Enzyme-catalysed Asymmetric Synthesis of a Spiro[3.3]heptane Derivative with Axial Chirality and Enzymatic Resolution of Racemic Spiro[3.3]heptane Derivatives

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2,6-Bis(acetoxymethyl)-2,6-bis(hydroxymethyl)spiro[3.3]heptane with axial chirality and moderate optical purity has been prepared in high chemical yield by pig liver esterase-catalysed asymmetric hydrolysis of 2,2,6,6-tetrakis(acetoxymethyl)spiro[3.3]heptane. Similarly, racemic 2,6-disubstituted spiro[3.3]heptane derivatives with axial chirality were resolved by enantioselective enzyme-catalysed hydrolysis.

Use of enzymes for kinetic resolution and asymmetric synthesis has been well studied.[1] However, although kinetic resolution of racemic compounds with axial chirality by enzyme-catalysed hydrolysis[2] has been described, there has been no report of the enzyme-catalysed asymmetric hydrolysis of an achiral compound to give an optically active compound with axial chirality. Here we report the first enzyme-catalysed asymmetric synthesis of an optically active compound with axial chirality by pig liver esterase-catalysed hydrolysis of 2,2,6,6-tetrakis(acetoxymethyl)-spiro[3.3]heptane **2** with D_{2d}-symmetry and also the kinetic resolution of the racemic 2,6-disubstituted spiro[3.3]heptanes **6**, **10** and **13** with axial chirality by enantioselective enzyme-catalysed hydrolysis.

Of the four possible acetates, 2,2,6-tris(acetoxymethyl)-6-(hydroxymethyl)spiro[3.3]heptane, 2,6-bis(acetoxymethyl)-2,6-bis(hydroxymethyl)spiro[3.3]heptane **3**, 2,2- bis(acetoxymethyl)-6,6-bis(hydroxymethyl)spiro[3,3]heptane of C_{2v}-symmetry, and 2-(acetoxymethyl)-2,6,6-tris(hydroxymethyl)spiro[3.3]heptane formed by partial hydrolysis of **2**, only the diacetate **3** of C_2-symmetry is chiral. Preparative-scale PLE-catalysed hydrolysis of **2**† [b.p. 170–171 °C (0.15 mmHg)], prepared from **1** [m.p. 184–186 °C] [3] was performed in phosphate buffer solution (pH 8.0) at room temperature for 4 h on a 2.0 mmol scale. Extraction with chloroform gave a 6:76:8:10 mixture of the triacetate, the C_2-diacetate **3**, the C_{2v}-diacetate,

† Structure of key compounds confirmed by ^{1}H NMR, IR, and HRMS. For **2**: δ($CDCl_3$) 1.99 (8 H, s), 2.04 (12 H, s), and 4.00 (8 H, s). For **3**: δ 1.94 (8 H, s), 2.07 (6 H, s), 2.16 (2 H, br s, OH), 3.48 (4 H, s), and 4.08 (4 H, s). For 2,2-bis(acetoxymethyl)-6,6-bis(hydroxymethyl)spiro-[3.3]heptane: δ 1.98 (4 H, s), 1.92 (4 H, s), 2.06 (6 H, s), 2.14 (2 H, br s, OH), 3.64 (4 H, s), and 4.00 (4 H, s). For **6**: δ 2.02 (6 H, s), 2.0–2.6 (8 H, m), and 4.90 (2 H, quin., J 8 Hz).

CD and UV spectra for **8**: CD (c 5.65×10^{-5} EtOH) $[\theta]_{320}$ $+3.01 \times 10^5$, $[\theta]_{309}$ 0, and $[\theta]_{297}$ -1.77×10^5; λ_{max}(EtOH) 314 (ε 4.81×10^4).

1 $R^1 = R^2 = H$
2 $R^1 = R^2 = Ac$
3 $R^1 = Ac$, $R^2 = H$
4 $R^1 = Ac$, $R^2 = COC_6H_3Cl_2$-3, **5**

5 $R^1 = R^2 = H$
6 $R^1 = R^2 = Ac$
7 $R^1 = Ac$, $R^2 = H$
8 $R^1 = Ac$, $R^2 = COC_6H_4NMe_2$-*p*

9 $R^1 = R^2 = H$
10 $R^1 = R^2 = Ac$
11 $R^1 = Ac$, $R^2 = H$

12 $R^1 = R^2 = H$
13 $R^1 = R^2 = Et$
14 $R^1 = Et$, $R^2 = H$

Table 1. Enzyme-catalysed asymmetric hydrolysis.

Enzyme	Reaction time (h)	Reaction temp.	C_2-Diacetate **3**: isolated yield (%)	E.e. (%)
PLE	4	R.t	59	56
PLE	50	0 °C	86	51
PPL	45	R.t.	37	9.2
CCL	49	R.t.	41	1.3
Lipase P	43	R.t.	63	4.0

and the monoacetate (by GLC); chromatography on silica gel afforded **3** in 59% yield, the enantiomeric excess (e.e.) of which was determined as 56% by HPLC analysis on **4**. It seems likely that **1** was formed under these conditions, but was not extracted with chloroform. The results of asymmetric hydrolysis of **2** are summarized in Table 1. PLE-catalysed reaction carried out at low temperature improved the regioselectivity to furnish a 5:87:7:1 mixture of the triacetate, the C_2-diacetate **3**, the C_{2v}-diacetate, and the monoacetate, and **3** with 51% e.e. (isolated in 86% yield after chromatography).

Next we turned our attention to enantioselective enzyme-catalysed hydrolyses of racemic **6**, **10** and **13**, the hydrolyses being terminated at, or close to, 50% of the hydrolysis point. 2,6-Diacetoxyspiro[3.3]heptane **6** [b.p. 142–143 °C (22 mmHg)], was prepared from **5** [m.p. 103.5–104.5 °C], which was obtained by $LiAlH_4$ reduction of spiro[3.3]heptane-2,6-dione.[4] The hydrolyses of **6** and **10** were carried out in phosphate buffer solution (pH 8.0) and the products were extracted with chloroform and purified by chromatography on silica gel. The results are summarized in Table 2. $LiAlH_4$ reduction of (−)-**6** ($[\alpha]_{435}$ −11.7°), and (+)-**7** ($[\alpha]_{435}$ +3.97°) gave (−)-**5** ($[\alpha]_{435}$ −3.99°) and (+)-**5** ($[\alpha]_{435}$ +4.17°), respectively, and the e.e. value of **5** ($[\alpha]_{435}$ −3.99°) was determined as 44% e.e. by HPLC analysis of its bis(phenylcarbamate). The absolute configuration of (−)-(*S*)-**5** was determined by the CD exciton chirality method with the corresponding bis(dimethylaminobenzoate) **8**.† The absolute configurations and the e.e. values of **10** and **11** were confirmed by conversion into the known diol **9**.[5] By $LiAlH_4$ reduction, (−)-**10** ($[\alpha]_D$ −0.201°) and (+)-**11** ($[\alpha]_D$ +0.274°) were converted into (−)-(*R*)-**9** (22% e.e.) and (+)-(*S*)-**9** (14% e.e.), respectively.

The hydrolysis of **13** was performed in phosphate buffer solution (pH 8.0), and worked up by extraction with ethyl acetate, first at pH 8.0 to extract **13** and **14**, and then at pH 1.0 to isolate **12**. Separation of **14** from **13** was achieved by extraction with aqueous sodium hydrogen carbonate. The results are given in Table 2. PLE-catalysed hydrolysis of **13** proceeded smoothly to give a considerable amount of **12**, but the e.e. values of the products were poor. Chemical hydrolysis (KOH in methanol) of (−)-**13** ($[\alpha]_D$ −0.252°) and (+)-**14** ($[\alpha]_D$ +0.527°) gave (−)-(*S*)-**12** (16% e.e) and (+)-(*R*)-**12** (21% e.e.), respectively, the optical rotation and the absolute configuration of which are described in the literature.[5]

† PLE: pig liver esterase (Boehringer Mannheim Gmbh Co.) PPL: porcine pancreas lipase (Sigma Chemical Co.); CCL: lipase from *Candida cylindracea* (Sigma Chemical Co.); lipase P: lipase from *Pseudomonas sp.* (Nagase Biochemicals, Ltd.).

Table 2. Enzyme-catalysed enantioselective hydrolysis.

Substrate	Enzyme	Reaction time/h	Reaction temp.	Products	Yield[a] (%)	E.e. (%)
6	PLE	3.5	0 °C	(−)-(*S*)-**6**	47	5.1
				(+)-(*R*)-**7**	50	6.0
6	PPL	3.5	R.t	(−)-(*S*)-**6**	50	44
				(+)-(*R*)-**7**	41	46
6	CCL	5.5	R.t	(−)-(*S*)-**6**	47	14
				(+)-(*R*)-**7**	47	18
10	PLE	4.5	0 °C	(−)-(*R*)-**10**	38	22
				(+)-(*S*)-**11**	53	14
10	PPL	0.7	R.t	(−)-(*R*)-**10**	36	8.8
				(+)-(*S*)-**11**	57	10
10	Lipase P	3.5	R.t	(+)-(*S*)-**10**	41	11
				(−)-(*R*)-**11**	50	10
13	PLE	0.5	0 °C	(+)-(*R*)-**12**	28	6.0
				(−)-(*S*)-**13**	32	2.2
				(−)-(*S*)-**14**	34	4.3
13	PPL	5.0	R.t	(−)-(*S*)-**13**	48	16
				(+)-(*R*)-**14**	34	21
13	CCL	3.5	R.t	(−)-(*S*)-**13**	41	28
				(+)-(*R*)-**14**	41	23
13	Lipase P	28	R.t	(−)-(*S*)-**13**	44	18
				(+)-(*R*)-**14**	50	16

[a] Isolated yield.

Experimental

Typical Procedure for Enzyme-catalysed Hydrolysis of Acetates: Asymmetric Hydrolysis of **2** *with PLE.*—To a solution of **2** (303 mg, 0.800 mmol) in 0.1M phosphate buffer solution (pH 8.0) (350 ml) was added PLE (35 μl, 100 units mg^{-1}) and the mixture was stirred at 0 °C. The reaction was monitored by GLC. After the mixture had been stirred for 50 h, it was extracted with chloroform and the extract was dried ($MgSO_4$) and concentrated. Silica gel chromatography of the residue furnished the triacetate ($CHCl_3$–MeOH, 100:1, as eluant) (13 mg, 5% yield), **3** ($CHCl_3$–MeOH, 50:1) (204 mg, 86%), and a 7:1 mixture of the C_{2v}-acetate and the monoacetate ($CHCl_3$–MeOH, 50:3) (19 mg). A mixture of **3** (20 mg, 0.070 mmol), 3,5-dichlorobenzoyl chloride (130 mg, 0.620 mmol), and pyridine (2 ml) was stirred at room temperature. After work-up, preparative TLC gave **4** (37 mg, 86%) as a viscous oil.

Enantioselective Hydrolysis of (±)-**6** *with PPL.*—A mixture of (±)-**6** (299 mg, 1.40 mmol) and PPL (300 mg) in 0.1M phosphate buffer solution (pH 8.0) (300 ml) was stirred at room temperature for 3.5 h and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated. Silica gel chromatography furnished (−)-**6** (benzene as eluant) (150 mg, 50% yield) and (+)-**7** (benzene–ether, 10:1) (99 mg, 41%). A mixture of (−)-**5** (20 mg, 0.16 mmol), prepared by treatment of (−)-**6** (135 mg, 0.635 mmol) with $LiAlH_4$ (90 mg, 2.4 mmol) in ether (40 ml), phenyl isocyanate (110 mg, 0.920 mmol), and pyridine (1 drop) was stirred at room temperature. After work-up, preparative TLC gave the bis(phenylcarbamate) (46 mg, 80%) as a white solid.

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