

CHELATION CONTROLLED ALDOL REACTION OF TETRONIC ACID
DIANION WITH KETONES

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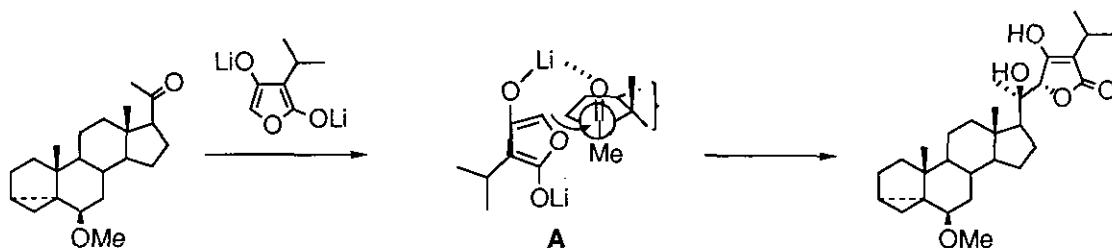
Abstract---The chelation effect in the aldol reaction of dianion of tetrionic acid with ketones was investigated to give the erythro adduct, predominantly, *via* the six-membered chelation transition state. The carbon-carbon bond formation occurred at the 5-position siteselectively in this reaction.

The aldol reaction has long been recognized as one of the most promising methods¹ for selective carbon-carbon bond formation, in which chelation control² has also been established to play an important role to determine the stereochemistry of the resulting hydroxy group.

During the course of our synthetic work on the polyhydroxysteroids, we have found³ that the reaction of the dianion of 3-isopropyltetrionic acid with 20-oxosteroid afforded the 22*R*-compound predominantly, where the chelation model **A** was reasonably assumed as a transition state to rationalize the stereoselectivity. As part of our ongoing interest in synthetic utility of tetrionic acid as a useful building block in natural product synthesis,⁴ we thought it worthwhile to investigate the

This paper is dedicated to Dr. Masatomo Hamana on the occasion of his 75th birthday.

further possibility of chelation effect of metal enolate derived from tetrone acid, although the reaction of methyl tetronate with achiral aldehyde, such as benzaldehyde, has been reported by Pelter and his co-workers,⁵ in which a stereochemical study has not been made yet.



Thus, the reaction of dianion of tetrone acid (**1**) (prepared from tetrone acid with 2.2 eq. mol of LDA) with 1-cyclohexyl-1-propanone (**2**) was carried out in tetrahydrofuran(THF) at $-78\text{ }^{\circ}\text{C}$ to afford the adduct which was then treated with chloromethyl methyl ether providing the erythro compound (**3**)⁶ predominantly in 43.5 % yield. The ratio of the diastereomers was determined by 400 MHz nmr spectrum to be 2.2 : 1 (erythro:threo). When this reaction was performed in THF-HMPA (10 : 1), the yield was increased to 79 % with the similar ratio of the aldol products. Magnesium and zinc enolates were prepared by direct transmetalation of the lithium enolate with magnesium bromide and zinc bromide in THF respectively, and their aldol reaction with **2** was again attempted. The results obtained were summarized in Table 1, indicating that the magnesium enolate was the most effective enolate in terms of conversion yield and stereoselectivity.

These results clearly suggested that the aldol reaction of dianion of tetrone acid with **2** proceeded *via* the six-membered chelation transition model (**B**) rather than the seven-membered chelation (**C**). It is also noteworthy that the carbon-carbon bond formation occurred at the 5-position siteselectively in this reaction and none of the aldol product at the 3-position was isolated.

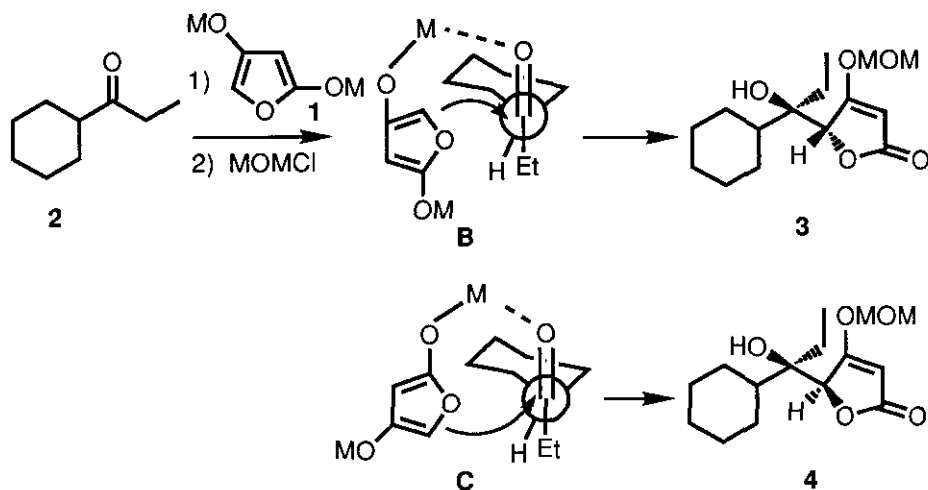
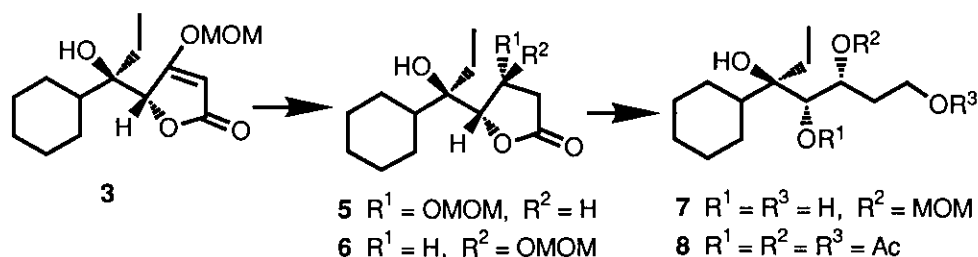


Table 1. Reaction of Metal Enolates with 1-Cyclohexyl-1-propanone

Base	Solvent	Products (3 : 4)	Yield (%)
LDA	THF	2.2 : 1	43.5
LDA	THF + HMPA	2.2 : 1	79.0
LDA + ZnBr ₂	THF	2.7 : 1	66.6
LDA + MgBr ₂	THF	6.3 : 1	81.0

This strategy would provide a useful route to construct a polyol system including a tertiary hydroxyl group, stereoselectively, hence the major compound (3) was converted into the substance with three contiguous chiral hydroxyl functionalities. Catalytic reduction of 3 over rhodium on alumina under 7 atm of hydrogen afforded the lactones (5) and (6) in 70 % yield in a ratio of 8 : 1, where the reduction occurred predominantly from the opposite side of the substituent at the 5-position. The major isomer (5) was further reduced with lithium aluminum hydride to give the



tetraol derivative (**7**), which was converted into the triacetate (**8**)⁷ by acetylation, deprotection of the MOM group, and again by acetylation.

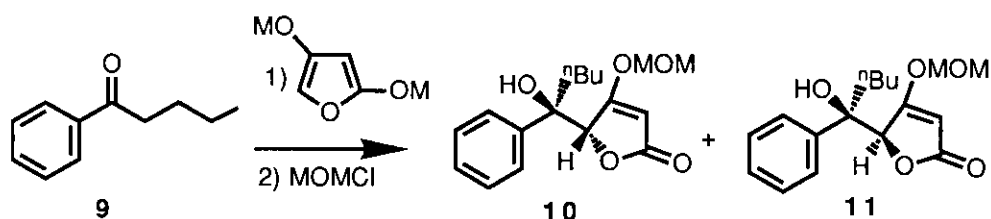


Table 2. Reaction of Metal Enolates with 1-Phenyl-1-pentanone

Base	Solvent	Products (10 : 11)	Yield (%)
LDA	THF	1 : 1	73.3
LDA	THF + HMPA	4.3 : 1	86.6
LDA + ZnBr ₂	THF	3.4 : 1	61.2
LDA + MgBr ₂	THF	8.6 : 1	64.2

We next examined the aldol reaction of dianion of tetronic acid with 1-phenyl-1-pentanone (**9**) having a sp^2 carbon at the α to carbonyl group and the results were summarized in Table 2. Although the stereoselectivity in the reaction of lithium enolate of tetronic acid with **9** in THF at -78°C was not observed, the same reaction in THF-HMPA(10 : 1) furnished the erythro isomer (**10**), determined by X-ray

analysis⁸ (Figure 1), as a major product, in 86.8 % yield, in a ratio of 4.3 : 1. The highest stereoselectivity was obtained with the use of magnesium enolate, due to its strong chelation ability, as expected.

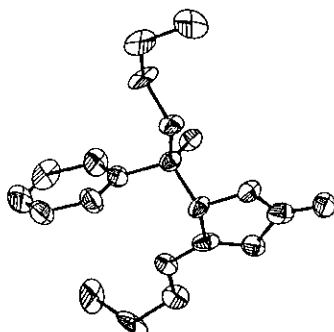


Figure 1. The ORTEP drawing of the compound (10).

Thus, we could disclose the chelation controlled stereoselective construction of polyol systems, and application of this strategy to the synthesis of natural products is currently under investigation.

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6. **3**: Ir(CHCl₃) v: 3300, 1720, 1610 cm⁻¹. ¹H Nmr(CDCl₃) δ: 3.53(3H, s), 4.96(1H, d, *J*=1.2 Hz), 5.19(2H, s), 5.30(1H, d, *J*=1.2 Hz). MS *m/z* : 255(M⁺-Et).
7. **8**: Ir(CHCl₃) v: 1710 cm⁻¹. ¹H Nmr(CDCl₃) δ: 2.05(3H,s), 2.06(3H,s), 2.12(3H, s), 4.08(2H, t, *J*=6.1 Hz), 5.11(1H, d, *J*=3.0 Hz), 5.45(1H, m). Ms *m/z*: 355(M⁺-OH).
8. All the measurements were performed on a Rigaku AFC-5 diffractometer using Cu K α radiation. The unit cell dimensions were determined by least-squares calculation from 20 high-angle reflections. Intensity data were collected by using the 2 θ / ω scan technique for 5° < 2 θ < 110° with an average scan rate of 3°/min. In total, 3621 independent reflections, satisfying the condition $F_o < 5\sigma(F)$ were used for calculation. The crystallographic data for **10**: C₁₇H₂₂O₅. *M_r*=306.36. Triclinic *a*=13.384(5)Å, *b*=14.969(6)Å, *c*=8.303(9)Å, α =95.85(6)°, β =93.76(6)°, γ =90.74(3)°, *D_c*=1.23, *V*=1650.8(2.0), *Z*=2. Space group *P* $\bar{1}$. The structure was solved by the direct method using MULTAN 80. The structure was refined by the block-diagonal least-squares method with anisotropic thermal parameters for all non-hydrogen atoms. The *R* factor was finally reduced to 0.122.

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