Synthesis of Methyl 3-(4-Methyl-3-oxo-1-cyclohexenyl)-butanoate

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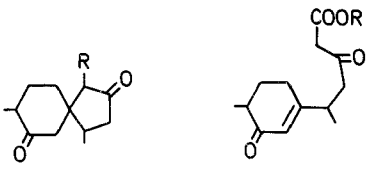
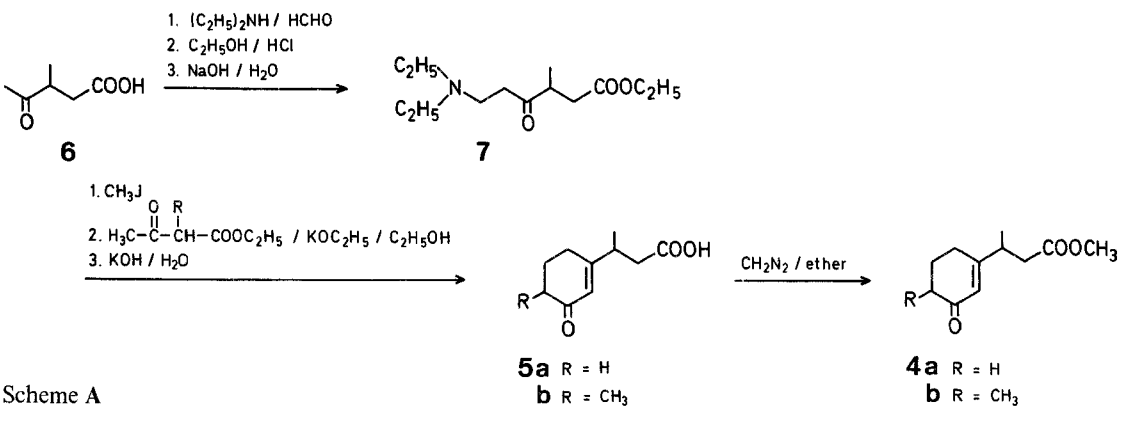
In a projected synthesis of acorone (**1**)[1], isolated from sweet flag oil, we envisioned[2] an intramolecular Michael reaction of the unsaturated β-keto-ester **2** to construct the spiro-[4.5]decane system **3**.



1 R = *i*-C_3H_7
3 R = $COOC_2H_5$ **2**

The synthesis of acorone could not be completed due to some difficulties at the final stage. In view of a recent publication of Pinder et al.[3] on an attempted synthesis of acorone (**1**) on essentially similar lines, we are prompted to report our alternative synthesis of the title compound **4b** (Scheme A), the precursor of the β-ketoester **2**. This constitutes the complementary information without duplication of the report by Pinder[3].

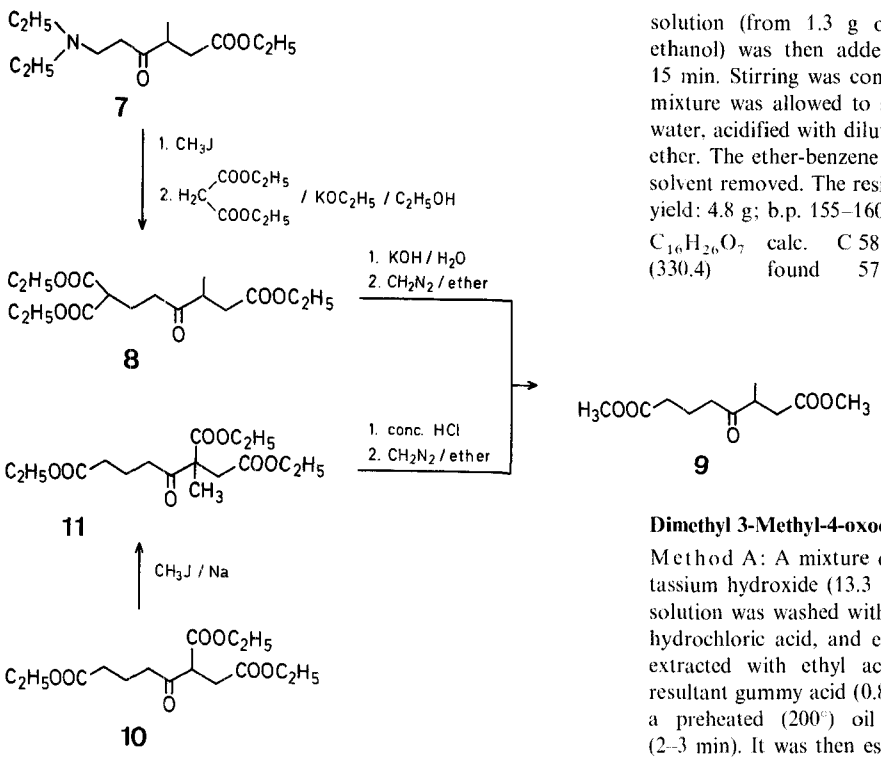


Scheme A

β-Methyllevulinic acid (**6**) was treated with diethylamine hydrochloride and paraformaldehyde to give the corresponding Mannich base hydrochloride which was converted into the aminoketoester **7** by esterification and subsequent basification. Since there are two reactive positions adjacent to the carbonyl group in β-methyllevulinic acid, the structure of the compound **7** was proved as follows (Scheme **B**).

The Mannich base **7** was converted into the methiodide and then condensed with diethyl malonate to give the keto-triester **8**. Hydrolysis/decarboxylation of **8** followed by esterification with diazomethane gave dimethyl 3-methyl-4-oxooctanedioate (**9**). Diester **9** was unambiguously synthesized from triester **10** via methylation, hydrolysis/decarboxylation, and esterification.

The methiodide prepared from the base **7** was condensed with ethyl α-methylacetoacetate in the presence of potassium ethoxide. The resultant product on treatment with 10% aqueous sodium hydroxide underwent simultaneous cyclization, hydrolysis, and decarboxylation to give the unsatur-



Scheme **B**

ated ketoacid **5b** which was esterified with diazomethane to give the unsaturated ketoester **4b**. Similar condensation of the methiodide of **7** with ethyl acetoacetate gave ester **4a** (Scheme A)[8].

β-Methyllevulinic Acid (6):
Condensation of ethyl acetoacetate with ethyl chloroacetate in the presence of sodium, instead of sodium ethoxide as reported earlier[4], yielded ethyl acetylsuccinate in better yield (74%). The latter on methylation followed by acid hydrolysis gave the acid **6** according to the reported procedures[5].

Ethyl 6-Diethylamino-3-methyl-4-oxohexanoate (7):
A mixture of β-methyllevulinic acid (49 g) and diethylamine hydrochloride (45 g) was heated on a steam bath for 15 min. To this solution was added paraformaldehyde (23 g) and heating was continued for 30 min. The resultant homogeneous viscous mass was heated under diminished pressure to remove the water formed during the reaction. The gummy Mannich base hydrochloride was esterified by refluxing with 5% ethanolic hydrogen chloride (150 ml) for 6 hr. The ethanol was removed and the residue was dissolved in water (45 ml). The solution was made alkaline by the cautious addition of 40% aqueous sodium hydroxide under cooling in ice. It was then saturated with potassium carbonate and repeatedly extracted with ether. The combined ether extract was washed with brine and the solvent removed. The yellow liquid was distilled. The fraction having b.p. 110–112°/15 torr (28 g, 31%) was collected and redistilled. The yield of this fraction was not consistent, presumably due to thermal decomposition, and a considerable amount of the product was found to polymerize on standing.

$C_{13}H_{25}O_3N$	calc.	C 64.19	H 10.29	N 5.76
(243.3)	found	64.41	10.64	6.1

Triethyl 2-Methyl-3-oxohexane-1,6,6-tricarboxylate (8):
A mixture of Mannich base **7** (6.5 g) and methyl iodide (2.5 ml) was allowed to stand at room temperature overnight. The resultant crystalline methiodide was isolated by filtration and washed with dry ether to remove excess methyl iodide. To the methiodide was added a cold solution of diethyl malonate (4.8 g) in benzene (15 ml) under nitrogen. Potassium ethoxide solution (from 1.3 g of potassium and 20 ml of absolute ethanol) was then added to the mixture with stirring within 15 min. Stirring was continued for a further 2 hr. The reaction mixture was allowed to stand overnight, then poured into cold water, acidified with dilute hydrochloric acid, and extracted with ether. The ether-benzene extract was washed with brine and the solvent removed. The residue distilled with slight decomposition; yield: 4.8 g; b.p. 155–160°/0.5 torr.

$C_{16}H_{26}O_7$	calc.	C 58.18	H 7.87
(330.4)	found	57.98	7.78

Dimethyl 3-Methyl-4-oxooctanedioate (9):
Method A: A mixture of triester **8** (2 g) and 10% aqueous potassium hydroxide (13.3 ml) was refluxed for 8 hr. The alkaline solution was washed with ether, acidified in the cold with dilute hydrochloric acid, and evaporated to dryness. The residue was extracted with ethyl acetate and the solvent removed. The resultant gummy acid (0.8 g) was decarboxylated by keeping it in a preheated (200°) oil bath until the effervescence ceased (2–3 min). It was then esterified with diazomethane in the usual way. The product was purified by repeated short-path distillation; yield: 0.5 g; b.p. 118–120°/1.5 torr; n_D^{25}: 1.4525.

$C_{11}H_{18}O_5$	calc.	C 57.4	H 7.82
(240.3)	found	57.71	7.89

Method B: A mixture of triester **8** (3 g) and conc. hydrochloric acid (18 ml) was refluxed for 20 hr. The hydrochloric acid was removed under reduced pressure and the gummy residue was treated with diazomethane in ether to give diester **9**; yield: 0.8 g; b.p. 118–120°/1.5 torr.

Triethyl 2-Methyl-3-oxohexane-1,2,6-tricarboxylate (11):
Triethyl 3-Oxohexane-1,2,6-tricarboxylate (**10**) was prepared from diethyl 3-oxoheptanedioate[6] following the procedure of Loewenthal[7].

Triethyl 2-Methyl-3-oxohexane-1,2,6-tricarboxylate (**11**): Triester **10** (4.7 g) was added with stirring to powdered sodium (0.4 g) in cold dry benzene (25) and the mixture was allowed to stand overnight. To the sodium salt thus formed, methyl iodide (5 g) was added and the mixture was refluxed for 8 hr. Water was then added and the reaction mixture extracted with ether. The ether solution was washed with sodium chloride solution, the solvent removed, and the residue distilled in vacuo; yield: 3.5 g; b.p. 161–164°/1 torr; $n_D^{28.5}$: 1.447.

$C_{16}H_{26}O_7$	calc.	C 58.18	H 7.87
(330.4)	found	57.88	7.69

Dimethyl 3-Methyl-4-oxooctanedioate (9):
A mixture of triester **11** (3 g) and conc. hydrochloric acid (18 ml) was refluxed for 20 hr. The hydrochloric acid was then removed under reduced pressure and the residue treated with ethereal diazomethane to give diester **9**; yield: 0.8 g; b.p. 120–122°/2 torr; n_D^{27}: 1.4453.

$C_{11}H_{18}O_5$	calc.	C 57.4	H 7.82
(240.3)	found	57.74	8.21

The I.R. spectrum was identical with that of compound **9** obtained from **8**.

3-(4-Methyl-3-oxocyclohexen-1-yl)-butanoic Acid (5b):
To the methiodide of the base **7**, prepared as described above from **7** (8.5 g) and methyl iodide (6.5 g), was added a solution of ethyl α-methylacetoacetate (5.7 g) in benzene (15 ml) under nitrogen. Ethanolic potassium ethoxide (from 2.4 g of potassium and 35 ml of dry ethanol) was then added during 10 min with stirring and cooling and stirring was continued for 1 hr. The

mixture was allowed to stand overnight. It was then refluxed for 3 hr, poured into cold water (200 ml), acidified with hydrochloric acid, saturated with ammonium chloride, and extracted with ether. The ethereal extract was washed with sodium chloride solution containing a little sodium thiosulfate and the solvent was removed. Excess ethyl α-methylacetoacetate was removed under diminished pressure and the residue was refluxed with 10% aqueous potassium hydroxide (90 ml) for 3 hr under nitrogen. The alkaline solution was washed with ether, acidified in the cold with dilute hydrochloric acid, saturated with ammonium chloride, and extracted with ether. The ethereal extract was washed with sodium chloride solution and the solvent removed. The residue was subjected to short-path distillation; yield: 2.8 g (41%); b.p. 130–135°/0.002 torr.

$C_{11}H_{16}O_3$	calc.	C 67.35	H 8.15
(196.2)	found	67.57	8.21

I.R. (CCl_4): $\nu_{max} = 1770, 1709, 1667\ cm^{-1}$.

U.V. (C_2H_5OH): $\lambda_{max} = 238$ nm ($\log \varepsilon = 3.98$).

Methyl 3-(4-Methyl-3-oxocyclohexen-1-yl)-butanoate (4b):
The foregoing acid (**5**; 2.8 g) was treated with diazomethane in ether and left in ice for 10 min and worked up to give ester **4b**; yield: 1.4 g; b.p. 121–123°/1 torr; n_D^{30}: 1.4826.

$C_{12}H_{18}O_3$	calc.	C 68.57	H 8.55
(210.3)	found	68.58	8.66

I.R. (CCl_4): $\nu_{max} = 1727, 1667, 1623\ cm^{-1}$.
U.V. (C_2H_5OH): $\lambda_{max} = 233$ nm ($\log \varepsilon = 4.12$).

3-(3-Oxocyclohexen-1-yl)-butanoic Acid (5a):
The acid was prepared by the procedure employed in the preparation of acid **4b** using the base **7** (8.5 g), methyl iodide (6.5 g), ethyl acetoacetate (4.5 g) in benzene (15 ml), and potassium ethoxide (from 2.1 g of potassium and 30 ml of ethanol). The product was obtained by short-path distillation; yield: 2.8 g (44%); b.p. 130–135°/0.002 torr; n_D^{26}: 1.4870.

$C_{10}H_{14}O_3$	calc.	C 65.94	H 7.69
(182.2)	found	65.85	8.04

I.R. (CCl_4): $\nu_{max} = 1770, 1709, 1667\ cm^{-1}$.

U.V. (C_2H_5OH): $\lambda_{max} = 236$ nm ($\log \varepsilon = 3.9$).

Methyl 3-(3-Oxocyclohexen-1-yl)-butanoate (4a):
Acid **5a** was esterified with ethereal diazomethane. Care was taken to keep the acid in contact with diazomethane only for 10 min. The product distilled at b.p. 130–132°/1.5 torr; n_D^{26}: 1.4870.

$C_{11}H_{16}O_3$	calc.	C 67.35	H 8.16
(196.2)	found	67.61	8.21

Received: December 28, 1972

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