Lipase-promoted asymmetric transesterification of 4-alkyloxetan-2-ones with ring-opening

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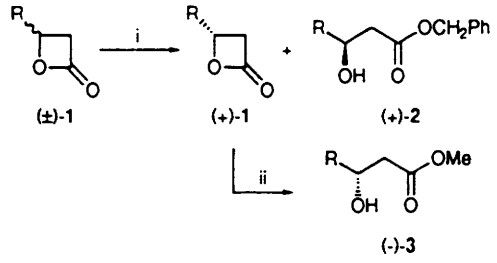
Lipase-catalysed reaction of (±)-4-alkyloxetan-2-ones **1a–c** with benzyl alcohol gave (*R*)-**1a** (R = Me) (36%, 96% ee) and benzyl (*S*)-3-hydroxybutanoate **2a** (51%, 85% ee), (*R*)-**1b** (R = Pr) (42%, 75% ee) and benzyl (*S*)-3-hydroxyhexanoate **2b** (45%, 69% ee) and (*S*)-**1c** (R = Pr^i, 41%, 95% ee) and benzyl (*R*)-3-hydroxy-4-methylpentanoate **2c** (43%, 90% ee), respectively.

Optically active oxetan-2-ones, β-lactones, of interest because of their ubiquity in biologically active natural products,[1,2] have been utilized as a monomer for biodegradable poly(hydroxyalkanoates).[3,4] They have, moreover, been employed as chiral building blocks having two electrophilic reaction centres.[1,5] Optically active 4-substituted oxetan-2-ones have been synthesized from optically active 3-halogeno[5] and 3-hydroxyalkanoic acids[6] and their asymmetric synthesis has been reported recently.[7–9] We undertook to develop the facile and preparative optical resolution of 4-alkyloxetan-2-ones with lipase and alcohols in organic solvents in which release of the 4-membered ring strain was expected to be the driving force of the reaction. Lipase has been widely used for asymmetric synthesis and optical resolution.[10] As to optically active lactones, asymmetric hydrolysis of lactones having over 5-membered rings[11] and asymmetric lactonization of hydroxy esters[12] have been reported. In the non-stereoselective acylation of alcohols with diketene, it has been suggested that catalysis occurs on the protein surface.[10b] Here, we describe the lipase-promoted asymmetric transesterification of 4-alkyloxetan-2-ones to give alkyl 3-hydroxyalkanoates.

4-Methyloxetan-2-one **1a** was chosen for an initial optimization study and treated with ethanol, butan-1-ol and benzyl alcohol to give alkyl 3-hydroxybutanoates in the presence of porcine pancreas lipase (PPL, Sigma, type II) and Amano PS (*Pseudomonas* sp. lipase, Amano Pharmaceutical Co.) in various organic solvents. The products are those expected from ordinary lipase-promoted transesterification and generated by acyl fission of **1a** which is observed in basic hydrolysis of oxetan-2-ones, while acidic hydrolysis proceeds with alkyl fission.[13] Among various combinations of lipases, alcohols and solvents, the reaction proceeded with very high stereoselectivity (E = 39) under the conditions using PPL, benzyl alcohol and acetone at 35 °C (Table 1, entry 1). Unchanged (*R*)-**1a** (96% ee) and product (*S*)-**2a** (85% ee) were separated by fractional distillation in good yields.

The reactions of **1b** (R = Pr) and **1c** (R = Pr^i) with PPL were very sluggish but effectively catalysed by Amano PS (E = 12 for **1b** and E = 81 for **1c**). Chromatographic separation afforded (*R*)-**1b** (75% ee) and (*S*)-**2b** (69% ee) in the former (entry 2) and (*S*)-**1c** (95% ee) and (*R*)-**2c** (90% ee) in the latter (entry 3) in good yields. Compounds (*R*)-**1b** and (*S*)-**1c** were converted into methyl esters (*R*)-**3b** and (*S*)-**3c**, respectively. The absolute configurations and ee's of these oxetanones were determined on the methyl esters. The change in *R*, *S*-notation of the compounds bearing isopropyl group is due to the change of the priority order of the substituents and the spatial orientation around chiral centres is the same.



Scheme 1 *Reagents and conditions:* i, $PhCH_2OH$, lipase, acetone, 35 °C; ii, MeOH, Et_3N, reflux

In conclusion, this report describes an efficient methodology providing optically active 4-alkyloxetan-2-ones and 2-hydroxyalkanoates. The enantiomeric pairs of the latter are readily available by the present method and are also useful chiral building blocks. In addition, it is very interesting that the natural products bearing an oxetan-2-one moiety are potent inhibitors of some lipases.[14] The present results and further application for oxetan-2-ones with long alkyl substituents are informative for elucidation of the catalysis and inhibition mechanism.

Experimental

Typical procedures for asymmetric transesterification of 4-alkyloxetan-2-ones

A mixture of (±)-**1a** (5.0 g, 58 mmol), benzyl alcohol (5.0 g, 46 mmol), PPL (5.0 g) and acetone (50 cm^3) was stirred at 35 °C during which the reaction conversion was assessed by GC. After 6 days, the lipase was filtered off and washed with ether (20 cm^3) and the combined filtrate and washing were evaporated. The residue was fractionally distilled to afford (*R*)-**1a** and (*S*)-**2a**. For (±)-**1b** and (±)-**1c**, Amano PS was employed in place of PPL, the reaction conversion was assessed by ^{1}H NMR, and the products were isolated by silica gel flash chromatography.

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Table 1 Optical resolution of 4-alkyloxetan-2-ones with benzyl alcohol and lipases

Entry	Substrate	Lipase	Reaction period (day)	Conv'n (%)	E^a	Lactone				Ester			
						Compd.	Yield (%)	$[\alpha]_D^{25}$ in $CHCl_3$[i]	ee (%)	Compd.	Yield (%)	$[\alpha]_D^{25}$ in $CHCl_3$[i]	ee (%)
1	(±)-**1a** (R = Me)	PPL	6	54	39	(*R*)-**1a**[b]	36	+28.0 (*c* 4.3)	96[e]	(*S*)-**2a**[g]	51	+25.7 (*c* 1.1)	85[h]
2	(±)-**1b** (R = Pr)	Amano PS	4	52	12	(*R*)-**1b**[c]	42	+32.8 (*c* 1.1)	75[c]	(*S*)-**2b**	45	+14.1 (*c* 1.1)	69[h]
3	(±)-**1c** (R = Pr^i)	Amano PS	12	51	81	(*S*)-**1c**[d]	41	+22.8 (*c* 1.1)	95[f]	(*R*)-**2c**	43	+27.4 (*c* 1.0)	90[h]

[a] Calculated from the ee's of the remaining lactones and the conversions.[15] [b] Reported: $[\alpha]_D^{22}$ +28.8 (*c* 4.3, $CHCl_3$), 95% ee.[16] [c] By converting into (*R*)-**3b**: $[\alpha]_D^{25}$ −3.5 (*c* 2.5, EtOH); reported *S*-isomer: $[\alpha]_D$ +4.6 (*c* 1.0, EtOH), 98% ee.[17] [d] By converting into (*S*)-**3c**: $[\alpha]_D^{25}$ −25.3 (*c* 2.2, EtOH); reported *S*-isomer: $[\alpha]_D$ −23.5 (*c* 5, EtOH), 87% ee.[18] [e] HPLC analysis of the amide derived from (*R*)-**1a** and (*S*)-1-phenylethylamine. [f] Determined on (*S*)-**3c** by ^1H NMR using $Eu(hfc)_3$. [g] Reported *R*-isomer: $[\alpha]_D^{25}$ −19.1 (*c* 5.0, $CHCl_3$).[19] [h] Determined by ^1H NMR using $Eu(hfc)_3$. [i] Values given in units of 10^{-1} deg cm^2 g^{-1}.

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