Preparation of 2-(6-Carboxyhexyl)- and 2-(6-Methoxycarbonylhexyl)cyclopent-2-en-1-one Using Free Radical Reactions

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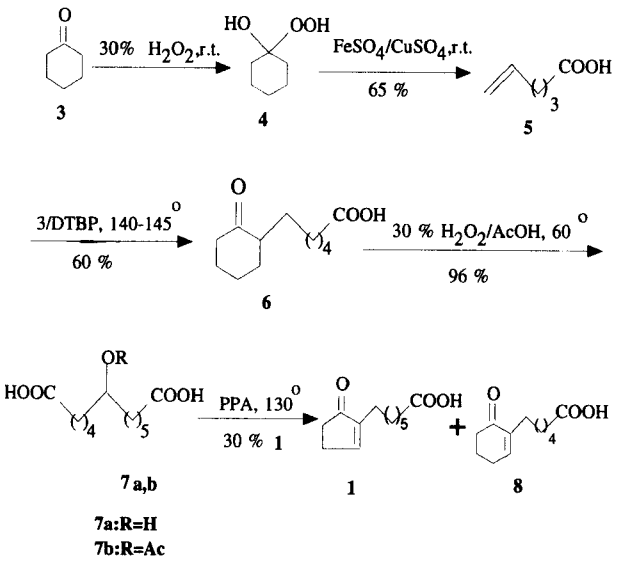
Two short and simple synthetic routes to the prostaglandin synthons 2-(6-carboxyhexyl)- and 2-(6-methoxycarbonylhexyl)cyclopent-2-en-1-one have been developed. The first is based on a cyclohexanone oxidative transformation with hydrogen peroxide and di-*tert*-butyl peroxide, the second on the free radical addition reaction of methyl 9-oxononanoate to acrylaldehyde diacylal.

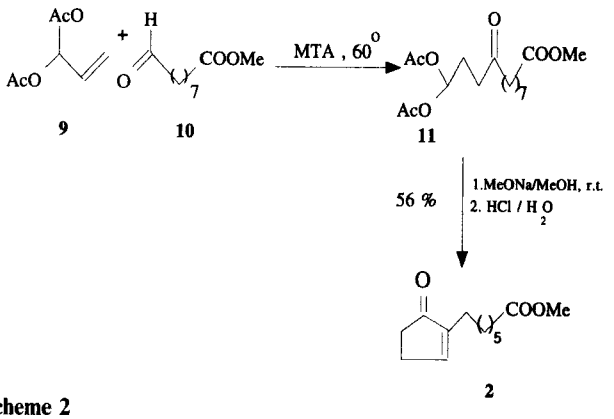
2-(6-Carboxyhexyl)cyclopent-2-en-1-one (**1**) and its ester (**2**) are the key intermediates in the synthesis of prostaglandins and their analogues.[1] Several approaches for preparation of **1** and **2** have been developed utilising various starting materials such as cyclopentanone derivatives,[2,3] fatty acids and their esters,[4-12] lactones,[11-13] and phenylsulfides and sulfones.[12-14] The shortest route described comprises 3 steps and starts from methyl 9-chloro-9-oxononanoate and 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide.[11] Other pathways are more lengthy and require the use of less available and expensive starting materials. Hence there is still a need to elaborate new simpler routes to **1** and **2** from easily available and cheap reagents. Here we describe two new procedures for preparation of **1** and **2** based on free radical reactions and involving only simple starting compounds like hydrogen peroxide, acrylaldehyde diacylal,[15] and methyl 9-oxononanoate.[16,17] The first approach is shown in Scheme 1.



Scheme 1

Hydroperoxide **4**, prepared in situ by reaction of cyclohexanone (**3**) with 30% hydrogen peroxide at room temperature, was decomposed under the action of a ferrous sulfate – copper sulfate system to give 5-hexenoic acid (**5**) in 65% yield. The decomposition of **4** proceeds via formation of α-hydroxycyclohexyloxyl and 6-carboxyhexyl radicals.[18] Acid **5** thus obtained was homolytically added to **3** at 140–150°C in the presence di-*tert*-butyl peroxide (DTBP) to give 2-(5-carboxypentyl)cyclohexanone (**6**) in 60% yield. The following oxidative cleavage of **6** under the action of hydrogen peroxide in acetic acid solution at 60°C gave a mixture of 6-hydroxy- and 6-acetoxy-1,12-dodecanedioic acids (**7a, b**) in a ratio of 3:1 in 96% yield. Cyclodehydration of the mixture in the presence of polyphosphoric acid (PPA) led to a mixture of **1** and 2-(5-carboxypentyl)cyclohex-2-en-1-one (**8**) in a ratio of 3:1. The target compound **1** was easily isolated from the mixture by low-temperature crystallisation from acetone. The overall yield of **1** for the whole sequence is 14% based on **3**. The conversion of **1** into **2** by ordinary esterification is known.[5]

The second route to **2**, which accesses the target compound in only two steps in a high yield, is based on manganese triacetate (MTA) initiated, free radical addition and is shown in Scheme 2.



Scheme 2

Some time ago, the high efficiency of MTA in the reactions of free radical addition of aldehydes to olefins was discovered in our laboratory.[19] Recently it was successfully used for initiation of the reactions between acrylaldehyde diacylal (**9**) and various aldehydes.[20] The addition of methyl 9-oxononanoate (**10**) to **9** initiated with MTA proceeds efficiently at 60°C and at molar ratios of **9**/MTA and **10**/**9** of 4:1 and 6:1, respectively. The reaction mixture was filtered to remove manganese(II) diacetate and then the excess of **10** and unreacted **9** (25%) were distilled off. An oily residue, consisting mainly of the corresponding adduct, methyl 12,12-diacetoxy-9-oxododecanoate (**11**), was used without additional purification in the next step of base-induced cyclisation. The target compound **2** was isolated by chromatography in a combined yield of 74% based on converted **9** (56% based on the starting **9**).

The basic feature of the preparation of **1** shown in Scheme 1 is the construction of the synthon **1** from two cyclohexanone molecules. The availability and low cost of the starting material as well as all other reagents, in spite of

the moderate overall yield of **1**, represents an advantage over the other known approaches to **1**. The good combined yield of **2** prepared as shown in Scheme 2, the shortness of the synthetic sequence, the simplicity of the experimental procedures, and the relative availability of the starting compounds and reagents allow us to consider this procedure as one of the most effective among the known routes to **2**.

The reaction products were identified either by comparison with authentic samples or ^{1}H NMR spectra ($CDCl_3$/TMS) using a Bruker WM-150 (250 MHz) instrument. Acrylaldehyde diacylal **9** was obtained from freshly distilled acrolein and acetic anhydride as described,[15] yield 90%. Methyl 9-oxononanoate 10 was the ozonolysis product of methyl oleate,[16] yield 60%.

5-Hexenoic acid (5):
Hydrogen peroxide (227 mL of 30% aqueous solution, 2 mol) was added over 30 min at 20–25 °C to a stirred solution of cyclohexanone **(3)** (98 g, 1 mol) in MeOH (100 mL). The mixture was then added over 2 h to a stirred solution of ferrous sulfate heptahydrate (278 g, 1 mmol) and cupric sulfate pentahydrate (250 g, 1 mol) in water (1.8 L), maintaining the reaction mixture at 18–20 °C. The aqueous phase was separated and extracted with Et_2O (3 × 200 mL). The organic phase and Et_2O extracts were washed with 20% aq NaOH (3 × 100 mL). The alkaline extract was acidified with 20% sulfuric acid to pH 2 and extracted with Et_2O (3 × 200 mL). Removal of solvent at reduced pressure gave the crude product **5** as a clear oil which was purified by fractional distillation; yield: 74 g (60%), bp 93–95 °C/10 Torr (Lit.[21] bp 91–94/8 Torr).

^{1}H NMR ($CDCl_3$): δ = 1.96–2.08 (m, 6H, 3 × CH_2), 5.01 (d, 2H, J = 15 Hz, H_2C=), 5.68 (m, 1H, =CH), 11.9 (br s, 1H, CO_2H).

2-(5-Carboxypentyl)cyclohexanone (6):
A solution of acid **5** (74 g, 0.65 mol) and di-*tert*-butyl peroxide (7.3 g, 0.05 mol) in cyclohexanone **(3)** (147 g, 1.5 mol) was added over 45 min to effectively stirred **3** (294 g, 3 mol) at 135–140 °C. After additional stirring for 1 h at 135–140 °C, the mixture was distilled under reduce pressure to give excess **3** and 2-(5-carboxypentyl)cyclohexanone **(6)**; yield: 89 g (60% based on **3**); bp 160–162 °C/0.2 Torr, mp 48 °C.

^{1}H NMR (CD_3OD): δ = 1.36 (m, 14H, 7 × CH_2), 2.12 (m, 5H, 2 × CH_2 + CH), 10.81 (br s, 1H, CO_2H).

6-Hydroxy- and 6-Acetoxy-1,12-dodecanedioic Acids (7a,b):
To a stirred mixture of acid **6** (21.2 g, 100 mmol), AcOH (20 mL) and 55% sulphuric acid (180 mL), 30% (w/v) hydrogen peroxide (11.3 mL, 125 mmol) was added dropwise over 45 min while keeping the temperature below 60 °C. After additional stirring for 2 h at r.t., 20% aq NaOH (450 mL) was added to pH 2, and the mixture was extracted with EtOAc (3 × 100 mL). The extract was washed with brine, dried (Na_2SO_4) and evaporated to leave a clear yellow oil, which, when methylated with diazomethane and analysed by GLC, was found to be composed of acids **7a** and **7b** in the proportion of 3:1; yield: 25 g (96%).

2-(6-Carboxyhexyl)cyclopent-2-en-1-one (1):
To effectively stirred polyphosphoric acid (250 g) heated to 85 °C, the mixture of acids **7a,b** (25 g, 10 mmol) was added in one portion. After stirring for 10 min, the reaction mixture was quenched by pouring it onto crushed ice, neutralised with 30% aq NaOH (300 mL) to pH 2 and extracted with 1:1 EtOAc/petroleum ether (bp 40–70 °C, 3 × 150 mL). The extract was washed with brine, evaporated and the residue (17 g) was fractionally distilled under reduced pressure to give a clear yellow oil (bp 120–190 °C/0.1 Torr, 8 g), which, as analysed by GLC (after diazomethane methylation), was composed mainly of acids **1** and **8** in the proportion of 3:1. Crystallisation of the mixture from acetone (150 mL, at −40 °C) gave **1**, yield: 3.1 g (14%); mp 39–40 °C (Lit.[3] mp 36–38 °C).

^{1}H NMR (CD_3OD): δ = 1.28 (m, 4H, 2 × CH_2), 1.43–1.55 (m, 4H), 2.10 (m, 2H, CH_2), 2.23 (m, 2H, CH_2), 2.33 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 4.85 (s, 1H, CO_2H), 7.40 (m, 1H, =CH).

2-(6-Methoxycarbonylhexyl)cyclopent-2-en-1-one (2):
A solution of acrylaldehyde diacylal **(9)** (3.2 g, 20 mmol) in methyl 9-oxononanoate **(10)** (11.2 g, 60 mmol) was added over 6 h to stirred **10** (11.2 g, 60 mmol) heated at 60 °C. Simultaneously MTA (1.34 g, 5 mmol) was added in small portions (ca. 0.1 g). Each subsequent portion of MTA was introduced only after the reaction mixture changed from brown to light yellow, which indicated the full consumption of MTA. The mixture was heated thereafter for 2 h at 60 °C, cooled, diluted with $CHCl_3$ (50 mL), filtered to remove $Mn(OAc)_2$, and evaporated to obtain a residual oil, from which the unreacted **9** (0.8 g, 25%) and the excess of **10** were distilled off under reduced pressure leaving crude **11** (6.5 g) as an oily residue, pure enough according to TLC (alumina, CH_2Cl_2). The product was dissolved in methanolic NaOMe (0.3 M, 500 mL) and the solution was stirred for 5 h at r.t., neutralised with concentrated hydrochloric acid and concentrated to leave an aqueous residue (100 mL), which was diluted with water (300 mL) and extracted with EtOAc (2 × 100 mL). The extract was dried (Na_2SO_4 and evaporated. Column chromatography of the residue on neutral alumina (CH_2Cl_2) gave **2**, yield: 2.5 g (56%), bp 146–150 °C/0.2 Torr.

IR (film): ν = 1735, 1700, 1630 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.35 (m, 4H, 2 × CH_2), 1.50 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.00–2.40 (m, 8H, 4 × CH_2), 3.60 (s, 3H, OCH_3), 7.30 (m, 1H, =CH).

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