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Synthesis of Novel Proline and γ-Lactam Derivatives as Non-Peptide Mimics of Somatostatin / Sandostatin®†

Dominique Damour, Frédéric Herman, Richard Labaudinière, Guy Pantel, Marc Vuilhorgne, and Serge Mignani. [&,*]

Rhône-Poulenc Rorer S.A. Centre de Recherche de Vitry-Alfortville, 13 Quai Jules Guesde BP 14, 94403 Vitry-sur-Seine Cedex, France

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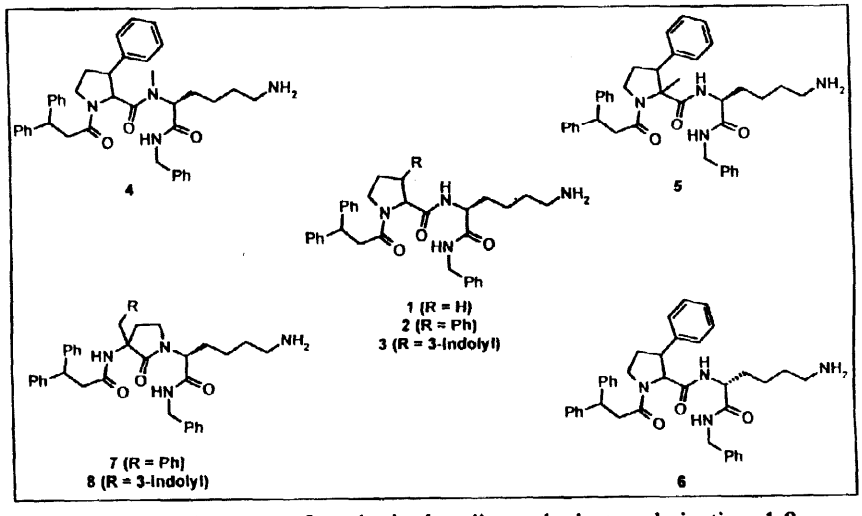
Abstract - Original proline or γ-lactam derivatives bearing either an aryl group such as a phenyl or a 3-indolyl in position 3 of the proline moiety or on the 3-methyl chain of the γ-lactam skeleton were prepared as non-peptide mimics of Somatostatin / Sandostatin®.

INTRODUCTION

Recently we reported on novel sugar-based [1a] and on spirocyclic lactam derivatives [1b] as non-peptide mimics of Somatostatin / Sandostatin®. Somatostatin-14 (SRIF-14, Figure 1) is a cyclic tetradecapeptide which is not used in clinical therapy due to its too short plasma half-life.[2] Extensive investigations of the structure-activity relationships of the SRIF-14 peptide showed that the sequence Phe[7]-Trp[8]-Lys[9]-Thr[10] was the most relevant for the biological activity. [3] Chemical derivation of SRIF-14 led to preparation of stable somatostatin analogues [4ab] such as Sandostatin® (Figure 1) which was the first drug to be marketed.[5] As part of our program based on conformational studies of Sandostatin® - using ^{1}H-NMR and molecular modeling [1a] - we focused our efforts on the synthesis of ambiscalemic [6] 3-functionalized-proline [7a] and γ-lactam [7b] derivatives **1-8** (Scheme1) as non-peptide mimics of Somatostatin / Sandostatin®.

This paper reports the convenient synthesis of proline and γ-lactam as non-peptide mimics of Sandostatin® **2**, **3**, **7** and **8**. In addition, with the aim to complete structure-activity relationships, the proline derivatives **1**, **4-6** were also synthetized. In most cases, these compounds have been prepared as enantiomerically pure *cis*- and *trans*-diastereoisomers.[8]



Scheme 1 : Structure of synthesized proline and γ-lactam derivatives **1-8**.

[&] Serge Mignani : Fax : 33 (1) 55 71 80 14, e-mail : serge.mignani@rp-rorer.fr

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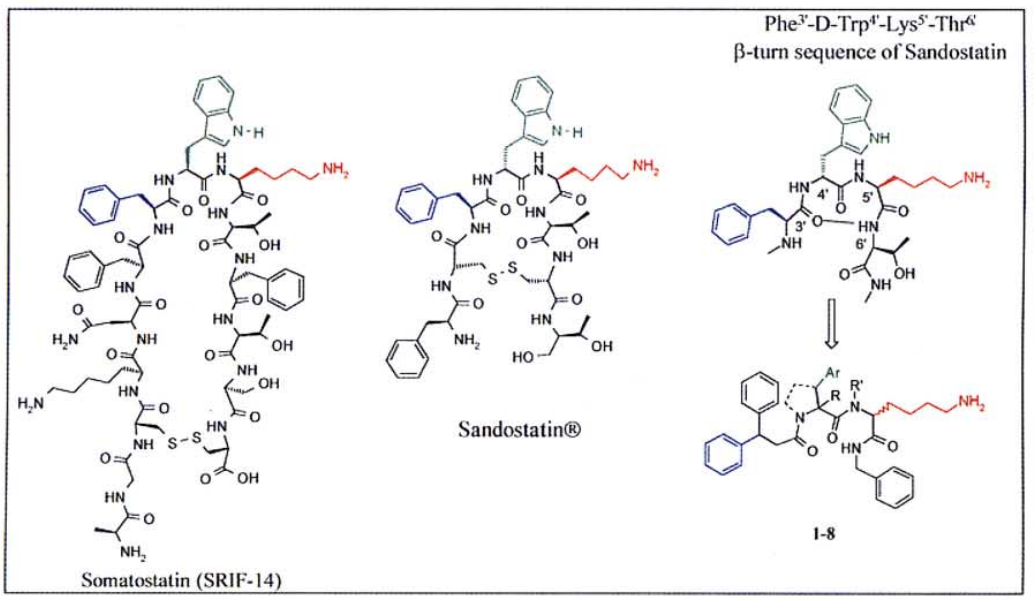


Figure 1: Chemical structure of SRIF-14, Sandostatin® and **1-8**.

CHEMISTRY

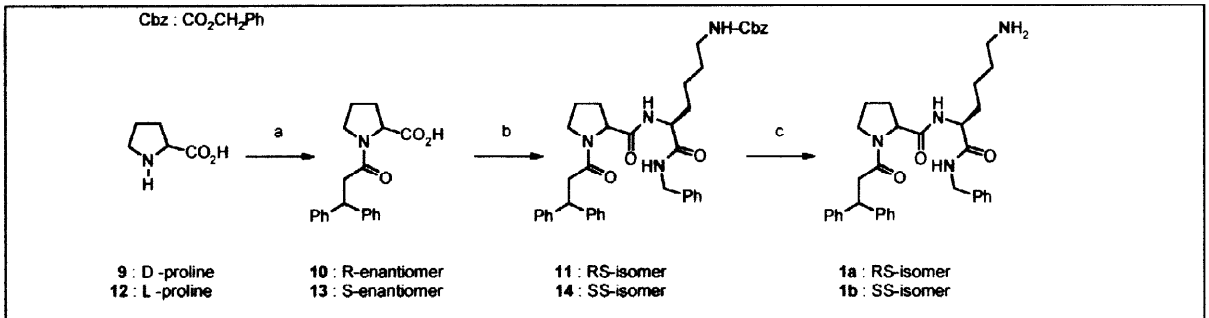
Synthesis of compounds 1-3 :

Compounds **1a** (RS-isomer) and **1b** (SS-isomer) were prepared respectively from the commercially available D- and L-proline (Scheme 2). As outlined in the next following Schemes, we prepared the 3-functionalized-proline derivatives **18** ***cis***, **18** ***trans***, **33** ***cis*** and **33** ***trans*** as precursors of compounds **2** and **3** (*cis*-isomers, form A and B[8]and *trans*-isomers, form A and B[8]) (Schemes 3-6).

a) Synthesis of 1a and 1b : the targeted compounds **1a** (RS-isomer) and **1b** (SS-isomer) were obtained as outlined in Scheme 2. *N*-acylation of commercially available D-proline **9** and L-proline **12** with 3,3-diphenylpropionyl chloride was followed by condensation of H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ [9] in the presence of EDCI/HOBT as a coupling agent to provide the requisite intermediates **11** and **14**. Then *N*-Bz deprotection using Pd/C (10%) with cyclohexene, afforded **1a** and **1b**.

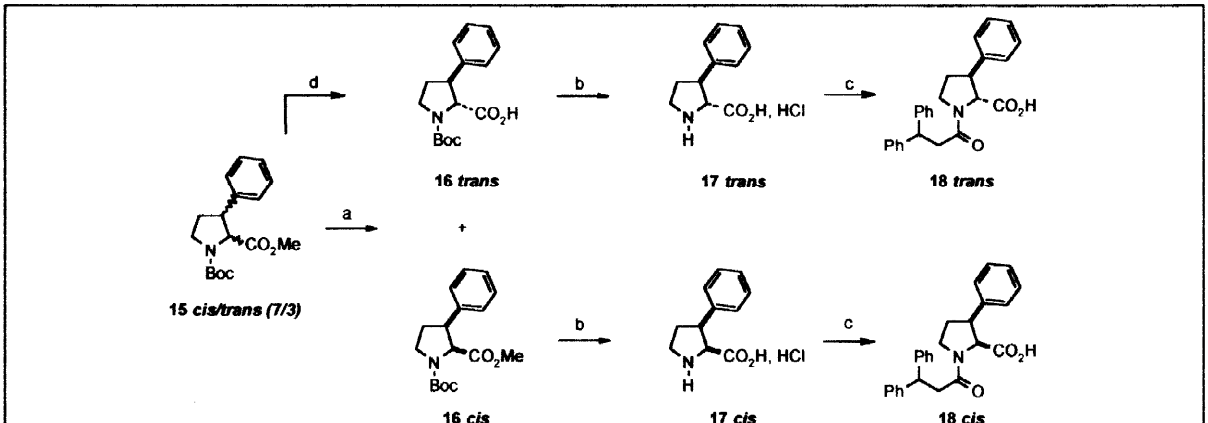
b) Synthesis of 2c, 2c', 2t and 2t' : as shown in Scheme 3, the preparation of the precursors **18** ***cis*** and **18** ***trans*** started from 3-phenyl-proline methyl ester **15** (*cis*/*trans* mixture : 7/3) which was prepared *via* 3-step synthesis from *trans*-cinnamaldehyde and diethyl acetamidomalonate with 59% overall yield based on a literature route[10] (~50g scale). Preferential alkaline saponification of **15** (0.5N NaOH) gave a clean separation into *cis*-3-phenyl-proline methyl ester **16** ***cis*** and *trans*-3-phenyl-proline **16** ***trans***. *N*-Boc deprotection and hydrolysis of **16** ***cis*** and **16** ***trans*** with 6N HCl gave *cis*-3-phenyl-proline **17** ***cis*** and *trans*-3-phenyl-proline **17** ***trans***. Then, condensation of 3,3-diphenylpropionyl chloride with **17** ***cis*** and **17** ***trans*** under standard experimental conditions afforded **18** ***cis*** and **18** ***trans***. Note that the action of excess of sodium methylate (1.2 eq.) at reflux with **15**, led to **16** ***trans***.

Compounds **2c** and **2t** were obtained under two isolated forms (A and B) as depicted in Schemes 4 and 5. The reaction of *cis*-3-phenyl-proline **18** ***cis*** with H_2N-L-Lys(ε- Cbz)-CO_2Me [11] in the presence of EDCI/HOBT as a coupling agent followed by flash chromatography purification furnished **19** (form A) and **19** (form B). Finally, the desired compounds **2c** (form A) and **2c'** (form B) were obtained by saponification (0.5N NaOH), condensation of benzylamine under standard experimental reaction conditions, and *N*-Bz deprotection reaction (HCO_2H, Pd/C).



Reagents and conditions : ***a)*** **9** or **12** (1eq.), Ph_2CHCH_2COCl (1eq.), Et_3N (~2eq.), CH_2Cl_2, 0°C to rt, 18h, **10** (18%); **13** (35%) ***b)*** **10** or **13** (1eq.), H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ (1eq.), HOBT (1eq.), EDCI (1eq.), CH_2Cl_2, rt, 18h, **11** (61%); **14** (79%) ***c)*** **11** or **14**, cyclohexene, Pd/C (10%), EtOH, reflux 2h, **1a** (19%); **1b** (41%).

Scheme 2 : Synthesis of proline derivatives **1a** and **1b**.

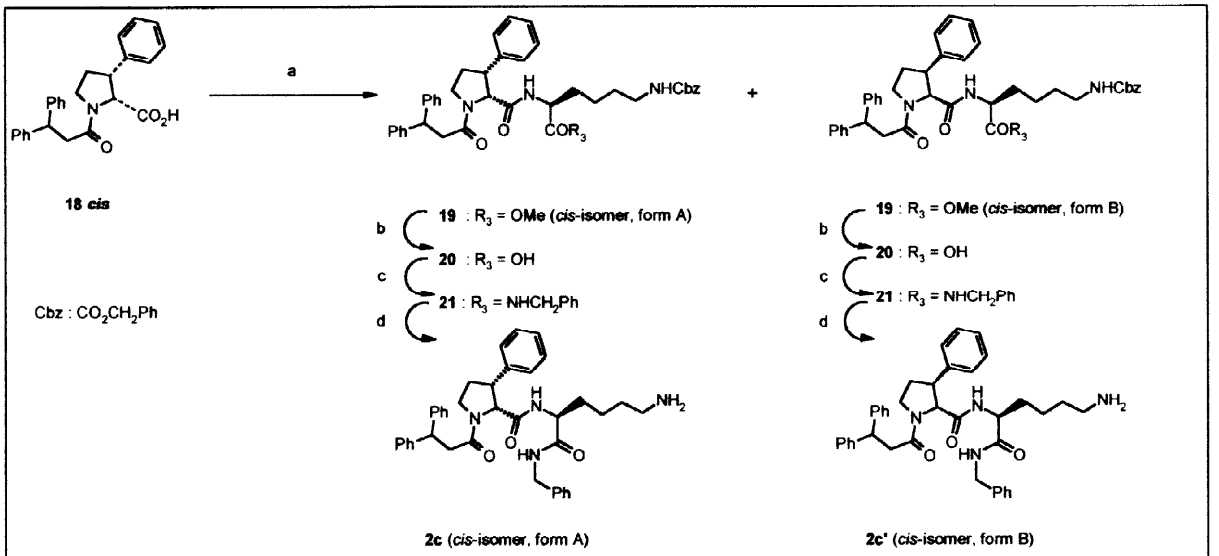


Reagents and conditions: ***a)*** 0.5N NaOH, THF, rt, 20h, **16** ***cis*** (63%), acidification of the aq. phase with citric acid (pH 4) gave **16** ***trans*** (21%) ***b)*** 6N HCl/AcOH, reflux, 3h, **17** ***cis*** (68%), **17** ***trans*** (75%) ***c)*** Ph_2CHCH_2COCl (1eq.), Na_2CO_3 (10%), 0°C to rt, 12h, **18** ***cis*** (87%), **18** ***trans*** (89%) ***d)*** MeONa (1.2eq.), MeOH, reflux, 2h, **16** ***trans*** (65%).

Scheme 3: Synthesis of *cis*- and *trans*-3-phenyl-proline derivatives **18**.

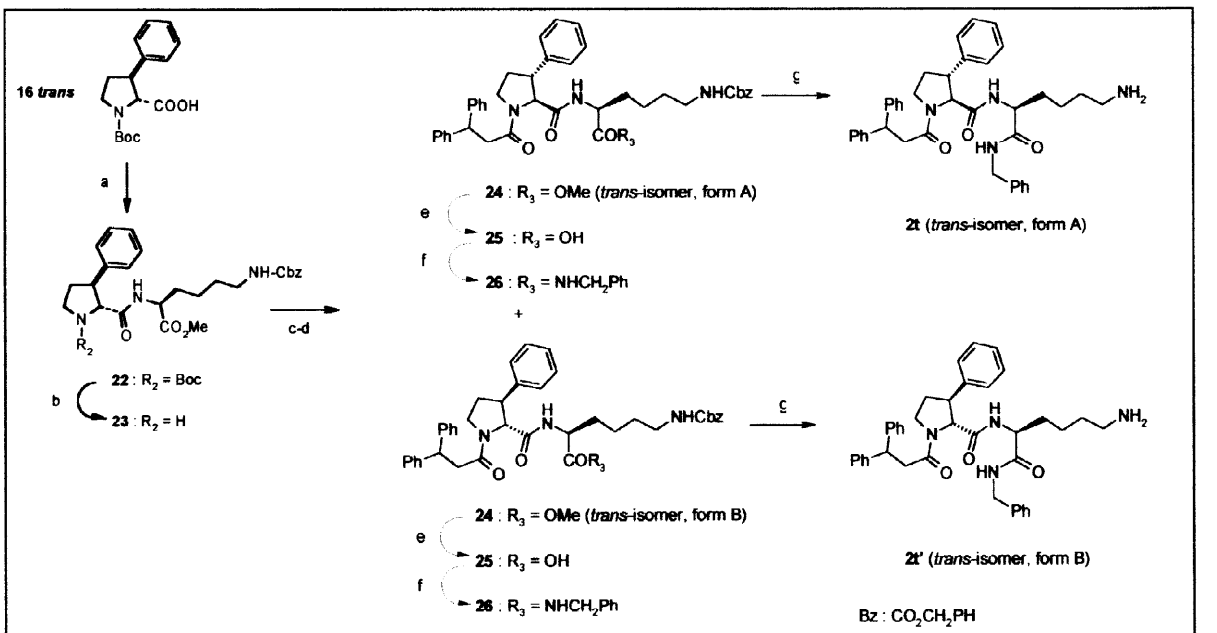
In order to obtain the corresponding *trans*-isomers **2t** and **2t'**, the preceding synthetic pathway has been lightly modified as illustrated in Scheme 5. The *trans-N*-Boc-3-phenyl-proline **16** ***trans*** was first quantitatively converted into the amide **22** as with H_2N-L-Lys(ε-Cbz)-CO_2Me [11] in the presence of EDCI/HOBT as coupling agent. Then, *N*-Boc deprotection in acidic medium (CF_3CO_2H), condensation of 3,3-diphenylpropionyl chloride and flash chromatography purification afforded **24** (form A) and **24** (form B). Finally, the desired compounds **2t** (form A) and **2t'** (form B) were obtained as before by saponification, condensation of benzylamine, and *N*-Cbz deprotection reaction.

c) Synthesis of 3c, 3c', 3t and 3t': original *cis*- and *trans*-3-(3-indolyl)-prolines **33** ***cis*** and **33** ***trans*** were synthesized in a 7-step synthesis from commercially available indole-3-carboxaldehyde **27** as shown in Scheme 6. According to the procedure described previously by us [12] : *i)* treatment of **27** with benzenesulfonyl chloride, *ii)* Wittig-olefination reaction giving **29**,[13] *iii)* [3+2] cycloaddition reaction with *N*-ethoxycarbonyl-diethoxycarbonylazomethine ylide generated *in situ* from diethyl (*N*-methoxymethyl-*N*-ethoxycarbonyl)aminomethyl malonate [14], *iv)* decarboxylation reaction with HBr affording **31** as a mixture of *cis* and *trans* isomers in a 7/3 ratio (^{1}H-NMR). Then, esterification of the acidic function of **31** *via* standard protocols and separation of each diastereoisomer by flash chromatography on silica gel provided pure 3-(3-indolyl)-proline derivatives **32** ***cis*** and **32** ***trans***. Finally, the desired proline derivatives **33** ***cis*** and **33** ***trans***



Reagents and conditions : ***a)*** H_2N-L-Lys(ε-Cbz)-CO_2Me (1eq.), HOBT (1eq.), EDCI (1eq.), CH_2Cl_2, rt, 0.5h then Et_3N (1eq.), rt, 18h, form A/form B : 1/1(^{1}H-NMR, 250MHz, DMSO-*d6*), then flash chromatography on silica gel (AcOEt/cyclohexane 45:55), **19** (form A): 10%, **19** (form B): 15% ***b)*** 0.5N NaOH, THF, rt, 18h, **20** form A : 90%, **20** form B : 95% ***c)*** EDCI (1eq.), HOBT (1eq.), H_2N-CH_2Ph (1eq.), CH_2Cl_2, **21** form A : 98%, **21** form B : 93% ***d)*** Pd(C) (5%), HCO_2H/MeOH 96:4, rt, 20h, **2c** (form A), oxalate salt : 24%, **2c'**(form B), oxalate salt: 53%.

Scheme 4 : Synthesis of 3-phenyl-proline derivatives **2c** and **2c'** (*cis*-isomers).



Reagents and conditions : ***a)*** H_2N-L-Lys(ε-Cbz)-CO_2Me (1eq.), HOBT (1eq.), EDCI (1eq.), CH_2Cl_2, rt, 0.5h then Et_3N (1eq.), rt, 18h, 100%, form A/form B 1/1(^{1}H-NMR, 250MHz, DMSO-*d6*) ***b)*** CF_3CO_2H, $CHCl_3$, rt, 5h, 100%, form A/form B 1/1 (^{1}H-NMR, 300MHz, DMSO-*d6*) ***c)*** Ph_2CHCH_2COCl (1eq.), Na_2CO_3 (10%) (1eq.), dioxane, rt, 18h, 54% ***d)*** flash chromatography on silica gel (AcOEt:cyclohexane 45:55), **24** form A : 15%, **24** form B : 23% ***e)*** 0.5N NaOH, THF, rt, 18h, **25** form A : 80%, **25** form B : 62% ***f)*** EDCI (1eq.), HOBT (1eq.), H_2N-CH_2Ph (1eq.), CH_2Cl_2, **26** form A : 87%, **26** form B : 97% ***g)*** Pd(C) (5%), HCO_2H/MeOH 96:4, rt, 20h, **2t** (form A), oxalate salt: 43%, **2t'** (form B), oxalate salt: 61%.

Scheme 5 : Synthesis of 3-phenyl-proline derivatives **2t** and **2t'** (*trans*-isomers).

were obtained with good overall yields by condensation of 3,3-diphenylpropionic acid in presence of BOP as a coupling agent followed by saponification reaction using NaOH/MeOH. In order to shorten the synthesis, we have directly condensed the precursors **33** ***cis*** and **33** ***trans*** with H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$[9] in the presence of BOP as a coupling agent. Then, separation of the two diastereoisomers (form A and form B) by preparative HPLC, and finally *N*-Cbz deprotection provided **3c** (form A), **3c'**(form B), **3t** (form A) and **3t'**(form B).

Synthesis of compounds 4 and 6 :

The proline derivatives **4** and **6** in which the L-lysine has been replaced by *N*-methyl-L-lysine or by D-lysine has been prepared using the same synthetic strategies as previously.

a) synthesis of 4c, 4c', 4t and 4t' : *via* the sequence shown in Scheme 7, **35** ***trans*** (form A and form B) were readily prepared from *trans*-3-phenyl-proline derivative **18** ***trans*** by condensation of MeNH-L-Lys-(ε-Cbz)CO_2Me[11] in presence of bromotris(dimethylamino)phophonium hexafluorophosphate as coupling agent followed by chromatographic purification affording pure **35** (form A) and **35** (form B). Then, treating **35** (form A and form B) with aqueous sodium hydroxide, followed by condensation of benzylamine and finally deprotection of the benzylcarbamate moiety yielded **4t** (form A) and **4t'** (form B). Compounds **4c** (form A) and **4c'** (form B) were prepared according to a similar synthetic pathway.

b) Synthesis of 6c, 6c', 6t and 6t': our synthesis of **6c** and **6t** (form A and form B) started from proline derivatives **18** ***cis*** and **18** ***trans*** as outlined in Scheme 8. This synthesis followed the same synthetic pathway than the preparation of **2c** (see Scheme 4) with H_2N-D-Lys-(ε-Cbz)-CO_2Me[11] in place of H_2N-L-Lys-(ε-Cbz)-CO_2Me.

Synthesis of compounds 5 :

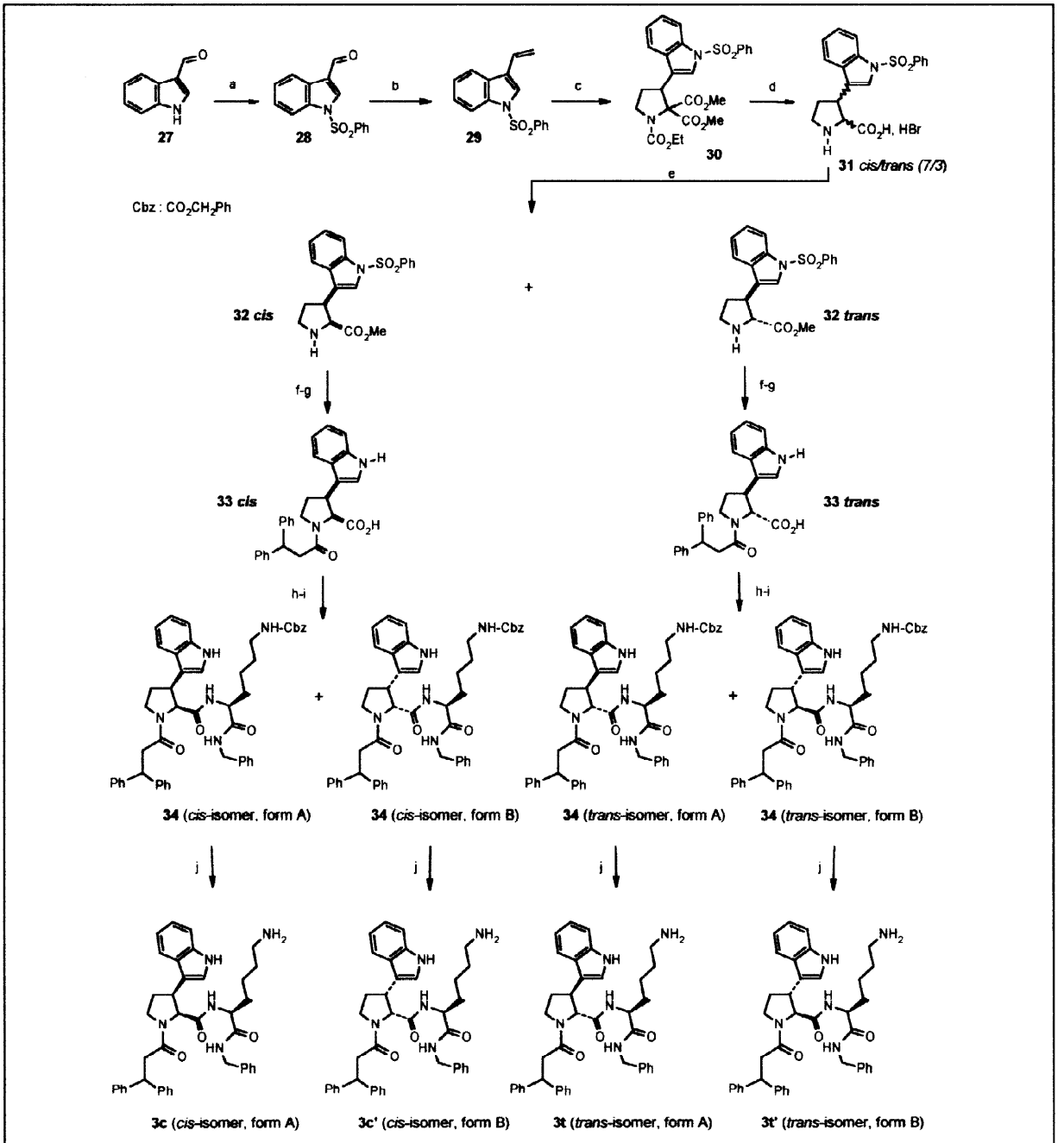
As outlined in Scheme 9 (Pathway A), our route to the *trans*-proline derivative **5t** bearing a methyl group in the α-position, using *trans*-2-methyl-3-phenyl-proline derivative **41** ***trans*** as a key intermediate. This synthesis required the condensation of D,L-*N*-acetyl-alanine ethyl ester **38** with *trans*-cinnamaldehyde according to the procedure previously described [10] affording new hydroxylactam **39** as a mixture of two major isomers in a 6/4 ratio (^{1}H-NMR), followed by quantitative acid-catalyzed silane reduction and finally diastereoselective saponification of **40** (1N NaOH) giving pure **41** ***trans*** and **42** ***cis***. Conversion of the *trans*-proline derivative **41** ***trans*** to **43** ***trans*** was achieved by acidic hydrolysis with aqueous (6N HCl) at 100°C. Then, condensation of 3,3-diphenylpropionyl chloride followed by H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ [9] gave *trans*-isomer **45** as a mixture of form A and form B in a 6/4 ratio (^{1}H-NMR). In spite of numerous attempts we were unable to separate both isomers. Finally, N-Bz deprotection reaction furnished **5t** as a mixture of diastereoisomers form A and form B in a 6/4 ratio (^{1}H-NMR).

Compound **5c** (form A and B mixture) was synthesized from **46** as depicted in Scheme 9 (Pathway B). Thus, 2-dealkoxycarbonylation of **46** followed by esterification reaction afforded the *cis*-proline ethyl ester derivative **47** which was then *N*-protected with ethylchloroformate giving **48**. Then alkylation reaction of **48** using lithium bis(trimethylsilyl)amide as base in presence of a large excess of iodomethane (~20 times) gave **49** as a 8/2 mixture of *cis*-, *trans*-diastereoisomers which was used in the next step without further purification. Acidic hydrolysis (HBr) followed by condensation of 3,3-diphenylpropionyl chloride gave pure *cis*-proline derivative **51**. Finally, condensation of H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ [9] afforded **52** and deprotection of the benzylcarbamate moiety of **52** yielded **5c** as a 6/4 mixture of diastereoisomers (^{1}H-NMR).

The synthesis of 2-methyl-3-phenyl-proline **40** from **38** represent a generalisation of the condensation-cyclization reaction described by M. W. Holladay et al.[10] and us[1b] and open the way to various 2,3-disubstituted proline derivatives.

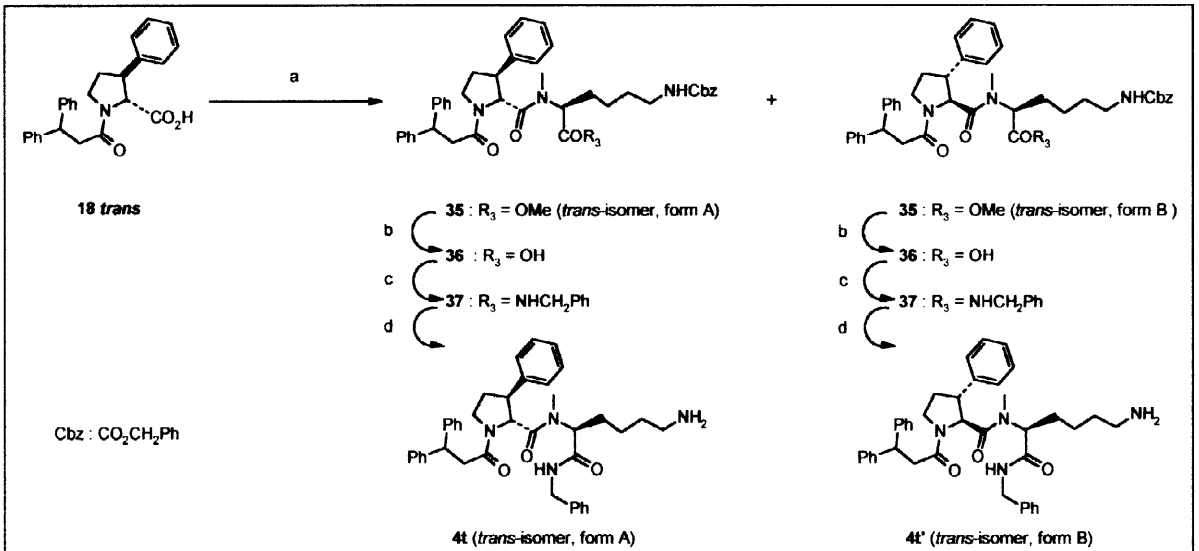
Synthesis of compounds 7 and 8 :

The synthesis of stereoisomers of γ-lactams **7** and **8** (form A and form B) was achieved starting from L-methionine methyl ester hydrochloride **53** as outlined in Scheme 10. Condensation of benzaldehyde, alkylation of the sodium or the lithium salt of *N*-benzylidene-methionine methyl esters **54** with benzyl bromide or gramine followed by an acidic workup gave **57** and **58**.

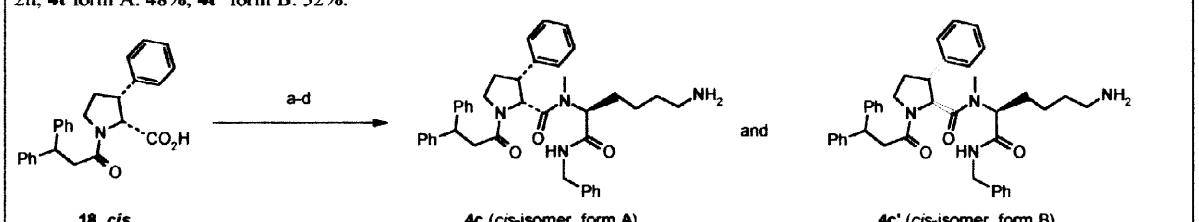


Reagents and conditions : ***a)*** $PhSO_2Cl$ (2 eq.), K_2CO_3, MEC, reflux, 2h, 86% ***b)*** n-BuLi (1.6M, 2eq.), DME, $Ph_3P^+CH_3Br^-$ (1.2eq.), -20°C to rt, 18h, 83% ***c)*** $MeOCH_2(EtOCO)NCH(CO_2Me)_2$ (1eq.), $TiCl_4$ (2eq.), TEA (1eq.), CH_2Cl_2, reflux, 1.5h, 70% ***d)*** HBr/AcOH (47%), reflux, 20h, 100% ***e)*** H_2SO_4 (95%), MeOH, reflux, 12h then flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5), **32** ***cis*** (40%), **32** ***trans*** (13%) ***f)*** $Ph_2CHCH_2CO_2H$ (1eq.), BOP (1eq.), TEA (1eq.), MeCN, 0°C, 1h then rt, 12h, 53-69% ***g)*** 3N NaOH, MeOH, reflux, 2h, **33** ***cis*** (65%), **33** ***trans*** (89%) ***h)*** H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ (1eq.), BOP (1eq.), TEA (2eq.), MeCN, rt, 12h, ***cis*** (92%), ***trans*** (84%) ***i)*** preparative HPLC (Porasil®/Waters) (AcOEt:cyclohexane:DEA:MeOH 30:63:5:2), **34** ***cis*** (form A): 30%, **34** ***cis*** (form B): 48%, **34** ***trans*** (form A): 49%, **34** ***trans*** (form B): 47% ***j)*** cyclohexene, Pd/C (10%), EtOH, reflux, 2h, **3c** (form A): 71%, **3c'** (form B): 19%, **3t** (form A): 90%, **3t'** (form B): 90%.

Scheme 6 : Synthesis of 3-(3-indolyl)-3-proline derivatives **3** (*cis*- and *trans*-isomers).

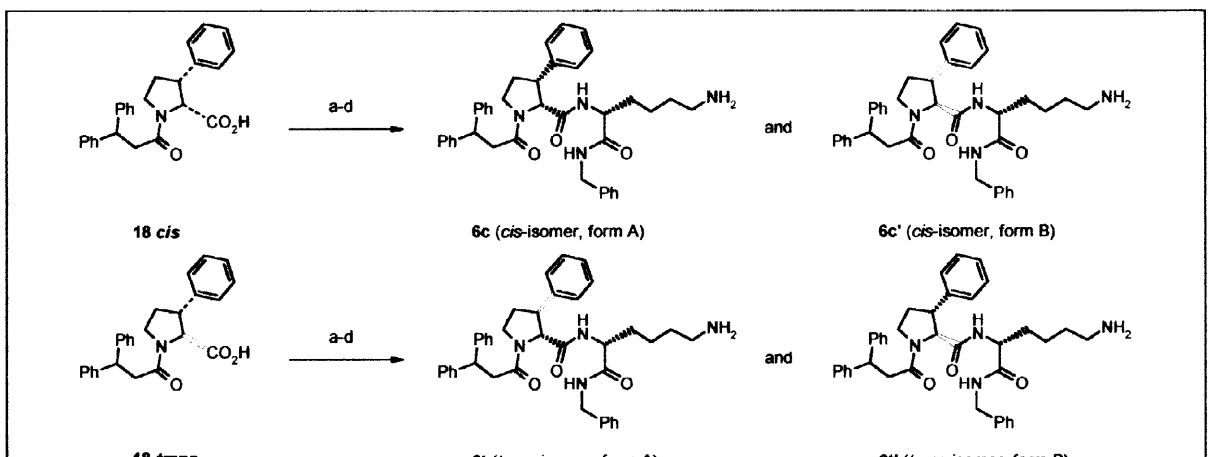


Reagents and conditions: ***a)*** MeNH-L-Lys(ε-Cbz)-CO_2Me (1.1eq.), *N,N*-diisopropylethylamine (1eq.), bromotris-(dimethylamino)-phosphonium hexafluorophosphate (1eq.), CH_2Cl_2, rt, 1h then flash chromatography on silica gel (toluene/DEA/EtOH 97.5:1.25:1.25), **35** form A: 48%, **35** form B: 52% ***b)*** 0.5N NaOH, THF, rt, 18h, **36** form A: 83%, **36** form B: 85% ***c)*** EDCI (1 eq.), HOBT (1 eq.), $PhCH_2NH_2$ (1eq.), CH_2Cl_2, rt, 18h, **37** form A: 98%, **37** form B: 83% ***d)*** cyclohexene, Pd/C (10%), EtOH, reflux, 2h, **4t** form A: 48%, **4t'** form B: 52%.



Reagents and conditions, idem than the preparation of **4t** : ***a)*** form A: 33%, form B: 44% ***b)*** form A: 39%, form B: 44% ***c)*** form A: 38%, form B: 64% ***d)*** **4c** form A: 35%, **4c'** form B: 23%.

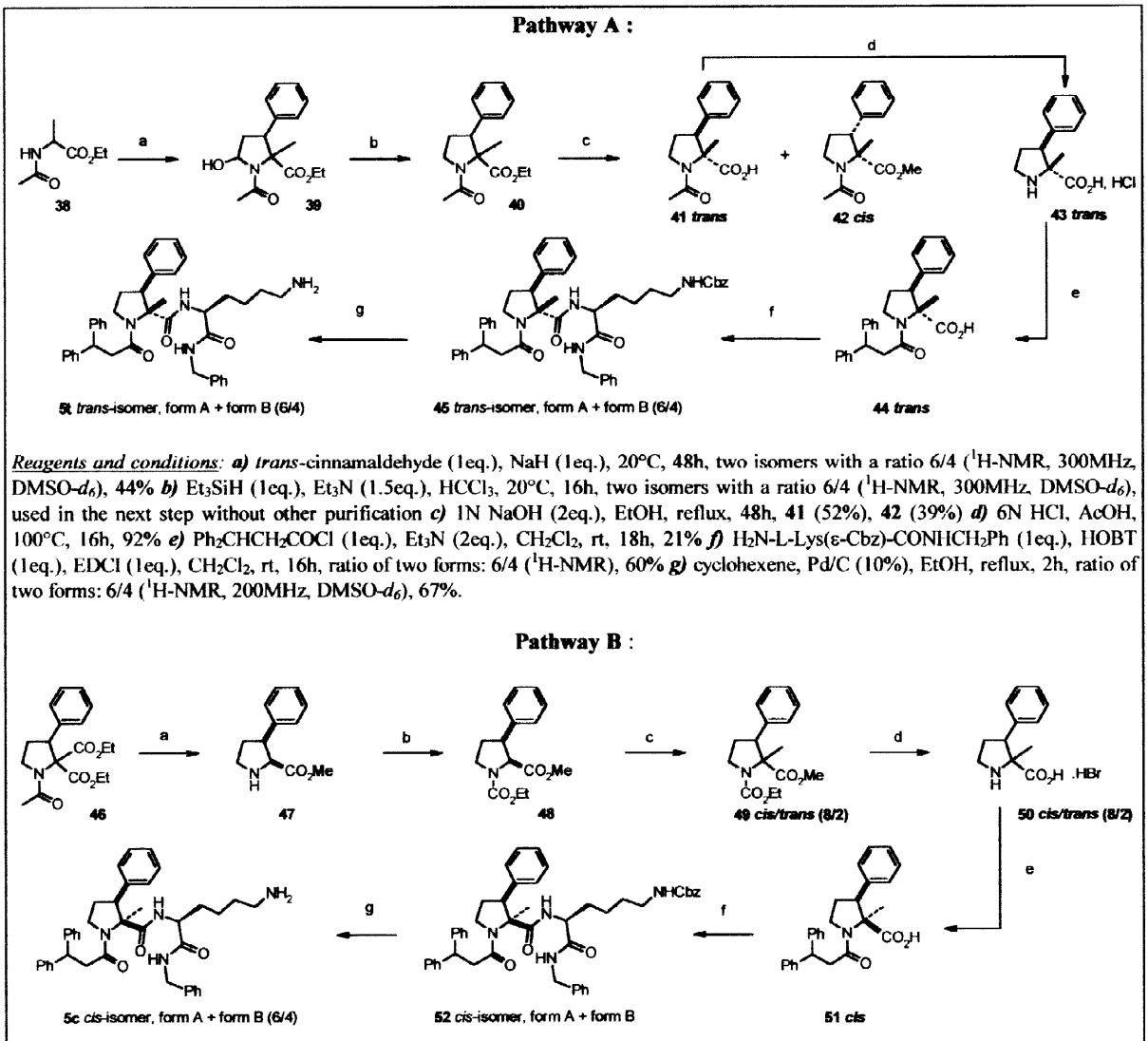
Scheme 7 : Synthesis of prolines derivatives **4** (*cis*- and *trans*-isomers).



Reagents and conditions : ***a)*** H_2N-D-Lys(ε-Cbz)-CO_2Me (1.1eq.), HOBT (1.1eq.),EDCI (1.1eq.), Et_3N (1.1eq.), CH_2Cl_2, rt, 18h then flash chromatography on silica gel (CH_2Cl_2:MeOH 99:1), *trans* series: form A: 23%, form B: 29%; *cis* series: form A: 43%, form B: 23% ***b)*** 0.5N NaOH, rt,12h, *trans* series: form A: 99%, form B: 70%; *cis* series: form A: 82%, form B: 55% ***c)*** EDCI (1eq.), HOBT (1eq.), H_2N-CH_2Ph (1eq.), CH_2Cl_2, *trans* series: form A: 81%, form B: 88%, *cis* series: form A: 82%, form B: 68% ***d)*** cyclohexene, Pd/C (10%), EtOH, reflux, 2h, **6c** (form A): 74%, **6c'** (form B): 73%, **6t** (form A): 78%, **6t'** (form B): 67%.

Scheme 8 : Synthesis of D-lysine derivatives **6** (*cis*- and *trans*-isomers).

The synthesis of **7a** (form A) and **7b** (form B) started by the protection of the amine **55** as the corresponding *N*-Boc derivative **59** followed by hydrolysis of the ester group to give **61**. Coupling of this acid with H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ [9] gave **63**, then pure diastereoisomeric methionine derivatives **65** (form A and form B) were easily separable by flash chromatography. Methylation on the sulphur of **65** (form A and form B) with an excess of iodomethane followed by action of NaH as base induced ring closure to give the γ-lactams **66**.[15]

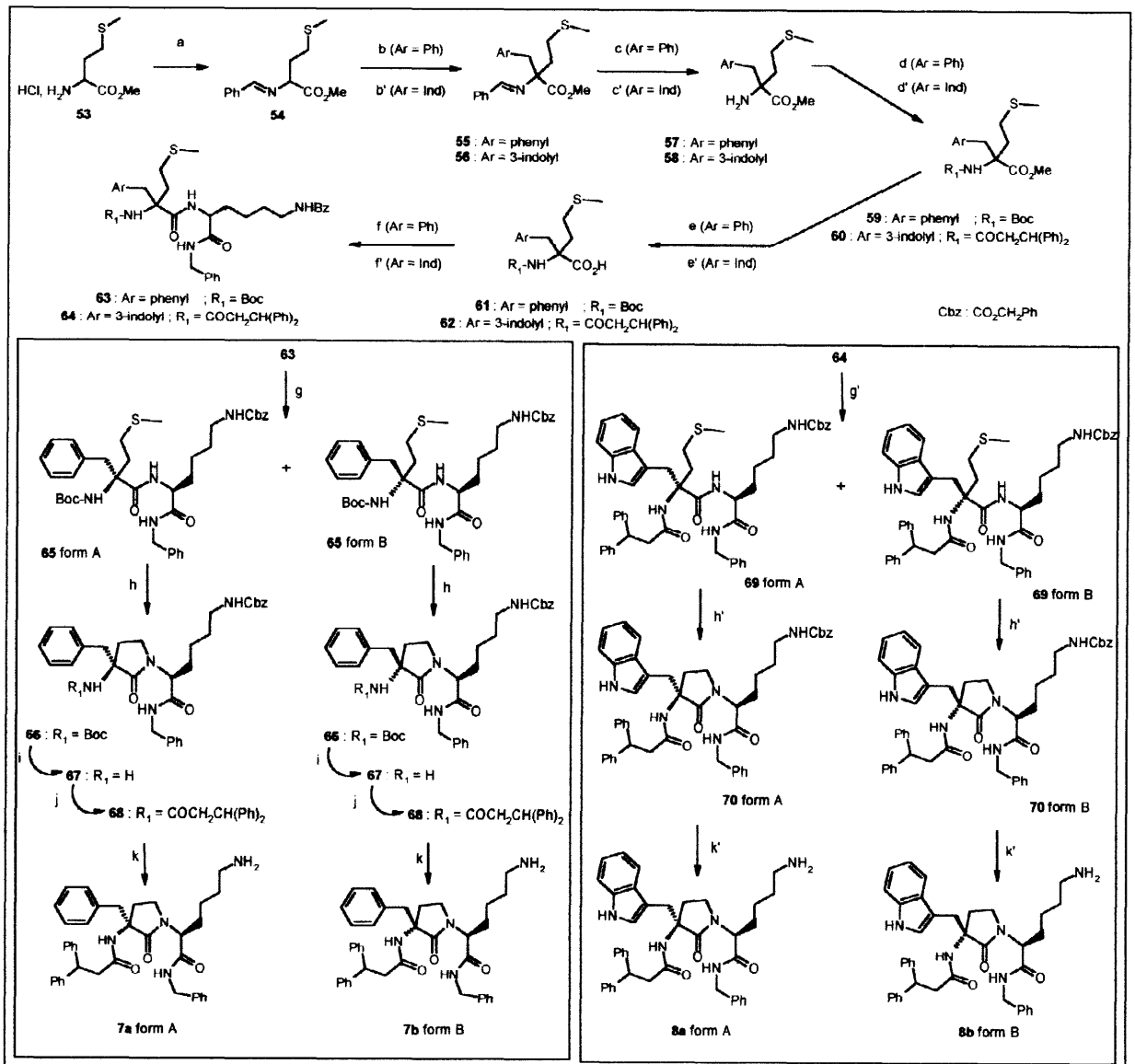


Reagents and conditions: ***a)*** *trans*-cinnamaldehyde (1eq.), NaH (1eq.), 20°C, 48h, two isomers with a ratio 6/4 (^{1}H-NMR, 300MHz, DMSO-d_6), 44% ***b)*** Et_3SiH (1eq.), Et_3N (1.5eq.), $HCCl_3$, 20°C, 16h, two isomers with a ratio 6/4 (^{1}H-NMR, 300MHz, DMSO-d_6), used in the next step without other purification ***c)*** 1N NaOH (2eq.), EtOH, reflux, 48h, **41** (52%), **42** (39%) ***d)*** 6N HCl, AcOH, 100°C, 16h, 92% ***e)*** Ph_2CHCH_2COCl (1eq.), Et_3N (2eq.), CH_2Cl_2, rt, 18h, 21% ***f)*** H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ (1eq.), HOBT (1eq.), EDCI (1eq.), CH_2Cl_2, rt, 16h, ratio of two forms: 6/4 (^{1}H-NMR), 60% ***g)*** cyclohexene, Pd/C (10%), EtOH, reflux, 2h, ratio of two forms: 6/4 (^{1}H-NMR, 200MHz, DMSO-d_6), 67%.

Reagents and conditions : ***a)*** 1N HCl, MeOH, reflux, 3h then H_2SO_4 conc., MeOH, reflux, 12h then 1N NaOH, rt, 2h, 67% ***b)*** EtOCOCl (1eq.), Et_3N (1eq.), CH_2Cl_2, 20°C, 18h, 95% ***c)*** $LiN(SiMe_3)_2$ (1eq.), MeI (22eq.), THF, -30°C, 1h then rt, 3h, *cis*- and *trans*-isomers with a 8/2 ratio (^{1}H-NMR, 200MHz, DMSO-d_6), used in the next step without other purifications ***d)*** HBr (47%), 110°C, 16h, *cis*- and *trans*-isomers with a 8/2 ratio (^{1}H-NMR, 300MHz, DMSO-d_6), 84% ***e)*** Ph_2CHCH_2COCl (1eq.), Et_3N (2eq.), toluene, rt, 24h, 14.5% ***f)*** H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ (1eq.), HOBT (1eq.), EDCI (1eq.), TEA (2eq.), CH_2Cl_2, rt, 16h, 55% ***g)*** cyclohexene, Pd/C (10%), EtOH, reflux, 2h, form A/form B: 6/4, ^{1}H-NMR, 200MHz, DMSO-d_6, 14%.

Scheme 9 : Synthesis of *trans* and *cis*-2-methyl -3-phenyl prolines derivatives **5** (forms A and B mixture).

Removal of the *tert*-butyloxy group of **68** (form A and form B) using CF_3CO_2H followed by the condensation of 3,3-diphenylpropionyl chloride lead to **68** (form A and form B). The removal of the carbobenzyloxy-protecting group of **68** was achieved easily by hydrogenolysis (Pd/C) to provide **7a** (form A) and **7b** (form B).



Reagents and conditions : ***a)*** PhCHO (1 eq.), TEA (1 eq.), $MgSO_4$, CH_2Cl_2, rt, 18h , 88%.
Synthesis of **7a** (form A) and **7b** (form B): ***b)*** $PhCH_2Br$ (1eq.), LDA (1eq.), THF, rt, 18h used in the next step without further purification ***c)*** 1N HCl, THF, H_2O, rt, 12h, 40% ***d)*** Boc_2O (1eq.), Et_3N (1eq.), THF, rt, 6h, 94% ***e)*** 1N NaOH, dioxane, reflux, 5h, 82% ***f)*** H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ (1.2eq.), HOBT (1.4eq.), EDCI (1.2eq.), CH_2Cl_2, 70% ***g)*** flash chromatography on silica gel (AcOEt:cyclohexane 40:60), **65** form A: 29%, **65** form B: 37% ***h)*** MeI (180eq.), rt, 20h, 94-100% then NaH (1eq.), DMF, CH_2Cl_2, 0°C, 2h, **66** form A: 100%, **66** form B: 86% ***i)*** CF_3CO_2H, $HCCl_3$, rt, 18h, **67** (form A): 98%, **67** (form B): 83% ***j)*** Ph_2CHCH_2COCl (2.5eq.), TEA (1eq.), CH_2Cl_2, rt, 18h, **68** form A: 68%, **68** form B: 40% ***k)*** 2.5N HCl/MeOH (1.2eq.), H_2 (14.7psi), Pd/C (10%), rt, 18h, **7a** (form A): 51%, **7b** (form B): 85%.
Synthesis of **8a** (form A) and **8b** (form B): ***b')*** gramine (1eq.), NaOH (0.3eq.), toluene, reflux, 18h, used in the next step without purification ***c')*** 1N HCl, Et_2O, rt, 3h , 72% ***d')*** Ph_2CHCH_2COCl (2eq.), TEA (2eq.), CH_2Cl_2, rt, 3h , 79% ***e')*** 1N NaOH, dioxane, rt, 18h, 93% ***f')*** H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ (1.2eq.), DPPA (1.2eq.), DMF, -5°C, 0.5h then TEA (2.2eq.), rt, 18h, two isomers, 1/1 ration (1H-NMR, 300MHz, $CDCl_3$), 48% ***g')*** flash chromatography on silica gel (AcOEt/cyclohexane 50:50), **69** form A: 17%, **69** form B: 14% ***h')*** **69** form A (1eq.), MeI (180eq.), rt, 20h, 100% then NaH (5eq.), DMF, CH_2Cl_2, -5°C to 0°C, 4h, **70** (form A): 15% ; **69** form B (1eq.), MeI (180eq.), rt, 20h, 100% then K_2CO_3 (5eq.), DMF, CH_2Cl_2, rt, 18h, **70** (form B): 32% ***k')*** 2.5N HCl/MeOH (1.2eq.), H_2 (14.7psi), Pd/C (10%), rt, 12h, **8a** (form A): 99%, **8b** (form B): 84%.

Scheme 10 : Synthesis of γ-lactam derivatives **7** and **8** (form A and form B).

Our synthetic plan to synthesize **8a** (form A) and **8b** (form B) was to utilize the both pure isomers **69** (form A and form B) as key intermediates. Thus, initially, coupling of the amine **58** with of 3,3-diphenylpropionyl chloride gave **60** and hydrolysis of this ester gave the corresponding acid **62**, which was transformed into the diastereoisomeric amide mixture **64** as a 1/1 mixture of two isomers. Pure diastereoisomers **69** (form A and form B) were isolated as single diastereoisomers by flash chromatography. Methylation of the methionine side chain in **69** (form A and form B) with an excess of iodomethane (~200 eq.), followed by cyclization using sodium hydride or potassium carbonate as base yielded the corresponding γ-lactams. Finally, **70** (form A and form B) were deprotected by hydrogenolysis and furnished the desired γ-lactams **8a** (form A) and **8b** (form B).

In conclusion, we have accomplished the synthesis of original 3-aryl proline derivatives **1-6** and γ-lactam derivatives **7** and **8**. These preparations involved rapid and efficient synthesis of new building blocks derived from proline skeleton. The synthesis of these unusual cyclic amino acids opens the way to design and to prepare peptidomimetics with new architectural motifs. Binding assays[16] have shown that the 3-functionalized-proline derivatives **2-6** and γ-lactam derivatives **7-8** showed weak affinity (IC_{50}: 7-64μM) for somatostatin receptors on membranes of rat cerebral cortex (3-[^{125}I]-Tyr^{11}-SRIF-14) *versus* SRIF-14 itself (IC_{50}: 0.002μM).

EXPERIMENTAL

General Methods

Solvents and other reagents were used without further purification. Flash chromatography was carried out on E.Merck silica gel 60 (0.04-0.063 mm). NMR spectra were recorded on Bruker AC200 , AC250 , AC300 or AM400 spectrometers operating at 200.13 , 250.13 , 300.13 or 400.13 MHz for proton observation. Chemical shifts are reported as δ values from internal tetramethylsilane standard. DCI mass spectra were obtained on a Finnigan SSQ with ammonia as reactant gas . FAB (glycerol/thioglycerol) was obtained using a VG-Autospec . FT-IR spectra were recorded as KBr pellet using a Nicolet 60 SX photospectrometer . Elemental analysis was carried out on a Fisons EA 1108 micro-analyser while polarimetry was obtained thanks to a Perkin Elmer 341 polarimeter equipped with a 350 microliter cell. Melting points were determined with a Reicher-Kofler apparatus and are uncorrected.

A / Proline derivatives.

Preparation of 1-(3,3-diphenylpropionyl)-pyrrolidine-2-carboxylic acid precursors 10, 13, 18 *cis*, 18 *trans*, 33 *cis*, 33 *trans*, 44 *trans and* 51 *cis*.

1-(3,3-Diphenylpropionyl)-pyrrolidine-2-(R)-carboxylic acid (10).

To a solution of D-proline **9** (5g, 43.5mmol) in CH_2Cl_2 (200ml) were added NEt_3 (6.1ml, 43.5mmol) and Ph_2CHCH_2COCl (freshly prepared from Ph_2CHCH_2COOH (9.8g, 43.4mmol) and $SOCl_2$ (20ml) at 0°C, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (100ml) and the product was extracted with CH_2Cl_2 (2x50ml). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification on silica gel (CH_2Cl_2 / MeOH : 97.5/2.5) gave **10** (2.5g, 18%) as a yellow solid; mp 50°C.

1-(3,3-Diphenylpropionyl)-pyrrolidine-2-(S)-carboxylic acid (13).

Prepared as above from L-proline **12** to give **13** (4.9g, 35%) as a yellow solid; mp 60°C.

cis-1-(3,3-Diphenylpropionyl)-3-phenyl-pyrrolidine-2-carboxylic acid (18 _cis_) and _trans_-1-(3,3-diphenylpropionyl)-3-phenyl-pyrrolidine-2-carboxylic acid (18 _trans_).

To a solution of **15** (_cis/trans_ :7/3) (107g, 0.35mol) in THF (500ml) were added 0.5N NaOH (700ml) and the mixture was stirred at room temperature overnight. After decantation, extraction with AcOEt (2x200ml), the combined organic layers were dried over $MgSO_4$, filtered and concentrated _in vacuo_ to afford **16 _cis_** (67g, 63%) as a white solid ; mp 72°C. Acidification of the aqueous phase with citric acid (pH 4), extraction with AcOEt (3x250 ml), then concentration _in vacuo_ gave **16 _trans_** (21.4g, 21%) as a white solid ; mp 137°C.

A mixture of compound **16 _cis_** (10g, 32mmol), 6N HCl (52ml) and AcOH (12.5ml) was heated at reflux for 3h. Upon cooling to 20°C, the reaction mixture was evaporated _in vacuo_. The resulting crude solid was washed with iPr_2O (100ml) to give **17 _cis_.HCl** (4.9g, 68%) as a white solid ; mp 188°C.

17 _trans_ was prepared as above from **16 _trans_** to give **17 _trans_.HCl** (7.5g, 75%) as a white solid ; mp 196°C.

To a solution of **17 _cis_.HCl** (10g, 43.95mmol) in 10% aqueous Na_2CO_3 solution (740ml) was added Ph_2CHCH_2COCl (prepared from $PhCHCH_2COOH$ (11g, 48.67mmol) and $SOCl_2$ (18ml) at 0°C and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with AcOEt (300ml), acidified to pH 2 with 1N HCl and the water layer was extracted with AcOEt (2x300ml). The combined extracts were washed with water, dried over $MgSO_4$, filtered and concentrated _in vacuo_. The crude solid was recrystallized from 2-propanol to give **18 _cis_** (15.25g, 87%) as a white solid; mp 120°C.

18 _trans_ was prepared as above from **17 _trans_.HCl** to give **18 _trans_** (5.5g, 89%) as a white solid; mp 106°C.

cis-1-(3,3-Diphenylpropionyl)-3-(3-indolyl)-pyrrolidine-2-carboxylic acid (33 _cis_) and _trans_-1-(3,3-diphenylpropionyl)-3-(3-indolyl)-pyrrolidine-2-carboxylic acid (33 _trans_).

To a suspension of **27** (14.5g, 0.1mol), K_2CO_3 (55.3g, 0.4mol) and $CH_3COC_2H_5$ (500ml) was added dropwise $PhSO_2Cl$ (25.6ml, 0.2mol) and the mixture was heated at reflux for 2h. Upon cooling to 20°C, the reaction was filtered and the filtrate was concentrated _in vacuo_. The resulting residue was washed with iPr_2O (250ml) to provide, after filtration, **28** (24.5g, 86%) as a cream solid; mp 156°C.

To a suspension of Ph_3P^+Me, Br^- (21.36g, 0.06mol) in DME (750ml) was added dropwise at -20°C n-BuLi (75.5ml of 1.6M in hexane, 0.12mol). The reaction mixture was stirred at room temperature for 2 h and cooled at -10°C to introduce **28** (14.25g, 0.05mol). The reaction mixture was then stirred at room temperature overnight, poured into water (2l) and extracted with AcOEt (3x200ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated _in vacuo_. Purification on silica gel (CH_2Cl_2) gave **29** (11.7g, 83%) as a yellow solid; mp 67°C.

To a solution of $MeOCH_2(EtOCO)NCH(CO_2Me)_2$ (4.36g, 15mmol) in CH_2Cl_2 (150ml) was added $TiCl_4$ (3.29ml, 30mmol). The reaction mixture was heated at reflux and a solution of TEA (2.1ml, 15mmol), **29** (8.49g, 30mmol) and CH_2Cl_2 (100ml) was added. After 1h at reflux, the reaction mixture was cooled at 20°C, diluted with water (750ml) and extracted with CH_2Cl_2 (3x190ml). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated _in vacuo_. Purification on silica gel (AcOEt/cyclohexane : 1/2) gave **30** (5.7g, 70%) as a yellow solid; mp 104°C.

A mixture of **30** (5.4g, 0.01mol), AcOH (50ml) and HBr 47% (50ml) was heated at reflux for 20h. Upon cooling to 20°C, the reaction mixture was evaporated _in vacuo_ and the resulting residue was washed successively with toluene, CH_2Cl_2, iPr_2O and MeOH to afford **31.HBr** as a brown solid (3.2g, 100%) ; mp 180°C.

A solution of **31.HBr** (12g, 0.03mol), MeOH (300ml) and H_2SO_4 (3ml) was heated at reflux for 12h then the reaction mixture was concentrated _in vacuo_. The resulting crude oil was diluted with water (300ml) and treated with NH_3 aq.. After extraction with CH_2Cl_2, the combined organics were dried ($MgSO_4$), filtered, and concentrated _in vacuo_. Purification on silica gel (CH_2Cl_2 / MeOH : 95/5) gave **32 _trans_** (1.5g, 13%) as a brown oil; _Rf_[CH_2Cl_2:MeOH (95:5)] 0.27 and **32 _cis_** (4.6g, 40%) as a yellow oil; _Rf_(CH_2Cl_2/MeOH 95:5)0.2.

To a solution of $Ph_2CHCH_2CO_2H$ (3.3g, 0.015mol) in CH_3CN (150ml) were added at 0°C a solution of **32 _cis_** (5.5g, 0.015mol) in CH_3CN (150ml), BOP (6.5g, 0.015mol) and TEA (2.1ml, 0.015mol).The reaction mixture was stirred at 0°C for 1h and finally at room temperature for 12h. After concentration _in vacuo_, the resulting residue was diluted with CH_2Cl_2 (300ml) and washed with water (2x50ml). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated _in vacuo_. Purification on silica gel using CH_2Cl_2/MeOH

(98/2) gave the corresponding ester (5.7g, 69%). Then, this compound was treated with 3N NaOH (40ml) in MeOH (80ml) at reflux overnight. After concentration *in vacuo*, the resulting residue was diluted with water and treated with a aqueous solution of $KHSO_4$. The resulting solid was filtrate and washed with CH_2Cl_2 (2x50ml) to afford **33** ***cis*** (2.1g, 65%) as a white solid ; mp254°C.

33 ***trans*** was prepared as above from **32** ***trans*** to give **33** ***trans*** (1.4g, 89%) as a beige solid; mp 264°C.

***trans*-1-(3,3-Diphenylpropionyl)-2-methyl-3-phenyl-pyrrolidine-2-carboxylic acid (44 *trans*).**

To a solution of **38** (15.9g, 0.1mol) in DMF (400ml) was added NaH (50%) (4.8g, 0.1mol) and the reaction mixture was stirred at room temperature for 3h. Upon cooling at 0-5°C, a solution of *trans*-cinnamaldehyde (13.2ml, 0.105mol) in DMF was added and the mixture was stirred at room temperature for 48h. The reaction mixture was poured into water (500ml) , CH_2Cl_2 (200ml) and 1N HCl (150ml). After decantation, the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide **39** (12.8g, 44%) as an oil; *Rf* (AcOEt)0.43.

To a solution of **39** (12.5g, 43mmol) in $HCCl_3$ (120ml) was added Et_3SiH (8.7ml, 54.8mmol). Upon cooling at 0-5°C, Et_3N (8.3g, 11.5ml, 82.8mmol), CF_3COOH (27ml) was added dropwise. The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo* to provide **40** used in the next step without further purification.

This intermediate was treated with 1N NaOH (74ml) in EtOH (100ml). The stirred reaction mixture was heated at reflux for 48h. Upon cooling to 20°C, the reaction mixture was concentrated *in vacuo*. The residue was diluted in water, extracted with AcOEt (3x100ml), then acidified to pH 1 with 1N HCl. The water layer was extracted with CH_2Cl_2 (2x75ml) and the combined organics was dried over Na_2SO_4, filtered, concentrated *in vacuo* to provide **41** ***trans*** (4.7g, 51.5%) as a white solid; mp 218°C.

A solution of **41** ***trans*** (4.5g, 18.2mmol), AcOH (7ml) and 6N HCl (28ml) was heated at reflux overnight. Upon cooling to room temperature, the reaction mixture was evaporated and the crude solid obtained was washed with acetone (2x30ml) to afford **43** ***trans*** (4g, 92%) as a white solid; mp 260°C.

Compound **44** ***trans*** was prepared in the same manner as compound **10** as a white solid (1.2g, 21%); mp 230°C.

***cis*-1-(3,3-Diphenylpropionyl)-2-methyl-3-phenyl-pyrrolidine-2-carboxylic acid (51 *trans*).**

To a solution of **47** (51.25g, 0.25mol) in CH_2Cl_2 (800ml) was added Et_3N (35ml, 0.25mol) then $ClCO_2Et$ (24ml, 0.25mol) at 10°C. The reaction mixture was stirred at room temperature overnight. After filtration, the filtrate was washed with water (3x100ml), dried over Na_2SO_4 and concentrated *in vacuo* to provide **48** (66g, 95%) as an oil which was used directly in the next step without further purification.

To a solution of lithiohexamethyldisilazane (prepared *in situ* at -35°C from $HNSiMe_3$ (11.2g, 0.127mol) in THF (200ml) and n-BuLi (44ml of 1.6M in hexane, 0.07mol)) was added at -30°C in one portion the methyl ester **48** (15g, 0.054mol) in THF (100ml). The reaction mixture was then stirred at -30°C for 1h and at 0°C for 1h and IMe (100ml, 1.59mol) was added. The reaction mixture was then stirred at room temperature for 3h, poured into saturated aqueous NH_4Cl (400ml). The water layer was extracted with CH_2Cl_2 (3x150ml) and the combined organic layers were washed with saturated aqueous NaCl solution (3x100ml) then with water (3x100ml), dried ($NaSO_4$), filtered and concentrated *in vacuo* to afford **49** as an oil which was used directly in the next step without further purification.

A mixture of **49** (2g, 6.87mmol) and 6N HBr/AcOH (20ml) was heated at 110°C and stirred for 16h. Upon cooling to 20°C, the reaction mixture was concentrated *in vacuo*, and the residue was washed with CH_2Cl_2 (3x50ml) to provide, after filtration, **50.HBr** (1.65g, 84%) as a grey solid; mp 230°C.

Compound **51** ***cis*** was prepared in the same manner as compound **10** as a white meringue (0.12g,14.5%); *Rf* (AcOEt/cyclohexane 1:1)0.2.

The compounds* 1, 3 *and* 5 *were synthesized according to Schemes 2,6 and 9 respectively. Illustrative synthetic procedure is given for the proline derivatives* 1a *as representative example of this series.

_N_-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-2-(R)-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide (1a).

To a solution of **10** (1.6g, 4.95mmol) in CH_2Cl_2 (65ml) were added H_2N-L-Lys(ε-Cbz)$CONHCH_2Ph$ (2g, 5.42mmol), HOBT (0.7g, 5.2mmol), EDCI (1g, 5.2mmol) at 0°C and the reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was diluted with water (70ml) and the product was extracted with CH_2Cl_2 (2x50ml). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification on silica gel (CH_2Cl_2 / MeOH : 97.5 / 2.5) to provide **11** (2g, 61%); *Rf* (CH_2Cl_2/MeOH 97.5:2.5)0.5.

A mixture of **11** (2g, 3.03mmol), Pd/C (10%) (2g), cyclohexene (38.5ml) and MeOH (77ml) was heated at reflux and stirred for 2h. Upon cooling to 20°C, the catalyst was removed by filtration. The filtrate was evaporated *in vacuo*. Purification on silica gel (toluene/DEA/MeOH 90:5:5) gave **1a** (0.5g, 19%) as a white solid; IR (KBr) 3410, 3300, 1650, 1545 cm^{-1} . ^1H NMR (DMSO-d_6, 300 MHz) T=413°K: δ 7.4 to 7.1 (m, 15H, $3xC_6H_5$), 4.5 (t, 1H, CH diphenylpropionyl), 4.1 (m, 4H, H_2, $H_{2'}$ and CH_2 benzyl), 3.5 (m, 2H, $H_{5'}$), 3 (m, 2H, CH_2 diphenylpropionyl), 2.8 (t, 2H, H_6), 2 to 1.3 (m complex, 10H, H_3, H_4, H_5, $H_{3'}$, $H_{4'}$). MS (DCI/NH_3) *m/z* 541 ($M + H^+$). Anal. calcd for $C_{33}H_{40}N_4O_3$: C, 73.30; H, 7.46; N, 10.36; O, 8.88; found: C, 73.3; H, 8.0; N, 9.9; O, 8.3. $[\alpha]_D^{20}$ -38° +/-0.9 (*c* 0.853; MeOH).

Compounds* 1b, 3c, 3c', 3t, 3t', 5c *and* 5t *were prepared in the same manner. Their physical data are summarized as follows.

_N_-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-2-(S)-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide (1b) :

IR, NMR and MS identical to that of **1a**. Anal. calcd for $C_{33}H_{40}N_4O_3$: C, 73.30; H, 7.46; N, 10.36; O, 8.88; found: C, 73.2; H, 7.9; N, 10.0; O, 9.1. $[\alpha]_D^{20}$ -81.9° +/-1 (*c* 1.011; MeOH).

***cis*-_N_-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-(3-indolyl)-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide . HCl , form A (3c):**

IR (KBr) 3410, 3300, 3000-2500, 1635, 1535 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) T=413°K: δ 7.7 (d, 1H, indole), 7.3 (d, 1H, indole), 7.1 (s, 1H, indole), 7.3 to 6.9 (m, 17H, C_6H_5 + indole), 4.7 (d, 1H, H_2'), 4.45 (bt, 1H, CH diphenylpropionyl), 4.2 (AB, 2H, CH_2 benzyl), 3.9 to 3.6 (m complex, 4H, H_2, H_5', and H_3'), 3.2 and 2.9 (dd, 2H, CH_2 diphenylpropionyl), 2.7 (m, 3H, H_6 and H_4'), 2.2 (m, 1H, H_4'), 1.5 to 1 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) *m/z* 656 ($M + H^+$). Anal. calcd for $C_{41}H_{46}ClN_5O_3$: C, 71,13; H, 6,70; Cl, 5,12; N, 10,12; found: C, 71,9; H, 7,2; Cl, 5,5; N, 10,1; $[\alpha]_D^{20}$ - 99,9° +/- 1,9 (*c* 0.5; MeOH).

***cis*-_N_-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-(3-indolyl)-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide . HCl , form B (3c'):**

IR (KBr) 3410, 3300, 3000-2500, 1640, 1525 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) T=413°K: δ 7.6 (d, 1H, indole), 7.3 to 7 (m, C_6H_5 + indole), 4.7 (bs, 1H, H_2'), 4.6 (bt, 1H, CH diphenylpropionyl), 4.1 (AB, 2H, CH_2 benzyl), 4 to 3.7 (m, 4H, H_2, H_5', and H_3'), 3.2 and 3.05 (vbs, 2H, CH_2 diphenylpropionyl), 2.7 (bm, 3H, H_6 and H_4'), 2.2 (vbs, 1H, H_4'), 1.6 to 1.1 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) *m/z* 656 ($M + H^+$). Anal. calcd for $C_{41}H_{46}ClN_5O_3$: C, 71,13; H, 6,70; Cl, 5,12; N, 10,12; found: C, 71,8; H, 7,1; Cl, 5,7; N, 9,9; $[\alpha]_D^{20}$ + 25,2° +/- 1 (*c* 0.4; MeOH).

***trans*-_N_-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-(3-indolyl)-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide . HCl , form A (3t):**

IR (KBr) 3415, 3300, 3000-2500, 1640, 1540 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) T=413°K: δ 7.5 (d, 1H, indole), 7.4 (d, 1H, indole), 7.3 to 7.1 (m, 16H, C_6H_5 + indole), 7.05 (s, 1H, indole), 7 (t, 1H, indole), 4.5 (bt, 1H, CH diphenylpropionyl), 4.4 (vbs, 1H, H_2'), 4.25 (AB, 2H, CH_2 benzyl), 3.8 (bm, 3H, H_5', and H_2), 3.2 and 3 (bm, 2H, CH_2 diphenylpropionyl), 2.7 (bt, 2H, H_6), 2.4 and 2 (bs, 2H, H_4'), 1.8 to 1.1 (m complex, 6H, H_3, H_4

and H_5). MS (DCI/NH_3) *m/z* 656 ($M + H^+$). Anal. calcd for $C_{41}H_{46}ClN_5O_3$, 2,89 H_2O: C, 71,13; H, 6,70; Cl; 5,12; N, 10,12; found: C, 71,2; H, 6,5; Cl, 6,0; N, 9,9; $[\alpha]_D^{20}$ - 8,9° +/- 0,8 (*c* 0.4; MeOH).

***trans-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-(3-indolyl)-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide . HCl , form B (3t'):**

IR (KBr) 3410, 3000-2500, 1640, 1525 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) T=413°K: δ 7.5 (d, 1H, indole), 7.4 (d, 1H, indole), 7.3 to 7.1 (m, 15H, 3xC_6H_5), 7.1 (t, 1H, indole), 7 (t, 1H, indole), 6.9 (s, 1H, indole), 4.6 (t, 1H, CH diphenylpropionyl), 4.5 (vbs, 1H, H_2'), 4.25 (bs, 2H, CH_2 benzyl), 3.7 (bm, 4H, H_5', H_3' and H_2), 3.3 and 3 (bm, 2H, CH_2 diphenylpropionyl), 2.8 (bt, 2H, H_6), 2.4 and 2 (bm, 2H, H_4'), 1.8 to 1.3 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) *m/z* 656 ($M + H^+$). Anal. calcd for $C_{41}H_{46}ClN_5O_3$: C, 71,13; H, 6,70; Cl, 5,12; N, 10,12; found: C, 71,1; H, 6,6; Cl, 5,5; N, 9,9; $[\alpha]_D^{20}$ - 13,9° +/- 0,8 (*c* 0.3; MeOH).The relative stereochemistry of the proline moiety of **3c** to **3t'** was obtained by comparison of nOe results observed on compounds **32** ***cis*** and ***trans***.

***cis-N*-benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-2-methyl-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide (5c).**

IR (KBr) 3420, 3320, 1635 1540, 1515 cm^{-1}. ^1H NMR (DMSO-*d6*, 200 MHz) T=413°K (2 isomers 60/40): δ 7.4 to 7.1 (m, 20H, 4xC_6H_5), 4.5 (bt, 1H, CH diphenylpropionyl),4.3 and 4.2 (2s, 2H, two CH_2 benzyl), 4.1 to 3.7 (m complex, 4H, H_5', H_2 and H_3'), 3.2 (m, 2H, CH_2 diphenylpropionyl), 2.75 and 2.65 (bt, 2H, H_6), 2.5 and 2 (m, 2H, H_4'), 1.7 to 0.8 (m complex, 9H, H_3, H_4, H_5 and Me_2' (1.5 and 1.4 ppm)). MS (DCI/NH_3) *m/z* 631 ($M + H^+$).

***trans-N*-benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-2-methyl-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide (5t).**

IR (KBr) 3425, 3305, 1630, 1540, 1515 cm^{-1}. ^1H NMR (DMSO-*d6*, 300 MHz) T=413°K (2 isomers 60/40): δ 7.4 to 7.1 (m, 20H, 4xC_6H_5), 4.5 (bt, 1H, CH diphenylpropionyl), 4.2 (bm, 2H, CH_2 benzyl), 4.1 to 3.7 (m, 4H, H_5', H_2 and H_3'), 3.2 and 2.8 (m, 2H, CH_2 diphenylpropionyl), 2.7 (bt, 2H, H_6), 2.3 and 2.1 (m, 2H, H_4'), 1.9 to 1.4 (m complex, 6H, H_3, H_4 and H_5), 0.9 and 0.8 (2s, 3H, CH_3 in 2'). MS (DCI/NH_3) *m/z* 631 ($M + H^+$). Anal. calcd for $C_{40}H_{46}N_4O_3$: C, 76,16; H, 7,35; N, 8,88; O, 7,61; found: C, 76,2; H, 7,4; N, 8,7). The relative stereochemistry of the proline moiety was secured by nOe experiments performed on **43** and **50** .

The compounds* 2, 4 *and* 6 *were synthesized according to Schemes 4-5,7 and 8 respectively. Illustrative synthetic procedure is given for the proline derivatives* 2c *as representative example of this series.

***cis-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide . $C_2H_2O_4$, form A (2c):**

To a solution of **18** ***cis*** (9.1g, 23mmol) in THF (255ml) were added H_2N-L-Lys(ε-Cbz)-CO_2Me·HCl (7.54g, 23mmol), TEA (3.2ml, 23mmol), HOBT (3.84g, 25mmol) and EDCI (4.8g, 25mmol). The reaction mixture was stirred at room temperature overnight, and then washed with water (150ml). The water layer was extracted with CH_2Cl_2 (150ml). The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The remaining residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 99 : 1) to afford **19** ***cis*, form A** (1.5g, 10%) as a white solid ; *Rf* [CH_2Cl_2/MeOH 95:5]0.48. The chromatography was pursued using CH_2Cl_2:MeOH (95 :5) as eluent to afford **19** ***cis*, form B** (2.25g, 14.5%) as a white solid ; *Rf* (CH_2Cl_2/MeOH 95:5)0.41.

A mixture of **19** ***cis*, form A** (1.5g, 2.2mmol), 0.5N NaOH (5ml) and THF (8.2ml) was stirred at room temperature overnight and then, concentrated *in vacuo*. The remaining residue was diluted with AcOEt (40ml), water (30ml) then acidified (pH 1) with N HCl . The water layer was extracted with AcOEt (3x20ml) and the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **20** ***cis*, form A** (1.33g, 90%) as a white solid ; mp ~70°C.

To a solution of **20** ***cis*** (1.33g, 2mmol) in CH_2Cl_2 (30ml) were added $PhCH_2NH_2$ (0.24ml, 2.2mmol), HOBT (0.34g, 2.2mmol) and EDCI (0.42g, 2.2mmol). The reaction mixture was stirred at room temperature overnight, diluted with water (20ml) and finally acidified (pH 1) with N HCl. The water layer was extracted with CH_2Cl_2 (3x15ml) and the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by chromatography on silica gel (CH_2Cl_2/MeOH 98:2) gave **21** ***cis*, form A** (1.48g, 98%) as a white solid; mp ~70°C.

A mixture of compound **21 *cis*, form A** (0.84g, 1.1mmol), (5%) Pd/C (0.84g) in HCO_2H:MeOH (96:4) (66.2ml) was stirred overnight. Then, the catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The remaining residue was diluted with CH_2Cl_2 (30ml), water (20ml), and then basified (pH 11) with 1N NaOH. The water layer was extracted with CH_2Cl_2 (3x10ml) and the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was treated with oxalic acid (54mg) in CH_3CN (9ml) to give **2c .$C_2H_2O_4$, form A** (190mg, 24%) as a white solid ; mp~85°C. IR (KBr) 3410, 3375, 3000-2500, 1640, 1530 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) T=413°K: δ 7.4 to 7.1, (m, 20H, 4xC_6H_5), 4.7 (bs, 1H, H_2'), 4.6 (t, 1H, CH diphenylpropionyl), 4.15 (d, 2H, CH_2 benzyl), 4 (bs, 1H, H_2), 3.8 and 3.5 (bm, 3H, H_5' and H_3'), 3.10 (vbs, 2H, CH_2 diphenylpropionyl), 2.65 (bt, 2H, H_6), 2.5 and 2.1 (bm, 2H, H_4'), 1.7 to 1.2 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) *m/z* 617 (M + H^+). Anal. calcd for $C_{39}H_{44}N_4O_3,C_2H_2O_4$: C, 69,67; H, 6,56; N, 7,93; found: C, 69,7; H, 6,9; N, 8,3; $[\alpha]_D^{20}$ - 11,9° +/- 0,5 (*c* 1; MeOH).

Compounds* 2c', 2t, 2t', 4c, 4c', 6c, 6c', 6t *and* 6t' *were prepared in the same manner. Their physical data are summarized as follows.

***cis-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide . $C_2H_2O_4$, form B (2c'):**

IR (KBr) 3400, 3300, 3000-2500, 1640, 1540 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) T=413°K: δ 7.4 to 7.1, (m, 20H, 4xC_6H_5), 4.7 (bd, 1H, H_2'), 4.55 (t, 1H, CH diphenylpropionyl), 4.2 (dd, 2H, CH_2 benzyl), 3.9 and 3.6 (bm, 4H, H_2, H_5' and H_3'), 3.1 (bm, 2H, CH_2 diphenylpropionyl), 2.7 (t, 2H, H_6), 2.6 and 2.1 (bm, 2H, H_4'), 1.6 to 0.8 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) *m/z* 617 (M + H^+). Anal. calcd for $C_{39}H_{44}N_4O_3$, $C_2H_2O_4$: C, 69,67; H, 6,56; N, 7,93; found: C, 69,6; H, 7,0; N, 7,8; $[\alpha]_D^{20}$ - 39° +/- 0,8 (*c* 1,13; MeOH).

***trans-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide . $C_2H_2O_4$, form A (2t):**

IR (KBr) 3410, 3300, 3000-2500, 1640, 1540 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) T=413°K: δ 7.4 to 7.1, (m, 20H, 4xC_6H_5), 4.6 (t, 1H, CH diphenylpropionyl), 4.45 (bs, 1H, H_2'), 4.30 (bt, 2H, CH_2 benzyl), 4.25 (bm, 1H, H_2), 3.7 and 3.5 (bm, 3H, H_5' and H_3'), 3.1 (vbs, 2H, CH_2 diphenylpropionyl), 2.75 (bt, 2H, H_6), 2.4 and 1.9 (bm, 2H, H_4'), 1.3 to 1.9 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) *m/z* 617 (M + H^+). Anal. calcd for $C_{39}H_{44}N_4O_3$, $C_2H_2O_4$: C, 69,67; H, 6,56; N, 7,93; O, 15,84; found: C, 69,4; H, 7,0; N, 7,9; O, 15,5; $[\alpha]_D^{20}$ = - 8,3° +/- 0,5 (*c*; MeOH).

***trans-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(S)-hexanamide . $C_2H_2O_4$, form B (2t'):**

IR (KBr) 3410, 3300, 3000-2500, 1640, 1540 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) T=413°K: δ 7.4 to 7.1, (m, 20H, 4xC_6H_5), 4.55 (bt, 1H, CH diphenylpropionyl), 4.4 to 4.2 (m, 4H, H_2, H_2' and CH_2 benzyl), 3.7 and 3.5 (m, 3H, H_5' and H_3'), 3.2 and 3 (bm, 2H, CH_2 diphenylpropionyl), 2.7 (bt, 2H, H_6), 2.4 and 2.1 (bm, 2H, H_4'), 1.8 and 1.6 (bm, 2H, H_3), 1.5 to 1.2 (m complex, 4H, H_4 and H_5). MS (DCI/NH_3) *m/z* 617 (M + H^+). Anal. calcd for $C_{39}H_{44}N_4O_3$, $C_2H_2O_4$: C, 69,67; H, 6,56; N, 7,93; O, 15,84; found: C, 69,5; H, 7,0; N, 8,2; O, 15,7; $[\alpha]_D^{20}$ - 31,9° +/- 0,6 (*c* 1; MeOH).

***cis-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolyl-*N*-methylcarboxamido]-2-(S)-hexanamide , form A (4c):**

IR (KBr) 3300, 1635, 1540 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) T=413°K: δ 7.4 to 7.1 (m, 20H, 4xC_6H_5), 4.8 to 4.4 (bm, 3H, H_2', H_2 and CH diphenylpropionyl), 4.3 (bs, 2H, CH_2 benzyl), 3.7 and 3.4 (bm, 3H, H_5' and H_3'), 3.2 and 3 (bm, 2H, CH_2 diphenylpropionyl), 2.7 (bm, 5H, NCH_3 and H_6), 2.4 and 2.1 (bm, 2H, H_4'), 1.9 to 1 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) m/z 631 (M + H+). Anal. calcd for $C_{40}H_{46}N_4O_3$: C, 76,16; H, 7,35; N, 8,88; O, 7,61; found: C, 75,8; H, 7,5; N, 8,6; O, 7,3; $[\alpha]_D^{20}$ - 13,1° +/- 1 (c 0.521; MeOH).

***cis-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolyl-*N*-methylcarboxamido]-2-(S)-hexanamide , form B (4c') :**

IR (KBr) 3300, 1640, 1525 cm^{-1}. ^1H NMR (DMSO-*d6*, 300 MHz) T=413°K: δ 7.4 to 7.1 (m, 20H, 4xC_6H_5), 4.8 to 4.4 (bm, 3H, H_2', H_2 and CH diphenylpropionyl), 4.3 (bs, 2H, CH_2 benzyl), 3.8 (bm, 3H, H_5'), 3.4 (m,

1H, H_3'), 3.2 and 3 (bm, 2H, CH_2 diphenylpropionyl), 2.7 (m, 5H, NCH_3 and H_6), 2.4 and 2 (bm, 2H, H_4'), 1.9 to 1.2 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) *m/z* 631 (M + H^+). Anal. calcd for $C_{40}H_{46}N_4O_3$: C, 76,16; H, 7,35; N, 8,88; O, 7,61; found: C, 76,8; H, 7,7; N, 8,9; O, 6,7; $[\alpha]_D^{20}$ - 35,2° +/- 1,3 (*c* 0.563; MeOH).

***trans-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolyl-*N*-methylcarboxamido]-2-(S)-hexanamide , form A (4t) :**

IR (KBr) 3325, 1645, 1635, 1525 cm^{-1}. ^1H NMR (DMSO-*d6*, 300 MHz) T=353°K: δ 7.4 to 7.1 (m, 20H, $4xC_6H_5$), 5 (bdd, 1H, H_2), 4.6 (bd, 1H, H_2'), 4.4 (bt, 1H, CH diphenylpropionyl), 4.3 and 4.1 (d, 2H, CH_2 benzyl), 3.9 and 3.7 (bm, 2H, H_5'), 3.4 (bm, 1H, H_3'), 3.2 and 3 (bdd, 2H, CH_2 diphenylpropionyl), 2.7 (bt, 2H, H_6), 2.5 (s, 3H, NCH_3), 2.3 and 2.1 (bm, 2H, H_4'), 1.9 to 0.9 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) *m/z* 631 (M + H^+). Anal. calcd for $C_{40}H_{46}N_4O_3$: C, 76,16; H, 7,35; N, 8,88; O, 7,61; found: C, 75,8; H, 7,7; N, 8,8; O, 8,3; $[\alpha]_D^{20}$ - 4,7° +/- 0.5 (*c* 0.927; MeOH).

***trans-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolyl-*N*-methylcarboxamido]-2-(S)-hexanamide , form B (4t') :**

IR (KBr) 3300, 1660, 1630, 1540 cm^{-1}. ^1H NMR (DMSO-*d6*, 300 MHz) T=413°K: δ 7.4 to 7.1 (m, 20H, $4xC_6H_5$), 5 (bd, 1H, H_2), 4.7 (bd, 1H, H_2'), 4.35 (bt, 1H, CH diphenylpropionyl), 4.3 and 4.1 (bm, 2H, CH_2 benzyl), 3.9 and 3.7 (bm, 2H, H_5'), 3.5 (bm, 1H, H_3'), 3.3 and 3 (m, 2H, CH_2 diphenylpropionyl), 2.7 (m, 5H, H_6 and NCH_3), 2.3 and 2.1 (m, 2H, H_4'), 1.9 to 0.9 (m complex, 6H, H_3, H_4 and H_5). MS (DCI/NH_3) *m/z* 631 (M + H^+). Anal. calcd for $C_{40}H_{46}N_4O_3$: C, 76,16; H, 7,35; N, 8,88; O, 7,61; found: C, 76,9; H, 7,8; N, 8,4; O, 7,0; $[\alpha]_D^{20}$ - 72,8° +/- 1,7 (*c* 0.38; MeOH).

***cis-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(R)-hexanamide , form A (6c):**

IR, NMR and MS identical to that of **2c**. Anal. calcd for $C_{39}H_{44}N_4O_3$: C, 75,95; H, 7,19; N, 9,08; O, 7,78; found: C, 75,4; H, 7,6; N, 8,9; O, 7,3; $[\alpha]_D^{20}$ + 12,8° +/- 0,7 (*c* 0,5; MeOH).

***cis-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(R)-hexanamide , form B (6c'):**

IR, NMR and MS identical to that of **2c'**. Anal. calcd for $C_{39}H_{44}N_4O_3$: C, 75,95; H, 7,19; N, 9,08; O, 7,78; found: C, 75,9; H, 7,4; N, 8,7; $[\alpha]_D^{20}$ + 48,0° +/- 1 (*c* 0,5; MeOH).

***trans-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(R)-hexanamide , form A (6t):**

IR, NMR and MS identical to that of **2t**. Anal. calcd for $C_{39}H_{44}N_4O_3$: C, 75,95; H, 7,19; N, 9,08; O, 7,78; found: C, 75,7; H, 7,7; N, 8,9; O, 7,6; $[\alpha]_D^{20}$ + 8,1° +/- 0,7 (c 0,5; MeOH).

***trans-N*-Benzyl-6-amino-2-[1-(3,3-diphenylpropionyl)-3-phenyl-perhydro-2-pyrrolylcarboxamido]-2-(R)-hexanamide , form B (6t'):** IR, NMR and MS identical to that of **2t'**. Anal. calcd for $C_{39}H_{44}N_4O_3$: C, 75,95; H, 7,19; N, 9,08; O, 7,78; found: C, 75,6; H, 7,6; N, 8,9; O, 7,9; $[\alpha]_D^{20}$ + 31,0° +/- 0,9 (*c* 0,5; MeOH).

B / γ-lactam derivatives.

To a suspension of **53** (19.97g, 0.1mol) in CH_2Cl_2 (200ml) were added TEA (13.94ml, 0.1mol), PhCHO (10.16ml, 0.1mol) and $MgSO_4$ (12g, 0.1mol). The mixture was stirred at room temperature overnight, filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with toluene (250ml), filtered and heated at reflux for 4h with azeotropic removal using a Dean-Stark trap. Removal of the solvent and purification of the oily residue by flash chromatography (CH_2Cl_2 / MeOH 95 :5) gave **54** (22.15g, 88%) as a colorless oil.

***N*-Benzyl-6-amino-2-(S)-{3-(3-indolylmethyl)-2-oxo-3-[(3,3-diphenylpropionyl) amino]-pyrrolidin-1-yl}-hexanamide (8a and 8b).**

A solution of **54** (10g, 40mmol), gramine (7g, 40mmol), NaOH (0.5g ; 12.5mmol) and toluene (200ml) was heated at reflux overnight, filtered and evaporated *in vacuo* to give **56** as a solid (*Rf* (AcOEt/cyclohexane 30:70)0.36) which was used in the next step without further purification.

To a solution of **56** (15,2g, 40mmol) in Et_2O (150ml) was added N HCl (150ml) and the reaction mixture was stirred at room temperature for 3h. After decantation, the aqueous layer was washed with Et_2O (4x150ml), basified with NH_4OH and extracted with AcOEt (3x150ml).The combined organic layers were washed with water (4x150ml), dried and filtered. Removal of solvent *in vacuo* gave **58** (*Rf* (CH_2Cl_2/MeOH 95:5)0.30) which was used in the next step without further purification.

Compound **60** was prepared in the same manner as compound **10** as a white solid (6.2g, 79%), (*Rf* (CH_2Cl_2)0.17).

A solution of **60** (6.2g, 12mmol) and 1N NaOH (40ml) in dioxane (100ml) was stirred at reflux for 6h. The reaction mixture was cooled , diluted with water (150ml) and acidified with 1N HCl (45ml). The mixture was then extracted with AcOEt (3x150ml) and the combined extracts were washed with water (3x150ml), dried over $MgSO_4$, filtered and evapored *in vacuo* to give **62** (5.6g, 93%) as a white solid.

A solution of **62** (8g, 16.5mmol) and H_2N-L-Lys(ε-Cbz)-$CONHCH_2Ph$ (7.4g, 20mmol) in DMF (200ml) was cooled at -5°C, then a solution of DPPA (2.3ml, 20mmol) in DMF (25ml) was added dropwise. After stirring at -5°C for 0.5h, TEA (4.93ml, 0.035mol) was added and the reaction mixture was stirred for 3h at the same temperature and 42h at room temperature. After concentration *in vacuo*, the residue was diluted in AcOEt (250ml). This organic layer was washed with 0.5N citric acid (2x100ml), aqueous $NaHCO_3$ (2x100ml) and aqueous saturated NaCl solution (2x100ml), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by chromatography on silica gel (AcOEt/cyclohexane 50 :50) to afford **69, form A** (2.3g, 17%) (*Rf* [AcOEt:cyclohexane(60:40)]0.06) and **69, form B** (1.9g, 14%) (*Rf* (AcOEt/cyclohexane 60:40)0.04).

A mixture of **69, form A** (2.3g, 2.7mmol) and IMe (30ml, 0.48mol) was stirred at room temperature for 20h and then concentrated *in vacuo*. The resulting residue was washed with CH_2Cl_2 (3x100ml) and concentrated *in vacuo* to give a solid which was dissolved with DMF (80ml) and CH_2Cl_2 (80ml). Then, NaH 50% (0.7g, 13.5mmol) was added by portions at -5°C and the reaction mixture was stirred at 0°C for 4h. Then, water (100ml) was cautiously added and the stirring was maintained overnight at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was washed with CH_2Cl_2 (250ml) and water (100ml). The aqueous layer was extracted with CH_2Cl_2 (3x100ml) and the combined extracts were washed with water (3x100ml), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The resulting residue was purified by chromatography on silica gel (AcOEt/cyclohexane :60/40) to afford **70, form A** (0.31g, 15%) (*Rf* (CH_2Cl_2/MeOH 95:5)0.30).

Compound **70, form B** was prepared in the same manner as compound **70, form A** but using K_2CO_3 as base in place of NaH ; *Rf* (CH_2Cl_2/MeOH 98:2)0.25.

A suspension of **70, form A** (0.3g, 0.38mmol) in 2.5N HCl/MeOH (0.18ml, 0.46mmol), Pd(C) 10% (60mg) and MeOH (10ml) was hydrogenated (14.7 psi) at room temperature for 6h, then filtered and concentrated *in vacuo*. The resulting residue was washed with iPr_2O to give **8a, form A** (0.27g, 99%) as a white solid ; mp 195°C.IR (KBr) 3410, 3300, 3000-2500, 1655, 1545, 1525 cm^{-1}. ^1H NMR (DMSO-*d6*, 250 MHz) : δ 11 (s, 1H, NH indole), 8.2 (t, 1H, NH), 8.1 (s, 1H, NH), 7.8 (bs, 3H, NH_3^+), 7.5 (d, 1H, indole), 7.35 (d, 1H, indole), 7.3 to 7.1 (m, 17H, $3xC_6H_5$ + indole), 7 (t, 1H, indole), 4.4 (dd, 1H, CH diphenylpropionyl), 4.25 (dd, 1H, H_2'), 4.15 (m, 2H, CH_2 benzylamino), 3.1 to 2.7 (m, 8H, H_6,H_5', CH_2 indole and CH_2 diphenylpropionyl), 2 to 1.2 (m complex, 8H, H_4', H_3, H_4 and H_5). MS (FAB) *m/z* 656 (M + H^+). Anal. calcd for $C_{41}H_{46}ClN_5O_3$: C, 71,13; H, 6,70; Cl, 5,12; N, 10,12; found: C, 71,1; H, 6,7; Cl, 5,4; N, 10,2; $[\alpha]_D^{20}$ - 42,2° +/- 1.2 (*c* 0,5; MeOH).

Compound **8b, form B** was prepared as above as a white solid ; mp 250°C. IR (KBr) 3405, 3290, 3000-2500, 1655, 1550 cm^{-1}. ^1H NMR (DMSO-*d6*, 400 MHz) : δ 11.1 (s, 1H, NH indole), 8.7 (s, 1H, NH), 8.6 (t, 1H, NH), 7.6 (vbs, 3H, NH_3^+), 7.5 (d, 1H, indole), 7.4 (d, 1H, indole), 7.35 to 7.2 (m, 16H, $3xC_6H_5$ + indole), 7.1 (t, 1H, indole), 7 (t, 1H, indole), 4.4 (dd, 1H, CH diphenylpropionyl), 4.3 and 4.1 (dd, 2H, CH_2 benzylamino), 4.08 (dd, 1H, H_2'), 3.1 and 2.8 (m, 2H, CH_2 diphenylpropionyl), 3.07 and 3 (AB, 2H, CH_2 indole), 2.8 and 2.2 (m, 2H, H_5'), 2.5 (bt, 2H, H_6), 2.2 and 1.8 (m, 2H, H_4'), 1.6 and 0.8 (m, 2H, H_3), 1.2 (bq, 2H, H_5), 0.4 and 0.1 (m, 2H, H_4). MS (FAB) *m/z* 656 (M + H^+). Anal. calcd for $C_{41}H_{46}ClN_5O_3$: C, 71,13; H, 6,70; Cl, 5,12; N, 10,12; O, 6,93; found: C, 70,7; H, 7,0; Cl, 5,3; N, 10,1; O, 6,9; $[\alpha]_D^{20}$ + 11,3° +/- 0.6 (*c* 0,5; MeOH).

N-Benzyl-6-amino-2-(S)-{3-benzyl-2-oxo-3-[(3,3-diphenylpropionyl) amino]-pyrrolidin-1-yl}-hexanamide (7a and 7b).

To a solution of n-BuLi (12ml, 24mmol) (1.6M solution in hexane) in THF (20ml) was added dropwise at -70°C a solution of **54** (5.9g, 23.5mmol) in THF (30ml). After 1h at -70°C, a solution of $PhCH_2Br$ (2.8ml, 23.5mmol) in THF (10ml) was added and the reaction mixture was allowed to room temperature and stirred overnight. The reaction mixture was poured into water and extracted with AcOEt(3x50ml). The combined extracts were dried over MgSO4, filtered and concentrated *in vacuo* to give **55** as a viscous oil which was used in the next step without further purification.

Compound **57** (2.4g, 40%) was obtained in a similar manner as **56** as a yellow oil, (*Rf* (CH_2Cl_2/MeOH 98:2) 0.23).

To a solution of **57** (9.5g, 37.5mmol) in THF (50ml) was added Boc_2O (8.3g, 38mmol) and the reaction mixture was stirred at room temperature overnight. Then, TEA (5.4ml, 37.4mmol) was added and the stirring was maintained for 10h. The reaction mixture was concentrated *in vacuo*. Then AcOEt (100ml) added, and the organic layer was washed with water (2x20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by chromatography (CH_2Cl_2/cyclohexane 80 :20) gave **59** (12.5g, 94%) as a colorless oil (*Rf* (CH_2Cl_2/cyclohexane 80:20)0.54).

A mixture of **59** (12.4g, 35mmol), 1N NaOH (120ml, 0.12mol) in dioxane (240ml) was heated at reflux for 5h. The reaction mixture was allowed to cool and then evaporated *in vacuo*. The residue was diluted with water (300ml) and acidified with 1N HCl (120ml). The resulting precipitate was collected by filtration and redissolved in AcOEt (200ml). This organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **61** (10.1g, 82%) as a yellow solid ; mp 137°C.

Compound **63** (3.57g, 70%) was obtained in the same manner as **1a** from **61** (2.5g, 7.4mmol). Pure diastereoisomers **65 form A** (1.6g) (*Rf* (AcOEt/cyclohexane 40:60)0.15) and **65 form B** (1.24g)) (*Rf* [AcOEt:cyclohexane (40:60)]0.09) were purified by chromatography on silica gel.

Compounds **66 form A** (0.88g, 61%) (*Rf* [AcOEt:cyclohexane (40:60)]0.28) and **66 form B** (0.8g, 74%) (*Rf* (CH_2Cl_2/MeOH 95:5)0.31) were obtained in the same manner as **70 form A** from **65 form A** (1.6g, 2.3mmol) and from **65 form B** (1g, 1.45mmol) respectively.

To a solution of **66 form A** (0.8g, 1.2mmol) in $HCCl_3$ (15ml) was added CF_3CO_2H (5ml) at 0°C. The reaction mixture was allowed at room temperature and stirred overnight. After concentration *in vacuo*, the residual oil was diluted with water, basicified with aqueous 28% NH_3 and extracted with CH_2Cl_2 (3x50ml). The combined extracts were washed with water (2x25ml), dried over $MgSO_4$, filtered and concantrated *in vacuo* to give **67 form A** (640mg, 98%) as a colorless oil (*Rf* (CH_2Cl_2/MeOH 95:5)0.28).

Compound **67 form B** (540mg, 83%) (*Rf* (CH_2Cl_2/MeOH/TEA 90:8:2)0.57) was obtained in the same manner as above from **65 form B** (0.78g, 1.2mmol).

Compounds **68 form A** (0.6g, 68%) and **68 form B** (0.3g, 40%) were obtained in the same manner as **10** from **67 form A** (0.6g, 1.18mmol) and from **67 form B** (0.54g, 1mmol) respectively.

Compound **7a.HCl form A** (267mg, 51%) was obtained in the same manner as **8a** from **68 form A** (0.6g, 0.8mmol) as a white solid ; mp 118°C. IR (Kbr) 3410, 3300, 3000-2500, 1660, 1545 cm^{-1}. ^1H NMR (DMSO-*d6*, 300 MHz) : δ 8.5 (t, 1H, NH benzyl), 8.2 (s, 1H, NH), 8 (bs, 3H, NH_3^+), 7.4 to 7.1 (m, 20H, $4xC_6H_5$), 4.5 (t, 1H, CH diphenylpropionyl), 4.4 (t, 1H, H_2), 4.3 (m, 2H, CH_2 benzylamino), 3.1 to 2.7 (m, 8H, H_6, H_5', CH_2 benzyl, CH_2 diphenylpropionyl), 2 to 1.3 (m, complex, 8H, H_4', H_3, H_4, H_5). MS (DCI/NH_3) *m/z* 617 ($M + H^+$). Anal. calcd for $C_{39}H_{45}ClN_4O_3$: C, 71,71; H, 6,94; Cl, 5,43; N, 8,58; found: C, 72,0; H, 7,4; Cl, 6,0; N, 8,7; $[\alpha]_D$ - 37° +/- 0.8 (*c* 1; MeOH).

Compound **7b.HCl form B** (1g, 85%) was obtained in the same manner as **8a** from **68 form B** (1.35g, 1.8mmol) as a white solid ; mp 150°C. IR (Kbr) 3420, 3300, 3000-2500, 1650, 1545 cm^{-1}. ^1H NMR (DMSO-*d6*, 300 MHz) : δ 8.7 (s, 1H, NH), 8.65 (t, 1H, NH), 7.4 to 7.1 (m, 20H, $4xC_6H_5$), 4.4 (dd, 1H, CH

diphenylpropionyl), 4.35 (dd, 1H, benzylamino),4.25 (dd, 1H, H_2), 4.10 (dd, 1H, benzylamino), 3.1 (dd, 1H, CH diphenylpropionyl), 2.9 (AB, 2H, CH_2 benzyl), 2.8 (dd, 1H, CH diphenylpropionyl), 2.6 (bt, 2H, H_6), 2.9 and 2.3 (m, 2H, H_5'), 2.2 and 1.9 (m, 2H, H_4'), 1.4 (q, 2H, H_5), 1.8 and 1.1 (m, 2H, H_3), 0.8 and 0.4 (m, 2H, H_4). MS (DCI/NH_3) *m/z* 617 ($M + H^+$). Anal. calcd for $C_{39}H_{45}ClN_4O_3$: C, 71,71; H, 6,94; Cl, 5,43; N, 8,58; found: C, 71,7; H, 7,0; Cl, 5,3; N, 8,4; $[\alpha]_D$ - 11,3° +/- 0.7 (*c* 0,62; MeOH).

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