SUPPORTING INFORMATION

Chiral Photocages based on Phthalimide Photochemistry

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1 Synthetic Procedures

**General remarks.** All NMR spectra were run on a a Bruker ARX 300 instrument. \(^1 \text{H}-\text{NMR: } 300 \text{ MHz; } ^{13} \text{C}-\text{NMR: } 63.4 \text{ MHz.} \) Carbon multiplicities were determined by APT. UV-vis spectra were recorded on a Hitachi U-3200 instrument. Mass spectroscopy (EI or CI) was performed on a Finnigan Incos 500; HR-mass spectroscopy in a Finnigan MAT H-SQ 30. Column chromatography was done on silica gel (Merck) 60-230 mesh. All melting points were determined with a Buchi melting point apparatus (type Nr. 535) and are uncorrected. Rayonet chamber photoreactors RPR-208 (8 × 3000 Å lamps, ca. 800 W, 300 ± 10 nm) and RPR-100 (16 × 3500 Å lamps, ca. 400 W, 350 ± 20 nm) were used for standard irradiations. For actinometry and for 365 nm irradiation, a medium-pressure mercury lamp and suitable liquid filter solutions were used. All solvents were reagent or HPLC grade and used as received. All other chemicals were purchased from Acros Organics and used as received.

**Synthesis of (2\text{S},3\text{R})-3-acetoxy-2-(1,3-dioxoisoindolin-2-yl)butanoic acid ((2\text{S},3\text{R})-1).**

The synthesis of \(N\)-Phthaloyl-threonine, (2\text{S},3\text{R})-3-hydroxy-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butyric acid, has been previously described.\(^2\) This compound was acetylated by dissolving 1 g (4.0 mmol) of it in 20 ml of acetyl chloride and stirring the solution for 4 hours at room temperature. Then the excess of acetyl chloride was evaporated in vacuo and the residue dissolved in 50 ml of a 1:1 mixture of acetone and water. After stirring 10 minutes, the acetone was evaporated and the product extracted with dichloromethane (3 × 50 ml). The organic phase was dried over magnesium sulphate, filtered, and the solvent removed in vacuo to afford 1.1 g (95% yield) of (2\text{S},3\text{R})-1 as a colorless oil.

\(^1 \text{H}-\text{NMR} \ (\text{CDCl}_3) \delta \ 1.41 \ (d, \ J = 6 \text{ Hz}, \ 3H), \ 1.91 \ (s, \ 3H), \ 4.91 \ (d, \ J = 6 \text{ Hz}, \ 1H), \ 5.72 \ (m, \ 1H), \ 7.75 \ (m, \ 2H), \ 7.89 \ (m, \ 2H), \ 10.32 \ (br \ s, \ 1H). \)

\(^{13} \text{C}-\text{NMR} \ (+\text{APT}, \text{CDCl}_3) \delta \ 18.4 \ (\text{CH}_3), \ 20.9 \ (\text{CH}_3), \ 55.1 \ (\text{CH}), \ 67.7 \ (\text{CH}), \ 123.7 \ (\text{CH}), \ 131.5 \ (\text{quaternary C}), \ 134.4 \ (\text{CH}), \ 167.1 \ (\text{C}=\text{O}), \ 170.0 \ (\text{C}=\text{O}), \ 170.7 \ (\text{C}=\text{O}). \)

**MS** HRMS (EI) Calcd for C\(_{14}\)H\(_{13}\)NO\(_6\)Na\(^+\) (M-Na\(^+\)) 314.0641. Found 314.063.

**UV** (CH\(_3\)CN, \(\lambda_{max} (\varepsilon) \)) 291.6 (1900), 222.6 (26500).

**Synthesis of \(\text{erythro}-3\)-acetoxy-2-(1,3-dioxoisoindolin-2-yl)butanoic acid (3).** The phthaloylation of racemic allo-threonine (erythronine) was performed according to the Nefkens’ procedure.\(^1\) Thus 2.38 g (20 mmol) of allo-threonine and 2.12 g (20 mmol) of Na\(_2\)CO\(_3\) were dissolved in 30 ml of water at room temperature and 4.5 g (20 mmol) of N-ethoxycarbonylphthalimide, previously powdered in a mortar, was added in small portions. After stirring during 30 minutes practically all the N-ethoxycarbonylphthalimide has gone into solution. The aqueous solution was extracted twice with diethyl ether and acidified with HCl 6 N until pH \(\approx 2\). Then the product is extracted with dichloromethane (3 × 50 ml), and the organic phase was dried over magnesium sulphate, filtered, and the solvent removed in vacuo to afford 1.1 g (95% yield) of (2\text{S},3\text{R})-1 as a colorless oil.

\(^1 \text{H}-\text{NMR} \ (\text{CDCl}_3) \delta \ 1.30 \ (d, \ J = 6 \text{ Hz}, \ 3H), \ 4.62 \ (m, \ 1H), \ 4.74 \ (d, \ J = 6 \text{ Hz}, \ 1H), \ 7.76 \ (m, \ 2H), \ 7.88 \ (m, \ 2H), \ 10.30 \ (br \ s, \ 1H). \)

\(^{13} \text{C}-\text{NMR} \ (+\text{DEPT, CDCl}_3) \delta \ 18.6 \ (\text{CH}_3), \ 52.0 \ (\text{CH}), \ 66.2 \ (\text{CH}), \ 124.0 \ (\text{CH}), \ 131.8 \ (\text{quaternary C}), \ 134.2 \ (\text{CH}), \ 168.8 \ (\text{C}=\text{O}), \ 172.0 \ (\text{C}=\text{O}). \)

This product was acetylated by the same procedure used in the synthesis of ((2\text{S},3\text{R})-1), affording 3 in 95% yield as a colorless oil.
$^1$H–NMR (CDCl$_3$) $\delta$ 1.27 (d, $J = 6$ Hz, 3H), 2.04 (s, 3H), 5.15 (d, $J = 6$ Hz, 1H), 5.68 (m, 1H), 7.75 (m, 2H), 7.89 (m, 2H), 10.30 (br s, 1H).

$^{13}$C–NMR (+DEPT, CDCl$_3$) $\delta$ 16.4 (CH$_3$), 21.0 (CH$_3$), 53.4 (CH), 68.6 (CH), 123.8 (CH), 131.5 (quaternary C), 134.4 (CH), 167.3 (C=O), 170.4 (C=O), 171.6 (C=O).

MS HRMS (EI) Calcd for C$_{14}$H$_{13}$NO$_6$Na$^+$ (M-Na$^+$) 314.0641. Found 314.063.

Synthesis of 1-(1,3-dioxoisoindolin-2-yl)propan-2-yl acetate (4). Phthalic anhydride was mixed with an excess of 1-amino-2-propanol, and the mixture heated in a microwave oven in an open vessel. After 3-4 minutes of interrupted heating, the reaction is completed, and 1-(1,3-dioxoisoindolin-2-yl)propan-2-ol is recrystallized from ethanol. The alcohol is then acetylated by the same procedure used for (2$^5$,3$^R$)-1 and 3, yielding 4 as a white solid (m. p. 96–97 °C).

$^1$H–NMR (CDCl$_3$) $\delta$ 1.27 (d, $J = 6$ Hz, 3H), 1.97 (s, 3H), 3.82 (d, $J = 6$ Hz, 2H), 5.20 (m, 1H), 7.71 (m, 2H), 7.85 (m, 2H).

$^{13}$C–NMR (+DEPT, CDCl$_3$) $\delta$ 17.7 (CH$_3$), 21.1 (CH$_3$), 41.9 (CH$_2$), 68.4 (CH), 123.3 (CH), 131.9 (quaternary C), 134.0 (CH), 168.2 (C=O), 170.6 (C=O).

MS HRMS (EI) Calcd for C$_{13}$H$_{13}$NO$_4$ (M$^+$) 247.0845. Found 247.084.

Synthesis of (S)-2-(1,3-dioxoisoindolin-yl)-3-(1H-pyrazol-1-yl)propanoic acid (6). Phthaloyl-serine β-lactone 5 was synthesized according to the literature.$^{[3]}$ This compound was reacted with pyrazole by heating at 50 °C an acetonitrile solution of both compounds for 24 hours, according to the procedure described for similar amino acid-derived β-lactones.$^{[4]}$ After work-up, 6 was obtained as a colorless oil.

$^1$H–NMR (CDCl$_3$) $\delta$ 4.98 (dd, $J_2 = 15$ Hz, $J_3 = 10$ Hz, 1H), 5.11 (dd, $J_2 = 15$ Hz, $J_3 = 6$ Hz, 1H), 5.40 (dd, $J_3 = 10$ Hz, $J'_3 = 6$ Hz, 1H), 6.16 (s, 1H), 7.38 (s, 1H), 7.50 (s, 1H), 7.66 (m, 1H), 7.76 (m, 2H), 7.86 (m, 2H).

$^{13}$C–NMR (+DEPT, CDCl$_3$) $\delta$ 49.6 (CH$_2$), 52.1 (CH), 41.9 (CH), 106.0 (CH), 123.6 (CH), 130.8 (quaternary C), 131.5 (CH), 134.2 (CH), 139.7 (CH), 167.1 (C=O), 169.0 (C=O).

MS HRMS (EI) Calcd for C$_{14}$H$_{11}$N$_3$O$_4$Na$^+$ (M-Na$^+$) 308.0647. Found 308.064.

Synthesis of (S)-3-acetoxy-2-(1,3-dioxoisoindolin-2-yl)propanoic acid (7). This caged acetate was prepared using the same route as for 1 and 3, but starting with serine. Compound 7 was obtained as a colourless oil that slowly crystallized on standing. By co-evaporation with toluene, remaining water can be eliminated, then obtaining a white solid with m. p. = 153–155 °C. Alternatively, 7 can be prepared from phthaloyl-serine β-lactone 5, following the literature method used for N-protected amino acid-derived β-lactones.$^{[3,4]}$

$^1$H–NMR (CDCl$_3$) $\delta$ 1.97 (s, 3H), 4.60 (dd, $J_2 = 12$ Hz, $J_3 = 10$ Hz, 1H), 4.87 (dd, $J_2 = 12$ Hz, $J_3 = 6$ Hz, 1H), 5.20 (dd, $J_3 = 10$ Hz, $J'_3 = 6$ Hz, 1H), 7.76 (m, 2H), 7.86 (m, 2H), 8.5 (bs, 1H).

$^{13}$C–NMR (+DEPT, CDCl$_3$) $\delta$ 20.6 (CH$_3$), 50.7 (CH$_2$), 60.9 (CH), 123.8 (CH), 131.6 (quaternary C), 134.4 (CH), 167.3 (C=O), 170.7 (C=O), 170.8 (C=O).

MS HRMS (EI) Calcd for C$_{13}$H$_{11}$NO$_6$Na$^+$ (M-Na$^+$) 300.0484. Found 300.048.
2 General Procedure for Photolyses

Solutions of 0.2 mmol of the starting materials (2S,3R)-1 or 3 in 50 ml of phosphate buffer at pH = 7 were irradiated at 15–20 °C for 2 h with phosphor-coated mercury low-pressure lamps (the emission maximum at 300 ± 10 nm or 350 ± 20 nm). The alkenyl-phthalimide formed was extracted with CH$_2$Cl$_2$ (3 × 50 ml). The organic phase was dried over MgSO$_4$, filtered and the solvent evaporated in vacuo. The residue was dissolved in CDCl$_3$ and analyzed by NMR.

In the aqueous phase, liberated acetate after irradiation was analyzed using a modification of a published method.$^5$ By addition of benzyl bromide and warming at 50 °C for 4 hours, acetate was derivatized as benzyl acetate. It was then extracted with dichloromethane and detected by GC, comparing with an authentic sample.

Photoreaction of caged pyrazole 6. Compound 6 was irradiated using the general procedure. After extraction, the decarboxylation product, 2-[2-(1H-pyrazol-1-yl)ethyl]isoindoline-1,3-dione, was isolated. The NMR and MS data were in accordance to those described in the literature.$^6$

Irradiation at 365 nm. To prove the photorelease process at longer wavelengths (Rayonet RPR-3500 lamps have a broad radiance profile), the 365 nm line of a medium-pressure mercury lamp was isolated by using a suitable liquid filter.$^7$ The samples were irradiated during 6 hours in 1 cm-path cuvettes, and the general work-up followed. The formation of insoluble material was observed, which was identified as N-(1-propenyl)-phthalimide by NMR after extraction.

Sensitized irradiations. First, acetone was used as triplet sensitizer, employing a large excess (30% vol. acetone mixed with the phosphate buffer was used as solvent). Parallel irradiations at 300 nm were performed on samples of (2S,3R)-1 with and without sensitizer. After 2 hours of irradiation, the general work-up was done, and the samples analyzed by NMR, using 1,4-dimethoxybenzene as internal standard. An increase of ca. 6% in the yield of N-(1-propenyl)-phthalimide was measured for the sensitized reaction.

For the sensitization using 350 nm lamps, 2 equivalents of 2-carboxybenzophenone (soluble in the phosphate buffer) was used as sensitizer. In this case, after 3 hours of irradiation, the amount of N-(1-propenyl)-phthalimide formed in the sensitized reaction was 5.8 times the amount formed in the reference reaction.

3 Azobenzene Actinometry

The procedure was adapted from the IUPAC technical report about chemical actinometry.$^8$ According to bibliography,$^7$ the 313 nm line of a medium-pressure mercury lamp was isolated by using a liquid filter composed of 126 g/l of CoCl$_2$·6 H$_2$O, 239 g/l of NiSO$_4$·6 H$_2$O and 2.44 g/l of resorcin. The lamp was pre-heated during 2 hours before the actinometric measurements, which were carried out in a standard quartz cuvette (1 cm optical path). Then, samples of (2S,3R)-1 and 3 (transmittance at 313 nm < 1%) were irradiated in the same cuvette, extracted, and analyzed by NMR using 1,4-dimethoxybenzene as internal standard. After the irradiations, actinometry was repeated to check the stability of the light intensity.

4 References

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