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Syntheses of the Terpenoid Precursors Cyclopent-2-enone and Cyclohex-2-enone Diesters

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Summary. Two reaction pathways were elaborated for the practical and convenient synthesis of the title compounds. The first route applies a bromination-dehydrobromination sequence to introduce the double bond into 1-alkoxycarbonyl-2-oxocycloalkylacetic and propionic esters (**4a–c**, **7a, b**). The application of 2,6-lutidine for dehydrobromination of α-bromocycloalkanones diesters (**5a–c**, **8a, b**) provides sufficient selectivity to carry out this step without affecting the sensitive ester group. Alternative pathways, involving *Michael* reaction of diethyl 2-acetylsuccinate or -glutarate with acrolein and subsequent intramolecular aldol condensation, are presented in the case of cyclohex-2-enone derivatives **2a, b**.

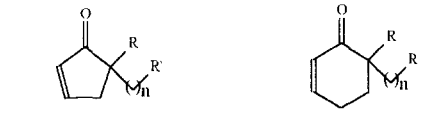
Keywords. Aldol condensation; Bromination; Cyclopent-2-enone and cyclohex-2-enone derivatives; Dehydrobromination; 2,6-Lutidine.

Zusammenfassung. Für praktische und bequeme Synthesen der Titelverbindungen werden zwei Reaktionswege präsentiert. Der erste Weg basiert auf einer Bromierungs-Dehydrobromierungs-Sequenz zur Einführung der Doppelbindung in die 1-Alkoxykarbonyl-2-oxocycloalkylessig- und -propionsäureester (**4a–c**, **7a, b**). Die Anwendung von 2,6-Lutidin zur Dehydrobromierung der α-Bromocycloalkanone-diester (**5a–c**, **8a, b**) sichert die ausreichende Selektivität, ohne die empfindlichen Estergruppen anzugreifen. Im Falle der Cyclohex-2-enon-Derivate (**2a, b**) zeigen wir einen alternativen Weg, der auf der *Michael*-Reaktion von Diethyl-2-acetyl-succinat bzw. -glutarat mit Acrolein basiert; die anschließende intramolekulare Aldol-Kondensation liefert die Zielprodukte.

Introduction

Cyclopent-2-enone and cyclohex-2-enone derivatives are valuable starting materials for the syntheses of terpenoids (*e.g.* jasmonoids [1, 2] and trichothecenes [3, 4]) and prostanoids [5]. Within our project [6] targeting an improved annulation method toward the plant germination stimulant strigol [7], we were interested in finding an efficient method for the preparation of cyclic enones **1a–c** and **2a, b** (Scheme 1).

The most straightforward methodology involves the alkylation of the cyclic β-ketoesters **3** and **6** (Scheme 2), followed by the introduction of the double bond adjacent to the keto group. This transformation generally comprises bromination



1a-d

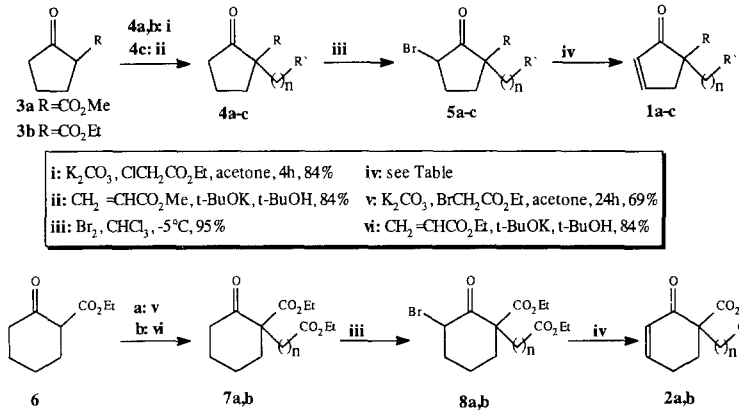
1	R	R'	n
a	CO_2Me	CO_2Et	1
b	CO_2Et	CO_2Et	1
c	CO_2Me	CO_2Me	2
d	Me	CO_2Et	0

2a,b

2	R	n
a	CO_2Et	1
b	CO_2Et	2

Scheme 1

and dehydrobromination steps, the latter usually accomplished by treating the corresponding α-bromoketone with lithium halogenide and/or lithium carbonate in *DMF* [8–10]. This method proved to be not suitable for substrates possessing sensitive ester groups, such as β-keto diesters **1a–c**. In this case the yields are low [1] or the corresponding α,β-unsaturated keto monoester is isolated as the main product [5]. Therefore we tried to find a more selective reagent for the elimination or to elaborate alternative pathways to circumvent this troublesome step.



Scheme 2

Results and Discussion

The α-bromoketones **5a–c** and **8a, b** were synthesized according to the sequence depicted in Scheme 2, starting from the readily available methyl and ethyl 2-oxocyclopentanecarboxylates (**3a, b**) and ethyl 2-oxocyclohexanecarboxylate (**6**). Alkylation of **3** and **6** was conveniently accomplished by the method of *Pollini et al.* [11] using ethyl chloro- or bromoacetate in the presence of potassium carbonate in acetone to afford the diesters **4a, b** and **7a**.

The homologous propionic esters **4c** and **7b** were prepared by *Michael* reaction of methyl and ethyl acrylate with **3a** and **6**, respectively [12, 13].

The cycloalkanone diesters **4a–c** and **7a, b** were brominated in $CHCl_3$ at −5 °C, and dehydrobromination of the resulting α-bromoketones was studied. The preparation of **1b** from the corresponding α-bromoketone with lithium bromide-lithium carbonate in *DMF* in 24% yield has been reported [1]. Our reproduction

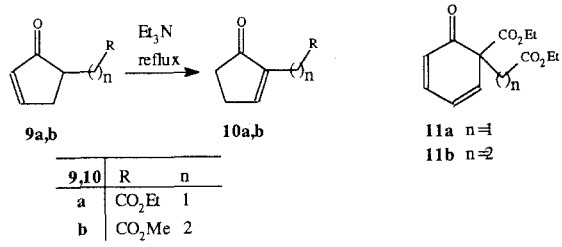
Table 1. Dehydrobromination of Cyclic α-Bromoketones **5a–c** and **8a, b**

Substrate	Method[a]	Reaction time[b] (h)	Product	Yield[c] (%)
5a	A	3	1a	7
5a	B	5.5	1a	25
5a	C	4	1a	28.7
5a	D	5	1a	25
5b	D	9	1b	61.8
5c	D	3	1c	37
8a	D	5	2a	46.5
8b	D	13	2b	53

[a] All reactions were carried out in dry solvent under the following conditions: **A**: 1.25 eq. quinoline, *o*-Cl_2–C_6H_4, 150 °C; **B**: 1.25 eq. collidine, *o*-Cl_2–C_6H_4, 150 °C; C: 1.25 eq. lutidine, *o*-Cl_2–C_6H_4, 150 °C; D: lutidine, 144 °C; [b] time required to achieve at least 95% conversion as monitored by GC; [c] isolated yields

achieved only 11% yield and application of this method to **5a, c** and **8a, b** produced complex reaction mixtures. However, in boiling quinoline **1d** was obtained in 65% yield [14]; this result prompted us to test quinoline and some related bases, *sym*-collidine [15, 16] and 2,6-lutidine, neat and in solution. For **1a–c** and **2a, b**, yields and conditions are summarized in Table 1.

Comparing the yields of **1a** under various conditions, 2,6-lutidine in *o*-dichlorobenzene proved to be the most efficient reagent. We found that the optimum temperature was about 150 °C providing a reaction time short enough to avoid excessive decomposition and sufficiently long to achieve at least 95% conversion. The boiling point of lutidine (144 °C) is close to the optimum temperature, hence the relatively inexpensive reagent proved to be an excellent solvent as well. The resulting enone **1a** was isolated by column chromatography. However, repeated fractional distillation also gave a sufficiently pure product. GC-MS analysis of the forerun of the distillation revealed the presence of monoesters **9a** [24] and **10a** [5] (Scheme 3) arising from demethoxycarbonylation and subsequent double bond migration, and a small amount of unreacted diester **4a**. The ^1H NMR spectrum of the mixture containing **9a** and **10a** showed peaks at $\delta = 7.75$, 6.14, and 7.58 ppm attributable to the olefinic protons. Transformation of this mixture to **10a** on treatment with triethylamine supported the proposed structures.



9,10	R	n
a	CO_2Et	1
b	CO_2Me	2

Scheme 3

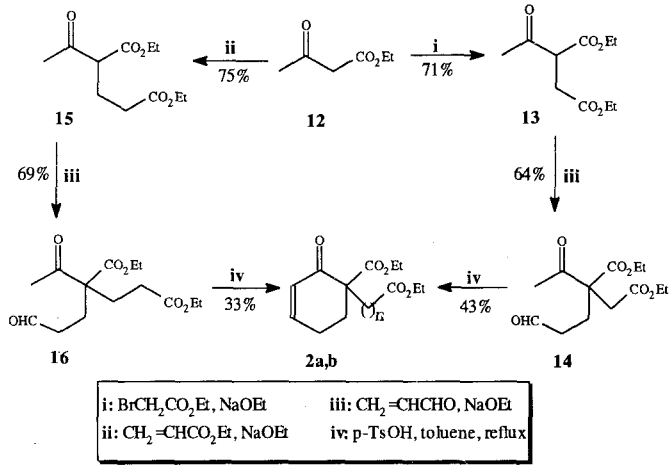
Similarly, dehydrobromination of **5c** was accomplished in refluxing lutidine in 37% yield. By-products of demethoxycarbonylation were also detected by GC analysis and isolated by fractional distillation. Again, a mixture of **9b** and **10b** [25] (^{1}H NMR: $\delta = 7.71$, 6.11 and 7.36 ppm) was readily converted to pure **10b** in the presence of triethylamine.

Upon dehydrobromination of diethyl esters **5b** and **8a, b**, desethoxycarbonylation was not significant. Yields (61.8% for **1b**, 46.6% for **2a**, and 53% for **2b**) were considerably higher than those of the analogous **1a, c**.

Although product **2b** yielded a single-peak GC chromatogram, ^{1}H NMR and ^{13}C NMR spectra proved the presence of an unexpected by-product. It showed olefinic signals at $\delta = 6.10$, 6.28, 6.43 and 7.08 ppm in the ^{1}H NMR spectrum, and 123.4, 126.5, 139.1, and 141.0 ppm in the ^{13}C NMR spectrum. These signals are characteristic for 6,6-disubstituted cyclohexa-2,4-diene-1-one systems [26–28], and the structure can be unambiguously assigned to **11b**. A similar by-product was detected on the preparation of **2a** as well. The structural assignment of the by-products **11a, b** was further confirmed by comparison of their spectral characteristics with those of the authentic samples prepared *via* allylic bromination of **2a, b** followed by dehydrobromination [29].

The isolated yields of cycloalkenone diesters **1a–c** and **2a, b** are generally higher than those obtained *via* the method with lithium carbonate in *DMF*. This is probably due to the low solubility of the formed lutidinium bromide (in lutidine), which in turn reduces the rate of dealkoxycarbonylation, since this side reaction starts with an O-alkyl cleavage induced by the nucleophilic attack of the solute bromide anion on the alkyl carbon of the ester group [5]. Furthermore, in the case of diethyl esters, the S_N2 reaction is sterically more hindered; consequently, the yields are enhanced.

In order to avoid the difficulties encountered during the elimination step, a novel three-step synthesis of **2a, b** was elaborated (Scheme 4). It starts with successive double alkylations of ethyl acetoacetate by standard methods [17–19] to afford the branched diesters **14, 16**. They were cyclized on treatment with *p*-toluenesulfonic acid in refluxing toluene, and solely the expected cyclohex-2-enone diesters **2a, b** were isolated. All intermediates were purified by distillation and showed satisfactory spectroscopic data. The combined yield of **2a, b** was somewhat increased up to 52% (based on acetyl diesters **13** and **15**) by omitting the purification of the keto aldehydes **14** and **16**.



Scheme 4

Experimental

Column chromatography: Merck Kieselgel 60 70-230 mesh; TLC: aluminium sheets coated with Kieselgel 60 F_{254}. Plates were stained with anisaldehyde solution (100 ml glacial acetic acid, 2 ml conc. sulfuric acid and 1 ml anisaldehyde) and heated at ca. 150 °C. Analytical gas chromatography: Chromatron GCHF 16.3 using a 1 m × 3 mm column packed with Chromosorb W/Silicone QF-1; 100–240 °C (24 °C/min); carrier gas: N_2; FID. GC-MS analysis: HP-5890 (capillary column 30 m × 0.32 mm coated with DB-5, 0.25 µm; temperature program: 2 min at 100 °C and 17 °C/min to 250 °C; carrier gas: He; FID) coupled with VG TRIO-2 mass spectrometer (electron ionization mode, 70 eV). IR: Specord75 IR, liquid film. ^1H and ^{13}C NMR: Perkin Elmer R12 60, Bruker AW 80, JEOL FX 100, Bruker AC 250, Varian Unity 300; $CDCl_3$; *TMS* as internal standard. Elementary analyses: Microanalytical Laboratory of EGIS Pharmaceuticals; boiling points: uncorrected. *o*-Dichlorobenzene was distilled from P_2O_5 and 2,6-lutidine from CaH_2 prior to use. Acrolein, ethyl and methyl acrylate were freshly distilled. Potassium carbonate was dried at 250 °C for 5 h.

Ethyl 1-methoxycarbonyl-2-oxocyclopent-1-ylacetate (**4a**)

To a suspension of potassium carbonate (76 g, 0.55 mol) and **3a** (71 g, 0.5 mol) in dry acetone (350 ml) ethyl chloroacetate (86.4 g, 0.7 mol) was slowly added. The mixture was refluxed for 4 h, cooled and filtered. The filtrate was concentrated and the excess reagent removed *in vacuo* (20 Torr). The residue was distilled to give a colourless oil. Yield 96.25 g (0.422 mol, 84%); b.p. 114–116 °C/0.3 Torr; $n_D^{30} = 1.4565$; IR: $\nu = 1750, 1730, 1200, 1020\,cm^{-1}$; ^1H NMR (60 MHz): $\delta = 1.18$ (t, 3H, OCH_2CH_3), 1.80–2.65 (m, 6H, ring CH_2) 2.74 (s, 2H, CH_2CO_2), 3.58 (s, 3H, OCH_3), 4.02 (q, 2H, OCH_2CH_3).

Ethyl 1-ethoxycarbonyl-2-oxocyclopent-1-ylacetate (**4b**)

Prepared as described for **4a** replacing **3a** by ethyl 2-oxocyclopentane carboxylate **3b**. Yield 85.7%; b.p. 120–124 °C/0.3 Torr (Ref. [1]: b.p. 109–110 °C/0.5 Torr); $n_D^{25} = 1.4638$; IR $\nu = 1750, 1730, 1190, 1020\,cm^{-1}$; ^1H NMR (250 MHz): $\delta = 1.30$ (t, 6H, OCH_2CH_3), 1.80–2.69 (m, 6H, ring CH_2) 2.80 and 2.97 (AB, $J_{AB} = 17$ Hz, 2H overall, CH_2CO_2), 4.13 and 4.19 (q each, 4H overall, OCH_2CH_3).

Ethyl 1-ethoxycarbonyl-2-oxocyclohex-1-ylacetate (**7a**)

A suspension of potassium carbonate (4.5 g, 32.3 mmol), ethyl 2-oxocyclohexanecarboxylate (**6**; 5 g, 29,5 mmol) and ethyl bromoacetate (6.85 g, 41.02 mmol) in dry acetone (30 ml) was refluxed for 24 h and worked up as described for **4a**. Fractional distillation afforded 5.16 g (20.2 mmol, 69%) of a colourless oil; b.p. 130–132 °C/0.4 Torr (Ref. [20]: b.p. 130–132 °C/1 Torr); $n_D^{24} = 1.4605$ (Ref. [20]: $n_D^{20} = 1.4613$); IR: $\nu = 1735, 1715, 1440, 1205, 1170\,cm^{-1}$; ^1H NMR (60 MHz): $\delta = 1.23$ (t, 6H, OCH_2CH_3) 1.40–2.60 (m, 8H, ring CH_2), 2.66 (s, 2H, CH_2CO_2), 4.20 (q, 4H, OCH_2CH_3).

Ethyl 3-(1-ethoxycarbonyl-2-oxocylohex-1-yl)propionate (**7b**)

To a solution of potassium *tert*-butoxide (0.8 g, 7 mmol) in *tert*-butanol (60 ml) β-oxoester **6** was added (19.81 g, 0.116 mol). The mixture was then treated with ethyl acrylate (12 g, 0.12 mol) dissolved in *tert*-butanol (10 ml). After stirring at room temperature for 10 h, the reaction mixture was partitioned between dil. aq. HCl (50 ml) and ether (50 ml). The aqueous phase was extracted with ether and the collected ethereal layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was distilled to furnish 26.51 g (0.0981 mol, 84%) of a colourless oil; b.p. 135–137 °C/0.1 Torr (Ref. [13]: b.p. 123–132 °C/0.12–0.22 Torr); $n_D^{24} = 1.4610$ (Ref. [13]: $n_D^{25} = 1.4622$); IR: $\nu = 1730, 1715, 1440, 1200, 1160\,cm^{-1}$; ^1H NMR (60 MHz): $\delta = 1.26$ (t, 6H, OCH_2CH_3) 1.40–2.60 (m, 12H, CH_2), 4.13 (q, 4H, OCH_2CH_3).

Methyl 3-(1-methoxycarbonyl-2-oxocyclopent-1-yl)propionate (**4c**)

Prepared in the same manner and at the same scale as above using **3a** and methyl acrylate. Yield 84%; b.p. 135–140 °C/0.2 Torr; $n_D^{25} = 1.4635$; IR: $\nu = 1750, 1730, 1435, 1185, 1150\,cm^{-1}$; ^1H NMR (60 MHz): $\delta = 1.66–2.80$ (m, 10H, CH_2), 3.65 and 3.68 (s, 3H each, OCH_3).

Bromination of Cycloalkanone Diesters **4a–c** *and* **7a, b**; *General Procedure*

A solution of diester (0.1 mol) in $CHCl_3$ (60 ml) was treated with bromine (17.58 g, 5.7 ml, 0.11 mol) at −5 °C and stirred for an hour. Then it was successively washed with sodium pyrosulfite and bicarbonate solutions, and dried over $MgSO_4$. Evaporation of the solvent gave a pale yellow oil which was used directly in the next step.

Ethyl 3-bromo-1-methoxycarbonyl-2-oxocyclopent-1-ylacetate (**5a**)

Yield 97%. An analytical sample was distilled; b.p. 146–152 °C/0.4 Torr; $n_D^{30} = 1.5021$; ^1H NMR (60 MHz): $\delta = 1.23$ (t, 3H, OCH_2CH_3), 1.80–2.90 (m, 4H, ring CH_2) 2.95 (s, 2H, CH_2CO_2), 3.70 (s, 3H, OCH_3), 4.13 (q, 2H, OCH_2CH_3), 4.55 (m, 1H, CHBr).

Ethyl 3-bromo-1-ethoxycarbonyl-2-oxocyclopent-1-ylacetate (**5b**)

Yield 95%. An analytical sample was distilled; b.p. 156–158 °C/0.2 Torr (Ref. [1]: b.p. 130–131 °C/1 Torr); $n_D^{25} = 1.5015$; ^1H NMR (250 MHz): $\delta = 1.24$ (2 × t, 6H, OCH_2CH_3), 2.05–2.88 (m, 4H, ring CH_2) 2.92–3.34 (m, 2H, CH_2CO_2), 4.15 (2 × q, 4H, OCH_2CH_3), 4.57 (m, 1H, CHBr).

Methyl 3-(3-bromo-1-methoxycarbonyl-2-oxocyclopent-1-yl)propionate (**5c**)

Yield 93%; $n_D^{25} = 1.5072$; ^1H NMR (60 MHz): $\delta = 2.0–2.80$ (m, 10H, CH_2), 3.60 and 3.70 (s, 3H each, OCH_3), 4.50 (m, 1H, CHBr).

Ethyl 3-bromo-1-ethoxycarbonyl-2-oxocyclohex-1-ylacetate (**8a**)

Yield 92%; $n_D^{21} = 1.5101$; ^1H NMR (60 MHz): $\delta = 1.25$ (t, 6H, OCH_2CH_3) 1.20–2.50 (m, 6H, ring CH_2), 2.65 (s, 2H, CH_2CO_2), 4.10 (q, 4H, OCH_2CH_3), 5.10 (m, 1H, CHBr).

Ethyl 3-(3-bromo-1-ethoxycarbonyl-2-oxocyclohex-1-yl)propionate (**8b**)

Yield 98.8%; $n_D^{24} = 1.5035$; ^1H NMR (60 MHz): $\delta = 1.26$ (t, 6H, OCH_2CH_3) 1.40–2.80 (m, 10H, CH_2), 4.15 (q, 4H, OCH_2CH_3), 4.88 (m, 1H, CHBr).

Dehydrobromination of **5a** *with various bases*

α-Bromoketone **5a** (2.26 g, 10 mmol) was dissolved in dry *o*-dichlorobenzene (25 ml) under nitrogen. The base (see Table 1 entries 1–3) was then added and the solution was stirred and heated. The progress of the elimination was monitored by GC analysis. After completion, the reaction mixture was cooled, poured into ether and washed with 5% aq. HCl and sodium bicarbonate solution. Drying over $MgSO_4$ and concentrating at reduced pressure afforded a dark oil which was purified by column chromatography (eluent hexane-ethyl acetate (7:3 v/v), $R_f = 0.36$). The results are summarized in the Table 1 (entries 1–3).

Dehydrobromination of α-Bromoketones **5a–c** *and* **7a, b** *in 2,6-Lutidine. General Procedure*

A solution of α-bromoketone (0.1 mol) in lutidine (120 ml) was refluxed with mechanical stirring. The progress of the reaction was checked by GC analysis. The thick suspension was cooled, lutidinium bromide was filtered and lutidine evaporated at reduced pressure (the solvent was recycled by drying over sodium hydroxide and distilling from CaH_2). The residue was taken up in ether and filtered through a short plug of silica gel to remove the most of the tarry materials. Evaporation of ether yielded a brown oil which was fractionated using a *Vigreux* column.

Ethyl 1-methoxycarbonyl-2-oxocyclopent-3-en-1-ylacetate (**1a**)

The fraction boiling at 84–94 °C/0.1 Torr (0.95 g) was a mixture of **9a** (43%), **10a** (43%), **1a** (10%), and **4a** (4%) according to GC analysis. ^{1}H NMR (60 MHz): $\delta = 6.14$ (dm), 7.58 (m), 7.55 (dm). The fraction collected between 94–104 °C/0.1 Torr (2.10 g) was analyzed by GC-MS. The GC showed the presence of **9a** (25.4%, M^+ 168), **10a** (32.5%, M^+ 168), **4a** (14.1%, M^+ 228), and **1a** (28%, M^+ 226). The fraction boiling at 104–120 °C/0.1 Torr (7.70 g, ca. 84% pure by GC) was redistilled to yield 5.63 g (0.0249 mol, 24.9%) of pure **1a**; b.p. 112–114/0.1 Torr; $n_D^{21} = 1.4754$; IR: $\nu = 3040$, 1730, 1705, 1595, 1430, 1190, 1160, 1020 cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 1.25$ (t, 3H, OCH_2CH_3), 2.58 and 3.22 (AB, $J_{AB} = 17$ Hz, 1H each, CH_2CO_2), 2.77 and 3.49 (ddd, $J = 19$, 3, 2 Hz, 1H each, 5-H), 3.70 (s, 3H, OCH_3), 4.14 (q, 2H, OCH_2CH_3), 6.19 (dt, $J = 6$, 2 Hz, 1H, 3-H), 7.84 (dt, $J = 6$, 3 Hz, 1H, 4-H); ^{13}C NMR (75 MHz): $\delta = 14.0$ (CH_3CH_2O), 38.4 (CH_2CO_2), 40.3 (C-5), 52.6 (OCH_3), 55.4 (C-1), 60.8 (CH_3CH_2O), 131.2 (C-3), 164.6 (C-4), 169.8 and 170.6 (CO esters), 203.6 (C-2); $C_{11}H_{14}O_5$ (226.23); calcd.: C 58.40, H 6.24; found: C 58.27, H 6.23.

Ethyl 1-ethoxycarbonyl-2-oxocyclopent-3-en-1-ylacetate (**1b**)

Yield 61.8%; b.p. 116–118/0.1 Torr (Ref. [1]: b.p. 104–106 °C/0.5 Torr); $n_D^{25} = 1.4765$; IR: $\nu = 3060$, 1740, 1710, 1590, 1345, 1210, 1180 cm^{-1}; ^{1}H NMR (250 MHz): $\delta = 1.22$ and 1.25 (t each, 6H overall, OCH_2CH_3), 2.57 and 3.22 (AB, $J_{AB} = 17$ Hz, 1H each, CH_2CO_2), 2.78 and 3.49 (dt, $J = 19.5$, 2.4 Hz, 1H each, 5-H), 4.14 (m, 4H, OCH_2CH_3), 6.20 (dt, $J = 5.5$, 2.2 Hz, 1H, 3-H), 7.85 (dt, $J = 5.5$, 2.7 Hz, 1H, 4-H); ^{13}C NMR (62.5 MHz): $\delta = 13.7$, 13.9 (CH_3CH_2O), 38.2 (CH_2CO_2), 40.3 (C-5), 55.4 (C-1), 60.6, 61.7 (CH_3CH_2O), 131.1 (C-3), 164.6 (C-4), 169.0 and 170.6 (CO esters), 203.7 (C-2).

Methyl 3-(1-methoxycarbonyl-2-oxocyclopent-3-en-1-yl)propionate (**1c**)

The fraction boiling at 85–100 °C/0.1 Torr weighed 2.50 g; the ^{1}H NMR spectrum showed a 65:35 mixture of **10b** and **9b**. ^{1}H NMR (80 MHz): $\delta = 6.11$ (dm), 7.35 (m), 7.71 (dm). The fraction boiling at 100–116 °C/0.1 Torr (0.64 g) was a mixture of **9b**, **10b**, **1c**, and **4c** according to GC analysis. The fraction collected between 116–120 °C/0.1 Torr gave 8.34 g (0.0369 mol, 36.9%) of pure **1c**; $n_D^{26} = 1.4820$; IR: $\nu = 3040$, 1730, 1705, 1600, 1430, 1195, 1170 cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 2.2$–2.5 (m, 4H, $CH_2CH_2CO_2$), 2.62 and 3.26 (ddd, $J = 19$, 3, 2 Hz, 1H each, 5-H), 3.66 and 3.72 (s, 3H each, OCH_3), 6.19 (dt, $J = 6$, 2 Hz, 1H, 3-H), 7.79 (dt, $J = 6$, 3 Hz, 1H, 4-H); ^{13}C NMR (75 MHz): $\delta = 29.2$ and 29.3 ($CH_2CH_2CO_2$), 39.6 (C-5), 51.6 and 52.7 (OCH_3), 56.7 (C-1), 132.0 (C-3), 163.5 (C-4), 173.0 and 170.6 (CO esters), 204.8 (C-2); $C_{11}H_{14}O_5$ (226.23); calcd.: C 58.40, H 6.24; found: C 58.22, H 6.15.

Ethyl 1-ethoxycarbonyl-2-oxocyclohex-3-en-1-ylacetate (**2a**)

Yield 46.5%; b.p. 120–126 °C/0.1 Torr; $n_D^{22} = 1.4848$; IR: $\nu = 3020$, 1740, 1680, 1645, 1200, 1175 cm^{-1}; ^{1}H NMR (100 MHz): $\delta = 1.25$ (t, 6H, OCH_2CH_3), 2.20–2.60 (m, 4H, ring CH_2), 2.81 (s, 2H, CH_2CO_2), 4.12 and 4.20 (q, 2H each, OCH_2CH_3), 6.05 (dm, $J = 10$ Hz, 1H, 3-H), 6.92 (dm, $J = 10$ Hz, 1H, 4-H); ^{13}C NMR (25 MHz): $\delta = 13.7$ (CH_3CH_2O), 23.4 (C-5), 30.7 (C-6), 38.4 (CH_2CO_2), 54.8 (C-1), 61.6 and

60.2 (CH_3CH_2O), 128.4 (C-3), 149.3 (C-4), 170.1 and 170.4 (CO esters), 194.3 (C-2). NMR spectra showed a 83:17 mixture of **2a** and **11a**. MS: m/z (%) = 254 (1.2) [M^+], 79 (36.7), 77 (24.6), 68 (100), 53 (20.9), 43 (39.1), 41 (21.1), 40 (32.7), 39 (60.2).

Ethyl 3-(1-ethoxycarbonyl-2-oxocyclohex-3-en-1-yl)propionate (**2b**)

Yield 53%; b.p. 137–140 °C/0.1 Torr; $n_D^{24} = 1.4810$. An analytical sample was purified by column chromatography (eluent hexane : ethyl acetate (7:3 v/v), $R_f = 0.46$). IR: $\nu = 3020, 1740, 1680, 1645, 1450, 1240, 1180\,cm^{-1}$; ^1H NMR (250 MHz): $\delta = 1.25$ (t, 6H, $OCH_2\mathbf{CH_3}$), 1.80–2.70 (m, 8H, CH_2), 4.15 (q, 4H, $\mathbf{OCH_2}CH_3$). 6.05 (dm, $J = 10$ Hz, 1H, H-3), 6.92 (dm, $J = 10$ Hz, 1H, 4-H); ^{13}C NMR (25 MHz): $\delta = 13.9$ and 14.0 ($\mathbf{CH_3}CH_2O$), 23.4 (C-5), 28.4, 29.6 ($\mathbf{CH_2}CH_2CO_2$), 30.4 (C-6), 55.9 (C-1), 60.3 and 61.2 ($CH_3\mathbf{CH_2}O$), 128.9 (C-3), 149.0 (C-4) 172.1 and 172.8 (CO esters), 195.7 (C-2). NMR spectra showed a 85:15 mixture of **2b** and **11b**.

Ethyl 5-oxocyclopent-1-enylacetate (**10a**)

A ca. 1:1 mixture of **9a** and **10a** (3.04 g) and triethylamine (5 ml) in ethanol (25 ml) was refluxed for 24 h. Solvent and triethylamine were evaporated and distillation of the residue gave 2.5 g (82.2%) of a colourless oil; b.p. 80–84 °C/0.2 Torr (Ref. [5]: b.p. 70–71 °C/0.12 Torr); $n_D^{24} = 1.4745$; IR: $\nu = 1735, 1705, 1645, 1260, 1165, 1025, 785\,cm^{-1}$; ^1H NMR (80 MHz): $\delta = 1.23$ (t, 3H, $OCH_2\mathbf{CH_3}$), 2.36 and 2.61 (m, 2H each, ring CH_2), 3.11 (broad s, 2H, CH_2CO_2), 4.10 (q, 2H, $\mathbf{OCH_2}CH_3$), 7.58 (m, 1H, 2-H); ^{13}C NMR (25 MHz): $\delta = 13.1$ ($\mathbf{CH_3}CH_2O$), 25.8, 29.3, 32.9 (CH_2), 59.7 ($CH_3\mathbf{CH_2}O$), 138.2 (C-1), 159.0 (C-2), 169.1 (CO ester), 206.4 (C-5).

Methyl 3-(5-oxocyclopent-1-enyl)propionate (**10b**)

A 35:65 mixture of **9b** and **10b** (2.57 g) and triethylamine (5 ml) in methanol (25 ml) was refluxed for 24 h. Concentration and distillation *in vacuo* afforded a pale yellow oil. Yield 2 g (77.8%); b.p. 74–76 °C/0.1 Torr; $n_D^{24} = 1.4795$; IR: $\nu = 1735, 1705, 1635, 1435, 1245, 1190, 795\,cm^{-1}$; ^1H NMR (80 MHz): $\delta = 2.25$–2.68 (m, 8H, CH_2), 3.65 (s, 3H, OCH_3), 7.35 (broad s, 1H, 2-H); ^{13}C NMR (25 MHz): $\delta = 20.6, 26.5, 32.1, 34.5$ (CH_2), 51.5 (OCH_3), 144.7 (C-1), 157.8 (C-2), 173.1 (CO ester), 208.8 (C-5).

Ethyl 1-ethoxycarbonyl-6-oxocyclohexa-2,4-diene-1-ylacetate (**11a**)

A suspension of **2a** (2.02 g, 7.95 mmol) and N-bromosuccinimide (1.69 g, 9.53 mmol) in CCl_4 (80 ml) was heated with a 150 W infralamp for 3 h. The supernatant succinimide was filtered and the solvent evaporated at reduced pressure. The residue was purified by column chromatography (eluent hexane-ethyl acetate (4:1 v/v)) to give ethyl 1-ethoxycarbonyl-5-bromo-2-oxocyclohex-3-en-1-ylacetate (1.14 g 3.4 mmol) in 43% yield. IR: $\nu = 3030, 1740, 1705, 1635, 1395, 1220, 1190, 1035, 845\,cm^{-1}$; ^1H NMR (80 MHz): $\delta = 1.23$ (t, 6H, $OCH_2\mathbf{CH_3}$), 2.45–3.26 (m, 4H, CH_2), 4.06 and 4.20 (q, 2H each, $\mathbf{OCH_2}CH_3$), 5.20 (m, 1H, CHBr), 5.95 (dd, $J = 10$, 2.5 Hz, 1H, 3-H), 6.96 (dm, $J = 10$ Hz, 1H, 4-H); ^{13}C NMR (25 MHz): $\delta = 13.6, 13.8$ ($\mathbf{CH_3}CH_2O$), 38.5 ($\mathbf{CH_2}CO_2$), 41.2 (CHBr), 41.3 (C-6), 56.7 (C-1), 60.5, 61.8 ($CH_3\mathbf{CH_2}O$), 127.9 (C-3), 148.8 (C-4), 169.6 and 169.0 (CO esters), 191.4 (C-2).

The bromo compound (0.73 g, 2.2 mmol) was refluxed in lutidine (5 ml) for 2.5 h under nitrogen. Then the resulting suspension was filtered and lutidine was evaporated *in vacuo*. The residue was purified by column chromatography (eluent hexane-ethyl acetate (7:3 v/v)) to furnish the requested cyclohexadienone **11a** (0.16 g, 0.635 mmol) in 28.8% yield. IR: $\nu = 3030, 1730, 1670, 1635, 1560, 1210, 1190, 850\,cm^{-1}$; ^1H NMR (300 MHz): $\delta = 1.20$ (t, 6H, $OCH_2\mathbf{CH_3}$), 3.16 and 3.26 (AB, $J_{AB} = 16$ Hz, 2H, $\mathbf{CH_2}CO_2Et$), 4.35 and 4.65 (q, 2H each, $\mathbf{OCH_2}CH_3$), 6.16 (d, $J = 9.8$ Hz, 1H), 6.40 (m, 2H), 7.06 (ddd, $J = 9.8$ Hz, 1H); ^{13}C NMR (25 MHz) δ: 13.7, 13.9 ($\mathbf{CH_3}CH_2O$), 40.8 ($\mathbf{CH_2}CO_2$), 59.7 (C-1), 123.5 (C-3), 126.4 (C-5), 138.4 (C-4), 140.6 (C-2), 169.6 and 167.3 (CO esters), 196.2 (C-6); $C_{13}H_{16}O_5$ (252.27); calcd.: C 61.90, H 6.39; found: C 61.72, H 6.41.

Ethyl 3-(1-ethoxycarbonyl-6-oxocyclohexa-2,4-diene-1-yl)propionate (**11b**)

Prepared in the same manner and at the same scale as described for **11a**. The allylic bromination afforded ethyl 3-(1-ethoxycarbonyl-5-bromo-2-oxocyclohex-3-en-1-yl)propionate in 40.5% yield. IR: $\nu = 3040, 1735, 1700, 1620, 1380, 1240, 1180, 1020\,cm^{-1}$; ^1H NMR (100 MHz): $\delta = 1.25$ and 1.22 (t, 3H each, $OCH_2\mathbf{CH_3}$), 2.0–2.60 (m, 5H), 3.06 (m, 1H), 4.08 and 4.20 (q, 2H each, $\mathbf{OCH_2}CH_3$), 5.08 (m, 1H, CHBr), 5.97 (dm, $J = 10$ Hz, 3-H, 1H), 6.92 (dm, $J = 10$ Hz, 1H, 4-H); ^{13}C NMR (25 MHz): $\delta = 13.7$, 14.0 ($\mathbf{CH_3}CH_2O$), 29.1, 29.2 ($\mathbf{CH_2}CH_2CO_2$), 41.1 (CHBr), 41.5 (C-6), 57.9 (C-1), 60.2, 61.7 ($CH_3\mathbf{CH_2}O$), 128.7 (C-3), 148.1 (C-4), 169.6 and 172.1 (CO esters), 192.6 (C-2).

The bromo compound was refluxed in lutidine for 3 h and the requested dienone **11b** was isolated after column cromatography (eluent hexane-ethyl acetate (7:3 v/v)) in 28% yield. IR: $\nu = 3030, 1735, 1670, 1640, 1220, 1180\,cm^{-1}$; ^1H NMR (250 MHz): $\delta = 1.17, 1.25$ (t, 3H each, $OCH_2\mathbf{CH_3}$), 2.20 (m, 2H), 2.34 (m, 1H), 2.56 (m, 1H), 4.12, 4.18 (q, 2H each, $\mathbf{OCH_2}CH_3$), 6.10 (d, $J = 10$ Hz, 1H, 5-H), 6.28 (dd, $J = 9$, 1.5 Hz, 1H, 2-H), 6.43 (dd, $J = 9$, 6 Hz, 1H, 3-H), 7.08 (ddd, $J = 10$, 5, 1.5 Hz, 1H, 4-H); ^{13}C NMR (25 MHz): $\delta = 14.0, 13.7$ ($\mathbf{CH_3}CH_2O$), 28.9 ($\mathbf{CH_2}CH_2CO_2$), 31.4 ($CH_2\mathbf{CH_2}CO_2$), 60.2 (C-1), 61.8, 61.9 ($CH_3\mathbf{CH_2}O$), 123.4 (C-3), 126.5 (C-5), 139.1 (C-4), 141.0 (C-2), 168.4 and 172.2 (CO esters), 197.2 (C-6). $C_{14}H_{18}O_5$ (266.29): calcd. C 63.15, H 6.81; found C 63.26, H 6.71.

Diethyl 2-acetylsuccinate (**13**)

Prepared at a 1 mol scale according to the procedure of *Adkins* [17]. Yield 71%; b.p. 140–146 °C/13 Torr (Ref. [21]: b.p. 140–142 °C/14 Torr); $n_D^{26} = 1.4325$ (Ref. [22]: $n_D^{16} = 1.438$); ^1H NMR (60 MHz): $\delta = 1.25$ (t, 6H, $OCH_2\mathbf{CH_3}$), 2.30 (s, 3H, CH_3CO), 2.85 (s, 2H, CH_2CO_2), 3.95 (t, 1H, $CHCO_2$), 4.13 (q, 4H, $\mathbf{OCH_2}CH_3$).

Diethyl 2-acetylglutarate (**15**)

Prepared at a 1 mol scale according to the method of *Korte* and *Machleidt* [18]. Yield 75%; b.p. 120–122 °C/0.5 Torr (Ref. [18]: b.p. 92–95 °C/0.05 Torr); $n_D^{22} = 1.4386$ (Ref. [23]: $n_D^{19} = 1.4420$); ^1H NMR (60 MHz): $\delta = 1.25$ (t, 6H, $OCH_2\mathbf{CH_3}$), 1.90–2.40 (m, 4H, $CH_2CH_2CO_2$), 2.20 (s, 3H, CH_3CO), 3.50 (t, 1H, $CHCO_2$), 4.10 (q, 4H, $\mathbf{OCH_2}CH_3$).

Diethyl 2-acetyl-2-(2-formylethyl)succinate (**14**)

To a solution of sodium ethoxide (prepared by dissolution of sodium (0.14 g, 6 mgatom) in dry ethanol (150 ml)) 2-acetylsuccinate (**13**; 30.6 g, 0.142 mol) was added. The mixture was cooled to 0 °C and acrolein (8.5 g, 0.153 mol) was slowly added. After stirring for 7 h at room temperature, GC analysis showed the consumption of the starting material. Usual aqueous workup gave the crude product which was purified by distillation. According to GC analysis, the distillate contained *ca.* 5% cyclized enone **2a**. Yield 24.5 g (90 mmol, 64%); b.p. 140–145 °C/0.4 Torr; $n_D^{26} = 1.4525$; IR: $\nu = 2720, 1730, 1715, 1200, 1170\,cm^{-1}$; ^1H NMR (100 MHz): $\delta = 1.04$ and 1.07 (t, 3H each, $OCH_2\mathbf{CH_3}$), 2.05 (s, 3H, CH_3CO), 2.16 and 2.45 (m, 2H each, $\mathbf{CH_2}CH_2CHO$), 2.68 (s, 2H, CH_2CO_2), 3.90 and 4.01 (q, 4H, $\mathbf{OCH_2}CH_3$), 9.51 (s, 1H, CHO); ^{13}C NMR (25 MHz): $\delta = 13.6$ and 13.7 ($\mathbf{CH_3}CH_2O$), 26.5 ($\mathbf{CH_3}CO$), 24.7 ($\mathbf{CH_2}CH_2CHO$), 37.0 and 38.5 ($\mathbf{CH_2}CHO$ and $\mathbf{CH_2}CO_2$), 59.9 (C_{quat}), 61.5 and 60.5 ($CH_3\mathbf{CH_2}O$), 170.5 and 170.1 (CO esters), 199.9 (CHO), 203.3 (CO ketone); MS: m/z (%) = 272 (5.7) [M^+], 184 (11.2), 174 (14.9), 141 (27.7), 140 (20.2), 128 (22.4), 113 (16.4), 83 (22.3), 43 (100).

Diethyl 2-acetyl-2-(2-formylethyl)glutarate (**16**)

Prepared at a 50 mmol scale in the same manner as described for **14**. Yield 69%; b.p. 150–152 °C/0.5 Torr; $n_D^{20} = 1.4632$; IR: $\nu = 2730, 1735, 1715, 1200, 1175\,cm^{-1}$; ^1H NMR (100 MHz): $\delta = 1.22, 1.35$ (t,

3H each, OCH_2CH_3), 2.16 (s, 3H, CH_3CO), 1.80–2.54 (m, 8H), 4.10, 4.20 (q, 2H each, OCH_2CH_3), 9.71 (s, 1H, CHO); ^{13}C NMR (25 MHz): $\delta = 13.6$ and 13.7 (CH_3CH_2O), 26.3 (CH_3CO), 23.6, 26.8, 28.3, 38.4 (CH_2), 60.2 (C_{quat}), 61.5 and 61.2 (CH_3CH_2O), 170.2 and 171.1 (CO esters), 199.7 (CHO), 203.7 (CO ketone).

General Procedure for the Cyclization of Diethyl 2-Acetyl-2-(2-formylethyl)-carboxylates **14** and **16**

A mixture of keto aldehyde (0.13 mol) and *p*-toluene-sulfonic acid (1 g) in toluene (300 ml) was refluxed for 2 h with continuous removal of water. Then the reaction mixture was washed with sodium bicarbonate solution and brine. Drying over $MgSO_4$ and evaporation of the solvent afforded the crude product which was purified by distillation. **2a**: Yield 43%; b.p. 122–126 °C/0.1 Torr; $n_D^{21} = 1.4841$; $C_{13}H_{18}O_5$ (254.28); calcd.: C 61.42, H 7.13; found: C 61.55, H 7.05. **2b**: Yield 33%; b.p. 138–140 °C/0.1 Torr; $n_D^{22} = 1.4852$; $C_{14}H_{20}O_5$ (268.31); calcd.: C 62.67, H 7.51; found: C 62.85, H 7.60. All spectral data were identical with those of the compounds synthesized *via* the bromination-dehydrobromination route.

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