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Kinetic resolution of 1,2-dihydroxy-3-ferrocenylpropane by sequential lipase-catalysed esterification

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Abstract

One-pot sequential esterification of 1,2-dihydroxy-3-ferrocenylpropane **1**, catalysed by lipase from *Pseudomonas cepacia*, allowed kinetic resolution of the racemate, affording (−)-(*R*)-1-acetoxy-2-hydroxy-3-ferrocenylpropane (−)-**2**, and (+)-(*S*)-1,2-diacetoxy-3-ferrocenylpropane (+)-**3**, in high chemical yield and enantiomeric excess.

Optically active ferrocene derivatives are widely employed as chiral ligands in asymmetric reactions[1] and there is continuing interest in the development of efficient procedures to prepare them in enantiopure form.[2] Planar chiral compounds are mainly accessible from diastereoselective metallation of suitable optically active ferrocene derivatives by means of *ortho*-lithiation–electrophilic quenching sequences.[3] Chiral ferrocenes possessing an α-stereogenic carbon on a side chain are generally prepared from enantiopure *N*,*N*-dimethylaminoethylferrocene, by stereospecific displacement of the dimethylamino group with nucleophiles.[4]

As a valid alternative, biocatalysed reduction of prochiral ferrocenyl ketones[5] or kinetic resolution of racemic mixtures of α-hydroxyalkylferrocenes[6] or 1-hydroxymethyl-2-substituted ferrocenes[7] by lipase-catalysed esterification has allowed access to several enantiopure alcohols.

Conversely, relatively few examples of optically active ferrocenes bearing vicinal hydroxy groups have been described, derived from pinacol coupling of planar chiral ferrocenecarboxyaldehydes[3c,8] or Sharpless' dihydroxylation of ferrocenyl olefins.[9] Since 1,2-diols are valuable as synthetic intermediates because they are readily transformed into epoxides, aziridines and aminoalcohols, we decided to investigate lipase-catalysed esterifications of the previously unreported 1,2-dihydroxy-3-ferrocenylpropane **1**, and we report herein the results obtained.

Preliminary esterifications of (±)-**1**[10,11] in *tert*-butyl methyl ether using vinyl acetate as acyl donor in the presence of lipases from different sources (porcine pancreas, *Candida cylindracea*, *Candida antarctica*, *Mucor miehei* and *Pseudomonas cepacia*) showed that all the enzymes converted the substrate,

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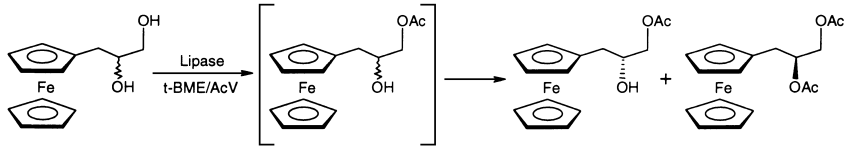
although with quite different rates, to give the primary monoacetate **2** with low enantiomeric excess. No trace of the isomeric monoacetate was detected.

Prolonging the reaction time, the formation of diacetate **3** occurred only in negligible amounts in the presence of lipases from porcine pancreas and *C. cylindracea*. With the other enzymes tested diester **3** in good yield and unconverted monoacetate **2**, both in nonracemic form, were obtained. Optimal kinetic resolution was achieved when lipase from *P. cepacia* was used as the catalyst and a satisfactory *E* value (*E*=73) relative to the second step of the esterification was calculated (Table 1).

Table 1
Enzymatic esterification of ferrocene diol (±)-**1a**[a]



(±)-**1** **2** (−)-**2** (+)-**3**

		Diol 1		Monoacetate 2		Diacetate 3		
Lipase	Time (h)	(%)[b]	ee (%)[c]	(%)[b]	ee (%)[c]	(%)[b]	ee (%)[c]	Confign.
C. cylindracea	18	18	6	82	--[d]	-	-	
Porcine pancreas	18	37	29	63	17	-	-	
M. miehei[e]	0.5	28	5	72	--[d]	-	-	
	18	-	-	49	87	51	85	*S*
P. cepacia	1	65	19	35	36	-	-	
	40	-	-	51	90	49	92	*S*
C. antarctica[f]	0.5	20	9	80	--[d]	-	-	
	60	-	-	65	29	35	54	*S*

[a]Experimental conditions: *tert*-butyl methyl ether as solvent; substrate 10 mg/ml; lipase 20 mg/ml; vinyl acetate 18μl/ml (2.5 eqv.), 300 rpm, 40 °C. [b]Determined by HPLC analysis. [c]Detemined by chiral-stationary phase HPLC after alkaline hydrolisys to diol **1**. [d]Values in a range from 1 to 2 were determined. [e]Immobilised (Lipozyme® IM, Novo Nordisk). [f]Immobilised (Novozym® 435, Novo Nordisk).

In a preparative run using *P. cepacia* lipase, the esterification of (±)-**1** was quenched after 40 h by filtering the enzyme, and following chromatographic purification, the compounds (−)-**2** and (+)-**3** in a ratio of almost 1:1 were obtained with ee values of 90 and 92%, respectively. Hydrolysis of the purified esters with K_2CO_3 in MeOH afforded the diols (−)-**1** and (+)-**1** in high yields.[12] The *S*-stereopreference of *P. cepacia* was assessed by comparison of the optical and chromatographic properties of (+)-**1** with those of a reference sample prepared from ferrocene and enantiopure (*S*)-benzylglycidyl ether.[13]

The observed behaviour indicated that the enzyme displays its enantioselectivity in the esterification of the secondary hydroxyl group of the monoacetate **2**, which is generated in situ with high regioselectivity but low enantioselection in the first step of the reaction and then subsequently acylated stereoselectively. The acylation course and lipase stereopreference are in agreement with reported data for the sequential kinetic resolution of the 1-aryl-1,2-ethandiols and 3-(aryloxy)-1,2-propanediols mediated by *P. cepacia* lipase,[14] allowing a similarity between the aryl and ferrocenyl moieties in the sterical features required for the enzyme recognition to be deduced.[15]

Further studies on the application of this enzymatic procedure to the kinetic resolution of other

dihydroxyferrocenyl derivatives and the use of enantiopure diols in the synthesis of bifunctionalised ferrocenes are in progress.

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10. Compound (±)-**1** was prepared from ferrocene, lithiated with *t*-BuLi according to Kagan's procedure,[11] and subsequently treated with benzylglycidyl ether to afford compound **1** protected at the primary hydroxyl group in about 40% yield. After purification on a silica gel column (hexane–ethyl acetate mixtures as eluant) the benzyl group was removed by hydrogenation (H_2/C in EtOH) to give (±)-**1** in nearly quantitative yield; mp 70–71°C; ^{1}H NMR (250.13 MHz, CD_3OD): δ 2.49 (1H, dd, *J*=7.0 and 14.2 Hz), 2.62 (1H, dd, *J*=5.7 and 14.2 Hz), 3.42 (1H, dd, *J*=6.2 and 11.0 Hz), 3.49 (1H, dd, *J*=4.2 and 11.0 Hz), 3.62 (1H, m), 4.09 (2H, m), 4.12 (5H, s), 4.17 (2H, m); ^{13}C NMR (62.9 MHz, CD_3OD): δ 35.10, 66.54, 68.34, 68.40, 69.45, 70.01, 70.30, 74.42, 85.95.
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12. In a typical experiment diol (±)-**1** (0.5 g) was dissolved in 50 ml of *t*-butyl methyl ether and to this solution *P. cepacia* lipase (1 g) and vinyl acetate (0.9 ml, 2.5 equiv.) were added. The mixture was shaken at 300 rpm and 40°C and the reaction course was monitored by chiral HPLC analysis (Ciclobond I 2000 column, CH_3CN:MeOH, 92:8, containing 0.25% triethylammonium acetate as eluant). After 40 h the enzyme was filtered off and the solution taken to dryness. The residue was purified by column chromatography (Si gel, hexane:ethyl acetate, 7:3) to give (−)-**2** (290 mg, 50% yield, 90% ee) and (+)-**3** (310 mg, 47% yield, 92% ee). Data for compound (−)-**2**: $[\alpha]_D$ −6.6 (*c* 0.6, EtOH); ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 2.13 (3H, s), 2.60 (2H, d, *J*=5.8 Hz), 3.90 (1H, m), 3.97 (2H, m), 4.14 (9H, bs); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.91, 34.06, 67.84, 68.04, 68.66, 68.83, 68.97, 70.53, 83.18, 171.50. Data for compound (+)-**3**: $[\alpha]_D$ +42.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 2.07 (3H, s), 2.09 (3H, s), 2.67 and 2.71 (AB system, each 1H, dd, *J*=14.2 and 6.5 Hz), 3.99 (1H, dd, *J*=12.0 and 6.5 Hz), 4.07 (2H, m), 4.09 (2H, m), 4.13 (5H, s), 4.21 (1H, dd, *J*=12.0 and 3.3 Hz), 5.06 (1H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.8, 21.1, 31.4, 64.4, 67.9, 68.6, 69.0, 72.1, 82.4, 170.3, 170.7.

Compound (+)-**3** was dissolved in MeOH and treated with K_2CO_3 to afford (+)-**1** with the same optical purity, $[\alpha]_D$ +3.3 (*c* 0.7, C_6H_6).

13. In the first step of esterification of (±)-**1** *P. cepacia* lipase displayed *R*-stereopreference affording (−)-**2** whose ee progressively lowered to give a quasi-racemic **2** that accumulated in the reaction mixture before subsequent enantioselective acylation. Selected experiments established that *C. antarctica* lipase and *M. miehei* lipase showed *S*-stereopreference in both steps of the acylation of (±)-**1**, so at very low levels of conversion monoacetate **2** was slightly enriched in the *S*-enantiomer (+)-**2**.
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