A facile route to (+)- and (−)-*trans*-tetrahydro-5-oxo-2-pentylfuran-3-carboxylic acid, precursors of (+)- and (−)-methylenolactocin

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The enantioselective synthesis of the title γ-lactone intermediates is easily achieved by employing *Porcine pancreas lipase* catalysed hydrolysis of the corresponding esters as the key step.

Many natural compounds possess the γ-butyrolactone structure as the basic skeleton.[1] Among them, the α-methylene-γ-butyrolactones have received particular attention owing to their antibiotic, antiviral and antitumour activities.[2] A few total syntheses of methylenolactocin (−)-**1**, an antitumour antibiotic,[3] have been reported (Fig. 1). The first one, proposed by Greene,[4] involved the enantiomerically pure lactone (−)-**2** as the key intermediate. More recently G. Zhu[2b] prepared (−)-methylenolactocin from optically active 1-acetoxy-2-nonyl-4(*R*)-ol in seven steps. Since the α-methylenation of the lactone (−)-**2** leading to (−)-**1** is a well settled reaction,[4] many authors focused their attention to the synthesis of (−)-**2**,[2c,5,6] which was generally accomplished by multistep processes.

In connection with our studies on the synthesis of enantiomerically pure bicyclic γ-butyrolactones,[7] we have developed an easy procedure for the synthesis of both enantiomers of methylenolactocin.

Their racemic precursor, ethyl *trans*-tetrahydro-5-oxo-2-pentylfuran-3-carboxylate **5** (Scheme 1) was prepared from diethyl hexanoylbutanedioate **3**[8]† in two steps. Reduction of the keto diester **3** with sodium borohydride in ethanol gave a 1 : 1 mixture of *cis* and *trans* lactones **4**‡ and **5** in high yield (90%). The relative configuration was assigned by analysis of their ^{13}C NMR spectra and also deduced from their stability. The chain methylene carbon atom linked to the lactone ring in **4** was shielded upfield relative to **5** (31.2 *vs.* 35.2 ppm), as a result of a steric compression. Similar shift differences have also been observed for the ring carbon atoms C-2, C-3 and C-4. The mixture of reduction products **4** and **5** was equilibrated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene for a few minutes. After equilibration, the *cis* : *trans* ratio was 1 : 9. Separation of the products by flash chromatography with light petroleum–ethyl acetate (9 : 1) as eluent yielded the major component **5** in 45% yield.

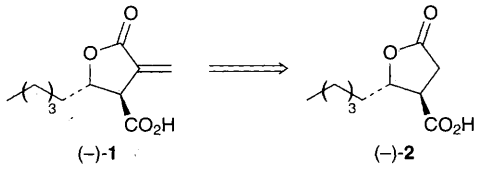
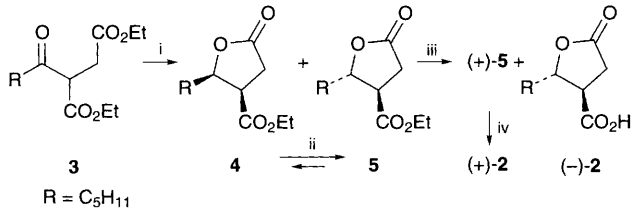


Fig. 1



Scheme 1 *Reagents and conditions*: i, $NaBH_4$, EtOH, room temp., 2 h (45% after chromatographic separation); ii, DBU, toluene, 100 °C, 20 min; iii, (*a*) PPL, 150 mg $mmol^{-1}$, pH 7.2, H_2O, room temp., 6 h (19%); (*b*) PPL, 300 mg $mmol^{-1}$, pH 7.2, H_2O, room temp., 42 h (29%); iv, 2 NaOH, H_2O, room temp., 48 h (98%)

Hydrolysis of the ethoxycarbonyl group in the lactone **5** by *Porcine pancreas lipase* (PPL) (150 mg $mmol^{-1}$) in phosphate buffer at room temperature for 6 h,§ gave the acid (−)-**2**[4] in 19% yield. The acid was found to have an enantiomeric excess (ee) of 92% (determined by chiral HRGC on a γ-cyclodextrin-based column of its ethyl ester¶). The unreacted ester (+)-**5** (75%) was found to have 27% ee.

When the lactone **5** was hydrolysed using 300 mg $mmol^{-1}$ of PPL for 42 h, the unreacted ester (+)-**5**‖ was shown to be enantiomerically pure (>99% ee, 29%), while the remaining acid (−)-**2** (40%) was found by chiral HRGC of its ethyl ester to have an ee of 57%. Hydrolysis of (+)-**5**, carried out under basic conditions at room temperature for 48 h, gave the acid (+)-**2** with 88% ee (by chiral HRGC of its ethyl ester) in quantitative yield. Hydrolysis performed in refluxing dioxane under acidic conditions for 2 h gave (+)-**2** with a lower ee.

The results obtained indicate that both enantiomers (+)- and (−)-**2** can be prepared by the same sequence of reactions and in good enantiomeric purity, simply varying the conditions of the biotransformation step. Since the acids can be methylenated at the α position by the Greene method,[4] this procedure constitutes the formal synthesis of (+) and (−)-methylenolactocin **1**.

Other enzymes were also used for the hydrolysis of the lactone (±)-**5** but unsuccessfully. *Pig liver esterase* (PLE) in fact afforded the acid **2** as a racemic compound and *Candida cylindracea lipase* (CCL) gave the ester (−)-**5** enantiomeric with that obtained using *Porcine pancreas lipase* but only in a low enantiomeric purity (12%).

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Footnotes

† Diethyl hexanoylbutanedioate **3**[8]: ν_{max}(neat)/cm^{-1} 1738 (CO_2Et) and 1720 (CO); δ_H (400 MHz) 4.21 (2 H, q, OCH_2CH_3), 4.04 (2 H, q, OCH_2CH_3), 3.90 (1 H, dd, $COCHCO_2Et$), 2.88 (1 H, pseudoq, $CHCO_2Et$), 2.74 (1 H, pseudoq, $CHCO_2Et$), 2.64 (1 H, m, C_4H_9CHCO), 2.53 (1 H, m, C_4H_9CHCO), 1.53 (2 H, quintet, CH_2CH_2CO), 1.25 – 1.15 (4 H, m, $CH_3CH_2CH_2$), 1.19 (3 H, t, OCH_2CH_3), 1.17 (3 H, t, OCH_2CH_3) and 0.81 (3 H, t, CH_2CH_3); δ_C (100.4 MHz) 203.9 (s), 171.2 (s), 168.3 (s), 61.5 (t), 60.7 (t), 53.9 (d), 42.5 (t), 32.2 (t), 31.0 (t), 22.9 (t), 22.2 (t), 13.9 (q), 13.8 (q) and 13.7 (q).

‡ Ethyl *cis*-5-oxo-2-pentyl-tetrahydrofuran-3-carboxylate **4**: ν_{max}(neat)/cm^{-1} 1785 (O–CO) and 1734 (CO_2Et); δ_H (400 MHz) 4.63 (1 H, m, 2-H), 4.21 (2 H, q, OCH_2CH_3), 3.42 (1 H, ddd, 3-H), 2.89 (1 H, dd, 4-H), 2.66 (1 H, dd, 4-H), 1.59 (3 H, m), 1.31–1.21 (5 H, m), 1.29 (3 H, t, OCH_2CH_3) and 0.89 (3 H, t, CH_3); δ_C (100.4 MHz) 175.0 (s), 170.3 (s), 80.4 (d, C-2), 61.4 (t), 44.3 (d, C-3), 31.8 (t, C-4), 31.3 (t), 31.2 (t), 25.4 (t), 22.4 (t), 14.1 (q) and 13.9 (q).

§ To a solution of the lactone (±)-**5** (420 mg, 1.8 mmol) in a buffer solution (0.1 mol dm^{-3} KH_2PO_4/Na_2HPO_4, 5.6 cm^3) was added PPL (*Porcine*

pancreas lipase type II, 61 units mg^{-1}, Sigma, 273 mg). The pH value was maintained at 7.2 by adding 2 mol dm^{-3} NaOH. The course of the reaction was monitored by chiral HRGC (trifluoroacetylated γ-cyclodextrine). The crude reaction mixture was then extracted with ether. After the usual work-up, the lactone (+)-**5**‖ (0.310 g, 75% yield) in 27% ee was obtained. The aqueous phase was acidified to pH 2 with 1 mol dm^{-3} HCl and extracted with ether. The usual work-up furnished the acid (−)-**2** (0.070 g, 19% yield), $[\alpha]_D^{25}$ − 54.5 (*c* 0.5, $CHCl_3$), $\Delta\varepsilon_{226}$ = −0.2, 92% ee.

¶ To determine the ee of the acid (−)-**2** by chiral HRGC, the acid was esterified; ethyl iodide (0.034 g, 0.22 mmol) was added to a solution of DBU (0.033 g, 0.22 mmol) and (−)-**2** (0.050 g, 0.22 mmol) in benzene (0.33 ml). After 2 h at room temperature the solution was washed with water, dried on anhydrous sodium sulfate and analysed by chiral HRGC. The same procedure was used to establish the ee of the acid (+)-**2**.

‖ (+)-(2*R*, 3*S*)-Ethyl *trans*-5-oxo-2-pentyltetrahydrofuran-3-carboxylate **5**: ν_{max}(neat)/cm^{-1} 1777 (O–CO) and 1732 (CO_2Et); δ_H (400 MHz) 4.54 (1 H, dt, 2-H), 4.20 (2 H, dq, OCH_2CH_3), 3.01 (1 H, m, 3-H), 2.98 (1 H, dd, 4-H), 2.75 (1 H, dd, 4-H), 1.74 (2 H, m, $C_4H_9CH_2$), 1.49–1.27 [6 H, m, $CH_3(CH_2)_3$], 1.28 (3 H, t, OCH_2CH_3) and 0.87 (3 H, m, CH_3); δ_C (100.4 MHz) 174.5 (s), 171.0 (s), 81.9 (d, C-2), 61.6 (t), 45.7 (d, C-3), 35.2 (t, C-4), 32.1 (t), 31.2 (t), 24.7 (t), 22.3 (t), 14.0 (q) and 13.8 (q); $[\alpha]_D^{25}$ +31.4 (*c* 0.7, $CHCl_3$), $\Delta\varepsilon_{222}$ = +0.2, >99% ee, by HRGC.

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