A Convenient Method of Preparing the Leukotriene Precursor Methyl 5-Oxopentanoate

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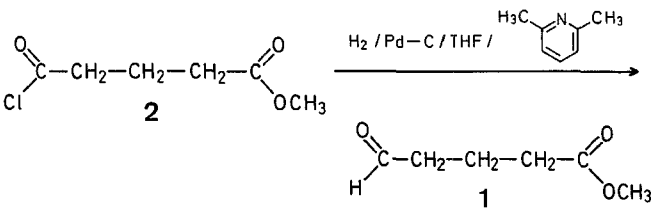
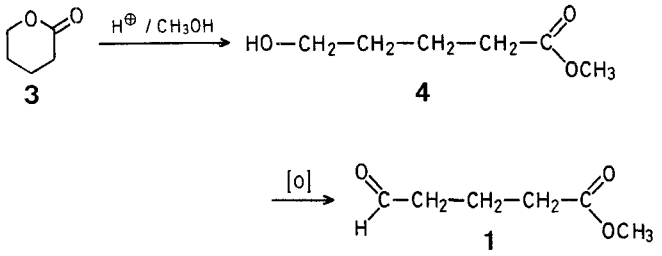
Methyl 5-oxopentanoate (**1**) has been employed in several recent syntheses of leukotrienes and related natural products[1,2,3]. To our knowledge, a detailed experimental procedure for the preparation of **1** has not been published although it has been reported[2] that **1** can be prepared from methyl 5-chloro-5-oxopentanoate (**2**) using Burgstahler's modified Rosenmund reduction procedure[4,5].



We have found that the acid chloride **2**, tetrahydrofuran, and 2,6-dimethylpyridine all have to be carefully dried and redistilled prior to use and that rigorous exclusion of moisture is necessary in order to obtain reproducible yields of aldehyde **1**. We therefore sought a straightforward procedure for preparing **1** from a less expensive and more accessible precursor. Methyl 5-hydroxypentanoate (**4**) seemed an ideal precursor to aldehyde **1** but a literature survey indicated that the existing methods[6] for its preparation were complex. However, we found that **4** could be obtained in near quantitative yield by the acid-catalysed transesterification of 5-pentanolide (**3**, valerolactone) with methanol[7]. Relactonisation was only observed when an aqueous work-up was employed or when ester **4** was distilled.



It has been reported[8] that 5-hydroxyalkanoic esters tend to relactonise rather than undergo oxidation to 5-oxoalkanoic esters but we found that a variety of chromium(VI) oxidising agents converted **4** into the required aldehyde **1**, although the yields of **1** isolated varied markedly according to the reagent and reaction conditions employed (Table). The use of pyridinium dichromate[9] and chromium(VI) oxide/pyridine[10] gave low yields of aldehyde **1** (Table, entries 1 and 2) whereas pyridinium chlorochromate[11] (Table, entry 3) gave a 70% yield of isolated product. This yield was reduced when more reagent, different reaction times, or a buffered reaction medium were employed.

Table. Oxidation of Methyl 5-Hydroxypentanoate (**4**) to Methyl 5-Oxopentanoate (**1**) under Various Reaction Conditions[a]

Entry	Reagent (equiv)	Reaction time [h]	Yield of isolated **1**[b] [%]
1	Pyridinium chromate (1.5)	24	41
2	$CrO_3 \cdot Py_2$ (6.0)	0.25	9
3	Pyridinium chlorochromate (1.5) + NaOAc (2.0)	2	39
4	Pyridinium chlorochromate (1.5)	2	70
5	Pyridinium chlorochromate (1.5)	1	29
6	Pyridinium chlorochromate (1.5)	4	24
7	Pyridinium chlorochromate (2.0)	2	41

[a] All reactions were carried out on 0.1 mol of **4** at room temperature using dichloromethane as solvent.

[b] G.L.C. purity: >99% (OV 17, 160 °C).

Methyl 5-Hydroxypentanoate (4):

Concentrated sulphuric acid (10 drops) is added to a magnetically stirred solution of 5-pentanolide (**3**; 10 g, 0.1 mol) in freshly distilled methanol (200 ml) and the mixture is boiled under reflux for 5 h. The mixture is then cooled in an ice/salt bath and sodium hydrogen carbonate (1 g) is added. The mixture is stirred for 10 min, the excess solid removed by filtration, and the solvent removed in vacuo at 25 °C; yield of **4**: 13.1 g (99%); b.p. 67–71 °C/0.2 torr. The product is normally oxidised directly without purification in view of the ease with which it relactonises; it should be noted that distillation causes extensive relactonisation.

I.R. (film): $\nu = 3420, 1735\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 3.70$ (s, 1H, OH); 3.65 (s, 3H, OCH_3); 3.8–3.3 (m, 2H, CH_2—O); 2.60–2.15 (m, 2H, CH_2—CO); 2.0–1.4 ppm (m, 2H, CH_2—CH_2—CH_2).

Methyl 5-Oxopentanoate (1):

Pyridinium chlorochromate (32 g, 0.15 mol) in dry dichloromethane (120 ml) is stirred mechanically and a solution of methyl 5-hydroxypentanoate (**4**; 13.2 g, 0.1 mol) in dichloromethane (60 ml) is added in one portion. The mixture is stirred for 2 h at room temperature and then dry diethyl ether (200 ml) is added. The solution is decanted off

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and the residue washed with diethyl ether (3 × 50 ml). The combined organic solutions are then filtered through Florisil® and the solvent removed in vacuo. The remaining oil is distilled in vacuo to give **1** as a colourless liquid; yield: 9.2 g (70%); b.p. 90–98 °C/10 torr (a b.p. of **1** has hitherto not been reported).

$C_6H_{10}O_3$	calc.	C 55.39	H 7.70
(130.1)	found	55.15	7.95

I.R. (film): $\nu = 1730$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 9.70$ (t, 1H, $J = 1.5$ Hz, CHO); 3.60 (s, 3H, $COOCH_3$); 1.7–2.7 ppm (m, 6H, remainder).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 201.3$ (d); 173.3 (s); 51.5 (t); 42.9 (t); 32.9 (t); 17.2 ppm (t).

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