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Synthesis of *threo*- and *erythro*-3-Pentulose by Aldol Type Reaction in Water

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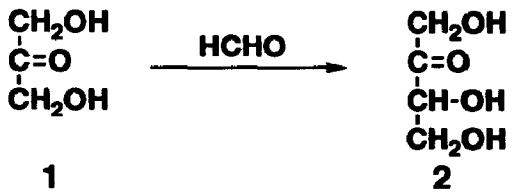
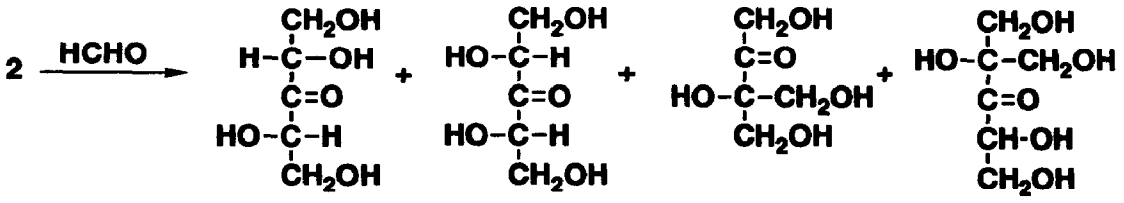
Abstract: The aldol condensation of *glycero*-tetrulose with formaldehyde was performed without protection of the hydroxyl groups to give 3-pentulose. *threo*-3-Pentulose was stereoselectively obtained in methanol, whereas the *erythro*-isomer was major in water. In addition, 3-*C*-(hydroxymethyl)tetrulose was obtained as a side product.

One-pot formation of saccharides and their derivatives from C_1 material, formaldehyde, is called formose reaction.[1] Among the several features of the formose reaction, it has received much attention in connection with the prebiotic synthesis of saccharides.[2-4] Previously, selective syntheses of C_3 and C_4 sugars such as 1,3-dihydroxyacetone (**1**)[5,6] and *glycero*-tetrulose (**2**)[7,8] from formaldehyde were reported. Although aldol type reaction in water is assumed to be one of the important ways for the prebiotic formation of the carbon-carbon bonds in saccharide,[9,10] there have been few studies on the stereochemical control of the reaction.[11,12] In this report, one- or two-carbon homologation of **1** or **2** in water and other polar solvents is investigated. We have found that the aldol condensation between



1 **2**



threo-**3** *erythro*-**3** **4** **5**

Table 1. Aldol Reaction of 2-Ketoses with Formaldehyde in Water or Alcohol[a)]

Ketose	HCHO	Base	Time	Conversion	Yield/%				3
	mmol		min	%	2	3	4	5	threo:erythro
1[b)]	9.0	NaOH	105	42	75	17			
2	9.0	NaOH	60	44		62	12	7	37:63
2	3.0	NaOH	60	48		52	11	7	36:64
2	3.0	KOH	60	40		60	14	7	35:65
2	3.0	$Ba(OH)_2$	20	43		60	17	11	40:60
2	3.0	$Ca(OH)_2$	30	64		46	18	13	39:61
2[c)]	3.0	$Ca(OH)_2$	240	27		37	7	0	84:16
2[d)]	3.0	$Ca(OH)_2$	240	18		22	6	0	76:24

a) Substrate, 1.5 mmol; base, 0.50 mmol; solvent, H_2O (50 mL); 0 °C; yield, based on the consumed substrate. b) Substrate, 3.0 mmol.
c) $Ca(OH)_2$, 5.0 mmol; solvent, MeOH:H_2O=250:1.
d) Solvent, 1-propanol:H_2O=250:1.

formaldehyde and **2** without protection of the hydroxyl groups gives 3-pentulose (**3**)[9,13] along with 3-*C*-(hydroxymethyl)tetrulose (**4**)[9] and that the ratio of *threo*- to *erythro*-**3** is dependent on the solvents.

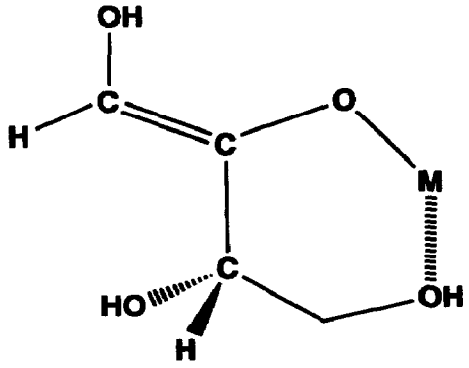
As shown in Table 1, a C_4 sugar **2** was obtained from a C_3 sugar **1** in a good yield. The aldol condensation between **2** and formaldehyde in water mainly gave a linear C_5 sugar, 3-pentulose (**3**), and a branched ketose **4** was obtained as a side product. The result means the preferential reaction at the C1 position of **2**. In addition, 2-*C*-(hydroxymethyl)-3-pentulose (**5**)[8,14] was also formed by the further condensation of formaldehyde with **3** or **4**.

A typical procedure is as follows. Under a nitrogen atmosphere, **2** (180 mg, 1.5 mmol) in water (50 mL) was stirred with an aqueous formaldehyde solution (ca. 0.20 mL, 3.0 mmol as HCHO) and calcium hydroxide (37 mg, 0.50 mmol) at 0°C. After 30 min, the reaction mixture was slightly acidified with hydrochloric acid (1 M), and then 0.5 mL of the quenched solution was treated with pyridine (2 mL) and hydroxylamine hydrochloride (30 mg, 0.40 mmol) at room temperature for 15 min. On the other hand, in order to estimate the ratio of *threo*- to *erythro*-**3**,[15,16] the reaction products were transformed into sugar alcohols by the treatment of the quenched solution (5 mL) with $NaBH_4$ (15 mg, 0.40 mmol) at room temperature for 1 h. Arabinitol is derived from *threo*-**3**. Xylitol and ribitol are derived from *erythro*-**3**. Therefore, the ratio of these alditols is corresponding to that of *threo*- to *erythro*-**3**. After trimethylsilylation, the oxime derivatives and reduced products were analyzed by gas chromatography (1,1,1-tris(hydroxymethyl)ethane as an internal standard) as described previously.[17,18]

As to the stereoselectivity in the formation of **3** in water, the ratio of *threo*- to *erythro*-**3** was approximately 40:60~35:65 independent of bases such as NaOH, KOH, $Ba(OH)_2$, or $Ca(OH)_2$. For the explanation of this phenomenon, we propose a chelated enolate **6** in which the interaction of C1-OH moiety with the bulky C3-C4 group is avoided. Formaldehyde approaches the less hindered face of the enolate to form *erythro*-**3**. Because an 84:16 mixture of *threo*- and *erythro*-**3** was treated with $Ca(OH)_2$ (0.50 mmol) in water (50 mL) at 0°C for 1 h to give a 48:52 mixture of them, there would be little difference between thermodynamic stability of *threo*-**3** and that of *erythro*-**3** under the reaction

conditions. These results mean that formation of slightly *erythro*-rich mixtures in water is attributed to the base induced isomerization of *erythro*-**3** into *threo*-**3** and/or rather large proportion of formation of **3** via a non-chelated enolate of **2**.

In contrast, the reaction carried out in methanol or 1-propanol preferentially gave *threo*-**3** when $Ca(OH)_2$ was employed.[19] Solvation of metal ions in the alcohols would be weaker than that in water. In this case, we propose a chelated enolate **7** in which the C1- and C3-hydroxyl groups of **2** coordinate to a metal cation. Formaldehyde approaches as to reduce the steric congestion and the consequent chair-type transition state leads to *threo*-**3**. Thus stereoselectivity is dependent on the configuration at C3 position of **2**.[20,21]



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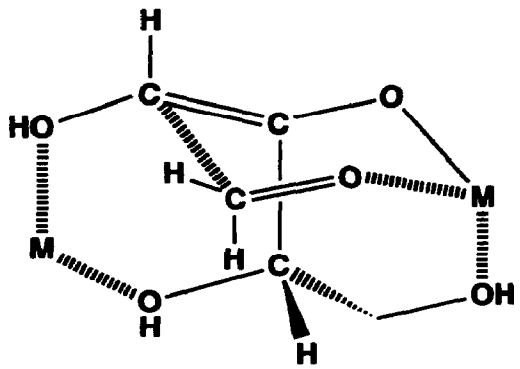

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In conclusion, we have demonstrated one of the possible reaction models for the stereoselective formation of sugar in a simple and primitive system in which metal hydroxides, water or alcohol, formaldehyde, and ketoses without protection of the hydroxyl groups were employed.[22]

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16. Fractionization of the products with HPLC gave **3**. A mixture of *threo*-**3**^{13,15} and *erythro*-**3**,^{9,15} the ratio being 2:3 based on gas chromatography, showed ^{1}H NMR (CD_3OD, * refer to *erythro*-**3**) δ 3.80 (dd, J = 4.1, 11.6 Hz, H-C1-**H**(OH) and H-C5-**H**(OH)), 3.83* (dd, J = 4.1, 11.6 Hz, H-C1-**H**(OH) and H-C5-**H**(OH)), 3.87 (dd, J = 4.7, 11.6 Hz, **H**-C1-H(OH) and **H**-C5-H(OH)), 3.88* (dd, J = 4.6, 11.6 Hz, **H**-C1-H(OH) and **H**-C5-H(OH)), 4.47* (t, J = 4.3 Hz, **H**-C2-OH and **H**-C4-OH), 4.50 (t, J = 4.4 Hz, **H**-C2-OH and **H**-C4-OH); ^{13}C NMR (CD_3OD, * refer to *erythro*-**3**) δ 64.6* (t, C1 and C5), 64.8 (t, C1 and C5), 77.5* (d, C2 and C4), 77.9 (d, C2 and C4), 212.9* (s, C3), 213.0 (s, C3); IR (neat) 3000-3700, 1720 cm^{-1}.
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