Horseradish Peroxidase-Catalyzed Enantioselective Reduction of Racemic Hydroperoxy Homoallylic Alcohols: A Novel Enzymatic Method for the Preparation of Optically Active, Unsaturated Diols and Hydroperoxy Alcohols

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The kinetic resolution of chiral diastereomeric hydroperoxy homoallylic alcohols **1** by horseradish peroxidase-catalyzed asymmetric reduction affords the optically active (*R*,*R*) or (*R*,*S*) allylic diols **2** and (*S*,*S*) or (*S*,*R*) hydroperoxy homoallylic alcohols **1** in high enantiomeric excess (up to 99%).

Introduction

Peroxidases (E.C. 1.11.1.7) are heme-containing enzymes which catalyze the reduction of hydrogen peroxide and organic hydroperoxides in the presence of structurally diverse electron-donating substrates.[1] Chloroperoxidase (CPO) and horseradish peroxidase (HRP) have been preferentially used as biocatalysts in asymmetric synthesis; for example, CPO catalyzes the enantioselective epoxidation of unfunctionalized alkenes,[2] the stereoselective sulfoxidation of prochiral thioethers by achiral[3] racemic 1-arylethyl hydroperoxides,[4] and the regio- and stereoselective halogenation of olefins.[4] Reports on enantioselective reactions catalyzed by HRP are rather scarce; only the asymmetric sulfoxidation of prochiral sulfides[5] is known.

We have reported that the kinetic resolution of chiral alkyl aryl hydroperoxides[6] by the HRP-catalyzed enantioselective reduction to the corresponding alcohols constitutes a convenient and efficient method to prepare optically active peroxides. Only recently[7] was this kinetic resolution applied to diastereomerically functionalized hydroperoxides with two chiral centers. To assess the potential of the commercially available HRP biocatalyst in asymmetric synthesis, we have now investigated the enzyme-catalyzed reduction of chiral diastereomeric hydroperoxy homoallylic alcohols **1**, which are versatile intermediates for the Ti^{IV}-mediated hydroxyepoxidation.[8] Herein, we report the details of the enzymatic preparation of optically active hydroperoxy homoallylic alcohols **1** and allylic diols **2** by enantioselective reduction of the former with HRP in the presence of guaiacol (Scheme 1).

Scheme 1. HRP-Catalyzed Enantioselective Reduction of Racemic Hydroperoxy Homoallylic Alcohols 1 in the Presence of Guaiacol

(*R**, *R**)-**1** (*R**, *S**)-**1**

HRP, guaiacol

(*R*, *R*)-**2** + (*S*, *S*)-**1** (*R*, *S*)-**2** + (*S*, *R*)-**1**

1, 2	a	b	c	d	e
R^1	Me	Et	Pr^i	Bu^t	Me
R^2	H	H	H	H	Me

Results and Discussion

The racemic *threo* hydroperoxides **1** were prepared diastereoselectively (90:10 *threo*/*erythro*) by the ene reaction of the corresponding *Z*-configured allylic alcohols with singlet oxygen.[9] Unfortunately, the *E*-configured alcohol gave a 50:50 *threo*/*erythro* mixture of the hydroperoxides **1**. To obtain the diastereomerically pure *erythro* compound **1b** for the HRP-catalyzed reduction to the corresponding diol **2b**, the *threo*/*erythro* mixture was

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Table 1. Kinetic Parameters for HRP-Catalyzed Enantioselective Reduction of Racemic Hydroperoxy Homoallylic Alcohols 1 in the Presence of Guaiacol[a]

entry		peroxide	K_m[b] (mM)	k_{cat}[c] (min^{-1})	k_{cat}/K_m (mM^{-1} min^{-1})
1		H_2O_2	0.05	4600	92000
		threo-**1** (>99%)			
2	**1a**		29	656	23
3	**1b**		45	643	14
4	**1c**		76	25	0.3
5	**1d**		250	15	0.1
6	**1e**		289	48	0.2
		erythro/threo-**1** (50:50)			
7	**1a**		33	1510	47
8	**1b**		19	1092	57
		erythro/threo-**1** (91:9)			
9	**1b**		19	1680	88

[a] The kinetic parameters were obtained at a fixed guaiacol concentration of 500 μM; the initial rates were monitored by following the appearance of the guaiacol oxidation product ($\varepsilon = 2.66 \times 10^4$ M^{-1} cm^{-1} at 470 nm) in 0.1 M phosphate buffer (pH 6.0); the data were processed with the Duggleby program to give K_m and k_{cat} values. [b] Error limits between 5% and 10% of the stated values. [c] Error limits between 1% and 5% of the stated values.

Scheme 2. Kinetic Resolution of Hydroperoxy Homoallylic Alcohol 1b (50:50 *Threo/Erythro* Mixture) by Diastereoselective Epoxidation with Ti(O*i*Pr)$_4$

OOH, OH, Et; **1b** *threo : erythro* 50 : 50 — Ti(O*i*Pr)$_4$ (0.1 equiv.), CH_2Cl_2, MS 4 Å, -25 °C, 15 h → (S^*,R^*,S^*)-**3b** + (R^*,S^*)-**1b** [24%]

chemically separated by diastereoselective Ti(O*i*Pr)$_4$-mediated epoxidation of *threo*-**1b** (Scheme 2). The much faster reacting *threo*-**1b** is epoxidized, while the diastereomeric *erythro*-**1b** is left behind.

To assess the catalytic efficiency of the enzymatic transformations, we have determined the kinetic parameters K_m (Michaelis constant) and k_{cat} (turnover number). The K_m value reflects the affinity of the enzyme for the hydroperoxide, whereas k_{cat} measures the number of substrate molecules turned over per enzyme molecule per minute. The kinetic parameters for the hydroperoxy alcohols **1** in the presence of guaiacol as electron donor are shown in Table 1; for comparison the values of H_2O_2 are also given.

The k_{cat}/K_m ratio represents the second-order rate constant for the enzyme–substrate reaction. For the *threo* hydroperoxy alcohols **1**, the highest k_{cat}/K_m value is obtained for the derivative *threo*-**1a** (Table 1; entry 2).

The homologous series *threo*-**1a–d** of the hydroperoxy homoallylic alcohols (Table 1, entries 2–5) reflects the sensitivity of HRP toward the steric demand of the R^1 substituent. The gradual increase of alkyl branching decreases the catalytic efficiency, presumably due to the size restrictions at the active site. The introduction of a methyl group as R^2 substituent decreases the catalytic efficiency dramatically in comparison to that of the R^1 substituent (Table 1; entries 3 and 6). Furthermore, for 50:50 *threo:erythro* mixtures of the hydroperoxy alcohol **1a** and **1b**, as well as for the diastereomerically pure *erythro*-**1b**, the K_m and k_{cat} values are higher than those for the diasteriomerically pure *threo* isomers **1a** and **1b** (Table 1; entries 7–9). These results reveal that the HRP exhibits a larger catalytic efficiency (k_{cat}/K_m) for the *erythro*- versus the *threo*-configured hydroperoxy alcohols **1**.

In view of these observed trends in the catalytic efficiency, the kinetic resolution of the hydroperoxy alcohols **1a–e** was conducted at optimized substrate/HRP

Table 2. Enantioselectivities of the HRP-Catalyzed Kinetic Resolution of Hydroxy-Functionalized Hydroperoxides 1 in the Presence of Guaiacol[a]

entry	peroxide	(mmol)	ROOH : HRP (mol ratio)	time[b] (h)	ee[c] (%)		E[d]
	threo-**1**[e]				(*S*,*S*)-**1**[f]	(*R*,*R*)-**2**	
1	**1a**	(0.06)	3400 : 1	3	63	67	10
2		(1.0)[g]	2933 : 1	44	77	40	5.1
3	**1b**	(0.06)	3040 : 1	3	>99	>99	>200
4		(3.03)	3040 : 1	48	>99	93	94
5	**1c**	(0.06)	1866 : 1	3	>99	>99	>200
6		(0.69)	997 : 1	44	>99	90	99
7	**1d**	(0.06)[g]	2500 : 1	20	91	84	30
8		(0.34)	2024 : 1	42	45	88	24
9	**1e**	(0.06)	400 : 1	24	14	18	2
10		(0.38)	557 : 1	43	30	29	2.4
	erythro-**1**[h]				(*S*,*R*)-**1**	(*R*,*S*)-**2**	
11	**1a**	(0.06)	3200 : 1	3	>99	84	30
12	**1b**	(0.06)	3040 : 1	3	>99	89	52
13		(0.46)[i]	1349 : 1	22	>99	89	52
14	**1c**	(0.06)	1866 : 1	3	>99	92	79
15	**1d**	(0.06)	2500 : 1	20	>99	89	52
16	**1e**	(0.06)	760 : 1	24	62	73	14

[a] The conversion of the peroxide was 50±1% as determined photometrically. [b] Not optimized. [c] The enantiomeric excess was established by MDGC. [d] Enantiomeric ratios (E values, ref 10). [e] For HRP-catalyzed reduction diastereomerically pure *threo*-**1** was used. [f] The absolute configurations were assigned by CD spectroscopy after benzoylation of the hydroxy groups after reduction (ref 11). [g] HRP-catalyzed reduction of *threo*-**1a** in the presence of ABTS (**4**). [h] For HRP-catalyzed reduction a 1:1 *threo*/*erythro* mixture was employed. [i] For HRP-catalyzed reduction a 16:84 *threo*/*erythro* mixture was employed.

ratios. These ratios, the absolute configurations, and the enantiomeric excess (ee) and enantiomeric ratio (E) values for the HRP-catalyzed kinetic resolution of hydroperoxides **1** are given in Table 2. Fortunately, hydroperoxides **1** did not react at room temperature with guaiacol in the absence of HRP; therefore, the enzymatic reactions could be conducted at room temperature (ca. 20 °C).

The HRP enzyme exhibited excellent stereoselectivity for the reduction of the *threo* and *erythro* diastereomers of the racemic hydroperoxides **1**, with high preference for the (*R*) configuration of the hydroperoxy group. Accordingly, the kinetic resolution afforded the (*R*,*R*) or (*R*,*S*) allylic diols **2** with ee values between 84 and 99%, while the (*S*,*S*) and (*S*,*R*) hydroperoxy homoallylic alcohols **1** were left behind nearly enantiomerically pure (ee >99%), cf. Table 2 (entries 3–6 and 11–15).

Significantly higher ee values were obtained for the *erythro*- versus *threo*-configured hydroperoxides **1a** and **1e**, while similar enantioselectivities were observed for both diastereomers of the derivatives **1b**–**d**. In contrast to *erythro*-**1a** (entry 11), its *threo* diastereomer (entry 1) displayed a significantly lower enantioselectivity (ee >99% versus 63%), which is also reflected in the values (30 versus 10) of the enantiomeric ratios (*E*). Apparently, the *erythro* configuration of the HOO and HO functional groups facilitates selective binding of the (*R*,*S*) enantiomer at the active site of the enzyme. Moreover, steric effects on the HRP selectivity are more pronounced for the *threo* than the *erythro* diastereomers, as shown by derivative **1e** (entries 9, 10, and16). Thus, methyl branching at the α position of the double bond lowers significantly the optical purity for the *threo* (entry 10) compared to the *erythro* congener (entry 16). The unfa-

Scheme 3. HRP-Catalyzed Oxidation of ABTS in the Presence of Hydroperoxide 1a

vorable influence of branched substituents on the HRP stereoselectivity was already observed for alkyl aryl hydroperoxides;[6] however, alkyl substituents adjacent to the hydroxy group do not significantly affect the enantioselectivity of HRP (entries 3−8 and 12−15).

To demonstrate the applicability of the enzymatic method for preparative purposes, *threo*-**1a**,**c**−**e** and *erythro*-**1b** were reduced on the semipreparative scale (46−108 mg, 0.34−1.0 mmol; cf. Table 2, entries 2, 6, 8, 10, and 13). Moreover, the results for a 50-fold quantity (400 mg, 3.03 mmol) of the *threo*-4-hydroperoxyhex-5-en-3-ol (**1b**) with equimolar amounts of guaiacol (376 mg, 3.03 mmol) demonstrate convincingly that the HRP-catalyzed kinetic resolution serves well for the preparation of the enantiomerically pure title compounds (entry 4). Thus, after conventional workup and purification by silica gel chromatography, the optically active allylic hydroperoxides **1** and the corresponding diols **2** were isolated in high yields (ca. 85% relative to 50% conversion). This implies, fortunately, that the guaiacol oxidation products do not affect adversely the reactivity and selectivity of this enzymatic reaction even on the preparative scale. Nevertheless, the guaiacol oxidation products complicate the purification of the hydroperoxy homoallylic alcohol **1a** and diol **2a** by silica gel chromatography. Therefore, we have substituted 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) or ABTS (**4**)[12] for the electron-donating substrate guaiacol (Scheme 3). Neither ABTS (**4**) nor its radical-cation oxidation product is extracted into the organic phase (ether) during the workup (Table 2; entry 2).

The enantioselectivities for the HRP-catalyzed reduction of the allylic hydroperoxides **1** was determined by employing multidimensional gas chromatography (MDGC) on chiral phases. The analytical protocol consisted of four steps: (i) extraction of the aqueous buffer solution with ether, (ii) separation of the unreacted hydroperoxides **1** from the corresponding diols **2** by normal-phase HPLC, (iii) reduction of the temperature-labile allylic hydroperoxides **1** with triphenylphosphine, and (iv) MDGC analysis on chiral columns. The absolute configurations of the allylic hydroperoxides **1** were assigned after triphenylphosphine reduction to the corresponding alcohols by employing the CD-spectral exciton-chirality method[11] developed by Nakanishi et al.[13]

In summary, HRP exhibited a high enantioselectivity for the (R^*,R^*) and (R^*,S^*) hydroperoxy homoallylic alcohols **1**. Kinetic and stereochemical studies establish that both the catalytic efficiency and the enantioselectivity of the HRP enzyme highly depend on the steric demand of the substituent adjacent to the stereogenic hydroperoxy group and on the diastereomeric configuration of the HOO and HO functional groups. For the first time we demonstrate that neither the hydroxy functionality nor the presence of additional chirality centers has any influence on the enantioselectivity. Important for synthetic applications is the fact that the present enzyme-catalyzed resolution may be performed on the preparative scale to provide readily and convenienty optically active α,β-unsaturated (*S*,*S*) and (*S*,*R*) hydroxy-functionalized hydroperoxides **1**, as well as (*R*,*R*) and (*R*,*S*) diols **2**, for asymmetric transformations. Attractive applications constitute their Ti(O*i*Pr)$_4$-catalyzed oxidation to optically active epoxy diols[14] or the epoxidation of allylic alcohols by optically active hydroperoxides.[15]

Experimental Section

Materials and Methods. Horseradish peroxidase (HRP) was purchased from Sigma (RZ 2.0) and used without further purification. All commercial chemicals were of analytical grade quality. All purchased solvents were of high purity and were redistilled before use. The racemic *threo* hydroperoxides **1** were obtained by the ene reaction of *Z*-configured allylic alcohols with singlet oxygen accordingly to the previously reported procedure.[16] The racemic *erythro* hydroperoxides **1** were prepared from the *E*-configured allylic alcohols by this method only as 50:50 *threo*/*erythro* mixtures. The spectral data of the hydroperoxides **1** and alcohols **2** have been previously reported.[16,17]

Preparation of the Diastereomerically Enriched 4-Hydroperoxy-5-hexen-3-ol (1b). To a solution of 309 mg (2.43 mmol) of a 50:50 *threo*/*erythro* mixture of 4-hydroperoxy-5-hexen-3-ol (**1b**) in 8 mL of CH_2Cl_2 was added 66.5 mg (23.4 μmol, 69 μL) Ti(O*i*Pr)$_4$ at −25 °C. After stirring over molecular sieves (4 Å) for 15 h at −25 °C, a 92:8 ratio of ($3R^*$,$4S^*$)-/($3S^*$,$4S^*$)-**1b** was determined by ^{1}H NMR analysis. Subsequently, the catalyst was destroyed by addition of 230 μL of water and stirred for 1 h at room temperature (ca. 20 °C). After removal of the suspended material by filtration and thorough washing of the residue with CH_2Cl_2 (5×1 mL), the solvent was evaporated (20 °C, 20 Torr). The crude product was purified by silica gel chromatography (1:1 petroleum ether−ethyl ether) to yield 73.0 mg (24%) of the *erythro* hydroperoxide **1b**. ($3R^*$,$4S^*$)-**1b**:^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 0.99$ (t, $J = 7.4$ Hz, 3 H), 1.41−1.59 (m, 2 H), 2.25 (br s, 1 H), 3.87 (ddd, $J = 7.4$, 5.8, 3.2 Hz, 1 H), 4.35 (dd, $J = 7.9$, 3.2 Hz, 1 H), 5.41 (d, $J = 11.1$ Hz, 1 H), 5.44 (d, $J = 16.6$ Hz, 1 H), 5.92 (ddd, $J = 16.6$, 11.1, 7.9 Hz, 1 H), 8.57 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 10.1$ (q), 25.4 (t), 72.7 (d), 89.5 (d), 121.9 (t), 131.6 (d); IR (neat) ν 3375 cm^{-1} (OH), 2968, 2926, 2884, 1723, 1639 (C=C), 1462, 1425, 1321, 1238, 1102, 1050, 972, 935, 841. Anal. Calcd for $C_6H_{12}O_3$ (132.2): C, 54.53; H, 9.15. Found: C, 54.14; H, 9.21.

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The triphenylphosphine reduction[17] of the *erythro* hydroperoxide **1b** afforded the alcohol (*3S**,*4R**)-**2b**: ^{1}H NMR (250 MHz, $CDCl_3$) δ = 0.99 (t, J = 7.3 Hz, 3 H), 1.37–1.57 (m, 2 H), 1.72 (br s, 2 H), 3.63 (ddd, J = 8.2, 4.7, 3.7 Hz, 1 H), 4.13 (ddt, J = 6.4, 3.7, 1.2 Hz, 1 H), 5.29 (dt, J = 10.5 Hz, 1 H), 5.34 (d, J = 17.1 Hz, 1 H), 5.94 (ddd, J = 17.1, 10.5, 6.4 Hz, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ = 10.2 (q), 25.0 (t), 75.6 (d), 75.7 (d), 117.6 (t), 136.0 (d); IR (neat) ν 3385 cm^{-1} (OH), 2968, 2926, 2884, 1644 (C=C), 1457, 1425, 1311, 1253, 1123, 1055, 972, 920, 847. Anal. Calcd for $C_6H_{12}O_2$ (116.2): C, 62.04; H, 10.41. Found: C, 61.58; H, 10.31.

Peroxidase Assay. Peroxidase activity was measured at pH 6.0 and 25 °C according to the method of Chance and Maehly[18] by using hydrogen peroxide as oxygen donor and guaiacol as cosubstrate.

Determination of the Kinetic Parameters for HRP. To determine the kinetic parameters K_m and k_{cat} for the hydroperoxides **1** (up to 35 mM), a 0.1 M stock solution of guaiacol in phosphate buffer (0.1 M, pH 6) was prepared. In each assay, the guaiacol concentration was adjusted to 0.5 mM by diluting 100 μL of the stock solution to a final volume of 2 mL, which contained the required amount of hydroperoxide, and the sample was placed into a quartz cuvette. After efficient mixing, 50 μg of enzyme was injected to start the reaction. The appearance of the guaiacol oxidation product, which has an absorption maximum at 470 nm ($\epsilon = 2.66 \times 10^4$ M^{-1} cm^{-1}), was monitored for 3 min to calculate the initial rate. Once all the initial rates were acquired, the data were processed with the Duggleby program to give K_m and k_{cat} values.

General Procedure for the Kinetic Resolution of Hydroperoxides 1a–e with HRP. In a typical reaction, racemic hydroperoxide and equimolar amounts of guaiacol (or ABTS for hydroperoxide **1a**; cf. Table 2, entry 2) were dissolved in 2–50 mL of 0.1 M phosphate buffer solution (pH 6) and subsequently HRP (cf. Table 2) was added. The reaction progress was followed photometrically[19] and terminated at a conversion rate of 50%. The mixture was extracted with ethyl ether, the combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum (ca. 20 °C, 17 Torr). A sample (5 mg) of the crude mixture was submitted to normal-phase HPLC for the separation of the unreacted hydroperoxide **1** from the corresponding diol **2**. After reduction of the temperature-labile allylic hydroperoxides **1** with triphenylphosphine, the enantiomeric excess of the hydroperoxide and alcohol was determined by MDGC analysis on chiral columns. For the enantiomerically enriched *threo*-**1a**–**e** and *erythro*-**1b** hydroperoxides and the corresponding alcohols **2**, the optical rotation values [α] were determined after purification by silica gel chromatography (1:1 pentane–ethyl ether) on a Perkin-Elmer polarimeter. The [α] values: (*S*,*S*)-**1a**, $[\alpha]^{20}_D$ −15 (*c* 0.3 in MeOH for ee 77%); (*S*,*S*)-**1b**, $[\alpha]^{20}_D$ −21 (*c* 0.8 in MeOH for ee >99%); (*S*,*S*)-**1c**, $[\alpha]^{20}_D$ −13 (*c* 0.8 in MeOH for ee >99%); (*S*,*S*)-**1d**, $[\alpha]^{20}_D$ +8 (*c* 1.1 in MeOH for ee 45%); (*S*,*S*)-**1e**, $[\alpha]^{20}_D$ −7 (*c* 0.5 in MeOH for ee 30%); (*S*,*R*)-**1b**, $[\alpha]^{20}_D$ −9 (*c* 1.1 in $CHCl_3$ for ee >99%); (*R*,*R*)-**2a**, $[\alpha]^{20}_D$ +23 (*c* 0.4 in MeOH for ee 40%); (*R*,*R*)-**2b**, $[\alpha]^{20}_D$ +44 (*c* 0.4 in MeOH for ee >99%); (*R*,*R*)-**2c**, $[\alpha]^{20}_D$ +29 (*c* 0.7 in MeOH for ee 90%); (*R*,*R*)-**2d**, $[\alpha]^{20}_D$ +4 (*c* 0.8 in MeOH for ee 88%); (*R*,*R*)-**2e**, $[\alpha]^{20}_D$ +2 (*c* 0.6 in MeOH for ee 29%); (*R*,*S*)-**2b**, $[\alpha]^{20}_D$ +8 (*c* 0.9 in $CHCl_3$ for ee 89%).

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