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Synthesis of optically active α-methylene γ-lactones through lipase-catalyzed kinetic resolution

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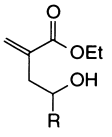
Abstract

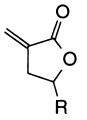
The lipase-catalyzed kinetic resolution of the γ-hydroxy esters **1a**,**b** and their subsequent acid-mediated cyclization afford the optically active α-methylene γ-lactones **2a**,**b** in high yields (71–89%) and in up to 95% enantiomeric excess. The direct enzymatic lactonization of the racemic γ-hydroxy esters **1a**,**b** to the lactones **2a**,**b** represents a less satisfactory alternative, since poor enantioselectivies have been obtained.

1. Introduction

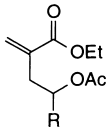
The α-methylene γ-lactone functionality is a key structural feature in numerous natural products and biologically active compounds.[1] Several methods have been developed for the synthesis of α-methylene γ-lactones,[1,2] even the asymmetric synthesis of these building blocks has been reported;[3] nevertheless, little is known on the biocatalytic preparation of optically active α-methylene γ-lactones. Herein we report the first-time synthesis of the optically active α-methylene γ-lactones **2a**,**b** through the kinetic resolution by lipases catalysis.



1a: R = Me
1b: R = Ph



2a
2b



3a
3b

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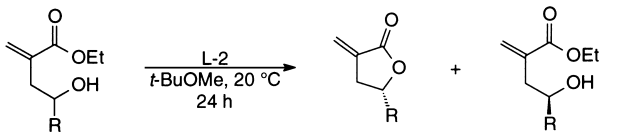
2. Results and discussion

The racemic γ-hydroxy esters **1a**,**b**, which were prepared according to literature procedure,[4] were submitted to enzyme screening for the biocatalytic cyclization. Only the lipase from *Candida antartica* (CHIRAZYME® L-2, Roche Diagnostics, formerly Boehringer Mannheim, Germany) was effective in catalyzing the lactone formation of these substrates (Scheme 1), while the other tested lipases from *Burkholderia* sp. (CHIRAZYME® L-6) and *Porcine pancreas* (CHIRAZYME® L-7) were ineffective. The enzymatic reaction of hydroxy ester **1a** (2.50 mg, 15.8 μmol) with the lipase L-2 (2.50 mg) gave at 54% conversion an enantiomeric excess (ee) of 11% for the *R*-**2a** lactone and 13% for the residual ester *S*-**1a**. For the sterically more demanding phenyl-substituted hydroxy ester **1b** (3.48 mg, 15.8 μmol), in about the same reaction time (24 h) but with a ten-fold amount of enzyme (25.0 mg of L-2), ee values of 16% for the lactone *S*-**2b** and 40% for the hydroxy ester *R*-**1b** were observed at 71% conversion. Although the latter substrate was converted more slowly due to the sterically larger phenyl group, the enantiodifferentiation between the groups at the stereogenic center are about the same for the γ-lactone products **2a**,**b**.



rac-**1**

	% convn		% ee		% ee
a: R = Me	54	*R*(+)-**2a**:	11	*S*(+)-**1a**:	13
b: R = Ph	71	*S*(+)-**2b**:	16	*R*(+)-**1b**:	40

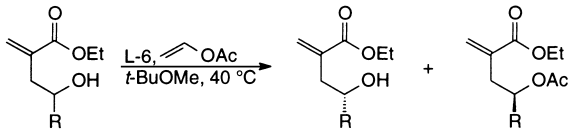
Scheme 1. Lipase-catalyzed lactonization of γ-hydroxy esters **1a**,**b**

Since the enzymatic cyclization of the racemic γ-hydroxy esters **1a**,**b** proved to be ineffective for the preparation of optically active α-methylene γ-lactones **2a**,**b**, an alternative route has been explored. This alternative consisted of the lipase-catalyzed kinetic resolution of hydroxy ester **1** and subsequent acid-mediated cyclization.

In the enzyme-catalyzed acetylation of the hydroxy esters **1a**,**b**, the lipase L-6 showed the best results for the tested enzymes L-1, L-7 and lipases from *Candida rugosa* (CHIRAZYME® L-3) and *Candida antarctica*, fraction A (CHIRAZYME® L-5). With this biocatalyst (Table 1), the hydroxy ester *R*-**1a** was obtained in high yield with an ee value of 64% and the acetate *S*-**3a** with 36% ee at 64% conversion. As in the case of the enzymatic cyclization by the lipase L-2 (Scheme 1), the phenyl-substituted hydroxy ester **1b** reacted more slowly in the biocatalytic transesterification by the lipase L-6 than the methyl derivative **1a** (Table 1). However, for the hydroxy ester **1b,** perfect kinetic resolution was achieved, which furnished the ester *S*-**1b** and the acetate *R*-**3b** in good yields and ee values of 99% at 50% conversion. For this substrate, the phenyl group at the stereogenic center effects a much better enantiomeric differentiation than the methyl group in ester **1a**. The unknown acetates **3a**,**b**, which were required as reference samples for HPLC analysis, were synthesized by acetylation of the racemic hydroxy esters **1a**,**b** with acetic anhydride and fully characterized.

Cyclization of the optically active hydroxy esters **1a**,**b** with trifluoroacetic acid (Scheme 2) afforded the γ-lactones **2a**,**b** in good yields. For the methyl-substituted product **2a**, no racemization occurred, while for the phenyl derivative **2b** a slight decrease of the ee value from 99% of the ester

Table 1
Lipase-catalyzed kinetic resolution of γ-hydroxy esters **1** on the preparative scale



rac-**1**
a: R = Me
b: R = Ph

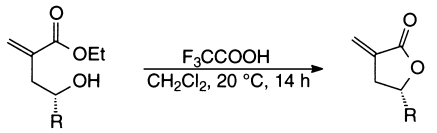
R(-)-**1a**
S(-)-**1b**

S(+)-**3a**
R(+)-**3b**

	time	convn[a)]	enantiomeric excess [% ee][b)]		yield [%][c)]		
substrate[d)]	[h]	[%]	(-)-**1**	(+)-**3**	(-)-**1**	(+)-**3**	E[e)]
1a	6	64	64	36	95	84	4
1b	27	50	99	99	72	70	>200

a) The % conversion was calculated from the enantiomeric excess of the starting material (ee_s) and the product (ee_p) according to % convn = ee_s / (ee_s + ee_p) [ref 5]; b) the enantiomeric excess (ee) was determined by HPLC analysis (Chiralcel OD and OB-H columns), error ca. 1% of the stated values; c) normalized to 100% convn ; d) 100 mg of L-6, 120 mg (758 μmol) of **1a** and 130 mg (590 μmol) of **1b** were used; e) the enantioselectivity (E) was calculated (ref 5) from the enantiomeric excess of the starting material (ee_s) and the conversion according to E = ln [(1 - convn) (1 – ee_s)] / ln [(1 – convn) (1 + ee_s)].

1b to 95% ee of the lactone **2b** was observed. This is presumably due to the fact that the stereogenic center is located at a benzylic position in the substrate **1b**, which is much more prone to racemization than the methyl-substituted ester **1a**.



	% ee	yield (%)		% ee
R(-)-**1a**:	64	71	*R*(+)-**2a**:	64
S(-)-**1b**:	99	89	*S*(+)-**2b**:	95

Scheme 2. Lactonization of the optically active γ-hydroxy esters **1a**,**b**

3. Conclusion

Our present studies have demonstrated that the lipase-catalyzed kinetic resolution of racemic γ-hydroxy ester **1**, coupled with subsequent acid-mediated cyclization, is an effective method for the synthesis of optically active α-methylene γ-lactone **2**. This enzymatic process represents an attractive and convenient alternative to the chiral-auxiliary-mediated preparation of the optically active α-methylene γ-lactones **2a**[3a] and **2b**[3b] since it affords higher enantiomeric excesses under mild reaction conditions and does not require optically active starting materials. Moreover, no alternative route to our enzymatic one appears to be known for the optically active lactone **2a**.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 250 (^1H: 250 MHz, ^{13}C: 63 MHz), with $CHCl_3$ as internal reference standard. HPLC analyses were performed on Kontron (Neufahrn, Germany) equipment, furnished with a spectrophotometer UVIKON 720 LC and a polarimetric detector CHIRALYSER 1.6 from IBZ Messtechnik (Hannover, Germany). The stationary phases were chiral columns (Daicel® CHIRALCEL OD and CHIRALCEL OB-H from Chiral Technologies Europe, Illkirch, France). IR spectra were recorded on a Perkin–Elmer 1420 ratio-recording infrared spectrophotometer. The specific rotation $[\alpha]_D^{25}$ was determined in $CHCl_3$ on a Perkin–Elmer 241 MC polarimeter. TLC analysis was conducted on precoated silica gel foils Polygram SIL G/UV_{254} from Macherey Nagel; the spots were visualized by phosphomolybdic acid. Silica gel (32–64 μm, Macherey Nagel) was used for flash chromatography. The commerically available lipases were obtained as gift samples from Roche Diagnostics (Penzberg, Germany, formerly Boehringer Mannheim GmbH) and used as received.

4.2. General procedure for the lipase-catalyzed lactonization

The lipase powder (2.50 mg for **1a** and 25.0 mg for **1b**) was added to a solution of the racemic hydroxy ester **1** (2.50 mg of **1a**, 15.8 μmol and 3.48 mg of **1b**, 15.8 μmol) in *tert*-butyl methyl ether (1 mL) and the reaction mixture was vigorously stirred at 20°C for ca. 24 h. Subsequently, the enzyme was removed by centrifugation and the residual solution was submitted to chiral HPLC analysis.

4.3. General procedure for the lipase-catalyzed transesterification of the hydroxy esters *1*

To a solution of the hydroxy ester **1** (758 μmol of **1a** and 590 μmol of **1b**) in *tert*-butyl methyl ether (100 mL) were added 100 mg of lipase L-6 and 10 equiv. of vinyl acetate. The mixture was vigorously stirred at 20°C for the time given in Table 1, the enzyme was removed by filtration, and the solvent was evaporated (20°C, 10 torr). The hydroxy esters **1** and the acetoxy esters **3** were separated by silica gel chromatography (1:1 petroleum ether:Et_2O for **1a** and 3:1 for **1b**) and submitted to HPLC analysis. The yields and ee values are given in Table 1.

Ethyl (*S*)-4-acetoxy 2-methylenepentanoate (*S*)-**3a**: $[\alpha]_D^{25} = +1.68$ (*c* 1.26, $CHCl_3$). Ethyl (*R*)-4-acetoxy 2-methylene-4-phenylbutanoate (*R*)-**3b**: $[\alpha]_D^{25} = +40.6$ (*c* 1.08, $CHCl_3$).

4.4. General procedure for the acid-catalyzed lactonization of the hydroxy esters *1*

To a solution of 210 μmol of the appropriate optically active hydroxy ester **1** in 1.5 mL of CH_2Cl_2 were added 16.2 μL of trifluoroacetic acid. After stirring for 14 h at 20°C, the reaction mixture was washed with saturated, aqueous $NaHCO_3$ (0.5 mL), dried over $MgSO_4$, and the solvent was removed (20°C, 10 torr). Silica gel chromatography of the residue with CH_2Cl_2 as eluent gave the lactones **2** in good yields (Scheme 1).

4.5. General procedure for the acetylation of the hydroxy esters *1*

To a solution of 525 μmol of the racemic hydroxy ester **1** in 5 mL of CH_2Cl_2 were added 59.0 mg (578 μmol) of acetic anhydride, 79.7 mg (788 μmol) of triethylamine and 1.00 mg of

4-(dimethylamino)pyridine (DMAP), and the reaction mixture was stirred at 20°C for 24–40 h. The reaction mixture was washed with dilute hydrochloric acid (1×1 mL) and water (1×1 mL), dried over $MgSO_4$, and concentrated (20°C, 10 torr). Flash chromatography (silica gel, 5:1 petroleum ether:Et_2O for **3a** and 10:1 for **3b**) afforded the esters **3a** and **3b** in 82 and 55% yields.

4.6. Ethyl 4-acetoxy-2-methylenepentanoate *3a*

Colorless oil; R_f (5:1 petroleum ether:Et_2O) = 0.41; ^{1}H NMR: δ 1.20 (d, J = 6.4 Hz, 3H, 5-H), 1.27 (t, J = 7.0 Hz, 3H, 2′H), 1.96 (s, 3H, 8-H), 2.42–2.60 (m, 2H, 3-H), 4.18 (q, J = 7.0 Hz, 2H, 1′-H), 5.00–5.13 (m, 1H, 4-H), 5.55 (m, 1H, 6-H), 6.18 (d, J = 1.5 Hz, 1H, 6-H); ^{13}C NMR: δ 14.1 (q, C-2′), 19.8 (q, C-8), 21.1 (q, C-5), 38.3 (t, C-3), 60.7 (t, C-1′), 69.2 (d, C-4), 127.1 (t, C-6), 136.8 (s, C-2), 166.6 (s, C-1), 170.4 (s, C-7); IR (neat): ν 3010, 2935, 2874, 1724, 1631 cm^{-1}; HPLC: t_R [CHIRALCEL OB-H (*n*-hexane:*iso*-propanol, 98:2), flow 0.60 mL/min, 220 nm)] = 16.8, 20.0. Anal. calcd for $C_{10}H_{16}O_4$ (200.2): C, 59.98; H, 8.05. Found: C, 60.15; H, 7.86.

4.7. Ethyl 4-acetoxy-2-methylene-4-phenylbutanoate *3b*

Colorless oil; R_f (10:1 petroleum ether:Et_2O) = 0.18; ^{1}H NMR: δ 1.33 (t, J = 7.3 Hz, 3H, 2′-H), 2.06 (s, 3H, 11-H); 2.85 (m, 2H, 3-H), 4.22 (q, J = 7.3 Hz, 2H, 1′-H); 5.55 (d, J = 1.2 Hz, 1H, 9-H); 6.00 (dd, J = 8.3, 8.0 Hz, 1H, 4-H), 6.22 (d, J = 1.2 Hz, 1H, 9-H), 7.35–7.37 (m, 5H, H_{aromat}); ^{13}C NMR: δ 14.1 (q, C-2′), 21.1 (q, C-11), 39.3 (t, C-3), 60.8 (t, C-1′), 74.1 (d, C-4), 126.3, 128.4 (2×d C-6, C-7), 127.7 (t, C-9), 127.9 (d, C-8), 136.3 (s, C-2), 140.0 (s, C-5), 166.5 (s, C-1), 170.0 (s, C-10); IR (CCl_4): ν 2960, 1760, 1700, 1540 cm^{-1}; HPLC: t_R [CHIRALCEL OD (*n*-hexane/*iso*-propanol 95:5), flow 1.00 mL/min, 220 nm)] = 6.75, 7.48. Anal. calcd for $C_{15}H_{18}O_4$ (262.3): C, 68.69; H, 6.92. Found: C, 68.96; H, 6.67.

Acknowledgements

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