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THE STEREOCHEMISTRY OF THE MICHAEL ADDITION OF MALONIC ESTERS TO 4-SUBSTITUTED CYCLOPENT-2-EN-1-ONES

A. ICHIHARA, J. MORITA, K. KOBAYASHI, S. KAGAWA, H. SHIRAHAMA and T. MATSUMOTO

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Japan

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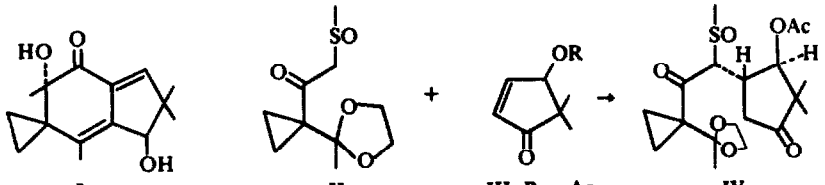
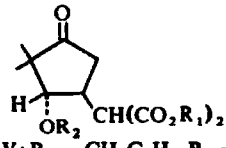
Abstract—The stereochemistry of the Michael addition of malonic esters to 4-substituted cyclopent-2-en-1-ones (III and XV) has been studied under various conditions of solvents, catalysts and temperature. Under conditions of kinetic control, the main product is a *trans* compound, for example, V, VI, XIII and XVI, while under conditions of thermodynamic control, the main product is a *cis* lactone (XIV). The mechanism of the formation of XIV is discussed.

IN THE course of the synthetic studies of illudin M(I),[1-3] it was found that the addition of a β-ketosulfoxide (II) to a cyclopentenone (III) proceed stereoselectively to give a single product (IV).[2,3] The stereochemistry of IV was tentatively assigned by NMR spectrum to be *trans*, since the J_{AX} value of 9 Hz in the adduct (IV) indicates that H_A and H_X are both quasi-axial.

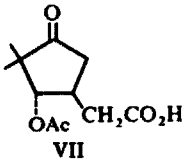


I II III: R = Ac XV: R = H IV

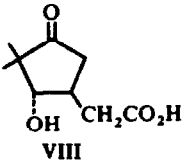
We now wish to report chemical evidence for the stereochemistry and to discuss the stereochemical course of the Michael addition to 4-substituted cyclopent-2-enones (III, XV) under several conditions. Very little is known concerning the stereochemistry of the Michael addition to substituted cyclopentenones.[4]



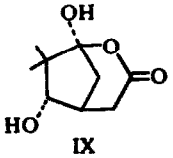
V: $R_1 = CH_2C_6H_5$, R_2 = Ac
VI: R_1 = H, R_2 = Ac
XIII: $R_1 = C_2H_5$, R_2 = Ac
XVI: $R_1 = C_2H_5$, R_2 = H



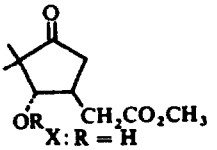
VII



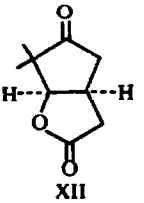
VIII



IX



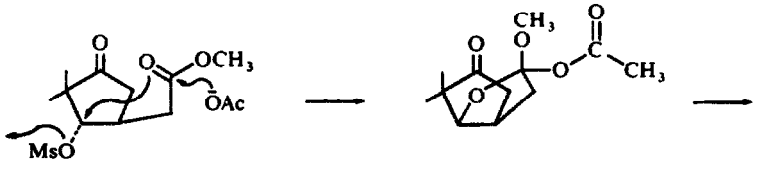
X: R = H
XI: R = Ms



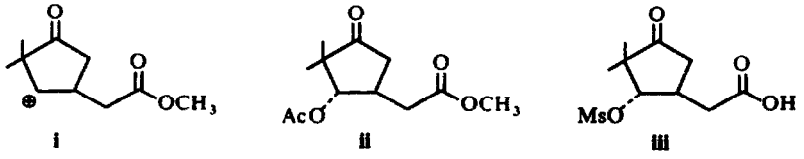
XII

For the investigation of the addition of dibenzyl malonate to 5,5-dimethyl-4-acetoxylcyclopent-2-en-1-one (III), the α,β-unsaturated cyclopentenone was prepared by the known procedure.[2,3] The Michael reaction was carried out in ethanol at room temperature for 30 min to give exclusively an adduct V, m.p. 95–96° in 61% yield. In the NMR spectrum of V, the coupling constant (J = 9 Hz) of the signal at τ 4·83 due to α proton to acetoxy group would mean that the proton has a *trans* disposition to a vicinal proton as in the case of IV.[2] The *trans*-orientation of the adduct (V) was confirmed chemically as follows. Hydrogenolysis of V on 5% Pd-C gave a diacid (VI), m.p. 153–155°, which in turn was decarboxylated by heating at 160° for 15 min to give a crystalline monoacid (VII), m.p. 123–124°. Hydrolysis of the acid (VII) with 10% sodium hydroxide in methanol produced a hydroxy acid (VIII), m.p. 100·5–101·5° in 82% yield. If the hydroxy acid had *cis* configuration, it should be spontaneously cyclized to a γ-lactone.[5] Since the product (VIII) has no absorption band due to γ-lactone carbonyl in the IR spectrum, the compound VIII must be a *trans* hydroxy acid. The stereochemistry of VIII is further discussed later. When the acid VIII was recrystallized from chloroform, the resultant compound, m.p. 91–93°, showed new absorption bands at 3430 cm^{-1} and at 1730 cm^{-1} due to an OH and a δ-lactone CO group respectively in place of absorption band due to a 5-membered ring ketone in the IR spectrum. Therefore, the compound must be an isomerized lactol (IX). The lactol (IX) was reversibly converted to VIII by recrystallization from benzene. Esterification of VIII with diazomethane gave a methyl ester (X) in 90% yield. Treatment of the ester (X) with mesyl chloride in dry pyridine afforded a mesylate (XI), m.p. 95·5–96·5°, which still has a signal at τ 5·18 due to α proton to mesyloxy group with the coupling constant, J = 8 Hz, corresponding to two vicinal protons oriented in *trans*.

The mesylate (XI) was then refluxed with anhydrous sodium acetate in anhydrous acetic acid to yield a compound, which was homogeneous on TLC and characterized as a 2,4-dinitrophenylhydrazone, m.p. 209–210°, $C_{15}H_{16}O_6N_4$. Since in the IR spectrum the compound shows an absorption band at 1785 cm^{-1} which is ascribable to a γ-lactone and in NMR spectrum a signal at 5·36 (J = 5 Hz) due to CH—O—CO, the structure XII was assigned. The formation of the lactone (XII) from the mesylate (XI) would be rationalized as follows.*

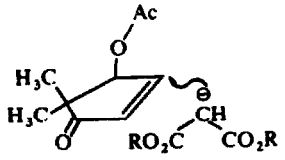


* Although for simplicity the mechanism is formulated as a concerted one, as a referee suggested, a stepwise mechanism through i cannot be excluded at this stage of study. However, as the positive charge of neopentyl type develops, it would be readily neutralized by the neighbouring ester CO group. Therefore the concerted or quasi-concerted mechanism may be more plausible. The compound ii, which would be formed through i, could not be detected. As another possibility could be that the compound XII is formed by acetolysis of the ester group in XI prior to lactonization to give iii, followed by lactonization.



i ii iii

These facts clearly indicate that the Michael addition occurred stereospecifically in a *trans* manner under the above conditions. Since the acetoxy cyclopentenone (III) is almost planar, malonate anion would attack from the opposite side of the acetoxy group as follows.

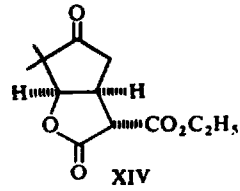


Next, we investigated the Michael reaction under several conditions in order to clarify the relationship between the stereospecificity and the reaction conditions. The results are summarized in Table 1.

TABLE 1. MICHAEL REACTIONS UNDER SEVERAL CONDITIONS

Reactions	Molar ratio of			Solvent	Temp	Product
	Na	Diethyl malonate	Cyclo-pentenone			
1	0·5	1·0	1·0 (III)	EtOH	r.t.	XIII (trans)
2	0·3	1·2	1·0 (III)	EtOH	r.t.	XIII
3	0·25	1·0	1·0 (III)	Benzene	r.t.	XIII
4	2·0	2·0	1·0 (III)	EtOH	60°	XIV (cis-lactone)
5	0·5	1·0	1·0 (XV)	EtOH	r.t.	XVI (trans)

For example, in reaction 3, the addition was carried out in benzene, using diethyl malonate as a nucleophile in the presence of $\frac{1}{4}$ molar equivalent of sodium ethoxide at room temperature. The reaction mixture was checked by gas chromatography at various intervals of time and showed throughout the reaction only a single product peak attributable to the *trans* compound (XIII), which, like other related *trans*-compounds,[2] has a coupling constant $J = 9$ Hz at τ 4·85 due to an α proton to acetoxyl group in the NMR spectrum. The results suggested that XIII was formed through a kinetically controlled process. However, under drastic conditions (reaction 4) in which the reaction was carried out in ethanol in the presence of two molar equivalents of sodium ethoxide at 60°, the reaction gave predominantly a new adduct. The adduct has bands at 1785 cm^{-1} due to a γ-lactone and at 1742 cm^{-1} due to a 5-membered cyclic ketone and an ester in the IR spectrum. In the NMR spectrum, the adduct shows signals at τ8·92 (3H, s, C—C$\underline{H}_3$), 8·82 (3H, s, C—C$\underline{H}_3$), 8·67 (3H, s, CH_2—C$\underline{H}_3$), 6·63 (1H, s, C$\underline{H}$—CO_2), 5·78 (2H, q, C$\underline{H}_2$—CH_3) and 5·29 (1H, d, $J = 5$ Hz, C$\underline{H}$—OCO). The coupling constants $J = 5$ Hz at 5·29 and $J \simeq 0$ Hz at 6·63 indicate the structure XIV for the adduct.

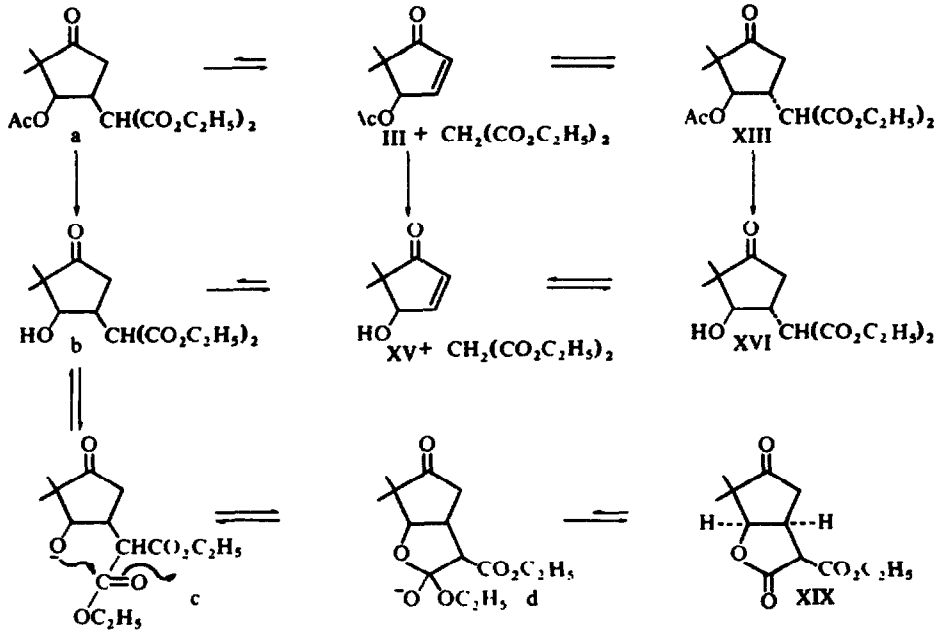


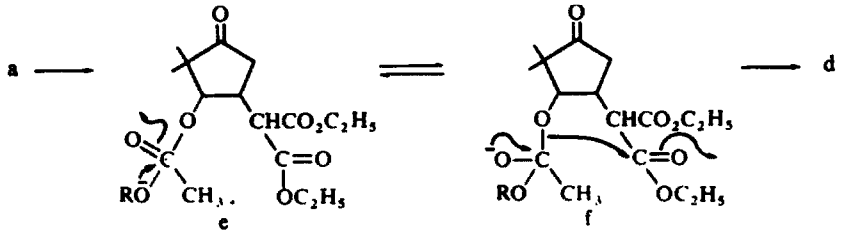
XIV

The structure XIV was unequivocally confirmed by the conversion of XIV to the γ-lactone (XII). Thus, the lactone ester (XIV) was refluxed for 2 hr in conc HCl to give a product which was identical with the previously obtained sample (XII) in all respects.

At first, the specific formation of the lactone ester (XIV) in reaction 4 was considered to be the result of the participation of a neighbouring OH group with an OH group adjacent to the attacking point in a hydroxy-cyclopentenone (XV), which could be derived from III by ethanolysis under the reaction conditions (excess base and high temp). Therefore, the hydroxy-cyclopentenone (XV) was prepared from III by hydrolysis with K_2CO_3 in MeOH-H_2O and the addition reaction of diethyl malonate to XV was examined under mild conditions (reaction 5). The addition reaction gave a product whose spectrum was identical with that of authentic *trans*-hydroxycyclopentyl malonate (XVI, J = 9 Hz at τ 6·30) derived from the acetate (XIII). Acetylation of the product gave an acetate which was identical with an authentic sample (XIII) by gas chromatography. The result mentioned above excluded the possibility of OH group participation in the formation of XVI from XV.

On the other hand, equilibration of the *trans*-adduct (XIII) under the same conditions as used for the addition reaction 4 gave the *cis*-lactone ester (XIV). Further, the same treatment of the *trans* compound (XVI) also yielded the *cis*-lactone ester (XIV). From these data, mechanism of the formation of the *cis*-γ-lactone ester (XIV) in reaction 4 would be explained as follows:





It is reasonable to assume formation of a *cis*-hydroxy compound (b) through *cis*-acetoxy compound (a) which is in equilibrium with the *trans* adduct (XIII) and through *trans*-hydroxy compound (XVI) by reversible equilibration (b) ⇌ XVI. Further a part of III can be alcoholyzed to the hydroxycyclopentenone (XV) which is also equilibrated with *trans* adduct (XVI) and *cis* adduct (b). The *cis* adduct (b) immediately would be converted to the γ-lactone (XIV) through the intermediates (c) and (d). In addition, formation of the *cis*-γ-lactone ester (XIV) through the sequence (a) → (e) → (f) → (d) is also possible.

Summarizing the results of this study it may be concluded that under mild conditions (reaction **1, 2, 3** and **5**) the Michael addition is kinetically controlled to give *trans* adducts (XIII, XVI), but under drastic conditions (reaction **4**), the kinetic control was lost and stable *cis*-lactone ester (XIV) through equilibrated *cis* adduct was formed.

EXPERIMENTAL

M.ps. are uncorrected. IR spectra were measured on a JASCO model IR-S instrument with NaCl optics. NMR spectra were measured on Hitachi model H-6013 and JEOLCO model JNM-3H-60 using TMS as internal standard.

5,5-Dimethyl-4-acetoxycyclopent-2-en-1-one (III). This was prepared by the procedure described.[2]

Dibenzyl trans-*1-oxo-2,2-dimethyl-3-acetoxy-4-cyclopentylmalonate* (V). A soln of 1·180 g of III and 2·160 g of benzyl malonate and ca. 40 mg NaOEt in 2 ml EtOH was allowed to stand for 30 min at room temp. The resultant crystalline material was collected and washed with n-hexane. Recrystallization of the crude product from n-hexane gave 1·892 g (61%) of Michael adduct (V), m.p. 95–96°; ν_{max}^{Nujol} 1760, 1740, 1220 cm^{-1}; τ^{CCl_4} 9·14 (3H, s), 8·95 (3H, s), 8·18 (3H, s), 6·42 (1H, d, J = 7 Hz), 4·99 (4H, s), 4·83 (1H, d, J = 9 Hz). (Found: C, 69·18; H, 6·26, $C_{26}H_{28}O_7$ requires: C, 69·01; H, 6·24%).

trans-*1-Oxo-2,2-dimethyl-3-acetoxy-4-cyclopentylmalonic acid* (VI). A mixture of 1·70 g of V and 1·5 g Pd-C (5%) in 40 ml ether and 40 ml benzene was shaken under H_2 (30 kg/cm^2) for 30 hr at room temp. The mixture was filtered and the filtrate was concentrated *in vacuo* to give 0·910 g (89%) of VI as a white powder, m.p. 153–155°; ν_{max}^{Nujol} 1740, 1720, 1700 cm^{-1}.

trans-*1-Oxo-2,2-dimethyl-3-acetoxy-4-cyclopentylacetic acid* (VII). The diacid VI, (910 mg) was decarboxylated by heating at 165° for 15 min. The product was dissolved in $NaHCO_3$ aq and the neutral material was extracted from the soln. After acidification with HCl, the soln was extracted by ether to give 554 mg (73%) of VII. Recrystallization from n-hexane-benzene gave pure VII, m.p. 123–124°; ν_{max}^{Nujol} 3170, 1735, 1250 cm^{-1}; τ^{CDCl_3} 8·97 (3H, s), 8·87 (3H, s), 7·83 (3H, s), 4·98 (1H, diffused), −0·25 (1H, s). (Found: C, 57·87; H, 7·05. $C_{11}H_{16}O_5$ requires: C, 57·85; H, 7·07%).

trans-*1-Oxo-2,2-dimethyl-3-hydroxy-4-cyclopentylacetic acid* (VIII). A mixture of 100 mg of VII and NaOH aq (3·3%) in 3 ml MeOH was allowed to stand for 1 hr at room temp. The mixture was concentrated *in vacuo*, acidified with HCl and extracted with ether. Evaporation of the solvent gave 63 mg of VIII in 82% yield. Recrystallization of the acid from benzene gave pure VIII, m.p. 100·5–101·5; ν_{max}^{Nujol} 3220, 1750, 1690 cm^{-1}. (Found: C, 58·35; H, 7·58. $C_9H_{14}O_4$ requires: C, 58·05; H, 7·58%).

Isomerization of VIII *to the lactol* (IX). Recrystallization of VIII from $CHCl_3$ gave IX, m.p. 91–93°; ν_{max}^{Nujol} 3430, 1730 cm^{-1}. (Found: C, 57·94; H, 7·71. $C_9H_{14}O_4$ requires: C, 58·05; H, 7·58%). The lactol was reversibly converted to VII by recrystallization from benzene.

Methyl trans-*1-oxo-2,3-dimethyl-3-hydroxy-4-cyclopentylacetate* (X). To a soln of 63 mg of VIII was

added excess ethereal soln of diazomethane and the whole was allowed to stand for 1 hr at room temp. The mixture was evaporated *in vacuo* to give 60 mg (90%) of X; ν_{max}^{neat} 3420, 1740 cm^{-1}; τ^{CCl_4} 8·96 (3H, s), 8·85 (3H, s), 6·23 (3H, s).

Methyl trans-1-*oxo*-2,2-*dimethyl*-3-*mesyloxy*-4-*cyclopentylacetate* (XI). A soln of 60 mg of X and 70 mg of MsCl in 0·1 ml dry pyridine was allowed to stand for 1 hr at room temp. A large amount of ether was added to the mixture and the ethereal soln was washed with $NaHCO_3$aq, dil HCl and sat salt soln, and dried with Na_2SO_4. The soln was evaporated *in vacuo* to give 81 mg (83%) of XI. Recrystallization from n-hexane-benzene gave pure XI m.p. 95·5–96·5; ν_{max}^{Nujol} 1755, 1730, 1330, 1170 cm^{-1}; τ^{CDCl_3} 8·87 (3H, s), 8·71 (3H, s), 6·82, 3H), 6·23 (3H, s), 5·18 (1H, d, J = 8 Hz). (Found: C, 47·43; H, 6·46. $C_{11}H_{18}O_6S$ requires: C, 47·48; H, 6·52%).

Lactonization of XI *to* XII. A soln of 103 mg of XII and 196 mg of anhyd AcONa in 2 ml of anhyd AcOH was refluxed for 2 hr. The mixture was neutralized by adding Na_2CO_3 and extracted with ether. Combined extracts were evaporated *in vacuo* to give 47 mg (74%) of XII; ν_{max}^{neat} 1785, 1745 cm^{-1}; τ^{CCl_4} 8·86 (3H, s), 8·71 (3H, s), 5·36 (1H, d, J = 5 Hz); 2,4-dinitrophenylhydrazone of XII, m.p. 209–210°. (Found: C, 51·57; H, 4·59; N, 16·11. $C_{15}H_{16}O_6N_4$ requires: C, 51·72; H, 4·63; N, 16·09%).

Diethyl trans-1-*oxo*-2,2-*dimethyl*-3-*acetoxy*-4-*cyclopentylmalonate* (XIII). A soln of 1·18 g (0·007 mole) of III and 1·13 g (0·0071 mole) diethyl malonate and 0·04 g Na in 4 ml EtOH was allowed to stand for 30 min at room temp. The reaction mixture was acidified with 1 ml AcOH and poured into water. The mixture was extracted with ether and the extract was washed with dil $NaHCO_3$aq and then with saturated salt soln and dried with Na_2SO_4. The extract was concentrated *in vacuo* to give a residue. The residue was chromatographed on silica gel using benzene-AcOEt (30:1) as solvent. The resultatnt crystals were recrystallized from n-hexane to give 478 mg of pure XIII, m.p. 65–66°; ν_{max}^{Nujol} 1745, 1728, 1235 cm^{-1}; τ^{CCl_4} 9·02 (3H, s), 8·91 (3H, s), 8·70 (6H, t, J = 7 Hz), 7·90 (3H, s), 6·50 (1H, d, J = 6 Hz), 5·78 (2H, q, J = 7 Hz), 5·75 (2H, q, J = 7 Hz), 4·85 (1H, d, J = 9 Hz). (Found: C, 58·67; H, 7·40. $C_{16}H_{24}O_7$ requires: C, 58·52; H, 7·37%).

Further elution of the column with the same solvent gave 660 mg of XVI; ν_{max}^{neat} 3400, 1730 cm^{-1}; τ^{CCl_4} 9·06 (3H, s), 8·97 (3H, s), 8·72 (6H, t, J = 7 Hz), 6·60 (1H, d, J = 7 Hz), 6·30 (1H, d, J = 9 Hz), 5·83 (4H, q, J = 7 Hz).

The compound XVI was not a reaction product, but a by-product formed by hydrolysis of XIII in the column during purification. This was confirmed by the facts that, before chromatography, the reaction mixture shows no peak due to XVI in GLC and pure XIII (430 mg) was converted to XVI (230 mg) by the chromatography on the silica gel column under the same condition used for the purification.

Compounds XIII and XVI were used as the authentic samples for the identification of the products of the Michael reaction under various conditions.

5,5-*Dimethyl*-4-*hydroxycyclopent*-2-*en*-1-*one* (XV). To a soln of 200 mg of III in 2 ml MeOH and 0·8 ml water was added 80 mg K_2CO_3. The mixture was allowed to stand for 50 min at room temp. The reaction mixture was concentrated *in vacuo* and the residue was extracted with ether. The ether extracts were evaporated to give 95 mg of product. Chromatography of the product on a silica gel colum using benzene-MeOH (50:1) as solvent gave 20 mg of XV; ν_{max}^{neat} 3400, 1700, 1590 cm^{-1}; τ^{CCl_4} 8·96 (3H, s), 8·85 (3H, s), 5·50 (1H, s), 3·88 (1H, d, J = 5 Hz), 2·60 (1H, d, J = 5 Hz).

Michael reactions under several conditions

Reaction 1. A soln of 168 mg of III and 160 mg (1 equiv) diethyl malonate in 0·8 ml EtOH was added to a soln of EtONa from Na (11·5 mg, 0·5 equiv) at room temp. The reaction mixture was sampled at various intervals of time (15, 30, 60, 120 min and 7 days), and each sample was acidified with AcOH and then extracted with ether. Combined extracts were washed with dil $NaHCO_3$aq and saturated salt soln and evaporated *in vacuo* to give the product. Each product was analyzed by GLC on a 10 ft × $\frac{3}{8}$ in SE-30 (30%) on a Chromosorb W column operated at 230°, with a He flow rate of 113 ml/min. Under these conditions, each product showed, beside peaks due to starting materials, single peak due to the *trans* adduct (XIII) which had a retention time of 25 min.

Reaction 2. A soln of 504 mg of III and 576 mg (1·2 equiv) diethyl malonate in 2·25 ml EtOH was added to a soln of EtONa from Na (23 mg, 0·3 equiv) and 2·25 ml EtOH at room temp. The reaction mixture was acidified with AcOH and extracted with ether. Combined extracts were concentrated *in vacuo* to give 621 mg of product which has chromatographed on silica gel column using benzene-AcOEt (30:1) to give 204 mg of XIII.

Reaction 3. A soln of 164 mg of III in 1·5 ml benzene was added to a mixture of 5·7 mg (0·25 equiv) Na and 160 mg diethyl malonate at room temp. The reaction mixture was treated and checked by GLC accord-

ing to the procedure described in reaction 1. The product was identified as XIII by the comparison of the retention time with authentic sample.

Reaction 4. A soln of 174 mg of III and 324 mg (2 equiv) diethyl malonate in 0·7 ml EtOH was added to a mixture of 46 mg Na (2 equiv) and 0·8 ml EtOH. The reaction mixture was allowed to stand for 2 hr at 60°. The mixture was acidified with AcOH and extracted with ether. The extracts were washed with $NaHCO_3$aq and then saturated salt soln. The solvent was evaporated to give 183 mg crude product which was purified on a silica gel column to yield 65 mg pure XIV; ν_{max}^{neat} 1770, 1750, 1730, 1160 cm^{-1}; τ^{CCl_4} 8·92 (3H, s), 8·82 (3H, s), 8·67 (3H, t, J = 7 Hz), 6·63 (1H, s), 5·78 (2H, q, J = 7 Hz) and 5·29 (1H, d, J = 5 Hz).

Reaction 5. To a soln of 11 mg of XV and 18 mg (1 equiv) of diethyl malonate in 0·1 ml of EtOH was added a soln of EtONa from 1·07 mg (0·5 equiv) Na and 0·1 ml EtOH. The mixture was allowed to stand for 2 hr at room temp. The reaction mixture was acidified with 1N HCl and extracted with ether. The extracts were washed with dil $NaHCO_3$aq and saturated salt soln, evaporated *in vacuo* to give 15 mg of an adduct. The product was acetylated with Ac_2O in pyridine to give an acetate which was identified as XIII by the comparison with authentic sample in the IR spectrum and GLC.

Decarbethoxylation of XIV. A soln of 55 mg of XIV in 2 ml conc HCl was refluxed for 2 hr. The reaction mixture was extracted with ether. Combined extracts were dried on Na_2SO_4 and evaporated to give 18 mg of crude product which was chromatographed on a silica gel column to yield XII. The IR spectra of the lactone and its 2,4-dinitrophenylhydrazone were identical with those of previously obtained samples.

Equilibration of XIII *and* XVI. To a mixture of 35 mg of XIII and 32 mg diethyl malonate (2 equiv) was added a soln of 4·3 mg (2 equiv) Na in 0·15 ml EtOH. The mixture was allowed to stand for 1 hr at 60°. The reaction mixture was acidified with AcOH and extracted with ether. Combined extracts were washed with dil $NaHCO_3$aq and evaporated *in vacuo* to give 29 mg product. The product was chromatographed on a silica gel column using benzene-AcOEt (5:1) as solvent to give 12 mg of a compound which identical with XIV in all respect.

The equilibrations of XVI were carried out analogously except that the following quantities of materials were used; XVI (30 mg), diethyl malonate (20 mg, 1·2 equiv), Na (2·5 mg, 1·2 equiv) and EtOH (0·4 ml). Under these conditions, after chromatography, the lactone (XIV) (6 mg) was obtained.

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