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Synthesis of ornithine lactams via diastereoselective photocyclization of 2-amino-4-oxo-4-phenyl-butanoyl amines

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Abstract

The diastereoselective synthesis of ornithine lactams **6–9** via photoinduced ε-hydrogen abstraction followed by cyclization of the corresponding 1,6-biradicals is described. A highly asymmetric 1,4-induction is observed.

1. Introduction

In recent years, diastereoselective photocyclization reactions have been developed as key steps in the synthesis of biologically interesting compounds.[1–4] The advantage of such ring closure reactions is the formation of a C–C bond, possibly along with two new asymmetric centers.

In an earlier report, we described the cyclization of 4-oxo-4-phenyl-butanoyl amines to δ-lactams via photoinduced hydrogen abstraction from the ε-position.[5] Herein we report the synthesis of *N*-protected (±)-2-amino- and (*S*)-2-amino-4-oxo-4-phenyl-butanoyl amines and their diastereoselective photocyclization to ornithine lactams. The interest in mono- and bicyclic ornithine lactams has grown in recent years owing to their utility as β-turn mimetics in peptide chemistry.[6–8]

2. Results and discussion

2.1. Synthesis of (±)-2-trifluoroacetylamino- and (S)-2-benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl amines 3 and 7

Trifluoroacetyl-protected amino acid **1** was synthesized in two steps, starting with L-aspartic acid according to the literature.[9–11] The appropriate amides **3** were afforded via the in situ generated acid

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chloride[12] (Eq. 1, Table 1) and under these conditions complete racemization occurs presumably as a result of the base-induced formation of a 5-oxo-1,3-oxazole from the acid chloride.[13,14]

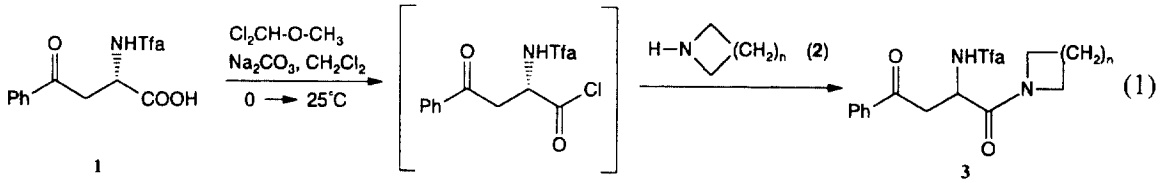
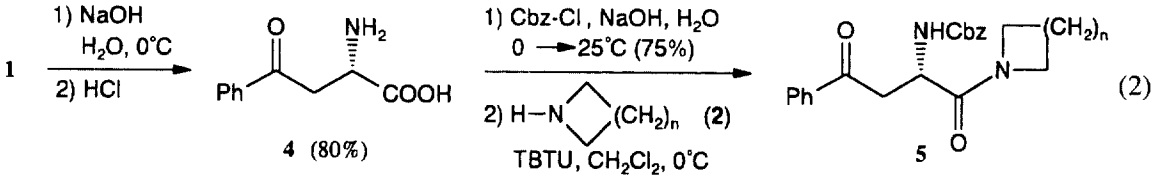


Table 1
Isolated yields of amides (±)-**3** and (*S*)-**5**

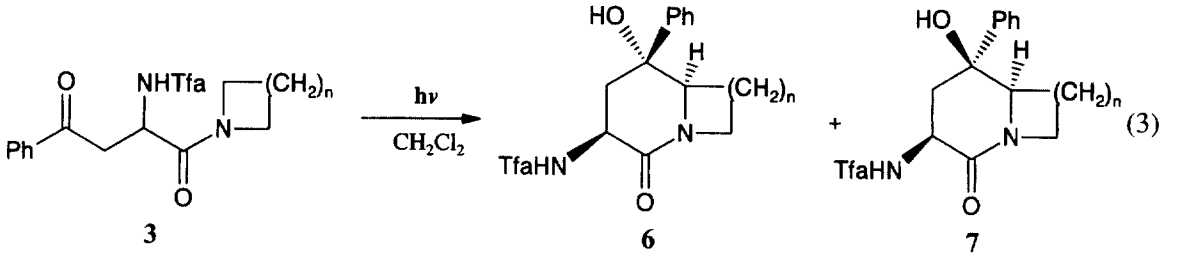
	n	(±)-3 [%]	(*S*)-5 [%]
a	1	44	8
b	2	66	65
c	3	71	79
d	4	48	80

We therefore decided to change the protecting group of amides **3**. The deprotection of acid **1** with NaOH to afford the known β-benzoylalanine **4**[15] could be accomplished in gram amounts (Eq. 2). Compound **4** was then protected with benzyloxycarbonyl chloride, followed by coupling with amines **2**, using TBTU[16] (Eq. 2, Table 1). Amides **5** were afforded with enantiomeric excesses >95%.



2.2. *Photocyclization of amides 3 and 5 to ornithine lactams 6–9*

For the following stage, we turned our attention to the investigation of the photocyclization of amides **3** and **5**. Irradiation of these compounds yielded the corresponding ornithine lactams **6–9** as a result of an intramolecular ε-hydrogen abstraction (Eqs. 3 and 4). Remarkably, this reaction yields in both cases only two (**6** and **7**; **8** and **9**) of the four possible diastereomers. Ornithine lactams **6** and **8** are the major products (Table 2).



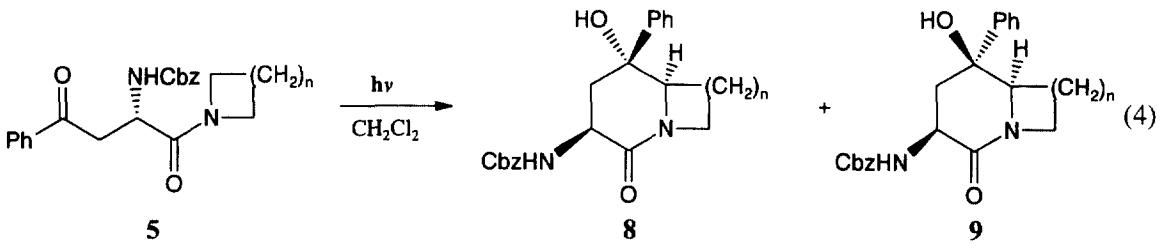


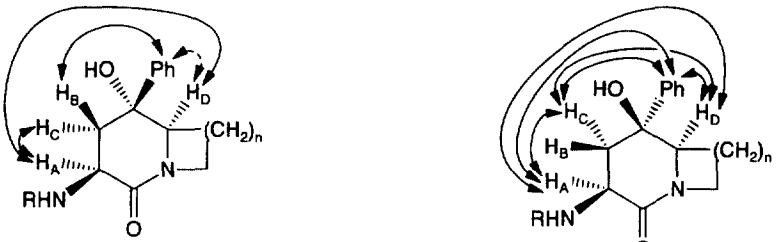
Table 2
Yields* and diastereoselectivities of ornithine lactams **6–9**

	n	(±)-6	(±)-7	*d.s.* (6) [%]	8	9	*d.s.* (8) [%]
a	1	52	28	67	67	29	70
b	2	74	22	77	54	16	77
c	3	53	15	78	41	9	82
d	4	72	9	89	68	26	72

* determined by HPLC

The amine substituent in reactants **3** and **5** effects a 1,4-induction on the newly formed stereocenter at the bridge head carbon atom of bicyclic products **6–9**. Thus, the methine proton on this carbon atom assumes a *trans*-position in relation to the protected amino groups in all photoproducts. The influence of 1,3-induction on the formation of the second new stereocenter is only moderate.

The relative configuration of products **6** and **7** and the absolute configuration of bicyclic compounds **8** and **9** were assigned by coupling constants in the ^{1}H NMR spectra and by NOE experiments. Coupling constants between H_A and H_B (9.4–13.2 Hz) and between H_A and H_C (3.0–7.0 Hz) indicate that proton H_A assumes a pseudo-axial position at the 6-ring. The results of NOE experiments are summarized in Fig. 1. Indeed, an NOE effect between protons H_A and H_C was observed for all ornithine lactams **6–9**. The broken line marks a small NOE effect between the aromatic *ortho*-protons with H_D of products **6** and **8**. This is smaller than that found with H_B of these compounds.



6 R:-Tfa
8 R:-Cbz

7 R:-Tfa
9 R:-Cbz

* NOE difference signals between H_B and H_C and between H_A and the nitrogen bonded proton are not included to simplify matters.

Figure 1. Observed NOE effects of ornithine lactams **6–9***

Additionally, the structure of product **6b** was established by X-ray analysis of compound **10** (Fig. 2), which was obtained after removal of the Tfa-group using $NaBH_4$.[17] The investigated crystal contained only one enantiomer (space group: $P2_12_12_1$). The small distance (2.33 Å) between H19 and H27 in the X-ray structure of **10** explains the NOE effect between the similiar protons H_A and H_D, which was observed for all ornithine lactams **6–9**.

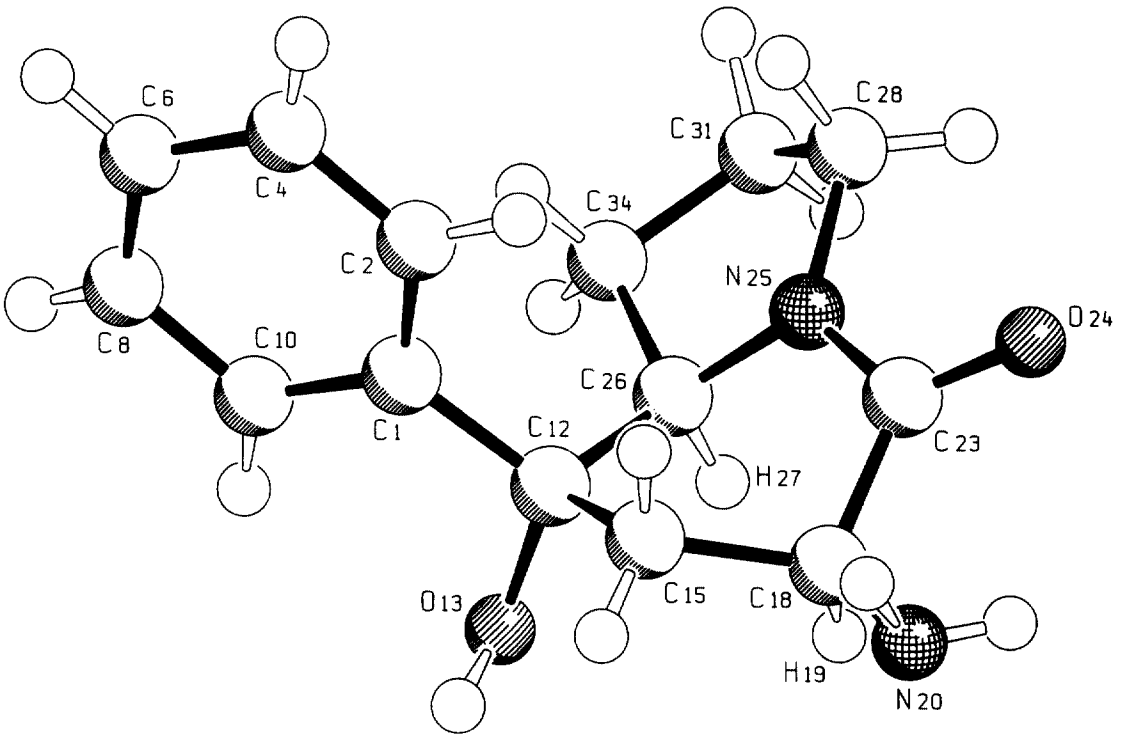


Figure 2. X-Ray structure of deprotected amine derivative **10**

Possible conformations of the triplet 1-hydroxyl-1,6-biradicals, which are formed by ε-hydrogen abstraction after irradiation, were calculated in order to explain the observed diastereoselectivities of the photocyclization. Fig. 3, shows the calculated structure of a low energy conformer of the biradical, which reflects convenient conditions for cyclization. The calculation was performed with the MM+ force field (Hyperchem). As seen in Fig. 3, a hydrogen bond between the hydroxyl group and the carbonyl oxygen atom of the amino-protecting group was found (formyl group was used to simplify the calculations). Its distance was calculated as 2.2 Å.

Products **6–9** were formed by combination of the two radical centers I and II from the *Re*-site. Presumably, the reason for this exclusive selectivity is the preferred conformation, as shown in Fig. 3, around the C–C bond between the stereogenic center and the amide carbon atom (black marked bond). The hydrogen atom H-2, the smallest substituent at the stereocenter, prefers a *syn*-orientation to H-1. This conformation involves the smallest amount of unfavorable steric interactions.

The conformational analysis of the *N*-alanyl-pyrrolidine-2-yl radical used as a model system, performed on a semi-empirical level (UHF/PM3), confirms that the energetically preferred conformer is characterized by a *syn*-orientation of the hydrogen atoms H-4 and H-5. The structure shown in Fig. 4 corresponds to the global minimum with a dihedral angle (N–C–C–N) of 150°.

The formation of both possible products **6** and **7/8** and **9** by radical combination from the *Re*-site can be explained by two contradictory effects. The intramolecular hydrogen bond can influence the diastereoselectivity of radical combination. The major products **6** and **8** are formed from the biradical conformation with the hydrogen bridge shown in Fig. 3.

In contrast, in these cases the steric hindrance between the hydrogen atom H-3 opposite the radical center I and the phenyl ring at the radical center II influences the cyclization (see Fig. 3). We have already discussed such an effect for the diastereoselective photocyclization of 4-oxo-4-phenyl-butanoyl

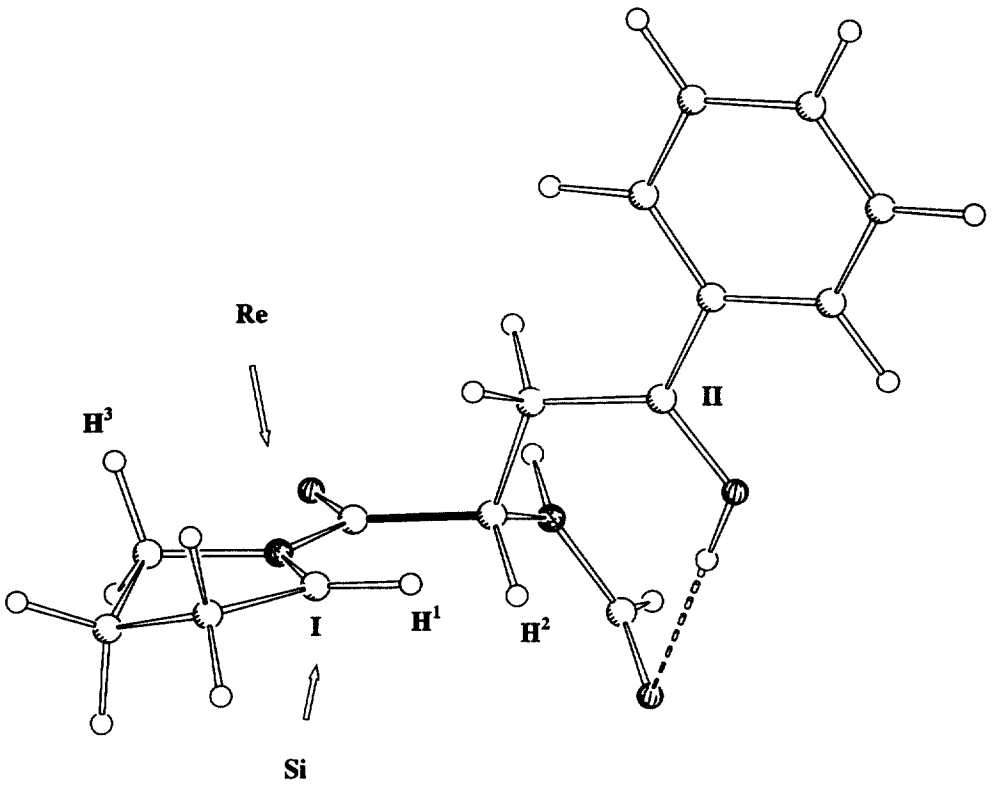


Figure 3. Calculated structure of 1,6-biradical

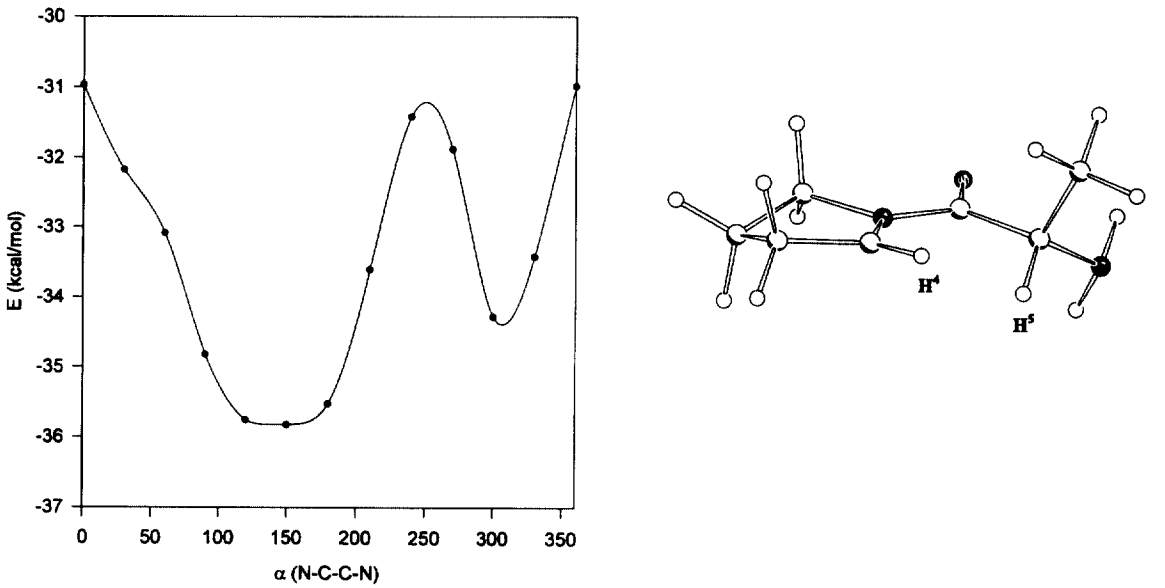


Figure 4. Calculated structure and conformational analysis of *N*-alanyl-pyrrolidine-2-yl radical

amines.[5] The steric repulsion during the formation of the C–C bond is smaller if the hydrogen atom H-3 interacts with the smaller hydroxyl group as opposed to the aromatic moiety. This steric interaction could be the force for breaking of the hydrogen bridge and rotation around the C–C bond between the radical center II and the neighboring CH_2 group to yield ornithine lactams **7** and **9**. Thus, the observed diastereoselectivities show that the calculated intramolecular hydrogen bond does not completely offset the steric shielding of the radical center I by the opposite hydrogen H-3.

In conclusion, we have reported the photocyclization of 2-amino-4-oxo-4-phenyl-butanoyl amines **3** and **5**, affording diastereoselectively ornithine lactams **6–9**. The effective asymmetric 1,4-induction is explained with a preferred conformation of the corresponding 1,6-biradicals, which is caused by the dominant influence of the amino-substituents.

3. Experimental

TLC was performed on alumina sheets with silica gel 60 F_{254} (Merck), detected by UV light. Silica gel 40–63 μm (Merck) and a mobile phase of dichloromethane:methanol (v/v) were used for flash chromatography (FC). High-pressure liquid chromatography (HPLC) was performed on an analytical SIX [NH_2] column (150×3.3 mm, 5 μm, Laboratorni Pristroje) under the following conditions: flow 1 ml/min, mobile phase *n*-hexane:2-propanol, 95:5 (v/v), UV detection at 220 and 230 nm. Enantiomeric excesses of amines **3b** and **5b** were determined on an OD-Chiralcel column (Daicel), detected by Chiralizer (IBZ Messelektronik). The uncorrected melting points (m.p.s) were determined on a Boetius micro melting point apparatus (Wagema). IR spectra were taken with a Perkin–Elmer 881 (solids as KBr pellets, oils on NaCl plates). NMR spectra were recorded with a Bruker DPX300 (^{1}H 300 MHz, ^{13}C 75.5 MHz), using $SiMe_4$ as an internal standard (0 ppm). EI-mass spectra were taken with a Hewlett Packard 5995 A, 70 eV at 293–593 K.

3.1. General procedure for the synthesis of 2-trifluoroacetylamino-4-oxo-4-phenyl-butanoyl amines **3**

(*S*)-2-Trifluoroacetylamino-4-oxo-4-phenyl-butanoic acid **1**[9–11] (20.0 mmol) dissolved in dried CH_2Cl_2 (100 ml) was treated with Na_2CO_3 (32.0 mmol) at 0°C. A solution of dichloromethylmethyl-ether (25.0 mmol) in dried CH_2Cl_2 (20 ml) was added at this temperature. After stirring for 2.5 h at 0°C, the amine **2** (40.0 mmol), dissolved in CH_2Cl_2 (20 ml), was added dropwise to the reaction mixture. The solution was stirred for 12 h at room temperature, then the precipitate was filtered off. The filtrate was washed with water, with diluted HCl, again with water, with saturated $NaHCO_3$ solution and again with water. Products **3** were afforded by flash chromatography after drying the organic layer over $MgSO_4$ and removal of the solvent in vacuo.

3.1.1. 2-Trifluoroacetylamino-4-oxo-4-phenyl-butanoyl azetidine ***3a***

(*S*)-2-Trifluoroacetylamino-4-oxo-4-phenyl-butanoic acid **1**[9–11] (1.00 g, 3.63 mmol) was treated with an ethanolic solution of azetidine **2a**, which was afforded by stirring of azetidine hydrochloride (0.42 g, 4.54 mmol) with *t*-BuOK (0.50 g, 4.54 mmol) in absolute ethanol (50 ml) for 30 min. Purification by FC (CH_2Cl_2:MeOH, 10:1) afforded **3a** (R_f=0.55) as a white solid (524 mg, 44%).

M.p.=104–106°C; IR (KBr): ν=3227, 1723, 1678, 1635, 1211, 1186, 1156 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.24 (m, 1H, NH), 7.98–7.35 (m, 5H, arom. H), 5.11–5.03 (m, 1H, 2-C*H*), 4.66–4.40 (m, 2H), 4.12–4.98 (m, 2H), 3.72 (dd, *J*=8.9, 17.7, 1H, 3-CH_AH$_B$), 3.39 (dd, *J*=4.1, 17.7, 1H, 3-CH$_A$$H_B$), 2.40–2.30 (m, 2H, C$H_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=196.8 (s, C-1), 169.1 (s, C-4), 157.0 (q,

CF_3), 135.8 (s, arom. C), 133.7, 128.7, 128.0 (d, arom. CH), 51.1 (t, N–*C*H_2), 48.3 (t, N–*C*H_2), 45.1 (d, C-2), 40.3 (t, C-3), 15.3 (t, *C*H_2); MS (EI, 70 eV): *m/z* (%)=328 (1), [M^+] 105 (74), [{CO–Ph}$^+$] 84 (58), [{CO–azetidinyl}$^+$] 77 (55), [Ph^+] 69 (14), 56 (100) [{azetidinyl}$^+$]. Anal. calcd for $C_{15}H_{15}N_2O_3F_3$: C 54.88, H 4.61, N 8.53; found: C 55.31, H 4.95, N 8.17.

3.1.2. 2-Trifluoroacetylamino-4-oxo-4-phenyl-butanoyl pyrrolidine 3b

The reaction of (*S*)-2-trifluoroacetylamino-4-oxo-4-phenyl-butanoic acid **1**[9–11] (5.50 g, 20.0 mmol) with pyrrolidine **2b** (2.06 ml, 25.0 mmol) yielded after FC (CH_2Cl_2:MeOH, 100:3) **3b** (R_f=0.46, CH_2Cl_2:MeOH, 100:4) as a white solid (3.86 g, 66%).

M.p.=141–143°C; UV/vis (MeCN): λ_{max} (lg ε)=242.0 (4.16), 278.5 (3.05), 318.5 (2.28); IR (KBr): ν=3223, 1715, 1679, 1627, 1201, 1185, 1167, 1153 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.22–8.14 (m, 1H, NH), 7.98–7.38 (m, 5H, arom. H), 5.37–5.30 (m, 2H, 2-C*H*), 3.93–3.67 (m, 3H, CH_2–N–C$H_A$$H_B$), 3.49–3.38 (m, 3H, N–C$H_A$$H_B$, 3-C$H_2$), 2.07–1.84 (m, 4H, 2×C$H_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=196.7 (s, C-1), 168.0 (s, C-4), 156.7 (q, *C*F_3), 136.0 (s, arom. C), 133.6, 128.7, 128.0 (d, arom. CH), 47.9 (d, 2-C), 46.9 (t, N–*C*H_2), 46.4 (t, N–*C*H_2), 41.0 (t, C-3), 25.9 (t, *C*H_2), 24.1 (t, *C*H_2); MS (EI, 70 eV): *m/z* (%)=342 (0), [M^+] 244 (0.5), [M^+–{CO–pyrrolidinyl}] 105 (48), [{CO–Ph}$^+$] 98 (79), [{CO–pyrrolidinyl}$^+$] 77 (60), [Ph^+] 70 (100) [{pyrrolidinyl}$^+$]. Anal. calcd for $C_{16}H_{17}N_2O_3F_3$: C 56.14, H 5.01, N 8.18; found: C 56.40, H 4.50, N 8.10.

3.1.3. 2-Trifluoroacetylamino-4-oxo-4-phenyl-butanoyl piperidine 3c

(*S*)-2-Trifluoroacetylamino-4-oxo-4-phenyl-butanoic acid **1**[9–11] (1.50 g, 5.45 mmol) was treated with piperidine **2c** (0.67 ml, 6.81 mmol). Purification by FC (CH_2Cl_2:MeOH, 100:4) gave **3c** (R_f=0.50) as a white solid (1.38 g, 71%).

M.p.=137–139°C; IR (KBr): ν=1719, 1684, 1622, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.04–7.42 (m, 6H, arom. H, NH), 5.52 (dt, *J*=5.2, 7.8, 1H, 2-C*H*), 3.66–3.44 (m, 5H, CH_2–N–CH_2, 3-C$H_A$$H_B$), 3.39 (dd, *J*=5.2, 17.1, 1H, 3-C$H_A$$H_B$), 1.84–1.44 (m, 6H, 3×C$H_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=196.5 (s, C-1), 167.7 (s, C-4), 156.7, 156.2 (q, *C*F_3), 136.1 (s, arom. C), 133.7, 128.7, 128.1 (d, arom. CH), 47.1 (t, N–*C*H_2), 46.0 (d, C-2), 43.8 (t, N–*C*H_2), 41.1 (t, C-3), 26.2 (t, *C*H_2), 25.4 (t, *C*H_2), 24.3 (t, *C*H_2); MS (EI, 70 eV): *m/z* (%)=356 (0.6), [M^+] 112 (100), [{CO–piperidinyl}$^+$] 105 (52), [{CO–Ph}$^+$] 84 (64), [{piperidinyl}$^+$] 77 (52), [Ph^+] 69 (75).

3.1.4. 2-Trifluoroacetylamino-4-oxo-4-phenyl-butanoyl azepanine 3d

Reaction of (*S*)-2-trifluoroacetylamino-4-oxo-4-phenyl-butanoic acid **1**[9–11] (1.50 g, 5.45 mmol) with hexamethylenimine **2d** (0.77 ml, 6.81 mmol), followed by FC (CH_2Cl_2:MeOH, 100:4), afforded **3d** (R_f=0.52) as a white solid (972 mg, 48%).

M.p.=132–134°C; IR (KBr): ν=3230, 1717, 1685, 1620, 1212, 1183, 1156 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.98–7.39 (m, 5H, arom. H), 7.80 (d, *J*=8.7, 1H, NH), 5.50 (dt, *J*=5.3, 8.1, 1H, 2-C*H*), 3.79–3.55 (m, 4H), 3.45–3.37 (m, 2H), 1.93–1.51 (m, 8H, 4×CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=196.5 (s, C-1), 169.2 (s, C-4), 156.7, 156.2 (q, *C*F_3), 136.2 (s, arom. C), 133.6, 128.7, 128.1 (d, arom. CH), 48.1 (t, N–*C*H_2), 46.8 (t, N–*C*H_2), 46.4 (d, C-2), 41.3 (t, C-3), 28.8 (t, *C*H_2), 27.2 (t, *C*H_2), 27.1 (t, *C*H_2), 26.5 (t, *C*H_2); MS (EI, 70 eV): *m/z* (%)=370 (3), [M^+] 265 (22), [M^+–{CO–Ph}] 126 (100), [{CO–azepanyl}$^+$] 105 (51), [{CO–Ph}$^+$] 98 (45), [{azepanyl}$^+$] 83 (18), 77 (39), [Ph^+] 55 (60).

3.2. (S)-2-Amino-4-oxo-4-phenyl-butanoic acid 4

(*S*)-2-Trifluoroacetylamino-4-oxo-4-phenyl-butanoic acid **1**[9–11] (35.13 g, 122 mmol) was stirred with NaOH (12.15 g, 305 mmol) in water (400 ml) for 4 h. At 0°C the mixture was acidified with HCl:water (1:10) to pH=4. The precipitate was filtered off. This procedure was repeated and the precipitate collected. After drying the white solid, **4**[15] (30.8 g, 80%) was afforded (R_f=0.62, EtOH:H_2O:NH_3, 20:5:2).

M.p.=60–62°C; $[\alpha]_D^{20}$ +4.6 (*c* 1, H_2O); IR (KBr): ν=3518, 3450, 1684, 1623, 1596, 1411, 1349 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ=7.93–7.45 (m, 5H, arom. H), 4.11–4.08 (m, 1H, 2-H), 3.69–3.66 (m, 2H, 3-CH_2); ^{13}C NMR (75.5 MHz, D_2O): δ=205.9 (s, C-4), 174.1 (s, CO), 170.6 (s, CO), 135.7 (s, arom. C), 134.9, 129.3, 128.6 (d, arom. CH), 50.8 (d, C-2), 39.0 (t, C-3); MS (EI, 70 eV): *m/z* (%)=193 (0), [M^+] 105 (100), [{CO–Ph}$^+$] 77 (69), [Ph^+] 51 (40), 44 (58).

3.3. (S)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoic acid 11

NaOH (5.40 g, 5% excess) was dissolved in water (120 ml) and (*S*)-2-amino-4-oxo-4-phenyl-butanoic acid **4**[15] (12.0 g, 62.2 mmol) was added followed by benzyloxycarbonylchloride (9.60 ml, 57.1 mmol) at 0°C. The mixture was stirred for 48 h at room temperature. Ethyl acetate was then added. The non-separated water layer was treated with 9 N aq. HCl until no precipitate formed. The organic layer was separated, dried over $MgSO_4$ and the solvent removed under reduced pressure. Product **11** (15.2 g, 75%) was isolated as viscous oil.

$[\alpha]_D^{20}$ +44.9 (*c* 1, CH_2Cl_2); IR (KBr): ν=3544, 3067, 3033, 1723, 1689, 1521, 1509, 1215, 1064, 755, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=10.01 (s, 1H, OH), 7.93–7.31 (m, 10H, arom. H), 5.99 (d, *J*=8.3, 1H, NH), 5.09 (s, 2H, Ph–CH_2), 4.82–4.79 (m, 1H, 2-C*H*), 3.76 (dd, *J*=3.8, 18.1, 1H, CH_AH$_B$), 3.56 (dd, *J*=3.8, 18.1, 1H, CH$_A$$H_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=197.7 (s, C-4), 176.1 (s, C-1), 156.3 (s, *C*OO), 135.9, 135.7 (s, arom. C), 133.8, 128.7, 128.5, 128.2, 128.1, 128.0 (d, arom. CH), 67.2 (t, Ph–CH_2), 49.8 (d, C-2), 40.7 (t, C-3); MS (EI, 70 eV): *m/z* (%)=327 (0), [M^+] 305 (0.3), 108 (48), 107 (31), 105 (100), [{CO–Ph}$^+$] 91 (92), [{CH_2–Ph}$^+$] 79 (95), 77 (91), [Ph^+] 65 (21), 51 (49).

3.4. General procedure for the synthesis of 2-benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl amines 5

(*S*)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoic acid **4** (4.00 mmol), TBTU (4.40 mmol) and Et*N*(*i*-Pr)$_2$ (8.00 mmol or 12.0 mmol in the case of amine hydrochloride) were stirred in CH_2Cl_2 (25 ml) at 0°C for 15 min. Then amine **2** (4.00 mmol) in 10 ml solvent was added dropwise. After stirring for 0.5–4 h, the reaction mixture was washed with citric acid in water (3×), with water (1×), with saturated $NaHCO_3$ solution (3×) and with water (1×). The organic layer was dried over $MgSO_4$. Removal of the solvent in vacuo followed by purification by FC afforded amide **5**.

3.4.1. (S)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl azetidine 5a

The reaction of (*S*)-2-benzyloxycarbonylamino-4-oxo-4-phenyl-butanoic acid **11** (1.42 g, 4.33 mmol) with azetidine hydrochloride **2a**·HCl (0.40 g, 4.33 mmol) gave, after purification by FC (R_f=0.22, CH_2Cl_2:MeOH, 100:4), product **5a** (50 mg, 8%) as a viscous oil.

$[\alpha]_D^{20}$ −12.0 (*c* 0.5, CH_2Cl_2); IR (KBr): ν=3421, 1719, 1682, 1651, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.95–7.30 (m, 10H, arom. H), 5.65 (d, *J*=9.0, 1H, NH), 5.10 (s, 2H, Ph–C*H*), 4.86–4.78 (m, 1H, 2-C*H*), 4.52–4.42 (m, 2H), 4.52–4.42 (m, 2H), 3.51 (dd, *J*=7.9, 17.3, 1H, 3-CH_AH$_B$), 3.40 (dd, *J*=4.1, 17.3, 1H, 3-CH$_A$$H_B$), 2.33–2.26 (m, 2H, C$H_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=197.6 (s, C-1), 170.4

(s, C-4), 136.3 136.2 (s, arom. C), 133.5, 128.6, 128.5, 128.2, 128.1 (d, arom. CH), 67.0 (t, Ph–CH_2), 51.0 (t, N–CH_2), 48.2 (t, N–CH_2), 46.9 (d, C-2), 41.3 (t, C-3), 15.4 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=366 (1), [M^+] 105 (71), [{CO–Ph}$^+$] 91 (100), [{CH_2–Ph}$^+$] 77 (20), [Ph^+] 56 (23) [{azetidinyl}$^+$].

3.4.2. (S)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl pyrrolidine **5b**

(*S*)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoic acid **11** (1.44 g, 4.39 mmol) was treated with pyrrolidine **2b** (0.36 ml, 4.39 mmol), providing, after purification by FC (R_f=0.44, CH_2Cl_2:MeOH, 100:4), product **5b** (1.11 g, 67%) as a viscous oil.

$[\alpha]_D^{20}$ −34.1 (*c* 1, CH_2Cl_2); UV/vis (MeCN): λ_{max} (lg ε)=242.0 (4.10), 278.0 (3.00), 311.5 (2.02); IR (KBr): ν=3262, 1717, 1683, 1628, 1449, 746, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.00–7.26 (m, 10H, arom. H), 5.81–5.66 (m, 1H, NH), 5.09 (m, 3H, 2-C*H*, Ph–CH_2), 3.88–3.58 (m, 3H), 3.44–3.30 (m, 3H), 1.98–1.72 (m, 4H, 2×CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=197.9 (s, C-1), 169.7 (s, C-4), 156.0 (q, COO), 136.8, 136.6 (s, arom. C), 133.8, 129.0, 128.9, 128.6, 128.5 (d, arom. CH), 67.4 (t, Ph–CH_2), 49.6 (d, C-2), 47.1 (t, N–CH_2), 46.5 (t, N–CH_2), 42.4 (t, C-3), 26.4 (t, CH_2), 24.6 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=380 (0.4), [M^+] 105 (71), [{CO–Ph}$^+$] 98 (24), [{CO–pyrrolidinyl}$^+$] 91 (100), [{CH_2–Ph}$^+$] 77 (16), [Ph^+] 70 (48), [{pyrrolidinyl}$^+$] 55 (21).

3.4.3. (S)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl piperidine **5c**

The reaction of (*S*)-2-benzyloxycarbonylamino-4-oxo-4-phenyl-butanoic acid **11** (1.01 g, 3.09 mmol) with piperidine **2c** (0.31 ml, 3.09 mmol), followed by purification by FC (R_f=0.31, CH_2Cl_2:MeOH, 100:4), yielded product **5c** (780 mg, 79%) as a viscous oil.

$[\alpha]_D^{20}$ −25.5 (*c* 1, CH_2Cl_2); IR (KBr): ν=3267, 2938, 1715, 1684, 1626, 1448, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.97–7.27 (m, 10H, arom. H), 5.89–5.83 (m, 1H, NH), 5.33–5.28 (m, 1H, 2-C*H*), 5.08 (s, 2H, Ph–CH_2), 3.69–3.48 (m, 5H, CH_2–N–CH_2, 3-CH_AH$_B$), 3.29 (dd, *J*=4.5, 17.0, 1H, 3-CH$_A$$H_B$), 1.72–1.45 (m, 6H, 3×C$H_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=197.3 (s, C-1), 163.1 (s, C-4), 155.5 (q, COO), 136.4, 136.2 (s, arom. C), 133.2, 128.5, 128.4, 128.1, 128.0 (d, arom. CH), 66.9 (t, Ph–CH_2), 47.1 (d, C-2), 47.0 (d, N–CH_2), 43.5 (t, N–CH_2), 41.9 (t, C-3), 26.2 (t, CH_2), 25.5 (t, CH_2), 24.4 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=394 (0.5), [M^+] 112 (23), [{CO–piperidinyl}$^+$] 105 (79), [{CO–Ph}$^+$] 91 (100), [{CH_2–Ph}$^+$] 84 (42), [{piperidinyl}$^+$] 77 (20), [Ph^+] 69 (22).

3.4.4. (S)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl azepanine ***5d***

(*S*)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoic acid **11** (1.24 g, 3.78 mmol) was treated with hexamethylenimine **2d** (0.43 ml, 3.78 mmol). Purification by FC (R_f=0.42, CH_2Cl_2:MeOH, 100:4) gave product **5d** (1.23 g, 80%) as a viscous oil.

$[\alpha]_D^{20}$ −28.8 (*c* 1, CH_2Cl_2); IR (KBr): ν=3412, 3266, 2928, 1715, 1683, 1626, 1284, 1241, 1213 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=8.03–7.26 (m, 10H, arom. H), 6.01 (d, *J*=9.4, 1H, NH), 5.37–5.22 (m, 1H, 2-C*H*), 5.08 (s, 2H, Ph–CH_2), 3.85–3.40 (m, 5H, 2×N–CH_2, 3-CH_AH$_B$), 3.29 (dd, *J*=4.5, 17.3, 1H, 3-CH$_A$$H_B$), 2.01–1.48 (m, 8H, 4×C$H_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=197.3 (s, C-1), 170.6 (s, C-4), 155.5 (q, COO), 136.3, 136.2 (s, arom. C), 133.1, 128.4, 128.3, 128.0 (d, arom. CH), 66.9 (CH_2–Ph), 47.9 (t, N–CH_2), 47.3 (d, C-2), 46.3 (t, N–CH_2), 42.1 (t, C-3), 28.7 (t, CH_2), 27.2 (t, CH_2), 26.9 (t, CH_2), 26.6 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=408 (0.4), [M^+] 126 (13), [{CO–azepanyl}$^+$] 105 (69), [{CO–Ph}$^+$] 98 (28), [{azepanyl}$^+$] 91 (100), [{CH_2–Ph}$^+$] 77 (17), [Ph^+] 53 (28).

3.5. General procedure for the photocyclization of amides 3 and 5

Irradiation of amides **3** and **5** was performed in dichloromethane with concentrations of nearly 1 mg/ml, using a 150 W high pressure mercury arc lamp. The solutions were degassed with argon for 30 min before irradiation, and stirred during irradiation. The products were separated by flash chromatography.

3.5.1. (3S,5R,5aR)-(±)-3-Trifluoroacetylamino-5-hydroxy-5-phenyl-1-aza-bicyclo[4.2.0]octan-2-one 6a and (3S,5S,5aR)-(±)-3-trifluoroacetylamino-5-hydroxy-5-phenyl-1-aza-bicyclo[4.2.0]octan-2-one 7a

Irradiation of 2-trifluoroacetylamino-4-oxo-4-phenyl-butanoyl azetidine **3a** (83 mg, 0.25 mmol) was performed in dichloromethane (120 ml). Purification by FC (CH_2Cl_2:MeOH, 100:3) yielded **6a** (29 mg, 35%), 9 mg (11%) of **7a** and a mixture of **6a** and **7a** (18 mg, 22%) as white solids.

6a: m.p.=50–52°C; IR (KBr): ν=3394, 1723, 1712, 1701, 1685, 1673, 1669, 1653, 1642, 1172, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.72 (s, 1H, NH), 7.35–7.21 (m, 5H, arom. H), 4.83–4.71 (m, 2H, 3-H, 5a-H), 3.86–3.81 (m, 2H, 7-CH_2), 2.73 (dd, J=4.0, 13.2, 1H, 4-CH_AH$_B$), 2.31 (dd, J=12.4, 13.2, 1H, 4-CH$_A$$H_B$), 1.87–1.69 (m, 3H, OH, 6-CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=169.6 (s, C-2), 141.4 (s, arom. C), 128.7, 128.3, 125.2 (d, arom. CH), 74.2 (s, C-5), 73.1 (d, C-5a), 48.6 (t, C-7), 47.2 (d, C-3), 38.4 (t, CH_2), 26.4 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=328 (0.3), [M^+] 105 (44), 91 (5), 84 (17), 77 (30), [Ph^+] 69 (14), 56 (100).

7a: m.p.=71–73°C; IR (KBr): ν=3389, 2923, 1721, 1710, 1666, 1659, 1641, 1214, 1183, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.64 (m, 1H, NH), 7.33–7.24 (m, 5H, arom. H), 4.71 (dd, J=5.6, 8.3, 1H, 5a-H), 4.51–4.45 (m, 1H, 3-H), 4.15–4.09 (m, 1H, 7-CH_AH$_B$), 3.94–3.89 (m, 1H, 7-CH_AH$_B$), 3.28 (s, 1H, OH), 3.02 (dd, J=10.2, 15.4, 1H, 4-CH_AH$_B$), 2.43–2.34 (m, 1H, 6-CH_AH$_B$), 2.30–2.22 (m, 1H, 6-CH$_A$$H_B$), 2.14 (dd, J=3.0, 15.4, 1H, 4-CH$_A$$H_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.1 (s, C-2), 140.5 (s, arom. C), 128.7, 128.1, 125.1 (d, arom. CH), 72.5 (s, C-5), 71.4 (d, C-5a), 49.5 (t, C-7), 46.8 (d, C-3), 44.4 (t, C-4), 19.2 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=328 (1), [M^+] 105 (59), 91 (9), 84 (13), 77 (31), [Ph^+] 69 (17), 56 (100).

3.5.2. (6S,8R,8aR)-(±)-6-Trifluoroacetylamino-8-hydroxy-8-phenyl-perhydro-indolizin-5-one 6b and (6S,8S,8aR)-(±)-6-trifluoroacetylamino-8-hydroxy-8-phenyl-perhydro-indolizin-5-one 7b

2-Trifluoroacetylamino-4-oxo-4-phenyl-butanoyl pyrrolidine **3b** (515 mg, 1.50 mmol) was irradiated in dichloromethane (500 ml). A white solid **6b** (282 mg, 55%) and a 1:0.57 mixture of **6b** and **7b** (109 mg, 21%) were isolated by FC (CH_2Cl_2:MeOH, 100:3).

6b: m.p.=69–71°C; IR (KBr): ν=3377, 1723, 1656, 1214, 1179, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.86 (s, 1H, NH), 7.36–7.29 (m, 5H, arom. H), 4.86–4.78 (m, 1H, 6-H), 3.89 (t, J=7.2, 1H, 8a-H), 3.53–3.34 (m, 3H, 3-CH_2, OH), 2.97 (dd, J=6.4, 13.9, 1H, 7-CH_AH$_B$), 2.28 (dd, J=11.8, 13.9, 1H, 7-CH$_A$$H_B$), 1.98–1.58 (m, 2H), 1.41–1.22 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=167.0 (s, C-5), 143.7 (s, arom. C), 128.3, 127.8, 125.5 (d, arom. CH), 74.5 (s, C-8), 65.9 (d, C-8a), 48.9 (d, C-6), 45.4 (t, C-3), 42.9 (t, C-7), 28.0 (t, CH_2), 22.5 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=342 (1), [M^+] 105 (12), 77 (12), [Ph^+] 70 (100), 28 (12). Anal. calcd for $C_{16}H_{17}N_2O_3F_3$: C 56.14, H 5.01, N 8.18; found C 55.99, H 5.06, N 8.02.

7b: ^1H NMR (300 MHz, $CDCl_3$): δ=8.05 (s, 1H, NH), 7.49–7.20 (m, 5H, arom. H), 4.72–4.63 (m, 1H, 6-H), 3.93 (t, J=7.3, 1H, 8a-H), 3.69–3.48 (m, 3H, 3-CH_2, OH), 3.08 (dd, J=9.4, 15.1, 1H, 7-CH_AH$_B$), 2.06 (dd, J=6.4, 15.1, 1H, 7-CH$_A$$H_B$), 1.94–1.53 (m, 4H, 1-C$H_2$, 2-C$H_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$):

δ=166.7 (s, C-5), 143.3 (s, arom. C), 128.2, 124.8 (d, arom. CH), 73.1 (s, C-8), 66.1 (d, C-8a), 48.3 (d, C-6), 47.0 (t, C-3), 44.4 (t, C-7), 26.3 (t, CH_2), 23.0 (t, CH_2).

3.5.3. (1R,3S,9aR)-(±)-3-Trifluoroacetylamino-1-hydroxy-1-phenyl-perhydro-quinolizin-4-one ***6c*** *and (1S,3S,9aR)-3-trifluoroacetylamino-1-hydroxy-1-phenyl-perhydro-quinolizin-4-one* ***7c***

Photoreaction of 2-trifluoroacetylamino-4-oxo-4-phenyl-butanoyl piperidine **3c** (207 mg, 0.58 mmol) in dichloromethane (230 ml) afforded, after purification by FC (CH_2Cl_2:MeOH, 100:3), a white solid **6c** (109 mg, 53%) and product **7c** (30 mg, 15%) as a viscous oil.

6c: m.p.=187–190°C; IR (KBr): ν=3462, 1702, 1622, 1211, 1200, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.71–7.66 (m, 1H, NH), 7.39–7.31 (m, 5H, arom. H), 4.83–4.75 (m, 1H, 3-H), 4.65–4.60 (m, 1H, 6-CH_AH$_B$), 3.50 (d, *J*=12.4, 1H, 9a-H), 3.22 (s, 1H, OH), 2.86 (ddd, *J*=1.1, 5.9, 11.8, 1H, 2-CH_AH$_B$), 2.59–2.51 (m, 2H, 6-CH$_A$$H_B$, 2-CH$_A$$H_B$), 1.78–0.88 (m, 6H, 7-$CH_2$, 8-$CH_2$, 9-$CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=165.2 (s, C-4), 157.7 (q, CF_3), 143.2 (s, arom. C), 128.7, 128.4, 125.3 (d, arom. CH), 73.2 (s, C-1), 68.4 (d, C-9a), 49.1 (d, C-3), 45.6 (t, C-6), 33.1 (t, C-2), 30.5 (t, CH_2), 25.2 (t, CH_2), 25.0 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=356 (0.3), [M^+] 236 (6), 112 (5), 105 (18), 77 (19), [Ph^+] 63 (12), 55 (20). Anal. calcd for $C_{17}H_{19}N_2O_3F_3$: C 57.31, H 5.38, N 7.82; found: C 56.93, H 5.60, N 6.35.

7c: IR (KBr): ν=3401, 1731, 1620, 1167, 1025 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=8.88–8.85 (m, 1H, NH), 7.79–7.27 (m, 5H, arom. H), 5.55 (s, 1H, OH), 4.67–4.62 (m, 1H, 6-CH_AH$_B$), 4.08–4.00 (m, 1H, 3-H), 3.71 (dd, 1H, 9a-H), 2.73–2.65 (m, 1H, 6-CH$_A$$H_B$), 2.41–2.38 (m, 2H, 2-$CH_2$), 1.96–1.51 (m, 6H, 7-$CH_2$, 8-$CH_2$, 9-$CH_2$); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ=164.2 (s, C-4), 144.0 (s, arom. C), 128.3, 127.5, 125.6 (d, arom. CH), 70.0 (s, C-1), 64.2 (d, C-9a), 47.8 (d, C-3), 44.1 (t, C-6), 37.0 (t, C-2), 27.2 (t, CH_2), 25.1 (t, CH_2), 24.4 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=356 (1), [M^+] 236 (9), 105 (19), 84 (100), 77 (16), [Ph^+] 69 (13), 66 (52).

3.5.4. (1R,3S,10aR)-(±)-3-Trifluoroacetylamino-1-hydroxy-1-phenyl-perhydro-pyrido[1,2-a]azepin-4-one ***6d*** *and (1S,3S,10aR)-(±)-3-trifluoroacetylamino-1-hydroxy-1-phenyl-perhydro-pyrido-[1,2-a]azepin-4-one* ***7d***

Irradiation of 2-trifluoroacetylamino-4-oxo-4-phenyl-butanoyl azepanine **3d** (126 mg, 0.34 mmol) in dichloromethane (120 ml), followed by purification by FC (CH_2Cl_2:MeOH, 100:3), gave **6d** (60 mg, 48%) and **7d** (16 mg, 9%) as white solids.

6d: m.p.=221–223°C; IR (KBr): ν=3437, 1705, 1620, 1220, 1190, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.92–7.88 (m, 1H, NH), 7.36–7.28 (m, 5H, arom. H), 4.77–4.71 (m, 1H, 3-H), 3.71–3.64 (m, 1H, 6-CH_AH$_B$), 3.62 (dd, *J*=3.4, 11.7, 1H, 10a-H), 3.50–3.42 (m, 1H, 6-CH$_A$$H_B$), 3.30 (s, 1H, OH), 2.80 (dd, *J*=6.4, 13.6, 1H, 2-CH_AH$_B$), 2.48 (dd, *J*=12.1, 13.6, 1H, 2-CH$_A$$H_B$), 1.96–1.04 (m, 8H, 7-$CH_2$, 8-$CH_2$, 9-$CH_2$, 10-$CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=168.3 (s, C-4), 157.6, 157.1 (q, CF_3), 143.7 (s, arom. C), 128.5, 127.9, 125.3 (d, arom. CH), 74.5 (s, C-1), 68.5 (d, C-10a), 49.1 (d, C-3), 46.2 (t, C-6), 38.4 (t, C-2), 30.5 (t, CH_2), 27.8 (t, CH_2), 27.2 (t, CH_2), 26.6 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=370 (9), [M^+] 265 (25), 250 (10), 126 (11), 105 (22), 98 (100), 77 (23), [Ph^+] 69 (18). Anal. calcd for $C_{18}H_{21}N_2O_3F_3$: C 58.37, H 5.72, N 7.56; found: C 57.75, H 5.48, N 7.34.

7d: m.p.=66–68°C; IR (KBr): ν=3369, 1718, 1640, 1212, 1187, 1163 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.86–7.80 (m, 1H, NH), 7.49–7.27 (m, 5H, arom. H), 4.79–4.68 (m, 1H, 3-H), 4.63–4.56 (m, 1H, 6-CH_AH$_B$), 3.64 (dd, *J*=3.2, *J*=11.4, 1H, 10a-H), 3.23 (dd, *J*=7.0, 14.0, 1H, 2-CH_AH$_B$), 3.10–3.02 (m, 1H, 6-CH$_A$$H_B$), 2.30 (s, 1H, OH), 2.22–2.16 (m, 1H), 1.89–1.11 (m, 8H, 2-CH$_A$$H_B$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=169.0 (s, C-4), 144.8 (s, arom. C), 128.7, 127.6, 124.6 (d, arom. CH), 67.0 (d, C-3), 49.1 (d, C-10a), 45.6 (t, C-2), 43.6 (t, C-6), 30.0 (t, CH_2), 29.1 (t, CH_2), 27.9 (t, CH_2), 25.1 (t, CH_2);

MS (EI, 70 eV): *m/z* (%)=370 (2), [M^+] 265 (10), 126 (19), 105 (45), 98 (100), 82 (18), 77 (45), [Ph^+] 68 (31).

3.5.5. (3S,5R,5aR)-3-Benzyloxycarbonylamino-5-hydroxy-5-phenyl-1-aza-bicyclo[4.2.0]octan-2-one ***8a*** *and (3S,5S,5aR)-3-benzyloxycarbonylamino-5-hydroxy-5-phenyl-1-aza-bicyclo[4.2.0]octan-2-one* ***9a***

(*S*)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl azetidine **5a** (100 mg, 0.27 mmol) was irradiated in dichloromethane (120 ml). Purification by FC (CH_2Cl_2:MeOH, 100:2) afforded products **8a** (30 mg, 30%), **9a** (10 mg, 10%) and a 2:1 mixture of **8a** and **9a** (20 mg, 20%) as viscous oils.

8a: $[\alpha]_D^{20}$ +78.5 (*c* 0.5, CH_2Cl_2); IR (NaCl): ν=3399, 1716, 1650, 1216, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.44–7.32 (m, 10H, arom. H), 6.12 (d, *J*=4.9, 1H, NH), 4.97 (s, 2H, Ph–CH_2), 4.81–4.87 (m, 1H, 5a-H), 4.69–4.62 (m, 1H, 3-H), 3.87–3.82 (m, 2H, 7-CH_2), 3.45–3.42 (m, 1H, OH), 2.73 (dd, *J*=4.1, 13.6, 1H, 4-CH_AH_B), 2.35 (dd, *J*=12.6, 13.6, 1H, 4-CH_AH_B), 1.86–1.73 (m, 2H, 6-CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.0 (s, C-2), 155.9 (s, CO–O), 142.1, 136.3 (s, arom. C), 128.6, 128.5, 128.3, 128.1, 128.0, 125.4 (d, arom. CH), 74.3 (s, C-5), 72.8 (d, C-5a), 66.8 (t, Ph–CH_2), 48.2 (t, C-7), 47.8 (d, C-3), 40.4 (t, C-4), 26.0 (t, C-6); MS (EI, 70 eV): *m/z* (%)=366 (1), [M^+] 105 (45), 91 (100), [{Ph–CH_2}$^+$] 77 (18), [Ph^+] 65 (13), 56 (71).

9a: $[\alpha]_D^{20}$ +11.4 (*c* 0.2, CH_2Cl_2); IR (NaCl): ν=3401, 2925, 1706, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.46–7.29 (m, 10H, arom. H), 5.89 (d, *J*=6.0, 1H, NH), 5.12 (s, 2H, Ph–CH_2), 4.74–4.69 (m, 1H, 5a-H), 4.28–4.16 (m, 2H, 3-H, 7-CH_AH_B), 3.96–3.88 (m, 2H, OH, 7-CH_AH_B), 2.99 (dd, *J*=4.7, 15.4, 1H, 4-CH_AH_B), 2.51–2.44 (m, 1H, 6-CH_AH_B), 2.31 (dd, *J*=1.4, 15.4, 1H, 4-CH_AH_B), 2.19–2.13 (m, 1H, 6-CH_AH_B); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=172.2 (s, C-2), 156.8 (s, CO–O), 141.5, 136.1 (s, arom. C), 128.6, 128.5, 127.8, 125.4 (d, arom. CH), 72.0 (s, C-5), 71.6 (d, C-5a), 67.0 (t, Ph–CH_2), 49.4 (t, C-7), 45.0 (t, C-4), 38.6 (d, C-3), 18.9 (t, C-6); MS (EI, 70 eV): *m/z* (%)=366 (8), [M^+] 148 (11), 105 (62), 91 (100), [{Ph–CH_2}$^+$] 77 (21), [Ph^+] 65 (14), 56 (99).

3.5.6. (6S,8R,8aR)-6-Benzyloxycarbonylamino-8-hydroxy-8-phenyl-perhydro-indolizin-5-one ***8b*** *and (6S,8S,8aR)-6-benzyloxycarbonylamino-8-hydroxy-8-phenyl-perhydro-indolizin-5-one* ***9b***

Photocyclization of (*S*)-2-benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl pyrrolidine **5b** (440 mg, 1.16 mmol) was performed in dichloromethane (500 ml). White solids **8b** (110 mg, 25%), **9b** (20 mg, 5%) and a 3:1 mixture of **8b** and **9b** (123 mg, 28%) were isolated by FC (CH_2Cl_2:MeOH, 100:2).

8b: m.p.=57–58°C; $[\alpha]_D^{20}$ +121.7 (*c* 1, CH_2Cl_2); IR (KBr): ν=3396, 1708, 1653, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.35–7.26 (m, 10H, arom. H), 6.17 (d, *J*=4.9, 1H, NH), 5.03 (s, 2H, Ph–CH_2), 4.71–4.63 (m, 1H, 6-H), 3.89–3.85 (m, 1H, 8a-H), 3.70 (s, 1H, OH), 3.47–3.34 (m, 2H, 3-CH_2), 2.90 (dd, *J*=6.6, 14.1, 1H, 7-CH_AH_B), 2.26 (dd, *J*=11.9, 14.1, 1H, 7-CH_AH_B), 1.83–1.72 (m, 1H, 1-CH_AH_B), 1.61–1.50 (m, 1H, 2-CH_AH_B), 1.40–1.29 (m, 1H, 1-CH_AH_B), 1.22–1.12 (m, 1H, 2-CH_AH_B); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=168.4 (s, C-5), 156.2 (s, CO–O), 144.3, 136.3 (s, arom. C), 128.5, 128.1, 128.0, 127.9, 127.4, 125.7 (d, arom. CH), 74.6 (s, C-8), 66.9 (t, Ph–CH_2), 65.5 (d, C-8a), 49.7 (d, C-6), 45.2 (t, C-7, C-3), 27.7 (t, CH_2), 22.7 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=380 (0.1), [M^+] 105 (22), 91 (37), [{Ph–CH_2}$^+$] 77 (10), [Ph^+] 70 (100).

9b: m.p.=50–52°C; $[\alpha]_D^{20}$ +12.0 (*c* 0.5, CH_2Cl_2); IR (KBr): ν=3410, 1714, 1701, 1652, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.55–7.25 (m, 10H, arom. H), 6.13 (d, *J*=6.0, 1H, NH), 5.11 (s, 2H, Ph–CH_2), 4.35–4.27 (m, 1H, 6-H), 3.86–3.81 (m, 2H, 8a-H, OH), 3.59, 3.55 (m, 2H, 2-CH_2), 3.02 (dd, *J*=9.8, 15.1, 1H, 7-CH_AH_B), 2.08 (dd, *J*=6.0, 15.1, 1H, 7-CH_AH_B), 1.95–1.84 (m, 2H), 1.78–1.67 (m, 1H), 1.59–1.50 (m, 1H, 1-CH_AH_B); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=168.0 (s, C-5), 156.8 (s, CO–O), 144.1, 136.2 (s, arom. C), 128.5, 128.4, 128.1, 127.3, 125.0 (d, arom. CH), 72.7 (s, C-8), 67.1 (t,

Ph–CH_2), 66.0 (d, C-8a), 49.4 (d, C-6), 46.9 (t, C-7), 45.6 (t, C-3), 26.3 (t, CH_2), 23.1 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=380 (0.2), [M^+] 105 (24), 91 (39), [{Ph–CH_2}$^+$] 77 (9), [Ph^+] 70 (100).

3.5.7. (1R,3S,9aR)-3-Benzyloxycarbonylamino-1-hydroxy-1-phenyl-perhydro-quinolizin-4-one **8c** *and (1S,3S,9aR)-3-benzyloxycarbonylamino-1-hydroxy-1-phenyl-perhydro-quinolizin-4-one* **9c**

(*S*)-2-Benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl piperidine **5c** (527 mg, 1.34 mmol) was irradiated in dichloromethane (500 ml). Purification by FC (twice, CH_2Cl_2:MeOH, 100:2 and 100:1) yielded white solids **8c** (151 mg, 29%) and **9c** (40 mg, 5%).

8c: m.p.=80–83°C; $[\alpha]_D^{20}$ +27.5 (*c* 1, CH_2Cl_2); IR (KBr): ν=3398, 1711, 1698, 1632, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.41–7.31 (m, 10H, arom. H), 5.92 (s, 1H, NH), 5.00 (s, 2H, Ph–CH_2), 4.60–4.48 (m, 2H, 3-H, 6-CH_AH_B), 4.25–4.13 (m, 1H, OH), 3.46–3.35 (m, 1H, 9a-H), 2.63–2.53 (m, 2H, 2-CH_2), 2.46–2.32 (m, 1H, 6-CH_AH_B), 1.76–1.62 (m, 1H), 1.58–1.23 (m, 3H), 1.17–0.96 (m, 1H), 0.94–0.83 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=166.6 (s, C-4), 156.6 (s, CO–O), 143.9, 136.3 (s, arom. C), 128.4, 128.0, 127.9, 125.5 (d, arom. CH), 73.0 (s, C-1), 68.3 (d, C-9a), 66.6 (t, Ph–CH_2), 49.3 (d, C-3), 45.4 (t, C-6), 34.4 (t, C-2), 30.0 (t, CH_2), 25.2 (t, CH_2), 25.0 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=394 (0.1), [M^+] 105 (24), 91 (48), [{Ph–CH_2}$^+$] 84 (100), 77 (12) [Ph^+].

9c: m.p.=42–45°C; $[\alpha]_D^{20}$ −35.4 (*c* 0.5, CH_2Cl_2); IR (KBr): ν=3412, 2927, 1716, 1631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.45–7.32 (m, 10H, arom. H), 5.89 (s, 1H, NH), 5.07 (s, 2H, Ph–CH_2), 4.65–4.58 (m, 1H, 6-CH_AH_B), 4.13–4.02 (m, 1H, 3-H), 3.68–3.60 (m, 1H, 9a-H), 2.78–2.60 (m, 3H, 6-CH_AH_B, 2-CH_AH_B, OH), 2.27–2.12 (m, 1H, 2-CH_AH_B), 1.87–1.26 (m, 6H, 7-CH_2, 8-CH_2, 9-CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=167.6 (s, C-4), 156.2 (s, CO–O), 144.1, 136.3 (s, arom. C), 128.7, 128.4, 128.0, 127.9, 124.9 (d, arom. CH), 72.6 (s, C-1), 66.9 (t, Ph–CH_2), 64.6 (d, C-9a), 49.7 (d, C-3), 45.7 (t, C-6), 40.1 (t, C-2), 25.8 (t, CH_2), 24.6 (t, CH_2), 23.6 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=394 (0.1), [M^+] 105 (30), 91 (60), [{Ph–CH_2}$^+$] 84 (100), 77 (14), [Ph^+] 55 (11).

3.5.8. (1R,3S,10aR)-3-Benzyloxycarbonylamino-1-hydroxy-1-phenyl-perhydro-pyrido[1,2-a]azepin-4-one **8d** *and (1S,3S,10aR)-3-benzyloxycarbonylamino-1-hydroxy-1-phenyl-perhydro-pyrido-[1,2-a]azepin-4-one* **9d**

Irradiation of (*S*)-2-benzyloxycarbonylamino-4-oxo-4-phenyl-butanoyl azepanine **5d** (450 mg, 1.10 mmol) in dichloromethane (500 ml) gave white solids **8d** (283 mg, 63%) and **9d** (66 mg, 15%) after purification by FC (CH_2Cl_2:MeOH, 100:2).

8d: m.p.=76–78°C; $[\alpha]_D^{20}$ +74.5 (*c* 1, CH_2Cl_2); IR (KBr): ν=3397, 2932, 1713, 1630, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.35–7.28 (m, 10H, arom. H), 6.08 (s, 1H, NH), 5.29 (s, 2H, Ph–CH_2), 4.60–4.52 (m, 1H, 3-H), 3.84 (s, 1H, OH), 3.78–3.65 (m, 1H, 6-CH_AH_B), 3.65–3.56 (m, 1H, 10a-H), 3.39–3.33 (m, 1H, 6-CH_AH_B), 2.71 (dd, *J*=6.0, 13.9, 1H, 2-CH_AH_B), 2.44 (dd, *J*=12.4, 13.9, 1H, 2-CH_AH_B), 1.96–1.85 (m, 1H), 1.75–1.54 (m, 1H), 1.38–1.24 (m, 1H), 1.07–0.99 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=169.9 (s, C-4), 156.3 (s, CO–O), 144.4, 136.3 (s, arom. C), 128.4, 128.2, 128.0, 127.9, 127.5, 125.4 (d, arom. CH), 74.5 (s, C-1), 68.4 (d, C-10a), 66.8 (t, Ph–CH_2), 49.6 (d, C-3), 45.6 (t, C-6), 40.4 (t, C-2), 30.2 (t, CH_2), 28.2 (t, CH_2), 27.4 (t, CH_2), 26.8 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=408 (1), [M^+] 105 (33), 98 (100), 91 (65), [{Ph–CH_2}$^+$] 77 (11) [Ph^+].

9d: m.p.=54–57°C; $[\alpha]_D^{20}$ +2.4 (*c* 1, CH_2Cl_2); IR (KBr): ν=3404, 1715, 1689, 1656, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.51–7.28 (m, 10H, arom. H), 6.13–6.11 (m, 1H, NH), 5.12 (s, 2H, Ph–CH_2), 4.64–4.57 (m, 2H, 3-H, 6-CH_AH_B), 3.63–3.59 (m, 1H, 10a-H), 3.16 (dd, *J*=6.6, 13.6, 1H, 2-CH_AH_B), 3.06–2.98 (m, 1H, 6-CH_AH_B), 2.21–2.17 (m, 1H, OH), 1.90–1.12 (m, 9H, 2-CH_AH_B, 7-CH_2, 8-CH_2, 9-CH_2, 10-CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.5 (s, C-4), 156.1 (s, CO–O), 145.4, 136.3 (s, arom. C), 128.7, 128.5, 128.3, 128.1, 127.9, 127.2, 124.6 (d, arom. CH), 76.3 (s, C-1), 67.0 (d,

C-10a), 66.8 (t, Ph–CH_2), 50.2 (d, C-3), 47.2 (t, C-2), 43.3 (t, C-6), 30.1 (t, CH_2), 29.2 (t, CH_2), 27.9 (t, CH_2), 25.1 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=408 (1), [M^+] 105 (41), 98 (100), 91 (73), [{Ph–CH_2}$^+$] 79 (12), 77 (26) [Ph^+].

3.5.9. (6S,8R,8aR)-(±)-3-Amino-8-hydroxy-8-phenyl-hexahydro-indolizin-5-one ***10***

According to the literature[12] (6*S*,8*R*,8a*R*)-(±)-3-trifluoroacetylamino-8-hydroxy-8-phenyl-hexahydro-indolizin-5-one **6b** (350 mg, 1.00 mmol) was treated with $NaBH_4$ (151 mg, 4 mmol) in 5 ml absolute EtOH at 0°C. After stirring for 2 h, acetone (5 ml) was added, followed by stirring for 20 min. The solvent was removed under reduced pressure. The residue was dissolved in K_2CO_3 solution and extracted with dichloromethane (3×). Drying of the organic layer over $MgSO_4$ followed by removal of the solvent in vacuo afforded **10** (210 mg, 85%) as a white solid.

M.p.=176°C; IR (KBr): ν=1657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.36–7.25 (m, 5H, arom. H), 3.88–3.80 (m, 2H, 6-H, 8a-H), 3.48–3.29 (m, 2H, 3-CH_2), 3.50 (dd, *J*=6.4, 13.9, 1H, 7-CH_AH_B), 2.35 (s, 1H, OH), 2.24 (dd, *J*=12.0, 13.9, 1H, 7-CH_AH_B), 1.80–1.69 (m, 1H, 1-CH_AH_B), 1.59–1.50 (m, 1H, 2-CH_AH_B), 1.39–1.13 (m, 2H, 1-CH_AH_B, 2-CH_AH_B); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=172.2 (s, C-5), 144.6 (s, arom. C), 128.2, 127.5, 125.6 (d, arom. CH), 74.7 (s, C-8), 65.7 (d, C-8a), 49.4 (d, C-6), 45.8 (t, C-7), 45.0 (t, C-3), 27.9 (t, CH_2), 22.6 (t, CH_2); MS (EI, 70 eV): *m/z* (%)=246 (0.1), [M^+] 148 (7), 124 (14), 105 (16), 77 (16), [Ph^+] 70 (100), 44 (12). Anal. calcd for $C_{14}H_{17}N_2O_4$: C 68.27, H 7.37, N 11.37; found: C 67.83, H 7.52, N 11.09.

Crystals suitable for X-ray structure determination have been grown from dichloromethane. $C_{14}H_{18}N_2O_2$, *M*=246 g mol^{-1}. Orthorhombic, *a*=5.8640(10), *b*=8.2110(10), *c*=26.397(4) Å, α=90, β=90, γ=90°, *V*=1271.0(3) $Å^3$, space group $P2_12_12_1$, *Z*=4, density (calculated)=1.287 g cm^{-1}. Crystal size 1.90×0.38×0.15 mm. *F*(000)=528, *T*=200(2) K, wavelength=0.71069 Å. Absorption coefficient 0.087 mm^{-1}, extinction coefficient 0.010(6), theta range for data collection 2.60–24.16°, index range $-6 \le h \le 6$, $-9 \le k \le 9$, $-30 \le l \le 30$. Collected reflections 9014, independent reflections 2029, [*R*(int)=0.0654] data/restraints/parameters 2026/0/236, goodness of fit F^2 1.072. Final *R* indices [*I*>2 sigma (*I*)]: R_1=0.0352, wR_2=0.0882. *R* indices (all data): R_1=0.0375, wR_2=0.0913. Largest difference peak and hole 0.393 to −0.153 $Å^{-3}$. Refinement method: full-matrix least-squares on F^2. Further details of the crystal structure investigations are available from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (Germany), on quoting the depository numbers CSD-410326.

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