Synthesis of the (2*S*,4*S*)-stereoisomers of 4-(indol-1-yl) and 4-arylamino derivatives of 5-oxoproline, proline, and 2-hydroxymethylpyrrolidine*

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Nucleophilic substitution of the halogen atom in dimethyl (*S*)-4-bromoglutamate followed by removal of the protecting groups and closure of a lactam ring afforded (2*S*,4*S*)-4-(indolin-1-yl)-5-oxoproline. The indoline fragment was oxidized into the indole fragment to give (2*S*,4*S*)-4-(indol-1-yl)-5-oxoproline; reduction of the carbonyl groups with BH_3 yielded (2*S*,4*S*)-4-(indol-1-yl)prolines and (2*S*,4*S*)-2-hydroxymethyl-4-(indol-1-yl)pyrrolidines. Reduction of (2*S*,4*S*)-4-arylamino-5-oxoprolines with BH_3 to the corresponding (2*S*,4*S*)-4-arylaminoprolines and (2*S*,4*S*)-4-arylamino-2-hydroxymethylpyrrolidines was studied.

Key words: 4-aminoproline, glutamic acid, indole, 5-oxoproline, proline, prolinol.

(*S*)-5-Oxoproline (pyroglutamic acid) plays an important role in metabolic processes occurring in living organisms. The 5-oxoproline fragment is part of thyroliberin and other neuropeptides and peptide hormones.[1] 4-Aminoproline and 4-amino-5-oxoproline derivatives, which are of special interest because they can be modified at the amino group and contain an additional chiral center, are used in organic synthesis as chiral building blocks,[2—6] also for the preparation of substituted prolinols (2-hydroxymethylpyrrolidines) employed as catalysts in asymmetric synthesis.[7,8] Some 4-aminoproline derivatives are known as metalloproteinase inhibitors[9] and antidiabetic agents.[10] When incorporated in a peptide chain, the 4-aminoproline fragment changes its conformation and hence biological activity.[11—13] *trans*-4-Aminoproline is a metabolite of the fungus *Ascochyta caulina* and exhibits herbicidal activity.[14] (2*R*,4*R*)-4-Amino-4-carboxyproline is a powerful and selective group II agonist of metabotropic glutamate receptors, which accounts for its anticonvulsant *in vivo* effect[15,16] and makes it promising for the treatment of neurodegenerative diseases.[17]

The goal of the present work was to develop a method for the synthesis of 5-oxoprolines, prolines, and 2-hydroxymethylpyrrolidines containing 4-arylamino or 4-indol-1-yl substituents, because the indole fragment is known to be part of some physiologically active compounds[18—20] and 4-(indol-1-yl)-5-oxoprolines and 4-(indol-1-yl)prolines have not been documented hitherto.

4-(Indol-1-yl)-5-oxoproline derivatives were synthesized from dimethyl (2*S*,4*RS*)-4-bromo-*N*-phthaloylglutamate (**1**)[21] *via* nucleophilic substitution of the bromine atom followed by removal of the protecting groups, closure of a lactam ring, and oxidation of the indoline fragment into an indole one.

Reflux of bromide **1** with indoline in acetonitrile gave a mixture of diastereomers of dimethyl (2*S*,4*RS*)-4-(indolin-1-yl)-*N*-phthaloylglutamate (**2a,b**) (Scheme 1).

The ratio of diastereomers **2a** and **2b** in the reaction mixture was 77 : 23 (^{1}H NMR and HPLC); *i.e.*, the nucleophilic substitution of the Br atom from bromide **1** under the action of indoline is a stereoselective process, much the same as with other arylamines.[22—24] Diastereomer **2a** (*de* 97%) was isolated by twofold crystallization from methanol.

To assign the diaminopentanedioic acid residue in diastereomers **2a** and **2b** to the *threo*- or *erythro*-configuration, we examined their ^{1}H NMR spectra, keeping in mind that the difference between the chemical shifts of the nonequivalent protons at the C(3) atom ($\Delta\delta_{AB} = \delta_{3A} - \delta_{3B}$) for 4-substituted *N*-phthaloylglutamic acids with the *erythro*-configuration is larger than that for *threo*-diastereomers.[22—24] However, for the mixture of diastereomers **2a,b**, $\Delta\delta_{AB}$ is difficult to determine because the ^{1}H NMR signal of the low-field $H_A(3)$ proton in minor isomer **2b** (δ 3.01) overlaps the signals of major isomer **2a**. Using a 1D TOCSY experiment (selective excitation of the signal at δ 2.43 for

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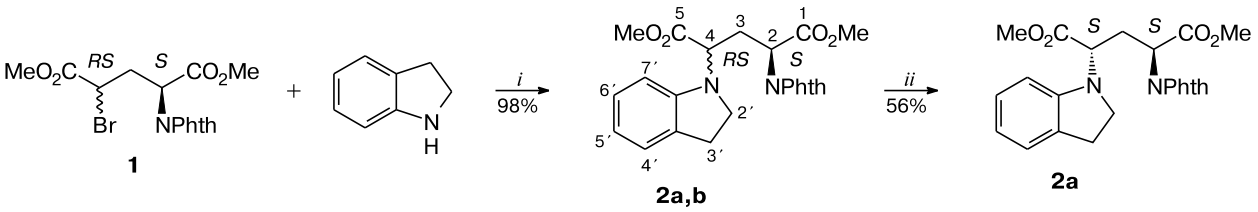
Scheme 1



Phth is phthaloyl.

Reagents and conditions: *i*. MeCN, reflux, 35 h; *ii*. Crystallization from MeOH.

the $H_B(3)$ proton in minor *erythro*-diastereomer **2b**), we found that $\Delta\delta_{AB}$ for compound **2b** is 0.58 ppm, which is substantially larger than that for *threo*-isomer **2a** ($\Delta\delta_{AB}$ = = 0.05 ppm), which was isolated in the individual state.

Earlier,[22—24] we have demonstrated that reactions of bromide **1** with aromatic amines (in particular, with 2-methylindoline[23]) are not accompanied by racemization. One could expect that a similar reaction with indoline would occur with retention of the (*S*)-configuration of the chiral C(2) center, which was confirmed by configuration assignment for the products of subsequent transformations.

The synthesis of 4-(indol-1-yl)-5-oxoprolines from compound **2a** includes three steps: (1) removal of the protecting groups, (2) closure of a lactam ring, and (3) oxidation of the indoline fragment into an indole one. We studied different pathways of the above transformations (Scheme 2).

We refluxed dimethyl ester **2a** in 6 *M* HCl; after removal of the acid, the dry residue was heated *in vacuo* to give (2*S*,4*S*)-4-(indolin-1-yl)-5-oxoproline (**3**). Esterification of amino acid **3** with methanol in the presence of thionyl chloride yielded methyl (2*S*,4*S*)-4-(indolin-1-yl)-5-oxoproline (**4**), which was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[25] in benzene into methyl (2*S*,4*S*)-4-(indol-1-yl)-5-oxoproline (**5**). The overall yield of compound **5** according to this method was 35% (with respect to **2a**).

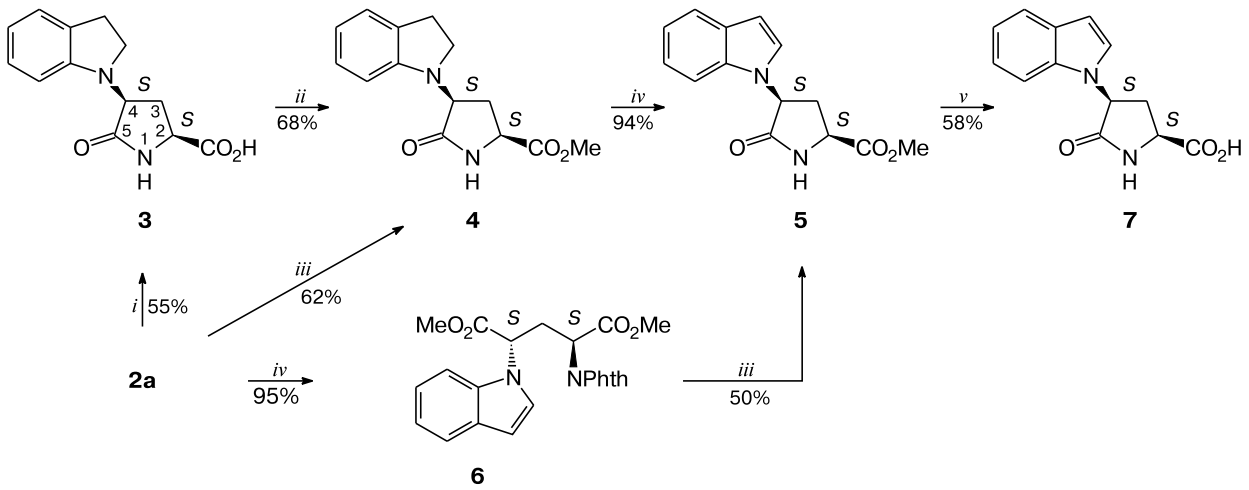
Hydrazinolysis of dimethyl ester **2a** followed by lactam ring formation in boiling toluene (see Scheme 2) led to methyl ester **4** in one step. Using this approach, we increased the overall yield of compound **5** to 58% (with respect to **2a**).

Oxidation of dimethyl ester **2a** with DDQ gave dimethyl (2*S*,4*S*)-4-(indol-1-yl)-*N*-phthaloylglutamate (**6**). Hydrazinolysis of compound **6** followed by lactam ring formation produced methyl ester **5** (see Scheme 2) in an overall yield of 48% with respect to **2a**.

Methyl ester **5** was transformed into (2*S*,4*S*)-4-(indol-1-yl)-5-oxoproline (**7**) by heating with bis(tributyltin) oxide in benzene as described earlier[26] (see Scheme 2).

To obtain 4-aminoproline derivatives from appropriate 4-amino-5-oxoprolines, we employed the complex

Scheme 2



Reagents and conditions: *i*. 1) 6 *M* HCl, reflux, 5 h; 2) 130 °C, vacuum, 4 h; *ii*. MeOH, $SOCl_2$; *iii*. 1) $N_2H_4 \cdot H_2O$, benzene—MeOH (1 : 1), 30 °C, 45 min; 2) toluene, reflux, 30 min; *iv*. DDQ, benzene, reflux, 15 min; *v*. $(Bu_3Sn)_2O$, benzene, reflux, 16 h.

$BH_3 \cdot Me_2S$ in THF (see Schemes 3 and 4), which is used for selective reduction of the lactam CO group in the presence of an ester function.[2,27] Qualitative analysis of the resulting mixtures of reduction products was performed by TLC and HPLC. For the products isolated in the individual state by chromatography, their quantitative ratio was determined from their yields. Otherwise, the structures and yields of the products were determined using ^{1}H NMR spectroscopy and HPLC and LC-MS experiments. It turned out that the reduction of methyl 4-substituted (2*S*,4*S*)-5-oxoprolines is not regioselective: apart from the corresponding methyl 4-substituted prolines, the reaction mixture contains 4-substituted 2-hydroxymethylpyrrolidines (prolinols) and other products. For instance, the reduction of compound **8** (obtained from methyl ester **5** and Boc_2O according to a known method)[28] with $BH_3 \cdot Me_2S$ in THF at −5 °C and 10 °C (Table 1, entries *1*—*3*) gave complex mixtures from which esters **9** and **10** and 2-hydroxymethylpyrrolidine **11** were isolated in low yields (Scheme 3). The same reaction at 40 °C mainly produced substituted pyrrolidine **11** (42% yield; see Table 1, entry *4*). Methyl (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-5-hydroxy-4-(indol-1-yl)proline (**10**) was isolated (in a mixture with ester **9**) as a single diastereomer. The configuration of the chiral center at C(5) in compound **10** was not determined.

Table 1. Reduction of compound **8** with the complex $BH_3 \cdot Me_2S$ in THF*

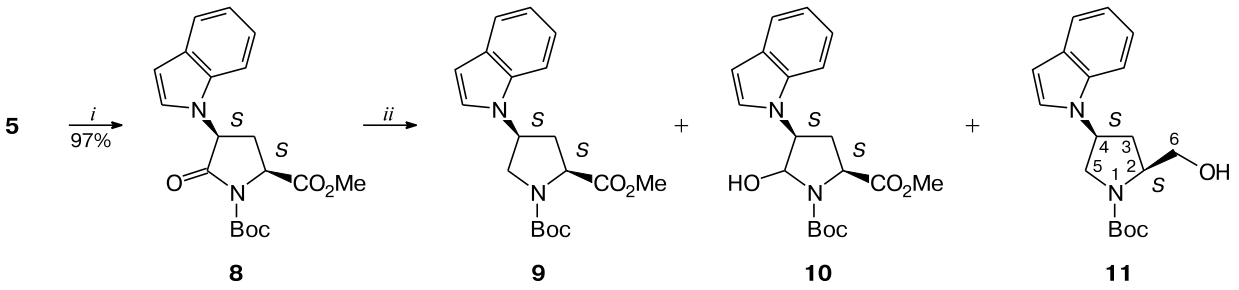
Entry	*T*/°C	τ/day	Yield (%)			
			8	**9**	**10**	**11**
1	−5	35	33	10	17	1
2	10	35	—	5	11	24
*3***	10	77	—	5	16	42
4	40	4	—	—	3	42

* The starting molar ratio BH_3 : **8** is 4 : 1.
** The starting molar ratio BH_3 : **8** is 5 : 1.

We extended this method to the reduction of the methyl (2*S*,4*S*)-4-arylamino-5-oxoprolines obtained previously.[29] Since reactions of esters **12** and **13** with $BH_3 \cdot Me_2S$ in THF gave complex mixtures, we additionally protected the lactam N atom in esters **12** and **13** with the *tert*-butoxycarbonyl group[28] (Scheme 4). Introduction of the Boc-protection to the N(1) atom in compound **12** was regiospecific, the N atom of the PhNH group being intact.

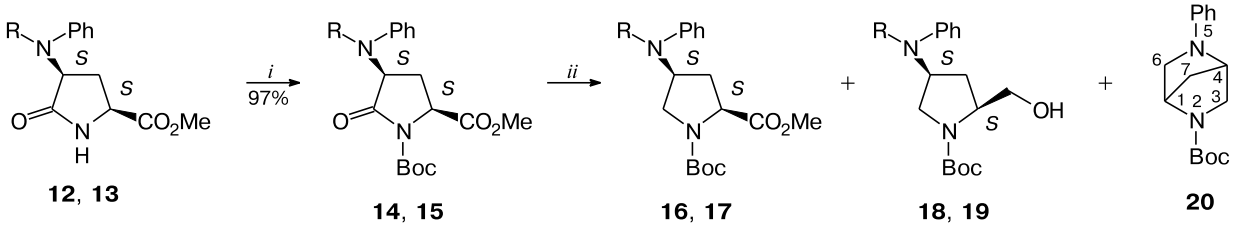
Reduction of substituted methyl 5-oxoproline **14** with $BH_3 \cdot Me_2S$ under mild conditions (−5 °C, 17 days) predominantly gave proline methyl ester **16** (63% yield) and substituted 2-hydroxymethylpyrrolidine **18** as a by-product (8%). At 40 °C, the yield of pyrrolidine **18** increased to

Scheme 3



Reagents and conditions: *i*. Boc_2O, Et_3N, DMAP, CH_2Cl_2, 20 °C, 2 h; *ii*. $BH_3 \cdot Me_2S$, THF.

Scheme 4



R = H (**12**, **14**, **16**, **18**), Me (**13**, **15**, **17**, **19**)

Reagents and conditions: *i*. Boc_2O, Et_3N, DMAP, CH_2Cl_2, 20 °C, 2 h; *ii*. $BH_3 \cdot Me_2S$, THF.

72% and bicyclic compound **20** was isolated as a by-product (8%) (see Scheme 4). The stereo configuration of compound **20** was not determined.

When studying the conditions for the reduction of methyl ester **15** with $BH_3 \cdot Me_2S$ (see Scheme 4) (compound **15** has a bulkier substituent in position 4 with respect to ester **14**), we found that the maximum yield of the methyl ester of the corresponding proline (**17**) is 31% (20 °C, 4 days). Under milder conditions (−5 °C, 35 days), the yield of compound **17** was low (15%) because of the low degree of conversion of methyl ester **15**. A longer reaction time (20 °C, 7 days) was favorable for the formation of 2-hydroxymethylpyrrolidine **19** (Table 2, entry *3*). The highest yield (64%) of prolinol **19** was achieved at 40 °C (see Table 2, entry *4*).

By comparing the results of the reduction of esters **8**, **14**, and **15** at −5 °C, one should notice that the bulky substituent in position 4 of the pyrrolidine ring negatively affects the yields of the proline esters. The reduction at 40 °C afforded the corresponding prolinols in moderate (42% for **11**) to good yields (72 and 64% for **18** and **19**, respectively).

The *cis*-configuration of 4-substituted 5-oxoprolines **3**—**5**, **7**, **8**, and **13**—**15** was confirmed by ^{1}H NMR spectroscopy according to known rules:[22,30] (1) the coupling constants $^3J_{2-3A}$ and $^3J_{2-3B}$ are close to each other and lie in the 7.7—9.2 Hz range and (2) the difference between the chemical shifts for the nonequivalent $C(3)H_AH_B$ protons in the 5-oxoproline ring is 0.70—1.06 ppm.

The room-temperature ^{1}H NMR spectra of 4-substituted 1-(*tert*-butoxycarbonyl)prolines and 2-hydroxymethylpyrrolidines **9**—**11** and **16**—**19** show substantial broadening of the signals in both $CDCl_3$ and DMSO-d_6, probably because of the presence of different conformers (by analogy with other esters of 1-protected 4-aminoprolines[31]). The resolution of the signals required for reliable interpretation was achieved by recording spectra at 70—100 °C in DMSO-d_6. Under these conditions, we recorded the ^{1}H and ^{13}C NMR spectra of compounds **9**—**11** and **16**—**20**. The *cis*-configuration of prolinol **19** was evident from a 2D ^{1}H—^{1}H NOESY experiment revealing cross peaks for the H(2) and H(4) protons only with one proton of the geminal pair (namely with $H_A(3)$). For compounds **2a**, **3**, **6**, **8**, **16**, and **19**, we managed to assign all signals for the protons and the carbon atoms by using a combination of 2D spectroscopic techniques (HSQC/HMBC).

Table 2. Reduction of compound **15** with the complex $BH_3 \cdot Me_2S$ in THF*

Entry	*T*/°C	τ/day	Yield (%)		
			15	**17**	**19**
1	−5	35	46	15	—
2	20	4	11	31	36
3	20	7	—	13	62
4	40	4	—	—	64

* The starting molar ratio BH_3 : **15** is 4 : 1.

The optical purity of the compounds obtained was confirmed by the absence of the corresponding *trans*-isomers in the reaction mixtures (NMR and GC-MS data).

The mass spectra of compounds **9**—**11**, **16**, **18**, and **20** (APCI, 400 °C) show relatively weak peaks of the molecular ions and relatively intense peaks of the fragmentation ions due to elimination of the *tert*-butyl and *tert*-butoxycarbonyl groups.

To sum up, we developed a method for the synthesis of the (2*S*,4*S*)-stereoisomers of previously unknown 5-oxoprolines, prolines, and 2-hydroxymethylpyrrolidines (prolinols) containing the phenylamino, [(methyl)(phenyl)]-amino, or indol-1-yl substituent in position 4 of the heterocycle.

Experimental

Dimethyl (2*S*,4*RS*)-4-bromo-*N*-phthaloylglutamate (**1**),[21] (2*S*,4*S*)-4-[(methyl)(phenyl)amino]-5-oxoproline,[22] and methyl (2*S*,4*S*)-5-oxo-4-phenylaminoproline (**12**)[29] were prepared according to known procedures. Indoline, DDQ, $(Bu_3Sn)_2O$, $BH_3 \cdot Me_2S$ (Lancaster), Boc_2O (Fluka), and DMAP (ICN Biomedicals, Inc.) were used. Tetrahydrofuran was dried and distilled over $LiAlH_4$. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 instrument (400 and 100 MHz, respectively) in $CDCl_3$ or DMSO-d_6 with $SiMe_4$ as the internal standard at room or elevated temperature (as specified below). Chemical shifts δ are quoted in parts per million. Melting points were determined on a Boetius instrument. IR spectra were recorded on an FT-IR Spectrometer Spectrum One instrument (Perkin—Elmer) either in Nujol or thin films (prepared by evaporation of solutions in $CHCl_3$), or with a diffuse reflection attachment (DRA). UV spectra were recorded on a UV-2401 PC instrument (Shimadzu) for solutions in MeOH ($c = 10^{-4}$ mol L^{-1}). Optical rotation was measured on a Perkin—Elmer Model 341 polarimeter. Mass spectra were recorded with preliminary chromatographic separation on a LCMS-2010 quadrupole LC-MS instrument (Shimadzu) (Supelcosil LC-18 column, 250×4.6 mm, reversed-phase C18 sorbent, 5 μm). The other parameters of the LC-MS experiment: elution rate 0.8 mL min^{-1}, working needle voltage 4.5 kV, chemical ionization under atmospheric pressure (APCI), 400 °C, nitrogen as a carrier gas, flow rate 2.5 L min^{-1}. The mixtures of products were analyzed by HPLC on a Merck—Hitachi chromatograph (L-4000A Intelligent Pump, L-4000A UV detector, D-2500A Chromato-Integrator, RT250-4 Hibar Pre-packed Column, 250×4 mm, LiChrosorb Si-60 sorbent, 5 μm, elution rate 1.0 mL min^{-1}, detection at a wavelength of 230 nm). The mobile phases and the retention times τ_R are specified for each compound. Flash chromatography was carried out on Silica gel 60 (0.063—0.040 mm, Lancaster; column 7×2 cm). For TLC, Sorbfil plates were used; spots were visualized under UV light and with the iodine vapor.

Dimethyl (2*S*,4*RS*)-4-(indolin-1-yl)-*N*-phthaloylglutamate (2a,b). A solution of bromide **1** ((2*S*,4*S*)-**1** : (2*S*,4*R*)-**1** = 1 : 1; 5.00 g, 13.01 mmol) and indoline (4.0 mL, 35.88 mmol) in acetonitrile (30 mL) was refluxed for 35 h. On cooling to room temperature, the precipitate that formed was filtered off and the mother liquor was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL), successively washed with water (1×30 mL), 1 *M* HCl (4×30 mL), aqueous NaCl (1×30 mL), 5% $NaHCO_3$ (1×30 mL), and again aqueous NaCl (2×30 mL), dried with Na_2SO_4, concentrated under reduced pressure, and dried *in vacuo* over P_2O_5 at 50—60 °C for 8 h. The yield of product **2a,b** was 5.39 g (98%), amorphous solid, **2a** : **2b** = 77 : 23 (^{1}H NMR and HPLC). Found (%): C, 65.69; H, 4.97; N, 6.44. $C_{23}H_{22}N_2O_6$. Calculated (%): C, 65.40; H, 5.25; N, 6.63. **2a** + **2b**. ^{1}H NMR ($CDCl_3$), δ: 2.43 (ddd, 1 H, H_B(3), *J* = 14.6 Hz, *J* = 10.4 Hz, *J* = 7.0 Hz, **2b**); 2.80—2.90 (m, 2 H, H_AH_B(3′), **2b**); 2.85—2.97 (m, 2 H, H_AH_B(3), **2a**); 3.01 (ddd, 1 H, H_A(3), *J* = 14.6 Hz, *J* = 7.4 Hz, *J* = 5.3 Hz, **2b**); 2.97—3.08 (m, 2 H, H_AH_B(3′), **2a**); 3.34 (td, 1 H, H_B(2′), *J* = 9.8 Hz, *J* = 8.4 Hz, **2b**); 3.47 (td, 1 H, H_B(2′), *J* = 9.3 Hz, *J* = 8.4 Hz, **2a**); 3.52 (ddd, 1 H, H_A(2′), *J* = 9.6 Hz, *J* = 8.3 Hz, *J* = 4.4 Hz, **2b**); 3.57 (s, 3 H, C(5)O_2Me, **2a**); 3.62 (ddd, 1 H, H_A(2′), *J* = 9.3 Hz, *J* = 8.2 Hz, *J* = 5.8 Hz, **2a**); 3.65 (s, 3 H, C(5)O_2Me, **2b**); 3.74 (s, 3 H, C(1)O_2Me, **2b**); 3.75 (s, 3 H, C(1)O_2Me, **2a**); 4.06 (m, 1 H, H(4), **2a**); 4.56 (dd, 1 H, H(4), *J* = 10.4 Hz, *J* = 5.3 Hz, **2b**); 5.16 (dd, 1 H, H(2), *J* = 7.4 Hz, *J* = 7.0 Hz, **2b**); 5.17 (m, 1 H, H(2), **2a**); 6.25 (d, 1 H, H(7′), *J* = 7.9 Hz, **2a**); 6.38 (d, 1 H, H(7′), *J* = 7.9 Hz, **2b**); 6.57 (td, 1 H, H(5′), *J* = 7.4 Hz, *J* = 0.9 Hz, **2b**); 6.63 (td, 1 H, H(5′), *J* = 7.5 Hz, *J* = 1.0 Hz, **2a**); 6.91—6.98 (m, 2 H, H(4′), H(6′), **2b**); 6.90 (td, 1 H, H(6′), *J* = 7.7 Hz, *J* = 1.1 Hz, **2a**); 7.05 (dd, 1 H, H(4′), *J* = 7.2 Hz, *J* = 1.1 Hz, **2a**); 7.69 (m, 2 H, Phth, **2b**); 7.76 (m, 2 H, Phth, **2a**); 7.79 (m, 2 H, Phth, **2b**); 7.85 (m, 2 H, Phth, **2a**). HPLC, τ_R/min: 16.4 (**2a**), 14.5 (**2b**) (hexane—propan-2-ol (80 : 1)).

Dimethyl (2*S*,4*S*)-4-(indolin-1-yl)-*N*-phthaloylglutamate (2a). Amorphous product **2a,b** (5.18 g) was crystallized twice from methanol to give compound **2a** (2.90 g, 56%), light yellow needle-like crystals (*de* 97%), m.p. 129—130 °C; $[\alpha]_D^{25}$ −68.9 (*c* 1.0, $CHCl_3$). Found (%): C, 65.67; H, 4.98; N, 6.58. $C_{23}H_{22}N_2O_6$. Calculated (%): C, 65.40; H, 5.25; N, 6.63. IR (Nujol), ν/cm^{-1}: 1773, 1740, 1713, 1687 (C=O); 1604 (Ar). UV, λ_{max}/nm: 208, 218, 232, 240, 252, 300. ^{1}H NMR ($CDCl_3$), δ: 2.88 (ddd, 1 H, H_B(3), *J* = 14.9 Hz, *J* = 9.9 Hz, *J* = 5.4 Hz); 2.93 (ddd, 1 H, H_A(3), *J* = 14.9 Hz, *J* = 9.2 Hz, *J* = 5.7 Hz); 2.97—3.08 (m, 2 H, H_AH_B(3′)); 3.47 (dt, 1 H, H_B(2′), *J* = 9.3 Hz, *J* = 8.4 Hz); 3.57 (s, 3 H, C(5)O_2Me); 3.62 (ddd, 1 H, H_A(2′), *J* = 9.3 Hz, *J* = 8.2 Hz, *J* = 5.8 Hz); 3.75 (s, 3 H, C(1)O_2Me); 4.06 (m, 1 H, H(4)), 5.17 (m, 1 H, H(2)); 6.25 (d, 1 H, H(7′), *J* = 7.9 Hz); 6.63 (td, 1 H, H(5′), *J* = 7.5 Hz, *J* = 1.0 Hz); 6.90 (td, 1 H, H(6′), *J* = 7.7 Hz, *J* = 1.1 Hz); 7.05 (dd, 1 H, H(4′), *J* = 7.2 Hz, *J* = 1.1 Hz); 7.76, 7.85 (both m, 2 H each, Phth). ^{13}C NMR ($CDCl_3$), δ: 28.29 (C(3′)); 28.76 (C(3)); 49.08 (C(2′)); 49.22 (C(2)); 51.83 (C(5)O_2<u>Me</u>); 52.98 (C(1)O_2<u>Me</u>); 55.68 (C(4)); 106.70 (C(7′)); 118.19 (C(5′)); 123.63 (C(3″), C(6″)); 124.57 (C(4′)); 127.06 (C(6′)); 129.87 (C(3′a)); 131.77 (C(2″a), C(6″a)); 134.30 (C(4″), C(5″)); 150.08 (C(7′a)); 167.48 (C(2″), C(7″)); 169.58 (C(1)); 171.20 (C(5)).

(2*S*,4*S*)-4-(Indolin-1-yl)-5-oxoproline (3). A mixture of ester **2a** (3.85 g, 9.11 mmol) and deoxygenated (by reflux in an open vessel for 5 min) 6 *M* HCl (25 mL) was refluxed for 5 h and then kept at −5 °C for 16 h. The precipitate that formed was filtered off and the mother liquor was concentrated under reduced pressure. The residue was dried *in vacuo* over P_2O_5 and KOH at 130 °C for 4 h and crystallized from 40% aqueous ethanol. The yield of amino acid **3** was 1.23 g (55%), m.p. 214—219 °C (decomp.); $[\alpha]_{546\ nm}^{25}$ +113.6 (*c* 0.5, MeOH). Found (%): C, 63.46; H, 5.73; N, 11.18. $C_{13}H_{14}N_2O_3$. Calculated (%): C, 63.40; H, 5.73; N, 11.38. IR (Nujol), ν/cm^{-1}: 3364 (NH); 1713 (C=O, lactam); 1660 (CO_2H...N); 1606 (Ar). UV, λ_{max}/nm: 206, 254, 302. ^{1}H NMR (DMSO-d_6), δ: 1.88 (ddd, 1 H, H_B(3), *J* = 12.7 Hz, *J* = 9.6 Hz, *J* = 8.5 Hz); 2.58 (ddd, 1 H, H_A(3), *J* = 12.7 Hz, *J* = 8.9 Hz, *J* = 8.0 Hz); 2.88 (m, 2 H, H_AH_B(3′)); 3.26 (dt, 1 H, H_B(2′), *J* = 9.0 Hz, *J* = 8.4 Hz); 3.34 (dt, 1 H, H_A(2′), *J* = 9.0 Hz, *J* = 8.3 Hz); 4.10 (t, 1 H, H(2), *J* = 8.1 Hz); 4.46 (t, 1 H, H(4), *J* = 9.3 Hz); 6.49 (d, 1 H, H(7′), *J* = 7.8 Hz); 6.55 (td, 1 H, H(5′), *J* = 7.3 Hz, *J* = 1.0 Hz); 6.94 (td, 1 H, H(6′), *J* = 7.7 Hz, *J* = 1.0 Hz); 7.00 (dd, 1 H, H(4′), *J* = 7.1 Hz, *J* = 1.0 Hz); 8.28 (s, 1 H, NH); 12.93 (br.s, 1 H, CO_2H). ^{13}C NMR (DMSO-d_6), δ: 26.31 (C(3)); 27.67 (C(3′)); 47.95 (C(2′)); 51.51 (C(2)); 55.94 (C(4)); 106.91 (C(7′)); 117.12 (C(5′)); 124.26 (C(4′)); 126.91 (C(6′)); 129.42 (C(3′a)); 150.83 (C(7′a); 173.15 (C(5)); 173.33 (CO_2H).

(2*S*,4*S*)-4-(Indolin-1-yl)-5-oxoproline methyl ester (4). ***A.*** Thionyl chloride (202 μL, 2.82 mmol) was added dropwise at −5 °C to a stirred suspension of amino acid **3** (278 mg, 1.13 mmol) in anhydrous methanol (4 mL). The mixture was kept at −5 °C for 1 h and then at 20 °C for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (15 mL). The resulting solution was washed with 5% aqueous $NaHCO_3$ (2×5 mL) and aqueous NaCl (2×5 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Ester **4** was isolated by column chromatography with $CHCl_3$—MeOH (100 : 1) as an eluent. The yield was 200 mg (68%), colorless crystals, m.p. 153—155 °C; $[\alpha]_D^{25}$ +127.8 (*c* 1.0, $CHCl_3$). Found (%): C, 64.63; H, 6.30; N, 10.64. $C_{14}H_{16}N_2O_3$. Calculated (%): C, 64.60; H, 6.20; N, 10.76. IR (Nujol), ν/cm^{-1}: 3220 (NH); 1749 (C=O, ester); 1708 (C=O, lactam); 1603 (Ar). UV, λ_{max}/nm: 208, 253, 301. ^{1}H NMR (DMSO-d_6), δ: 1.90 (ddd, 1 H, H_B(3), *J* = 12.8 Hz, *J* = 9.6 Hz, *J* = 8.4 Hz); 2.60 (ddd, 1 H, H_A(3), *J* = 12.8 Hz, *J* = 9.1 Hz, *J* = 7.9 Hz); 2.88 (m, 2 H, H_AH_B(3′)); 3.24 (dt, 1 H, H_B(2′), *J* = 9.0 Hz, *J* = 8.0 Hz); 3.32 (dt, 1 H, H_A(2′), *J* = 9.0 Hz, *J* = 7.9 Hz); 3.68 (s, 3 H, CO_2Me); 4.22 (t, 1 H, H(2), *J* = 8.1 Hz); 4.48 (t, 1 H, H(4), *J* = 9.3 Hz); 6.49 (d, 1 H, H(7′), *J* = 7.7 Hz); 6.55 (td, 1 H, H(5′), *J* = 7.3 Hz, *J* = 1.0 Hz); 6.95 (td, 1 H, H(6′), *J* = 7.7 Hz, *J* = 1.3 Hz); 7.01 (dd, 1 H, H(4′), *J* = 7.2 Hz, *J* = 1.3 Hz); 8.37 (s, 1 H, NH).

B. A 64% aqueous solution of hydrazine hydrate (0.23 mL, 2.94 mmol) was added to a solution of ester **2a** (500 mg, 1.18 mmol) in benzene—MeOH (1 : 1, 13 mL). The reaction mixture was stirred at 30 °C for 45 min, cooled, and acidified with 10 *M* HCl to pH 6. The precipitate of phthalohydrazide was filtered off and the mother liquor was concentrated under reduced pressure. The residue was dried *in vacuo* at 60 °C and refluxed in toluene (15 mL) for 30 min. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$ (10 mL). On cooling to 0 °C, an additional amount of phthalohydrazide was filtered off. The mother liquor was concentrated under reduced pressure and ester **4** was isolated by flash chromatography with benzene—ethyl acetate (7 : 3 → 1 : 1) as an eluent. The yield was 190 mg (62%). The ^{1}H NMR spec-

trum (DMSO-d_6) of the product is identical with that of ester **4** obtained by method ***A***.

(2*S*,4*S*)-4-(Indol-1-yl)-5-oxoproline methyl ester (5). ***A.*** 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (169 mg, 0.74 mmol) was added to a solution of ester **4** (184 mg, 0.71 mmol) in benzene (10 mL). The mixture was refluxed for 15 min and cooled. The precipitate of 2,3-dichloro-5,6-dicyanohydroquinone was filtered off and the mother liquor was concentrated. Ester **5** was isolated by flash chromatography with $CHCl_3$—MeOH (100 : 1) as an eluent. The yield of compound **5** was 172 mg (94%), light yellow amorphous solid, $[\alpha]_D^{25}$ +109.5 (*c* 1.0, $CHCl_3$). Found (%): C, 65.27; H, 5.28; N, 10.54. $C_{14}H_{14}N_2O_3$. Calculated (%): C, 65.11; H, 5.46; N, 10.85. IR (Nujol), ν/cm^{-1}: 3220 (NH); 1745 (C=O, ester); 1715 (C=O, lactam); 1610 (Ar). UV, λ_{max}/nm: 221, 268, 280, 292. ^{1}H NMR (DMSO-d_6), δ: 2.20 (ddd, 1 H, H_B(3), J = 12.9 Hz, J = 9.7 Hz, J = 8.4 Hz); 2.98 (ddd, 1 H, H_A(3), J = 12.9 Hz, J = 9.4 Hz, J = 7.7 Hz); 3.72 (s, 3 H, CO_2Me); 4.40 (t, 1 H, H(2), J = 8.1 Hz); 5.40 (t, 1 H, H(4), J = 9.5 Hz); 6.47 (dd, 1 H, H(3′), $^3J_{3'-2'}$ = 3.2 Hz, $^5J_{3'-7'}$ = = 0.9 Hz); 7.04 (ddd, 1 H, H(5′), J = 7.8 Hz, J = 7.0 Hz, J = 1.0 Hz); 7.13 (ddd, 1 H, H(6′), J = 8.3 Hz, J = 7.0 Hz, J = 1.2 Hz); 7.28 (d, 1 H, H(2′), $^3J_{2'-3'}$ = 3.2 Hz); 7.40 (dq, 1 H, H(7′), J = 8.3 Hz, J = 0.9 Hz); 7.56 (dt, 1 H, H(4′), J = 7.8 Hz, J = 1.0 Hz); 8.73 (s, 1 H, NH).

B. Hydrazinolysis of ester **6** was carried out as described above for the synthesis of compound **4** (method ***B***). The yield was 50%. The ^{1}H NMR spectrum (DMSO-d_6) of the product is identical with that of ester **5** obtained by method ***A***.

Dimethyl (2*S*,4*S*)-4-(indol-1-yl)-*N*-phthaloylglutamate (6). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (125 mg, 0.55 mmol) was added to a solution of ester **2a** (219 mg, 0.52 mmol) in benzene (10 mL). The mixture was refluxed for 15 min and cooled. The precipitate that formed was filtered off and the mother liquor was concentrated. Compound **6** was isolated by flash chromatography with benzene—ethyl acetate (30 : 1 → 15 : 1) as an eluent. The yield was 208 mg (95%), light yellow crystals, m.p. 54—55 °C; $[\alpha]_D^{20}$ −3.4 (*c* 1.0, $CHCl_3$). Found (%): C, 66.10; H, 4.69; N, 6.50. $C_{23}H_{20}N_2O_6$. Calculated (%): C, 65.71; H, 4.80; N, 6.66. IR (Nujol), ν/cm^{-1}: 1779, 1745, 1715 (C=O); 1611 (Ar). UV, λ_{max}/nm: 222, 239, 268, 279, 291. ^{1}H NMR ($CDCl_3$), δ: 3.20 (ddd, 1 H, H_B(3), $^2J_{3B-3A}$ = 14.9 Hz, $^3J_{3B-4}$ = = 9.9 Hz, $^3J_{3B-2}$ = 5.2 Hz); 3.26 (ddd, 1 H, H_A(3), $^2J_{3A-3B}$ = = 14.9 Hz, $^3J_{3A-2}$ = 10.0 Hz, $^3J_{3A-4}$ = 5.8 Hz); 3.63 (s, 3 H, C(5)O_2Me); 3.70 (s, 3 H, C(1)O_2Me); 4.67 (dd, 1 H, H(2), $^3J_{2-3A}$ = 10.0 Hz, $^3J_{2-3B}$ = 5.2 Hz); 5.02 (dd, 1 H, H(4), $^3J_{4-3B}$ = 9.9 Hz, $^3J_{2-3A}$ = 5.8 Hz); 6.62 (dd, 1 H, H(3′), $^3J_{3'-2'}$ = 3.3 Hz, $^5J_{3'-7'}$ = 0.7 Hz); 7.02—7.12 (m, 3 H, H(5′), H(6′), H(7′)); 7.24 (d, 1 H, H(2′), $^3J_{2'-3'}$ = 3.3 Hz); 7.62 (ddd, 1 H, H(4′), $^3J_{4'-5'}$ = 7.5 Hz, $^4J_{4'-6'}$ = 1.5 Hz, $^5J_{4'-7'}$ = 0.9 Hz); 7.76, 7.83 (both m, 2 H each, Phth). ^{13}C NMR ($CDCl_3$), δ: 30.96 (C(3)); 48.82 (C(2)); 52.78 (C(5)O_2Me); 53.09 (C(1)O_2Me); 55.43 (C(4)); 103.65 (C(3′)); 109.02 (C(7′)); 120.10 (C(5′)); 121.29 (C(4′)); 122.09 (C(6′)); 123.68 (C(3″), C(6″)); 125.54 (C(2′)); 128.79 (C(3′a)); 131.68 (C(2″a), C(6″a)); 134.40 (C(4″), C(5″)); 136.11 (C(7′a)); 167.24 (C(2″), C(7″)); 168.90 (C(1)); 170.18 (C(5)).

(2*S*,4*S*)-4-(Indol-1-yl)-5-oxoproline (7). Bis(tributyltin) oxide (415 μL, 0.814 mmol) was added to a solution of ester **5** (105 mg, 0.407 mmol) in dry benzene (10 mL). The reaction mixture was refluxed for 16 h and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and subjected to extraction with 5% aqueous $NaHCO_3$ (3×5 mL). The aqueous extracts were combined and acidified with 10 *M* HCl to pH 2. The product was extracted with ethyl acetate (3×20 mL). The organic extracts were combined, washed with aqueous NaCl (3×5 mL), dried with Na_2SO_4, and concentrated. The yield of acid **7** was 58 mg (58%), light brown amorphous solid, $[\alpha]_D^{20}$ +40.4 (*c* 0.5, MeOH). Found (%): C, 63.62; H, 4.98; N, 11.21. $C_{13}H_{12}N_2O_3$. Calculated (%): C, 63.93; H, 4.95; N, 11.47. IR (DRA), ν/cm^{-1}: 3265, 3054, 2929, 1715, 1675, 1613. UV, λ_{max}/nm: 220, 269, 280, 292. ^{1}H NMR (DMSO-d_6), δ: 2.16 (ddd, 1 H, H_B(3), J = 12.9 Hz, J = 9.7 Hz, J = 8.4 Hz); 2.97 (ddd, 1 H, H_A(3), J = 12.9 Hz, J = 9.2 Hz, J = 7.7 Hz); 4.28 (t, 1 H, H(2), J = 8.2 Hz); 5.38 (t, 1 H, H(4), J = 9.5 Hz); 6.47 (dd, 1 H, H(3′), $^3J_{3'-2'}$ = 3.2 Hz, $^5J_{3'-7'}$ = 0.9 Hz); 7.04 (ddd, 1 H, H(5′), J = 7.9 Hz, J = 7.0 Hz, J = 1.1 Hz); 7.12 (ddd, 1 H, H(6′), J = 8.2 Hz, J = 7.0 Hz, J = 1.2 Hz); 7.28 (d, 1 H, H(2′), $^3J_{2'-3'}$ = 3.2 Hz); 7.41 (dq, 1 H, H(7′), J = 8.2 Hz, J = 0.9 Hz); 7.56 (ddd, 1 H, H(4′), J = 7.9 Hz, J = 1.2 Hz, J = 0.9 Hz); 8.66 (s, 1 H, NH); 13.04 (br.s, 1 H, CO_2H). ^{13}C NMR (DMSO-d_6), δ: 31.43 (C(3)); 51.68, 55.88 (C(2), C(4)); 101.52 (C(3′)); 109.96 (C(7′)); 119.30, 120.61, 121.16 (C(5), C(4), C(6)); 127.43 (C(3′a)); 128.39 (C(2′)); 135.48 (C(7′a)); 172.16, 173.10 (CO, CO_2H).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(indol-1-yl)-5-oxoproline methyl ester (8). Triethylamine (110 μL, 0.789 mmol), Boc_2O (270 mg, 1.24 mmol), and DMAP (76 mg, 0.622 mmol) were added to a solution of ester **5** (160 mg, 0.619 mmol) in CH_2Cl_2 (2.5 mL). The mixture was stirred at 20 °C for 2 h, diluted with ethyl acetate to 20 mL, washed with 5% aqueous citric acid (3×5 mL), aqueous NaCl (1×5 mL), 5% aqueous $NaHCO_3$ (2×5 mL), and again aqueous NaCl to a neutral reaction, dried with Na_2SO_4, and concentrated. The yield of compound **8** was 215 mg (97%), colorless small crystals, m.p. 170—172 °C (decomp.); $[\alpha]_D^{30}$ +48.2 (*c* 1.0, $CHCl_3$). Found (%): C, 63.28; H, 6.00; N, 7.54. $C_{19}H_{22}N_2O_5$. Calculated (%): C, 63.68; H, 6.18; N, 7.82. IR (Nujol), ν/cm^{-1}: 1778, 1733, 1701 (C=O); 1610 (Ar). UV, λ_{max}/nm: 220, 266, 292. ^{1}H NMR (DMSO-d_6), δ: 1.44 (s, 9 H, Boc); 2.21 (ddd, 1 H, H_B(3), $^2J_{3B-3A}$ = 12.8 Hz, $^3J_{3B-4}$ = 10.9 Hz, $^3J_{3B-2}$ = 9.2 Hz); 2.96 (ddd, 1 H, H_A(3), $^2J_{3A-3B}$ = 12.8 Hz, $^3J_{3A-4}$ = 9.6 Hz, $^3J_{3A-2}$ = 7.8 Hz); 3.77 (s, 3 H, OMe); 4.69 (dd, 1 H, H(2), $^3J_{2-3B}$ = 9.2 Hz, $^3J_{2-3A}$ = = 7.8 Hz); 5.66 (dd, 1 H, H(4), $^3J_{4-3B}$ = 10.9 Hz, $^3J_{4-3A}$ = 9.6 Hz); 6.52 (dd, 1 H, H(3′), $^3J_{3'-2'}$ = 3.2 Hz, $^5J_{3'-7'}$ = 0.9 Hz); 7.06 (ddd, 1 H, H(5′), J = 7.9 Hz, J = 7.0 Hz, J = 1.0 Hz); 7.16 (ddd, 1 H, H(6′), J = 8.3 Hz, J = 7.0 Hz, J = 1.2 Hz); 7.33 (dq, 1 H, H(7′), J = 8.3 Hz, J = 0.9 Hz); 7.34 (d, 1 H, H(2′), $^3J_{2'-3'}$ = 3.2 Hz); 7.58 (dt, 1 H, H(4′), J = 7.9 Hz, J = 1.0 Hz). ^{13}C NMR (DMSO-d_6), δ: 27.26 (C(3)); 27.37 (Me, Boc); 52.57 (OMe); 55.32 (C(2)); 56.38 (C(4)); 83.26 (C, Boc); 102.17 (C(3′)); 109.77 (C(7′)); 119.60 (C(5′)); 120.80 (C(4′)); 121.52 (C(6′)); 127.40 (C(2′)); 128.43 (C(3′a)); 135.32 (C(7′a)); 148.49 (CO, Boc); 169.43 (COO); 171.20 (C(5)). HPLC, τ_R/min: 17.6 (hexane—propan-2-ol (40 : 1)).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(indol-1-yl)proline methyl ester (9). The complex $BH_3 \cdot Me_2S$ (282 μL, 2.973 mmol) was added under argon to a solution of ester **8** (266 mg, 0.742 mmol) in dry THF (3 mL). The reaction mixture was kept at −5 °C for 35 days. Then methanol was added until gas evolution ceased. The mixture was refluxed for 5 min and concentrated. The residue was separated by flash chromatography with benzene—ethyl acetate (100 : 1 → 10 : 1) as an eluent. The eluates contained the

starting ester **8** (89 mg, 33%), ester **9** (10 mg, 4%), and a mixture of compounds **9**, **10**, and **11** in a ratio of 25 : 71 : 4 (63 mg). Ester **9** is a colorless amorphous solid. UV, λ_{max}/nm: 202, 218, 270, 279, 292. ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.40 (s, 9 H, Boc); 2.26 (dt, 1 H, H_B(3), J = 12.6 Hz, J = 8.6 Hz); 2.85 (dt, 1 H, H_A(3), J = 12.6 Hz, J = 7.7 Hz); 3.55 (dd, 1 H, H_B(5), J = 10.5 Hz, J = 8.6 Hz); 3.68 (s, 3 H, CO_2Me); 4.02 (dd, 1 H, H_A(5), J = 10.5 Hz, J = 7.7 Hz); 4.40 (t, 1 H, H(2), J = 8.2 Hz); 5.22 (tt, 1 H, H(4), J = 8.6 Hz, J = 8.0 Hz); 6.47 (dd, 1 H, H(3′), $^3J_{3'-2'}$ = 3.4 Hz, $^5J_{3'-7'}$ = 0.8 Hz); 7.03 (ddd, 1 H, H(5′), J = 7.9 Hz, J = 7.0 Hz, J = 0.9 Hz); 7.14 (ddd, 1 H, H(6′), J = 8.3 Hz, J = 7.0 Hz, J = 1.2 Hz); 7.43 (d, 1 H, H(2′), $^3J_{2'-3'}$ = 3.4 Hz); 7.52 (dq, 1 H, H(7′), J = 8.3 Hz, J = 0.9 Hz); 7.54 (dt, 1 H, H(4′), J = 7.9 Hz, J = 1.0 Hz). LC-MS (MeOH—H_2O (7 : 3), τ_R = 9.2 min, CI), m/z (I_{rel} (%)): 245 [M – Boc + 2 H]$^+$ (78), 277 [M – Boc + 2 H + MeOH]$^+$ (38), 289 [M – Bu^t + 2 H]$^+$ (100), 345 [M + H]$^+$ (9); calculated for $C_{19}H_{24}N_2O_4$: M = 344.41. HPLC, τ_R/min: 5.0 (hexane—propan-2-ol (40 : 1)).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-5-hydroxy-4-(indol-1-yl)-proline methyl ester (10) was obtained in a mixture with compounds **9** and **11** (**9** : **10** : **11** = 25 : 71 : 4; for the synthetic procedure, see above). ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.41 (s, 9 H, Boc); 2.51—2.71 (m, 2 H, H_AH_B(3)); 3.71 (s, 3 H, CO_2Me); 4.32 (dd, 1 H, H(2), J = 10.0 Hz, J = 7.4 Hz); 4.95 (ddd, 1 H, H(4), J = 12.2 Hz, J = 7.2 Hz, J = 4.9 Hz); 5.45 (t, 1 H, H(5), J = 4.9 Hz); 5.76 (br.d, 1 H, OH, J = 4.9 Hz); 6.41 (dd, 1 H, H(3′), J = 3.3 Hz, J = 0.8 Hz); 7.01 (ddd, 1 H, H(5′), J = 7.8 Hz, J = 7.0 Hz, J = 1.0 Hz); 7.12 (ddd, 1 H, H(6′), J = 8.3 Hz, J = 7.0 Hz, J = 1.3 Hz); 7.46 (d, 1 H, H(2′), $J_{2'-3'}$ = 3.3 Hz); 7.50—7.56 (m, 2 H, H(4′), H(7′)). LC-MS (MeOH—H_2O (7 : 3), τ_R = 6.7 min, CI), m/z (I_{rel} (%)): 183 [M – Boc – CO_2Me – – H_2O + H]$^+$ (5), 243 [M – Boc – H_2O + 2 H]$^+$ (100), 244 [M – indole anion]$^+$ (16), 275 [M – Boc – H_2O + 2 H + MeOH]$^+$ (87), 276 [M – indole anion + MeOH]$^+$ (15), 287 [M – Bu^t – – H_2O + 2 H]$^+$ (5), 299 (20), 305 [M – Bu^t + 2 H]$^+$ (22), 319 [M – Bu^t – H_2O + 2 H + MeOH]$^+$ (10), 361 [M + H]$^+$ (9); calculated for $C_{19}H_{24}N_2O_5$: M = 360.41. HPLC, τ_R/min: 5.7 (hexane—propan-2-ol (40 : 1)).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-2-hydroxymethyl-4-(indol-1-yl)pyrrolidine (11). The complex $BH_3 \cdot Me_2S$ (87 μL, 0.917 mmol) was added to a solution of ester **8** (82 mg, 0.229 mmol) in dry THF (2 mL). The mixture was kept in a sealed tube under argon at 40 °C for 4 days. Then methanol was added until gas evolution ceased. The mixture was refluxed for 5 min and concentrated. The residue was separated by flash chromatography with benzene—ethyl acetate (100 : 1 → 10 : 1) as an eluent. The yield of compound **11** was 30.5 mg (42%), colorless amorphous solid, $[\alpha]_D^{25}$ –27.5 (*c* 1.0, $CHCl_3$). Found (%): C, 68.15; H, 7.70; N, 8.72. $C_{18}H_{24}N_2O_3$. Calculated (%): C, 68.33; H, 7.65; N, 8.85. IR (thin film), ν/cm^{-1}: 3413 (OH); 1690 (C=O, Boc); 1611 (Ar). UV, λ_{max}/nm: 221, 272, 280, 291. ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.44 (s, 9 H, Boc); 2.34 (ddd, 1 H, H_B(3), J = 12.8 Hz, J = 9.5 Hz, J = 7.5 Hz); 2.56 (dtd, 1 H, H_A(3), J = 12.8 Hz, J = 7.8 Hz, J = 1.0 Hz); 3.44 (dd, 1 H, H_B(5), J = 10.7 Hz, J = 8.8 Hz); 3.59 (dd, 1 H, H_B(6), J = 10.7 Hz, J = 5.9 Hz); 3.65 (dd, 1 H, H_A(6), J = 10.7 Hz, J = 3.6 Hz); 3.93 (tdd, 1 H, H(2), J = 7.7 Hz, J = 5.7 Hz, J = 3.6 Hz); 4.03 (ddd, 1 H, H_A(5), J = 10.7 Hz, J = 7.6 Hz, J = 1.0 Hz); 4.51 (br.s, 1 H, OH); 5.04 (tt, 1 H, H(4), J = 9.2 Hz, J = 7.7 Hz); 6.47 (dd, 1 H, H(3′), $^3J_{3'-2'}$ = 3.3 Hz, $^5J_{3'-7'}$ = 0.9 Hz); 7.02 (ddd, 1 H, H(5′), J = 7.9 Hz, J = 7.0 Hz, J = 0.9 Hz); 7.13 (ddd, 1 H, H(6′), J = 8.3 Hz, J = 7.0 Hz, J = 1.2 Hz); 7.42 (d, 1 H, H(2′), $^3J_{2'-3'}$ = 3.3 Hz); 7.53 (ddd, 1 H, H(4′), J = 7.9 Hz, J = 1.2 Hz, J = 0.9 Hz); 7.54 (dq, 1 H, H(7′), J = 8.3 Hz, J = 0.9 Hz). ^{13}C NMR (DMSO-d_6, 70 °C), δ: 27.73 (Me, Boc); 33.05 (C(3)); 50.29 (C(5)); 52.31 (C(2)); 57.20 (C(4)); 62.00 (C(6)); 78.42 (C, Boc); 101.05 (C(3′)); 109.53 (C(7′)); 118.75 (C(6′)); 119.99 (C(4′)); 120.69 (C(5′)); 124.59 (C(2′)); 128.01 (C(3′a)); 135.67 (C(7′a)); 153.30 (CO, Boc). LC-MS (MeOH—H_2O (7 : 3), τ_R = 8.4 min, CI), m/z (I_{rel} (%)): 217 [M – Boc + 2 H]$^+$ (48), 243 [M – Bu^t – H_2O + 2 H]$^+$ (34), 249 [M – Boc + 2 H + + MeOH]$^+$ (28), 261 [M – Bu^t + 2 H]$^+$ (100), 317 [M + H]$^+$ (2). HPLC, τ_R/min: 14.0 (hexane—propan-2-ol (40 : 1)).

(2*S*,4*S*)-4-[(Methyl)(phenyl)amino]-5-oxoproline methyl ester (13) was obtained as described for compound **4** (method ***A***) by esterification of (2*S*,4*S*)-4-[(methyl)(phenyl)amino]-5-oxoproline. The yield was 70%, colorless crystals, m.p. 142—144 °C; $[\alpha]_D^{20}$ +155.8 (*c* 1.0, $CHCl_3$). Found (%): C, 62.88; H, 6.46; N, 11.42. $C_{13}H_{16}N_2O_3$. Calculated (%): C, 62.89; H, 6.50; N, 11.28. IR (Nujol), ν/cm^{-1}: 3231 (NH); 1747 (C=O, ester); 1716 (C=O, lactam); 1599 (Ph). UV, λ_{max}/nm: 206, 250, 295. ^{1}H NMR (DMSO-d_6), δ: 1.84 (ddd, 1 H, H_B(3), J = 12.8 Hz, J = 9.5 Hz, J = 8.5 Hz); 2.68 (s, 3 H, NMe); 2.68 (ddd, 1 H, H_A(3), J = 12.8 Hz, J = 9.0 Hz, J = 7.9 Hz); 3.69 (s, 3 H, CO_2Me); 4.21 (t, 1 H, H(2) or H(4), J = 8.2 Hz); 4.69 (t, 1 H, H(4) or H(2), J = 9.2 Hz); 6.66 (tt, 1 H, H_p, J = 7.3 Hz, J = 1.0 Hz); 6.79 (dd, 2 H, H_o, J = 8.8 Hz, J = 1.0 Hz); 7.17 (dd, 2 H, H_m, J = 8.8 Hz, J = 7.3 Hz); 8.36 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 27.27 (C(3)); 33.15 (NMe); 51.26 (OMe); 52.16 (C(2)), 59.15 (C(4)); 112.79 (C_o); 116.70 (C_p); 128.93 (C_m); 149.47 (C_i); 172.36, 173.53 ($\underline{C}O_2$Me, C(5)).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-5-oxo-4-phenylaminoproline methyl ester (14) was obtained from ester **12** as described for the synthesis of compound **8**. The yield was 97%, colorless crystals, m.p. 144—145 °C; $[\alpha]_D^{25}$ +48.7 (*c* 1.0, $CHCl_3$). Found (%): C, 61.10; H, 6.76; N, 8.20. $C_{17}H_{22}N_2O_5$. Calculated (%): C, 61.07; H, 6.63; N, 8.38. IR (Nujol), ν/cm^{-1}: 3403, 3377 (NH); 1780, 1753, 1740, 1705 (C=O); 1603 (Ph). UV, λ_{max}/nm: 208, 242, 290. ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.46 (s, 9 H, Boc); 1.74 (ddd, 1 H, H_B(3), $^2J_{3B-3A}$ = 12.5 Hz, $^3J_{3B-4}$ = 10.0 Hz, $^3J_{3B-2}$ = 9.0 Hz); 2.80 (ddd, 1 H, H_A(3), $^2J_{3A-3B}$ = 12.5 Hz, $^3J_{3A-4}$ = 8.8 Hz, $^3J_{3A-2}$ = 7.7 Hz); 3.74 (s, 3 H, CO_2Me); 4.40 (ddd, 1 H, H(4), $^3J_{4-3B}$ = 10.0 Hz, $^3J_{4-3A}$ = 8.8 Hz, $^3J_{4-NH}$ = = 7.4 Hz); 4.56 (dd, 1 H, H(2), $^3J_{2-3B}$ = 9.0 Hz, $^3J_{2-3A}$ = 7.7 Hz); 5.64 (br.d, 1 H, NH, $^3J_{NH-4}$ = 7.4 Hz); 6.62 (tt, 1 H, H_p, J = 7.2 Hz, J = 1.1 Hz); 6.68 (dd, 2 H, H_o, J = 8.6 Hz, J = 1.1 Hz); 7.10 (dd, 2 H, H_m, J = 8.6 Hz, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 70 °C), δ: 27.10 (Me, Boc); 28.42 (C(3)); 51.65 (OMe); 53.61 and 55.01 (C(2), C(4)); 82.28 (C, Boc); 112.60 (C_o); 116.44 (C_p); 128.28 (C_m); 146.93 (C_i); 148.34 (CO, Boc); 171.24, 170.86 ($\underline{C}O_2$Me, C(5)). HPLC, τ_R/min: 10.3 (hexane—propan-2-ol (40 : 1)).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-[(methyl)(phenyl)amino]-5-oxoproline methyl ester (15) was obtained from ester **13** as described for the synthesis of compound **8**. The yield was 97%, colorless crystals, m.p. 170—173 °C; $[\alpha]_D^{25}$ +53.5 (*c* 1.0, $CHCl_3$). Found (%): C, 62.00; H, 7.05; N, 8.09. $C_{18}H_{24}N_2O_5$. Calculated (%): C, 62.06; H, 6.94; N, 8.04. IR (Nujol), ν/cm^{-1}: 1781, 1738, 1706 (C=O); 1602 (Ph). UV, λ_{max}/nm: 206, 248, 290. ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.43 (s, 9 H, Me, Boc); 1.83 (ddd, 1 H, H_B(3), J = 12.8 Hz, J = 10.1 Hz, J = 8.8 Hz); 2.66 (ddd, 1 H, H_A(3), J = 12.8 Hz, J = 9.5 Hz, J = 8.3 Hz); 2.74

(s, 3 H, NMe); 3.73 (s, 3 H, OMe); 4.54 (t, 1 H, H(2) or H(4), J = 8.6 Hz); 4.91 (t, 1 H, H(4) or H(2), J = 9.8 Hz); 6.70 (tt, 1 H, H_p, J = 7.2 Hz, J = 1.0 Hz); 6.80 (dd, 2 H, H_o, J = 8.9 Hz, J = 1.0 Hz); 7.17 (dd, 2 H, H_m, J = 8.9 Hz, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 70 °C), δ: 23.55 (C(3)); 27.08 (Me, Boc); 33.26 (NMe); 51.71 (OMe); 54.73, 59.98 (C(2), C(4)); 82.44 (C, Boc); 113.10 (C_o); 117.03 (C_p); 128.42 (C_m); 148.26, 148.83 (C_i, CO, Boc); 169.93, 170.93 ($\underline{C}O_2Me$, C(5)). HPLC, τ_R/min: 9.4 (hexane—propan-2-ol (40 : 1)).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-phenylaminoproline methyl ester (16). The complex $BH_3 \cdot Me_2S$ (69 μL, 0.728 mmol) was added to a solution of ester **14** (60.4 mg, 0.181 mmol) in THF (1.2 mL). The reaction mixture was kept under argon at −5 °C for 17 days. Then methanol was added until gas evolution ceased. The mixture was refluxed for 5 min and concentrated. The product was isolated by flash chromatography with benzene—ethyl acetate (10 : 0.1 → 10 : 2.0) as an eluent. The yield of ester **16** was 36.7 mg (63%), colorless amorphous solid, $[\alpha]_D^{20}$ +16.8 (*c* 0.97, $CHCl_3$). IR (thin film), ν/cm^{-1}: 3363 (NH); 1744 (C=O, ester); 1692 (C=O, Boc); 1603 (Ph). UV, λ_{max}/nm: 206, 246, 292. ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.38 (s, 9 H, Me, Boc); 1.82 (dt, 1 H, H_B(3), J = 12.8 Hz, J = 6.7 Hz); 2.60 (ddd, 1 H, H_A(3), J = 12.8 Hz, J = 8.6 Hz, J = 6.7 Hz); 3.15 (dd, 1 H, H_B(5), J = 10.6 Hz, J = 6.6 Hz); 3.65 (s, 3 H, OMe); 3.80 (dd, 1 H, H_A(5), J = 10.6 Hz, J = 6.7 Hz); 4.02 (sextet, 1 H, H(4), J = 6.9 Hz); 4.25 (dd, 1 H, H(2), J = 8.6 Hz, J = 6.6 Hz); 5.24 (br.d, 1 H, NH, J = 7.0 Hz); 6.57 (tt, 1 H, H_p, J = 7.3 Hz, J = 1.1 Hz); 6.59 (dd, 2 H, H_o, J = 8.6 Hz, J = 1.1 Hz); 7.07 (dd, 2 H, H_m, J = 8.6 Hz, J = 7.3 Hz). ^{13}C NMR (DMSO-d_6, 100 °C), δ: 27.49 (Me, Boc); 35.19 (C(3)); 50.75 (C(4)); 51.01 (OMe); 51.12 (C(5)); 57.19 (C(2)); 78.64 (C, Boc); 112.54 (C_o); 116.09 (C_p); 128.30 (C_m); 147.17 (C_i); 152.64 (CO, Boc); 172.33 ($\underline{C}O_2Me$). LC-MS (MeCN—H_2O (7 : 3), τ_R = 13.7 min, CI), *m*/*z* (I_{rel} (%)): 221 $[M - Boc + 2 H]^+$ (15), 262 $[M - Boc + 2 H + MeCN]^+$ (93), 265 $[M - Bu^t + 2 H]^+$ (14), 306 $[M - Bu^t + 2 H + MeCN]^+$ (100), 321 $[M + H]^+$ (48), 362 $[M + H + MeCN]^+$ (95). $C_{17}H_{24}N_2O_4$ (320.39). HPLC, τ_R/min: 7.2 (hexane—propan-2-ol (40 : 1)).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-[(methyl)(phenyl)amino]proline methyl ester (17). The complex $BH_3 \cdot Me_2S$ (275 μL, 2.899 mmol) was added to a solution of ester **15** (252 mg, 0.723 mmol) in THF (1.2 mL). The reaction mixture was kept under argon at 20 °C for 4 days. Then methanol was added until gas evolution ceased. The mixture was refluxed for 5 min and concentrated. The products were isolated by flash chromatography with benzene—ethyl acetate (10 : 0.3 → 10 : 1.5) as an eluent. A mixture of esters **17** and **15** (119 mg) was isolated. The mixture was dissolved in ethyl acetate (0.7 mL), diluted with hot hexane (7 mL), and kept at −5 °C for 3 h. The precipitate of the starting ester **15** (27 mg, 11%) was filtered off. The mother liquor was concentrated and the residue was separated by flash chromatography with hexane—ethyl acetate (10 : 0.3 → 10 : 1.5) as an eluent. The yield of ester **17** was 74.9 mg (31%), colorless amorphous solid, $[\alpha]_D^{25}$ −55.4 (*c* 1.0, $CHCl_3$). Found (%): C, 64.46; H, 7.95; N, 8.68. $C_{18}H_{26}N_2O_4$. Calculated (%): C, 64.65; H, 7.83; N, 8.38. IR (thin film), ν/cm^{-1}: 1750 (C=O, ester); 1698 (C=O, Boc); 1598 (Ph). ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.37 (s, 9 H, Me, Boc); 1.91 (ddd, 1 H, H_B(3), J = 12.5 Hz, J = 9.6 Hz, J = 8.4 Hz); 2.45 (ddd, 1 H, H_A(3), J = 12.5 Hz, J = 8.0 Hz, J = 7.4 Hz); 2.74 (s, 3 H, NMe); 3.24 (dd, 1 H, H_B(5), J = 10.7 Hz, J = 8.9 Hz); 3.65 (dd, 1 H, H_A(5), J = 10.7 Hz, J = 7.6 Hz); 3.67 (s, 3 H, OMe); 4.24 (t, 1 H, H(2), J = 8.3 Hz); 4.39 (tt, 1 H, H(4), J = 9.2 Hz, J = 7.5 Hz); 6.73 (tt, 1 H, H_p, J = 7.2 Hz, J = 1.0 Hz); 6.88 (dd, 2 H, H_o, J = 8.8 Hz, J = 1.0 Hz); 7.18 (dd, 2 H, H_m, J = 8.8 Hz, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 70 °C), δ: 27.55 (Me, Boc); 31.60 (C(3)); 32.93 (NMe); 46.66 (C(5)); 51.16 (OMe); 56.28 and 57.01 (C(2), C(4)); 78.82 (C, Boc); 114.91 (C_o); 117.70 (C_p); 128.42 (C_m); 149.95 (C_i); 152.74 (CO, Boc); 172.23 ($\underline{C}O_2Me$). HPLC, τ_R/min: 5.1 (hexane—propan-2-ol (40 : 1)).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-2-hydroxymethyl-4-phenylaminopyrrolidine (18). The complex $BH_3 \cdot Me_2S$ (80 μL, 0.843 mmol) was added to a solution of ester **14** (70.1 mg, 0.210 mmol) in THF (1.0 mL). The reaction mixture was kept in a sealed tube under argon at 40 °C for 4 days. Then methanol was added until gas evolution ceased. The mixture was refluxed for 5 min and concentrated. The product was isolated by flash chromatography with benzene—ethyl acetate (10 : 0.1 → 10 : 2.0) as an eluent. The yield of compound **18** was 44.1 mg (72%), colorless amorphous solid, $[\alpha]_D^{20}$ −40.0 (*c* 1.0, $CHCl_3$). Found (%): C, 65.78; H, 8.20; N, 9.38. $C_{16}H_{24}N_2O_3$. Calculated (%): C, 65.73; H, 8.27; N, 9.58. IR (thin film), ν/cm^{-1}: 3349 (OH, NH); 1678 (C=O, Boc); 1603 (Ph). UV, λ_{max}/nm: 208, 246, 294. ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.41 (s, 9 H, Me, Boc); 1.80 (dt, 1 H, H_B(3), J = 13.1 Hz, J = 6.0 Hz); 2.36 (dddd, 1 H, H_A(3), J = 13.1 Hz, J = 8.3 Hz, J = 7.3 Hz, J = 0.9 Hz); 3.01 (dd, 1 H, H_B(5), J = 10.7 Hz, J = 5.9 Hz); 3.57 (t, 2 H, H(6), J = 5.0 Hz); 3.76—3.83 (m, 2 H, H_A(5), H(2)); 3.88 (sextet, 1 H, H(4), J = 6.7 Hz); 4.44 (t, 1 H, OH, J = 5.3 Hz); 5.41 (d, 1 H, NH, J = 6.7 Hz); 6.55 (tt, 1 H, H_p, J = 7.2 Hz, J = 1.1 Hz); 6.58 (dd, 2 H, H_o, J = 8.6 Hz, J = 1.1 Hz); 7.06 (dd, 2 H, H_m, J = 8.6 Hz, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 70 °C), δ: 27.81 (Me, Boc); 33.91 (C(3)); 50.56 (C(4)); 52.04 (C(5)); 57.60 (C(2)); 62.32 (C(6)); 78.09 (C, Boc); 112.46 (C_o); 115.75 (C_p); 128.41 (C_m); 147.68 (C_i); 153.56 (CO, Boc). LC-MS (MeCN—H_2O (1 : 9), τ_R = 18.3 min, CI), *m*/*z* (I_{rel} (%)): 193 $[M - Boc + 2 H]^+$ (10), 234 $[M - Boc + 2 H + MeCN]^+$ (62), 237 $[M - Bu^t + 2 H]^+$ (13), 278 $[M - Bu^t + 2 H + MeCN]^+$ (100), 293 $[M + H]^+$ (27), 334 $[M + H + MeCN]^+$ (80). HPLC, τ_R/min: 22.9 (hexane—propan-2-ol (40 : 1)).

(2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-2-hydroxymethyl-4-[(methyl)(phenyl)amino]pyrrolidine (19). The complex $BH_3 \cdot Me_2S$ (127 μL, 1.339 mmol) was added to a solution of ester **15** (116 mg, 0.333 mmol) in dry THF (2 mL). The reaction mixture was kept in a sealed tube under argon at 40 °C for 4 days. Then methanol was added until gas evolution ceased. The mixture was refluxed for 5 min and concentrated. The product was isolated by flash chromatography with benzene—ethyl acetate (10 : 0.3 → 10 : 1.5) as an eluent. The yield of compound **19** was 65 mg (64%), colorless amorphous solid, $[\alpha]_D^{20}$ −54.1 (*c* 1.0, $CHCl_3$). Found (%): C, 66.87; H, 8.54; N, 8.90. $C_{17}H_{26}N_2O_3$. Calculated (%): C, 66.64; H, 8.55; N, 9.14. IR (thin film), ν/cm^{-1}: 3416 (OH); 1693, 1670 (C=O, Boc); 1599 (Ph). UV, λ_{max}/nm: 210, 252, 297. ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.41 (s, 9 H, Me, Boc); 1.98 (ddd, 1 H, H_B(3), J = 12.8 Hz, J = 9.9 Hz, J = 8.0 Hz); 2.16 (dt, 1 H, H_A(3), J = 12.8 Hz, J = 7.6 Hz); 2.78 (s, 3 H, NMe); 3.10 (dd, 1 H, H_B(5), J = 10.6 Hz, J = 9.4 Hz); 3.56 (dt, 1 H, H_B(6), J = 10.5 Hz, J = 5.4 Hz); 3.60 (ddd, 1 H, H_A(6) J = 10.5 Hz, J = 5.3 Hz, J = 3.7 Hz); 3.66 (dd, 1 H, H_A(5), J = 10.6 Hz, J = 7.6 Hz); 3.78 (tdd, 1 H, H(2), J = 7.9 Hz, J = 5.3 Hz, J = 3.8 Hz); 4.18 (tt, 1 H, H(4), J = 9.6 Hz, J = 7.6 Hz); 4.39 (t, 1 H, OH, J = 5.5 Hz); 6.71 (tt, 1 H, H_p, J = 7.2 Hz, J = 1.0 Hz);

6.87 (dd, 2 H, H_o, J = 8.8 Hz, J = 1.0 Hz); 7.17 (dd, 2 H, H_m, J = 8.8 Hz, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 70 °C), δ: 27.75 (Me, Boc); 30.00 (C(3)); 33.02 (NMe); 47.26 (C(5)); 56.21 (C(4)); 56.90 (C(2)); 62.25 (C(6)); 78.08 (C, Boc); 114.71 (C_o); 117.32 (C_p); 128.33 (C_m); 150.26 (C_i); 153.51 (CO, Boc). HPLC, τ_R/min: 18.4 (hexane—propan-2-ol (40 : 1)).

2-(*tert*-Butoxycarbonyl)-5-phenyl-2,5-diazabicyclo[2.2.1]-heptane (20) was isolated by flash chromatography while separating the reduction products from ester **14** (see the synthesis of compound **18**). The yield was 4.5 mg (8%), colorless crystals, m.p. 133—136 °C. UV, λ_{max}/nm: 206, 250, 297. ^{1}H NMR (DMSO-d_6, 70 °C), δ: 1.36 (s, 9 H, Me, Boc); 1.86 (dm, 1 H, $H_B(7)$, J = 9.8 Hz); 1.90 (dm, 1 H, $H_A(7)$, J = 9.8 Hz); 3.00 (dm, 1 H, $H_B(3)$ or $H_B(6)$, J = 8.9 Hz); 3.23 (dd, 1 H, $H_B(6)$ or $H_B(3)$, J = 9.8 Hz, J = 1.4 Hz); 3.30 (dd, 1 H, $H_A(6)$ or $H_A(3)$, J = 9.8 Hz, J = 1.9 Hz); 3.50 (dd, 1 H, $H_A(3)$ or $H_A(6)$, J = 8.9 Hz, J = 2.0 Hz); 4.43, 4.46 (both m, 1 H each, H(1), H(4)); 6.57 (dd, 2 H, H_o, J = 8.7 Hz, J = 1.0 Hz); 6.60 (tt, 1 H, H_p, J = 7.3 Hz, J = 1.0 Hz); 7.14 (dd, 2 H, H_m, J = 8.7 Hz, J = 7.3 Hz). LC-MS (MeCN—H_2O (7 : 3), τ_R = 5.4 min, CI), m/z (I_{rel} (%)): 175 $[M - Boc + 2 H]^+$ (16), 216 $[M - Boc + 2 H + MeCN]^+$ (68), 219 $[M - Bu^t + 2 H]$ (16), 257 (54), 260 $[M - Bu^t + 2 H + MeCN]^+$ (75), 275 $[M + H]^+$ (38), 316 $[M + H + MeCN]^+$ (100); calculated for $C_{16}H_{22}N_2O_2$: M = 274.36. HPLC, τ_R/min: 5.4 (hexane—propan-2-ol (40 : 1)).

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