Application of Meldrum's acid in natural product synthesis. Synthesis of ar-turmerone and α-curcumene†‡

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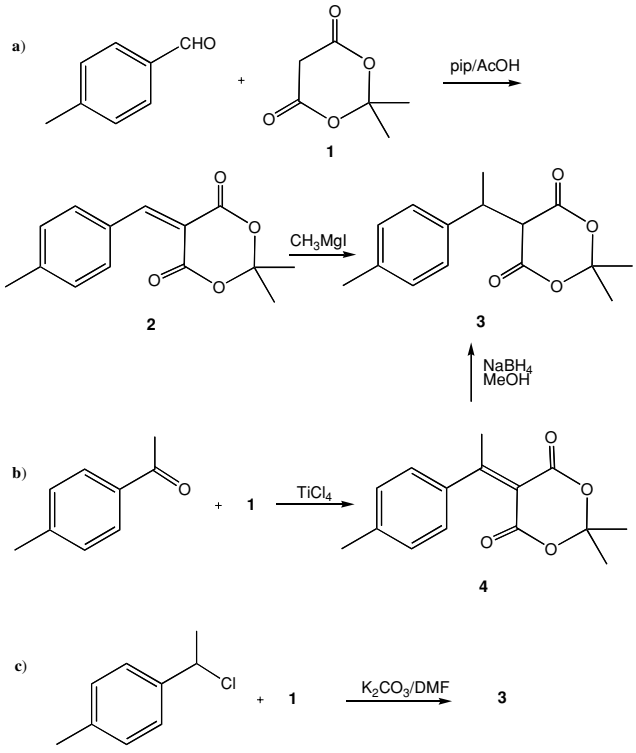
Meldrum's acid (**1**) is employed in the synthesis of ar-turmerone (**6**) and α-curcumene (**12**). 1-(*p*-Tolyl)ethyl Meldrum's acid (**3**), synthesised by three different routes, was the key intermediate in these syntheses.

Keywords: Meldrum's acid, cinnamic acids, malonic acids, coumarins, indan-1-ones

The rhizomes of *Curcuma longa* Linn., which are widely used, particularly as condiments and for dyeing of wool, silk and unmordanted cotton,[1] yield an essential oil whose constituents have been extensively studied.[2,3] The oil contains a high percentage of ketones, the closely related ar-turmerones, and mainly turmerones. After the proposal of structure **6** for ar-turmerone,[4] it has been synthesised by several methods in good yields.[4,5-12] The monocyclic sesquiterpene α-curcumene (**12**) was first isolated[13,14] from the essential oil of rhizomes of *Curcuma aromatica* Salisb. A large number of essential oils have been shown to contain α-curcumene[15,16]. After structure assignment[17] as **12**, it has been synthesised by various routes.[2,12,17-20]

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione, isopropylidene malonate, **1**) is a cyclic bifunctional ester containing an active methylene group (pK_a 5.1), and behaving as a C_3O_2 synthon, is a versatile reagent which has attracted considerable attention in synthetic organic chemistry.[21-27] A number of novel reactions[23,24] associated with the rigid ring structure of Meldrum's acid have been identified which have not been documented in the chemistry of acyclic malonates. On the other hand, however, some seemingly obvious but important transformations such as the 1, 3-dioxane-4, 6-dione ring opening reactions[28] have been less studied. The presence of a highly active methylene group adjacent to an ester function allows the Meldrum's acid to be manipulated to give a wide range of possible products. Our interest in the applications of Meldrum's acid prompted us to demonstrate its utility in the synthesis of natural products, through the synthesis of monocyclic aromatic sesquiterpenes, namely, ar-turmerone (**6**) and α-curcumene (**12**).

The key intermediate in these syntheses, 5-[1-(*p*-tolyl)ethyl] Meldrum's acid (**3**), has been synthesised using three different approaches, all involving characteristic reactions of Meldrum's acid (**1**). In the first approach, Knoevenagel condensation[29] of Meldrum's acid (**1**) with *p*-tolualdehyde using piperidine and acetic acid gave 5-*p*-tolylidene Meldrum's acid (**2**). Alkylidene Meldrum's acids such as **2** are highly reactive electrophilic olefins and readily undergo Michael addition reactions with nucleophiles. Conjugate Grignard addition[30, 31] of methyl magnesium iodide to **2** yielded 1-(*p*-tolyl)ethyl Meldrum's acid (**3**), (Scheme 1, path a). In a second approach to the intermediate **3**, Meldrum's acid (**1**) on Knoevenagel condensation[32] with *p*-methylacetophenone using titanium tetrachloride gave 5-[(1-*p*-tolyl)ethyl]methylene Meldrum's acid (**4**). The compound **4**, being a highly electrophilic olefin, undergoes reduction of the double bond with sodium borohydride[33] by hydride addition, to give **3** in good yield (Scheme 1, path b). The third approach is the monoalkylation[25,27] of Meldrum's acid with 1-*p*-tolylethyl chloride using potassium carbonate in DMF (Scheme 1, path c).



Scheme 1

We have adopted two approaches for the synthesis of ar-turmerone (**6**) from the key intermediate **3**. In the first approach, compound **3** was hydrolysed and decarboxylated by heating with pyridine and water to give 3-*p*-tolylbutyric acid (**5**). The acid **5** was then reacted with isobutenyl lithium to give ar-turmerone (**6**) (Scheme 2, path a). In another approach to **6**, we planned the acylation of key intermediate (**3**); which would demonstrate the utility of Meldrum's acid (**1**) in the synthesis of desired ketones. The reaction in fact, represents the stepwise monoalkylation[27] and acylation[34-36] of Meldrum's acid. The key intermediate **3** was condensed with 3,3-dimethylacryloyl chloride in dichloromethane and pyridine to give the alkyl acyl Meldrum's acid **7**. Hydrolysis[37] of **7** with aqueous acetic acid, aqueous pyridine, dilute hydrochloric acid or with dilute sodium hydroxide gave a product (**6**), which was purified by preparative TLC (Scheme 2, path b). In view of the problems of achieving the smooth hydrolysis of the alkyl acyl Meldrum's acid **7**, it was decided to carry out ethanolysis. Alcoholysis[34,37] of acyl Meldrum's acids to give β–ketoesters is a well-documented reaction. Ethanolysis

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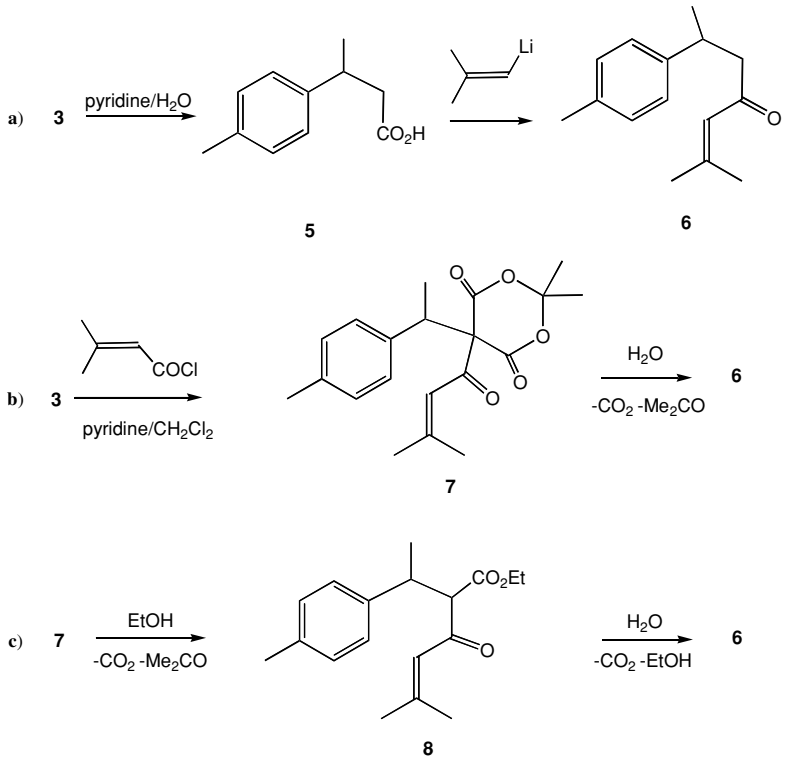


Scheme 2 Synthesis of ar-turmerone.

of **7** gave the β-ketoester **8**, which on mild hydrolysis afforded the desired ar-turmerone (**6**) in good yield (Scheme 2, path c).

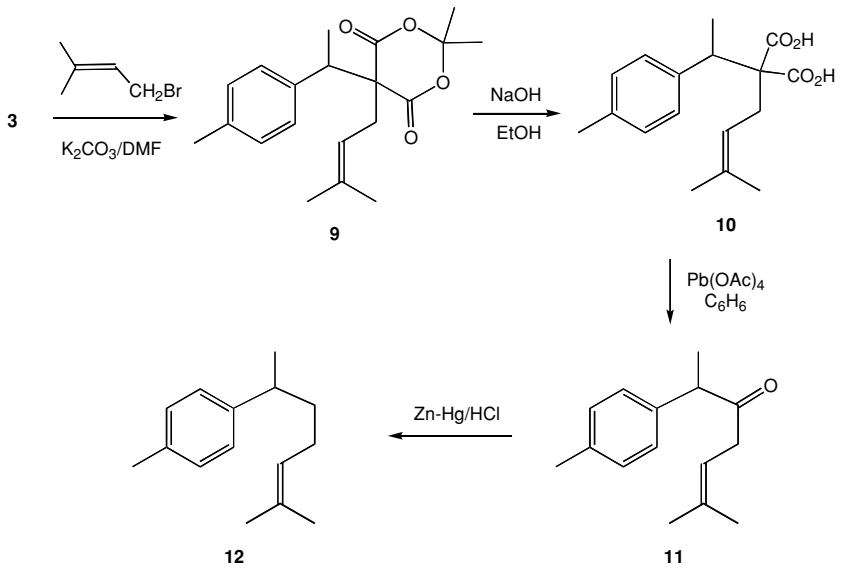
The approach adopted for the synthesis of second natural product, α-curcumene (**12**), was the stepwise alkylation of Meldrum's acid (**1**) with different alkylating agents. The key intermediate **3** was further alkylated[27] with 3,3-dimethyl-allyl bromide to give the dialkyl Meldrum's acid **9**. Alkaline hydrolysis[37] of **9** yielded the corresponding dialkylmalonic acid **10**, which underwent oxidative decarboxylation[38,39] with lead tetraacetate to give the ketone **11**. This ketone on Clemmensen reduction[37] afforded the desired product, α-curcumene (**12**) in good yield (Scheme 3).

Experimental

1-*p*-Tolylethyl chloride, isobutenyl bromide and 3,3-dimethyl-acryloyl chloride were prepared[37,40] in the laboratory. All other chemicals were commercial products and used after proper purification and drying.

5-p-Tolylidene Meldrum's acid [5-(p-tolyl)methylene Meldrum's acid] (**2**)

A mixture of Meldrum's acid (2.4 g, 0.016 mol), *p*-tolualdehyde (2.4 g, 0.020 mol), piperidine (0.2 ml) and glacial acetic acid (0.5 ml) in dry benzene (80 ml) was refluxed for 3 h using a Dean-Stark apparatus. Benzene was removed at 50 °C under vacuum by rotary evaporator to give viscous material, which was crystallised from ethanol to yield a slightly yellow product **2** (2.67 g, 65%), m.p. 126 °C, (lit.[29] m.p. 125–126 °C). ^{1}H NMR ($CDCl_3$): δ 1.80 (6H, s, gem-Me_2), 2.45 (3H, s, Ar–Me), 7.37 (2H, d, J = 8.5 Hz, Ar–H ortho to Me),



Scheme 3 Synthesis of α-curcumene.

8.13 (2H, d, J = 8.5 Hz, Ar–H), 8.51 (1H, s, CH). IR (KBr): 1762, 1725,1615,1600 cm^{-1}.

1-(p-Tolyl)ethyl Meldrum's acid (**3**): *(a) By Grignard reaction*: To a suspension of **2** (2.46 g, 0.01 mol) in 20 ml of dry ether at 0–5 °C, methylmagnesium iodide (0.014 mol) [prepared from magnesium turnings (0.341 g, 0.014 mol) and methyl iodide (1.99 g, 0.014 mol) in dry ether (20 ml)] was added over five min with stirring, and stirring was continued for 20 min in the same ice-bath and for a further 30 min at room temperature. To this reaction mixture 1N HCl (60 ml) was added with stirring, and the ether was removed under reduced pressure. The residual mixture was chilled with stirring to give a crystalline product which was filtered off, washed with ice-cold water, and dried. Recrystallisation of the crude product from ethanol gave white crystalline **3** (2.4 g, 92%), m.p. 130 °C dec. ^{1}H NMR ($CDCl_3$): δ 1.34 (3H, s, one Me of gem-Me_2),1.62 (3H, d, J = 7 Hz, secondary Me), 1.67 (3H, s, one Me of gem–Me_2), 2.30 (3H, s, Ar–Me), 3.65 (1H, d, J = 7Hz, CH), 4.00 (1H, m, benzylic CH), 7.19 (4H, AA′BB′ q, Ar–H). IR (KBr): 1780, 1740 cm^{-1}. Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.88. Found: C, 68.70; H, 6.67 %.

(b) By reduction of the unsaturated compound **4**: *(i) 5-(1-p-Tolyl)ethylidene Meldrum's acid* (**4**): Titanium tetrachloride (2.2 ml, 0.02 mol) in CCl_4 (5 ml) was added dropwise to dry THF (40 ml) at 0 °C, and a solution of *p*-methylacetophenone (1.33 ml, 0.01 mol) and Meldrum's acid (1.44 g, 0.01 mol) in THF (5 ml) was added slowly with stirring, followed by pyridine (3.2 ml, 0.05 mol) in THF (5 ml). The reaction mixture was stirred for 1 h at 0 °C and then at room temperature overnight. Water (10 ml) and ether (20 ml) were added and stirring was continued until the solid material dissolved. The organic later was separated and washed with brine, saturated sodium bicarbonate solution, and water, and dried over anhydrous sodium sulfate. Removal of solvent using rotary evaporator at 50 °C under vacuum gave a solid product which was recrystallised from ethanol to give a slight yellow solid **4** (1.56 g, 60 %), m.p. 103 °C. ^{1}H NMR ($CDCl_3$): δ 1.81 (6H, s, gem–Me_2), 2.35 (3H, s, Ar–Me), 2.65 (3H, s, vinylic Me), 6.90 (2H, d, J = 8 Hz, Ar–H ortho to Me), 7.30 (2H, d, J = 8 Hz, Ar-H). IR (KBr): 1760, 1730, 1610 cm^{-1}. Anal. calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.15. Found C, 69.24; H, 6.28 %.

(ii) Reduction of **3**: The product **4** (1.3 g, 0.005 mol) was dissolved in methanol (75 ml), and sodium borohydride (100 mg, 0.0025 mol) was added slowly while stirring over 10 min with cooling to *ca* 10–15 °C. After stirring for a further 10 min, 1N HCl (200 ml) was added and the resultant suspension was chilled. The crystalline product was recrystallised from ethanol to give a colourless solid **3** (0.920 g, 70%), m.p. 130 °C dec.

(c) Formation of **3** *by monoalkylation*[25,27] *of* **1**: To a solution of Meldrum's acid (**1**) (1.44 g, 0.01 mol) in dry DMF (10 ml) anhydrous potassium carbonate (0.692 g, 0.005 mol) was added and the mixture was stirred for 1 h. Into this solution was added dropwise, with stirring, 1-*p*-tolylethyl chloride (1.54 g, 0.01 mol) in DMF (10 ml) over 1.5 h at room temperature The reaction mixture was further stirred for 5–6 h; the contents were poured into water (30 ml) and acidified with acetic acid. The organic material was extracted with ether and the ether layer then extracted with sodium bicarbonate solution. Acidification of the aqueous extract with dil. HCl gave a crude product which was filtered off, washed with ice-cold water and dried. Recrystallisation from chloroform – pet. ether or ethanol furnished a white crystalline product **3** (1.88 g, 72%), m.p. 130 °C dec.

3-p-Tolylbutyric acid (**5**): A mixture of compound **3** (2 g), water (2 ml) and pyridine (20 ml) was refluxed for 6 h. The cooled solution was poured into ice-cold water (50 ml) and acidified with dil. HCl (the Py-HCl should be dissolved completely). It was then extracted with ether, the ether extract washed with water and dried over anhydrous sodium sulfate. Removal of ether gave a crude product which was recrystallised from pet. ether to yield a colourless acid (**5**) (1.255 g, 92%), m.p. 92 °C. ^{1}H NMR($CDCl_3$): δ 1.30 (3H, d, J = 7 Hz, secondary Me), 2.34 (3H, s, Ar–Me), 2.60 (2H, m, CH_2), 3.24 (1H, sextet, J = 7 Hz, CH), 7.15 (4H, s, Ar–H), 10.8 (1H, s, COOH). IR (KBr): 3400–3300, 1700 cm^{-1}. Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.17, H, 7.84. Found: C, 74.16; H, 7.88 %.

ar-Turmerone (**6**)[11]: Isobutenyl bromide[40] (3.3 g, 0.025 mol) in dry ether (25 ml) was added dropwise to finely cut lithium (0.694 g, 0.1 mol) in dry ether (50 ml) with stirring during 0.5 h under nitrogen. The solution was stirred for further 2 h at room temperature. The acid **5** (0.89 g, 0.005 mol) in ether (15 ml) was added dropwise at 0 °C with stirring over 15 min. The mixture was stirred for 4 h at room temperature and then poured into ice-water (60 ml). The organic layer was separated and aqueous layer extracted with ether. The combined organic layer and ether extract was successively washed with saturated aqueous sodium bicarbonate, then water, and dried over anhydrous sodium sulfate. Removal of ether gave ar-turmerone (**6**), which was purified by preparative TLC over silica gel (95% pet. ether + 5% ethyl acetate) to yield pure **6** as a yellowish liquid (0.972 g, 90%), b.p. 160–165 °C /10 mm, (lit.[8,12] b.p. 150–155 °C /8mm). ^{1}H NMR (CCl_4): δ 1.18 (3H, d, J = 7 Hz, secondary Me), 1.80 and 2.06(3H each s, two vinylic Me), 2.25(3H, s, Ar–Me), 2.52(2H, m, CH_2), 3.20(1H, sextet, J = 7 Hz, benzylic CH), 5.88(1H, s, vinylic CH), 6.98(4H, s, Ar–H). IR (CCl_4): 1685,1620 cm^{-1}. Anal. Calcd. for $C_{15}H_{20}O$: C, 83.33; H, 9.25. Found: C, 83.21; H, 9.29 %.

5-(1-p-Tolylethyl)-5-(3,3-dimethylacryloyl) Meldrum's acid (**7**): To a solution of **3** (2.62 g, 0.01 mol) in dry dichloromethane (20 ml), dry pyridine (1.58 g, 0.02 mol) was added under nitrogen atmosphere and stirred for 0.5 h. 3,3-Dimethylacryloyl chloride (1.20 g, 0.011 mol) in dry dichloromethane (5 ml) was added dropwise with stirring at 0 °C during 30 min and the reaction mixture was stirred in the same ice-bath for 1 h and then at room temperature for 6 h. The contents were poured into water (30 ml) and the organic material was extracted into dichloromethane. The organic extract was washed repeatedly with water, sodium bicarbonate solution, water and dried over anhydrous calcium chloride. The removal of solvent by distillation gave a crude product which was purified by TLC over silica gel (90% pet.ether + 10% ethyl acetate) to furnish a yellow viscous product **7** (2.83 g, 85%). ^{1}H NMR (CCl_4): δ 1.05 (3H, s, Me of gem–Me_2), 1.30(3H, d, J = 6.5 Hz, secondary Me), 1.70 (3H, s, Me of gem–Me_2), 1.91 and 2.10 (3H each, each s, two vinylic Me), 2.30 (3H, s, Ar–Me), 4.11 (1H, m, benzylic CH), 6.00 (1H, bs, vinylic CH), 7.10 (4H, s, Ar–H). IR (CCl_4): 1790, 1720, 1630 cm^{-1}. Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.76; H, 6.97. Found: C, 69.53; H, 6.74 %.

Ethyl 2-(p-tolylethyl)-2-(3,3-dimethylacryloyl)acetate (**8**): A solution of **7** (2 g) in 20 ml of ethanol was refluxed for 5 h on water bath. Ethanol was distilled off and the product (1.385 g, 83%) so obtained was purified by TLC over silica gel (90% pet.ether + 10% ethyl acetate) to give **8** as a yellow viscous liquid. ^{1}H NMR (CCl_4): δ 1.10 (3H, t, J = 7 Hz, Me of ester group), 1.35 (3H, d, J = 7 Hz, sec. Me), 1.81 and 2.11 (3H each, s, two vinylic Me), 2.25 (3H, s, Ar–Me), 3.26 (2H, q, J = 7 Hz, CH_2 of ester group), 4.20 (2H, m, two CH), 5.62 (1H, s, vinyl CH), 7.05 (4H, AA′BB′q, Ar–H). IR (neat): 1720, 1685, 1610 cm^{-1}. Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.00; H, 8.33. Found: C, 74.80; H, 8.12 %.

ar-Turmerone (**6**): The hydrolysis of alkyl-acyl Meldrum's acid (**7**) or its ethanolysis product (**8**) was achieved using the following approaches to give **6** in 43-60% yields.

(a) With aqueous HCl: A solution of **7** (or **8**) (1 g), 1N HCl (5 ml) in dioxan (10 ml) was heated on a water bath for 6 h The cooled contents were poured into water (20 ml) and extracted with ether as described above for ar-turmerone to give **6** (0.31 g, 50%).

(b) With aqueous CH_3COOH: A solution of **7** (or **8**) (1 g), water (3 ml), glacial CH_3COOH (2 ml) in dioxan (10 ml) was treated as above to yield **6** (0.332 g, 53%).

(c) With aqueous pyridine: Compound **7** (1 g), water (1 ml) and pyridine (5 ml) were refluxed together for 6 h. The cooled reaction mixture poured into water (20 ml), acidified with dil. HCl and extracted with ether to afford **6** (0.270 g, 43%).

(d) With NaOH–EtOH: Compound **7** (or **8**) (1 g) and 5% aqueous NaOH (5 ml) in ethanol (15 ml), were refluxed for 6 h on a water bath. The reaction mixture was diluted with water (15 ml) and ethanol was distilled off. The cooled residue was acidified with dil. H_2SO_4 and left for 2 h for decarboxylation. The usual work up with ether afforded ar-turmerone, **6** (0.338 g, 54%).

5-(1-p-Tolylethyl)-5-(3,3-dimethylallyl) Meldrum's acid (**9**): Anhydrous potassium carbonate (0.69 g, 5 mmol) was added with stirring to a solution of **3** (2.62 g, 0.01 mol) in dry DMF (10 ml), and stirring was continued for 1 h at r.t. Then 3,3-dimethylallyl bromide (1.49 g, 1 mmol) in dry DMF (5 ml) was added dropwise with stirring and the stirring was continued for 6 h; the reaction mixture was then left overnight. The contents were poured into water (30 ml) and extracted with chloroform. The chloroform extract was successively washed with water, aqueous sodium bicarbonate, and water, and dried over anhydrous calcium chloride. Removal of solvent left the crude product, which was recrystallised from chloroform – pet. ether to give the colourless product **9** (2.6 g, 80%) m.p. 110 °C. ^{1}H NMR ($CDCl_3$): δ 0.80 (3H, s, Me of Meldrum's acid unit), 1.48 (3H, s, vinyl Me), 1.56 (3H, d, J = 6.5 Hz, sec. Me), 1.67 (6H, s, Me of Meldrum's acid unit and vinyl Me), 2.29 (3H, s, Ar–Me), 2.50–3.20 (2H, m, allylic CH_2), 3.53 (1H, q, methine H), 5.04 (1H, bt, vinylic CH), 7.10 (4H, s, Ar–H). IR (KBr): 1765, 1732, 1510 cm^{-1}. Anal. Calcd. for $C_{20}H_{26}O_4$. C, 72.72; H, 7.87. Found: C, 72.69; H, 7.89 %.

(1-p-Tolylethyl)-(3,3-dimethylallyl)malonic acid (**10**): A mixture of **9** (2 g), 10% aqueous NaOH (10 ml) and ethanol (20 ml) was refluxed for 6 h. on a water bath. Ethanol was then removed, the cooled contents were poured into cold water (30 ml), acidified with dil. HCl, and extracted with ether. The ether layer was extracted with saturated aqueous sodium bicarbonate. The combined bicarbonate washings then acidified with dil. HCl and the obtained crude solid product was recrystallised from ethanol to give colourless acid **10** (1.520 g, 86%), m.p. 120 °C. IR (KBr): 3500–3300, 1700, 1680 cm^{-1}. Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.34; H, 7.58. Found: C, 70.30; H, 7.61 %.

2-p-Tolyl-6-methylhept-5-en-3-one (**11**): A mixture of the acid **10** (1 g) and pyridine (0.38 g) in dry benzene (20 ml) was stirred at 0 °C for 15 min. Lead tetraacetate (1.85 g) was then added in three lots with stirring over 20 min. The reaction mixture was stirred for 1 h at 0 °C, 1 h at room temperature, and then refluxed for 5 h on a water bath. The cooled contents were filtered and the residue washed with dry benzene (10 ml). The filtrate was then washed successively with water, 1 N NaOH, water, 1N HCl, water and dried over anhydrous sodium sulfate. The removal of benzene under vacuum by rotary evaporator furnished a crude product which was purified by preparative TLC over silica gel (95% pet. ether + 5% ethyl acetate) to give the ketone **11** as a slightly yellow oil (0.535 g, 71%). ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, d, benzylic Me), 1.60 and 1.65 (6H, each s, two vinylic Me), 2.32 (3H, s, Ar–Me), 3.65 (2H, m, CH_2), 4.00 (1H, m, benzylic CH), 5.02 (1H, bt, vinyl CH), 7.10 (4H, s, Ar–H). IR (CCl_4): 1715, 1510 cm^{-1}. Anal. Calcd. for $C_{15}H_{20}O$: C, 83.33; H, 9.25. Found: C, 83.38; H, 9.19 %.

*Clemmensen reduction of **11**; α-curcumene* (**12**)
Amalgamated zinc was prepared by shaking a mixture of zinc wool (0.925 g), $HgCl_2$ (0.7 g), conc. HCl (0.45 ml) and water (1.25 ml) for 15 min in a three-necked flask. The supernatant liquid was decanted, and to the residue conc. HCl (0.95 ml), water (0.75 ml), toluene (0.75 ml) and ketone **11** (0.5 g) were added. The flask was fitted with a vertical condenser connected to a gas absorption trap and the mixture was refluxed vigorously for 45 h. After each 6 h interval, conc. HCl (0.25 ml) was added. After cooling, water (20 ml) was added and the whole was extracted with ether. The ether extract was washed with water, saturated aqueous sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude product which was purified by preparative TLC over silica gel (95% pet. ether + 5% ethyl acetate) to give α-curcumene, **12** (0.39 g, 85%), b.p. 140–142 °C/20mm (lit.[12,18] b.p. 125–127 °C/ 15mm). ^{1}H NMR ($CDCl_3$): δ 1.20 (3H, d, J = 7 Hz, sec Me), 1.50 and 1.65 (6H, each s, two vinylic Me), 1.40–2.00 (4H, m, CH_2CH_2), 2.30 (3H, s, Ar–Me), 2.64 (1H, sextet, benzylic CH), 5.06 (1H, bt, vinylic CH), 7.02 (4H, s, Ar–H). IR (neat): 2945, 2900, 2840, 1510, 1450 cm^{-1}. Anal. Calcd. for $C_{15}H_{22}$: C, 89.10; H, 10.89. Found: C, 89.05; H, 10.92 %.

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