Methyl 4-Oxothiolane-3-carboxylate and Methyl 2-Methyl-4-oxothiolane-3-carboxylate Anions as Synthetic Equivalents of α-Acrylate and α-Crotonate Anions. Formal Synthesis of Integerrinecic Acid

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The base-promoted fragmentation of the *C*-alkylation products (**6a—h**) and (**8a—e**) of methyl 4-oxothiolane-3-carboxylate (**4**) and methyl 2-methyl-4-oxothiolane-3-carboxylate (**5**) gave good yields of the α-substituted acrylates (**7a—h**) and α-substituted crotonates (**9a—e**); thus the corresponding heterocyclic anions (**1a**) and (**1b**) could be considered to be synthetic equivalents of α-acrylate and α-crotonate anions respectively. A formal synthesis of integerrinecic acid (**10**) is reported, demonstrating the usefulness of this strategy in natural product chemistry.

A number of methods have been developed for the preparation of esters of α-substituted acrylic acids, important substructures in a variety of natural compounds and valuable intermediates in organic synthesis.[1]

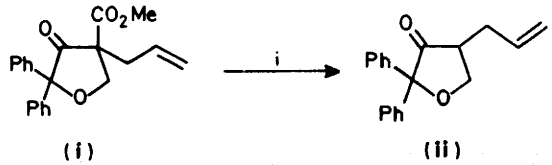
In a recent communication,[2] we described a new method for the preparation of α-substituted acrylic esters based on the discovery that the heterocyclic anion (**1a**) could be used for generating the α-acrylate anion (**2**). Similarly, α-substituted alk-2-enoic esters could be obtained by generating the α-crotonate anion (**3**) utilizing the heterocyclic carbanion (**1b**). In this paper we give a detailed account of our previous investigations adding new examples, and we illustrate the interesting features of the synthon (**3**) through its application to the formal synthesis of a natural target molecule.

The preparation of the starting materials, methyl 4-oxothiolane-3-carboxylate (**4**) and methyl 2-methyl-4-oxothiolane-3-carboxylate (**5**), by (a) piperidine-catalysed Michael addition of methyl thioglycolate to methyl acrylate or crotonate respectively, followed by (b) Dieckmann cyclization of the resulting adducts, which proceeds easily in satisfactory overall yield following known procedures.[3,4]

The reaction of compound (**4**) with a variety of alkyl halides in acetone solution in the presence of anhydrous K_2CO_3 leads to the *C*-alkylated products (**6a—h**): the yields are good with reactive allylic and benzylic halides, and lower but acceptable with less reactive halides. *O*-Alkylation was a minor problem and all the products were purified by column chromatography in order to remove these by-products.

The *C*-alkylated products (**6a—h**) were then exposed to 5% aqueous sodium hydroxide solution in a two-phase ethereal system to promote fragmentation to give in good yields the corresponding α-substituted acrylates (**7a—h**). The complete sequence is depicted in Scheme 1.

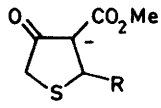
These experimental conditions were found to be the best, although other basic systems were investigated. The critical fragmentation was rationalized in terms of a series of retrograde Dieckmann–Michael reactions, the ability of sulphur to act as a leaving group playing a determining role. For instance, the similar oxygenated heterocycle (**i**) showed the usual behaviour of a β-oxoester when subjected to treatment with base, undergoing demethoxycarboxylation to yield (**ii**).[5]



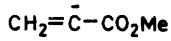
(**i**) (**ii**)

Reagents: i, NaOH, 100 °C

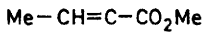
This sequence shows that the *C*-alkylated products (**6a—h**) may be considered to be masked α-substituted acrylates, which are successively unmasked under very mild basic conditions.



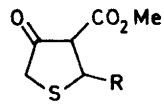
(**1**) a; R = H
b; R = Me



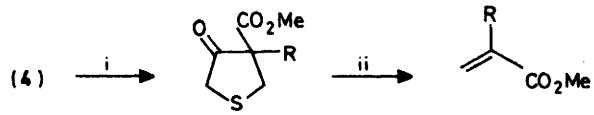
(**2**)



(**3**)



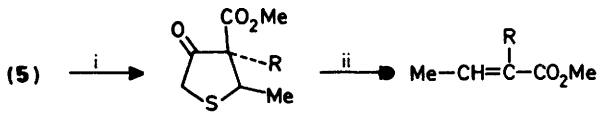
(**4**) R = H
(**5**) R = Me



(**6**) (**7**)

a; R = CH_2Ph
b; R = CH_2CO_2Et
c; R = $CH_2C{\equiv}CH$
d; R = $CH_2CH{=}CH_2$
e; R = $CH_2C_6H_4NO_2$-*p*
f; R = $CH_2C(OEt){=}CH{-}CO_2Et$
g; R = n-C_6H_{13}
h; R = CH_2–Phthaloyl

Scheme 1. *Reagents:* i, RX, K_2CO_3; ii, 5% NaOH



(8) (9)

a; R = CH_2Ph
b; R = CH_2CO_2Et
c; R = $CH_2C{\equiv}CH$
d; R = $CH_2CH{=}CH_2$
e; R = $CH_2C_6H_4NO_2$-*p*

Scheme 2. *Reagents:* i, RX, K_2CO_3; ii, 5% NaOH

The fragmentation step occurs with negligible concomitant hydrolysis of the ester function, and, moreover, suitable acidic conditions may also be tolerated: for instance the enol-ether moiety of compound (**6f**) was easily transformed into the corresponding keto group by treatment with aqueous perchloric acid at room temperature. However, under more drastic acid conditions the behaviour of these compounds parallels that of a β-oxoester, and hydrolysis and subsequent decarboxylation take place in refluxing hydrochloric acid.

These results paved the way to the possible utilization of the parent compound (**1b**) as an anion equivalent of the methyl crotonate (**3**). Methods and reagents suitable for generating anions such as (**3**) have enjoyed less attention than (**2**). This synthon cannot be directly generated by removal of a proton from C-2 of alk-2-enoic esters, as this tends to afford an allyl anion rather than a vinyl anion, and is extensively utilized for deconjugative alkylation of such compounds.[6]

To the best of our knowledge, the only method which implies the formation of an anion such as (**3**) was recently reported by Sato and Takeuchi;[7] their process involves fluoride ion induced desilylation of t-butyl 2-trimethylsilylalk-2-enoate followed by successive coupling with aldehydes to produce the corresponding 2-(1-hydroxyalkyl)alkenoates as an *E*/*Z* mixture.

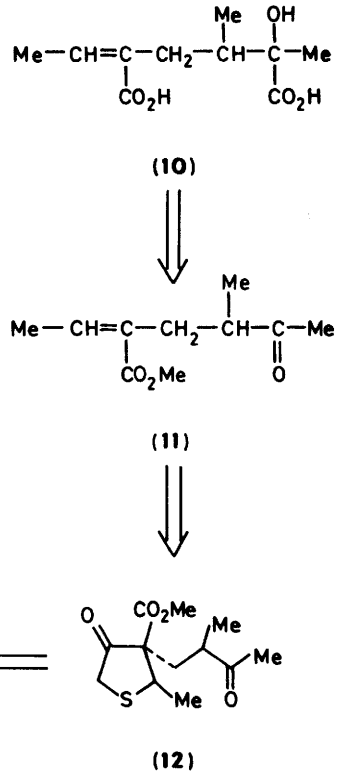
Thus, we subjected compound (**5**) to (a) alkylation with alkyl halides; and (b) base-promoted fragmentation; this resulted in a formal, direct α-alkylation of methyl crotonate, as summarized in Scheme 2.

The behaviour of compound (**5**) towards the alkylating agents parallels that of the parent compound (**4**), and some *O*-alkylated products formed may be easily removed by column chromatography. It is noteworthy that this purification led to the isolation of only one diastereoisomer of the alkylation product (the ^1H n.m.r. spectra did not show any duplication of signals). The configuration assigned to these compounds was based on the attack of the alkyl halide occurring from the side opposite to the methyl group.

The mechanism of the fragmentation step might be expected to proceed either *via* a multistep mechanism involving carbanions as intermediates or *via* a one-step concerted elimination. The fact that the ratio of the *E*/*Z* mixture of the α-substituted crotonates varied was better accounted for by the former hypothesis, which would probably be non-stereospecific.

Compounds (**8a—f**) underwent base-promoted fragmentation on treatment with 5% aqueous sodium hydroxide in ethereal two-phase systems, giving good yields of the corresponding crotonates (see Experimental section).*

* The effect of the addition of a phase transfer catalyst, which in the first experiments seemed to be crucial for a fast reaction, appears to be less important after a more careful investigation of the reaction conditions.



(10) (11) (12)

Scheme 3.

In order to highlight further the importance of the method, we decided to study its application to the synthesis of a natural target molecule. Necic acids, a family of C_{10} acids which form esters with the pyrrolizidine alkaloids, serve well for the purpose, as there is much interest in finding general methods for their synthesis at present.[8,9]

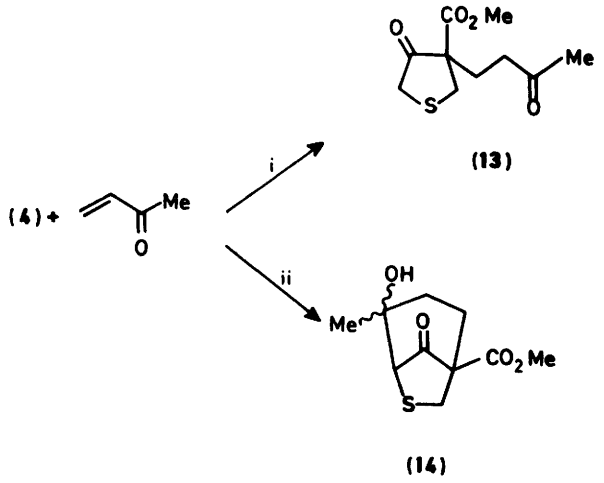
We chose integerrinecic acid (**10**) as the first target molecule and our projected synthesis, retrosynthetically outlined in Scheme 3, requires a starting material that is easily derivable from compound (**5**).

To this end, we investigated the Michael reaction of the model compound (**4**) with the commercially available methyl vinyl ketone (MVK) in order to determine the optimum conditions. We found that the simple adduct (**13**) from the β-oxoester (**4**) and the α,β-unsaturated moiety can only be obtained in good yield in the presence of the weak base triphenylphosphine[10] (Scheme 4).

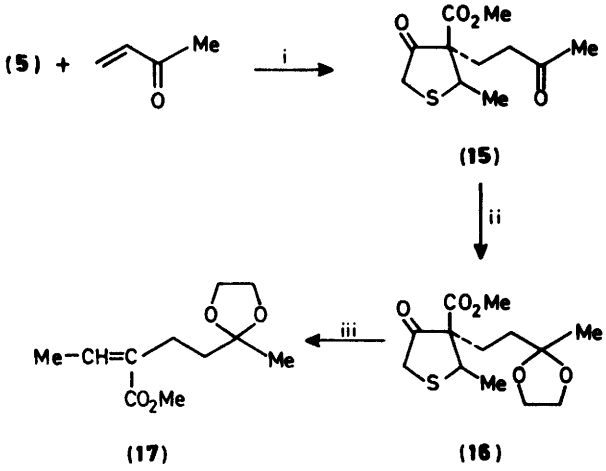
Other catalysts, for instance 18-crown-K_2CO_3[11] or tetramethylguanidine,[12] gave rise to the bicyclic compounds (**14**), which were recently reported[13] to be formed by acid treatment of (**13**), but without experimental details. Analogously the reaction of compound (**5**) with methyl vinyl ketone in the presence of triphenylphosphine led to the adduct (**15**) in good yield.

In order to avoid problems associated with the presence of two carbonyl groups in the following fragmentation step, compound (**15**) was transformed into the monoacetal (**16**) by treatment with equimolecular quantities of ethylene glycol in the presence of toluene-*p*-sulphonic acid (Scheme 5).

On exposure to basic conditions as above, the acetal (**16**) underwent clean fragmentation to produce the α-crotonate (**17**) as an *E*/*Z* mixture in the ratio 4:6, as determined both by gas-chromatography and by ^1H n.m.r. spectroscopy [the vinylic proton in the *E*-form (6.8—6.9 p.p.m.) was to lower field than that of the *Z*-isomer (6—6.1 p.p.m.)].



Scheme 4. *Reagents:* i, Ph_3P; ii, 18-crown-K_2CO_3



Scheme 5. *Reagents:* i, Ph_3P; ii, ethylene glycol, H^+; iii, KOH, MeOH, reflux

We then turned our attention to the reaction of compound (**5**) with methyl isopropenyl ketone to produce the expected intermediate (**12**). Although the catalysts used previously were unsuccessful in promoting Michael addition with the more hindered and less reactive isopropenyl methyl ketone, the use of more forcing conditions (refluxing equimolecular amounts of methanolic KOH) not only promotes the Michael addition to give (**12**), but led directly to the fragmented compound (**11**) in 34% overall yield, as an *E*/*Z* mixture in the ratio 1:6 (^{1}H n.m.r.). Treatment of the crude mixture with a catalytic amount of iodine in refluxing xylene for 10 h resulted in complete conversion of the unwanted *Z*-isomer into the *E*-analogue. The latter isomer has been already transformed[8,14] into the target compound (**10**), and this therefore represents a new formal synthesis of integerrinecic acid.

Experimental*

M.p.s and b.p.s are uncorrected. The course of the reactions and the product mixtures were routinely monitored by t.l.c. on silica gel pre-coated 60 F_{254} Merck plates. I.r. spectra were measured on a Perkin-Elmer 297 spectrometer. ^{1}H N.m.r. spectra were obtained with a Perkin-Elmer R32 spectrometer for solutions in $CDCl_3$, and peak positions are given in p.p.m. downfield from tetramethylsilane as the internal standard. Gas chromatography was carried out with a Carlo Erba 4200 instrument equipped with a flame ionization detector using an OV17 column. All drying was carried out with anhydrous magnesium sulphate.

Light petroleum refers to the fraction of boiling range 40—60 °C, and ether to diethyl ether. All reactions were carried out under nitrogen.

General Procedure for the Alkylation of Methyl 4-Oxothiolane-3-carboxylate (**4**) *and Methyl 2-Methyl-4-oxothiolane-3-carboxylate* (**5**).—To a suspension of anhydrous K_2CO_3 (30 mmol) and compound (**4**) (10 mmol) or (**5**) (10 mmol) in dry acetone, was added the alkyl halide (10 mmol) and the mixture refluxed for the appropriate time (t.l.c.). After cooling, the mixture was filtered and the solvent removed at 25 mmHg. The residue was diluted with water (50 ml), extracted with ether, and dried. Removal of the solvent left a residue which was purified by column chromatography on silica gel eluting with ether–light petroleum solutions. This procedure was used to give the following *methyl 4-oxothiolane-3-carboxylates*: 3-*benzyl*- (**6a**) (80%); $\nu_{max.}$ ($CHCl_3$) 1 750, 1 730, and 1 600 cm^{-1}; m.p. 69—70 °C; δ 2.95—3.5 (6 H, m), 3.75 (3 H, s), and 7.25 (5 H, m) (Found: C, 62.1; H, 5.6; S, 12.6. $C_{13}H_{14}O_3S$ requires C, 62.39; H, 5.64; S, 12.79%).

3-*Ethoxycarbonylmethyl*- (**6b**) (78%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 730br cm^{-1}; δ 1.22 (3 H, t, *J* 7 Hz), 2.95 (2 H, s), 3.2—3.7 (4 H, m), 3.75 (3 H, s, 4.15 (2 H, q, *J* 7 Hz) (Found: C, 48.6; H, 5.6; S, 12.8. $C_{10}H_{14}O_5S$ requires C, 48.78; H, 5.73; S, 13.00%).

3-*Prop*-2-*ynyl*- (**6c**) (75%) as an oil; $\nu_{max.}$ ($CHCl_3$) 3 280, 1 750, and 1 730 cm^{-1}; δ 2.1 (1 H, m), 2.8 (2 H, m), 3.1—3.7 (4 H, m), and 3.8 (3 H, s) (Found: C, 54.4; H, 5.0; S, 16.1. $C_9H_{10}O_3S$ requires C, 54.54; H, 5.09; S, 16.15%).

3-*Prop*-2-*enyl* (**6d**) (78%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 750, 1 730, and 1 640 cm^{-1}; δ 2.5—2.7 (2 H, m), 2.9—3.7 (4 H, m), 3.75 (3 H, s), 5.07 (1 H, m), 5.20 (1 H, m), and 5.75 (1 H, m) (Found: C, 53.8; H, 6.1; S, 16.1. $C_9H_{12}O_3S$ requires C, 53.99; H, 6.04; S, 15.98%).

3-(4-*Nitrobenzyl*)- (**6e**) (86%), $\nu_{max.}$ ($CHCl_3$) 1 730, 1 610, 1 520, 1 350, and 860 cm^{-1}; m.p. 72—73 °C; δ 2.75—3.5 (6 H, m), 3.75 (3 H, s), 7.35 (2 H, m), and 8.2 (2 H, m) (Found: C, 52.55; H, 4.4; N, 4.7; S, 10.7. $C_{13}H_{13}NO_5S$ requires C, 52.88; H, 4.44; N, 4.74; S, 10.84%).

3-(2-*Ethoxy*-3-*ethoxycarbonylprop*-2-*enyl*)- (**6f**) (68%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 730, 1 700, and 1 620 cm^{-1}; δ 1.25 (3 H, t, *J* 7 Hz), 1.27 (3 H, t, *J* 7 Hz), 3.75 (3 H, s), 3.85 (2 H, q, *J* 7 Hz), 4.15 (2 H, q, *J* 7 Hz), and 5.10 (1 H, s) (Found C, 53.1; H, 6.3; S, 10.0. $C_{14}H_{20}O_6S$ requires C, 53.16; H, 6.37; S, 10.12%).

3-*Hexyl*- (**6g**) (50%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 750 and 1 730 cm^{-1}; δ 0.9 (3 H, t), 1.1—1.4 (10 H, m), 2.85—3.60 (4 H, m), and 3.75 (3 H, s) (Found: C, 59.2; H, 8.3; S, 13.2. $C_{12}H_{20}O_3S$ requires C, 59.00; H, 8.25; S, 13.10%).

3-*Phthaloylmethyl*- (**6h**) (62%); $\nu_{max.}$ ($CHCl_3$) 1 790, 1 730 cm^{-1}; m.p. 132—133 °C; δ 3.75 (3 H, s), 3.10—4.45 (6 H, m) and 7.80 (4 H, m) (Found: C, 56.3; H, 4.1; S, 10.1. $C_{15}H_{13}NO_5S$ requires C, 56.43; H, 4.10; S, 10.03%).

3-*Benzyl*-2-*methyl*- (**8a**) (77%), as an oil; $\nu_{max.}$ ($CHCl_3$) 1 750 and 1 730 cm^{-1}; δ 1.35 (3 H, d, *J* 7 Hz), 2.9—3.6 (5 H, m), 3.75 (s, 3 H), and 7.1—7.5 (5 H, m) (Found: C, 63.6; H, 6.1; S, 12.1. $C_{14}H_{16}O_3S$ requires C, 63.62; H, 6.10; S, 12.11%).

3-*Ethoxycarbonylmethyl*-2-*methyl*- (**8b**) (68%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 730br cm^{-1}; δ 1.3 (3 H, t, *J* 7 Hz) 1.35 (3 H, d, *J* 7 Hz), 2.7—3.3 (3 H, m), 3.75 (3 H, s), and 4.1 (2 H, q, *J* 7 Hz) (Found: C, 50.6; H, 6.25; S, 12.3. $C_{11}H_{16}O_5S$ requires C, 50.77; H, 6.20; S, 12.30%).

* In collaboration with Dr. Sandra Toso.

2-*Methyl*-3-*prop*-2-*ynyl*- (**8c**) (65%) as an oil; $\nu_{max.}$ ($CHCl_3$) 3 200, 1 750, and 1 730 cm^{-1}; δ 1.35 (3 H, d *J* 7 Hz), 2.00 (1 H, m), 2.85 (2 H, m,); 3.3—4.1 (3 H, m), and 3.75 (3 H, s) (Found C, 56.7; H, 5.75; S, 15.2. $C_{10}H_{12}O_3S$ requires C, 56.60; H, 5.70; S, 15.08%).

2-*Methyl*-3-*prop*-2-*enyl*- (**8d**) (70%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 750, 1 730, and 1 640 cm^{-1}; δ 1.35 (3 H, d, *J* 7 Hz), 2.6—2.8 (2 H, m), 3.2—3.7 (3 H, m), 3.75 (3 H, s), 5.1 (1 H, m), 5.2 (1 H, m), and 5.5—5.8 (1 H, m) (Found: C, 55.85; H, 6.4; S, 14.9. $C_{10}H_{14}O_3S$ requires C, 56.07; H, 6.59; S, 14.94%).

2-*Methyl*-3-(4-*nitrobenzyl*)- (**8e**) (72%); $\nu_{max.}$ ($CHCl_3$) 1 750, 1 730, 1 610, 1 520, and 1 350 cm^{-1}; m.p. 141—142 °C; δ 1.4 (3 H, d, *J* 7 Hz), 3.1—3.6 (5 H, m), 3.75 (3 H, s), 7.35 (2 H, d, *J* 9 Hz), and 8.1 (2 H, d, *J* 9 Hz) (Found: C, 54.2; H, 4.8; N, 4.6; S, 10.2. $C_{14}H_{15}O_5NS$ requires C, 54.37; H, 4.89; N, 4.53; S, 10.35%).

General Procedure for the Fragmentation of Compounds (**6**) *and* (**8**).—A solution of compound (**6**) (5 mmol) or (**8**) (5 mmol) in ether (30 ml) was vigorously stirred with 5% NaOH (80 ml) at room temperature until the fragmentation was complete (0.5—2 h; t.l.c.). The organic phase was separated, dried, and evaporated under reduced pressure at room temperature to leave the practically pure product (**7a—h**) or (**9a—e**) (as an *E*/*Z* mixture).

The following methyl acrylates were prepared by this procedure and purified by bulb-to-bulb distillation: 2-*benzyl*- (**7a**) (81%) b.p. 69.70 °C/0.8 mmHg (lit.,[15] b.p. 62 °C/0.7 mmHg); $\nu_{max.}$ (neat) 1 720, 1 640 cm^{-1}; δ 3.6 (2 H, m), 3.7 (3 H, s), 5.43 (1 H, m), 6.2 (1 H, s) and 7.2 (5 H, m) (Found: C, 74.85; H, 6.7. Calc. for $C_{11}H_{12}O_2$: C. 74.97; H, 6.86%).

2-*Ethoxycarbonylmethyl*- (**7b**) (78%); b.p. 120 °C/20 mmHg; $\nu_{max.}$ (neat) 1 730br, 1 640 cm^{-1}; δ 1.22 (3 H, t, *J* 7 Hz), 3.3 (2 H, s), 3.75 (3 H, s), 4.2 (2 H, q, *J* 7 Hz), 5.7 (1 H, m), and 6.3 (1 H, s) (Found: C, 55.7; H, 6.9. $C_8H_{12}O_4$ requires C, 55.80; H, 7.03%).

2-*Prop*-2-*ynyl*- (**7c**) (76%), b.p. 105 °C/25 mmHg; $\nu_{max.}$ (neat) 3 270, 1 720 and 1 630 cm^{-1}; δ 2.20 (1 H, m), 3.25 (2 H, m), 3.75 (3 H, s), 6.08 (1 H, m), and 6.35 (1 H, m) (Found: C, 67.85; H, 6.5. $C_7H_8O_2$ requires C, 67.73; H, 6.50%).

2-Prop-2-enyl- (**7d**) (78%), b.p. 104 °C/25 mmHg (lit.,[15] 100 °C/20 mmHg); $\nu_{max.}$ (neat) 1 720 and 1 630 cm^{-1}; δ 3.10 (2 H, m), 3.75 (3 H, s), 5.00 (1 H, m), 5.15 (1 H, m), 5.7—6.1 (1 H, m), 5.60 (1 H, m), and 6.2 (1 H, m) (Found: C, 66.5; H, 7.9. Calc. for $C_7H_{10}O_2$: C, 66.64; H, 7.99%).

2-(4-*Nitrobenzyl*)- (**7e**) (90%); b.p. 81 °C/0.8 mmHg; $\nu_{max.}$ (neat) 1 720, 1 630, 1 520, and 1 345 cm^{-1}; δ 3.7 (2 H, m), 3.75 (3 H, s), 5.60 (1 H, m), 6.30 (1 H, s), 7.35 (2 H, d, *J* 9 Hz), and 8.15 (2 H, d, *J* 9 Hz) (Found: C, 59.8; H, 5.1; N, 6.3. $C_{11}H_{11}NO_4$ requires C, 59.72; H, 5.01; N, 6.33%).

2-(2-*Ethoxy*-3-*ethoxycarbonylprop*-2-*enyl*)- (**7f**) (75%), b.p. 117 °C/1 mmHg; $\nu_{max.}$ (neat) 1 730, 1 710 and 1 630 cm^{-1}; δ 1.25 (3 H, t, *J* 7 Hz), 1.27 (3 H, t, *J* 7 Hz), 3.7—3.95 (7 H, m), 4.15 (2 H, q, *J* 7 Hz), 5.10 (1 H, s), 5.60 (1 H, m), and 6.20 (1 H, m) (Found: C, 59.3; H, 7.6; $C_{12}H_{18}O_5$ requires C, 59.49; H, 7.49%).

2-Hexyl- (**7g**) (80%), b.p. 140 °C/20 mmHg (lit.,[15] b.p. 135 °C/15 mmHg); $\nu_{max.}$ (neat) 1 720, 1 630 cm^{-1}; δ 0.90 (3 H, t), 1.1—1.4 (10 H, m), 3.7 (3 H, s), 5.50 (1 H, m), and 6.10 (1 H, m) (Found: C, 70.3; H, 10.6. Calc. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%).

2-*Phthaloylmethyl*- (**7h**) (41%) m.p. 99—100 °C; $\nu_{max.}$ ($CHCl_3$) 1 750, 1 730, and 1 670 cm^{-1}; δ 3.80 (3 H, s), 4.60 (2 H, m), 5.60 (1 H, m), 6.30 (1 H, m), and 7.80 (4 H, m) (Found: C, 63.5; H, 4.5; N, 5.6. $C_{13}H_{11}NO_4$ requires C, 63.67; H, 4.52; N, 5.71%).

The following methyl crotonates were also prepared by this procedure and purified by short silica gel column chromatography. The ^1H n.m.r. spectral data refer only to the more significant vinylic and methylic protons.

2-*Benzyl*- (**9a**) (85%), *E*:*Z* ratio 20:80; $\nu_{max.}$ ($CHCl_3$) 1 720, 1 640, and 1 600 cm^{-1}; δ (*Z*) 1.90 (3 H, d, *J* 7 Hz), 6.05 (1 H, q, *J* 7 Hz) δ (*E*) 2.00 (3 H, d, *J* 7 Hz), 7.05 (1 H, m) (Found: C, 75.6; H, 7.3. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%).

2-*Ethoxycarbonylmethyl*- (**9b**) (67%) (*E*:*Z* ratio 74:26; $\nu_{max.}$ ($CHCl_3$) 1 725, 1 640 cm^{-1}; δ (*E*) 1.85 (3 H, d, *J* 7 Hz), 7.08 (1 H, q, *J* 7 Hz); δ (*Z*) 2.1 (3 H, d, *J* 7 Hz), 6.50 (1 H, q, *J* 7 Hz) (Found: C, 58.25; H, 7.9. $C_9H_{14}O_4$ requires C, 58.05; H, 7.58%).

2-*Prop*-2-*ynyl*- (**9c**) (67%) *E*:*Z* ratio 65:35; $\nu_{max.}$ ($CHCl_3$) 3 280, 1 720, and 1 640 cm^{-1}; δ (*E*) 1.90 (3 H, d, *J* 7 Hz), 7.00 (1 H, q, *J* 7 Hz); δ (*Z*) 2.1 (3 H, d, *J* 7 Hz), 6.50 (1 H, q, *J* 7 Hz) (Found: C, 69.3; H, 7.2. $C_8H_{10}O_2$ requires C, 69.54; H, 7.30%).

2-*Prop*-2-*enyl*- (**9d**) (71%), *E*:*Z* ratio 70:30; $\nu_{max.}$ ($CHCl_3$) 1 720, 1 640 cm^{-1}; δ (*E*) 1.80 (3 H, d, *J* 7 Hz), 6.95 (1 H, q, *J* 7 Hz); δ (*Z*) 2.00 (3 H, d, *J* 7 Hz), 6.05 (1 H, m) (Found: C, 68.4; H, 8.5. $C_8H_{12}O_2$ requires C, 68.54; H, 8.63%).

2-(4-*Nitrobenzyl*)- (**9e**) (83%), *E*:*Z* ratio 25:75; $\nu_{max.}$ ($CHCl_3$) 1 715, 1 645, 1 520, and 1 350 cm^{-1}; δ (*Z*) 2.05 (3 H, d, *J* 7 Hz), 6.2 (1 H, q, *J* 7 Hz); δ (*E*) 1.90 (3 H, d, *J* 7 Hz), 7.15 (1 H, q, *J* 7 Hz) (Found: C, 61.2; H, 5.5; N, 5.8. $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.96%).

2-(3-*Methylenedioxybutyl*)- (**17**) (83%) *E*:*Z* ratio 40:60; $\nu_{max.}$ ($CHCl_3$) 1 720, 1 640 cm^{-1}; δ (*Z*) 1.85 (3 H, d, *J* 7 Hz), 6.05 (1 H, q, *J* 7 Hz); δ (*E*) 1.95 (3 H, d, *J* 7 Hz), 6.85 (1 H,q, *J* 7 Hz) (Found: C, 61.5; H, 8.3. $C_{11}H_{18}O_4$ requires C, 61.66; H, 8.47%).

Methyl 4-*Oxo*-3-(3-*oxobutyl*)*thiolane*-3-*carboxylate* (**13**).—To a solution of compound (**4**) (1.0 g, 6.3 mmol) and freshly distilled methyl vinyl ketone (0.8 g, 11.4 mmol) in acetonitrile (10 ml) was added triphenylphosphine (0.1 g, 0.3 mmol) and the mixture stirred for 5 h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel eluting with ether–light petroleum (7:3) to give the *ester* (**13**) (1.05 g, 73%), m.p. 42—43 °C $\nu_{max.}$ ($CHCl_3$) 1 755 and 1 735 cm^{-1}; δ 2.10 (3 H, s), 2.90—3.55 (4 H, m), and 3.75 (3 H, s) (Found: C, 52.5; H, 6.3. $C_{10}H_{14}O_4S$ requires C, 52.17; H, 6.13%).

Methyl 4-*Hydroxy*-4-*methyl*-8-*oxo*-6-*thiabicyclo*[3.2.1]-*octane*-1-*carboxylate* (**14**).—A solution of compound (**4**) (1.0 g, 6.3 mmol) and freshly distilled methyl vinyl ketone (0.8 g, 11.4 mmol) in toluene (10 ml) was cooled in an ice-bath and 18-crown-6 (0.17 g, 6 mmol) and potassium carbonate (0.085 g, 0.61 mmol) were added. The mixture was stirred for 3 h, then water was added and the organic layer was separated. The aqueous phase was extracted with ether (2 × 20 ml), and the combined organic extracts washed with brine and dried. The solvents were removed and the product was purified by column chromatography with ether–light petroleum (7:3) as eluant, to give the *ester* (**14**) (0.72 g, 50.3%), m.p. 88—89 °C, $\nu_{max.}$ (KBr), 3 350, 3 290, 1 750, and 1 730 cm^{-1}; δ 1.30 (3 H, s), 1.50—2.15 (4 H, m), 2.25—2.45 (1 H, m), 2.60—3.60 (3 H, m), and 3.75 (3 H, s) (Found: C, 52.1; H, 6.2. $C_{10}H_{14}O_4S$ requires C, 52.17; H, 6.13%).

Methyl 2-*Methyl*-4-*oxo*-3-(3-*oxobutyl*)*thiolane*-3-*carboxylate* (**15**).—This was prepared following the procedure reported above for (**14**); the *product* (**15**) was obtained as an oil (78.5%) after column chromatography on silica gel using ether–light petroleum, 7:3 as eluant; $\nu_{max.}$ ($CHCl_3$) 1 750, 1 730, and 1 720 cm^{-1}; δ 1.35 (3 H, d, *J* 7 Hz), 2.12 (3 H, s), 2.1—2.7 (4 H, m), 3.3—3.7 (3 H, m), and 3.75 (3 H, s) (Found: C, 53.9; H, 6.5. $C_{11}H_{16}O_4S$ requires C, 54.09; H, 6.60%).

The corresponding monoacetal (**16**) was obtained by refluxing (**15**) (0.7 g, 2.8 mmol) in a Dean–Stark apparatus in benzene (30 ml) containing ethylene glycol (0.3 ml, 5.3 mmol) in the presence of toluene-*p*-sulphonic acid. The cooled mixture was washed successively with 5% sodium hydrogen carbonate (20 ml), water (20 ml), and the organic layer was separated and

dried. Removal of the solvent left the *acetal* (**16**) as a homogeneous oil (0.78 g, 94%); $\nu_{max.}$ ($CHCl_3$) 1 760 and 1 730 cm^{-1}; δ 1.30 (3 H, s), 1.35 (3 H, d, *J* 7 Hz), 1.60—2.10 (4 H, m), 3.20—3.70 (3 H, m), 3.75 (3 H, s), and 4.95 (4 H, s) (Found: C, 53.9; H, 6.9. $C_{13}H_{20}O_5S$ requires C, 54.16; H, 6.92%).

Attempted Preparation of Methyl 2-*Methyl*-3-(2-*methyl*-3-*oxobutyl*)-4-*oxothiolane*-3-*carboxylate* (**12**). *Preparation of Methyl* (2E)-2-*Ethylidene*-4-*methyl*-5-*oxohexanoate* (**11**).—To a solution of compound (**5**) (1 g, 5.7 mmol) in methanol (2 ml) containing potassium hydroxide (0.32 g, 5.7 mmol) was added methyl isopropenyl ketone (0.6 g, 7.1 mmol) and the mixture was refluxed for 4 h. The cooled mixture was neutralized with aqueous acetic acid, extracted with ether (3 × 20 ml), dried and evaporated under reduced pressure. The crude residue was purified by column chromatography (eluant ether–light petroleum 2:8) giving a 6:4 mixture of the *Z*/*E* isomers (0.36 g, 34%) as indicated by g.l.c. and ^1H n.m.r. spectroscopy. A solution of this *Z*/*E* mixture (0.26 g, 1.4 mmol) in xylene (5 ml) containing a catalytic amount of iodine was refluxed for 10 h, monitored by g.l.c. The cooled solution was washed successively with 5% sodium thiosulphate solution and water and dried. Removal of the solvent left a residue which was chromatographed on silica gel column eluting with ether–light petroleum (8:2) to give the E-*isomer* (0.18 g, 69%); $\nu_{max.}$ ($CHCl_3$) 1 715 and 1 650 cm^{-1}; δ 1.03 (3 H, d, *J* 7 Hz), 1.82 (3 H, d, *J* 7 Hz), 2.15 (3 H, s), 2.20—2.90 (3 H, m), 3.70 (3 H, s), and 6.95 (1 H, q, *J* 7 Hz) (Found: C, 65.0; H, 8.7. $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75%).

References

1 H. M. R. Hoffmann and J. Rabe, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 795 and references listed therein.
2 Preliminary communication: P. G. Baraldi, A. Barco, S. Benetti, F. Moroder, G. P. Pollini, D. Simoni, and V. Zanirato, *J. Chem. Soc., Chem. Commun.* 1982, 1265.
3 R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, 1946, **68**, 2229.
4 F. Duus, *Tetrahedron*, 1981, **37**, 2633.
5 M. T. Flavin and M. C. Lu, *Tetrahedron Lett.*, 1983, 2335.
6 A. S. Kende and B. H. Toder, *J. Org. Chem.*, 1982, **47**, 167.
7 Y. Sato and S. Takeuchi, *Synthesis*, 1983, 734.
8 S. E. Drewes and N. D. Emslic, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2079.
9 K. Narasaka and T. Uchimaru, *Chem. Lett.*, 1982, 57.
10 D. A. White and M. M. Baizer, *Tetrahedron Lett.*, 1973, 3597.
11 D. J. Cram and D. Y. Sogah, *J. Chem. Soc., Chem. Commun.*, 1981, 625.
12 G. P. Pollini, A. Barco, and G. De Giuli, *Synthesis*, 1972, 44.
13 E. H. Evans, A. T. Hewson, L. A. March, and I. W. Nowell, *J. Chem. Soc., Chem. Commun.*, 1982, 1342.
14 U. Pastewka, H. Wiedenfeld, and E. Roder, *Arch. Pharm.*, 1980, **313**, 846.
15 D. Seebach, R. Henning, and T. Mukhopadhyay, *Chem. Ber.*, 1982, **115**, 1705.

Received 27*th February* 1984; *Paper* 4/325