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Diastereoselective synthesis of 3-hydroxy-3-phenyl-cyclobutanoic derivatives by photocyclization

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Abstract

Irradiation of 2-substituted 4-oxo-4-phenyl-butanoic amide **1a** and esters **1b–f** affords the corresponding cyclobutanols **4**, **5** and **6**. The diastereoselectivity of photocyclization depends on carboxyl and γ-substituents. In the case of pyrrolidide **10** products **13** and **14** which are formed via a competitive ε-hydrogen transfer are obtained along with **2**, **11** and **12** which are the result of γ-hydrogen abstraction. The relative configurations of the photoproducts **4–6** and **12–14** are established by NMR and X-ray analysis. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Photocyclization; Cyclobutanols; Competitive γ-; ε-Hydrogen abstraction

1. Introduction

During our study of the synthesis of unnatural amino acids via a selective photochemical key step, we became interested in investigating the diastereoselectivity of photocyclizations. Alkyl aryl ketones play an important role in our research because they afford after irradiation triplet states with ISC quantum yields nearly unity. Due to the six-membered triplet transition state γ-hydrogen transfer is the main chemical deactivation process. The photoreaction of excited alkyl aryl ketones with hydrogen atoms in γ-position has been extensively studied [1,2]. Products of Norrish type II reactions (cyclization and cleavage) are observed as a result of γ-hydrogen abstraction from the triplet excited keto carbonyl group (see Scheme 1).

The ratio of cyclization to cleavage is decisively influenced by substituents and solvent. The cyclization of alkyl aryl ketones is preferred over cleavage in the case of α, α-dialkyl derivatives, α-fluoroketones, α-diketones, β-alkoxy-ketones [1] and cyclic ketones [4,5], but the cleavage dominates for β-substituted butyrophenones [3,6,7]. Now we wish to report the first example of β-substituted butyrophenones, which yield cyclobutanols after irradiation.

The photolysis of alkyl aryl ketones, bearing a δ- as well as a γ-hydrogen atom, usually provides a 20 : 1 mixture of the corresponding cyclobutanols and cyclopentanols [8]. ε-hydrogen transfer of excited alkyl aryl ketones was previously only observed in the absence of γ- and δ-hydrogen atoms, for example, in the case of 4-oxo-4-phenyl-butanoyl amines [9]. Thus, 2-methyl-4-oxo-4-phenyl-butanoyl pyrrolidine **10** is the first alkyl phenyl ketone, in which the irradiation gives both ε- and γ-hydrogen abstraction reactions.

2. Experimental

2.1. Equipment and methods

TLC: Alumina sheets with silica gel 60 F_{254} (Merck), detection UV light. Flash chromatography (FC): silica gel 40–63 μm (Merck). High-pressure liquid chromatography (HPLC): analytical SIX [NH_2] column (150 × 3.3 mm, 5 μm Laboratorni Pristroje) and analytical Chiralcel OD-column (250 × 4 mm, Daicel), flow 1 ml/min, mobile phase *n*-hexane: 2-propanol = 95 : 5 and 98 : 2, UV detection at 220 and 230 nm. m.p.: Boetius micro melting point apparatus (Wagema), uncorrected. IR: Perkin-Elmer-881, solids as KBr-pastills, oils on NaCl crystals. NMR: Bruker DPX300 (^{1}H 300 MHz, ^{13}C 75.5 MHz) and Bruker AMX600 (^{1}H 600 MHz), internal reference $SiMe_4$ (=0 ppm). EI–MS: Hewlett-Packard 5995 A, 70 eV at 293–593 K. UV: Uvikon 930 (Kontron instruments).

Photochemistry: Preparative irradiations with a 150 W high-pressure mercury-arc lamp (Hanau), analytical irradiations with a 500 W high-pressure mercury-arc lamp

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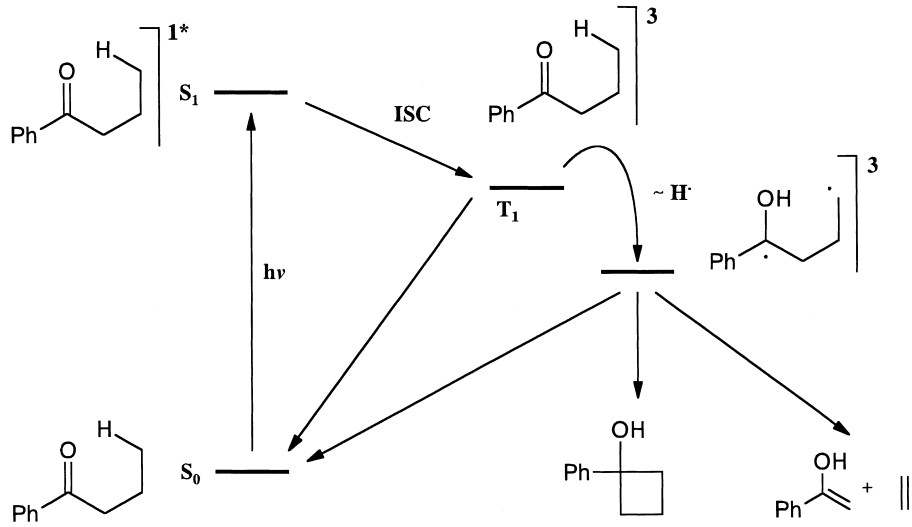


Scheme 1. Photoreaction of butyrophenone.

(OSRAM HBO-500), UV cuvet 1 × 1 cm and filter WG 295 (Schott).

All solvents were distilled and dried. The reagents were of reagent grade and used without further purification. Organic extracts were dried over $MgSO_4$ and evaporated. Most of the described compounds were purified by flash chromatography (FC).

2.2. Reactants

Derivatives **1a–f** and **10** were obtained from the appropriate acids. 2-methyl-4-oxo-4-phenyl-butanoic acid was prepared as described in the literature [10]. 2-Ethyl- and 2-Benzyl-4-oxo-4-phenyl-butanoic acids were obtained according to the reported method [11] unless xylol was used as a solvent for the decarboxylation. 4-oxo-2-isopropyl-4-phenyl-butanoic acid was synthesized in analogy to the described procedure [10] from isopropyl–butanoic anhydride [12,13]. Synthesis via the mixed anhydride afforded dimethylamide **1a** according to literature [14]. Methylesters **1b–f** were obtained after refluxing the corresponding acids in dry methanol with few drops of concentrated sulphuric acid.

*2-methyl-4-oxo-4-phenyl-butanoyl dimethylamine (***1a**): 43%; m.p. 57°C–59°C; IR (KBr): 1681, and 1642; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.00$–7.41 (m 5 H, Ph), 3.67 (dd, $J = 8.8$ and 17.8 Hz, 1 H, 3-H_A), 3.47–3.40 (m, $J = 4.0$, 8.8 and 7.0 Hz, 1 H, 2-H), 3.19 (s, 3 H, N–CH_3), 2.96 (s, 3 H, N–CH_3), 2.90 (dd, $J = 4.0$ and 17.8 Hz, 1 H, 3-H_B), 1.21 (d, $J = 7.0$ Hz, 3 H, 2-CH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 199.1$ (CO), 175.7 (CO–N), 136.6/133.0/128.4/128.0 (Ph), 42.9 (3-C), 37.2 (CH_3–N), 35.7 (CH_3–N), 31.2 (2-C), 17.4 (3-CH_3); EI–MS (70 eV): *m/z* (%) = 219 (M^+, 1), 175 (15), 114 (26), 77 (52), 72 (37); UV/VIS (MeCN): λ_{max} (lg ε) = 240.0 (4.12), 277.5 (3.03), and 317 (sh).

*Methyl, 2-methyl-4-oxo-4-phenyl-butanoate (***1b**) [15]: 65%; IR (NaCl): 1736, 1687, and 1215; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.98$–7.44 (m, 5 H, Ph), 3.70 (s, 3 H CH_3–O–CO), 3.49 (dd, $J = 7.4$ and 16.9 Hz, 1 H, 3-H_A), 3.17–3.11 (m, $J = 5.1$, and 6.6 Hz, 1 H, 2-H) 3.03 (dd, $J = 5.1$ and 16.9 Hz, 1 H, 3-H_B), 1.28 (d, $J = 6.6$ Hz, 3 H, 2-CH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 198.0$ (CO), 176.4 (CO–O), 136.6/133.2/128.7/128.1 (Ph), 51.9 (CH_3–O–CO), 41.9 (3-C), 34.8 (2-C), 17.2 (2-CH_3); EI–MS (70 eV): *m/z* (%) = 206 (M^+, 1), 146 (8), 120 (3), 105 (100), 77 (49), and 51 (23).

*Benzyl, 2-methyl-4-oxo-4-phenyl-butanoate (***1c**): 282 mg (10.4 mmol) KO*t*Bu was added to a stirred solution of 2 g (10.4 mmol) 2-methyl-4-oxo-4-phenyl-butanoic acid [10] in 50 ml abs. EtOH. 0.3 ml (10.4 mmol) Benzyl bromide was added and the solution was refluxed for 7 h. After evaporation the residue was dissolved in CH_2Cl_2, washed with water and saturated $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated again. The pure product was obtained after FC. 801 mg (27%); IR (NaCl): 1734, 1688, 1213, 1165, and 692; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.93$–7.29 (mm 10 H, Ph and Ph–CH_2), 5.18–5.09 (m, 2 H, CH_2–Ph), 3.50 (dd, $J = 8.1$ and 17.7 Hz, 1 H, 3-H_A), 3.23–3.16 (m, $J = 5.2$, 8.1 and 7.4 Hz, 1 H, 2-H), 3.03 (dd, $J = 5.2$ and 17.7 Hz, 1 H, 3-H_B), 1.29 (d, $J = 7.4$ Hz, 3 H, 2-CH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 197.9$ (CO), 175.7 (CO-O), 136.0/136.6/133.1/128.5/128.4/128.0 (Ph and Ph–CH_2, 66.3 (CH_2–Ph), 41.8 (3-C), 34.9 (2-C), 17.2 (CH_3–CH); EI–MS (70 eV): *m/z* (%) = 283 ($M^+ + 1$, 0.1), 175 (21), 148 (19), 120 (11), 105 (100), 91 (62), 77 (67), and 51 (27).

*Methyl 2-ethyl-4-oxo-4-phenyl-butanoate (***1d**) [15]: 85%; IR (NaCl): 2967, 1754, 1686, and 1215; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.98$–7.43 (m, 5 H, Ph), 3.70 (s, 3 H, CH_3–O–CO), 3.52–3.42 (m. 1 H, 2-H), 3.09–2.97 (m, 2 H, 3-H_A and 3-H_B), 1.77–1.65 (m, 2 H, CH_3–CH_2 0.97 (*t*, $J = 7.7$ Hz, 3 H, CH_3–CH_2); ^{13}C-NMR (75.5 MHz, $CDCl_3$):

$\delta = 198.2$ (CO), 175.9 (CO–O), 136.6/133.1/128.4/128.0 (Ph), 51.7 (CH_3–O–CO), 41.6 (2-C), 40.0 (3-C). 25.2 (CH3–CH_2); 11.6 (CH_3–CH_2)EI–MS (70 eV): *m/z* (%) = 220 (M^+, 1), 120 (45), 105 (100), 77 (49), and 51 (19).

*Methyl 2-benzyl-4-oxo-4-butanoate (***1e**) [16]: 91%; m.p. 59°C–60°C; IR (KBr): 1737, 1677, 1215, 1165, 760, and 703; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.91$–7.18 (m, 10 H, Ph and Ph–CH_2), 3.66 (s, 3 H, CH_3–O–CO), 3.46–3.33 (m, 2 H, 2-H), 3.11 (dd, $J = 5.9$ and 13.2 Hz, 1 H), 3.00 (dd, $J = 3.3$ and 16.6 Hz, 1 H), 2.85 (dd, $J = 8.5$ and 13.2 Hz, 1 H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 198.0$ (CO), 175.2 (CO–O), 138.4/136.4/133.1/128.9/128.5/127.9/126.6 (Ph and Ph–CH_2), 42.1 (2-C), 39.3 (CH_2), 37.7 (CH_2); EI–MS (70 eV): *m/z* (%) = 282 (M^+, 5) 163 (31), 131 (37), 120 (100), 105 (94), 91 (37), 77 (75), and 51 (25); UV/VIS (MeCN): λ_{max} (lg ε) = 241.0 (4.10), 278.0 (2.98), and 310.0 (1.83).

*Methyl 2-isopropyl-4-oxo-4-phenyl-butanoate (***1f**): 86%; m.p. 22°C–24°C; IR (KBr): 2963, 1733, 1687, and 1167; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.59$–7.44 (m, 5 H, Ph), 3.70 (s, 3 H, CH_3–O–CO), 3.61–3.45 (m, 1 H, 2-H) 3.05–2.93 (m, 2 H_A and 3-H_B), 2.07 (m, 1 H, CH_3–CH–CH_3), 1.02 (d, $J = 6.8$ Hz, 3 H, CH_3–CH), 1.00 (d, $J = 6.8$ Hz, 3 H, CH_3–CH); ^{13}C-NMR (75.5 MHz $CDCl_3$): $\delta = 198.6$ (CO), 175.3 (CO–O), 136.8/133.1/128.5/128.0 (Ph), 51.7 (CH_3–O–CO), 46.5 (2-C), 37.5 (3-C), 30.2 (CH_3–CH–CH_3), 20.2/19.9 (CH_3–CH and CH_3–CH); EI–MS (70 eV): *m/z* (%) = 234 (M^+, 0.2), 120 (38), 115 (14), 105 (100), 77 (51), and 51 (23); UV/VIS (MeCN): λ_{max} (lg ε) = 240.0 (4.07), 277.5 (2.95), and 309.0 (1.79).

*2-methyl-4-oxo-4-phenyl-butanoyl pyrrolidine (***10**): 1-(2-bromo-propionyl)-pyrrolidine [17] was prepared by treating 5.40 g (25.0 mmol) 2-bromo-propionyl-chloride with 4.13 ml (50 mmol) pyrrolidine and 3.47 ml (25 mmol) Et_3N in 80 ml CH_2Cl_2 at −20°C. After stirring for 2 h at room temperature the organic layer was washed with water, aqueous HCl and again with water, dried over $MgSO_4$ and evaporated. Purification with FC provides 4.02 g (78%) of 1-(2-bromo-propionyl)-pyrrolidine. Second, 2.73 ml (19.4 mmol) (iPr)$_2$NH was treated with 12.1 ml (19 mmol) BuLi (1.6 M in hexane) in 50 ml THF at −70°C under N_2. After stirring for 20 min 2.3 ml (19.4 mmol) acetophenone was added at this temperature. The solution was stirred for 5 min and then added to 4.00 g (19.4 mmol) 1-(2-bromo-propionyl) pyrrolidine in 80 ml THF at −70°C. The reaction mixture was allowed to warm up to room temperature and was stirred at this temperature for 44 h. After evaporation the residue was treated with water. The water phase was washed with CH_2Cl_2, dried over $MgSO_4$ and evaporated. Purification via FC affords 1.18 g (25%) of **10**. m.p. 72°C–80°C; IR (KBr): 1687, 1636, 1438, and 1210; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.99$–7.42 (m, H, Ph), 3.64 (dd, $J = 9.2$ and 17.7 Hz, 1 H, 3-H_B), 3.54–3.38 (m, 4 H, CH_2–N–CH_2), 3.30–3.19 (m, $J = 4.4$, 9.2 and 7.6 Hz, 1 H, 2-H), 2.94 (dd, $J = 4.4$ and 17.7 Hz, 1 H, 3-H_A), 2.08–1.81 (m, 4 H, CH_2 and CH_2), 1.22 (d, $J = 7.6$ Hz, 3 H, 2-CH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 199.1$ (CO), 174.2 (N–CO), 136.6/133.0/128.4/128.0 (Ph), 46.3 (N–CH_2), 45.7 (N–CH_2) 42.7 (3-C), 33.3 (2-C), 26.0 (CH_2), 24.3 (CH_2), 17.4 (2-CH_3); EI–MS (70 eV): *m/z*(%) = 245 (M^+, 2), 175 (19), 147 (4), 140 (5), 105 (96), 98 (18), 77 (49), 70 (100); UV/VIS (MeCN): λ_{max} (lg ε) = 240.0 (4.08), 277.0 (2.91), and 310.0 (2.01).

*4-oxo-4-phenyl-2-trideuterio-butanoyl pyrrolidine ([D$_3$]−***10**): The reaction of 15 g (103 mmol [D_3]-methyl iodide with 8.27 g (51.7. mmol) diethyl malonoate gave 6.41 g (70%) diethyl trideuteriomethyl-malonoate according to Braendsroem et al. [18]. 6.41 g (36.2 mmol) diethyl trideuteriomethyl-malonoate was treated with 7.24 g (36.2 mmol) phenacyl bromide, [19] affording 5.26 g (40%) diethyl phenacyl-trideuteriomethyl-malonoate. 554 mg (16%) 4-oxo-4-phenyl-2-trideuterio-butanoic acid was prepared by alkaline saponification, followed by decarboxylation [20] of 5.26 g (17.8 mmol) diethyl phenacyl-trideuteriomethyl-malonoate. The reaction of 554 mg (2.84 mmol) 4-oxo-4-phenyl-2-trideuterio-butanoic acid with 0.23 ml (2.84 mmol) pyrrolidine as described in literature [14]. Purification via FC affords 282 mg (40%) of [D_3]−**10**. The ^{1}H- and ^{13}C-NMR data are identical to those described for **10** with the exception of the septett of CD_3 at 16.0 ppm.

2.3. Photoproducts

Solutions with approximately 1 mg reactant/1 ml solvent (except **1e**: 2 mg/1 ml) were rinsed with dry O_2-free argon for 30 min before photolysis. The solutions were irradiated until no reactant was detectable by TLC. Non-isolated yields were determined by analytical HPLC (correlation between peak areas and concentration): acetophenone **2** on a Chiralcel OD-column, the other photoproducts on a SIX [NH_2] column. The analytically pure products or mixtures of two diastereomers were isolated by purification with FC. The irradiation of reactant **10** was carried out in CH_2Cl_2 and *t*-butanol. Compound **14** was only isolated after irradiation in *t*-butanol.

*Cis-3-hydroxy-3-phenyl-cyclobutanoyl dimethylamine (***4a**): 52%; m.p. 104°C–106°C; IR (KBr): 3342, 1621, 773, and 709 ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.55$–7.25 (m, 5 H, Ph), 4.62 (s, 1 H, OH), 3.16–3.10 (m, 1 H, 1-H), 3.00 (s, 3 H, N–CH_3), 2.99 (s, 3 H, N–CH_3), 2.90–2.83 (m, 2 H, 2-H_A and 4-H_A), 2.65–2.59 (m, 2 H, 2-H_B and 4-H_B); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 175.7$ (N–CO) 145.4/128.3/127.1/125.0 (Ph), 73.8 (3-C), 40.6 (2-C and 4-C), 37.2 (N–CH_3), 35.9 (N–CH_3), 28.4 (1-C); EI–MS (70 eV): *m/z* (%) = 219 (M^+, 4), 202 (4), 175, (16) 149 (91), 147 (14), 120 (12), 114 (74), 105 (64), 100 (100), 91 (19), 87 (18), 77 (42), 72 (56), and 55 (46).

*Cis-methyl 3-hydroxy-3-phenyl-cyclobutanoate (***4b**) [21]: 48%; IR (NaCl): 3433, 1728, 1247, 1207, and 700; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.52$–7.26 (m, 5 H, Ph), 3.72 (s, 3 H, CH_3–O–CO), 3.25 (s, 1 H, OH), 2.91–2.78 (m, 3 H, 1-H

2-H_A and 4-H_A), 2.69–2.60 (m, 2 H, 2-H_B and 4-H_B); ^{13}C-NMR (75.5 MHz, $CDCl_3$) $\delta = 176.5$ (CO–O), 144.7/128.5/127.5/125.0 (Ph), 73.3 (3-C), 52.0 (CH_3–O–CO), 40.7 (2-C and 4-C), 29.5 (1-C); EI–MS 70 eV): *m/z* (%) = 206 (B^+, 1), 175 (7), 146 (13), 129 (16), 120 (62), 105 (100), 91 (22), 77 (49), and 65 (11).

Cis-benzyl 3-hydroxy-3-phenyl-cyclobutanoate (**4c**): 6%; IR (NaCl): 3433, 1727, 1157, and 698; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.51$–7.25 (m, 10 H, Ph and Ph–Ch_2), 5.16 (s, 2 H CH_2–Ph), 3.16 (s, 1 H, OH), 2.92–2.82 (m, 3 H, 1-H, 2-H_A and 4-H_A), 2.71–2.60 (m, 2 H, 2-H_B and 4-H_B); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 175.8$ (CO–O), 144.6/135.7/128.6/128.5/128.3/127.5/125.0 (Ph and Ph–CH_2), 73.7 (3-C), 66.7 (CH_2–Ph), 40.7 (2-C and 4-C), 29.7 (1-C); EI–MS (70 eV): *m/z* (%) = 191 (12), 120 (52), 105 (64), 91 (100), 77 (31), and 65 (13).

Trans-benzyl 3-hydroxy-3-phenyl-cyclobutanoate (**6c**): 4% (mixture of **4c**: **6c** = 2.9 : 1); ^{1}H-NMR (300 MHz, $CDCl_3$: $\delta = 7.51$–7.26 (m, 10 H, Ph and Ph–CH_2), 5.11 (s, 2 H, CH_2–Ph), 2.91–2.82 (m, 3 H, 1-H, 2-H_A and 4-H_A), 2.69–2.57 (m, 2 H, 2-H_B and 4-H_B), 2.25 (s, 1 H, OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 175.0$ (CO–O), 144.7/135.9/128.4/128.2/127.4/124.7 (Ph and Ph–CH_2), 75.0 (3-C), 66.3 (CH_2–Ph), 39.4 (2-C and 4-C), 31.7 (1-C).

Methyl (1R, 2R, 3S)-(±)-3-hydroxy-2-methyl-3-phenyl-cyclobutanoate (**4d**): 8%; IR (NaCl): 3448, 2953, 1733, 1705, 1208, 1177, 700; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–7.22 (m, 5 H, Ph), 4.16 (s, 1 H, OH), 3.76 (s, 3 H, CH_3–O–CO), 3.21–3.11 (m, 2 H, 1-H and 2-H), 2.82–2.75 (m, 1 H, 4-H_A), 2.50 (dd, $J = 3.3$ and 12.9 Hz, 1 H, 4-H_B), 1.05 (d, $J = 6.6$ Hz, 3 H, 2-CH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 177.6$ (CO–O), 145.1/128.2/127.1/124.8 (Ph), 76.9 (3-C), 52.0 (CH_3–O–CO), 43.7 (2-C), 37.8 (1-C), 37.3 (4-C), 9.8 (2-CH_3); EI–MS) (70 eV): *m/z* (%) = 282 (M^+, 0), 220 (1), 160 (7), 133 (30), 131 (12), 120 (94), 115 (10), 105 (100), 101 (11), 91 (19), 77 (71), 69 (22), and 51 (36).

Methyl (1R, 2S, 3S)-(±)-3-hydroxy-2-methyl-3-phenyl-cyclobutanoate (**5d**): 8% (1 : 4 mixture of **6d** and **5d**); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.19 (m, 5 H, Ph), 3.64 (s, 3 H, CH_3–O–CO), 2.95–2.87 (m, 1 H, 4-H_A), 2.79–2.73 (m, 1 H, 2-H), 2.47–2.40 (m, 1 H, 4-H_B), 2.36–2.27 (m, 1 H, 1-H), 0.59 (d, $J = 6.6$ Hz, 3 H, 2-CH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 175.4$ (CO–O), 141.3/128.2/125.9/124.7 (Ph), 75.7 (3-C), 51.9 (CH_3–O–CO), 48.6 (2-C), 37.2 (1-C), 37.5 (4-C), and 15.5 (2-CH_3).

Methyl (1R, 2S, 3R)-(±)-3-hydroxy-2-methyl-3-phenyl-cyclobutanoate (**6d**): 2% (1 : 1.8 mixture of **6d** and **4d**); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–7.23 (m, 5 H, Ph), 4.13 (s, 1 H, OH), 3.70 (s, 3 H, CH_3–O–CO), 3.07–2.90 (m, 2 H, 1-H and 2-H), 2.66 (ddd, $J = 0.7$, 8.1 and 12.1 Hz, 1 H, 4-H_A), 2.40 (dd, $J = 8.1$ and 12.1 Hz, 1 H, 4-H_B), 1.22 (d, $J = 6.6$ Hz, 3 H, 2-CH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 175.4$ (CO–O), 145.2/128.5/127.5/124.8 (Ph), 76.1 (3-C), 51.7 (CH_3–O–CO), 44.5 (2-C), 40.2 (1-C), 37.0 (4-C), 12.7 (2-CH_3).

Methyl (1R, 2R, 3S)-(±)-2,3-diphenyl-3-hydroxy-cyclobutanoate (**5e**): 23%; m.p. 130°C–37°C; IR (KBr): 3498, 1705, 1236, and 697; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.19$–6.84 (m, 12 H, Ph and Ph–CH), 4.11 (d, $J = 2.0$ Hz, 1 H, 2-H), 3.69 (s, 3 H, CH_3–O–CO), 3.21–3.04 (m, 2 H, 1-H and 4-H_A), 2.67 (dd, $J = 9.6$ and 11.0 Hz, 1 H, 4-H_B), 1.94 (s, 1 H, OH) ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 174.7$ (CO–O), 140.4/137.2/128.7/128.1/127.8/127.7/127.5/127.3/126.5/126.1 (Ph and Ph–CH), 77.6 (3-C), 52.1 (CH_3–O–CO), 37.6 (4-C), 33.7 (1-C); EI–MS (70 eV): *m/z* (%) = 282 (M^+, 1), 163 (26), 131 (52), 120 (100), 115 (10), 103 (16), 91 (16), 77 (45), and 51 (15).

Methyl (1R, 2R, 3R)-(±)-2,3-diphenyl-3-hydroxy-cyclobutanoate (**6e**): 5%, IR NaCl): 3475, 1729, and 699; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.82$–7.20 (m, 10 H, Ph and Ph–CH), 4.23 (d, $J = 10.0$ Hz, 1 H, 2-H), 3.87–3.74 (m, 1 H, 1-H), 3.71 (s, 3 H, CH_3–O–CO), 2.77 (dd, $J = 9.6$ and 11.8 Hz, 1 H, 4- H_A), 2.52 (dd, $J = 8.8$ and 11.8 Hz, 1 H, 4-H_B), 1.89 (s, 1 H, OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 175.0$ (CO–O), 145.3/136.0/129.8/128.8/128.5/128.1/127.5/127.4/125.0 (Ph and Ph–CH), 53.9 (2-C), 52.0 (CH_3–O–CO), 37.5 (4-C), 37.3 (1-C); EI–MS (70 eV): *m/z* (%) = 282 (M^+, 0.4), 149 (16), 131 (12), 120 (27), 115 (12), 105 (100), 91 (17), 77 (63), and 51 (21).

Cis-methyl 2,2-dimethyl-3-hydroxy-3-phenyl-cyclobutanoate (**4f**): 10%; IR (NaCl); 3486, 1733, and 1198, ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.24 (m, 5 H, Ph), 3.75 (s, 3 H, CH_3–O–CO), 3.45 (s, 1 H, OH), 3.01 (ddd, $J = 4.4$, 8.3 and 13.2 Hz, 1 H, 4-H_A), 2.70 (ddd, $J = 4.4$, 6.5 and 8.3 Hz, 1 H, 1-H), 2.48 (ddd, $J = 4.4$, 6.5 and 13.2 Hz, 1 H, 4-H_B), 1.78 (d, $J = 4.4$ Hz, 3 H, CH_3), 0.78 (d, $J = 4.4$ Hz, 3 H, CH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 175.9$ (CO–O), 142.4/128.1/127.3/125.8 (Ph), 78.6 (3-C), 51.8 (CH_3–O–CO), 48.6 (2-C), 43.7 (1-C), 33.0 (4-C), 27.2 (CH_3), 18.8 (CH_3); EI–MS (70 eV): *m/z* (%) = 234 (M^+, 0.3), 148 (11), 120 (100), 115 (40), 105 (69), 91 (11), 83 (35.8), 78 (35.8), 77 (34), and 55 (19).

Trans-methyl 2,2-dimethyl-3-hydroxy-3-phenyl-cyclobutanoate (**6f**): 6% (1 : 1.6 mixture of **6f** and **4f**); ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.23 (m, 5 H, Ph), 3.69 (s, 3 H, CH_3–O–CO), 3.25 (ddd, $J = 5.3$, 7.9 and 10.2 Hz, 1 H, 1-H), 3.09 (ddd, $J = 5.3$, 10.2 and 12.1 Hz, 1 H, 4-H_A), 2.07 (ddd, $J = 5.3$, 7.9 and 12.1 Hz, 2 H, 4-H_B and OH), 1.38 (d, $J = 5.3$ Hz 3 H, CH_3), 0.65 (d, $J = 5.3$ Hz, 3 H CH_3); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 173.9$ (CO–O), 142.7/128.3/127.6/125.9 (Ph), 79.2 (3-C), 51.3 (CH_3–O–CO), 48.0 (2-C), 43.9 (1-C), 30.7 (4-C), 22.1 (CH_3), 21.5 (CH_3).

Cis-3-hydroxy-3-phenyl-cyclobutanoyl pyrrolidine (**12**): 12%; m.p. 93°C–95°C; IR (KBr): 3392, 1607, and 1441,; ^{1}H-NMR (300 MHz $CDCl_3$): $\delta = 7.56$–7.23 (m, 5 H, Ph), 5.45 (s, 1 H, OH), 3.55–3.39 (m, 4 H, CH_2–N–CH_2), 3.09–3.01 (m, 1 H, 1-H), 2.91–2.83 (m, 2 H, 2-H_A and 4-H_A), 2.67–2.60 (m, 2 H, 2-H_B and 4-H_B), 2.01–1.64 (m, 4 H, CH_2-CH_2); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 174.5$ (CO–N), 145.5/128.1/126.9/124.9 (Ph), 73.9 (3-C), 46.5 (N–

CH_2), 46.3 (N–CH_2), 40.5 (2-C and (4-C), 30.0 (1-C), 25.9 (CH_2), 24.2 (CH_2); EI–MS (70 eV): *m/z* (%) = 245 (M^+, 0.2), 140 (18), 126 (86), 105 (39), 98 (28), 77 (40), 70 (100), and 55 (65).

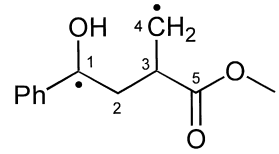
*(8S, 8aR)-(±)-8-hydroxy-6-methyl-8-phenyl-hexahydro-indolizin-5-one (***13**): 14%; m.p. 112°C–15°C IR (KBr): 3380, 1625, 1614, and 1445; ^{1}H-NMR (600 MHz, [D_5]-pyridine): $\delta = 7.82$–7.31 (m, 5 H, Ph) 6.80 (s, 1 H, OH), 3.87 (dd, $J = 6.9$ and 8.1 Hz, 1 H, 8a-H), 3.73–3.62 (m, 2 H, 3-H_A and 3-H_B), 2.77 (m, 1 H, 6-H), 2.74 (dd, $J = 8.9$ and 13.6 Hz, 1 H, 7-H_A), 2.15–2.08 (m, 1 H, 1-H_A), 2.01 (dd, $J = 5.4$ and 13.6 Hz, 1 H, 7-H_B), 1.78–1.70 (m, 1 H, 2-H_A), 1.53–1.41 (m, 2 H, 1-H_B and 2-H_B), 1.49 (d, $J = 6.6$ Hz, 3 H, 6-CH_3); ^{13}C-NMR (75.5 MHz, [D_5]-pyridine): $\delta = 172.4$ (5-CO), 147.7/128.7/127.3/126.1 (Ph), 73.9 (8-C), 66.9 (8a-C), 46.8 (3-C), 46.5 (7-C), 35.2 (6-C), 27.0 (1-C), 23.5 (2-C), 18.7 (6-CH_3); EI–MS (70 eV): *m/z* (%) = 245 (M^+, 2), 125 (7), 105 (16), 97 (19), 77 (17), and 70 (100).

*(6S, 8R, 8aR)-(±)-8-hydroxy-6-methyl-8-phenyl-hexahydro-indolizin-5-one (***14**): 32%; m.p. 107°C-29°C IR (KBr): 3394, 1640, and 1624; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.27$–7.26 (m, 5 H, Ph), 3.88–3.83 (m, 1 H, 8a-CH), 3.42–3.28 (m, 2 H, 3-H_A and 3-H_B), 2.91–2.85 (m, 2 H, OH, 6-H), 2.30 (dd, $J = 7.0$ and 14.7 Hz, 1 H, 7-H_A), 2.20 (dd, $J = 11.7$ and 14.7 Hz, 1 H, 7-H_B), 1.84–1.74 (m, 1 H, 1-H_A), 1.57–1.48 (m, 1 H, 2-H_A), 1.42–1.30 (m, 1 H, 1-H_B), 1.24 (d, $J = 6.8$ Hz, 3 H, 6-CH_3), 1.19–1.12 (m, 1 H, 2-H_B); ^{13}C-NMR (75.5 MHz, $CDCl_3$): $\delta = 173.4$ (5-CO), 145.0/128.2/127.2/125.7 (Ph), 75.6 (8-C), 65.9 (8a-C), 47.2 (7-C), 44.8 (3-C), 34.1 (6-C), 27.7 (1-C), 22.7 (2-C), 14.8 (6-CH_3); EI–MS (70 eV): *m/z* (%) = 245 (M^+, 1), 105 (17), 97 (25), 77 (20), 70 (100), and 69 (9).

2.4. Calculation methods

Semi-empirical calculations were performed using the program MOPAC7 [22], the PM3 hamiltonian [23] and the spin-unrestricted Hartree–Fock method (UHF). Ab initio calculations were performed with the program package Gaussian 94 [24].

The conformational analysis of 1-hydroxy-1-phenyl-3-methoxycarbonyl-butan-1,4-diyl triplet biradical was performed as follows. For each of the three staggered conformations of the 1,4-biradical with respect to the C(2)–C(3)-bond a two dimensional grid was calculated by rotating around the bonds between C(1), C(2) and C(3), C(5) (step size 24°). The method used for this was UHF/PM3. Afterwards the minima seen in a contour plot were fully optimized at the same level of theory. Finally the two *gauche*-conformers with the lowest energy (**A** and **B**) and the *anti*-conformer with the lowest energy (**C**) were optimized by ab initio methods (UHF/3-21 G). The zero point vibrational energies were calculated at this level. More accurate electronic energies were obtained by single point calculations using density functional theory methods (UB3Lyp [25]/6–31 G* [26]). **A**, **B** and **C** were characterized as minima by UHF/3-21 G.



2.5. X-ray crystallographic data

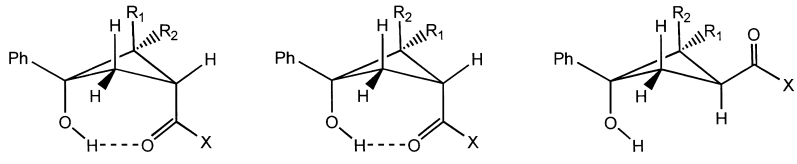
See Table 1.

3. Results

3.1. Norrish type II cleavage versus cyclization

2-Substituted 4-oxo-4-phenyl-butanoic derivatives **1** and **10** can be regarded as β- and γ-disubstituted butyrophenone derivatives. These compounds exhibit UV absorption at ≈310 nm for the n, π^* excitation of the keto carbonyl group. As excepted, amide **1a** and esters **1b–f** undergo γ-hydrogen transfer after irradiation at $\lambda \geq 300$ nm to give the corresponding products **2–6** (Scheme 2). Amazingly, the photocyclization dominates over the Norrish type II cleavage in most cases (Table 2). Dimethyl amide **1a** and methyl ester **1b**, bearing primary γ-hydrogen atoms, afford the highest yields of cyclobutanols **4a** and **4b**, respectively.

Besides, the diastereoselectivity for most irradiations is remarkably high. We obtained mainly products **4** and **5**. The highest diastereoselectivities of photocyclization are observed for the amide **1a** and the methylester **1b**. *Cis*-configuration of the hydroxyl group and the carboxyl substituent is preferred. The relative configuration of the cyclobutanols **4**, **5** and **6** were assigned on the basis of NOE difference spectra.



4 **5** **6**

Commonly, cyclobutanols **9** with the hydroxyl group and the substituent at the 2-position in a *cis*-configuration are obtained [27] Scheme 3. Nevertheless, upon irradiation of

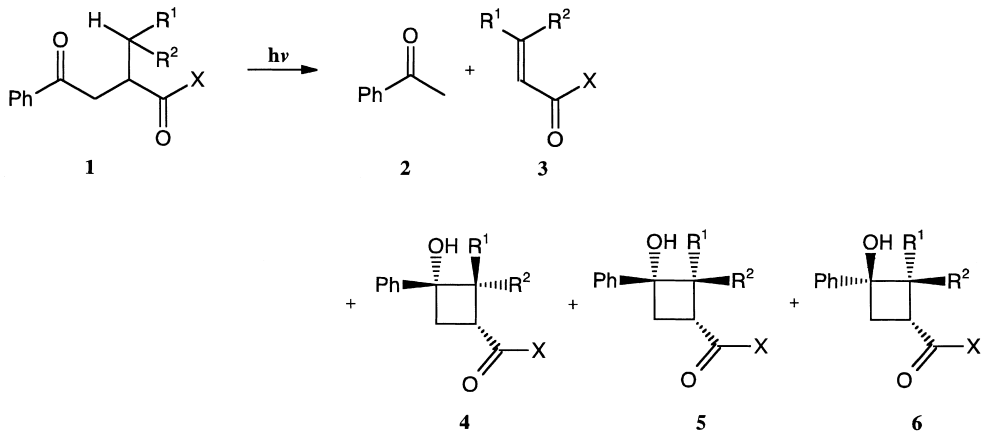
Table 1
Crystal data and structure refinement of *cis*-3-hydroxy-3-phenyl-cyclo-butanoyl pyrrolidine **12** and (6*S*, 8*R*, 8a*S*)-(±)-8-hydroxy-6-methyl-8-phenyl-hexahydro-indolizin-5-one **14**

	12	**14**
CDS number	407 278	407 277
Formula	$C_{15}H_{19}NO_2$	$C_{15}H_{19}NO_2$
Temperature (K)	293 (2)	293 (2)
Wavelength (Å)	0.71069	0.71069
Crystal system	Monoclinic	Monoclinic
Space group	*P*	*P* $2_1/n$
a (Å)	10.420 (2)	7.533 (2)
b (Å)	11.632 (3)	21.428 (3)
c (Å)	11.155 (2)	8.062 (2)
α (°)	90	90
β (°)	104.690 (10)	90.46 (2)
γ (°)	90	90
V (Å^3)	1307.9 (5)	1301.4 (5)
Z	4	4
F (0 0 0)	528	528
Density (calculated [g × cm^{-1}]	1.246	1.252
Absorption coefficient (mm^{-1})	0.082	0.083
Theta range for data collection (°)	1.89–24.96	2.87–24.16
Index ranges	$-12 \le h \le 12$, $0 \le k \le 13$, $13 \le 1 \le 13$	$-8 \le h \le 8$, $-24 \le k \le 24$, $-9 \le 1 \le 9$
Reflections collected	3173	8851
Independent reflections	2299 [R(int) = 0.0448]	2043 [R(int) = 0.0474]
Data/restraints/parameters	1874/0/240	2036/0/239
Goodness of fit F^2	1.068	1.036
Final R indices [$I > 2$sigma (I)]	$R_1 = 0.0393$, $wR_2 = 0.0943$	$R_1 = 0.0382$, $wR^2 = 0.0959$
R indices (all data)	R_1=0.0538,= wR2=0.1158	$R_1 = 0.0429$, $wR_2 = 0.1000$
Extinction coefficient	0.064 (4)	
Largest differential peak and hole [Å^{-3}]	0.138–0.111	0.152–0.122
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Crystal size [mm]	0.76 × 0.57 × 0.19	1.75 × 0.57 × 0.46

compound **1e** formation of *cis*-product **5e** with regard to the two neighbouring phenyl groups is favored.

3.2. γ-Hydrogen abstraction versus ε-transfer

In the case of 2-methyl-4-oxo-4-phenyl-butanoyl pyrrolidine (**10**) we studied the influence of the cyclic amide substituent on the diastereoselectivity of the cyclization. Surprisingly, along with perhydro-indolizinones **13** and **14** the γ-hydrogen abstraction products **2**, **11** and **12** were also obtained (Scheme 4). Products **13** and **14** are the results of an ε-hydrogen transfer via an eight-membered transition state. Photocyclizations with an ε-hydrogen abstraction are only known, if alkyl aryl ketones without γ- and δ-hydrogens are irradiated, for instance 4-oxo-4-phenyl-butanoyl amines [9]. Due to the chiral center at the 2-C of racemic **10** the



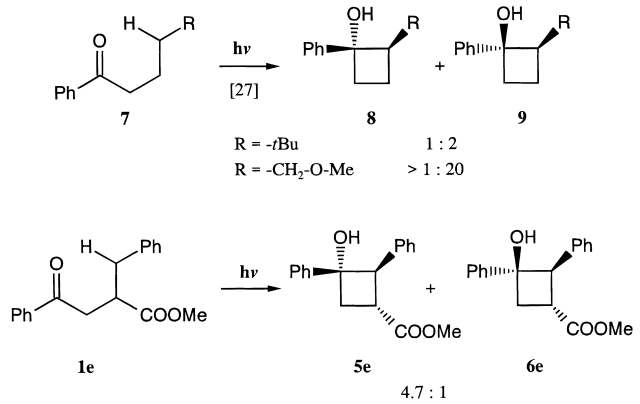
1 **2** **3** **4** **5** **6**

Scheme 2. Photoreaction of derivatives **1**.

Table 2
Yields of the photoreaction of derivatives **1**[a]

	Reactants **1**			*2* (%)	**4**, **5** (%)[b]	**6** (%)	*Cis*[c] : *trans*[d]	**2**/ (**4** + **5** + **6**)[b]
	R^1	R^2	*X*					
a	H	H	NMe_2	33	67	–	>20 : 1	0.49
b	H	H	OMe	31	69	–	>20 : 1	0.46
c	H	H	OBn	25	34	3	11.3 : 1	0.68
d	H	Me	OMe	36	15, 21	5	7.2 : 1	0.88
e	H	Ph	OMe	40	0, 28	6	4.5 : 1	1.20
f	Me	Me	OMe	42	10	5	2 : 1	2.91

[a] Determined by HPLC.
[b] If $R^1 = R^2$ then products **4** and **5** are identical.
[c] *Cis* with respect to the hydroxyl- and the carboxyl group (**4** and **5**).
[d] *Trans* with respect to the hydroxyl- and the carboxyl group (**6**).



7 8 9 1e 5e 6e

Scheme 3. Photoreaction of γ-substituted butyrophenones [27] and ester **1e**.

formation of four diastereomeric indolizinones is possible. After irradiation of pyrrolidide **10** in dichloromethane we found besides **2**, **11** and **12** only product **13**, while the photolysis of reactant **10** in *t*-butanol affords preferably the indolizinones **13** and **14** (Table 3).

Table 3
Yields of the photoreaction of **10** in CH_2Cl_2 and *t*-butanol[a]

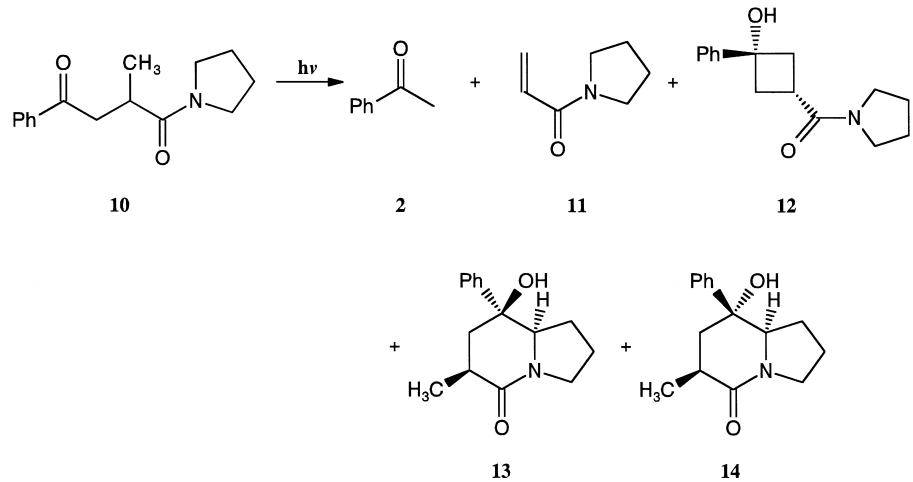
Solvent	**2** (%)	**12** (%)	**13** (%)	**14** (%)	[**2** + **12**] (%)	[**13** + **14**] (%)
CH_2Cl_2	20	28	23	0	48	23
t-Butanol	8	11	14	39	19	53

[a]Determined by HPLC.

The relative configuration of products **12** and **14** were assigned on the basis of NOE experiments and confirmed by X-ray analysis. Cyclobutanol **9** exhibits the same configuration, elucidated for products **4a–c**, resulting from the irradiation of compounds **1a–c** (Fig. 1). The amide substituent and the hydroxyl group are found to be *cis*-configured.

The methyl substituent and the phenyl group of indolizinone **14** are *cis*-configured (Fig. 2). Fig. 2 show the *trans*-relationship of the 8a-proton (H28) with respect to the above mentioned groups.

NOE experiments performed with **13** indicate the *cis*-relationship of the phenyl ring and the 8a-methine proton.



10 2 11 12 13 14

Scheme 4. Photoreaction of pyrrolidide **10**.

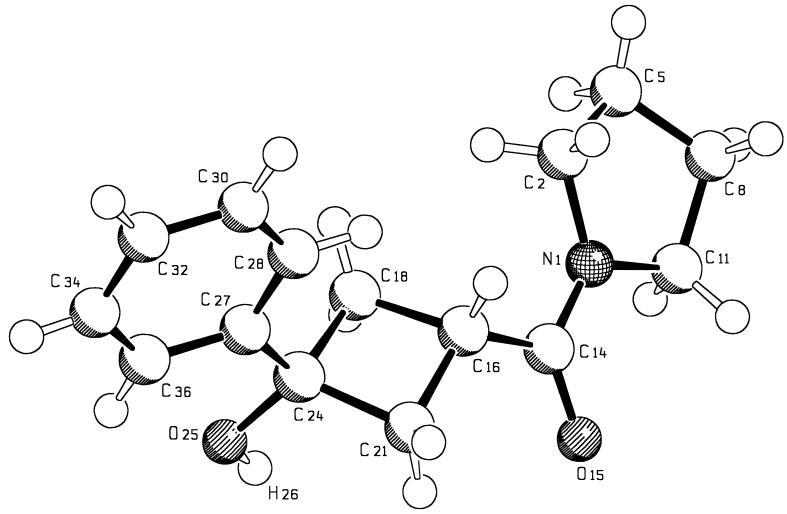


Fig. 1. X-ray structure of cyclobutanol **12**.

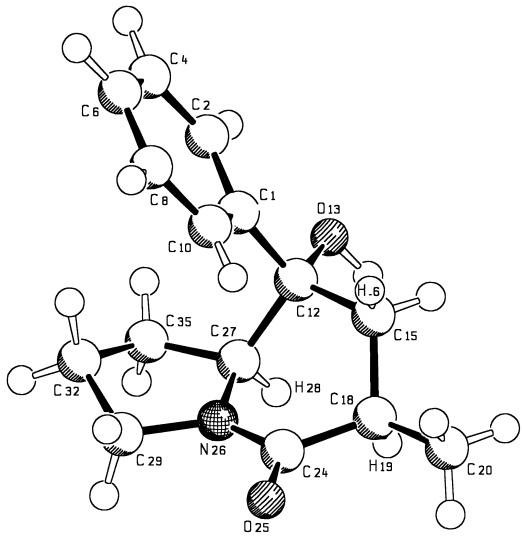


Fig. 2. X-ray structure of indolizinone **14**.

These results refer to one of the two relative configurations **13-A** or **13-B** (Fig. 3). In the 300 MHz ^{1}H-NMR spectra the multiplet which can be assigned to 6-H is superimposed with the signal of proton H_B at the 7-C. Only when acquiring the ^{1}H-NMR spectra at 600 MHz are the signals separated which allows the determination of the relative configuration

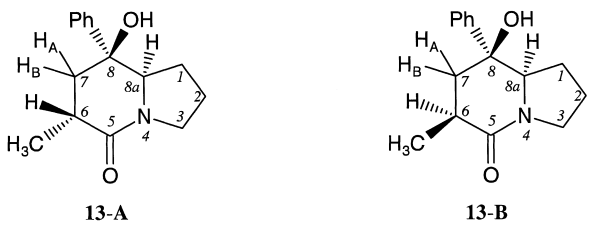


Fig. 3. Possible relative configurations of indolizinone **13**.

at 6-C and 8-C. NOESY experiments clearly prove the *trans*-arrangement of the methyl group at C-6 and the phenyl group at C-8 (13-B). Molecular mechanics calculations (MM2) suggest a pseudo-equatorial orientation of both the methyl and the phenyl group.

4. Discussion

4.1. Norrish type II cleavage versus cyclization

It is remarkable, that the irradiation of amide **1a** and esters **1b–f** affords mainly the *cis*-configurated cyclobutanols **4** and **5** with respect to the carboxyl substituent and the hydroxy group. Additionally, the diastereoselectivity of the cyclization and the ratio of cyclization to Norrish type II cleavage products decrease with an increase in the size of the γ-substituent. We assume a hydrogen bond between the carboxyl and the hydroxy group as reason for these unexpected observations. The influence of an intramolecular hydrogen bond on the diastereoselectivity of photocyclizations has been reported for several examples [4,8]. In one case [28] the existence of an intramolecular hydrogen bridge in 1-hydroxy-1,4-biradicals is determined by kinetic studies.

The diastereoselectivity of photochemical ring closure of triplet ketones is determined by mainly two factors: triplet biradical conformational distribution and variable ISC rates of different biradical conformations [1]. Although, the latter factor should not be ignored the former one is often able to explain experimental results. Thus we calculated the appropriate triplet biradical *gauche*-conformers **A** and **B** and the *anti*-conformer **C** with respect to the radical centers **I** and **II** as described in the experimental part (Fig. 4). We obtained an energy difference of 5.5 kcal/mol for the two biradical conformers **A** and **B** and of 5.2 kcal/mol for the two biradical conformers **B** and **C**.

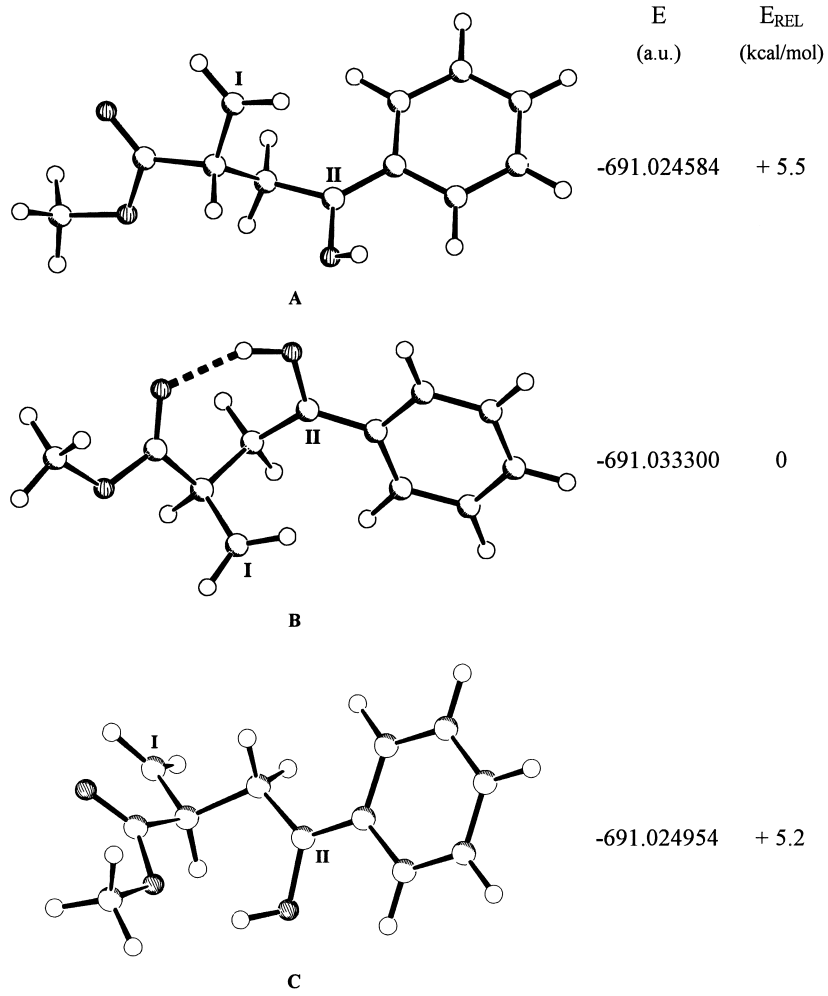


Fig. 4. Calculated triplet hydroxy biradical conformers **A**, **B** and **C**(UB3Lyp/6-31 G*//UHF/3-21 G).

Geometry **A** corresponds to the not observed product **6b** (Fig. 5). Conformer **B** with the lower energy forms the obtained cyclobutanol **4b** by preservation of the assumed hydrogen bond, which fixes the molecule. It is noteworthy that Norrish type II cleavage is not possible from conformer **B**, because the spin bearing *p*-orbitals do not overlap with the breaking σ-bond [2]. Stabilization of 1-hydroxy-1,4-biradicals like **B** by a hydrogen bridge explains the preferred formation of the *cis*-cyclobutanols **4** and **5**.

Irradiation of derivatives **1a**, **1b** and **10** gives the *cis*-cyclobutanols with high diastereoselectivity (de > 99%). In the irradiation of esters **1d** and **1e**, bearing a γ-substituent, a decreased diastereoselectivity of cyclization is observed. The substituents effect a steric hindrance to the phenyl ring and/or to the intramolecular hydrogen bond in the formed 1-hydroxy-1,4-biradicals, leading to lower yields of the corresponding cyclobutanols **4d** and **5e**.

The hydrogen bond also influences the preferred formation of *cis*-product **5e** with regard to the two phenyl groups during the irradiation of reactant **1e**. The steric interaction

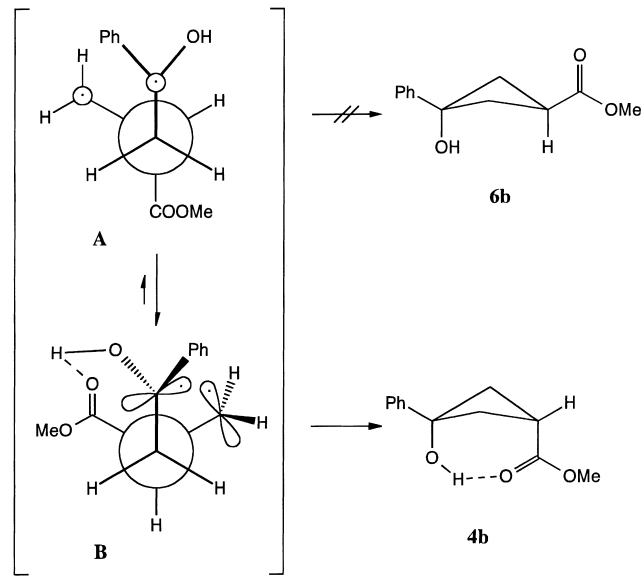


Fig. 5. Cyclization of *gauche*-conformers **A** and **B.**

between the benzyl group and the intramolecular hydrogen bond results in the observed diastereoselectivity (**4e** : **5e** = 0 : 28). On the other hand, the steric influence of the methyl substituent at the radical carbon is smaller (**4d** : **5d** = 15 : 21).

Two methyl groups, like those in photoreactant **1f**, considerably disturb the formation of *gauche*-conformations. The decreased yield of cyclobutanols **4f** and **6f** (15%) and the decreased diastereoselectivity (33%) show the influence of these substituents.

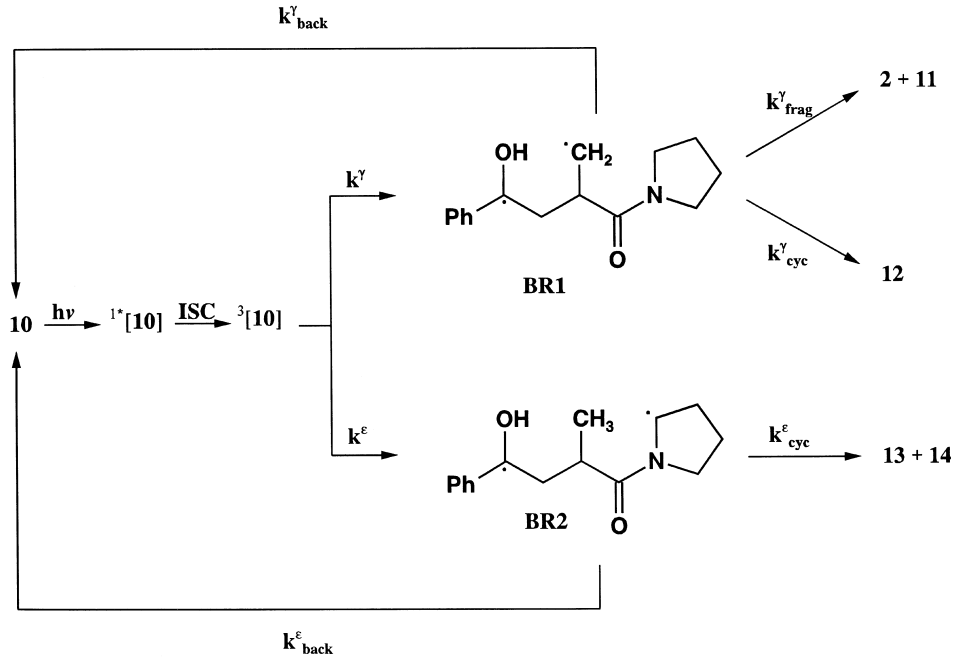
There exists an effect on the diastereoselectivity by the carbonyl substituent of the reactants **1a–c**. The benzylester group at this position decreases the diastereoselectivity from > 99% (for the amide **1a** and ester **1b**) to 84% (for **1c**) and the yield of all Norrish type II products by 35%. Presently no explanation for this fact has been found, but decreasing yields for photocyclizations of alkyl aryl ketones bearing a second aromatic substituent we have also observed. Perhaps, CT-quenching of the excited state occurs.

4.2. γ-Hydrogen abstraction versus ε-transfer

After irradiation of the pyrrolidide **10** we observed the cyclobutanol **12**, as well as, the indolizinones **13** and **14** besides the cleavage products **2** and **11**. Irradiation of cyclodecanone provides a similiar results, namely, the γ-abstraction product bicyclo[6.2.0]decan-1-ol and ε-abstraction product bicyclo[4.4.0]decan-1-ol [29]. Sauers and Huang [29] assumed that differences in the ratios $k_{cyc}^{\gamma}/k_{back}^{\gamma}$ and $k_{cyc}^{\varepsilon}/k_{back}^{\varepsilon}$ are an explanation of the exceptional behavior of cyclodecanone, which means that the 1-hydroxy-1,4-biradical and 1-hydroxy-1,6-biradical undergo hydrogen transfer back to the reactant with different rates and that this hydrogen back transfer competes with the recombination of the radical centers to give cyclization products (see Scheme 5).

Photoreaction of **10** in dichloromethane affords increased yield of γ-abstraction products **2**, **11** and **12**. Obviously, in dichloromethane the greater amount of 1,6-biradical **BR2** undergoes preferred hydrogen transfer back to the pyrrolidide **7**.

Hydrogen back transfer can be suppressed by irradiation in *t*-butanol which solvates the hydroxyl group. Irradiation of **10** in this solvent gives as major products **13** and **14** of ε-hydrogen abstraction (53%, Table 3) and suggest that $k^{\varepsilon} \geq k^{\gamma}$. Nevertheless, some qualifying remarks are necessary. Summation of all determined yields do not total 100%. Thus, we cannot exclude unknown reactions, for instance of the biradicals **BR1** and **BR2**. Second, we cannot exclude the fact that different populations of reactant conformations influence regioselectivity. Last the possibility of radical isomerization must be taken into consideration. In order to investigate this we have synthesized **10** with a CD_3-group instead of the CH_3-group ([D_3]-**10**). Upon irradiation both in CH_2Cl_2 and in *t*-BuOH we isolated the same products **2, 12, 13** and **14**. The yields of ε-hydrogen transfer products **13** and **14** were clearly increased (41% in CH_2Cl_2, 62% in *t*-BuOH) whereas lower yields of γ-hydrogen transfer products were obtained (12% in CH_2Cl_2, 2% in *t*-BuOH). This results reflects the expected H–D kinetic isotope effect of hydrogen abstraction. In the ^{1}H-NMR spectra of δ-lactams no signals of a CHD_2-group were shown which proved that no isomerization of the biradicals occurs.



Scheme 5. Regioselective photoreaction of pyrrolidide **10**.

5. Conclusions

Photoreaction of 2-substituted 4-oxo-4-phenyl-butanoic derivatives **1a–d** mainly provides cyclobutanols **4–6**, in the case of photoreactants **1e** and **1f** the Norrish type II cleavage is preferred. The diastereomers **4** and **5** with a *cis*-relationship between the carboxyl substituent and the hydroxyl group dominate due to an intramolecular hydrogen bond. This relationship already exists in the 1-hydroxy-1,4-biradicals. The cyclobutanols **4a** and **4b** were obtained with a diastereoselectivity > 99% and a yield of 68%. The competition between γ- and ε-hydrogen abstraction after irradiation of pyrrolidide **10** is explained by the difference in the ratios of rates for transfer of γ- and ε-hydrogen atoms and hydrogen back transfer of the 1,4- and 1,6-biradicals.

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