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# New Amino Acids Derived from *L*-Pyroglutamic Acid: Synthesis of *Trans*-4-Benzyl-*Cis*-5-Phenyl-*L*-Proline, *L*-α-(2-Benzyl-3-Phenylpropyl)-Glycine and *L*-α-(3-Phenylpropyl)-Glycine

Jo Van Betsbrugge, Wim Van Den Nest, Patricia Verheyden, Dirk Tourwé*

Vrije Universiteit Brussel, Eenheid Organische Chemie, Pleinlaan 2, 1050 Brussel, Belgium

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***Abstract:*** A convenient synthesis of three new amino acids, *L*-α-(3-phenylpropyl)-glycine, *L*-α-(2-benzyl-3-phenylpropyl)-glycine and its conformationally constrained analog, *trans*-4-benzyl-*cis*-5-phenyl-*L*-proline is reported. All compounds were prepared in good diastereomeric or enantiomeric purity from *L*-pyroglutamic acid. *Trans*-4-benzyl-*cis*-5-phenyl-*L*-proline was prepared by benzylation of Boc-*L*-Pyr-OBn, ring opening with phenyllithium and subsequent cyclisation. Hydrogenolysis under mild conditions then furnished *L*-α-(2-benzyl-3-phenylpropyl)-glycine. In a similar way, *L*-α-(3-phenylpropyl)-glycine was prepared from *cis*-5-phenyl-*L*-proline by catalytic hydrogenolysis.

## INTRODUCTION

Artificial amino acids are of great importance in medicinal chemistry. The use of unnatural amino acids as building blocks has already resulted in a variety of products with interesting biological properties. Growing interest for substituted prolines is reflected in an increasing number of publications dealing with the asymmetric synthesis of various substituted prolines.[1-7] One area of interest in which substituted prolines play a major role, is the domain of peptides and peptidomimetics. Substituted prolines, for example, have been used to restrict the conformational behaviour of flexible, small peptides.[4,8-10] Recently, the utility of *cis*-5-phenylproline was also demonstrated for ACE inhibitors.[11] Several examples of peptidomimetics which are based on a proline skeleton are also cited in the literature.[4,11-16]

In the present paper, *trans*-4-benzyl-*cis*-5-phenyl-*L*-proline is presented as a new proline analog, together with two new amino acids, i.e. *L*-α-(2-benzyl-3-phenylpropyl)-glycine and *L*-α-(3-phenylpropyl)-glycine. We believe these new amino acids to be of use in the field of peptides, especially where amino acids which have long flexible and hydrophobic side chains are required. The new amino acids presented here were all synthesised from *L*-pyroglutamic acid as the starting material. Pyroglutamic acid has been used before in the synthesis of chiral α-amino acids such as 4- and 5-substituted proline analogs. Prolines substituted at position 4 are rapidly accessible by alkylation of urethane-protected pyroglutamates and by subsequent reduction of the pyroglutamate to the corresponding proline, as was demonstrated by Baldwin and Ezquerra.[3,17,18] On the other hand, 5-substituted prolines are conveniently obtained by ring opening of pyroglutamates by organometallic reagents and subsequent ring closure.[19-22] In the present paper it is demonstrated how the methods for the synthesis of 4- and 5-substituted prolines can be combined to prepare the reported new amino acid derivatives in high enantiomeric and diastereomeric purity.

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*E-mail: datourwe@vub.ac.be     Fax: +32 2 629 33 04

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## RESULTS AND DISCUSSION

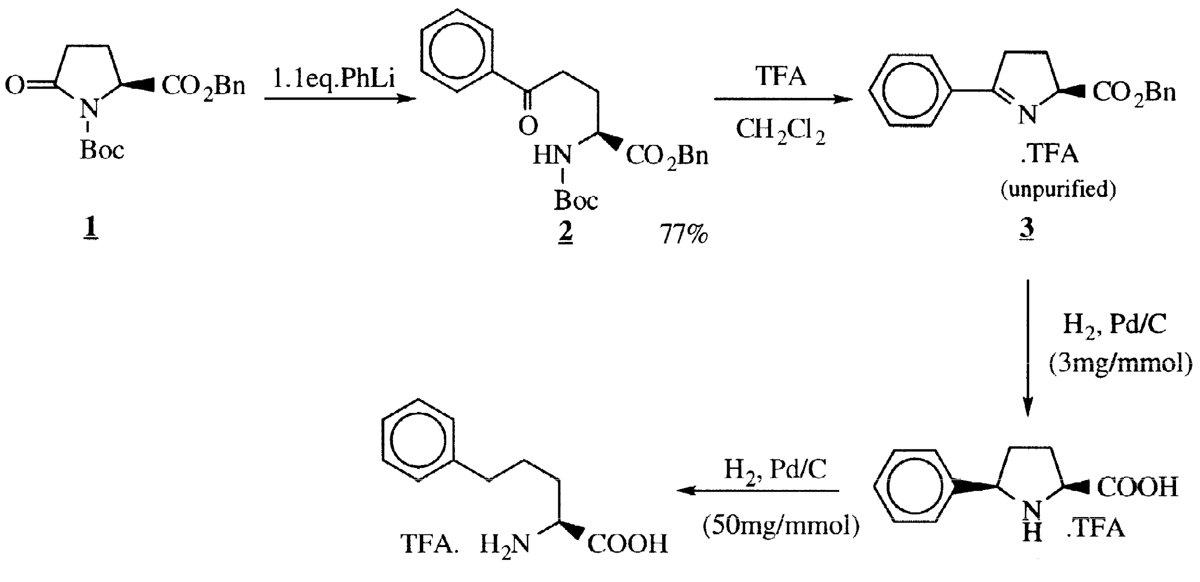
All compounds were obtained from benzyl N-Boc-*L*-pyroglutamate. This chiral starting material was obtained in good yield by esterification ($NEt_3/PhCH_2Cl$) and N-Boc-protection ($Boc_2O/DMAP$) of pyroglutamic acid.

***Synthesis of L-α-(3-phenylpropyl)-glycine (scheme 1)***

A convenient synthesis strategy for this new amino acid was elaborated based on the catalytic hydrogenolysis of the endocyclic N-benzyl bond of *cis*-5-phenyl-*L*-proline 4. Endocyclic N-benzyl bonds in amino acids are known to cleave under catalytic hydrogenation conditions. The reaction conditions under which cleavage of the N-benzyl bond is accomplished can be rather drastic. For example, the hydrogenolysis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids to the corresponding 2'-methylphenylalanine requires a reaction temperature of 90°C. Under these conditions, epimerisation of the α-carbon atom is observed.[24]

We examined the reaction conditions on the reductive cleavage of the endocyclic N-benzyl bond of *cis*-5-phenyl-*L*-proline with the aim to reduce the amount of epimerisation of the α-carbon atom.

*Cis*-5-phenyl-*L*-proline 4 was first prepared by ring opening of Boc-*L*-Pyr-OBn 1 using 1.1eq. PhLi 1.8M at -78°C in 77% yield, according to known literature procedures.[23,24] The hydrogenation of the pyrroline 3 was carried out in dry methanol using 3mg/mmol 10% Pd/C. The diastereomeric excess of the *cis*-5-phenyl-*L*-proline 4 was found to be 86% as determined by GCMS. No peaks of the corresponding D-enantiomers were detected using a chiral GC column, indicating either that no racemization has occured or that the enantiomers are not resolved. The high enantiomeric purity of 5 argues in favour of the former case.



*Scheme 1* 5 85% 4 65%

Our efforts to hydrogenolyse *cis*-5-phenyl-*L*-proline 4 demonstrated that this compound is converted to the corresponding *L*-α-(3-phenylpropyl)-glycine 5 under very mild conditions, i.e. catalytic hydrogenolysis at room temperature using 50mg/mmol 10% Pd/C in MeOH(10)/water(1). Full conversion was obtained after 18 hours (yield = 85%). The use of these mild conditions has the obvious advantage that the configuration of the αcenter is preserved. Indeed, GCMS analysis performed using a Chirasil-Val column demonstrated the obtained *L*-α-(3-phenylpropyl)-glycine 5 to be of high enantiomeric purity (e.e. = 98%).[28]

*L*-α-(3-Phenylpropyl)-glycine can also be obtained by direct hydrogenation of the pyrroline 3 using 50mg/mmol 10% Pd/C. The pyrroline is first reduced to *cis*-5-phenyl-*L*-proline and then further reduced to give the desired *L*-α-(3-phenylpropyl)-glycine.

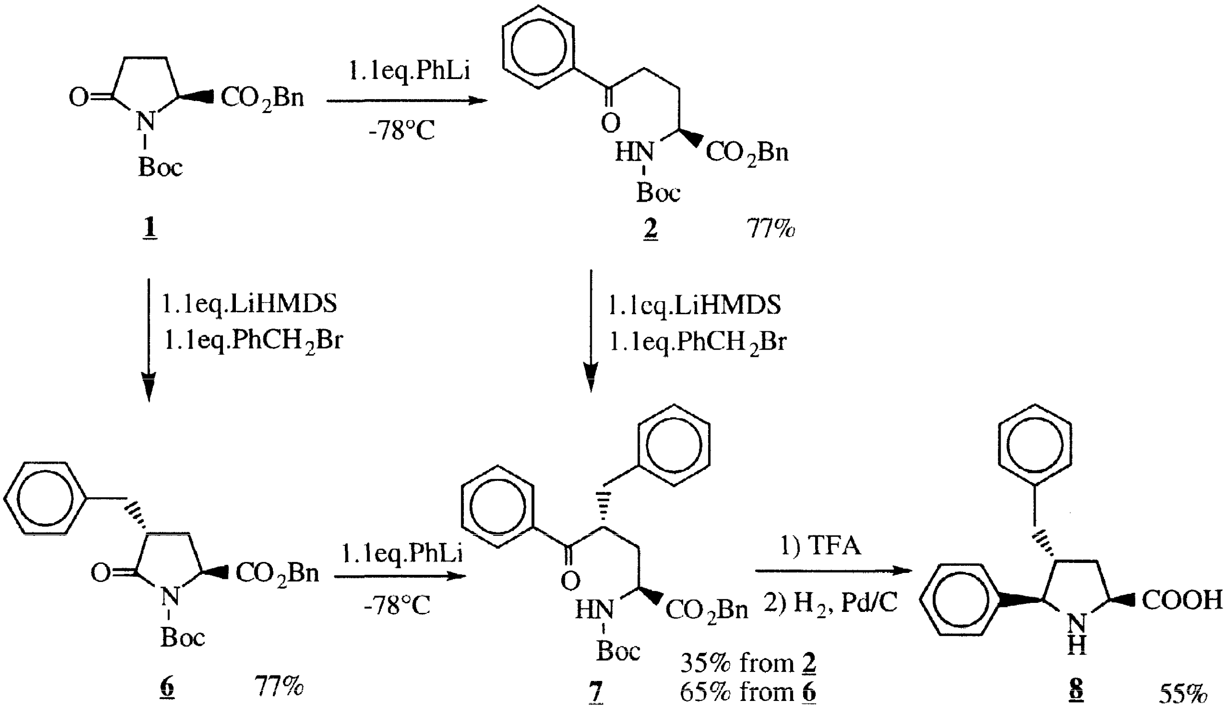
### *Synthesis of trans-4-benzyl-cis-5-phenyl-L-proline (scheme 2)*

Synthetic efforts to obtain this novel 4,5-substituted amino acid involved a combination of both methods used in the preparation of respectively 4- and 5-substituted prolines.[3,17,20-22,24]

Two approaches were investigated in order to prepare this δ-oxo-α-amino acid derivative 7. The first approach (scheme 2) involved ring opening of benzyl N-Boc-*L*-pyroglutamate 1 with phenyllithium at -78°C and subsequent benzylation of the obtained benzyl 2-(N-Boc-amino)-5-oxo-5-phenyl-*L*-pentanoate 2 using the sterically hindered base LiHMDS. This kind of alkylation performed on glutamates was recently reported to proceed with high diastereoselectivity[25-27], furnishing 4-*trans*-substituted glutamates.

A second approach consisted in the application of the same reactions but in a reversed order, i.e. a benzylation of the 4-position of pyroglutamate 1 leading to compound 6 followed by regioselective ring opening with phenyllithium.

The key compound of both strategies was the δ-oxo-α-amino acid derivative 7.



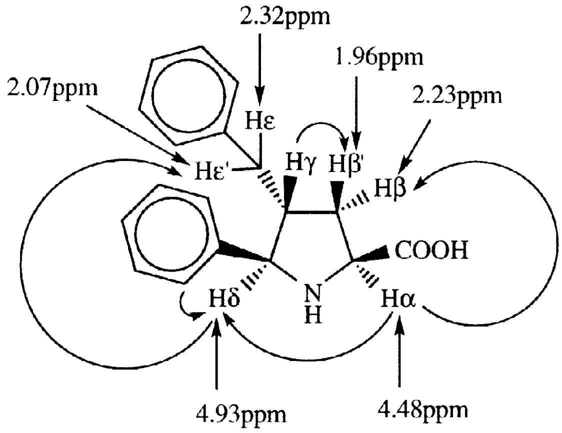
**Scheme 2**

Using the first approach, the δ-oxo-α-amino acid ester 2 was again obtained in 77% yield after purification by column chromatography. The benzylation, however, proceeded with very low yield (35%) when 2 was first added to a solution containing two equivalents LiHMDS. The reverse order of manipulations, *i.e* the addition of the base to the δ-oxo-α-amino-acid derivative 2 did not give higher yields. Instead, a complex mixture was obtained.

The second approach proved to be much more convenient. Boc-*L*-Pyr-OBn 1 was first benzylated using known procedures to furnish the *trans*-4-benzyl-*L*-pyroglutamate 6 in 77% yield. The *trans*-configuration of the 4-benzyl substitutent in 6 was unambiguously assigned based on 1D and 2D $^1$H NMR experiments.
The ring opening of *trans*-4-benzyl-*L*-pyroglutamate 6 using PhLi proceeded well, furnishing the desired benzyl 2-(N-Boc-amino)-*trans*-4-benzyl-5-oxo-5-phenyl-*L*-pentanoate 7 in 65% yield after purification by column chromatography. Hence, this second approach clearly is the most convenient way to obtain the desired δ-oxo-α-amino-acid derivative 7.

The next step in the synthesis of *trans*-4-benzyl-*cis*-5-phenyl-*L*-proline 8 involved conversion to a pyrroline by reaction of 7 with TFA/$CH_2Cl_2$ and subsequent hydrogenation of the imine, affording the corresponding *trans*-4-benzyl-*cis*-5-phenyl-*L*-proline 8. The conversion of 7 to 8 was accomplished in 55% yield.

The relative configurations of the 4- and 5-substituents were assigned based on 1D and 2D $^1$H NMR experiments. All protons were assigned based on a COSY-spectrum, recorded in DMSO at 303K. A NOESY-spectrum, recorded in DMSO at 303K, was used to assign the *cis*-2,5-configuration. This *cis*-configuration was established by the presence of characteristic NOe's between $H_\alpha$ and $H_\delta$. The NOe between $H_\delta$ and one of the benzylic protons of the 4-benzyl substituent suggest the 5-phenyl ring to be *trans* relative to the 4-benzyl group. The resulting trans orientation between the 4-benzyl substituent and the α-carboxyl group is further substantiated by the NOe's between the α,β and γ ring protons. Besides a *cis*-5-phenyl substituted proline analog, some *trans*-product was observed in the NMR spectrum.

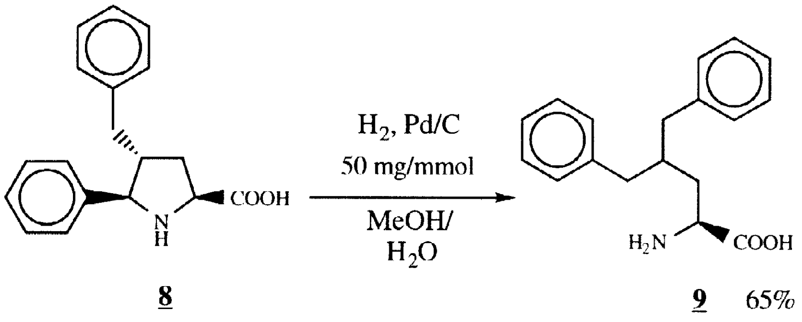


Observed NOe's and chemical shifts δ(ppm)
of *trans*-4-benzyl-*cis*-5-phenylproline

The diastereomeric excess was calculated by integration of the $H_\delta$'s in respectively the *cis* and the *trans* isomer. A cis/trans ratio of 90/10 was observed (d.e. 80%). When compared to the d.e. observed for *cis*-5-phenyl-*L*-proline (d.e. = 86%), this means that the extra 4-benzyl group has only a limited influence on the stereochemical outcome of the reductive cyclisation of δ-oxo-α-amino acid derivative 7.

### *Synthesis of L-α-(2-benzyl-3-phenylpropyl)-glycine (scheme 3)*

Similar to the synthesis of *L*-α-(3-phenylpropyl)glycine, the catalytic hydrogenolysis of the endocyclic benzylic bond was investigated. Our experiments showed the 4,5-disubstituted proline derivative <u>8</u> to convert easily at room temperature to the corresponding *L*-α-(2-benzyl-3-phenylpropyl)-glycine <u>9</u>. Its enantiomeric purity was analyzed via GCMS analysis on a Chirasil-Val column and was found to be 97%. This method can in principle lead to unsymmetrically γ-substituted α-(3-phenylpropyl)glycines with good control of the configuration.



*Scheme 3*

## CONCLUSION

*L*-Pyroglutamic acid has proven to be an excellent chiral starting block for the synthesis of 4,5-disubstituted prolines. Chiral 4,5-substituted prolines are now readily accessible starting form benzyl Boc-*L*-pyroglutamate using a combination of methods that have been used previously with success in the synthesis of 4- and 5-substituted prolines. We were able to demonstrate that both methods can be easily combined, furnishing a new *trans*-4-*cis*-5-disubstituted proline analog in a very limited number of steps.

The hydrogenolysis of the benzylic bond of 5-substituted prolines proceeded easily in presence of catalyst at the concentration of 50mg/mmol. This observation was used in the preparation of two new amino acids with long and flexible side chains, i.e. *L*-α-(3-phenylpropyl)-glycine and *L*-α-(2-benzyl-3-phenylpropyl)-glycine.

## EXPERIMENTAL SECTION

### *General procedures*

$^1H$ NMR spectra were recorded in DMSO or $CDCl_3$ on a Bruker AC-250 spectrometer, using the residual isotopic solvent signal as internal reference. Chemical shifts are given in δ(ppm). HOHAHA, ROESY, COSY and NOESY spectra were recorded on a Bruker AMS500 spectrometer equipped with an X32 computer and a Eurotherm temperature control unit.

Mass spectra were recorded on a VG Quattro II spectrometer (electrospray ionisation, ESP). GCMS analyses performed in order to determine e.e or d.e values using a Chirasil-Val column were performed on a Fisons MD800 system, inject port 250°C, split injection (1:30), He carrier gas (13psi head pressure), electron impact detection. Amino acids were therefore derivatised prior to GCMS analysis. The amino acids (1mg) were dissolved in 400µL 3N HCl in isobutanol (prepared by bubbling HCl in isobutanol, analytical grade). The reaction mixture (in Pierce Reacti-Vials of 1mL) was purged by Ar-stream, tightly capped and kept at 110°C for

60 minutes. After evaporation of the solvent, the residue was taken up in 100µL acetonitrile and 70µL trifluoroacetic acid anhydride (Pierce, 99+%) and allowed to react at 110°C for 10 minutes. Reactions were performed in a Pierce Reacti-block. The resulting solution was evaporated under a gentle Ar-stream at 25°C. The residue was then dissolved in acetonitrile (analytical grade).

HPLC analyses were performed on a Spectra-Physics P-4000 or an a Gilson system run by a Gilson 712 HPLC System Controller. Analytical runs used a Vydac 218 TP 54 column (RP-C18, 5µm, d=0.46cm, l=25cm) at a flow rate of 1.0mL/min. Preparative separations were performed on a Vydac 218 TP 152022 column (RP-C-18, 15-20µm, d=2.5cm, l=25cm) at a flow rate of 13mL/min.

Analytical thin layer chromatographies were performed using precoated glass-backed plates (Merck kieselgel 60 $F_{254}$) and visualised with ultraviolet light or iodine.

Column chromatographies were performed using Merck kieselgel 60 (0.040-0.063mm particle size, 230-400mesh). THF was dried by distillation over sodium/benzophenone. MeOH was dried by distillation over magnesium.

### ***Benzyl Boc-L-pyroglutamate (1)***

*L*-Pyroglutamic acid (5g, 38.75mmol) was suspended in 50mL THF. To the suspension was added 1 eq. $NEt_3$ (5.4mL), followed by 1.1 eq. benzyl chloride (43mmol, 4.9mL). The solution was refluxed for 5 days. After cooling, 50mL water was added and THF was removed under reduced pressure. Three extractions with $CH_2Cl_2$ afforded the crude benzyl pyroglutamate as an oil. The oil was then dissolved in 150mL $CH_2Cl_2$. The solution was cooled to 0°C, followed by the addition of 1 eq. $NEt_3$ (5.4mL), 2 eq. $Boc_2O$ (17.8mL) and 1 eq. DMAP (2.8g). After stirring for 18 hours, the solution was evaporated under reduced pressure. The resulting slurry was dissolved in 50mL hot cyclohexane. The solution was left standing in the refrigerator overnight. The crystals that had formed were filtered off and dried in a dessicator. Benzyl Boc-*L*-pyroglutamate was obtained as soft white crystalline needles. *Yield:* 9.52g (29.8mmol, 77%) ; *TLC:* $R_f$ = 0.76 (petroleumether(3)/EtOAc(1)) ; *m.p.: 57-59°C* ; *ESP/MS (m/z, % RA): 320($M^+$+1, 15), 220(50), 100(100)* ; *NMR (250MHz, $CDCl_3$):* 7.33(m, 5H, $H_{arom}$), 5.2(s, 2H, $OCH_2Ph$), 4.6(dd, 1H, $H_\alpha$, J = 8.8Hz, 3.14Hz), 2.65-1.9(m, 4H, $H_\beta$, $H_{\beta'}$, $H_\gamma$, $H_{\gamma'}$), 1.4(s, 9H, t-Bu).

### ***Benzyl 2-(N-Boc-amino)-5-oxo-5-phenyl-L-pentanoate (2)***

3g Boc-*L*-Pyr benzyl ester **1** (9.4mmol) was dissolved in 20mL dry THF. To this solution was added 1.1 eq. PhLi (10.34mmol, 5.75mL 1.8M solution) at -78°C. The reaction was allowed to reach -40°C. After further reaction for 2 hours at -40°C, the reaction was quenched by addition of a saturated solution of ammonium chloride. To the solution was added 50mL EtOAc and 50mL water. The organic layer was washed with 10% $KHSO_4$, 6% $NaHCO_3$ and brine. The organic layer was evaporated under reduced pressure and the resulting oil (which solidifies upon standing) was purified by column chromatography (Merck kieselgel 60) using petroleumether(3)/EtOAc(1) as eluent. Benzyl 2-(N-Boc-amino)-5-oxo-5-phenyl-*L*-pentanoate **2** was obtained as a white powder. *Yield:* 2.87g (7.24mmol, 77%) ; *TLC:* :$R_f$ = 0.62 (petroleum ether(3)/EtOAc(1)) ; *m.p.: 72-74°C* ; *ESP/MS (m/z, % RA):* 398($M^+$+1, 100), 342(100), 298(25) ; *NMR (250MHz, $CDCl_3$)* : 7.9-7.2(m, 10H, $H_{arom}$), 5.15(s, 2H, $OCH_2Ph$), 4.4(m, 1H, $H_\alpha$), 3.1-2.9(m, 2H, $H_\gamma$, $H_{\gamma'}$), 2.5-2.3(m, 2H, $H_\beta$, $H_{\beta'}$), 1.4(s, 9H, t-Bu).

### *Cis-5-phenyl-L-proline* (4)

Benzyl 2-(Boc-amino)-5-oxo-5-phenyl-*L*-pentanoate 2 (1g, 2.5mmol) was dissolved in 30mL $CH_2Cl_2$. To this solution was added 10mL TFA. The reaction was allowed to proceed at room temperature for 30 minutes. After evaporation of all solvents, the remaining oil was dried overnight in a dessicator.

The crude 2-phenylpyrroline-5-carboxylic benzyl ester (TFA-salt) 3 was dissolved in 30mL dry MeOH. To this solution was added 10% Pd/C (3mg/mmol). The reaction flask was filled with $H_2$ (4 atm.) in a Parr apparatus and the reaction was continued for 3 hours. The catalyst was filtered off and the solution was evaporated. The resulting oil was crystallized from MeOH/diisopropyl ether. *Cis*-5-phenylproline TFA-salt was obtained as a white, hygroscopic powder. *Yield:* 495mg (1.6mmol, 65%) ; *TLC:* $R_f$ = 0.72 ($CH_3CN(4)/MeOH(1)/H_2O(1)$) ; *HPLC:* $R_t$=29.7 min, $\lambda$=215nm (t=0, 90%A; t=60, 100%B ; A=100%$H_2O$,0.1%TFA ; B=80%$H_2O$, 20%$CH_3CN$,0.1%TFA) ; *ESP/MS (m/z, % RA):* 192 (M+$^+$1, 100) ; *NMR (500MHz, DMSO):* 7.51-7.42(m, 5H, $H_{arom}$), 4.63(dd, 1H, $H_\delta$, J=11Hz, J=6.47Hz), 4.35(m, 1H, $H_\alpha$), 2.33-1.99(m, 4H, $H_\beta$'s, $H_\gamma$'s) ; *GCMS (Chirasil-Val):* $R_t$=54.7 min (trans) and 55.3 min (cis) (gradient: 80°-200°C, 2°/min). d.e.86% .

### *L-α-(3-Phenylpropyl)-glycine* (5) *from* (3).

200mg of crude *L*-2-phenylpyrroline-5-carboxylic benzyl ester TFA-salt 3 (0.51mmol), prepared as described above, was dissolved in 15mL MeOH and 2mL water. To this solution was added 10% Pd/C (50mg/mmol). The reaction flask was filled with $H_2$ (4 atm.) and the reaction was continued for 8 hours. The catalyst was filtered off and the solution was evaporated. An analytical sample was purified by RP-HPLC and characterized. *L*-α-(3-Phenylpropyl)-glycine 5 (TFA-salt) was obtained as a white, hygroscopic powder. *Yield:* 133mg (0.43mmol, 85%) ; *TLC:* $R_f$ = 0.76 ($CH_3CN(4)/MeOH(1)/H_2O(1)$) ; *HPLC:* $R_t$=22.9 min, $\lambda$=215nm (t=0, 90%A; t=60,100%B ; A=100%$H_2O$,0.1%TFA ; B=80%$H_2O$, 20%$CH_3CN$,0.1%TFA) ; *ESP/MS (m/z, %RA):* 194($M^+$+1, 100) ; *NMR (500MHz, DMSO):* 7.29-7.16(m, 5H, $H_{arom}$), 3.84(t, 1H, $H_\alpha$, J=5.8Hz), 2.60(t, 2H, $PhCH_2$, J=7Hz), 1.78-1.61(m, 4H, $H_\beta$'s, $H_\gamma$'s) ; *GCMS (Chirasil-Val column):* $R_t$= 26.0 min (D) and 26.3 min (L) (gradient: 80°-200°C, 5°/min). e.e = 98% .

### *L-α-(3-Phenylpropyl)-glycine* (5) *from* (4).

100mg cis-5-phenyl-L-proline TFA-salt 4 (0.33mmol) was dissolved in 10mL MeOH and 1mL water. To this solution was added 10% Pd/C (50mg/mmol). The reaction flask was filled with hydrogen (4 atm.) and the reaction mixture was shaken for 8 hours. The catalyst was filtered off and the solvent was evaporated : 5 (TFA) salt was obtained as a white hygroscopic powder. *Yield :* 86mg (0.28mmol, 85%).

### *Benzyl Boc-trans-4-benzyl-L-pyroglutamate* (6)

2g benzyl Boc-*L*-pyroglutamate 1 (6.26mmol) was dissolved in 40mL anhydrous THF and the solution was cooled to -78°C under inert atmosphere. LiHMDS (1.1 eq, 6.9mmol, 6.9mL 1N solution) was slowly added at -78°C and the enolisation was continued for 1 hour. Benzyl bromide (1.1 eq, 6.9mmol, 810μL) was added. After 2 hours at -78°C, the reaction was quenched with a saturated solution of $NH_4Cl$. After 30 minutes of stirring, water (30mL) was added. The solution was extracted with three portions of EtOAc and washed with $KHSO_4$ (10%), brine and water. After drying over $MgSO_4$, the organic layer was evaporated to yield a light yellow oil. This oil was purified by silicagel column chromatography (Merck kieselgel 60) using petroleumether(3)/EtOAc(1) as eluent. The purified benzyl Boc-*trans*-4-benzyl-*L*-pyroglutamate was recrystallized from $Et_2O$ and was finally obtained as a white powder. *Yield:* 1.97g (4.8mmol, 77%) ; *TLC:* $R_f$ = 0.63 (petroleumether(3)/EtOAc(1)) ; *m.p.:* 119-121°C ; *ESP (m/z, % RA):* 410($M^+$+1,20), 310(100) ; *NMR (250MHz, $CDCl_3$):* 7.4-7.1(m, 10H, $H_{arom}$), 5.15(s, 2H, $OCH_2Ph$), 4.5(dd, $H_\alpha$, J=8.33Hz, 2.98Hz), 3.25(dd, 1H, PhCH-, J=13.5Hz, 3.9Hz), 2.85(m, 1H, $H_\gamma$), 2.6(dd, 1H, PhCH-, J=13.5Hz, J=9.5Hz), 2.09(m, 1H, $H_\beta$), 1.95(m, 1H, $H_{\beta'}$), 1.4(s, 9H, tBu) ; d.e.>95% (according to 500MHz NMR).

***Benzyl 2-(Boc-amino)-trans-4-benzyl-5-oxo-5-phenyl-L-pentanoate (7)***

1.5g benzyl Boc-*trans*-4-benzyl-*L*-pyroglutamate **6** (3.67mmol) was dissolved in 10mL dry THF and 1.1 eq. PhLi (4.03mmol, 2.24mL 1.8M solution) was added at -78°C. The mixture was allowed to attain -40°C. After stirring for two hours at -40°C, 30ml of a saturated $NH_4Cl$ solution was added. This mixture was stirred for 30 minutes and then extracted three times with EtOAc. The organic layer was washed with water and brine. After evaporation of the organic layer, the crude oil was finally purified by silicagel column chromatography (Merck kieselgel 60) using petroleumether (9)/EtOAc(1) as eluent. Benzyl *trans*-4-benzyl-5-oxo-5-phenyl-*L*-pentanoate 7 was obtained as a colourless oil. *Yield:* 1.16g (2.38mmol, 65% ) ; *TLC :* $R_f$ = 0.61 (petroleumether(3) /EtOAc(1)) ; *ESP/MS (m/z, % RA) :* 488($M^+$+1, 30), 388(100) ; *NMR (250MHz, $CDCl_3$):* 7.5-6.9 (m, 15H, $H_{arom}$), 5.1 (1H, $NH_{amide}$), 5.0 (s, 2H, O-$CH_2$Ph), 4.4 (dd, 1H, $H_\alpha$, J=7.8Hz, J=3.0Hz), 3.3-3.1 (dd, 1H, PhCH-, J=13.8Hz, J=4.0Hz), 3.1-2.95 (m, 1H, $H_\gamma$), 2.6 (dd, 1H, -CHPh, J=13.8Hz, J=4.3Hz), 2.5(m, 1H, $H_\beta$), 1.8(m, 1H, $H_{\beta'}$), 1.2(s, 9H, t-butyl).

***Trans-4-benzyl-cis-5-phenyl-L-proline (8)***

500mg benzyl 2-(Boc-amino)-*trans*-4-benzyl-5-oxo-5-phenyl-*L*-pentanoate 7 (1.03mmol) was dissolved in 20mL $CH_2Cl_2$(2)/TFA(1) and the solution was stirred for 30 minutes. After evaporation of the solvent, the crude pyrroline was dissolved in 25mL MeOH. To the clear solution was added 3mg 10% Pd/C (i.e. 3mg/mmol). The reaction flask was filled with $H_2$ (4 atm) and the hydrogenation was continued for 5 hours. The catalyst was filtered off and the solvents were evaporated. The remaining residue was dried in a dessicator under NaOH pellets. Purification by reversed-phase HPLC afforded the desired *trans*-4-benzyl-*cis*-5-phenyl-*L*-proline TFA-salt as a white powder. *Yield:* 223mg (0.56mmol, 55%) ; *TLC:* $R_f$=0.67 ($CH_3CN$(4)/MeOH(1) /$H_2O$(1)) ; *HPLC:* $R_t$=33.8 min, $\lambda$=215nm (t=0, 90%A; t=60,100%B ; A=100%$H_2O$,0.1%TFA ; B=80%$H_2O$, 20%$CH_3CN$,0.1%TFA) ; *ESP/MS (m/z, % RA):* 282($M^+$+1, 100) ; *NMR (500MHz, DMSO):* 7.33-7.05(10H, $H_{arom}$), 4.93(d, 1H, $H_\delta$,J=7.87Hz), 4.48 (dd, 1H,$H_\alpha$, J=9.13Hz, J=9.02Hz), 2.93(m, 1H, $H_g$), 2.32(dd, 1H, PhCH-, J=13.35Hz, J=3.63Hz), 2.23(dd, 1H, $H_{\beta'}$, J=21Hz, J=9.95Hz), 2.07(dd, 1H, PhCH-, J=12.56Hz, J=12.49Hz), 1.96(m, 1H, $H_\beta$) ; d.e 80% (determined by NMR).

***L-α-(2-Benzyl-3-phenylpropyl)-glycine* (9)**

100mg *trans*-4-benzyl-*cis*-5-phenyl-*L*-proline TFA-salt **8** (0.25mmol) was dissolved in 15mL MeOH and 2mL water. To this solution was added 16mg 10% Pd/C. The reaction flask was filled with $H_2$ (4 atm) in a Parr apparatus and the reaction was continued for 18 hours at room temperature. MeOH was evaporated and an analytical sample was purified by HPLC for characterization. *L*-α-(2-Benzyl-3-phenylpropyl)-glycine was obtained as a white hygroscopic powder. *Yield:* 65mg (0.16mmol, 65%) ; *TLC:* $R_f$=0.75 ($CH_3CN$(4)/MeOH(1)/$H_2O$(1)) ; *HPLC:* $R_t$=27.8min, λ=215nm (t=0, 90%A; t=60,100%B ; A=100%$H_2O$,0.1%TFA ; B=80%$H_2O$, 20%$CH_3CN$,0.1%TFA) ; *ESP/MS (m/z, % RA) :* 284($M^+$+1, 100) ; *NMR (500MHz, DMSO):* 8.38(m, 10H, $H_{arom}$), 3.95(m, 1H, $H_\alpha$), 2.6-2.4(m, 4H, 2xPh$CH_2$-), 1.8-1.5(m, 3H, $H_\beta$, $H_{\beta'}$, $H_\gamma$) ; *GCMS (Chirasil-Val column):* $R_t$=62.7 minutes (gradient: 80°-200°C, 5°/min). e.e 98% .

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28. Note that both cis- and trans-diastereomers of **4** (d.e. 86%) lead to **5** in an e.e. of 98%.

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