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Photooxygenation Catalysis with a Polyol-Decorated Disc-Shaped Porphyrin Sensitizer: Shell-Recognition Effects

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Abstract: Polar *meso*-tetraarylporphyrins **2**–**4** were synthesized from tetrakis-4-hydroxyphenylporphyrin **1** as the central building block by consecutive base-induced reactions with glycidol. The decorating units form a polar hydrogen-bonded shell around the sensitizer core which is proposed as the binding site for polar substrates in photocatalyzed oxygenation reactions. As substrate, the polarity-sensor mesitylol (**5**) was applied and the reaction constrained in a polystyrene matrix. Increasing shell dimensions lead to increased diastereoselectivities for the allylic hydroperoxides **6** and thus clearly demonstrate the concept of shell-induced substrate stereoselectivity in singlet oxygen reactions.

Keywords: diastereoselectivity; ene reaction; photooxygenation; porphyrine catalyst; singlet oxygen

Singlet oxygen ($^1\Delta_g$-$^1O_2$) is the reactive oxidant in catalytic type II photooxygenation and is formed by energy transfer either from an electronically excited sensitizer molecule or by various chemical methods.[1] These reactions are highly selective and show all kinetic properties of pericyclic reactions,[2] with the most important reaction modes: ene reaction,[3] [4+2][4] and [2+2] cycloaddition,[5] as well as heteroatom oxidation.[6] These modes represent efficient synthetic routes to a broad variety of oxyfunctionalized products. Singlet oxygen is most conveniently generated in solution phase by photochemical sensitization from appropriate dyestuffs with high chemical stability and singlet oxygen quantum yields.[7] Concerning *green chemistry* concepts,[8] photooxygenation is the most promising oxidation route with complete atom economy[9] when both oxygen atoms are incorporated in the final products,[10] as such the archetype reaction for solar chemistry applications.[11] The disadvantage of $^1O_2$ as a reactant is its moderate lifetime: 2–3 μsec in water and several msec in non-polar halogenated solvents. Thus, the generation of the excited state has to occur repeatedly without photobleaching of the sensitizer. On the other hand, $^1O_2$ lifetimes are high enough to establish long diffusive path lengths separating the areas of sensitization and reaction by several hundreds of nanometers. Even in a living cell, the lifetime of $^1O_2$ is about 3 μsec which allows extensive traveling through cell compartments.[12]

Photocatalysts that are designed to influence also the stereochemical course of a photooxygenation, for example, by introduction of stereogenic elements, suffer from a diffusive path length that is much too high for imprinting stereochemical information on the substrate. A solution can be the chiral template idea, recently also described for photochemical applications, combining light-absorbing unit with substrate-binding motifs.[13] Hydrogen-bonding networks are the most efficient glues because they are weak enough to release the products after reaction but strong enough by cooperative effects to bind substrates in proper geometries. In our ongoing project on the synthesis of new antimalarial peroxides, we have recently developed a photochemical method for the photooxygenation of allylic alcohols in polymer matrices.[14] This method was applied for the synthesis of new generations of spirobicyclic[15] and bicyclic[16] 1,2,4-trioxanes and was also studied with respect to changes in the photooxygenation diastereoselectivities.[17] Because of the apparent hydrogen-bonding interaction of $^1O_2$ with allylic alcohols, the photooxygenation is highly dependent on the environment of the substrate and shows solvent-solute interactions as well as substrate aggregation and competitive substrate-product aggregation.[18]

The following trends have been observed for the $^1O_2$ reaction with chiral allylic alcohols: (a) non-hydrogen-bonding solvents give rise to the highest diastereoselectivities, (b) low conversions lead to high diastereoselectivities indicating substrate-product aggregation with increasing conversion, and (c) low substrate concentrations also favor high diastereoselectivities indicating substrate aggregation in non-polar solvents. These trends make chiral allylic alcohols excellent sensors for the solvent environment and for the

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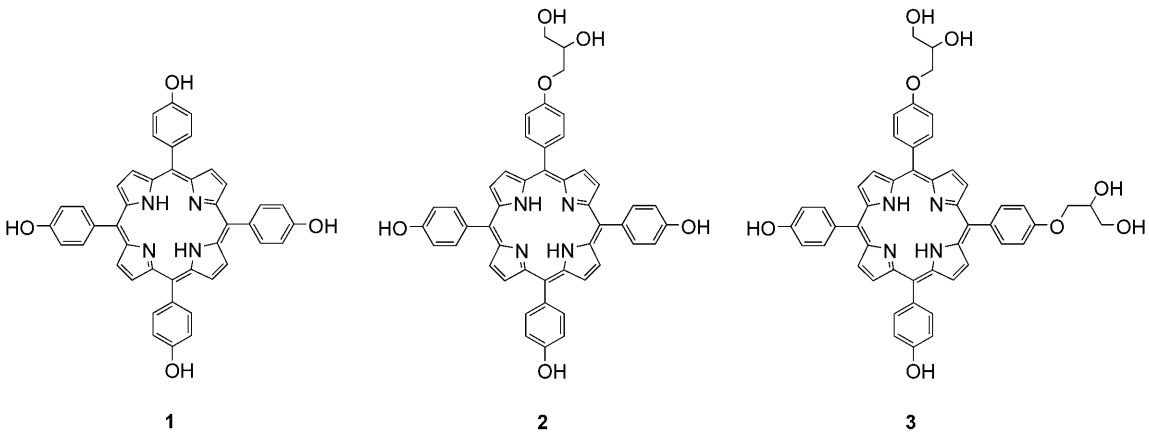
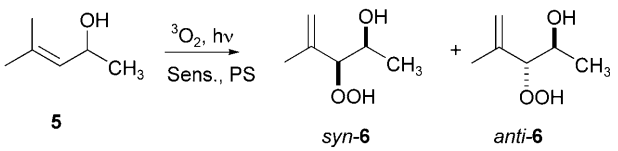


Scheme 1. Porphyrin core **1** and hydroxylated derivatives **2** and **3**.

interaction with other hydrogen-bonding substrate and product molecules, respectively. If the sensitizer itself has a strong hydrogen-bonding capacity and the $^1O_2$ ene reaction occurs preferentially in the vicinity of the photocatalyst, the stereoselectivity is expected to differ from solution phase experiments and serves as an indication of the reaction area. For these experiments, a non-polar solvent environment is crucial to avoid competing hydrogen-bonding. The polystyrene matrix was therefore considered as suitable because the sensitizers can be covalently immobilized and the substrate environment mimics non-polar solvents such as toluene.

We thus envisaged a sensitizer system that combines high singlet oxygen quantum yields, a hydrogen-bonding shell and an anchor for covalent binding to the polystyrene bead matrix. The sensitizer core is tetrakis-4-hydroxyphenylporphyrin **1** (Scheme 1) with a literature singlet oxygen quantum yield (determined for ethanol solution) of $\Phi_\Delta = 0.58$.[19] In the solution phase (benzene), photooxygenation of the polarity sensor 2,4-dimethylbut-2-en-4-ol (**5**, mesitylol) gives a 2:1 *dr* with the *syn*-diastereoisomer *syn*-**6** favored due to hydrogen-bonding interaction with the reacting singlet oxygen molecule (Scheme 2).[20] Not much changed when this sensitizer was bound in a polystyrene matrix (Table 1 and Table 2). Subsequently, the porphyrine **1** was treated with five equivalents of glycidol in the presence of triethylamine. Depending on the base concentration, the mono- and disubstituted porphyrins **2** and **3**, respectively, were isolated in moderate yields. When embedded in polystyrene



Scheme 2. Singlet oxygen reaction with mesitylol.

Table 1. Diastereoselectivities and conversions (in brackets) for 5 photooxygenation (*syn*:*anti*) after 1 h of irradiation.

Substrate amount:	0.64 mmol g^{-1}	1.2 mmol g^{-1}	2.5 mmol g^{-1}
14-HPP (**1**)	2.0:1 (47%)	2.1:1 (34%)	1.8:1 (26%)
Monomer (**2**)	2.5:1 (48%)	2.3:1 (34%)	2.2:1 (28%)
Dimer (**3**)	2.7:1 (44%)	2.2:1 (35%)	2.2:1 (26%)
Polyglycerol (**4**)	***3.3:1 (47%)***	3.0:1 (36%)	2.6:1 (18%)

Table 2. Diastereoselectivities and conversions (in brackets) for 5 photooxygenation (*syn*:*anti*) after 3.5 h of irradiation.

Substrate amount:	0.64 mmol g^{-1}	1.2 mmol g^{-1}	2.5 mmol g^{-1}
14-HPP (**1**)	2.2:1 (93%)	2.2:1 (73%)	2.2:1 (68%)
Monomer (**2**)	2.6:1 (87%)	2.6:1 (72%)	1.9:1 (65%)
Dimer (**3**)	2.5:1 (82%)	2.6:1 (74%)	2.3:1 (64%)
Polyglycerol (**4**)	***3.5:1 (83%)***	3.2:1 (69%)	2.8:1 (60%)

beads, an appreciable ***increase*** in diastereoselectivity was observed.

As can be see from Table 1 and Table 2, substrate concentrations were critical and the highest *dr* was observed for the lowest concentrations of **5** in the polymer beads. The conversion, however, showed no substantial influence on the diastereoisomeric ratios. Following a patent procedure,[21] substrate **1** was treated with an excess of glycidol and sodium hydride. This process results in a mixture of polyol-decorated porphyrins as indicated by the MALDI mass spectrum (see Experimental Section). In a broad distribution centered on penta- and hexamers, oligomers with up to 25 glycidol units could be identified. This mixture was deprotonated again and reacted with chloromethylated polystyrene beads to give the PS-bond porphyrin **4** (Scheme 3). Photooxygenation with this

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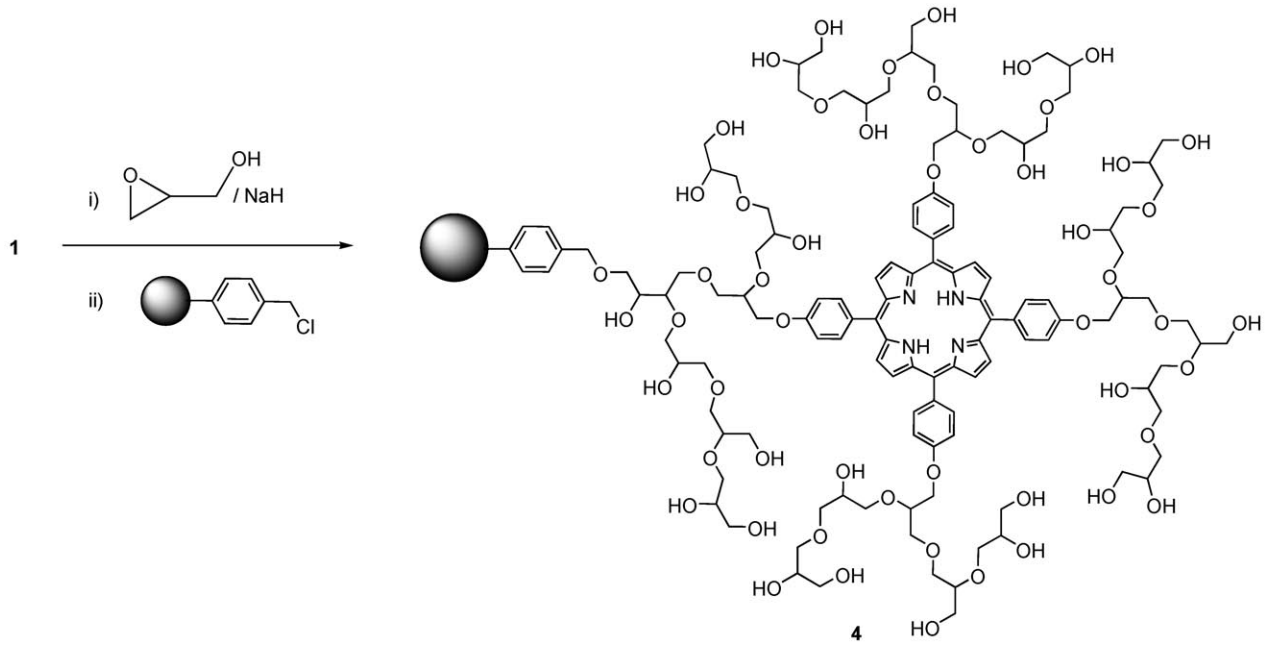
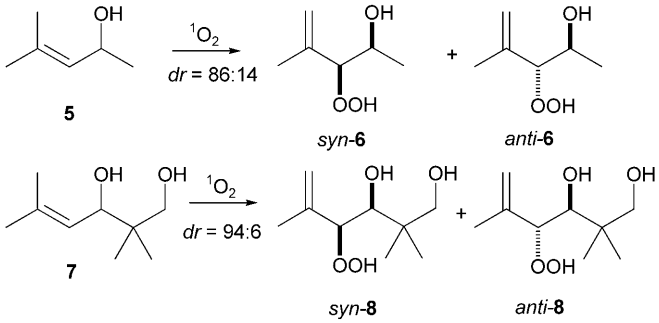


Scheme 3. Synthesis of the polyol-decorated porphyrin ($n = 20$ shown).

sensitizer is possible several times without loss of activity or changes in diastereoselectivity.

Substrate-sensitizer ratios of 500–1000 were calculated from the loading degree of the polystyrene beads (*ca.* 5% in weight). With the sensitizer system **4**, diastereoselectivities as high as 78:23 were detected, that is, selectivities are considerably higher (up to 65%) for coordinating, polyol-decorated porphyrins in comparison with the tetrahydroxylated porphyrine sensitizer **1**. Consequently, singlet oxygen generated by collision energy transfer at the porphyrin site, recognizes hydrogen-bonded substrates in the exterior of the sensitizer when incorporated in a polymer network. Even high conversions or high substrate concentrations did not alter this effect, indicating that the binding sites at the sensitizer are not occupied by product molecules with progressing reaction.

What is the reason that the diastereoselectivity of the ene reaction increases with increasing shell interactions with the sensitizer? At first hand, one might interpret this effect as contra-intuitive because the *syn*-selectivity decreases in protic solvents due to competing hydrogen-bond interactions with the solvent molecules. We have, however, discovered that one additional hydrogen bond donor/acceptor as realized in an unsaturated 1,3-diol, does indeed increase the *syn*-selectivity of the $^1O_2$ ene reaction (Scheme 4).[16] Thus, the stereoselectivity trend as observed for the polyol-substituted sensitizers is in excellent accord with the conception of a shell-induced substrate binding and activation of allylic alcohols. Additionally, these effects could also be useful for the selective localization of a sensitizer in heterogeneous materials.



Scheme 4. Singlet oxygen reaction with allylic alcohols: effect of an intramolecular hydrogen bond (CCl_4).

Experimental Section

Chloromethylated polystyrene beads (1% divinylbenzene copolymer, 100–200 mesh) were purchased from Acros Organics.

Synthesis of Tetrakis-4-hydroxyphenylporphyrin (1)[22]

Freshly distilled pyrrole (12.5 g, 186 mmol) was slowly added to 4-hydroxybenzaldehyde (22.7 g, 186 mmol) in 425 mL of refluxing propionic acid. After 30 min of vigorous stirring the solvent was removed by vacuum distillation. The resulting black residue was purified by flash column chromatography (chloroform/ethanol, 20:1). The product was obtained as a purple powder; yield: 3.0 g (4.42 mmol, 9.5%).

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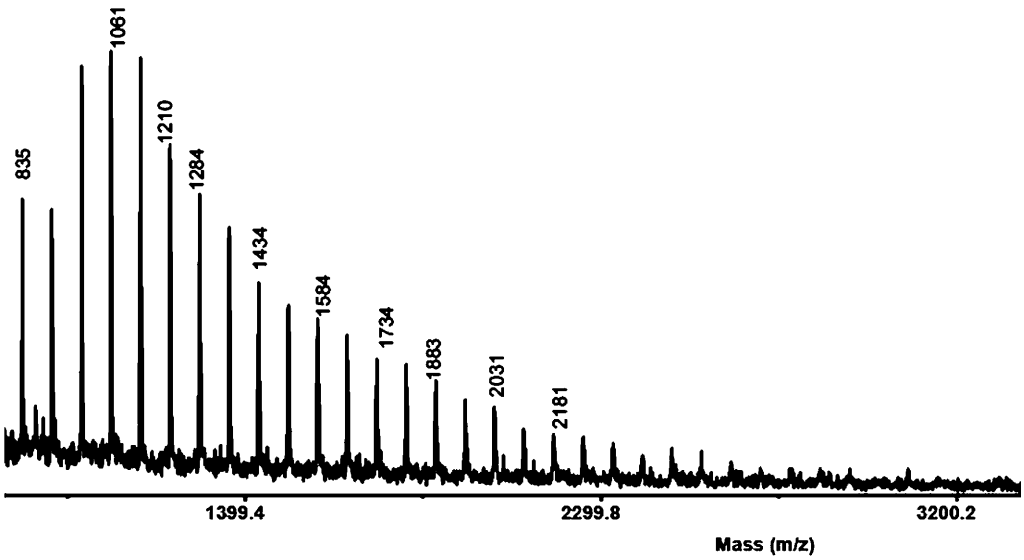

Figure 1. UV-MALDI-TOF spectrum of the polyol-porpyrin mixture **4**.

^{1}H NMR (acetone-d_6, 300 MHz): $\delta = 8.93$ (br, OH) 8.07 (d, 8H, 2,6-phenyl-H, $J = 8.4$ Hz), 7.30 (d, 8H, 3,5-phenyl-H, $J = 8.4$ Hz), 2.98 (s, 8H, β-pyrrole); IR: $\nu = 3317$ (OH), 2918 (CH), 1606 (C=C), 1508 (C=C), 1170 (CO), 800 cm^{-1} (CH); ESI-MS (HR): $m/z = 679.16$ (100%) [M−H$^+$], 680.16 (66%), 681.16 (33%).

Synthesis of the Mono-glycerol Substituted Porphyrin (2)

Tetrakis-4-hydroxyphenylporphyrin **1** (30 mg, 0.044 mmol) and *rac*-glycidol (17 mg, 0.22 mmol) were dissolved in 10 mL of dry ethanol. After addition of triethylamine (47 mg, 0.46 mmol) the mixture was refluxed for 4 h. Evaporation of the solvent and flash column chromatography afforded of a purple powder; yield: 11 mg (0.015 mmol, 33%). ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 7.82$ (d, 8H, 2,6-phenyl-H, $J =$ 6.0 Hz), 7.90 (d, 8H, 3,5-phenyl-H, $J = 6.9$ Hz), 4.20–3.35 (m, C-H, C-H_2), 3.28 (s, 8H, β-pyrrole); IR: $\nu = 3331$ (OH), 2944 (CH), 1600 (C=C), 1508 (C=C), 1174 (CO), 802 cm^{-1} (CH); ESI-MS (HR): $m/z = 753.20$ (100%) [M−H$^+$]: 754.20 (44%); mp > 250 °C.

Disubstituted porphyrin **3** was found as a side product.

Synthesis of the Di-glycerol Substituted Porphyrin (3)

Tetrakis-4-hydroxyphenylporphyrin **1** (51 mg, 0.075 mmol) and *rac*-glycidol (27.8 mg, 0.38 mmol) were dissolved in 10 mL of dry ethanol. After addition of triethylamine (47 mg, 0.46 mmol) the mixture was refluxed for 4 h. Evaporation of the solvent and flash column chromatography afforded a purple powder; yield: 13 mg (0.015 mmol, 21%). ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 7.72$ (d, 8H, 2,6-phenyl-H, $J = 7.8$ Hz), 7.09 (d, 8H, 3,5-phenyl-H, $J = 7.8$ Hz), 4.13–3.30 (m, C-H, C-H_2), 3.27 (s, 8H, β-pyrrole); IR: $\nu = 3331$ (OH), 2944 (CH), 1600 (C=C), 1508 (C=C), 1174 (CO), 802 cm^{-1} (C-H); ESI-MS (HR): $m/z = 827.22$ (100%) [M−H$^+$], 828.22 (52%); mp > 250 °C.

Synthesis of Polyglycerol-Bound Porphyrin (4)

Tetrakis-4-hydroxyphenylporphyrin **1** (380 mg, 0.256 mmol) in 12 mL dry THF were added to sodium hydride (60% in mineral oil, 54 mg, 2.24 mmol). The solution was heated to 65 °C and *rac*-glycidol (2.27 g, 30.3 mmol) in 5 mL of dimethoxyethane were added over 12 h *via* a syringe pump. After evaporation of the solvent, the residue was dissolved in methanol and recrystallized from acetone, then dried for 10 h at 50 mbar and 70 °C. The product was obtained as a viscous, purple oil; yield:900 mg. ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 7.90$ (d, 8H, 2,6-phenyl-H, $J = 7.8$ Hz), 7.06 (d, 8H, 3,5-phenyl-H, $J = 7.2$ Hz), 4.45–2.70 (m, CH; CH_2; β-pyrrole); IR: $\nu = 3391$ (OH), 2919–2873 (CH), 1558 (C=C), 1113–1071 cm^{-1} (CO).

UV-MALDI-TOF mass spectra were recorded in positive polarity on an Applied Biosystems Voyager STR (Applied Biosystems, Framingham, MA, USA) instrument equipped with an N_2-UV-laser (337 nm), delayed extraction and reflectron technology. MS analysis of the sample was performed utilizing a saturated solution of α-cyano-4-hydroxycinnamic acid (HCCA) in TFA 0.1%-ACN 80/20 as matrix, by the classic dried drop method: 1–2μL of a sample/matrix solution mixture (1:1, v/v) was deposited onto a stainless-steel MALDI sample plate (Applied Biosystems, Framingham, MA, USA) and left to dry at room temperature. MALDI-mass spectra, resulting from the sum of 400 laser shots, were acquired in the reflectron mode after external calibration of the mass accuracy (≈150 ppm) with a peptide/protein mixture (Figure 1).

Synthesis of Polymer Beads with Covalently Bound Porphyrins 2 and 3

Chloromethylated polystyrene beads (2.10 g, 1.4–1.7 mmol Cl/g, 1% divinylbenzene copolymer, 100–200 mesh) were swollen in 38 mL of dry DMF for 20 min. The flask was heated to 63 °C and a solution of 0.015 mmol of porphyrins **2** or **3**, respectively, potassium carbonate (0.35 g, 2.53 mmol) and 18-crown-6 (0.035 mg) in 10 mL of DMF, was added.

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The mixture was stirred for 20 h at 63 °C. After cooling to room temperature the resin was thoroughly washed with water, ethanol and ethyl acetate and dried for 3 h (50 mbar, 70 °C).

Synthesis of Polymer Beads with Covalently Bound Porphyrin 4

Porphyrin **4** (25 mg) was dissolved in 10 mL of dry DMF and deprotonated with sodium hydride (5 mg, 0.21 mmol). After 1 h, chloromethylated polystyrene beads (2.50 g, mmol Cl/g, 1% divinylbenzene copolymer, 100–200 mesh) in 10 mL of dry DMF were added and the mixture was stirred for 3 d at 80 °C. After cooling to room temperature the resin was thoroughly washed with water, ethanol and ethyl acetate and dried for 3 h (50 mbar, 70 °C).

General Procedure for the Photooxygenation of Mesitylol (5) in Polystyrene Beads

A slurry of 2 g of polystyrene beads with a solution of mesitylol in 20 mL of dichloromethane was dispersed on a Petri dish (Ø 19 cm). The excess solvent was evaporated by leaving the Petri dish for a few minutes in a well ventilated hood. The sandy solid which was obtained was irradiated in the loosely covered Petri dish by a sodium street lamp or a halogen lamp without external cooling and without external oxygen purging. The polymer beads were subsequently rinsed with 3×20 mL of ether and filtered. After careful evaporation of the solvent (no hydroperoxide decomposition was observed when the temperature was kept < 40 °C), the crude product was analyzed by ^{1}H NMR spectroscopy. As the significant ^{1}H NMR (300 MHz, $CDCl_3$) signals were used: *syn*-diastereoisomer: $\delta = 0.89$ (t, 3 H, $J = 7.42$ Hz, 3 H, CH_2CH_3), 1.17–1.52 (m, 2 H, CH_2CH_3), 1.65 (s, 3 H, CH_3), 3.52 (ddd, 1 H, $J = 8.53$, 8.53, 3.24 Hz, C*H*-OH), 4.12 (d, 1 H, $J = 8.53$ Hz, C*H*-OOH), 4.97 (m, 2 H, $=CH_2$); *anti*-diastereoisomer: $\delta = 0.90$ (t, 3 H, $J = 7.42$ Hz, 3 H, CH_2CH_3), 1.17–1.52 (m, 2 H, CH_2CH_3), 1.73 (s, 3 H, CH_3), 3.65 (m, 1 H, CH-OH), 4.27 (d, 1 H, $J = 4.55$ Hz, CH-OOH), 5.00 (m, 2 H, $=CH_2$). The residual polystyrene beads could be used for further photooxygenations without loss of activity for at least six times.

Acknowledgements

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