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Singlet oxygen addition to chiral allylic alcohols and subsequent peroxyacetalization with β-naphthaldehyde: synthesis of diastereomerically pure 3-β-naphthyl-substituted 1,2,4-trioxanes

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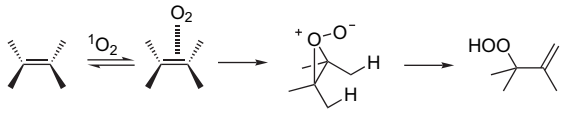
Abstract—The synthesis of a series of eight β-naphthyl-substituted 1,2,4-trioxanes **3a–h** by a sequence of singlet oxygen ene reaction of allylic alcohols **1a–h** and Lewis acid catalyzed peroxyacetalization of the allylic hydroperoxides **2a–h** with β-naphthaldehyde is reported. The ene reactions were performed by solid-state photooxygenation in dye-crosslinked polystyrene beads and resulted in mixtures of diastereoisomeric hydroperoxides **2**. Boron trifluoride catalyzed peroxyacetalization resulted in the formation of **3**, as well as the 1,2,4-trioxanes **4** and **5**, which were formed via acid catalyzed β-hydroperoxy alcohol cleavage.

1. Introduction

1.1. Singlet oxygen chemistry

In 1948, Schenck was the first to describe the singlet oxygen ene reaction[1] (therefore often termed Schenck reaction).[2] In the course of this reaction, $^1O_2$ attacks one center of a CC double bond with abstraction of an allylic hydrogen atom or an allylic silyl group (from a silyl enolether in case of the *silyl–ene reaction*) with simultaneous allylic shift of the double bond. As a result of this reaction, allylic hydroperoxides or *O*-silylated α-hydroperoxy carbonyl compounds are formed (Scheme 1). Since the first report, the $^1O_2$ ene reaction has attracted major interest not only in the mechanistic photochemistry but also in modern organic synthesis. Several mechanisms have been postulated for this reaction with concerted or 'concerted two-stage' mechanisms,[3] as well as 1,4-biradicals,[4] 1,4-zwitterions,[5] perepoxide, dioxetane[6] or exciplex intermediates.



Scheme 1. Singlet oxygen ene reaction.

The results of Stephenson's elegant inter- and intramolecular isotope effect experiment[7] with isotopically labeled tetramethylethylenes provided evidence for the perepoxide intermediate. Also, the small negative activation enthalpies and highly negative activation entropies observed for the singlet oxygen ene reaction from kinetic measurements have shown that the reaction of $^1O_2$ with electron-rich olefins proceed 10^3 times slower than the diffusion rate, which accounts for the presence of non-productive encounters between $^1O_2$ and the alkene favoring the participation of a reversibly formed exciplex as intermediate.[8] As a result, a three-step mechanism involving exciplex and perepoxide can be assumed for the ene reaction.

The *regiochemistry* of the ene reaction with substrates with multiple sites for allylic hydrogen transfer was extensively studied and several general effects can predict the regioselective introduction of the hydroperoxy group: (a) the cis-effect[9] (*syn*-effect): in the reaction of $^1O_2$ with trisubstituted alkenes[10] or enol ethers,[11] the allylic hydrogen atoms on the more substituted side of the double bond are more reactive for H-abstraction by $^1O_2$; (b) the *gem*-effect[12] that leads to highly selective abstraction of an allylic hydrogen atom from a substituent in α position of an α,β-unsaturated carbonyl compound; (c) the large-group effect[13] that leads to selective (moderate) abstraction of an allylic hydrogen from the substituent geminal to a large group.

Several factors that control the π-facial selectivity of singlet oxygen ene reaction are known and can be summarized as follows: (a) steric factors: in view of the small size of the

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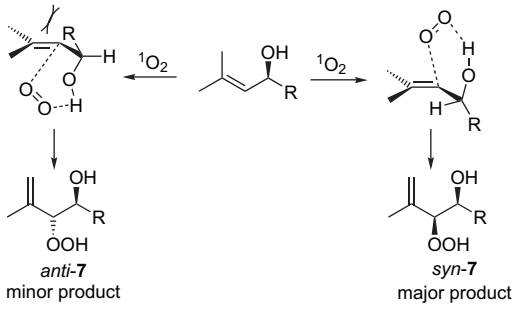
reactive molecule singlet oxygen, steric interactions are expected to be less important in directing the facial approach. However, in rigid (cyclic and polycyclic) substrates where changes in conformation that minimize steric factors are restricted, this effect is more pronounced and steric shielding of one face of the double bond may bias $^1O_2$ attack to occur predominantly on the other face of the π-system;[14] (b) conformational effects: for an efficient hydrogen abstraction to occur, the reactive allylic hydrogen atoms must adopt a conformation, which places them perpendicular to the alkene plane.[15] This factor is often highly effective in rigid compounds in which allylic hydrogen atoms can be conformationally fixed in an optimal transfer geometry on one face of the double bond; (c) electronic effects and hydrogen bonding: the simplest tetrasubstituted alkene, 2,3-dimethyl-2-butene with a highly nucleophilic double bond reacts more than 30 times faster than the corresponding trisubstituted alkene, 2-methyl-2-butene, and the latter reacts about 15 times faster than the disubstituted alkene *Z*-2-butene. Adam and Brünker elegantly used hydrogen bonding interactions between the substrate and the incoming singlet oxygen for control of the diastereoselectivity in the photooxygenation of allylic alcohols and other substrates.[16] The coordination of singlet oxygen to the hydroxy group in the more stable conformer (not destabilized by 1,3-allylic strain) directs the approach of the electrophilic $^1O_2$ to one face of the double bond (Scheme 2).



Scheme 2. Mechanism of the singlet oxygen ene reaction with chiral allylic alcohols.

We have recently demonstrated that the use of polymer support as reaction media with non-covalently adsorbed or covalently linked porphyrin dyes are convenient processes for the solvent-free photooxygenation of unsaturated organic substrates.[17] Especially the use of chiral allylic alcohols is informative in that the diastereoselectivity is a tool for analyzing the reaction environment and supramolecular effects.[18] We have used this concept for the synthesis of β-hydroperoxy alcohols, which we have applied as substrates for the synthesis of a series of 1,2,4-trioxanes in the context of a study on antimalarial peroxides.

1.2. Artemisinin and antimalarial peroxides

One of the major drawbacks of artemisinin is its poor solubility in both water and oil.[19] To overcome this problem artemisinin is reduced to dihydroartemisinin, which leads to the preparation of a series of semisynthetic first-generation artemisinin analogues, including artemether, arteether, and artesunate, which are used broadly in many areas of the world where malaria is endemic (Fig. 1).[20] Venugopalan et al. synthesized various ethers and thioethers of dihydroartemisinin

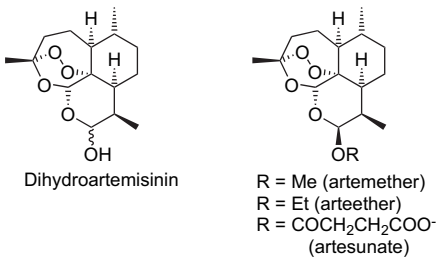


Figure 1. Artemisinin-derivatives with improved pharmacological properties.

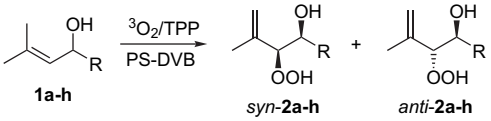
by treatment with alkyl, aryl, alkynyl, and heteroalkyl alcohols or thiols in the presence of boron trifluoride. The products were tested in vivo and some show antimalarial activity comparable to arteether.[21]

The moderate bioavailability and rapid clearance (short pharmacological half-life) observed with these artemisinin-derived drugs are the major disadvantages. This often results from the poor chemical and metabolic stability of the additional acetal functional group present in such derivatives. To overcome this problem, many C-10-carba analogues and C-10-aryl analogues of dihydroartemisinin that are metabolically more robust were synthesized. Of relevance are the C-10-alkyl and the C-10-aryl or heteroaromatic derivatives prepared by Haynes,[22] Posner,[23] O'Neill,[24] Jung,[25] and Ziffer.[26] The development of the artemisinin combination therapy concept was recently achieved by the synthesis of effective drugs that simultaneously contain the 1,2,4-trioxane moiety covalently bound with another active antimalarial pharmacophore, such as aminoquinolines[27] or aliphatic diamines.[28] The high activity of these molecules, termed trioxaquines, is rationalized by the combination of a peroxidic entity that is a fast and potential alkylating agent, in the same molecule with the aminoquinoline unit, which is characterized by easy penetration of the infected erythrocytes.[29]

The goal of the present work is to show that aromatic side groups can be easily incorporated into 1,2,4-trioxanes that are produced by a sequence of $^1O_2$ ene reaction with chiral allylic alcohols and subsequent peroxyacetalization. As a model compound for aromatic and heteroaromatic carbonyl compounds, β-naphthaldehyde was applied.

2. Results and discussion

The photooxygenation of a series of allylic alcohols **1a–h** using PS–DVB polymer matrix doped with adsorbed porphyrin sensitizers resulted in the formation of a *syn* (or *threo*) and *anti* (or *erythro*) diastereomeric mixture of the *vic*-hydroperoxy alcohols in good yields (Scheme 3). The β-hydroperoxy alcohols are stable at rt and can be kept in the refrigerator for weeks without decomposition.



Scheme 3. Solvent-free photooxygenation of the allylic alcohols **1a–h** using TPP embedded in PS–DVB matrix.

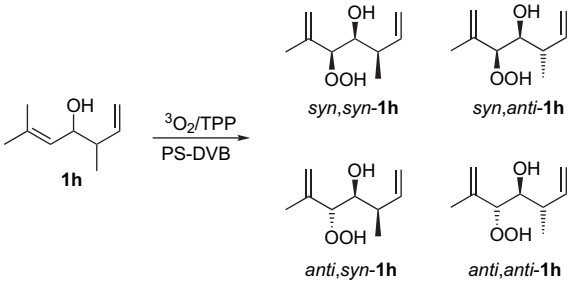
The diastereoselectivity of the ene reaction using the commercial PS–DVB that were modified with adsorbed porphyrin sensitizer (Table 1) showed similar values to that obtained with the polymer-bound sensitizer systems, TSP–S–DVB or PP–S–DVB (TSP=tetrastyrylporphyrin; PP=protoporphyrin IX),[30] but lower than for solution phase (e.g., tetrachloromethane), accounting for an intermolecular hydrogen bonding between the concentrated substrate molecules in both polymer systems. Comparison of the chemical yields and the diastereoselectivities in the solvent-free photooxygenation reaction of the allylic alcohols **1a–h** is shown in Table 1.

Table 1. Photooxygenation of the allylic alcohols **1a–h** using solvent-free approach with PS–DVB copolymer

Compound	R	d.r.[a] *syn*:*anti*	Yield (%)
2a	Et	77:23	72
2b	*n*-Pr	79:21	78
2c	*n*-Bu	79:21	78
2d	*i*-Bu	80:20	77
2e	*c*-Pr	62:38	80
2f	*c*-Hex	88:12	65
2g	$CH_2CH{=}CH_2$	75:25	69
2h	$CH(Me)CH{=}CH_2$	[b]	63

[a] The diastereoselectivity was determined from the integration of the characteristic signals in the NMR of the crude reaction mixture.
[b] Four diastereomers were obtained in a ratio of 39:39:11:11.

The photooxygenation of the allylic alcohol **1h** (possessing two stereogenic centers, applied as a 1:1 diastereoisomeric mixture) afforded four diastereomers of the β-hydroxy allylic hydroperoxides, two correspond to the major products with reaction-induced *syn* configuration (assigned as *syn*,*syn*-**2h** and *syn*,*anti*-**2h**) and two to the minor compounds with reaction-induced *anti* configuration (assigned as *anti*,*syn*-**2h** and *anti*,*anti*-**2h**). The photooxygenation of **1h** is depicted in Scheme 4. The diastereomeric ratio of the individual pairs of major and minor isomers is about 1:1. The major diastereomers constitute about 85% of the product mixture (determined from ^{13}C NMR).



Scheme 4. Solvent-free photooxygenation of the allylic alcohol **1h**.

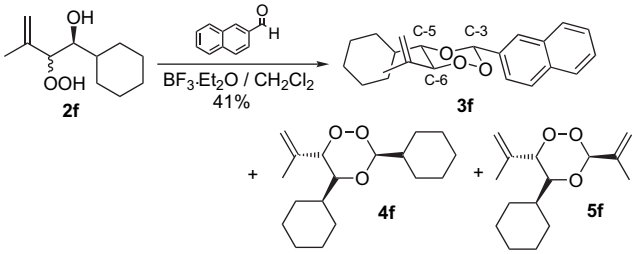
The peroxyacetalization reaction of 2-naphthaldehyde with the β-hydroperoxy alcohols proceeded under standard reaction conditions[31] with boron trifluoride as Lewis acid catalyst and resulted in the 1,2,4-trioxanes **3a–h** in moderate yields (Table 2). The carbonyl component was applied in slight excess and thus, appreciable amounts of the BF_3-catalyzed cleavage and cross-peroxyacetalization products were isolated in each case. This is shown for the reaction of the cyclohexyl-substituted β-hydroperoxy alcohol **2f** (Scheme 5)

Table 2. Peroxyacetalization of the allylic hydroperoxides **2a–h** with β-naphthaldehyde

Compound	R	Yield[a] (%)
3a	Et	24
3b	*n*-Pr	40
3c	*n*-Bu	43
3d	*i*-Bu	21
3e	*c*-Pr	31
3f	*c*-Hex	41
3g	$CH_2CH{=}CH_2$	14
3h	$CH(Me)CH{=}CH_2$	15

[a] Yields after purification of the crude materials.

with β-naphthaldehyde. The hydroperoxy alcohol **2f** is reacted with 1.1 equiv of the aldehyde in CH_2Cl_2 in the presence of a catalytic amount of BF_3 to form the 1,2,4-trioxane **3f** in 41% yield in addition to the cross-peroxyacetalization products **4f** and **5f** in 22 and 16% yields, respectively. In most cases, these side-products were not isolated and characterized solely from the NMR spectra (not reported in Section 4). It is, however, possible to obtain these compounds (also 1,2,4-trioxane structures) in good yields by BF_3-catalyzed oxidative cleavage and cross-peroxyacetalization of the hydroperoxides in the absence of an additional carbonyl component. The assignment of the structure of **3f** is based on ^1H as well as ^{13}C NMR spectra, IR, elemental, and HRMS analyses. The IR spectrum shows the characteristic C–O stretching at 1112, 1074 cm^{-1} and O–O at 906, 822 cm^{-1}. The ^1H NMR shows the characteristic singlet at 6.38 ppm corresponding to the peroxyacetal proton (H-3) and the doublet at 4.87 ppm related to the peroxy proton (H-6) due to coupling with H-5 ($^3J_{HH}$=9.5 Hz) indicating trans configuration. Surprisingly, H-5 appears also as doublet (and not doublet of doublet as expected); this can be ascribed to a dihedral angle of roughly 90° between this proton and the CH proton of the cyclohexyl group. The 2-naphthyl group is located also in equatorial position as confirmed by X-ray for the two analogous examples **3a** and **3b** (Fig. 2 and Table 3). In no case were the products from the minor diastereoisomeric allylic hydroperoxides (*anti* isomers) isolated from the crude reaction mixtures (where they appear with about 5–10% relative yields).



Scheme 5. Lewis acid catalyzed peroxyacetalization of the β-hydroperoxy alcohol **2f** with β-naphthaldehyde.

3. Conclusion

In summary, the singlet oxygen ene reaction with chiral allylic alcohols **1** in polystyrene matrices proceeds with excellent yields and gives the allylic hydroperoxides **2** with good (*syn*) diastereoselectivities. Subsequent Lewis acid catalyzed peroxyacetalization with β-naphthaldehyde results

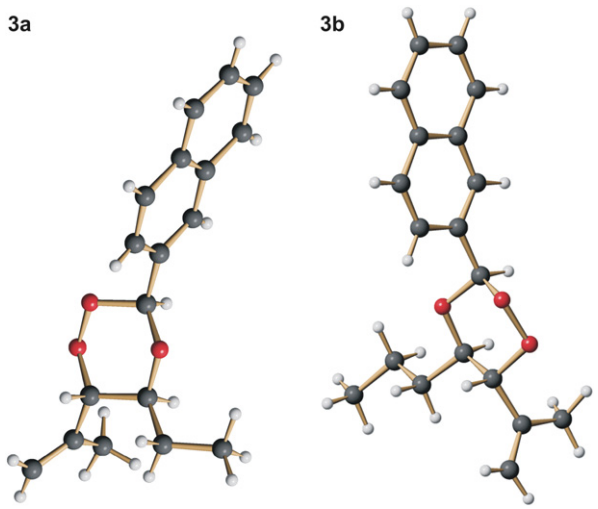


Figure 2. Structure of 1,2,4-trioxanes **3a** and **3b** in the crystal.

Table 3. Crystal structure analyses data for 1,2,4-trioxanes **3a** and **3b**

Crystal data	**3a**	**3b**
Empirical formula	$C_{18}H_{20}O_3$	$C_{19}H_{22}O_3$
Formula weight	284.34	298.37
Temperature [K]	100(2)	100(2)
Crystal system	Monoclinic	Monoclinic
Space group	*P*21/*c*	*C*2/*c*
a [Å]	13.614(2)	34.338(1)
b [Å]	5.6245(5)	5.362(1)
c [Å]	19.903(3)	20.740(1)
α [°]	90	90
β [°]	97.456(4)	121.32(1)
γ [°]	90	90
Volume [Å^3]	1511.1(4)	3262.2(6)
Z	4	8
d_{calcd} [g cm^{-3}]	1.250	1.215
Crystal size [mm]	0.1×0.1×0.3	0.35×0.25×0.25
No. refl. collected	6492	10220
No. unique refl.	3146	3554
No. obsd refl.	1251	2305
*R*1	0.0663	0.0427
*wR*2	0.1452	0.0900
Largest diff. peak/hole [e/Å^{-3}]	0.428/−0.215	0.232/−0.166

in the formation of diastereomerically pure (all-equatorial) 3-naphthyl-1,2,4-trioxanes **3** in moderate yields besides the cross-peroxyacetalization products **4** and **5**.

4. Experimental

4.1. General procedures (GP)

4.1.1. GP 1. Solvent-free type-II photooxygenation reaction in polymer matrices.

4.1.1.1. Using commercial PS–DVB copolymer. The polymer beads (ca. 2–3 g, Fluka, polystyrene copolymer with 1% divinylbenzene) were introduced into a Petri dish (19 cm diameter) and were pretreated with CH_2Cl_2 (20 mL) and the excess solvent evaporated by a vacuum line. The substrate (ca. 10 mmol) and the non-polar sensitizer (tetraphenylporphyrin, TPP, or tetratolylporphyrin, TTP, ca. 3–6 mg) in ethyl acetate (20 mL) were subsequently added and the excess solvent evaporated by leaving the Petri dish in a well ventilated hood. The Petri dish is covered with a glass plate and the sandy solid is irradiated with halogen lamp or sodium street lamp. The polymer beads were subsequently washed with ethanol (3×30 mL) and filtered (the beads can be used again for at least six cycles without pre-swelling). The solvent was evaporated under reduced pressure (CAUTION: water bath temperature should not exceed 30 °C.) and the composition of the product was determined by ^{1}H as well as ^{13}C NMR and the crude products applied directly for peroxyacetalization.

4.1.1.2. Using synthetic TSP–S–DVB or PP–S–DVB copolymers.[30] The dye-cross-linked polymer beads (TSP–S–DVB or PP–S–DVB, ca. 0.60 g) in a Petri dish (14 cm in diameter) were swollen by CH_2Cl_2 (20 mL), then the substrate (ca. 5 mmol) in ethyl acetate (20 mL) was added. Subsequent treatment as in Section 4.1.1.1 affords the product.

4.1.2. GP 2. General procedure for the peroxyacetalization reaction and 1,2,4-trioxanes synthesis. To a stirred solution of β-hydroxy hydroperoxides and the carbonyl reagent in dry CH_2Cl_2 (100 mL) was added at rt a catalytic amount of boron trifluoride etherate (ca. 0.2 mL) and the mixture was further stirred for about 12 h (overnight) at the same temperature. Volatile carbonyl compounds were used in 5–10-fold molar excess, less volatile carbonyl compounds were used in 1.2–1.5-fold molar excess. The reaction mixture was then partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL) and the combined organic phases were washed with brine, water, and dried over Na_2SO_4. Solvent evaporation (CAUTION: water bath temperature should not exceed 30 °C.) followed by chromatographic purification afforded the 1,2,4-trioxane as pure product.

4.1.2.1. 4-Hydroperoxy-5-methylhex-5-en-3-ol (2a). Photooxygenation of 5-methylhex-4-en-3-ol (**1a**) (1.0 g, 8.77 mmol) for 48 h according to GP 1 afforded a diastereomeric mixture (d.r. *syn*:*anti*, 77:23) of β-hydroxy allylic hydroperoxides **2a** (0.92 g, 6.30 mmol, 72%) as colorless oil.

syn-**2a**: ^{1}H NMR: *δ* 0.92 (t, 3H, *J*=7.5 Hz, C*H*$_3$CH$_2$), 1.23–1.58 (m, 2H, CH$_2$CH$_3$), 1.68 (m, 3H, C*H*$_3$C=), 3.55 (ddd, 1H, *J*=5.9, 5.9, 8.5 Hz, C*H*–OH), 4.15 (d, 1H, *J*=8.5 Hz, C*H*–OOH), 5.01 (m, 2H, C*H*$_2$=C). ^{13}C NMR: *δ* 9.6 (q, *C*H$_3$CH$_2$), 17.8 (q, *C*H$_3$C=), 25.5 (t, *C*H$_2$CH$_3$), 71.8 (d, *C*H–OH), 93.4 (d, *C*H–OOH), 116.5 (t, *C*H$_2$=C), 141.4 (s, *C*=CH$_2$).

anti-**2a**: ^{1}H NMR additional significant signals: *δ* 0.93 (t, 3H, *J*=7.4 Hz, C*H*$_3$CH$_2$), 1.76 (s, 3H, C*H*$_3$C=), 3.69 (m, 1H, C*H*–OH), 4.30 (d, 1H, *J*=4.7 Hz, C*H*–OOH), 5.04 (m, 2H, C*H*$_2$=C). ^{13}C NMR: *δ* 10.3 (q, *C*H$_3$CH$_2$), 19.3 (q, *C*H$_3$C=), 25.0 (t, *C*H$_2$CH$_3$), 72.2 (d, *C*H–OH), 91.4 (d, *C*H–OOH), 115.3 (t, *C*H$_2$=C), 141.2 (s, *C*=CH$_2$).

4.1.2.2. 3-Hydroperoxy-2-methylhept-1-en-4-ol (2b). Photooxygenation of 2-methylhept-2-en-4-ol (**1b**) (1.0 g, 7.81 mmol) for 48 h according to GP 1 afforded a diastereomeric mixture (d.r. *syn*:*anti*, 79:21) of β-hydroxy allylic hydroperoxides **2b** (0.98 g, 6.13 mmol, 78%) as colorless oil.

syn-**2b**: ^{1}H NMR: δ 0.87 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.20–1.58 (m, 4H, CH$_2$CH_2), 1.68 (m, 3H, CH_3C=), 3.63 (m, 1H, CH–OH), 4.13 (d, 1H, J=8.5 Hz, CH–OOH), 5.01 (m, 2H, CH_2=C). ^{13}C NMR: δ 13.8 (q, CH$_3$CH$_2$), 17.8 (t, CH$_2$CH$_3$), 18.3 (q, CH$_3$C=), 34.6 (t, CH$_2$CH$_2$), 70.3 (d, CH–OH), 93.8 (d, CH–OOH), 116.6 (t, CH$_2$=C), 141.4 (s, C=CH$_2$).

anti-**2b**: ^{1}H NMR additional significant signals: δ 0.87 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.76 (m, 3H, CH_3C=), 3.78 (m, 1H, CH–OH), 4.29 (d, 1H, J=4.4 Hz, CH–OOH). ^{13}C NMR: δ=13.9 (q, CH$_3$CH$_2$), 19.0 (t, CH$_2$CH$_3$), 19.4 (q, CH$_3$C=), 34.0 (t, CH$_2$CH$_2$), 70.5 (d, CH–OH), 91.6 (d, CH–OOH), 115.2 (t, CH$_2$=C), 141.2 (s, C=CH$_2$).

4.1.2.3. 3-Hydroperoxy-2-methyloct-1-en-4-ol (2c). Photooxygenation of 2-methyloct-2-en-4-ol (**1c**) (1.19 g, 8.38 mmol) for 60 h according to GP 1 afforded a diastereomeric mixture (d.r. *syn*:*anti*, 79:21) of β-hydroxy allylic hydroperoxides **2c** (1.14 g, 6.55 mmol, 78%) as faint yellow oil.

syn-**2c**: ^{1}H NMR: δ 0.85 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.21–1.57 (m, 6H, CH$_2$CH_2CH_2), 1.70 (s, 3H, CH_3C=), 3.64 (m, 1H, CH–OH), 4.15 (d, 1H, J=8.4 Hz, CH–OOH), 5.03 (m, 2H, CH_2=C). ^{13}C NMR: δ 13.9 (q, CH$_3$CH$_2$), 17.9 (q, CH$_3$C=), 22.5 (t, CH$_2$CH$_3$), 27.3 (t, CH$_2$CH$_2$), 32.2 (t, CH$_2$CH$_2$), 70.6 (d, CH–OH), 93.7 (d, CH–OOH), 116.6 (t, CH$_2$=C), 141.3 (s, C=CH$_2$).

anti-**2c**: ^{1}H NMR additional significant signals: δ 1.77 (s, 3H, CH_3C=), 3.75 (m, 1H, CH–OH), 4.30 (d, 1H, J= 4.7 Hz, CH–OOH). ^{13}C NMR: δ 13.9 (q, CH$_3$CH$_2$), 19.3 (q, CH$_3$C=), 22.5 (t, CH$_2$CH$_3$), 28.0 (t, CH$_2$CH$_2$), 32.2 (t, CH$_2$CH$_2$), 70.7 (d, CH–OH), 91.7 (d, CH–OOH), 116.6 (t, CH$_2$=C), 141.2 (s, C=CH$_2$).

4.1.2.4. 3-Hydroperoxy-2,6-dimethylhept-1-en-4-ol (2d). Photooxygenation of 2,6-dimethylhept-2-en-4-ol (**1d**) (1.25 g, 8.80 mmol) for 60 h according to GP 1 afforded a diastereomeric mixture (d.r. *syn*:*anti*, 80:20) of β-hydroxy allylic hydroperoxides **2d** (1.18 g, 6.78 mmol, 77%) as colorless oil.

syn-**2d**: ^{1}H NMR: δ 0.83 (d, 3H, J=6.5 Hz, CH_3CH), 0.87 (d, 3H, J=6.8 Hz, CH_3CH), 1.03 (m, 1H, CH_2CH), 1.32 (m, 1H, CH_2CH), 1.68 (s, 3H, CH_3C=), 1.81 (m, 1H, CHCH$_2$), 3.68 (m, 1H, CH–OH), 4.09 (d, 1H, J=8.4 Hz, CH–OOH), 5.0 (m, 2H, CH_2=C). ^{13}C NMR: δ 17.9 (q, CH$_3$CH), 21.1 (q, CH$_3$C=), 23.8 (d, CHCH$_2$), 24.0 (q, CH$_3$CH), 41.6 (t, CH$_2$CH), 68.7 (d, CH–OH), 94.2 (d, CH–OOH), 116.6 (t, CH$_2$=C), 141.4 (s, C=CH$_2$).

anti-**2d**: ^{1}H NMR additional significant signals: δ 0.84 (d, 3H, J=6.7 Hz, CH_3CH), 1.76 (s, 3H, CH_3C=), 3.83 (m, 1H, CH–OH), 4.26 (d, 1H, J=4.5 Hz, CH–OOH), 5.05 (m, 2H, CH_2=C). ^{13}C NMR: δ 19.4 (q, CH$_3$CH), 21.4 (q, CH$_3$C=), 23.6 (d, CHCH$_2$), 24.7 (q, CH$_3$CH), 41.1 (t, CH$_2$CH), 68.9 (d, CH–OH), 92.0 (d, CH–OOH), 115.2 (t, CH$_2$=C), 141.3 (s, C=CH$_2$).

4.1.2.5. 1-Cyclopropyl-2-hydroperoxy-3-methylbut-3-en-1-ol (2e). Photooxygenation of 1-cyclopropyl-3-methylbut-2-en-1-ol (**1e**) (1.0 g, 7.94 mmol) for 60 h according to GP 1 afforded a diastereomeric mixture (d.r. *syn*:*anti*, 62:38) of β-hydroxy allylic hydroperoxides **2e** (1.0 g, 6.33 mmol, 80%) as colorless oil.

syn-**2e**: ^{1}H NMR: δ 0.20–0.52 (m, 4H, CH_2CH_2), 0.78–0.99 (m, 1H, CH), 1.75 (m, 3H, CH_3C=), 3.07 (dd, 1H, J=7.9, 7.9 Hz, CH–OH), 4.29 (d, 1H, J=9.3 Hz, CH–OOH), 5.05 (m, 2H, CH_2=C). ^{13}C NMR: δ 1.8 (t, CH$_2$CH$_2$), 3.2 (t, CH$_2$CH$_2$), 14.0 (d, CH), 18.9 (q, CH$_3$C=), 75.0 (d, CH–OH), 93.3 (d, CH–OOH), 115.5 (t, CH$_2$=C), 141.6 (s, C=CH$_2$).

anti-**2e**: ^{1}H NMR additional significant signals: δ 1.82 (m, 3H, CH_3C=), 3.14 (dd, 1H, J=4.3, 8.8 Hz, CH–OH), 4.41 (d, 1H, J=4.3 Hz, CH–OOH). ^{13}C NMR: δ 2.6 (t, CH$_2$CH$_2$), 2.9 (t, CH$_2$CH$_2$), 13.3 (d, CH), 19.6 (q, CH$_3$C=), 75.6 (d, CH–OH), 91.2 (d, CH–OOH), 115.4 (t, CH$_2$=C), 141.3 (s, C=CH$_2$).

4.1.2.6. 1-Cyclohexyl-2-hydroperoxy-3-methylbut-3-en-1-ol (2f). Photooxygenation of 1-cyclohexyl-3-methylbut-2-en-1-ol (**1f**) (1.30 g, 7.74 mmol) for 60 h according to GP 1 afforded a diastereomeric mixture (d.r. *syn*:*anti*, 88:12) of β-hydroxy allylic hydroperoxides **2f** (1.0 g, 5.0 mmol, 65%) as faint yellow oil.

syn-**2f**: ^{1}H NMR: δ 0.83–1.90 (m, 11H, CH and CH_2), 1.64 (s, 3H, CH_3C=), 3.43 (m, 1H, CH–OH), 4.24 (d, 1H, J=8.5 Hz, CH–OOH), 4.97 (s, 2H, CH_2=C). ^{13}C NMR: δ 17.7 (q, CH$_3$C=), 25.3 (t, CH$_2$), 25.9 (t, CH$_2$), 26.1 (t, CH$_2$), 26.4 (t, CH$_2$), 30.3, 30.5 (t, CH$_2$), 39.1 (d, CH), 74.3 (d, CH–OH), 91.0 (d, CH–OOH), 115.9 (t, CH$_2$=C), 141.6 (s, C=CH$_2$).

anti-**2f**: ^{1}H NMR additional significant signals: δ 4.29 (d, 1H, J=6.0 Hz, CH–OOH). ^{13}C NMR additional significant signals: δ 39.3 (d, CH), 89.2 (d, CH–OOH), 112.9 (t, CH$_2$=C).

4.1.2.7. 3-Hydroperoxy-2-methylhepta-1,6-dien-4-ol (2g). Photooxygenation of 6-methylhepta-1,5-dien-4-ol (**1g**) (1.16 g, 9.21 mmol) for 60 h according to GP 1 afforded a diastereomeric mixture (d.r. *syn*:*anti*, 75:25) of β-hydroxy allylic hydroperoxides **2g** (1.0 g, 6.33 mmol, 69%) as faint yellow oil.

syn-**2g**: ^{1}H NMR: δ 1.70 (m, 3H, CH_3C=), 2.02–2.37 (m, 2H, CH_2), 3.71 (ddd, 1H, J=3.7, 8.3, 8.3 Hz, CH–OH), 4.17 (d, 1H, J=8.4 Hz, CH–OOH), 5.05 (m, 4H, CH_2=C and CH_2=CH), 5.79 (m, 1H, CH=CH$_2$). ^{13}C NMR: δ 17.9 (q, CH$_3$C=), 37.1 (t, CH$_2$), 70.0 (d, CH–OH), 92.8 (d, CH–OOH), 116.8 (t, CH$_2$=CH), 118.1 (t, CH$_2$=C), 133.8 (d, CH=CH$_2$), 141.1 (s, C=CH$_2$).

anti-**2g**: ^{1}H NMR additional significant signals: δ 1.76 (m, 3H, CH_3C=), 3.82 (m, 1H, CH–OH), 4.31 (d, 1H, J=4.9 Hz, CH–OOH). ^{13}C NMR: δ 19.1 (q, CH$_3$C=), 36.6 (t, CH$_2$), 69.9 (d, CH–OH), 91.0 (d, CH–OOH), 115.6 (t, CH$_2$=CH), 117.9 (t, CH$_2$=C), 134.5 (d, CH=CH$_2$), 141.0 (s, C=CH$_2$).

4.1.2.8. 3-Hydroperoxy-2,5-dimethylhepta-1,6-dien-4-ol (2h). Photooxygenation of 3,6-dimethylhepta-1,5-dien-4-ol

(**1h**) (1.20 g, 8.57 mmol) for 60 h according to GP 1 afforded an oil composed of the inseparable diastereomeric mixture (0.92 g, 5.35 mmol, 63%) composed of *syn*,*syn*-**2h**, *syn*,*anti*-**2h** (d.r. 1:1) as major product and a diastereomeric mixture of *anti*,*syn*-**2h** and *anti*,*anti*-**2h** (d.r. 1:1) as minor products (major/minor: 78:22 ratio).

syn,*syn*-**2h**: ^{1}H NMR: δ 0.90 (d, 3H, J=6.9 Hz, CH_3CH), 1.63 (s, 3H, CH_3C=), 2.17 (m, 1H, CHCH$_3$), 3.50 (m, 1H, CH–OH), 4.12 (d, 1H, J=8.8 Hz, CH–OOH), 4.94 (m, 4H, CH_2=C and CH_2=CH), 5.74 (m, 1H, CH=CH$_2$). ^{13}C NMR: δ 12.1 (q, CH$_3$CH), 17.8 (q, CH$_3$C=), 38.7 (d, CHCH$_3$), 73.1 (d, CH–OH), 90.8 (d, CH–OOH), 114.3 (t, CH$_2$=CH), 116.2 (t, CH$_2$=C), 141.1 (s, C=CH$_2$), 141.2 (d, CH=CH$_2$).

syn,*anti*-**2h**: ^{1}H NMR additional significant signals: δ 0.99 (d, 3H, J=5.4 Hz, CH_3CH), 3.52 (m, 1H, CH–OH), 4.22 (d, 1H, J=8.0 Hz, CH–OOH). ^{13}C NMR: δ 17.6 (q, CH$_3$C=), 39.0 (d, CHCH$_3$), 73.4 (d, CH–OH), 91.3 (d, CH–OOH), 116.2 (t, CH$_2$=CH), 116.8 (t, CH$_2$=C), 137.8 (d, CH=CH$_2$), 140.6 (s, C=CH$_2$).

anti,*syn*-**2h**: ^{13}C NMR significant signals: δ 72.5 (d, CH–OH), 89.2 (d, CH–OOH).

anti,*anti*-**2h**: ^{13}C NMR significant signals: δ 72.5 (d, CH–OH), 89.5 (d, CH–OOH).

4.1.2.9. (3*RS*,5*RS*,6*RS*)-5-Ethyl-3-(naphthalen-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane (3a). Following GP 2, a solution of 4-hydroperoxy-5-methylhex-5-en-3-ol (**2a**) (1.22 g, 8.36 mmol) and β-naphthaldehyde (1.30 g, 8.33 mmol) in CH_2Cl_2 was treated with a catalytic amount of $BF_3\cdot Et_2O$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EA/*n*-hex, 1:10, R_f=0.71) affords the 1,2,4-trioxane (0.57 g, 2.0 mmol, 24%) as viscous oil, which crystallizes into white solid on standing, mp 73–75 °C. ^{1}H NMR: δ 1.14 (dd, 3H, J=7.4, 7.4 Hz, CH_3CH$_2$), 1.70 (m, 2H, CH_2CH$_3$), 1.86 (m, 3H, CH_3C=), 3.96 (ddd, 1H, J=3.8, 7.9, 9.3 Hz, OCH), 4.67 (d, 1H, J=9.3 Hz, OOCH), 5.18 (m, 1H, CH_2=), 5.23 (s, 1H, CH_2=), 6.43 (s, 1H, OCHOO), 7.48–8.07 (m, 7H, H_{arom}); ^{13}C NMR: δ 9.4 (q, CH$_3$CH$_2$), 19.9 (q, CH$_3$C=), 23.6 (t, CH$_2$CH$_3$), 78.5 (d, OCH), 87.4 (d, OOCH), 104.0 (d, OCHOO), 118.4 (t, CH$_2$=C), 124.0 (d, CH$_{arom}$), 126.1 (d, CH$_{arom}$), 126.6 (d, CH$_{arom}$), 126.8 (d, CH$_{arom}$), 127.6 (d, CH$_{arom}$), 128.0 (d, CH$_{arom}$), 128.3 (d, CH$_{arom}$), 131.9 (s, Cq$_{arom}$), 132.8 (s, Cq$_{arom}$), 133.9 (s, Cq$_{arom}$), 138.7 (s, C=CH$_2$); IR: (CsI) ν (cm^{-1})=3064, 2980, 2925, 2898, 1664, 1605, 1071, 908, 824; MS: (EI, 70 eV) m/z (%)=284 (M$^+$, 4), 156 ($C_{11}H_8O^+$, 100), 155 ($C_{11}H_7O^+$, 95), 128 ($C_{10}H_8^+$, 22), 127 ($C_{10}H_7^+$, 73), 96 ($C_7H_{12}^+$, 47), 81 ($C_6H_9^+$, 17); HRMS: (EI, 70 eV, $C_{18}H_{20}O_3$) calcd: M=284.141 g/mol, found: M=284.141±0.005 g/mol; CH-analysis: ($C_{18}H_{20}O_3$, M=284.35 g/mol) calcd: C, 76.03; H, 7.09, found: C, 75.53; H, 7.11.

4.1.2.10. (3*RS*,5*RS*,6*RS*)-3-(Naphthalen-2-yl)-6-(prop-1-en-2-yl)-5-propyl-1,2,4-trioxane (3b). Following GP 2, a solution of 3-hydroperoxy-2-methylhept-1-en-4-ol (**2b**) (1.20 g, 7.50 mmol) and β-naphthaldehyde (1.18 g, 7.56 mmol) in CH_2Cl_2 was treated with a catalytic amount of $BF_3\cdot Et_2O$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EA/*n*-hex, 1:10, R_f=0.66) afforded the pure 1,2,4-trioxane (0.89 g, 2.99 mmol, 40%) as colorless oil, which crystallizes on standing, mp 78–80 °C. ^{1}H NMR: δ 1.02 (t, 3H, J=7.1 Hz, CH_3CH$_2$), 1.47–1.79 (m, 4H, CH_2CH_2), 1.86 (m, 3H, CH_3C=), 4.04 (ddd, 1H, J=3.1, 8.1, 9.3 Hz, OCH), 4.67 (d, 1H, J=9.3 Hz, OOCH), 5.19 (m, 1H, CH_2=), 5.24 (s, 1H, CH_2=), 6.43 (s, 1H, OCHOO), 7.47–8.07 (m, 7H, H_{arom}); ^{13}C NMR: δ 13.9 (q, CH$_3$CH$_2$), 18.1 (t, CH$_2$CH$_3$), 19.7 (q, CH$_3$C=), 32.5 (t, CH$_2$CH$_2$), 77.1 (d, OCH), 87.7 (d, OOCH), 104.0 (d, OCHOO), 118.5 (t, CH$_2$=), 124.0 (d, CH$_{arom}$), 126.1 (d, CH$_{arom}$), 126.6 (d, CH$_{arom}$), 126.7 (d, CH$_{arom}$), 127.6 (d, CH$_{arom}$), 128.0 (d, CH$_{arom}$), 128.3 (d, CH$_{arom}$), 131.9 (s, Cq$_{arom}$), 132.8 (s, Cq$_{arom}$), 133.9 (s, Cq$_{arom}$), 138.7 (s, C=CH$_2$); IR: (CsI) ν (cm^{-1})=2957, 2934, 1664, 1605, 1576, 1362, 1340, 1092, 1075, 907; MS: (EI, 70 eV) m/z (%)=298 (M$^+$, 3), 226 (M$^+$−C_4H_8O, 2), 156 ($C_{11}H_8O^+$, 92), 155 ($C_{11}H_7O^+$, 100), 128 ($C_{10}H_8^+$, 22), 127 ($C_{10}H_7^+$, 77), 110 ($C_8H_{14}^+$, 27), 95 ($C_7H_{11}^+$, 8); HRMS: (EI, 70 eV, $C_{19}H_{22}O_3$) calcd: M=298.157 g/mol, found: M=298.157±0.005 g/mol; CH-analysis: ($C_{19}H_{22}O_3$, M=298.39) calcd: C, 76.48; H, 7.43, found: C, 76.25; H, 7.27.

4.1.2.11. (3*RS*,5*RS*,6*RS*)-5-Butyl-3-(naphthalen-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane (3c). Following GP 2, a solution of 3-hydroperoxy-2-methyloct-1-en-4-ol (**2c**) (1.24 g, 7.13 mmol) and β-naphthaldehyde (1.11 g, 7.12 mmol) in CH_2Cl_2 was treated with a catalytic amount of $BF_3\cdot Et_2O$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EA/*n*-hex, 1:10, R_f=0.85) afforded the pure 1,2,4-trioxane (0.96 g, 3.08 mmol, 43%) as viscous oil, which crystallizes on standing, mp 51–53 °C. ^{1}H NMR: δ 0.96 (t, 3H, J=7.2 Hz, CH_3CH$_2$), 1.25–1.70 (m, 6H, CH_2), 1.85 (s, 3H, CH_3C=), 4.01 (m, 1H, OCH), 4.64 (d, 1H, J=9.3 Hz, OOCH), 5.18 (m, 1H, CH_2=), 5.22 (s, 1H, CH_2=), 6.41 (s, 1H, OCHOO), 7.49–8.05 (m, 7H, H_{arom}); ^{13}C NMR: δ 13.9 (q, CH$_3$CH$_2$), 19.7 (q, CH$_3$C=), 22.6 (t, CH$_2$CH$_3$), 27.0 (t, CH$_2$CH$_2$), 30.1 (t, CH$_2$CH$_2$), 77.4 (d, OCH), 87.7 (d, OOCH), 104.1 (d, OCHOO), 118.5 (t, CH$_2$=C), 124.1 (d, CH$_{arom}$), 126.1 (d, CH$_{arom}$), 126.6 (d, CH$_{arom}$), 126.8 (d, CH$_{arom}$), 127.6 (d, CH$_{arom}$), 128.1 (d, CH$_{arom}$), 128.4 (d, CH$_{arom}$), 132.0 (s, Cq$_{arom}$), 132.8 (s, Cq$_{arom}$), 133.9 (s, Cq$_{arom}$), 138.8 (s, C=CH$_2$); MS: (EI, 70 eV) m/z (%)=312 (M$^+$, 1), 226 (M$^+$−$C_5H_{10}O$, less than 1), 156 ($C_{11}H_8O^+$, 100), 155 ($C_{11}H_7O^+$, 93), 127 ($C_{10}H_7^+$, 72), 124 ($C_9H_{16}^+$, 38); HRMS: (EI, 70 eV, $C_{20}H_{24}O_3$) calcd: M=312.173 g/mol, found: M=312.173±0.005 g/mol; CH-analysis: ($C_{20}H_{24}O_3$, M=312.40) calcd: C, 76.89; H, 7.74, found: C, 76.61; H, 7.78.

4.1.2.12. (3*RS*,5*RS*,6*RS*)-5-Isobutyl-3-(naphthalen-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane (3d). Following GP 2, a solution of 3-hydroperoxy-2,6-dimethylhept-1-en-4-ol (**2d**) (1.21 g, 6.95 mmol) and β-naphthaldehyde (1.09 g, 6.99 mmol) in CH_2Cl_2 was treated with a catalytic amount of $BF_3\cdot Et_2O$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EA/*n*-hex, 1:10, R_f=0.71) affords the 1,2,4-trioxane (0.46 g, 1.47 mmol, 21%) as an oil, which crystallizes on standing to white solid, mp 60–62 °C.

^{1}H NMR: δ 1.01 (d, 3H, J=6.6 Hz, CH_3CH), 1.04 (d, 3H, J=6.8 Hz, CH_3CH), 1.33 (m, 1H, CH_2CH), 1.70 (m, 1H, CH_2CH), 1.87 (s, 3H, CH_3C=), 2.08 (m, 1H, CHCH$_2$), 4.12 (ddd, 1H, J=2.3, 9.1, 10.3 Hz, OCH), 4.65 (d, 1H, J=9.1 Hz, OOCH), 5.19 (m, 1H, CH_2=), 5.24 (m, 1H, CH_2=), 6.45 (s, 1H, OCHOO), 7.49–8.07 (m, 5H, H$_{arom}$); ^{13}C NMR: δ 19.6 (q, CH$_3$C=), 21.5 (q, CH$_3$CH), 23.6 (d, CHCH$_2$), 23.7 (q, CH$_3$CH), 39.2 (t, CH$_2$CH), 75.6 (d, OCH), 88.0 (d, OOCH), 104.0 (d, OCHOO), 118.7 (t, CH$_2$=), 124.0 (d, CH$_{arom}$), 126.1 (d, CH$_{arom}$), 126.6 (d, CH$_{arom}$), 126.7 (d, CH$_{arom}$), 127.6 (d, CH$_{arom}$), 128.0 (d, CH$_{arom}$), 128.3 (d, CH$_{arom}$), 131.9 (s, Cq$_{arom}$), 132.8 (s, Cq$_{arom}$), 133.9 (s, Cq$_{arom}$), 138.6 (s, C=CH$_2$); IR: (CsI) ν (cm^{-1})=3095, 2956, 2934, 1605, 1347, 1098, 1080, 997, 863, 817; MS: (EI, 70 eV) m/z (%)=312 (M$^+$, 3), 226 (M$^+$−C$_5$H$_{10}$O, 2), 156 (C$_{11}$H$_8$O$^+$, 100), 155 (C$_{11}$H$_7$O$^+$, 97), 128 (C$_{10}$H$_8^+$, 30), 127 (C$_{10}$H$_7^+$, 70), 124 (C$_9$H$_{16}^+$, 27), 109 (C$_8$H$_{13}^+$, 17); HRMS: (EI, 70 eV, C$_{20}$H$_{24}$O$_3$) calcd: M=312.173 g/mol, found: M=312.173±0.005 g/mol; CH-analysis: (C$_{20}$H$_{24}$O$_3$, M=312.40 g/mol) calcd: C, 76.89; H, 7.74, found: C, 76.61; H, 7.63.

4.1.2.13. (3*RS*,5*RS*,6*RS*)-5-Cyclopropyl-3-(naphthalen-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane (3e). Following GP 2, a solution of 1-cyclopropyl-2-hydroperoxy-3-methylbut-3-en-1-ol (**2e**) (1.25 g, 7.91 mmol) and β-naphthaldehyde (1.23 g, 7.88 mmol) in CH_2Cl_2 was treated with a catalytic amount of $BF_3\cdot Et_2O$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EA/*n*-hex, 1:10, R_f=0.67) affords the pure 1,2,4-trioxane as yellow oil, which crystallizes upon standing (0.72 g, 2.43 mmol, 31%). ^{1}H NMR: δ 0.39–0.64 (m, 4H, CH_2CH_2), 0.98 (m, 1H, CH(CH$_2$)$_2$), 1.87 (m, 3H, CH_3C=), 3.44 (dd, 1H, J=7.4, 9.1 Hz, OCH), 4.68 (d, 1H, J=9.12 Hz, OOCH), 5.14 (m, 2H, CH_2=), 6.31 (s, 1H, OCHOO), 7.46–7.98 (m, 7H, H$_{arom}$); ^{13}C NMR: δ 2.0 (t, CH$_2$), 2.8 (t, CH$_2$), 11.6 (d, CH(CH$_2$)$_2$), 20.7 (q, CH$_3$C=), 81.0 (d, OCH), 87.8 (d, OOCH), 104.0 (d, OCHOO), 117.5 (t, CH$_2$=), 124.2 (d, CH$_{arom}$), 126.2 (d, CH$_{arom}$), 126.7 (d, CH$_{arom}$), 127.0 (d, CH$_{arom}$), 127.7 (d, CH$_{arom}$), 128.2 (d, CH$_{arom}$), 128.5 (d, CH$_{arom}$), 131.8 (s, Cq$_{arom}$), 132.9 (s, Cq$_{arom}$), 134.1 (s, Cq$_{arom}$), 139.9 (s, C=CH$_2$); IR: (Film) ν (cm^{-1})=3088, 3011, 2968, 2934, 1647, 1603, 1126, 1071, 904, 859, 814; HRMS: (EI, 70 eV, C$_{19}$H$_{20}$O$_3$) calcd: M=296.141 g/mol, found: M=296.141±0.005 g/mol; CH-analysis: (C$_{19}$H$_{20}$O$_3$, M=296.36) calcd: C, 77.00; H, 6.80, found: C, 76.47; H, 6.83.

4.1.2.14. (3*RS*,5*RS*,6*RS*)-5-Cyclohexyl-3-(naphthalen-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane (3f). Following GP 2, a solution of 1-cyclohexyl-2-hydroperoxy-3-methylbut-3-en-1-ol (**2f**) (1.20 g, 6.0 mmol) and β-naphthaldehyde (0.94 g, 6.03 mmol) in CH_2Cl_2 was treated with a catalytic amount of $BF_3\cdot Et_2O$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EA/*n*-hex, 1:10, R_f=0.65) afforded the pure 1,2,4-trioxanes (0.83 mg, 2.46 mmol, 41%) as white solid, mp 88–90 °C. Additionally, the cross-peroxyacetalization products **4f** and **5**, were isolated in 22 and 16% yields, respectively (by NMR from the crude reaction mixture). ^{1}H NMR: δ 1.06–1.94 (m, 11H, CH and CH_2), 1.85 (s, 3H, CH_3C=), 3.87 (d, 1H, J=9.5 Hz, OCH), 4.87 (d, 1H, J=9.5 Hz, OOCH), 5.18 (m, 2H, CH_2=), 6.38 (s, 1H, OCHOO), 7.47–8.02 (m, 7H, H$_{arom}$); ^{13}C NMR: δ 19.7 (q, CH$_3$C=), 26.2 (t, CH$_2$), 26.2 (t, CH$_2$), 26.3 (t, CH$_2$), 26.5 (t, CH$_2$), 30.1 (t, CH$_2$), 38.4 (d, CH), 81.4 (d, OCH), 85.2 (d, OOCH), 104.1 (d, OCHOO), 118.5 (t, CH$_2$=C), 124.1 (d, CH$_{arom}$), 126.1 (d, CH$_{arom}$), 126.6 (d, CH$_{arom}$), 126.9 (d, CH$_{arom}$), 127.6 (d, CH$_{arom}$), 128.0 (d, CH$_{arom}$), 128.4 (d, CH$_{arom}$), 132.1 (s, Cq$_{arom}$), 132.8 (s, Cq$_{arom}$), 133.9 (s, Cq$_{arom}$), 138.9 (s, C=CH$_2$); IR: (CsI) ν (cm^{-1})=2933, 2856, 1653, 1647, 1605, 1560, 1112, 1074, 1004, 906, 822; MS: (EI, 70 eV) m/z (%)=338 (M$^+$, 1), 226 (M$^+$−C$_5$H$_{10}$O, 2), 156 (C$_{11}$H$_8$O$^+$, 95), 155 (C$_{11}$H$_7$O$^+$, 96), 128 (C$_{10}$H$_8^+$, 27), 127 (C$_{10}$H$_7^+$, 100), 83 (C$_6$H$_{11}^+$, 17); HRMS: (EI, 70 eV, C$_{22}$H$_{26}$O$_3$) calcd: M=338.188 g/mol, found: M=338.188± 0.005 g/mol; CH-analysis: (C$_{22}$H$_{26}$O$_3$, M=338.44) calcd: C, 78.07; H, 7.74, found: C, 77.49; H, 7.90.

4.1.2.15. (3*RS*,5*RS*,6*RS*)-3,5-Dicyclohexyl-6-(prop-1-en-2-yl)-1,2,4-trioxane (4f). ^{1}H NMR: δ 0.92–2.12 (m, 22H, CH and CH_2), 1.71 (s, 3H, CH_3C=), 3.48 (d, 1H, J=9.6 Hz, OCH), 4.54 (d, 1H, J=9.5 Hz, OOCH), 4.95 (d, 1H, J=5.6 Hz, OCHOO), 5.05 (m, 2H, CH_2=). ^{13}C NMR: δ 19.7 (q, CH$_3$C=), 25.7 (t, CH$_2$), 25.7 (t, CH$_2$), 25.8 (t, CH$_2$), 26.0 (t, CH$_2$), 26.2 (t, CH$_2$), 26.3 (t, CH$_2$), 26.5 (t, CH$_2$), 27.1 (t, CH$_2$), 27.3 (t, CH$_2$), 30.1 (t, CH$_2$), 38.3 (d, CH), 40.6 (d, CH), 80.6 (d, OCH), 85.2 (d, OOCH), 107.1 (d, OCHOO), 118.1 (t, CH$_2$=C), 139.1 (s, C=CH$_2$).

4.1.2.16. (3*RS*,5*RS*,6*RS*)-5-Allyl-3-(naphthalen-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane (3g). Following GP 2, a solution of 3-hydroperoxy-2-methylhepta-1,6-dien-4-ol (**2g**) (0.39 g, 2.47 mmol) and β-naphthaldehyde (388 mg, 2.49 mmol) in CH_2Cl_2 was treated with a catalytic amount of $BF_3\cdot Et_2O$ (0.2 mL). Usual work-up and further purification of the crude product by preparative thick-layer chromatography (SiO_2, EA/*n*-hex, 1:10, R_f=0.69) afforded the pure 1,2,4-trioxanes (30 mg, 0.10 mmol, 4%) as viscous colorless oil, which crystallizes on standing, mp 55–57 °C. ^{1}H NMR: δ 1.82 (m, 3H, CH_3C=), 2.47 (m, 2H, CH_2), 4.06 (ddd, 1H, J=3.9, 7.2, 9.2 Hz, OCH), 4.64 (d, 1H, J=9.2 Hz, OOCH), 5.15 (m, 4H, CH_2=CH and CH_2=C), 6.0 (m, 1H, CH=CH$_2$), 6.37 (s, 1H, OCHOO), 7.45–8.0 (m, 7H, H$_{arom}$); ^{13}C NMR: δ 19.7 (q, CH$_3$C=), 35.1 (t, CH_2), 76.8 (d, OCH), 87.1 (d, OOCH), 104.1 (d, OCHOO), 117.7 (t, CH$_2$=CH), 119.0 (t, CH$_2$=C), 124.1 (d, CH$_{arom}$), 126.2 (d, CH$_{arom}$), 126.7 (d, CH$_{arom}$), 126.9 (d, CH$_{arom}$), 127.7 (d, CH$_{arom}$), 128.2 (d, CH$_{arom}$), 128.5 (d, CH$_{arom}$), 131.8 (s, Cq$_{arom}$), 132.9 (s, Cq$_{arom}$), 133.4 (d, CH=CH$_2$), 134.0 (s, Cq$_{arom}$), 138.5 (s, C=CH$_2$); MS: (EI, 70 eV) m/z (%)=296 (M$^+$, 7), 156 (C$_{11}$H$_8$O$^+$, 100), 155 (C$_{11}$H$_7$O$^+$, 86), 127 (C$_{10}$H$_7^+$, 62); HRMS: (EI, 70 eV, C$_{19}$H$_{20}$O$_3$) calcd: M=296.141 g/mol, found: M=296.141±0.005 g/mol; CH-analysis: (C$_{19}$H$_{20}$O$_3$, M=296.36) calcd: C, 77.00; H, 6.80, found: C, 76.85; H, 6.71.

4.1.2.17. (3*RS*,5*RS*,6*RS*)-5-((*RS*)-But-3-en-2-yl)-3-(naphthalen-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane and (3*RS*,5*RS*,6*RS*)-5-((*SR*)-but-3-en-2-yl)-3-(naphthalen-2-yl)-6-(prop-1-en-2-yl)-1,2,4-trioxane (3h). Following GP 2, a solution of 3-hydroperoxy-2,5-dimethylhepta-1,6-dien-4-ol (**2h**) (1.16 g, 6.74 mmol) and 2-naphthaldehyde (1.07 g, 6.86 mmol) in CH_2Cl_2 was treated with a catalytic amount of $BF_3\cdot Et_2O$ (0.2 mL). Usual work-up and further

purification of the crude product (1.62 g, 5.23 mmol, 77.5%) by preparative thick-layer chromatography (SiO_2, EA/*n*-hex, 1:10, R_f=0.69) afforded a diastereomeric mixture of the pure 1,2,4-trioxanes **3h** in a ratio 1:1 (0.31 g, 1.0 mmol, 15%) as white solid. ^{1}H NMR first diastereomer: δ 1.30 (d, 3H, J=7.0 Hz, C*H*$_3$CH), 1.88 (t, 3H, J=1.5 Hz, C*H*$_3$C=), 2.55 (m, 1H, C*H*CH$_3$), 4.02 (dd, 1H, J=1.9, 9.5 Hz, OC*H*), 4.83 (d, 1H, J=9.5 Hz, OOC*H*), 5.20 (m, 4H, C*H*$_2$=CH and C*H*$_2$=), 6.15 (m, 1H, C*H*=CH$_2$), 6.40 (s, 1H, OC*H*OO), 7.50–8.10 (m, 7H, H$_{arom}$); ^{13}C NMR first diastereomer: δ 13.5 (q, *C*H$_3$CH), 19.5 (q, *C*H$_3$C=), 38.1 (d, *C*HCH$_3$), 79.9 (d, O*C*H), 85.4 (d, OO*C*H), 103.9 (d, O*C*HOO), 114.3 (t, *C*H$_2$=CH), 118.9 (t, *C*H$_2$=C), 124.0 (d, CH$_{arom}$), 126.1 (d, CH$_{arom}$), 126.6 (d, CH$_{arom}$), 126.8 (d, CH$_{arom}$), 126.9 (d, CH$_{arom}$), 127.6 (d, CH$_{arom}$), 128.0 (d, CH$_{arom}$), 131.9 (s, Cq$_{arom}$), 132.7 (s, Cq$_{arom}$), 133.9 (s, Cq$_{arom}$), 138.5 (d, *C*H=CH$_2$), 138.6 (s, *C*=CH$_2$); ^{1}H NMR additional signals of the other diastereomer: δ 4.12 (dd, 1H, J=2.51, 9.6 Hz, OC*H*), 4.89 (d, 1H, J=9.6 Hz, OOC*H*), 6.41 (s, 1H, OC*H*OO); ^{13}C NMR other diastereomer: δ 18.2 (q, *C*H$_3$CH), 19.5 (q, *C*H$_3$C=), 38.8 (d, *C*HCH$_3$), 80.0 (d, O*C*H), 85.6 (d, OO*C*H), 104.0 (d, O*C*HOO), 116.1 (t, *C*H$_2$=CH), 118.9 (t, *C*H$_2$=C), 124.0 (d, CH$_{arom}$), 126.1 (d, CH$_{arom}$), 126.6 (d, CH$_{arom}$), 126.8 (d, CH$_{arom}$), 126.9 (d, CH$_{arom}$), 127.6 (d, CH$_{arom}$), 128.3 (d, CH$_{arom}$), 131.9 (s, Cq$_{arom}$), 132.7 (s, Cq$_{arom}$), 133.9 (s, Cq$_{arom}$), 138.4 (s, *C*=CH$_2$), 140.8 (d, *C*H=CH$_2$); IR: (CsI) ν (cm^{-1})=3078, 2978, 2923, 1653, 1647, 1605, 1127, 1076, 999, 987, 904, 866, 818; MS: (EI, 70 eV) *m*/*z* (%)=310 (M$^+$, 2), 226 (M$^+$−C$_5$H$_8$O, 1), 156 (C$_{11}$H$_8$O$^+$, 100), 155 (C$_{11}$H$_7$O$^+$, 89), 128 (C$_{10}$H$_8^+$, 20), 127 (C$_{10}$H$_7^+$, 68), 107 (C$_8$H$_{11}^+$, 20); HRMS: (EI, 70 eV, C$_{20}$H$_{22}$O$_3$) calcd: M=310.157 g/mol, found: M=310.157±0.005 g/mol; CH-analysis: (C$_{20}$H$_{22}$O$_3$, M=310.39) calcd: C, 77.39; H, 7.14, found: C, 77.28; H, 7.02.

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References and notes

1. Schenck, G. O. *Naturwissenschaften* **1948**, *35*, 28–29.
2. Recent reviews: Clennan, E. L. *Tetrahedron* **2005**, *61*, 6665–6691; Clennan, E. L. *Tetrahedron* **2000**, *56*, 9151–9179.
3. Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 1319–1328.
4. Maranzana, A.; Canepa, C.; Ghigo, G.; Tonachini, G. *Eur. J. Org. Chem.* **2005**, 3643–3649.
5. Jefford, C. W.; Kohmoto, S.; Boukouvalas, J.; Burger, U. *J. Am. Chem. Soc.* **1983**, *105*, 6498–6500.
6. Gollnick, K.; Kuhn, H. J. *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic: New York, NY, 1979; pp 287–427.
7. Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1980**, *102*, 1417–1418.
8. Hurst, J. R.; Wilson, S. L.; Schuster, G. B. *Tetrahedron* **1985**, *41*, 2191–2197.
9. Adam, W.; Prein, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 477–494.
10. (a) Orfanopoulos, M.; Gardina, M. B.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 275–276; (b) Rautenstrauch, V.; Thommen, W.; Schulte-Elte, K. H. *Helv. Chim. Acta* **1986**, *69*, 1638–1643.
11. (a) Rousseau, G.; Le Perchec, P.; Conia, J. M. *Tetrahedron Lett.* **1977**, *18*, 2517–2520; (b) Jefford, C. W. *Tetrahedron Lett.* **1979**, *20*, 985–988.
12. (a) Adam, W.; Griesbeck, A. G. *Synthesis* **1986**, 1050–1052; (b) Orfanopoulos, M.; Foote, C. S. *Tetrahedron Lett.* **1985**, *26*, 5991–5994.
13. (a) Clennan, E. L.; Chen, X. *J. Am. Chem. Soc.* **1989**, *111*, 5787–5792; (b) Orfanopoulos, M.; Stratakis, M.; Elemis, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6417–6419.
14. (a) Jefford, C. W.; Laffer, M. H.; Boschung, A. F. *J. Am. Chem. Soc.* **1972**, *94*, 8904–8905; (b) Jefford, C. W.; Boschung, A. F. *Helv. Chim. Acta* **1974**, *57*, 2242–2257.
15. Kropf, H.; Reichwaldt, R. *J. Chem. Res.* **1987**, 412–413.
16. Adam, W.; Brünker, H.-G. *J. Am. Chem. Soc.* **1995**, *117*, 3976–3982.
17. Griesbeck, A. G.; Bartoschek, A. *Chem. Commun.* **2002**, 1594–1595.
18. Griesbeck, A. G.; Bartoschek, A.; Brodwolf, A.; Miara, C. *Photochem. Photobiol.* **2006**, *82*, in press.
19. China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials. *J. Tradit. Chin. Med.* **1982**, *2*, 9–16.
20. Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301–315.
21. Venugopalan, B.; Karnik, P. J.; Bapat, C. P.; Chatterjee, D. K.; Iyer, N.; Lepcha, D. *Eur. J. Med. Chem.* **1995**, *30*, 697–706.
22. Haynes, R. K.; Chan, H.-W.; Cheung, M.-K.; Chung, S. T.; Lam, W.-L.; Tsang, H.-W.; Voerste, A.; Williams, I. D. *Eur. J. Org. Chem.* **2003**, 2098–2114.
23. (a) Posner, G. H.; Paik, I. H.; Sur, S.; McRiner, A. J.; Borstnik, K. *J. Med. Chem.* **2003**, *46*, 1060–1065; (b) Borstnik, K.; Paik, I. H.; Posner, G. H. *Int. J. Parasitol.* **2002**, *32*, 1661–1667.
24. O'Neill, P. M.; Searle, N. L.; Kan, K. W.; Storr, R. C.; Maggs, J. L. *J. Med. Chem.* **1999**, *42*, 5487–5493.
25. Jung, M.; Bae, J. *Heterocycles* **2000**, *45*, 1055–1058.
26. Pu, Y. M.; Ziffer, H. *J. Med. Chem.* **1995**, *38*, 613–616.
27. (a) Robert, A.; Dechy-Cabaret, O.; Cazelles, J.; Meunier, B. *Acc. Chem. Res.* **2002**, *35*, 167–174; (b) Dechy-Cabaret, O.; Benoitvical, F.; Robert, A.; Meunier, B. *ChemBioChem* **2000**, *1*, 281–283.
28. Hindley, S.; Ward, S. A.; Storr, R. C.; Searle, N. L.; Bray, P. G.; Park, B. K.; Davies, J.; O'Neill, P. M. *J. Med. Chem.* **2002**, *45*, 1052–1063.
29. Meunier, B. *J. Porphyrins Phthalocyanines* **2002**, *6*, 271–273.
30. Griesbeck, A. G.; El-Idreesy, T. T. *Photochem. Photobiol. Sci.* **2005**, *5*, 205–209.
31. Griesbeck, A. G.; El-Idreesy, T. T.; Fiege, M.; Brun, R. *Org. Lett.* **2002**, *4*, 4193–4195.