Diastereo- and Enantioselective Synthesis of Pyrrolo[1,4]benzodiazepines through Decarboxylative Photocyclization**

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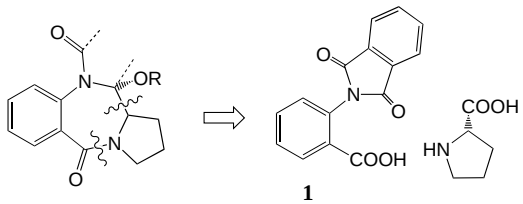
The concept of "memory of chirality" has recently been introduced by Fuji and Kawabata as a useful principle for asymmetric synthesis.[1] It involves the planarization of a stereogenic center during a multistep reaction with subsequent formation of chiral nonracemic products. No asymmetric induction by chiral auxiliaries controls the transformation, only the remaining chirality memory of the intermediates. The lifetime of these intermediates and their conformational flexibilty is decisive for the degree of stereoselectivity. Besides reactions with carbanions,[1] monoradicals,[2] or carbenium ions,[3] combination reactions of diradicals are promising due to the very low (if present at all) activation barriers. This approach was described recently by Giese and co-workers for the cyclization of photochemically generated 1,5-diradicals with singlet multiplicity.[4] The lifetimes of these intermediates are extremely short and near complete memory of chirality resulted. The corresponding triplet diradicals are expected to show strongly reduced memory effects due to their higher lifetimes.[5] In order to corroborate this assumption, we investigated the decarboxylative photocyclization of phthaloylanthranilic acid derivatives[6] and now report surprisingly high enantiomeric excesses for the radical combination of a triplet 1,7-diradical.

The decarboxylative photocyclization of ω-phthalimido carboxylates is initiated in the triplet channel of the electronically excited phthalimido chromophore.[7] Intramolecular electron transfer and extrusion of carbon dioxide lead to the 1,($\omega+1$)-triplet diradical which, after spin inversion, combines to form the closed-shell products. This process allows, for example, the synthesis of diastereo- and enantiomerically pure benzopyrrolizidines from glutamic acid derivatives.[8] Another interesting target family in this context are pyrrolo[1,4]-benzodiazepines. These molecules show highly selective bindung to DNA and thus exhibit a strong potential as regulators for gene expression.[9] Taking our photocyclization method into consideration, the retrosynthesis showed C,N-activated anthranilic acid building blocks to be suitable substrates (Scheme 1).[10]



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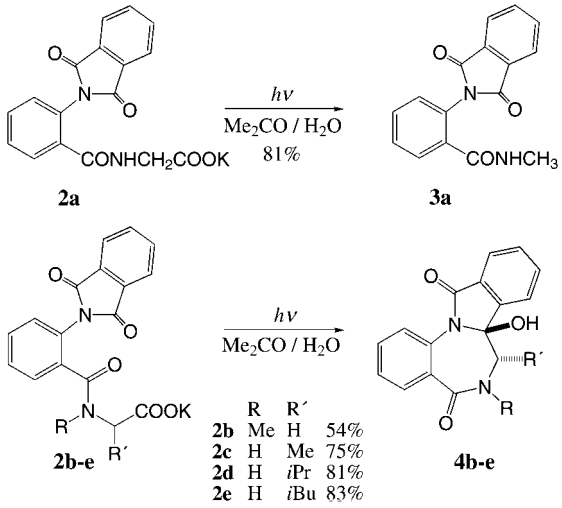
Scheme 1. Retrosynthesis for pyrrolo[1,4]benzodiazepines.

N-Phthaloyl anthranilic acid (**1**) is a photolabile substance under basic conditions. When it was irradiated in acetone/water mixtures (95/5), only *N*-phenyl phthalimide resulted as a reduction product and no cyclization was observed. If **1** was condensed with glycine to give **2a**, the photochemical reactivity was decreased and only after prolonged irradiation was the reduction product **3a** formed (Scheme 2). These results are in agreement with the photochemistry of *N*-phthaloyl dipeptides.[6b] The increased photostability of these substrates is probably caused by an intramolecular hydrogen bond between the amide-NH group and one of the imido carbonyl groups. Thus, *N*-alkylated substrates should exhibit higher reactivities.



Scheme 2. Photochemistry of the anthranilic acid derivatives **2a–e** of acyclic amino acids.

The switch to sarcosine as the amino acid component did in fact drastically change the (secondary) reactivity: Substrate **2b** cyclized efficiently to give the benzodiazepine **4b** in 54% yield. It was surprising to notice that not only *N*-alkylation favored ring formation but branching of the amino acid component also had the same effect: Irradiation of the alanine, valine, and leucine derivatives **2c–e** gave the corresponding benzodiazepines **4c–e** in good yields. The products were formed diastereoselectively as the pure *trans* isomers, but only when the photolyses were performed on a small scale. Large-scale (0.1 mol) irradiation of **2e** using a 3 kW XeCl excimer system resulted in **4e** as a 1:1 mixture of diastereoisomers.[11] This mixture could also produced from pure *trans*-**4e** by treatment with catalytic amounts of trifluoroacetic acid (via the corresponding acyl iminium cation)[12] which clearly shows, that the photocyclization is kinetically controlled. As we had now established the structural requirements for efficient and selective photocyclization, we started to investigate cyclic α-amino acids as substrate components.

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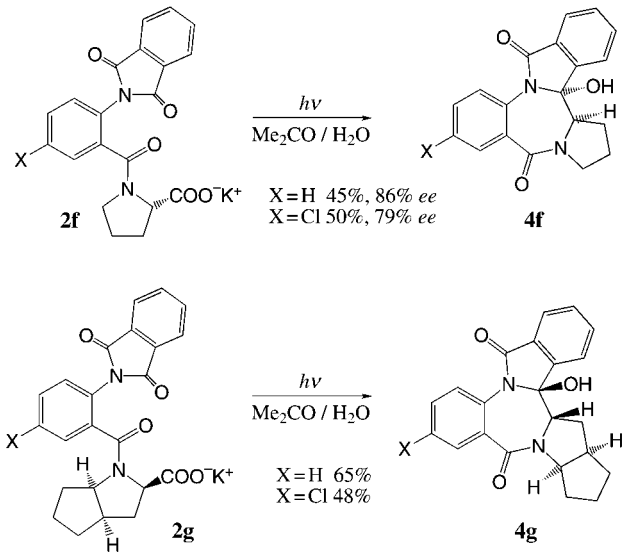
The proline derivative **2f**-H (X = H) was synthesized with *ee* > 95% by coupling its benzyl ester and *N*-phthaloyl anthranilic acid (**1**) with DCC/HOBT and subsequent debenzylation with H_2/Pd. Photodecarboxylation of the corresponding potassium salt in an acetone/water mixture (1/1) resulted in the formation of the pentacyclic product **4f**-H (Scheme 3 and Table 1) in 45% yield and with a diastereoselectivity of



Scheme 3. Decarboxylative photocyclization of anthranilic acid derivatives **2f**-H, **g**-H.

Table 1. Characteristic data for **4f**-H und **4g**-H.[a]

4f-H: mp 113–116 °C (acetone); $[\alpha]_D^{20}$: +71.2° (methanol, $c = 1$); IR (CsI): $\tilde{\nu}$ = 3460, 2363, 1717, 1616, 1559, 1506 cm^{-1}; ^{1}H NMR: δ = 1.1–1.30 (m, 1H), 1.71 (dt, J = 12.7, 7.2 Hz, 1H), 2.06–2.20 (m, 1H), 2.50 (dd, J = 13.7, 7.1 Hz, 1H), 3.05 (dt, J = 11.2, 8.7 Hz, 1H), 3.21–3.31 (m, 1H), 4.00 (d, J = 8.6 Hz, 1H), 4.96 (s, 1H; OH), 7.29 (dd, J = 7.7, 1.1 Hz, 1H), 7.43–7.77 (m, 7H); ^{13}C NMR: δ = 22.7 (CH_2), 26.8 (CH_2), 45.2 (CH_2), 63.4 (CH), 96.9 (C_q), 123.9 (CH), 124.1 (CH), 129.2 (CH), 129.9 (CH), 130.4 (CH), 131.1 (CH), 132.2 (C_q), 132.3 (CH), 132.8 (C_q), 134.0 (CH), 134.6 (C_q), 143.2 (C_q), 167.5 (C_q), 167.9 (C_q); HR-MS (ESI, reference = PPG): m/z calcd for [M + Na]: 343.10586, found: 343.1060.

4g-H: mp 131–135 °C (acetone); $[\alpha]_D^{20}$: −96.5° (methanol, $c = 1$); IR (CsI): $\tilde{\nu}$ = 3345, 2958, 1716, 1622, 1486, 1405 cm^{-1}; ^{1}H NMR: δ = 1.39–1.49 (m, 2H), 1.58–1.65 (m, 2H), 1.81–1.89 (m, 2H), 2.03–2.17 (m, 2H), 2.54 (dd, J = 14.0, 8.3 Hz, 1H), 3.57 (dt, J = 8.1, 4.3 Hz, 1H), 4.04 (d, J = 9.0 Hz, 1H), 7.22–7.71 (m, 8H); ^{13}C NMR: δ = 23.7 (CH_2), 30.1 (CH_2), 31.5 (CH_2), 32.2 (CH_2), 40.9 (CH), 63.8 (CH), 65.8 (CH), 96.8 (C_q), 123.5 (CH), 124.2 (CH), 128.8 (CH), 128.9 (CH), 129.8 (CH), 130.6 (CH), 131.5 (C_q), 131.9 (CH), 132.6 (C_q), 133.6 (CH), 135.6 (C_q), 143.8 (C_q), 166.6 (C_q), 167.6 (C_q); HR-MS (ESI, reference = PPG): m/z calcd for [M + H]: 361.15532, found: 361.15522.

[a] ^{1}H NMR spectra were measured at 300 MHz in $CDCl_3$; ^{13}C NMR spectra were measured at 75 MHz in $CDCl_3$ with distortionless enhancement by polarization transfer. PPG = polypropyleneglycol.

> 98% (*trans* with respect to the hydroxy group and the anulated pyrrolidine ring). Its relative configuration was also proven by X-ray crystal structure analysis.[13] Compound **4f**-H crystallized in nonracemic form in the space group $P2_12_12_1$; the crude material showed an optical rotation of +71.2 ($c = 1$, MeOH). HPLC comparison of racemic (±)-**4f**-H (from (±)-**2f**-H) with the product from enantiomerically pure (+)-**2f**-H resulted in a surprisingly high *ee* value of 86%.[14] This result was unexpected because **4f**-H results from the combination of a 1,7-triplet diradical.

The absolute configuration of **4f**-H could not be determined despite several derivatization experiments. Identical results concerning the enantioselectivity of the photocyclization were obtained with the 4-chloro derivative **4f**-Cl (from 4-chloroanthranilic acid). We did not succeed, however, in crystallizing this material. Consequently, a substrate analogous to proline with additional chiral information had to be applied. We did not succeed in isolating the photoproduct from 4-hydroxyproline. The application of (all-*R*)-2-azabicyclo-[3.3.0]octan-3-oic acid was successful. This waste product from the industrial synthesis of the ACE-inhibitor Ramipril[15] could be readily transformed into the substrate **2g**-H. Photodecarboxylation resulted in 65% yield of the hexacyclic product **4g**-H, whose relative (and thus also absolute) configuration was determined by X-ray crystal structure analysis.[13] This analysis showed unambigously that the diradical combination proceeded with complete inversion of configuration at the stereogenic α center.

In order to rule out the possibility that this effect is related to the sterically shielding bicyclooctane skeleton, the CD spectra of the substrates **2f**-H, **g**-H, as well as the products **4f**-H, **g**-H, were compared. As a consequence of the different configurations at the stereogenic α centers, the CD spectra of the starting materials **2f**-H, **g**-H showed opposite Cotton effects at 244 ($\Delta\varepsilon = -20.6$) and 243 nm ($\Delta\varepsilon = +27.3$), respectively (Figure 1). The size and direction of these Cotton

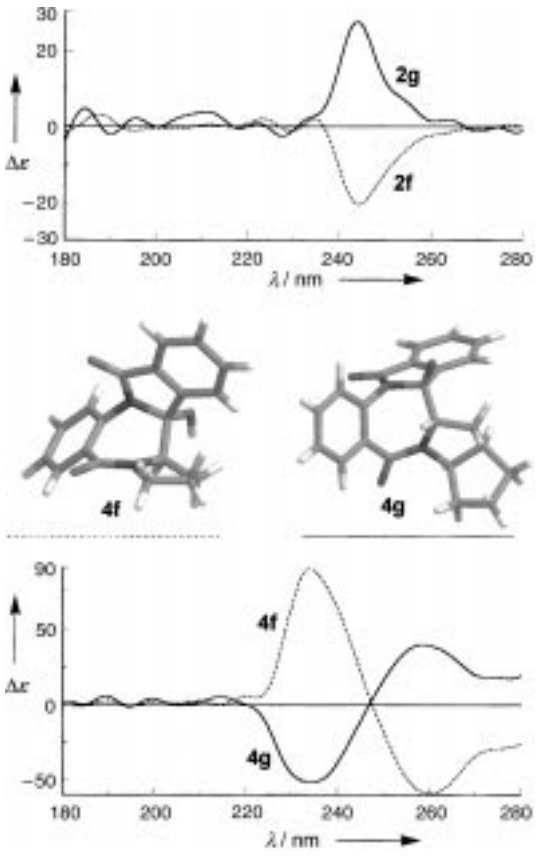


Figure 1. CD Spectra of **2f**-H, **g**-H (top); CD spectra (middle) and X-ray structures (bottom) of **4f**-H, **g**-H.

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effects were in agreement with those reported by Gawronski and co-workers for several *N*-phthaloyl amino acids.[16] Due to the photocyclization, the long-wavelength absorption maximum of the chromophore is shifted hypsochromic (from 290 to <250 nm)[7] and consequently the maxima in the CD spectra were also shifted to 233 nm (**4f**-H, $\Delta\varepsilon = +88.9$) and 234 nm (**4g**-H, $\Delta\varepsilon = -51.9$). The absolute configuration of the products were determined through the exciton rule:[17] Compound **4g**-H shows positive exciton chirality (and thus a negative Cotton effect in the short-wavelength region). The mirror-image behavior of the CD spectra of substrates and products when comparing proline and 2-azabicyclo[3.3.0]octanoic acid derivatives clearly proved that inversion of configuration also occurs for the photocyclization of the proline substrate **2f**-H (Figure 1).

As an explanation for the high degree of memory of chirality, we assume that the intermediary (atropisomeric) 1,7-triplet diradicals exhibit high activation barriers for rotation about the central C–N single bond and thus preserve their absolute axial chirality during the course of the reaction. Force-field calculations for the proline substrate **2f**-H resulted in an activation barrier of approximately 55 kJ mol^{-1}.[18] This classifies these substrates as non-diaryl atropisomers with restricted single bond rotations in the arylimide, as well as the amide moiety.[19] The kinetically controlled simple diastereoselectivity (see above) most probably results from diradical conformations determined by spin-orbit coupling that are capable of rapid spin inversion. This model was already successfully applied to cyclization reactions involving 1,4-[20] and 1,6-diradicals.[21]

Experimental Section

A solution of carboxylic acid **2** (3.00 mmol) in acetone (10 mL) was treated with a solution of potassium carbonate (1.5 mmol) in water (15 mL) and heated to 50 °C for 2 min. After dilution with acetone (90 mL) and water (90 mL), the solution is irradiated for 12 h under a nitrogen atmosphere in a Rayonet photoreactor ($\lambda = 300 \pm 10$ nm, ca. 800 W) at 15 °C. After treatment with saturated sodium bicarbonate solution (10 mL) and extraction with ethyl acetate (3×40 mL), the organic phase was separated, washed with diluted aqueous sodium bicarbonate, and dried. After evaporation of the solvent, **4** was recrystallized or purified by column chromatography.

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[13] X-ray crystal structure analyses of **4f**-H and **4g**-H. Data collection: Enraf-Nonius-CAD4 diffractometer, $Mo_{K\alpha}$, graphite monochromator, Wyckoff-Scan, θ-range [°]: 1.75 – 27.5. Structure analysis und refinement: Solution by direct phase determination, refinement by full matrix least square fit techniques against F^2 with Siemens SHELXL-93. Crystal data: **4f**-H ($C_{19}H_{16}N_2O_3$, from acetone): $M = 320.3$, orthorhombic, $a = 8.987(1)$, $b = 11.098(1)$, $c = 15.338(1)$ Å, space group $P2_12_12_1$, 5037 reflections measured, 2093 reflections with $F > 2\sigma(F)$, $R = 0.069$, $R_w = 0.041$. **4g**-H ($C_{22}H_{20}N_2O_3xC_3H_6O$, from acetone): $M = 418.48$, orthorhombic, $a = 10.043(1)$, $b = 11.512(1)$, $c = 18.511(1)$ Å, space group $P2_12_12_1$, 12515 reflections measured, 3038 reflections with $F > 2\sigma(F)$, $R = 0.065$, $R_w = 0.040$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-150112 (**4f**-H) and -150113 (**4g**-H). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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