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Synthesis of Optically Active α-Methyl β-Hydroperoxy Esters by Diastereoselective Singlet Oxygen Ene Reaction and Horseradish Peroxidase Catalyzed Kinetic Resolution

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Summary. Optically active diastereomeric β-hydroperoxy esters **4** have been prepared by singlet oxygen ene reaction of β,γ-unsaturated esters **3** and subsequent horseradish peroxidase (HRP) catalyzed kinetic resolution of the ene product. The highest enantiomeric excess (up to 95%) has been obtained for the isopropyl ester *threo*-**4c**, which establishes that the size of the remote ester functionality exercises appreciable control in the enantioselectivity of the enzymatic kinetic resolution.

Keywords. γ,δ-Unsaturated β-hydroperoxy esters; Horseradish peroxidase; Kinetic resolution; *Schenck* ene reaction; Singlet oxygen.

Introduction

During the last two decades, metal-activated hydroperoxides have been widely used as oxidants in enantioselective synthesis under catalytic conditions [1]. An achiral peroxide, *e.g.* *t*BuOOH or cumyl hydroperoxide, is usually employed in combination with a chiral auxiliary for asymmetric induction. Only recently [2] have optically active hydroperoxides been applied for the direct enantioselective oxygen transfer without chiral auxiliaries, because few methods are known for the preparation of enantiomerically enriched or even pure hydroperoxides, most notably enzymatic resolution [3]. In this context we have developed a convenient, versatile, and quite general kinetic resolution of racemic hydroperoxides by horseradish peroxidase (HRP) in the presence of guajacol [4]. Substrates with varying size as well as structure and with diverse functionalities have been extensively examined by this method; however, the influence of remote groups of different size on the stereochemical consequences on the efficacy of the kinetic resolution has not yet been addressed. For this purpose, we have studied by HRP-catalyzed kinetic resolution of α-methyl β-hydroperoxy esters in which the size of the ester group (-CO_2R), remote from the chirality center, has been varied in the increasing order of methyl, ethyl, isopropyl, and isobutyl.

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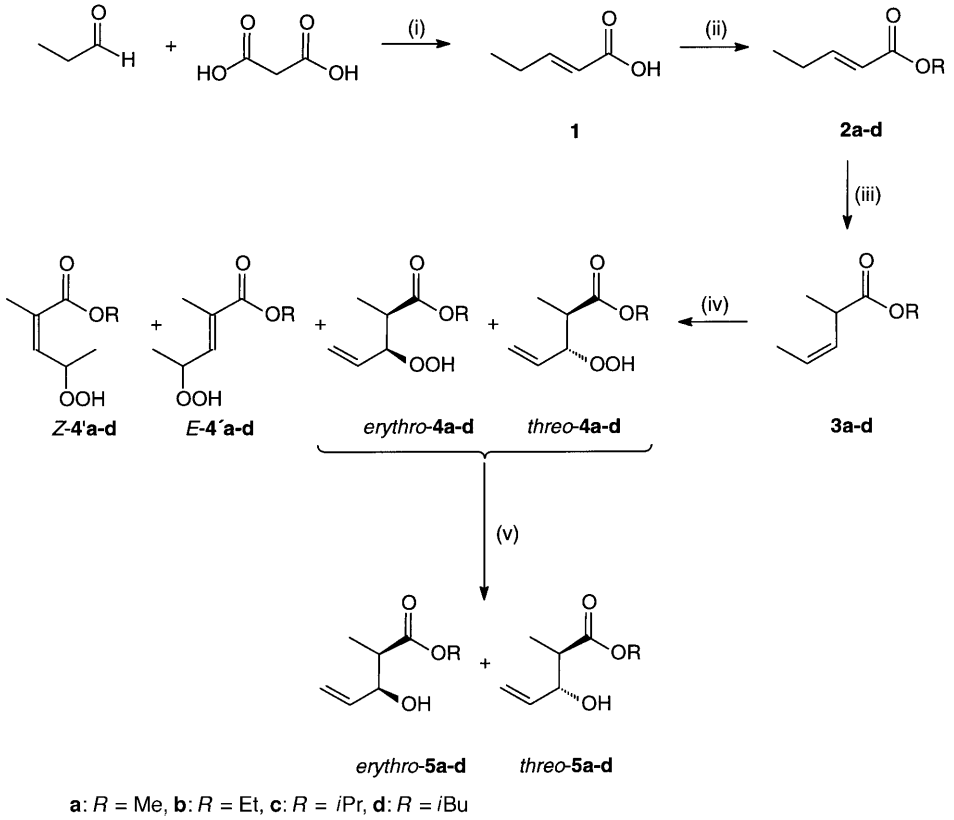
Results and Discussion

The photooxygenation of the *Z*-configured β,γ-unsaturated esters **3a–d** afforded the diastereomeric β-hydroperoxy esters **4a–d** in good yields by the singlet oxygen ene reaction (Scheme 1). Additionally, minor amounts of the regioisomeric acrylic acid derivatives **4a′–d′** were formed. The starting materials were prepared according to literature procedures. By starting from malonic acid and propionic aldehyde (*i*), (*E*)-2-pentenoic acid was formed [5] which was esterified in two ways (*ii*): the methyl, ethyl, and isopropyl esters were synthesized by means of the acid-catalyzed method of *Buchta* and *Burger* [6]; for the isobutyl derivative, to avoid possible rearrangement, the inverse method of *Johnstone* and *Rose* [7] was applied, *i.e.* alkylation of the carboxylate by isobutyl bromide. The deconjugative alkylation (*iii*) was performed in analogy to the literature procedure [8], in which the lithium enolate was allowed to react with methyl iodide; however, *HMPT* was replaced by the cyclic urea *DMPU* [9] without significant loss of yield.

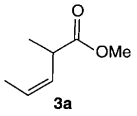
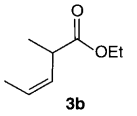
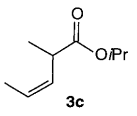
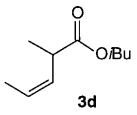
The photooxygenation [10] (*iv*) of the *Z*-configured β,γ-unsaturated esters **3a–d** was performed in CCl_4 at $-20°C$ (Table 1) and afforded the diastereomeric



(*i*) Pyridine, 6d, 20°C, exclusion of light, 53% (Ref. [5]: 88%); (*ii*) $R = $ Me, Et, *i*Pr: *R*OH, H_2SO_4, reflux [6]; $R = i$Bu: a) KOH, H_2O, 20°C, 2 h, b) *i*BuBr, *DMSO*, 20°C [7]; (*iii*) a) *LDA*/*DMPU*, *THF*, −78°C, 30 min, b) MeI, *THF*, −78°C, 45 min [8]; (*iv*) O_2, *TPP*, $h\nu$ (500 W), CCl_4, −20°C, 17 h [10]; (*v*) Ph_3P, Et_2O, 0°C, 30 min [11]

Scheme 1. Synthesis of β,γ-unsaturated esters, photooxygenation, and triphenylphosphine reduction

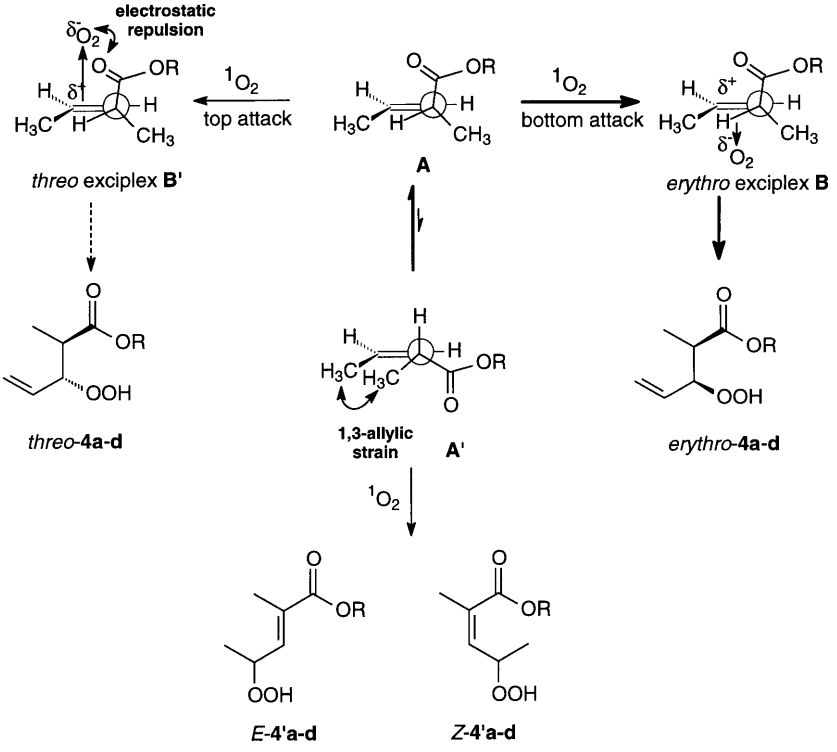
Table 1. Regio- and diastereoselectivities for the photooxygenation of the β, γ-unsaturated esters **3a–d**

Entry	Substrate	Conversion[a] [%]	Yield[b] [%]	Selectivity[a] Regioselectivity **4**:**4′**	Diastereoselectivity[c] *erythro*:*threo*	*E*:*Z*
1	 **3a**	92	65	90:10	77:23	34:66
2	 **3b**	> 95	60	90:10	77:23	33:67
3	 **3c**	> 95	70	90:10	76:24	22:78
4	 **3d**	> 95	67	> 95:5	80:20	–[d]

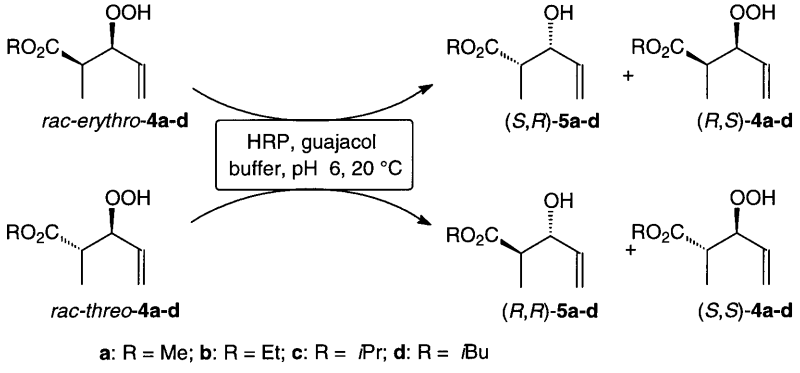
[a] Determined by ^{1}H NMR spectroscopy, error $\pm 5\%$; [b] yield of isolated product **4** after silica gel chromatography; [c] relative configuration was assigned according to Ref. [10]. [d] *E/Z* isomers not detected

hydroperoxy esters **4a–d** in 60–70% yield, with the *erythro* isomers as the main products. Due to the 1,3-allylic strain in the *cis*-configured esters **3**, the conformer **A′** (Scheme 2) is less favoured, and **A** dominates. The incoming $^1O_2$ may attack from the two diastereomeric π faces. In exciplex **B′** (top attack), the electrostatic repulsion between the dioxygen molecule and the carbonyl group disfavours this attack and, therefore, the resulting *thero* hydroperoxy esters are formed as the minor isomers (20–23%); in exciplex **B** (bottom attack), such electrostatic interaction is avoided; consequently, the *erythro* isomers are formed as the main products (76–80%). Since in the exciplex **B** the ester group points away from the reaction center, the diastereomeric ratios are unaffected by the size of this group, as demonstrated by the fact that the *threo*/*erythro* ratio is approximately the same for the whole series of hydroperoxy esters **4a–d** (Table 1). Minor amounts (*ca.* 10%) of the **4′** regioisomers were also formed, which were separated from the main **4** regioisomers by flash chromatography on silica gel. All attempts to separate the diastereomers **4a–d** by any chromatographic method failed; therefore, the hydroperoxy esters were used as mixture for further transformations. For GC analysis, the hydroperoxy esters **4a–d** were reduced (Scheme 1, step *v*) by triphenylphosphine in ether at 0°C to afford the hydroxy esters **5a–d** in high yields (80–98%) [11].

The HRP-catalyzed kinetic resolution [4] of the hydroperoxy esters **4a–d** as *erythro*/*threo* diastereomeric mixtures (*ca.* 77:23, Table 1) was performed on a semi-preparative scale. The methyl, ethyl, and isopropyl esters were converted to



Scheme 2. Mechanism of the singlet oxygen ene reaction for the β,γ-unsaturated esters **3a–d**

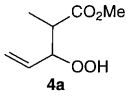
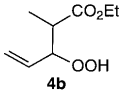
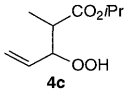
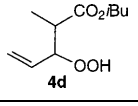


Scheme 3. HRP-catalyzed kinetic resolution of the racemic hydroperoxy esters **4a–d**; for the assignment of the absolute configuration, consult Scheme 4

the extent of *ca.* 50% within 4–6 h at ambient temperature (*ca.* 20°C) in a 0.1 *M* aqueous phosphate buffer ($pH = 6$) with 0.5 equiv. of guajacol and 1/10000 equiv. of enzyme (Scheme 3); in contrast, the isobutyl ester **4d** did not react under these conditions (Table 2). The conversions were determined by ^{1}H NMR spectroscopy on the crude product mixture and, for comparison, also calculated from the *ee* values of the hydroperoxides **4** and alcohols **5** (Table 2) according to

$$convn = 100 \times (ee_{ROOH}/ee_{ROOH} + ee_{ROH}) \quad (1)$$

Table 2. Enantioselectivities for the kinetic resolution of the hydroperoxy esters **4a–d**

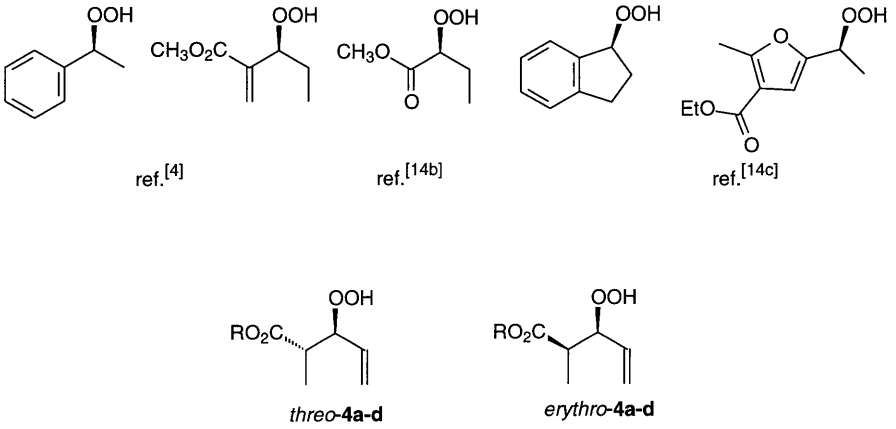
Entry	Substrate		*t*/h	Conversion (%) ^{1}H NMR[b]	Eq. (1)[c]	*ee*[a](%) **5**	**4**	*E*[d]
1	 **4a**	*erythro*	4	40	39	86 ± 1	53 ± 1	18
		threo			41	88 ± 1	60 ± 2	25
2[e]		*erythro*	4	24	23	82 ± 1	25 ± 1	14
		threo			23	82 ± 1	24 ± 1	12
3	 **4b**	*erythro*	4	60	48	81 ± 1	76 ± 2	23
		threo			–	–[f]	80 ± 1	34
4	 **4c**	*erythro*	6	46	49	93 ± 1	88 ± 1	66
		threo			49	>95	93 ± 1	>200
5	 **4d**	*erythro*	6	–[g]	–	–	–	
		threo						

[a] The *ee* values were determined by chiral GC analysis, error limits refer to several determinations, absolute configuration was not determined; [b] yield determined by ^{1}H NMR spectroscopy on the crude product mixture, error *ca*. 5%; [c] conversion calculated according to Eq. (1), [d] values for **4** calculated according to $E = \ln((1 - convn) \times (1 - ee))/\ln((1 - convn) \times (1 + ee))$ [12]; [e] reaction performed in a 1:1 phosphate buffer (*pH* 6)/EtOH mixture; [f] the *threo* diastereomer was not detected; [g] no conversion

The *ee* values of the hydroxy esters **5**, which were separated from the hydroperoxy esters **4** by silica gel chromatography, were determined by GC analysis on a chiral adsorbent. The *ee* values of the hydroperoxy esters **4** were determined in the same way, but after triphenylphosphine reduction.

The size of the remote ester group does influence the enantioselectivity of the HRP-catalyzed resolution of the hydroperoxides **4** (Table 2), since for the methyl *vs*. isopropyl substrates the *ee* values of the alcohols and hydroperoxides rose from 86% (**5a**) and 53% (**4a**) to 93% (**5c**) and 88% (**4c**). However, in all cases no significant difference in *ee* values was observed for the *erythro* and *threo* diastereomers. Unfortunately, the large isobutyl group (**4d**) was not accepted by the enzyme. To enhance the solubility of the substrate **4a**, the pure phosphate buffer was replaced by a 1:1-mixture of buffer and EtOH; however, the conversion was significantly decreased (Table 2, entry 2). This may be ascribed to the favoured active conformation of the enzyme under the natural conditions of the aqueous buffered medium [13].

The determination of the absolute configuration by spectroscopic and/or chemical means was made difficult by the fact that the diastereomeric mixtures of the hydroperoxy (**4**) and hydroxy (**5**) esters could not be separated and, thus, the pure diastereomers were not accessible. For this reason, the configurations, given in Scheme 3 were tentatively assigned by analogy to the established configurations of optically active hydroperoxides obtained previously by HRP-catalyzed kinetic resolutions. The following empirical rule has been proposed [14]: The two α



Scheme 4. Correlation of the absolute configuration of the hydroperoxy esters **4** with hydroperoxides of known configuration

carbon atoms of the chiral hydroperoxid are placed in the plane of the paper, with the small substituent on the right-hand and the larger one on the left-hand side (Scheme 4). The enantiomer with the hydroperoxy group above the paper plane is less likely reduced by the enzyme and, therefore, accumulates enantiomerically enriched in the HRP-catalyzed kinetic resolution. Application of this empirical rule leads to the absolute configurations of *threo-* and *etythro-***4a–c** as depicted in Scheme 4, in which the vinyl group unquestionably qualifies as the smaller substituent compared to the ester-bearing group.

In conclusion, the present study clearly demonstrates that besides α substituents, also remote groups may influence the stereochemical course of the HRP-catalyzed reduction of chiral hydroperoxides. This affords attractive opportunities of controlling the enantioselectivity of such enzymatic transformations by attaching easily removable groups remote from the reaction center.

Experimental

THF was distilled from potassium metal, diisopropyl amine was refluxed over CaH_2 for one week and distilled subsequently. *DMPU* was dried according to literature [9]. For the photooxygenation, CCl_4 was distilled from P_2O_5 and the oxygen gas was dried over $CaCl_2$ and P_2O_5. Other commercially available reagents were used without further purification. The photooxygenations were performed at $-20^{\circ}C$ by irradiation with two 500 W sodium vapor lamps (Osram Vialox NAV-E) without filter. The horseradish peroxidase was obtained from Sigma (peroxidase type II, 1.5–2 U/mg).

Preparation of the starting materials

E-2-Pentenoic acid (**1**) was prepared from propionoic aldehyde and malonic acid in 53% yield [5]. The esters **2a–c** were synthesized according to literature in 73–80% yield. **2d** [7] and the *Z*-2-methylpentenoic esters **3a–d** [8] were obtained in yields of 91 and 46–70%, respectively. Photooxygenations were performed as reported [10] to afford the hydroperoxy esters **4a–d** in 60–70% yields as a 90:10-mixture of the regioisomers **4** and **4′** and a 77:23 mixture of the *erythro/threo* diastereomers. The reduction to the hydroxy esters **5a–d** was performed as described [11] in 80–98% yield. Compounds **1** [5], **2a** [6], **b** [5], **c** [15], **d** [15], **3a** [16], **b** [8], **c** [16], **d** [16], **4b** [10], **5a**[17], **b**

[18] are known. No satisfactory elemental analyses could be obtained for the labile hydroperoxides **4a** and **4d**; the peroxide content was therefore determined iodometrically.

Methyl erythro, threo-3-hydroperoxy-2-methyl-4-pentenoates (**4a**; $C_7H_{12}O_4$)
and *(E,Z)-4-Hydroperoxy-2-methyl-2-pentenoates* (**4a′**; $C_7H_{12}O_4$)

Peroxide content: >95%; *erythro*-**4a**: ^{1}H NMR ($CDCl_3$, δ, 250 MHz): 1.19 (d, $J_{6,2} = 7.2$ Hz, 3H, 6-H), 2.84 (qd, $J_{2,6} = 7.2$ Hz, $J_{2,3} = 6.5$ Hz, 1H, 2-H), 3.69 (s, 3H, 7-H), 4.58 (ddm, $J_{3,4} = 7.5$ Hz, $J_{3,2} = 6.5$ Hz, 1H, 3-H), 5.32 (m, 1H, 5-H_b), 5.38 (ddd, $J_{5a,4} = 17.4$ Hz, $J_{5a,5b} = J_{5a,3} = 0.9$ Hz, 1H, 5-H_a), 5.82 (ddd, $J_{4,5a} = 17.4$ Hz, $J_{4,5b} = 10.4$ Hz, $J_{4,3} = 7.5$ Hz, 1H, 4-H), 8.49 (s, 1H, OOH) ppm; ^{13}C NMR ($CDCl_3$, δ, 63 MHz): 12.2 (q, C-6), 42.3 (d, C-2), 52.0 (q, C-7), 87.3 (d, C-3), 120.7 (t, C-5), 133.4 (d, C-4), 174.2 (C-1) ppm; *threo*-**4a**: ^{1}H NMR ($CDCl_3$, δ, 250 MHz): 1.12 (d, $J_{6,2} = 7.2$ Hz, 3H, 6-H), 2.84 (qd, $J_{2,6} = 7.2$ Hz, $J_{2,3} = 6.5$ Hz, 1H, 2-H), 3.69 (s, 3H, 7-H), 4.50 (ddm, $J_{3,4} = 7.9$ Hz, $J_{3,2} = 6.5$ Hz, 1H, 3-H), 5.32 (m, 1H, 5-H_b), 5.38 (ddd, $J_{5a,4} = 17.4$ Hz, $J_{5a,5b} = J_{5a,3} = 0.9$ Hz, 1H, 5-H_a), 5.77 (ddd, $J_{4,5a} = 17.4$ Hz, $J_{4,5b} = 10.4$ Hz, $J_{4,3} = 7.9$ Hz, 1H, 4-H), 8.49 (s, 1H, OOH) ppm; ^{13}C NMR ($CDCl_3$, δ, 63 MHz): 13.2 (q, C-6), 41.9 (d, C-2), 52.0 (q, C-7), 88.2 (d, C-3), 121.4 (t, C-5), 133.4 (d, C-4), 174.2 (C-1) ppm; the signals for the regioisomers (*E*)-**4a′** and (*Z*)-**4a′** could not be assigned due to severe overlap in the NMR spectrum of the crude product; IR (neat): $\nu = 3640$-3020 (OOH), 2940, 2910, 1700 (C=O), 1435, 1410, 1360, 1330, 1240, 1190, 1040, 980, 920, 860 cm^{-1}.

Isopropyl erythro, threo-3-hydroperoxy-2-methyl-4-pentenoates (**4c**; $C_9H_{16}O_4$)
and (E,Z)-4-hydroperoxy-2-methyl-2-pentenoates (**4c′**; $C_9H_{16}O_4$)

Calcd.: C 57.43, H 8.57; found: C 57.16, H 8.80; *erythro*-**4c**: ^{1}H NMR ($CDCl_3$, δ, 250 MHz): 1.23 (d, $J_{6,2} = 7.2$ Hz, 3H, 6-H), 1.23 (d, $J_{8,7} = 6.3$ Hz, 6H, 8-H), 2.78 (qd, $J_{2,6} = 7.2$ Hz, $J_{2,3} = 6.4$ Hz, 1H, 2-H), 4.57 (ddm, $J_{3,4} = 7.4$ Hz, $J_{3,2} = 6.4$ Hz, 1H, 3-H), 5.02 (sept, $J_{7,8} = 6.3$ Hz, 1H, 7-H), 5.33 (dm, $J_{5b,4} = 10.2$ Hz, 1H, 5-H_b), 5.39 (dm, $J_{5a,4} = 18.9$ Hz, 1H, 5-H_a), 5.83 (ddd, $J_{4,5a} = 18.9$ Hz, $J_{4,5b} = 10.2$ Hz, $J_{4,3} = 7.4$ Hz, 1H, 4-H), 8.43 (s, 1H, 3-OOH) ppm; ^{13}C NMR ($CDCl_3$, δ, 63 MHz): 12.3 (q, C-6), 21.7 (2q, C-8), 42.5 (d, C-2), 68.2 (d, C-7), 87.3 (d, C-3), 120.5 (t, C-5), 133.6 (d, C-4), 173.3 (s, C-1) ppm; *threo*-**4c**: ^{1}H NMR ($CDCl_3$, δ, 250 MHz): 1.19 (d, $J_{6,2} = 7.2$ Hz, 3H, 6-H), 1.23 (d, $J_{8,7} = 6.3$ Hz, 6H, 8-H), 2.78 (qd, $J_{2,6} = 7.2$ Hz, $J_{2,3} = 6.4$ Hz, 1H, 2-H), 4.48 (ddm, $J_{3,4} = 8.0$ Hz, $J_{3,2} = 6.4$ Hz, 1H, 3-H), 5.02 (sept, $J_{7,8} = 6.3$ Hz, 1H, 7-H), 5.33 (dm, $J_{5b,4} = 10.2$ Hz, 1H, 5-H_b), 5.39 (dm, $J_{5a,4} = 18.9$ Hz, 1H, 5-H_a), 5.83 (ddd, $J_{4,5a} = 18.9$ Hz, $J_{4,5b} = 10.2$ Hz, $J_{4,3} = 8.0$ Hz, 1H, 4-H), 8.43 (s, 1H, OOH) ppm; ^{13}C NMR ($CDCl_3$, δ, 63 MHz): 12.3 (q, C-6), 21.7 (2q, C-8), 42.5 (d, C-2), 68.2 (d, C-7), 88.2 (d, C-3), 121.2 (t, C-5), 133.6 (d, C-4), 173.3 (s, C-1) ppm; the signals for the regioisomers (*E*)-**4c′** and (*Z*)-**4c′** could not be assigned due to severe overlap in the NMR spectrum of the crude product; IR (neat): $\nu = 3680$-3100 (OOH), 2960, 2920, 2860, 1710 (C=O), 1690, 1440, 1365, 1100, 985, 820 cm^{-1}.

Isobutyl erythro, threo-3-hydroperoxy-2-methyl-4-pentenoates (**4d**; $C_{10}H_{18}O_4$)

Peroxide content: 91%; *erythro*-**4d**: ^{1}H NMR ($CDCl_3$, δ, 250 MHz): 0.93 (d, $J_{9,8} = 6.7$ Hz, 6H, 9-H), 1.21 (d, $J_{6,2} = 7.0$ Hz, 3H, 6-H), 1.94 (m, 1H, 8-H), 2.84 (qd, $J_{2,6} = 7.0$ Hz, $J_{2,3} = 6.2$ Hz, 1H, 2-H), 3.90 (d, $J_{7,8} = 6.7$ Hz, 2H, 7-H), 4.58 (ddm, $J_{3,4} = 7.4$ Hz, $J_{3,2} = 6.2$ Hz, 1H, 3-H), 5.33 (ddd, $J_{5b,4} = 4.3$ Hz, $J_{5b,5a} = 1.5$ Hz, $J_{5b,3} = 0.9$ Hz, 1H, 5-H_b), 5.39 (ddd, $J_{5a,4} = 11.3$ Hz, $J_{5a,5b} = 1.5$ Hz, $J_{5a,3} = 0.9$ Hz, 1H, 5-H_a), 5.84 (ddd, $J_{4,5a} = 11.3$ Hz, $J_{4,3} = 7.4$ Hz, $J_{4,5b} = 4.3$ Hz, 1H, 4-H), 8.46 (s, 1H, OOH) ppm; ^{13}C NMR ($CDCl_3$, δ, 63 MHz): 12.1 (q, C-6), 19.0 (2q, C-9), 27.7 (d, C-8), 42.1 (d, C-2), 71.0 (t, C-8), 87.2 (d, C-3), 120.5 (t, C-5), 133.7 (d, C-4), 173.9 (s, C-9) ppm; *threo*-**4d**: ^{1}H NMR ($CDCl_3$, δ, 250 MHz): 0.94 (d, $J_{9,8} = 6.7$ Hz, 6H, 9-H), 1.12 (d, $J_{6,2} = 7.0$ Hz, 3H, 6-H), 1.94 (m, 1H, 8-H), 2.75 (qd, $J_{2,6} = 7.0$ Hz, $J_{2,3} = 6.2$ Hz, 1H, 2-H), 3.87 (d, $J_{7,8} = 6.7$ Hz, 2H, 7-H), 4.52 (ddm, $J_{3,4} = 8.5$ Hz, $J_{3,2} = 6.2$ Hz, 1H, 3-H), 5.33 (ddd, $J_{5b,4} = 4.3$ Hz, $J_{5b,5a} = 1.5$ Hz, $J_{5b,3} = 0.9$ Hz, 1H,

5-H_b), 5.39 (ddd, $J_{5a,4} = 11.3$ Hz, $J_{5a,5b} = 1.5$ Hz, $J_{5a,3} = 0.9$ Hz, 1H, 5-H_a), 5.80 (ddd, $J_{4,5a} = 11.3$ Hz, $J_{4,3} = 8.5$ Hz, $J_{4,5b} = 4.3$ Hz, 1H, 4-H), 8.46 (s, 1H, OOH) ppm; ^{13}C NMR ($CDCl_3$, δ, 63 MHz): 13.2 (q, C-6), 19.0 (2q, C-9), 27.7 (d, C-8), 42.5 (d, C-2), 71.0 (t, C-7), 88.2 (d, C-3), 121.2 (t, C-5), 133.7 (d, C-4), 174.3 (s, C-9) ppm; IR (neat): $\nu = 3620$-3100 (OOH), 2920, 2820, 1700 (C=O), 1620, 1440, 1410, 1230, 1175, 1030, 975, 910, 850 cm^{-1}.

Isopropyl erythro, threo-3-hydroxy-2-methyl-4-pentenoates (**5c**; $C_9H_{16}O_3$)

Calcd.: C 62.77, H 9.36; found: C 62.88, H 9.27; *erythro*-**5c**: ^{1}H NMR ($CDCl_3$, δ, 250 MHz): 1.15 (d, $J_{6,2} = 7.3$ Hz, 3H, 6-H), 1.23 (d, $J_{8,7} = 6.3$ Hz, 6H, 8-H), 2.58 (qd, $J_{2,6} = 7.3$ Hz, $J_{2,3} = 4.0$ Hz, 1H, 2-H), 4.38 (m, 1H, 3-H), 5.04 (sept, $J_{7,8} = 6.3$ Hz, 1H, 7-H), 5.19 (ddd, $J_{5b,4} = 10.5$ Hz, $J_{5b,5a} = J_{5b,3} = 1.6$ Hz, 1H, 5-H_b), 5.32 (ddd, $J_{5a,4} = 17.2$ Hz, $J_{5a,5b} = J_{5a,3} = 1.6$ Hz, 1H, 5-H_a), 5.82 (ddd, $J_{4,5a} = 17.2$ Hz, $J_{4,5b} = 10.5$ Hz, $J_{4,3} = 5.5$ Hz, 1H, 4-H) ppm, OH not detected; ^{13}C NMR ($CDCl_3$, δ, 63 MHz): 11.2 (q, C-6), 21.7 (2q, C-8), 44.6 (d, C-2), 68.1 (d, C-7), 73.0 (d, C-3), 116.2 (t, C-5), 137.3 (d, C-4), 174.9 (s, C-1) ppm; *threo*-**5c**: ^{1}H NMR ($CDCl_3$, δ, 250 MHz): 1.17 (d, $J_{6,2} = 7.3$ Hz, 3H, 6-H), 1.40 (d, $J_{8,7} = 6.7$ Hz, 6H, 8-H), 2.58 (qd, $J_{2,6} = 7.3$ Hz, $J_{2,3} = 4.0$ Hz, 1H, 2-H), 4.38 (m, 1H, 3-H), 5.04 (sept, $J_{7,8} = 6.7$ Hz, 1H, 7-H), 5.19 (ddd, $J_{5b,4} = 10.5$ Hz, $J_{5b,5a} = J_{5b,3} = 1.6$ Hz, 1H, 5-H_b), 5.30 (ddd, $J_{5a,4} = 17.1$ Hz, $J_{5a,5b} = J_{5a,3} = 1.6$ Hz, 1H, 5-H_a), 5.83 (ddd, $J_{4,5a} = 17.1$ Hz, $J_{4,5b} = 10.5$ Hz, $J_{4,3} = 5.5$ Hz, 1H, 4-H) ppm, OH not detected; ^{13}C NMR ($CDCl_3$, δ, 63 MHz): 14.0 (q, C-6), 30.9 (2q, C-8), 45.2 (d, C-2), 68.1 (d, C-7), 74.7 (d, C-3), 116.7 (t, C-5), 138.2 (d, C-4), 174.9 (s, C-1) ppm; IR (neat): $\nu = 3620$-3100 (OH), 2960, 2920, 2860, 1710 (C=O), 1690 (C=C), 1440, 1365, 1250, 1185, 1100, 920 cm^{-1}.

Isobutyl erythro,threo-3-hydroxy-2-methyl-4-pentenoates (**5d**; $C_{10}H_{18}O_3$)

Calcd.: C 64.49, H 9.74; found: C 64.22, H 9.56; *erythro*-**5d**: ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 0.86 (d, $J_{9,8} = 6.7$ Hz, 6H, 9-H), 1.11 (d, $J_{6,2} = 7.2$ Hz, 3H, 6-H), 1.87 (septm, $J_{8,9} = 6.7$ Hz, 1H, 8-H), 2.55 (qd, $J_{2,6} = 7.2$ Hz, $J_{2,3} = 4.6$ Hz, 1H, 2-H), 3.81 (d, $J_{7,8} = 6.6$ Hz, 2H, 7-H), 4.32 (m, 1H, 3-H), 5.10 (ddd, $J_{5b,4} = 10.5$ Hz, $J_{5b,5a} = J_{5b,3} = 1.5$ Hz, 1H, 5-H_b), 5.23 (ddd, $J_{5a,4} = 17.2$ Hz, $J_{5a,5b} = J_{5a,3} = 1.5$ Hz, 1H, 5-H_a), 5.77 (ddd, $J_{4,5a} = 17.2$ Hz, $J_{4,5b} = 10.5$ Hz, $J_{4,3} = 5.6$ Hz, 1H, 4-H), ppm, OH not detected; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 11.3 (q, C-6), 18.9 (2q, C-9), 27.5 (d, C-8), 44.7 (d, C-2), 70.5 (t, C-7), 73.0 (d, C-3), 115.9 (t, C-5), 137.5 (d, C-4), 175.1 (s, C-1) ppm; *threo*-**5d**: ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 0.86 (d, $J_{9,8} = 6.7$ Hz, 6H, 9-H), 1.10 (d, $J_{6,2} = 7.2$ Hz, 3H, 6-H), 1.87 (septm, $J_{8,9} = 6.7$ Hz, 1H, 8-H), 2.55 (qd, $J_{2,6} = 7.2$ Hz, $J_{2,3} = 4.6$ Hz, 1H, 2-H), 3.82 (d, $J_{7,8} = 6.6$ Hz, 2H, 7-H), 4.32 (m, 1H, 3-H), 5.10 (ddd, $J_{5b,4} = 10.5$ Hz, $J_{5b,5a} = J_{5b,3} = 1.5$ Hz, 1H, 5-H_b), 5.23 (ddd, $J_{5a,4} = 17.2$ Hz, $J_{5a,5b} = J_{5a,3} = 1.5$ Hz, 1H, 5-H_a), 5.77 (ddd, $J_{4,5a} = 17.2$ Hz, $J_{4,5b} = 10.5$ Hz, $J_{4,3} = 5.6$ Hz, 1H, 4-H), ppm, OH not detected; ^{13}C NMR ($CDCl_3$, δ, 50 MHz): 13.7 (q, C-6), 18.9 (2q, C-9), 27.5 (d, C-8), 45.2 (d, C-2), 70.6 (t, C-6), 74.5 (d, C-3), 116.7 (t, C-5), 138.0 (d, C-4), 175.3 (s, C-1) ppm; IR (neat): $\nu = 3600$-3120, 2940, 2850, 1710 (C=O), 1690 (C=C), 1450, 1360, 1330, 1250, 1180, 1040, 980, 910 cm^{-1}.

General procedure for HRP-catalyzed kinetic resolution on a semi-preparative scale

Guajacol (0.05–0.30 mmol, 0.5 equiv.) and HRP ($1–3 \times 10^{-5}$ mmol, 1/10000 equiv.) were dissolved in 2 cm^3 of 0.1 *M* phosphate buffer ($pH = 6$), and subsequently 0.1–0.6 mmol of the particular hydroperoxy esters **4** (as diastereomeric mixture) were added. The reaction was stirred at *ca.* 20°C until about 50% conversion was achieved (*ca.* 4–6 h) and then extracted with CH_2Cl_2 (5×10 cm^3). The combined organic phases were dried over $MgSO_4$, and the solvent was evaporated (0°C, 12 torr). The products were separated by flash chromatography (40 g silica gel (0.063–0.200 mm), petroleum ether (30–50): ethyl ether = 9:1 as eluent) to afford the enantiomerically enriched hydroperoxy esters

4a–d and the corresponding hydroxy esters **5a–d**. The enantiomeric excess was determined by GC analysis on a Cyclodex-B column (30 m, 0,25 mm ID, H_2 gas). Conditions **5a**: 60°C (5 min), 5°C/min, 90°C; **5b**: 60°C (1 min), 5°C/min, 90°C; **5c**,**d**: 60°C (1 min), 5°C/min, 80°C.

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