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Synthesis of new bicyclic lactam peptidomimetics by ring-closing metathesis reactions

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Abstract—An efficient and versatile synthetic method for the preparation of new fused bicyclic lactams **3a** and **3b** is described. The spirane cyclopentane nucleus was easily installed by diallylation of the pyroglutamate derivative **18** followed by ring-closing metathesis (RCM). A more practical and stereoselective method for the allylation of the α-methoxy carbamate **21**, involving the use of $InCl_3$ as a Lewis acid, was developed. In the crucial coupling reaction of the diastereomeric mixture of *cis*- and *trans*-pirrolidine derivatives **5a** and **5b** with *N*-Cbz vinyl phenylalanine only the *cis* isomer was found to react. An RCM reaction on the dipeptides **25a** and **25b** followed by catalytic hydrogenation, gave the final epimeric bicyclic lactams **3a** and **3b**. The same synthetic sequence on the model compound **7**, lacking the spiro cyclopentane nucleus, is also reported.

1. Introduction

Bradykinin (**1**) is a natural nonapeptide implicated in a great variety of physiological disorders such as hyperalgesia, inflammation and asthma.[1] A rational design of potential antagonists is made difficult by the lack of any knowledge on a 3D structure of the ligand–receptor complex.[2] Therefore, the synthesis of modified bradykinins could provide useful information on the structural features essential for receptor binding. One of the most active nonnatural bradykinin antagonist, derived from a modification of the peptide chain, is Hoe-140 (**2**, Icatibant)[3] in which Pro,[3] Phe,[5] Pro,[7] and Phe[8] are replaced by Hyp, Thi, D-Tic, and Oic respectively. One additional unit of D-Arg is also linked to the peptide N terminus. It has been hypothesized that the D-Tic[7]-Oic[8] moiety is crucial for the bioactive conformation of the whole peptide as a site of a β-turn.[4] Interest in bradykinin B2 receptor antagonists has been further stimulated by the recent discovery that HOE-140 exhibits mitogenic agonism in various tumour cell lines.[5]

HArg[1]-Pro[2]-Pro[3]-Gly[4]-Phe[5]-Ser[6]- Pro[7]-Phe[8]-Arg[9]OH

1

D-Arg[0]-Arg[1]-Pro[2]-Hyp[3]-Gly[4]-Thi[5]-Ser[6]- D-Tic[7]-Oic[8]-Arg[9]

2

Our continuing interest in the synthesis of conformationally restricted peptidomimetics,[6] based on bicyclic lactam derivatives, led us to consider whether the unnatural dipeptide D-Tic-Oic could be mimicked by more constrained structures like **3**. The design of such molecules was based on the observation of a fairly good overlapping between some families of minimum energy conformations of the D-Tic-Oic fragment and 5,7-fused bicyclic lactams **11**. However, these dipeptide mimetics completely lack a lipophilic portion that should mimic the fused cyclohexane ring of the octahydroindole nucleus. The presence of this structural unit may be important as a site of hydrophobic interactions with the receptor. Thus we modified our original targets by appending a spirocyclopentane moiety to the C-4 position of the proline ring. Molecular mechanics calculations[7] showed a fairly good overlapping of some families of minimum energy conformations of the *N*-acetyl *N*′-methyl amide derivative of the D-Tic-Oic dipeptide and the bicyclic peptidomimetic scaffold **3b** (Fig. 1). It is interesting to note that the bicyclic scaffold is able to adopt a reverse-turn conformation. The RMS deviation in rigid

Keywords: ring-closing metathesis reaction; bicyclic lactam; Lewis acid.
Abbreviations: Hyp, *trans*-4-hydroxy-L-proline; Thi, 3-(2-thienyl)-L-alanine; D-Tic, (*R*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; Oic, (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid; PyBroP®, bromotripyrrolidinophosphoniumhexafluorophosphate.
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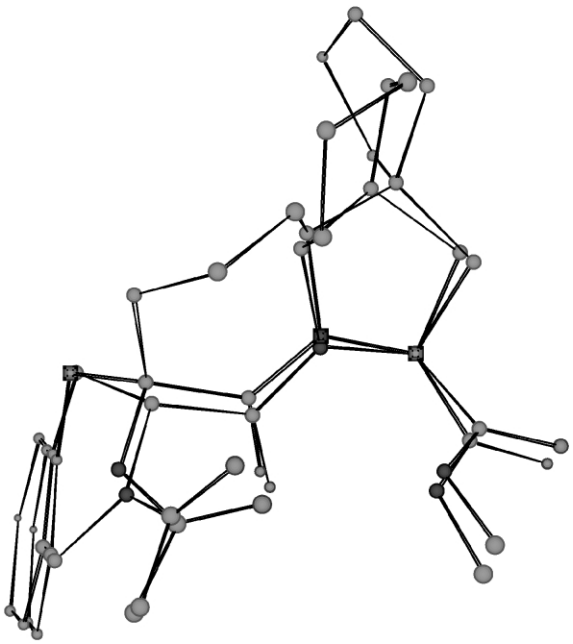
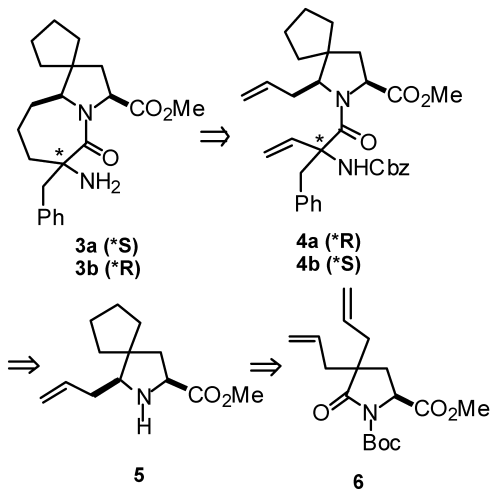


Figure 1.

superimposition between energy minimized conformations featuring a β-turn is 0.15 Å for the dipeptide backbone atoms.

Here we report on the synthesis of **3a** and **3b** by taking advantage of ring closing metathesis (RCM) reactions[8] for constructing both the spirane cyclopentane moiety and the 5,7-fused bicyclic nucleus, as indicated in the retrosynthetic sequence depicted in Scheme 1.

RCM reactions have been already applied to the synthesis of bicyclic lactams like **3**,[9–12] but no examples are known in which the vinyl component is linked to a quaternary α-amino acid center. A major concern arises from the coupling of the two amino acid units to give **4a**,**b**. Extensive literature search as SciFinder and Beilstein x-fire databases, revealed the absence of any report on the peptide bond formation between a 5-substituted proline and an *N*-protected α,α-disubstituted amino acid. Therefore, we decided to test the synthetic sequence on the model



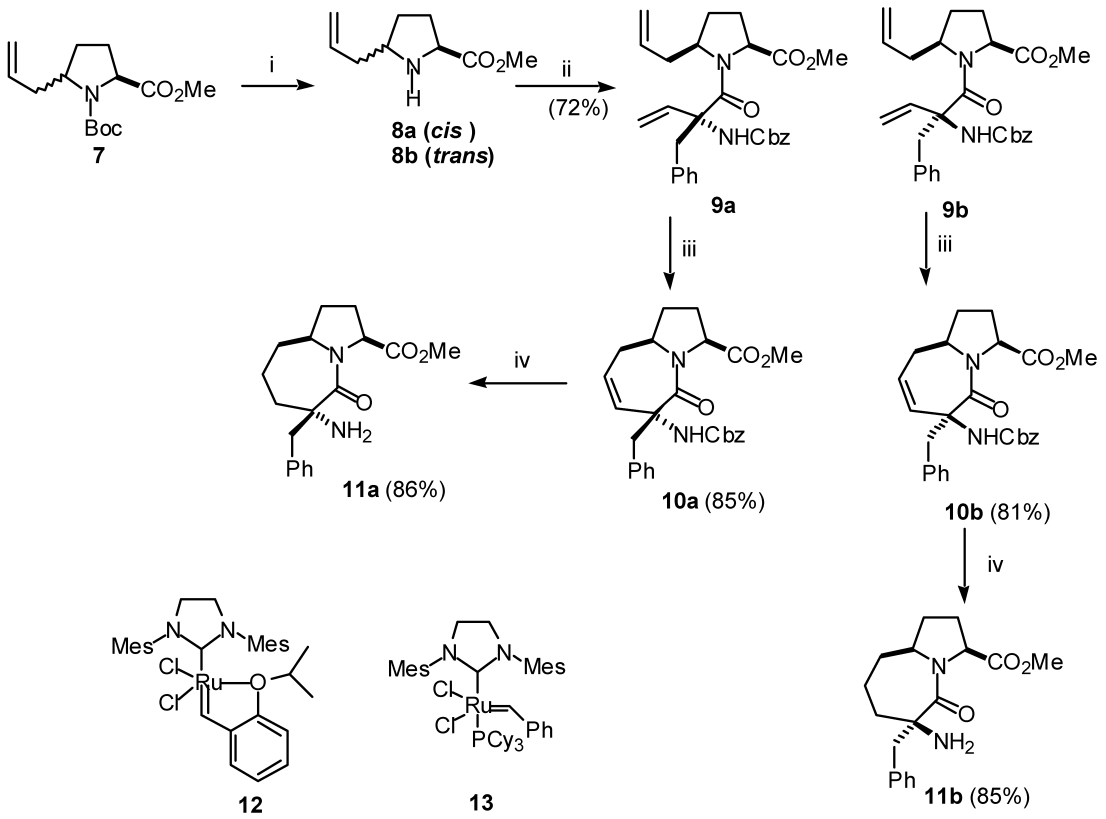
Scheme 1. Retrosynthetic analysis.

compound **7**, lacking the spiro cyclopentane nucleus. On the other hand, the simplified final products **11a** and **11b** would be valuable per se as constrained mimics of the Phe-Pro dipeptide.

2. Results and discussion

The starting *N*-Boc-5-allyl-L-proline methylester **7** (Scheme 2) was prepared according to a literature procedure as an inseparable mixture of *cis* and *trans* isomers.[9,10,13,14] Deprotection of the nitrogen protecting group allowed the separation of the isomeric free amines **8a** and **8b** through careful chromatographic purification. The subsequent coupling with *N*-Cbz-vinyl phenylalanine **17** was attempted using the amino acid in a racemic form. This choice was dictated primarily by our need of preparing both epimers of the final compound at the quaternary stereocenter. It seemed more practical to rely on a chromatographic separation of the diastereomeric pair of a suitable advanced intermediate rather than to prepare both enantiomers of vinyl phenylalanine, whose reported syntheses are lenghty and laborious, particularly for gram scale preparations.[15–20] Racemic **17** was prepared through a simplified modification of a literature enantioselective method (Scheme 3).[18] Benzylation of the lithium enolate derived from methyl 2-benzamido crotonate **14**[21] gave mainly the α-alkylated product **15**, whose treatment with 6N HCl gave the fully deprotected amino acid **16**. Protection of the amine function as an *N*-Cbz derivative was found to be not a trivial operation. High yields could be obtained only through the use of non aqueous conditions and di-benzyl dicarbonate as a reagent.[22] The key coupling reaction between the *cis*-proline derivative **8a** and *N*-Cbz vinyl phenylalanine **17** required extensive experimentation. Among the numerous activating agents and reaction conditions tested,[23] only PyBroP®[24] gave satisfactory results affording the dipeptides **9a** and **9b** in an acceptable 72% yield. The diastereomeric pair of coupled products was obtained in an approximately 1:1 ratio and, fortunately, their ΔR_f (0.37 vs. 0.28, *n*-Hex/EtOAc 75:25) allowed an easy separation by flash chromatography. When the same reaction was performed on the *trans*-proline derivative **8b** under identical experimental conditions, no coupled product was obtained, suggesting the occurrence of a strong kinetic resolution effect. This was also proved by reacting an approximately equimolar mixture of **8a** and **8b** with racemic *N*-Cbz vinyl phenylalanine. Careful analysis of the reaction mixture revealed the formation of the dipeptides deriving only from the *cis* proline derivative **8a**, while the *trans* isomer was recovered unchanged in a yield close to 90%. Configurational assignment of the quaternary stereocenter was assured by correlation with a diastereomerically pure sample of **9a**, obtained by the same procedure but starting from enantiomerically enriched (>95% e.e.) (*R*)-vinyl phenylalanine, prepared on milligram scale according to the method reported by Seebach.[16]

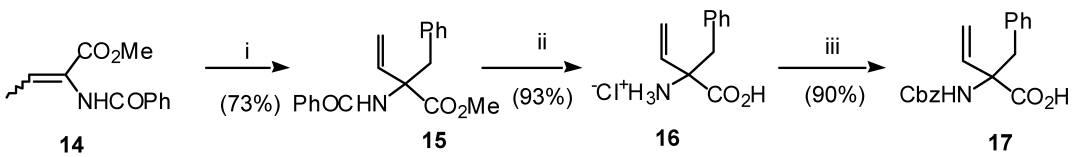
The following RCM reaction was initially carried out separately on each diastereomer. Good yields could be obtained only by the use of the more thermally stable second generation Grubbs catalyst **13**[25] or Hoveyda catalyst **12**.[26] The last one has the great advantage of being recoverable by



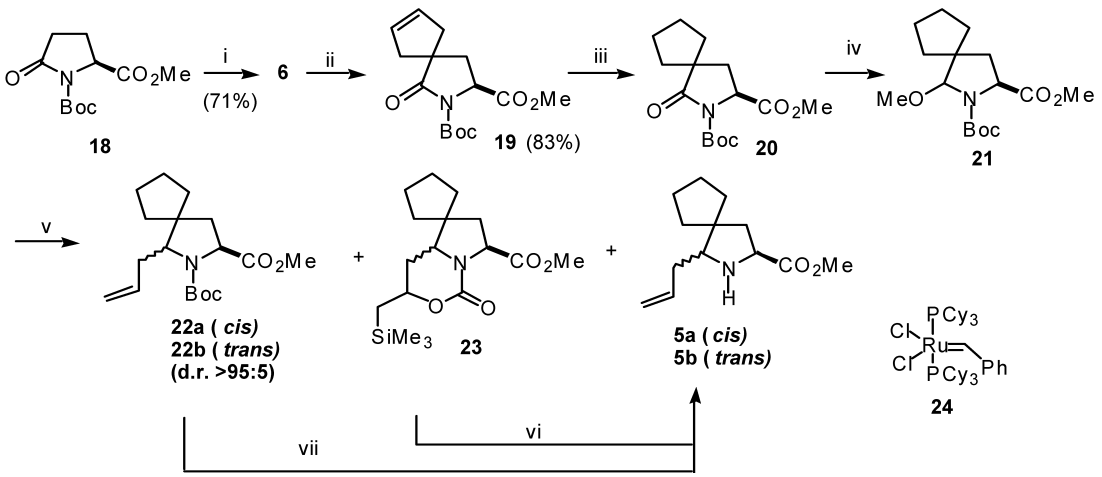
Scheme 2. (i) HCl/MeOH. (ii) PyBroP®, **17**, DIEA, DMAP, CH_2Cl_2. (iii) **13**, toluene, reflux. (iv) 10% Pd/C, H_2, EtOH.

chromatography and hence reusable for further cycles. As the ΔR_f of the cyclized products **10a**,**b** was higher than that of their acyclic precursors (0.16, *n*-Hex/EtOAc 3:2, vs. 0.08, *n*-Hex/EtOAc 3:1), we routinely performed the RCM step on the diastereomeric mixture, postponing the chromatographic separation of diastereoisomers to the cyclized products. Saturation of the double bond and removal of the *N*-Cbz prtotecting group was then effected in one operation by standard catalytic hydrogenation, giving **11a** and **11b** in 85 and 86% yield, respectively.

Having established the feasibility of the proposed synthetic sequence on the model compound, the stage was set for its application to the spiro compounds **3a**,**b**. Attachment of a spirocyclopentane to the 4-position of methyl *N*-Boc pyroglutamate was first attempted by bis-alkylation of the imide enolate with 1,4-dihalo butanes and 1,4-dihalo-*cis*-2-butenes, but only mediocre results were obtained. The problem was circumvented by resorting to a double allylation reaction of the pyroglutamate **18**[27] to give **6**, followed by a high yielding RCM reaction promoted by **24** (Scheme 4). By adjustment of the experimental conditions we were able to increase the yields of the bis-allylation step in comparison to those reported for an almost identical substrate.[27] Although it was reported that enolate formation in pyroglutamates is highly regioselective and no epimerization occurs at the stereocenter adjacent to the ester function,[27,28] the optical rotation value we measured for **6** was much lower than that reported for the corresponding ethyl ester.[27] In order to verify that no epimerization had occurred under our modified conditions, the enantiomeric excess of the advanced intermediate **20** was determined by chiral HPLC and shown to be 99.6% (see Section 3 for details). The spiro compound **20** was prepared by RCM of **6** followed by standard catalytic hydrogenation. Selective reduction of the imide carbonyl with Et_3LiBH[29] was followed, without purification, by treatment with trimethyl orthoformate in methanol to give the *N*-Boc-*N*,*O*-acetal **21** in a diastereomeric ratio >95:5 (300 MHz NMR). The configuration of the newly formed stereocenter was not determined, since it should be converted into an sp^2 center in the subsequent allylation reaction that is known to proceed via an intermediate acyliminium ion.[30] Such species are usually formed in situ by treatment of hemiaminal derivatives with air sensitive Lewis acids at low temperature. In order to make the allylation step more practical, we briefly surveyed the use of Lewis acids which could be effective for promoting the acyliminium ion formation in less drastic conditions and possibly avoiding the use of strictly anhydrous solvents. The screening was



Scheme 3. (i) BnBr, LDA, THF/HMPA. (ii) 6N HCl, reflux. (iii) $(Cbz)_2O$, Me_4NOH, CH_3CN.



Scheme 4. (i) Allyl Br, LiHMDS, THF/DMPU, −78°C. (ii) **24**, DCM. (iii) 10% Pd/C, H_2, EtOH. (iv) (a) $LiEt_3BH$, THF, −78°C; (b) $CH(OMe)_3$, PPTS, MeOH. (v) Allyltrimethylsilane, $InCl_3$, DCM. (vi) Bu_4NF, THF. (vii) TFA/DCM.

restricted to indium and ytterbium salts and $InCl_3$ was found to give the best results in terms of yield and mildness of the reaction conditions.[31] Reaction of the crude α-methoxy carbamate **21** with excess allyltrimethylsilane in the presence of an equimolar amount of $InCl_3$ in CH_2Cl_2 at room temperature afforded the allylated adduct **22** in good yields. Although all allylation reactions were run in anhydrous CH_2Cl_2 (distilled over CaH_2), the same transformations also worked with reagent grade solvent in comparable yields.

The reaction is highly diastereoselective, affording one predominant diastereomer in a ratio >95:5 (400 MHz NMR). 1D NOE and NOESY experiments were of no avail for determining the relative configuration of the new stereocenter. A tentative assignment was thought possible by comparison of NMR data with those of the analogous *cis* and *trans* compounds **7** lacking the spirocyclopentane nucleus (Scheme 2). To this end, a method that could give access to both diastereoisomers of **22** was needed. Taking advantage of our previous experience on similar systems,[6] we were able to obtain a 3:1 mixture of **22a** and **22b** by reacting the crude reduction product from **20** with tributyl allylstannane in the presence of *t*-butyl dimethylsilyl triflate at −78°C, without prior conversion into the α-methoxy carbamate derivative **21**. Removal of the *N*-Boc protecting group with TFA gave a chromatographically separable mixture of **5a** and **5b** in the same ratio as the starting material with the major isomer being identical to that produced in the $InCl_3$ promoted reaction. This was assigned a *cis*-relative configuration by comparing chemical shifts of relevant protons in **5a**,**b** with the corresponding protons in **8a**,**b**, whose relative configurations were known from literature data (Table 1).[32] A confirmation of this tentative assignment was obtained from NOESY experiments on the final compounds **3a** and **3b** (see below).

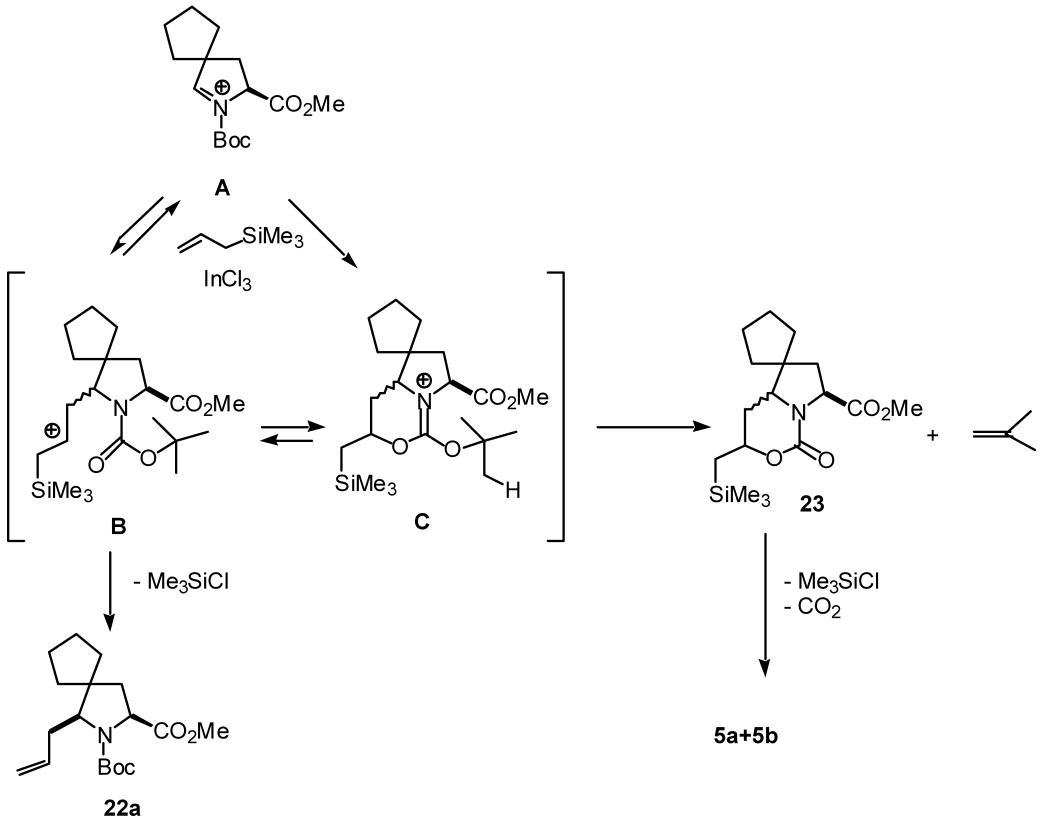
Table 1. Comparison of chemical shifts of H-2 and H-5 in compounds **5a**,**b** and **8a**,**b**

	δH-5[a] (ppm)	δH-2[a] (ppm)
8a	3.15	3.78
5a	2.87	3.79
8b	3.25	3.81
5b	3.09	3.83

[a] H-5 and H-2 are referred to the protons linked to carbons adjacent to the allyl and carbomethoxy groups, respectively.

Beside the desired product, the $InCl_3$ catalyzed allylation reaction gave two side-products in 18 and 10% yield, respectively. The former was immediately recognized as the deprotected free amine **5** while the latter resulted from intramolecular trapping of a β-silyl carbenium ion by the *N*-Boc group, followed by the loss of 2-methylpropene.The formation of such an oxazinone **23** from α-methoxycarbamates has already been reported in reactions catalyzed by $TiCl_4$.[13] The stereochemical course of this reaction deserves some comments. While the *N*-Boc protected allyl derivative **22** was formed with high stereoselectivity, the free amine **5** was produced as a 6:4 mixture of *cis* and *trans* isomers. This result suggests that the deprotected allyl derivative **5** derives from the trimethylsilyl oxazinone **23** through an elimination reaction promoted by the attack of chloride ions on the silicon atom of the cyclized intermediate (Scheme 5). This hypothesis was corroborated by the following experiments. Treatment of **22** with $InCl_3$ under the same experimental conditions as the allylation reaction did not afford any deprotected product, excluding the hypothesis that **5a**,**b** could directly derive from **22** through the catalysis of the Lewis acid. Moreover, the ratio between **5** and **22** is considerably increased in favor of the desilylated product when using longer reaction times. The intermediate silyl oxazinone **23**, that was formed as a mixture of only two out of four possible diastereoisomers, by reaction with Bu_4NF in THF gave the N-deprotected allyl derivatives **5a**,**b** with the same diasteromeric ratio as the oxazinone **23**. The use of indium salts with non nucleophilic counterions such as $In(OTf)_3$ did not afford any deprotected product, supporting the role of chloride ions as nucleophilic species that promote the elimination of Me_3SiCl from **23**. However, the $In(OTf)_3$ catalyzed allylation was of no synthetic value as the allylated product was formed in very poor yield.

Two possible explanations of the stereochemical divergence in the formation of **22** with respect to **23** and **5** may be advanced. The accepted mechanism[33] of the allylation of

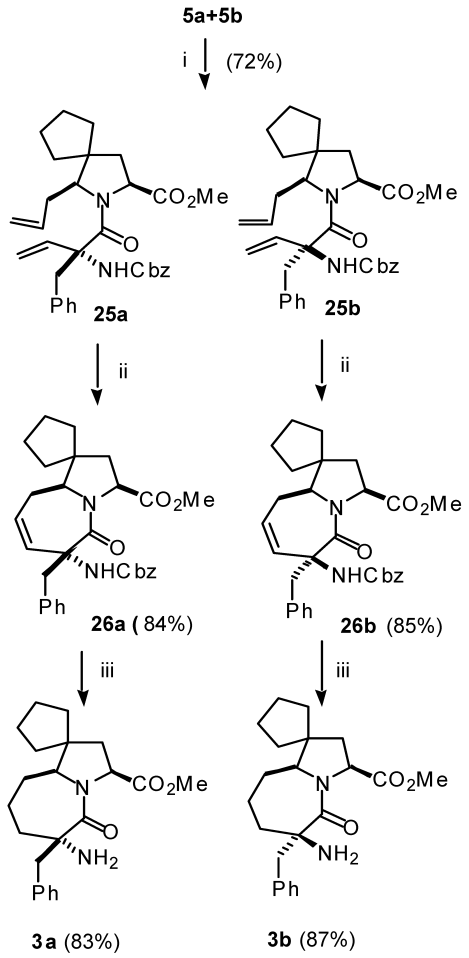


Scheme 5.

iminium ions and carbonyl compounds by allyltrimethylsilane involves the formation of an intermediate β-silyl carbenium ion (intermediate **B** in Scheme 5) that undergoes an elimination reaction by attack of a nucleophile on the silicon center. In our particular case the carbenium ion **B** can also follow a pathway leading to the iminium ion **C** and, after elimination of 2-methyl-2-propene, to the final oxazinone **23**. If this mechanistic picture is true, the only possible explanation of the stereoselective formation of **22** is that the elimination of Me_3SiCl from the carbenium ion **B** is much more faster on the *cis* than the *trans* isomer. At present we cannot explain this kinetic resolution effect. We can only speculate that the relative rate by which the intermediate **B** can be converted in either **C** or **22a** may be dependent on the conformational preference of the Boc carbonyl group. A *trans* conformational arrangement of the proline peptide bond places the carbonyl oxygen far from the carbocation, making more difficult the formation of adduct **C**. It is, however, unclear how the conformational properties of the intermediate **B** could be influenced by the relative configuration of C-2 and C-5. An alternative, simpler explanation is that the bicyclic intermediate **C** is formed directly from the iminium ion **A** via a [4+2] cycloaddition with the double bond of the silane acting as a dienophile. A concerted mechanism for the addition of cyclic *N*-acyliminium ions and 2-silyloxy-1,3-dienes has been already hypothesized.[34]

In practice, we treated the crude allylation reaction mixture with Bu_4NF and, after aqueous workup without purification, submitted the crude product to reaction with TFA in order to remove the residual carbamate protecting group. The sequence from the spiro bicyclic pyroglutamate derivative **19** to the allylated free proline derivatives **5a**,**b** was routinely carried out without any purification in 59% yield, that corresponds to a 88% average yield for each step. The coupling reaction with racemic vinyl phenylalanine proceeded using the same experimental conditions as in the model study. Again, a remarkably higher reactivity of the *cis* isomer allowed the use of the diastereomeric mixture of **5a** and **5b**. The reaction of the separated *trans* isomer did not proceed at a detectable rate under the usual conditions allowing an almost complete recovery of the unaffected starting material. The ensuing RCM reaction, as in the case of the model compound, was performed on the mixture of the two diastereomers, since the ΔR_f of the cyclized products was higher than that of the acyclic dipeptides. The assignment of the configuration of the quaternary stereocenter was assigned as before by correlation with a diastereomerically pure compound prepared from enantio-enriched *N*-Cbz vinyl phenyl alanine (>95% e.e.).[16]

Repetition of the last two steps, under the same conditions as the model study, gave without, any difficulties, the final compounds **3a** and **3b** with the yields indicated in Scheme 6. Molecular mechanics calculations performed on the *R* isomer **3b** showed that in some minimum energy conformations the distance between the benzylic protons and the hydrogen atom linked to the bicyclic lactam fusion carbon was short enough to observe an NOE correlation. As a matter of fact, the NOESY spectrum of **3b** showed a small



Scheme 6. (i) PyBroP®, **17**, DIEA, DMAP, CH_2Cl_2. (ii) **12**, DCE. (iii) 10% Pd/C, H_2, MeOH.

but unequivocal cross peak correlating these protons. No such correlation was evidenced by the NOESY spectrum of the *S* isomer. This is a definite proof of the *cis* relationship between the two hydrogen atoms flanking the proline nitrogen, thus confirming the tentative stereochemical assignment discussed above.

In conclusion we have developed an efficient approach toward new bicyclic lactams. The novel elements introduced in this synthetic sequence are a practical and stereoselective allylation reaction on an acyliminium ion catalyzed by $InCl_3$ and a peptide bond formation between 5-substituted proline derivatives and a *N*-protected α,α-disubstituted amino acid. The conformationally constrained peptidomimetics we have so prepared have been inserted in place of the D-Tic-Oic fragment in HOE-140 analogues. The solid phase synthesis of these nonapeptides and their biological activity as bradykinin antagonists will be reported elsewhere.

3. Experimental

3.1. General

THF was distilled from sodium/benzophenone ketyl and MeCN from P_2O_5 under nitrogen. TLC was performed on Kieselgel 60 F_{254} (Merck) glass Plate with detection by UV light, iodine, or a solution of 4,4′- methylenebys-*N*,*N*-dimethylaniline, ninidrine, KI in an aqueous ethanolic solution of AcOH. Flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Melting points were determined on a Kofler apparatus and are uncorrected. Optical rotations were measured at 20°C with a Perkin–Elmer 343 polarimeter. The ^1H (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded with Bruker Avance 300 and 400 instruments, respectively. In the peak listing of ^{13}C spectra abbreviations s and t refer to zero and two protons attached to the carbons, as determined by DEPT experiments. Infrared spectra were recorded on a Perkin–Elmer FTIR 1600 series spectrometer. Mass spectra were recorded on a Finnigan LCQ-DECA mass spectrometer. Elemental analyses were performed on a Carlo Erba Elemental Analyzer Mod. 1106.

3.1.1. (5*R* and 5*S*,2*S*)-5-Allyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (7a and 7b). A 1.0 M solution of lithium triethylborohydride in THF (9.86 mL, 9.86 mmol) was added to a solution of (*S*)-*N*-Boc pyroglutamic acid methyl ester (**18**) (2.0 g, 8.22 mmol) in THF (50 mL) at −78°C under a nitrogen atmosphere. After 30 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and warmed to 0°C. Thirty percent H_2O_2 (1.5 mL) was added, and the mixture was stirred at 0°C. After 20 min the organic solvent was removed in vacuo, and the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried, filtered and evaporated to dryness. The crude reaction mixture was used without purification and dissolved in CH_2Cl_2 (80 mL) under nitrogen. After the addition of allyltributyltin (3.06 mL, 9.86 mmol) the solution was cooled to −78°C and *t*-butyldimethylsilyl trifluoromethanesulphonate (2.26 mL, 9.86 mmol) was added. After 20 min the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL), extracted with CH_2Cl_2 (3×30 mL), dried and evaporated. Purification by flash chromatography eluting first with C_6H_{14} and then C_6H_{14}/AcOEt 85:15 gave 1.66 g (75%) of an inseparable 65:35 mixture of **7a** and **7b** as a colorless oil. TLC R_f 0.35 (C_6H_{14}/AcOEt 85:15). ^1H NMR ($CDCl_3$, 400 MHz, mixture of diatereoisomers and conformers) δ: 1.40 and 1.47 (2s, 9H: 1.9:1), 1.56–1.83 (m, 1H), 1.83–2.29 (m, 4H), 2.38–2.78 (bm, 1H), 3.71 and 3.73 (s, 3H: 1:1.9), 3.80–4.12 (3m, 1H), 4.16–4.36 (m, 1H), 4.99–5.12 (m, 2H), 5.67–5.87 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, mixture of diatereoisomers and conformers) δ: 28.4, 28.6, 28.7, 29.1 (t), 29.9 (t), 38.5 (t), 38.6 (t), 39.3 (t), 39.5 (t), 52.2, 52.4, 57.8, 57.9, 58.3, 58.4, 59.9, 60.1, 60.2, 60.5, 80.2 (s), 80.3 (s), 117.2 (t), 117.6 (t), 117.7 (t), 135.4, 135.5, 135.7, 153.9 (s), 154.0 (s), 154.6 (s), 154.7 (s), 173.7 (s), 174.0 (2 peaks, s), 174.2 (s). IR (neat) 1752, 1701, 1655, 1640, 1391, 1172 cm^{-1}. MS (ESI) *m*/*z* 270.2 $[M+H]^+$, 292.2 $[M+Na]^+$. Anal. calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.31; H, 8.54; N, 5.12.

3.1.2. (5*R* and 5*S*,2*S*)-5-Allyl-pyrrolidine-2-carboxylic acid methyl ester (8a and 8b). A solution of the 65:35 mixture of **7a** and **7b** (1.540 g, 5.72 mmol) in saturated HCl methanol was stirred at 0°C for 10 min. The reaction mixture was evaporated and the solid residue was used

without purification for the next reaction. For sake of characterization, a sample of the crude hydrochloride salt (205 mg) was dissolved in 2 mL of water, treated with solid Na_2CO_3 until pH 8–9, and extracted with AcOEt (5×5 mL). The combined organic layers were dried and evaporated to give an oily residue that was purified by flash chromatography (Et_2O/MeOH 97:3) to give **8a** (0.352 g, 36.4%) and **8b** (0.170 g, 17.6%). (spectroscopic data of **8a** and **8b** were in agreement with those provided to us by Professor K. Moeller).[32]

Compound **8a**. Pale yellow oil. TLC R_f 0.38 (Et_2O/MeOH 97:3). $[\alpha]_D$=−23.4 (*c* 0.7, $CHCl_3$). IR (film) 3347, 3074, 2953, 1737, 1639, 1436 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.29–1.42 (m, 1H), 1.85–1.98 (m, 2H); 2.05–2.17 (m, 1H), 2.19–2.37 (m, 3H, 2H after exchange with D_2O), 3.15 (m, 1H), 3.74 (s, 3H), 3.78 (dd, 1H, *J*=5.8, 8.8 Hz), 5.06 (broad d, 1H, *J*=10.1 Hz), 5.12 (dd, 1H, *J*=17.1, 1.5 Hz), 5.83 (ten lines system, *J*=10.1, 17.1, 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 29.9 (t), 30.8 (t), 39.9 (t), 52.0, 59.0, 59.6, 116.7 (t), 135.4, 175.3 (s). MS (ESI) *m/z* 170.2 $[M+H]^+$, 192.2 $[M+Na]^+$. Anal. calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.71; H, 8.97; N, 8.12.

Compound **8b**. TLC R_f 0.47 (Et_2O/MeOH 97:3). $[\alpha]_D$=−38.8 (*c* 0.7, $CHCl_3$). IR (film) 3349, 3074, 2956, 1736, 1641, 1437 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.31–1.44 (m, 1H), 1.75–1.91 (m, 2H), 2.05–2.23 (m, 3H), 2.35 (bs, 1H, exchanges with D_2O), 3.25 (m, 1H), 3.67 (s, 3H), 3.81 (dd, 1H, *J*=5.8, 8.6 Hz), 4.99 (d, 1H, *J*=10.2 Hz), 5.03 (dd, 1H, *J*=17.1, 1.5 Hz), 5.76 (ten lines system, *J*=10.1, 17.2, 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 29.3 (t), 30.7 (t), 40.6 (t), 51.9, 57.6, 58.8, 116.4 (t), 135.8, 176.0 (s). MS (ESI) *m/z* 170.2 $[M+H]^+$, 192.2 $[M+Na]^+$. Anal. calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.71; H, 9.02; N, 8.20.

3.1.3. (5*R*)-5-Allyl-1-[(2*R* and 2*S*)-2-benzyl-2-benzyloxycarbonylamino-but-3-enoyl]-pyrrolidine-(2*S*)-2-carboxylic acid methyl ester (9a and 9b). To a CH_2Cl_2 solution (16 mL) of **17** (1.152 g, 3.54 mmol) was added PyBroP® (1.980 g, 4.25 mmol) and DIEA (1.85 mL, 10.62 mmol), and the mixture was stirred at room temperature for 1 h under nitrogen. The crude 1:1.9 mixture of the hydrochloride salt of **8a** and **8b** (728 mg, 3.54 mmol) obtained from the previous reaction was added, followed by the addition of DIEA (1.85 mL, 10.62 mmol) and DMAP (216 mg, 1.77 mmol). The resulting mixture was stirred at room temperature for 4 days. (The reaction time could be decreased by refluxing for 12 h, without substantially affecting the yield.) The solvent was reduced to a small volume by evaporation and the residue, after dilution with AcOEt (30 mL), was washed with an aqueous 5% solution of $KHSO_4$, saturated $NaHCO_3$ and water. Evaporation of the solvent gave an oily residue that was purified by flash chromatography (C_6H_{14}/AcOEt 75:25) to give 790 mg of an approximately 1:1 mixture of **9a** and **9b** (72% with respect to the amount of **8a**). For sake of characterization a sample of the above mixture (204 mg) was submitted to further flash chromatography (C_6H_{14}/AcOEt 73:27) giving pure **9a** (96 mg) and **9b** (101 mg).

Compound **9a**. Foamy solid. TLC R_f 0.37 (C_6H_{14}/AcOEt 75:25). $[\alpha]_D$=−63.5 (*c* 1.1, MeOH). IR (nujol) 3311, 1751, 1735, 1654, 1637 cm^{-1}. ^1H NMR (DMSO-d_6, 80°C, 400 MHz) δ: 1.54 (bs, 1H), 1.86 (bs, 3H), 2.08–2.26 (bm, 1H), 2.76 (bs, 1H), 3.02 (s, 1H), 3.07 (d, 1H, *J*=13.3 Hz), 3.60 (s, 3H), 3.56–3.69 (m, 1H), 4.15 (bs, 1H), 4.57 (bs, 1H), 4.87–5.27 (m, 5H), 5.22 (d, 1H, *J*=11.0 Hz), 5.70–5.91 (m, 1H), 5.93 (dd, 1H, *J*=10.9, 17.7 Hz), 6.92–7.01 (m, 2H), 7.11–7.21 (m, 4H), 7.30–7.44 (m, 4H). ^{13}C NMR (DMSO-d_6, 80°C, 100 MHz) δ: 28.6 (t), 38.6 (bt), 42.6 (bt), 51.8, 59.1 (b), 60.8 (b), 64.8 (s), 66.1 (t), 115.4 (bt), 116.5 (bt), 126.4, 127.9, 128.2, 128.4, 128.6, 131.2, 136.2, 137.1 (s), 137.3 (s), 138.4, 154.6 (s), 170.2 (s), 172.7 (s) (one broad signal is obscured by the solvent). MS (ESI) *m/z* 477.2 $[M+H]^+$, 499.3 $[M+Na]^+$. Anal. calcd for $C_{28}H_{32}N_2O_5$: C, 70.57; H, 6.77; N, 5.88. Found: C, 70.41; H, 6.58; N, 5.61.

Compound **9b**. Glassy solid. TLC R_f 0.29 (C_6H_{14}/AcOEt 75:25). $[\alpha]_D$=+19.4 (*c* 0.9, MeOH). IR (nujol) 3369, 1728, 1636 cm^{-1}. ^1H NMR (DMSO-d_6, 80°C, 400 MHz) δ: 1.63 (bs, 2H), 1.79–1.95 (m, 1H), 1.95–2.22 (m, 2H), 2.39–2.62 (bs, 1H), 3.02 (bs, 1H), 3.11 (d, 1H, *J*=13.5 Hz), 3.52 (bd, 1H), 3.62 (s, 3H), 4.02–4.13 (bm, 1H), 4.62 (bs, 1H), 4.96–5.13 (m, 5H), 5.16 (d, 1H, *J*=11.0 Hz), 5.69–5.85 (m, 1H), 5.93 (dd, 1H, *J*=11.0, 17.6 Hz), 6.96–7.04 (m, 2H), 7.14–7.24 (m, 3H), 7.28–7.43 (m, 5H).). ^{13}C NMR (DMSO-d_6, 80°C, 100 MHz) δ: 28.2 (t), 38.1 (bt), 42.5 (bt), 51.8, 58.9 (b), 60.4 (b), 64.7 (bs), 66.1 (t), 115.0 (t), 117.0 (bt), 126.5, 128.0, 128.2, 128.4, 128.6, 131.2, 136.0, 136.9 (s), 137.3 (s), 138.4, 154.7 (s), 169.8 (s), 172.8 (s) (one broad signal is obscured by the solvent). MS (ESI) *m/z* 477.2 $[M+H]^+$, 499.3 $[M+Na]^+$. Anal. calcd for $C_{28}H_{32}N_2O_5$: C, 70.57; H, 6.77; N, 5.88. Found: C, 70.41; H, 6.58; N, 5.71.

3.1.4. (6*R* and 6*S*)-6-Benzyl-6-benzyloxycarbonylamino-5-oxo-(2*R*)-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-(3*S*)-3-carboxylic acid methyl ester (10a and 10b). A solution of **9a** (165 mg, 0.35 mmol) and catalyst **13** (14 mg, 0.02 mmol) in toluene was refluxed under nitrogen for 2 h. Lead (IV) acetate (18 mg, 0.04 mmol) was added and the stirring continued overnight.[35] The solvent was evaporated and the crude mixture was chromatographed (C_6H_{14}/AcOEt 6:4) to give pure **10a** (132 mg, 85%). The same procedure, applied to **9b** (172 mg, 0.36 mmol) gave, after flash chromatography (C_6H_{14}/AcOEt 75:25), 131 mg (81%) of **10b** and 12 mg of starting material **9b**.

Compound **10a**. White amorphous solid, mp 37–38°C. TLC R_f 0.30 (C_6H_{14}/AcOEt 6:4). $[\alpha]_D$=−144.9 (*c* 0.8, $CDCl_3$). IR (nujol) 3323, 1717, 1653 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.63–1.78 (bm, 1H), 1.94 (bs, 2H), 2.12 (bs, 1H), 2.22–2.32 (m, 1H), 2.39–2.51 (m, 1H), 3.13 (d, 1H, *J*=14.0 Hz), 3.61 (d, 1H, *J*=14.0 Hz), 3.77 (s, 3H), 4.51–4.72 (bm, 2H), 4.94 (bs, 1H), 5.02–5.50 (bm, 2H), 5.68 (apparent d, 1H, *J*=11.9 Hz), 5.75–5.84 (m, 1H), 7.06–7.13 (bm, 2H), 7.20–7.28 (bm, 3H), 7.32–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.4, 32.8, 35.8, 40.9, 52.5, 54.5, 60.1, 61.8, 67.1, 127.0, 127.1, 128.5, 128.8, 129.0 (2 peaks), 132.0, 133.5, 136.8, 154.1, 170.0, 173.8. MS (ESI) *m/z* 449.3 $[M+H]^+$, 471.2 $[M+Na]^+$. Anal. calcd for $C_{26}H_{28}N_2O_5$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.81; H, 6.42; N, 6.44.

Compound **10b**. White prisms, mp 119–120°C (from

EtOH). TLC R_f 0.46 (C_6H_{14}/AcOEt 6:4). $[\alpha]_D=-120.3$ (*c* 0.7, $CDCl_3$). IR (nujol) 3373, 1747, 1715, 1643 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.80–1.93 (m, 1H), 2.02–2.19 (m, 2H), 2.23–2.40 (m, 2H), 2.54–2.66 (m, 1H), 3.24 (d, 1H, *J*=13.8 Hz), 3.71 (s, 3H), 3.85 (d, 1H, *J*=13.8 Hz), 4.27 (bm, 1H), 4.49 (dd, 1H, *J*=2.9, 8.2 Hz), 5.09 (d, 1H, *J*=12.5 Hz), 5.21 (d, 1H, *J*=12.5 Hz), 5.75 (ddd, 1H, *J*=2.3, 6.9, 12.4 Hz), 6.33 (d, 1H, *J*=12.4 Hz), 6.57 (s, 1H), 6.88–6.94 (m, 2H), 7.14–7.24 (m, 3H), 7.30–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 27.7 (t), 32.7 (t), 34.9 (t), 42.3 (t), 52.6, 56.6, 62.7, 64.8 (s), 66.3 (t), 126.7, 127.5, 128.3, 128.6, 128.8, 129.0, 130.1, 135.8 (s), 137.4 (s), 154.9 (s), 169.9 (s), 172.9 (s). MS (ESI) *m/z* 449.3 $[M+H]^+$, 471.2 $[M+Na]^+$. Anal. calcd for $C_{26}H_{28}N_2O_5$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.68; H, 6.34; N, 6.21.

3.1.5. (6*R* and 6*S*)-6-Benzyl-6-amino-5-oxo-(2*R*)-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-(3*S*)-3-carboxylic acid methyl ester (11a and 11b). A solution of **10a** (60 mg, 0.13 mmol) in EtOH (2 mL) was added of Pd, 10% wt on activated carbon, (6 mg) and stirred under a positive pressure of hydrogen for 24 h. After filtration on celite® and careful washing with the same solvent the colorless solution was evaporated. The crude product (40 mg) was purified by flash chromatography (AcOEt/Et_3N 95:5) to give pure **11a** (36 mg, 86%) as an oil. The same procedure, applied to **10b** (58 mg, 0.13 mmol) gave, after flash chromatography (C_6H_{14}/AcOEt 75:25), 35 mg (85%) of **11b** as a white solid.

Compound **11a**. TLC R_f 0.42 (EtOAc/Et_3N 95:5). $[\alpha]_D=-73.8$ (*c* 0.3, $CDCl_3$). IR (nujol) 3364, 1740, 1629 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.72–2.24 (m, 8H), 2.33–2.49 (bs, 1H), 2.60–2.79 (bs, 1H), 3.25 (d, 1H, *J*=13.8 Hz), 3.25 (bs, 1H, exchanges with D_2O), 3.38 (d, 1H, *J*=13.8 Hz), 3.53–3.67 (bs, 1H, exchanges with D_2O), 3.77 (s, 3H), 4.01 (bs, 1H), 4.61 (d, 1H, *J*=7.8 Hz), 7.17–7.52 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.4 (t), 27.5 (t), 30.3 (t), 31.5 (t), 33.5 (t), 42.3 (t), 52.8, 59.0, 62.5, 62,6 (s), 128.0, 128.7, 132.0, 133.5 (s), 169.5 (s), 173.2 (s). MS (ESI) *m/z* 449.3 $[M+H]^+$, 471.2 $[M+Na]^+$. Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.54; H, 7.38; N, 8.69.

Compound **11b**. White needles, mp 96–97°C (from C_6H_{14}). TLC R_f 0.37 (EtOAc/Et_3N 95:5). $[\alpha]_D=-90.5$ (*c* 0.9, $CDCl_3$). IR (nujol) 3363, 1744, 1634 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.56–2.32 (m, 10H), 3.04 (d, 1H, *J*=13.4 Hz), 3.31 (bd, 1H, *J*=13.4 Hz), 3.76 (s, 3H), 3.88 (bm, 1H), 4.49 (d, 1H, *J*=7.1 Hz), 4.83 (bs, 2H, exchange with D_2O), 7.01–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.1 (bt), 27.5 (t), 33.7 (t), 34.8 (bt), 40.7 (bt), 52.9, 59.3 (b), 62.7, 63.5 (s), 127.6, 129.0, 130.3, 135.2 (s), 172.9 (s), 173.2 (s).). MS (ESI) *m/z* 449.3 $[M+H]^+$, 471.2 $[M+Na]^+$. Anal. calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.41; H, 7.59; N, 8.93.

3.1.6. 2-Benzoylamino-2-benzyl-but-3-enoic acid methyl ester (15). To a 0.2 M solution of LDA (12 mmol) in a 1:2 mixture of THF/HMPA (60 mL) maintained under nitrogen at −78°C was added **14** (2.475 g, 11.3 mmol) in THF (50 ml) via cannula, followed by butyllithium (14 mL, 1.6 M in *n*-hexane). The resulting deep-red solution was stirred for 5 min at −78°C. Benzyl bromide (2.90 mL, 24.5 mmol) in THF (11 mL) at −78°C was then added via cannula. After 40 min the reaction mixture was poured in ether (100 mL) and saturated aqueous NH_4Cl (150 mL). After further extraction of the aqueous phase with ether (3×50 mL), the combined organic layers were dried and evaporated. Flash chromatography (C_6H_{14}/AcOEt 82:18) provided **15** (2.558 g, 73%) as a white solid. Mp 104–106°C. TLC R_f 0.35 (C_6H_{14}/AcOEt 82:18). IR (nujol) 3285, 1745, 1647, 1541 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.46 (d, 1H, *J*=13.5 Hz), 3.85 (s, 3H), 3.94 (d, 1H, *J*=13.5 Hz), 5.34 (d, 1H, *J*=17.3 Hz), 5.37 (d, 1H, *J*=10.6 Hz), 6.22 (dd, 1H, *J*=10.6, 17.3 Hz), 7.03 (bs, 1H), 7.08–7.14 (m, 2H), 7.21–7.27 (m, 3H), 7.40–7.54 (m, 3H), 7.70–7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 40.4 (t), 53.5, 66.2 (s), 116.7 (t), 127.4, 127.5, 128.7, 129.1, 130.4, 132.1, 135.1 (s), 136.1 (s), 136.7, 166.7 (s), 172.8 (s). MS (ESI) *m/z* 310.2 $[M+H]^+$, 332.2 $[M+Na]^+$. Anal. calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.68; H, 6.25; N, 4.61.

3.1.7. 2-Amino-2-benzyl-but-3-enoic acid hydrochloride salt (16). A suspension of **15** (2.258 g, 7.30 mmol) in 6N HCl (60 mL) was refluxed under vigorous stirring for 4 h. The reaction mixture was cooled to room temperature and extracted with CH_2Cl_2 (3×30 mL). The aqueous phase was evaporated and the white solid residue dried under vacuum in a dessicator in the presence of abundant P_2O_5 until constant weight (1.546 g, 93%). The spectral data were in accordance with those reported for enantiomerically enriched (*R*)-**16**.[16]

3.1.8. 2-Benzyl-2-benzyloxycarbonylamino-but-3-enoic acid (17). To a stirred solution of **16** (1.363 g, 5.99 mmol) in anhydrous CH_3CN (60 mL) under nitrogen was added tetramethylammonium hydroxide pentahydrate (2.168 g, 12.0 mmol). The solution slowly becomes gelatinous and after 30 min dibenzyl dicarbonate (2.576 g, 9.0 mmol) was added, causing the conversion of the gel into an almost clear solution. After 4 h a further portion of dibenzyldicarbonate was added and the stirring continued for 16 h. The solvent was evaporated and the residue, dissolved in aqueous sodium carbonate, washed with ether (2×30 mL) and slowly acidified to pH 1–2. The aqueous phase was then extracted with EtOAc (3×30 mL) and the combined organics dried and evaporated to give 1.748 g of **17** (90%), sufficiently pure to be used in the following coupling reaction. For the sake of characterization a sample of crude **17** (158 mg) was purified by flash chromatography (EtOAc/MeOH 99:1) to give 146 mg of pure compound as a colorless oil. TLC R_f 0.42 (EtOAc/MeOH 99:1). IR (nujol) 3400, 3033, 1709, 1495, 1446 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.39 (d, 1H, *J*=13.4 Hz), 3.60 (d, 1H, *J*=13.4 Hz), 5.11 (d, 1H, *J*=12.2 Hz), 5.21 (d, 1H, *J*=12.2 Hz), 5.34 (d, 1H, *J*=17.3 Hz), 5.37 (d, 1H, *J*=10.6 Hz), 5.59 (bs, 1H), 5.67–6.37 (bs, 1H), 6.11 (dd, 1H, *J*=10.6, 17.3 Hz), 7.04–7.11 (m, 2H), 7.16–7.26 (m, 3H), 7.35–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 40.8 (t), 65.4 (s), 67.3 (t), 116.8 (t), 127.5, 128.2, 128.7 (2 peaks), 129.0, 130.5, 135.6 (s), 136.6, 136.7 (s), 155.1 (s), 176.3 (s). MS (ESI) *m/z* 326.2 $[M+H]^+$, 348.3 $[M+Na]^+$. Anal. calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.27; H, 5.92; N, 4.53.

3.1.9. (2*S*)-4,4-Diallyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (6). To a solution of **18** (2.5 g, 10.3 mmol) in dry THF (100 mL) stirred at −78°C under nitrogen was added a 1 M solution of lithium hexamethyldisilazide in THF (22.6 mL, 22.6 mmol), followed, after 15 min, by the addition of dry DMPU (6.2 mL, 51.5 mmol) and freshly distilled alllyl bromide (1.78 mL, 20.6 mmol). After stirring for 30 min, the temperature was slowly raised to −30°C and the mixture stirred at this temperature for 90 min, after which time the pale yellow solution was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3×60 mL). The combined organic phases were dried and evaporated. The product was purified by flash chromatography (C_6H_{14}/AcOEt 85:15) giving the diallylated product (**6**) (1.366 g, 41%) as a colorless oil and a mixture of *cis*- and *trans*- monoallylated products (1.263 g, 43%) whose spectral data were in full agreement with those reported in the literature.[6,36] This diastereomeric mixture was submitted to a further allylation using the same procedure as above (1.1 equiv. of base and 1.2 equiv. of allyl bromide, quenching at −60°C) to give, after chromatography, 1.010 g of **6** (70%), corresponding to a global yield of 71%. TLC R_f 0.61 (C_6H_{14}/AcOEt 7:3). $[\alpha]_D$=−18.7 (*c* 1.0, $CHCl_3$). The lit. value of the corresponding ethyl ester is: $[\alpha]_D$=−169.7 (*c* 0.35, $CHCl_3$). IR (film) 1788, 1753, 1438, 1370 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.51 (s, 9H), 1.93 (dd, 1H, *J*=5.8, 13.7 Hz), 2.19–2.33 (m, 3H), 2.36–2.45 (m, 2H), 3.78 (s, 3H), 4.48 (dd, 1H, *J*=5.8, 9.8 Hz), 5.08 (ddd, 1H, *J*=1.5, 3.4, 17.0 Hz), 5.12–5.20 (m, 3H), 5.67–5.80 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 28.3, 30.0 (t), 41.4 (t), 41.8 (t), 49.2 (s), 52.9, 56.6, 84.1 (s), 119.8 (t), 120.2 (t), 132.9, 133.2, 149.6 (s), 172.5 (s), 176.8 (s). MS (ESI) *m/z* 669.1 $[2M+Na]^+$ (20%), 345.9 $[M+Na]^+$ (100%), 246.1 (67%). Anal. calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.24; H, 7.68; N, 4.44.

3.1.10. (3*S*)-1-Oxo-2-aza-spiro[4,4]non-7-ene-2,3-dicarboxylic acid 2-*tert*-butyl ester 3-methyl ester (19). To a 0.04 M solution of **6** (2.962 g, 9.16 mmol) in dry CH_2Cl_2 under nitrogen was added the catalyst **24** (379 mg, 0.46 mmol) and the mixture stirred for 24 h. Lead (IV) acetate (408 mg, 0.92 mmol) was added and the stirring continued overnight. The solvent was evaporated and the crude black residue purified by flash chromatography (C_6H_{14}/AcOEt 77:23) to give **19** (2.245 g, 83%) as a white solid. Mp 72–73°C (white needles from C_6H_{14}). TLC R_f 0.44 (C_6H_{14}/AcOEt 7:3). $[\alpha]_D$=−18.0 (*c* 1.1, $CDCl_3$). IR (nujol) 1779, 1738, 1358, 1318 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (s, 9H), 2.11 (dd, 1H, *J*=4.4, 13.3 Hz), 2.19–2.35 (m, 2H), 2.34 (dd, 1H, *J*=9.0, 13.3 Hz), 2.84–3.01 (m, 2H), 3.79 (s, 3H), 4.58 (dd, 1H, *J*=4.4, 9.0 Hz), 5.55–5.61 (m, 1H), 5.61–5.67 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 27.9, 38.1 (t), 44.9 (t), 45.0 (t), 50.6 (s), 52.5, 56.4, 83.6 (s), 127.9, 128.1, 149.6 (s), 172.0 (s), 177.8 (s). MS (ESI) *m/z* 613.0 $[2M+Na]^+$ (17%), 317.9 $[M+Na]^+$ (100%), 288.3 (44%), 218.1 (65%). Anal. calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.08; H, 7.24; N, 4.69.

3.1.11. (3*S*)-1-Oxo-2-aza-spiro[4,4]nonane-2,3-dicarboxylic acid 2-*tert*-butyl ester 3-methyl ester (20). A solution of **19** (2.120 g, 7.18 mmol) in EtOH (50 mL) was hydrogenated under pressure (3 atm of H_2) overnight in the presence of Pd, 10% wt on activated carbon (200 mg). After filtration on celite® and careful washing with the same solvent the colorless solution was evaporated to give 2.092 g (98%) of **20** as a white solid, sufficiently pure to be processed in the next reaction. Mp 43–44°C (white needles from C_6H_{14}). TLC R_f 0.46 (C_6H_{14}/AcOEt 7:3). $[\alpha]_D$=−16.8 (*c* 1.0, $CDCl_3$). IR (nujol) 1779, 1732, 1355, 1304 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.44–174 (m+s, 13H), 1.75–1.92 (m, 2H), 1.99 (dd, 1H, *J*=4.5, 13.2 Hz), 1.99–2.13 (m, 2H), 2.25 (dd, 1H, *J*=9.2, 13.2 Hz), 3.78 (s, 3H), 4.55 (dd, 1H, *J*=4.5, 9.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.4, 25.6, 27.9; 36.7, 37.8, 38.0, 51.8, 52.4, 56.5, 83.4, 149.6, 172.1, 178.4. MS (ESI) *m/z* 617.2 $[2M+Na]^+$ (100%), 320.0 $[M+Na]^+$ (22%). Anal. calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.47; H, 7.61; N, 4.83. The enantiomeric excess was determined to be 99.6% by hplc (Chiracel OD, *n*-hexane/2-propanol 99:1, 1 mL min^{-1}, *T*=35°C), by comparison with a racemic sample obtained by racemization of the (*S*)-enantiomer with LDA [R_t (*S*-enantiomer)=17.82 min, R_t (*R*-enantiomer)=19.30 min)].

3.1.12. (3*S*)-1-Methoxy-2-aza-spiro[4,4]nonane-2,3-dicarboxylic acid 2-*tert*-butyl ester 3-methyl ester (21). A 1.0 M solution of lithium triethylborohydride in THF (6.42 mL, 6.42 mmol) was added to a solution of **20** (1.592 g, 5.35 mmol) in THF (22 mL) at −78°C under a nitrogen atmosphere. After 45 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and warmed to 0°C. Thirty percent H_2O_2 (1.0 mL) was added, and the mixture was stirred at 0°C. After 20 min the organic solvent was removed in vacuo, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried, filtered and evaporated to dryness to give 1.605 g of the corresponding 1-hydroxy derivative as a 70:30 mixture (NMR) of two isomers, that was used without purification for the next reaction. A sample was purified by chromatography for characterization (C_6H_{14}/AcOEt 7:3). TLC R_f 0.40 (C_6H_{14}/AcOEt 65:35). IR (neat) 3457, 1759, 1703, 1436, 1391 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.43 (s, 6.3H), 1.49 (s, 2.7H), 1.35–1.74 (m, 7H), 1.98–2.19 (m, 3H), 3.06 (d, 0.7H, *J*=3.5 Hz, exchanges with D_2O), 3.75 (s, 2.1H), 3.76 (s, 0.9H), 4.19 (dd, 0.7H, *J*=7.6, 9.7 Hz), 4.28 (dd, 0.3H, *J*=7.9, 9.4 Hz), 4.92 (d, 0.3H, *J*=4.7 Hz), 4.98 (d, 0.3H, *J*=4.7 Hz, exchanges with D_2O), 5.06 (d, 0.7H, *J*=3.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: (m and M indicate a tentative assignment of the major and the minor isomer, respectively, based on the relative signal intensities) 24.7 (m), 24.8 (M), 24.9, 25.0, 28.2 (M), 28.4 (m), 31.8 (M), 32.0 (m), 36.2 (M), 36.4 (m), 39.1 (m), 39.8 (M), 52.2 (M), 52.5 (m), 53.6, 58.0 (m), 58.5 (M), 80.9 (M), 81.2 (m), 87.3 (M), 87.7 (m), 153.7 (m), 153.9 (M), 173.6 (M), 174.1 (m). MS (ESI) *m/z* 322.0 $[M+Na]^+$. The crude product derived from the reduction of **20** (1.498 g) was dissolved in MeOH (50 mlL) and trimethyl orthoformate (2.93 mL, 26.75 mmol) was added followed by addition of pyridinium tosylate (200 mg, 0.75 mmol). After stirring for 2 h the solvent was evaporated and the residue treated with an aqueous saturated solution of $NaHCO_3$ that was extracted with ether (3×30 mL). The combined organic layers, dried and evaporated, gave **21** (colorless oil, 1.560 g) with a diastereomeric ratio >95:5 (only one isomer detected by ^1H

(200 MHz) and ^{13}C (75 MHz) NMR). A sample was purified by chromatography for characterization (C_6H_{14}/AcOEt 85:15). TLC R_f 0.47 (C_6H_{14}/AcOEt 8:2). $[\alpha]_D=-47.1$ (*c* 1.1, $CDCl_3$). IR (film) 1759, 1710, 1380, 1304 cm^{-1}. ^1H NMR (DMSO-d_6, 80°C, 200 MHz) δ: 1.41 (s, 9H), 1.24–1.47 (m, 2H), 1.48–1.71 (m, 5H), 1.77–1.98 (m, 2H), 2.08 (dd, 1H, *J*=7.8, 11.8 Hz), 3.35 (s, 3H), 3.66 (s, 3H), 4.20 (dd, 1H, *J*=7.8, 10.1 Hz), 4.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 23.8 (t), 24.0 (t), 27.5, 31.0 (t), 34.6 (t), 38.3 (t), 51.1, 53.2 (s), 54.5, 57.4, 79.3, 93.5, 153.5 (s), 171.9 (s). MS (ESI) *m/z* 649.0 $[2M+Na]^+$ (9%), 336.0 $[M+Na]^+$ (100%). Anal. calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.53; H, 8.49; N, 4.55.

3.1.13. (1*S* and 1*R*,3*S*)-1-Allyl-2-aza-spiro[4,4]nonane-3-carboxylic acid methyl ester (5a and 5b). To a solution of the crude **21** (1.560 g), derived from the previous reaction, in CH_2Cl_2 (44 mL) at 0°C were added allyltrimethylsilane (3.96 mL, 24.8 mmol) and $InCl_3$ (971 mg, 4.39 mmol). After 1.5 h the solvent was removed and to the residue was added water (10 mL), solid Na_2CO_3 until pH 8–9 and AcOEt (30 ml). The two phase mixture was filtered on celite®, washing abundantly with AcOEt. The aqueous phase was extracted with AcOEt (3×15 mL) and the combined organic layers dried and evaporated. The crude reddish residue (1.131 g) was dissolved in THF and treated with tetrabutylammonium fluoride (1 M solution in THF, 0.65 mL) with stirring for 30 min. The solvent was evaporated, the residue taken up in a small volume of water and extracted with AcOEt (3×30 ml). Evaporation of the combined organic phases gave an oily residue (1.017 g) that was dissolved in CH_2Cl_2 (4 mL) and treated at 0°C with trifluoroacetic acid (4 mL). After 2 h stirring at the same temperature, the volatiles were removed by evaporation and the residue suspended in a small volume of water to which solid Na_2CO_3 was added to pH 8–9. Extraction with AcOEt (5×15 mL) and CH_2Cl_2 (2×10 mL) followed by evaporation gave an oily mixture that, finally, was purified by flash chromatography (gradient elution, C_6H_{14}/AcOEt from 1:1 to 0:100) to give **5a** (626 mg) and **5b** (102 mg), both as colorless oils (global yield from **19**: 61%). A sample of the reaction mixture derived from the allylation reaction (352 mg) was chromatographed (gradient elution C_6H_{14}/AcOEt from 9:1 to 0:100) to give **22a** (170 mg), **23** (6:4 ratio of two stereoisomers, 31 mg), and **5a**,**b** (6:4 ratio of two stereoisomers, 38 mg).

Compound **22a**. Colorless oil. TLC R_f 0.49 (C_6H_6/di-*iso*-propyl ether 7:3). $[\alpha]_D=-42.1$ (*c* 1.0, $CDCl_3$). IR (film) 1755, 1697, 1454, 1390 cm^{-1}. ^1H NMR (DMSO-d_6, 80°C, 400 MHz) δ: 1.37 (s, 9H), 1.39–1.75 (m, 8H), 1.83 (bt, 1H, *J*=11.0 Hz), 2.06 (dd, 1H, *J*=7.8, 12.4 Hz), 2.17–2.38 (m, 2H), 3.58 (bt, 1H, *J*=6.3 Hz), 3.66 (s, 3H), 4.14 (dd, 1H, *J*=7.8, 10.2 Hz), 4.98 (d, 1H, *J*=9.8 Hz), 5.09 (dd, 1H, *J*=2.0, 17.1 Hz), 5.88–6.00 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 28.2 (t), 28.9 (t), 33.0, 36.9 (t), 41.9 (t), 43.1 (t), 44.1 (t), 56.5, 57.8 (s), 63.0, 70.6, 83.9 (s), 120.6, 141.6 (t), 158.3 (s), 178.0 (s). MS (ESI) *m/z* 346.1 $[M+Na]^+$. Anal. calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33. Found: C, 66.98; H, 8.86; N, 4.42.

Compound **23** (6:4 mixture of stereoisomers). Colorless oil. TLC R_f 0.44 (C_6H_{14}/AcOEt 1:1). IR (film) 1748, 1698, 1431, 1367 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.10 and 0.11 (2 s, 9H), 0.97 and 1.01 (2dd, 1H, *J*=7.2, 14.6 Hz, *J*=7.6, 14.5 Hz), 1.15–1.96 (m, 12H), 2.22 and 2.25 (2dd, 1H, *J*=7.5, 12.4, 7.8, 12.4 Hz), 3.69 (dd, 0.6H, *J*=4.4, 11.8 Hz), 3.77 (s, 3H), 3.79 (dd, 0.4H, *J*=5.7, 11.1 Hz), 4.36 (dd, 0.4H, *J*=7.4, 10.6 Hz), 4.42 (dd, 0.6H, *J*=7.8, 10.3 Hz), 4.45–4.53 (m, 0.4H,), 4.68–4.77 (m, 0.6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 1.0, 1.3, 22.0 (t), 24.2 (t), 24.5 (t), 25.1 (t), 27.7 (t), 31.2 (t), 31.5 (t), 34.1 (t), 34.2 (t), 42.2 (t), 42.3 (t), 52.0 (s), 52.1 (s), 58.0, 58.1, 59.1, 63.4, 75.1, 75.9, 152.1 (s), 152.9 (s), 172.6 (s). MS (ESI) *m/z* 701.0 $[2M+Na]^+$ (8%), 362.1 $[M+Na]^+$ (100%). Anal. calcd for $C_{17}H_{29}NO_4Si$: C, 60.14; H, 8.61; N, 4.13. Found: C, 60.39; H, 8.73; N, 4.21.

Compound **5a**. Colorless oil. TLC R_f 0.28 (C_6H_{14}/AcOEt 1:1). $[\alpha]_D=-18.9$ (*c* 1.0, MeOH). IR (film) 3329, 1742, 1589 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.20–1.31 (m, 1H), 1.49–1.69 (m, 7H), 1.81 (dd, 1H, *J*=7.2, 12.6 Hz), 1.93–2.05 (m, 2H), 2.23–2.32 (m, 1H), 2.41 (bs, 1H, exchanges with D_2O), 2.87 (dd, 1H, *J*=3.5, 10.5 Hz), 3.72 (s, 3H), 3.79 (dd, 1H, *J*=7.3, 8.7 Hz), 5.08 (d, 1H, *J*=10.1 Hz), 5.16 (dd, 1H, *J*=1.2, 17.1 Hz), 5.77–5.90 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.4 (t), 25.1 (t), 33.1 (t), 37.0 (t), 37.7 (t) 43.7 (t), 52.5, 53.3 (s), 58.4, 66.2, 117.3 (t), 136.9, 176.3 (s). MS (ESI) *m/z* 224.1 $[M+H]^+$. Anal. calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.81; H, 9.65; N, 6.01.

Compound **5b**. Colorless oil. TLC R_f 0.40 (C_6H_{14}/AcOEt 1:1). $[\alpha]_D=+1.0$ (*c* 1.0, MeOH). IR (film) 3333, 1736, 1209 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.29–1.38 (m, 1H), 1.40–150 (m, 1H), 1.53–1.67 (m, 6H), 1.73 (dd, 1H, *J*=7.7, 12.5 Hz), 1.94–2.04 (m, 1H), 2.14 (dd, 1H, *J*=8.5, 12.5 Hz), 2.18–2.26 (m, 1H), 2.40 (bs, 1H, exchanges with D_2O), 3.09 (dd, 1H, *J*=3.2, 10.1 Hz), 3.72 (s, 3H), 3.83 (t, 1H, *J*=8.2 Hz), 5.05 (d, 1H, *J*=10.1 Hz), 5.12 (dd, 1H, *J*=1.4, 17.1 Hz), 5.77–5.90 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.6 (t), 25.2 (t), 32.2 (t), 36.3 (t), 36.6 (t), 44.5 (t), 52.4, 52.9 (s), 57.4, 64.6, 116.8 (t), 137.3, 176.9 (s). MS (ESI) *m/z* 224.1 $[M+H]^+$. Anal. calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.74; H, 9.62; N, 5.98.

3.1.14. (1*S*)-1-Allyl-2-(2*R* and 2*S*)-(2-benzyl-2-benzyloxycarbonylamino-but-3-enoil)-2-aza-spiro[4,4]nonane-(3*S*)-3-carboxylic acid methyl ester (25a and 25b). To a 2 M solution of racemic **17** (650 mg, 2.0 mmol) in dry CH_2Cl_2 PyBroP® (1.120 g, 2.4 mmol) and DIEA (0.675 mL, 4.0 mmol) were added under nitrogen and the solution stirred at room temperature for 2 h. A 1 M CH_2Cl_2 solution of **5a** (232 mg, 1.0 mmol) was then added, followed by addtion of DMAP (1.0 mmol, 122 mg) and the mixture was stirred for 4 days. The solvent was evaporated and the crude directly flash chromatographed (gradient elution, C_6H_{14}/AcOEt from 85:15 to 0:100) to afford pure **25a** (164 mg, 31%), **25b** (218 mg, 41%) and unreacted **5a** (30 mg, 13%).

Compound **25a**. Colorless oil. TLC R_f 0.48 (C_6H_{14}/AcOEt 7:3). $[\alpha]_D=-71.0$ (*c* 0.5, $CDCl_3$). IR (film) 3305, 3062, 1746, 1729, 1634, 1496, 1450 cm^{-1}. ^1H NMR (DMSO-d_6, 80°C, 400 MHz, mixture of conformers): 1.26–1.44 (m,

3H), 1.47–1.64 (m, 4H), 1.65–1.75 (m, 1H), 1.81 (bt, 1H, J=10.6 Hz), 2.01 (bt, 1H), 2.32 (q, 1H, J=15.8, 7.8, 7.8 Hz), 2.45–2.56 (bm, 1H), 3.10 (d, 1H, J=13.6 Hz), 3.63 (s, 3H), 3.68 (d, 1H, J=13.6 Hz), 4.14–4.25 (bm, 1H), 4.35 (bs, 0.8H), 4.78 (bs, 0.2H), 4.95 (bd, 1H, J=10.2 Hz), 4.96 (bs, 1H), 5.05 (bd, 1H, d, J=17.0 Hz), 5.18 (d, 1H, J=12.5 Hz), 5.26 (bs, 1H), 5.28 (d, 1H, J=11.0 Hz), 5.84–6.03 (m, 2H), 6.95–7.02 (m, 1.8H), 7.11–7.26 (m, 3.2H), 7.29–7.45 (m, 6H). ^{13}C NMR (DMSO-d_6, 80°C, 50 MHz, mixture of conformers): 23.9, 24.6, 32.8, 43.0 (b), 52.1, 60.0 (b), 63.9, 65.3, 66.6, 116,3, 116.9, 126.9, 127.3, 127.4, 128.3, 128.7, 128.8, 128.9, 129.1, 131.8, 137.7, 137.9, 138.4, 155, 3, 170.5, 173.6. MS (ESI) m/z 553.4 $[M+Na]^+$ (66%), 531.1 $[M+H]^+$ (100%). Anal. calcd for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.09; H, 7.43; N, 5.45.

Compound **25b**. White solid: mp 34–36°C. TLC R_f 0.40 (C_6H_{14}/AcOEt 7:3). $[\alpha]_D$=−5.5 (c 0.5, $CDCl_3$). IR (nujol) 3329, 1782, 1727, 1623 cm^{-1}. ^{1}H NMR (DMSO-d_6, 80°C, 400 MHz, mixture of conformers) δ: 1.19–1.42 (m, 3H), 1.43–1.63 (m, 4H), 1.64–1.77 (m, 1H), 1.83 (dd, 1H, J=10.3, 12.4 Hz), 2.00 (dd, 1H, J=8.3, 12.4 Hz), 2.35–2.41 (m, 2H), 3.00 (d, 0.5H, J=13.9 Hz), 3.11 (d, 0.5H, J=13.7 Hz), 3.29 (d, 0.5H, J=13.9 Hz), 3.62 (s, 3H), 3.65 (d, 0.5H, J=13.7 Hz), 3.92 (bs, 1H), 4.39 (bs, 1H), 4.92 (dd, 1H, J=1.8, 10.4 Hz), 5.05 (dd, 1H, J=1.8, 17.3 Hz), 4.96–5.29 (m, 3H), 5.44 (d, 0.5H, J=10.5 Hz), 5.51 (d, 0.5H, J=17.2 Hz), 5.81–6.05 (m, 1.5H), 6.13 (dd, 0.5H, J=10.5, 17.2 Hz), 6.91–7.03 (m, 1.5H), 7.09–7.25 (m, 4H), 7.25–7.45 (m, 5.5H). ^{13}C NMR (DMSO-d_6, 80°C, 50 MHz, mixture of conformers) δ: 22.5 (t), 23.1 (t), 31.6 (t), 36.3 (t), 37.7 (t), 41.4 (t), 41.7 (t), 51.0, 54.9 (s), 58.9, 63.4, 64.0, 65.3 (t), 68.2 (s), 114.9 (t), 115.4 (t), 117.1 (t), 125.1, 127.1, 127.4, 127.7, 127.8, 127.9, 129.8, 130.5, 133.2 (s), 134.5, 137.0, 137.4 (s), 154.2 (s), 169.4 (s), 172.2 (s). MS (ESI) m/z 553.4 $[M+Na]^+$ (100%), 531.1 $[M+H]^+$ (80%). Anal. calcd for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.51; H, 7.41; N, 5.12.

3.1.15. Methyl (6*R* and 6*S*)-6-benzyl-6-{[(benzyloxy)carbonyl]amino}-5-oxo-(2*S*)-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-(3*S*)-3-carboxylate-cyclopentane (1:1) (26a and 26b). A solution of **25a** (231 mg, 0.44 mmol) and catalyst **12** (13 mg, 0.02 mmol) in 1,2-dichloroethane (9 mL) was refluxed under nitrogen for 4 h. The solvent was evaporated and the crude mixture was chromatographed (C_6H_{14}/AcOEt 6:4) to give pure **26a** (183 mg, 84%). The same procedure, applied to **25b** (294 mg, 0.55 mmol) gave, after flash chromatography (C_6H_{14}/AcOEt 75:25), 236 mg (85%) of **26b**.

Compound **26a**. White solid: mp 59–61°C. TLC R_f 0.32 (C_6H_{14}/AcOEt 6:4). $[\alpha]_D$=−153.8 (c 0.5, $CDCl_3$). IR (nujol) 3326, 1722, 1654 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18–1.71 (m, 8H), 1.73–1.89 (bm, 1H), 1.92–2.10 (bm, 1H), 2.12–2.25 (m, 1H), 2.31–2.47 (m, 1H), 3.07 (d, 1H, J=14.1 Hz), 3.71 (d, 1H, J=14.1 Hz), 3.78 (s, 3H), 4.47 (dd, 1H, J=2.8, 12.8 Hz), 4.39–4.53 (bs, 1H), 4.86 (bs, 1H), 5.14 (d, 1H, J=12.0 Hz), 5.11–5.26 (bs, 1H), 5.70 (dt, 1H, J=2.3, 12.1 Hz), 5.86 (ddd, 1H, J=3.0, 4.8, 12.1 Hz), 7.07–7.16 (m, 2H), 7.21–7.50 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.9 (t), 24.4 (t), 31.7 (t), 33.0 (t), 38.2 (t), 39.2 (t), 40.3 (bt), 52.6, 53.6 (s), 59.6 (s), 60.0, 62.1, 67.4 (t), 126.6, 126.9, 128.5, 128.8, 129.0, 129.3, 131.9, 134.5, 136.7 (bs), 137.1 (s), 153.7 (bs), 169.5 (s), 174.0 (s). MS (ESI) m/z 525.2 $[M+Na]^+$ (12%), 503.2 $[M+H]^+$ (100%), 352.2 (22%). Anal. calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.78; H, 6.69; N, 5.46.

Compound **26b**. White solid: mp 52–54°C. TLC R_f 0.41 (C_6H_{14}/AcOEt 7:3). $[\alpha]_D$=−52.6 (c 0.6, $CDCl_3$). IR (nujol) 3368, 1717, 1639 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23–1.91 (m, 9H), 2.11 (dd, 1H, J=7.5, 12.5 Hz), 2.25–2.38 (m, 1H), 2.42–255 (m, 1H), 3.28 (d, 1H, J=14.2 Hz), 3.70 (s, 3H), 3.98 (d, 1H, J=14.2 Hz), 4.33 (bd, 1H, J=12.1 Hz), 4.42 (dd, 1H, J=7.5, 10.0 Hz), 5.07 (d, 1H, J=12.5 Hz), 5.20 (d, 1H, J=12.5 Hz), 5.80 (ddd, 1H, J=2.3, 6.1, 12.5 Hz), 6.31 (bd, 1H, J=12.5 Hz), 6.55 (bs, 1H), 6.91–6.98 (m, 2H), 7.12–7.23 (m, 3H), 7.30–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.8 (t), 24.2 (t), 31.0 (t), 33.6 (t), 37.9 (t), 39.4 (t), 41.8 (t), 52.7, 54.2 (s), 61.1, 64.4 (s), 65.0, 66.4 (t), 127.3, 127.5, 128.3, 128.4, 128.7, 128.8, 129.3, 130.0, 135.8 (s), 137.4 (s), 154.7 (s), 169.8 (s), 173.1 (s). MS (ESI) m/z 525.3 $[M+Na]^+$ (68%), 503.1 $[M+H]^+$ (100%), 352.2 (29%). Anal. calcd for $C_{30}H_{34}N_2O_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.73; H, 6.75; N, 5.50.

3.1.16. Methyl (6*S* and 6*R*)-6-benzyl-6-{[(benzyloxy)carbonyl]amino}-(2*S*)-5-oxooctahydro-1*H*-pyrrolo[1,2-*a*]azepine-(3*S*)-3-carboxylate-cyclopentane (1:1) (3a and 3b). To a solution of **26a** (143 mg, 0.28 mmol) in MeOH (2 mL) was added Pd, 10% wt on activated carbon (14 mg), and stirred under a positive pressure of hydrogen overnight. After filtration on celite® and careful washing with the same solvent, the colorless solution was evaporated. The crude product was purified by flash chromatography (AcOEt/Et_3N 95:5) to give pure **3a** (88 mg, 83%) as an oil. The same procedure, applied to **26b** (182 mg, 0.36 mmol) gave, after flash chromatography (AcOEt/Et_3N 9:1), 117 mg (87%) of **3b** as an oil.

Compound **3a**. TLC R_f 0.41 (AcOEt/Et_3N 97:3). $[\alpha]_D$=−41.5 (c 0.6, $CDCl_3$). IR (neat) 3366, 1743, 1627 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.33–1.80 (m, 16H, 14H after exchange with D2O), 1.79 (dd, 1H, J=9.4, 12.2 Hz), 1.98 (dd, 1H, J=7.5, 12.2 Hz), 3.04 (d, 1H, J=13.7 Hz), 3.14 (d, 1H, J=13.7 Hz), 3.78 (s, 3H), 4.43 (dd, 1H, J=7.5, 9.4 Hz), 4.50 (d, 1H, J=10.9 Hz), 7.20–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.3 (t), 24.2 (t), 24.9 (t), 29.3 (t), 33.1 (t), 37.7 (t), 38.8 (t), 39.1 (t), 47.2 (t), 52.6, 53.8 (s), 60.3 (s), 60.8, 65.9, 126.9, 128.4, 132.1, 137.7 (s), 173.7 (s), 174.7 (s). MS (ESI) m/z 741.0 $[2M+H]^+$ (79%), 371.1 $[M+H]^+$ (100%). Anal. calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.43; H, 8.28; N, 7.72.

Compound **3b**. TLC R_f 0.38 (AcOEt/Et_3N 9:1). $[\alpha]_D$=−80.0 (c 0.9, $CDCl_3$). IR (neat) 3362, 3025, 1745,1621 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (bs, 1H), 1.28–1.66 (m, 9H), 1.66–1.95 (m, 5H), 1.96–2.05 (m, 3H, 1H after exchange with D_2O), 2.88 (bd, 1H, J=13.0 Hz), 2.96 (d, 1H, J=13.0 Hz), 3.17 (bs, 1H), 3.74 (s, 3H), 4.31 (dd, 1H, J=7.3, 10.1 Hz), 7.14–7.19 (m, 2H), 7.19–7.31 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 20.6 (bt), 24.0 (t), 24.3 (t), 29.4 (t), 33.1 (t), 33.4 (bt), 38.1 (t), 38.9 (t), 46.4 (bt), 52.7, 53.6 (s), 60.4, 63.4 (s), 64.3 (b),

127.4, 129.0, 130.7, 136.5 (s), 173.3 (s), 175.0 (s). MS (ESI) *m/z* 741.1 $[2M+H]^+$ (94%), 371.2 $[M+H]^+$ (100%). Anal. calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.49; H, 8.27; N, 7.69.

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