An Improved Synthesis of Methyl 7-(2-Hydroxy-5-oxo-1-cyclopentenyl)heptanoate

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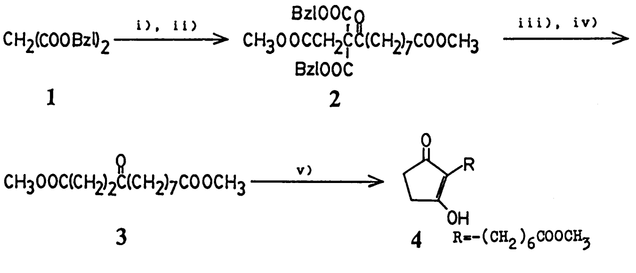
Synopsis. Methyl 7-(2-hydroxy-5-oxo-1-cyclopentenyl)-heptanoate, which is a valuable synthon for prostanoids, was prepared in a good yield from dibenzyl malonate via three steps.

A polymeric prostaglandin, PGB$_X$, with biochemical and physiological properties very different from those of any other prostaglandin derivatives, was first synthesised by Polis et al.[1] PGB$_X$ has such biological properties as restoring the oxidative phosphorylation of isolated degraded rat liver mitochondria in vitro and increasing in survival after otherwise lethal episodes of myocardial ischemia in monkeys and hypocia in dogs in vivo.[2] PGB$_X$ is an oligomeric mixture (4—6 monomer units) of the 15-dehydro-PGB$_1$ methyl ester. The total syntheses of PGB$_1$ or its equivalents have already been known,[3] and methyl 7-(2-hydroxy-5-oxo-1-cyclopentenyl)heptanoate (**4**) is a key intermediate in all cases. **4** is a valuable synthon not only for PGB$_1$ but also for other prostanoids, for other synthetic intermediates for primary prostaglandins can easily be derived from **4**.[4] We thought that a simple method of preparing a large quantity of **4** would be of significant synthetic and pharmaceutical interest and so started to investigate it.

We modified Bowmann's general method of ketone synthesis[5] and obtained **4** from dibenzyl malonate in a short time and in a good yield. In our method, **4** was prepared in only three steps because the tetraester **2**, which is difficult to prepare by Bowmann's method, was obtained in a single step.



i) NaH, $BrCH_2CO_2CH_3$ ii) NaH, $CH_3O_2C(CH_2)_7COCl$ iii) H_2, Pd/C iv) Δ v) $NaOCH_3$

Tetraester **2** was prepared from dibenzyl malonate (**1**) in one pot by base-promoted alkylation with methyl bromoacetate, followed by acylation with methyl 8-chloroformyloctanoate. The crude yield of this one pot reaction was 92% from dibenzyl malonate (**1**). Although the tetraester **2** was used in the next step without further purification, it can be purified by silica-gel column chromatography if necessary. The structure of **2** was elucidated by means of the spectroscopic data.

Thermal decarboxylation after the removal of the benzyl groups of the tetraester **2** gave the keto diester[3] **3** in a 58% yield. This step was achieved by hydrogenolysis in mixture of 10% palladium on charcoal and by subsequent thermal decomposition under reflux in ethyl alcohol. All the spectroscopic data of **3** support its structure.

The keto diester **3** was cyclized with sodium methoxide to give methyl 7-(2-hydroxy-5-oxo-1-cyclopentenyl)heptanoate[3,4] (**4**) in a 94% yield. The IR and NMR spectra of **4** were identical with those of an authentic sample.[3]

Experimental

Dimethyl 3-Bis(benzyloxycarbonyl)-4-oxo-1,12-dodecanedioate (2). A solution of 40 g of dibenzyl malonate (**1**: Aldrich No. 16040-7) in 100 ml of benzene was added to a suspension of 3.36 g (0.14 mol) of sodium hydride in 400 ml of benzene dropwisely. Benzene (200 ml) was then added to the reaction mixture, after which it was gently heated to reflux. After 15 min, a solution of 21.6 g (0.14 mol) of methyl bromoacetate in 100 ml of benzene was added at 50 °C, and then the reaction mixture was heated under reflux for 90 min.

The resultant mixture was added dropwise to a suspension of 3.36 g (0.14 mol) of sodium hydride in 400 ml of benzene with stirring at room temperature. The reaction mixture was kept at 50 °C for 30 min during the evolution of hydrogen gas and then heated under reflux for 15 additional min.

At 50 °C, to the stirred mixture was added a solution of 30.8 g (0.14 mol) of methyl 8-chloroformyloctanoate in 100 ml of benzene dropwisely. The mixture was then cooled to room temperature after refluxing for 2 h. The organic materials were extracted with 1000 ml of ether, and the ethereal layer was washed with 500 ml of water, 300 ml of aq. sat. $NaHCO_3$, 500 ml of water (three times), and brine, and then dried over $MgSO_4$. The removal of the solvents and volatile components under 0.4 mmHg (1 mmHg=133.322 Pa) at 160 °C for 2 h gave 70 g of crude **2** in a 92% yield. Crude **2** can be used for the next step without further purification. Column chromatography (LiCroprep Si 60; hexane–ethyl acetate=3:1) gave pure **2**: ^1H NMR (90 MHz, chloroform-d_1, TMS) δ=7.29 (br., 10H), 5.16 (s, 4H), 3.66 (s, 3H), 3.58 (s, 3H), 3.13 (s, 2H), 2.55 (t, J=7.5 Hz, 2H), 2.27 (t, J=7.5 Hz, 2H), 1.4—1.8 (br., 4H), and 1.0—1.4 (br., 6H); IR (film) 2940, 2850, 1735, 1455, and 1440 cm^{-1}; MS (LREI) 540 (M^+), 509 (M−MeO), 508 (M−MeOH), 477 (M−MeO−MeOH), and 449 (M−Bzl); (HREI) Found: m/z 540.2347. Calcd for $C_{30}H_{36}O_9$: M, 540.2336.

Dimethyl 4-Oxo-1,12-dodecanedioate[3] (3). The hydrogenolysis of 25.5 g (0.047 mol) of **2** was carried out in 150 ml of 95% ethyl alcohol with hydrogen gas at atmospheric pressure over 2 g of 10% palladium on charcoal for 24 h. After the removal of the catalyst by filtration, the reaction mixture was heated under reflux for 2 h. The resultant product was distilled at 159—160 °C (0.7 mmHg) to give 7.47 g of **3** in a 58% yield: ^{1}H NMR (100 MHz, chloroform-d_1, TMS) δ=3.63 (s, 6H), 2.80—2.08 (m, 8H), and 1.80—1.05 (m, 10H); IR (KBr) 2940, 2850, 1740, 1710, and 1440 cm^{-1}.

Methyl 7-(2-Hydroxy-5-oxo-1-cyclopentenyl)heptanoate[3,4] **(4).** Dimethyl 4-oxo-1,12-dodecanedioate (**3**: 2.72 g; 10 mmol) in 20 ml of dry toluene was added dropwise to a suspension of 20 mmol of sodium methoxide in 50 ml of dry toluene under reflux. The reaction mixture was then heated under reflux for 30 min, followed by the azeotropic removal of the generating methyl alcohol for 2 h. After it had then been cooled to room temperature, the resultant mixture was diluted with 20 ml of water and acidified with 1 M HCl (1 M=1 mol dm^{-3}) between pH 1 and pH 2. The organic materials were extracted with 20 ml of ethyl acetate twice. The organic layer was washed successively with equal volumes of 1 M HCl, water, and brine. The subsequent removal of the solvents gave 2.26 g (94% yield) of **4**: ^{1}H NMR (90 MHz, chloroform-d_1, TMS) δ=4.75—4.0 (br., 1H), 3.66 (s, 3H), 2.66 (br., 4H), 2.75—1.95 (m, 4H), and 1.9—1.0 (m, 8H); IR (KBr) 2910, 2860, and 1740 cm^{-1}.

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