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Selective Cyclization of the 1,2-Cyclohexanediacetaldehyde Derivatives through the Intramolecular Aldol Condensation Reaction

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In connection with the synthesis of serratinine (A), the selective cyclization reaction of the 1,2-cyclohexanediacetaldehyde derivatives, IIIa and IIIb, through the intramolecular aldol condensation reaction was investigated.

Cyclization reaction of IIIa or IIIb by basic alumina or by the enamine method[2] using piperidine acetate in dry benzene gave selectively IVa or IVb. On the other hand, cyclization reaction of IIIa or IIIb using excess pyrrolidine acetate in abs. MeOH afforded selectively Va or Vb which is suitable for the present purpose.

In connection with the synthesis of serratinine (A),[3] we have reported the syntheses of the compounds, IIa and IIb, by the Diels–Alder reaction of 2-methyl-5-(2-ethoxycarbonyl-*trans*-vinyl)-1,4-benzoquinone (Ia) and 2-(2-ethoxycarbonyl-*trans*-vinyl)-1,4-benzoquinone (Ib), respectively, with butadiene.[4] An attempt was then made to obtain the V type α,β-unsaturated aldehydes, which possess two rings leading to the ring A and B of the serratinine molecule and an aldehyde group situated suitably for the further synthesis, from the compounds, IIa and IIb. Thus, osmylation of VIIIa or VIIIb, followed by catalytic hydrogenation, periodic acid oxidation and the intramolecular aldol condensation will provide the desired α,β-unsaturated aldehyde (Va or Vb). It is however easy to presume that this aldol condensation will occur in two ways, (route a and route b), to furnish two kinds of aldehydes, *i.e.* the IV type and the V type compounds. For the present purpose, it is therefore necessary to find such a suitable reaction condition as permits to give selectively the V type aldehydes. We have now achieved the syntheses of the key intermediates, Va and Vb, for the serratinine synthesis and the details of the selective cyclization reactions are reported in this paper.

Syntheses of the Dialdehydes, IIIa and IIIb

Reduction of the Diels–Alder adduct (IIa) with Zn-acetic acid furnished quantitatively the dione (VIa)[5] which without purification was reduced with $NaBH_4$ and the chromatographic separation of the product gave the diol (VIIa), mp 94—95°, in 40% yield. The infrared (IR) spectrum of VIIa revealed the hydroxy bands at 3550, 3500 cm^{-1} and the bands due to the α,β-unsaturated ester group at 1710 and 1650 cm^{-1}. The stereostructure of VIIa was estimated as shown in Chart 2 by means of the decoupling experiments in the nuclear magnetic resonance (NMR) using Eu $(DPM)_3$ as a shift reagent. On addition of the shift reagent, all signals were clearly resolved and the signals due to the methylene protons (H_C

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[1] Location: *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*

[2] R.B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W.M. McLamore, *J. Amer. Chem. Soc.*, **74**, 4223 (1952).

[3] Y. Inubushi, H. Ishii, B. Yasui, M. Hashimoto, and T. Harayama, *Chem. Pharm. Bull.* (Tokyo), **16**, 82, 92, 101 (1968); K. Nishio, T. Fujiwara, K. Tomita, H. Ishii, Y. Inubushi, and T. Harayama, *Tetrahedron Letters*, **1969**, 861.

[4] T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *Chem. Pharm. Bull.* (Tokyo), **21**, 25 (1973).

[5] From the NMR spectrum, this compound was proved to be an epimeric mixture due to the secondary methyl group in a 3: 2 ratio.

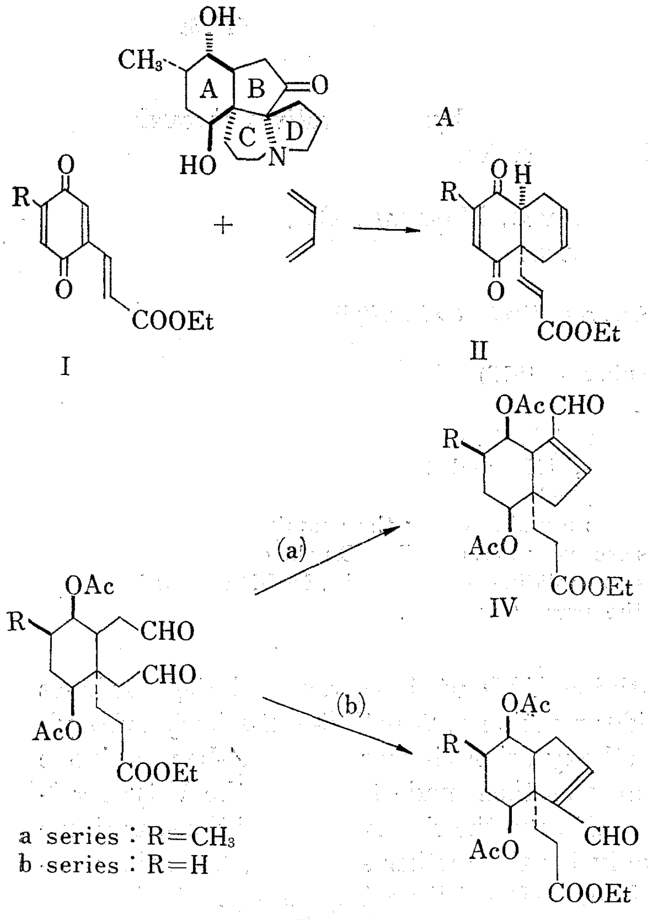

Chart 1

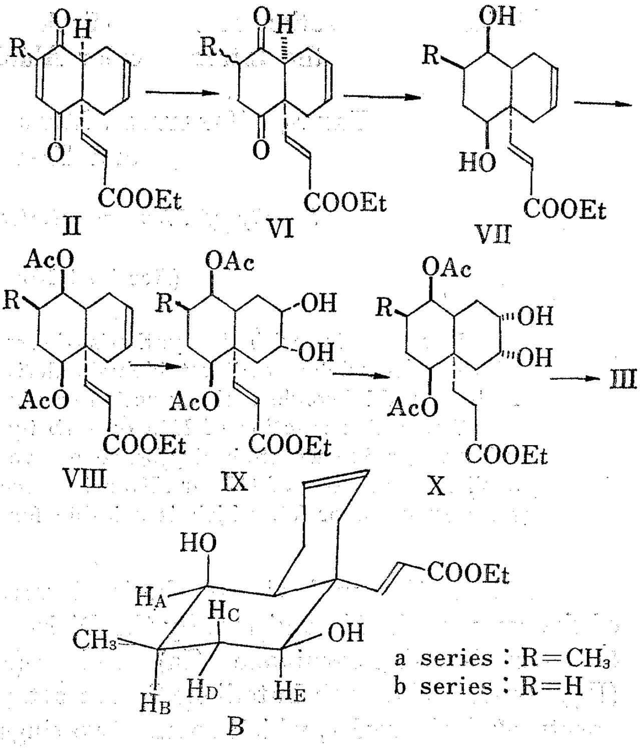

Chart 2

and H$_D$) were observed as a quartet (J=12 Hz) and a doublet of triplets (J_1=12 Hz and J_2=4 Hz). When irradiated on the signal due to the proton H$_E$ geminal to an equatorial hydroxy group, the signal of H$_C$ proton changed from the quartet to the triplet (J=12 Hz) and the signal of the proton H$_D$ from the doublet of triplets to the doublet of doublets (J_1=12 Hz and J_2=4 Hz) (see Formula (B)). These observations suggest that the H$_C$ and H$_D$ protons show the geminal coupling pattern (J=12 Hz) and the proton H$_C$ couples with the H$_B$ and H$_E$ protons in the axial-axial relationship (J=12 Hz), respectively, and the proton H$_D$ couples with the protons H$_B$ and H$_E$ in the equatorial-axial relationship (J=4 Hz), respectively. Consequently, the secondary methyl group should have the equatorial conformation. Since it was estimated by its NMR spectrum that the diol (VIIa) possesses one equatorial and one axial hydroxy group (see Experimental, VIIIa), the stereostructure of the diol is represented by the formula (VIIa) shown in Chart 2.

The diol (VIIa) was then acetylated by the usual manner and the diacetate (VIIIa) was oxidized with OsO$_4$-NaClO$_3$[6] in THF to give the desired diol (IXa), mp 133—135°, in 35% yield. The diol (IXa) revealed the hydroxy bands at 3550, 3500 cm^{-1}, the bands due to the α,β-unsaturated ester group at 1710, 1645 cm^{-1} and the acetate band at 1730 cm^{-1} in the IR spectrum and signals attributable to the *trans* olefinic protons appeared at 2.71 τ (1H, d, J=16 Hz) and 4.20 τ (1H, d, J=16 Hz), and signals of two protons geminal to the two hydroxy groups at 5.65—6.40 τ (2H, m) in the NMR spectrum. Treatment of IXa with active carbon afforded the hydroxy ether (XII), mp 148—149°, the IR spectrum of which showed the hydroxy band at 3400—3500 cm^{-1} and no α,β-unsaturated ester bands. Treatment of IXa with NaBH$_4$

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[6] K. Wiesner, Wen-ling Kao, and J. Šantroch, *Can. J. Chem.*, 47, 2431 (1969).

gave also the hydroxy ether. It is sure that the Michael addition of one of two hydroxy groups to the α,β-unsaturated ester double bond produced the hydroxy ether. This observation together with the structure proof of the ketol (XI) (*vide infra*) permitted to assign the formula (XII) for this hydroxy ether. This result established in turn the *cis* relationship of the two hydroxy groups to the α,β-unsaturated ester substituent at the angular position as shown in the formula (IXa). Catalytic reduction of IXa over PtO_2 furnished the dihydrodiol (Xa), mp 119—120° which was in turn converted to the dialdehyde (IIIa) by periodic acid oxidation. Besides the diol (IXa), careful separation of the OsO_4-$NaClO_3$ oxidation product gave the ketol (XI), mp 174—176°, which revealed the hydroxy band at 3500, the ketone band at 1715, and the α,β-unsaturated ester bands at 1715 and 1650 cm^{-1} in the IR spectrum. Reduction of XI with $NaBH_4$ afforded the hydroxy ether (XII) in high yield, indicating that the ketol was produced by oxidation of one of two hydroxy groups of the diol (IXa) and that the hydride attacked the ketone group from the concave face of the compound (XI). It is well known that the attack of the reagent to the *cis*-decalin derivatives occurs generally from their convex faces. The anomalous hydride attack in the present case will be explained by assuming that the ketone group is situated in the β position to the angular substituent and the hydride approach from the convex face gives rise to a serious non-bonded interaction between the reagent and the angular substituent to prevent the hydride attack from this face as shown in Fig. 1. The above assumption concerning the position of the ketone group was also supported by the following results. Treatment of the diol (IXa) with active carbon gave the hydroxy ether (XII) whereas the same treatment of the ketol (XI) recovered the starting material quantitatively. Sodium borohydride reduction of the dihydroketol (XIII), mp 144—146°, which was obtained by catalytic hydrogenation of the compound (XI), provided the dihydrodiol (X) in good yield but not the hydroxy ether (XII), and $NaBH_4$ reduction of the ketol (XI) gave the hydroxy ether (XII).

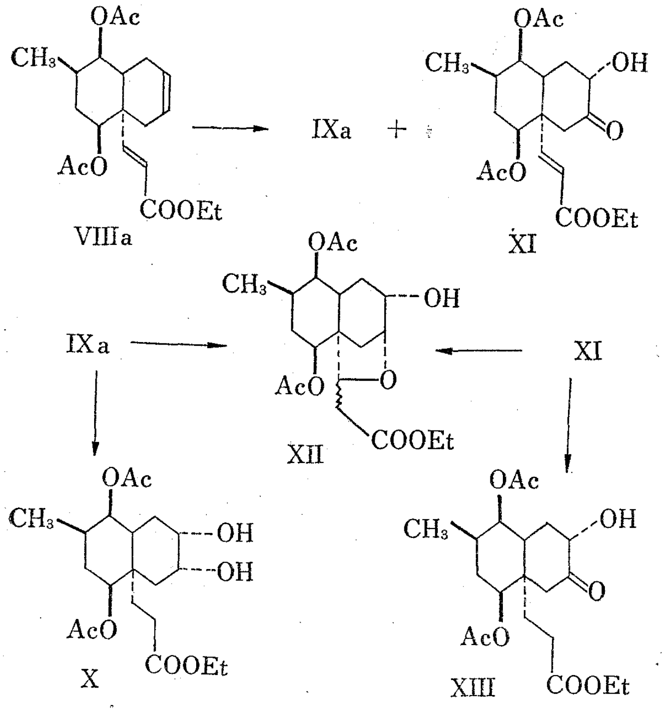

Chart 3

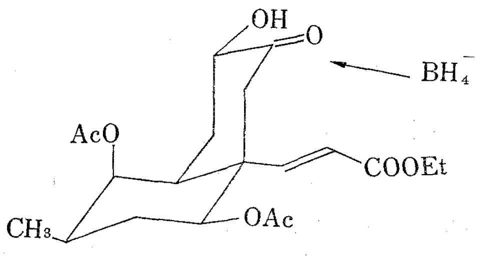

Fig. 1.

The similar treatments of IIb to those of IIa afforded the dialdehyde (IIIb).

Selective Cyclization Reaction of 1,2-Cyclohexanediacetaldehyde Derivatives [Syntheses of IV and V]

Since the dialdehyde (IIIa) obtained above seemed to be unstable for the further purification, the dialdehyde in $CHCl_3$ solution was passed immediately through the basic alumina column and elution with the same solvent afforded the α,β-unsaturated aldehyde (IVa), mp 122—124°, in 50% yield. Its IR spectrum showed the α,β-unsaturated aldehyde bands at 1680 and 1620 cm^{-1} and the NMR spectrum (100 MHz) exhibited a singlet (1H) due to an aldehyde proton at 0.35 τ, a quartet (1H, J_1=2 Hz, J_2=4 Hz) of an olefinic proton at 3.10 τ, a doublet (1H, J=4 Hz) of an allylic methine proton at 7.07 τ, and two quartets (1H, J_1=2 Hz, J_2=18 Hz at 7.14 τ: 1H, J_1=4 Hz, J_2=18 Hz at 7.88 τ) due to the allylic methylene protons. Irradiation on the signal due to a proton geminal to an acetoxy group at 4.82 τ resulted in the change of the doublet at 7.07 τ into the singlet and irradiation on the signal at 3.10 τ changed the signals of two quartets at 7.14 and 7.88 τ to the two sharp doublets (J=18 Hz). These observations suggest the structure of the α,β-unsaturated aldehyde as shown in the formula (IVa). The formation of IVa is rationalized by assuming that the carbanion derived from the less hindered active methylene with basic alumina may attack the other aldehyde carbonyl group and the resulting alcohol is dehydrated. Treatment of IIIa with AcOH gave also the same α,β-unsaturated aldehyde. Since any (V) type aldehyde could not be detected in the mother liquor removed the compound (IVa), the other reaction condition must be explored.

It is well known that Woodward, *et al.*[2] have succeeded in the formation of the D ring in their steroid synthesis using the enamine method which resulted in the selective cyclization of 1,2-cyclohexanediacetaldehyde derivative. We tried to apply this method to our cyclization reaction of the dialdehyde (IIIa). Thus, the dialdehyde (IIIa) and piperidine acetate were dissolved in dry benzene and the reaction mixture was then heated at 60° for 1 hr under nitrogen atmosphere. The conventional work up gave solely the α,β-unsaturated aldehyde which was identified with a sample of the unsaturated aldehyde (IVa) obtained from the basic alumina method. The formation of IVa in the enamine method is explainable by assuming that the nucleophilic attack of the enamine, formed from the less hindered aldehyde group and piperidine, to the other aldehyde group takes place to give the compound (IVa). In our case, this reaction condition was therefore not suitable.

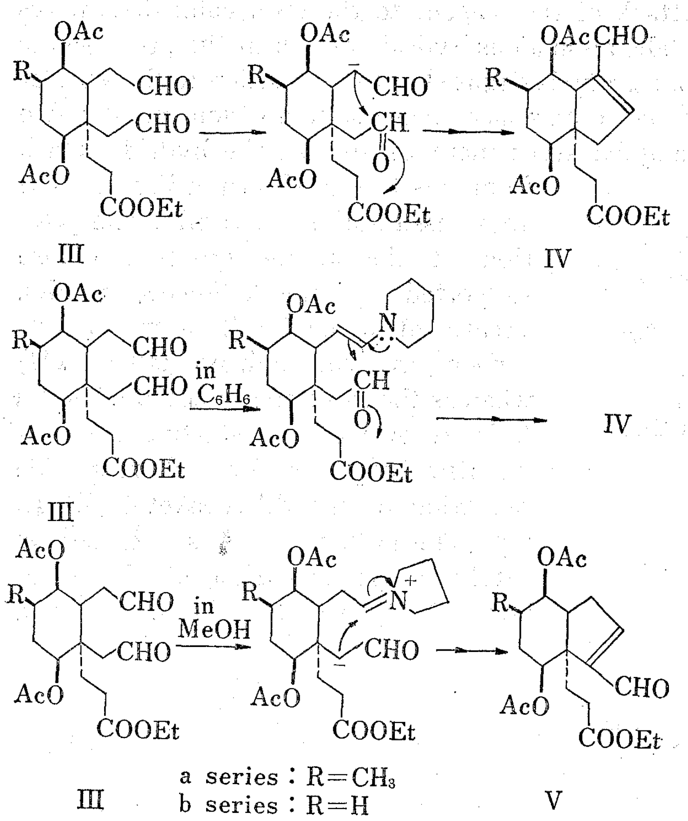

Chart 4

From the reaction mechanism described above, it is presumed that if the immonium salt, which is formed first from the less hindered aldehyde group and the amine, is maintained as such in the reaction mixture and the concentration of this salt is sufficient to cause the nucleophilic attack of the carbanion arised from the other acetaldehyde substituent to this immonium portion, the desired type α,β-unsaturated aldehyde would be obtained (see Chart 4). On the basis of this consideration, subsequent experiments were carried out using the polar solvent. Thus, the dialdehyde (IIIa) was treated with excess of pyrrolidine acetate in absolute methanol and the reaction mixture was kept on standing overnight at 0° under nitrogen atmosphere. The usual work up gave a mixture of aldehydes which was found to consist of two kinds of aldehydes in a 8: 1 ratio from its NMR spectrum examination. The major product showed a signal due to an aldehyde proton (1H, s) at 0.25 τ and a signal of an olefinic proton (1H, t, J=3 Hz) at 3.05 τ in the NMR spectrum. The signal pattern due to the allylic protons around 7.5 τ of this compound differed clearly from that of the compound (IVa). From these observations, the structure of the major product could be represented by the formula (Va). On the other hand, the NMR data of the minor product were identical with those of the compound (IVa). Consequently, the reaction condition described above serves the present purpose.

These two reaction conditions using basic alumina and pyrrolidine acetate in abs. MeOH, were applied to the compound (IIIb) and the similar results to those from the compound (IIIa) were obtained. Thus, the α,β-unsaturated aldehyde (IVb) was solely obtained in 70% yield by the former method and the latter method gave a mixture of two kinds of aldehydes which consists of IVb and Vb in a ratio of 1: 20. The structures of IVb and Vb were assigned by comparing their spectral data with those of IVa and Va, respectively.

The solvent effects for the cyclization reactions of the compound (IIIb) were examined using DMF, DMSO and AcOH as the solvent. The results are shown in the Table I and any significant effect was not observed.

Table I. The Relative Ratio of IVb and Vb in the Aldol Condensation Product Obtained from IIIb by the Pyrrolidine Acetate Method in Three Different Solvents

Solvent	Yield (%)	IVb/Vb Ratio
DMF	48	1/1
DMSO	36	2/3
AcOH	37	5/4
abs. MeOH	90	1/20

Experimental

All melting points were observed on a microscopic hotstage and uncorrected. All NMR spectra were obtained in $CDCl_3$ solution with tetramethylsilane as an internal standard on a Varian A-60 spectrometer or Varian HA-100 spectrometer when otherwise stated and IR spectra were measured for a solution in $CHCl_3$ with a Hitachi EPI spectrometer. Mass spectra were taken with a Hitachi RMU-6C spectrometer with a heated direct inlet system.

The Diol (VIIa)——To a suspension of 20 g of zinc powder in 40 ml of water was added a solution of 5 g of the enedione (IIa) in 40 ml of acetic acid and the mixture was stirred for 40 min at 60°. After removal of the precipitates by filtration, the filtrate was diluted with water and extracted with ether. The extract was washed with an aqueous sodium bicarbonate solution and dried over $MgSO_4$. Evaporation of the solvent left 5 g of the dione (VIa). To a stirred solution of 5 g of VIa in 100 ml of MeOH was gradually added a solution of 600 mg of $NaBH_4$ in 100 ml of EtOH under ice cooling. After 1 hr, the reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue in $CHCl_3$ was chromatographed on silica gel and elution with the same solvent gave a crystalline mass which was recrystallized from ether–petroleum ether to give 2.0 g of the diol (VIIa) as colorless needles, mp 94—95°. IR cm^{-1}: ν_{OH} 3550, 3500; ν_{CO} 1710; $\nu_{C=C}$ 1650. NMR τ: 3.15 (1H, d, J=16 Hz, olefinic proton), 4.11 (1H, d, J=16 Hz, olefinic proton), 4.18 (2H, m, olefinic protons), 5.80 (2H, q, J=7 Hz, OCH_2CH_3), 6.15—6.50 (2H, m, 2×$\rangle$CH–OH), 8.70 (3H, t, J=7 Hz, OCH_2CH_3), 8.95 (3H, d, J=6 Hz, $\rangle$CH–CH_3). *Anal.* Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.59; H, 8.64.

Oxidation of the Diacetate (VIIIa) with OsO_4–$NaClO_3$——A solution of 24 g of the diol (VIIa) in 150 ml of pyridine and 150 ml of Ac_2O was heated for 8 hr at 85° and evaporated to dryness *in vacuo*. The residue in $CHCl_3$ was chromatographed on silica gel and elution with the same solvent gave 30 g of the diacetate (VIIIa). IR cm^{-1}: ν_{CO} 1730, 1710; $\nu_{C=C}$ 1655. NMR τ: 4.85 (1H, t, J=2 Hz, $\rangle$CH–OAc), 5.10 (1H, q, J_1=6 Hz, J_2=9 Hz, $\rangle$CH–OAc). Mass Spectrum *m/e*: 364 (M$^+$). To a solution of 30 g of the diacetate (VIIIa) in 1700 ml of freshly distilled THF were added a solution of 2.5 g of OsO_4 in 50 ml of THF and a solution of 11.12 g of $NaClO_3$ in 290 ml of water. The mixture was stirred for 5 days at room temperature and the osmate was decomposed with H_2S gas. After removal of the precipitates by filtration, the filtrate was diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from ether to give 10.9 g of the diol (IXa), mp 133—135°, as colorless needles. IR cm^{-1}: ν_{OH} 3550, 3500; ν_{CO} 1730, 1710; $\nu_{C=C}$ 1645. NMR τ: 2.71 (1H, d, J=16 Hz, olefinic proton), 4.20

(1H, d, $J=16$ Hz, olefinic proton), 4.70 (1H, t, $J=2$ Hz, >CH–OAc), 5.35 (1H, t, $J=8$ Hz, >CH–OAc), 5.81 (2H, q, $J=7$ Hz, OCH_2CH_3), 5.65—6.40 (2H, m, 2×>CH–OH), 7.88 (3H, s, $OCOCH_3$), 7.95 (3H, s, OAc), 8.71 (3H, t, $J=7$ Hz, OCH_2CH_3), 9.13 (3H, d, $J=6$ Hz, >CH–CH_3). *Anal.* Calcd. for $C_{20}H_{30}O_8$: C, 60.29; H, 7.59. Found: C, 59.99; H, 7.67. The mother liquor from recrystallization of IXa was evaporated and the residue in $CHCl_3$ was chromatographed on silica gel and elution with the same solvent afforded 5 g of VIIIa in the earlier eluate and the successive elution with $CHCl_3$ gave 3.5 g of the ketol (XI), which was recrystallized from ether to give colorless prisms, mp 174—176°. IR cm^{-1}: ν_{OH} 3500; ν_{CO} 1735, 1715; $\nu_{C=C}$ 1650. NMR τ: 3.43 (1H, d, $J=16$ Hz, olefinic proton), 4.20 (1H, d, $J=16$ Hz, olefinic proton), 4.58 (1H, m, >CH–OAc), 5.18 (1H, q, $J_1=6$ Hz, $J_2=9$ Hz, >CH–OAc), 5.70—6.05 (1H, m, >CH–OH), 5.85 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.90 (3H, s, $OCOCH_3$), 8.03 (3H, s, $OCOCH_3$), 8.75 (3H, t, $J=7$ Hz, OCH_2CH_3), 9.10 (3H, d, $J=6$ Hz, >CH–CH_3). *Anal.* Calcd. for $C_{20}H_{28}O_8$: C, 60.59; H, 7.12. Found: C, 60.53; H, 7.17.

The Dihydrodiol (Xa)——1) From the Diol (IXa): To a solution of 2 g of IXa in 100 ml of EtOH was added 150 mg of PtO_2. The mixture was stirred under hydrogen at room temperature and atmospheric pressure. After the absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was evaporated to give 2 g of the dihydrodiol (Xa). Recrystallization from ether–petroleum ether afforded colorless needles, mp 119—120°. IR cm^{-1}: ν_{OH} 3500, 3400; ν_{CO} 1725. NMR τ: 4.77 (1H, t, $J=2$ Hz, >CH–OAc), 5.22 (1H, t, $J=8$ Hz, >CH–OAc), 5.70—6.40 (2H, m, >CH–OH), 5.88 (2H, q, $J=7$ Hz, OCH_2CH_3), 8.77 (3H, t, $J=7$ Hz, OCH_2CH_3), 9.19 (3H, d, $J=6$ Hz, >CH–CH_3). *Anal.* Calcd. for $C_{20}H_{32}O_8$: C, 59.98; H, 8.05. Found: C, 60.01; H, 8.09.

2) From the Dihydroketol (XIII): To a solution of 100 mg of XIII in 10 ml of EtOH was added 20 mg of $NaBH_4$. The mixture was stirred for 30 min, diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated. The residue in $CHCl_3$ was chromatographed on silica gel and elution with $CHCl_3$ afforded 60 mg of Xa which was identified with an authentic sample.

The Hydroxy Ether (XII)——1) From the Ketol (XI): To a solution of 350 mg of the ketol (XI) in 20 ml of MeOH was added a solution of 100 mg of $NaBH_4$ in 10 ml of EtOH. The mixture was stirred for 2 hr at room temperature, diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated. The residue was recrystallized from ether to give 300 mg of the hydroxy ether (XII), mp 148—149°, as colorless plates. IR cm^{-1}: ν_{OH} 3400—3500; ν_{CO} 1730. NMR τ: 4.80 (1H, t, $J=3$ Hz, >CH–OAc), 5.31 (1H, q, $J_1=5$ Hz, $J_2=10$ Hz, >CH–OAc), 5.60—5.90 (2H, m, 2×>CH–O–), 5.83 (2H, q, $J=7$ Hz, OCH_2CH_3), 6.50 (1H, m, >CH–O–), 7.90 (3H, s, $OCOCH_3$), 7.96 (3H, s, $OCOCH_3$), 8.75 (3H, t, $J=7$ Hz, OCH_2CH_3), 9.15 (3H, d, $J=6$ Hz, >CH–CH_3). *Anal.* Calcd. for $C_{20}H_{30}O_8$: C, 60.29; H, 7.59. Found: C, 60.19; H, 7.47.

2) From the Diol (IXa): To a solution of 60 mg of IXa in 10 ml of EtOH was added 20 mg of $NaBH_4$. The mixture was stirred for 2 hr. After the usual work up, the residue was recrystallized from ether to give 51 mg of XII, mp 148°, which was identified with an authentic sample in all respects.

3) From the Diol (IXa): To a solution of 60 mg of IXa in 10 ml of EtOH was added 100 mg of activated charcoal and the mixture was refluxed for 5 hr. After the usual work up, the residue was recrystallized from ether to give 50 mg of XII, mp 147—148°, which was identical with an authentic sample in all respects.

The Dihydroketol (XIII)——To a solution of 130 mg of the ketol (XI) in 20 ml of AcOEt was added 20 mg of PtO_2. After the usual hydrogenation and work up, the residue was recrystallized from ether to afford 120 mg of XIII, mp 144—146°, as colorless prisms. IR cm^{-1}: ν_{OH} 3500; ν_{CO} 1730. *Anal.* Calcd. for $C_{20}H_{30}O_8$: C, 60.29; H, 7.59. Found: C, 60.40; H, 7.70.

The α,β-Unsaturated Aldehyde (IVa)——1) Basic Alumina Method: A solution of 600 mg of periodic acid in 10 ml of water was added to a solution of 450 mg of the dihydrodiol (XIIa) in 30 ml of dioxane. The mixture was stirred at room temperature under nitrogen atmosphere for 15 min, diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to dryness at room temperature under reduced pressure. The residue without purification was immediately chromatographed on basic alumina in $CHCl_3$ and elution with the same solvent gave 210 mg of a crystalline mass and recrystallization from ether–petroleum ether gave colorless needles (IVa), mp 122—124°. IR cm^{-1}: ν_{CO} 1725, 1680; $\nu_{C=C}$ 1620. NMR τ: 0.35 (1H, s, –CHO), 3.10 (1H, q, $J_1=4$ Hz, $J_2=2$ Hz, olefinic proton), 4.82 (1H, d, $J=4$ Hz, >CH–OAc), 5.02 (1H, q, $J_1=10$ Hz, $J_2=8$ Hz, >CH–OAc), 5.96 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.07 (1H, d, $J=4$ Hz, allylic methine), 7.14 (1H, q, $J_1=18$ Hz, $J_2=2$ Hz, allylic methylene), 7.88 (1H, q, $J_1=18$ Hz, $J_2=4$ Hz, allylic methylene), 7.96 (3H, s, $OCOCH_3$), 8.10 (3H, s, $OCOCH_3$), 8.80 (3H, t, $J=7$ Hz, OCH_2CH_3), 9.11 (3H, d, $J=6$ Hz, >CH–CH_3) (Varian HA-100 spectrometer). *Anal.* Calcd. for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 62.92; H, 7.67.

2) Acetic Acid Method: A solution of 80 mg of the aldehyde (IIIa) in 10 ml of AcOH was stirred for 66 hr under ice cooling and nitrogen atmosphere. After the usual work up, the residue in $CHCl_3$ was chromatographed on silica gel and elution with $CHCl_3$ gave 50 mg of the α,β-unsaturated aldehyde, mp 125°, which was identical with an authentic sample of IVa in all respects.

3) Piperidine Acetate Method: To a solution of 180 mg of the aldehyde (IIIa) in 10 ml of anhydrous benzene was added a trace of piperidine acetate and the mixture was stirred for 1 hr at 60° under nitrogen

atmosphere. The solvent was evaporated and the residue was chromatographed on silica gel in $CHCl_3$ and elution with the same solvent gave 65 mg of IVa, mp 122°, which was identical with an authentic sample in all respects.

The α,β-Unsaturated Aldehyde (Va)——To a solution of 1.9 g of IIIa in 280 ml of dry MeOH were added 2 g of pyrrolidine and 2 g of AcOH under nitrogen atmosphere. The mixture was stirred overnight under ice cooling, diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated. The residue in $CHCl_3$ was chromatographed on silica gel and elution with the same solvent gave 1.4 g of the oily α,β-unsaturated aldehyde (Va). IR cm^{-1}: ν_{CO} 1725, 1680; $\nu_{C=C}$ 1620. NMR τ: 0.25 (1H, s, –CHO), 3.05 (1H, t, J=3 Hz, olefinic proton), 4.70—5.30 (2H, m, 2×$>$CH–OAc), 5.90 (2H, q, J=7 Hz, OCH_2CH_3), 7.92 (3H, s, $OCOCH_3$), 8.06 (3H, s, $OCOCH_3$), 8.77 (3H, t, J=7 Hz, OCH_2CH_3), 9.01 (3H, d, J=6 Hz, $>$CH–CH_3). This α,β-unsaturated aldehyde gave quantitatively the oily ethylene acetal by the usual method. Mass Spectrum *m/e*: 424 (M^+).

The Diol (VIIb)——To a stirred suspension of 40 g of zinc powder in 100 ml of water was added at 60° a solution of 10 g of the enedione (IIb) in 100 ml of acetic acid. The mixture was stirred vigorously for 30 min at the same temperature and the precipitates were removed by filtration. The filtrate was diluted with water and extracted with ether. The extract was washed with water and dried over $MgSO_4$. Removal of the solvent yielded 10 g of crude crystalline mass which was recrystallized from ether to give 7 g of the dione (VIb) as colorless needles, mp 99—100°. IR cm^{-1}: ν_{CO} 1710; $\nu_{C=C}$ 1640. *Anal.* Calcd. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.75; H, 6.70. To a solution of 7 g of the dione (VIb) in 400 ml of MeOH was added dropwise a solution of 920 mg of $NaBH_4$ in 100 ml of EtOH under stirring and ice cooling. The mixture was stirred for 30 min, diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated. The residue in $CHCl_3$ was chromatographed on silica gel and elution with the same solvent afforded 5.68 g of the diol (VIIb). Recrystallization from acetone–ether gave colorless plates, mp 88—90°. IR cm^{-1}: ν_{OH} 3510; ν_{CO} 1705; $\nu_{C=C}$ 1650. NMR τ: 3.12 (1H, d, J=16 Hz, olefinic proton), 4.10 (1H, d, J=16 Hz, olefinic proton), 4.05—4.25 (2H, m, olefinic protons), 5.80 (2H, q, J=7 Hz, OCH_2CH_3), 6.05—6.45 (2H, m, $>$CH–OH), 8.72 (3H, t, J=7 Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.36; H, 8.19.

The Diacetate (VIIIb)——A mixture of 3.61 g of the diol (VIIb) in 15 ml of pyridine and 15 ml of acetic anhydride was heated on a steam bath for 5 hr and evaporated *in vacuo*. The residue in $CHCl_3$ was chromatographed on silica gel and elution with $CHCl_3$ afforded 4.43 g of the diacetate (VIIIb), which was recrystallized from ether to give colorless plates, mp 110°. IR cm^{-1}: ν_{CO} 1720, 1700 (sh); $\nu_{C=C}$ 1650. *Anal.* Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.12; H, 7.46.

The Diol (IXb)——To a solution of 200 mg of VIIIb in 10 ml of freshly distilled THF were added a solution of 36 mg of OsO_4 in 6 ml of THF and a solution of 100 mg of $NaClO_3$ in 4 ml of water. The reaction mixture was stirred for 20 hr. After decomposition of the osmate with H_2S gas, the precipitates were filtered off. The filtrate was diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to leave the residue which was recrystallized from ether to give 140 mg of IXb as colorless prisms, mp 182—185°. IR cm^{-1}: ν_{OH} 3500; ν_{CO} 1725, 1705; $\nu_{C=C}$ 1645. *Anal.* Calcd. for $C_{19}H_{28}O_8 \cdot 1/4H_2O$: C, 58.68; H, 7.38. Found: C, 58.84; H, 7.20.

The Dihydrodiol (Xb)——To a solution of 612 mg of IXb in 150 ml of 99% EtOH was added 135 mg of PtO_2. The mixture was stirred under hydrogen at room temperature and atmospheric pressure until the absorption had ceased. After removal of the catalyst by filtration, the filtrate was evaporated to leave 587 mg of Xb which was recrystallized from acetone–ether to afford colorless pillars, mp 132—135°. IR cm^{-1}: ν_{OH} 3500; ν_{CO} 1725. *Anal.* Calcd. for $C_{19}H_{30}O_8$: C, 59.05; H, 7.83. Found: C, 59.31; H, 7.88.

The α,β-Unsaturated Aldehyde (IVb)——To a solution of 50 mg of Xb in 6 ml of dioxan was added a solution of 40 mg of $HIO_4 \cdot 2H_2O$ in 2 ml of distilled water at room temperature. The mixture was stirred for 1 hr under nitrogen atmosphere and diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated under reduced pressure at room temperature to give the crude aldehyde (IIIb). To a solution of IIIb in 15 ml of $CHCl_3$ was added 1 g of basic alumina and the mixture was stirred overnight under nitrogen. After removal of alumina by filtration, the solvent was evaporated. The residue in $CHCl_3$ was chromatographed on silica gel and elution with the same solvent gave 33 mg of the oily α,β-unsaturated aldehyde (IVb). IR cm^{-1}: ν_{CO} 1720, 1670; $\nu_{C=C}$ 1614. NMR τ: 0.32 (1H, s, aldehyde proton), 3.07 (1H, t, J=3 Hz, olefinic proton), 4.67—5.28 (2H, m, 2×$>$CH–OAc), 5.92 (2H, q, J=7 Hz, OCH_2CH_3), 7.92 (3H, s, $OCOCH_3$), 8.09 (3H, s, $OCOCH_3$), 8.73 (3H, t, J=7 Hz, OCH_2CH_3). For analysis, the ethylene acetal of this α,β-unsaturated aldehyde was derived by the usual procedure. Mass Spectrum *m/e*: 410 (M^+).

The α,β-Unsaturated Aldehyde (Vb)——A mixture of 370 mg of the dialdehyde (IIIb), 70 ml of MeOH, 15 drops of pyrrolidine and 15 drops of acetic acid was stirred for 1 hr at 0° under nitrogen atmosphere. The reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated. The residue in $CHCl_3$ was chromatographed on silica gel and elution with $CHCl_3$ gave 332 mg of Vb which was recrystallized from ether–petroleum ether to give colorless pillars, mp 97—99°. IR cm^{-1}: ν_{CO} 1724, 1675; $\nu_{C=C}$ 1610. NMR τ: 0.33 (1H, s, aldehyde proton), 2.97 (1H, t, J=2 Hz, olefinic proton), 4.72—5.25 (2H, m, 2×$>$CH–OAc), 5.88 (2H, q, J=7 Hz, OCH_2CH_3), 7.95 (3H, s, $OCOCH_3$), 8.08 (3H, s, $OCOCH_3$), 8.77 (3H, t, $J=7$ Hz, OCH_2CH_3). *Anal.* Calcd. for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.22; H, 6.92.

Aldol Condensation of (IIIb) in Three Different Solvents——1) In DMF: A mixture of 50 mg of IIIb in 14 ml of DMF and each two drops of AcOH and pyrrolidine was stirred for 2 hr under ice cooling and nitrogen atmosphere. The reaction mixture was then diluted with water and extracted with ether. The extract was washed with water, dried over $MgSO_4$ and evaporated. The residue in $CHCl_3$ was passed through the short column of silica gel and evaporation of the solvent gave 23 mg of a mixture of IVb and Vb.

2) In AcOH: To a solution of 50 mg of IIIb in 10 ml of AcOH was added a solution of three drops of pyrrolidine in 17 ml of AcOH under nitrogen atmosphere. The mixture was stirred for 18 hr at room temperature. The usual work up gave 18 mg of a mixture of IVb and Vb.

3) In DMSO: To a solution of 50 mg of IIIb in 10 ml of freshly distilled DMSO were added two drops of AcOH and two drops of pyrrolidine. The mixture was stirred for 1.5 hr under cooling and nitrogen atmosphere. The usual work up afforded 17 mg of a mixture of IVb and Vb.

In these three experiments, the relative ratio of IVb and Vb in each reaction product was estimated by the relative intensity of the signal due to $COOC\underline{H}_2CH_3$ protons corresponding to IVb and Vb, respectively, and shown in Table I.