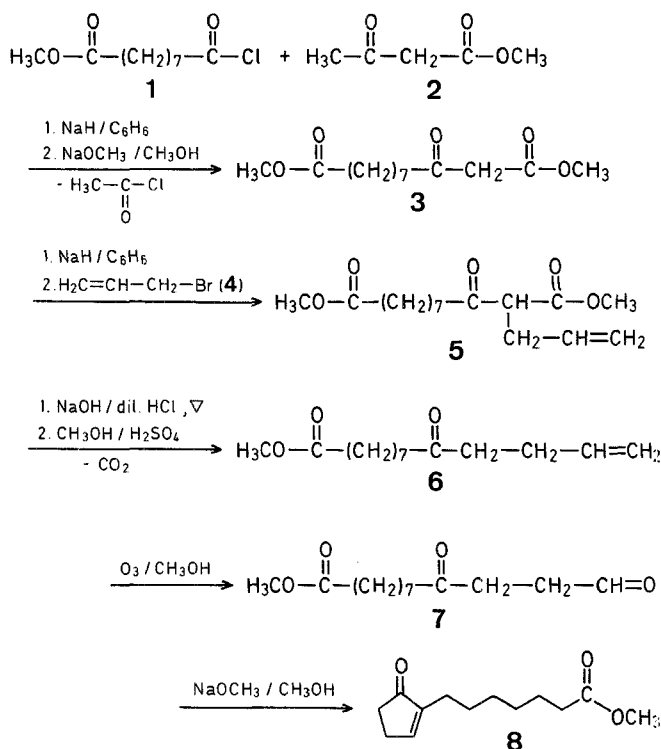


We have therefore developed a new method which enables **8** to be obtained in good yields starting from inexpensive and easily available materials. The reaction sequence is shown below.



Acylation of methyl acetoacetate (**2**) with methyl 8-chlorocarboxyloctanoate¹² (**1**) gave **3** in 60% yield. Subsequent alkylation of **3** with allyl bromide (**4**) gave **5** in 85% yield. Decarboxylative hydrolysis by 10% sodium hydroxide followed by esterification with methanol and sulphuric acid were then carried out to give **6** in 90% yield.

The terminal double bond was then cleaved by ozonolysis in 95% yield and the γ -keto-aldehyde **7** thus obtained was cyclized to **8**. Conversely, ozonolysis may also be carried out directly on **5** followed by a one-pot hydrolytic decarboxylation and cyclization to **8**. In this case, in spite of the lesser number of steps, the yield is lower than the one described above.

Dimethyl 3-Oxoundecanedioate (**3**):

To a solution of methyl acetoacetate (**2**; 44.3 g, 0.382 mol) in benzene (630 ml) is added sodium hydride (9.16 g, 0.382 mol) and the resulting mixture is stirred for 1 h at 22 °C. After cooling to 5 °C, a solution of methyl 8-chlorocarboxyloctanoate¹² (**1**; 76.9 g, 0.348 mol) in benzene (350 ml) is added. After the addition is complete, stirring is continued for 30 min at reflux temperature. The reaction mixture is then cooled and extracted with 10% sulphuric acid (2 × 200 ml), 5% sodium hydrogen carbonate (2 × 100 ml), and water (2 × 100 ml). The organic phase is then dried with sodium sulphate and evaporated to give an oily residue (111.5 g) which is dissolved in methanol (150 ml) and treated with a solution of sodium methoxide, obtained by addition of sodium (8.77 g, 0.382 mol) in methanol (250 ml). The reaction mixture is left overnight at room temperature, the solvent is evaporated under reduced pressure and water (80 ml) is added to the resulting residue. After acidification to congo red by 10% sulphuric acid, extraction is carried out with dichloromethane (3 × 200 ml). The organic phase is then washed with 5% sodium hydrogen carbonate (2 × 100 ml), water (2 × 100 ml), dried with sodium sulphate, and evaporated. The oily residue is distilled under reduced pressure to give **3** as a liquid; yield:

A New Synthesis of 2-(6-Methoxycarbonylhexyl)-cyclopent-2-en-1-one, An Important Prostanoid Synthone

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The synthesis of 2-(6-methoxycarbonylhexyl)-cyclopent-2-en-1-one (**8**), an important intermediate for the preparation of prostanoids, has been studied by many groups. The synthetic strategies devised for **8** rely on the cyclization of linear, appropriately functionalized C₁₂ acid derivatives¹⁻⁷ or on the alkylation of cyclopentenone derivatives with alkyl 7-bromo- or 7-oxoheptanoate⁸⁻¹¹. These routes have, however, some drawbacks such as lack of industrial applicability due to unavailability of the starting materials in sufficient amounts and consequent high costs or due to the inconvenient reagents employed¹².

60.16 g (61%); b.p. 150–155 °C/0.5 torr. The product is pure according to T.L.C. analysis (silica gel, hexane/ethyl acetate, 6:4).

$C_{13}H_{22}O_5$	calc.	C 60.44	H 8.58
(258.3)	found	60.53	8.61

I.R. (neat): $\nu = 1720\text{--}1745\text{ cm}^{-1}$ (C=O).

$^1\text{H-N.M.R. (CDCl}_3\text{)}$: $\delta = 1.15$ (br. s, 10H); 2.25 (m, 4H); 3.20 (s, 2H); 3.40 (s, 3H); 3.45 ppm (s, 3H).

Dimethyl 2-Allyl-3-oxoundecanedioate (5):

To a solution of **3** (51.7 g, 0.2 mol) in benzene (300 ml), sodium hydride (4.8 g, 0.2 mol) is added and the resulting mixture is stirred at room temperature for 1 h. After addition of allyl bromide (**4**; 33.9 g, 0.28 mol), the mixture is stirred for 18 h at reflux temperature. After cooling, the reaction mixture is washed with 5% hydrochloric acid (2 \times 100 ml), water (2 \times 100 ml), and the organic phase is dried with sodium sulphate. The solvent is evaporated under reduced pressure and the oily residue (59.5 g) obtained is distilled under reduced pressure to give **5**; yield: 50.5 g (85%); b.p. 150–152 °C/1 torr. T.L.C.: hexane/ethyl acetate, 6:4; $R_f = 0.8$.

$C_{16}H_{26}O_5$	calc.	C 64.40	H 8.78
(298.4)	found	64.32	8.89

I.R. (neat): $\nu = 1720\text{--}1740$ (C=O); 1640 cm^{-1} (C=C).

$^1\text{H-N.M.R. (CDCl}_3\text{)}$: $\delta = 1.15$ (br. s, 10H); 2.1–2.6 (m, 6H); 3.4 (m, 1H); 3.55 (s, 3H); 3.65 (s, 3H); 4.8–5.1 (m, 2H); 5.4–6.0 ppm (m, 1H).

Methyl 9-Oxo-12-tridecenoate (6):

Dimethyl 2-allyl-3-oxoundecanedioate (**5**; 48.4 g, 0.162 mol) is refluxed with 10% sodium hydroxide solution (700 ml) for 20 h. After cooling to 10 °C, the precipitated white solid is removed by filtration, washed with 10% sodium hydroxide (70 ml), and dissolved in water (200 ml). After acidification to congo red with 5% hydrochloric acid (~180 ml), the white crystalline solid is filtered, washed with water (100 ml), and dried in the presence of phosphorus pentoxide to give the 9-oxo-12-tridecenoic acid; yield: 35 g (96%); m.p. 54–56 °C. A sample of the product is crystallized from ether/hexane; m.p. 55–56 °C.

$C_{13}H_{22}O_3$	calc.	C 69.06	H 9.80
(226.3)	found	68.92	9.83

I.R. (Nujol): $\nu = 1720\text{--}1690$ (C=O); 1645 cm^{-1} (C=C).

The crude product (35 g) is directly esterified with methanol (360 ml) and 98% sulphuric acid (7 ml) at room temperature for 3 h. The mixture is poured into ice/water (2 l), extracted with ether (3 \times 400 ml), the extract washed with brine (4 \times 200 ml), and dried with sodium sulphate, filtered, and evaporated to leave a pale yellow liquid; yield: 35 g (90%); a sample of which is distilled; b.p. 108–110 °C/0.1 torr (Ref.⁷, b.p. 108–110 °C/0.17 torr). The product is used in the next step without further purification.

$C_{14}H_{24}O_3$	calc.	C 69.96	H 10.06
(240.3)	found	70.05	10.01

I.R. (neat): $\nu = 1745\text{--}1720$ (C=O); 1645 cm^{-1} (C=C).

$^1\text{H-N.M.R. (CDCl}_3\text{)}$: $\delta = 1.05$ (m, 10H); 2.0–2.7 (m, 8H); 3.60 (s, 3H); 4.7–5.15 (m, 2H); 5.35–6.0 ppm (1H, m).

Methyl 9,12-Dioxododecanoate (7):

To a solution of **6** (10 g, 0.0416 mol) in methanol (200 ml), cooled to –50 °C, ozone is bubbled until a pale blue color is formed. The reaction mixture is then treated with a saturated sodium metabisulphite solution (40 ml) and stirred overnight at room temperature. After evaporation of the methanol, the mixture is diluted with water (100 ml) and treated with 30% sodium hydroxide (20 ml). The aqueous phase is extracted thoroughly with ethyl acetate (4 \times 100 ml). The organic layers are collected together, washed to neutrality with water, dried with sodium sulphate and evaporated; **7** is obtained as an oily residue, pure according to T.L.C. (silica gel, hexane/ethyl acetate, 3:1); yield: 9.6 g (95%).

I.R. (neat): $\nu = 1730\text{--}1710\text{ cm}^{-1}$ (C=O).

$^1\text{H-N.M.R. (CDCl}_3\text{)}$: $\delta = 1.05\text{--}1.8$ (br. s, 10H); 2.25 (t, 2H); 2.4 (t, 2H); 2.75 (s, 4H); 3.65 (s, 3H); 9.7 ppm (s, 1H).

2-(6-Methoxycarbonylhexyl)-cyclopent-2-en-1-one (8):

Compound **8** is obtained starting from **7** (20 g, 0.0825 mol) under the same conditions using sodium methoxide in methanol as reported¹²; yield: 70%; b.p. 152 °C/1 torr (Ref.¹², b.p. 145–148 °C/0.7 torr). T.L.C.: (hexane/ethyl acetate), $R_f = 0.5$.

I.R. (neat): $\nu = 1740\text{--}1705$ (C=O); 1630 cm^{-1} (C=C).

$^1\text{H-N.M.R. (CDCl}_3\text{)}$: $\delta = 1.35\text{--}2.4$ (m, 16H); 3.60 (s, 3H); 7.26 ppm (m, 1H).

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- ¹ P. D. Gokhale et al., *Synthesis* **1974**, 718.
- ² A. S. C. Prakasa Rao, U. R. Nayak, S. Dev, *Synthesis* **1975**, 608.
- ³ S. B. Thakur et al., *Indian J. Chem.* **12**, 893 (1974).
- ⁴ K. Kondo, D. Tunemoto, *Tetrahedron Lett.* **1975**, 1397.
- ⁵ V. B. Deodhar et al., *Org. Prep. Proced. Int.* **9**, 155 (1977).
- ⁶ J. M. Reuter, R. G. Salomon, *J. Org. Chem.* **43**, 4247 (1978).
- ⁷ Y. Naoshima, S. Mizobuchi, S. Wakabayashi, *Agric. Biol. Chem.* **43**, 1765 (1979).
- ⁸ A. Barco et al., *Synthesis* **1981**, 199.
- ⁹ N. Ono, H. Miyake, A. Kaji, *Synthesis* **1981**, 1003.
- ¹⁰ L. Novak, C. Szantay, *Synthesis* **1974**, 353.
- ¹¹ K. F. Bernady et al., *German Patent* 2 234 706, American Cyanamid Co.; *C. A.* **78**, 147439 (1973).
- ¹² E. Wenkert et al., *J. Am. Chem. Soc.* **100**, 1267 (1978).