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Synthesis of 4-Amino Derivatives of 5-Oxoproline

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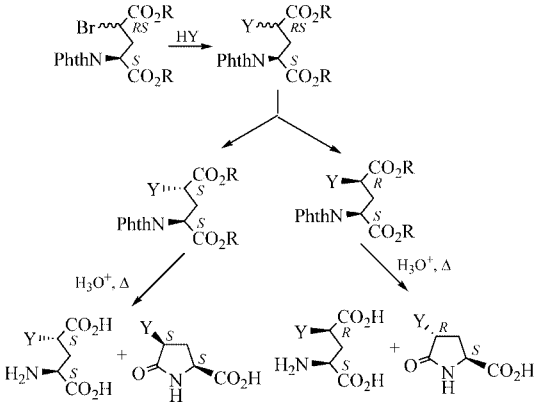
The possibility of obtaining the stereoisomeric derivatives of 5-oxoproline and glutamic acid with a tertiary amino group at C-4, using the nucleophilic substitution of bromine in dimethyl (2*S*,4*RS*)-4-bromo-*N*-phthaloylglutamate with secondary amines followed by resolution of diastereomers and removal of protecting groups has been studied. We have shown that the reaction with arylamines results in optically pure 5-oxoproline derivatives in high yields. In the case of more basic amines, the reaction is accompanied by racemization, and the target products can be isolated only as diastereomeric racemates.

Introduction

(*S*)-5-Oxoproline (pyroglutamic acid) plays an important role in metabolic processes in living beings. 5-Oxoproline is part of a number of neuropeptides and peptide hormones.[1] Many 5-oxoproline derivatives exhibit biological activity and have been used as probes for studying the action of enzymes and cellular membrane receptors.[2] Consequently, the conformationally restricted analogues of biologically active peptides have been obtained.[2c,3] Stereoisomers of 5-oxoproline derivatives have been used as convenient chiral synthons and efficient chiral resolving agents.[4] The carbonyl group of the lactam cycle in substituted 5-oxoprolines can be selectively reduced,[4b] which opens the way to the corresponding optically pure substituted prolines. Derivatives of 5-oxoproline possess significant synthetic potential and are promising both for asymmetrical syntheses on their basis, and for obtaining new physiologically active compounds.

This discussion also applies to the 4-substituted derivatives of proline. The electrophilic addition to lactam enolates generated from 5-oxoproline,[5] or the transformation of the hydroxy group in 4-hydroxyproline followed by oxidation[6] have been applied for the synthesis of the stereoisomers of 4-substituted 5-oxoprolines. Using these methods 4-substituted 5-oxoprolines containing C-4–C, C-4–O and C-4–N bonds have been prepared. However, up to now a limited number of 4-amino-substituted 5-oxoprolines have been obtained using these methods as well as other methods of less importance,[3a,4b,5e,6a,7] while communications concerning the synthesis of 4-amino derivatives of 5-oxoproline have described only the preparation of compounds with a primary amino group in position 4 (in some cases an acylated one).

Previously, we have developed synthetic routes for 4-substituted derivatives of glutamic acid which are based on the nucleophilic substitution of a halogen atom in (*S* or *R*)-4-halogen-*N*-phthaloylglutamates[8] followed by the resolution of diastereomers and the removal of protecting groups. According to the above methods we prepared glutamic acid derivatives containing nitrogen,[9] oxygen,[10] sulfur,[11] and phosphorus[12] atoms in position 4. When there is a functional group (OH, SH, or NH_2) in position 4 of glutamic acid able to undergo ring formation, protecting groups removal by acidic hydrolysis can be accompanied by heterocyclic ring closure (Scheme 1).[11,13] Moreover, any of the process steps can be accompanied by racemisation.



Scheme 1.

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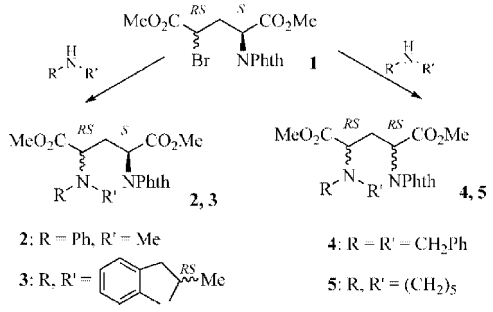
For the purpose of obtaining the stereoisomers of 5-oxoproline and glutamic acid derivatives with tertiary amino groups at C-4, we have studied and report herein the possibility of applying the nucleophilic substitution of Br in a 4-bromo derivative of glutamic acid with subsequent resolution of diastereomers, deprotection of functional groups, and then lactam ring closure.

Results and Discussion

The starting compound for the synthesis of 4-substituted 5-oxoprolines was dimethyl (2*S*,4*RS*)-4-bromo-*N*-phthaloylglutamate [(2*S*,4*RS*)-**1**].[8a] Since the optical purity of the starting compound was very essential in our study, we have verified that starting compound (2*S*,4*RS*)-**1** does not contain detectable amounts of (2*R*) isomers by using HPLC performed with a chiral column (Chiralcel OD-H).

The nucleophilic substitution of Br in (2*S*,4*RS*)-**1** by secondary amines of different basicity such as *N*-methylaniline, 2-methylindoline, dibenzylamine, and piperidine, resulted in diastereomers of dimethyl 4-amino-*N*-phthaloyl-substituted glutamates (**2**–**5**, Scheme 2).



Scheme 2.

Product **2** was formed while refluxing (2*S*,4*RS*)-**1** and *N*-methylaniline in CH_3CN. It has been found that the interaction of derivative (2*S*,4*RS*)-**1** and *N*-methylaniline proceeds diastereoselectively resulting in the predominant formation of the *threo* diastereomer similar to the reaction of (2*S*,4*RS*)-**1** with primary aromatic amines.[9b–9d] The ratio of (2*S*,4*S*)-**2**/(2*S*,4*R*)-**2** in the reaction mixture was 83:17, according to ^{1}H NMR and HPLC data. When the reaction of (2*S*,4*RS*)-**1** with *N*-methylaniline was carried out in EtOH the yield (about 90%) and the diastereomeric composition of product **2** were practically the same.

Stereoisomer (2*S*,4*S*)-**2** (96% *de*) was isolated by twice crystallizing it from MeOH. The configuration of (2*S*,4*S*)-**2** was determined by X-ray crystallography (Figure 1). According to the X-ray data, (2*S*,4*S*)-**2** crystallized in the $P2_12_12_1$ space group.

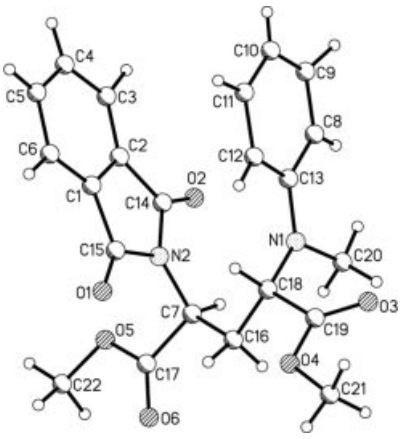
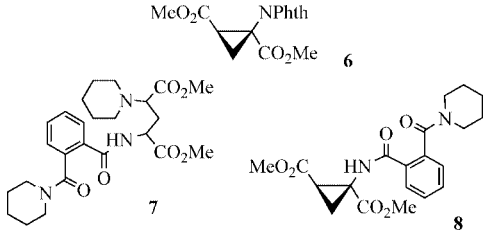


Figure 1. X-ray structure of glutamic acid derivative (2*S*,4*S*)-**2**.

Compounds **3** and (2*S*,4*S*,2′*S*)-**3** were obtained previously starting from (2*S*,4*RS*)-**1** and 2-methylindoline.[9e]

Interest in preparing compounds combining fragments of dibenzylamine and amino acids is caused by the fact that the dibenzylamine fragment is incorporated into compounds possessing neuroprotective activity, improving memory and cognitive abilities in the experiments in animals.[14]

It has been found that interaction of (2*S*,4*RS*)-**1** and dibenzylamine results not only in the target product **4**, but also in the product of the γ-elimination of HBr, dimethyl (*Z*)-1-phthalimidocyclopropane-1,2-dicarboxylate (**6**, Scheme 3), similar to a previous report.[15]



Scheme 3.

To optimise the preparative method for **4**, we studied the effect of the reaction conditions on the product ratio. The reaction was carried out in refluxing benzene, dioxane, CH_3CN, EtOH or MeOH for 10 h. The reaction mixtures were analysed by HPLC and ^{1}H NMR spectroscopy.

It has been found that the degree of conversion of starting (2*S*,4*RS*)-**1** increases with increasing solvent polarity, but the yield of side product **6** also grows (Table 1). Compound **6** is practically not formed in benzene and dioxane; in CH_3CN, EtOH and MeOH the yield of **6** was 10%, 58%, and 81%, respectively. Moreover, the reaction in EtOH was accompanied by the partial transesterification (up to 30%, according to ^{1}H NMR), which was not observed during the interaction of (2*S*,4*RS*)-**1** and arylamines.[9b,9c]

Thus, the optimum conditions for the preparation of **4** are refluxing of (2*S*,4*RS*)-**1** and dibenzylamine in benzene for 20 h, to yield 94% of target product **4**. The diastereomer ratio of *threo*-/*erythro*-**4** was 43:57.

Table 1. Composition of the reaction mixture after refluxing **1** and dibenzylamine[a] for 10 h according to ^{1}H NMR spectroscopy.

Entry	Solvent	Temperature [°C]	Content of the compounds in the reaction mixture (molar ratio)		
			1	**4** (*threo*-**4**/*erythro*-**4**)	**6**
1	benzene	80	22	78 (50:50)	–
2	dioxane	101	25	75 (50:50)	–
3	CH_3CN	82	14	76 (50:50)	10
4	EtOH	78	–	42[b] (50:50)	58[c]
5	MeOH	65	–	19 (45:55)	81

[a] The starting molar ratio of **1**/dibenzylamine was 1:2.8. [b] Overall content of **4** and products of its transesterification. [c] Overall content of **6** and products of its transesterification.

threo-**4** was isolated from the reaction mixture by repeated crystallization from MeOH. According to X-ray crystallographic data, this compound crystallized in the centrosymmetrical $P2_1/n$ space group (Figure 2), which suggests that *threo*-**4** is a diastereomeric racemate. *threo*-**4** was optically inactive. Thus, it may be concluded that the synthesis of **4** from (2*S*,4*RS*)-**1** was accompanied by racemisation.

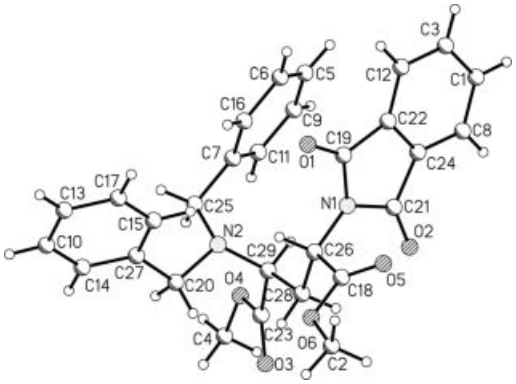


Figure 2. X-ray structure of glutamic acid derivative *threo*-**4**.

The piperidine fragment is present in many biologically active species, and this is responsible for the interest in compounds containing this fragment. 4-(1-Piperidyl)glutamic acid was obtained earlier;[16] its moderate radio-protective activity was found,[9a] and inhibition towards glutamine synthetase of *Chlorella* was studied.[17]

To select the optimum conditions for obtaining **5**, we studied the interaction of (2*S*,4*RS*)-**1** and piperidine at room temperature in benzene and MeOH, and in refluxing benzene (Table 2). The reaction of (2*S*,4*RS*)-**1** and piperidine, which is more basic than dibenzylamine, led to the product of the γ-elimination of HBr, **6**, and **7** and **8** in addition to the target product (Scheme 3). Compound **6** was isolated from the reaction mixture after washing with 3 N HCl followed by crystallization from MeOH. The diastereoisomeric racemates of **7** and **8** were isolated by flash chromatography. Their structures were confirmed by comparison with the compounds obtained from the reaction of piperidine with **5** or **6**. Heating of **7** in vacuo at 130 °C for 4 h resulted in **5**. The content of the compounds formed was determined by ^{1}H NMR spectroscopy after the removal of excess piperidine and its hydrobromide from the reaction mixture.

It has been found that the highest yield (78%) of **5** was observed when the reaction was carried out in refluxing benzene. When the reaction was carried out at room temperature in benzene or MeOH, the ratio of **5**/**6**/**7**/**8** was 26:9:65:0 or 3:72:13:12, respectively. Thus, the γ-elimination of HBr is dominant in the interaction of (2*S*,4*RS*)-**1** with dibenzylamine and piperidine in alcohols.

Dimethyl *N*-phthaloyl-4-(1-piperidyl)glutamate (**5**) was isolated from the reaction mixture by crystallization from MeOH or column chromatography in a 69% yield. *erythro*-**5** (>99% *de*) was obtained by multiple crystallizations of the diastereomeric mixture, and *threo*-**5** (94% *de*) was obtained by crystallization from the mother liquors with fast cooling.

The configuration of *erythro*-**5** was confirmed by X-ray crystallography (Figure 3). According to X-ray data, *erythro*-**5** crystallized in the $P2_1/n$ space group, which suggests that *erythro*-**5** was a diastereomeric racemate. Compounds *erythro*- and *threo*-**5** were optically inactive. It follows that in this case the reaction is also accompanied by racemisation.

threo- and *erythro*-**5** are readily epimerized, which is likely due to the high basicity of the piperidine nitrogen atom. Thus, the refluxing of a 3:97 mixture of *threo*-**5**/*erythro*-**5** in benzene for 10 h gave a 22:78 mixture of *threo*-**5**/*erythro*-**5**. Epimerization proceeds faster in MeOH; thus, a 40:60 mixture of *threo*-/*erythro*-**5** was formed after refluxing for 3 h. The ready epimerization of **5** makes it possible to obtain the *erythro* isomer of **5** in an 85% yield with a slow concentration of an MeOH solution of a 1:1 mixture of diastereomers.

Table 2. Composition of the reaction mixture after interaction between **1** and piperidine[a] according to ^{1}H NMR spectroscopy.

Entry	Solvent	Reaction conditions		Content of the compounds in the reaction mixture (molar ratio)				
		Temperature [°C]	Time [h]	**1**	**5** (*threo*-**5**/*erythro*-**5**)	**6**	**7**	**8**
1	benzene	20	48	–	26 (40:60)	9	65	–
2	benzene	80	1.5	3	78 (40:60)	9	10	–
3	MeOH	20	48	–	3 (50:50)	72	13	12

[a] The starting molar ratio of **1**/piperidine was 1:2.8.

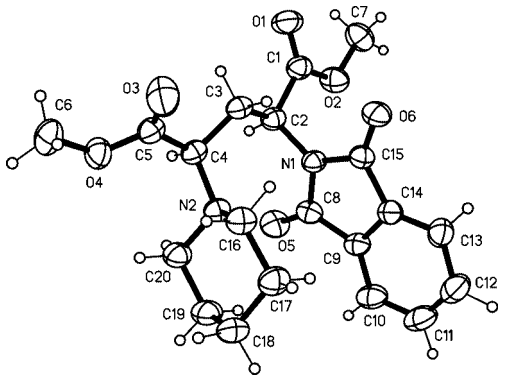
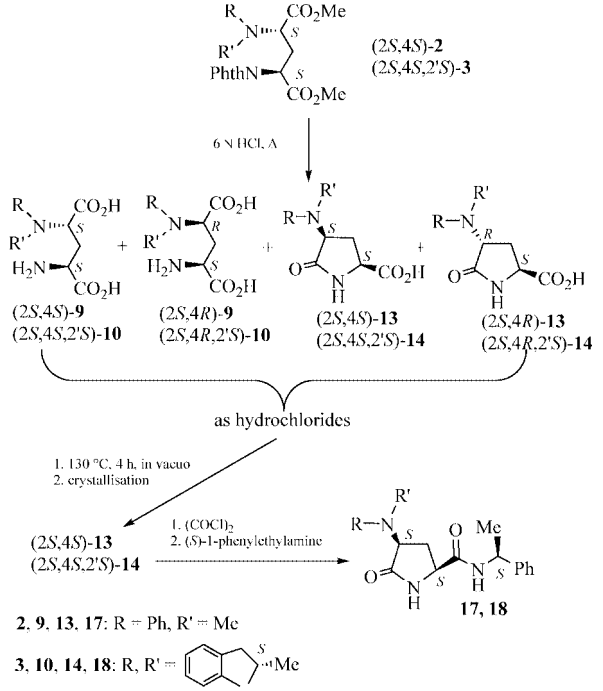
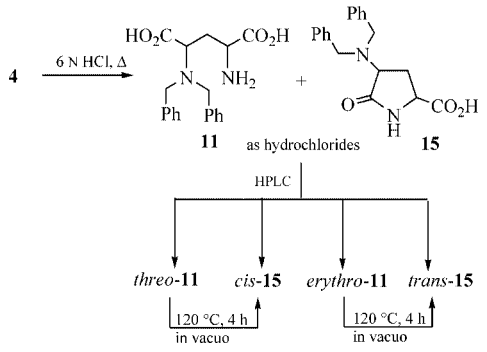


Figure 3. X-ray structure of glutamic acid derivative *erythro*-**5**.

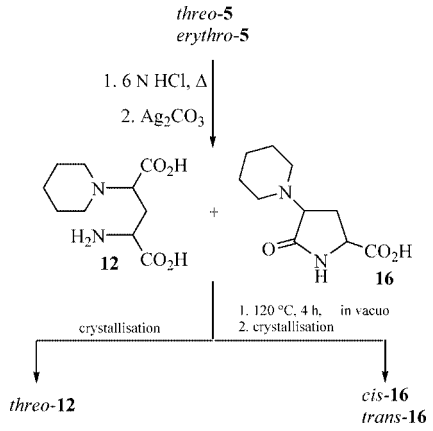
The next step of our study was the removal of the protecting groups from **2**–**5** by acidic hydrolysis. Refluxing of **2**–**5** in 6 N HCl resulted in mixtures of hydrochlorides of 4-substituted glutamic acids **9**–**12** and their lactams, 4-substituted 5-oxoprolines **13**–**16** (Schemes 4, 5, and 6).



Scheme 4.



Scheme 5.



Scheme 6.

We carried out the acidic hydrolysis of (2*S*,4*S*)-**2**, (2*S*,4*S*,2′*S*)-**3**, **4**, *threo*-**5** and *erythro*-**5**. It has been found that partial racemisation takes place during the acidic hydrolysis of individual diastereomers. Thus, the hydrolysis of *erythro*-**5** (96% *de*) in 6 N HCl for 8 h gave a 7:30:10:53 mixture of *threo*-/*erythro*-**12**/*cis*-/*trans*-**16**. That is, in the course of the hydrolysis of *erythro*-**5** the diastereomeric products, *threo*-**12** and *cis*-**16** (in an overall 17% yield), were formed in addition to *erythro*-**12** and the product of its dehydration, *trans*-**16**. Partial epimerization during acidic hydrolysis of C-4-substituted glutamic acids has been previously observed for some derivatives of 2,4-diaminoglutaric acid,[13d] and 4-thio- and 4-mercaptoglutamic acids.[11] The epimerization degree decreases with decreasing duration of acidic hydrolysis. Thus, when *erythro*-**5** was hydrolyzed for 5 h, the overall yield of epimerization products *threo*-**12** and *cis*-**16** was about 10%. The refluxing of **2**–**5** in 6 N HCl for 5 h was chosen as the standard reaction conditions.

The acidic hydrolysis of (2*S*,4*S*)-**2** under the aforementioned conditions was also accompanied by epimerization. A 32:6:52:10 mixture of the hydrochlorides of (2*S*,4*S*)-/(2*S*,4*R*)-**9**/(2*S*,4*S*)-/(2*S*,4*R*)-**13** was formed from (2*S*,4*S*)-**2** (99% *de*), and the heating of this mixture in vacuo gave a 84:16 mixture of lactams (2*S*,4*S*)-/(2*S*,4*R*)-**13** (Scheme 4). We did not observe any epimerization during the dehydration. Compound (2*S*,4*S*)-**13** was obtained in a 61% yield [taking into account the starting (2*S*,4*S*)-**2**] by crystallization from 40% EtOH in H_2O. The configuration of (2*S*,4*S*)-**13** was confirmed by a 2D NOESY spectrum. Lactam (2*S*,4*R*)-**13** was isolated from a mixture of **9** and **13** by preparative RP HPLC. Heating in vacuo and crystallization of (2*S*,4*S*,2′*S*)-**3** as described above gave lactam (2*S*,4*S*,2′*S*)-**14** in a 56% yield.

The optical purity (99% *ee*) of lactams (2*S*,4*S*)-**13** and (2*S*,4*S*,2′*S*)-**14** was determined by HPLC and ^{1}H NMR spectroscopy after preliminary derivatization with [(*S*)-1-phenylethyl]amine. The derivatization was carried out through the acyl chlorides and gave optically pure **17** and **18** (Scheme 4).

We suppose that the isolation of optically pure lactams (2*S*,4*S*)-**13** and (2*S*,4*S*,2′*S*)-**14** from a mixture of stereoiso-

mers is due to two reasons. The first is the enrichment of the (2*S*,4*S*) diastereomer during crystallization, and the second is the fact that partial racemisation takes place at either of the chiral centres under conditions of acidic hydrolysis of (2*S*,4*S*)-**2** and (2*S*,4*S*,2′*S*)-**3**.

The correctness of the above statement was confirmed by the following experiment. Heating of (2*S*,4*S*)-**13** in 6 N DCl in D_2O for 8 h resulted in a mixture of (2*S*,4*S*)- and (2*S*,4*R*)-**9**, and (2*S*,4*S*)- and (2*S*,4*R*)-**13**, all compounds being partially deuterated at C-2 and C-4. Due to the partial overlapping of the CH signals, the integration was not quite accurate, but for (2*S*,4*S*)-**9** and (2*S*,4*S*)-**13** we observed predominant (about 25%) deuteration of the C-4 protons [4-CH–N(Me)Ph] while deuteration of the C-2 protons was less than 5%.

To obtain amino acids **11** and **15**, we carried out the acidic hydrolysis of a diastereomeric mixture of **4** without the pre-resolution of diastereomers. The acidic hydrolysis resulted in a mixture of the hydrochlorides of diastereomeric 4-(dibenzylamino)glutamic acids **11** and 4-(dibenzylamino)-5-oxoprolines **15** (Scheme 5). The resolution of diastereomers of **11** and **15** was also performed by preparative RP HPLC.

The configuration of *cis*-**15** was confirmed by a 2D NOESY spectrum, in which cross-peaks between 3A-H and both 2-H and 4-H were observed.

To assign the configuration of *threo*-**11** and *erythro*-**11**, we used their ability to form lactams (Scheme 5). We have shown that the heating of *threo*-**11** at 120 °C in vacuo for 4 h leads to *cis*-**15**, and *erythro*-**11** gives *trans*-**15** under the same conditions. That is, the formation of lactams proceeds without epimerization in this case also.

The acidic hydrolysis of *threo*-**5** and *erythro*-**5** followed by the removal of chloride ions using Ag_2CO_3 gave mixtures of amino acids **12** and lactams **16** enriched with the starting *threo* and *erythro* configurations (Scheme 6). *threo*-4-(1-piperidyl)glutamic acid (*threo*-**12**, 96% *de*) was isolated from the reaction mixture due to its low solubility in EtOH.

The complete conversion of **12** to lactams **16** took place while heating of their mixture in vacuo at 120 °C for 4 h or while refluxing in toluene for 4 h similar to a previous report.[18] No epimerization was observed. *cis*-5-Oxo-4-(1-piperidyl)proline *cis*-**16** (99% *de*) was obtained in a 65% yield by crystallization of a mixture of *cis*- and *trans*-**16** from EtOH.

By following the above procedure and starting from *erythro*-**5**, we obtained *trans*-5-oxo-4-(1-piperidyl)proline *trans*-**16** (>99% *de*) in a 75% yield, and a mixture enriched with *erythro*-(4-1-piperidyl)glutamic acid (*erythro*-**12**). Configuration of *trans*-**16** was confirmed by a 2D NOESY spectrum.

Comparison of the ^{1}H NMR spectra of the *cis* and *trans* diastereomers of 4-substituted 5-oxoprolines **13**–**16** made it possible to reveal the following common features. For the *cis* diastereomers of **13**–**16**, the values of the coupling constants $^3J_{2,3A}$ and $^3J_{2,3B}$ are close and fall within the range of 7.9–9.2 Hz; for the *trans* diastereomers of **13**, **15**, **16** these constants are much different from each other, the value of one being 9.0–9.5 Hz and that of another being 0–2.6 Hz. The difference in chemical shifts of non-equivalent protons of the 3-CH_2 group of the 5-oxoproline ring ($\Delta\delta_{AB} = \delta_{3A} - \delta_{3B}$) is much larger for the *cis* diastereomers ($\Delta\delta_{AB}$ = 0.51–0.87 ppm) than for the *trans* diastereomers ($\Delta\delta_{AB}$ = 0.11–0.21 ppm).

Similar rules have been pointed out previously[5d,19] for ^{1}H NMR spectra of 5-oxoprolines containing C and O substituents at position 4.

Thus, the parameters of the ^{1}H NMR spectra [the difference in chemical shifts ($\Delta\delta_{AB}$), and the coupling constants $^3J_{2,3A}$ and $^3J_{2,3B}$] can serve as useful tools for distinguishing between the relative configurations of 4-substituted 5-oxoprolines.

Previously,[20] we reported a similar methodology for the synthesis of 4-arylamino derivatives of glutamic acid, the acidic hydrolysis of which resulted in the spontaneous formation of 5-oxoproline derivatives without any additional dehydration step, and we supposed that lactamisation proceeded at the C-2 nitrogen atom. But the results of the present study have forced us to revise these data. At present, we are carefully re-checking the results obtained previously. We will complete these studies and report the results in due course.

Conclusions

The results of the interaction of dimethyl (2*S*,4*RS*)-4-bromo-*N*-phthaloylglutamate with secondary amines essentially depend on the amine character and the reaction conditions. The reaction with arylamines proceeds in high yields without racemisation. It is accompanied by epimerization at C-4, but the configuration of C-2 remains unchanged; as a result, mixtures of diastereomers of the (*S*) series are formed. The reaction with more basic amines is accompanied by the formation of side products, especially in polar solvents and by racemisation at both chiral centres. The acidic hydrolysis of the products of nucleophilic substitution is also accompanied by partial racemisation and leads to mixtures of 4-amino-5-oxoprolines and 4-aminoglutamic acids. Diastereomers of the latter can be obtained by preparative RP HPLC. Diastereomers of 4-amino-5-oxoproline derivatives were obtained after dehydration of the aforementioned mixtures by heating in vacuo at 120–130 °C, no racemisation being observed. (2*S*,4*S*)-4-[(Methyl)(phenyl)amino]-5-oxoproline and (2*S*,4*S*)-4-[(2′*S*)-2-methylindolin-1-yl]-5-oxoproline were obtained as individual stereoisomers.

Thus, by using dimethyl (2*S*,4*RS*)-4-bromo-*N*-phthaloylglutamate as the starting material one can manage to obtain diastereomeric racemates of 4-amino-5-oxoproline and 4-aminoglutamic acid derivatives, although the preparation of individual stereoisomers has some limitations.

Experimental Section

General: Dimethyl (2*S*,4*RS*)-4-bromo-*N*-phthaloylglutamate [(2*S*,4*RS*)-**1**] was prepared according to a literature procedure.[8a]

All other reagents were of commercial quality. Solvents were dried and purified by standard methods. Routine monitoring of reaction mixtures was carried out 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, and by using a tuneable UV detector set at 230 nm. Mixtures of hexane (solvent A), *i*PrOH (solvent B) and MeOH (solvent C) were used as mobile phases. Analytical RP-HPLC was performed with a LiChrosorb RP-18 (4.6 × 250 mm, 5 μm) column, with a flow rate of 0.7 mL/min, in a gradient mode, and by using a tuneable UV detector set at 230 or 254 nm. Mixtures of MeOH (solvent C) and 0.005 M TFA in H_2O (solvent D) or 0.01 M KH_2PO_4 in H_2O (solvent E) were used as mobile phases. Preparative RP-HPLC was performed with a Reprosil-Pur C_{18} (20 × 250 mm, 10 μm) column, with a flow rate of 8 mL/min, and by using a UV detector at 254 nm. Mixtures of H_2O (solvent F), MeOH (solvent C), CH_3CN (solvent G), and AcOH (solvent H) were used as mobile phases. ^1H NMR spectra were recorded at 400 MHz using TMS or DSS as references. ^{13}C NMR spectra were recorded at 100 MHz. MS data were obtained by using a quadrupole Shimadzu LCMS-2010 system in positive mode with an APCI probe installed with MeOH or 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. Optical rotations were measured with a Perkin–Elmer M 341 polarimeter.

Dimethyl (2*S*,4*RS*)-4-[(Methyl)(phenyl)amino]-*N*-phthaloylglutamate (2): *N*-Methylaniline (8.5 mL, 78 mmol) was added to a solution of (2*S*,4*RS*)-**1** (10.0 g, 26.0 mmol) in CH_3CN (100 mL). After 90 h of refluxing, the precipitate was filtered off, the filtrate was concentrated under reduced pressure, and the residue was dissolved in EtOAc (100 mL). This solution was successively washed with 1 N HCl, H_2O, 5% aq. $NaHCO_3$, and H_2O. The organic solution was dried with Na_2SO_4, the solvent was evaporated to dryness, and the residue was purified by flash chromatography with the use of benzene as the eluent to obtain **2** as an amorphous brown solid (9.50 g, 89% yield). (2*S*,4*S*)-**2**/(2*S*,4*R*)-**2**, 83:17. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B = 100:1]: t_R = 16.5 min [(2*S*,4*R*)-**2**]; t_R = 17.2 min [(2*S*,4*S*)-**2**]. In the ^1H NMR spectrum two sets of signals corresponding to (2*S*,4*S*)-**2** and (2*S*,4*R*)-**2** were observed. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (ddd, $J_{3B,3A}$ = 14.6, $J_{3B,4}$ = 9.7, $J_{3B,2}$ = 6.8 Hz, 1 H, 3B-H, 17%), 2.82 (s, 3 H, NMe, 17%), 2.89 (ddd, $J_{3B,3A}$ = 15.0, $J_{3B,4}$ = 10.4, $J_{3B,2}$ = 4.9 Hz, 1 H, 3B-H, 83%), 2.94 (s, 3 H, NMe, 83%), 3.01 (ddd, $J_{3A,3B}$ = 15.0, $J_{3A,2}$ = 10.8, $J_{3A,4}$ = 5.6 Hz, 1 H, 3A-H, 83%), 3.02–3.10 (m, 1 H, 3A-H, 17%), 3.62 (s, 3 H, OMe, 83%), 3.69 (s, 3 H, OMe, 17%), 3.72 (s, 3 H, OMe, 17%), 3.74 (s, 3 H, OMe, 83%), 4.37 (dd, $J_{4,3B}$ = 10.4, $J_{4,3A}$ = 5.6 Hz, 1 H, 4-H, 83%), 4.80 (dd, $J_{4,3B}$ = 9.7, $J_{4,3A}$ = 5.3 Hz, 1 H, 4-H, 17%), 4.97 (dd, $J_{2,3A}$ = 10.8, $J_{2,3B}$ = 4.9 Hz, 1 H, 2-H, 83%), 5.04 (dd, $J_{2,3A}$ = 7.3, $J_{2,3B}$ = 6.8 Hz, 1 H, 2-H, 17%), 6.63–6.70 (m, 3 H, Ar, 83%), 6.68–6.74 (m, 3 H, Ar, 17%), 7.02–7.09 (m, 2 H, Ar, 83%), 7.08–7.14 (m, 2 H, Ar, 17%), 7.69–7.73 (m, 2 H, Ar-Phth, 100%, both isomers), 7.75–7.80 (m, 2 H, Ar-Phth, 83%), 7.77–7.82 (m, 2 H, Ar-Phth, 17%) ppm. $C_{22}H_{22}N_2O_6$ (410.43): calcd. C 64.38, H 5.40, N 6.83; found C 64.68, H 5.20, N 6.67.

Dimethyl (2*S*,4*S*)-4-[(Methyl)(phenyl)amino]-*N*-phthaloylglutamate [(2*S*,4*S*)-2]: A mixture of (2*S*,4*S*)-**2** and (2*S*,4*R*)-**2** (9.18 g) was twice crystallized from MeOH to give (2*S*,4*S*)-**2** as a yellow solid (5.05 g, 55% yield, 96% *de*). An additional crystallization from MeOH gave (2*S*,4*S*)-**2** in >99% *de*. M.p. 109–111 °C. $[\alpha]_D^{20}$ = –85.8 (*c* = 1.0, acetone, 99% *de*). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.89 (ddd, $J_{3B,3A}$ = 15.0, $J_{3B,2}$ = 4.9, $J_{3B,4}$ = 10.4 Hz, 1 H, 3B-H), 2.94 (s, 3 H, NMe), 3.01 (ddd, $J_{3A,3B}$ = 15.0, $J_{3A,2}$ = 10.8, $J_{3A,4}$ = 5.6 Hz, 1 H, 3A-H), 3.62 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 4.37 (dd, $J_{4,3B}$ = 10.4, $J_{4,3A}$ = 5.6 Hz, 1 H, 4-H), 4.97, (dd, $J_{2,3A}$ = 10.8, $J_{2,3B}$ = 4.9 Hz, 1 H, 2-H), 6.63–6.70 (m, 3 H, Ar), 7.02–7.09 (m, 2 H, Ar), 7.69–7.73 (m, 2 H, Ar-Phth), 7.75–7.80 (m, 2 H, Ar-Phth) ppm. $C_{22}H_{22}N_2O_6$ (410.43): calcd. C 64.38, H 5.40, N 6.83; found C 64.32, H 5.38, N 6.64.

Dimethyl 4-(Dibenzylamino)-*N*-phthaloylglutamate (4): Dibenzylamine (7.2 mL, 37.4 mmol) was added to a solution of (2*S*,4*RS*)-**1** (5.0 g, 13.0 mmol) in benzene (50 mL). After 20 h of refluxing, the precipitate was filtered off, the filtrate was concentrated under reduced pressure and treated with hexane, and the residue was dried under reduced pressure to give **4** as an amorphous yellow solid (6.15 g, 94% yield). *threo*-**4**/*erythro*-**4**, 43:57. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B = 160:1]: t_R = 19.0 min (*threo*-**4**); t_R = 20.4 min (*erythro*-**4**). In the ^1H NMR spectrum two sets of signals corresponding to *threo*-**4** and *erythro*-**4** were observed. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.20 (ddd, $J_{3B,3A}$ = 14.3, $J_{3B,4}$ = $J_{3B,2}$ = 7.2 Hz, 1 H, 3B-H, 57%), 2.74 (ddd, $J_{3B,3A}$ = 15.3, $J_{3B,4}$ = 11.7, $J_{3B,2}$ = 4.2 Hz, 1 H, 3B-H, 43%), 2.86 (ddd, $J_{3A,3B}$ = 14.3, $J_{3A,2}$ = $J_{3A,4}$ = 7.2 Hz, 1 H, 3A-H, 57%), 2.95 (ddd, $J_{3A,3B}$ = 15.3, $J_{3A,2}$ = 12.0, $J_{3A,4}$ = 4.4 Hz, 1 H, 3A-H, 43%), 3.39 (dd, $J_{4,3A}$ = 11.7, $J_{4,3B}$ = 4.4 Hz, 1 H, 4-H, 43%), 3.48 (dd, $J_{4,3A}$ = $J_{4,3B}$ = 7.2 Hz, 1 H, 4-H, 57%), 3.50 (d, ^2J = 13.5 Hz, 2 H, 2 × CH-Ph, 43%), 3.53 (d, ^2J = 13.3 Hz, 2 H, 2 × CH-Ph, 57%), 3.54 (s, 3 H, OMe, 57%), 3.66 (s, 3 H, OMe, 43%), 3.76 (s, 3 H, OMe, 43%), 3.80 (d, ^2J = 13.3 Hz, 2 H, 2 × CH-Ph, 57%), 3.83 (s, 3 H, OMe, 57%), 3.97 (d, ^2J = 13.5 Hz, 2 H, 2 × CH-Ph, 43%), 5.06 (dd, $J_{2,3A}$ = $J_{2,3B}$ = 7.2 Hz, 1 H, 2-H, 57%), 5.21 (dd, $J_{2,3A}$ = 12.0, $J_{2,3B}$ = 4.2 Hz, 1 H, 2-H, 43%), 6.96–7.01 (m, 2 H, Ar, 43%), 7.04–7.10 (m, 2 H, Ar, 57%), 7.12–7.17 (m, 4 H, Ar, 43%), 7.16–7.21 (m, 4 H, Ar, 57%), 7.31–7.35 (m, 4 H, Ar, 100%, both isomers), 7.70–7.75 (m, 2 H, Ar-Phth, 100%, both isomers), 7.76–7.80 (m, 2 H, Ar-Phth, 43%), 7.78–7.83 (m, 2 H, Ar-Phth, 57%) ppm. $C_{29}H_{28}N_2O_6$ (500.55): calcd. C 69.59, H 5.64, N 5.60; found C 69.35, H 5.42, N 5.94.

Dimethyl *threo*-4-(Dibenzylamino)-*N*-phthaloylglutamate (*threo*-4): A mixture of *threo*-**4** and *erythro*-**4** (6.15 g) was crystallized three times from MeOH to give *threo*-**4** as a white solid (0.74 g, 12% yield). M.p. 137–141 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.74 (ddd, $J_{3B,3A}$ = 15.3, $J_{3B,4}$ = 11.7, $J_{3B,2}$ = 4.2 Hz, 1 H, 3B-H), 2.95 (ddd, $J_{3A,3B}$ = 15.3, $J_{3A,2}$ = 12.0, $J_{3A,4}$ = 4.4 Hz, 1 H, 3A-H), 3.39 (dd, $J_{4,3A}$ = 11.7, $J_{4,3B}$ = 4.4 Hz, 1 H, 4-H), 3.50 (d, ^2J = 13.5 Hz, 2 H, 2 × CH-Ph), 3.66 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.97 (d, ^2J = 13.5 Hz, 2 H, 2 × CH-Ph), 5.21 (dd, $J_{2,3A}$ = 12.0, $J_{2,3B}$ = 4.2 Hz, 1 H, 2-H), 6.96–7.01 (m, 2 H, Ar), 7.12–7.17 (m, 4 H, Ar), 7.31–7.35 (m, 4 H, Ar), 7.70–7.75 (m, 2 H, Ar-Phth), 7.76–7.80 (m, 2 H, Ar-Phth) ppm. $C_{29}H_{28}N_2O_6$ (500.55): calcd. C 69.59, H 5.64, N 5.60; found C 69.66, H 5.40, N 5.62. 97% *de*. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B = 160:1]: t_R = 19.0 min.

Dimethyl *N*-Phthaloyl-4-(1-piperidyl)glutamate (5): Piperidine (2.7 mL, 27.6 mmol) was added to a solution of (2*S*,4*RS*)-**1** (3.84 g, 10.0 mmol) in benzene (35 mL). After 2 h of refluxing, the precipitate was filtered off, the filtrate was washed with H_2O to neutral pH, dried with Na_2SO_4, and the solvent was evaporated to dryness. The residue was dissolved in MeOH (5 mL), and the solution was stored at –10 °C for 24 h. The filtration of the precipitate gave a mixture of *threo*-**5** and *erythro*-**5** as a yellow solid (0.84 g). The mother liquor was concentrated to dryness; the residue was dissolved in EtOAc (40 mL) and extracted with HCl (3 N, 2 × 15 mL). The combined acidic extracts were adjusted with Na_2CO_3 to pH =

9 and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water to neutral pH, dried with Na_2SO_4 and the solvents were evaporated to dryness. The residue (2.41 g) was dissolved in MeOH (2.6 mL) under heating, a seed of the first precipitate was added, and the solution was stored at –10 °C for 24 h. The filtration of the precipitate gave an additional 1.42 g of a *threo*-**5**/*erythro*-**5** mixture. An additional amount of the *threo*-**5**/*erythro*-**5** mixture was isolated from the mother liquor by flash chromatography (hexane/*i*BuOH from 20:1 to 4:1). Overall yield 2.67 g (69%). *threo*-**5**/*erythro*-**5**, 1:1. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B/C = 80:0.7:0.3]: t_R = 15.9 min (*threo*-**5**); t_R = 17.6 min (*erythro*-**5**). $C_{20}H_{24}N_2O_6$ (388.42): calcd. C 61.85, H 6.23, N 7.21; found C 61.94, H 6.28, N 6.83.

Dimethyl *threo*-*N*-Phthaloyl-4-(1-piperidyl)glutamate (*threo*-5): A 1:1 mixture of *threo*-**5**/*erythro*-**5** (2.20 g) was dissolved in MeOH (30 mL). After slow evaporation of 25 mL of MeOH at 20 °C in an open vial, the precipitate was filtered off to give *erythro*-**5** (1.4 g, 64% yield). After 2 h of cooling of the mother liquor at –10 °C, the precipitate was filtered off to give *threo*-**5** as a white solid (0.55 g, 25% yield). M.p. 91–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (m, 2 H, piperidyl), 1.53 (m, 2 H, piperidyl), 1.60 (m, 2 H, piperidyl), 2.27 (m, 2 H, piperidyl), 2.58 (ddd, J = 15.1, $J_{3B,2}$ = 10.9, $J_{3B,4}$ = 4.8 Hz, 1 H, 3B-H), 2.63–2.77 (m, 3 H, 3A-H, piperidyl), 3.01 (dd, J = 11.2, $J_{4,3B}$ = 4.9 Hz, 1 H, 4-H), 3.62 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 5.31 (dd, $J_{2,3B}$ = 11.0, J = 3.8 Hz, 1 H, 2-H), 7.75 (m, 2 H, Ar-Phth), 7.88 (m, 2 H, Ar-Phth) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.47, 26.33, 27.82, 49.13, 50.50, 50.86, 52.68, 64.08, 123.39, 131.71, 134.12, 167.46, 170.11, 171.20 ppm. $C_{20}H_{24}N_2O_6$ (388.42): calcd. C 61.85, H 6.23, N 7.21; found C 61.84, H 6.33, N 7.06. 94% *de*. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B/C = 80:0.7:0.3]: t_R = 15.9 min.

Dimethyl *erythro*-*N*-Phthaloyl-4-(1-piperidyl)glutamate (*erythro*-5): A 1:1 mixture of *threo*-**5**/*erythro*-**5** (2.67 g) was dissolved in MeOH (30 mL). The solvent was slowly evaporated to dryness, and the residue was crystallized from MeOH to give *eryhtro*-**5** as a yellow solid (2.27 g, 85% yield). M.p. 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (m, 6 H, piperidyl), 2.26 (m, 2 H, piperidyl), 2.41 (ddd, $J_{3B,3A}$ = 14.8, $J_{3B,4}$ = 9.8, $J_{3B,2}$ = 8.4 Hz, 1 H, 3B-H), 2.60 (m, 2 H, piperidyl), 2.62 (ddd, $J_{3A,3B}$ = 14.8, $J_{3A,2}$ = 6.0, $J_{3A,4}$ = 5.3 Hz, 1 H, 3A-H), 3.42 (dd, $J_{4,3B}$ = 9.8, $J_{4,3A}$ = 5.3 Hz, 1 H, 4-H), 3.70 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 5.14 (dd, $J_{2,3B}$ = 8.4, $J_{2,3A}$ = 6.0 Hz, 1 H, 2-H); 7.75 (m, 2 H, Ar-Phth), 7.87 (m, 2 H, Ar-Phth) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.25, 26.08, 27.87, 49.38, 50.60, 50.95, 52.67, 65.60, 123.40, 132.01, 134.06, 167.35, 169.60, 171.11 ppm. $C_{20}H_{24}N_2O_6$ (388.42): calcd. C 61.85, H 6.23, N 7.21; found C 61.90, H 6.55, N 7.00. 99% *de*. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B/C = 80:0.7:0.3]: t_R = 17.6 min.

Dimethyl (*Z*)-1-(Phthalimido)cyclopropane-1,2-dicarboxylate (6): The organic layers obtained after the extraction of an EtOAc solution with 3 N HCl (see the above procedure for **5**) was washed with H_2O to neutral pH and dried with Na_2SO_4. The solvent was evaporated to dryness under reduced pressure; the residue was dissolved in MeOH (1 mL) and kept at –10 °C for 24 h. The precipitate was filtered off to give cyclopropane **6** as a white solid [0.16 g, 5% yield taking into account the starting (2*S*,4*RS*)-**1**]. M.p. 98–100 °C (MeOH) [ref.[15] m.p. 83.5–85.5 °C (heptane/*s*BuOH, 4:1)]. The ^{1}H NMR spectrum is identical to the literature data.[15] HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B/C = 80:0.7:0.3]: t_R = 15.9 min. $C_{15}H_{13}NO_6$ (303.27): calcd. C 59.41, H 4.32, N 4.62; found C 59.37, H 4.50, N 4.68.

Dimethyl *threo*-4-(1-Piperidyl)-*N*-[2-(1-piperidylcarbonyl)benzoyl]-glutamate (*threo*-7): Piperidine (0.10 mL, 1.02 mmol) was added to a solution of *threo*-**5** (0.10 g, 0.257 mmol) in benzene (0.5 mL). The reaction mixture was kept at room temperature for 4 d and then diluted with benzene (5.5 mL), washed with H_2O to neutral pH, and dried with Na_2SO_4. The solvent was evaporated to dryness under reduced pressure to yield a 81:19 mixture of *threo*-**7**/*erythro*-**7** as an amorphous white solid (0.102 g, 77% yield). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.31–1.61 (m, 12 H, piperidyl), 1.89 (m, 1 H, C^3H_B), 2.13 (ddd, J = 14.4, 11.2, 3.4 Hz, 1 H, C^3H_A), 2.32 (m, 2 H, piperidyl), 2.63 (m, 2 H, piperidyl), 3.06 (m, 2 H, piperidyl), 3.29 (dd, J = 11.3, 3.7 Hz, 1 H, C^4H), 3.49 (m, 2 H, piperidyl), 3.63 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 4.72 (m, 1 H, C^2H), 7.26 (dd, J = 7.3, 1.3 Hz, 1 H, Ar), 7.48 (td, J = 7.4, 1.5 Hz, 1 H, Ar), 7.53 (td, J = 7.4, 1.4 Hz, 1 H, Ar), 7.61–7.66 (m, 1 H, Ar), 8.64 (d, 1 H, NH, J = 8.1 Hz) ppm. MS (in CH_3CN, Q-array scan): m/z (%) = 474 (100) [M + H]$^+$. MS (in CH_3CN, Q-array voltage 80 V): m/z (%) = 474 (24) [M + H]$^+$, 389 (100) [M – $C_5H_{10}N$]$^+$, 329 (8) [M – $C_5H_{10}NH$ – CO_2CH_3]$^+$, 304 (6) [M – 2 $C_5H_{10}N$ – H]$^+$, 242 (8) [M – $C_5H_{10}NH$ – PhthN]$^+$, 216 (31) [OCC_6H_4 – CO – NC_5H_{10}]$^+$, 182 (8) [M – $C_5H_{10}NH$ – PhthNH – CO_2CH_3]$^+$, 156 (6) [M – 2 $C_5H_{10}NH$ – PhthNH]$^+$. $C_{25}H_{35}N_3O_6$·0.5C_6H_6 (512.63): calcd. C 65.60, H 7.47, N 8.20; found C 65.47, H 7.64, N 8.24. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B/C = 10:0.5:0.5]: t_R = 14.2 min.

Dimethyl *erythro*-4-(1-Piperidyl)-*N*-[2-(1-piperidylcarbonyl)benzoyl]-glutamate (*erythro*-7): According to the above procedure and starting from *erythro*-**5**, a 19:81 mixture of *threo*-**7**/*erythro*-**7** as an amorphous white solid (0.107 g, 81% yield) was obtained. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.30–1.61 (m, 12 H, piperidyl), 2.00 (ddd, J = 14.4, 7.3, 7.3 Hz, 1 H, C^3H_B), 2.18 (ddd, J = 13.9, 7.2, 6.3 Hz, 1 H, C^3H_A), 2.32 (m, 2 H, piperidyl), 2.59 (m, 2 H, piperidyl), 3.04 (m, 2 H, piperidyl), 3.39 (dd, J = 7.4, 7.3 Hz, 1 H, C^4H), 3.51 (m, 2 H, piperidyl), 3.63 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 4.48 (q, J = 7.1 Hz, 1 H, C^2H), 7.26 (dd, J = 7.4, 1.4 Hz, 1 H, Ar), 7.48 (td, J = 7.5, 1.4 Hz, 1 H, Ar), 7.54 (td, J = 7.4, 1.3 Hz, 1 H, Ar), 7.68 (d, J = 7.3 Hz, 1 H, Ar), 8.72 (d, J = 7.6 Hz, 1 H, NH) ppm. MS (in CH_3CN, Q-array scan): m/z = 474 (100) [M + H]$^+$. MS (in CH_3CN, Q-array voltage 80 V): m/z (%) = 474 (28) [M + H]$^+$, 389 (100) [M – $C_5H_{10}N$]$^+$, 329 (8) [M – $C_5H_{10}NH$ – CO_2CH_3]$^+$, 304 (8) [M – 2 $C_5H_{10}N$ – H]$^+$, 242 (9) [M – $C_5H_{10}NH$ – PhthN]$^+$, 216 (33) [OCC_6H_4 – CO – NC_5H_{10}]$^+$, 182 (7) [M – $C_5H_{10}NH$ – PhthNH – CO_2CH_3]$^+$, 156 (6) [M – 2 $C_5H_{10}NH$ – PhthNH]$^+$. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B/C = 10:0.5:0.5]: t_R = 18.4 min.

Dimethyl (*Z*)-1-{[2-(1-Piperidylcarbonyl)benzoyl]amino}cyclopropane-1,2-dicarboxylate (8): A solution of dimethyl (*Z*)-1-(phthalimido)cyclopropane-1,2-dicarboxylate (**6**, 0.30 g, 1.0 mmol) and piperidine (0.67 mL, 6.84 mmol) in benzene (4 mL) was kept at 5 °C for 5 d, washed with H_2O to neutral pH, and dried with Na_2SO_4. The solvent was evaporated to dryness under reduced pressure; the residue was purified by flash chromatography (hexane/acetone from 50:1 to 4:1) to give **8** as a white solid (192 mg, 49% yield). M.p. 155–157 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.21–1.68 (m, 6 H, piperidyl), 1.76 (m, 2 H, CH_2), 2.64 (dd, J = 8.6, 7.8 Hz, 1 H, CH), 3.02 (m, 2 H, piperidyl), 3.19 (m, 1 H, piperidyl), 3.56 (br. s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.81 (m, 1 H, piperidyl), 7.24 (dd, J = 7.4, 1.2 Hz, 1 H, Ar), 7.47 (td, J = 7.5, 1.3 Hz, 1 H, Ar), 7.54 (td, J = 7.5, 1.3 Hz, 1 H, Ar), 7.66 (dd, J = 7.4, 0.9 Hz, 1 H, Ar), 9.11 (s, 1 H, NH) ppm. $C_{20}H_{24}N_2O_6$ (388.42): calcd. C 61.85, H 6.23, N 7.21; found C 62.10, H 6.42, N 6.99. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B/C = 10:0.8:0.2]: t_R = 17.2 min.

***threo*-4-(Dibenzylamino)glutamic Acid (*threo*-11), *erythro*-4-(Dibenzylamino)glutamic Acid (*erythro*-11), *cis*-4-(Dibenzylamino)-**

5-oxoproline (*cis*-15), and *trans*-4-(Dibenzylamino)-5-oxoproline (*trans*-15): Compound **4** (1.24 g, 2.48 mmol) was refluxed in HCl (6 N, 12 mL) for 5 h. After cooling the mixture to room temperature, the precipitate of phthalic acid was filtered off, and the filtrate was concentrated to dryness under reduced pressure to give a mixture of the hydrochlorides of *threo*- and *erythro*-**11**, and *cis*- and *trans*-**15** (1.0 g). The mixture (120 mg) was separated by using preparative RP HPLC [Reprosil-Pur C_{18} (20 × 250 mm, 10 μm)] in a gradient mode (F/C/G/H from 90:5:5:0.5 to 30:35:35:0.5) to give *threo*-**11** (13 mg, 11% yield), *erythro*-**11** (15 mg, 12% yield), *cis*-**15** (20 mg, 17% yield), and *trans*-**15** (25 mg, 21% yield) as amorphous solids.

***threo*-4-(Dibenzylamino)glutamic Acid (*threo*-11):** ^{1}H NMR (400 MHz, D_2O, NaOD): δ = 1.52 (ddd, $J_{3B,3A}$ = 14.3, J = 10.7, 4.6 Hz, 1 H, 3B-H), 2.18 (ddd, $J_{3A,3B}$ = 14.3, J = 11.3, 3.3 Hz, 1 H, 3A-H), 3.19 [dd, J = 11.4, 4.3 Hz, 1 H, 2(4)-H], 3.50 [dd, J = 10.8, 3.3 Hz, 1 H, 4(2)-H], 3.59 (d, ^2J = 13.7 Hz, 2 H, CH-Ph), 3.89 (d, ^2J = 13.7 Hz, 2 H, CH-Ph), 7.29–7.47 (m, 10 H, Ar) ppm. MS (in CH_3CN, Q-array scan): *m*/*z* (%) = 343 (100) $[M + H]^+$. MS (in CH_3CN, Q-array voltage 60 V): *m*/*z* (%) = 343 (100) $[M + H]^+$, 325 (41) $[M + H – H_2O]^+$, 299 (31) $[M + H – CO_2]^+$, 251 (18) $[M + H – CH_2Ph]^+$, 224 (28) $[M – 2\ CO_2 – CH_2NH_2]^+$, 132 (42) $[M – 2\ CO_2 – CH_2NH_2 – CH_2Ph]^+$, 91 (31) $[CH_2Ph]^+$. RP HPLC [LiChrosorb RP-18 (4.6 × 250 mm, 5 μm), C/E from 10:90 to 80:20]: t_R = 23.6 min.

***erythro*-4-(Dibenzylamino)glutamic Acid (*erythro*-11):** ^{1}H NMR (400 MHz, D_2O, NaOD): δ = 1.74 (ddd, $J_{3B,3A}$ = 13.6, J = 9.5, 6.5 Hz, 1 H, 3B-H), 2.18 (ddd, $J_{3A,3B}$ = 13.6, J = 8.7, 4.4 Hz, 1 H, 3A-H), 3.18 [dd, J = 9.4, 3.8 Hz, 1 H, 2(4)-H], 3.33 [dd, J = 8.4, 6.4 Hz, 1 H, 4(2)-H], 3.60 (d, ^2J = 13.8 Hz, 2 H, CH-Ph), 3.92 (d, ^2J = 13.8 Hz, 2 H, CH-Ph), 7.27–7.41 (m, 10 H, Ar) ppm. MS (in CH_3CN, Q-array scan): *m*/*z* (%) = 343 (100) $[M + H]^+$. MS (in CH_3CN, Q-array voltage 60 V): *m*/*z* (%) = 343 (100) $[M + H]^+$, 325 (38) $[M + H – H_2O]^+$, 299 (30) $[M + H – CO_2]^+$, 251 (17) $[M + H – CH_2Ph]^+$, 224 (31) $[M – 2\ CO_2 – CH_2NH_2]^+$, 132 (42) $[M – 2\ CO_2 – CH_2NH_2 – CH_2Ph]^+$, 91 (33) $[CH_2Ph]^+$. RP HPLC [LiChrosorb RP-18 (4.6 × 250 mm, 5 μm), C/E from 10:90 to 80:20]: t_R = 23.8 min.

***cis*-4-(Dibenzylamino)-5-oxoproline (*cis*-15):** ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 1.87 (ddd, $J_{3B,3A}$ = 12.4, $J_{3B,4}$ = 9.1, $J_{3B,2}$ = 7.9 Hz, 1 H, 3B-H), 2.44 (ddd, $J_{3A,3B}$ = 12.4, $J_{3A,4}$ = 9.1, $J_{3A,2}$ = 7.9 Hz, 1 H, 3A-H), 3.43 (t, $J_{4,3A}$ = $J_{4,3B}$ = 9.1 Hz, 1 H, 4-H), 3.52 (d, ^2J = 13.9 Hz, 2 H, CH-Ph), 3.72 (d, ^2J = 13.9 Hz, 2 H, CH-Ph), 3.91 (t, $J_{2,3A}$ = $J_{2,3B}$ = 7.9 Hz, 1 H, 2-H), 7.22 (m, 2 H, Ar), 7.31 (m, 4 H, Ar), 7.39 (m, 4 H, Ar), 8.01 (s, 1 H, NH) ppm. MS (in CH_3CN, Q-array scan): *m*/*z* (%) = 325 (100) $[M + H]^+$. MS (in CH_3CN, Q-array voltage 60 V): *m*/*z* (%) = 325 (25.7) $[M + H]^+$, 233 (97.6) $[M – CH_2Ph]^+$, 222 (23.8) $[M – CO_2 – CONHCH_2]^+$, 181 (45.9), 132 (40.2) $[M – CH_2Ph – CO_2 – CONHCH_2]^+$, 91 (100) $[CH_2Ph]^+$. RP HPLC [LiChrosorb RP-18 (4.6 × 250 mm, 5 μm), C/E from 10:90 to 80:20]: t_R = 31.5 min.

***trans*-4-(Dibenzylamino)-5-oxoproline (*trans*-15):** ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 2.11 (dd, $J_{3B,3A}$ = 12.8, $J_{3B,4}$ = 9.2 Hz, 1 H, 3B-H), 2.32 (ddd, $J_{3A,3B}$ = 12.8, $J_{3A,2}$ = 9.7, $J_{3A,4}$ = 9.2 Hz, 1 H, 3A-H), 3.41 (t, $J_{4,3A}$ = $J_{4,3B}$ = 9.2 Hz, 1 H, 4-H), 3.55 (d, ^2J = 13.9 Hz, 2 H, CH-Ph), 3.72 (d, ^2J = 13.9 Hz, 2 H, CH-Ph), 3.96 (d, $J_{4,3A}$ = 9.7 Hz, 1 H, 2-H), 7.22 (m, 2 H, Ar), 7.31 (m, 4 H, Ar), 7.39 (m, 4 H, Ar), 8.10 (s, 1 H, NH) ppm. MS (in CH_3CN, Q-array scan): *m*/*z* (%) = 325 (100) $[M + H]^+$. MS (in CH_3CN, Q-array voltage 60 V): *m*/*z* (%) = 325 (25.7) $[M + H]^+$, 233 (95.7) $[M – CH_2Ph]^+$, 222 (16.4) $[M – CO_2 – CONHCH_2]^+$, 181 (38.6), 132 (52.8) $[M – CH_2Ph – CO_2 – CONHCH_2]^+$, 91 (100) $[CH_2Ph]^+$. RP HPLC [LiChrosorb RP-18 (4.6 × 250 mm, 5 μm), C/E from 10:90 to 80:20]: t_R = 30.4 min.

***threo*-4-(1-Piperidyl)glutamic Acid (*threo*-12):** Compound *threo*-**5** (1.16 g, 2.99 mmol) was refluxed in HCl (20%, 12 mL) for 5 h. After cooling the mixture to room temperature, the precipitate of phthalic acid was filtered off, the filtrate was concentrated to dryness under reduced pressure, and the residue was dried with P_2O_5 and KOH under reduced pressure at room temperature to give a 39:6:46:10 mixture of the hydrochlorides (0.85 g) of *threo*-/*erythro*-**12**/*cis*-/*trans*-**16**. Ag_2CO_3 (0.69 g, 2.5 mmol) was added to a solution of the above mixture in H_2O (2 mL). The reaction mixture was stirred at room temperature for 30 min, the precipitate was filtered off, the filtrate was treated with H_2S, the precipitate was filtered off, and the filtrate was concentrated to dryness under reduced pressure. The residue (0.67 g) was crystallized from EtOH to give *threo*-**12** as a white solid (0.19 g, 28% yield). M.p. 234–239 °C (decomp.). 96% *de* according to ^{1}H NMR spectroscopy. ^{1}H NMR (400 MHz, D_2O, NaOD): δ = 1.43 (m, 2 H, piperidyl), 1.54 (m, 4 H, piperidyl), 1.82 (ddd, J = 13.4, 9.4, 6.7 Hz, 1 H, 3B-H), 1.89 (ddd, J = 13.4, 7.2, 4.7 Hz, 1 H, 3A-H), 2.53 (m, 4 H, piperidyl), 2.98 [dd, J = 9.4, 4.7 Hz, 1 H, 2(4)-H], 3.15 [dd, J = 7.1, 7.0 Hz, 1 H, 4(2)-H] ppm. $C_{10}H_{18}N_2O_4$ (230.26): calcd. C 52.16, H 7.88, N 12.17; found C 52.09, H 7.94, N 11.98.

***erythro*-4-(1-Piperidyl)glutamic Acid (*erythro*-12):** According to the above procedure and starting from a 4:37:7:52 mixture (2.57 g) of *threo*-/*erythro*-**12**/*cis*-/*trans*-**16**, a 17:78:5 mixture (0.41 g, 16% yield) of *threo*-/*erythro*-**12**/*trans*-**16** was obtained. *erythro*-**12**: ^{1}H NMR (400 MHz, D_2O, NaOD): δ = 1.43 (m, 2 H, piperidyl), 1.47–1.62 (m, 4 H, piperidyl), 1.56 (ddd, J = 13.3, 10.8, 3.4 Hz, 1 H, 3B-H), 2.15 (ddd, J = 13.3, 11.5, 2.8 Hz, 1 H, 3A-H), 2.49–2.61 (m, 4 H, piperidyl), 3.08 [dd, J = 11.5, 3.4 Hz, 1 H, 2(4)-H], 3.11 [dd, J = 10.9, 2.8 Hz, 1 H, 4(2)-H] ppm.

(2*S*,4*S*)-4-[(Methyl)(phenyl)amino]-5-oxoproline [(2*S*,4*S*)-13]: Compound (2*S*,4*S*)-**2** (2.14 g, 5.21 mmol) was refluxed in HCl (6 N, 25 mL) for 5 h. After cooling the mixture to room temperature, the precipitate of phthalic acid was filtered off, and the filtrate was concentrated to dryness under reduced pressure to give a 32:6:52:10 mixture of the hydrochlorides of *threo*-/*erythro*-**9**/(2*S*,4*S*)-/(2*S*,4*R*)-**13** (^{1}H NMR). The mixture was heated under reduced pressure at 130 °C for 4 h, and then crystallized from 40% EtOH in H_2O to give amino acid (2*S*,4*S*)-**13** as a white solid (0.75 g, 61% yield). M.p. 215–220 °C (decomp.). $[\alpha]_D^{20}$ = 152.5 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 1.81 (ddd, $J_{3B,3A}$ = 12.7, $J_{3B,4}$ = 9.1, $J_{3B,2}$ = 8.2 Hz, 1 H, 3B-H), 2.68 (ddd, $J_{3A,3B}$ = 12.7, $J_{3A,4}$ = 9.1, $J_{3A,2}$ = 8.2 Hz, 1 H, 3A-H), 2.69 (s, 3 H, NMe), 4.09 (t, $J_{2,3A}$ = $J_{2,3B}$ = 8.2 Hz, 1 H, 2-H), 4.68, (t, $J_{4,3A}$ = $J_{4,3B}$ = 9.1 Hz, 1 H, 4-H), 6.66 (t, J = 7.2 Hz, 1 H, *para*-Ar), 6.79 (d, J = 8.1 Hz, 2 H, *ortho*-Ar), 7.16 (m, 2 H, *meta*-Ar), 8.27 (s, 1 H, NH), 12.92 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 27.47 (C^3H_2), 33.22 (CH_3N), 51.37 (CH), 59.32 (CH), 112.80 (*ortho*-Ar), 116.69 (*para*-Ar), 128.98 (*meta*-Ar), 149.54 (*ipso*-Ar), 173.48 (CO), 173.58 (CO) ppm. $C_{12}H_{14}N_2O_3$ (234.26): calcd. C 61.53, H 6.02, N 11.96; found C 61.48, H 6.16, N 11.89. 99% *de*. RP HPLC [LiChrosorb RP-18 (4.6 × 250 mm, 5 μm), C/D from 5:95 to 80:20]: t_R = 30.7 min.

(2*S*,4*R*)-4-[(Methyl)(phenyl)amino]-5-oxoproline [(2*S*,4*R*)-13]: According to the above procedure and starting from a 64:36 mixture of (2*S*,4*S*)-**2**/(2*S*,4*R*)-**2** (2.29 g, 5.58 mmol), a 23:16:35:26 mixture of the hydrochlorides of *threo*-/*erythro*-**9**/(2*S*,4*S*)-/(2*S*,4*R*)-**13** (^{1}H NMR) was obtained. Amino acid (2*S*,4*R*)-**13** (22 mg, 18% yield) was isolated from the above mixture (120 mg) as an amorphous solid by using preparative RP HPLC [Reprosil-Pur C_{18}

(20 × 250 mm, 10 μm)] in a gradient mode (F/C/G/H from 90:5:5:0.5 to 60:20:20:0.5). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.26 (ddd, $J_{3B,3A}$ = 13.3, $J_{3B,2}$ = J_{3B-4} = 9.2 Hz, 1 H, 3B-H), 2.37 (dd, $J_{3A,3B}$ = 13.3, $J_{3A,4}$ = 9.2 Hz, 1 H, 3A-H), 2.70 (s, 3 H, NMe), 4.06 (d, $J_{2,3B}$ = 9.2 Hz, 1 H, 2-H), 4.54, (dd, $J_{4,3A}$ = $J_{4,3B}$ = 9.2 Hz, 1 H, 4-H), 6.66 (t, J = 7.2 Hz, 1 H, *para*-Ar), 6.76 (d, J = 8.0 Hz, 2 H, *ortho*-Ar), 7.16 (m, 2 H, *meta*-Ar), 8.28 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 27.39 (C^{3}H$_2$), 33.11 (CH$_3$N), 52.03 (CH), 58.59 (CH), 112.95 (*ortho*-Ar), 116.73 (*para*-Ar), 128.96 (*meta*-Ar), 149.61 (*ipso*-Ar), 173.95 (CO), 174.42 (CO) ppm. MS (in CH$_3$CN, Q-array scan): *m*/*z* (%) = 276 (13) [M + H + CH$_3$CN]$^+$, 235 (100) [M + H]$^+$. MS (in CH$_3$CN, Q-array voltage 70 V): *m*/*z* (%) = 276 (8) [M + H + CH$_3$CN]$^+$, 235 (55) [M + H]$^+$, 190 (28) [M – CO$_2$]$^+$, 175 (29) [M – CO$_2$ – NH]$^+$, 148 (100) [M + H – CO$_2$ – CONH]$^+$, 134 (74) [M + H – CO$_2$ – CONHCH$_2$]$^+$, 107 (75) [PhNCH$_3$]$^+$. 99% *de*. RP HPLC [LiChrosorb RP-18 (4.6 × 250 mm, 5 μm), C/D from 5:95 to 80:20]: t_R = 31.4 min.

(2*S*,4*S*)-4-[(2′*S*)-2-Methylindolin-1-yl]-5-oxoproline [(2*S*,4*S*,2′*S*)-14]: According to the procedure described for amino acid (2*S*,4*S*)-**13** and starting from (2*S*,4*S*,2′*S*)-**3**,[9e] lactam (2*S*,4*S*,2′*S*)-**14** was obtained in a 56% yield as a white solid. M.p. 222–226 °C (decomp.). $[\alpha]_D^{20}$ (578 nm) = 141.1 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.25 (d, $J_{Me,2'}$ = 6.5 Hz, 3 H, Me), 1.88 (ddd, $J_{3B,3A}$ = 12.2, $J_{3B,4}$ = 9.8, $J_{3B,2}$ = 9.2 Hz, 1 H, 3B-H), 2.50 (dd, $J_{3'B,3'A}$ = 15.5, $J_{3'B,2'}$ = 9.3 Hz, 1 H, 3′B-H), 2.56 (ddd, $J_{3A,3B}$ = 12.2, $J_{3A,4}$ = 9.0, $J_{3A,2}$ = 8.6 Hz, 1 H, 3A-H), 3.09 (dd, $J_{3'A,3'B}$ = 15.5, $J_{3'A,2'}$ = 8.7 Hz, 1 H, 3′A-H), 3.72 (ddq, $J_{2',3'B}$ = 9.3, $J_{2',3'A}$ = 8.7, $J_{2',Me}$ = 6.5 Hz, 1 H, 2′-H), 4.10 (dd, $J_{2,3B}$ = 9.2, $J_{2,3A}$ = 8.6 Hz, 1 H, 2-H), 4.20 (dd, $J_{4,3B}$ = 9.8, $J_{4,3A}$ = 9.0 Hz, 1 H, 4-H), 6.26 (d, $J_{7',6'}$ = 7.7 Hz, 1 H, 7′-H), 6.54 (dd, $J_{5',6'}$ = 7.3, $J_{5',4'}$ = 7.0 Hz, 1 H, 5′-H), 6.89 (dd, $J_{6',7'}$ = 7.7, $J_{6',5'}$ = 7.3 Hz, 1 H, 6′-H), 6.98 (d, $J_{4',5'}$ = 7.0 Hz, 1 H, 4′-H), 8.28 (s, 1 H, NH), 12.89 (br. s, 1 H, CO$_2$H) ppm. C$_{14}$H$_{16}$N$_2$O$_3$ (260.29): calcd. C 64.60, H 6.20, N 10.76; found C 64.61, H 6.20, N 10.64.

***cis*-5-Oxo-4-(1-piperidyl)proline (*cis*-16):** Compound *threo*-**5** (1.16 g, 2.99 mmol) was refluxed in HCl (6 N, 12 mL) for 5 h. Then according to the procedure described for amino acid (2*S*,4*S*)-**13**, a 39:6:46:10 mixture of hydrochlorides of *threo*-/*erythro*-**12**/*cis*-/*trans*-**16** (0.85 g) was obtained. Ag_2CO_3 (0.69 g, 2.5 mmol) was added to a solution of the above mixture in H$_2$O (2 mL). The reaction mixture was stirred at room temperature for 30 min, the precipitate was filtered off, the filtrate was treated with H$_2$S, the precipitate was filtered off, and the filtrate was concentrated to dryness under reduced pressure. The residue (0.67 g) was heated under reduced pressure at 120–130 °C over P$_2$O$_5$ for 4 h. Crystallization from EtOH gave *cis*-**16** as a white solid (0.41 g, 65% yield, 99% *de*). M.p. 204–211 °C (decomp.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.37 (m, 2 H, H-piperidyl), 1.47 (m, 4 H, H-piperidyl), 1.87 (ddd, J = 13.0, 8.0, 8.0 Hz, 1 H, 3B-H), 2.38 (ddd, J = 13.3, 8.7, 8.7 Hz, 1 H, 3A-H), 2.42 (m, 2 H, H-piperidyl), 2.65 (m, 2 H, H-piperidyl), 3.36 (dd, J = 8.7, 8.6 Hz, 1 H, 4-H), 3.96 (dd, J = 7.9, 7.9 Hz, 1 H, 2-H), 8.09 (s, 1 H, NH) ppm. C$_{10}$H$_{16}$N$_2$O$_3$ (212.25): calcd. C 56.59, H 7.60, N 13.20; found C 56.53, H 7.79, N 13.18.

***trans*-5-Oxo-4-(1-piperidyl)proline (*trans*-16):** According to the above procedure and starting from *erythro*-**5**, lactams *trans*-**16** were obtained in a 75% yield (99% *de*). M.p. 133–136 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.37 (m, 2 H, piperidyl), 1.46 (m, 4 H, piperidyl), 2.07 (ddd, J = 13.2, 8.9, 2.7 Hz, 1 H, 3B-H), 2.27 (ddd, J = 13.2, 9.2, 9.2 Hz, 1 H, 3A-H), 2.38 (m, 2 H, piperidyl), 2.70 (m, 2 H, piperidyl), 3.31 (dd, J = 8.9, 8.6 Hz, 1 H, 4-H), 3.97 (ddd, J = 9.5, 2.6, 1.0 Hz, 1 H, 2-H), 8.07 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 23.61 (CH$_2$ piperidyl), 25.20 (2 CH$_2$ piperidyl), 26.66 (C^{3}H$_2$), 49.52 (2 CH$_2$N piperidyl), 52.65 (CH), 62.81 (CH), 174.11 (CO), 174.62 (CO) ppm. MS (in MeOH, Q-array scan): *m*/*z* (%) = 245 (16) [M + H + MeOH]$^+$, 213 (100) [M + H]$^+$. MS (in MeOH, Q-array voltage 80 V): *m*/*z* (%) = 245 (9) [M + H + MeOH]$^+$, 213 (100) [M + H]$^+$, 185 (26) [M + H – CO]$^+$, 168 (53) [M + H – CO$_2$]$^+$, 113 (92) [C$_5$H$_{10}$NCO]$^+$.

{(2*S*,4*S*)-4-[(Methyl)(phenyl)amino]-5-oxoprolyl}[(1*S*)-1-phenylethyl]-amine (17): Oxalyl chloride (0.35 mL, 4.0 mmol) and DMF (5 μL) were added to a solution of *cis*-**13** (206 mg, 0.88 mmol) in CHCl$_3$ (10 mL) whilst stirring and cooling (to 0 °C). After complete dissolution, the reaction mixture was concentrated to dryness under reduced pressure. The residue was suspended in dry benzene (10 mL), and [(*S*)-1-phenylethyl]amine (0.5 mL, 3.91 mmol) was added whilst stirring and cooling. The reaction mixture was stirred at room temperature for 3 h, and the precipitate was filtered off. The filtrate was washed successively with 5% aq. citric acid, H$_2$O, 5% aq. NaHCO$_3$, and then dried with Na$_2$SO$_4$. Evaporation of the solvent under reduced pressure to dryness gave **17** as an amorphous yellow solid (148 mg, 50% yield). >99% *de*. HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B/C = 5:0.5:0.5]: t_R = 11.0 min. Crystallization from EtOAc gave **17** as a yellow solid (74 mg, 25% yield). M.p. 174–177 °C. $[\alpha]_D^{20}$ = 71.2 (*c* = 0.64, acetone). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.46 (d, $J_{Me,CH}$ = 7.1 Hz, 3 H, Me), 2.03 (ddd, $J_{3B,3A}$ = 13.2, $J_{3B,H}$ = 9.4, $J_{3B,H}$ = 8.4 Hz, 1 H, 3B-H), 2.72 (ddd, $J_{3A,3B}$ = 13.2, $J_{3A,H}$ = 9.4, $J_{3A,H}$ = 8.4 Hz, 1 H, 3A-H), 2.82 (s, 3 H, NMe), 4.00 [t, $J_{H,3A}$ = $J_{H,3B}$ = 8.4 Hz, 1 H, 2(4)-H], 4.54 [t, $J_{H,3A}$ = $J_{H,3B}$ = 9.4 Hz, 1 H, 4(2)-H], 5.09, (dq, $J_{CH,NH}$ = 7.8, $J_{CH,Me}$ = 7.1 Hz, 1 H, CH-Phe), 6.64 (d, $J_{NH,CH}$ = 7.8 Hz, 1 H, NH), 6.81–6.76 (m, 3 H, Ar), 7.06 (s, 1 H, NH-lactam), 7.29–7.20 (m, 7 H, Ar) ppm. C$_{20}$H$_{23}$N$_3$O$_2$ (337.42): calcd. C 71.19, H 6.87, N 12.45; found C 70.83, H 6.90, N 12.36.

{(2*S*,4*S*)-4-[(2*S*)-2-Methylindolin-1-yl]-5-oxoprolyl}[(1*S*)-1-phenylethyl]amine (18): According to the above procedure and starting from amino acid *cis*-**14**, derivative **18** was obtained in 54% yield. M.p. 106–110 °C. $[\alpha]_D^{20}$ = 82.1 (*c* = 1.0, CHCl$_3$). >99% *de*; HPLC [LiChrosorb Si-60 (4 × 250 mm, 5 μm), A/B/C = 5:0.7:0.3]: t_R = 15.6 min. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.34 (d, $J_{Me,CH}$ = 7.2 Hz, 3 H, Me), 1.38 (d, J = 6.1 Hz, 3 H, Me-Ind), 2.23 (ddd, $J_{3B,3A}$ = 12.9, J = 10.5, 9.2 Hz, 1 H, 3B-H), 2.62 (ddd, $J_{3A,3B}$ = 12.9, J = 9.2, 8.4 Hz, 1 H, 3A-H), 2.66 (dd, $J_{3'B,3'A}$ = 15.5, J = 10.1 Hz, 1 H, 3′B-H), 3.13 (dd, $J_{3'A,3'B}$ = 15.5, J = 8.6 Hz, 1 H, 3′A-H), 3.72 (m, 1 H, 2′-H), 4.05 [dd, J = 9.2, 8.4 Hz, 1 H, 2(4)-H], 4.10 [dd, J = 10.5, 9.2 Hz, 1 H, 4(2)-H], 5.02 (dq, $J_{CH,NH}$ = 8.2, $J_{CH,Me}$ = 7.2 Hz, 1 H, CH-Phe), 6.39 (d, $J_{7',6'}$ = 7.8 Hz, 1 H, 7′-H), 6.70 (dd, $J_{5',6'}$ = 7.5, $J_{5',4'}$ = 7.2 Hz, 1 H, 5′-H), 6.79 (d, $J_{NH,CH}$ = 8.2 Hz, 1 H, NH), 6.90 (s, 1 H, NH-lactam), 7.00 (dd, $J_{6',7'}$ = 7.8, $J_{6',5'}$ = 7.5 Hz, 1 H, 6′-H), 7.05 (d, $J_{4',5'}$ = 7.2 Hz, 1 H, 4′-H), 7.32–7.20 (m, 5 H, Ph) ppm. C$_{22}$H$_{25}$N$_3$O$_2$ (363.46): calcd. C 72.70, H 6.93, N 11.56; found C 72.61, H 6.99, N 11.42.

X-ray Analysis: Data for (2*S*,4*S*)-**2** and *threo*-**4** were collected with an XCALIBUR-3 diffractometer, and that for *erythro*-**5** was collected with a Bruker P4 diffractometer with graphite-monochromated Mo-K_α radiation. The structures were solved by direct methods and expanded using Fourier techniques. 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 idealised positions and allowed to ride on the C atoms to which they are bonded.

Crystal Data for (2*S*,4*S*)-2: M_r = 410.42; 0.50 × 0.43 × 0.23 mm; yellow prism; T = 295 K; orthorhombic; space group $P2_12_12_1$; a = 10.1205(4) Å, b = 11.3428(4) Å, c = 17.8131(7) Å; β = 90.00°; V = 2044.85(13) Å^3; $\rho_{calcd.}$ = 1.333 g cm^{-3}; θ_{max} = 26.37°; R_1 = 3.76%.

CCDC-643957 contains the supplementary crystallographic data for this compound.

Crystal Data for *threo*-4: M_r = 500.53; 0.48 × 0.37 × 0.22 mm; colourless plate; T = 295 K; monoclinic; space group $P2_1/n$; a = 17.3292(10) Å, b = 9.6538(5) Å, c = 31.7835(18) Å; β = 100.055(5)°; V = 5235.5(5) Å^3; $\rho_{calcd.}$ = 1.270 g cm^{-3}; θ_{max} = 26.00; R_1 = 5.90%. CCDC-643956 contains the supplementary crystallographic data for this compound.

Crystal Data for *erythro*-5: M_r = 388.41; 1.10 × 0.46 × 0.24 mm; colourless prism; T = 298 K; monoclinic; space group $P2_1/n$; a = 9.3423(8) Å, b = 9.3345(10) Å, c = 23.018(2) Å; β = 96.249(7)°; V = 1995.3(3) Å^3; $\rho_{calcd.}$ = 1.293 g cm^{-3}; θ_{max} = 26.00; R_1 = 4.47%. CCDC-617321 contains the supplementary crystallographic data for this compound.

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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