78. Asymmetric Synthesis of 3-Hydroxyprolines by Photocyclization of *N*-(2-Benzoylethyl)glycinamides

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Dedicated to Professor Dr. *Hans-Georg Henning* on the occasion of his 65th birthday

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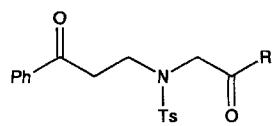
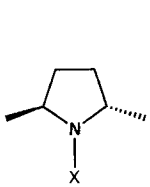
The chiral *N*-(2-benzoylethyl)-*N*-tosylglycinamides **1a–c** were prepared from the C_2-symmetric pyrrolidines **5a–c**. Irradiation of these ketones **1a–c** gave *cis*-3-hydroxyprolinamides **10–12** in moderate to good yields (*Scheme 3*). The *de* of the photocyclizations depended on the size of the substituents in positions C(2) and C(5) of the chiral pyrrolidine auxiliaries. In addition, the *de* varied with the reaction temperature, allowing the determination of activation-parameter differences. The structure of products **10–12** were established by NMR and X-ray analyses.

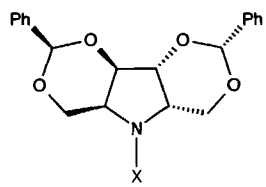
Introduction. – The stereoselective synthesis of α-amino acids is a challenging problem of modern organic synthesis. Particularly, unnatural α-amino acids are of great interest as components of modified peptides with unusual properties. Synthetic routes



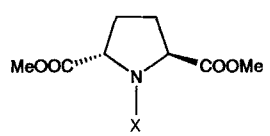
1 (= RX; for *R* see below)
2 R = R'O, R'R'N



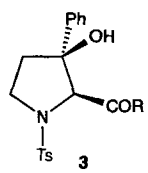
1a X = $PhCO(CH_2)_2N(Ts)CH_2CO$
5a X = H



1b X = $PhCO(CH_2)_2N(Ts)CH_2CO$
5b X = H



1c X = $PhCO(CH_2)_2N(Ts)CH_2CO$
5c X = H



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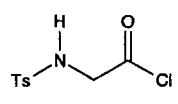

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with chiral glycine derivatives like imidazolidinones [1] or oxazinones [2] proved to be valuable methods. On the other hand, acyclic glycine derivatives were used only in a few cases (see, *e.g.*, [3]).

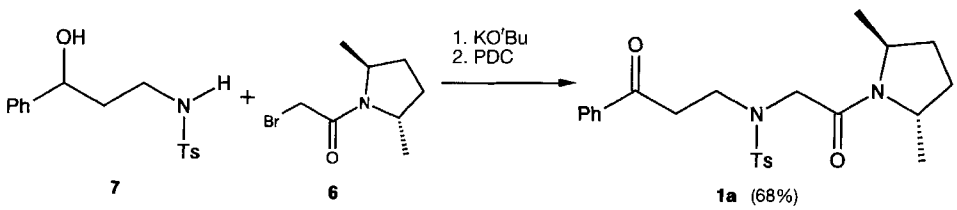
With regard to the development of new peptide pharmaceuticals, proline derivatives are of particular importance [4]. Recently, *Henning et al.* [5–7] published a method for the diastereoselective synthesis of 3-hydroxy-3-phenylproline derivatives **3** by photocyclization of glycine derivatives **2**. During the reaction **2** → **3**, a 1,5-biradical is formed, which undergoes intramolecular recombination to the pyrrolidinol **3** with high diastereoselectivity.

In this paper, we report on similar photocyclizations of glycine derivatives **1a–c** with chiral substituents R inducing stereogenic centers at C(2) and C(3) of the new proline ring. According to *Giese* and coworkers [8a] and *Porter et al.* [8b], C_2-symmetric pyrrolidine derivatives are suitable auxiliaries in asymmetric syntheses with radicals. So we decided to synthesize compounds **1a–c** as educts for UV irradiation.

Results and Discussion. – *Synthesis of* **1**. *Walther et al.* [7] synthesized *N*-(2-benzoylethyl)-*N*-tosylglycinamides by treating β-bromopropiophenone with *N*-tosylglycinamides, which were prepared from *N*-tosylglycyl chloride (**4**) with amines. The reaction of **4** with the pyrrolidines **5a–c** gave only *N*,*N*′-ditosyl-2,5-diketopiperazine instead of corresponding *N*-tosylglycinamides. Obviously, *Walther*'s method failes with steric hindered amines like **5a–c**.

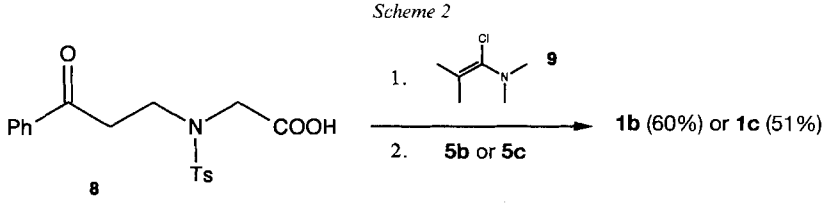
We found that (2*S*,5*S*)-2,5-dimethylpyrrolidine [9] (**5a**) reacted easily with bromoacetyl bromide yielding the bromoacetamide **6**, which then *N*-alkylated *N*-(3-hydroxy-3-phenylpropyl)tosylamide (**7**), after deprotonation. Oxidation of the intermediate product with pyridinium dichromate (PDC) gave **1a** in 68% overall yield (*Scheme 1*).

Scheme 1



Unfortunately, bromoacetyl bromide did not give a stable bromoacetamide with bis(dioxino)pyrrolidine [10] **5b**. But *N*-(2-benzoylethyl)-*N*-tosylglycine (**8**) gave the desired amide **1b**, after reaction with the chloroenamine [11] [12] **9** and treatment of the non-isolated acyl chloride with **5b**. The same method was used to transform dimethyl (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylate [13] (**5c**) to amide **1c** (*Scheme 2*).

Scheme 2



Photochemical Behavior of Compounds **1**. The keto amides **1a–c** exhibit UV absorption at *ca.* 320 nm (n → π*-excitation of the keto carbonyl group). In the relatively long-lived T_1-state, the ketones **1a–c** should form 1,5-biradicals by intramolecular H-abstraction as the most important deactivation process [5–7]. Intramolecular recombination of the biradicals would then give the 3-hydroxyprolines **10–12**. Indeed, after irradiation of **1a** at 20°, we isolated two products **10a, b** in a ratio 2.1:1 (*Scheme 3*). Their ^{1}H-NMR spectra were interpreted by COSY experiments (see *Exper. Part*), and NOE experiments established *cis*-configuration for the tetrasubstituted pyrrolidine ring of both **10a** and **10b** (see *Fig. 1*) in contrast to the assignments published by *Henning* and coworkers [5–7].

Scheme 3

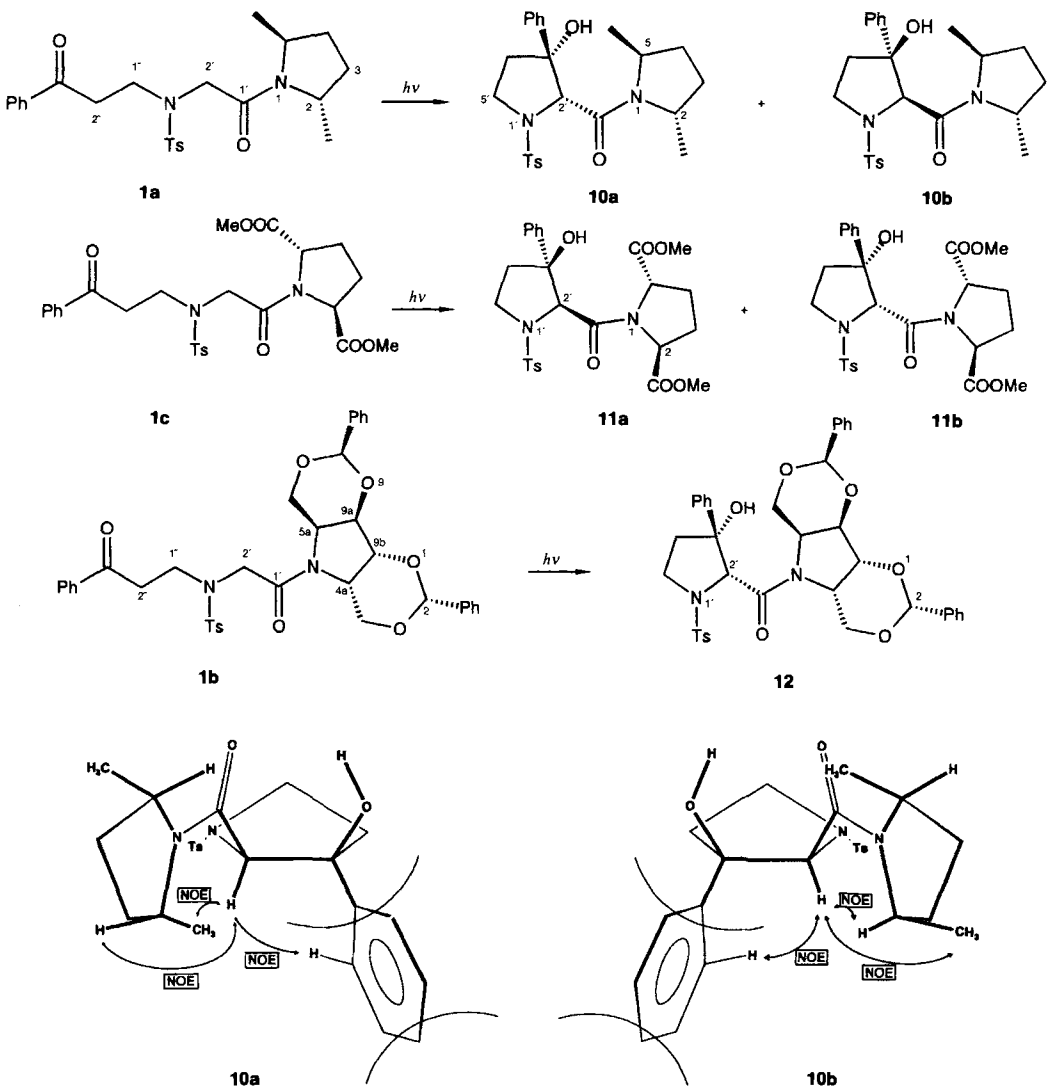


Fig. 1. *Configuration of* **10a, b**

The ^{1}H-NMR signals of the H-atoms and Me groups at C(2) and C(5) of **10a,b** are of special interest. The signal of 1 CH of **10a** is shifted by *ca.* 0.7 ppm to high field, as compared to **1a**. In contrast, in the case of **10b**, the signal of 1 Me group is high-field-shifted by *ca.* 0.8 ppm, as compared to **1a**. Obviously, these shifts are caused by the anisotropic effect of the Ph substituent at C(3'). In NOE experiments, irradiation of H–C(2') (**10a**: 4.67 ppm; **10b**: 4.44 ppm) produces NOE's at 1 Me and 1 CH signal, proving the near orthogonal position of both pyrrolidine rings. In addition, NOE difference signals appear in the region above 7 ppm caused by the Ts groups (*cf.* X-ray structure analysis below). A second NOE difference signal in this region (**10a**: 7.55 ppm; **10b**: 7.4 ppm) indicates the relatively small distance between H–C(2') and Ph–C(3'). It should be mentioned that the NOE effects are observed at the same Me and CH protons which suffer the strong high-field shift.

The photocyclization of **1c** occurred with a considerable higher *de*; at 20°, the isomers **11a** and **11b** were formed in a 7.3:1 ratio (*Scheme 3*). In comparison with **1a** → **10a**/**10b**, the reaction was slower and gave a lower yield. Irradiation of **1b** gave an impressive result; in more than 70% yield the proline amide **12** was formed. The other isomer could not be detected. The structure determination of **12** by ^{1}H-NMR was complicated by the superposition of some signals although the spectrum is similar to those of **10a,b** and **11a,b**. The relative configuration of **12** was definitely determined by X-ray structure analysis (*Fig. 2*) which shows an excellent agreement with the conclusions from the NMR spectra described above.

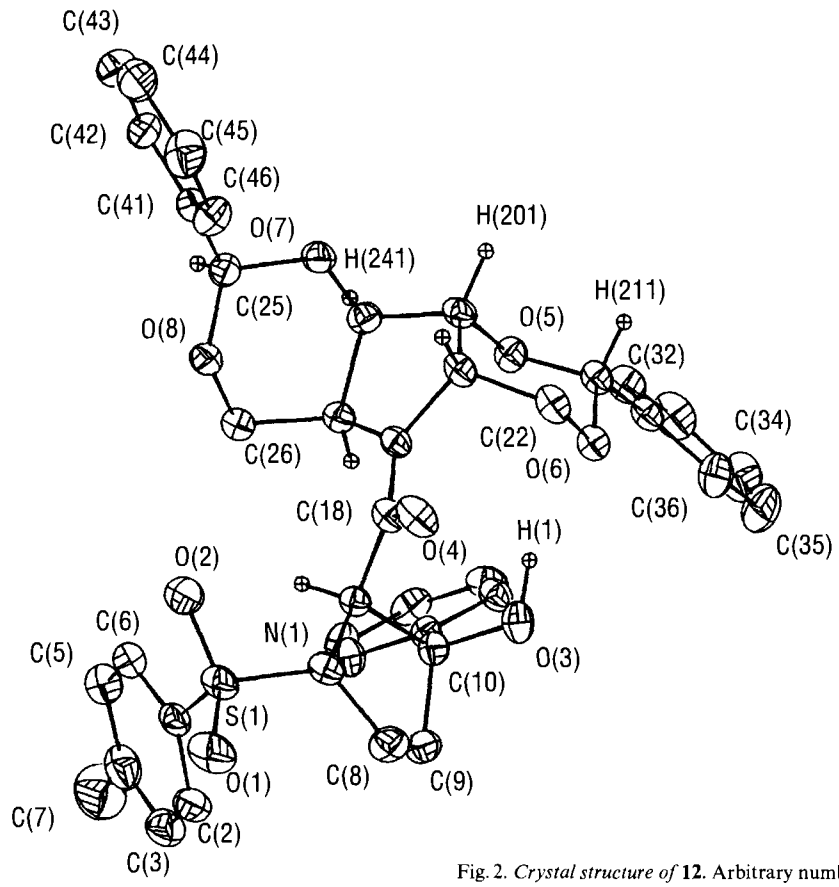
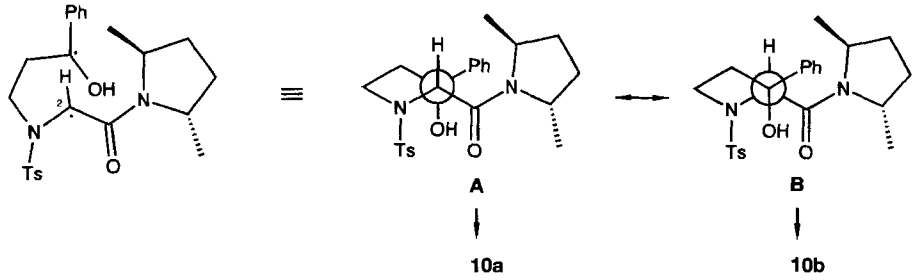


Fig. 2. *Crystal structure of* **12**. Arbitrary numbering.

The observed stereoselectivities of the photocyclizations can be explained by the preferred conformations of the intermediate biradical, as exemplified by conformations **A** and **B** formed from amide **1a** (*Scheme 4*). Conformation **A** gives the major product **10a** because of attack of radical $CH_2C(Ph)(OH)^{\cdot}$ from the less shielded side of the glycine radical at C(2).

Scheme 4



Temperature Dependence of the Stereoselectivity in the Photocyclizations of **1a** *and* **1c**. Irradiation of **1a** and **1c** at lower temperature led to an increased *de* (*Table 1*). But the

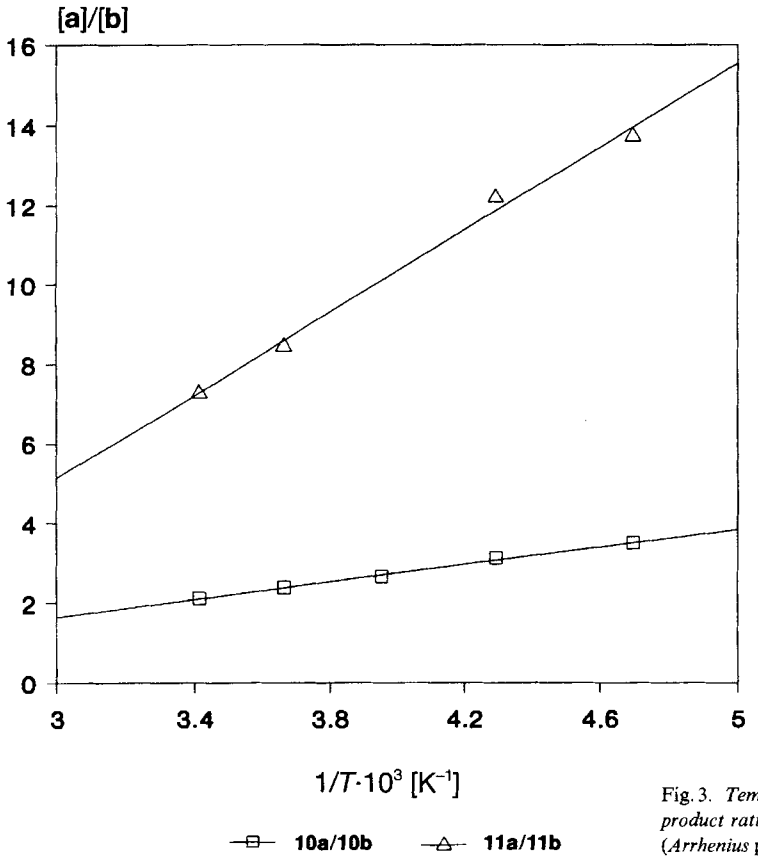


Fig. 3. *Temperature dependence of product ratios* **10a**/**10b** *and* **11a**/**11b** (*Arrhenius* plot)

Table 1. *Temperature Dependence of Photoproduct Ratio* **10a,b** *and* **11a,b**, *Obtained from* **1a** *and* **1c**, *Respectively*

T [K]	**10a/10b**	*de*(**10a**) [%]	**11a/11b**	*de*(**11a**) [%]
293	2.10:1	35.5	7.28:1	75.8
273	2.37:1	40.6	8.45:1	78.8
253	2.63:1	44.9	–	–
233	3.10:1	51.2	12.20:1	84.8
213	3.48:1	55.3	13.75:1	86.4

concomittant decrease of the reaction rates restricted the practical application of this effect. We determined the differences of the activation enthalpy and entropy between the photolysis products **10a** and **10b**, respectively, and **11a** and **11b**, respectively, by an *Arrhenius* plot (*Fig. 3*, *Eqn. 1*) and obtained the following results: for **10a/10b**, $\Delta\Delta H^{\neq} = 1.01$ kcal/mol and $\Delta\Delta S^{\neq} = -0.533$ cal/mol·K, and for **11a/11b**, $\Delta\Delta H^{\neq} = 0.791$ kcal/mol and $\Delta\Delta S^{\neq} = 1.2$ cal/mol·K.

$$\ln \frac{k_a}{k_b} = \ln \frac{[\mathbf{a}]}{[\mathbf{b}]} = \frac{\Delta H_a^{\#} - \Delta H_b^{\#}}{RT} - \frac{\Delta S_a^{\#} - \Delta S_b^{\#}}{R}, \quad \mathbf{a} \cong \mathbf{10a}, \mathbf{11a} \quad \mathbf{b} \cong \mathbf{10b}, \mathbf{11b} \qquad (1)$$

Conclusion. – Photocyclization of *N*-(2-benzoylethyl)-*N*-tosylglycinamides **1a–c** provides *cis*-configurated 3-hydroxyprolinamides **10–12** with high stereoselectivity. The asymmetric induction by chiral C_2-symmetric pyrrolidine groups as auxiliaries increases from the 2′,5′-dimethylpyrrolidine derivative **1a** to the bis(dioxino)pyrrolidine derivative **1b** and can be considered as a convenient method for the asymmetric synthesis of 3-hydroxyprolines.

We would like to thank Prof. Dr. *H.-G. Henning* for valuable discussions and suggestions. Furthermore, we thank the *Fond der Chemischen Industrie* for financial support.

Experimental Part

General. All solvents were distilled and dried. The reagents were of reagent grade and used without further purification. Org. extracts were dried (Mg_2SO_4) and evaporated below 50°. TLC: silica gel *60* F_{254} (*Merck*). Column chromatography (CC): silica gel (35–70 μm; *Chemische Fabrik Uetikon*); FC = flash chromatography. Medium-pressure liquid chromatography (MPLC): column *B-685* (*Büchi*), silica gel *C 490* (15–35 μm, *Uetikon*). Photochemistry: prep. irradiations with a 150-W mercury-arc lamp (*Hanau*); anal. irradiations with a 500-W mercury-arc lamp (*OSRAM HBO-500*); UV cuvet 1 × 1 cm; filter *WG 295* (*Schott*). M.p.: *Büchi 530*; uncorrected. Polarimetry: *Perkin Elmer 141*; $d = 9.999$ cm. UV: *Perkin-Elmer-Lamda-2* UV spectrometer; λ_{max} (lg ε) in nm. IR: *Perkin-Elmer-1600* series FTIR; in cm^{-1}. NMR: *Varian Gemini 300* (^1H, 300 MHz; ^{13}C, 75.5 MHz); chemical shifts δ in ppm rel. to internal SiMe (= 0 ppm), J in Hz; where necessary, assignments were corroborated by $^1H,^1H$-COSY. NOE Experiments: *Varian VXR-400* (^1H, 400 MHz). MS (Dr. *H. Nadig*): *VG-70-250.*

N-(3-Hydroxy-3-phenylpropyl)tosylamide (**7**). *N*-(3-Oxo-3-phenylpropyl)tosylamide [14] (6.8 g, 22.4 mmol) was suspended in EtOH (50 ml) and treated with $NaBH_4$ (0.8 g, 21.2 mmol) in portions. After additional 30 min and evaporation, H_2O (20 ml) and $CHCl_3$ (50 ml) were added. Dil. HCl soln. was added dropwise until foaming ceased. The aq. phase was extracted with $CHCl_3$ (2 × 20 ml), the combined org. phase dried and evaporated, and the residue recrystallized (MeOH/H_2O): 6.1 g (90%) of **7**. M.p. 101–103°. IR (KBr): 3465, 3179, 1597, 1322, 1156, 1095, 697. ^1H-NMR (300 MHz, $CDCl_3$): 7.78–7.21 (*m*, 9 arom. H); 5.34 (*s*, OH); 4.79 (*t*, $J_{vic} = 6.62$, 2 H–C(1)); 3.13–2.93 (*m*, H–C(3)); 2.42 (*s*, MeC_6H_4); 1.87–1.81 (*m*, 2 H–C(2)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 143.7, 143.3, 136.8, 129.7, 128.5, 127.7, 127.1, 125.5 (arom. C); 72.9 (C(3)); 40.7 (C(1)); 37.6 (C(2)); 21.5 (MeC_6H_4). EI-MS: 199 (4, $[M - 106]^+$), 184 (12), 171 (17), 155 (30, $[Ts]^+$), 150 (26), 121 (20), 105 (32), 91 (100).

*(2S,5S)-1-[*N*-(2-Benzoylethyl)-*N*-tosylglycyl]-2,5-dimethylpyrrolidine* (**1a**). A soln. of (2*S*,5*S*)-2,5-dimethylpyrrolidine (**5a**; 0.73 g, 7.4 mmol) in CH_2Cl_2 (10 ml) containing dry Na_2CO_3 (1.3 g) was treated with a soln. of bromoacetyl bromide (1.5 g, 7.4 mmol) at –40° during 2 h. After additional stirring for 10 h, the mixture was filtered and evaporated: oily (bromoacetyl)pyrrolidine **6** (1.44 g, 88%) which was used in the next step without further purification.

In a soln. of **7** (2 g, 6.55 mmol) in dry DMF (12 ml) was introduced K(*t*-BuO) (0.73 g, 6.55 mmol) in portions. After stirring for 1 h, a soln. of crude **6** in DMF (5 ml) was added dropwise. The mixture was stirred overnight at 50°, cooled, and treated with crushed ice. Extraction with Et_2O gave *(2S,5S)-1-[*N*-(3-hydroxy-3-phenylpropyl)-*N*-tosylglycyl]-2,5-dimethylpyrrolidine* (2.65 g, 91%) which was used in the next step without further purification.

A mixture of the glycylpyrrolidine (2.65 g) prepared above, PDC (2.7 g, 7.2 mmol), and CH_2Cl_2 (50 ml) was stirred overnight. Solvent was evaporated and the residue suspended in Et_2O and filtrated through a plug of silica gel (60–200 μm, *Merck*; 10 g). Evaporation and purification by FC (silica gel (35–70 μm), CH_2Cl_2/MeOH 100:2) gave 2.46 g (75%) of **1a**. Colorless oil. UV (MeCN): 237 (4.28). IR (film): 3062, 2969, 1682, 1650, 1333, 1157. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.95–7.26 (*m*, 9 arom. H); 4.30 (*d*, J_{gem} = 16.6, 1 H–C(2′)); 4.17–4.07 (*m*, 1 H–C(2′), H–C(2), H–C(5)); 3.8–3.6 (*m*, 2 H–C(1″)); 3.6–3.37 (*m*, 2 H–C(2″)); 2.40 (*s*, *Me*C_6H_4); 2.22–2.05 (*m*, 1 H–C(3), 1 H–C(4)); 1.65–1.48 (*m*, 1 H–C(3), 1 H–C(4)); 1.22 (*d*, *J* = 6.4, Me); 1.07 (*d*, *J* = 6.34, Me). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 198.9 (Ph*C*O); 166.0 (C(1′)); 143.4, 136.6, 136.4, 133.3, 129.5, 128.6, 128.1, 127.6 (arom. C); 53.6, 53.0 (C(2), C(5)); 51.0, 44.6, 39.1, 31.1, 28.7 (C(3), C(4), C(2′), C(1″), C(2″)); 21.7 (Me); 21.6 (*Me*C_6H_4); 19.0 (Me). EI-MS: 316 (7), 287 (37, [*M* – Ts]$^+$), 184 (11), 155 (36, [Zs]$^+$), 133 (23), 126 (33), 105 (64, [PhCO]$^+$), 98 (11), 91 (100), 83 (30).

N-(2-Benzoylethyl)-N-tosylglycine (**8**). A soln. of **7** (10.3 g, 33.8 mmol) in dry DMF (30 ml) was treated with K(*t*-BuO) (3.8 g, 33.8 mmol) in portions. After stirring for 30 min, a soln. of 2-(trimethylsilyl)ethyl bromoacetate [15] (8.5 g, 35.5 mmol) in dry DMF (15 ml) was added dropwise. The soln. was stirred for 20 h at 50–60°. Then crushed ice was introduced and the product extracted with Et_2O. Evaporation of the dried extract gave 17.4 g of crude *2-(trimethylsilyl)ethyl* N-*(3-hydroxy-3-phenylpropyl)*-N-*tosylglycinate* which was used in the next step without further purification.

A mixture of the glycinate (17.4 g) prepared above, PDC (21.2 g, 56 mmol), and CH_2Cl_2 (150 ml) was treated as described for **1a** (plug of silica gel (120 g)). FC (silica gel (35–70 μm), pentane/AcOEt 5:1) gave 12.3 g (71%) of *2-(trimethylsilyl)ethyl* N-*(2-benzoylethyl)*-N-*tosylglycinate*.

To a soln. of this glycinate (12.3 g) in dry THF (15 ml) was added dropwise 1M Bu_4NF in THF (16.7 ml, 26.6 mmol) during 2 h. After 14 h stirring, solid $Bu_4NF \cdot 3\,H_2O$ (8.4 g, 26.6 mmol) was added and stirring continued for 13 h. The soln. was poured into 0.1M HCl (500 ml) and extracted with Et_2O (3 × 240 ml). The combined extracts were washed with sat. NH_4Cl soln. (50 ml), dried ($MgSO_4$), and evaporated. Purification of crude **8** (8.2 g) by FC (silica gel (35–70 μm), CH_2Cl_2/MeOH/AcOH 200:10:1) gave 6.2 g (51% rel. to **7**) of **8**. M.p. 105–107°. IR (KBr): 3057, 2927, 1728, 1682, 1346, 1155. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.94–7.27 (*m*, 9 arom. H); 4.18 (*s*, NCH_2COO); 3.64 (*t*, *J* = 6.4, PhCOCH_2); 3.44 (*t*, *J* = 6.4, CH_2CH_2N); 2.42 (*s*, *Me*C_6H_4). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 198.7 (Ph*C*O); 174.5 (COOH); 143.8, 136.3, 133.5, 129.7, 128.6, 128.0, 127.2, 50.1, 44.6, 38.9 (CH_2CH_2); 21.5 (*Me*C_6H_4). FAB-MS: 362 (100, [*M* + H]$^+$), 242 (47), 206 (25), 162 (20), 155 (18, Ts$^+$), 133 (22), 105 (59, [PhCO]$^+$), 91 (59), 77 (35), 42 (78).

*(2R,4aS,5a S,8R,9aR,9bR)-1-[*N*-(2-Benzoylethyl)-*N*-tosylglycyl]perhydro-2,8-diphenyl-2*H*,5*H*,8*H*-bis-[1,3]dioxino[5,4-b:4′,5′-d]pyrrolidine* (**1b**). A soln. of **8** (0.4 g, 1.1 mmol) in dry CH_2Cl_2 (2.5 ml) was treated with 1-chloro-1-(dimethylamino)-2-methylpropene [11] (**9**; 157 μl, 1.1 mmol) during 2 h. After stirring overnight and cooling to –5°, dry pyridine (180 μl, 2.2 mmol) was added, followed by addition of **5b** (0.375 g, 1.1 mmol). After 20 h additional stirring at 20°, the soln. was diluted with CH_2Cl_2 (40 ml), extracted with H_2O (3 × 50 ml), dried, and evaporated. Purification of the crude yellow oil by FC (silica gel (35–70 μm), CH_2Cl_2/MeOH 100:1) gave 0.453 g (60%) of **1b**. White solid. M.p. 75–77°. IR (KBr): 2922, 1684, 1654, 1450, 1338, 1155. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.82–7.15 (*m*, 19 arom. H); 5.55, 5.48 (2*s*, H–C(2), H–C(8)); 5.21, 4.85 (2*d*, *J*(4A,4B) = 13.7, *J*(6A,6B) = 13.2, H_A–C(4), H_A–C(6)); 4.49, 4.44 (2*s*, H–C(9a), H–C(9b)); 4.47, 4.16 (2*d*, J_{gem} = 15.8, 2 H–C(2′)); 4.30, 4.15 (2 br. *s*, H–C(4a), H–C(5a)); 4.25 (2*d*, *J*(4A,4B) = 13.7, *J*(4B,4a) = 1.95, H_B–C(4)); 3.91 (2*d*, *J*(6A,6B) = 13.2, *J*(6B,5a) = 2.3, H_B–C(6)); 3.65 (*t*, J_{gem} = 7.3, 2 H–C(2″)); 3.42–3.24 (*m*, 2 H–C(1″)); 2.36 (*s*, *Me*C_6H_4). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 198.3 (Ph*C*O); 168.5 (C(1′)); 143.5, 137.4, 137.2, 136.5, 135.4, 133.0, 129.6, 192.4, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 126.0 (arom. C); 100.0, 99.9 (C(2), C(8)); 78.5, 77.3 (C(9a), C(9b)); 67.2, 64.4 (C(4), C(6)); 57.1, 54.8 (C(4a), C(5a)); 52.5, 38.4 (C(1″), C(2″)); 44.1 (C(2′)); 21.5 (*Me*C_6H_4). FAB-MS: 683 (21, [*M* + H]$^+$), 445 (29), 316 (27), 155 (46, [Ts]$^+$), 133 (21), 105 (88, [PhCO]$^+$), 91 (100, [PhCH_2]$^+$), 89 (22), 77 (50).

*Dimethyl (2S,5S)-1-[*N*-(2-Benzoylethyl)-*N*-tosylglycyl]pyrrolidine-2,5-dicarboxylate* (**1c**) was prepared as described for **1b**, from **8** (0.78 g, 2.16 mmol), **9** (366 µl, 2.59 mmol), and dimethyl (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylate (**5c**; 0.449 g, 2.4 mmol): 0.582 g (51%) of **1c**, after FC purification. Pale yellow resin. IR (KBr): 2955, 1743, 1679, 1449, 1340, 1156. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.95–7.15 (*m*, 9 arom. H); 4.87, 4.60 (*2d*, $J(2,3) = 8.51$, $J(5,4) = 8.52$, H–C(2), H–C(5)); 4.30, 3.97 (*2d*, $J_{gem} = 16.2$, 2 H–C(2′)); 3.84, 3.66 (*2s*, 2 COOMe); 3.76–3.48 (*m*, 2 H–C(1″)); 3.40 (*t*, $J(1'',2'') = 7.4$, 2 H–C(2″)); 2.40 (*s*, *Me*C_6H_4); 2.29–1.95 (*m*, 2 H–C(3), 2 H–C(4)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 198.4 (Ph*C*O); 172.0, 171.8 (2 *C*OOMe); 167.1 (C(1′)); 143.5, 136.5, 135.4, 133.1, 129.6, 129.0, 128.4, 128.1, 128.0, 127.9, 127.6, 125.2 (arom. C); 59.6, 59.3 (C(2), C(5)); 52.9, 52.2 (2 COOMe); 51.4, 44.6, 38.4 (C(2′), C(1″), C(2″)); 29.8, 26.81 (C(3), C(4)); 21.5 (*Me*C_6H_4). FAB-MS: 531 (39, $[M + H]^+$), 399 (70), 375 (35), 316 (31), 155 (42, $[Ts]^+$), 128 (50), 105 (73), 91 (100), 77 (37), 42 (37).

Preparation of **10–12**: *General Procedure*. A soln. of ketone **1a–c** in cyclohexane/benzene 4:1 (*ca.* 10^{-2} mol/l) was rinsed with dry, O_2-free Ar for 30 min. The soln. was irradiated until practically no educt was detectable by TLC (*ca.* 1 h). After evaporation, the crude photoproducts were separated by FC and purified by MPLC.

*(2S,5S)-1-[(2R,3R)- and -(2S,3S)-3-Hydroxy-3-phenyl-*N*-tosylprolyl]-2,5-dimethylpyrrolidine* (**10a** and **10b**, resp.). From **1a** (1 g). FC (CH_2Cl_2/MeOH 100:2) gave 0.47 g (47%) of **10a** and 0.23 g (23%) of **10b**.

Data of **10a**: M.p. 55–58°. IR (KBr): 3421, 2968, 1624, 1448, 1328, 1160, 702, 666, 549. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.94–7.12 (*m*, 9 arom. H); 5.14 (*s*, OH); 4.67 (*s*, H–C(2′)); 4.28–4.19 (*m*, H–C(5)); 3.84–3.78 (*t*, 1 H–C(5′)); 3.51–3.42 (*m*, 1 H–C(5′)); 2.80–2.72 (*m*, H–C(2)); 2.68–2.57 (*m*, 1 H–C(4′)); 2.43 (*s*, *Me*C_6H_4); 2.17–2.11 (*m*, 1 H–C(4′)); 2.07–1.75 (*m*); 1.5–1.2 (*m*, 2 H–C(3), 2 H–C(4)); 1.18 (*d*, $J = 6.5$, Me); 1.10 (*d*, $J = 6.4$, Me). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 167.3 (CO); 143.5, 140.8, 136.4, 129.5, 128.5, 128.0, 125.5 (arom. C); 81.5 (C(3′)); 68.5 (C(2′)); 54.3, 53.6 (C(2), (C(5)); 46.5, 39.9, 30.7, 28.5 (C(4′), C(5′), C(3), C(4)); 21.6 (*Me*C_6H_4); 20.7, 18.9 (2 Me). EI-MS: 316 (18), 287 (21, $[M - Ts]^+$), 155 (30, $[Ts]^+$), 132 (28), 126 (63), 105 (100, $[PhCO]^+$), 98 (33), 91 (67), 77 (83).

Data of **10b**: M.p. 120–125°. IR (KBr): 3357, 3261, 2975, 1626, 1439, 1338, 1162, 670. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.83–7.14 (*m*, 9 arom. H); 6.81 (*s*, OH); 4.44 (*s*, H–C(2′)); 4.32–4.22 (*m*, H–C(5)); 4.22–4.13 (*m*, H–C(2)); 3.81–3.62 (*m*, 2 H–C(5′)); 2.44 (*s*, *Me*C_6H_4); 2.24–1.77 (*m*, 2 H–C(4″), 1 H–C(3), 1 H–C(4)); 1.51–1.40 (*m*, 1 H–C(3), 1 H–C(4)); 1.14 (*s*, $J = 6.4$, Me); 0.27 (*s*, $J = 6.6$, Me). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 169.2 (CO); 143.7, 142.3, 129.7, 128.6, 127.8, 127.5, 126.5, 125.4 (arom. C); 82.0 (C(3′)); 65.1 (C(2′)); 54.7, 53.8 (C(2), C(5)); 47.5, 40.2, 30.7, 29.1 (C(4′), C(5′), C(3), C(4)); 21.6 (*Me*C_6H_4); 21.5, 17.9 (2 Me). EI-MS: 316 (18), 287 (24, $[M - Ts]^+$), 155 (39, $[Ts]^+$), 133 (13), 126 (54), 105 (40, $[PhCO]^+$), 98 (24), 91 (100), 83 (29), 77 (28).

*Dimethyl (2S,5S)-1-[(2S,3S)- and -(2R,3R)-3-Hydroxy-3-phenyl-*N*-tosylprolyl]pyrrolidine-2,5-dicarboxylate* (**11a** and **11b**, resp.). From **1c** (0.744 g). The crude photolysis mixture was separated by MPLC (CH_2Cl_2/MeOH 250:1): 159 mg (22%) of **11a** and 74.4 mg (10%) of **11b**.

Data of **11a**: Viscous oil. IR (KBr): 3447, 2956, 1735, 1670, 1437, 1348, 1163. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.76–7.26 (*m*, 9 arom. H); 4.90 (*s*, H–C(2′)); 4.69, 4.17 (*2d*, $J(2,3) = 9.89$, $J(5,4) = 7.97$, H–C(2), H–C(5)); 4.35 (*s*, OH); 3.81, 3.76 (*2s*, 2 COOMe); 3.63–3.50 (*m*, 2 H–C(5′)); 2.42 (*s*, *Me*C_6H_4); 2.39–1.93 (*m*, 2 H–C(3), 2 H–C(4), 2 H–C(4′)). ^{13}C-NMR ($CDCl_3$): 173.1, 171.4 (2 *C*OOMe); 168.4 (CO, amide); 143.2, 142.9, 136.4, 129.4, 128.6, 127.9, 127.5, 125.0 (arom. C); 82.1 (C(3′)); 67.7 (C(2′)); 59.8, 59.1 (C(2), C(5)); 53.0, 52.8 (2 COOMe); 46.0, 40.6 (C(5′), C(4′)); 29.2, 26.8 (C(3), C(4)); 21.5 (*Me*C_6H_4). FAB-MS: 531 (93, $[M + H]^+$), 375 (49), 316 (88), 200 (14), 188 (29), 186 (100), 162 (14), 155 (12), 149 (36), 144 (26), 128 (56), 126 (25), 105 (36), 91 (83), 77 (32), 68 (26).

Data of **11b**: Viscous oil. IR (KBr): 3448, 2955, 1742, 1648, 1438, 1356, 1164. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.83–7.21 (*m*, 9 arom. H); 5.13, 4.68 (*2d*, $J(2,3) = 9.34$, $J(5,4) = 7.35$, H–C(2), H–C(5)); 4.67 (*s*, H–C(2′)); 4.62 (*s*, OH); 3.73, 3.34 (*2s*, 2 COOMe); 3.51 (*t*, $J_{vic} = 6.84$, 2 H–C(5′)); 2.44 (*s*, *Me*C_6H_4); 2.35–1.84 (*m*, 2 H–C(3), 2 H–C(4), 2 H–C(4′)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 173.6, 172.7 (2 *C*OOMe); 169.1 (CO, amide); 144.3, 143.9, 135.2, 129.7, 129.6, 128.5, 128.0, 127.7, 127.6, 124.5, 124.4 (arom. C); 82.0 (C(3′)); 68.5 (C(2′)); 60.6, 59.7 (C(2), C(5)); 52.7, 52.4 (2 COO*Me*); 46.4, 40.6 (C(5′), C(4′)); 30.0, 26.8 (C(3), C(4)); 21.6 (*Me*C_6H_4). FAB-MS: 531 (50, $[M + H]^+$), 375 (34), 316 (100), 298 (49), 200 (19), 188 (51), 186 (58), 162 (15), 155 (29, $[Ts]^+$), 144 (28), 128 (68), 105 (36), 91 (94), 77 (24).

*(2R,4aS,5aS,8R,9aR,9bR)-Perhydro-1-[(2R,3R)-3-hydroxy-3-phenyl-*N*-tosylprolyl]-2,8-diphenyl-2*H*,5*H*,8*H*-bis[1,3]dioxino[5,4-*b*:4′,5′-*d*]pyrroline* (**12**). From **1b** (0.345 g). During photolysis, 0.17 g (49%) of pure **12** precipitated. Evaporation and FC (silica gel (35–70 µm), CH_2Cl_2/MeOH 100:1) gave additional 65 mg (19%). Total yield, 0.235 g (68%). Colorless solid. M.p. 222–225°. IR (KBr): 3436, 2924, 1676, 1349, 1138. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.85–7.01 (*m*, 19 arom. H); 5.57, 5.41 (*2s*, H–C(2), H–C(8)); 5.55, 5.03 (*2d*, $J(4A,4B) = 13.46$, $J(6A,6B) = 16.21$, H_A–C(4), H_A–C(6)); 5.06 (*s*, H–C(2′)); 4.39, 4.12 (*2s*, H–C(9a), H–C(9b)); 4.28 (*d*, $J(4a,6B) = 2.32$, H–C(4a)); 4.00–3.94 (*m*, H_B–C(4), H_B–C(6)); 3.85–3.63 (*m*, 2 H–C(5′)); 3.66 (*s*, OH); 3.22 (*s*, H–C(5a)); 2.40 (*s*, *Me*C_6H_4); 2.28–2.16 (*m*, 2 H–C(4′)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 168.9 (C=O); 144.2, 143.3,

137.5, 137.0, 129.5, 129.2, 129.1, 128.5, 128.3, 128.2, 127.6, 127.5, 126.1, 126.0, 124.5 (arom. C); 100.0, 99.2 (C(2), C(8)); 83.6 (C(3')); 78.4, 77.2 (C(9a), C(9b)); 71.0 (C(2')); 67.3, 64.3 (C(4), C(6)); 57.2, 54.3 (C(4a), C(5a)); 47.6, 43.6 (C(4'), C(5')); 21.6 (MeC_6H_4). FAB-MS: 683 (81, $[M + H]^+$), 577 (20), 527 (20), 316 (100), 144 (33), 105 (62), 91 (96), 77 (22).

X-Ray Structure Analysis of **12**. The X-ray structure of **12** is shown *Fig. 2*. Crystal data and parameters of the data collection are compiled in *Table 2*. Unit-cell parameters were determined by accurate centering of 25 strong independent reflections by the least-squares method. Reflection intensities were collected at r.t. on a four-circle diffractometer *Enraf-Nonius CAD4* equipped with a graphite monochromator and using CuK_α radiation. Three standard reflections monitored every h during data collection showed no intensity loss. The usual corrections were applied. Diffraction absorption direct-method strategies using the program SHELXS-86 [16]. Anisotropic least-squares refinement was carried out on all non-H-atoms using the program CRYSTALS [17]. Positions of H-atoms were calculated. Scattering factors were taken from International Tables of Crystallography, Vol. IV. Fractional coordinates are deposited in the *Cambridge Crystallographic Data Base*.

Table 2. *Crystal Data and Parameters of Data Collection for* **12**

Molecular formula	$C_{38}H_{38}N_2O_8S$	Crystal dimensions [mm]	0.15 × 0.15 × 0.42
Crystal system	orthorhombic	Temperature [K]	298
Space group	*P*212121	Θ_{max} [°]	74.3
a [Å]	11.401(8)	Radiation	CuK_α, λ = 1.54178 Å
b [Å]	15.109(9)	Scan type	$\omega/2\Theta$
c [Å]	19.324(12)	No. of independent refl.	3792
α [°]	90(0)	No. of refl. in refinement	2983
β [°]	90(0)	No. of variables	447
γ [°]	90(0)	Final *R*	3.37
V [Å^3]	3328.64(3.72)	Final R_w	4.01
Z	4	Weighting scheme	weight $\cdot [1 - (\Delta F/6\sigma F)^2]^2$

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