Preparation of Optically Active Allylic Hydroperoxy Alcohols and 1,3-Diols by Enzyme-Catalyzed Kinetic Resolution and Photooxygenation of Chiral Homoallylic Alcohols

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Received October 7, 1999

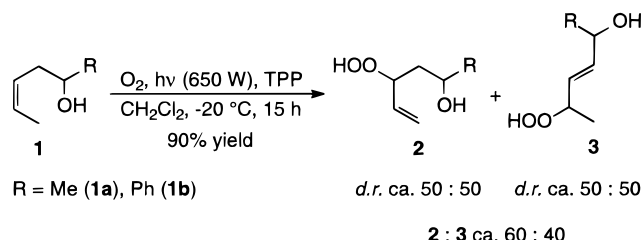
All four possible enantiomers of the 3-hydroperoxy-4-penten-1-ols **2a**,**b** and their corresponding 4-pentene-1,3-diols **4a**,**b** have been prepared for the first time in high enantiomeric purity (up to 98% ee) and in preparative amounts according to two distinct ways: First the photooxygenation of the racemic homoallylic alcohols **1** gave the racemic hydroperoxy alcohols **2**, which have subsequently been kinetically resolved by horseradish peroxidase (HRP); alternatively, first the lipase-catalyzed resolution afforded the optically active homoallylic alcohols **1** and subsequent photooxygenation led to the enantiomerically enriched hydroperoxy alcohols **2**.

Introduction

During the last years, the enzyme-catalyzed kinetic resolution of organic substrates has become a subject of intensive activity and interest, in view of the need of optically active building blocks for the synthesis of natural products and biologically active compounds.[1] Furthermore, enantiomerically pure hydroperoxides are potentially attractive oxygen-atom donors for asymmetric oxidations.[2] For the latter purpose, we have developed a convenient preparative-scale method for the enantioselective reduction of racemic hydroperoxides by horseradish peroxidase (HRP) in the presence of guaiacol,[3] which includes the HRP-catalyzed kinetic resolution of alkyl aryl hydroperoxides[4] and hydroperoxy homoallylic alcohols.[5] Also lipases, which generally serve well for the preparation of a wide range of optically active alcohols and esters,[6] have been successfully employed as convenient and efficient biocatalysts in the kinetic resolution of hydroperoxides.[7]

In this work, we report on the asymmetric synthesis of the allylic hydroperoxy alcohols **2** as potential chiral building blocks for highly oxy functionalized hydrocarbons. The racemic hydroperoxy alcohols **2** are readily available by photooxygenation (Schenck ene reaction)[8] of the homoallylic alcohols **1**[9] (Scheme 1). Kinetic resolution of the racemic hydroperoxy alcohols **2** by HRP-catalyzed reduction affords the enantiomerically pure (3*S*)-1,3-diols **4** and leaves behind the enantiomerically pure (3*R*)-hydroperoxy alcohols **2**.

Scheme 1



Results and Discussion

In the photooxygenation of the homoallylic alcohols **1** both diastereomeric pairs of the regioisomers **2** and **3** were formed in equal amounts and with no diastereoselectivity, as expected on account of the lacking 1,3-allylic strain in these substrates (Scheme 1).[10] The regioisomers **2** and **3** were readily separated by silica gel chromatography, whereas the diastereomers of **2** are only separable by MPLC.[11] Subsequent kinetic resolution of the racemic hydroperoxy alcohols **2** with HRP in the presence of guaiacol[3,12] led to the enantiomerically enriched hydroperoxides (*l*,*u*)-**2** and diols (*l*,*u*)-**4** (Scheme 2). The results are summarized in Table 1. At 50%

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(11) The diastereomers of **2a** were separated on a LiChroprep Si60 column (15−25 μm, $N = 8000$, SI = 1.1, 70:30 petroleum ether/ethyl acetate), and those of **2b**, in two cycles on a Europrep 60-30 C18 reversed-phase column, 60 Å (20−45 μm, $N = 2000$, SI = 1.05, 3:1 = H_2O/acetonitrile).

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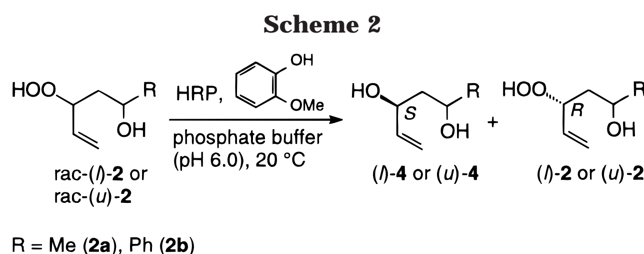
10.1021/jo9915630 CCC: $19.00 © 2000 American Chemical Society
Published on Web 02/11/2000

Table 1. Kinetic Resolution of the Hydroperoxy Alcohols 2 by Catalytic Reduction with Horseradish Peroxidase (HRP) in the Presence of Guaiacol

entry	substrate		enzyme:substrate[b]	time (min)	convn[c] (%)	enantiomeric excess (%)[a]		
						diol **4**[d]	ROOH **2**[d]	*E*[e]
1	**2a** (Me)	*like*	1:5000	80	50	>98, (−)-(2*S*,4*S*)-**4a**	98, (−)-(2*R*,4*R*)-**2a**	>200
2	**2a** (Me)	*like*	1:1400	5	44	>98, (−)-(2*S*,4*S*)-**4a**	78, (−)-(2*R*,4*R*)-**2a**	>200
3	**2a** (Me)	*unlike*	1:5000	80	54	84, (−)-(2*R*,4*S*)-**4a**	>98, (+)-(2*S*,4*R*)-**2a**	50
4	**2a** (Me)	*unlike*	1:1400	10	42	>98, (−)-(2*R*,4*S*)-**4a**	>72, (+)-(2*S*,4*R*)-**2a**	>200
5	**2b** (Ph)	*like*	1:1400	2	48	98, (−)-(1*S*,3*S*)-**4b**	90, (+)-(1*R*,3*R*)-**2b**	>200
6	**2b** (Ph)	*like*	1:5000	3	28	96, (−)-(1*S*,3*S*)-**4b**	38, (+)-(1*R*,3*R*)-**2b**	126
7	**2b** (Ph)	*unlike*	1:1400	5	51	94, (+)-(1*R*,3*S*)-**4b**	>98, (−)-(1*S*,3*R*)-**2b**	150
8	**2b** (Ph)	*unlike*	1:5000	5	42	95, (+)-(1*R*,3*S*)-**4b**	68, (−)-(1*S*,3*R*)-**2b**	65

[a] The enantiomeric excess (ee) was determined by multidimensional gas chromatography (MDGC) on a achiral OV 1701 and a permethylated β-cyclodextrin column packed with DB 1701 for **2a**/**4a** or by HPLC analysis (CHIRACEL OD-H, Daicel Chemical Industries Ltd.) for **2b**/**4b**. [b] Ratio of enzyme to substrate; semipreparative (ca. 300 μmol of substrate) scale, except entries 6 and 8 are on analytical scale (60 μmol of substrate). [c] The % conversion was calculated from the enantiomeric excess of the starting material (ee_s) and the product (ee_p) according to % convn = $ee_s/(ee_s + ee_p)$; cf. ref 13. [d] The absolute configuration was assessed by chemical correlation (see text). [e] The enantioselectivity (*E*) was calculated from the enantiomeric excess of the starting material (ee_s) and the conversion according to $E = \ln[(1 - \text{convn})(1 - ee_s)]/\ln[(1 - \text{convn})(1 + ee_s)]$; cf. ref 13.

Scheme 2



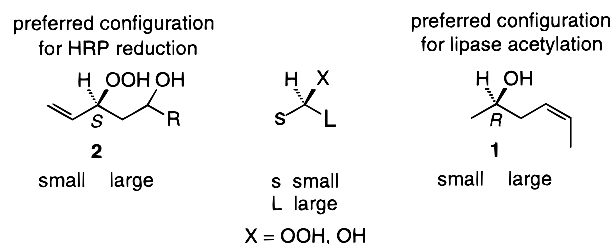


Figure 1. Preferred enantiomers in the HPR-catalyzed reduction of hydroperoxides and in the lipase-catalyzed acetylation of alcohols.

conversion of rac-(*l*)-**2a**, the diol (2*S*,4*S*)-**4a** and the hydroperoxide (2*R*,4*R*)-**2a** were obtained enantiomerically pure (Table 1, entry 1) in a very fast reaction (80 min). These results imply that the hydroperoxy alcohol (*l*)-**2a** is an excellent substrate for the HRP enzyme and one enantiomer of the hydroperoxide is selectively recognized by HRP. Also the *unlike* diastereomer (*u*)-**2a** and the phenyl-substituted hydroperoxy alcohols (*l*)-**2b** and (*u*)-**2b** are readily reduced by the enzyme in high enantioselectivity. At ≤50% conversion, the diols **4a**,**b** were obtained essentially enantiomerically pure (Table 1, entries 1, 2, 4, 5, 6, and 8), whereas at ≥50% conversion the optically pure hydroperoxy alcohols **2a**,**b** are left behind (entries 1, 3, and 7).

For a good fit of a substrate in the enzyme pocket, the steric features of the substrate are decisive. To assess the steric effects, it was of interest to test whether both diastereomers of the hydroperoxides **2a** are accepted well by the HRP enzyme and whether the large substituent phenyl in the substrate **2b** fits into the enzyme pocket. Comparison of entries 2 and 4 in Table 1 show no influence of the relative configuration of the alcohol functionality at the additional stereogenic center (C-1) since both *like* and *unlike* diastereomers are reduced by HRP in similar conversions with nearly equal stereodifferentiation. Moreover, the change of the substituent size from methyl (**2a**) to phenyl (**2b**) had no significant influence on the reactivity nor on the enantioselectivity (Table 1, entries 2, 4 and 5, 7).

For the *like* and *unlike* diastereomers of both **2a**,**b**, the enantiomer with the *S* configuration at the hydroperoxy group was preferably reduced to the diol by the horseradish peroxidase. This configurational preference in the present HRP-catalyzed kinetic resolution matches that for other alkyl aryl hydroperoxides,[4] hydroperoxy homoallylic alcohols,[5] and α-methylene β-hydroperoxy esters.[3] Moreover, it fits nicely into the established model[6a] for the molecular recognition of the preferred enantiomer by lipases (Figure 1). It is remarkable that two such distinct enzyme systems, namely the hydrolases (lipases) and oxidoreductases (peroxidases), are subject to the same steric control.

These optically active hydroperoxy alcohols **2** are also available by permutation of the photooxygenation and kinetic-resolution sequence, i.e., first to resolve enzymatically the racemic homoallylic alcohols **1** and subsequently to photooxygenate the optically active alcohols. The enantiomerically enriched homoallylic alcohols **1** were readily accessible by lipase-catalyzed kinetic resolution (ee up to 98%).[9] Subsequent photooxygenation of the optically active homoallylic alcohols **1** gave a diastereomeric mixture of both regioisomers **2** and **3** (analogous to Scheme 1). Since the chirality center of the homoallylic alcohol **1** is not involved in the photooxygenation reaction, the oxidation products hydroperoxy alcohols **2** and **3** possess the same enantiomeric excess as the starting homoallylic alcohols **1** (Figure 2). By following this sequence, all enantiomers of the hydroperoxy alcohols **2a**,**b** were obtained in high enantiomeric excess (ee ≥ 94%), except the phenyl-substituted hydroperoxy alcohols (*u*)-(1*R*,3*S*)-**2b** and (*l*)-(1*R*,3*R*)-**2b**, which were formed in only 48% ee. For the preparation of these two enantiomers, kinetic resolution of the separate racemic hydroperoxy alcohols (*u*)-**2b** and (*l*)-**2b** with HRP is superior (ee ≥ 95%). It should be emphasized that the *S*-configured hydroperoxides (*l*)-(2*S*,4*S*)-**2a**, (*u*)-(2*R*,4*S*)-**2a**, (*l*)-(1*S*,3*S*)-**2b**, and (*u*)-(1*R*,3*S*)-**2b**, which cannot be obtained by HRP-catalyzed kinetic resolution, are made available by the alternative route, namely first enzymatic resolution of the racemic homoallylic alcohols **1** and subsequent photooxygenation. Triphenylphosphine reduction of the enantiomerically pure hydroperoxy alcohols **2** (cf. Figure

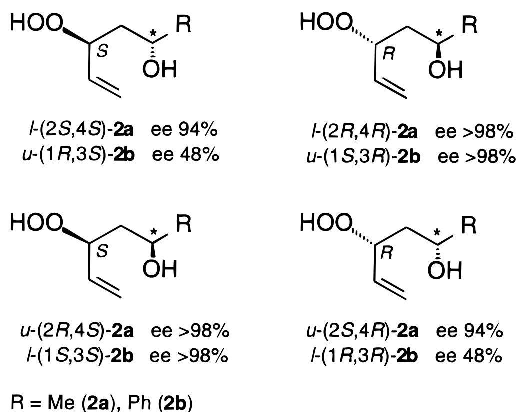
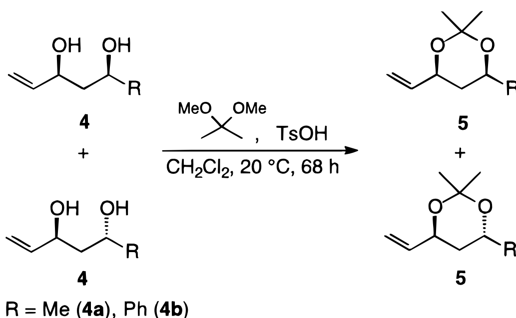


Figure 2. Enantiomeric excess of the hydroperoxy alcohols **2** obtained by photooxygenation of the optically active homoallylic alcohols **1**.

Scheme 3. Determination of the Relative Configuration of the 1,3-Diols 4



2) afford the whole set of all possible enantiomers of the 1,3-diols **4**.

The absolute configurations of the optically active homoallylic alcohols **1** of the lipase-catalyzed kinetic resolution are known.[9] The relative configuration of the new stereogenic center at the hydroperoxy group of **2** was assigned by chemical correlation. For this purpose, after photooxygenation of the enantiomerically pure homoallylic alcohol (*R*)-**1a**, the diastereomers (2*R*,4*R*)-**2a** and (2*R*,4*S*)-**2a** were reduced to the diols (2*R*,4*R*)-**4a** and (2*R*,4*S*)-**4a**. These diols were transformed into the corresponding cyclic acetals (2*R*,4*R*)-**5a** and (2*R*,4*S*)-**5a** by 2,2-dimethoxypropane/*p*-TsOH (Scheme 3).[14] The configurations of the *like* [(2*R*,4*R*)-**5a**] and *unlike* [(2*R*,4*S*)-**5a**] diastereomers were determined by NMR spectroscopy (cf. Supporting Information).

(13) The conversion and the enantioselectivity (*E* value) was calculated as described in: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Shi, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299.

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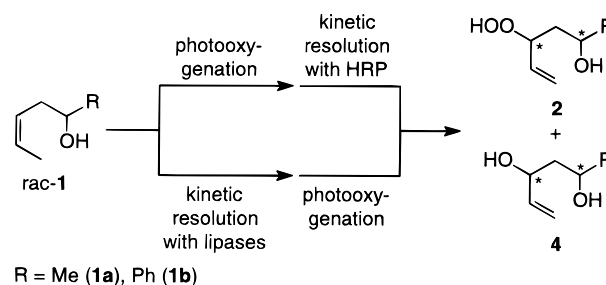
Scheme 4. Preparation of Optically Active Hydroperoxy Alcohols 2 and Their Corresponding 1,3-Diols 4 by a Combination and Permutation of Photooxygenation and Enzyme-Catalyzed Kinetic Resolution



Conclusions

By means of the appropriate combination and permutation of enzyme-catalyzed kinetic resolution and photooxygenation, all four possible optically active stereoisomers of the hydroperoxy alcohols **2** and their corresponding 1,3-diols **4** have been prepared for the first time (Scheme 4). In the upper route, the homoallylic alcohols **1** were first photooxygenated to the racemic hydroperoxy alcohols **2**, followed by their HRP-catalyzed enantioselective reduction to the optically active 1,3-diols **4**. Alternatively (lower route), lipase-catalyzed kinetic resolution afforded first the enantiomerically enriched homoallylic alcohols **1**, which were subsequently converted to the optically active hydroperoxy alcohols **2** by photooxygenation. Although both sequences make available for the first time these enantiomerically pure building blocks in preparative amounts, the sequence with the kinetic resolution by horseradish peroxidase is more efficient and applicable to various R substituents; however, the drawback of this method is that only *R*-configured hydroperoxides are made available.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (SFB-347, “Selektive Reaktionen Metall-aktivierter Moleküle”) and the Fonds der Chemischen Industrie. We also thank Boehringer Mannheim GmbH for the generous gift of enzymes.

Supporting Information Available: Text providing full experimental details and the characterization of the 1,3-diols **4a**,**b** and the 1,3-dioxanes (*l*,*u*)-**5a**,**b**, as well as for the kinetic resolution of the hydroperoxy alcohols **2a**,**b** by HRP, and structures **1**−**5**. This material is available free of charge in the Internet under http://pubs.acs.org.

JO9915630