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Lipase-catalyzed kinetic resolution of racemic seven-membered substituted lactones

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Abstract

Optically active 3-, 4-, 5-, or 6-methyl substituted seven-membered lactones were prepared by *Candida antarctica* lipase (CAL)-catalyzed kinetic resolution of the racemic lactones. Among these lactones, only in the case of 5-methylhexanolide (*R*)-isomer reacts faster than the other enantiomer, while the rest of lactones show (*S*)-selectivity.

Keywords: enzymes and enzyme reaction; hydrolysis; lactone.

Lipase-catalyzed enantioselective hydrolysis has been known as a method for preparing optically active five- or six-membered substituted lactones.[1] Rousseau and co-workers reported that enzymatic hydrolysis of γ- and δ-lactones using commercially available horse liver esterase (HLE), pig liver esterase (PLE), or pig pancreatic lipase (PPL), gave optically active lactones.[2] On the contrary, substituted seven-membered lactones can be utilized for the kinetic resolution only if they are substituted at the 6-position. Fellous and co-workers have reported the hydrolysis of 6-substituted hexanolide by esterase (PLE and HLE).[3] They have stated that the stereoselectivity of the reaction was influenced by the bulkiness of the substituents at the 6-position. Thus, although the ethyl derivative showed high selectivity, the methyl analog afforded poor selectivity. Until now, there has been no report on enantioselective hydrolysis of seven-membered lactones which have a chiral carbon at the 3-, 4-, or 5-position.[4] In this communication, we report the lipase-catalyzed kinetic resolution of 3-, 4-, 5-, or 6-methyl substituted seven-membered lactones.

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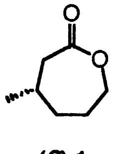
The substrates, racemic methylhexanolides (**1a–d**), were synthesized with Baeyer–Villiger oxidation of the corresponding methylcyclohexanones.[5] Kinetic resolution of the lactones (**1a–d**) with *Candida antarctica* lipase (CAL) was examined in water-saturated diisopropyl ether (IPE) and the results are summarized in Table 1.

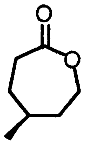
Table 1
CAL catalyzed hydrolysis of methyl substituted seven-membered lactones **1**[a]

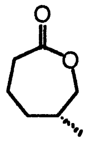
Position of methyl group	Conversion of **1** (%)	Ee of recovered **1** (%)[b] (configuration)	*E*[c]
1a; 3-	47	82 (*R*)	53
1b; 4-	50	72 (*R*)	13
1c; 5-	50	92 (*S*)	79
1d; 6-	50	94 (*R*)	>100

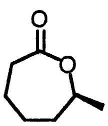
[a] Lactone; 8 mg, CAL; 2 mg, in 2 ml of IPE/H_2O at 36°C for 24 h.
[b] Determined by GC (CYCLODEX β 236M 25 m × 0.25 μm).
[c] Calculated from conversion and substrate's ee value.

Thus, in the reaction of **1b**, the (*S*)-isomer reacted faster than the (*R*)-isomer.[6] In the resolution of lactone **1d**, the lipase also has the (*S*)-preferency. Previously, PLE-catalyzed hydrolysis of **1d** was reported,[3,7] and we have found that the stereoselectivity of CAL is better than that of PLE. The oxidation of 3-methylcyclohexanone afforded a 1:1 mixture of **1a** and **1c**. Attempted isolation of **1a** and **1c** by distillation, HPLC, and GPC was unsuccessful. Since the separation of **1a** and **1b** was difficult, CAL-catalyzed hydrolysis of the mixture was examined. The reaction afforded the hydroxyhexanoic acid (*S*)-**2a** and (*R*)**-2c** along with the recovered two enantiomers, (*R*)-**1a** and (*S*)-**1c**. The absolute configurations of the recovered **1a** and **1c** were determined by comparing their retention times of GC with those of (*R*)-3- and (*R*)-5-methylhexanolide derived from commercially available (*R*)-3-methylcyclohexanone.[8] The stereoselectivity in the hydrolysis of **1b** using CAL was lower than that of hydrolysis of **1a** and **1c**. Only the (*R*)-isomer of **1c** reacts faster than the (*S*)-isomer while the rest of lactones show (*S*)-selectivity.

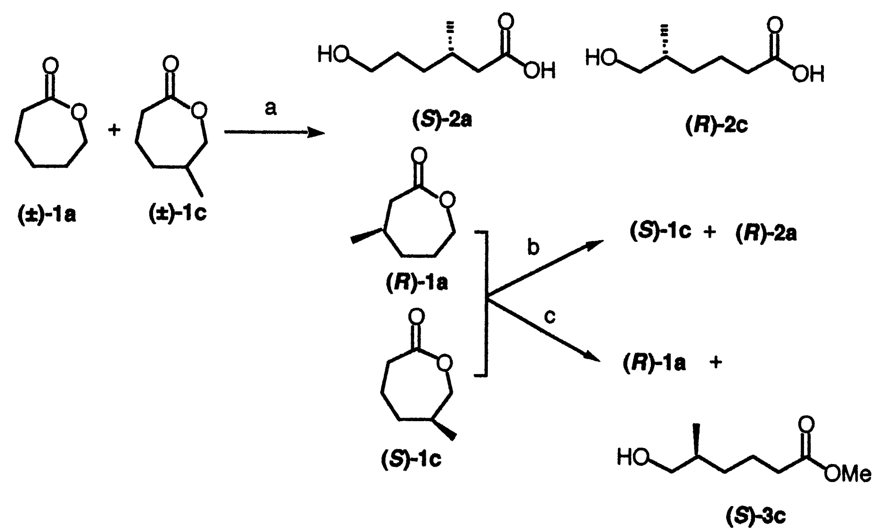

(*S*)-1a


(*S*)-1b


(*R*)-1c


(*S*)-1d

The kinetic resolution with CAL on a preparative scale provided an enantiomerically pure 1.5 g of (*R*)-**1a** and (*S*)-**1c**, starting from 4.0 g of the mixture of **1a**, **c** (800 ml IPE/H_2O, 1.0 g CAL). The resolution of the mixture of (*R*)-**1a** and (*S*)-**1c** with PLE afforded (*R*)-**2a** and (*S*)-**1c**.[9] Compounds (*R*)-**1a** and (*S*)-**1c** were also separated by using extrelut® as a solid acid to give methyl ester (*S*)-**3c** and (*R*)-**1a** (Scheme 1).[10]



Scheme 1. (a) With CAL in $\mathrm{Pr}^{i}_{2}\mathrm{O}/\mathrm{H}_2\mathrm{O}$ at 36°C. (b) With PLE in phosphate buffer (pH 7.4) at 36°C. (c) In the presence of extrelut® in MeOH at 30°C for 4 h

Thus, the resolution with CAL resulted in the first successful synthesis of optically active 3-, 4-, or 5-methyl substituted lactones in a gram scale. These lactones are of great potential value as synthons for the synthesis of natural products.

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5. The oxidation of 4-methylcyclohexanone afforded 4-methylhexanolide (**1b**). Yield 65%, ^{1}H NMR (CDCl$_3$) $\delta = 4.31$–4.15 (m, 2H), 2.71–2.58 (m, 2H), 1.96–1.85 (m, 2H), 1.82–1.73 (m, 1H), 1.56–1.46 (m, 1H), 1.00 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CDCl$_3$) $\delta = 175.78$, 69.26, 42.01, 37.23, 29.41, 27.89, 22.17. The oxidation of 2-methylcyclohexanone gave 6-methylhexanolide (**1d**) contaminated by 2-methylhexanolide (5%). We applied this mixture to CAL-catalyzed kinetic resolution without separation. The oxidation of 3-methylcyclohexanone gave 3-methylhexanolide (**1a**) and 5-methylhexanolide (**1c**) (1:1). Total yield 65%, (±)-**1a**; ^{1}H NMR (CDCl$_3$) $\delta = 4.29$–4.16 (m, 2H), 2.65–2.52 (m, 2H), 1.85–1.76 (m, 3H), 1.74–1.58 (m, 1H), 1.49–1.36 (m, 1H), 1.10 (d $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl$_3$) $\delta = 175.13$, 69.26, 42.01, 37.23, 29.41, 27.89, 22.17. (±)-**1c**; ^{1}H NMR (CDCl$_3$) $\delta = 4.11$–3.96 (m, 2H), 2.65–2.57 (m, 2H), 1.94–1.88 (m, 3H), 1.68–1.62 (m, 1H), 1.37–1.36 (m, 1H), 0.97 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (CDCl$_3$) $\delta = 176.00$, 73.99, 36.36, 34.42, 33.85, 21.64, 17.74.
6. The absolute configuration of the unreacted lactone **1b** was determined by comparison of the sign of the optical rotation with that reported. A pure enantiomer (*R*)-**1b** was obtained at a conversion of 72%. $[\alpha]_{\mathrm{D}}^{25}$ +44.9 (*c* 0.99, CHCl$_3$), ee>98%. Kayser, M.; Chen, G.; Stewart, J. *Synlett* **1999**, 153; Stewart, J. D.; Reed, K. W.; Martinez, C. A.; Zhu, J.; Chen, G.; Kayser, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 3541.

7. A small amount of 2-methylhexanolide was not hydrolyzed under these reaction conditions.
8. Retention times of GC with those enantiomers of (±)-**1a** and (±)-**1c** were 39.6, 42.0, 43.3, and 43.8 min, respectively. Retention times of GC with (*R*)-**1a** and (*R*)-**1c**, derived from 3-methylcyclohexanone, were 40.6 and 42.4 min, respectively.
9. A mixture of (*R*)-**1a** and (*S*)-**1c** (1.0 g) was dissolved in 250 ml of phosphate buffer (pH 7.4), 1.0 g of PLE was added and the mixture was stirred at 36°C for 3 h. The PLE was removed by filtration with extrelut®. The crude residue was purified by silica gel chromatography. Elution with CH_2Cl_2 afforded (*S*)-**1c** in 35% yield. $[\alpha]_D^{25}$ +41.3 (*c* 0.35, $CHCl_3$). The optical rotation of (*S*)-**1c** differed from the literature value in Ref. 9, while the ee (>98%) and configuration of (*S*)-**1c** determined in this experiment were confirmed by GC analysis.
10. Powdered extrelut® (25 g) was added to a solution of (*R*)-**1a** and (*S*)-**1c** (1.0 g) in CH_3OH (1000 ml) at 30°C. The resulting mixture was stirred for 4 h. After the removal of extrelut® by filtration, the reaction mixture was concentrated in vacuo. The crude residue was purified by silica gel flash column chromatography. Elution with CH_2Cl_2 afforded (*R*)-**1a** and methyl ester (*S*)-**3c**. (*R*)-**1a**; yield 30% (based on the total amount of the mixture). $[\alpha]_D^{25}$ −15.1 (*c* 0.35, $CHCl_3$). (*S*)-**3c** was contaminated by (*R*)-**3a** (23%).