g), b.p. 79°, and *B* (4.65 g), b.p. 87–90°. *A* and *B* were mixtures of **4** and **5**, and they were resolved as in (*a*), to give **4** (1.32 g, 15%) and **5** (5.20 g, 59%).

Reaction of **1** *with* α*-methylacetoacetic acid* (**3**). — Ethyl α-methylacetoacetate[12] (15 g, 0.1 mol) was hydrolysed at room temperature in M sodium hydroxide (110 mL). The alkaline solution was extracted with ether (2 × 50 mL), and then chilled and acidified with cold sulfuric acid (3.5 mL of the conc. acid in 15 mL of water). The solution was saturated with sodium chloride and extracted with ether until the ether extract gave only a faint reaction with aqueous ferric chloride. The ether extracts were combined, dried, and concentrated under diminished pressure, to give a residue (7 g, 58%), the ^{1}H-n.m.r. spectrum of which indicated it to be slightly impure α-methylacetoacetic acid (**3**).

(*a*) To a solution of **3** (6 g, 0.05 mol) in pyridine (15 mL) at −10° was added a solution of **1** (5 g, 0.045 mol) in pyridine (15 mL) at −10°. The mixture was kept at 5° for 24 h, and then for 5 h at room temperature. Evaporation of the solvent and the catalyst gave a residue, a solution of which in chloroform (50 mL) was washed with aqueous 10% sodium hydrogensulfate, saturated, aqueous sodium hydrogencarbonate, and water. T.l.c. (solvent *A*) then revealed components with R_F 0.49, 0.33, and 0.25. The solvent was evaporated, and the residue was subjected to column chromatography (ether–hexane mixtures 1:2→2:1). Concentration of the fractions which contained the component with R_F 0.49 gave *trans*-1,3,4-trideoxy-5,6-*O*-isopropylidene-3-*C*-methyl-D-*glycero*-hex-3-enulose (**6**; 4.5 g, 64%), b.p. 68°/0.5 mmHg, $[\alpha]_D$ +36° (*c* 1.12, chloroform); λ_{max}^{MeOH} 230 nm (ε 11830); ν_{max}^{film} 1685 (C=O), 1635 (C=C), 1375 (C-H), 1250 (C-O-C), 1150, 1065, and 870 cm^{-1} (O-C-O).

Anal. Calc. for $C_{10}H_{16}O_3$: C, 65.22; H, 8.70. Found: C, 65.24; H, 8.84.

Concentration of the fractions containing the component with R_F 0.33 yielded 1,3-dideoxy-5,6-*O*-isopropylidene-3-*C*-methyl-D-*ribo*-hexulose (**7**; 0.5 g, 6.5%), b.p.

71–72°/0.1 mmHg, $[\alpha]_D$ +22° (*c* 1.74, chloroform); $\nu_{\max}^{\text{film}}$ 3500 (O-H), 1720 (C=O), 1385 (C-H), 1165, 1070, and 850 cm^{-1} (O-C-O).

Anal. Calc. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.62; H, 9.06.

Compound **7** (0.3 g, 1.5 mmol) was acetylated in the usual manner and the product was purified by column chromatography, to give 4-*O*-acetyl-1,3-dideoxy-5,6-*O*-isopropylidene-3-*C*-methyl-D-*ribo*-hexulose (**9**; 0.3 g, 83%), R_F 0.41 (solvent *A*), $[\alpha]_D$ −14° (*c* 1.5, chloroform); $\nu_{\max}^{\text{film}}$ 1755 (C=O, acetate), 1725 (C=O, ketone), 1385 (C-H), 1240 (C-O-C), 1165, 1065, and 850 cm^{-1} (O-C-O).

Anal. Calc. for $C_{12}H_{20}O_5$: C, 59.01; H, 8.20. Found: C, 58.69; H, 8.15.

The component with R_F 0.25, obtained by concentration of the corresponding fractions, was 1,3-dideoxy-5,6-*O*-isopropylidene-3-*C*-methyl-D-*lyxo*-hexulose (**8**; 0.3 g, 4%), b.p. 79°/0.1 mmHg, $[\alpha]_D$ −15° (*c* 1.3, chloroform); $\nu_{\max}^{\text{film}}$ 3500 (O-H), 1720 (C=O), 1385 (C-H), 1165, 1065, and 855 cm^{-1} (O-C-O).

Anal. Calc. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.00; H, 8.91.

Acetylation of **8** (0.5 g, 2.5 mmol) yielded 4-*O*-acetyl-1,3-dideoxy-5,6-*O*-isopropylidene-3-*C*-methyl-D-*lyxo*-hexulose (**10**; 0.5 g, 83%), R_F 0.50 (solvent *A*), $[\alpha]_D$ +52° (*c* 1.6, chloroform); $\nu_{\max}^{\text{film}}$ 1755 (C=O, acetate), 1725 (C=O, ketone), 1375 (C-H), 1240 (C-O-C), 1160, 1070, and 840 cm^{-1} (O-C-O).

Anal. Calc. for $C_{12}H_{20}O_5$: 59.01; H, 8.20. Found: C, 59.37; H, 8.46.

(*b*) To a solution of **3** (14 g, 0.1 mol) in toluene (50 mL) at −10° was added a solution of **1** (11 g, 0.09 mol) in toluene (50 mL) and diethylamine (2 mL) at −10°. The procedure in (*a*) then gave **6** (0.5 g, 3.2%), **7** (4.31 g, 25%), and **8** (3.57 g, 21%).

trans-*2,3-Dideoxy-4,5-*O*-isopropylidene-2-*C*-methyl-*D-glycero-*pent-2-enonic acid.* — A suspension of **5*A*** (1.07 g, 5 mmol) in M sodium hydroxide (5 mL) was heated under reflux. After 3 h, t.l.c. showed that **5** had disappeared. The reaction mixture was cooled to 0°, acidified (Congo Red), and extracted with ether (5 × 10 mL). Concentration of the extract and distillation of the residue gave the title compound (0.6 g, 72%), b.p. 128°/0.7 mmHg.

Synthesis of **6A**. — To a stirred suspension of small pieces of lithium (42 mg, 6 mmol) in anhydrous ether (5 mL) were added a few drops of methyl iodide. When reaction started, a solution of methyl iodide (0.426 g, 3 mmol) in anhydrous ether (10 mL) was added slowly to maintain gentle boiling. The mixture was then stirred and heated under reflux for 2 h, and cooled, and a solution of the foregoing acid (186 mg, 1 mmol) in ether (5 mL) was added slowly with stirring. The mixture was stirred and heated under reflux for a further 6 h. Water was added with stirring until two layers were obtained. The ethereal phase was washed with water and concentrated, to give a mobile oil (150 mg) that was shown by t.l.c. to be impure **6**. Column chromatography gave pure material (65 mg, 37%).

Configurational assignment at C-4 in **7** *and* **8**. — A solution of **7** (100.4 mg, 0.5 mmol) and (±)-α-phenylbutyric anhydride (315.41 mg, 1 mmol) in dry pyridine (2 mL) was kept overnight at room temperature. Water (2 mL) was added, and the mixture was stored for 5 h and then extracted with ether (15 mL). The extract was washed with saturated, aqueous sodium hydrogencarbonate and water. The combined aqueous extracts were acidified with hydrochloric acid and extracted with chloroform. Concentration of the extract gave α-phenylbutyric acid (248.8 mg), $[\alpha]_{365}$ −6.67° (*c* 2.5, chloroform).

Application of the above method to **8** (117.20 mg, 0.58 mmol) and the anhydride (348.80 mg) gave α-phenylbutyric acid (250.4 mg), $[\alpha]_{365}$ +9.15° (*c* 2.5, chloroform).

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