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Structure and Properties of 4-Amino Derivatives of 5-Oxoproline

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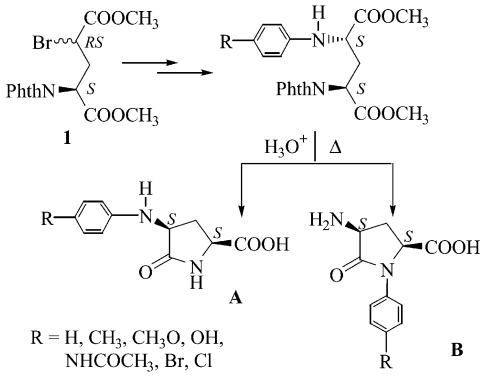
On the basis of the results obtained from NMR spectroscopy, X-ray analysis and chemical transformations, it was established that acidic hydrolysis of (2*S*,4*S*)-4-arylaminoglutamates results in the formation of lactams in which ring closure occurs with the participation of the γ-amino and α-COOH groups; but isomeric lactams resulting from the participation of the α-amino and γ-COOH groups are not formed. Isomeric lactams, that is, (2*S*,4*S*)-4-arylamino-5-oxoprolines, can be easily converted in acidic medium into more stable 4-amino-1-aryl-5-oxoprolines.

Introduction

The exceptionally important biological role of both glutamic acid and the product of its cyclization, 5-oxoproline (pyroglutamic acid), in metabolic processes[1] on the one hand, and the wide use of 5-oxoproline as a chiral building block on the other hand,[2] is reason for interest in the modification of these compounds by introducing various substituents into glutamic and pyroglutamic acids.

One of the most important chemical properties of glutamic acid and its C derivatives is the ability to form lactams, which are derivatives of pyroglutamic acid. Glutamic acid in aqueous solutions with pH values close to neutral is converted into pyroglutamic acid.[3] The derivatives of glutamic acid with 4-substituents, such as amino,[4] phenyl,[5] arylamino,[6] thiopyridinyl[7] and others,[8] are able to form lactams in acidic and neutral media. It should be noted that the amount of lactam formed increases when the glutamic acid contains aromatic and heterocyclic substituents. Acidic hydrolysis of dimethyl (2*S*,4*S*)-4-arylamino-*N*-phthaloylglutamates obtained from (2*S*,4*RS*)-4-bromoglutamate derivative **1** (Scheme 1) resulted in lactams (4-substituted 5-oxoprolines) as the only reaction products.[6] When the substituent is a fragment of a primary amine, in particular arylamine, both γ- and α-carboxylic groups can participate in the lactam-formation process to give **A** and **B** pyroglutamic acids, respectively (Scheme 1).

Earlier, we assigned a structure of type **A** to these formed lactams;[6] this assignment did not contradict the available data regarding the properties of these compounds. However, the results obtained recently, in particular on the synthesis of 4-arylaminoglutamate derivatives with a tertiary amino group,[8b] made it necessary to critically examine that data. The purpose of the present work was the synthesis and study of the structure of lactams derived from 4-arylaminoglutamates.



Scheme 1.

Results and Discussion

At first, we studied the hydrolysis of dimethyl (2*S*,4*S*)-4-phenylamino- (**2**) and (2*S*,4*S*)-4-(4-methoxyphenyl)amino-*N*-phthaloylglutamates (**3**) obtained according to the described method.[9] It was established that heating of compounds **2** or **3** in 10 N HCl for 1 h at 70 °C resulted in the selective hydrolysis of ester groups with the formation of compounds **4** and **5**, respectively (Scheme 2). Acids **4** and **5**, which were isolated from the reaction mixture, contained crystallized water that was removed while heating under reduced pressure. Comparison of the ^{1}H NMR spectra of the reaction products with those of the dehydrated products at-

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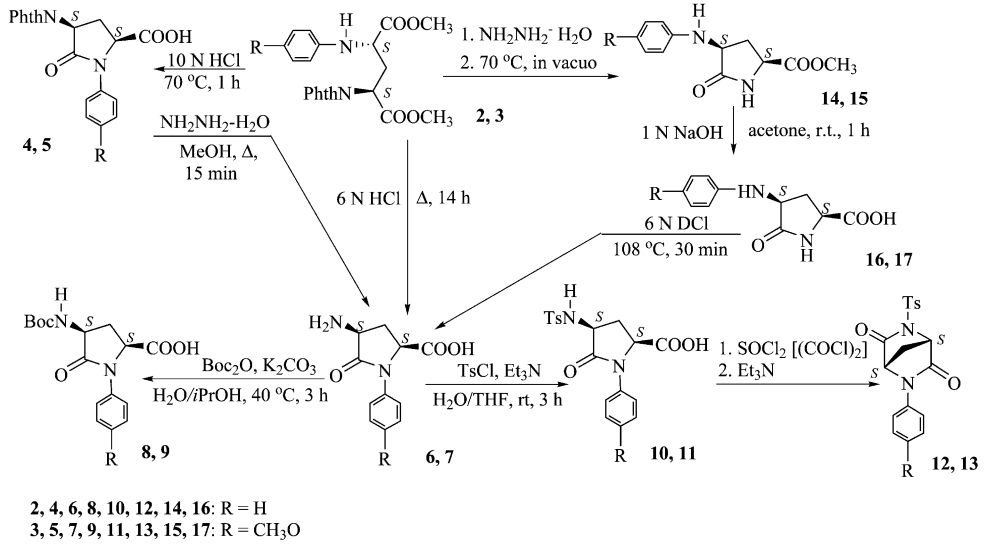


Scheme 2.

tested to the fact that the cyclization reaction resulting in the formation of 5-oxoproline derivatives has already occurred at the stage of hydrolysis (Scheme 2).

The structure of compound **4** was determined by both X-ray crystallography and NMR spectroscopy. Single crystals of compound **4** were obtained by crystallization from MeOH. It was established that the monoclinic unit cell ($P2_1$ space group, chiral) is formed by two crystallographic independent molecules of compound **4** together with two molecules of MeOH. In this case, MeOH molecules in the crystal fill the channels between the piles of compound **4**. They form pairs of hydrogen bonds and are the acceptors of bonds for carboxylic groups and the donors of bonds for the carbonyl groups of the lactam and phthalimide. X-ray data (Figure 1) and NMR spectra confirm the *cis* arrangement of the protected amino and carboxylic groups in this compound. In the 2D NOESY spectra of acid **4**, the cross peaks between 3A-H and both 2-H and 4-H, and also between 2-H and 4-H, were observed. Similar conclusions on the structure of compound **5** were made on the basis of its NMR spectra.

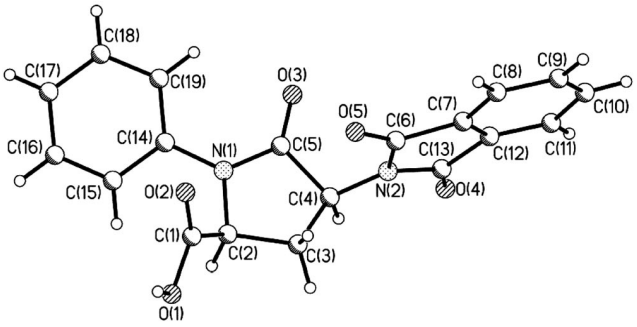


Figure 1. X-ray structure of compound **4**.

Acidic hydrolysis of compounds **4** and **5** under refluxing in 6 N HCl for 12 h led to the removal of the phthaloyl group and to the formation of pyroglutamic acid derivatives. However, because both ring opening and repeated closure are possible during the hydrolysis of the lactam, the reaction products could have a structure of type **A** or **B** (Scheme 1) and their ^{1}H NMR spectra are essentially identical.

We established that the hydrolysis of compounds **4** and **5**, as well as the hydrolysis of compounds **2** and **3**, under the conditions of prolonged (12–14 h) refluxing in 6 N HCl leads to compounds **6** and **7**, which possess the **B**-type structure. The lactams thus formed resulted from the formation of a bond between the carbon atom of the α-carboxy group and the nitrogen atom of the arylamino group.

Because the ^{1}H and ^{13}C NMR spectra of compounds **6** and **7** in D_2O and [D_6]DMSO are inconclusive with regard to the cyclization direction of the lactam ring (decision between **A** or **B** structures), to solve this problem we specially synthesized acid **6*** starting from ^{15}N-glutamic acid. In the ^{15}N NMR spectrum of compound **6***, only one signal at δ = 40.85 ppm, undoubtedly related to the NH_2 group, was observed, which testifies to the formation of a lactam of type **B**.

The next step in our investigation was the NMR study of *N*-*tert*-butyloxycarbonyl (compounds **8** and **9**) and *N*-tosyl (compounds **10** and **11**) derivatives of lactams **6** and **7**. In the ^{1}H NMR spectra of compounds **8**–**11**, the signals of the methylene protons of the pyrrolidone cycle were observed in the range δ = 2.5–2.7 (3A-H) and 1.6–1.9 (3B–H) ppm as a doublet of doublets of doublets with a geminal coupling constant $^2J_{3A,3B}$ = 11–12 Hz and a vicinal constant J = 7–10 Hz due to the spin–spin coupling of the 2-H and 4-H protons. The 2-H and 4-H protons resonated in the range δ = 4–5 ppm, and each of them are coupled to the nonequivalent protons at C-3. Moreover, the higher-field CH (δ = 4.2–4.4 ppm) was additionally split into the doublet owing to the coupling with the NH proton, $^3J_{CH,NH}$ = 8.5–9.2 Hz. However, this multiplicity pattern is

possible in both **A** and **B** structures (Scheme 1), which served as the reason for the erroneous interpretation of the data in the previous work.[10]

The ^{13}C NMR spectroscopic data for compounds **8**–**11**, obtained in the present work, also provide evidence for alternative assignments of the signals as a result of the closeness of the chemical shifts of the C-2 and C-4 carbon atoms, and the C-5 and COOH carbonyl carbon atoms; therefore, the data supports the hypothesis that both **A** and **B** structures are possible.

In order to unambiguously determine the direction of the formation of the pyrrolidone cycle and to prove the structure of the final products, we carried out extensive multinuclear NMR (^1H, ^{13}C and ^{15}N) spectroscopic studies of compounds **8**–**11**, including 2D homo- and heteronuclear experiments.

In the ^1H coupled ^{13}C NMR spectrum of compound **8**, the signal of the Boc carbonyl carbon atom (δ = 155.48 ppm) was a doublet with a coupling constant J = 4.9 Hz. In the 2D ^1H–^{13}C HMBC spectra of compounds **8** and **9**, the cross peak between the signal of the Boc carbonyl carbon atom and the upfield signal of the CH proton of pyrrolidone was observed; the latter in turn was coupled with the NH proton. Consequently, the upfield proton and the connected upfield carbon atom (according to 2D ^1H–^{13}C HSQC experiments) are related to C-4–H of oxoproline. Such a combination of homo- and heteronuclear spin–spin couplings is possible only for the **B**-type structure (Scheme 1).

Analysis of the 2D HMBC spectra made it possible to unambiguously assign the signals of the COOH group and the C-5 carbon atom by considering the corresponding cross peaks with the 2-H and 4-H protons. Additional confirmation of the assignment of the cyclic carbon atoms and determination of the $^1J_{C,C}$ coupling constants were obtained from 1D INADEQUATE experiments. The following values of coupling constants were measured for compound **8**: $^1J_{C2,COOH}$ = 61.6 Hz, $^1J_{C2,C3}$ = 45.1 Hz, $^1J_{C3,C4}$ = 45.5 Hz, $^1J_{C4,C5}$ = 61.6 Hz.

In the ^{15}N NMR spectra of compounds **8** and **10**, the chemical shifts of N-1 had almost similar values (δ = 135 ppm), whereas the chemical shift of the NH nitrogen atom changed from δ = 88 ppm (compound **8**) to δ = 103 ppm (compound **10**). X-ray crystallography data also confirmed the structure of compound **10** (Figure 2).

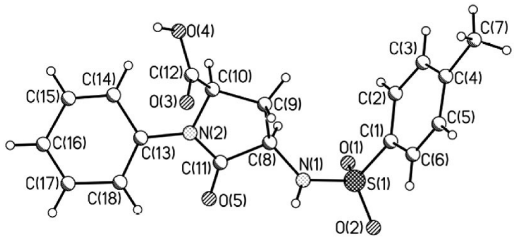


Figure 2. X-ray structure of compound **10**.

It was found that acyl chlorides obtained from *N*-tosyl pyroglutamic acids **10** and **11** undergo intramolecular cyclization in the presence of tertiary amines, which results in bicyclic compounds **12** and **13** (Scheme 2); however, this cyclization is only possible if the molecule contains a Ts-NH group. The structure of compound **12** was confirmed by X-ray analysis (Figure 3).

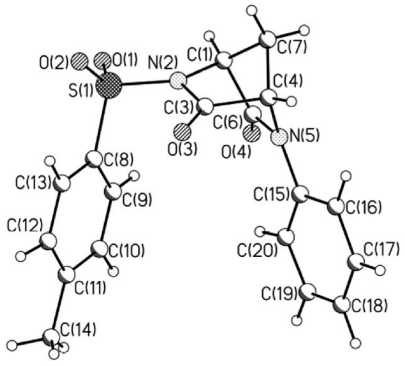


Figure 3. X-ray structure of compound **12**.

Removal of the phthaloyl group in compounds **4** and **5** by hydrazinolysis under mild conditions resulted in compounds **6** and **7**; their formation can be taken as additional evidence that **6** and **7** have the **B**-type structure.

Thus, it was established that acidic hydrolysis of protected 4-arylaminoglutamates in acidic and neutral media resulted in stable lactams formed as a result of the interaction between the α-COOH and γ-NH groups.

Synthesis of 4-substituted pyroglutamic acids **16** and **17** (Scheme 2) having the alternative type **A** structure was the final accent in the determination of the structure of the pyroglutamic acid derivatives obtained from arylamino glutamic acids. Thus, hydrazinolysis of compounds **2** and **3** yielded dimethyl 4-aminosubstituted glutamates, which were already partially converted into methyl 4-aminosubstituted pyroglutamates **14** and **15** in the course of the reaction; the complete ring closure occurred under heating at 70 °C in vacuo. The structures of compounds **14** and **15** were confirmed by ^1H and ^{13}C NMR spectroscopy, including 2D NOESY, HSQC and HMBC experiments. The characteristic feature of the ^1H NMR spectra was the presence of two signals for the NH protons, that is, a singlet at δ = 8.3 ppm (N-1–H) and a doublet at δ = 5–6 ppm (C-4–NH). The cross peaks observed in the 2D HMBC spectrum between the pairs of signals (4-H, C_i), (NH, C_o) and (NH, C-5) unambiguously proved a type **A** structure (Scheme 1). The structure of compound **14** was also established on the basis of the X-ray data (Figure 4).

Hydrolysis of the ester group in compounds **14** and **15** by 1 N NaOH in acetone yielded pyroglutamic acids **16** and **17**. The pyrrolidone ring was not affected in this case, which was confirmed by ^1H and ^{13}C NMR spectra. In the ^1H NMR spectra of compounds **16** and **17**, the signals of both the NH groups had approximately the same chemical shifts

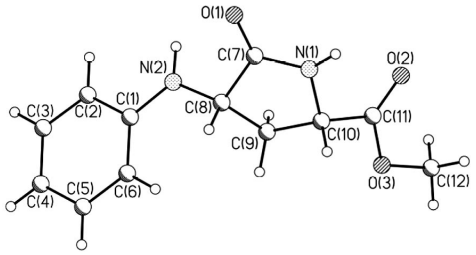


Figure 4. X-ray structure of compound **14**.

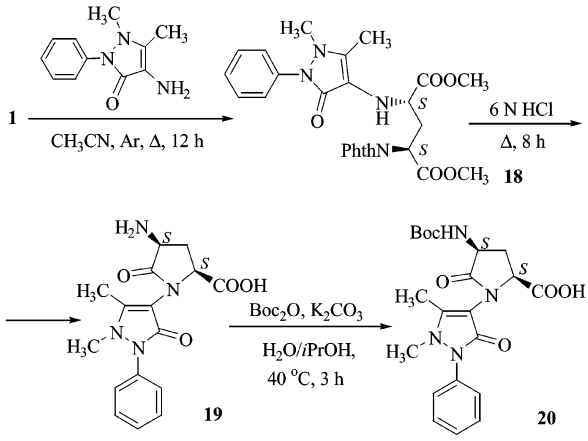
as in esters **14** and **15**; moreover, the signal of the C-4–NH proton was considerably broadened due to the chemical exchange with the protons of COOH and solvent water.

The pyrrolidone rings of *cis*-4-arylamino and *cis*-1-aryl-4-amino pyroglutamates (**A** and **B** types, respectively) had different hydrolytic stabilities. Thus, heating of compounds **16** and **17** in 6 N DCl at 108 °C for 30 min resulted in complete conversion into acids **6** and **7**, whereas the latter did not undergo any transformation under those conditions.

Thus, having compounds of both **A** and **B** types at hand we carried out a comparative analysis of their ^{1}H and ^{13}C NMR spectra. The spectral parameters (δ and J) of cyclic carbon atoms and protons do not have characteristic differences that make it possible to differentiate **A** or **B** structures (Table 1). At the same time, chemical shifts of the protons of the aryl moiety markedly differ in complete accordance with the known regularities. In the ^{1}H NMR spectra of the 4-arylamino derivatives, the aromatic protons were shifted upfield by 0.5–0.9 ppm (similar to aniline) relative to those of the 1-aryl-4-amino derivatives (similar to acetanilide). Another characteristic feature of the ^{1}H NMR spectra of 4-arylamino derivatives is the presence of two signals for the NH protons in aprotic solvents.

It was also found that some other 4-aminosubstituted glutamic acids tend to form lactams with a **B**-type structure, in which the nitrogen atom of the pyrrolidone ring is substituted, and these compounds are stable in acidic and neutral media.

In particular, we observed the formation of similar pyroglutamic acids under hydrolysis of dimethyl (2*S*,4*S*)-4-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)amino-*N*-phthaloylglutamate (**18**). Nucleophilic substitution of bromine in compound **1** by 4-aminoantipyrine (4-amino-2,3-dimethyl-5-oxo-1-phenyl-3-pyrazoline) (Scheme 3) resulted in a mixture of diastereoisomers **18** that was enriched with the (2*S*,4*S*)-isomer (according to HPLC data); the latter was isolated from the product mixture by repeated precipitation. The structure of compound **18** was confirmed by ^{1}H NMR spectroscopic data and X-ray crystallography (Figure 5). (2*S*,4*S*)-4-Amino-1-(2,3-dimethyl-5-oxo-1-phenyl-3-pyraz-



Scheme 3.

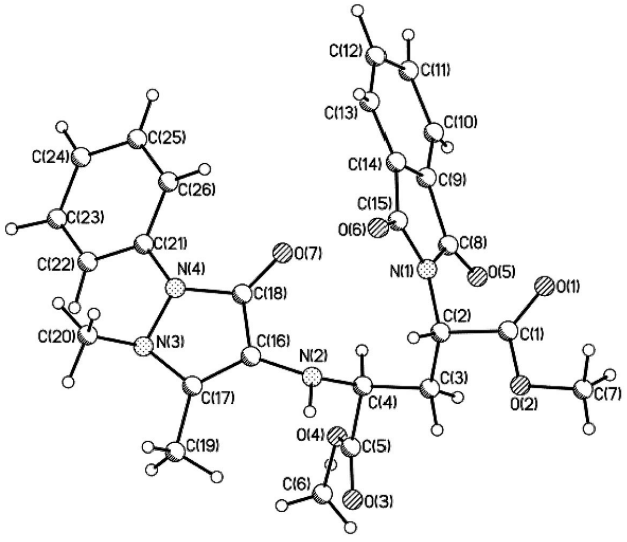


Figure 5. X-ray structure of compound **18**.

Table 1. Selected ^{1}H and ^{13}C NMR spectroscopic data for **A** (compounds **6** and **7**) and **B** structures (compounds **16** and **17**) in [D$_6$]-DMSO.

Compound	^{1}H chemical shifts (δ, ppm) and coupling constants (J, Hz)			^{13}C chemical shifts (δ, ppm)[a]		
	2-H	4-H	*ortho*–H	C-2	C-4	C-*o*
6	4.38 J = 7.9, 2.9	3.92 J = 8.1, 3.2	7.63	60.92	50.19	121.74
7	4.31 J = 7.9, 3.0	3.87 J = 7.9, 3.4	6.94	61.57	49.97	123.84
16	3.82 J = 9.2, 6.9	3.95 J = 9.9, 7.9	6.65	53.95	54.14	112.73
17	4.10 J = 9.0, 7.3	3.95 J = 9.5, 8.2	6.61	51.70	54.02	114.45

[a] ^{13}C chemical shifts for compounds **6** and **7** were measured in D$_2$O.

olin-4-yl)-5-oxoproline (**19**) and its Boc derivative **20** exhibited the same features in their 1D and 2D NMR spectra as did compounds **8** and **9**.

Conclusions

On the basis of the results of NMR spectroscopy, X-ray analysis and chemical transformation, it was established that lactams of type **B** (ring closure occurs with the participation of the γ-amino and α-COOH groups) are formed during the deprotection of α-amino and carboxylic groups in (2*S*,4*S*)-4-aminoglutamate derivatives (compounds **2**, **3**, and **18**) by heating in 6 N HCl. Lactams of type **A**, which result from the participation of the α-amino and γ-COOH groups are not formed, as it was considered earlier.[6,10] Isomeric lactams, that is, 4-arylamino-5-oxoprolines **16** and **17**, were easily converted in acidic medium into more stable compounds **6** and **7**.

Thus, it was established that 4-aminoglutamic acid derivatives in acidic and neutral solutions exist solely as lactams, and the closure into the lactam occurs with the participation of the α-COOH and γ-amino groups.

Experimental Section

General: Dimethyl (2*S*,4*RS*)-4-bromo-*N*-phthaloylglutamate (**1**),[11] dimethyl (2*S*,4*S*)-4-phenylamino-*N*-phthaloylglutamate (**2**) and dimethyl (2*S*,4*S*)-4-(4-methoxyphenyl)amino-*N*-phthaloylglutamate (**3**)[9] were prepared according to literature procedures. All other reagents were of commercial quality. Solvents were dried and purified by standard methods. Routine monitoring of reaction mixtures was carried out by using Sorbfil UV 254 (Russia) TLC aluminium-plated silica gel. Silica gel 60 (230–400 mesh) was used for flash chromatography. Analytical HPLC was performed with a LiChrosorb Si-60 (4 × 250 mm, 5 μm) column, with a flow rate of 1 mL min^{-1} and by using a tunable UV detector set at 230 nm. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, by using TMS or DSS as references. ^{15}N NMR spectra were recorded at 40.6 MHz by using liquid ammonia as external standard. Assignment of the δ values was based on standard 2D NMR techniques (^{1}H–^{13}C HSQC and HMBC, ^{1}H–^{1}H NOESY). Optical rotation values were measured with a Perkin–Elmer M 341 polarimeter. All optical rotations were obtained at room temperature. MS data were obtained by using a quadrupole Shimadzu LCMS-2010 system in negative mode with an APCI probe installed with CH_3CN as the solvent. Quadrupole array and curved desolvation line (CDL) were used in scan-mode according to the parameters stored in the auto-tune file. The probe voltage was set to 4.5 kV, and the APCI probe temperature was set to 400 °C. The CDL and block heater were set at 250 °C and 200 °C, respectively.

(2*S*,4*S*)-5-Oxo-1-phenyl-4-phthalimidoproline (4): A solution of compound **2** (2.00 g, 5.05 mmol) in HCl (10 N, 10 mL) was stirred at 70 °C for 1 h. The precipitate was filtered off, washed with water and dried in vacuo at 70 °C to give compound **4** (1.06 g, 60%) as a white solid. M.p. 229–231 °C. $[\alpha]_D$ = +49.1 (c = 0.45, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.47 (ddd, $^2J_{3B,3A}$ = 12.0 Hz, $^3J_{3B,4}$ = 11.0 Hz, $^3J_{3B,2}$ = 9.5 Hz, 1 H, 3B-H), 2.82 (ddd, $^2J_{3A,3B}$ = 12.0 Hz, $^3J_{3A,4}$ = 9.4 Hz, $^3J_{3A,2}$ = 7.3 Hz, 1 H, 3A-H), 5.01 (dd, $^3J_{2,3B}$ = 9.5 Hz, $^3J_{2,3A}$ = 7.3 Hz, 1 H, 2-H), 5.24 (dd, $^3J_{4,3B}$ = 11.0 Hz, $^3J_{4,3A}$ = 9.4 Hz, 1 H, 4-H), 7.21 (tt, ^3J = 7.1 Hz, ^4J = 1.4 Hz, 1 H, *p*-H), 7.38–7.46 (m, 4 H, Ph), 7.92 (m, AA′BB′, 4 H, Phth), 13.13 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 26.92 (C-3), 49.70 (C-4), 57.13 (C-2), 121.53 (C-*o*), 123.37 (C-3′, C-6′), 125.21 (C-*p*), 128.57 (C-*m*), 131.24 (C-4′, C-5′), 134.86 (C-2′a, C-6′a), 138.39 (C-*i*), 167.03 (C-2′, C-7′), 169.02 (C-5), 171.57 (COOH) ppm. $C_{19}H_{14}N_2O_5$ (350.33): calcd. C 65.14, H 4.03, N 8.00; found C 65.10, H 3.96, N 7.84.

(2*S*,4*S*)-1-(4-Methoxyphenyl)-5-oxo-4-phthalimidoproline (5): According to the above procedure and starting from compound **3**, compound **5** (64% yield) was obtained as a white solid. M.p. 276–282 °C. $[\alpha]_D$ = +45.8 (c = 0.3, MeOH). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.46 (ddd, $^2J_{3B,3A}$ = 12.0 Hz, $^3J_{3B,4}$ = 11.0 Hz, $^3J_{3B,2}$ = 9.5 Hz, 1 H, 3B-H), 2.80 (ddd, $^2J_{3A,3B}$ = 12.0 Hz, $^3J_{3A,4}$ = 9.3 Hz, $^3J_{3A,2}$ = 7.3 Hz, 1 H, 3A-H), 3.75 (s, 3 H, OCH_3), 5.01 (dd, $^3J_{2,3B}$ = 9.5 Hz, $^3J_{2,3A}$ = 7.3 Hz, 1 H, 2-H), 5.24 (dd, $^3J_{4,3B}$ = 11.0 Hz, $^3J_{4,3A}$ = 9.3 Hz, 1 H, 4-H), 6.97 (d, ^3J = 9.2 Hz, 2 H, *m*-H), 7.34 (d, ^3J = 9.2 Hz, 2 H, *o*-H), 7.92 (m, AA′BB′, 4 H, Phth), 13.08 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 27.02 (C-3), 49.54 (C-4), 55.22 (OCH_3), 57.60 (C-2), 113.80 (C-*m*), 123.35 (C-3′, C-6′), 123.79 (C-*o*), 131.24 (C-4′, C-5′), 131.27 (C-*i*), 134.86 (C-2′a, C-6′a), 156.85 (C-*p*), 167.05 (C-2′, C-7′), 168.93 (C-5), 171.65 (CO_2H) ppm. $C_{20}H_{16}N_2O_6$ (380.36): calcd. C 63.16, H 4.24, N 7.36; found C 63.06, H 3.99, N 7.15.

(2*S*,4*S*)-4-Amino-5-oxo-1-phenylproline (6)

Procedure A: A mixture of compound **2** (4.7 g, 11.86 mmol) and HCl (6 N, 50 mL) was heated at reflux for 14 h and then cooled. The precipitate of phthalic acid was filtered off; the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in EtOH (30 mL) and pyridine (1.2 mL) was added to the solution. The reaction mixture was kept for 3 h at –10 °C. The precipitate was filtered off and dried in vacuo to give compound **6** (2.45 g, 90%) as a white solid.

Procedure B: To a suspension of compound **4** (0.995 g, 2.84 mmol) in MeOH (10 mL) was added an aqueous solution of hydrazine hydrate (64%, 0.9 mL, 11.5 mmol). The reaction mixture was heated at reflux for 15 min and then concentrated HCl was added up to pH 3–4. The precipitate was filtered off. The filtrate was evaporated to dryness, and the residue was dried in vacuo, dissolved in EtOH (5 mL) and then cooled to –10 °C. The precipitate of hydrazinium chloride was filtered off. Pyridine was added to the filtrate up to pH 6. The reaction mixture was kept at –10 °C overnight. The precipitate was filtered off and dried in vacuo to give compound **6** (0.357 g, 55%) as a white solid. M.p. 224–227 °C (decomp.). $[\alpha]_D$ = –39.4 (c = 1.0, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 2.11 (ddd, $^2J_{3B,3A}$ = 13.1 Hz, $^3J_{3B,4}$ = 9.3 Hz, $^3J_{3B,2}$ = 8.3 Hz, 1 H, 3B-H), 3.05 (ddd, $^2J_{3A,3B}$ = 13.1 Hz, $^3J_{3A,4}$ = 9.3 Hz, $^3J_{3A,2}$ = 7.1 Hz, 1 H, 3A-H), 4.33 (t, $^3J_{4,3B}$ = $^3J_{4,3A}$ = 9.3 Hz, 1 H, 4-H), 4.44 (dd, $^3J_{2,3B}$ = 8.3 Hz, $^3J_{2,3A}$ = 7.1 Hz, 1 H, 2-H), 7.35 (tt, ^3J = 7.1 Hz, ^4J = 1.4 Hz, 1 H, *p*-H), 7.43 (dd, ^3J = 8.7 Hz, ^4J = 1.4 Hz, 2 H, *o*-H), 7.49 (dd, ^3J = 8.7 Hz, ^3J = 7.1 Hz, 2 H, *m*-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 27.33 (C-3), 50.19 (C-4), 60.92 (C-2), 121.74 (C-*o*), 126.30 (C-*p*), 128.44 (C-*m*), 135.77 (C-*i*), 169.08 (C-5), 175.85 (CO_2H) ppm. $C_{11}H_{12}N_2O_3 \cdot 0.5H_2O$ (229.24): calcd. C 57.63, H 5.72, N 12.22; found C 57.65, H 5.62, N 12.34.

(2*S*,4*S*)-4-Amino-1-(4-methoxyphenyl)-5-oxoproline (7): According to the above Procedure A and starting from compound **3**, compound **7** (89% yield) was obtained as a white solid. According to the above Procedure B and starting from compound **5**, compound **7** (75% yield) was obtained as a white solid. M.p. 229–231 °C (decomp.) (H_2O/EtOH). $[\alpha]_D$ = –19.8 (c = 1.0, H_2O). ^{1}H NMR

(400 MHz, D_2O): δ = 2.13 (ddd, $^2J_{3B,3A}$ = 13.2 Hz, $^3J_{3B,4}$ = 9.1 Hz, $^3J_{3B,2}$ = 7.8 Hz, 1 H, 3B-H), 3.04 (ddd, $^2J_{3A,3B}$ = 13.2 Hz, $^3J_{3A,4}$ = 9.1 Hz, $^3J_{3A,2}$ = 7.3 Hz, 1 H, 3A-H), 3.83 (s, 3 H, OCH_3), 4.33 (t, $^3J_{4,3B}$ = $^3J_{4,3A}$ = 9.1 Hz, 1 H, 4-H), 4.70 (dd, $^3J_{2,3B}$ = 7.8 Hz, $^3J_{2,3A}$ = 7.3 Hz, 1 H, 2-H), 7.05 (d, ^3J = 9.0 Hz, 2 H, *m*-H), 7.36 (d, ^3J = 9.0 Hz, 2 H, *o*-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 27.21 (C-3), 49.97 (C-4), 54.67 (OCH_3), 61.57 (C-2), 113.73 (C-*m*), 123.84 (C-*o*), 128.91 (C-*i*), 156.81 (C-*p*), 169.14 (C-5), 175.99 (CO_2H) ppm. $C_{12}H_{14}N_2O_4$ (250.26): calcd. C 57.60, H 5.64, N 11.19; found C 57.57, H 5.72, N 11.36.

(2*S*,4*S*)-4-(*tert*-Butyloxycarbonyl)amino-5-oxo-1-phenylproline (8): To a stirred solution of **6** (5.0 g, 22.7 mmol) and K_2CO_3 (3.41 g, 24.7 mmol) in water (22 mL) was added a solution of Boc_2O (6.27 g, 22.8 mmol) in *i*PrOH (9 mL), and the reaction mixture was stirred at 40 °C for 3 h. The reaction mixture was diluted with water and extracted with hexane (2 × 15 mL). The aqueous layer was acidified with citric acid to pH 4. The precipitate was filtered off and recrystallized from EtOH to give compound **8** as a white solid (5.24 g, 72%). M.p. 220–222 °C (decomp.). $[\alpha]_D$ = –29.5 (*c* = 1.0, acetone). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.41 (s, 9 H, CH_3 Boc), 1.91 (ddd, $^2J_{3B,3A}$ = 11.7 Hz, $^3J_{3B,4}$ = 11.0 Hz, $^3J_{3B,2}$ = 9.6 Hz, 1 H, 3B-H), 2.70 (ddd, $^2J_{3A,3B}$ = 11.7 Hz, $^3J_{3A,4}$ = 8.9 Hz, $^3J_{3A,2}$ = 7.0 Hz, 1 H, 3A-H), 4.42 (dt, $^3J_{4,3B}$ = 11.0 Hz, $^3J_{4,3A}$ = $^3J_{4,NH}$ = 8.9 Hz, 1 H, 4-H), 4.83 (dd, $^3J_{2,3B}$ = 9.6 Hz, $^3J_{2,3A}$ = 7.0 Hz, 1 H, 2-H), 7.16 (tt, ^3J = 7.0 Hz, ^4J = 1.6 Hz, 1 H, *p*-H), 7.32 (d, $^3J_{NH,4}$ = 8.9 Hz, 1 H, NH), 7.37 (dd, ^3J = 8.9 Hz, ^3J = 7.0 Hz, 2 H, *m*-H), 7.41 (dd, ^3J = 8.9 Hz, ^4J = 1.6 Hz, 2 H, *o*-H), 13.05 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 28.32 (CH_3 Boc), 29.63 (C-3), 51.52 (C-4), 56.70 (C-2), 78.40 (C Boc), 121.19 (C-*o*), 124.94 (C-*p*), 128.63 (C-*m*), 138.83 (C-*i*), 155.48 (CO Boc), 171.86 (C-5), 172.30 (CO_2H) ppm. ^{15}N NMR (40.6 MHz, [D$_6$]DMSO): δ = 88.22 (NH–C-4), 135.08 (N-1) ppm. $C_{16}H_{20}N_2O_5$ (320.34): calcd. C 59.99, H 6.29, N 8.74; found C 60.17, H 6.27, N 8.45.

(2*S*,4*S*)-4-(*tert*-Butyloxycarbonyl)amino-1-(4-methoxyphenyl)-5-oxoproline (9): According to the procedure outlined for **8** and starting from compound **7**, compound **9** (65% yield) was obtained as a white solid. M.p. 225–228 °C (decomp.) (EtOH). $[\alpha]_D$ = –26.2 (*c* = 0.4, acetone). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.40 (s, 9 H, CH_3 Boc), 1.90 (ddd, $^2J_{3B,3A}$ = 11.9 Hz, $^3J_{3B,4}$ = 10.8 Hz, $^3J_{3B,2}$ = 9.6 Hz, 1 H, 3B-H), 2.68 (ddd, $^2J_{3A,3B}$ = 11.9 Hz, $^3J_{3A,4}$ = 8.8 Hz, $^3J_{3A,2}$ = 7.0 Hz, 1 H, 3A-H), 3.74 (s, 3 H, OCH_3), 4.40 (ddd, $^3J_{4,3B}$ = 10.8 Hz, $^3J_{4,3A}$ = 8.8 Hz, $^3J_{4,NH}$ = 9.1 Hz, 1 H, 4-H), 4.75 (dd, $^3J_{2,3B}$ = 9.6 Hz, $^3J_{2,3A}$ = 7.0 Hz, 1 H, 2-H), 6.94 (d, ^3J = 9.0 Hz, 2 H, *m*-H), 7.27 (d, $^3J_{NH,4}$ = 9.1 Hz, 1 H, NH), 7.30 (d, ^3J = 9.0 Hz, 2 H, *o*-H), 12.97 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 28.18 [$(CH_3)_3$ Boc], 29.61 (C-3), 51.12 (C-4), 55.18 (OCH_3), 56.97 (C-2), 78.17 (C Boc), 113.73 (C-*m*), 123.26 (C-*o*), 131.60 (C-*i*), 155.30 (CO Boc), 156.54 (C-*p*), 171.56 (C-5), 172.19 (CO_2H) ppm. $C_{17}H_{22}N_2O_6$ (350.38): calcd. C 58.28, H 6.33, N 7.99; found C 58.12, H 6.28, N 7.94.

(2*S*,4*S*)-4-[(4-Methylbenzenesulfonyl)amino]-5-oxo-1-phenylproline (10): To a stirred solution of compound **6** (5.0 g, 22.7 mmol) and Et_3N (10 mL, 71.7 mmol) in a mixture of water (90 mL) and THF (45 mL) was portionwise added *para*-toluenesulfonyl chloride (6.5 g, 34.1 mmol) over 30 min, and the reaction mixture was stirred at room temperature for 2–5 h. The organic solvent was evaporated under reduced pressure, and the residual solution was diluted with water followed by filtration. The pH of the filtrate was adjusted to 2 with HCl (1 N). The precipitate was filtered off to give compound **10** as a white solid (5.36 g, 63%). M.p. 241–243 °C. $[\alpha]_D$ = –6.8 (*c* = 1.0, acetone). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.70 (ddd, $^2J_{3B,3A}$ = 12.0 Hz, $^3J_{3B,4}$ = 10.4 Hz, $^3J_{3B,2}$ = 9.4 Hz, 1 H, 3B-H), 2.37 (s, 3 H, CH_3), 2.47 (ddd, $^2J_{3A,3B}$ = 12.0 Hz, $^3J_{3A,4}$ = 8.8 Hz, $^3J_{3A,2}$ = 7.0 Hz, 1 H, 3A-H), 4.29 (dt, $^3J_{4,3B}$ = 10.4 Hz, $^3J_{4,3A}$ = $^3J_{4,NH}$ = 8.8 Hz, 1 H, 4-H), 4.76 (dd, $^3J_{2,3B}$ = 9.4 Hz, $^3J_{2,3A}$ = 7.0 Hz, 1 H, 2-H), 7.16 (tt, ^3J = 6.4 Hz, ^4J = 2.0 Hz, 1 H, *p*-H), 7.33–7.39 (m, 6 H, *m*-H Ph, *o*-H Ph, *m*-H Ts), 7.78 (d, ^3J = 8.2 Hz, 2 H, *o*-H Ts), 8.34 (d, $^3J_{NH,4}$ = 8.8 Hz, 1 H, NH), 13.20 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.02 (CH_3), 30.59 (C-3), 53.62 (C-4), 56.81 (C-2), 121.40 (C-*o* Ph), 125.20 (C-*p*), 126.60 (C-*o* Ts), 128.62 (C-*m* Ph), 129.58 (C-*m* Ts), 138.37, 138.86 (C-*i* Ph, C-*i* Ts), 142.73 (C-*p* Ts), 170.39 (C-5), 171.92 (CO_2H) ppm. ^{15}N NMR (40.6 MHz, [D$_6$]DMSO): δ = 103.29 (NH–C-4), 135.31 (N-1) ppm. $C_{18}H_{18}N_2O_5S$ (374.42): calcd. C 57.74, H 4.84, N 7.48, S 8.56; found C 57.90, H 4.85, N 7.49, S 8.42.

(2*S*,4*S*)-1-(4-Methoxyphenyl)-4-[(4-methylbenzenesulfonyl)amino]-5-oxoproline (11): According to the procedure outlined for **10** and starting from compound **7**, compound **11** (87% yield) was obtained as a pale-yellow solid. M.p. 219–222 °C (acetone/hexane). $[\alpha]_D$ = –5.7 (*c* = 1.0, acetone). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.66 (ddd, $^2J_{3B,3A}$ = 12.0 Hz, $^3J_{3B,4}$ = 10.4 Hz, $^3J_{3B,2}$ = 9.3 Hz, 1 H, 3B-H), 2.38 (s, 3 H, CH_3), 2.43 (ddd, $^2J_{3A,3B}$ = 12.0 Hz, $^3J_{3A,4}$ = 8.7 Hz, $^3J_{3A,2}$ = 7.0 Hz, 1 H, 3A-H), 3.73 (s, 3 H, OCH_3), 4.24 (dt, $^3J_{4,3B}$ = 10.4 Hz, $^3J_{4,3A}$ = $^3J_{4,NH}$ = 8.7 Hz, 1 H, 4-H), 4.64 (dd, $^3J_{2,3B}$ = 9.3 Hz, $^3J_{2,3A}$ = 7.0 Hz, 1 H, 2-H), 6.93 (d, ^3J = 9.0 Hz, 2 H, *m*-H Ts), 7.25 (d, ^3J = 9.0 Hz, 2 H, *o*-H Ts), 7.40 (d, ^3J = 8.0 Hz, 2 H, *m*-H Ph), 7.76 (d, ^3J = 8.0 Hz, 2 H, *o*-H Ph), 8.27 (d, $^3J_{NH,4}$ = 8.7 Hz, 1 H, NH), 13.06 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 20.96 (CH_3), 30.68 (C-3), 53.35 (C-4), 55.20 (OCH_3), 57.20 (C-2), 113.81 (C-*m* Ph), 123.60 (C-*o* Ph), 126.54 (C-*o* Ts), 129.51 (C-*m* Ts), 131.18 (C-*i* Ph), 138.80 (C-*i* Ts), 142.65 (C-*p* Ts), 156.80 (C-*p* Ph), 170.21 (C-5), 171.97 (CO_2H) ppm. $C_{19}H_{20}N_2O_6S$ (404.45): calcd. C 56.43, H 4.98, N 6.93, S 7.93; found C 56.08, H 4.90, N 6.95, S 7.59.

(1*S*,4*S*)-2-(4-Methylbenzenesulfonyl)-5-phenyl-2,5-diazabicyclo[2.2.1]-heptane-3,6-dione (12): $SOCl_2$ (1 mL) was added to a solution of compound **10** (0.5 g, 1.33 mmol) in dry benzene (2 mL). The reaction mixture was heated at reflux for 3 h and then evaporated to dryness under reduced pressure. The residue was treated with hexane (10 mL) at 0 °C for 1 h. The precipitate of acyl chloride was filtered off and dried in vacuo over P_2O_5 to give the acyl chloride (0.48 g, 95%) as a white solid that was used for further reaction without additional purification. Et_3N (0.14 mL, 1.0 mmol) was added to a solution of the acyl chloride (0.393 g, 1.0 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was kept at room temperature for 1 d, then washed with aqueous HCl (5%, 3 × 1 mL), water (3 × 1 mL), aqueous Na_2CO_3 (5%, 3 × 1 mL) and water (3 × 1 mL) and then dried with Na_2SO_4. The solvent was evaporated to dryness under reduced pressure. Crystallization from EtOAc gave compound **12** (0.28 g, 59%) as a white solid. M.p. 159–164 °C. $[\alpha]_D$ = +63.2 (*c* = 0.9, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 2.57 (dt, $^2J_{7B,7A}$ = 10.7 Hz, $^3J_{7B,4}$ = $^3J_{7B,1}$ = 1.9 Hz, 1 H, 7B-H), 2.60 (dt, $^2J_{7A,7B}$ = 10.7 Hz, $^3J_{7A,4}$ = $^3J_{7A,1}$ = 1.9 Hz, 1 H, 7A-H), 4.42 (q, $^3J_{4,7B}$ = $^3J_{4,7A}$ = $^4J_{4,1}$ = 1.9 Hz, 1 H, 4-H), 4.88 (q, $^3J_{1,7B}$ = $^3J_{1,7A}$ = $^4J_{1,4}$ = 1.9 Hz, 1 H, 1-H), 6.99 (d, ^3J = 8.5 Hz, 2 H, *m*-H Ts), 7.11 (m, 1 H, *p*-H), 7.16–7.25 (m, 4 H, *m*-H, *o*-H Ph), 7.83 (d, ^3J = 8.5 Hz, 2 H, *o*-H Ts) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.55 (CH_3), 42.31 (C-7), 64.38 (C-1), 65.23 (C-4), 120.51 (C-*o* Ph), 125.72 (C-*p* Ph), 128.27 (C-*o* Ts), 128.98 (C-*m* Ph), 129.53 (C-*m* Ts), 133.76 (C-*i* Ts), 136.43 (C-*i* Ph) 145.70 (C-*p*-Ts), 168.95, 169.03 (C-3, C-6) ppm. $C_{18}H_{16}N_2O_4S$ (356.40): calcd. C 60.67, H 4.49, N 7.87, S 8.99; found C 60.60, H 4.46, N 7.92, S 8.93.

(1*S*,4*S*)-5-(4-Methoxyphenyl)-2-(4-methylbenzenesulfonyl)-2,5-diazabicyclo[2.2.1]heptane-3,6-dione (13): Oxalyl chloride (0.4 mL, 4.6 mmol) and DMF (0.01 mL) were added to a suspension of compound **11** (0.404 g, 1.0 mmol) in dry benzene (5 mL). The reaction mixture was stirred at room temperature for 1 h and then evaporated to dryness under reduced pressure. The residue was dried in vacuo over P_2O_5 and then dissolved in dry benzene (6 mL). Et_3N (0.3 mL, 2.17 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 1 h, then diluted with EtOAc (20 mL) and washed with aqueous HCl (5%, 3 × 3 mL), water (3 × 5 mL), aqueous Na_2CO_3 (5%, 3 × 5 mL) and brine (3 × 5 mL) and dried with Na_2SO_4. The solvent was evaporated to dryness under reduced pressure to give compound **13** (0.317 g, 82%) as a pale-yellow solid. M.p. 179–182 °C (EtOAc). $[\alpha]_D$ = +55.4 (*c* = 0.9, acetone). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.39 (s, 3 H, CH_3), 2.61 (dt, $^2J_{7B,7A}$ = 10.8 Hz, $^3J_{7B,4}$ = $^3J_{7B,1}$ = 1.9 Hz, 1 H, 7B-H), 2.64 (dt, $^2J_{7A,7B}$ = 10.8 Hz, $^3J_{7A,4}$ = $^3J_{7A,1}$ = 1.9 Hz, 1 H, 7A-H), 3.71 (s, 3 H, OCH_3), 4.76 (q, $^3J_{4,7B}$ = $^3J_{4,7A}$ = $^4J_{4,1}$ = 1.9 Hz, 1 H, 4-H), 4.84 (q, $^3J_{1,7B}$ = $^3J_{1,7A}$ = $^4J_{1,4}$ = 1.9 Hz, 1 H, 1-H), 6.83 (m, AA′BB′, 4 H Ph), 7.40 (d, ^3J = 8.6 Hz, 2 H, *m*-H Ts), 7.75 (d, ^3J = 8.6 Hz, 2 H, *o*-H Ts) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 21.04 (CH_3), 41.58 (C-7), 55.26 (OCH_3), 64.71 (C-1), 65.42 (C-4), 114.05 (C-*m* Ph), 122.50 (C-*o* Ph), 127.86 (C-*o* Ts), 129.50 (C-*i* Ph), 129.74 (C-*m* Ts), 133.93 (C-*i* Ts) 145.66 (C-*p*-Ts), 156.85 (C-*p* Ph), 169.62, 169.74 (C-3, C-6) ppm. $C_{19}H_{18}N_2O_5S$ (386.43): calcd. C 59.06, H 4.69, N 7.25, S 8.30; found C 59.07, H 4.49, N 7.28, S 8.40.

Methyl (2*S*,4*S*)-5-Oxo-4-phenylaminoprolinate (14): An aqueous solution of hydrazine hydrate (64%, 0.3 mL, 3.80 mmol) was added to a solution of compound **2** (0.72 g, 1.81 mmol) in MeOH/benzene (1:1, 20 mL). The reaction mixture was stirred at room temperature for 1 h and then acidified with concentrated HCl to pH 6–7. The precipitate was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was heated in vacuo at 70 °C for 2 h and then treated with $CHCl_3$ (20 mL). The precipitate was filtered off, the filtrate was evaporated to dryness under reduced pressure and the residue was purified by flash-column chromatography (benzene/$CHCl_3$) to afford compound **14** (0.243 g, 57%) as a white solid. M.p. 159–161 °C. $[\alpha]_D$ = +159.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.72 (ddd, $^2J_{3B,3A}$ = 12.2 Hz, $^3J_{3B,4}$ = 9.6 Hz, $^3J_{3B,2}$ = 8.8 Hz, 1 H, 3B-H), 2.86 (ddd, $^2J_{3A,3B}$ = 12.2 Hz, $^3J_{3A,4}$ = 8.3 Hz, $^3J_{3A,2}$ = 7.5 Hz, 1 H, 3A-H), 3.68 (s, 3 H, CO_2CH_3), 4.09 (ddd, $^3J_{4,3B}$ = 9.6 Hz, $^3J_{4,3A}$ = 8.3 Hz, $^3J_{4,NH}$ = 6.6 Hz, 1 H, 4-H), 4.24 (dd, $^3J_{2,3B}$ = 8.8 Hz, $^3J_{2,3A}$ = 7.5 Hz, 1 H, 2-H), 5.72 (d, $^3J_{NH,4}$ = 6.6 Hz, 1 H, Ph-NH), 6.56 (tt, ^3J = 7.3 Hz, ^4J = 1.1 Hz, 1 H, *p*-H), 6.65 (dd, ^3J = 8.7 Hz, ^4J = 1.1 Hz, 2 H, *o*-H), 7.06 (dd, ^3J = 8.7 Hz, ^3J = 7.3 Hz, 2 H, *m*-H), 8.35 (s, 1 H, N-1–H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 32.88 (C-3), 51.61 (C-2), 52.12 (CO_2CH_3), 53.01 (C-4), 112.64 (C-*o*), 116.27 (C-*p*), 128.76 (C-*m*), 147.88 (C-*i*), 172.27 (CO_2H), 174.85 (C-5) ppm. $C_{12}H_{14}N_2O_3$ (234.26): calcd. C 61.53, H 6.02, N 11.96; found C 61.15, H 5.64, N 11.72.

Methyl (2*S*,4*S*)-4-(4-Methoxyphenyl)amino-5-oxoprolinate (15): According to the procedure outlined for **14** and starting from compound **3** (1.50 g, 3.52 mmol), compound **15** (0.251 g, 27%) was obtained as a white solid. M.p. 144–146 °C. $[\alpha]_D$ = +145.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.70 (ddd, $^2J_{3B,3A}$ = 12.7 Hz, $^3J_{3B,4}$ = 9.4 Hz, $^3J_{3B,2}$ = 8.8 Hz, 1 H, 3B-H), 2.85 (ddd, $^2J_{3A,3B}$ = 12.7 Hz, $^3J_{3A,4}$ = 8.3 Hz, $^3J_{3A,2}$ = 7.5 Hz, 1 H, 3A-H), 3.64 (s, 3 H, OCH_3), 3.68 (s, 3 H, CO_2CH_3), 3.97 (ddd, $^3J_{4,3B}$ = 9.4 Hz, $^3J_{4,3A}$ = 8.3 Hz, $^3J_{4,NH}$ = 6.1 Hz, 1 H, 4-H), 4.23 (dd, $^3J_{2,3B}$ = 8.8 Hz, $^3J_{2,3A}$ = 7.5 Hz, 1 H, 2-H), 5.28 (d, $^3J_{NH,4}$ = 6.1 Hz, 1 H, Ph-NH), 6.62 (d, ^3J = 9.1 Hz, 2 H, *o*-H), 6.71 (d, ^3J = 9.1 Hz, 2 H, *m*-H), 8.32 (s, 1 H, N-1–H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 33.17 (C-3), 51.65 (C-2), 52.11 (CO_2CH_3), 53.84 (C-4), 55.28 (OCH_3), 113.85 (C-*o*), 114.45 (C-*m*), 141.99 (C-*i*), 151.13 (C-*p*), 172.32 (CO_2H), 175.06 (C-5) ppm. $C_{13}H_{16}N_2O_4$ (264.28): calcd. C 59.08, H 6.10, N 10.60; found C 59.16, H 5.95, N 10.54.

(2*S*,4*S*)-5-Oxo-4-phenylaminoproline (16): NaOH (1 N, 1.2 mL, 1.2 mmol) was added to a solution of compound **14** (0.117 g, 0.50 mmol) in acetone (1.5 mL). The reaction mixture was stirred at room temperature for 1 h. Acetone was evaporated under reduced pressure. The aqueous solution was acidified with concentrated HCl to pH 6–7 and evaporated to dryness under reduced pressure, and the residue was purified by flash-column chromatography ($CHCl_3$/MeOH) to afford compound **16** (0.042 g, 38%) as a pale-yellow solid. M.p. 157–162 °C. $[\alpha]_D$ = +88.9 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.64 (ddd, $^2J_{3B,3A}$ = 12.2 Hz, $^3J_{3B,4}$ = 9.9 Hz, $^3J_{3B,2}$ = 9.2 Hz, 1 H, 3B-H), 2.74 (ddd, $^2J_{3A,3B}$ = 12.2 Hz, $^3J_{3A,4}$ = 7.9 Hz, $^3J_{3A,2}$ = 6.9 Hz, 1 H, 3A-H), 3.82 (dd, $^3J_{2,3B}$ = 9.2 Hz, $^3J_{2,3A}$ = 6.9 Hz, 1 H, 2-H), 3.95 (dd, $^3J_{4,3B}$ = 9.9 Hz, $^3J_{4,3A}$ = 7.9 Hz, 1 H, 4-H), 4.5 (br. s, 1 H, CO_2H), 5.60 (br. s, 1 H, Ph-NH), 6.54 (tt, ^3J = 7.2 Hz, ^4J = 1.1 Hz, 1 H, *p*-H), 6.65 (dd, ^3J = 8.7 Hz, ^4J = 1.1 Hz, 2 H, *o*-H), 7.05 (dd, ^3J = 8.7 Hz, ^3J = 7.2 Hz, 2 H, *m*-H), 7.99 (s, 1 H, N-1–H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 34.55 (C-3), 53.95 (C-2), 54.14 (C-4), 112.73 (C-*o*), 116.05 (C-*p*), 128.74 (C-*m*), 148.23 (C-*i*), 174.71, 177.79 (C-5, CO_2H) ppm. MS (Q-array scan, MeCN): *m*/*z* (%) = 219 (100) [M – H]$^-$, 260 (15.8) [M – H + MeCN]$^-$.

(2*S*,4*S*)-4-(4-Methoxyphenyl)amino-5-oxoproline (17): According to the procedure outlined for **16** and starting from compound **15** (0.132 g, 0.50 mmol), compound **17** (0.055 g, 44%) was obtained as a slightly coloured solid. M.p. 164–166 °C. $[\alpha]_{578}$ = +40.4 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.67 (ddd, $^2J_{3B,3A}$ = 12.3 Hz, $^3J_{3B,4}$ = 9.5 Hz, $^3J_{3B,2}$ = 9.0 Hz, 1 H, 3B-H), 2.84 (ddd, $^2J_{3A,3B}$ = 12.3 Hz, $^3J_{3A,4}$ = 8.2 Hz, $^3J_{3A,2}$ = 7.3 Hz, 1 H, 3A-H), 3.64 (s, 3 H, OCH_3), 3.95 (dd, $^3J_{4,3B}$ = 9.5 Hz, $^3J_{4,3A}$ = 8.2 Hz, 1 H, 4-H), 4.10 (dd, $^3J_{2,3B}$ = 9.0 Hz, $^3J_{2,3A}$ = 7.3 Hz, 1 H, 2-H), 5.3 (br. s, 1 H, Ph-NH), 6.61 (d, ^3J = 9.1 Hz, 2 H, *o*-H) 6.70 (d, ^3J = 9.1 Hz, 2 H, *m*-H), 8.24 (s, 1 H, N-1–H), 12.3 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 33.38 (C-3), 51.70 (C-2), 54.02 (C-4), 55.29 (OCH_3), 113.84 (C-*m*), 114.45 (C-*o*), 142.06 (C-*i*), 151.10 (C-*p*), 173.37 (CO_2H), 175.02 (C-5) ppm. MS (Q-array scan, MeCN): *m*/*z* (%) = 249 (100) [M – H]$^-$, 290 (17.8) [M – H + MeCN]$^-$. $C_{12}H_{14}N_2O_4$ (250.26): calcd. C 57.60, H 5.64, N 11.19; found C 57.20, H 5.62, N 11.08.

Dimethyl (2*S*,4*S*)-4-(2,3-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-amino-*N*-phthaloylglutamate (18): 4-Aminoantipyrine (8.46 g, 41.7 mmol) was added to a solution of compound **1** (4.0 g, 10.4 mmol) in MeCN (40 mL). The reaction mixture was heated at reflux under an Ar atmosphere for 12 h. The reaction mixture contained (2*S*,4*S*)-/(2*R*,4*S*)-diastereoisomers in a ratio of 78:22 according to HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm); hexane/*i*PrOH, 3:1]: t_R = 10.74 [(2*S*,4*S*)], 13.71 [(2*R*,4*S*)] min. The reaction mixture was evaporated under reduced pressure to a volume of 10 mL, poured into water (50 mL) and kept at 0 °C for 1 d. The mother solution was decanted from the oily precipitate. The latter was twice reprecipitated with water from acetone solution to give compound **18** (2.1 g, 40%). M.p. 178–181 °C (MeOH). $[\alpha]_D$ = –102.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.12 (s, 3 H, C-3′-CH_3), 2.43 (ddd, $^2J_{3B,3A}$ = 14.0 Hz, $^3J_{3B,4}$ = 11.3 Hz, $^3J_{3B,2}$ = 4.3 Hz, 1 H, 3B-H), 2.76 (s, 3 H, N-2′-CH_3), 2.78 (ddd, $^2J_{3A,3B}$ = 14.0 Hz, $^3J_{3A,2}$ = 11.9 Hz, $^3J_{3A,4}$ = 4.1 Hz, 1 H, 3A-H), 3.51 (s, 3 H, C-5-OCH_3), 3.68 (s, 3 H, C-1-OCH_3), 4.25 (ddd, $^3J_{4,3B}$ = 11.3 Hz, $^3J_{4,NH}$ = 10.9 Hz, $^3J_{4,3A}$ = 4.1, Hz, 1 H, 4-H), 4.57

(d, $^3J_{NH,4}$ = 10.9 Hz, 1 H, NH), 5.28 (dd, $^3J_{2,3A}$ = 11.9 Hz, $^3J_{2,3B}$ = 4.3 Hz, 1 H, 2-H), 7.16 (dd, ^3J = 8.5 Hz, ^4J = 1.3 Hz, 2 H, *o*-H), 7.20 (tt, ^3J = 7.4 Hz, ^4J = 1.3 Hz, 1 H, *p*-H), 7.37 (dd, ^3J = 8.5 Hz, ^4J = 1.3 Hz, 2 H, *m*-H), 7.87 (m, 4 H, Phth) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 9.83 (C-5′-*C*H$_3$), 30.60 (C-3), 37.52 (N-1′-CH$_3$), 48.83 (C-2), 51.62 (C-5-O*C*H$_3$), 52.82 (C-1-O*C*H$_3$), 53.20 (C-4), 118.31 (C-4′), 122.09 (C-*o*), 123.30 (C-3 Phth), 125.23 (C-*p*), 128.74 (C-*m*), 131.35 (C-2a Phth), 134.66 (C-4 Phth), 135.22 (C-*i*), 141.85 (C-3′), 160.92 (C-5′), 167.33 (C-2 Phth), 169.81 (C-1), 173.83 (C-5) ppm. $C_{26}H_{26}N_4O_7$ (506.52): calcd. C 61.66, H 5.17, N 11.06; found C 61.46, H 5.23, N 11.08. *de* 100% HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm); hexane/*i*PrOH, 3:1]: t_R = 10.74 min.

(2*S*,4*S*)-4-Amino-1-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-5-oxoproline (19): Solution of compound **18** (2.3 g, 4.5 mmol) in HCl (6 N, 20 mL) was heated at reflux for 8 h. The reaction mixture was cooled to room temperature, and the precipitate of phthalic acid was filtered off. The filtrate was evaporated to dryness under reduced pressure. The dried residue was dissolved in EtOH (15 mL) and Et$_3$N was added to the solution to pH 6–7. The reaction mixture was kept at 0 °C for 1 d, and the precipitate was filtered off and dried in vacuo over P_2O_5 to give compound **19** (0.65 g, 42%) as a white solid. M.p. 220–222 °C. $[\alpha]_D$ = –29.3 (*c* = 1.0, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 2.22 (ddd, $^2J_{3B,3A}$ = 13.5 Hz, $^3J_{3B,4}$ = 8.3 Hz, $^3J_{3B,2}$ = 7.4 Hz, 1 H, 3B-H), 2.29 (s, 3 H, CH$_3$), 3.04 (ddd, $^2J_{3A,3B}$ = 13.5 Hz, $^3J_{3A,4}$ = 9.2 Hz, $^3J_{3A,2}$ = 7.4 Hz, 1 H, 3A-H), 3.31 (s, 3 H, N-CH$_3$), 4.39 (dd, $^3J_{4,3A}$ = 9.2 Hz, $^3J_{4,3B}$ = 8.3 Hz, 1 H, 4-H), 4.53 (t, $^3J_{2,3A}$ = $^3J_{2,3B}$ = 7.4 Hz, 1 H, 2-H), 7.41 (m, 2 H, Ph), 7.57–7.64 (m, 3 H, Ph) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 12.63 (CH$_3$), 30.80 (C-3), 35.90 (NCH$_3$), 52.79 (C-4), 64.34 (C-2), 103.92 (C-4′), 131.00 (C-*o*), 132.65 (C-*m*), 133.12 (C-*p*), 134.62 (C-*i*), 151.76 (C-3′), 162.58 (C-5′), 174.64 (C-5), 179.25 (CO_2H) ppm. $C_{16}H_{18}N_4O_4{\cdot}H_2O$ (348.36): calcd. C 55.17, H 5.79. N 16.08; found C 55.13, H 5.74, N 16.02.

(2*S*,4*S*)-4-(*tert*-Butyloxycarbonyl)amino-1-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-5-oxoproline (20): To a solution of compound **19** (0.5 g, 1.43 mmol) and K_2CO_3 (0.22 g, 1.59 mmol) in water (1.5 mL) was added a solution of Boc_2O (0.40 g, 1.82 mmol) in *i*PrOH (1 mL). The reaction mixture was stirred at 40 °C for 3 h, cooled and then water (7.5 mL) was added. The reaction mixture was treated with hexane (2 × 1.5 mL). The aqueous layer was acidified with citric acid to pH 4. The precipitate was filtered off and crystallized from EtOH to give compound **20** (0.43 g, 67%) as a white solid. M.p. 235–238 °C (decomp.). $[\alpha]_D$ = –19.1 (*c* = 1.0, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO$_6$): δ = 1.40 (s, 9 H, Boc), 1.92 (br. q, *J* = 10.6 Hz, 1 H, 3B-H), 2.20 (s, 3 H, CH$_3$), 2.72 (ddd, $^2J_{3A,3B}$ = 11.7 Hz, $^3J_{3A,4}$ = 8.9 Hz, $^3J_{3A,2}$ = 7.4 Hz, 1 H, 3A-H), 3.10 (s, 3 H, NCH$_3$), 4.26 (br. q, *J* = 9.2 Hz, 1 H, 4-H), 4.62 (dd, $^3J_{2,3B}$ = 9.3 Hz, $^3J_{2,3A}$ = 7.4 Hz, 1 H, 2-H), 7.31–7.36 (m, 4 H, *o*-H, *p*-H, NH), 7.50 (m, 2 H, *m*-H), 12.9 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO$_6$): δ = 11.20 (CH$_3$), 28.24 [(CH$_3$)$_3$ Boc], 29.97 (C-3), 35.61 (NCH$_3$), 50.52 (C-4), 55.64 (C-2), 78.33 (C Boc), 106.42 (C-4′), 124.00 (C-*o*), 126.69 (C-*p*), 129.21 (C-*m*), 134.66 (C-*i*),154.37 (C-3′), 155.29 (CO Boc), 160.88 (C-5′), 172.08 (CO_2H), 172.29 (C-5) ppm. $C_{21}H_{26}N_4O_6{\cdot}H_2O$ (448.48): calcd. C 56.24, H 6.29, N 12.49; found C 56.37, H 6.11, N 12.17.

X-ray Analysis: Data for compounds **4**, **10** and **14** were collected with a XCALIBUR-3 diffractometer (CCD) by using graphite-monochromated Mo-K_α radiation. Absorption and anomalous dispersion effects were not taken into consideration due to its insignificance. Data for compound **12** were collected with a Bruker P4 diffractometer by using graphite-monochromated Mo-K_α radiation. Absorption correction is calculated by integration in model of multifaceted crystal. Data for compound **18** were collected with a Syntex P21 diffractometer by using graphite-monochromated Mo-K_α radiation. Absorption correction was calculated by integration in model of multifaceted crystal. The structures were solved by direct methods and expanded by using Fourier techniques. Refinement of the structure was accomplished with the SHELXL-97 program. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms involved in hydrogen bonding were located in electron-density maps. The remainder of the hydrogen atoms were placed in idealized positions and allowed to ride on the C atoms to which they are bonded.

Crystal Data for 4: From MeOH (solvate with MeOH 1:1); M_r = 382.36; 0.35 × 0.24 × 0.18 mm; colourless fragment; *T* = 295 K; monoclinic; space group $P2_1$; *a* = 5.1198(8) Å, *b* = 20.399(3) Å, *c* = 18.056(3) Å; β = 95.337(13)°; *V* = 1877.6(5) Å^3; $\rho_{calcd.}$ = 1.353 g cm^{-3}; θ_{max} = 26.37°; R_1 = 3.23% [$I > \sigma(I)$], wR_2 = 3.28%, *S* = 0.988.

Crystal Data for 10: M_r = 374.40; 0.43 × 0.37 × 0.29 mm; colourless prism; *T* = 295 K; triclinic; space group *P*1; *a* = 5.3741(16) Å, *b* = 6.2299(4) Å, *c* = 14.592(4) Å; α = 101.34(2)°, β = 99.041(4)°, *V* = 469.28(18) Å^3; $\rho_{calcd.}$ = 1.325 g cm^{-3}; θ_{max} = 26.36°; R_1 = 5.02% [$I > \sigma(I)$], wR_2 = 9.02%, *S* = 1.005.

Crystal Data for 12: 1.2 × 0.48 × 0.31 mm; colourless prism; *T* = 295 K; orthorhombic; space group $P2_12_12_1$; *a* = 6.3867(6) Å, *b* = 13.377(1) Å, *c* = 20.039(1) Å; *V* = 1712.0(2) Å^3; μ = 0.215 mm^{-1}, transmission 0.9129–0.9420, $\rho_{calcd.}$ = 1.383 g cm^{-3}; θ_{max} = 25.00°; R_1 = 2.90% [$I > \sigma(I)$], wR_2 = 8.21%, *S* = 1.064; Flack parameter –0.3(1); Flack parameter for inverted structure 1.1(1).

Crystal Data for 14: M_r = 234.25; 0.35 × 0.24 × 0.12 mm; colourless prism; *T* = 295 K; orthorhombic; space group $P2_12_12_1$; *a* = 6.3613(9) Å, *b* = 10.3157(12) Å, *c* = 18.145(5) Å; *V* = 1190.7(4) Å^3; $\rho_{calcd.}$ = 1.307 g cm^{-3}; θ_{max} = 26.38°; R_1 = 3.26% [$I > \sigma(I)$], wR_2 = 3.92%, *S* = 1.001.

Crystal Data for 18: M_r = 506.51; 1.00 × 0.75 × 0.08 mm; yellow plate; *T* = 296 K; monoclinic; space group $P2_12_12_1$; *a* = 11.409(4) Å, *b* = 8.170(3) Å, *c* = 14.595(5) Å; β = 111.71(3)°, *V* = 1263.9(8) Å^3; μ = 0.098 mm^{-1}, transmission 0.9418–0.99920, $\rho_{calcd.}$ = 1.331 g cm^{-3}; θ_{max} = 25.02°; R_1 = 5.01% [$I > \sigma(I)$], wR_2 = 11.87%, *S* = 1.099.

CCDC-669786, -669787, -669788, -669789 and -669790 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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