The chemoselective cyclisation of unsymmetrical γ-diketones to cyclopentenones by directed aldol reaction using a magnesium chelate

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The feasibility of synthesising disubstituted cyclopent-2-enones chemoselectively from unsymmetrical γ-diketones, using an aldol reaction directed by magnesium chelation, has been studied. Treatment of 3,3-dimethylhexane-2,5-dione **15** with aqueous sodium hydroxide (0.5 mol dm^{-3}) gives a mixture of 3,5,5-trimethyl- **12** and 3,4,4-trimethylcyclopent-2-enone **14** in an isomer ratio of 2.2:1. Insertion of an α-methoxycarbonyl grouping as a control element allows formation of a magnesium chelate **17** when treated with magnesium methoxide, and the major product is then mainly the undehydrated aldol **21**. This, when treated with aqueous sodium hydroxide (0.5 mol dm^{-3}) to dehydrate, hydrolyse and decarboxylate, gives the 3,5,5-trimethyl- and 3,4,4-trimethylcyclopent-2-enones in a nearly chemospecific ratio of 1:49. When 3-methoxycarbonyl-4,4-dimethylhexane-2,5-dione **16** is treated with aqueous sodium hydroxide (0.5 mol dm^{-3}), omitting the magnesium methoxide treatment, the corresponding ratio of cyclopentenones was still an interesting 1:7.3. Treatment with sodium methoxide in methanol gives, by contrast, γ-lactone **27**.

Treatment of undecane-4,7-dione **34** with aqueous sodium hydroxide (0.5 mol dm^{-3}) at reflux gives 2,3-dipropylcyclopent-2-enone **36** and 3-butyl-2-ethylcyclopent-2-enones **35** in a ratio of almost 1:1. Treatment of 6-methoxycarbonylundecane-4,7-dione **33** with magnesium methoxide in methanol gives undehydrated aldol which when treated with aqueous sodium hydroxide gives the dipropylcyclopent-2-enone **36** and 3-butyl-2-ethylcyclopent-2-enones **35** in 9:1 ratio. Conversely, the 5-methoxycarbonyldione **32** gives a corresponding ratio of **36** to **35** of 1:9. The best ratios attained, 1:15 for **36** and **35** from **32** and 20:1 for **36** and **35** from **33**, were when magnesium methoxide in refluxing benzene or toluene were employed. There is still a strong chemoselective effect when the magnesium treatment is omitted.

Preliminary examination of the corresponding cyclohex-2-enone systems gave poorer chemoselectivities when either procedure was employed. 6-Methoxycarbonyldodecane-5,9-dione **52** gave 2,3-dipropyl- **54** and 3-butyl-2-ethyl-cyclohex-2-enone **55** in a ratio of ~4:1 whilst the 5-methoxycarbonyldodecane-4,8-dione **53** gave a 1: ~4 ratio.

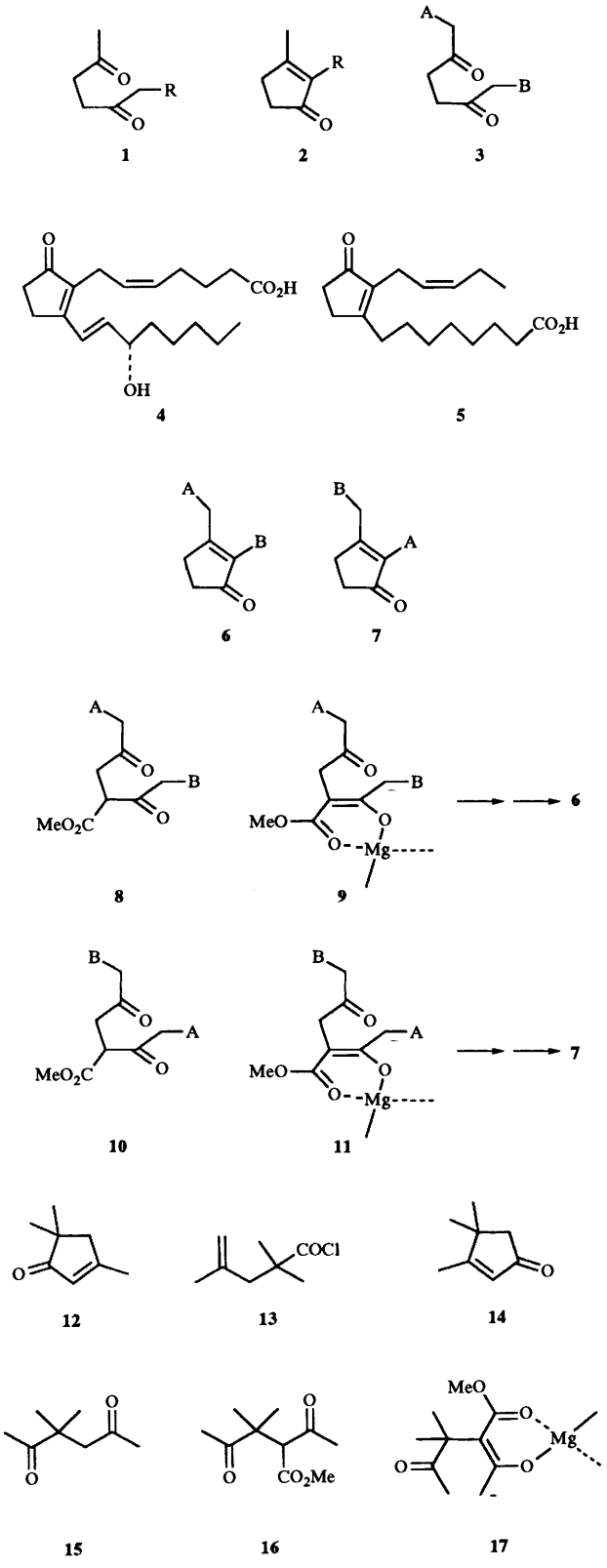
Base-catalysed cyclisation of 2,5-diketones **1**[1,2] provides the terminal step in many cyclopent-2-enone **2** syntheses. This type of structure is of significant interest in connection with the chemistry of various natural product groups, among them jasmonoids,[3] and pyrethrins.[4] However, the more general case of the γ-diketone **3** has been much less studied although it is represented by natural products such as prostaglandin B_2 (PGB_2)[5] **4** and the dicranenones, *e.g.* tetrahydrodicranenone[6] **5**. Where the cyclopentenone substituents are similar, intramolecular aldol leads to mixtures of **6** and **7**, often in near equal amounts (see below). The aim of the present investigation was the development of a method based on magnesium chelation to achieve chemoselective or chemospecific cyclisation processes. A methoxycarbonyl group is introduced as a control element internally adjacent to one or other of the carbonyl groups as in **8** and **10**. During cyclisation using the chelating base magnesium alkoxide in methanol, the β-keto ester becomes protected as an aldol acceptor by magnesium chelation (see **9** and **11**), and the second carbonyl then becomes the aldol acceptor.[7] Such a magnesio-chelate directed aldol cyclisation to form cyclopentenones has not previously been reported.

Cyclisation of 3,3-dimethylhexane-2,5-dione and its methoxycarbonyl derivative

Our investigation commenced with the study of a chemoselective aldol reaction to form certain trimethylcyclopent-2-enones of natural product interest,[8] which in early work were isolated synthetically as mixtures of isomers.[9] However, Hayashi and his colleagues[10] reported a chemospecific synthesis of 3,5,5-trimethylcyclopent-2-enone **12** by cyclisation of the intermediate **13** with aluminium chloride. Our interest was focussed on the isomer **14**, 3,4,4-trimethylcyclopent-2-enone. Aldol cyclisation of 3,3-dimethylhexanedione **15** might be expected to give a mixture of cyclopentenones **12** and **14**, and insertion of an α-methoxycarbonyl grouping, as in **16**, as a control element allowed us to form a magnesio-chelate anion **17** to direct the aldol cyclisation.[11]

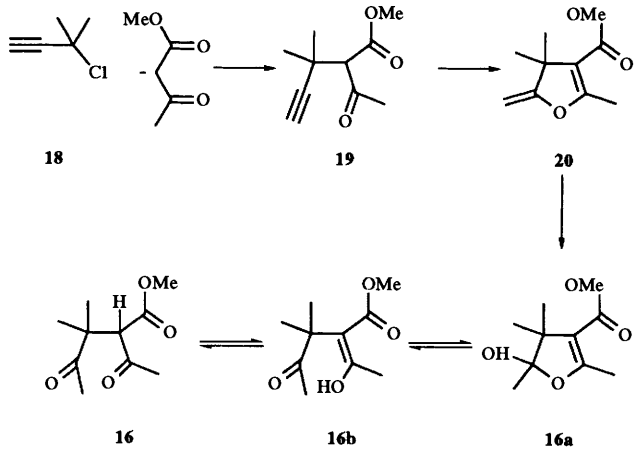
The starting substrate for study was made as in Scheme 1.[12,13] Reaction of 3-chloro-3-methylbutyne **18** in refluxing methanol with the anion from methyl acetoacetate forms the intermediate **19**, derived from α-attack on the presumed allene–carbene,[13] which cyclises spontaneously to give the methylene-dihydrofuran **20** in 75% yield. Subsequent hydration under acid conditions then produces the substrate required which exists as a pure liquid in the open ketone form **16** to the extent of 79% as shown by ^1H NMR examination. The other tautomer was the cyclic hemi-acetal form **16a** (21%), but no evidence was found for a detectable stationary concentration of the open-chain enol. As Table 1 shows, there is some variation in the concentrations of the relevant tautomers in different NMR solvents.

The pair of trimethylcyclopent-2-enones **12** and **14** required for study as products, were obtained as follows. Hydrolysis of the methylene dihydrofuroate **20** with 10% methanolic potassium hydroxide gave the corresponding acid and this was then decarboxylated and hydrolysed with aqueous sulfuric acid (1 mol dm^{-3}) to give the acyclic dione **15** (77%). Reaction of the latter with refluxing sodium hydroxide (0.5 mol dm^{-3}) gave a



mixture of the two isomeric cyclopentenones[12,13] which were initially separated by HPLC (Poropak silica, eluting with hexane–diethyl ether, 4:1) but later were routinely separated using flash column chromatography[14] (silica, eluent diethyl ether–light petroleum, 1:3) to give the 3,5,5-trimethyl isomer **12** (69%) and the 3,4,4-trimethyl isomer **3** (26%). As determined gas chromatographically, the ratio was 2.2:1 (Table 2).

Historically, the assignment of structure to the two cyclopentenones was made by Wallach[9] on the basis that one



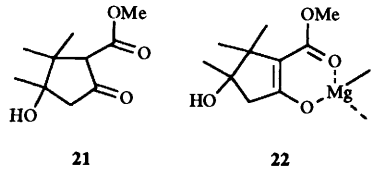
Scheme 1 Synthesis and tautomerism of 3-methoxycarbonyl-4,4-dimethylhexane-2,5-dione

Table 1 Equilibrium position for the hemiketal **16a** and the diketone **16** system in various solvents

	% Tautomer	
Solvent	**16a**	**16**
Neat liquid	21	79
$CDCl_3$	8	92
CCl_4	12	88
CD_3OD	13	87

isomer formed a semicarbazone slowly, the other rapidly, the latter being assigned the 3,4,4-trimethyl structure **14** on account of the expected lessened steric hindrance to its formation. Wallach's view receives unequivocal confirmation from a single crystal X-ray structure carried out for us by the late Dr M. Begley in our laboratory. The rapidly formed semicarbazone from **14** proved to be of the 3,4,4-trimethylcyclopent-2-enone structure.

The product from treatment of the keto ester **16** with an excess of magnesium methoxide (12 mol) was isolated, after acidification, as a pale yellow oil and purified by HPLC. The major isolable product was subjected to GLC–MS analysis which indicated a molecular weight of 200 and a fragmentation which showed loss of water from the parent ion (182) and loss of a methoxy group (169). The IR spectrum showed absorptions at 3470 (hydroxyl), 1750 (saturated ester) and 1705 (saturated ketone) and the NMR data were also consistent with the hydroxycyclopentanone structure **21**. This indicates that the magnesium chelate **22** had formed from the β-keto ester portion of **16** and that a directed aldol condensation to give **22** had taken place, but without much subsequent dehydration.

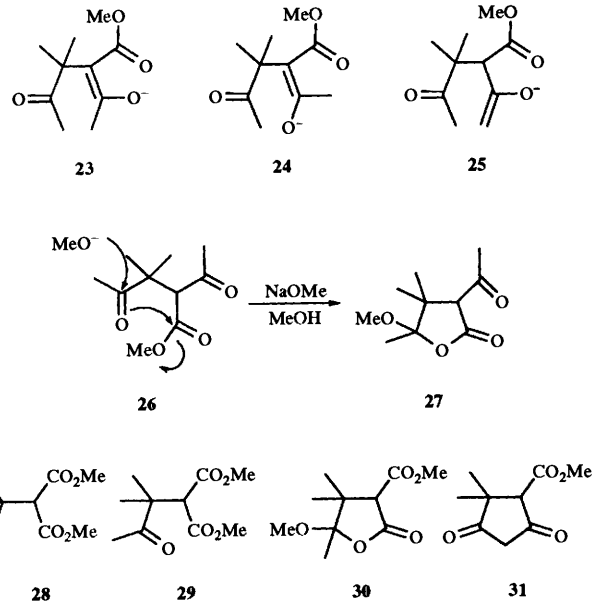


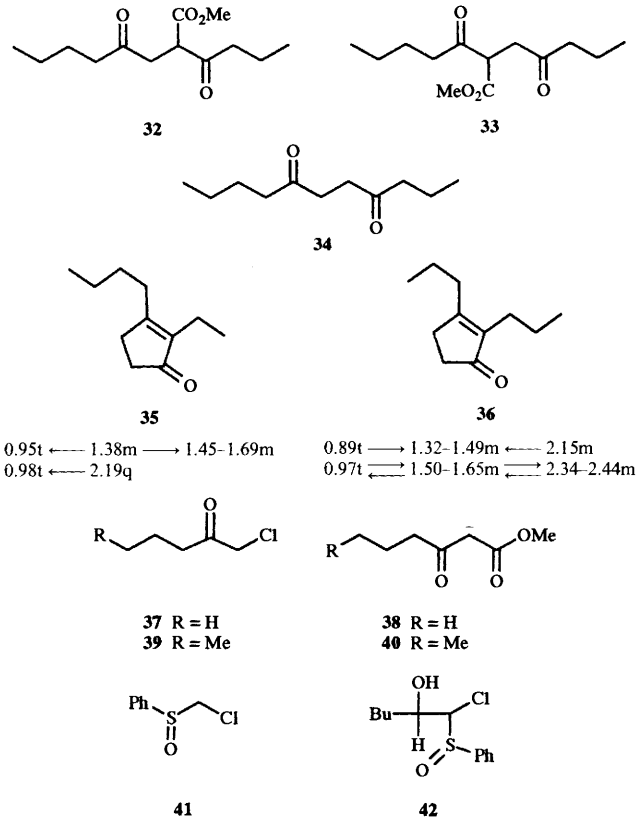
The pale yellow oil (above) was therefore refluxed with 0.5 mol dm^{-3} aqueous sodium hydroxide for 2 h to effect dehydration, hydrolysis and decarboxylation to give a colourless oil. Analysis by GLC (50 ft column, OV17) showed the product to contain 98% of the 3,4,4-trimethyl isomer and 2% of the 3,5,5-trimethyl isomer (Table 2). To ensure that no interconversion of cyclopentenones had taken place through alkaline isomerisation, each pure isomer was refluxed with

Table 2 Products from the treatment of the diones **15** and **16** with bases

		Isomers %				
		12	**14**	Ratio	Anal. method	Yield (%)
15	0.5 mol dm^{-3} aq. NaOH	69	31	2.2:1	GLC	—
		69	26	2.7:1	Isolation	95
16	1. $Mg(OMe)_2$ (12 mol)/MeOH; 2. 0.5 mol dm^{-3} aq. NaOH	2	98	1:49	GLC	81[a]
16	0.5 mol dm^{-3} aq. NaOH	12	88	1:7.3	GLC	54
16	0.5 mol dm^{-3} methanolic NaOH	Compound **27**			Isolation	48

[a] Yield based on magnesium methoxide product.





0.5 mol dm^{-3} aqueous sodium hydroxide for 2 h. No interconversion of the isomers could be detected—nor indeed after more prolonged refluxing.

It seemed of interest to find out how chemospecific the cyclisation of **16** would be if the magnesium methoxide step was omitted. Treatment of **16** directly with refluxing aqueous sodium hydroxide (0.5 mol dm^{-3}) for 4 h gave the 3,4,4-trimethyl isomer **14** and the 3,5,5-trimethyl isomer **12** in a ratio of 7.3:1. Rather surprisingly, introduction of the α-methoxycarbonyl grouping thus brings about a very marked increase in 3,4,4-trimethyl-directed specificity relative to similar cyclisation of the diketone **15**. A possible explanation is that whilst the ionised α-enolate **23** or **24** does not act efficiently as an aldol acceptor because of its charged situation, it undergoes equilibration with the βγ form **25** which now acts as the donor just as in the magnesium chelated case. The overall reaction is, of course, relatively complex as four reactions proceed in the one experimental stage: aldol condensation, dehydration, ester hydrolysis and decarboxylation, and some of the minor isomer could arise from diketone **15** formed ahead of the cyclisation.

Treatment of the diketo ester **16** with sodium methoxide in dry methanol for 2 h gave no evidence of cyclopentenone formation. Instead, the major product (56%) was the γ-lactonic ether **27**, a product of *O*-Claisen attack formed as shown in **26**. The compound showed IR absorptions at 1775 (γ-lactone), 1705 (dialkyl ketone) and 1645 cm^{-1} (β-diketone) and NMR and other data are in agreement.

During this work no *C*-Claisen product was encountered and this point was examined further using the ester **29**[15] in place of its acetyl relative **16**. The ester **29** was made by a method similar to that of Scheme 1 except that malonate anion replaces acetoacetate anion and the acetylenic product **28** (65%) did not cyclise spontaneously. It was therefore converted into the methyl ketone **29** by mercury-catalysed hydration using boron trifluoride–diethyl ether (75% yield).[16] Treated with either sodium methoxide in methanol or magnesium methoxide in methanol it gave the lactone **30** (47 and 59% yields, respectively), a product of *O*-Claisen attack rather than *C*-Claisen attack. The expected product from the latter type of reaction **31** was not found.

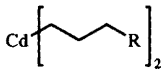
Cyclisation of undecane-4,7-dione and its carboxylated derivatives

The system selected for study was undecane-4,7-dione **34** which when cyclised with 0.5 mol dm^{-3} sodium hydroxide at reflux gives 2,3-dipropylcyclopent-2-enone **36** and 3-butyl-2-ethylcyclopent-2-enone **35** in almost equal amounts (Table 3). For the control element, a methoxycarbonyl was placed at position 5-, as **32**, and then at position 6-, as **33**. These latter compounds were made by condensing the chloro ketone **37** wtih the β-keto ester anion **40**, and the chloro ketone **39** with the β-keto ester **38**, in the presence of sodium hydride. The β-keto esters themselves are readily available by treatment of the corresponding ketones

Table 3 Products from the treatment of the diones **32**, **33** and **34** with bases

		Isomers %				
		35	**36**	Ratio	Anal. method	Yield (%)
34	0.5 mol dm^{-3} aq. NaOH	49	51	1:1	GLC	—
		49	51	1:1	Isolation	85
33	1. $Mg(OMe)_2$ (12 mol)/MeOH 2. 0.5 mol dm^{-3} aq. NaOH	10	90	1:9	Isolation	80
		12.5	87.5	1:7	GLC	64
32	1. $Mg(OMe)_2$ (12 mol)/MeOH 2. 0.5 mol dm^{-3} aq. NaOH	90	10	9:1	GLC	72
33	1. $Mg(OMe)_2$ (12 mol)/benzene) 2. 0.5 mol dm^{-3} aq. NaOH	4.8	95.2	1:20	Isolation	73
32	1. $Mg(OMe)_2$ (12 mol)/benzene 2. 0.5 mol dm^{-3} aq. NaOH	94	6	15:1	Isolation	72
33	0.5 mol dm^{-3} aq. NaOH	11	89	1:8	GLC	74
32	0.5 mol dm^{-3} aq. NaOH	87	13	7:1	GLC	71

with dimethyl carbonate in the presence of sodium hydride. Two methods were used to obtain the chloro ketone components **37** and **39**. In the first of these,[17] thioanisole was oxidised to its sulfoxide by sodium metaperiodate[18] and then chlorinated by *N*-chlorosuccinimide[19] to give the reagent **41**. This was treated with butyllithium in THF at −70 °C, followed by the appropriate aldehyde. Thermolysis of the product **42** in xylene then gave the desired chloro ketone, *e.g.* **39**. In our hands this method gave rather poor yields at the condensation stage, so instead, we later used a more conventional reaction between the appropriate alkylcadmium **43** and chloroacetyl chloride.[20]



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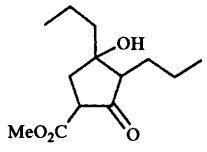
Undecane-4,7-dione **34** was obtained from the dione ester **32** or **33** by demethoxycarbonylation using cold 5 mol dm^{-3} aqueous potassium hydroxide in methanol,[21] and on cyclisation using aqueous sodium hydroxide (0.5 mol dm^{-3}) under reflux gave a mixture of the two cyclopent-2-enones **35** and **36** which were required as reference materials. The cyclopent-2-enones could be separated by flash column chromatography as isomeric oils and, on isolation, were obtained in 43.5:41.5% (**36**:**35**) (Table 3). A similar ratio, 1.05:1, was determined by GLC (OV 17 capillary). The identities of the two cyclopent-2-enones were determined by ^1H NMR, in particular by decoupling experiments as summarised below the formulae **35** and **36**. The results show that one isomer has one alkyl chain of two carbons and one of greater than three carbons in length, in support of structure **35**. The other has both methyl groups separated from the methylene carbons adjacent to the double bonds by a methylene carbon, and this isomer is, therefore, **36**.

In order to assess the influence of the chelating base magnesium methoxide on the cyclisation of **33**, it was treated in methanol with an excess (12 mol) of magnesium methoxide for 12 h at room temperature, and worked up under acid conditions. The product was found to be a mixture, as examined by ^1H NMR, TLC or gas chromatography (Carbowax 20M). There was evidence of some unchanged starting material but a strong hydroxyl peak in the IR spectrum indicated that, as in the previous example, large amounts of undehydrated aldol **44** were present. This suggests that the condensation does not proceed beyond formation of the chelate **45**, though some dehydration may occur during work-up. In order to complete dehydration, as well as to hydrolyse and decarboxylate the ester the crude



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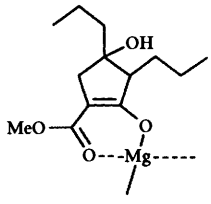

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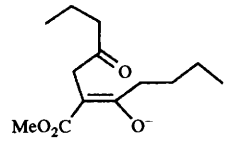
product from the magnesium complex was refluxed for 4 h with 0.5 mol dm^{-3} aqueous sodium hydroxide. Isolation by flash chromatography gave 2,3-dipropylcyclopent-2-enone **36** in 72% yield and 3-butyl-2-ethylcyclopent-2-enone **35** in 8% yield, an isomer ratio of 9:1 at an overall yield of 80%. GLC analysis in a similar experiment gave a ratio of 7:1 (64%) (Table 3). In the same way, when treated with magnesium methoxide (12 mol) in methanol, the isomeric precursory dione ester **32** also gave a mixture of products which on similar treatment with 0.5 mol dm^{-3} sodium hydroxide gave 2,3-dipropylcyclopent-2-enone **36** and 3-butyl-2-ethylcyclopent-2-enone **35** in an isomer ratio of 1:9 (72%) (Table 3).

Although an encouraging degree of directional control over cyclopentenone formation is achieved in the two reactions, unwanted isomer still remains in each case. As one possible source of this, the stability of the product cyclopentenones to refluxing aqueous base, under the conditions employed above, was tested. There was, however, no detectable retro-aldol reaction and recyclisation (this has been reported for the rearrangement of 3-substituted cyclopent-2-enones to 2,3-disubstituted cyclopent-2-enones,[2] and can occur with cyclohex-2-enones—see below). Experiments using 24 mol and 1.1 mol of magnesium methoxide in reactions with **33** gave the same 9:1 ratio of 2,3-dipropylcyclopent-2-enone **36** to 3-butyl-2-ethylcyclopent-2-enone **35** as did the 12 mol reaction. Using refluxing conditions for 36 h in a 12 mol reaction had no major effect on the ratio, though there was some deterioration (5.7:1), and neither the addition of anhydrous sodium sulfate nor molecular sieves to the standard reaction caused any major change in ratios.

Replacement of magnesium methoxide in methanol by magnesium methoxide (12 mol) in benzene, refluxing for 18 h and then working up by refluxing with sodium hydroxide (0.5 mol dm^{-3}) as before, produced from **33** an isolated yield of 69.5% of 2,3-dipropylcyclopent-2-enone **36** and 3.5% of 2-ethyl-3-butylcyclopent-2-enone **35** (ratio 20:1) (Table 3). A similar reaction in benzene using the dione ester **32** gave an isolated yield of 4.4% of 2,3-dipropylcyclopent-2-enone **36** and 67.1% 3-butyl-2-ethylcyclopent-2-enone **35**, *i.e.* an isomer ratio of 1:15,

and a reaction using toluene at reflux gave a similar result. A similar reaction in benzene at room temperature gave a ratio of 1:11.5 as determined by GLC. In order to encourage dehydration of the putative magnesium intermediate **45** the reaction using **32** was carried out in refluxing benzene using 12 mol of magnesium methoxide and a Soxhlet apparatus containing molecular sieves. On work-up, however, the ratio of **36** to **35** was still 1:9.

As pointed out above, cyclisation of the diketone **34** by hot 0.5 mol dm^{-3} aqueous sodium hydroxide gives the cyclopentenones **35** and **36** in approximately 1:1 ratio. Omitting preliminary magnesium methoxide treatment, we found that on similar treatment of the methoxycarbonylated relatives **32** and **33** there is still a strongly chemoselective effect as found in the case of **16**. Thus, **32** gave **35** and **36** at a ratio of 7:1 yield 71%). Similarly **33** gave **35** and **36** in a ratio of 1:8 (yield 74%) (Table 3). It is suggested that under alkaline conditions the αβ-double bond of the enolate **46** equilibrates with the βγ-double bond of the enolate **47** and that it is the



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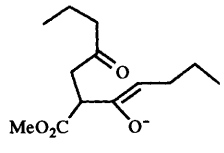

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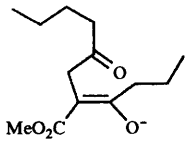

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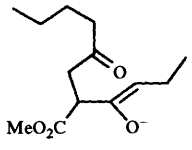

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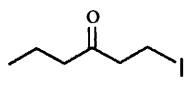
latter that initiates aldol condensation: similarly **48** gives **49**. As pointed out earlier, the aqueous sodium hydroxide treatment which follows magnesium methoxide treatment involves at least three processes—dehydration, ester hydrolysis and decarboxylation. Our results suggest that in the direct procedure using only sodium hydroxide, much of the cyclisation has occurred before ester hydrolysis and decarboxylation, but premature hydrolysis and decarboxylation before cyclisation may be a source of the minor isomer. A retro-aldol process involving the aldol, *e.g.* **44** might also reduce the chemoselectivity in the magnesium method and these various factors require further study.

Cyclisation of dodecane-4,8-dione and its carboxylated derivatives

In order to make a preliminary examination of the complementary cyclohex-2-enone systems, the diketo esters **52** and **53** were needed. These were made by a method similar to that used for **32** and **33**, the necessary halides being obtained as follows. Hept-1-en-3-ol was oxidised to the ketone (83%) with manganese dioxide, and trimethylsilyl iodide in dichloromethane at −40 °C was added to the unsaturated ketone to give 1-iodoheptan-3-one **51** (72%).[22] 1-Iodohexan-3-one **50** was made similarly.

6-Methoxycarbonyldodecane-5,9-dione **52** was refluxed for 12 h with aqueous sodium hydroxide (0.5 mol dm^{-3}) and gave a yellow oil which was purified by column chromatography and shown (GLC) to be a mixture of two components in the ratio ~4:1. Since these proved difficult to separate by HPLC, characterisation was continued by GLC–MS. The two components were isomeric, accurate masses being correct for $C_{12}H_{20}O$, and the loss of an ethyl and a butyl group (fragments 151 and 123) from the minor component suggested that it is **55**:



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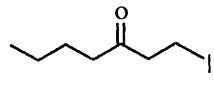

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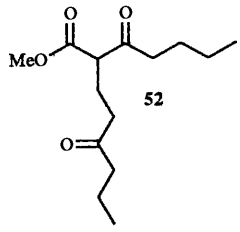

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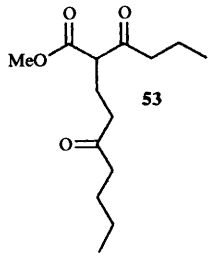

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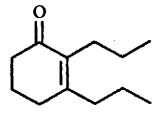

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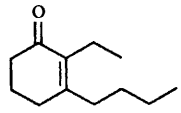

55

the major component **54** showed losses of methyl (165), ethyl (151) and propyl (137) only. This direction of cyclisation is, therefore, the same as in the five-membered series. Similar results were obtained with 5-methoxycarbonyldodecane-4,8-dione **53** when a *ca.* 4:1 mixture of cyclohexenones was obtained. However the major product was now 3-butyl-2-ethylcyclohex-2-enone **55**, 2,3-dipropylcyclohex-2-enone **54** being the minor product. ^{13}C NMR assignments for the major isomer in each mixture are also consistent with the structures proposed.

6-Methoxycarbonyldodecane-5,9-dione **52** when treated with magnesium methoxide (12 ml) in methanol for 12 h at room temperature, was recovered essentially unchanged on acidification; the recovered material, when treated with 0.5 mol dm^{-3} sodium hydroxide, gave **54** and **55** in *ca.* 4:1 ratio by GLC. It is presumed that a largely uncyclised magnesium chelate is formed in methanol solution though methoxycarbonyl dione may be present in reversible undehydrated aldol form as before. The action of magnesium methoxide thus appears largely protective of the β-keto-ester system in this system. 5-Methoxycarbonyldodecane-4,8-dione **53** showed similar behaviour when treated with magnesium methoxide, the sodium hydroxide treatment giving **54** and **55**, but in a ~1:4 ratio. Refluxing the dione ester **53** with magnesium methoxide (12 mol) in benzene for 16 h again left it unchanged after work-up.

In contrast to the cyclopent-2-enones examined above, the cyclohex-2-enones can equilibrate in base as has been reported,[23,24] causing disturbance of isomer ratios. Thus, a mixture of 2,3-dipropylcyclohex-2-enone **54** (79%) and 3-butyl-2-ethylcyclohex-2-enone **55** (21%), when refluxed with 0.5 mol dm^{-3} aqueous sodium hydroxide for 24 h, conditions that leave 2,3-dipropylcyclopent-2-enone unchanged, shifted in composition to 2,3-dipropylcyclohex-2-enone (65%) and 3-butyl-2-ethylcyclohex-2-enone (35%).

In summary, when a methoxycarbonyl is employed as a directing group for formation of a magnesium chelate in the cyclopent-2-enone-producing series, either the 2,3-dipropyl- or the 3-butyl-2-ethyl isomer can be formed chemoselectively in ratios of >9:<1 or <1:>9, according to its positioning on the undecane-4,7-dione. Even direct cyclisation, omitting the magnesium methoxide treatment, gives very substantial bias to the isomer ratio. Control in the cyclohex-2-enone series was less effective in preliminary studies, with chemoselection between the 2,3-dipropyl- and 3-butyl-2-ethyl isomers being ~4:1 or 1:~4 according to the positioning of the methoxycarbonyl group on the dodecane-4,8-dione chain.

Experimental

Melting points are uncorrected and were determined by a Reichert hot-stage microscope. Refractive indices were measured using a Bellingham and Stanley ABBE 60 refractometer and IR spectra were recorded on a Pye-Unicam SP3-100 or SP 200 spectrophotometer as either a liquid film, a solution in chloroform, or a KBr disc. UV spectra were measured on a Unicam SP 800 spectrophotometer in the solvent as stated. Routine ^{1}H NMR spectra were determined on a Perkin-Elmer R32 machine at 90 MHz, others being obtained on Bruker instruments at 80, 250 and 400 MHz. ^{13}C Spectra were measured using a Bruker FT instrument at 63.1 MHz. Mass spectra were obtained using a VG Micromass 7070E mass spectrometer. Preparative HPLC employed a Waters Associates PREP LC/system 500 instrument, whilst analytical HPLC employed a Waters Associates M6000 Series machine. Methanol was dried by the magnesium methoxide method. The GLC instrument used was a Pye series 104 machine, usually with an OV 17 capillary column.

Methyl 2,4,4-trimethyl-5-methylene-4,5-dihydro-3-furoate 20

3-Chloro-3-methylbutyne **18** (51.3 g, 0.5 mol) in dry methanol (50 cm^3) was added dropwise to a stirred and refluxing methyl acetoacetate solution [from sodium (22.9 g, 1.0 mol), methyl acetoacetate (116 g, 1.0 mol) and methanol (350 cm^3)]. The resulting mixture was stirred and refluxed for a further 24 h, after which it was evaporated to remove most of the solvent. The residue was poured into water (400 cm^3) and the mixture acidified to pH 6 with hydrochloric acid (1 mol dm^{-3}) and extracted with diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), evaporated and distilled to give the title furoate (69.5 g, 75%); bp 74–76 °C/16 mmHg (lit.,[12] bp 98 °C/20 mmHg), n_D^{20} 1.4815 (lit.,[12] n_D^{20} 1.4810); *m/z* 182 (M^+); ν_{max}(film)/cm^{-1} 1695 (unsaturated ester), 1660 (alkene) and 1640 (enol); λ_{max}(EtOH)/nm 266 (log ε 4.15); δ_H($CDCl_3$) 1.40 (6 H, s, CMe_2), 2.30 (3 H, s, OCMe), 3.78 (3 H, s, CO_2Me), 4.20 (1 H, d, *J* 3, HC=CO) and 4.57 (1 H, d, *J* 3, HC=CO).

3-Methoxycarbonyl-4,4-dimethylhexane-2,5-dione/methyl 5-hydroxy-2,4,4,5-tetramethyl 4,5-dihydro-3-furoate tautomers 16, 16a

The furoate **20** (30 g, 0.165 mol) was stirred overnight with 5% aq. sulfuric acid (250 cm^3) and then thoroughly extracted with diethyl ether. The ethereal extracts were washed with brine, dried (Na_2SO_4), evaporated and distilled to give the title compound as a colourless oil (24.4 g, 73%), bp 78–80 °C/0.1 mmHg, n_D^{20} 1.4520 (lit.,[12] bp 72–73 °C/0.07 mmHg; n_D^{19} 1.4550); ν_{max}(film)/cm^{-1} 3450 (OH), 1740 (saturated ester), 1715sh (dialkyl ketone), 1705 (unsaturated ester) and 1635; λ_{max}(EtOH)/nm 253 (log ε 3.34); λ_{max}(0.01 mol dm^{-3} ethanolic KOH) 252 and 280 (log ε 3.34); δ_H($CDCl_3$) 1.22 (3 H, s, 4-Me), 1.36 (3 H, s, 4-Me), 1.48 (0.076 H, s, *H*OCMe), 2.21 (*ca.* 6 H, s, MeCO and OCMe=C), 3.74 (3 H, s, CO_2Me) and 4.10 (0.92 H, s, $HCCO_2Me$).

3-Acetyl-5-methoxy-4,4,5-trimethylfuran-2-one 27

The dione **16**, **16a** (2.0 g, 0.01 mol) in dry methanol (5 cm^3) was added under nitrogen to a stirred solution of sodium methoxide [from sodium (2.76 g, 0.12 mol) in dry methanol (45 cm^3)] and stirring continued (2 h). After this the mixture was poured into water, neutralised with hydrochloric acid (1 mol dm^{-3}), saturated with salt, and extracted with diethyl ether. The ethereal extracts were washed with water and brine and then dried (Na_2SO_4) and evaporated. The resultant oil was chromatographed on silica, eluting with chloroform, to give the *title lactone* as an oil (1.40 g, 56%), n_D^{21} 1.4579 (Found: C, 60.25; H, 8.2; M^+, 200. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.05%; *M*, 200); ν_{max}(film)/cm^{-1} 1775 (γ-lactone), 1705 (methyl ketone) and 1645; δ_H($CDCl_3$) 1.06 (3 H, s, 4-Me), 1.25 (3 H, s, 4-Me), 1.42 (3 H, s, MeC), 2.38 (3 H, s, MeCO), 3.38 (3 H, s, OMe) and 3.72 (1 H, s, C*H*COMe).

2,4,4-Trimethyl-5-methylene-4,5-dihydro-3-furoic acid

The ester **20** (12.0 g, 0.066 mol) was refluxed with 10% methanolic potassium hydroxide (30 cm^3) for 7 h and then poured into water. Any unhydrolysed material was extracted with diethyl ether and the aq. solution was warmed to expel entrained diethyl ether and acidified to pH 6 (indicator paper) with HCl (1 mol dm^{-3}). The precipitated acid (6.01 g, 54%) was filtered off and recrystallised from light petroleum (bp 60–80 °C) to afford needles, mp 125–126 °C (lit.,[12] 124–125 °C); λ_{max}(EtOH)/nm 263 (log ε 4.06); δ_H($CDCl_3$) 1.41 (6 H, s, CMe_2), 2.31 (3 H, s, MeC=C), 4.18 (1 H, d, *J* 3, CH=C–O), 4.56 (1 H, d, *J* 3, C*H*=C–O) and 12.02 (1 H, br s, exch., CO_2H).

3,3-Dimethylhexane-2,5-dione 15

The above 3-furoic acid (16.8 g, 0.1 mol) was suspended in sulfuric acid (1 mol dm^{-3}; 56 cm^3) and heated at 90 °C for 25 min. The resulting solution was then cooled, saturated with sodium chloride and extracted with diethyl ether. The combined extracts were washed with water and saturated brine, dried and distilled to give the title compound (10.9 g, 77%), bp 76–78 °C/19 mmHg, n_D^{20} 1.4360 (lit.,[12] bp 93 °C/20 mmHg); ν_{max}(film)/cm^{-1} 1710; δ_H($CDCl_3$) 1.23 (6 H, s, CMe_2), 2.13 (3 H, s, COMe), 2.21 (3 H, s, COMe) and 2.80 (2 H, s, CH_2). The dione formed a di-semicarbazone, mp 204–205 °C from aq. ethanol (lit.,[12] mp 205–206 °C).

Sodium hydroxide-catalysed cyclisation of 3,3-dimethylhexane-2,5-dione 15

The hexanedione **15** (1.5 g, 0.105 mol) was refluxed with aq. sodium hydroxide (0.5 mol dm^{-3}; 30 cm^3) for 30 min, after which it was cooled, saturated with sodium chloride and extracted with diethyl ether. The combined extracts were washed with water and saturated brine, dried (Na_2SO_4), and evaporated to give a mixture of 3,4,4- and 3,5,5-trimethylcyclopenten-2-enones which were separated using flash chromatography on silica,[14] eluting with diethyl ether–light petroleum (bp 40–60 °C) (1:3). The 3,5,5-trimethylcyclopentenone (640 mg) isomer **12** (640 mg, 69%) was an oil, n_D^{19} 1.4650 (lit.,[15] n_D^{20} 1.4670); ν_{max}(film)/cm^{-1} 1710 and 1620; λ_{max}(EtOH)/nm 226 (log ε 4.06); δ_H($CDCl_3$) 1.10 (6 H, s, CMe_2), 2.12 (3 H, s, MeC=), 2.46 (2 H, br s, CH_2C=) and 5.86 (1 H, br s, CH=). The cyclopentenone formed a semicarbazone (very slowly), mp 205–206 °C from aq. ethanol (lit.,[15] mp 205.5–206 °C). It also formed an oxime, mp 107–108 °C from ethanol (lit.,[15] mp 108–108.2 °C).

The 3,4,4-trimethyl isomer **14** was next eluted as an oil (240 mg, 26%), n_D^{20} 1.4627 (lit.,[15] n_D^{20} 1.4720); ν_{max}(film)/cm^{-1} 1710 and 1625; λ_{max}(EtOH)/nm 226 (log ε 4.04); δ_H($CDCl_3$) 1.26 (6 H, s, CMe_2), 2.09 (3 H, s, MeC=C), 2.31 (2 H, bs, CH_2CO) and 5.85 (1 H, br s, CH=C). This isomer formed a semicarbazone rapidly from ethanol, mp 200–201 °C (lit.,[15] 199.5–200 °C). On mixed mp with the semicarbazone of the 3,5,5-isomer a clear depression of 8 °C was observed. Gas chromatographic analysis of the mixture of cyclopentenones produced on cyclisation of the title dimethyl dione showed that it consisted of 69%, 3,5,5-trimethylcyclopenten-2-one **12** and 31% of 3,4,4-trimethylcyclopenten-2-one **14**.

Cyclisation of the diketone/hydroxytetramethylfuroate 16, 16a using magnesium methoxide in methanol

The diketone/furoate (10 g, 0.05 mol) in dry methanol was added to a solution of magnesium methoxide [from magnesium (14.4 g, 0.6 atom) and dry methanol (600 cm^3)] and stirred

under nitrogen for 24 h at room temp. Most of the solvent was evaporated and the residue was poured into iced water and slowly just acidified with ice-cold hydrochloric acid (1 mol dm^{-3}). An excess of sodium chloride was added to the mixture which was then thoroughly extracted with diethyl ether. The combined organic extracts were washed with water and saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure, the water-bath temperature being kept < 30 °C, to give an unstable yellowish oil. The latter was purified by HPLC to give the hydroxy compound **21** (4.82 g, 48%); *m/z* 200 (M^+); ν_{max}(film)/cm^{-1} 3470, 1750, 1715 and 1705; δ_H($CDCl_3$) 1.12 and 1.24 (6 H, *gem*-dimethyls), 1.32 (3 H, s, *Me*COH), 2.08 (2 H, m, CH_2CO), 3.66 (1 H, s, C*H*CO_2Me) and 3.74 (3 H, s, CO_2Me).

Treatment of the magnesium methoxide product 21 with aq. sodium hydroxide

The hydroxy compound **21** (100 mg, 0.5 mmol) was heated under reflux for 2 h with aq. sodium hydroxide (0.5 mol dm^{-3}) and then cooled, diluted with water (100 cm^3), saturated with sodium chloride, and extracted with diethyl ether. The combined extracts were then washed with water and brine and evaporated to give a colourless oil (50 mg, 81%). GLC analysis using a 50 ft OV17 column showed that the oil contained 3,4,4-trimethylcyclopent-2-enone **14** (98%) and 3,5,5-trimethylcyclopent-2-enone **12** (2%).

Cyclisation of the diketone/hydroxytetramethylfuroate 16, 16a with aq. sodium hydroxide

The diketo ester **16**, **16a** (15 g, 0.075 mol) was refluxed with aq. sodium hydroxide (0.5 mol dm^{-3}; 300 cm^3) for 4 h, after which the mixture was cooled, saturated with sodium chloride and extracted with diethyl ether. The combined extracts were washed with water and brine, dried (Na_2SO_4) and evaporated to afford an oil. This was subjected to HPLC using a silica Prep-Pak 500 column, eluting with diethyl ether–hexane (1:4) to provide the cyclopentenones **12** (0.75 g, 8%) and **14** (4.30 g, 46%) as oils having ^{1}H NMR, UV and IR spectra identical with those given above. Gas chromatographic analysis of the mixture of products showed that the ratio of **12** to **14** was 12:88 (1:7.3).

Methyl 2-methoxycarbonyl-3,3-dimethyl-4-oxopentanoate 29

3-Chloro-3-methylbutyne **18** (19.40 g, 0.189 mol) was added to a solution of dimethyl sodiomalonate [prepared from sodium (4.60 g, 0.20 mol) and dimethyl malonate (21.70 g, 0.206 mol)] in dry methanol (100 cm^3). The mixture was first stirred at 60 °C for 1 h, then gently heated under reflux for 4 h, and then finally stirred at 60 °C for a further 14 h. After cooling, the sodium chloride was filtered off and the filtrate was evaporated under reduced pressure to give a red syrup to which ice-cold 1 mol dm^{-3} aq. hydrochloric acid (200 cm^3) was added. The mixture was then worked-up to afford a reddish oil (29.05 g) which was purified by distillation to give the diester **28** (22.60 g, 60.3%), bp 82–86 °C/1 mmHg; *m/z* 198 (M^+); ν_{max}(film)/cm^{-1} 2140 (terminal acetylene); δ_H($CDCl_3$) 1.38 (6 H, s, *gem*-dimethyl) 2.16 (1 H, s, terminal methine), 3.40 [1 H, s, C*H*(CO_2Me)$_2$] and 3.68 (6 H, s, 2 × CO_2Me).

A catalyst solution was prepared by gently heating a mixture of red mercury oxide (0.5 g, 2.31 mmol), boron trifluoride–diethyl ether (0.2 cm^3), trichloroacetic acid (10 mg) and methanol (1 cm^3).[16] A solution of the acetylenic diester **28** (7.15 g, 36.1 mmol) in dry methanol (150 cm^3) was then added slowly to the cooled catalyst. After the exothermic reaction had subsided the mixture was shaken at room temp. for 2 h and then poured into 2 mol dm^{-3} aq. sulfuric acid (70 cm^3). The mixture obtained was extracted with diethyl ether and the combined extracts were washed with water, dried (Na_2SO_4) and concentrated to give an oil. The soil was chromatographed on silica, with chloroform as eluent, to afford the title diester ketone **29** as a colourless oil (5.9 g, 75.6%); ν_{max}(film)/cm^{-1} 1710; δ_H($CDCl_3$) 1.32 (6 H, s, *gem*-dimethyl), 2.18 (3 H, s, MeCO) 3.64 (6 H, s, 2 × CO_2Me) and 3.92 (1 H, s, CH).

5-Methoxy-3-methoxycarbonyl-4,4,5-trimethylfuran-2-one 30

The malonic ester **29** (1.05 g, 4.86 mmol) in dry methanol (10 cm^3) was added to a stirred solution of sodium methoxide in methanol [from sodium (1.34 g, 58.3 mmol) and dry methanol (50 cm^3)]. After the mixture had been stirred at room temp. for 48 h under nitrogen it was evaporated and the residue was acidified to pH 6 (litmus paper) with 1 mol dm^{-3} hydrochloric acid. The solution was then saturated with sodium chloride and extracted with diethyl ether. Work-up of the extract gave a brownish oil which was purified by flash chromatography on silica with chloroform as eluent to give the title *lactone* **30** (500 mg, 48%) as a colourless oil (Found: C, 55.4; H, 7.55; M^+, 216. $C_{10}H_{16}O_5$ requires C, 55.55; H, 7.45%; *M*, 216; ν_{max}(film)/cm^{-1} 1780 and 1740; δ_H($CDCl_3$) 1.04 (3 H, s, 4β-Me), 1.24 (3 H, s, 4α-Me), 1.46 (3 H, s, MeC), 3.36 (3 H, s, OMe) and 3.78 (4 H, s, CH and CO_2Me).

Treatment of the acetylmalonic ester 29 with magnesium methoxide

The acetylmalonic ester **29** (1.05 g, 4.86 mmol) in dry methanol (10 cm^3) was added to a stirred methanolic solution of magnesium methoxide [from magnesium (1.42 g, 58.4 mol) and dry methanol (50 cm^3)]. The resultant mixture was stirred under nitrogen for 96 h, after which it was evaporated and the solid residue was acidified to pH 6 (pH paper) with 1 mol dm^{-3} hydrochloric acid. Extraction and work-up as above gave the lactone **30** (620 mg, 59%) spectrally identical with the specimen above.

Chloromethyl phenyl sulfoxide 41

Methyl phenyl sulfoxide, prepared from methyl phenyl sulfide (55 g) and sodium metaperiodate according to the method of Johnson and Keiser,[18] was obtained in 78% yield, bp 80–82 °C/0.1 mmHg, mp 36–37 °C (lit.,[18] bp 78–79 °C/0.1 mmHg, mp 33–34 °C). The sulfoxide (32.4 g, 0.231 mol) in dry dichloromethane (450 cm^3) was treated with *N*-chlorosuccinimide[19] (32.4 g, 0.243 mol) and the mixture kept overnight at 20 °C. It was then washed with saturated brine and evaporated to give an oil. The oil was purified by chromatography on silica, with chloroform as eluent to afford the title chloro sulfoxide **41** (37.4 g, 93%), bp 120–122 °C/1 mmHg (lit.,[25] 120–121 °C/4 mmHg); δ_H($CDCl_3$) 4.39 (2 H, s, $SOCH_2$) and 7.56 (5 H, m, ArH).

1-Chloro-1-phenylsulfinylhexan-1-ol 42

Butyllithium (1.61 mol dm^{-3}; 20.4 cm^3, 32.84 mmol) in tetrahydrofuran was added to a cooled (−85 °C) solution of chloromethyl phenyl sulfoxide **41** (5.73 g, 32.81 mmol) in dry THF (200 cm^3) under nitrogen. After pentanal (2.82 g, 32.74 mmol) had been added to the mixture it was first maintained at −85 °C for 30 min, then warmed to −30 °C and finally stirred for 30 min. The mixture was then diluted with water (200 cm^3), saturated with sodium chloride and extracted with diethyl ether. The combined extracts were dried and evaporated to produce a brown oil which crystallised from chloroform–light petroleum (bp 40–60 °C) to afford the title compound **42** as pale yellow crystals (2.80 g, 33%), mp 88–89 °C (lit.,[17] mp 88–89 °C) (Found: C, 55.45; H, 6.5; Cl, 13.4. Calc. for $C_{12}H_{17}O_2S$: C, 55.25; H, 6.5; Cl, 13.6%); δ_H($CDCl_3$) 0.92 (3 H, t, Me), 1.12–1.96 (6 H, m, 3 × CH_2), 3.80 (1 H, br d, OH), 4.18 (1 H, br m, C*H*OH, sharpened on addition of D_2O), 4.58 (1 H, m, CHCl) and 7.56–7.96 (5 H, m, ArH).

1-Chlorohexan-2-one 39

First method. 1-Chloro-1-(phenylsulfinyl-hexan-2-ol **42** (2.80 g, 10.74 mmol) was refluxed in dry xylene (75 cm^3) under nitrogen for 48 h and then evaporated under reduced pressure to produce a black oil which was purified by column chromatography on silica using chloroform as eluent. The title chlorohexanone (330 mg, 57.5%) was obtained as a liquid, n_D^{24} 1.4360 (lit.,[26] n_D^{25} 1.4356); ν_{max}(film)/cm^{-1} 1710; δ_H($CDCl_3$) 0.92 (3 H, t, Me), 1.13–1.79 (4 H, m, 2 × CH_2), 2.60 (2 H, t, CH_2CO) and 4.13 (2 H, s, $COCH_2Cl$).

Second method. Butylmagnesium bromide [from magnesium turnings (8.1 g, 0.33 mol), 1-bromobutane (46 g, 0.33 mol) and anhydrous diethyl ether (110 cm^3), prepared under nitrogen], was cooled to 5 °C and anhydrous cadmium chloride (32.7 g, 0.178 mol) added in portions to the vigorously stirred suspension held at 5–10 °C. The suspension was stirred (5 min) and then heated under reflux with stirring for a further 2.5 h when the bulk of the solvent was distilled off. Dry benzene (125 cm^3) was added to the dark viscous residue and further distillate (40 cm^3) was then collected. Further benzene (125 cm^3) was added to the mixture which was then heated under reflux with vigorous stirring to break up the solid cake. The product **43** (R = Me) was cooled to 5 °C when freshly distilled chloroacetyl chloride (38 g, 0.33 mol) in dry benzene (70 cm^3) was added to it over 5 min. The mixture was then stirred at 15–20 °C for 3 h and then at 20–25 °C for 2 h. Crushed ice and 2 mol dm^{-3} sulfuric acid were added to the mixture which was then extracted with benzene. The extract was washed with aq. sodium hydrogen-carbonate, water and brine, dried (Na_2SO_4) and evaporated to give an oil. This was distilled to give the title compound **39** (22.9 g, 52%), bp 68–70 °C/12 mmHg, n_D^{20} 1.4360 (lit.,[20,26] bp 67–71 °C, n_D 1.4356) (Found: C, 53.65; H, 8.0; Cl, 26.1; M^+, 134.050. Calc. for $C_6H_{11}ClO$: C, 53.55; H, 8.25; Cl, 26.35%; M, 134.050). Spectroscopic data were identical with the previously prepared compound **39**.

1-Chloropentan-2-one 37

The title compound was prepared in a similar fashion to the hexanone **39** from magnesium (8.1 g, 0.33 mol), 1-bromopropane (41.33 g, 0.33 mol), diethyl ether (110 cm^3) and cadmium chloride (32.7 g, 0.178 mol). The chloropentanone (18.8 g, 47%) had bp 59–60 °C/12 mmHg, n_D^{20} 1.4340 (lit.,[28,29] bp 53 °C/16 mmHg, n_D^{16} 1.4386) (Found: M^+, 120.032. Calc. for C_5H_9ClO: *M*, 120.034); ν_{max}(film)/cm^{-1} 1725; δ_H($CDCl_3$) 0.94 (3 H, t, *J* 8, Me), 1.40–1.85 (2 H, m, CH_2Me), 2.59 (2 H, t, *J* 8, CH_2CO) and 4.17 (2 H, s, $ClCH_2CO$). The 2,4-dinitrophenylhydrazone had mp 138–139 °C from aq. ethanol (lit.,[30] mp 138 °C).

Methyl 3-oxohexanoate 38

Sodium hydride (60% dispersion; 40 g, 1 mol) was washed free of oil with dry diethyl ether and suspended in dry diethyl ether (125 cm^3). Dimethyl carbonate (90 g, 1.0 mol) was added to the suspension which was then refluxed and stirred under nitrogen for 2 h, after which time pentan-2-one (43 g, 0.5 mol) in dry diethyl ether (125 cm^3) was added dropwise to it over 4.5 h. The suspension was stirred and refluxed for a further 5 h and then cooled to 5 °C. Glacial acetic acid (125 cm^3) and water (300 cm^3) were gradually added to the mixture after which the organic phase was separated, saturated with salt and extracted with diethyl ether. The combined extracts were washed with saturated aq. sodium hydrogen carbonate and water, dried (Na_2SO_4) and evaporated. Distillation of the residue gave the title ester (41.7 g, 58%), bp 82–84 °C/12 mmHg (lit.,[27,31] bp 85 °C/14 mmHg); (M^+, 144. Calc. for $C_7H_{12}O_3$: *M*, 144); ν_{max}(film)/cm^{-1} 1745 (ester) and 1715 (ketone); δ_H($CDCl_3$) 0.91 (3 H, t, *J* 8, Me), 1.42–1.72 (2 H, m, CH_2Me), 2.53 (2 H, t, *J* 8, CH_2CO), 3.46 (*ca.* 2 H, s, $COCH_2CO$), 3.72 (3 H, s, CO_2Me), 4.99 (br s, alkene) and 12.08 (br s, chelated OH).

Methyl 3-oxoheptanoate 40

Prepared in a manner analogous to the oxo ester **38**, hexan-2-one (50 g, 0.5 mol), sodium hydride (60% dispersion; 40 g, 1 mol) and dimethyl carbonate (90 g, 1.0 mol) gave the title ester **40** (48.0 g, 60%), bp 92–95 °C/12 mmHg (lit.,[32] 45.5–47 °C/0.2 mmHg) (M^+, 158. Calc. for $C_8H_{14}O_3$: *M*, 158); ν_{max}(film)/cm^{-1} 1750 and 1720; δ_H($CDCl_3$) 0.92 (3 H, t, *J* 8, Me), 1.15–1.85 (4 H, m, CH_2CH_2Me), 2.55 (2 H, t, *J* 8, CH_2CO), 3.46 (*ca.* 2 H, s, $COCH_2CO$), 3.57 (3 H, s, CO_2Me), 4.91 (br s, alkene) and 12.20 (br s, chelated OH).

5-Methoxycarbonylundecane-4,7-dione 32

Methyl 3-oxohexanoate **38** (8.65 g, 0.06 mol) in dry diethyl ether (50 cm^3) was added under nitrogen to a stirred and refluxing suspension of sodium hydride (60% dispersion; 2.0 g, 0.05 mol) in diethyl ether (100 cm^3). The resultant mixture was then heated under reflux for 2 h after which 1-chlorohexan-2-one **39** (7.4 g, 0.055 mol) in diethyl ether (50 cm^3) was added dropwise to it. The suspension was stirred and refluxed for a further 24 h and then cooled. Water (200 cm^3) and 4 mol dm^{-3} hydrochloric acid (50 cm^3) were added to the mixture after which the organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phase and extracts were washed with water and saturated brine, and then evaporated. Distillation of the residue gave the *title ester* **32** (11.95 g, 90%), bp 102–104 °C/0.2 mmHg (M^+, 242.148. $C_{13}H_{22}O_4$ requires *M*, 242.152); ν_{max}(film)/cm^{-1} 1740 and 1710; λ_{max}(EtOH)/nm 251 (ε 660) and 279.5 infl. (285); δ_H($CDCl_3$) 0.91 (6 H, t, 2 × alkyl Me), 1.24–1.39 (2 H, m, CH_2), 1.52–1.65 (4 H, m, 2 × CH_2), 2.44 (2 H, t, *J* 7.3, CH_2CO), 2.65–2.73 (2 H, m, CH_2CO), 2.92 and 3.13 (2 H, dq, AB part of ABX, J_{AB} 18), 3.73 (3 H, s, CO_2Me) and 4.04 (1 H, q, X part of ABX, $J_{AX} = J_{BX}$ 6).

6-Methoxycarbonylundecane-4,7-dione 33

The ester dione **33** was prepared essentially as described for compound **32** from methyl 3-oxoheptanoate **40** (17.9 g, 0.12 mol), 1-chloropentan-2-one **37** (13.25 g, 0.11 mol) and sodium hydride (4.0 g). Distillation gave the *ester-dione* **33** (21.80 g, 82%), bp 90–92 °C/0.05 mmHg (M^+, 242.148. $C_{13}H_{22}O_4$ requires *M*, 242.152); ν_{max}(film)/cm^{-1} 1740 and 1710; λ_{max}(EtOH) 251 (ε 375) and 277 infl. (280); δ_H($CDCl_3$) 0.75–0.82 (6 H, m, 2 × alkyl Me), 1.11–1.25 (2 H, m, CH_2), 1.37–1.57 (4 H, m, 2 × CH_2), 2.33 (2 H, t, *J* 7.3, CH_2CO), 2.50–2.57 (2 H, m, CH_2CO), 2.95 and 3.00 (2 H, dq, AB part of ABX, J_{AB} 18), 3.60 (3 H, s, CO_2Me), 3.91 (1 H, d, X part of ABX, $J_{AX} = J_{BX}$ 6).

Undecane-4,7-dione 34

The 6-methoxycarbonyl compound **33** (0.5 g, 2.06 mmol) was stirred with 5 mol dm^{-3} aq. potassium hydroxide (1.5 cm^3) in methanol (20 cm^3) at room temp. for 16 h. After adjustment of the pH to 6 with aq. hydrochloric acid (1 mol dm^{-3}) the product was extracted with diethyl ether. The combined extracts were then washed, dried (Na_2SO_4) and evaporated. The residue obtained was purified by chromatography on silica gel with hexane as eluent to afford the title *undecane*-4,7-*dione* **34** (0.34 g, 89%) (Found: C, 71.6; H, 10.95. $C_{11}H_{20}O_2$ requires C, 71.7; H, 10.95%); ν_{max}(film)/cm^{-1} 1710 (ketone); δ_H($CDCl_3$) 0.90 (3 H, t, *J* 8, Me), 0.91 (3 H, t, *J* 8, Me), 1.10–1.85 (6 H, m, 3 × CH_2), 2.45 (2 H, t, *J* 8, CH_2CO), 2.47 (2 H, t, *J* 8, CH_2CO) and 2.69 (4 H, apparent s at 80 MHz, $COCH_2CH_2CO$); δ_C($CDCl_3$) 13.73 (Me), 13.79 (Me), 17.41, 22.38, 26.08, 36.08, 36.15, 42.64, 44.84 (7 × CH_2), 209.46 (CO) and 209.58 (CO).

2,3-Dipropylcyclopent-2-enone 36 and 3-butyl-2-ethylcyclopent-2-enone 35

Undecane-4,7-dione **34** (300 mg, 1.6 mmol) was stirred with aq. sodium hydroxide (0.5 mol dm^{-3}; 10 cm^3) under reflux for 4 h and then cooled to room temp. The mixture was then acidified

(pH 6) with hydrochloric acid (2 mol dm^{-3}), saturated with sodium chloride and thoroughly extracted with diethyl ether. The combined extracts were washed with water and saturated brine, dried (Na_2SO_4) and evaporated. The resultant residue was chromatographed on flash silica with hexane containing 4% ethyl acetate as eluent. This gave the title *enone* **36** (115 mg, 43.5%) as a colourless oil (Found: C, 79.05; H, 10.9. M^+, 166.136. $C_{11}H_{18}O$ requires C, 79.45; H, 10.9%; *M*, 166.136); ν_{max}(film)/cm^{-1} 1700 (C=O) and 1640 (C=C); δ_H($CDCl_3$, 250 MHz) 0.89 (3 H, t, *J* 8, Me), 0.97 (3 H, t, *J* 8, Me), 1.32–1.49 (2 H, m, CH_2), 1.50–1.65 (2 H, m, CH_2), 2.15 (2 H, t, *J* 8, CH_2C=C), 2.34–2.51 (4 H, m, CH_2C=C and CH_2C=C in the ring) and 2.47–2.51 (2 H, m, CH_2CO).

A second colourless oil (110 mg, 41.5%) was also isolated from the chromatogram and identified as the *enone* **35** (Found: C, 79.15; H, 10.8; M^+, 166.135. $C_{11}H_{18}O$ requires C, 79.45; H, 10.9%; *M*, 166.136); ν_{max}(film)/cm^{-1} 1695 (C=O) and 1640 (C=C); δ_H($CDCl_3$, 250 MHz) 0.95 (3 H, t, *J* 8, Me), 0.98 (3 H, t, *J* 8, Me), 1.14–1.69 (4 H, m, CH_2CH_2), 2.19 (2 H, q, side-chain CH_2C=C) and 2.30–2.50 (6 H, m, CH_2CO and 2 × CH_2C=C).

The ratio of the enones **36**:**35** was 1.05:1 by isolation and 1.05:1 by GLC (OV 17).

GLC conditions

A 20 or 50 ft OV17 (methyl phenyl silicone) capillary column was employed. For assessment of yields, geraniol was used as an internal standard. The R_t of the enone **36** was 15.30 and that of **35** 16.40 [helium flow rate 2 cm^3 min^{-1}, injector temp. 150 °C, oven temp. 135 °C]. Other analyses employed a Carbowax 20 M capillary column: a Perkin-Elmer Sigma 2B instrument was used.

Treatment of 5-methoxycarbonylundecane-4,7-dione 32 with aq. sodium hydroxide (0.5 mol dm^{-3})

The diketo ester **32** (250 mg, 1.03 mmol) was stirred with sodium hydroxide (0.5 mol dm^{-3}; 25 cm^3) under reflux for 4 h after which the mixture was cooled, acidified with hydrochloric acid (2 mol dm^{-3}), saturated with sodium chloride and extracted with diethyl ether. The combined extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography on silica with hexane containing 4% ethyl acetate as eluent to afford the enones **35** and **36**. The compounds were spectroscopically identical with the previously prepared samples. In a similar experiment the products were estimated by GLC (OV 17). This gave the enones **36** (9%) and **35** (62%) (ratio 1:6.9), combined yield 71%.

Treatment of 6-methoxycarbonylundecane-4,7-dione 33 with aq. sodium hydroxide (0.5 mol dm^{-3})

The diketo ester **33** (250 mg, 1.03 mmol) was stirred with sodium hydroxide (0.5 mol dm^{-3}, 25 cm^3) under reflux for 4 h. Work-up as for compound **32** and flash column chromatography on silica with hexane containing 4% ethyl acetate as eluent, gave the enones **35** and **36**. The compounds were spectroscopically identical with the samples previously prepared. In a similar experiment the products were estimated by GLC (OV 17). This gave the enones **36** (66%) and **35** (8%) (8.25:1), combined yield 74%.

Treatment of the dione 32 with magnesium methoxide in methanol

Magnesium methoxide in methanol was prepared from magnesium (0.65 g, 27 mol), dry methanol (25 cm^3) and a trace of iodine. The title dione ester **32** (0.52 g, 2.16 mmol) in methanol (3 cm^3) was added to this solution at 20 °C and the resulting mixture stirred for 48 h. After concentration of the mixture by solvent evaporation the residue was diluted with water, acidified (4 mol dm^{-3} HCl) and extracted with diethyl ether. The combined extracts were washed with water and saturated brine, dried (Na_2SO_4) and evaporated to afford a brown oil. The oil was heated under reflux for 4 h with sodium hydroxide (0.5 mol dm^{-3}) and then extracted with diethyl ether. Work-up of the extract followed by chromatography on silica, with hexane containing 4% ethyl acetate as eluent gave an oil containing the enones **35** (65%) and **36** (7%) (9.3:1), as estimated by GLC (OV 17).

Treatment of the dione 33 with magnesium methoxide in methanol

Magnesium methoxide was prepared from magnesium (0.3 g, 12.4 mol), dry methanol (12 cm^3) and a trace of iodine. To the methanolic solution at 20 °C the title dione **33** (0.25 g, 1.03 mmol) in methanol (1 cm^3) was added and the mixture was stirred for 24 h. Work-up, treatment with sodium hydroxide (0.5 mol dm^{-3}), and chromatography, gave the enones **36** (123 mg, 72%) and **35** (14 mg, 8%) (9:1). The compounds were spectroscopically identical with the preceding samples. A similar experiment using GLC (OV 17) gave a product ratio **36**:**35** of 7:1 (64%).

Other experiments at 20 °C using magnesium methoxide (1.1 mol) and magnesium methoxide (24 mol) and hydrolysis with sodium hydroxide (0.5 mol dm^{-3}) gave the enones **35** and **36** in the 1:9 ratio by GLC (Carbowax 20M). A similar experiment using magnesium methoxide (12 mol), but refluxing for 36 h before the sodium hydroxide treatment gave the enones **35** and **36** in a ratio of 1:5.6.

Treatment of the enone 36 with aqueous sodium hydroxide

The enone **36** (100 mg, 0.6 mmol) was heated under reflux with aqueous sodium hydroxide (0.5 mol dm^{-3}; 10 cm^3) with stirring for 12 h. Re-isolation (95 mg) with diethyl ether, and examination using a Carbowax 20M capillary column at 100–150 °C (1 °C min^{-1}) using standard reference samples, indicated that the solution containing only the enone **36**.

Treatment of the enone 35 with aqueous sodium hydroxide

The enone **35** (100 mg, 0.6 mmol) was stirred and heated under reflux with aqueous sodium hydroxide (0.5 mol dm^{-3}; 10 cm^3) for 12 h. Re-isolation (95 mg) with diethyl ether, and examination using a Carbowax 20M capillary column at 100–150 °C (1 °C min^{-1}) using standard reference samples, indicated that the solution contained only the enone **35**.

Treatment of the dione 33 with magnesium methoxide (12 mol) in refluxing benzene

Magnesium methoxide in methanol was prepared under nitrogen from magnesium (0.3 g, 12.4 mol), dry methanol (10 cm^3) and a trace of iodine. The methanol was distilled off and the title dione ester **33** (250 mg, 1.03 mmol) in dry benzene (12 cm^3) was added to the residue. The mixture was heated under reflux for 18 h with vigorous stirring and then acidified with HCl (2 mol dm^{-3}) and extracted with diethyl ether. The extract was evaporated and the residue heated under reflux for 4 h with aqueous sodium hydroxide (0.5 mol dm^{-3}; 12 cm^3) for 4 h. Work-up followed by flash chromatography on silica with 4% ethyl acetate in hexane as eluent gave the enones **36** (119 mg, 69.5%) and **35** (6 mg, 3.5%) (ratio 19.9:1). The compounds were compared with authentic specimens by their ^1H NMR spectra and GLC.

Treatment of the dione 32 with magnesium methoxide (12 mol) in refluxing benzene and other solvents and conditions

Magnesium methoxide in methanol was prepared under nitrogen from magnesium (0.3 g, 12.4 g atom), dry methanol (10 cm^3) and a trace of iodine. The methanol was distilled off and the dione **32** (250 mg, 1.03 mmol) in dry benzene (12 cm^3)

was added to the residue. The mixture was then refluxed with vigorous stirring for 18 h, after which it was acidified with HCl (2 mol dm^{-3}) and extracted with diethyl ether. Evaporation of the extract gave a product which was refluxed (4 h) with aqueous sodium hydroxide (0.5 mol dm^{-3}; 12 cm^3). Work-up followed by flash chromatography on silica with 4% ethyl acetate in hexane as eluent gave the enones **36** (7.5 mg, 4.4%) and **35** (115 mg, 67.1%) (ratio 1:15.3), combined yield 71.5%.

A similar reaction in which the refluxing was omitted and the mixture in benzene was allowed to stand at room temperature for 24 h before sodium hydroxide treatment gave the enones **36** (8%) and **35** (92%) (ratio 1:11.5) by GLC analysis.

A similar reaction in which refluxing benzene was replaced by refluxing toluene gave a product shown by GLC analysis (Carbowax 20M/100 °C) to consist of the enones **36** (6%) and **35** (94%) (ratio 1:15.7).

A similar reaction in which refluxing benzene was replaced by refluxing hexane followed by treatment with sodium hydroxide gave a product consisting of the enones **36** (10%) and **35** (90%) (ratio 1:9) as analysed by GLC (Carbowax).

1-Iodohexan-3-one 50

A solution of hex-1-en-3-one (4.5 g, 46 mmol) in dry dichloromethane (150 cm^3) under nitrogen at −40 °C was treated dropwise with trimethylsilyl iodide (10 g, 50 mmol). After the mixture had been stirred under nitrogen for 2 h it was diluted with diethyl ether (200 cm^3) and poured into cold 5% aqueous sodium thiosulfate. The organic layer was separated, washed with saturated brine, dried ($MgSO_4$) and evaporated to yield the crude title compound **50** (18.8 g, 83%) as a purple oil (contamination with iodine) (Found: M^+, 225.985. $C_6H_{11}IO$ requires *M*, 225.985); ν_{max}(film)/cm^{-1} 1720 (C=O); δ_H($CDCl_3$) 0.92 (3 H, t, *J* 8, Me), 1.4–1.85 (2 H, m, CH_2Me), 2.40 (2 H, t, *J* 8, CH_2CH_2CO) and 2.97–3.42 (4 H, m, $COCH_2CH_2I$).

1-Iodoheptan-3-one 51

Hept-1-en-3-ol (10 g, 87.7 mmol) was stirred with active manganese dioxide (100 g) in dichloromethane for 16 h at room temperature, after which the solution was filtered through silica gel and evaporated to give hept-1-en-3-one (8.16 g, 83%) (Found: M^+, 112.089. $C_7H_{12}O$ requires *M*, 112.089). Prepared as above from hept-1-en-3-one (6.0 g, 54 mmol) and trimethylsilyl iodide (12.86 g, 64 mmol) the title iodo ketone (9.3 g, 72%) was obtained as a purple oil (Found: M^+, 240.003. $C_7H_{13}IO$ requires *M*, 240.001); ν_{max}(film)/cm^{-1} 1710; δ_H($CDCl_3$) 0.90 (3 H, t, Me), 1.1–1.70 (4 H, m, CH_2CH_2), 2.40 (CH_2CO), 2.9–3.4 (4 H, m, $COCH_2CH_2I$).

6-Methoxycarbonyldodecane-5,9-dione 52

Methyl 3-oxoheptanoate (*cf.* **40**) (4.74 g, 30 mmol) in dry diethyl ether (50 cm^3) was added slowly to a stirred and refluxing suspension of sodium hydride (50% dispersion; 1.44 g, 30 mmol) in diethyl ether (50 cm^3) under nitrogen, and the mixture was refluxed for 2 h. 1-Iodohexan-3-one **50** (6.0 g, 27 mmol) in diethyl ether was then added dropwise to the mixture and the resulting suspension was stirred and refluxed for a further 2 h. After the mixture had cooled, water (50 cm^3) and then hydrochloric acid (4 mol dm^{-3}; 30 cm^3) were added to it, the nitrogen stream being continued. Isolation of the organic phase using diethyl ether, followed by washing and evaporation in the usual way, gave a purple oil. This was chromatographed on silica (HF 254) with 20% diethyl ether in hexane as eluent to give the title compound **52** (2.98 g, 43%) as a colourless oil (Found: M^+, 256.170. $C_{14}H_{24}O_4$ requires *M*, 256.167); ν_{max}(film)/cm^{-1} 1728 (carbonyl) and 1760 (ester); δ_H(80 MHz, $CDCl_3$) 0.90 (6 H, t, *J* 8, 2 × Me), 1.18–1.73 (6 H, m, 3 × CH_2), 1.93–2.61 (8 H, m, 4 × CH_2), 3.55 (1 H, t, *J* 8, CH) and 3.72 (3 H, s, CO_2Me); δ_C(20.1 MHz, $CDCl_3$) 14.23 (2 × Me), 17.81, 22.43, 22.67, 26.10, 40.12, 42.28, 45.25 (7 × CH_2), 52.82 (OMe), 57.89 (CH), 170.62 (CO_2) and 205.57 and 210.29 (2 × CO).

5-Methoxycarbonyldodecane-4,8-dione 53

Methyl 3-oxohexanoate (*cf.* **38**) (4.4 g, 30 mmol) in dry diethyl ether (50 cm^3) was added slowly to a stirred and refluxing suspension of sodium hydride (50% dispersion; 1.44 g, 30 mmol) in diethyl ether (50 cm^3) under nitrogen, and the mixture was refluxed for 2 h. 1-Iodoheptan-3-one **51** (6.4 g, 27 mmol) in diethyl ether was then added dropwise to the mixture and the resulting suspension was stirred and refluxed for a further 2 h. Work-up as described above gave the title compound **53** (2.5 g, 36%) as a colourless oil (Found: M^+, 256.168. $C_{14}H_{24}O_4$ requires *M*, 256.167); ν_{max}(film)/cm^{-1} 1760 (ester) and 1730 (ketone); δ_H(80 MHz, $CDCl_3$) 0.91 (6 H, t, *J* 8, 2 × Me), 1.17–1.75 (6 H, m, 3 × CH_2), 1.85–2.61 (8 H, m, 4 × CH_2), 3.54 (1 H, t, *J* 8, CH) and 3.72 (3 H, s, CO_2Me; δ_C(20.1 MHz, $CDCl_3$) 14.03, 14.32 (2 × Me), 17.46, 22.42, 22.82, 26.45, 40.07, 43.05, 44.43 (7 × CH_2), 52.78 (OMe), 57.89 (CH), 170.61 (CO_2) and 204.44 and 210.40 (2 × CO).

Treatment of the dione 52 with aqueous sodium hydroxide

The title δ-diketone (200 mg, 0.8 mmol) was stirred with aqueous sodium hydroxide (0.5 mol dm^{-3}; 50 cm^3) under reflux for 12 h, after which the mixture was cooled, acidified with HCl (2 mol dm^{-3}) saturated with sodium chloride and extracted with diethyl ether. Work-up and chromatography on Kieselgel 60, with 20% diethyl ether in hexane as eluent, gave an oil (48 mg). GLC (OV 17) showed it to contain two compounds in the ratio ~4:1. The major compound was 2,3-dipropylcyclohex-2-enone **54** and since it proved difficult to separate it from the minor isomer, 2-ethyl-3-butylcyclohex-2-enone **55**, its data below are from observations on the major component of the mixture (Found: M^+, 180.151. $C_{12}H_{20}O$ requires *M*, 180.151); ν_{max}(film)/cm^{-1} 1675 (C=O) and 1630 (C=C); δ_H(80 MHz, $CDCl_3$) 0.96 (6 H, t, *J* 8, 2 × Me), 1.10–1.72 (4 H, m, 2 × CH_2), 1.82–2.11 (2 H, m, CH_2) and 2.15–2.48 (8 H, m, 4 × CH_2); δ_C 14.26 (2 × Me), 21.29, 22.70, 22.90, 27.20, 30.68, 36.99, 38.23 (7 × CH_2), 135.83, 158.61 (2 × quaternary C) and 199.07 (C=O).

Treatment of the dione 53 with aqueous sodium hydroxide

The title δ-diketone (200 mg, 0.8 mmol) was stirred with aqueous sodium hydroxide (0.5 mol dm^{-3}; 50 cm^3) under reflux for 12 h, after which the mixture was cooled and acidified with HCl (2 mol dm^{-3}). Work-up and chromatography as above gave an oil (48 mg) which GLC (OV 17) showed to contain two compounds in the ratio ~4:1. The major component was the enone **55** and the minor component was the enone **54** which were not separated except by GLC; the data below for **55** were extracted from the spectra of the mixure (M^+, 180.150. $C_{12}H_{20}O$ requires *M*, 180.151); ν_{max}(film)/cm^{-1} 1665 (C=O) and 1625 (C=C); δ_H(80 MHz, $CDCl_3$) 0.94 (6 H, t, *J* 8, 2 × Me), 1.18–1.54 (4 H, m, 2 × CH_2), 1.82–2.07 (2 H, m, CH_2) and 2.16–2.45 (8 H, m, 4 × CH_2); δ_C($CDCl_3$) 13.93, 14.14 (2 × Me), 18.38, 22.70, 23.05, 30.32, 30.75, 34.61, 38.21 (7 × CH_2), 137.09, 158.54 (2 × quaternary C) and 198.96 (C=O).

Treatment of the dione 52 with magnesium methoxide, then sodium hydroxide

The dione (256 mg, 1 mmol) was stirred with magnesium methoxide [from magnesium (0.288 g, 12 mmol)] under nitrogen for 24 h at room temperature. Work-up gave an oil, consisting largely of recovered dione, which was refluxed for 12 h with aqueous sodium hydroxide (0.5 mol dm^{-3}). The product (23 mg) consisted of the enones **54** and **55** in a ratio of ~4:1 as determined by GLC analysis. Employment of magnesium methoxide in benzene gave a similar result.

Equilibration of the enones 54 and 55 with aqueous sodium hydroxide

A 79:21 (3.8:1) mixture of the title enones was refluxed with aq. sodium hydroxide (0.5 mol dm^{-3}; 5 cm^3) for 24 h. Work-up gave a 65:35 ratio (1.86:1) for the mixture of **54** and **55** as determined by GLC.

Acknowledgements

We thank the SERC for a postgraduate studentship (to S. F.) and the Boots Company plc for awards to M. L. F. C. and J. M.

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Paper 4/07447E
Received 6*th December* 1994
Accepted 8*th February* 1995