SUPPORTING INFORMATION

Cholesterol-Diaryl ketone Stereoisomeric Dyads as Models for "Clean" Type I and Type II Photooxygenation Mechanisms

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(*R*)-2-(3-Benzoylphenyl)propionic acid, (*R*)-KP.

A mixture of (±)-ketoprofen, (1.5 g, 5.91 mmol) and PCl_5 (1.35 g, 6.50 mmol, 1.2 eq) in CCl_4 (9 mL) was heated at 40º C with magnetic stirring for 30 min. Evaporation of the volatile products under reduced pressure gave the corresponding acid chloride (1.60 g, 99%) as a brownish solid.[1] To a solution of (*R*)-3-hydroxy-1-phenyl-4,4-dimethylpirrolidin-2-one (1.10 g, 5.37 mmol) in anhydrous CH_2Cl_2 (18 mL), a solution of the above acid chloride (1.60 g, 5.87 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (18 mL) and a solution of anhydrous triethylamine (1.81 mL, 1.32 g, 13.0 mmol, 2.4 equiv) in anhydrous CH_2Cl_2 (52 mL) were successively added and the mixture was stirred at 0 ºC for 3 h. All of the above solutions were previously dried by stirring with 3 Å molecular sieves (3–4 g/mL) for 45 min. The reaction mixture was washed with 1 N HCl (2×30 mL) and saturated aqueous solution of $NaHCO_3$ (2×30 mL). The organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to give a brown oily residue (2.58 g). Column chromatography of this residue (eluent: hexane/diethyl ether mixtures) gave a diastereomeric mixture of (3*R*)-1-phenyl-4,4-dimethyl-2-oxopirrolidin-3-yl (α*R*)-2-(3-benzoylphenyl)propionate, **(7),** and its isomer α*S*,3*R*. (1.79 g, 73%, dr = 95/5, by ^{1}H-NMR), as a brown oil. This product was subjected to a new column chromatography (eluent: hexane/diethyl ether 60:40) obtaining in order of elution the following fractions: (i) (α*R*,3*R*)-**7** (0.64 g, 24%), colorless foam, >98/2 dr, (ii) mixture of (α*R*,3*R*)- and (α*S*,3*R*)-**7**, 0.46 g, colorless oil, 95/5 dr, (iii) mixture of (α*R*,3*R*)- and (α*S*,3*R*)-**7**, 0.52 g, colorless oil, 82/18 dr. R_f = 0.23 (silica gel, 8 cm, hexane/diethyl ether 3:2). The ^{1}H and ^{13}C NMR data of (α*R*,3*R*)-**7** coincide with those of its enantiomer.[1] Elemental analysis: calcd for $C_{28}H_{27}NO_4$ (441.53): C 76.17, H 6.16, N 3.17. Found: C 76.11, H 6.38, N 3.10. A suspension of (α*R*,3*R*)-**7** (558 mg, 1.27 mmol, >98/2 dr) in a mixture of acetic acid and 2 N HCl in the ratio of 2.5:1 (14 mL) was heated to 120 ºC for 2.5 h. The solution was concentrated in vacuo, water (10 mL) was added to the residue and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were treated with cyclohexylamine (0.14 mL, 121 mg, 1.27 mmol) and were concentrated in vacuo. The solid residue was extracted with diethyl ether (10 mL) to remove the chiral auxiliary, and the solid salt was

collected by filtration in vacuo. The filtrate was concentrated to give the chiral auxiliary (250 mg, 96%, >99% ee, by chiral HPLC) as a white solid. The precipitated salt was dissolved in 1 N HCl (5 mL) and the aqueous solution was extracted with diethyl ether (3×10 mL). The combined organic layers were washed with water (2×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **(*R*)-KP**, (201 mg, 63% yield, >99% ee, by chiral HPLC) as a white solid, whose spectroscopic data coincide with those described for its enantiomer.[1] R_f = 0.09 (silica gel, 8 cm, hexane / AcOEt 1:1); HPLC: Chiralcel OD-H, hexane / isopropanol / trifluoroacetic acid in the ratio of 99:1:0.1, flow: 0.8 mL/min; rt 32.68 min.[1]

[1] Camps, P.; Giménez, S. *Tetrahedron: Asymmetry* **1995**, *6*, 991-1000.

α-Cholesterol (α-Ch).

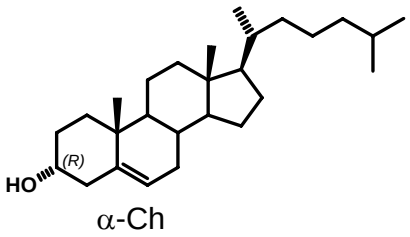
To a cold (0ºC) solution of β-cholesterol (1.00 g, 2.59 mmol), in THF (33 mL), triphenyl phosphine (748 mg, 2.85 mmol, 1.1 eq), chloroacetic acid (269 mg, 2.85 mmol, 1.1 eq) and diethyl azodicarboxylate (0.55 mL, 0.57 g, 2.85 mmol, 1.1 eq) were added and the mixture was stirred at room temperature for 16 h. The solvent was removed by distillation under reduced pressure and the residue was subjected to column chromatography (eluent: hexane/diethyl ether 95:5) to give a yellowish semisolid residue (500 mg). Crystallization of the above residue (900 mg, from two runs) from isopropanol (4 mL) gave a beige solid (680 mg), which was used as such in the next step. A mixture of the above crystallized product (667 mg, 1.44 mmol), MeOH (15 mL) and K_2CO_3 (218 mg, 1.58 mmol, 1.1 eq) was heated under reflux for 1 h. The solvent was distilled under reduced pressure, water (10 mL) was added to the residue and the mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a residue (649 mg) containing mainly α-cholesterol and a small amount of β-cholesterol. Column chromatography of this residue (eluent: hexane/diethyl ether 1:1) gave **α-Ch** (398 mg, 20% global yield) as a beige solid, whose ^1H and ^{13}C NMR data coincide with those described.[2] TLC (silica gel, 8 cm, hexane /diethyl ether 50:50): β-cholesterol: R_f 0.27; α-cholesterol: R_f 0.41

[2] Yan, J.; Bittman, R. *J. Lipid Res.* **1990**, *31*, 160-162.

Steady-state photolysis of dyad 1 under aerobic conditions.

A dichloromethane (12 mL) solution of (*S*)-KP-α-Ch (58 mg, 0.09 mmol) was irradiated under oxygen, through Pyrex, with a 400 W medium pressure mercury lamp. The reaction was monitored by TLC. After 4 hours, the reaction mixture was concentrated under reduced pressure and submitted to silica gel column chromatography, using hexane/ethyl acetate/dichloromethane (90:5:5 v/v/v) as eluent. This afforded in addition to **8** and **9**, the 7-oxo derivative of (*S*)-KP-α-Ch as yellow oil (15 mg, 26%). Selected NMR signals: ^{1}H NMR (300 MHz, $CDCl_3$) δ =5.59 (olefinic C<u>H</u>-6), 5.11(C<u>H</u>-3), 3.78 (C<u>H</u>-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ =201.2 (C=O aliphatic ketone), 196.6 (C=O aromatic ketone), 173.6 (C=O ester), 164.1 (olefinic C-6), 70.6 (C-3); HRMS (FAB) $C_{43}H_{57}O_4$ m/z calcd: 637.42424 [M+1]; found 637.42568.

(CDCl$_3$, 300 MHz)



α-Ch

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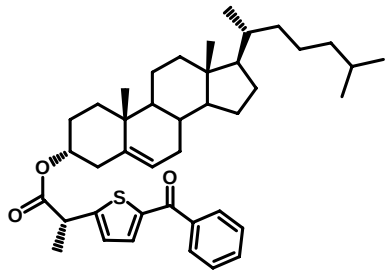

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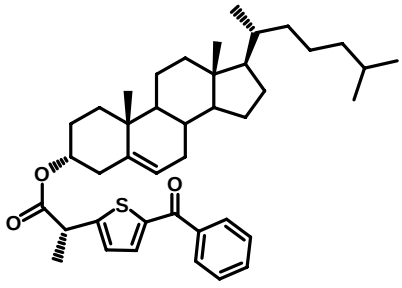

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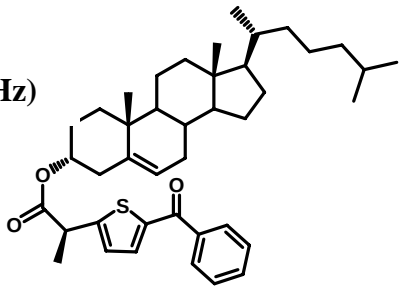
(CDCl$_3$, 75 MHz)

(CDCl$_3$, 300 MHz)



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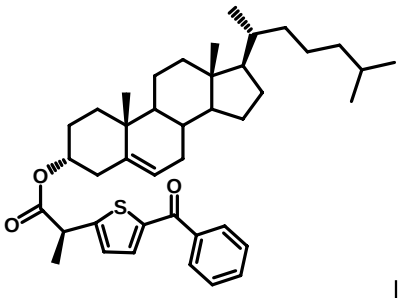

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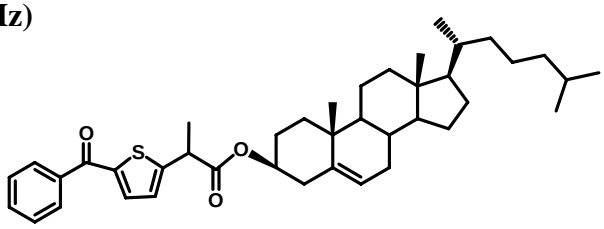

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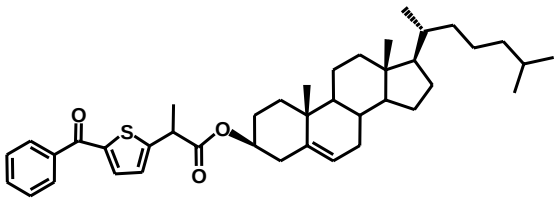
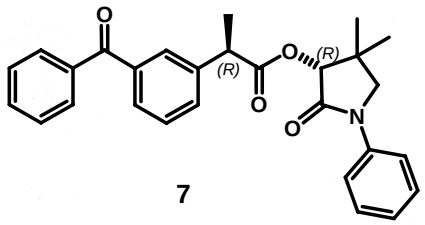


(CDCl₃, 75 MHz)

TPA-β-Ch (6)

(CDCl₃, 300 MHz)



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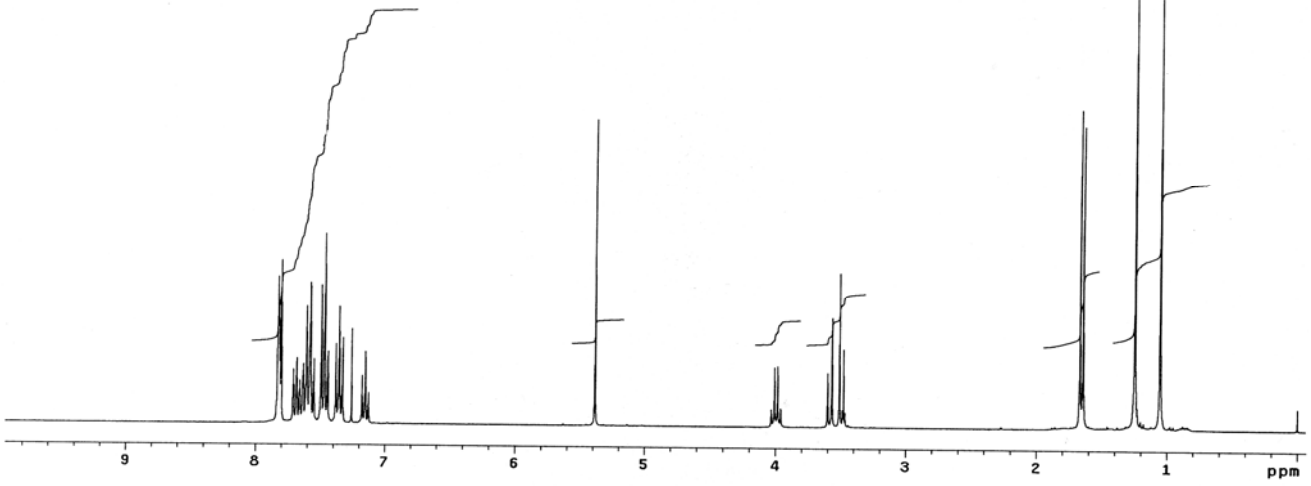

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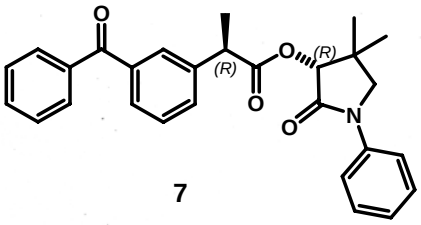

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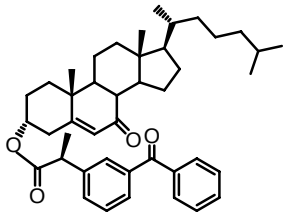
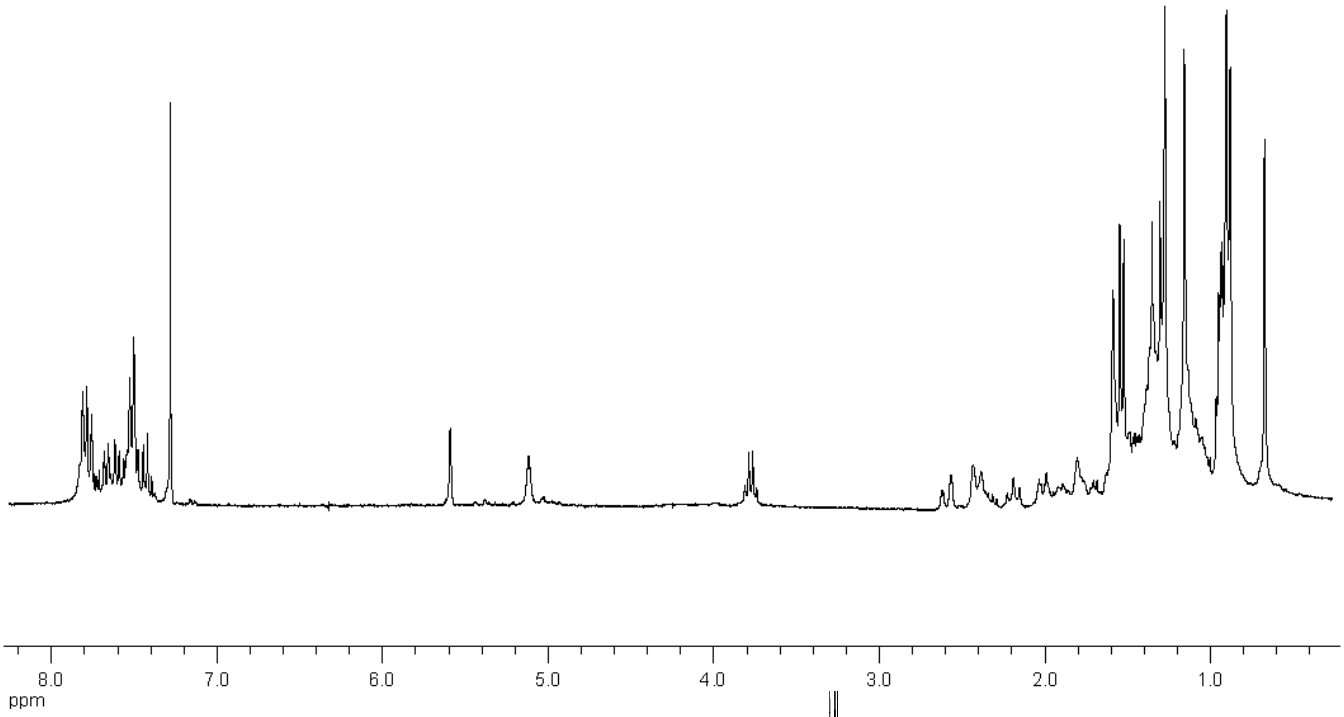
($CDCl_3$, 300MHz)





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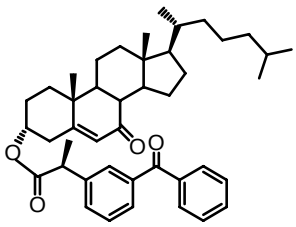
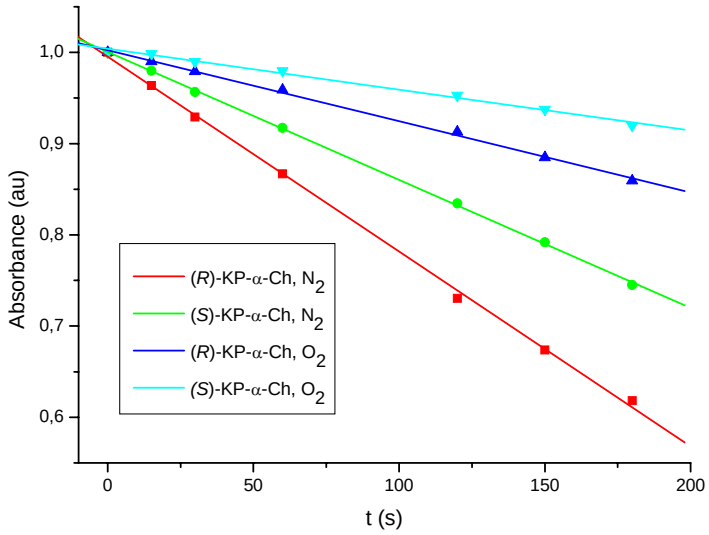
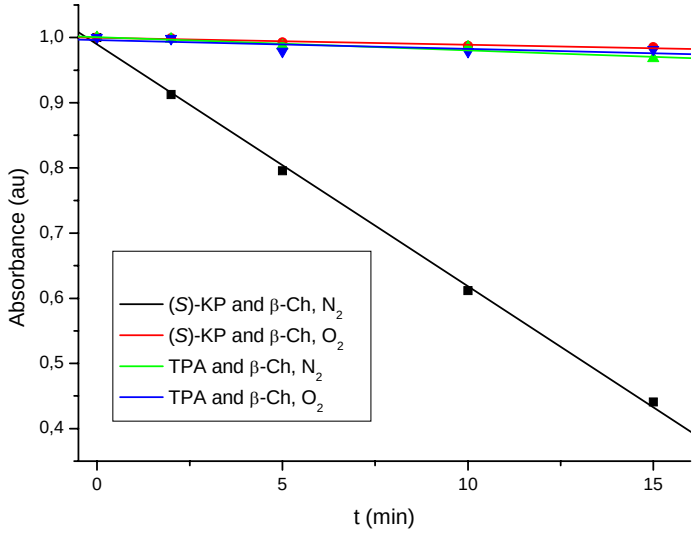
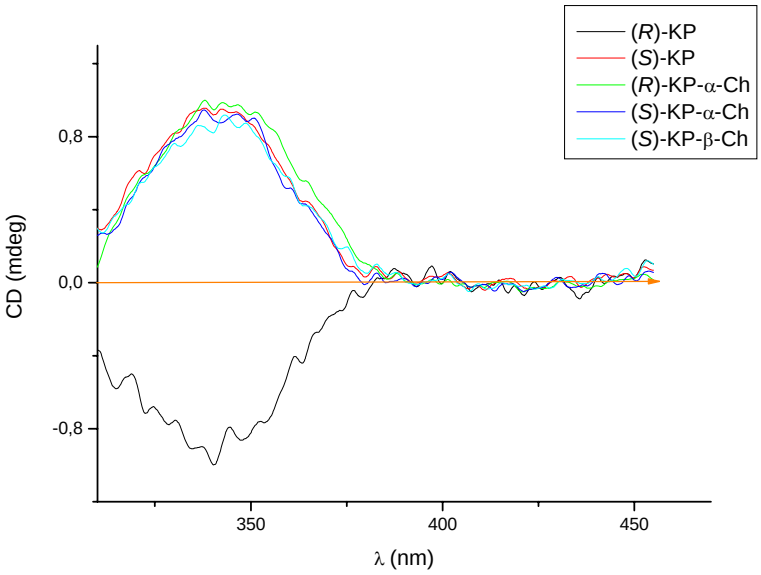




Irradiation of dyads **1** and **2** (ca. 10^{-5} M in dichloromethane solution), at λ_{max}= 350 nm (Gaussian distribution) with a multilamp photoreactor, both under anaerobic and aerobic conditions. The progress of the reaction was monitored by UV-spectrophotometry, following the disappearance of the benzophenone absorption band at 254 nm.



Irradiation of (S)-KP and racemic TPA in the presence of equimolar amounts of β-Ch (ca. 10^{-5} M in dichloromethane solution), at λ_{max}= 350 nm (Gaussian distribution) with a multilamp photoreactor, both under anaerobic and aerobic conditions. The progress of the reaction was monitored by UV-spectrophotometry, following the disappearance of the decrease of absorbance at 254 nm (KP) or 301 nm (TPA).



Circular dichroism (CD) spectra of (*S*)- and (*R*)-KP, as well as dyads **1-3**, in dichloromethane solution (ca. 2 x 10^{-4} M).