Lipase-catalysed Asymmetric and Enantioselective Esterification of Spiro[3.3]heptanes in Organic Solvents

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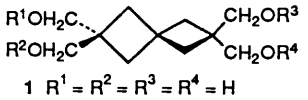
Lipase-catalysed asymmetric esterification of 2,2,6,6-tetrakis(hydroxymethyl)spiro[3.3]heptane in both isopropyl ether and pyridine gave regiospecifically 2,6-bis(acetoxymethyl)-2,6-bis-(hydroxymethyl)spiro[3.3]heptane having axial chirality and moderate optical purity. Similarly, racemic diols of spiro compounds having axial chirality were resolved by lipase-catalysed enantioselective esterification in isopropyl ether.

It is well established that hydrolytic enzymes such as lipases and esterases can also function in organic solvents,[1] and there have been many reports describing the resolution of racemic alcohols, having central chirality, by hydrolytic enzyme-catalysed esterification in organic solvents. Although lipase-catalysed enantioselective esterification of racemic allenic alcohols with axial chirality has also been described,[2] the asymmetric synthesis of an optically active alcohol, having axial chirality, by enzyme-catalysed esterification has not been reported. Here we report both the lipase-catalysed asymmetric esterification of 2,2,6,6-tetrakis(hydroxymethyl)spiro[3.3]heptane **1** with D_{2d} symmetry in organic solvents to give the optically active diacetate **3**, having axial chirality, and kinetic resolution of spiro compounds, having axial chirality, by lipase-catalysed enantioselective esterification.

Esterification of the D_{2d} tetraol **1**[3] could give five acetates: the monoacetate **2**, the C_2 diacetate **3**, the C_{2v} diacetate **4**, the triacetate **5**, and the tetraacetate **6**; only the diacetate **3** is chiral. The lipase P-catalysed asymmetric esterification of **1** was carried out with vinyl acetate as an acyl transfer reagent in isopropyl ether and pyridine (1:1, v/v) at room temperature. The progress was monitored by GLC and the reaction was terminated when the chemical yield of the diacetates reached their optimum. After filtration, the filtrate was concentrated to yield a 5:86:2:7:0 mixture of **2**:**3**:**4**:**5**:**6** (by GLC and HPLC). The results implied that further esterification of the prochiral monoacetate **2** proceeded highly regiospecifically to give the diacetate **3** of C_2-symmetry in high diastereoisomeric ratio.



1 $R^1 = R^2 = R^3 = R^4 = H$
2 $R^1 = R^2 = R^3 = H$, $R^4 = Ac$
3 $R^1 = R^3 = H$, $R^2 = R^4 = Ac$
4 $R^1 = R^2 = H$, $R^3 = R^4 = Ac$
5 $R^1 = H$, $R^2 = R^3 = R^4 = Ac$
6 $R^1 = R^2 = R^3 = R^4 = Ac$

The product was chromatographed on silica gel to furnish **3** ($CHCl_3$–MeOH, 50:1 as eluent). The enantiomeric excess (ee) of **3** was determined by HPLC analysis of its bis(3,5-dichlorobenzoate),† the analysis also revealed that the optically active diacetate **3** obtained by asymmetric esterification with both lipases used here was the antipode of that prepared by the PLE-catalysed asymmetric hydrolysis of **6**.[4] The results of asymmetric esterification of **1** are summarized in Table 1.

Table 1 Enzyme-catalysed asymmetric esterification of **1**

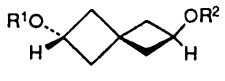
Enzyme*	Reaction time (d)	Diastereoisomer ratio **3**:**4**	C_2-Diacetate **3** Isolated yield (%)	Ee (%)
Lipase P[a]	5	43:1	60	59
Lipase YS[a]	5	24:1	52	28
Lipase YS[b]	10	26:1	46	29

* Lipase M, lipase YS, and lipase AY were supplied by the Amano pharmaceutical Co. and lipase from *Candida cylindracea* (CCL) and porcine pancreas lipase (PPL) were purchased from the Sigma Chemical Co. [a] With vinyl acetate in isopropyl ether–pyridine (1:1, v/v). [b] With vinyl acetate in pyridine.

Next we turned our attention to kinetic resolutions of the racemic diols **7**, **10**, **13** and **16** by lipase-catalysed enantioselective esterification. The lipase-catalysed esterifications were carried out with vinyl acetate in isopropyl ether and terminated at, or close to, 50% of the esterification point. Separation and purification of the products were performed on column and thin layer chromatography and, in the cases of esterifications of **7** and **16**, the formation of the corresponding diacetates **9** and **18** were not detected by GLC. The results are summarized in Table 2.

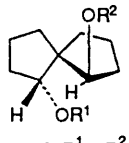
The absolute configuration of the 2,6-disubstituted spiro-[3.3]heptanes are described in the literature,‡ and ee values of **7**, **8**, **10**, **11** and **12** were confirmed on the basis of their specific rotations.§ As the absolute configurations and the rotations of

(–)-**7** $R^1 = R^2 = H$
(–)-**8** $R^1 = H$, $R^2 = Ac$
9 $R^1 = R^2 = Ac$



(–)-**10** $R^1 = R^2 = H$
(–)-**11** $R^1 = H$, $R^2 = Ac$
(–)-**12** $R^1 = R^2 = Ac$

13 $R^1 = R^2 = H$
14 $R^1 = H$, $R^2 = Ac$
15 $R^1 = R^2 = Ac$



(–)-**16** $R^1 = R^2 = H$
(–)-**17** $R^1 = H$, $R^2 = Ac$
18 $R^1 = R^2 = Ac$

† HPLC analysis of the bis(3,5-dichlorobenzoate) of **3** was carried out on Simazu LC-6A using a chiral column (Opti-Pak XC, Waters, 250 × 4.6 mm) [hexane–isopropyl ether, 97:3 (v/v), 2.4 × 10^{-1} ml min^{-1}] and showed two peaks at elution time 64 (major peak) and 73 (minor peak) min.

‡ The configurations of **7** and **8** reported in our recent communication[4] which were assigned according to the literature[7] were wrong. Wyberg *et al.* described the correct configurations of these compounds in a later paper.[8]

§ $[\alpha]_D$ Values are recorded in 10^{-1} deg cm^2 g^{-1}.

Table 2 Enzyme-catalysed enantioselective esterification[a]

Substrate	Enzyme	Reaction time (h)	Products	Yield (%)	Ee (%)
7	CCL	10	(+)-(*R*)-**7**	57	10
			(−)-(*S*)-**8**	31	14
7	Lipase M	96	(−)-(*S*)-**7**	49	17
			(+)-(*R*)-**8**	43	19
10	CCL	7	(+)-(*R*)-**10**	32	23
			(−)-(*S*)-**11**	46	25
			(−)-(*S*)-**12**	5	12
10	Lipase YS	6	(−)-(*S*)-**10**	47	14
			(+)-(*R*)-**11**	41	17
			(+)-(*R*)-**12**	4	14
13	CCL	8	(−)-**13**	46	15
			(+)-**14**	43	25
			(−)-**15**	8	52
13	CCL	90	(+)-**14**	47	40
			(−)-**15**	46	38
13	Lipase AY	48	(−)-**13**	49	11
			(+)-**14**	43	17
			(−)-**15**	6	56
16	CCL	120	(+)-(1*S*,5*R*,6*S*)-**16**	58	31
			(−)-(1*R*,5*S*,6*R*)-**17**	29	38
16	Lipase YS	102	(+)-(1*S*,5*R*,6*S*)-**16**	40	89
			(−)-(1*R*,5*S*,6*R*)-**17**	41	62
16	PPL	120	(+)-(1*S*,5*R*,6*S*)-**16**	56	70
			(−)-(1*R*,5*S*,6*R*)-**17**	37	83

[a] All reactions were carried out with vinyl acetate in isopropyl ether at room temperature.

the spiro[5.5]undecanes[5] were unknown, their configurational relationship and ee values were established as follows. By $LiAlH_4$ reduction, (+)-**14**, $[\alpha]_D$ +1.93 and (−)-**15**, $[\alpha]_D$ −3.51 were converted into (+)-**13**, $[\alpha]_D$ +3.33 and (−)-**13**, $[\alpha]_D$ −7.95, respectively, and the ee value of **13** was determined by HPLC analysis of its bis(phenylcarbamate). The absolute configuration and the maximum rotation of **16** are known[6] and $LiAlH_4$ reduction of (−)-**17**, $[\alpha]_D$ −66.4 gave (−)-(1*R*,5*S*,6*R*)-**16**, $[\alpha]_D$ −50.9 (83% ee).

As shown in Table 2, in contrast to the fact that the diacetate **12** obtained by esterification of **10** had the same configuration as that of the monoacetate **11**, esterification of **13** with CCL gave the monoacetate (+)-**14** (47%) and the diacetate (−)-**15** (46%), the chirality of each being in the opposite sense to that of the other.

Experimental

Typical Procedure for Enzyme-catalysed Esterification of Alcohols: Asymmetric Esterification of **1** *with Lipase P.*—To a solution of **1** (200 mg, 0.926 mmol) and vinyl acetate (750 mg, 8.72 mmol) in isopropyl ether–pyridine (1:1, v/v; 80 ml) was added lipase P (800 mg) and the mixture was stirred at room temperature. After 96 h, vinyl acetate (375 mg, 4.36 mmol) and lipase P (400 mg) were added to the reaction mixture and the mixture was stirred for further 24 h. After the solid had been filtered off, the filtrate was concentrated under reduced pressure. Silica gel chromatography of the residue furnished **5** ($CHCl_3$–MeOH 100:1 v/v as eluent) (16 mg, 5% yield), **3** ($CHCl_3$–MeOH, 50:1) (168 mg, 60%), and a 5:13 mixture of **4** and **2** ($CHCl_3$–MeOH 50:3) (14 mg).

Enantioselective Esterification of (±)-**16** *with Lipase YS.*—To a solution of (±)-**16** (200 mg, 1.28 mmol) and vinyl acetate (880 mg, 1.02 mmol) in isopropyl ether (80 ml) was added lipase YS (800 mg) and the mixture was stirred for 102 h at room temperature. The mixture was then filtered and the filtrate was concentrated under reduced pressure; silica gel chromatography of the residue gave **17** (benzene–ether, 50:1), $[\alpha]_D^{25}$ −49.6 (*c* 1.46, EtOH) (62% ee) (104 mg, 41%) and **16** (benzene–ether, 1:1), $[\alpha]_D^{25}$ +54.4 (*c* 0.320, EtOH) (89% ee) (79 mg, 40%).

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