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A convenient chemoenzymatic synthesis of (1*S*,7a*S*)-1-hydroxy-5-oxo-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane—a key intermediate of steroids

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Abstract

A porcine pancreatic lipase mediated enzymatic hydrolysis of (±)-1-acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5b**) furnished (1*S*,7a*S*)-1-acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**9**) and (1*R*,7a*R*)-1-hydroxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**8**) with >99% e.e. which on further chemical hydrolysis gave **1** and **ent-1**, key intermediates of steroids.

Keywords: Chemoenzymatic method; Enzymatic hydrolysis; Terpenoids; Steroids

1. Introduction

(1*S*,7a*S*)-1-Hydroxy-5-oxo-4-(2′-carboxyethyl)-7a-methyl-tetrahydro-indane (**1**) and its enantiomer are important key intermediates in the syntheses of a variety of natural occuring terpenoids and steroids (Fig. 1) [1]. A few approaches have been reported to obtain optically active **1** by involving asymmetric cyclization of methyl-7-(1-methyl-2,5-dioxo-cyclopentyl)-5-oxo-heptanoate (**2**) [2].

Asymmetric cyclization of achiral methyl-7-(1-methyl-2,5-dioxo-cyclopentyl)-5-oxo-heptanoate (**2**) mediated by (*S*)-(−)-proline offers optically enriched (1*S*,7a*S*)-1,5-dioxo-4-(2′-carboxyethyl)-7a-methyl tetrahydro-indane (**4**). However, this approach is not only time consuming but more importantly exhibits low optical induction. Although the chemical resolution of (±)-1,5-dioxo-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane (**3**) with ephedrine [1,3] in benzene afforded (1*S*,7a*S*)-1,5-dioxo-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane (**4**) in good optical purity, the use of benzene and L-ephedrine are not commercially viable due to carcinogenicity of benzene and restricted availability of ephedrine, respectively.

Consequent to the results of our earlier work in enzymatic studies with lipases [4,5], we expected that the enzymatic esterification or hydrolysis of (±)-1-hydroxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5a**) and (±)-1-acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5b**), respectively would be a feasible proposition.

2. Experimental

2.1. Materials and equipment

Enantiomeric excess (e.e.) were determined by chiral HPLC. HPLC was performed under the following condition: Chiracel OD (4.6 mm I.d. × 25 cm] λ = 254 nm, flow rate: 1 mL/min; mobile phase: hexane:isopropanol 95:05. Pig liver esterase (PLE), porcine pancreatic lipase (PPL), candida cylindracea lipase (CCL) candida antartica lipase (CAL) were procured from Sigma; lipozyme from Novo-Nordisk, chirazyme from Boehringer Manheim and *Trichosporium* sp. was grown in the laboratory. Infrared spectra were recorded with ATI MATT-SON RS-1 FT-IR spectrometer. Proton NMR spectra were recorded on

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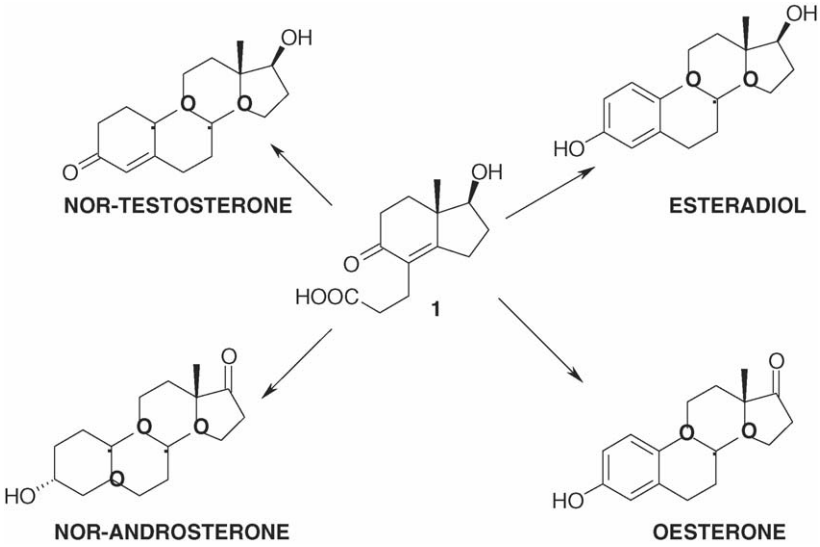


Fig. 1.

Bruker AC-200 machine in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained with Finningen MAT mass spectrometer.

2.2. Preparation of methyl 7-(1-methyl-2,5-dioxo-cyclopentyl)-5-oxo-heptanoate (2)

Methyl-5-oxo-6-heptenoate [6] (**6**, 5.4 g, 0.035 mol), 2-methylcyclo-pentane-1,3-dione (4.2 g, 0.037 mol) and anhydrous pyridine (1 eq.) were placed in dry toluene, refluxed under nitrogen for 18 h. After usual work-up gave crude Michael adduct 6.82 g, purified by column chromatography (**2**, 5.69 g, 61.5%); Liquid, IR (KBr): 1721, 2953, 1106 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.61 (S, 3H), 2.76 (t, 2H), 2.72 (t, 2H), 2.35–2.40 (m, 4H), 2.25 (t, 2H), 1.77–1.86 (m, 4H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.3 (s), 208.6 (s), 172.9 (s), 54.6 (s), 50.9 (q), 40.9 (t), 36.0 (t), 34.2 (t), 32.3 (t), 27.4 (t), 18.3 (q), 18.2 (t).

2.3. Preparation of 1,5-dioxo-4-(2′-carboxyethyl)-7a-methyl tetrahydro-indane (3a)

7-(1-Methyl-2,5-dioxo-cyclopentyl)-5-oxo-heptanoic acid (**2**, 4.5 g, 0.016 mol) was heated for 6 h at 50 °C in HCl (5N, 45 mL). After completion of the reaction, it was extracted with chloroform. Organic layer was separated, dried over anhydrous sodium sulphate and evaporated under vacuum to obtain **3a** (4.1 g) which on column chromatography afforded 1,5-dioxo-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane (**3a**, 3.61 g, 91.1%), solid, m.p. 126 °C: IR (KBr): 1743.40, 1709.20, 1663, 1660, 1217 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.09 (dd, 1H), 2.83 (q, 2H), 2.39–2.75 (m, 7H), 2.03–2.12 (m, 1H), 1.83 (dd, 2H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.1 (s), 197.4 (s), 178.3 (s), 164.8 (s), 131.7 (s), 48.8 (s), 35.3 (t), 32.6 (t), 32.4 (t), 28.3 (t), 24.2 (t), 20.9 (q), 20.7(t). MS: $(M+1)^+$: 237.1, $(M)^+$: 236.33.

2.4. Preparation of 1,5-dioxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (3b)

1,5-Dioxo-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane (**3a**, 3.5 g, 0.015 mol) in dry methanol (50 mL) was refluxed for 4 h under nitrogen in presence of catalytic H_2SO_4. After completion of the reaction, the reaction mixture was quenched with ice-water and extracted with chloroform. The organic layer was separated, dried over anhydrous sodium sulphate and the solvent evaporated under vacuum to obtain 1,5-dioxo-4-(2′-carbomethoxy-ethyl)-7a-methyltetrahydro-indane which on column chromatography afforded liquid (**3b**, 3.4 g, 86.30%); IR (KBr): 1740, 1664, 1663, 2953, 1216 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.54 (s, 3H), 2.95 (dd, 1H), 2.61–2.76 (m, 2H), 2.24–2.55 (broad m, 7H), 1.93–2.03 (m, 1H), 1.7–1.8 (dd, 1H), 1.20 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.8 (s), 196.7 (s), 172.9 (s), 164.2 (s), 131.7 (s), 51.0 (q), 48.5 (s), 35.1 (t), 32.5 (t), 32.3 (t), 28.2 (t), 24.0 (t), 20.8 (q), 20.7 (t).

2.5. Preparation of (±) (cis)-1-hydroxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (5a)

1,5-Dioxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**3b**, 3.0 g, 0.012 mol) in dry methanol (50 mL) was heated to 50 °C under nitrogen, $NaBH_4$ (0.28 g, 0.007 mol) was added. After 6 h methanol was evaporated under vacuum and crude reaction mass was extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulphate and the solvent evaporated under vacuum to obtain crude **5a**. The purification of crude **5a** was carried out by column chromatography to obtain (±) (*cis*)-1-hydroxy-5-oxo-4-(2′-carbomethoxy-ethyl)-7a-methyltetrahydro-indane (**5a**, 2.94 g, 97.32%); liquid, ^1H NMR (200 MHz, $CDCl_3 + CCl_4$): δ 3.72 (q, 1H), 3.55 (s, 3H), 2.25–2.53 (m, 8H), 1.96–2.04 (m, 2H), 1.64–1.90 (m, 2H), 1.02 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.6 (s), 173.5 (s), 169.0 (s), 131.8 (s), 80.9 (d),

51.3 (q), 45.2 (s), 33.9 (t), 33.4 (t), 32.6 (t), 29.6 (t), 25.2 (t), 21.6 (t), and 15.40 (q); MS: $(M+1)^+$: 253.16.

2.6. Preparation of (±) (cis)-1-acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5b**)

(±) (*cis*)-1-Hydroxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5a**, 2.8 g, 0.011 mol) was treated with acetic anhydride (1.41 g, 0.0138 mol) in presence of pyridine to obtain crude **5b** (3 g), purification by column chromatography afforded (±) (*cis*)-1-acetoxy-5-oxo-4-(2′-carbomethoxy-ethyl)-7a-methyltetrahydro-indane (**5b**, 2.8 g, 85.8%). Liquid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.77(dd, 1H), 3.62 (s, 3H), 2.66 (dd, 1H), 2.36–2.57 (m, 7H), 2.23–2.28 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.98 (dd, 1H), 1.8–1.86 (m, 2H), 1.23 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.2 (s), 173.3 (s), 170.2 (s), 167.1 (s), 131.7 (s), 80.9 (d), 51.3 (q), 44.5 (s), 33.7 (t), 33.0 (t), 32.3 (t), 26.3 (t), 25.2 (t), 21.4 (t), 20.8 (q), and 16.6 (q). HRMS: $(M+1)^+$: 295.16.

2.7. Enzymatic hydrolysis of (±) (cis)-1-acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5b**)

(±) (*cis*)-1-Acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5b**, 340 mg) ester was stirred at 30 ± 1 °C in phosphate buffer (27 mL, pH 7, 0.1M), ethanol (3 mL) and PPL (340 mg). After 24 h reaction mixture was passed through celite and extracted with chloroform. The organic layer was separated, dried over sodium sulphate and evaporated under vacuum to obtain crude mass (300 mg). It was chromatgraphed to obtain fraction I (154 mg, 45.2%) and fraction II (105 mg, 36.0%) ***Fraction I***: Solid; (1*S*,7*aS*)-1-acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**9**): $[\alpha]^{25}_D$ = +32.03° (c = 1.0, $CHCl_3$); e.e. 99.2% (determined by chiral HPLC of **ent-8**, which was prepared from **9**, column: Chiracel OD [4.6 mm I.d. × 25 cm] λ = 254 nm, flow rate: 1 mL/min; mobile phase: hexane:isopropanol 95:05; retention time for **ent-8** = 23.00, retention time for racemic: 20.86 and 22.70 (50.14: 49.86 ratio)). IR (KBr): 1733, 1660, 1659, 2977, 1215 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.78 (dd, 1H), 3.64 (s, 3H), 2.64 (dd, 1H), 2.25–2.53 (m, 7H), 2.17–2.33 (m, 2H), 2.09 (s, 3H), 1.86–1.98 (dd, 1H), 1.8–1.85 (dd, 1H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.6 (s), 172.70 (s), 169.7 (s), 166.8 (s), 131.1 (s), 80.4 (d), 50.7 (q), 44.0 (s), 33.2 (t), 32.2 (t), 31.8 (t), 25.9 (t), 24.7 (t), 20.9 (t), 20.2 (q), and 16.0 (q). ***Fraction II***: Liquid (1*R*,7*aR*)-1-hydroxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**8**): $[\alpha]^{25}_D$ = −36.68° (c = 1.0, $CHCl_3$); e.e. 99.1% (determined by chiral HPLC, column: Chiracel OD [4.6 mm I.d. × 25 cm] λ = 254 nm, flow rate: 1 mL/min; mobile phase: hexane:isopropanol 95:05; retention time for **8** = 21.07, retention time for racemic: 20.86 and 22.70 (50.14: 49.86 ratio); IR (KBr): 1733, 1646, 1647, 3448, 2952, 1215 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.79 (dd, 1H), 3.61 (s, 3H), 2.23–2.56 (m, 8H), 2.02–2.1 (m, 2H), 1.74–1.8 (m, 2H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3 + CCl_4$): δ 197.6 (s), 173.5 (s), 169.0 (s), 131.8 (s), 80.9 (d), 51.0 (q), 45.0 (s), 33.9 (t), 33.4 (t), 32.6 (t), 29.6 (t), 25.0 (t), 21.6 (t), 15.4 (q).

2.8. Preparation of (1S,7aS)-1-hydroxy-5-oxo-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane (**1**)

A mixture of (1*S*,7*aS*)-1-acetoxy-5-one-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**9**, 112 mg) and HCl (6.5N, 12 mL) was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was extracted with chloroform. The organic layer was separated, dried over anhydrous sodium sulphate and evaporated under vacuum to obtain crude mass (79 mg) which on column chromatography afforded (1*S*,7*aS*)-1-hydroxy-5-oxo-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane (**1**, 64 mg, 70.5%); solid; $[\alpha]^{25}_D$ = +31.5° ± 1 (c = 1.0, acetone)[1]; observed $[\alpha]^{25}_D$ = +30.9 (c = 1.0, acetone); ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 3.58 (dd, 1H), 2.3–2.65 (m, 3H), 2–2.3 (m, 5H), 1.75–2 (m, 2H), 1.5–1.75 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): δ 197.1 (s), 174.0 (s), 170.0 (s), 130.8 (s), 79.41 (d), 44.8 (s), 43.4 (t), 43.0 (t), 42.3 (t), 38.7 (t), 34.6 (t), 30.9 (t), 25.0 (q); MS: $(M+1)^+$: 239.14.

2.9. Preparation of (1R,7aR)-1-hydroxy-5-oxo-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane (***ent 1***)

A mixture of (1*R*,7*aR*)-1-hydroxy-5-one-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**8**, 80 mg) and HCl (6.5N, 8 mL) was stirred at room temperature for 12 h. After the completion of the reaction, the reaction mixture was extracted with chloroform. The organic layer was separated, dried over anhydrous sodium sulphate, and evaporated under vacuum to obtain crude mass (84 mg), which on purification by column chromatography afforded (1*R*,7*aR*) 1-hydroxy-5-one-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane (**ent-1**, 53 mg, 70.1%). Solid; m.p. 112 °C, $[\alpha]^{25}_D$ = −30.8 (c = 1.0, acetone); IR (KBr): 1708, 1632, 3307, 3400 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.55 (dd, 1H), 2.3–2.65 (m, 8H), 2.0–2.3 (m, 2H), 1.70–2 (m, 2H), 1.1 (s, 3H); MS $(M+1)^+$: 239.14.

2.10. Preparation of (1S,7aS)-1-hydroxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (***ent-8***)

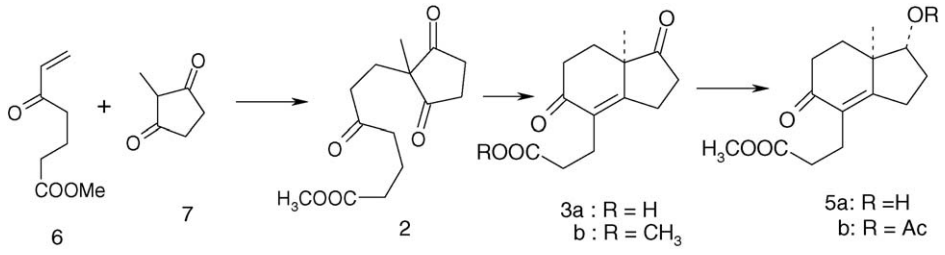
(1*S*,7*aS*)-1-hydoxy-5-oxo-4-(2′-carboxyethyl)-7a-methyl tetrahydro-indane (**1**) was treated with diazomethane to afford **ent-8**. e.e. 99.2% (determined by chiral HPLC, column: Chiracel OD [4.6 mm I.d. × 25 cm] λ = 254 nm, flow rate: 1 mL/min; mobile phase: hexane:isopropanol 95:05; retention time for **ent-8** = 23.00, retention time for racemic: 20.56 and 22.20 (50.14: 49.86 ratio); IR (KBr): 1733, 1646, 1647, 3448, 2952, 1215 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.78 (dd, 1H), 3.59 (s, 3H), 2.34–2.60 (m, 8H), 2.02–2.09 (m, 2H), 1.6–1.95 (dd, 2H), 1.07 (s, 3H).

3. Results and discussion

The synthesis of the substrate **5a** and **5b** commenced from **6**. Accordingly Michael addition of methyl-5-oxo-6-heptenoate (**6**) [6] on 2-methylcyclopentane-1,3-dione (**7**) gave methyl-7-(1-methyl-2,5-dioxo-cyclopentyl)-5-oxo-heptanoate (**2**). Subsequently **2** underwent aldol and elimination reaction in the presence of acid to generate a 1,5-dioxo-4-(2′-carboxyethyl)-7a-methyltetrahydro-indane (**3a**), which on esterification gave 1, 5 - dioxo - 4 - (2′ - carbo-methoxyethyl)-7a-methyltetrahydro-indane (**3b**). The reduction of 1,5-dioxo-4-(2′-carbomethoxy ethyl)-7a-methyltetrahydro-indane (**3b**) with $NaBH_4$ gave (±) (*cis*)-1 - hydroxy - 5 - oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5a**) (Scheme 1).

During the last three decades, many examples of the lipase catalysed hydrolysis of esters and amides have been reported with unprecedented success [7–10]. Our interest in preparing (1*S*,7a*S*) enantiomer of **5** from its racemic precursor led us to investigate first the enzymatic hydrolysis of ester. Thus, the acetoxy derivative (**5b**) was treated with various enzymes sequentially in phosphate buffer (pH 7). However, even after 72 h, low enantioselectivity was observed even though hydrolysis was taking place. This failure led us to investigate the medium engineering approach which involved the use of a co-solvent.

(±) (*cis*)-1-Acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5b**) was treated with different enzymes in phosphate buffer (pH 7) with 10% ethanol as a co-solvent (Table 1, Scheme 2). In case of PPL enzyme (±) **5b** was effectively hydrolysed to (1*R*,7a*R*) derivative (**8**) thus giving rise to the acetoxy derivative **9** with >99.2% e.e. The optical purity of **8** was determined by chiral HPLC using Chiracel OD [4.6 mm I.d. × 25 cm] column (λ = 254 nm, flow rate: 1 mL/min; mobile phase: hexane: isopropanol 95:05). The acetoxy derivative **9** was converted into **ent 8** by HCl hydrolysis and subsequent esterification. X-ray structure of **9** showed *cis* configuration (Fig. 2). In order to establish the absolute configuration, we tried to make ester of **8** with chiral acids but failed to get the crystals for X-ray study. In order to know absolute configuration of **8** and **9**, these were hydrolysed with 6.5N HCl to obtain the product **ent 1** and **1**, respectively (Table 2). Specific rotation of **1** was found to be

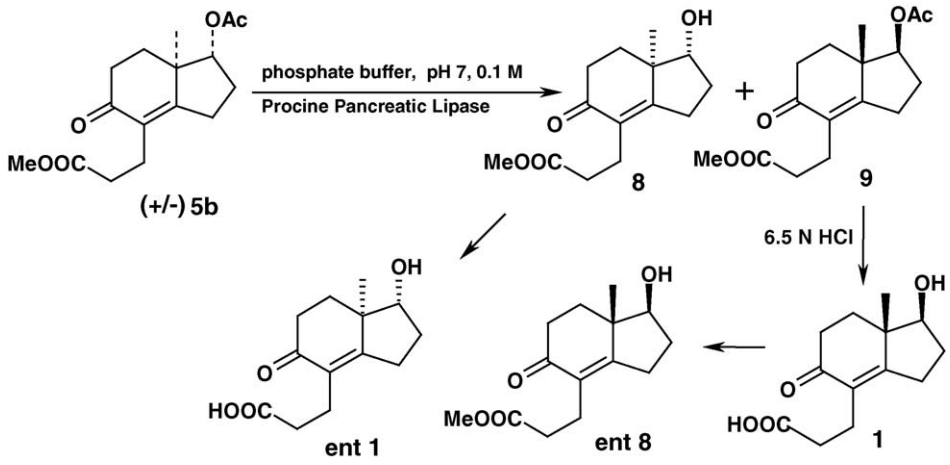


Scheme 1.

Table 1
Hydrolysis of **5b** with lipases

Lipase	Solvent[a]	Time (h)	8		9	
			% yield	e.e[b]	% yield	e.e[c]
Lipozyme	Phosphate buffer	76	31	7.7	38	28.4
Pig liver esterase (PLE)	Phosphate buffer	24	0.0		0.0	
Pig liver esterase (PLE)	Phosphate buffer: ethanol	24	95	0.0	–	–
Porcine pancreatic lipase (PPL)	Phosphate buffer	38	32	49.8	41	35.6
Porcine pancreatic lipase (PPL)	Phosphate buffer: ethanol	24	36	99.1	45	99.2
Trichosporium sp.	Phosphate buffer	24	99	0.0	–	–
Trichosporium sp.	Phosphate buffer: ethanol	24	99	0.0	–	–
Chirazyme	Phosphate buffer	24	37	9.1	26	7.6
Chirazyme	Phosphate buffer: ethanol	24	37	9.1	26	27.6
Candida cylindracea lipase (CCL)	Phosphate buffer	24	29	6.1	35	4.1
Candida cylindracea lipase (CCL)	Phosphate buffer: ethanol	24	22	25.2	38	29.1
Candida antartica lipase (CAL)	Phosphate buffer	24	25	8.3	31	5.2
Candida antartica lipase (CAL)	Phosphate buffer: ethanol	24	33	18.7	36	4.1

[a] (**5b**, 100 mg), phosphate buffer (10 mL, pH 7, 0.1 M) or phosphate buffer (9 mL, pH 7, 0.1 M) + ethanol (1 ml), lipase (100 mg) at 30 ± 1 °C.
[b] Determined by HPLC Chiracel OD (4.6 mm I.d. × 25 cm, λ = 254 nm, 1 mL/min; hexane: isopropanol 95:05).
[c] Determined by HPLC Chiracel OD (4.6 mm I.d. × 25 cm, λ = 254 nm, 1 mL/min; hexane: isopropanol 95:05) as **ent-8**.



Scheme 2. Enzymatic hydrolysis of **5b** in phosphate buffer (7 pH) and 10% ethanol as co-solvent.

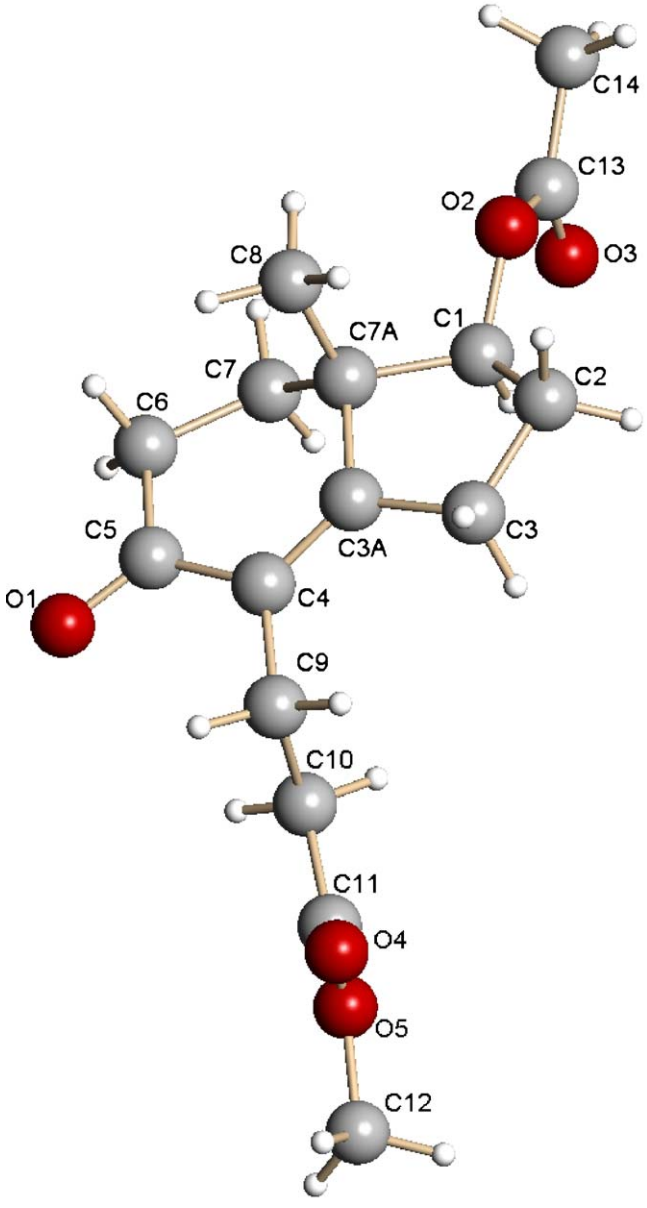


Fig. 2. PLUTO diagram single crystal structure of **9**, ellipsoids are drawn at 40% probability.

Table 2
Hydrolysis of **5b**[a] with lipases

Lipase	Time (h)	8		9	
		%	e.e[b]	%	e.e[c]
Porcine pancreatic lipase (PPL)	24	36	99.1	45	99.2
Pig liver esterase (PLE)	24	95	0.0	–	–
Trichosporium sp.	24	99	0.0	–	–
Chirazyme	24	37	9.1	26	27.6
Candida cylindracea lipase (CCL)	24	22	25.2	38	29.1
Candida antartica lipase (CAL)	24	33	18.7	36	4.1

[a] (**5b**, 100 mg), phosphate buffer (9 mL, pH 7, 0.1 M), ethanol (1 ml), lipase (100 mg) at 30 ± 1 °C.
[b] Determined by HPLC Chiracel OD (4.6 mm I.d. × 25 cm, λ = 254 nm, 1 mL/min; hexane: isopropanol 95:05).
[c] Determined by HPLC Chiracel OD (4.6 mm I.d. × 25 cm, λ = 254 nm, 1 mL/min; hexane: isopropanol 95:05) as **ent-8**.

identical with that reported for (1*S*,7a*S*)-1-hydroxy-5-oxo-4-(2′-carboxyehtyl)-7a-methyltetrahydro-indane (**1**) [1a].

4. Conclusion

In conclusion, we have established an efficient enzymatic hydrolysis of (±)-1-acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**5b**) to furnish (1*S*,7a*S*)-1-acetoxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**9**) in 99.2% e.e. and (1*R*,7a*R*)-1-hydroxy-5-oxo-4-(2′-carbomethoxyethyl)-7a-methyltetrahydro-indane (**8**) 99.1% e.e. with porcine pancreatic lipase in a phosphate buffer (pH 7) and 10% ethanol as a co-solvent, which on chemical hydrolysis gave **1** and **ent-1**, respectively.

Acknowledgement

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