Dienediolates from Unsaturated Carboxylic Acids: Michael Addition of Dilithium Buta-1,3-diene-1,1-diolate (from Crotonic Acid) to Unsaturated Ketones

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Conjugate addition of the lithium dienediolate derived from crotonic acid to several α,β-unsaturated ketones gave 7-oxocarboxylic acids. Styryl ketones (**2a**—**g**) afforded mixtures of 1,4-α- and 1,4-γ-adducts, in proportions depending on the bulk of the substituents attached to the carbonyl group. The reaction with the styryl ketones occurs through a tandem 1,2-addition–oxy-Cope rearrangement mechanism. On the other hand, α- and β-methyl styryl phenones (**2h** and **i**) afforded 1,4-γ-products through 1,2-addition with subsequent retro-aldol and Michael-type addition.

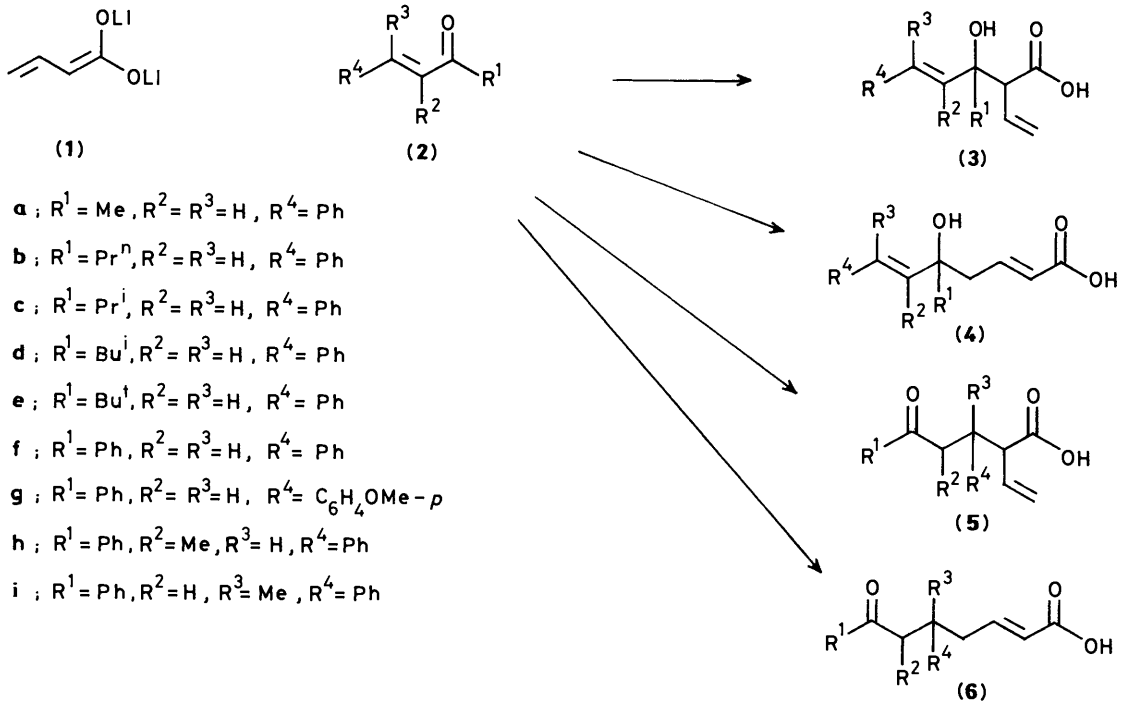
Deprotonation of unsaturated carboxylic acids by two equivalents of a lithium amide gives dilithium dienediolates. The aldol-like reactions of these dianions with aldehydes and ketones and their conjugate additions to unsaturated ketones conveniently afford 5- and 7-functionalized carboxylic acids. Unfortunately, they also react with electrophiles at the α-carbon atom. Thus, alkylation and protonation of the dienediolates afford unconjugated carboxylic acids. The aldol-like reaction with aldehydes and unhindered ketones under kinetically controlled conditions gives largely the product of addition at the α-carbon atom. However, at elevated temperatures, where the reaction becomes reversible, the thermodynamically more stable γ-adduct predominates, and good yields of 5-hydroxy acids result.[1-5] As a continuation of our previous work, we show now that, with a few exceptions, 1,4-γ-regioselectivity predominates for the reactions of crotonic acid (*via* its dienediolate) with enones, and that 7-oxo carboxylic acids can be conveniently obtained. We have found as well that the final Michael-type adducts are the result of a tandem 1,2-addition–oxy-Cope rearrangement for some enones. The present work has been restricted to the dienediolate (**1**) from crotonic acid; equivalent results have been obtained previously for dimethylacrylic acid.[1,2]

We had observed previously that the addition of the dienediolate (**1**) to some enones at low temperature led to complex mixtures, the ^{1}H n.m.r. spectra of which suggested that all possible regioisomers (**3**)—(**6**) were present (Scheme 1). Simpler mixtures were obtained on heating, and compounds resulting from 1,4-γ-addition were found to predominate largely. Although the equivalent enolates of saturated carboxylic acids have been reported to add irreversibly to enones,[6] the foregoing observations suggested that reversible 1,2- and 1,4-additions were leading in the end to the thermodynamically more stable compounds. Surprisingly, 1,3-diphenylpropenone (**2f**) gave almost exclusively the 1,4-α-adduct (**5f**), instead of the expected 1,4-γ-compound (**6f**).[2] Aldol and Michael addition equilibria could not account for this exceptional behaviour. This finding moved us to extend the study[7] to some other styryl ketones and cyclic enones, in order to identify the structural effects which determine the regioselectivity of the reaction.

Crude yields and product ratios (^{1}H n.m.r. and g.l.c.) for additions of the dienediolate (**1**) to styryl ketones (**2**) are given in Table 1. Yields of purified compounds are not included, as poor crystallization recoveries were attained even for pure samples. No improved preparative conditions were attempted. In fact, better yields and simpler crude mixtures were frequently obtained at 0 °C or at room temperature. The results for the enones (**2a**—**f**) reveal a linear correlation of the α:γ ratios with the Taft steric parameters E_S for the substituents R^1 attached to the carbonyl group.[8] This trend is opposite to that previously observed for the aldol-like addition of the dienediolate to saturated ketones: large groups were then found to favour addition at the α-carbon atom.[1,3,9] Taken as a whole, these regioselectivity trends suggested that the present Michael adducts were the result of a 1,2-addition and a subsequent intramolecular rearrangement (Scheme 2). Thus, an anionic oxy-Cope rearrangement would transform the intermediate 1,2-α-adducts into 1,4-γ-compounds (as observed for small R^1 groups), and conversely, 1,2-γ-adducts into the corresponding 1,4-α-regioisomers (for bulky R^1 groups).

Anionic oxy-Cope rearrangements have been found to give predominantly the diastereoisomers expected from a chair transition state in which as many substituents as possible are equatorially oriented.[10] It was interesting then to find that the addition of the dienediolate (**1**) to the diphenylpropenone (**2f**) occurred regio- as well as diastereo-selectively, to give the *R,R*- (or *S,S*-) 1,4-α-compound (**5f**). The configuration assigned to this adduct is in agreement with the stereochemistry expected for the tandem addition–rearrangement mechanism (Scheme 3). The *R,S*-isomer had been previously isolated,[2] and could just be observed in the ^{1}H n.m.r. spectrum of the present reaction mixture. For assignment of configurations, the ^{1}H n.m.r. spectrum of the methyl ester of the stereoisomer obtained here showed ester methoxy and vinyl protons to resonate 0.25 p.p.m. upfield and 0.1—0.2 p.p.m. downfield, respectively, relative to the equivalent signals of the minor isomer. It is known that acyclic compounds having vicinal stereocentres, each bearing one hydrogen atom, exist predominantly in the conformation having the hydrogen atoms *anti* (Figure), and that in such compounds a substituent *gauche* to phenyl usually experiences an upfield shift due to the net shielding effect of the aromatic ring.[11] The relative shifts observed here are in agreement with the phenyl ring being *gauche* to the methoxycarbonyl group of the major compound, and to the vinyl group of the minor isomer. These relations can be seen, respectively, in the predominant conformations (**I**) for the *R,R*- and (**II**) for the *R,S*-diastereoisomer of structure (**5f**).

When attempting to attain evidence for the addition–rearrangement mechanism, we were lucky to find that the addition of the dienediolate (**1**) to 1,3-diphenylpropenone (**2f**)



Scheme 1.

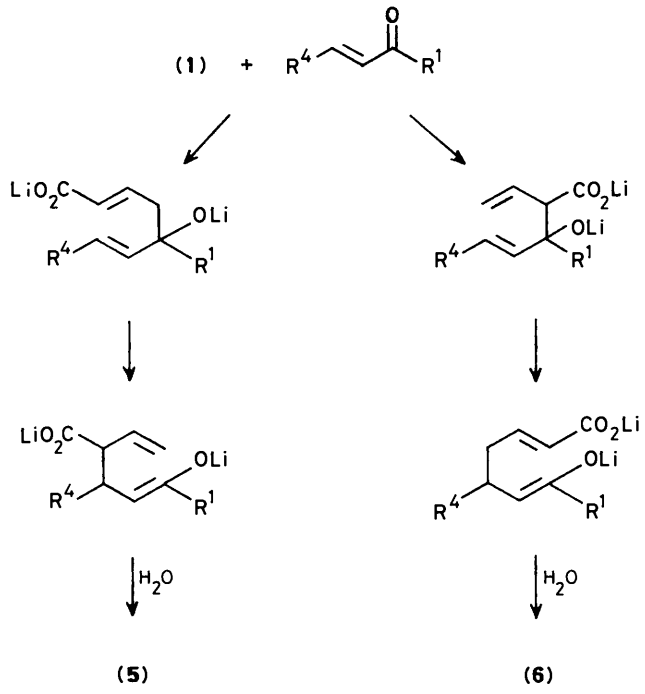
Table 1. Addition of the dienediolate (**1**) to styryl ketones

Substrate	Time (h)	Temp. (°C)	Crude yield (%)	Major adducts	Regioselectivity (1,4-α:1,4-γ)	E_s for R^1
(**2a**)	2	65		(**6a**)[a]	20:80	0.00
(**2b**)	2	65	87	(**6b**)	36:61	−0.36
(**2c**)	2	65	70	(**6c**), (**5c**)[b]	47:53	−0.47
(**2d**)	2	65	71	(**5d**), (**6d**)[b]	55:45	−0.93
(**2e**)	2	65	92	(**5e**),[c] (**6e**)	85:15	−1.54
(**2f**)	2	65	81	(**5f**)[c]	99:1	−2.55
(**2f**)	0.3	−90	90	(**4f**)		
(**2g**)	2	65	75	(**5g**)[c]	99:1	
(**2g**)	0.3	−90	80	(**4g**)		
(**2h**)	3	45		(**6h**)[a,d]	0:100	
(**2h**)	0.3	−70	67	(**4h**)		
(**2i**)	2	65	68	(**6i**)	0:100	
(**2i**)	0.3	−70	63	(**4i**)		

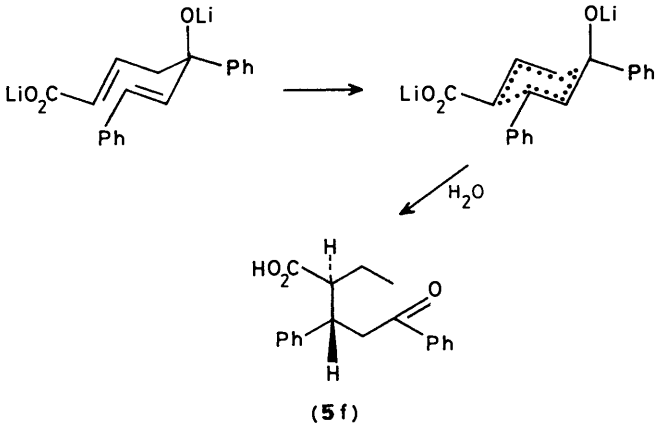
[a] See ref. 2. [b] Not isolated in pure form. [c] One single diastereoisomer obtained. [d] Obtained as a diastereoisomeric mixture.

at −90 °C gave the *E,E*-1,2-γ-adduct (**4f**) (Scheme 4). Although spectroscopically homogeneous samples of this compound were obtained, no good analytical determinations resulted. Further attempts at purification caused partial dehydration (see ref. 12). When the hydroxy acid (**4f**) was deprotonated in the cold and heated as usual, the *R,R*-1,4-α-adduct (**5f**) was obtained. The reaction gave the latter adduct more selectively than the addition of the dienediolate (**1**) to the diphenylpropenone (**2f**). Thus, the *R,S*-isomer was not observed in the n.m.r. spectrum of the crude reaction mixture. This result showed that the 1,2-γ-adduct was an intermediate that, under the conditions of the reaction, led regio- and stereo-selectively to the final *R,R*-1,4-α-adduct. A crossover experiment confirmed the intramolecular character of the rearrangement. The methoxy-diphenylpropenone (**2g**) was chosen as trapping reagent. On reaction with the dienediolate, this methoxy-propenone gave the 1,4-α-adduct (**5g**) as one single stereoisomer (most probably *R,R*) under the usual conditions, and the *E,E*-1,4-γ-adduct (**4g**) at −90 °C. The latter led to the 1,4-α-adduct (**5g**) by deprotonation at −70 °C and heating for 2 h. These experiments confirmed that the methoxy-enone (**2g**) was comparable in reactivity to the unsubstituted diphenylpropenone (**2f**). When the hydroxy acid (**4f**) was deprotonated at −70 °C and heated in the presence of the trapping enone (**2g**), no ether methoxy group was found in the ^{1}H n.m.r. spectrum of the crude reaction mixture; only the usual adduct (**5f**) was observed (Scheme 4). The absence of the crossover product (within experimental error) indicates that a stepwise rearrangement is not occurring.

The correlation of α:γ ratios found for the styryl ketones with the steric parameters for the groups R^1 suggests that the same mechanism is operative for all the enones (**2a**—**e**). On the other hand, the methyl-substituted styryl phenones (**2h** and **i**) (Table 1) were found to give the 1,4-γ-adducts (**6h** and **i**).[2] Comparison with diphenylpropenone (**2f**) led us to expect instead the 1,4-α-adducts as the result of 1,2-γ-addition and intramolecular rearrangement. This change of regioselectivity suggested that a different mechanism was involved. The same method as before was followed in order to establish this mechanism. In attempt-



Scheme 2.



Scheme 3.

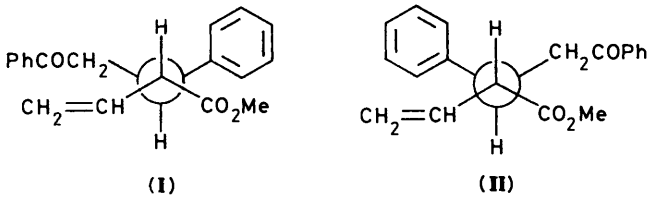
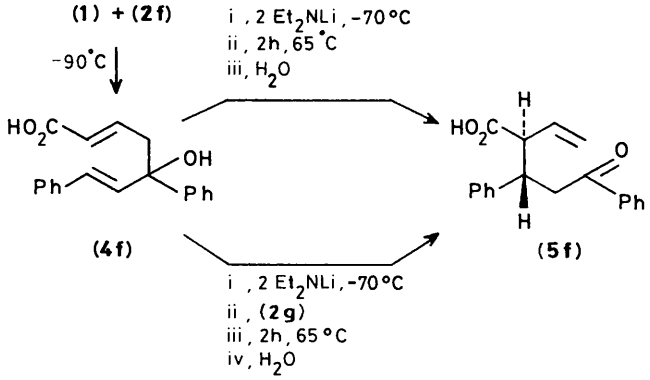
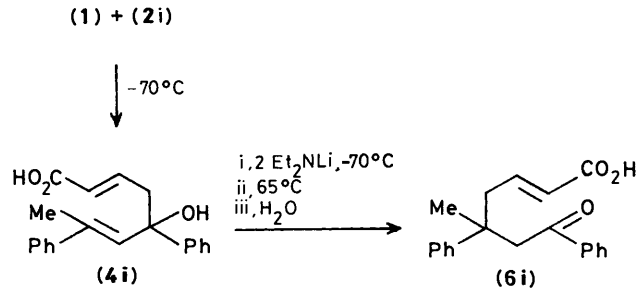


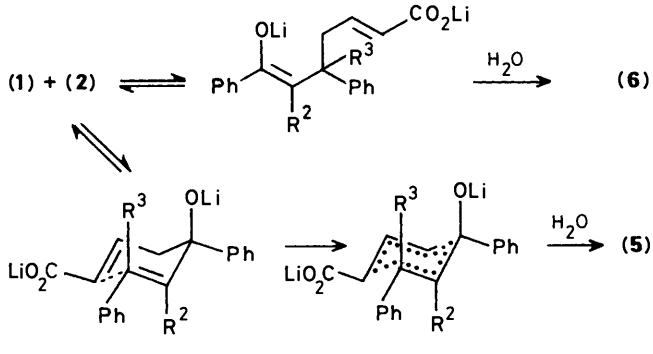
Figure.



Scheme 4.



Scheme 5.



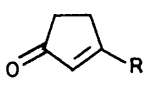
Scheme 6.

ing to obtain the 1,2-adducts, temperatures as low as −90 °C were not required, and the methyl-diphenylpropenones (**2h** and **i**) afforded selectively the *E,E*-1,2-γ-compounds (**4h** and **i**) at −70 °C. When the 1,2-γ-adduct (**4i**) was deprotonated at −70 °C and heated in presence of the methoxy-enone (**2g**), as before (Scheme 5), only the 1,4-α-adduct (**5g**) derived from the trapping methoxy-enone was obtained. This finding was clearly indicative of the dienediolate becoming free in the course of the 1,2- to 1,4-adduct rearrangement. It may then be concluded that two mechanisms are operative for the Michael addition of the dienediolate (**1**) to enones. They have in common a fast aldol-like addition, but differ in the subsequent rearrangement to the Michael-type compound. This rearrangement occurs either through a retro-aldol reaction and conjugate addition, or through a [3,3]sigmatropic shift. For the acyclic β-substituted enones studied, the oxy-Cope rearrangement occurs, whereas the stepwise process is found for α,β- and β,β-disubstituted unsaturated ketones. The occurrence of the stepwise rearrangement for the 1,2-γ-adducts (**4h** and **i**) is probably due to steric congestion in the transition state for the sigmatropic shift (Scheme 6), as the substituent methyl group must be axially

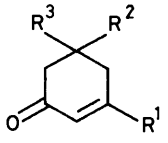
Table 2. Addition of the dienediolate (**1**) to cyclic enones

Substrate	Temp.[a] (°C)	Crude yield (%)	Adduct
(**7**)	25	76	(**15**)
(**8**)	25	87	(**16**)
(**9**)	25	77	(**17**)
(**10**)	25	78	(**18**)
(**11**)	65	91	(**19**)[b]
(**12**)	0	87	(**20**)
(**12**)	65	90	(**21**)
(**13**)	65	88	(**23**)
(**14**)	65	81	(**24**)

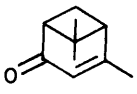
[a] All runs started at −70 °C and continued for 2 h. [b] Unresolved diastereoisomeric mixture.



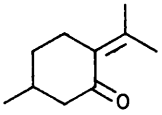
(**7**) R = H
(**8**) R = Me



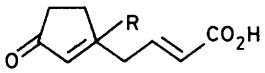
(**9**) $R^1 = R^2 = R^3 = H$
(**10**) R^1 = Me, $R^2 = R^3 = H$
(**11**) $R^1 = R^2$ = Me, $R^3 = H$
(**12**) $R^1 = R^2 = R^3$ = Me



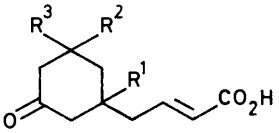
(**13**)



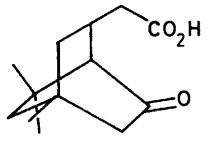
(**14**)



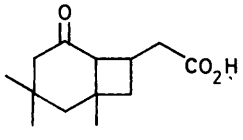
(**15**) R = H
(**16** R = Me



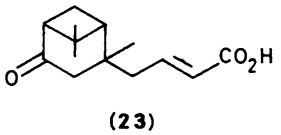
(**17**) $R^1 = R^2 = R^3 = H$
(**18**) R^1 = Me, $R^2 = R^3 = H$
(**19**) $R^1 = R^2$ = Me, $R^3 = H$
(**20**) $R^1 = R^2 = R^3$ = Me



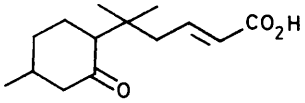
(**21**)



(**22**)

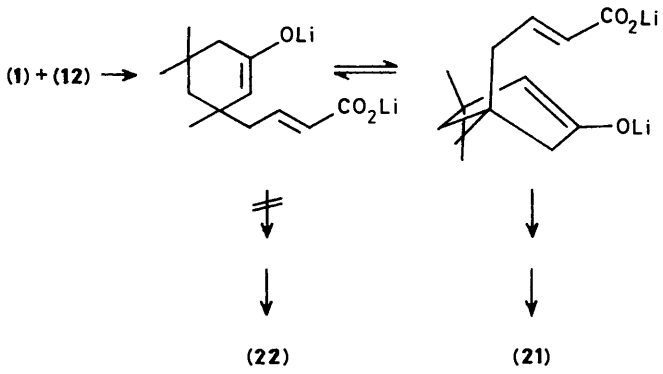


(**23**)

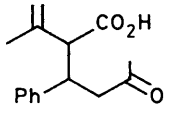


(**24**)

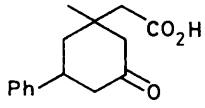
oriented, and strong 1,3-diaxial repulsions are then to be expected. Evans has already reported that anionic oxy-Cope rearrangements are sensitive to the degree of substitution, competitive processes being observed for congested systems.[10] On the contrary, the methyl substituents present in the 1,2-γ-



Scheme 7.



(**25**)



(**26**)

adducts (**4h** and **i**) should not be expected to cause a significant modification of the transition state energy of the retro-aldol process, and the stepwise rearrangement would then become energetically favoured over the concerted process. The observation of higher stability for the ionized forms of the 1,2-adducts (**4h** and **i**) relative to (**4f**) under the reaction conditions affords some support for this interpretation.

When the dienediolate (**1**) reacted with the cyclic enones (**7**)—(**14**), higher yields of crude product were found than with the acyclic systems (Table 2), and 1,4-γ-adducts (**15**)—(**20**), (**23**), and (**24**) were conveniently obtained. 1,2-γ-Adducts, or their dehydration products were observed occasionally. No attempts were made to establish the mechanism of these additions. However, the absence of 1,4-α-products in the crude mixtures inclines us to accept that the stepwise rearrangement mechanism predominates.

The addition to isophorone (**12**) deserves comment, as it leads to the bicyclic oxo acid (**21**) when the mixture is heated under reflux for 2 h. The oxobicyclo[2.2.2]octane structure (**21**) is in agreement with the 500 MHz n.m.r. spectrum, and with the results of two-dimensional n.m.r. experiments.[13] An especially significant feature is the long-range coupling (2.5—3.1 Hz) found for all the protons of the bicyclic structure, except for that at the bridgehead. All the methylene protons in the bicyclo[2.2.2]octane have the coplanar W-orientation required for effective long-range spin–spin coupling. However these W-orientations are found for only one pair of protons in the bicyclo[4.2.0]octanone (**22**). The bicyclo[2.2.2]octanone (**21**) most probably results from an α-to-α′ equilibration of the primary 1,4-γ-adduct (Scheme 7), and subsequent intramolecular Michael addition. The cyclization is not entirely stereospecific: small amounts of the geometric isomer have been observed. Haynes has recently reported a similar cyclization of the 1,4-adducts obtained by the reaction of allylic phosphine oxide carbanions with cyclic enones.[14]

Other bicyclic systems resulting from reactions of crotonic acid and cyclic enones have not been found, although the dienediolate of dimethylacrylic acid and the phenylbutenone (**2a**) afford a diastereoisomeric mixture of the 1,4-γ-compound (**25**) along with the carboxymethylcyclohexanone (**26**).

Comparison between our results and those of Hudlicky for the vinylogous Reformatsky reaction with enones[12] reveals that 1,4-γ-compounds can be prepared conveniently by both procedures. However, the present method seems more convenient to us, because crotonic acid is more easily handled than

the corresponding bromo ester, and because the resulting adducts are frequently better isolated as solid free acids. On the other hand, 1,2-adducts and compounds derived from very reactive enones are better obtained by the Reformatsky reaction.

Experimental

I.r. spectral data were obtained for potassium bromide discs, unless otherwise stated, with a Hitachi 269-10 spectrophotometer. N.m.r. spectra were recorded for solutions in $CDCl_3$, with $SiMe_4$ as internal reference, with a Varian CFT-80 (80 MHz) instrument, unless otherwise stated. G.l.c. analyses were performed with Perkin-Elmer Sigma 2 and Hewlett-Packard 5830-A chromatographs, on packed columns of SE-30 (1%) Chromosorb W-HP, 80—100 mesh (2 ft × $\frac{1}{8}$ in), under isothermal conditions: injector and detector temperature 250 °C; column temperature 170 °C; carrier gas nitrogen at 23 ml min^{-1}).

M.p.s were determined with a Büchi SMP-20 apparatus. Elemental analyses were determined by Servicio de Semimicroanálisis del Instituto de Química Bio-Orgánica de Barcelona.

Distillations of adducts were performed with a Büchi GKR-50 bulb-to-bulb distillation apparatus. Silica gel HF 254 (Merck) was used for column chromatography separations.

Esterifications were carried out with diazomethane. Tetrahydrofuran (THF) was distilled from sodium diphenylketyl immediately before use. Diethylamine was dried over CaH_2 and distilled before use. Generation and reactions of the dienediolate (**1**) were carried out in argon, under standard conditions for exclusion of moisture.

The generation of the dilithium dienediolate from crotonic acid with 2 equiv. of lithium diethylamide, as well as the addition conditions and general work-up procedures, have already been described.[1,4] The reaction temperatures −70, −90, and 65 °C were achieved with solid CO_2–Me_2CO bath, liquid N_2–MeOH bath, and THF under reflux, respectively.

(E)-5-*Phenyl*-7-*oxodec*-2-*enoic Acid* (**6b**).—1-Phenylhex-1-en-3-one (**2b**) (3.24 g, 18.6 mmol) and the dienediolate (**1**) [from crotonic acid (1.6 g, 18.6 mmol)] were treated for 2 h at 65 °C, according to the general procedure. Work-up gave an oil (4.21 g, 87%). Esterification of a sample (2.86 g) and chromatography allowed isolation of the *methyl ester* of the *oxo acid* (**6b**) (1.09 g) as an oil (Found: C, 74.5; H, 8.3. $C_{17}H_{22}O_3$ requires C, 74.4; H, 8.1%); t_R 2.8 min; $\nu_{max.}$(neat) 1 725 (C=O), 1 660 (C=C), and 770 and 710 (Ph) cm^{-1}; δ_H 7.22 (5 H, s, Ph), 6.77 (1 H, m, C*H*=C*CO*$_2$Me), 5.73 (1 H, d, *J* 15.7 Hz, C=C*H*CO$_2$Me), 3.67 (3 H, s, CO_2Me), 3.33 (1 H, m, PhC*H*), 2.70 (2 H, d, *J* 7.1 Hz, CH_2COPr^n), 2.50 (2 H, dd, *J* 7.1 and 6.8 Hz, CH_2C=C), 2.24 (2 H, dd, *J* 7.0 and 6.6 Hz, COCH_2Et), 1.44 (2 H, m, COCCH_2Me), and 0.8 (3 H, 2 × d, *J* 7.3 and 6.9 Hz, 2 × Me).

(E)-8-*Methyl*-5-*phenyl*-7-*oxonon*-2-*enoic Acid* (**6c**).—4-Methyl-1-phenylpent-1-en-3-one (**2c**) (6.47 g, 37.2 mmol) and the dienediolate (**1**) [from crotonic acid (3.2 g, 37.2 mmol)] in 0.5 h at −70 °C and 2 h at 65 °C gave an oil which solidified (6.77 g, 70%). Crystallization led to white prisms of the *oxo acid* (**6c**), m.p. 86—87 °C (Found: C, 73.95; H, 8.0. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%); $\nu_{max.}$ 3 600—3 200 (OH), 1 710 and 1 690 (C=O), and 1 655 (C=C) cm^{-1}. The methyl ester had t_R 2.2 min; δ_H 7.20 (5 H, s, Ph), 6.75 (1 H, m, C*H*=CCO$_2$Me), 5.74 (1 H, d, *J* 16 Hz, C=C*H*CO$_2$Me), 3.67 (3 H, s, CO_2Me), 3.4 (1 H, m, PhC*H*), 2.75 (2 H, d, *J* 7 Hz, CH_2CO), 2.55 (1 H, m, C*H*Me$_2$), 2.50 (2 H, t, *J* 8 Hz, CH_2C=C), and 1.00 and 0.93 (6 H, 2 × d, *J* 6.8 and 6.7 Hz, 2 × Me).

(E)-9-*Methyl*-5-*phenyl*-7-*oxodec*-2-*enoic Acid* (**6d**).—5-Methyl-1-phenylhex-1-en-3-one (**2d**) (7.0 g, 37.2 mmol) and crotonic acid (3.2 g, 37.2 mmol) for 0.5 h at −70 °C and 2 h at 65 °C gave an oil (7.24 g, 71%). A sample (1.44 g) of this was esterified. Chromatography and distillation gave the *methyl ester* of the *oxo acid* (**6d**) (0.62 g) as an oil (Found: C, 74.95; H, 8.6. $C_{18}H_{24}O_3$ requires C, 75.0; H, 8.4%); t_R 2.8 min; $\nu_{max.}$(CCl_4) 1 725 (C=O) and 1 660 (C=C) cm^{-1}; δ_H 7.22 (5 H, s, Ph), 6.8 (1 H, m, C*H*=CCO$_2$Me), 5.75 (1 H, d, *J* 15.7 Hz, C=C*H*CO$_2$Me), 3.67 (3 H, s, CO_2Me), 3.33 (1 H, m, PhC*H*), 2.68 (2 H, d, *J* 7 Hz, PhC–CH_2CO), 2.49 (2 H, dd, *J* 8.2 and 6.8 Hz, CH_2C=C), 1.75—2.3 (3 H, m, CH_2C*H*Me$_2$), and 0.80 (6 H, d, *J* 6.2 Hz, Me_2).

(E)-8,8-*Dimethyl*-5-*phenyl*-7-*oxonon*-2-*enoic Acid* (**6e**) *and* (R,R)- *and* (R,S)-6,6-*Dimethyl*-3-*phenyl*-5-*oxo*-2-*vinylheptanoic Acid* (**5e**).—4,4-Dimethyl-1-phenylpent-1-en-3-one (**2e**) (7.0 g, 37.2 mmol) and crotonic acid (3.2 g, 37.2 mmol) as before gave an oil which solidified (9.38 g, 92%). Crystallization from diethyl ether led to the *oxo acid* (**6e**), m.p. 123—124 °C (Found: C, 74.25; H, 8.2. $C_{17}H_{22}O_3$ requires C, 74.45; H, 8.0%); $\nu_{max.}$ 3 500 (OH) and 1 700 (C=O) cm^{-1}. The methyl ester had t_R 2.8 min; δ_H 7.20 (5 H, s, Ph), 6.80 (1 H, m, C*H*=CCO$_2$Me), 5.75 (1 H, d, *J* 15.7 Hz, C=C*H*CO$_2$Me), 3.67 (3 H, s, CO_2Me), 3.42 (1 H, m, PhC*H*), 2.79 and 2.77 (2 H, 2 × d, *J* 7.3 and 6.4 Hz, PhCOCH_2), 2.5 (2 H, t, *J* 7 Hz, CH_2C=C), and 1.02 (9 H, s, Bu^t).

On crystallization from benzene, material from the mother liquors gave white prisms of the *vinyl oxo acid* (**5e**), m.p. 116—117 °C (Found: C, 74.3; H, 8.35. $C_{17}H_{22}O_3$ requires C, 74.45; H, 8.0%); $\nu_{max.}$ 3 650—3 250 (OH), 1 700 (C=O), and 1 635 cm^{-1} (C=C). The methyl ester had t_R 1.1 min; δ_H 7.19 (5 H, s, Ph), 5.6 (1 H, m C*H*=CH_2), 4.94 and 5.01 (2 H, 2 × d, *J* 15.8 and 8.8 Hz, C=CH_2), 3.67 (3 H, s, CO_2Me), 3.65 (1 H, m, PhC*H*), 3.41 (1 H, m, C*H*CO$_2$Me), 2.91 and 2.81 (2 H, 2 × d, *J* 10.8 and 8.7 Hz, CH_2COBu^t), and 0.99 (9 H, s, Bu^t).

(R,R)-5-*Oxo*-3,5-*diphenyl*-2-*vinylpentanoic Acid* (**5f**).—1,3-Diphenylprop-2-enone (**2f**) (7.74 g, 37.2 mmol) and crotonic acid (3.2 g, 37.2 mmol) as before yielded a solid (8.86 g, 81%). Crystallization from benzene gave white prisms of the *vinyl oxo acid* (**5f**), m.p. 164—166 °C (Found: C, 77.7; H, 6.15. $C_{19}H_{18}O_3$ requires C, 77.5; H, 6.2%). The methyl ester had m.p. 74.75 °C; t_R 5 min; δ_H 7.40 and 7.79 (5 H, 2 × m, COPh), 7.22 (5 H, s, Ph), 5.90 (1 H, dt, *J* 15 and 9.1 Hz, C*H*=CH_2), 5.19 and 5.21 (2 H, 2 × d, *J* 15 and 9.1 Hz, C=CH_2), 3.78 (1 H, m, C*H*Ph), 3.42 (3 H, s, CO_2Me), and 3.39 (3 H, m, PhCOCH_2 and C*H*CO$_2$Me).

(E,E)-5-*Hydroxy*-5,7-*diphenylhepta*-2,6-*dienoic Acid* (**4f**).—Addition of 1,3-diphenylpropenone (**2f**) (7.74 g, 37.2 mmol) to deprotonated crotonic acid (3.2 g, 37.2 mmol) at −90 °C, with stirring at the same temperature for 20 min, gave a yellow oil, which solidified (9.85 g, 90%). Crystallization from diethyl ether yielded white prisms of the hydroxyheptadienoic acid (**4f**), m.p. 150—151 °C; $\nu_{max.}$ 3 500—3 200 (OH), 1 695 (C=O), and 1 660 and 1 640 cm^{-1} (C=C). The methyl ester had δ_H 7.30 and 7.46 (10 H, m, 2 × Ph), 6.85 (1 H, m, C*H*=CCO$_2$Me), 6.40, and 6.61 (2 H, 2 × d, *J* 15.2 and 15.2 Hz, PhC*H*=C*H*). 5.86 (1 H, d, *J* 13.5 Hz, C=C*H*CO$_2$Me), 3.67 (3 H, s, CO_2Me), and 2.91 (2 H, dd, *J* 7.4 and 7.3 Hz, CH_2C=C).

(R,R)- *or* (R,S)-3-(4-*Methoxyphenyl*)-5-*oxo*-5-*phenyl*-2-*vinylpentanoic Acid* (**5g**).—3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (**2g**) (4.42 g, 18.6 mmol) and crotonic acid (1.6 g, 18.6 mmol) at −70 °C for 0.5 h and 65 °C for 2 h gave a solid (4.52 g, 75%), which yielded white prisms of the *oxo acid* (**5g**), m.p. 163—164 °C (from diethyl ether) (Found: C, 73.9; H, 6.0. $C_{20}H_{20}O_4$ requires C, 74.05; H, 6.2%); $\nu_{max.}$ 3 600—3 250 (OH), 1 705 (C=O), 1 675 (C=O), and 1 640 cm^{-1} (C=C). The methyl ester had δ_H 7.8 and 7.4 (5 H, m, Ph), 7.15 (2 H, d, *J* 8.7 Hz, *o*-C_6H_2OMe), 6.75 (2 H, d, *J* 8.7 Hz, *m*-C_6H_2OMe), 5.93 (1 H, dt,

J 9 and 8 Hz, C*H*=CH_2), 5.23 (2 H, m, C=CH_2), 3.80 (1 H, m, PhC*H*), 3.73 (3 H, s, C_6H_4OMe), 3.44 (3 H, s, CO_2Me), and 3.35 (3 H, m, PhCH_2CO and C*H*CO_2Me).

(E,E)-5-*Hydroxy*-7-(4-*methoxyphenyl*)-5-*phenylhepta*-2,6-*dienoic Acid* (**4g**).—3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (**2g**) (8.85 g, 37.2 mmol) and crotonic acid (3.2 g, 37.2 mmol) at −90 °C for 20 min gave a solid (9.64 g, 80%), which crystallized from diethyl ether, affording white prisms of the *methoxyhydroxy-heptadienoic acid* (**4g**), m.p. 152—153 °C (Found: C, 74.0; H, 6.3. $C_{20}H_{20}O_4$ requires C, 74.05; H, 6.2%); $\nu_{max.}$ 3 500—3 200 (OH), 1 690 (C=O), and 1 655 and 1 635 cm^{-1} (C=C). The methyl ester had δ_H 7.32 (7 H, m, Ph and m-C_6H_2OMe), 6.84 (1 H, m, C*H*=CCO_2Me), 6.83 (2 H, d, *J* 8.7 Hz, *o*-C_6H_2OMe), 6.59 and 6.30 (2 H, 2 × d, *J* 15.2 Hz, $MeOC_6H_4CH$=C*H*), 5.88 (1 H, d, *J* 15.2 Hz, C=C*H*CO_2Me), 3.79 (3 H, s, C_6H_4OMe), 3.68 (3 H, s, CO_2Me), and 2.90 (2 H, d, *J* 7.4 Hz, CH_2C=C).

(E,E)-5-*Hydroxy*-6-*methyl*-5,7-*diphenylhepta*-2,6-*dienoic Acid* (**4h**).—Crotonic acid (0.8 g) and 1,3-diphenyl-2-methylpropenone (**2h**) (2.06 g) at −70 °C, with careful work-up (below 35 °C), gave a syrup (1.92 g, 67%), which crystallized from diethyl ether affording white prisms of the *methyl-hydroxyheptadienoic acid* (**4h**), m.p. 135—136 °C (Found: C, 77.9; H, 6.6. $C_{20}H_{20}O_3$ requires C, 77.9; H, 6.5%); $\nu_{max.}$ 3 420 (OH), 1 710 (C=O), and 1660 cm^{-1} (C=C). The methyl ester had δ_H 7.23 (10 H, m, 2 × Ph), 7.07 (1 H, dt, *J* 15.7 and 6.9 Hz, C*H*=CCO_2Me), 6.84 (1 H, br s, PhC*H*=C), 5.90 (1 H, d, *J* 15.7 Hz, C=C*H*CO_2Me), 3.69 (3 H, s, CO_2Me), 3.05 (2 H, d, *J* 6.9 Hz, CH_2C=C), and 1.67 (3 H, d, *J* 1 Hz, C=CMe).

(E,E)-5-*Hydroxy*-5,7-*diphenylocta*-2,6-*dienoic Acid* (**4i**).—Crotonic acid (1.6 g) and 1,3-diphenylbut-2-en-1-one (**2i**) (4.12 g) reacted for 20 min at −70 °C. Work-up led to an oil, which on crystallization from diethyl ether afforded white prisms of the *hydroxyoctadienoic acid* (**4i**), m.p. 133—134 °C (Found: C, 77.9; H, 6.45. $C_{20}H_{20}O_3$ requires C, 77.9; H, 6.5%); $\nu_{max.}$ 3 490 (OH), 1 680 (C=O), and 1 635 and 1 625 cm^{-1} (C=C). The methyl ester had δ_H 7.32 (10 H, m, 2 × Ph), 7.03 (1 H, dt, *J* 16 and 7.1 Hz, C*H*=CCO_2Me), 6.24 (1 H, br s, PhC*H*), 5.86 (1 H, d, *J* 16 Hz, C=C*H*CO_2Me), 3.69 (3 H, s, CO_2Me), 2.80 (2 H, d, *J* 7.1 Hz, CH_2C=C), and 1.90 (3 H, d, *J* 1 Hz, C=CMe).

(E)-5-*Methyl*-7-*oxo*-5,7-*diphenylhept*-2-*enoic Acid* (**6i**).—Crotonic acid (0.8 g) and 1,3-diphenylbut-2-enone (**2i**) (2.06 g) reacted as usual for 15 min at −70 °C and for 2 h at 65 °C. Work-up gave an oil (1.95 g, 68%). Esterification of a sample (1.5 g) and chromatography gave a colourless oil (1.1 g), the *methyl ester* of the *oxoheptenoic acid* (**6i**) (Found: C, 78.25; H, 7.0. $C_{21}H_{22}O_3$ requires C, 78.3; H, 6.8%); $\nu_{max.}$(neat) 1 720 and 1 695 (C=O) and 1 595 cm^{-1} (C=C); δ_H 7.8 and 7.35 (10 H, 2 × m, 2 × Ph), 6.85 (1 H, dt, *J* 15.7 and 7.2 Hz, C*H*=CCO_2Me), 5.82 (1 H, d, *J* 15.7 Hz, C=C*H*CO_2Me), 3.65 (3 H, s, CO_2Me), 3.38 (1 H, d, *J* 17 Hz, CH_ACOPh), 3.30 (1 H, d, *J* 17 Hz, CH_BCOPh), 2.81 (2 H, d, *J* 7.2 Hz, CH_2C=C), and 1.53 (3 H, s, CMe).

(E)-4-(3-*Oxocyclopentyl*)*but*-2-*enoic Acid* (**15**).—Crotonic acid (1.44 g) and cyclopentenone (1.20 g) reacted first at −70 °C and then at room temperature for 2 h. Usual work-up, and continuous extraction of the acidic aqueous solution, gave an oil (2.02 g, 76%). A sample of this was esterified and distilled (b.p. 150—155 °C at 5 mmHg) to give the methyl ester of the oxocyclopentylbutenoic acid (**15**), as a colourless oil; δ_H 6.95 (1 H, dt, *J* 15.7 and 7.8 Hz, C*H*=CCO_2Me), 5.86 (1 H, d, *J* 15.7 Hz, C=C*H*CO_2Me), 3.73 (3 H, s, CO_2Me), and 2.21—1.38 (9 H, m, CH_2C=C and C_5H_7). The *semicarbazone* had m.p. 156—157 °C (Found: C, 55.55; H, 7.2; N, 17.25. $C_{11}H_{17}N_3O_3$ requires C, 55.2; H, 7.1; N, 17.6%).

(E)-4-(1-*Methyl*-3-*oxocyclopentyl*)*but*-2-*enoic Acid* (**16**).—Crotonic acid (1.6 g) and 3-methylcyclopentenone (1.8 g) at room temperature gave an oil (2.7 g, 87%). Chromatography of an esterified sample (0.5 g) allowed isolation of the *methyl ester* of the *oxocyclopentylbutenoic acid* (**16**) (0.27 g), b.p. 150 °C at 1 mmHg (Found: C, 67.2; H, 8.1. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%); $\nu_{max.}$(neat) 1 735 and 1 720 (C=O) and 1 650 cm^{-1} (C=C); δ_H 6.91 (1 H, dt, *J* 15.7 and 7.8 Hz, C*H*=CCO_2Me), 5.87 (1 H, d, *J* 15.7 Hz, C=C*H*CO_2Me), 3.74 (3 H, s, CO_2Me), 2.31 (2 H, m, CH_2C=C), 2.26—1.3 (6 H, br s, C_5H_6), and 1.11 (3 H, s, CMe).

(E)-4-(3-*Oxocyclohexyl*)*but*-2-*enoic Acid* (**17**).—Crotonic acid (3.2 g) and cyclohex-2-enone (3.58 g) at −70 °C for 15 min and at room temperature for 2 h gave an oil (5.27 g). Esterification of a sample (1 g) and chromatography allowed isolation of the *methyl ester* of the *oxocyclohexylbutenoic acid* (**17**) as an oil, b.p. 150 °C at 1 mmHg (Found: C, 67.9; H, 8.4. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%); $\nu_{max.}$(neat) 1 730 and 1 720 (C=O) and 1 660 cm^{-1} (C=C); δ_H 6.95 (1 H, dt, *J* 15.7 and 7.8 Hz, C*H*=CCO_2Me), 5.87 (1 H, d, *J* 15.7 Hz, C=C*H*CO_2Me), 3.73 (3 H, s, CO_2Me), and 2.51—1.95 (11 H, br s, CH_2C=C and C_6H_7).

(E)-4-(1-*Methyl*-3-*oxocyclohexyl*)*but*-2-*enoic Acid* (**18**).—Crotonic acid (3.2 g) and 3-methylcyclohex-2-enone (4.09 g) on reaction as usual gave a yellow oil (5.70 g, 78%). Esterification and chromatography led to isolation of the *methyl ester* of the *oxocyclohexylcarboxylic acid* (**18**), b.p. 155 °C at 1 mmHg (Found: C, 67.9; H, 8.55. $C_{11}H_{16}O_3$ requires C, 68.5; H, 8.6%); $\nu_{max.}$(neat) 1 720 (C=O) and 1 660 cm^{-1} (C=C); δ_H 6.85 (1 H, dt, *J* 16 and 7 Hz, C*H*=CCO_2Me), 5.77 (1 H, d, *J* 16 Hz, C=C*H*CO_2Me), 3.73 (3 H, s, CO_2Me), 2.19 (2 H, m, CH_2C=C), 2.13—1.6 (8 H, m, C_6H_8), and 0.97 (3 H, s, CMe).

(E)-4-(1,5-*Dimethyl*-3-*oxocyclohexyl*)*but*-2-*enoic Acid* (**19**).—Crotonic acid (1.6 g) and 3,5-dimethylcyclohex-2-enone (2.3 g) for 2 h at 45 °C gave a syrup (3.55 g, 91%). A sample (3 g) was esterified. Chromatography and distillation gave a diastereoisomeric mixture of the *methyl esters* of the *oxocyclohexylbutenoic acid* (**19**), b.p. 160 °C at 1 mmHg (Found: C, 69.6; H, 8.8. $C_{13}H_{20}O_3$ requires C, 69.6; H, 8.9%); $\nu_{max.}$(neat) 1 720 (C=O) and 1 650 cm^{-1} (C=C); δ_H 6.98 (1 H, dt, *J* 15.5 and 7.8 Hz, C*H*=CCO_2Me), 5.81 (1 H, d, *J* 15.5 Hz, C=C*H*CO_2Me), 3.73 (3 H, s, CO_2Me), 2.15—1.6 (9 H, m, CH_2C=C and C_6H_7), 1.04 (3 H, s, CMe), and 0.95 (3 H, d, *J* 4.6 Hz, CMe).

(E)-4-(1,5,5-*Trimethyl*-3-*oxocyclohexyl*)*but*-2-*enoic Acid* (**20**).—Crotonic acid (1.6 g) and isophorone (2.5 g) on reaction as usual for 15 min at −70 °C and 2 h at 0 °C gave a syrup (3.6 g, 87%), which on crystallization from benzene afforded white prisms of the carboxylic acid (**20**), m.p. 98—99 °C (lit.,[1] 98—99 °C). The methyl ester had $\nu_{max.}$ 1 715 (C=O) and 1 650 cm^{-1}; δ_H 7.04 (1 H, dt, *J* 16 and 8 Hz, C*H*=CCO_2Me), 5.87 (1 H, d, *J* 16 Hz, C=C*H*CO_2Me), 3.73 (3 H, s, CO_2Me), 2.24 (2 H, d, *J* 8 Hz, CH_2C=C), 2.2 (4 H, s, C_6H_4), 1.62 (2 H, s, C_6H_2), and 1.07 (9 H, s, 3 × CMe).

4,6,6-*Trimethyl*-7-*oxobicyclo*[2.2.2]*octan*-2-*ylacetic Acid* (**21**).—Crotonic acid (1.6 g) and isophorone (2.5 g) reacted at −70 °C and then at 65 °C for 2 h. Work-up led to a solid (3.7 g, 90%), which gave white prisms of the *oxobicyclo-octylacetic acid* (**21**), m.p. 130—131 °C (from diethyl ether) (Found: C, 69.3; H, 9.2%; *m/z*, 224. $C_{13}H_{20}O_3$ requires C, 69.6; H, 8.9%; *M*, 224); $\nu_{max.}$ 1 720 (C=O) and 1 700 cm^{-1} (C=O); δ_H(500 MHz)

2.720 (1 H, ddddd, *J* 10.7, 9.5, 6.1, 5.0, and 2.6 Hz, 6-H), 2.280 (1 H, dd, *J* 16 and 6.1 Hz, C$H_A$$CO_2$H), 2.150 (1 H, dd, *J* 16 and 9.2 Hz, C$H_B$$CO_2$H), 2.022 (1 H, dd, *J* 19 and 3.5 Hz, 3-H_B), 1.891 (1 H, dd, *J* 19 and 2.5 Hz, 3-H_A), 1.830 (1 H, d, *J* 2.5 Hz, 1-H), 1.795 (1 H, ddd, *J* 13.6, 10.7, and 3.1 Hz, 5-H_C), 1.310 (1 H, dd, *J* 13.5 and 2.5 Hz, 8-H_C), 1.270 (1 H, dd, *J* 13.5 and 2.5 Hz, 8-H_B), 1.126 (3 H, s, CMe), 0.981 (1 H, ddd *J* 13.6, 5, and 2.5 Hz, 5-H_A), 0.947 (3 H, s, CMe), and 0.925 (3 H, s, CMe).

(E)-4-(2,7,7-*Trimethyl*-4-*oxobicyclo*[3.1.1]*heptan*-2-*yl*)*but*-2-*enoic Acid*.—Crotonic acid and verbenone (**13**) (2.79 g) reacted first at −70 °C and then at 65 °C for 2 h. Work-up as usual led to an oil (3.89 g, 88%), which on crystallization from diethyl ether yielded white prisms of the *bicycloheptylbutenoic acid* (**23**), m.p. 132—133 °C (Found: C, 70.5; H, 8.3. $C_{13}H_{18}O_3$ requires C, 70.3; H, 8.1%); $\nu_{max.}$ 3 400 (OH), 1 690 (C=O), and 1 640 cm^{-1} (C=C). The methyl ester had δ_H 6.92 (1 H, dt, *J* 15.5 and 7.8 Hz, C*H*=CO_2Me), 5.48 (1 H, d, *J* 15.5 Hz, C=C*H*CO_2Me), 3.74 (3 H, s, CO_2Me), 2.07—1.05 (6 H, m, CH_2C=C and C_6H_4), 1.37, 1.21, and 1.03 (9 H, 3 × s, 3 × CMe).

(E)-5-(4-*Methyl*-2-*oxocyclohexyl*)*hex*-2-*enoic Acid* (**24**).—Crotonic acid (1.44 g) and pulegone (**14**) (2.54 g) reacted for 2 h at 65 °C. Work-up led to a syrup (3.27 g, 81%). Esterification of a sample (2 g), chromatography, and distillation gave a colourless oil (1.12 g), the *methyl ester* of the *oxocyclohexylhexenoic acid* (**24**), b.p. 170 °C at 1 mmHg (Found: C, 71.3; H, 9.75. $C_{15}H_{24}O_3$ requires C, 71.45; H, 9.5%); $\nu_{max.}$(neat) 1 720 (C=O) and 1 640 cm^{-1} (C=C); δ_H 6.90 (1 H, dt, *J* 16.5 and 7.8 Hz, C*H*=CCO_2Me), 5.80 (1 H, d, *J* 16.5 Hz, C=C*H*CO_2Me), 3.72 (3 H, s, CO_2Me), 2.5—1.64 (10 H, m, CH_2C=C and C_6H_8), and 1.04 and 0.99 (9 H, 2 × s, 3 × CMe).

2-*Isopropenyl*-3-*phenyl*-5-*oxohexanoic Acid* (**25**) *and* 1-*Methyl*-3-*oxo*-5-*phenylcyclohexylacetic Acid* (**26**).—2-Methylbut-2-enoic acid (3.72 g) and 4-phenylbut-3-en-2-one (5.43 g) for 2 h at 40 °C afforded a syrup (7.7 g, 80%). Chromatography of an esterified sample (1.8 g) gave a solid (0.76 g), which on crystallization gave fairly pure samples of *erythro*- and *threo*-methyl esters of the oxohexanoic acid (**25**); δ_H 7.25 (5 H, s, Ph), 5.05 (2 H, m, C=CH_2), 3.66 (1 H, m, PhC*H*), 3.3 (3 H, s, CO_2Me), 3.37 (1 H, d, *J* 8 Hz, C*H*CO_2Me), 2.68 (2 H, d, *J* 6.8 Hz, CH_2COMe), 1.92 (3 H, s, COMe), and 1.83 (3 H, s, C=CMe). Further elution gave an oil (0.5 g), the *methyl ester* of the *oxocyclohexylacetic acid* (**26**), b.p. 170 °C at 1 mmHg (Found: C, 73.75; H, 8.0. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%); $\nu_{max.}$(neat) 1 730 and 1 710 cm^{-1} (C=O); δ_H 7.26 (5 H, s, Ph), 3.67 (3 H, s, CO_2Me), 3.33 (1 H, m, PhC*H*), 2.59 (2 H, C$H_2$$CO_2$Me), 2.36 (4 H, m, CH_2COCH_2), 2.01 (2 H, m, CH_2), and 1.22 (3 H, s, CMe).

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