Aldol Type Condensations of β-Keto Ester Dianions

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The dianion of methyl acetoacetate reacts with ketones and aldehydes to yield δ-hydroxy-β-keto esters. These hydroxy esters can be dehydrated to the corresponding γ,δ-unsaturated-β-keto esters which are useful in annelation reactions to form cyclic β-keto esters. The dianion of methyl acetoacetate does not appear to undergo conjugate addition to simple α,β-unsaturated ketones, instead only carbonyl addition occurs.

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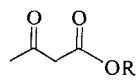
Le dianion de l'acétoacétate de méthyle réagit avec les cétones et les aldéhydes pour fournir des esters δ hydroxylés β-cétoniques. Ces esters hydroxylés peuvent se déshydrater pour conduire aux β-cétoesters nonsaturés correspondant qui sont utiles dans des réactions d'annélation conduisant à des esters β-cétoniques cycliques. Le dianion de l'acétoacétate de méthyle réagit avec les cétones α,β nonsaturés simple pour conduire uniquement à des produits d'addition; il ne semble pas que l'addition conjuguée se produise. [Traduit par le journal]

Recently we have been interested in utilizing the basic four carbon unit of β-keto esters (**1**) as



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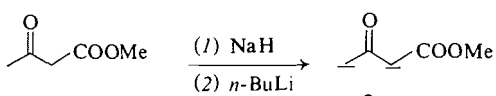
a foundation for an array of synthetic reactions. The introduction of this unit is relevant to the synthesis of a range of natural products, particularly the acetogenins (1). We have already described the ready generation of dianions from β-keto esters (2) and the alkylation (2, 3) and acylation (4, 5) of these intermediates. Now we would like to present some details of the reaction of these dianions with aldehydes and ketones.[2]

The dianion **2** can be prepared from methyl acetoacetate in a variety of ways; however, the most efficient method we have developed involves treating the β-keto ester with 1 equiv. of sodium hydride to generate the monoanion and subsequently treatment with 1 equiv. of *n*-butyllithium produces the dianion **2** (2, 3). This reaction



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can be performed in a range of solvents (7) but most of the present results are for reactions in tetrahydrofuran. Not unexpectedly dianion **2** reacts with an electrophile at the terminal γ-carbon (8). One of the reactions of particular use in our proposed synthesis of some aromatic antibiotics was the aldol type condensation of **2** shown in reaction 1.

We found that dianion **2** did react with a series of aldehydes and ketones to give the addition product **4** in reasonable yields for most substrates investigated (Table 1). The spectral data for each reaction product was compatible only with the δ-hydroxy-β-keto ester structure **4**, another ex-

TABLE 1. Addition of dianion **2** to ketones and aldehydes

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R	R′	Yield of **4** (%)[a]
CH_3	H	26
CH_3CH_2	H	73
$CH_3CH_2CH_2CH_2$	H	36
$(CH_3)_3C$	H	82
C_6H_5	H	89
o-$CH_3OC_6H_4$	H	73
2,3-$(CH_3O)_2C_6H_3$	H	68
2-Furyl	H	68
CH_3	CH_3	70
CH_3CH_2	CH_3	56
—$(CH_2)_5$—		63
—$(CH_2)_4$—		25
C_6H_5	CH_3	77
o-$CH_3OC_6H_4$	CH_3	79
C_6H_5	C_6H_5	93

[a]Isolated yield.

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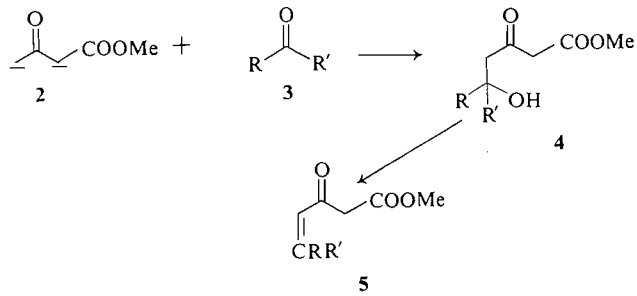
[2]A preliminary communication of a portion of this work has appeared (6).

[1] 

ample of reaction at the more nucleophilic terminal carbon in a multiple anion (1–8). In the case of acetaldyde, pentanal, and cyclopentanone a large amount of methyl acetoacetate was recovered. It may be that proton transfer is a competing side reaction in these cases, since self-condensation products of cyclopentanone were also formed in the reaction of **2** and cyclopentanone. Similar difficulties involving proton transfer have been reported during the reaction of dianions from β-diketones with ketones and aldehydes (9). Earlier it has been found that reaction of the dianion from ethyl acetoacetate with benzophenone gave the corresponding δ-hydroxy-β-keto ester in 50% (10). Using the above method this product was obtained in 81% from ethyl acetoacetate or 93% from methyl acetoacetate.

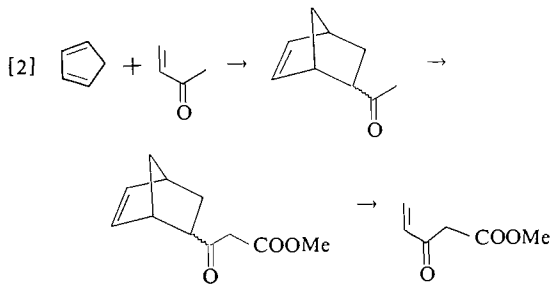
With some of the aromatic aldehydes and ketones, difficulty was encountered when attempts were made to purify the adducts **4** by distillation. Many of these products were liquids and they were readily purified by chromatography for spectral analysis; however, they were converted to the corresponding trimethylsilyl ethers (**6**) for further spectral analyses and elemental analyses. These ethers were readily distilled and could easily be hydrolyzed back to **4** by refluxing in methanol for a short period.

A brief study of the temperature dependence of this aldol addition was made, using the reaction of dianion **2** with propanal as the model. At temperatures below 0 °C, the reaction became very sluggish and finally at −78° only 11% of the desired product could be isolated after 1-h reaction period (79% recovery of methyl acetoacetate). When the reaction was performed at 25° for ½ h adduct **4** ($R = C_2H_5$; $R' = H$) was isolated in 57% yield. Whereas, this same product was isolated in 73% yield after 10 min reaction time at 0°. A similar temperature dependence was noted for alkylation (2, 3, 7) and acylation (4, 5, 7) of **2**.

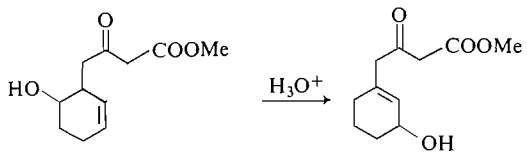
The dianion **2** could also be generated from methyl acetoacetate and **2** equiv. of lithium diisopropylamide, and subsequent reaction with benzophenone gave **4** ($R = R' = C_6H_5$) in 62%. Hence, it would appear that the dilithio intermediate **2** does not have the same reactivity as the sodio lithio intermediate **2**. Lithium bis(trimethylsilyl)amide was not a sufficiently strong enough base to generate the dianion **2**. The lower basicity of lithium bis(trimethylsilyl)amide compared to lithium dialkylamides parallels the lower basicity of silylamines compared to alkylamines (11). This has been attributed to dπ–pπ bonding between the nitrogen lone pairs and the adjacent silicon atom.

Several procedures were investigated to convert the adducts **4** into the corresponding unsaturated keto esters **5**. Treatment of these adducts (**4**) with phosphorus oxychloride in pyridine, *p*-toluenesulfonic acid in refluxing benzene, and refluxing 10% aqueous sulfuric acid gave complex mixtures of products. However, it was found that treatment of the product **4** with anhydrous hydrogen chloride in chloroform resulted in smooth conversion to the unsaturated keto ester (**5**). In those adducts (**4**) in which $R \neq R'$ a mixture of two isomeric unsaturated products (**5**) was obtained, these were not separated but estimates of the relative amounts of two isomers were obtained from the n.m.r. spectra (7). Recently synthetic interest in simple γ,δ-unsaturated-β-keto esters (**5**) has been revived and these esters appear to be very useful in annelation reactions to synthesize cyclic β-keto esters (12). Together with the renewed interest in these esters (**5**), was a need for an efficient synthesis of these materials; the above dianion route provides an efficient route to all but the simplest (**5**, $R = R' = H$) of these esters. Stork and Guthikonda have also developed an efficient route to these esters, which is outlined in eq. 2 (12).

We also undertook a limited study of the



possible conjugate addition of dianion **2** to α,β-unsaturated ketones. However, dianion **2** gave only carbonyl addition products with methyl vinyl ketone and cyclohex-2-enone. Addition of a variety of stoichiometries of cuprous iodide again gave only carbonyl addition products, although it is believed that some form of copper dianion complex was formed, as evidenced by the dissolution of the cuprous iodide and formation of a brown solution. The failure of the conjugate addition is attributed to the high nucleophilic reactivity of dianion **2**. It was found, however, that under acid work-up the initially formed carbonyl adduct of **2** and cyclohex-2-enone rearranged to the secondary alcohol **7**.



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Experimental[3]

Aldol Reactions of the Dianion of β-Keto Esters

Methyl 5-Hydroxy-5-methyl-3-oxohexanoate (4a)

Sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, was weighed into an oven-dried 50 ml flask and tetrahydrofuran (*ca.* 25 ml) was distilled directly into this flask from lithium aluminum hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice to 0 °C, and flushed with nitrogen. Methyl acetoacetate (1.161 g, 10.0 mmol) was added dropwise to the cooled slurry and the reaction allowed to stir for 10 min after the addition was complete. A solution of *n*-butyllithium (5 ml, 2.1 *M* in hexane, 10.5 mmol) was added dropwise to the solution and the reaction allowed to stir at 0° for a further 10 min. Acetone (0.638 g, 11.0 mmol) was added in one portion and the reaction allowed to stir for 10 min at 0° before being quenched with concentrated hydrochloric acid (*ca.* 2 ml). The reaction was worked up by the addition of water (10 ml) and diethyl ether (35 ml). The aqueous layer was separated and further extracted with ether (2 × 35 ml). The organic extracts were combined, washed with saturated sodium chloride solution (6 × 15 ml), dried over anhydrous sodium sulfate, and filtered. The solvents were removed by evaporation under reduced pressure and distillation of the resulting oil gave 1.162 g (72%) of **4a**, b.p. 51–52° (14 mm); i.r. ($CHCl_3$) 3500, 1740, and 1705 cm^{-1}; n.m.r. ($CDCl_3$) δ 3.76 (s, 3H), 3.48 (s, 2H), 3.27 (broad s, exchangeable D_2O, 1H), 2.70 (s, 2H), and 1.30 p.p.m. (s, 6H); mass spectrum, *m/e* (relative intensity) 174(4), 159(48), 128(71), 116(100), 85(62), 59(87), and 43(87).

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.97; H, 8.32.

Methyl 5-Hydroxy-5-methyl-3-oxoheptanoate (4b)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4a**). The reagents used in the preparation were: sodium hydride (0.467 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), *n*-butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, and 2-butanone (0.792 g, 11.0 mmol), which gave 1.052 g (56%) of **4b**, b.p. 88–89° (14 mm); i.r. (neat film) 3500, 1740, and 1705 cm^{-1}; n.m.r. ($CDCl_3$) δ 3.77 (s, 3H), 3.51 (s, 2H), 3.15 (broad s, exchangeable D_2O, 1H), 2.71 (s, 2H), 1.60 (distorted q, J = 8 Hz, 2H), 1.27 (s, 3H), and 0.92 p.p.m. (distorted t, J = 8 Hz, 3H); mass spectrum, *m/e* (relative intensity) 188(0.2), 170(10), 159(49), 128(75), 116(50), 85(47), 73(47), and 43(100).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.27; H, 8.71.

Methyl 4-(1-Hydroxycyclohexyl)-3-oxobutanoate (4c)

This compound was also prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4a**). The reagents used in the preparation were: sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), *n*-butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, and cyclohexanone (1.078 g, 11.0 mmol), which gave 1.348 g (63%) of **4c**, b.p. 95–96° (0.3 mm); i.r. (neat film) 3500, 1740, and 1705 cm^{-1}; n.m.r. ($CDCl_3$) δ 3.75 (s, 3H), 3.50 (s, 2H), 3.11 (broad s, exchangeable D_2O, 1H), (s, 2H), and 1.52 p.p.m. (m, 10H); mass spectrum, *m/e* (relative intensity) 214(3), 196(18), 182(12), 138(61), 123(40), 122(47), 116(44), 98(63), 95(60), 80(53), 69(69), 55(84), and 43(100).

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.84; H, 8.47.

Methyl 4-(1-Hydroxycyclopentyl)-3-oxobutanoate (4d)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4a**). The reagents used in the preparation were: sodium hydride (0.466 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), *n*-butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, and cyclopentanone (0.924 g, 11.0 mmol), which gave 0.502 g (25%) of **4d**, b.p. 67–68° (0.3 mm); i.r. (neat film) 3500, 1740, and 1705 cm^{-1}; n.m.r. (CDCl) δ 3.77 (s, 3H), 3.52 (s, 2H), 3.10 (broad s, exchangeable D_2O, 1H), 2.90 (s, 2H), and 1.72 p.p.m. (m, 8H); mass spectrum, *m/e* (relative intensity) 200(4), 182(12), 159(89), 126(62), 116(89), 109(51), 198(65), 101(84), 85(89), 84(98), 67(62), 59(62), 55(100), and 43(100).

[3]See refs. 3, 5, or 7 for general details.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.14; H, 7.94.

Methyl 5-Hydroxy-3-oxoheptanoate (4e)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4***a*). The reagents used in the preparation were: sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), *n*-butyllithium (5.0 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, and propanal (0.639 g, 11.0 mmol), which gave 1.270 g (73%) of **4***e*, b.p. 86–87° (0.5 mm); i.r. (neat film) 3500, 1740, and 1705 cm^{-1}; n.m.r. ($CDCl_3$) δ 4.00 (m, 1H), 3.76 (s, 3H), 3.52 (s, 2H), 2.66 (m, 2H), 2.43 (broad s, exchangeable D_2O, 1H), 1.45 (m, 2H), and 0.95 p.p.m. (m, 3H); mass spectrum, *m/e* (relative intensity) 174(1), 156(6), 145(17), 116(16), 114(38), 101(32), 83(59), 71(49), 69(53), 59(52), and 43(100).

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.95; H, 8.09.

Methyl 5-Hydroxy-3-oxononanoate (4f)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4***a*). The reagents used in the preparation were: sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), *n*-butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, and pentanal (0.946 g, 11.0 mmol), which gave 0.727 g (36%) of **4***f*, b.p. 55–56° (0.2 mm); i.r. (neat film) 3500, 1740, and 1705 cm^{-1}; n.m.r. (CDCl) δ 4.00 (m, 1H), 3.76 (s, 3H), 3.50 (s, 2H), 2.66 (m, 2H), 2.42 (broad s, exchangeable D_2O, 1H), and 1.52–0.77 p.p.m. (m, 9H); mass spectrum, *m/e* (relative intensity) 202(1), 184(9), 145(38), 127(9), 116(36), 113(35), 101(23), 97(14), 85(27), 84(19), 58(32), and 43(100).

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.19; H, 8.96.

Methyl 5-Hydroxy-3-oxohexanoate (4g)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4***a*). The reagents used in the preparation were: sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), *n*-butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, and acetaldehyde (0.484 g, 11.0 mmol), which gave 0.416 g (26%) of **4***g*, b.p. 42–43° (0.3 mm); i.r. ($CHCl_3$) 3500, 1740, and 1705 cm^{-1}; n.m.r. (CCl_4) δ 4.10 (m, 1H), 3.70 (s, 3H), (s, 2H), 3.00 (broad s, exchangeable D_2O, 1H), 2.62 (m, 2H), and 1.12 p.p.m. (m, 3H); mass spectrum, *m/e* (relative intensity) 160(40), 142(54), 127(33), 116(60), 101(73), 85(42), 59(64), and 43(100).

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.65; H, 7.39.

Methyl 5-Hydroxy-6,6-dimethyl-3-oxoheptanoate (4h)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4***a*). The reagents used in the preparation were: sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), *n*-butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, and 2,2-dimethylpropanol (0.946 g, 11.0 mmol), which gave 1.654 g (82%) of **4***h*, b.p. 68–69° (0.2 mm); i.r. ($CHCl_3$) 3500, 1740, and 1705 cm^{-1}; n.m.r. (CCl_4) δ 3.70 (s, 3H), 3.63 (m, 1H), 3.42 (s, 2H), 3.00 (broad s, exchangeable D_2O, 1H), 2.58 (m, 2H), and 0.87 p.p.m. (s, 9H); mass spectrum *m/e* (relative intensity) 202(1), 184(10), 170(22), 155(23), 145(90), 127(42), 116(48), 115(48), 113(92), 111(94), 101(60), 56(96), 83(87), 71(100), 69(94), 59(77), 55(100), and 43(100).

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.15; H, 8.95.

Methyl 5-Hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (4i)

This compound was prepared by the same procedure as that employed in the preparation of **4***a*. The reagents used were: sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), *n*-butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, and *o*-methoxyacetophenone (1.650 g, 11.0 mmol), which gave 2.550 g of pale yellow oil. Purification of this oil was achieved by t.l.c.: crude **4***i* (544 mg) was chromatographed on a 20 × 20 cm silica coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (9:1, v/v) as eluent. After elution, the band lying in the region R_f 0.25–0.33 was removed and extracted with ether (15 ml). The solvent was removed by evaporation under reduced pressure to give 471 mg (73%) of **4***i*; i.r. ($CHCl_3$) 3500, 1740, and 1705 cm^{-1}; u.v. (CH_3OH) 276, 270, and 264 nm (shoulder); n.m.r. (CCl_3) δ 7.70–6.70 (m, 4H), 4.10 (broad s, exchangeable D_2O, 1H), 3.82 (s, 3H), 3.63 (s, 3H), 3.33–1.65 (m, 4H), and 1.50 p.p.m. (s, 3H); mass spectrum (*a*) high resolution calcd. for $C_{14}H_{18}O_5$: 266.1154 a.m.u.; found: 266.1135 a.m.u.; (*b*) *m/e* (relative intensity) 266(10), 251(8), 234(16), 208(10), 159(34), 151(78), 135(94), 115(52), 91(25), 77(80), 59(47), and 43(100).

Methyl 5-(2-Methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (6i). Methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (**4***i*) (0.257 g, 0.99 mmol), chlorotrimethylsilane (0.108 g, 1.00 mmol), and hexamethyldisilazane (0.081 g, 0.50 mmol) were dissolved in dry pyridine (*ca.* 5 ml) and the solution stirred for 10 min. A fine white precipitate was thrown down and this was filtered off and washed with ether (3 × 10 ml). The washings were added to the filtrate and the solvents removed by evaporation under reduced pressure. The resulting oil was distilled under high vacuum to give 0.176 g (65%) of **6***i*, b.p. 83–85° (0.3 mm); i.r. ($CHCl_3$) 1740, 1705, and 1075 cm^{-1}; n.m.r. (CCl_4, ext TMS) 7.55–6.67 (m, 4H), 3.80 (s, 3H), 3.53 (s, 3H), 3.20 (m, 2H), 2.80 (m, 2H), 1.67 (2, 3H), and 0.00 p.p.m. (s, 9H); mass spectrum, *m/e* (relative intensity) 338(3), 323(2), 308(2), 265(2), 223(98), 173(35), 151(19), 135(80), 115(17), 105(46), 91(19), 75(100), 59(30), and 43(76).

Anal. Calcd. for $C_{17}H_{26}O_5Si$: C, 60.33; H, 7.74. Found: C, 60.20; H, 7.49.

Hydrolysis of Methyl 5-(2-Methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (6i). Methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (**6***i*) (0.170 g, 0.50 mmol) was dissolved in methanol (10 ml) and the solution heated to reflux. After a period of 30 min at reflux the solution was cooled and filtered. The methanol was removed by evaporation under reduced pressure and the resulting oil purified by preparative t.l.c., using a 20 × 20 cm silica coated plate, adsorbant thickness 0.5 mm, and employing a mixture of chloroform and ethyl acetate (9:1, v/v) as eluent. The band lying

in the region R_f 0.25–0.33 was removed and extracted with ether. The solvent was removed by evaporation under reduced pressure to give 95 mg (71%) of methyl 5-hydroxy-5-(2-methoxyphenyl) 3-oxohexanoate (**4*i***), which showed identical i.r. and n.m.r. spectra to **4*i*** obtained above.

Methyl 5-(2-Methoxyphenyl)-3-oxohex-4-enoate (5i). Chloroform (*ca.* 10 ml) was saturated with anhydrous hydrogen chloride, by direct passage of the gas through the solvent. Methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (**4*i***) (0.051 g, 0.19 mmol) was dissolved in this chloroform and the solution stirred for 30 min. The solution was washed with saturated sodium hydrogen carbonate solution (4 × 5 ml) and with saturated sodium chloride solution (2 × 5 ml), dried over anhydrous sodium sulfate, and filtered. The chloroform was removed by distillation to give 0.040 g (85%) of a mixture of *Z* and *E* isomers of **5*i*** (ratio of isomers, *Z*:*E* 1.0:2.3, by n.m.r.); i.r. ($CHCl_3$) 1740, 1680, and 1600 cm^{-1}; u.v. (CH_3OH) 320 (shoulder) and 278 nm; n.m.r. (CCl_4) δ 7.40–6.67 (m, 4H), 6.20 (m, 0.7H, *E*), 6.10 (m, 0.3H, *Z*), 3.82 (s, 3H), 3.70 (d, J = 1 Hz, 2.1H, *E*), 3.60 (d, J = 1 Hz, 0.9H, *Z*), 3.40 (s, 2H), 2.43 (d, J = 1 Hz, 2.1H, *E*), and 2.12 p.p.m. (d, J = 1 Hz, 0.9H, *Z*); mass spectrum: (*a*) high resolution calcd. for $C_{14}H_{16}O_4$: 248.1048 a.m.u.; found: 248.1064 a.m.u.; (*b*) *m/e* (relative intensity) 248(2), 217(14), 189(3), 175(11), 160(13), 159(100), 150(5), 136(17), 119(4), 115(4), 105(6), 91(9), 77(4), 69(2), 59(2), and 43(22).

Methyl 5-Hydroxy-3-oxo-5-phenylpentanoate (4j)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (**4*i***). The reagents used in the preparation were: sodium hydride (0.466 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.35 *M* solution in hexane, and benzaldehyde (1.168 g, 11.0 mmol), which gave 2.553 g of crude **4*j***, as a yellow oil. The crude product was purified by chromatography on a silica gel (200 g) column using a mixture of chloroform and ethyl acetate (9:1 v/v) as eluent. The major component from the chromatography was **4*j*** (1.973 g, 89%); i.r. ($CHCl_3$) 3500, 1740, and 1705 cm^{-1}; u.v. (CH_3OH) 280 (shoulder), 264, 258, 252, and 247 nm; n.m.r. (CCl_4) δ 7.22 (s, 5H), 5.05 (m, 1H), 3.65 (s, 3H), 3.33 (s, 2H), 3.30 (broad s, exchangeable D_2O, 1H), and 2.79 p.p.m. (m, 2H); mass spectrum: (*a*) high resolution calcd. for $C_{12}H_{14}O_4$: 222.089 a.m.u.; found: 222.086 a.m.u.; (*b*) *m/e* (relative intensity) 222(20), 204(74), 190(21), 188(18), 162(30), 149(58), 131(77), 116(86), 107(98), 106(88), 105(90), 91(32), 85(53), 84(72), 77(94), 58(90), 51(78), and 43(100)

Methyl 3-Oxo-5-phenyl-5-trimethylsiloxypentanoate (6j). This compound was prepared by the same procedure as that employed in the preparation of methyl 5-(2-methoxyphenyl)-3-oxo-trimethylsiloxyhexanoate (**6*i***). The reagents used were: methyl 5-hydroxy-3-oxo-5-phenylpentanoate (**4*j***) (0.208 g, 0.93 mmol), chlorotrimethylsilane (0.108 g, 1.00 mmol), and hexamethyldisilazane (0.080 g, 0.50 mmol), which gave 0.153 g (52%) of **6*j***, b.p. 60–62° (0.2 mm); i.r. ($CHCl_3$) 1740, 1705, and 1080 cm^{-1}; n.m.r. (CCl_4, ext TMS) δ 7.23 (s, 5H), 5.20–4.87 (m, 1H), 3.63 (s, 3H), 3.27 (s, 2H), 2.93–2.27 (m, 2H), and 0.00 p.p.m. (s, 9H); mass spectrum, *m/e* (relative intensity) 294(1), 279(4), 264(3), 249(8), 221(16), 204(51), 189(12), 179(53), 162(34), 149(38), 144(52), 131(62), 117(45), 116(66), 105(76), 91(68), 85(54), 77(82), 69(62), 59(100), and 43(83).

Anal. Calcd. for $C_{15}H_{22}O_4Si$: C, 61.19; H, 7.53. Found: C, 61.40; H, 7.32.

Methyl 5-Hydroxy-5-(2-methoxyphenyl)-3-oxopentanoate (4k)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (**4*i***). The reagents used were: sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.160 g, 10.0 mmol), *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.34 *M* solution in hexane, and *o*-methoxybenzaldehyde (1.498 g, 11.0 mmol), which gave 2.830 g of crude **4*k*** as a yellow oil. Purification of this oil was achieved by t.l.c.: crude **4*k*** (374 mg) was chromatographed on a 20 × 20 cm silica coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (9:1 v/v) as eluent. After elution, the band lying in the region R_f 0.2–0.3 was removed and extracted with ether (20 ml). The solvent was removed by evaporation under reduced pressure to give 243 mg (73%) of **4*k***; i.r. ($CHCl_3$) 3600, 1740, and 1705 cm^{-1}; n.m.r. (CCl_4) δ 7.50–6.67 (m, 4H), 5.30 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.50 (broad s, exchangeable D_2O, 1H), 3.36 (s, 2H), and 2.77 p.p.m. (m, 2H); u.v. (CH_3OH) 276, 271, and 257 nm; mass spectrum: (*a*) high resolution: calcd. for $C_{13}H_{16}O_5$: 252.099 a.m.u.; found: 252.102 a.m.u.; (*b*) *m/e* (relative intensity) 252(4), 234(36), 203(26), 179(16), 175(19), 161(43), 151(44), 137(60), 133(100), 127(36), 121(51), 116(39), 105(58), 91(47), 85(65), 77(54), 59(50), and 43(70).

Methyl 5-(2-Methoxyphenyl)-3-oxo-5-trimethylsiloxypentanoate (6k). This compound was prepared by the same procedure as that employed in the preparation of methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (**6*i***). The reagents used in the preparation were: methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxopentanoate (**4*k***) (149 mg, 0.59 mmol), chlorotrimethylsilane (69 mg, 0.64 mmol), and hexamethyldisilazane (52 mg, 0.32 mmol), which gave 138 mg (71%) of **6*k***, b.p. 64–65° (0.5 mm); i.r. ($CHCl_3$) 1740, 1705, and 1070 cm^{-1}; n.m.r. (CCl_4, ext TMS) δ 7.47–6.60 (m, 4H), 5.43 (m, 1H), 3.80 (s, 3H), 3.63 (s, 3H), 3.30 (s, 2H), 2.63 (m, 2H), and 0.00 p.p.m. (s, 9H); mass spectrum, *m/e* (relative intensity) 324(7), 306(45), 293(10), 266(8), 251(15), 241(31), 209(97), 199(24), 195(17), 179(25), 173(95), 161(33), 145(25), 135(53), 127(24), 115(37), 105(53), 91(69), 85(20), 77(68), 75(92), 73(100), 60(22), 59(66), and 43(88).

Anal. Calcd. for $C_{16}H_{24}O_5Si$: C, 59.23; H, 7.46. Found: C, 59.46; H, 7.48.

Methyl 5-(2-Furyl)-5-hydroxy-3-oxopentanoate (4l)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4*a***). The reagents used in the preparation were sodium hydride (0.463 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.160 g, 10.0 mmol), *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.34 *M* solution in hexane, and 2-furfuraldehyde (1.061 g, 11.0 mmol), which gave 1.445 g (68%) of **4*l***, b.p. 82–84° (0.1 mm); i.r. ($CHCl_3$) 3600, 1740, and 1710 cm^{-1}; n.m.r. (CCl_4) δ 7.32 (m, 1H), 6.23 (m, 2H), 5.05 (m, 1H), 3.82 (broad s, exchangeable D_2O, 1H), 3.69 (s, 3H), 3.42 (s, 2H), and 2.93 p.p.m. (m, 2H); mass spectrum, *m/e* (relative intensity) 212(12), 194(11), 149(11), 121(50),

116(30), 101(13), 97(75), 96(71), 95(76), 69(26), 65(21), 59(35), and 43(100).

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.66; H, 5.35.

Methyl 5-Hydroxy-3-oxo-5-phenylhexanoate (4m)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (**4***i*). The reagents used were: sodium hydride (0.461 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.163 g, 10 mmol), *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.34 *M* solution in hexane, and acetophenone (1.318 g, 11.0 mmol), which gave 2.801 g of crude **4***m* as a yellow oil. Purification of this oil was achieved by t.l.c.: 563 mg of crude **4***m* was chromatographed on a 20 × 20 cm silica coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (9:1 v/v) as eluent. After elution, the band lying in the region R_f 0.25–0.40 was removed and extracted with ether (20 ml). The solvent was removed under reduced pressure to give 367 mg of **4***m* (77% yield); i.r. ($CHCl_3$) 2550, 1740, and 1705 cm^{-1}; u.v. (CH_3OH) 294 (shoulder), 278, and 273 nm; n.m.r. (CCl_4) δ 7.30 (m, 5H), 3.85 (broad s, exchangeable D_2O, 1H), 3.63 (s, 3H), 3.25 (m, 2H), 2.67 (m, 2H), and 1.65 p.p.m. (s, 3H); mass spectrum: (*a*) high resolution calcd. for $C_{13}H_{16}O_4$: 236.104 a.m.u.; found: 236.105 a.m.u.; (*b*) *m/e* (relative intensity) 236(2), 221(5), 218(5), 190(6), 170(2), 159(11), 145(12), 127(17), 121(64), 120(95), 116(88), 106(50), 105(88), 101(45), 85(95), 77(100), 74(95), 69(64), 59(97), and 43(100).

Methyl 3-Oxo-5-phenyl-5-trimethylsiloxyhexanoate (6m). This compound was prepared by the same procedure as that employed for the preparation of methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (**6***i*). The reagents used were: methyl 5-hydroxy-3-oxo-5-phenylhexanoate (**4***m*) (305 mg, 1.30 mmol), chlorotrimethylsilane (155 mg, 1.43 mmol), and hexamethyldisilazane (115 mg, 0.72 mmol), which gave 242 mg (61%) of **6***m*, b.p. 82–83° (0.3 mm); i.r. ($CHCl_3$) 1740, 1705, and 1075 cm^{-1}; n.m.r. (CCl_4, ext TMS) δ 7.20 (m, 5H), 3.57 (s, 3H), 3.03 (m, 2H), 2.53 (m, 2H), 1.66 (s, 3H), and 0.00 p.p.m. (s, 9H); mass spectrum, *m/e* (relative intensity) 308(1), 295(9), 279(7), 264(9), 250(4), 233(11), 221(5), 211(6), 185(100), 179(11), 169(46), 156(28), 146(12), 126(17), 113(48), 101(31), 91(9), 77(26), and 73(62).

Anal. Calcd. for $C_{16}H_{24}O_4Si$: C, 62.30; H, 7.84. Found: C, 62.33; H, 7.77.

Methyl 5-(2,3-Dimethoxyphenyl)-5-hydroxy-3-oxopentanoate (4n)

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (**4***i*). The reagents used were: sodium hydride (0.466 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.162 g, 10.0 mmol), *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.34 *M* solution in hexane, and 2,3-dimethoxybenzaldehyde (1.823 g, 11.0 mmol), which gave 3.044 g of crude **4***n*, as a pale brown oil. Purification of **4***n* was achieved by t.l.c.: 306 mg of crude **4***n* was chromatographed on a 20 × 20 cm silica coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (9:1 v/v) as eluent. After elution, the band lying in the region R_f 0.30–0.40 was removed and extracted with ether (20 ml). The solvent was removed by evaporation under reduced pressure to give 194 mg of **4***n* (68% yield); i.r. ($CHCl_3$) 3550, 1740, and 1705 cm^{-1}; u.v. (CH_3OH) 264 (shoulder), 256, 252, and 246 nm; n.m.r. (CCl_4) δ 6.93 (m, 3H), 5.20 (m, 1H), 4.03 (broad s, exchangeable D_2O, 1H), 3.80 (s, 6H), 3.67 (s, 3H), 3.37 (s, 2H), and 2.77 p.p.m. (m, 2H); mass spectrum: (*a*) high resolution calcd. for $C_{14}H_{18}O_6$: 282.110 a.m.u.; found: 282.111 a.m.u.; (*b*) *m/e* (relative intensity) 282(19), 264(7), 250(15), 233(11), 222(2), 217(2), 209(5), 205(4), 191(9), 182(3), 191(9), 182(3), 167(100), 166(46), 151(21), 139(22), 137(21), 116(11), 107(11), 91(7), 85(10), 77(21), 69(9), 59(15), and 43(73).

Methyl 5-(2,3-Dimethoxyphenyl)-3-oxo-5-trimethylsiloxypentanoate (6n). This compound was prepared by the same procedure as that employed for the preparation of methyl 5-(2-methoxyphenyl)-3-oxo-5-trimethylsiloxyhexanoate (**6***i*). The reagents used were: methyl 5-(2,3-dimethoxyphenyl)-5-hydroxy-3-oxopentanoate (**4***n*) (173 mg, 0.61 mmol), chlorotrimethylsilane (74 mg, 0.68 mmol), and hexamethyldisilazane (55 mg, 0.34 mmol) which gave 114 mg (53%) of **6***n*, b.p. 89–91° (0.4 mm); i.r. ($CHCl_3$) 1740, 1705, and 1075 cm^{-1}; n.m.r. (CCl_4, ext TMS) δ 6.87 (m, 3H), 5.42 (m, 1H), 3.80 (s, 6H), 3.63 (s, 3H), 3.29 (s, 2H), 2.70 (m, 2H), and 0.00 p.p.m. (s, 9H); mass spectrum, *m/e* (relative intensity 354(16), 323(8), 304(4), 241(14), 236(100), 223(4), 209(8), 193(22), 183(47), 165(24), 151(13), 149(11), 135(13), 121(25), 115(21), 105(11), 91(11), 89(19), 75(44), 73(52), 59(17), and 43(11).

Anal. Calcd. for $C_{17}H_{26}O_6Si$: C, 57.60; H, 7.40. Found: C, 57.80; H, 7.29.

Methyl 5-Hydroxy-3-oxo-5,5-diphenylpentanoate (4p)

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (**4***i*). The reagents used were: sodium hydride (0.466 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.160 g, 10.0 mmol), *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.35 *M* solution in hexane, and benzophenone (2.003 g, 11.0 mmol), which gave 3.124 g of a semisolid. Recrystallisation from a hexane–ether mixture gave a first crop of **4***p* (1.831 g). Subsequent concentration of the mother liquors gave a second crop of **4***p* (0.321 g) and finally chromatography of the residual solution on silica gel (50 g) using chloroform as eluent gave 0.622 g of **4***p*, to total 2.774 g (93%) of product as colorless needles, m.p. 77–79 °C; i.r. ($CHCl_3$) 3550, 1740, and 1710 cm^{-1}; u.v. (CH_3OH) 253 (785), 259 (820), 265 (685), and 269 nm (52); n.m.r. (CCl_4) δ 7.27 (m, 10H), 4.43 (broad s, exchangeable D_2O, 1H), 3.67 (s, 3H), 3.40 (s, 2H), and 3.27 p.p.m. (s, 2H); mass spectrum, *m/e* (relative intensity) 298(6), 207(22), 189(14), 184(66), 183(98), 165(11), 154(18), 116(10), 105(100), 91(19), 77(85), 69(22), 59(45), 51(59), and 43(60).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.47; H, 6.05.

Ethyl 5-Hydroxy-3-oxo-5,5-diphenylpentanoate (4q)

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-hydroxy-5-(2-methoxyphenyl)-3-oxohexanoate (**4***a*). The reagents used were: sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, ethyl acetoacetate (1.303 g, 10.0 mmol), and benzophenone (2.001 g, 11.0 mmol), which gave 3.642 g of a yellow oil. This oil was dissolved in cyclohexane and addition of a small quantity of methanol to the solution precipitated **4***q* (2.510 g, 81%) as colorless needles, m.p. 68–69 °C (lit. (10) m.p. 68.5–69.5 °C).

Methyl 4-(1-Hydroxycyclohex-2-enyl)-3-oxobutanoate (4r)

This compound was prepared by the same procedure as that employed for the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4***a*). The reagents used were: sodium hydride (0.467 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.162 g, 10.0 mmol), *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.35 *M* solution in hexane, and cyclohex-2-enone (0.962 g, 10.0 mmol), which gave 2.210 g of pale yellow oil. Careful distillation of this oil in base-washed apparatus gave 1.229 g (58%) of **4***r*, b.p. 83–85 °C (0.1 mm) as a colorless oil which rapidly darkened on standing; i.r. (CCl_4) 3600, 1740, 1705, and 1630 cm^{-1}; n.m.r. (CCl_4) δ 5.67 (m, 2H), 3.70 (s, 3H), 3.40 (s, 2H), 2.83 (broad s, exchangeable D_2O, 1H), 2.67 (s, 2H), and 2.10–1.46 p.p.m. (m, 6H); mass spectrum: (*a*) high resolution calcd. for $C_{11}H_{16}O_4$: 212.1048 a.m.u.; found: 212.1063 a.m.u.; (*b*) *m/e* (relative intensity) 212(8), 197(12), 194(13), 180(15), 169(23), 136(27), 135(100), 134(15), 121(85), 108(58), 97(85), 96(54), 91(46), 84(38), 79(69), 77(58), 68(69), 55(43), and 43(77).

Attempted Conjugate Addition of Dianion 2 to Cyclohex-2-enone

Sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, was weighed into an oven-dried 50 ml flask and tetrahydrofuran (*ca.* 25 ml) was distilled, from lithium aluminum hydride, directly into this flask. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice to 0 °C, and flushed with nitrogen. Methyl acetoacetate (1.160 g, 10.0 mmol) was added dropwise to the cooled slurry and the reaction allowed to stir for 10 min after the addition was complete. A solution of *n*-butyllithium (4.5 ml 2.35 *M* in hexane, 10.6 mmol) was added dropwise to the solution and the mixture allowed to stir for an additional 10 min, to allow complete formation of the dianion. Cuprous iodide (4.208 g, 22.0 mmol), dried at 110° *in vacuo* (0.1 mm) for 20 h prior to use, was weighed under dry conditions into a 100 ml flask and tetrahydrofuran distilled directly into this flask from lithium aluminum hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), and flushed with nitrogen. Both the solution of dianion and the cuprous iodide suspension were cooled in a Dry Ice – acetone slurry to −78 °C. The dianion solution was transferred, via a stainless steel cannula, in a dropwise manner to the flask containing the cuprous iodide. The resulting dark brown mixture was stirred for 1 h at the end of which time most of the solid had dissolved. Cyclohex-2-enone (0.963 g, 10.0 mmol) dissolved in tetrahydrofuran (*ca.* 5 ml) was added to the reaction which was maintained at −78 °C for an additional hour before being allowed to warm to 0 °C. The reaction was quenched by dropwise addition of it to a vigorously stirred mixture of ether (50 ml) and hydrochloric acid (12 ml, 2 *M* solution). The aqueous phase was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (6 × 25 ml), dried over anhydrous sodium sulfate, and filtered. The solvents were removed by evaporation under reduced pressure and the resulting oil chromatographed on silica gel using a mixture of hexane, ether and acetic acid as eluent. The major fractions were identified, by comparison of i.r. and n.m.r. spectra with authentic or previously prepared materials, as methyl acetoacetate (0.708 g, 61%), cyclohex-2-enone (0.564 g, 59%), methyl 4-(1-hydroxycyclohex-2-enyl)-3-oxobutanoate (**4***r*) (0.360 g, 17%), and methyl 4-(3-hydroxycyclohex-1-enyl)-3-oxobutanoate (0.276 g, 13%).

Methyl 5-Hydroxy-5-methyl-3-oxohept-6-enoate (4s)

This compound was prepared by the same procedure as that employed in the preparation of methyl 5-hydroxy-5-methyl-3-oxohexanoate (**4***a*). The reagents used in the preparation were: sodium hydride (0.466 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.163 g, 10.00 mmol), *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.35 *M* solution in hexane, and methyl vinyl ketone (0.661 g, 11.0 mmol), which gave 1.450 g (78%) of **4***s*, b.p. 101–103 °C (0.3 mm); i.r. ($CHCl_3$) 3550, 1740, 1705, and 1630 cm^{-1}; n.m.r. (CCl_4) δ 5.87 (m, 1H), 5.10 (m, 2H), 3.72 (s, 3H), 3.36 (s, 2H), 3.20 (broad s, exchangeable D_2O, 1H), 2.20 (m, 2H), and 1.27 p.p.m. (s, 3H); mass spectrum (*a*) high resolution, calcd. for $C_9H_{14}O_4$: 186.0891 a.m.u.; found: 186.0921 a.m.u; (*b*) *m/e* (relative intensity) 186(1), 171(1), 168(3), 139(4), 127(6), 116(15), 101(10), 97(9), 95(8), 85(20), 84(14), 74(12), 71(31), 69(16), 59(26), 55(60), and 43(100).

Base Dependency Study

(a) Generation of Dianion 2 by means of Lithium Diisopropylamide

Diispropylamine (1.129 g, 11.3 mmol), which has been dried by distillation and stored over potassium hydroxide pellets prior to use, was weighed into a 50 ml oven dried flask and tetrahydrofuran (*ca.* 25 ml) distilled directly into this flask from lithium aluminum hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice, and flushed with nitrogen. *n*-Butyllithium (5 ml, 11.75 mmol), as a 2.35 *M* solution in hexane, was added dropwise to the solution and the reaction allowed to stir for 10 min after the addition was complete, to ensure complete formation of the amide. Methyl acetoacetate (0.638 g, 5.5 mmol) was added dropwise to solution and after a further 10 min, benzophenone (1.003 g, 5.5 mmol) dissolved in tetrahydrofuran (5 ml) was added. The reaction was quenched after 10 min by addition of concentrated hydrochloric acid (2 ml) and worked up by the addition of ether (50 ml) and water (15 ml). The aqueous phase was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with ether (50 ml) and water (15 ml). The aqueous phase was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 × 35 ml), dried over anhydrous sodium sulfate and filtered. The solvents were removed by evaporation under reduced pressure to give a semisolid which was recrystallised from a mixture of hexane and ether to give 0.827 g of methyl 5-hydroxy-3-oxo-5,5-diphenylpentanoate (**4***p*). Chromatography of the mother liquors on silica gel using chloroform as eluent gave an additional 0.184 g of **4***p*, to total 1.011 g (62%) as colorless needles, m.p. 77–79 °C.

(b) Attempted Generation of Dianion 2 by Means of Lithium Bis(trimethylsilyl)amide

Lithium bis(trimethylsilyl)amide was prepared from hexamethyldisilazane and *n*-butyllithium (13) and dissolved in tetrahydrofuran. This solution was standardised by titration against hydrochloric acid to determine its total base equivalence. An aliquot of this solution, which

had been found to be 1.52 *M* (5 ml, 7.60 mmol) was diluted to 25 ml with tetrahydrofuran and transferred to a 50 ml oven dried flask. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice, and flushed with nitrogen. Methyl acetoacetate (0.420 g, 3.62 mmol) was added dropwise to the solution of base and the reaction allowed to stir for 1 h after the addition was complete. Benzophenone (0.655 g, 3.65 mmol) dissolved in tetrahydrofuran (3 ml) was added to the reaction which was quenched after a further 15 min by addition of concentrated hydrochloric acid (0.75 ml). The reaction was worked up by the addition of ether (25 ml) and water (5 ml). The aqueous layer was separated and further extracted with ether (2 × 25 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 × 25 ml), dried over anhydrous sodium sulfate, and filtered. The solvents were removed by evaporation under reduced pressure to a pale yellow oil. Vapor phase chromatography analysis indicated that this oil was mainly methyl acetoacetate contaminated with hexamethyldisilazane and benzophenone, and distillation at reduced pressure gave essentially pure methyl acetoacetate (0.352 g, 84%). No product could be detected by v.p.c. or t.l.c. either in the crude oil or the residue from the distillation, that was not starting materials or hexamethyldisilazane.

Temperature Dependency Study

The dianion of methyl acetoacetate was generated as outlined above and then treated with propanal at low and room temperature.

Reaction of Dianion **2** *with Propanal at −78 °C*

The solution of dianion **2** was cooled to −78 °C in a Dry Ice – acetone slurry and propanal (0.640 g, 11.0 mmol) added. The reaction was stirred at −78 °C for 1 h and then allowed to warm to 0 °C before being quenched with concentrated hydrochloric acid (2 ml). The reaction was worked up by the addition of ether (25 ml) and water (5 ml). The aqueous phase was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (6 × 25 ml), dried over sodium sulfate, and filtered. The solvents were removed by evaporation at reduced pressure and the resulting oil distilled under high vacuum to give methyl acetoacetate (0.915 g, 79% recovery), identified by v.p.c. analysis and by its i.r. spectrum, and methyl 5-hydroxy-3-oxoheptanoate (**4***e*) (0.191 g, 11%), identified by comparison of its i.r. and n.m.r. spectra with those of previously prepared **4***e*.

Reaction of Dianion **2** *with Propanal at 25 °C*

The solution of dianion **2** was allowed to warm to room temperature before propanal (0.641 g, 11.0 mmol) was added. The reaction was stirred at room temperature for ½ h before being quenched with concentrated hydrochloric acid (2 ml). The reaction was worked up in an identical manner to the previous low temperature reaction to give 0.993 g (57%) of **4***e*, b.p. 48–49 °C (0.2 mm), which showed identical i.r. and n.m.r. spectra to that prepared previously.

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