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Stereocontrolled Photooxygenations—A Valuable Synthetic Tool§

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ABSTRACT

The stereochemical course of the singlet-oxygen ene reaction with acyclic olefins may be controlled if in the substrate conformational fixation (1,3-allylic strain) an allylic substituent for interaction with the attacking oxygen enophile aligns. Various substrates were chosen to elucidate the features of the olefin that are necessary to control the sense (*threo versus erythro*) and the extent of the π-facial preference of the singlet-oxygen attack. Depending on the electronic properties of the double bond and the nature of the allylic substituent, *threo* or *erythro* selectivity may be imposed through hydrogen bonding, electrostatic and steric effects and stereoelectronic alignment. Such directing properties, especially that of the hydroxy group, were also confirmed in the other reaction modes of singlet oxygen, namely the [4+2] cycloaddition to chiral naphthylenic alcohols and the [2+2] cycloaddition to an adamantylidene-substituted allylic alcohol. The syntheses of the natural products Merucathin and Isodihydromahubanolide B are two examples in which such stereocontrolled photooxygenations have been used as key steps to build up the required chirality diastereoselectively.

INTRODUCTION

Molecular oxygen is the most abundant and readily accessible oxidizing agent; however, in its triplet ground state, this oxidant is not particularly useful in organic synthesis due to the lack of selectivity in its characteristic radical-type reactions (*e.g.* autoxidation). To serve as a convenient reagent for mild and selective oxyfunctionalization, the triplet dioxygen molecule is electronically excited to its first singlet state (O_2 [$^1\Delta_g$]). Beside the chemical generation of singlet oxygen ($^1O_2$)‡ (1,2), the more convenient and widely used *in situ* method of preparation is through photosensitization with visible light and a suitable dyestuff (*e.g.* porphines, rose bengal, methylene blue). The three characteristic reaction modes of $^1O_2$ with olefins are displayed in Scheme 1, namely [4+2] cycloaddition of conjugated dienes to give endoperoxides (path A) (3–6), [2+2] cycloaddition with electron-rich olefins to yield 1,2-dioxetanes (path B) (3,6) and the ene process (Schenck ene reaction) for allylic substrates to afford allylic hydroperoxides (path C) (3,5–7). Of these three photooxygenation modes, the ene reaction is the most valuable for synthetic purposes. In view of this, in recent years much effort has been invested in the elucidation of the reaction mechanism to develop diastereoselective photooxygenations (8,9), the subject of this contribution.

MATERIALS AND METHODS

Chemicals. The allylic alcohols **3a–d** were prepared according to already published procedures (10).

Photooxygenations. A solution of the particular substrate (~0.1 *M*) and sensitizer (10^{-4} *M*) was irradiated with two 250-W sodium lamps, while a stream of dry oxygen gas was passed continuously through the reaction mixture and the temperature was kept constant by cooling the solution with a cryostat. The composition of the crude reaction mixture was determined by ^{1}H-NMR spectroscopy (error ± 5%). Further purification of the products was performed by removal of the solvent (20°C, 20 torr) and flash column chromatography on silica gel (solvents are given in brackets).

Photooxygenation of 400 mg (3.99 mmol) of *(Z)*-4-hexen-2-ol (**3a**) in dichloromethane (40 mL) at −20°C with tetraphenylporphine (TPP) as sensitizer for 5 h yielded **4a** and **5a** in a 56:44 mixture. The products were isolated as mixtures of diastereomers by silica-gel chromatography (4:1 petroleum ether/ethyl acetate).

4-Hydroperoxy-5-hexen-2-ol (4a). Colorless oil, 56:44 mixture of ***l*-4a** and ***u*-4a**. Diastereomer ***l*-4a**: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, *J* = 6.1 Hz, 3 H, 1-H), 1.65 (ddd, *J* = 15.0, 5.0, 3.0 Hz, 1 H, 3-H), 1.87 (dt, *J* = 15.0, 9.0 Hz, 1 H, 3-H), 2.92 (br s, 1 H, OH), 3.98–4.09 (m, 1 H, 2-H), 4.48–4.59 (m, 1 H, 4-H), 5.30 (dt, *J* = 10.4, 1.2 Hz, 1 H, 6-H [*cis*]), 5.35 (dt, *J* = 17.4, 1.2 Hz, 1 H, 6-H [*trans*]), 5.87 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1 H, 5-H), 9.75 (br s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ 24.1 (q, C-1), 41.6 (t, C-3), 66.6 (d, C-2), 86.0 (d, C-4), 118.6 (t, C-6), 136.7 (d, C-5). Diastereomer ***u*-4a**: ^{1}H NMR ($CDCl_3$) δ 1.24 (d, *J* = 6.4 Hz, 3 H, 1-H), 1.76 (dd, *J* = 6.1 Hz, 2 H, 3-H), 2.92 (br s, 1 H, OH), 3.98–4.09 (m, 1 H, 2-H), 4.64 (q, *J* = 6.7 Hz, 1 H, 4-H), 5.30 (dt, *J* = 10.4, 1.2 Hz, 1 H, 6-H [*cis*]), 5.35 (dt, *J* = 17.4, 1.2 Hz, 1 H, 6-H [*trans*]), 5.88 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1 H, 5-H), 9.75 (br s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ 23.2 (q, C-1), 41.6 (t, C-3), 67.9 (d, C-2), 86.4 (d, C-4), 118.5 (t, C-6), 138.2 (d, C-5). IR of diastereomeric mixture (neat) 3740, 3600–3100, 1460, 1425, 1385; analysis calculated for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.11; H, 8.86.

(E)-5-hydroperoxy-3-hexen-2-ol (5a). Colorless oil, 56:44 mix-

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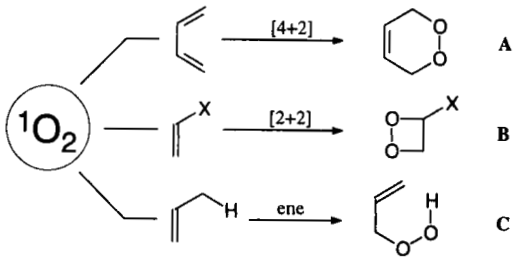
‡*Abbreviations:* $^1O_2$, singlet oxygen; d.r., diastereomeric ratio; TPP, tetraphenylporphine; TS, transition state.



Scheme 1.

ture of diastereomers **A** and **B**. Diastereomer **A**: ^{1}H NMR ($CDCl_3$) δ = 1.25 (d, *J* = 6.7 Hz, 3 H, 6-H), 1.30 (d, *J* = 6.4 Hz, 3 H, 1-H), 2.83 (br s, 1 H, OH), 4.35 (sext, *J* = 6.4 Hz, 1 H, 2-H), 4.49 (sext, *J* = 6.7 Hz, 1 H, 5-H), 5.61 (ddd, *J* = 15.6, 7.3, 0.9 Hz, 1 H, 4-H), 5.79 (ddd, *J* = 15.6, 7.3, 0.9 Hz, 1 H, 3-H), 9.32 (br s, 1 H, OOH). Diastereomer **B**: ^{1}H NMR ($CDCl_3$) δ = 1.27 (d, *J* = 6.7 Hz, 3 H, 6-H), 1.30 (d, *J* = 6.4 Hz, 3 H, 1-H), 2.83 (br s, 1 H, OH), 4.35 (sext, *J* = 6.4 Hz, 1 H, 2-H), 4.49 (sext, *J* = 6.7 Hz, 1 H, 5-H), 5.60 (ddd, *J* = 15.6, 7.3, 0.9 Hz, 1 H, 4-H), 5.83 (ddd, *J* = 15.6, 7.3, 0.9 Hz, 1 H, 3-H); (br s, 1 H, OOH). ^{13}C NMR ($CDCl_3$) of diastereomers **A** and **B**: δ = 18.2 (q, 2 × C-6), 23.1 (q, 2 × C-1), 67.9 and 68.3 (d, C-2), 81.5 and 81.7 (d, C-5), 129.2 and 130.0 (d, C-3 or C-4), 137.8 and 138.1 (d, C-3 or C-4). IR of diastereomeric mixture (neat) 3740, 3600–3100, 1450, 1375; analysis calculated for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.68; H, 9.42.

The photooxygenation of 350 mg (3.07 mmol) of (*Z*)-5-hepten-3-ol (**3b**) in CCl_4 (40 mL) at −20°C (TPP as sensitizer) for 8 h yielded a 51:49 mixture of **4b** and **5b**. The products were isolated as mixtures of diastereomers (silica-gel chromatography; 4:1 petroleum ether/ethyl acetate).

*5-Hydroperoxy-6-hepten-3-ol (**4b**).* Colorless oil, 44:56 mixture of ***l*-4b** and ***u*-4b**. Diastereomer ***l*-4b**: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, *J* = 7.3 Hz, 3 H, 1-H), 1.54 (dq, *J* = 7.3, 6.2 Hz, 2 H, 2-H), 1.67 (ddd, *J* = 14.7, 5.2, 2.5 Hz, 1 H, 4-H), 1.82 (ddd, *J* = 14.7, 9.2, 8.6 Hz, 1 H, 4-H), 3.77 (dq, *J* = 9.2, 6.2 Hz, 1 H, 3-H), 4.54 (dtt, *J* = 7.5, 5.5, 0.9 Hz, 1 H, 5-H), 5.30 (dt, *J* = 10.4, 1.2 Hz, 1 H, 7-H [*cis*]), 5.35 (dt, *J* = 17.4, 1.2 Hz, 1 H, 7-H [*trans*]), 5.88 (ddd, *J* = 17.4, 10.4, 7.3 Hz, 1 H, 6-H); OOH and OH were not detected; ^{13}C NMR ($CDCl_3$) δ 9.7 (q, C-1), 30.3 (t, C-2), 39.4 (t, C-4), 71.8 (d, C-3), 86.1 (d, C-5), 118.5 (t, C-7), 136.8 (d, C-6). Diastereomer ***u*-4b**: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, *J* = 7.3 Hz, 3 H, 1-H), 1.52 (dq, *J* = 7.3, 6.4 Hz, 2 H, 2-H), 1.77 (m, 2 H, 4-H), 3.82 (dq, *J* = 6.4, 4.4 Hz, 1 H, 3-H), 4.67 (dtt, *J* = 7.0, 5.8, 0.9 Hz, 1 H, 5-H), 5.30 (dt, *J* = 10.4, 1.2 Hz, 1 H, 7-H [*cis*]), 5.35 (dt, *J* = 17.4, 1.2 Hz, 1 H, 7-H (*trans*]), 5.88 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1 H, 6-H); OOH and OH were not detected; ^{13}C NMR ($CDCl_3$) δ 9.9 (q, C-1), 30.6 (t, C-2), 39.2 (t, C-4), 69.7 (d, C-3), 83.5 (d, C-5), 118.5 (t, C-7), 136.8 (d, C-6). IR of diastereomeric mixture (neat) 3600, 3540, 3500–3250, 2970, 2940, 2880, 1465, 1420, 1335, 1265, 1120, 1000, 940; analysis calculated for $C_7H_{14}O_3$: C, 57.51: H, 9.65. Found: C, 56.97; H, 9.71.

*(E)-6-Hydroperoxy-4-hepten-3-ol (**5b**).* Colorless oil, 59:41 mixture of diastereomers **A** and **B**. Diastereomer **A**: ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 3 H, 1-H), 1.27 (d, *J* = 6.1 Hz, 3 H, 7-H), 1.55 (q, *J* = 6.1 Hz, 1 H, 2-H), 1.57 (d, *J* = 6.1 Hz, 1 H, 2-H), 4.07 (quin, *J* = 6.1 Hz, 1 H, 3-H), 4.50 (quin, *J* = 6.4 Hz, 1 H, 6-H), 5.66 (ddd, *J* = 15.6, 6.4, 0.9 Hz, 1 H, 5-H), 5.76 (ddd, *J* = 15.6, 6.1, 0.9 Hz, 1 H, 4-H); OOH and OH were not detected; ^{13}C NMR ($CDCl_3$) δ 9.6 (q, C-1), 18.3 (q, C-7), 29.9 (t, C-2), 73.6 (d, C-3), 80.7 (d, C-6), 130.7 (d, C-4 or C-5), 136.7 (d, C-4 or C-5). Diastereomer **B**: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, 3 H, 1-H), 1.27 (d, *J* = 6.4 Hz, 3 H, 7-H), 1.56 (q, *J* = 6.4 Hz, 1 H, 2-H), 1.59 (q, *J* = 6.4 Hz, 1 H, 2-H), 4.10 (q, *J* = 6.4 Hz, 1 H, 3-H), 4.52 (quin, *J* = 6.4 Hz, 1 H, 6-H), 5.69 (ddd, *J* = 15.6, 6.4, 0.9 Hz, 1 H, 5-H), 5.79 (dd, *J* = 15.6, 5.8 Hz, 1 H, 4-H); OOH and OH were not detected; ^{13}C NMR ($CDCl_3$) δ 9.6 (q, C-1), 18.3 (q, C-7), 29.9 (t, C-2), 73.3 (d, C-3), 81.6 (d, C-6), 130.2 (d, C-4 or C-5), 136.5 (d, C-4 or C-5). IR of diastereomeric mixture (neat) 3600–3150, 2980, 2940, 2880, 1455, 1375, 1140, 1060, 1015, 975; analysis calculated for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 56.97; H, 9.71.

The photooxygenation of 130 mg (0.914 mmol) of (*Z*)-2,2-dimethyl-5-hexen-3-ol (**3c**) in dichloromethane (30 mL) at −20°C (TPP as sensitizer) for 18 h gave a 58:42 mixture of the hydroperoxides **4c** and **5c**.

*2,2-Dimethyl-5-hydroperoxy-6-hepten-3-ol (**4c**).* Colorless oil, 49:51 mixture of ***u*-4c** and ***l*-4c**. Diastereomer ***u*-4c**: ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 9 H, 1-H), 1.67–1.78 (m, 2 H, 4-H), 2.19 (br. s, 1 H, OH), 3.45 (dd, *J* = 9.2, 2.7 Hz, 1H, 3-H), 4.50 (tqt, *J* = 7.2, 6.2, 0.9 Hz, 1 H, 5-H), 5.29 (dt, *J* = 10.4, 1.5 Hz, 1 H, 7-H [*cis*]), 5.34 (dt, *J* = 17.4, 1.5 Hz, 1 H, 7-H [*trans*]), 5.89 (ddd, *J* = 17.5, 10.5, 7.2 Hz, 1 H, 6-H), 9.54 (s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ 25.5 (q, C-1), 34.3 (t, C-4), 34.7 (s, C-2), 75.3 (d, C-3), 86.6 (d, C-5), 118.5 (t, C-7), 136.8 (d, C-6). Diastereomer ***l*-4c**: ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 9 H, 1-H), 1.67–1.78 (m, 2 H, 4-H), 2.19 (br. s, 1 H, OH), 3.56 (dd, *J* = 10.1, 1.9 Hz, 1H, 3-H), 4.71 (tqt, *J* = 7.0, 4.2, 1.0 Hz, 1 H, 5-H), 5.30 (dt, *J* = 10.4, 1.5 Hz, 1 H, 7-H [*cis*]), 5.36 (dt, *J* = 17.4, 1.5 Hz, 1 H, 7-H [*trans*]), 5.86 (ddd, *J* = 17.3, 10.2, 7.0 Hz, 1 H, 6-H), 9.22 (s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ 25.5 (q, C-1), 34.3 (t, C-4), 34.7 (s, C-2), 78.2 (d, C-3), 83.7 (d, C-5), 118.1 (t, C-7), 136.8 (d, C-6); analysis calculated for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.48; H, 10.01.

*(E)-2,2-Dimethyl-6-hydroperoxy-4-hepten-3-ol (**5c**).* Colorless oil, 58:42 mixture of diastereomers **A** and **B**. Diastereomer **A**: ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 9 H, 1-H), 1.24 (d, *J* = 6.4 Hz, 3 H, 7-H), 2.31 (br. s, 1 H, OH), 3.77 (dd, *J* = 7.3, 0.6 Hz, 3-H), 4.48 (quin, *J* = 7.3 Hz, 1 H, 6-H), 5.61 (ddd, *J* = 15.9, 7.3, 0.9 Hz, 1 H, 4-H), 5.81 (dd, *J* = 15.6, 7.3 Hz, 1 H, 5-H), 9.03 (s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ = 18.4 (q, C-7), 25.6 (q, C-1), 34.7 (s, C-2), 80.5 (d, C-3), 81.6 (d, C-6), 132.7 (d, C-4 or C-5), 134.0 (d, C-4 or C-5). Diastereomer **B**: ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 9 H, 1-H), 1.26 (d, *J* = 6.4 Hz, 3 H, 7-H), 1.96 (br. s, 1 H, OH), 3.81 (dd, *J* = 6.1, 0.6 Hz, 3-H), 4.52 (quin, *J* = 6.7 Hz, 1 H, 6-H), 5.68 (ddd, *J* = 15.6, 7.0, 0.9 Hz, 1 H, 4-H), 5.86 (dd, *J* = 15.6, 6.4 Hz, 1 H, 5-H), 8.54 (s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ 18.4 (q, C-7), 25.6 (q, C-1), 34.9 (s, C-2), 79.9 (d, C-3), 81.7 (d, C-6), 131.8 (d, C-4 or C-5), 133.7 (d, C-4 or C-5); analysis calculated for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.31; H, 10.40.

The photooxygenation of 600 mg (3.70 mmol) 1-phenyl-3-pentenol (**3d**) was carried out in CH_2Cl_2 at −15°C (TPP as sensitizer) and yielded a mixture of **4d** and **5d** (63:37). The products were isolated as mixtures of diastereomers (silica-gel chromatography; 3:1 petroleum ether/ethyl acetate).

*3-Hydroperoxy-1-phenyl-4-penten-1-ol (**4d**).* Colorless oil, 45:55 mixture of ***u*-4d** and ***l*-4d**. Diastereomer ***u*-4d**: ^{1}H NMR ($CDCl_3$) δ 1.86 (ddd, *J* = 14.7, 4.8, 3.7 Hz, 1 H, 2-H), 2.24 (dt, *J* = 14.7, 9.2 Hz, 1 H, 2-H), 2.55 (br s, 1 H, OH), 4.54 (ddd, *J* = 8.7, 7.0, 4.8 Hz, 1 H, 3-H), 4.91 (dd, *J* = 9.2, 3.7 Hz, 1H, 1-H), 5.31 (ddd, *J* = 10.4, 2.2, 0.9 Hz, 1 H, 5-H (*cis*]), 5.35 (ddd, *J* = 17.4, 2.2, 0.9 Hz, 1 H, 5-H (*trans*]), 5.90 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1 H, 4-H), 7.20–7.30 (m, 5 H, aromatic), 8.85 (s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ 41.7 (t, C-2), 72.0 (d, C-1), 85.5 (d, C-3), 118.8 (t, C-5), 125.7 (d, aromatic), 126.4 (d, aromatic), 128.6 (d, aromatic), 136.1 (d, C-4), 142.3 (s, aromatic). Diastereomer ***l*-4d**: ^{1}H NMR ($CDCl_3$) δ 1.93–2.16 (ddd, *J* = 14.9, 7.8, 3.7 Hz, 2 H, 2-H), 2.40 (br s, 1 H, OH), 4.65 (ddd, *J* = 7.8, 7.0, 4.9 Hz, 1 H, 3-H), 4.97 (dd, *J* = 8.9, 3.7 Hz, 1 H, 1-H), 5.31 (ddd, *J* = 10.4, 2.2, 0.9 Hz, 1 H, 5-H [*cis*]), 5.35 (ddd, *J* = 17.4, 2.2, 0.9 Hz, 1 H, 5-H (*trans*]), 5.89 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1 H, 4-H), 7.20–7.30 (m, 5 H, aromatic), 8.60 (s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ 41.5 (t, C-2), 70.6 (d, C-1), 83.3 (d, C-3), 118.7 (t, C-5), 125.7 (d, aromatic), 126.9 (d, aromatic), 128.6 (d, aromatic), 135.9 (d, C-4), 142.3 (s, aromatic). IR of diastereomeric mixture (neat) 3610, 3540, 3500–3240, 3040, 3020, 2980, 2940, 1730, 1695, 1680, 1455, 1420, 1380, 1335, 1305, 1265, 1120, 1075, 1020, 980, 945; analysis calculated for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.48; H, 7.17.

*(E)-4-hydroperoxy-1-phenyl-2-penten-1-ol (**5d**).* Colorless oil, 58:42 diastereomers **A** and **B**. Diastereomer **A**: ^{1}H NMR ($CDCl_3$) δ 1.24 (d, *J* = 6.4 Hz, 3 H, 5-H), 2.80 (br s, 1 H, OH), 4.49 (quin, *J* = 6.7 Hz, 1 H, 4-H), 5.20 (dd, *J* = 5.6, 0.9 Hz, 1 H, 1-H), 5.75 (ddd, *J* = 15.6, 6.7, 1.2 Hz, 1 H, 3-H), 5.95 (ddd, *J* = 15.4, 5.6, 0.6 Hz, 1 H, 2-H), 7.20–7.30 (m, 5 H, aromatic), 8.96 (s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ 17.9 (q, C-5), 74.5 (d, C-1), 81.5 (d, C-4), 126.3 (d, aromatic), 126.4 (d, aromatic), 127.9 (d, aromatic), 128.6 (d, aromatic), 131.2 (d, C-3), 136.1 (d, C-2), 142.2 (s, aromatic).

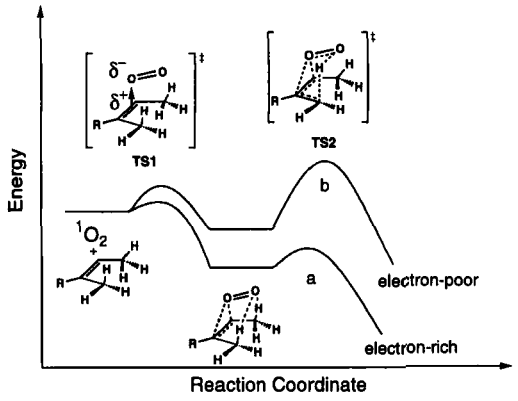


Figure 1. Reaction coordinate for the ene reaction of singlet oxygen with electron-rich (a) and electron-poor (b) olefins.

Diastereomer **B**: ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 6.4 Hz, 3 H, 5-H), 2.27 (br s, 1 H, OH), 4.53 (quin, J = 6.4 Hz, 1 H, 4-H), 5.20 (dd, J = 6.1, 0.9 Hz, 1 H, 1-H), 5.80 (ddd, J = 15.6, 6.7, 1.2 Hz, 1 H, 3-H), 5.98 (ddd, J = 15.6, 6.1, 0.6 Hz, 1 H, 4-H), 7.20–7.30 (m, 5 H, aromatic), 8.49 (s, 1 H, OOH); ^{13}C NMR ($CDCl_3$) δ 18.2 (q, C-5), 74.2 (d, C-1), 81.6 (d, C-4), 126.4 (d, aromatic), 127.9 (d, aromatic), 128.7 (d, aromatic), 130.5 (d, C-3), 135.8 (d, C-2), 142.3 (s, aromatic). IR of diastereomeric mixture (neat) 3620, 3540, 3480–3240, 3100, 3080, 3040, 2940, 1630, 1595, 1580, 1495, 1455, 1420, 1335, 1205, 1065, 1040, 1000, 940; analysis calculated for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.42; H, 6.90.

RESULTS AND DISCUSSION

Mechanism of the ene-reaction mode

Experimental (11–13) and theoretical (14) work favor a two-step mechanism for the Schenck ene reaction: In the first step an exciplex with perepoxide-like geometry is formed (Fig. 1) (8,15,16); in the second step one of the allylic hydrogen atoms is abstracted to afford the hydroperoxide product. The electronic properties of the reacting alkene determine which of these steps controls the rate of the process (16,17). In the case of electron-rich olefins, the exciplex formation is rate determining (path a in Fig. 1), whereas for electron-poor substrates it is hydrogen abstraction (path b in Fig. 1). This mechanistic difference has been demonstrated unambiguously by kinetic isotope effects observed in the photooxygenation of tetramethylethylene and methyl tiglate (Fig. 2). Thus, for the electron-rich tetramethylethylene, the rate-determining step does not involve hydrogen abstraction (k_H/k_D = 1.07) (16), and the highly polarized transition state TS1 applies (Fig. 1). In contrast, in the reaction of the electron-poor tiglate, a significant isotope effect is observed (k_H/k_D = 1.48) (17) that demands the less polar TS2. This means that for electron-poor substrates the first step (exciplex formation) is reversible and hydrogen abstraction in the second step determines the rate of the ene reaction. In view of this, fundamentally different mechanisms operate in the photooxygenation of allylic substrates and, thus, it is advantageous to present the diastereoselectivity data for the ene reaction of electron-rich and electron-poor olefins separately.

Electron-rich alkenes

While stereocontrol may be exercised readily in the photooxygenation of cyclic substrates (18,19) by imposing conformational rigidity on the ring system, the discrimination

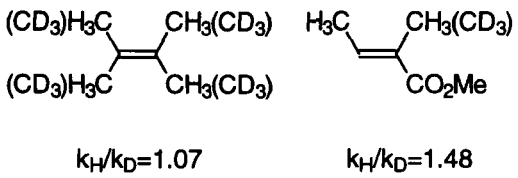
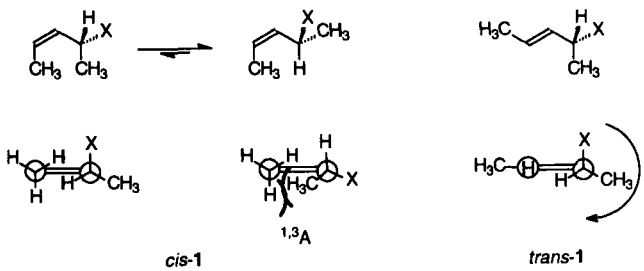


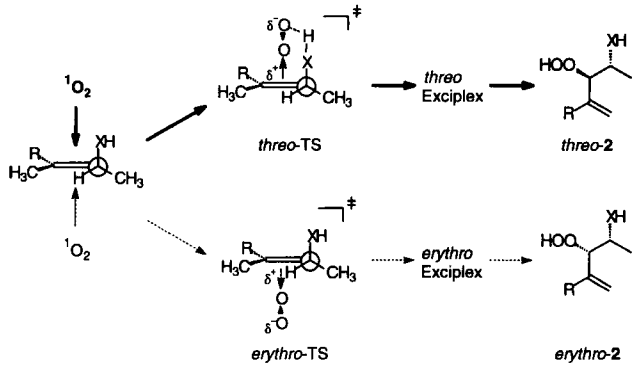
Figure 2. Isotopic effects in the reaction of singlet oxygen with electron-rich and electron-poor olefins.

of the π faces in acyclic compounds may also be achieved by populating one conformer preferably and by introducing a substituent that directs the incoming oxygen. A way to achieve the necessary conformational fixation is 1,3-allylic strain: In the *cis*-substituted alkene *cis*-**1** (Scheme 2), the rotation around the C2–C3 bond is restricted because there is a repulsive interaction between the allylic methyl group and the substituents on the chirality center (1,3-allylic strain, ^{1,3}A). The steric demand of the substituent obliges the population of the conformer with the smallest substituent (*i.e.* hydrogen) in the inside position to minimize repulsion with the juxtaposed methyl group. Thus, in this conformational alignment the X substituent at the chirality center is placed in a position well suited to interact with an incoming reagent and thereby π-facial differentiation is achieved; indeed, photooxygenations of such allylic substrates generally show high diastereoselectivities (20,21). In contrast, in the *trans*-substituted isomer *trans*-**1** no allylic strain exists and, therefore, the conformers are nearly equal in energy; consequently, little if any diastereoselectivity is observed in the ene reactions of these olefins (20).

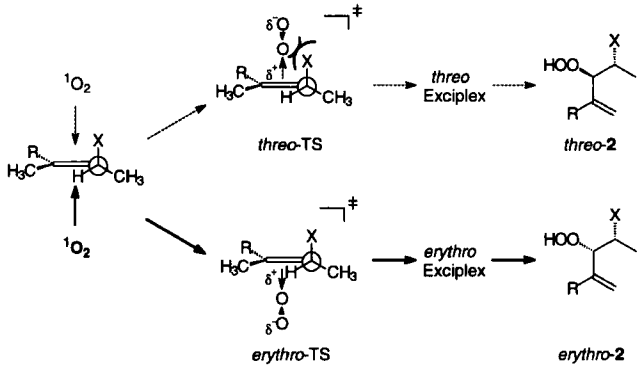
A variety of allylic substituents X has been tested for their directing properties in the Schenck ene reaction of $^1O_2$ in chiral acyclic alkenes (20,22–24). The substituents may be classified into two classes with regard to their propensity to direct the $^1O_2$ attack either with *threo* or *erythro* diastereoselectivity, in the former electronic association in the latter steric and electrostatic repulsion operates. As already stated previously for the reaction of $^1O_2$ with electron-rich olefins, the polarized TS1 (Fig. 1) applies. Thus, when the substituent (X = OH, NH_2, NH_3^+) can hydrogen bond to the negatively polarized oxygen, this hydrogen bond stabilizes the negative charge on the oxygen and thereby reduces the energy of the corresponding TS (Scheme 3). Because the conformation at the stereogenic center is fixed due to 1,3-allylic strain, such hydrogen bonding is effective in the *threo* TS and a high *threo* diastereoselectivity is observed (Table 1, entries 1–4). The favorable hydrogen bonding in the TS is disturbed in protic solvents (MeOH) through competing as-



Scheme 2.



Scheme 3.



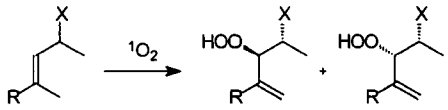
Scheme 4.

sociation of the substrate with the solvent and, hence, the diastereoselectivity drops significantly (*cf.* entries 5 and 6). Important for a high selectivity is a geometry that favors efficient hydrogen bonding. If the hydroxy group is placed one atom further away from the stereogenic center, hydrogen bonding is not effective for such homoallylic substrates and the *threo* diastereoselectivity drops dramatically (entry 7); in fact, for the hydroperoxy substituent even a slight preference for the *erythro* diastereomer is expressed (entry 8).

Electron-accepting substituents (X = CO_2Et, CO_2H, NHBoc, $NBoc_2$, Hal, SOPh, SO_2Ph) carry a partial negative charge that disfavors the interaction with the partially negatively charged external oxygen atom in the perepoxide-like exciplex (Scheme 4) due to electrostatic repulsion, particularly in the *threo* TS. Therefore, the attack occurs mainly from the opposite π face and *erythro* selectivity is observed (entries 9–16 in Table 1). Additionally, steric effects between the bulky X group and $^1O_2$ operate, because *erythro* selectivity is also observed for the bulky *tert*-butyl and phenyl substituents (*cf.* entries 17 and 18). These X groups cannot interact electrostatically with the incoming oxygen molecule and, thus, steric repulsion with the incoming $^1O_2$ molecule is the *erythro*-controlling feature.

Our new work addressed the question, whether a substituent at a stereogenic center in homoallylic position is capable of controlling the stereochemical outcome in photooxygenations. As shown in Table 2, the observed diastereoselectivities for such substrates without allylic strain are very low and no definitive trend in the π-facial sense of the attack is expressed; moreover, the regioselectivity is also low. These results show once more the importance of a suitable geometry through conformational fixation.

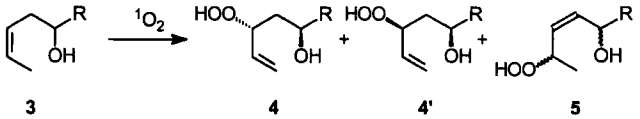
Table 1. Diastereoselectivities in the ene reaction of $^1O_2$ with electron-rich olefins **1***



Entry		X	R	Solvent	Yield (%)	d.r. *threo*-**2**: *erythro*-**2**
Entry						
1†	**1a**	OH	H	CCl_4	73	93:7
2	**1b**	OH	Me	CCl_4	89	93:7
3‡	**1c**	NH_2	Me	CCl_4	87	>95:5
4‡	**1d**	NH_3^+	Me	$CDCl_3$	90	94:6
5	**1b**	OH	Me	CH_3OH	>95	73:27
6‡	**1c**	NH_2	Me	CD_3OD	87	85:15
7	**1e**	OOH	Me	CCl_4	>95	34:66
8	**1f**	CH_2OH	H	CCl_4	79§	55:45
9	**1g**	COOH	H	CCl_4	>95	15:85
10	**1h**	CO_2Et	H	CCl_4	77§	22:78
11‡	**1i**	NHBoc	Me	CCl_4	76	24:76
12‡	**1j**	$NBoc_2$	Me	CCl_4	91§	5:95
13	**1k**	Cl	Me	$CDCl_3$	81	15:85
14	**1l**	Br	Me	$CDCl_3$	78	11:89
15	**1m**	SOPh	Me	$CDCl_3$	94	15:85
16‖	**1n**	SO_2Ph	Me	$CDCl_3$	87§	<5:95
17	**1o**	Ph	Me	Acetone	72§	18:82
18¶	**1p**	*t*Bu	Me	CCl_4	88§	29:71

*Unless otherwise stated, photooxygenations were carried out at −25°C, in CCl_4 and $CDCl_3$ TPP was used as sensitizer, in methanol rose bengal was used.
†0°C.
‡−20°C.
§Yield of isolated product.
‖Photooxygenation was carried out on a 1:1 mixture of the diastereomeric sulfoxides.
¶Kropf and Reichwaldt (24).

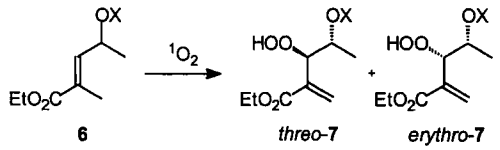
Table 2. Diastereoselectivities in the photooxygenation reactions of homoallylic alcohols **3***



Entry	R		Diastereoselectivity **4**:**4'**	Regioselectivity **4**:**5**
1	Me	**3a**	56 (*l*):44 (*u*)	56:44
2	Et	**3b**	44 (*l*):56 (*u*)	51:49
3	*t*Bu	**3c**	49 (*u*):51 (*l*)	58:42
4	Ph	**3d**	45 (*u*):55 (*l*)	63:37

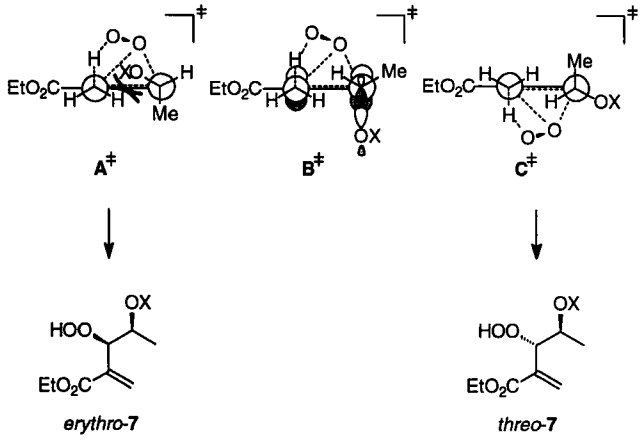
*These results have not been published before.

Table 3. Diastereoselectivities in the ene reaction of $^1O_2$ with electron-poor olefins **6***



Entry		X	Solvent	T (°C)	Yield (%)	*threo*-7 : *erythro*-7
1*	**6a**	H	CCl_4	−5	>95	84:16
2†	**6a**	H	CD_3OD	−7	61	86:14
3*	**6b**	CH_2Ph	CCl_4	−10	85	83:17
4*	**6c**	$SiMe_2tBu$	CCl_4	−5	>95	93:7
5*	**6d**	$Si(iPr)_3$	CCl_4	0	>95	>95:5

*Tetraphenylporphine as sensitizer.
†Methylene blue as sensitizer.



Scheme 5.

Electron-poor alkenes

For electron-poor substrates, *e.g.* α,β-unsaturated esters, exciplex formation is reversible in the ene reaction. The π-facial selectivity is controlled by the second TS (TS2 in Fig. 1), in which abstraction of the less polarized hydrogen atom determines the rate and, therefore, the diastereoselectivity. As a consequence of the lower polarization of the TS2, hydrogen bonding plays a less important role as evidenced by the lack of a solvent effect on the diastereoselectivity in the protic methanol (entries 1 and 2 in Table 3) for the photooxygenation of the allylic alcohol **6a** (25). More convincing that hydrogen bonding does not operate is that capping of the hydroxy functionality by silyl or alkyl groups even increases the *threo* preference (entries 3–5).

These results are understood in terms of Houk's stereoelectronic model (26,27) that is illustrated in Scheme 5 by means of the three possible TS conformers **A‡**, **B‡** and **C‡** for the hydrogen abstraction in the ene reaction of the unsaturated ester **6**. In TS **A‡** there is steric repulsion between the OX substituent and the methyl group on account of 1,3-allylic strain, which destabilizes this conformation. Still worse for stereoelectronic reasons is the conformation in the transition-state conformer **B‡**, because of the unfavorable interaction of the π orbital of the double bond and the σ* orbital of the C–X bond that withdraws electron density from the already electron-poor π system. Thus, the reaction proceeds mainly through TS **C‡** that leads to the *threo* diastereomer. The increase in *threo* selectivity in the order X = H ≈ CH_2Ph < $SiMe_2tBu$ < $Si(iPr)_3$ (*cf.* entries 3–5 in Table 3) is caused by the larger 1,3-allylic strain in that order for TS **A‡**. The repulsive interaction becomes more severe as the size of OX increases and in the case of the $OSi(iPr)_3$ substituent the steric effect is strong enough to suppress this reaction channel completely.

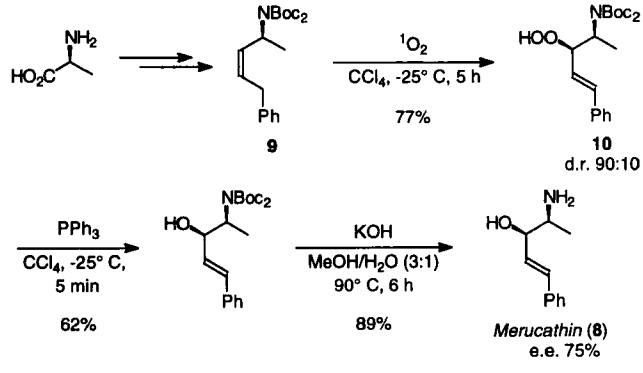
Synthetic applications

The high diastereoselectivity found for the ene reaction of $^1O_2$ with chiral acyclic olefins has been utilized in the stereoselective synthesis of natural products, namely Merucathin (28) and Isodihydromahubanolide B (25). For the synthesis of Merucathin (**8**), the protected phenyl-substituted amino alcohol **9** (Scheme 6) was prepared by starting from L-alanine. The photooxygenation of **9** yielded diastereoselectively (diastereomeric ratio [d.r.] = 90:10) the *erythro*/*E*-**10** hydroperoxide that was reduced and deprotected to give Merucathin (**8**) in 75% enantiomeric excess (overall yield over eight steps was ~20%).

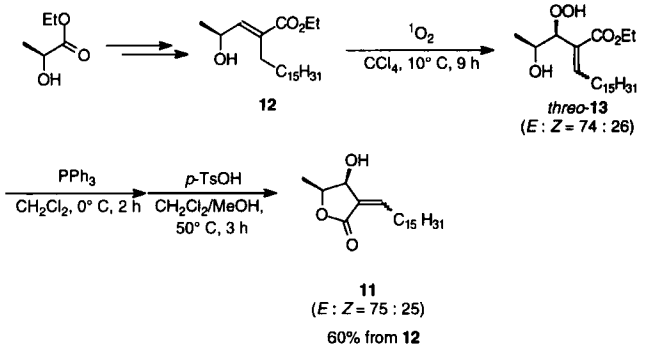
Similarly, the diastereoselectivity in the photooxygenation of electron-poor alkenes has been exploited in the synthesis of enantiomerically pure Isodihydromahubanolide B (*E*-**11**) and Dihydromahubanolide B (*Z*-**11**). The synthesis started with ethyl (*S*)-lactate that was converted into the allylic alcohol **12** in three steps (Scheme 7). The reaction of **12** with $^1O_2$ gave a mixture of the *threo* hydroperoxides **13** (*E*-**13** : *Z*-**13** = 74:26); reduction and acid-catalyzed cyclization yielded the naturally occuring *E* and *Z* lactones **11** in enantiomerically pure form.

Stereoselective directing effects in the [4+2]- and [2+2]-cycloaddition modes

Although the diastereoselectivity of singlet-oxygen reactions has been studied most extensively for the Schenck ene reaction, similar observations were also made for the other reaction modes. The diastereoselectivity in the [4+2] cycloaddition was determined for the chiral naphthylenic alcohols **14** (Scheme 8) (29). In these substrates exists a steric interaction between the substituents on the stereogenic center and



Scheme 6.

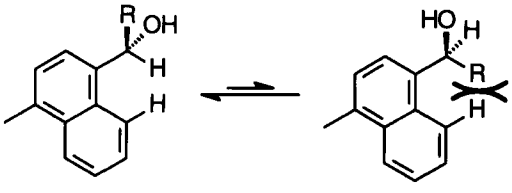


Scheme 7.

the *peri* hydrogen, similar to the 1,3-allylic strain. This *peri* strain aligns the hydroxy group in a position that is favorable for hydrogen bonding with the attacking $^1O_2$ and, thus, a preference for the like diastereomer is expressed during the formation of the endoperoxides **15**. Table 4 summarizes the observed selectivities in these [4+2] cycloaddition of $^1O_2$. As in the case of the ene reaction of chiral allylic alcohols, the diastereoselectivity is higher in the unpolar $CDCl_3$ solvent (entries 1, 3 and 4) than in the protic methanol. This is due to the disturbance of the intramolecular hydrogen bonding with the hydroxy group at the chirality center (entry 2) through competitive intermolecular hydrogen bonding with the solvent.

Recently, also the hydroxy-group-directed diastereoselectivity has been tested in the [2+2] cycloaddition mode by using the adamantylidene-substituted chiral allylic alcohol **16** (30). As shown in Table 5, the *threo*-**17** dioxetane was only formed in the photooxygenation of **16** in $CDCl_3$, whereas the diastereoselectivity drops in the more polar methanol/CCl_4 mixture. Again, the experimental results imply that the reaction proceeds through a hydrogen-bonded TS, conditioned conformationally through 1,3-allylic strain.

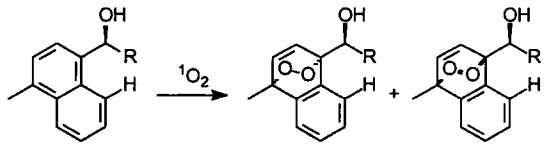
The parallelism of the stereochemical results in all three reaction modes of $^1O_2$ makes a hydrogen-bonded intermediate very likely for diastereomeric control (30,31). This intermediate is thought to be an exciplex in all cases, *i.e.* a complex between the olefin and $^1O_2$ with significant charge transfer from the π system to the oxygen. Thus, the oxygen molecule bears a partial negative charge and acts, therefore, as an acceptor for hydrogen bonding with a geometrically favorable allylic or naphthylenic hydroxy substituent. Effective hydrogen bonding lowers the energy already in the preceding TS (Scheme 9) and, thus, high diasteroselectivities result, but π-facial discrimination must be conditioned through some sterically promoted conformational bias.



14

Scheme 8.

Table 4. Diastereoselectivities in the [4+2] cycloaddition of $^1O_2$ with chiral naphthylenic alcohols **14***



14 *like*-**15** *unlike*-**15**

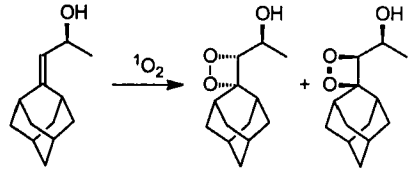
Entry		R	Solvent	Yield (%)	d.r. *like*-**15** : *unlike*-**15**
1	**14a**	Me	$CDCl_3$	>95	85:15
2	**14a**	Me	CD_3OD	95	55:45
3	**14b**	Et	$CDCl_3$	>95	88:12
4	**14c**	*t*Bu	$CDCl_3$	30†	87:13

*Photooxygenations were carried out at −35°C (entries 1–3) or −30°C (entry 4), and TPP was used as sensitizer except in entry 2, where rose bengal was used.
†Low yield due to low conversion (30%).

CONCLUSIONS

The present results demonstrate that the diastereoselectivity in the oxyfunctionalization of chiral acyclic alkenes may be controlled for $^1O_2$, if conformational fixation to provide π-facial discrimination is achieved (for example, by allylic or *peri* strain). Once this requisite is fulfilled, in the ene reaction mode, the sense (*threo versus erythro*) of the selectivity is determined by the electronic properties of the double bond: For electron-rich substrates, the photooxygenation is *threo*-selective if hydrogen bonding operates and *erythro*-selective if the allylic substituent exercises electrostatic and/or steric repulsion, whereas electron-poor olefins also yield the *threo* hydroperoxides predominantly, but Houk's stereoelectronic effect operates. Diastereoselective photooxygenations may be utilized as the key step of oxyfunctionalization in the synthesis of naturally occurring compounds, as illustrated in the efficient and convenient stereoselective

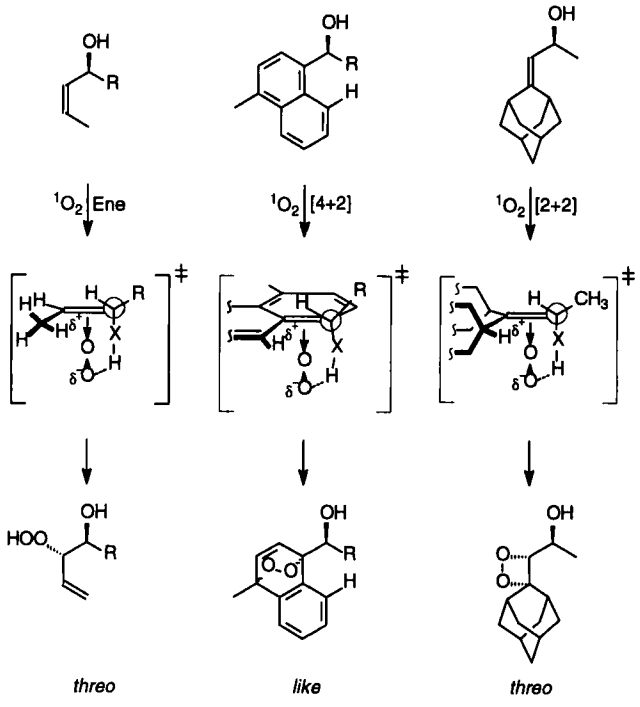
Table 5. Diastereoselectivities in the [2+2] cycloaddition of $^1O_2$ with the chiral allylic alcohol **16***



16 *threo*-**17** *erythro*-**17**

Entry	Solvent	Yield (%)	d.r. *threo*-**17** : *erythro*-**17**
1*	$CDCl_3$	47†	>95:5
2*	CD_3OD/CCl_4 (7:2)	>95	89:11

*Photooxygenations were performed with tetrakis(pentafluorophenyl)porphine as sensitizer.
†The ene product was also observed.



Scheme 9.

preparation of Merucathin and Isodihydromahubanolide B. Also the [4+2]- and [2+2]-cycloaddition modes of $^1O_2$ are subject to such hydroxy-directed stereocontrol, as long as conformation bias is provided through appropriate steric interaction, as illustrated in the photooxygenation of chiral naphthylenic (*peri* strain) and adamantylidene-substituted (1,3-allylic strain) allylic alcohols.

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