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Reaction of C_3 and C_4 ketoses with alkenals and alkenones in water

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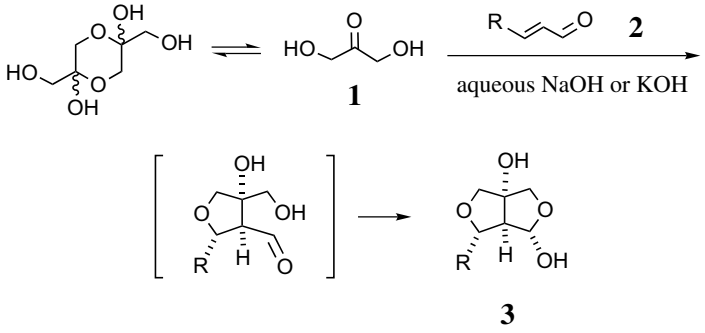
Abstract—Treatment of 1,3-dihydroxyacetone and acrolein with aqueous KOH gave a tetrahydrofuran derivative, 1,4-dihydroxy-3,7-dioxabicyclo[3.3.0]octane, in 80% yield. Similarly, 6-alkyl substituted 1,4-dihydroxy-3,7-dioxabicyclo[3.3.0]octanes were obtained by reaction of 1,3-dihydroxyacetone with various α,β-unsaturated aldehydes. In the cases of long chain alkenals, the reaction was effectively accelerated in the presence of organic co-solvent. On the other hand, the corresponding tricyclic products were synthesized by reaction of 1,3-dihydroxyacetone with cyclic enones, such as 2-cyclopentenone and 2-cyclohexenone. This method was successfully applied to the reaction of a tetrulose in the absence of any protecting groups.

The unique reactivity and usefulness as a synthetic block of triose and tetrulose have attracted wide attention in the field of synthetic and evolutional chemistry.[1–6] As an extension of our study on the reaction of unprotected sugars,[7,8] we found that treatment of 1,3-dihydroxyacetone (**1**) and α,β-unsaturated aldehydes **2** with aqueous NaOH or KOH gave bicyclic tetrahydrofuran derivatives **3** in one-pot as shown in Scheme 1. The formation of bicyclic compound **3** is explained by Michael addition of the hydroxy group of **1** to alkenals **2**, intramolecular aldol reaction, and subsequent hemiacetal formation.

As exemplified in entry 1 of Table 1, treatment of 1,3-dihydroxyacetone (**1**) with acrolein (**2a**) in aqueous KOH gave 1,4-dihydroxy-3,7-dioxabicyclo[3.3.0]octane (**3a**)[9] in 80% yield as a 4:1 mixture of diastereomers. According to studies on the stereochemistry of dioxabicyclo[3.3.0]octane derivatives,[10–12] the *cis* fusion of two five-membered rings is necessitated by the strain that a *trans* fusion would impose. Therefore, the diastereomeric ratio would depend on the configuration of the C(4)–OH group. As the α-face of the *cis*-fused bicyclo[3.3.0]octane is sterically less hindered, *cis*-1,4-diol,



Scheme 1.

Keywords: Dihydroxyacetone; Erythrulose; Water; One-pot reaction; Tetrahydrofurans.
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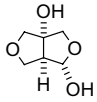
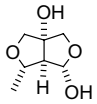
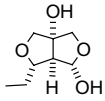
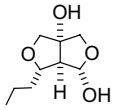
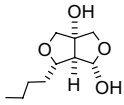
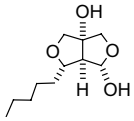
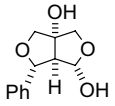
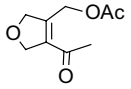
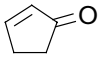
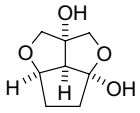
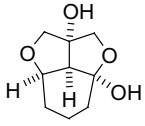
Table 1. Reaction of 1,3-dihydroxyacetone and α,β-unsaturated carbonyl compounds[a]

Entry	Alkenal **2** or alkenone		Base/mol/L		Solvent	Time/h	Isolated yield/% (diastereomer ratio)		
1	R = H	**2a**	KOH	0.02	H_2O	7		**3a**	82 (4:1)
2	R = Me	**2b**	NaOH	0.01	H_2O	14		**3b**	83 (12:1)
3	R = Et	**2c**	NaOH	0.01	H_2O	15		**3c**	76 (12:1)
4	R = *n*-Pr	**2d**	NaOH	0.01	H_2O	16		**3d**	52
5					H_2O/1,4-dioxane 1/1 (v/v)	19			85 (12:1)
6	R = *n*-Bu	**2e**	NaOH	0.01	H_2O	19		**3e**	35
7					H_2O/1,4-dioxane 1/1 (v/v)	19			90 (10:1)
8	R = *n*-pentyl	**2f**	NaOH	0.01	H_2O	21		**3f**	35
9					H_2O/1,4-dioxane 1/1 (v/v)	21			88 (10:1)
10	R = Ph	**2g**	LiOH	0.1	H_2O/1,4-dioxane 1/1 (v/v)	24		**3g**	33[b]
11		**4**	KOH	0.01	H_2O	2[c]		**5**	68[d]
12		**6**	NaOH	0.01	H_2O	20		**7**	64[e]
13		**8**	NaOH	0.01	H_2O	19		**9**	70[b]

[a] 1,3-Dihydroxyacetone dimer: 0.1 mol/L as monomer; α,β-unsaturated aldehyde or ketone: 0.12 mol/L; temperature: 0 °C.
[b] Other isomers were not observed.
[c] Temperature, 20 °C.
[d] Overall yield after acetylation.
[e] Bicyclic product without hemiacetal formation was observed, 9%.

which has the C(4)–α-OH group, should be a major isomer. The α configuration of the C(4)–OH group was also supported by ^{1}H NMR analysis, in which the absorption (δ 5.18, d, $J = 1.3$ Hz) corresponding to the C(4)–β-H of the major isomer **3a** showed a small spin–spin coupling constant between C(4)–β-H and C(5)–α-H, because the dihedral angle of the H–C–C–H linkage is close to 90°. On the other hand, the minor isomer showed a C(4)–α-H signal with a larger coupling constant (δ 5.55, d, $J = 6.1$ Hz). Similar phenomena were observed in other bicyclic products **3** shown in Table 1.

As to the configuration of the substituent at the C(6)-position of **3**, a product with a C(6)-α-substituent is thermodynamically favored because the α-face of the *cis*-fused bicyclo[3.3.0]octane **3** is sterically less hindered. Compared with short chain alkenals **2a**,**b**, and **2c** in entries 1, 2, and 3 in Table 1, relatively hydrophobic alkenals **2d**,**e**, and **2f** (entries 4, 6, and 8) were subjected to the reaction in water to give the corresponding bicyclic products in lower yields. These yields were much improved by the use of a 1:1 mixture of water and 1,4-dioxane as a solvent as shown in entries 5, 7, and 9 of

Table 1. However, formation of **3g** from cinnamaldehyde had a low yield, because of the poor water solubility of cinnamaldehyde.

In contrast to acrolein (Table 1, entry 1), which led to stable hemiacetal product **3a**, methyl vinyl ketone (**4**) (Table 1, entry 11) did not promote hemiacetal formation in the last stage of the one-pot transformation, instead, it led to a complex mixture. Therefore, the neutralized reaction mixture was then concentrated, lyophilized, and acetylated with acetyl chloride to yield 3-acetoxymethyl-4-acetyl-2,5-dihydrofuran (**5**). In addition, the reaction of 4-methyl-3-penten-2-one with **1** gave the corresponding tetrahydrofuran derivative in a poor yield. These results mean that hemiacetal formation plays an important role to obtain the tetrahydrofuran derivatives. When cyclic α,β-unsaturated ketones **6** and **8** were employed as a Michael accepter (Table 1, entries 12 and 13), tricyclic tetrahydrofuran derivatives **7**[13] and **9**[14] were obtained in one pot. As shown in Figure 1, X-ray analysis of 1,4-dihydroxy-2,6-dioxatricyclo[5.3.1.$0^{4,11}$]undecane (**9**) recrystallized from ethanol confirmed the all *cis* fusion of every ring.[15] Similarly, diol **7** might have all *cis* fusion of every five-membered ring.

This method was successfully applied to the reaction of a tetrulose, L-(*S*)-erythrulose (**10**), in the absence of any protecting groups as shown in Scheme 2. Although the reaction of **10** with **6** led to a mixture of several diastereomers, purification by column chromatography gave 1,4-dihydroxy-3-hydroxymethyl-2,6-dioxatricyclo[5.2.1.$0^{4,10}$]decane (**11**)[16] (30% yield; $[\alpha]_D$ −8.57, *c* 0.043 g/mL, H_2O, 20 °C) as a major isomer along with a minor isomer **12** (8% yield; $[\alpha]_D$ −39.11, *c* 0.043 g/mL, H_2O, 20 °C). Although the stereochemistry of **12** is still unclear, X-ray analysis of the main isomer revealed that every five-membered ring is fused in a *cis* manner and the hydroxymethyl group derived from L-(*S*)-**10** is in the *cis* position relative to the two hydroxy groups as shown in Figure 2.[15]

In conclusion, tetrahydrofuran derivatives were synthesized by the one-pot reaction of 1,3-dihydroxyacetone with α,β-unsaturated aldehydes and ketones in aqueous NaOH or KOH. This sequence is successfully applied to the reaction of L-(*S*)-erythrulose with 2-cyclopentenone to give tricyclic tetrahydrofuran derivatives in the absence of any protecting groups.

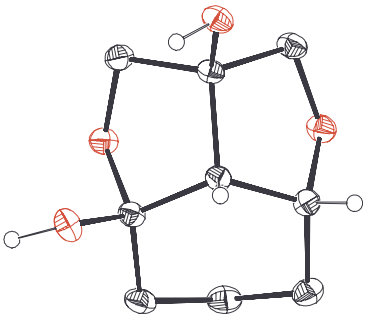
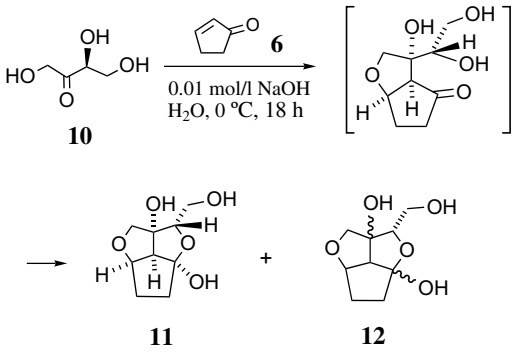


Figure 1. ORTEP plot of the X-ray structure of tricyclic undecane **9**.



Scheme 2.

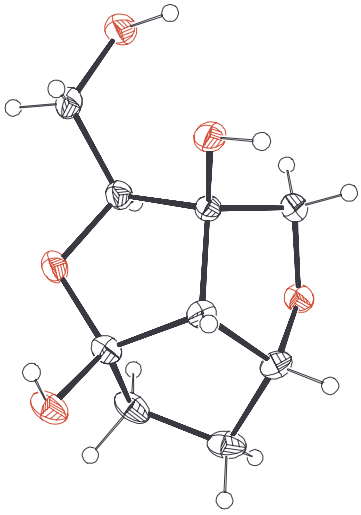


Figure 2. ORTEP plot of the X-ray structure of tricyclic decane **11**.

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9. In a typical procedure, aqueous NaOH (1 mol/L, 10 mL, 10 mmol) was added to a mixture of 1,3-dihydroxyacetone dimer (9.00 g, 100 mmol as **1**) and acrolein (**2a**) (6.80 g, 120 mmol) in water (482 mL) at 0 °C. After stirring at 0 °C for 7 h, the reaction mixture was slightly acidified with aqueous HCl, concentrated under reduced pressure, and lyophilized to give crude solid (16.8 g). The crude products were dissolved in a mixture of methanol and chloroform, and the insoluble compounds were eliminated by filtration. After concentration of the solution, recrystallization from ethanol gave **3a** (11.9 g, 82% yield) as colorless blocks. Compound **3a**: mp 76–78 °C; ^{1}H NMR (D_2O): δ 2.54 (ddd, J = 1.5, 5.0, 8.0 Hz, 1H), 3.62 (dd, J = 5.0, 10.0 Hz, 1H), 3.68 (d, J = 10.0 Hz, 1H), 3.73 (d, J = 10.0 Hz, 1H), 3.87 (d, J = 10.0 Hz, 1H), 3.89 (d, J = 10.0 Hz, 1H), 4.12 (dd, J = 5.0, 10.0 Hz, 1H), 5.18 (d, J = 1.3 Hz, 1H); IR (KBr) 3100–3600, 2880, 1061, 1003 cm^{-1}. Found: C, 49.08; H, 6.99%. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90.
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13. Compound **7**: colorless syrup; ^{1}H NMR (D_2O): δ 1.70–1.82 (m, 2H), 1.95–2.06 (m, 2H), 2.80 (d, J = 7.6 Hz, 1H), 3.83 (d, J = 9.9 Hz, 1H), 3.88 (d, J = 9.9 Hz, 1H), 3.95 (d, J = 9.3 Hz, 1H), 4.05 (d, J = 9.3 Hz, 1H), 4.83-4.89 (m, 1H); IR (neat) 3100–3600, 1267, 1043, 1018 cm^{-1}. Found: C, 55.65; H, 6.99. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03.
14. Compound **9**: mp 135–136 °C; ^{1}H NMR (D_2O): δ 1.31–1.57 (m, 4H), 1.81–1.95 (m, 2H), 2.27 (d, J = 7.2 Hz, 1H), 3.56 (dd, J = 2.5, 9.2 Hz, 1H), 3.94 (d, J = 9.2 Hz, 1H), 3.99 (d, J = 9.2 Hz, 1H), 4.05 (dd, J = 2.5, 9.2 Hz, 1H), 4.18–4.23 (m, 1H); IR (KBr) 3400, 3300, 1090, 1057, 893 cm^{-1}. Found: C, 57.77; H, 7.30%. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58.
15. Crystallographic data (excluding structure factors) for **9** and **11** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 249660 for **9**, CCDC 249661 for **11**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
16. Compound **11**: mp 136–137 °C; ^{1}H NMR (D_2O): δ 1.78–1.87 (m, 2H), 1.88-1.99 (m, 1H), 2.01–2.09 (m, 1H), 2.80 (d, J = 7.1 Hz, 1H), 3.73 (d, J = 9.9 Hz, 1H), 3.77 (dd, J = 4.0, 12.1 Hz, 1H), 3.83 (dd, J = 6.1, 12.1 Hz, 1H), 3.88 (d, J = 9.9 Hz, 1H), 3.98 (dd, J = 4.0, 6.1 Hz, 1H), 4.79–4.83 (m, 1H); IR (KBr) 3460, 3333, 1273, 1069, 1045, 995 cm^{-1}. Found: C, 53.32; H, 7.02. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98.