Synthesis of a Prostanoid Intermediate

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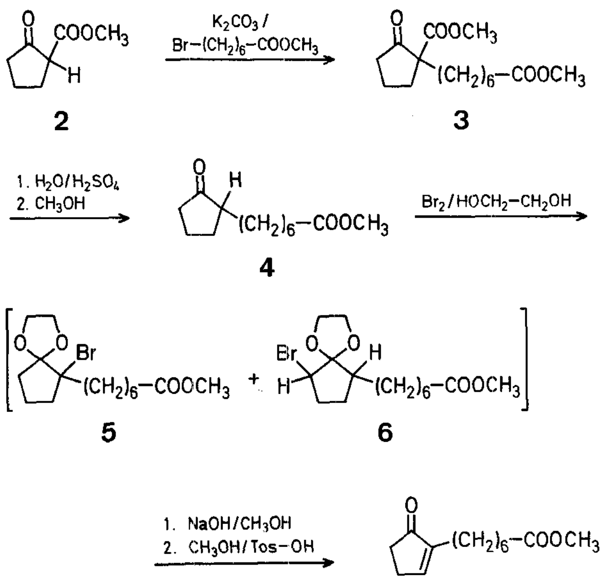
During the last few years, much effort has been concentrated on the synthesis of the biologically important prostanoids[1]. Several approaches have used methyl 3-oxocyclopentene-2-heptanoate (**1**) as an intermediate[2,3].

We worked out a new method for the preparation of the important intermediate **1**. Methyl 2-oxocyclopentanecarboxylate[4] (**2**) is alkylated with methyl 7-bromo- or 7-iodoheptanoate following, with modifications, a procedure[2] for the synthesis of the corresponding ethyl ester. The resultant compound **3** is hydrolyzed with 30% sulfuric acid; subsequent esterification with methanol yields **4**.

The enol silyl ester of **4** was also prepared, but bromination of the lithium enolate obtained from that ether did not proceed regioselectively, as has been reported for examples[5].

Using the method of Garbisch[6], compound **4** was brominated in glycol. The procedure yielded a mixture of **5** (65%) and **6** (35%) in 80% yield. The mixture can be stored at refrigerator temperature but decomposes vehemently at ~60°. Separation of the isomeric compounds **5** and **6** is not necessary. Treatment of the mixture with boiling methanolic sodium hydroxide followed by esterification of the intermediate isomeric unsaturated acids with methanol in benzene in the presence of *p*-toluenesulfonic acid gives ester **1** in 40% yield (based on **2**).



Methyl 1-(6-Methoxycarbonylhexyl)-2-oxocyclopentanecarboxylate (3):

A mixture of methyl 2-oxocyclopentanecarboxylate (**2**; 10 g, 0.077 mol), anhydrous potassium carbonate (27.5 g, 0.19 mol), and methyl 6-bromoheptanoate (22.3 g, 0.1 mol) was refluxed with stirring for 20 h in dry acetone (200 ml). After being cooled, the solution was filtered and evaporated to give an oil which was distilled in vacuo to give pure **3**; yield: 14.1 g (70%); b.p. 175–180°/0.2 torr.; $n_D^{20} = 1.4664$.

$C_{15}H_{24}O_5$	calc.	C 62.68	H 8.80
(284.3)	found	62.40	H 8.83

I.R. (film): $\nu_{max} = 1730\ cm^{-1}$ (C=O).

^{1}H-N.M.R. (CDCl$_3$): $\delta = 3.7$ (s, 3H, —OCH$_3$), 3.64 (s, 3H, —OCH$_3$), 2.3 (t, 4H, $J = 10$ Hz), 2.1–1.2 ppm (m, 14H).

Methyl 2-Oxocyclopentaneheptanoate (4):

Product **3** (40 g, 0.14 mol) was refluxed in water/sulfuric acid (2:1, 180 ml) for 20 h with stirring. The cooled reaction mixture was extracted with ether (4 × 400 ml). The combined ether layers were washed with water, dried, and evaporated. The residue was esterified in a mixture of dry methanol (80 ml) and dry benzene (400 ml) in the usual manner to give **4**; yield: 25 g (79%); b.p. 135–140°/0.4 torr.; n_D^{26}: 1.4567.

I.R. (film): $\nu_{max} = 1730\ cm^{-1}$ (C=O).

^{1}H-N.M.R. (CDCl$_3$): $\delta = 3.7$ (s, 3H, —OCH$_3$), 2.5–2 (m, 5H), 1.4 ppm (m, 14H).

Methyl 2-Trimethylsiloxycyclopentene-1-heptanoate (Enol Silyl Ether of 4):

To a stirred mixture of **4** (18.1 g, 0.08 mol) and triethylamine (10 g, 0.1 mol) in dry benzene (100 ml) was added trimethylchlorosilane (10 g, 0.09 mol) and the resulting solution was refluxed under anhydrous condition for 5 h. The mixture was then cooled and the precipitate filtered off. Evaporation of the solvent followed by distillation gave the pure silyl ether; yield: 16 g (67%); b.p. 170–175°/11 torr.

^{1}H-N.M.R. (CDCl$_3$): $\delta = 0.05$–0.15 [9H, —Si(CH$_3$)$_3$], 1.1–2.5 (m, 16H), 3.7 ppm (s, 3H, —OCH$_3$).

Methyl 3-Oxocyclopentene-2-heptanoate (1):

To a stirred solution of **4** (20.4 g, 0.09 mol) in dry ethylene glycol (200 ml), bromine (18 g, 0.11 mol) was added dropwise at 15°, during 7 h. The mixture was then cooled to 5° and poured into a stirred mixture of anhydrous sodium carbonate (12 g, 0.11 mol) in hexane (250 ml), precooled to 5°. The hexane layer was separated, dried with magnesium sulfate, and the hexane evaporated under reduced pressure to give 24.8 g (80%) crude bromo-acetals; $n_D^{20} = 1.4886$. The mixture consisted of 65% **5** and 35% **6**, as determined by N.M.R. analysis. The compounds must be stored in a refrigerator if not required for immediate use.

$C_{15}H_{25}BrO_4$	calc.	C 51.57	H 7.21	Br 22.88
(347.2)	found	51.05	7.12	24.10

I.R. (film): $\nu_{max} = 1735\ cm^{-1}$ (C=O).

^{1}H-N.M.R. (CDCl$_3$): $\delta = 4.2$ (t, $J = 2$ Hz, 1.4H, —O—CH$_2$—CH$_2$—O—), 4.1 (t, $J = 2$ Hz, 2.6H, —O—CH$_2$—CH$_2$—O—), 3.67 (s, 3H, —OCH$_3$), 3.18 (m, 0.35 H, Br-CH), 1.2–2.5 ppm (18H).

The mixture of the crude bromo-acetals was added to a solution of sodium hydroxide (9 g, 0.225 mol) in dry methanol (80 ml), and the mixture refluxed for 3 h. After standing at room temperature overnight, the solution was acidified with 10% acetic acid and the acid solution was extracted twice with ether. Removal of the solvent gave a light-brown oil which was esterified in a mixture of dry methanol (80 ml) and dry benzene (400 ml) using *p*-toluenesulfonic acid (0.5 g) as catalyst to give **1**; yield 8.1 g (40%); b.p. 145–150°/0.2 torr; $n_D^{27} = 1.4695$.

$C_{13}H_{20}O_3$	calc.	C 69.61	H 8.98
(224.3)	found	69.40	9.22

I.R. (film): $\nu_{max} = 1730$, 1700 (C=C), 1630 cm^{-1} (C=O).

^{1}H-N.M.R. (CDCl$_3$): $\delta = 7.15$ (poorly resolved t, 1H, =CH—), 3.6 (s, 3H, —OCH$_3$), 2.14–2.48 (m, 6H), 1.28–1.4 ppm (m, 10H).

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