$(1\beta,4\alpha,12\beta)$-2-Methoxytricyclo[5.4.2.$0^{4,12}$]tridecane-10,13-dione (23). Into a three-necked round-bottom flask fitted with dry nitrogen gas inlet, rubber septum, and mercury seal was introduced *n*-BuLi (0.15 mL) in hexane. It was cooled to −78 °C, and hexamethyldisilazane (0.1 mL) was added. The mixture was stirred for 20 min, and then THF (1 mL) was added to dissolve the solid material formed. After 10 min the bis-acetal **22** (30 mg, 0.095 mmol) in THF (2 mL) was slowly added, and the mixture was stirred for 20 min. Then freshly distilled trimethylsilyl chloride (0.1 mL) was added to quench the enolate. After 20 min $NaHCO_3$ solution was added to the reaction mixture, and it was extracted with ether (3 × 5 mL). The organic layer was washed and dried. The silyl enol ether obtained after removing the solvent was dissolved in dry dichloromethane (5 mL) and was taken into another three-necked round-bottom flask fitted with dry nitrogen set up. The reaction mixture was cooled to −78 °C, and $TiCl_4$ (0.1 mL) in dry dichloromethane (1 mL) was introduced. After being stirred for 30 min at −78 °C and for 1 h at 0 °C, the reaction mixture was quenched with $NaHCO_3$ solution. The organic layer was diluted and extracted with dichloromethane (3 × 5 mL). The crude material obtained after removing the solvent was charged on a small silica gel column. Careful elution with 60% ethyl acetate–petroleum ether furnished the cyclized diketone **23** (8 mg, 35.5%): IR (neat) ν_{max} 2950, 1700 (carbonyl), 1460, 1280, and 1100 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.0–2.9 (16 H, m), 3.26 (3 H, s, OCH_3), and 3.68 (1 H, t, J = 8 Hz, $CHOCH_3$); ^{13}C NMR spectrum (25.0 MHz, $CDCl_3$), δ 215.9, 214.8, 81.9, 58.6, 56.3, 54.4, 45.8, 43.2, 36.7, 35.9, 33.1, 29.6(2C) and 27.8. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.42; H, 8.40.

Further elution with 70% ethyl acetate–petroleum ether yielded the diketo aldehyde **24** (10 mg, 47%): IR (neat) ν_{max} 2950, 2775 (aldehyde), 1700 (carbonyl), 1460, and 1280 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.8–3.6 (16 H, m), 3.6–3.9 (1 H, m), and 9.49 (1 H, d, J = 2 Hz, CHO); ^{13}C NMR (25.0, MHz, $CDCl_3$) δ 214.2, 213.1, 201.8, 58.7, 49.2, 44.7, 43.7, 42.7, 40.3, 34.1, 32.5, 30.5, and 22.8.

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Registry No. **5**, 90955-44-5; (±)-**12**, 126543-04-2; (±)-(*E*)-**13**, 126543-05-3; (±)-(*Z*)-**13**, 126543-14-4; (±)-**14**, 126543-06-4; (±)-**15a**, 126543-07-5; (±)-**15b**, 126640-54-8; (±)-**16a**, 126543-08-6; (±)-**16b**, 126640-55-9; (±)-**16b** (R = $(CH_2)_2OH$), 126640-53-7; (±)-**17a**, 126543-09-7; (±)-**17b**, 126640-56-0; (±)-**18**, 126543-10-0; (±)-**19**, 126640-57-1; (±)-**20**, 126543-11-1; (±)-**20** (ethylene dithioacetal), 126543-03-1; (±)-**21**, 126543-02-0; (±)-**22**, 126543-12-2; (±)-**22** (TMS enol ether), 126578-19-6; **23**, 126543-13-3; (±)-**24**, 126543-15-5; $HS(CH_2)_2SH$, 540-63-6.

Evidence for Ketene Intermediates in the Reactions of 2-Oxobutanedioic Acid Diesters with Alcohols and Water

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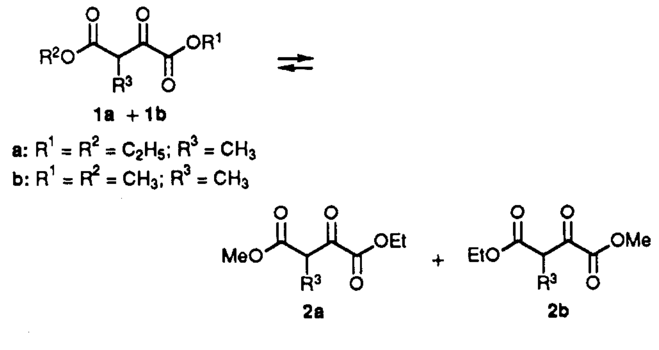
The reactions of the diethyl ester (**1a**) and dimethyl ester (**1b**) of 3-methyl-2-oxobutanedioic acid with excess ethanol, methanol, or water in a sealed tube at approximately 125 °C were studied. With methanol, **1a** yielded mainly 3-methyl-2-oxobutanedioic acid 1-ethyl 4-methyl diester, **2a**; with ethanol, **1b** yielded mainly the 4-ethyl 1-methyl diester, **2b**, while reaction of **1a** with water yielded carbon dioxide, 2-oxobutanoic acid ethyl ester, **6**, and 2-methyl-3-oxopropanoic acid ethyl ester, **7**. These results suggested that the ketene intermediates 3-methyl-2,4-dioxo-3-butenoic acid ethyl or methyl ester, **4a** and **4b**, respectively, are implicated. The similarity of these reactions to those exhibited by ethyl acetoacetate, such as alkoxy group exchange, and formation of dehydroacetic acid, now thought to proceed by way of acetylketene, was demonstrated.

The decarbonylation of α-oxobutanedioic acid diesters,[1] **1**, at temperatures on the order of 175 °C, has long been the subject of mechanism studies[2] and has synthetic utility.[3] It has been established that decarbonylation is a first-order reaction,[2,4] that an enolizable hydrogen on the β-carbon atom is required,[5] and that the carbon atom lost as carbon monoxide is the ester carbonyl adjacent to the α-keto group.[2]

Scheme I



More recently a lower temperature reaction was observed which leads to alkoxy group scrambling without loss of carbon monoxide. Mixtures of the diethyl and dimethyl esters of 3-methyl-2-oxobutanedioic acid, **1a** and **1b**, heated to 120 °C, were reported to yield the mixed diesters, **2a** and **2b**[6] (Scheme I). The results were attributed to cyclic intermediates such as those shown in Scheme II.

Not mentioned in that study[6] is the close resemblance of the alkoxy exchange reaction to ones occurring when ethyl acetoacetate or diethyl malonates and alcohols other

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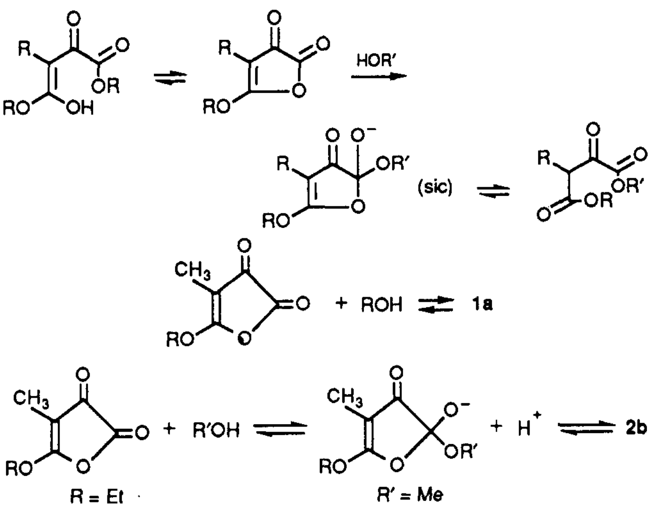
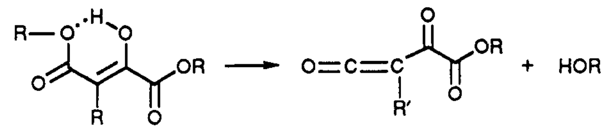
Scheme II



Scheme III



3a: R = C_2H_5; R' = CH_3
b: R = CH_3; R' = CH_3

4a: R = C_2H_5; R' = CH_3
b: R = CH_3; R' = CH_3

than ethanol are heated to about 100 °C or more.[7] The alkoxy group exchange has been shown to be a pseudo-first-order reaction probably involving a ketene intermediate.[8] The formation of dehydroacetic acid from ethyl acetoacetate very likely results from dimerization of acetylketene.[9]

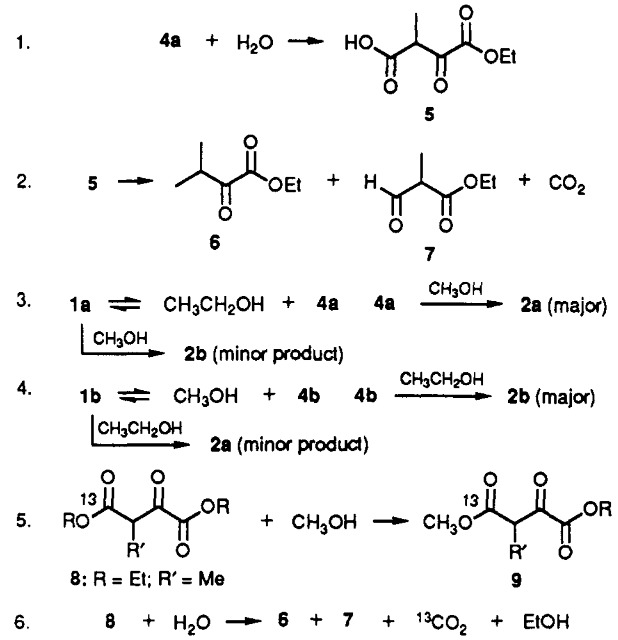
Compounds **1** and **2** can be regarded as β-keto esters if the carbon bearing the methyl substituent on the main chain is designated as the α-carbon. Either **1a** or **1b** in the hydrogen bonded enol form,[8e] **3**, could thus eliminate ethanol or methanol, respectively, to form the ketenes, 3-methyl-2,4-dioxo-3-butenoic acid ethyl ester, **4a**, or methyl ester, **4b** (Scheme III). Either alcohol can add to the ketene, **4a** or **4b**, to yield the observed mixed esters, **2a** and **2b**.

The hypothesis that a ketene intermediate is involved was tested in different ways. These include the reaction of **1a** with water or with methanol, the reaction of **1b** with ethanol, and the reaction of 2-methyl-3-oxobutanedioic-*1*-^{13}C acid diethyl ester, **8**, with methanol or water. These reactions are summarized in Scheme IV.

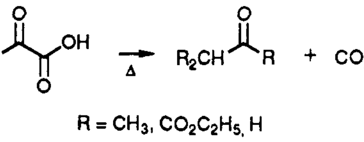
Results and Discussion

When **1a** was heated with a 4-fold molar excess of methanol in a sealed tube under nitrogen, the major product formed was 3-methyl-2-oxobutanedioic acid 1-ethyl 4-methyl diester, **2a**, and not the 4-ethyl, 1-methyl diester, **2b** (reaction 3, Scheme IV). When **1b** was heated with a 20-fold excess of ethanol under nitrogen, the predominant product was **2b**, mass 188. When **8** was heated with methanol, the major product was 2-methyl-3-oxobutanedioic-*1*-^{13}C acid 1-methyl 4-ethyl diester, **9**.

Scheme IV



Scheme V



When water was present, **1a** produced two esters, 2-oxobutanoic acid ethyl ester,[10] **6** (major product), and the isomeric 2-methyl-3-oxopropanoic acid ethyl ester,[11] **7** (minor product), were formed. (reactions 1 and 2 Scheme IV). The ester **6** could be accounted for by reaction of the ketene **4a** with water to form **5** with subsequent decarboxylation. The pathway for the rearrangement leading to **7** is unknown to us, but apparently it is not analogous to the one described for the rearrangement of 3,3-disubstituted 2-oxo acids[12] which entails migration of one of the three R groups. In our system, such a pathway would yield some ethyl acetoacetate; none was formed, however (Scheme V). When **8** was heated to 125 °C with 10-fold excess of water in dioxane, $^{13}CO_2$ was produced and none of the ^{13}C label appeared in either **6** or **7**. This finding too rules out a pathway to **7** via Scheme V.

The hydrolysis and decarboxylation of β-keto esters having an enolizable hydrogen has been carried out at 200–255 °C with water alone or water and a cosolvent.[13a–d] In our hands, heating ethyl benzoylacetate with water at 125 °C yielded carbon dioxide, acetophenone, and ethanol. Accordingly we suggest that the reaction pathway proposed here accounts for the earlier observations.[13a–d]

The course of alkoxy group exchange when **1a** or **1b** is heated with an alcohol is a subtly difficult matter to dis-

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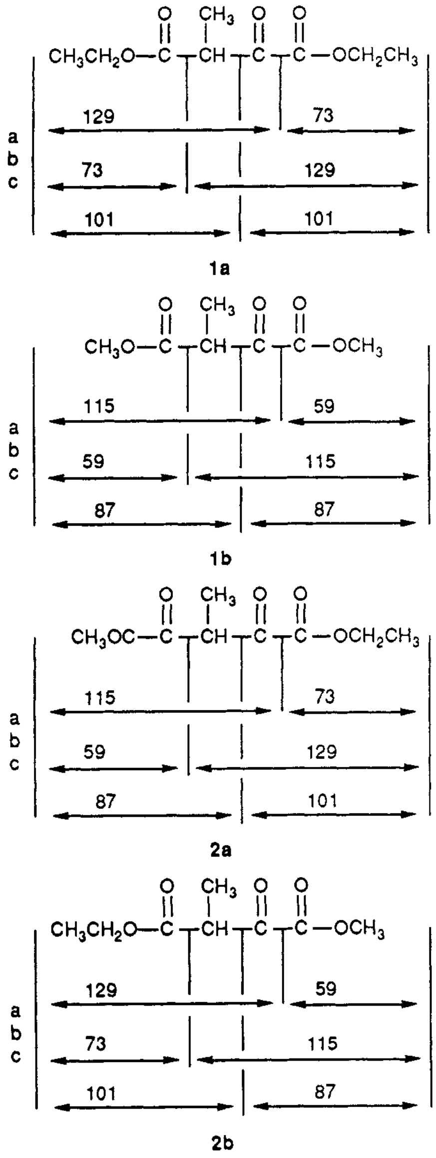
Chart I. MS Fragmentation Patterns of Oxalyl Diesters



cern. It was disentangled by GC–MS techniques, by isotopic labeling, and by a two-step series of reactions. It was determined that **1a** (mass 202) and **1b** (mass 174) would pass through the temperature-programmed capillary GC column virtually without decomposition. The diester, **1a**, yielded a major fragment ion at m/z 129 and fragments of lesser intensity at 101, 73, and 57. Major fragment ions from **1b** included m/z 115 and 59 with less intense fragment peaks at 88 and 87. Ambiguity exists for **1a** because the 129 and 73 fragments might arise from cleavage either between C-1 and C-2 or between C-3 and C-4 (Chart I). Similar ambiguity exists for **1b** where either C-1–C-2 cleavage or C-3–C-4 cleavage yields 115 and 59. Two exchange products, **2a** and **2b** (m/z 188), were obtained when **1a** was heated to $\approx$125 °C with a 4-fold excess of methanol or when **1b** was heated with a 20-fold excess of ethanol. The two isomers were partially separated by the GC column, were obtained in unequal amounts, and had quite different fragmentation patterns. The faster eluting minor component had a major m/z 129 fragment ion while the slower eluting major component had a major 115 m/z fragment ion. Again, because of the uncertainity about where the major fragmentation occurs (Chart I), it wasn't possible to know with certainty which isomer was which. Accordingly, we undertook unequivocal syntheses of **2a** and **2b**. Methyl propionate was allowed to react with diethyl oxalate in the presence of a solution of potassium *tert*-butoxide in THF. We reasoned that the major product of this reaction having mass 188 would be **2a**. It had the fragmentation pattern of the slower eluting component (m/z 115 and 59), thus establishing that the major component of mass 188 which results from the reaction of **1a** with excess methanol is **2a**. Similarly, **2b** was synthesized by the action of potassium *tert*-butoxide in THF on a mixture of excess ethyl propionate and dimethyl oxalate. The major product of mass 188 was the faster eluting component and had the fragmentation pattern of the major component (m/z 129) which results from reaction of **1b** with excess ethanol at $\approx$125 °C.

Further confirmation of these assignments was obtained by synthesizing 2-methyl-3-oxobutanedioic-*1*-^{13}C acid diethyl ester, **8**, and observing its mass spectrum and reactions. Its mass spectrum displayed the major fragment at m/z 130 thus establishing unequivocally that the m/z 129 fragment in the unlabeled **1a** arises from fragmentation path a for **1a** (Chart I) and, by analogy, path a for **2b**. Again by analogy, the m/z 115 must arise by path a for both **1b** and **2a**. Consequently there can be no doubt that the major products of alkoxy group scrambling occur by reaction at C-4, not at C-1 in the unlabeled compounds.

In another experiment **1a** was heated with methanol to give exchange of methoxy for ethoxy at C-4 as confirmed by GC–MS analysis. Water was added to the reaction mixture and it was again heated. The reaction mixture was analyzed by GC–MS, and the main hydrolysis products were **6** and **7** with only minor amounts of 2-oxobutanoic acid methyl ester and 2-methyl-3-oxopropanoic acid methyl ester. The mechanistic scheme previously proposed for the scrambling reaction[6] cannot be the correct one because the exchange of alkoxy groups would occur exclusively at C-1 (Scheme II).

How do the minor components arise? It was determined that ethyl pyruvate undergoes partial transesterification with a 20-fold excess of methanol under the reaction conditions. The resulting mixture contained ethyl and methyl pyruvate in the ratio of about 3:1. Thus, a transesterification pathway is available for simple 2-oxo esters which cannot involve the proposed cyclic mechanism[6] or a ketene intermediate.

The pathway for forming the ketene **4a** is analogous to that for the formation of acetylketene from ethyl acetoacetate[8e] and may be described as a cheletropic elimination of ethanol from **3a** to yield, at 105–125 °C, 2,4-dioxo-3-methyl-3-butenoic acid ethyl ester, **4a**.

In view of this experimental evidence, we submit that the alkoxy group scrambling of 3-methyl-2-oxobutanedioic acid diesters may be explained by the formation of a ketene intermediate perhaps formed by the cheletropic elimination of an alcohol and subsequent reaction of the ketene with other reaction mixture components. This interpretation is supported by the observed need for an enolizable hydrogen on the β-carbon of the diester,[5] and, in the case of ethyl acetoacetate, first-order kinetics,[2,4] alkoxy group exchange,[7,8e] and isolation of dehydroacetic acid.[8e]

A number of scattered observations reported in the literature are readily interpretable once the existence of acylketene intermediates arising from β-keto esters is recognized. The acylketenes produced by elimination of an alcohol or alkoxide ion from the keto ester, or anion thereof, can undergo any one of several reactions, depending on what else is present. If water is present, an acid, ketone, or aldehyde is formed.[13] If an alcohol is present, an ester different from the starting material is produced.[7,8e,14] The absence of an enolizable hydrogen on the β-carbon which prevents the cheletropic elimination of alcohol from the keto ester,[5] the acylketene intermediate cannot form, and other processes supervene.

Experimental Section

Analysis of Reaction Mixtures. Reaction mixtures were analyzed using a Hewlett-Packard Model 5988 GC–MS system employing a 30 m × 0.32 mm DB-5 column. The MS was operated at 70 eV. The programmed temperature capillary GC permitted rapid, efficient separation of reaction components. The starting oxalyl esters passed through the GC column virtually without decomposition. Gases were analyzed using a Carle Model 6500G gas chromatograph equipped with dual columns; 4 ft × $^1/_8$ in. packed with molecular sieve and 39 in. × $^1/_8$ in. packed with silica gel. The columns were operated in parallel, and a thermistor detector was employed. The relative molar response factors for CO_2 and CO were 1:(0.275 ± 0.004). NMR spectra were generated on a Varian VXR-300 with TMS or $CDCl_3$ internal references. IR spectra were obtained on an Analect 6200 FTIR spectrometer.

Reactions in a Sealed Reactor. A 316 stainless steel reactor 30 cm × 1.27 cm i.d. with a capacity of 36 mL was fabricated. It was fitted with a pipe union at one end. Closure of the reactor was accomplished using the mating parts of the union, washers, and sturdy septa of either Viton or silicone. The reactants and a cosolvent (freshly distilled dioxane) were mixed and placed in the reactor which was then purged with nitrogen or argon and sealed. It was then placed in a temperature-controlled oven with the closure end slightly elevated. After the heating period, the reactor was cooled. Gaseous products could be sampled by inserting a hypodermic needle through the septum. After gas sampling (if needed) was completed, the reactor was opened and the liquid products were dissolved in dichloromethane, dried over anhydrous sodium sulfate, and subjected to analysis.

Preparation of 3-Methyl-2-oxobutanedioic Acid Diethyl Ester (1a). To a mixture of ethyl propionate (10.2 g, 100 mmol) and diethyl oxalate (14.6 g, 100 mmol) in a mixture of ethyl ether and petroleum ether were added 2 mL of absolute ethanol and sodium hydride (4.4 g, 183 mmol). The side-arm flask containing the mixture was stoppered, and a drying tube containing Drierite and soda lime was attached to the side arm. The mixture was shaken occasionally over a period of 48 h. The reddish brown oil was filtered to remove a small quantity of solid residue, and the resulting oil was then treated with an ice-cold mixture of 3 mL of concentrated sulfuric acid and 60 mL of water. The layers were separated, and the acid layer was extracted with two portions of ethyl ether. The combined extract was extracted with dilute sodium bicarbonate followed by an extraction with concentrated brine. The extract was dried over anhydrous sodium sulfate and concentrated to 9.5 g on a rotary evaporator. A 4.0-g portion of the concentrate was subjected to a Kugelrohr distillation at <1 Torr. The yield of distillate boiling at 103–105 °C (lit.[3b] 114–116 °C (10 Torr)) was 3.5 g. The following spectral data were obtained: 300-MHz ^1H NMR δ 4.35 (q, CH_2), 4.20 (q, CH_2), 4.11 (q, CH), 1.41 (d, CH_3), 1.38 (t, CH_3), 1.26 (t, CH_3); 75-MHz ^{13}C NMR δ 189.56 (s, CO), 169.52 (s, CO), 160.16 (s, CO), 62.55 (t, CH_2), 61.40 (t, CH_2), 48.23 (d, CH), 13.79 (q, 2 CH_3), 11.60 (q, CH_3); IR 2989, 1755, 1734, 1657, 1456, 1369, 1303, 1253, 1203, 1121, 1093, 1046, 860 cm^{-1}; MS m/z 202 (0.3), 129 (100), 102 (25), 101 (28), 74 (19), 73 (21), 57 (35), 56 (16).

Preparation of 3-Methyl-2-oxobutanedioic Acid Dimethyl Ester (1b). To a mixture of methyl propionate (8.8 g, 100 mmol) and dimethyl oxalate (11.8 g, 100 mmol) in 30 mL of ether were added sodium hydride (4.25 g, 177 mmol), 1 mL of absolute methanol, and petroleum ether. The mixture, contained in a side-arm flask with a Drierite–soda lime drying tube, was shaken occasionally over a period of 24 h. The reaction mixture consisted of a liquid and a solid which were separated. The liquid was treated with 100 mL of 2 M sulfuric acid whereupon an intractable emulsion formed which was extracted with four 25-mL portions of ether. The solid was treated with 2 M sulfuric acid and extracted with ether. The ether extracts from both the liquid and the solid were combined, extracted with concentrated brine, and dried over anhydrous sodium sulfate. The extract was concentrated, and Kugelrohr distillation of the concentrate yielded 0.70 g of liquid: bp 77–83 °C (<1 Torr) (lit.[1,2] bp 110 °C (8 Torr)). Spectral data: 300-MHz ^1H NMR δ 4.15 (q, CH), 3.91 (s, CH_3), 3.74 (s, CH_3), 1.42 (d, CH_3); 75-MHz ^{13}C NMR δ 188.92 (s, CO), 170.09 (s, CO), 160.48 (s, CO), 52.97 (q, OCH_3), 52.40 (q, OCH_3), 48.00 (d, CH), 11.39 (q, CH_3); IR 2960, 1736, 1665, 1440, 1308, 1258, 1214, 1122, 1085, 1048 cm^{-1}; MS m/z 174 (0.3), 146 (12), 115 (92), 87 (23), 59 (100), 55 (11), 43 (13).

Preparation of 3-Methyl-2-oxobutanedioic Acid 1-Ethyl 4-Methyl Diester (2a). To a 125-mL suction flask equipped with a drying tube containing soda lime and Drierite were added 25 mL of anhydrous, freshly distilled THF and 0.41 g (10.5 mmol) of potassium. To the flask was added 0.80 g (10.8 mmol) of freshly distilled *tert*-butyl alcohol. Methyl propionate, 0.88 g (10 mmol), and 1.46 g of freshly distilled diethyl oxalate (10 mmol) were mixed and added to the flask containing the potassium *tert*-butoxide. A yellow color developed at once. After 16 h the reaction mixture was treated with 40 mL of water and 10 mL of 2 M sulfuric acid. The mixture was extracted twice with dichloromethane. The combined extract was extracted with water, dried over anhydrous sodium sulfate, and subjected to GC–MS analysis. The preponderance of the two partly resolved isomers of mass 188 was the slower eluting isomer whose mass spectrum showed very strong fragment ion peaks at m/z 115 and 59 and smaller peaks at 88 and 87.

Preparation of 3-Methyl-2-oxobutanedioic Acid 4-Ethyl 1-Methyl Diester (2b). To a 50-mL suction flask equipped with a drying tube containing soda lime and Drierite were added 20 mL of freshly distilled THF, 0.13 g (3.3 mmol) of potassium, and 0.55 g (7.4 mmol) of *tert*-butyl alcohol. After most of the potassium had dissolved, a solution of 0.42 g (3.7 mmol) of recently distilled dimethyl oxalate in 3.8 g (37 mmol) of freshly distilled ethyl propionate was added. A precipitate formed at once in the brownish yellow solution. After 5 min the reaction was quenched using 40 mL of a solution made from cold water and 5 mL of 2 M sulfuric acid. The reaction mixture was worked up as in **2a**.

The GC–MS analysis showed two partly resolved components of mass 188 with a preponderance of the faster eluting component which displayed a fragment ion of m/z 129 as the major feature. When the synthesis was attempted with equimolar amounts of the oxalate and propionate esters, more of the slower eluting component of mass 188 (**2a**) was obtained along with a considerable amount of **1b** and a little **1a**. As the mole ratio of ethyl propionate to dimethyl oxalate was increased, the amount of **1b** decreased and **1a** increased.

Preparation of Propanoic-*1*-^{13}*C* Acid Ethyl Ester.[15] To 1.00 g of dried propanoic-*1*-^{13}C acid sodium salt (Aldrich 99 atom % ^{13}C) (1.03 mmol) was added 10 mL of triethyl phosphate. The mixture was refluxed for 3.5 h and then allowed to cool and stand overnight. A trap cooled in liquid nitrogen was attached to the reflux condenser, and the system was evacuated. The product was obtained in 97% yield; ^1H NMR ($CDCl_3$) δ 1.14 (3 H, dt, CH_3CH_2CO, J = 7.5, 5.4 Hz), 1.26 (3 H, t, OCH_2CH_3, J = 7.2 Hz), 2.32 (2 H, q, CH_3CH_2CO, J = 7.5 Hz), 4.13 (2 H, dq, OCH_2CH_3, J = 7.2, 3.0 Hz); IR (neat) 1699, 1464, 1345, 1177, 1085, 1035 cm^{-1}.

2-Methyl-3-oxobutanedioic-*1*-^{13}*C* Acid Diethyl Ester (8). To 1.03 g (10.0 mmol) of ethyl propionate-*1*-^{13}C and 1.46 g (10.0 mmol) of diethyl oxalate in 11 mL of ether was added 1.0 mL of absolute ethanol and, in portions, 0.54 g of sodium hydride, 50% in mineral oil (11.2 mmoles). The flask was connected to a drying tube and allowed to stand at room temperature for 4 $^1/_2$ days. Ether was added to the solidified mixture, and the solid was broken up and filtered off. To the solid was added 2 M sulfuric acid, and the mixture was extracted with three portions of ether. The ether extract was dried over anhydrous sodium sulfate, and the ether was removed. The residue was subjected to a Kugelrohr distillation at <1 Torr. The material boiling at an oven temperature of 95–100 °C was shown to be pure by GC–MS analysis: yield 0.94 g, 46%; ^1H NMR ($CDCl_3$) $J(^{13}CCH)$ = 3.3 Hz, $J(^{13}CCCH_3)$ = 5.1 Hz; ^{13}C NMR ($CDCl_3$) δ 169.77 (s, CO (keto)), 173.50 (s, CO (enol)); IR (neat) 1736, 1705, 1636, 1456, 1369, 1248, 1200, 1048 cm^{-1}; MS (m/z) 203 (0.2), 130 (100), 103 (22), 102 (16),

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101 (10), 75 (16), 74 (10), 73 (9), 58 (12), 57 (21), 56 (9). The ether filtrate was shaken with 2 M sulfuric acid, dried, and distilled after removal of the ether. The product, boiling at 70–100 °C, contained less pure **8** and weighed 0.74 g.

Preparation of 2-Oxobutanoic Acid Ethyl Ester (6). The ester, **6**, was prepared by the method of Vogel and Schinz.[10] 3-Methyl-2-oxobutanedioic acid diethyl ester, **1a**, 0.60 g (3.0 mmol), was refluxed with 6 M hydrochloric acid for 2 h. The flask was attached to a continuous extractor, and extraction was carried out with ether. After evaporation of the ether, the residue was taken up in absolute alcohol to which 3 drops of concentrated hydrochloric acid was added. After 5 h of refluxing the solution was treated with decolorizing carbon and sodium hydrogen carbonate. The solvent was removed on the rotary evaporator, and the residue was subjected to a Kugelrohr distillation at reduced pressure. At an oven temperature of 67–70 °C, 0.01 g of **6** was obtained, 2.6%. Spectral data: MS *m/z* 130 (7), 75 (1), 58 (3), 57 (100), 56 (4), 45 (2).

Preparation of 2-Methyl-3-oxopropanoic Acid Ethyl Ester (7). The ester, **7**, was prepared by a method analogous to that of Holmes and Trevoy[11] using ethyl formate and ethyl propionate. To 1.00 g of sodium hydride (2.5 mmol) suspended in ether were added 2.55 mL of ethanol in 5 mL of ether, 2.95 g (40 mmol) of ethyl formate in 10 mL of ether, and, in portions, 2.04 g (20 mmol) of ethyl propionate in 5 mL of ether. After 2 days the reaction mixture was transferred to a separatory funnel and 20 mL of water was added followed by enough sulfuric acid to bring the pH to 1. Four extractions with 20, 10, 10, and 10 mL of ether were performed. The extracts were concentrated, and a molecular distillation was carried out on the residue. Fraction 4, bath temperature 120–140 °C, was about 80% pure by GC–MS analysis. A portion of this fraction was subjected to preparative GLC to obtain the sample for spectroscopic analysis which showed the presence of keto and enol forms. Analysis by GC/MS yielded two components in the chromatogram. It is believed that the first component is the keto form and the second the enol form; MS *m/z* (keto) 130 (23), 102 (25), 85 (44), 83 (14), 56 (100); (enol) 130 (4), 102 (62), 85 (85), 74 (88), 73 (37), 57 (50), 56 (100).

Reaction of 3-Oxo-3-phenylpropanoic Acid Ethyl Ester with Water. The reactor was charged with (0.40 g, 2 mmol) of ethyl benzoylacetate (Aldrich tech grade), 1.60 g of diglyme, recently distilled, and 0.36 g (20 mmol) of water. The mixture was heated for 16 h at 105 °C. The products consisted mainly of carbon dioxide and acetophenone, which was identified by its mass spectrum and comparison with the mass spectrum of an authentic sample. On a preparative scale, a mixture of 0.96 g (5.0 mmol) of ethyl benzoylacetate and 3 g of water was refluxed for 16 h and then extracted with methylene chloride. The extract was dried by shaking with anhydrous sodium sulfate, concentrated on a rotary evaporator, and subjected to Kugelrohr distillation. Acetophenone boiling at an oven temperature of 95–108 °C (14 Torr) was collected. Yield 0.42 g, 70%.

Reaction of Ethyl Pyruvate with Methanol. Ethyl pyruvate, 0.12 g (1.0 mmol) and 0.64 g of methanol (20 mmol) were heated to 110 °C in the reactor for 16 h and then subjected to GC–MS analysis. The relative peak areas for the methyl to ethyl esters were 19:50.

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Registry No. **1a**, 759-65-9; **1b**, 63921-06-2; **2a**, 99380-59-3; **2b**, 99380-58-2; **6**, 15933-07-0; **7**, 27772-62-9; **8**, 126615-15-4; $H_3CCH_2CO_2Et$, 105-37-3; EtO_2CCO_2Et, 95-92-1; $H_3CO_2CCO_2CH_3$, 553-90-2; $H_3CCH_2CO_2CH_3$, 554-12-1; $PhCOCH_2CO_2Et$, 94-02-0; HCO_2Et, 109-94-4; $PhCOCH_3$, 98-86-2; H_3CCOCO_2Et, 617-35-6; propanoic-1-^{13}C acid sodium salt, 62601-06-3; propanoic-1-^{13}C acid ethyl ester, 78217-95-5.

Transition-State Modeling of the Aldol Reaction of Boron Enolates: A Force Field Approach

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A force field model for the aldol reactions of ketone-derived enol borinates with aldehydes has been developed, based on MM2 and ab initio calculations, which can reproduce the geometries and energies of the ab initio transition structures **1–14** (±0.2 kcal mol^{-1}). It reproduces the experimental syn:anti stereoselectivity for the aldol additions of simple *Z* and *E* substituted enol borinates derived from ethyl ketones, and it shows that unsubstituted enol borinates (methyl ketone derived) have a greater degree of flexibility with a larger number of accessible chair and boat transition structures found. The force field also reproduces the aldehyde *si*/*re* face selectivity in the aldol reactions of a range of chiral *Z* enol borinates for which experimental data is available, and it may be a useful predictive tool for assessing stereoselection in new reactions. New ab initio calculations (RHF/3-21G) are described, which indicate the existence, not only of the chair and the twist-boat (boat A) reported by Houk, but also of an additional boat transition structure (boat B) found by the force field. In the aldol reactions of unsubstituted and *E* substituted enol borinates, boat B is likely to be involved as well as the chair and boat A; its omission from the development of the force field may explain the poor treatment of methyl ketone reactions.

Aldol reactions of metal enolates with aldehydes are among the most useful methods for stereocontrolled carbon–carbon bond formation in organic synthesis.[1,2] For example, the aldol reaction of an ethyl ketone with an aldehyde introduces two new chiral centers producing four possible stereoisomers (see Scheme I). For synthetic purposes, controlled formation of each individual stereo-

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