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An access to (*Z*)-ethylenic pseudodipeptides based on ring-closing metathesis

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Abstract—A new access to enantiopure (*Z*)-ethylenic pseudopeptides, starting from the chiral pool of amino acids and enantiopure 2-substituted-but-3-enoic acids is proposed and illustrated by the syntheses of the (*Z*)-ethylenic pseudopeptidic analogs of L-Phe-L-Phe, L-Phe-D-Phe, L-Phe-L-Val, L-Phe-D-Val and racemic (LL,DD) and (LD,DL) (phenyl)Gly-Phe. The key-steps of these syntheses are a ring-closing metathesis, catalysed by Grubbs' ruthenium alkykidene complexes, on diethylenic amides and the hydrolytic cleavage of the resulting dihydropyridones under mild conditions through intermediate formation of cyclic imidates.

1. Introduction

Backbone modifications of peptides constitute an important tool which may be directed towards several goals such as the stabilisation of biologically active peptide against enzymatic degradation, the development of peptidic hormone analogs with agonistic or antagonistic properties, the development of enzyme inhibitors or a better understanding of structure–activity relationships.[1] Among such modifications, the isosteric replacement of the amide bond by a carbon–carbon double bond is of special interest. Indeed, in terms of bond length and bond angles, (*E*) and (*Z*)-olefinic pseudopeptides are close, and at the same time configurationally locked mimics of peptides with a *trans* and *cis*-amide bond, respectively.[2] Although thermodynamically disfavoured compared to the *trans* ones, *cis*-amide bonds are nevertheless encountered in naturally occurring peptides, in particular in those which contain *N*-methyl amino acids or proline residues because the energy gap between the *cis* and *trans* forms of the amide bond *N*-terminal to these residues is greatly reduced ($\Delta H \leq 2$ kcal mol^{-1})[3] as compared to what is observed for other proteinogenic amino acids (ca. 5 kcal mol^{-1}, see Fig. 1).[4] The unique conformational properties of the Xaa-Pro link play an important role in the structure and function of peptides and proteins. In particular, *cis*-prolyl residues often induce[5] the formation of type VI β-turns, a special class of reverse turn motifs in which they occupy the $i+2$ position among the four residues involved and which constitute a basic recognition feature for peptide binding. Isomerisation of Xaa-Pro epitopes and binding of proline are the principal function of a vast and ubiquitously occurring group of enzymes termed peptidyl-prolyl *cis*/*trans* isomerases (PPPIases).[6] PPIases are implicated in a wide array of biologically important processes such as the folding of nascent proteins, the modulation of immunosuppression, the control of HIV infectivity or the regulation of calcium release receptors.

Given the importance of conformation effects on the

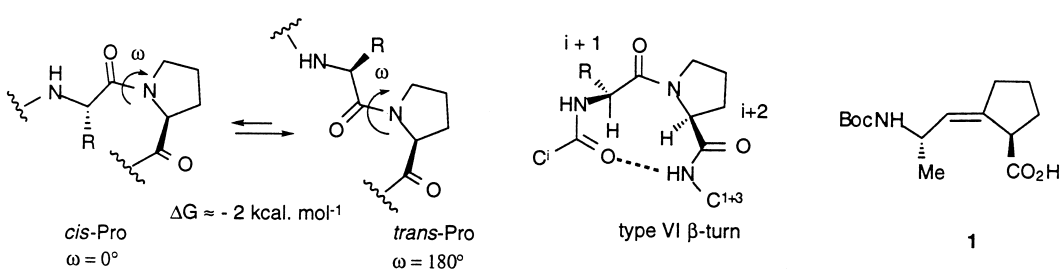

Figure 1.

Keywords: peptidomimetics; (*Z*-ethylenic)-pseudopeptides; (olefin) metathesis; ring-closing metathesis.

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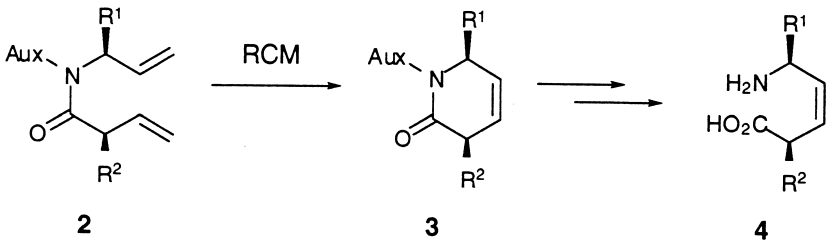


Scheme 1.

biological activity of peptidyl prolylamides, it is not surprising that much effort has been devoted to the obtention of surrogates of *cis*- (and also *trans*) Xaa-Pro units as well as of *cis*-peptidic bonds in general. Thus, properly substituted analogs of proline have been devised in order to shift the *cis–trans* equilibrium of the amide bond in favour either of the *cis*[7] or the *trans*[8] form. Conformationally rigid surrogates of *trans*[9] and *cis* prolylamides have also been proposed.[10] In particular, a number of Gly-Pro, sometimes Xaa-Pro type VI β-turn peptidomimetics in the form of functionalised azabicycloalkanes have been described. Other rigid surrogates of the *cis* amide bond in general include[11] cyclocystine, 1,5-tetrazoles, 1,2-disubstituted pyrroles, *o*-aminomethylphenylacetic acid derivatives, β-lactam derivatives and cyclic peptides but, to the best of our knowledge, only very few examples of the utilisation of the *Z*-alkene bond have been reported.†

Rich and co-workers[12] have prepared the (*Z*)-ethylenic pseudopeptidic analog of [*N*-(methyl)-L-leucyl]-L-leucine by alkylation with isobutyl iodide of [*N*-(methyl)-L-leucyl]glycine. The reaction exhibits almost no diastereoselectivity but the two diastereoisomers were separated by flash chromatography. Etzkorn and co-workers[13] have reported the stereoselective synthesis of the (*Z*)-alkene isostere of L-Ala-*cis*-L-Pro, but the strategy used remains limited to Xaa-Pro sequences. The synthesis of the (*Z*)-alkenic analog of L-Pro-D, L-Phe was recently described by Mann and co-workers[14] and the two diastereoisomers were also separated by chromatography.

The devising, some years ago, by Schrock and Grubbs of new ruthenium and molybdenum-based catalysts with high tolerance towards a number of polar functional groups including the amide function considerably increased the scope of utilisation of olefin metathesis in synthetic organic chemistry.[15] This has led us to propose[16a] a convergent approach to enantiopure (*Z*)-ethylenic pseudopeptides **4** whose key-steps are (Scheme 1) an intramolecular alkene metathesis (ring-closing metathesis) on diethylenic amides of general formula **2** followed by hydrolytic ring opening of the dihydropyridone **3** thus formed. We already described, in preliminary communications,[16] the obtention of the *Z*-ethylenic pseudopeptidic analogs of L-Phe-Gly and L-Phe-L-Phe. We present here a detailed report of our investigation which include the preparation of enantiopure *Z*-alkene isosteres of L-Phe-L-Phe, L-Phe-D-Phe, L-Phe-L-Val, L-Phe-D-Val and racemic R^*R^* and R^*S^* diastereoisomeric *Z*-alkene isosteres of (phenyl)Gly-Phe.

2. Results and discussion

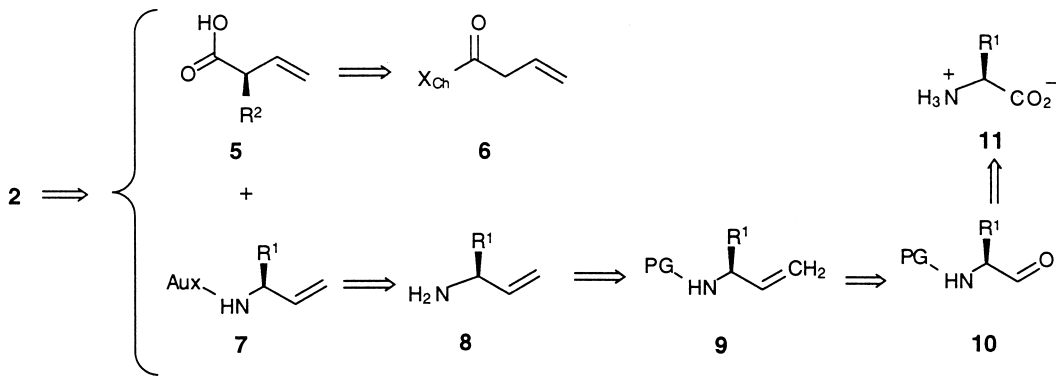
2.1. Preparation of bis-olefinic amides

The preparation of diethylenic amides **2** was planned according to retrosynthetic Scheme 2. In anticipation of the results concerning olefin metathesis, it should be noted, that the presence of an auxiliary group Aux on the nitrogen atom of dialkenic amides **2** is necessary for the RCM (ring-closing metathesis) process to take place. Its role is probably to ensure a sufficient proportion of the rotamer with a *syn* orientation (as represented in **2**) of the two ethylenic appendages.

The most obvious way to obtain dialkenic amides of general structure **2** is by coupling 2-substituted but-3-enoic acids **5** with N-substituted allylamines **7**. As to enantiopure allylamines **8**, many of them may be obtained in a straightforward and well-documented way from the chiral pool of aminoacids through reduction to the corresponding aldehydes followed by Wittig olefination.[17] However, α-aminoaldehydes **10** are notoriously very prone to racemisation.[17] At the present time, only a limited number of protecting groups on nitrogen are known to ensure satisfactory configurational stability.[18] None of these protections on nitrogen is compatible with the coupling reaction envisioned next. Therefore, our synthetic strategy entails a transprotection at the allylamine stage as represented in Scheme 2 (**9**→**8**→**7**).

For the obtention of (*S*)-1-benzyl-prop-2-enylamine from L-phenylalanine and following the recommendation of Albeck and Persky,[19] the trityl group was chosen in preference to the Boc group for temporary protection of

† By contrast, since the first report by Sammes and co-workers,[2a] several strategies have been proposed for the obtention of *E*-ethylenic isosteres.[41a] However, those which incorporate stereocontrol at both the C(2) and the C(5) positions of the 5-amino-pent-3-enoic acid are still relatively few and, as a rule, either lack generality and/or require many steps. Hopkin's convergent approach[41b] starts from independantly prepared optically active aldehydes and sulfones and utilises the Julia–Lythgoe reaction for construction of the double bond. In Procter's protocol[41c] the *E*-double bond is obtained through concerted fluoride ion-induced desilylation and ring-opening of an appropriately and stereoselectively substituted β-trimethylsilyl-γ-lactone. Many recent approaches utilise enantiopure allylic precursors on which repositioning of the double-bond and enantioselective construction of the C(2) or the C(5) chiral centres are achieved simultaneously. This can be done by way of sigmatropic rearrangements including Claisen–Ireland,[41d] Claisen–Johnson,[41e] Still–Wittig[41f,13] and trichloroacetamidate[41g,h] rearrangements, by way of anti-S_N2' alkylation of allylic mesylates[41i] or alkenyl aziridines[41j] with organocopper reagents or by way of stereoselective electrophilic anti-hydroxymethylation,[41k] -nitration[41l] or -aziridination[41l] of allylic silanes. However, the optically pure allylic precursors which are needed in all these strategies are usually of difficult or lengthy access.

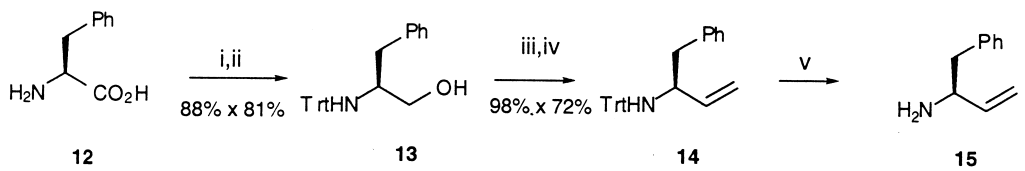


Scheme 2.

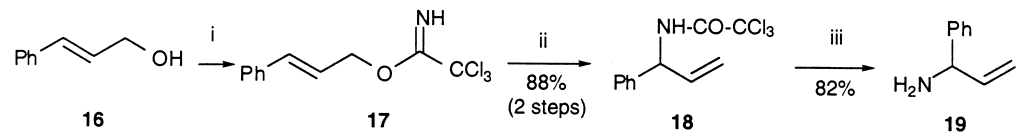
the nitrogen atom. Indeed, Wittig reaction on *N*-Boc-α-aminoaldehydes are known to give poorly reproducible results. *N*-trityl-(*S*)-1-benzyl-prop-2-enylamine **15** was synthesised (Scheme 3) in 50% overall yield and in four steps including reduction of L-phenylalanine to L-phenylalaninol, N-tritylation, Swern oxidation and Wittig reaction. *N*-trityl-(*R*)-1-benzyl-prop-2-enylamine **ent-15** was obtained in the same way from D-phenylalanine. The trityl group was removed by HCl in aqueous acetone.[19] The enantiomeric purities (ee >98%) of (*S*)- and (*R*)-1-benzyl-prop-2-enylamine **15** and **ent-15** were checked on aliquots by HPLC after *N*-*tert*-butoxycarbonylation.

Due to the high cost of enantiomerically pure phenylglycine, 1-phenyl-prop-2-enylamine **19** was synthesised in racemic form. It was obtained in 72% overall yield, starting from cinnamic alcohol and by rearrangement of the corresponding trichloracetimidate according to Overman (Scheme 4).[20]

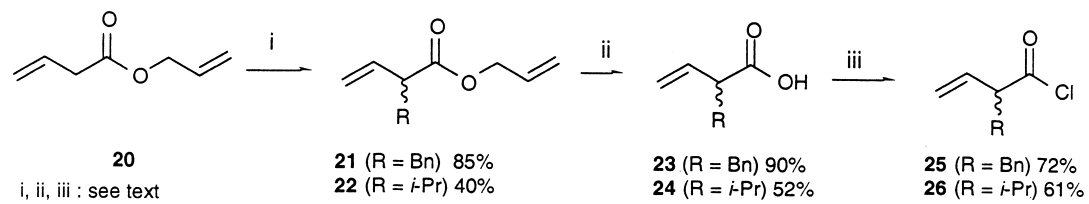
For the obtention of racemic α-substituted vinylacetic acids, direct alkylation of the dianion of vinylacetic acid[21] (LDA, alkylating agent, THF/HMPA, low temperature) was first attempted, but in our hands this reaction gave very poor results. On the contrary, alkylation of the enolate derived from vinylacetic methyl ester[22] was successsfully achieved but difficulties were subsequently encountered in the removal of the methyl ester group. A variety of conditions[23] were investigated such as acidic hydrolysis in concentrated hydrochloric acid, classical or hydrogen peroxide-assisted saponification, iodotrimethylsilane- or boron trichloride-induced demethylation, but in all cases partial or even total reconjugation of the double bond to give crotonic acid derivatives were observed. Replacement of the methyl group by the more easily removable *tert*-butyl group was then considered. However, the lithium enolate of *tert*-butyl vinylacetate proved unreactive. Since the lithium enolate of *tert*-butyl acetate is readily alkylated,[24] this lack of reactivity must be due to a cumulative effect of steric hindrance brought about by the *tert*-butyl group and of lowering of nucleophilicity due to charge delocalisation across the vinylacetyl group. The alkylation reactions were finally performed on the allyl ester of vinylacetic acid (Scheme 5). An excess of allyl vinylacetate over the



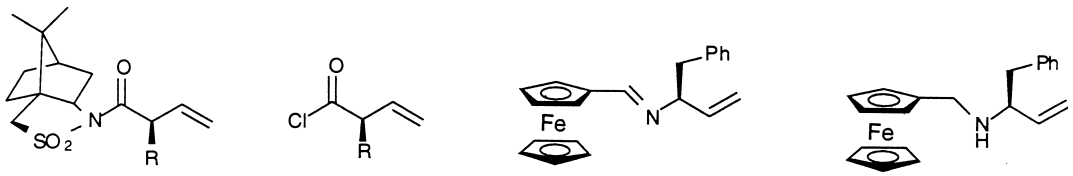
Scheme 3. (i): $NaBH_4$, H_2SO_4/Et_2O, 0°C, then MeOH, NaOH 5N, rfx; (ii): TrtCl, Et_3N, CH_2Cl_2, rt; $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; (iv): $Ph_3PCH_3^+Br^-$, *n*-BuLi, THF, −78°C; (v): HCl 32%, acetone, rfx.



Scheme 4. (i): HNa (10 mol%), CCl_3CN, Et_2O, 0°C then rt; (ii) xylene, rfx, 14 h; (iii): NaOH 6N, EtOH, rt, 40 h.



Scheme 5. (i), (ii), (iii): see text.



27 (R = H)
28 (R = Bn)
29 (R = *i*-Pr)

30 (R = Bn)
31 (R = *i*-Pr)

32

33

Figure 2.

deprotonating agent (lithium diisopropylamide) had to be used in order to avoid the concurrent formation of α,α-dialkylated products. Alkylations with benzyl bromide and isopropyl iodide gave, respectively, α-benzyl and α-isopropyl vinylacetic acid allyl esters **21** and **22** in 85 and 40% yields (based on LDA). Deallylation under neutral conditions was effected by resorting to catalytic π-allyl palladium chemistry.[25] Thus, α-benzyl and α-isopropyl vinylacetic acids **23** and **24** were obtained, respectively, in 90 and 52% yield by exposure of the allyl esters to phenylsilane as the allyl group scavenger and 0.5 mol% of palladium (tetrakis)triphenylphosphine as the catalyst.[26] Final conversion to acyl chlorides was achieved in 72% (R=Bn) and 61% (R=*i*-Pr) yields by reaction with dichloromethyl methyl ether.[27]

(*R*)-2-benzyl-but-3-enoic acid and (*R*)-2-isopropyl-but-3-enoic acid were prepared according to Oppolzer,[28] by regioselective and diastereoselective (de >99% as checked by HPLC) alkylation of the (1*S*)-(−)-2,10-camphor-sultam derivative of vinylacetic acid **27** with benzyl bromide (62% yield) or isopropyl iodide (43% yield) followed by hydrogen peroxide-mediated saponification[29] of the alkylation adducts **28** and **29** (Fig. 2). Fortunately, no reconjugation of the double bond was observed during this process. The carboxylic acids were finally reacted with dichloromethyl methyl ether to give (*R*)-2-benzyl-but-3-enoyl chloride **30** and (*R*)-2-isopropyl-but-3-enoyl chloride **31** in, respectively, 80×72=58% and 51×70=36% yields from intermediates **28** and **29**. Their enantiomeric purities (ee>98%) were checked after recondensation with (1*R*)-(+)-2,10-camphor-sultam and examination of the diastereomeric purity of the adduct. In order to verify that no significant kinetic resolution ocurred in this reaction, a control experiment was carried out in which racemic (*R*,*S*)-2-benzyl-but-3-enoyl chloride was reacted with a limited amount (0.5 equiv.) of (1*S*)-(−)-bornane-10,2-sultam. This reaction was found to lead to an equimolecular mixture of the two diastereoisomeric sulfonimides.

Concerning the auxiliary group on nitrogen, several groups were considered. In the first stage of our investigations dealing with the synthesis of the (*Z*)-ethylenic pseudopeptidic analog of L-Phe-Gly,[16a] the ferrocenylmethyl (Fcm) group had been selected. Indeed, unlike many other N-substituted aminoacids, *N*-Fcm derivatives of aminoacids have been described as reactive in conventional (DCC/DMAP) peptidic coupling reactions.[30] (*S*)-1-benzyl-prop-2-enylamine **15** was converted to ferrocenylimine **32** by reaction for 6 h at room temperature with ferrocenecarboxaldehyde in dichloromethane and in the presence of molecular sieves. The crude imine was reduced with $NaBH_4$ at room temperature in absolute EtOH to give the *N*-ferrocenylmethylamine **33** in 86% overall yield from **15**. At this stage, we were disappointed to find that the enantiomeric purity of **33** (measured on an aliquot after trifluoroacetolytic deprotection followed by *tert*-butoxycarbonylation) had dropped to 62%. Suspecting that this partial racemisation had occurred at the imine stage under the basic conditions of its formation and/or reduction with $NaBH_4$, we tried to obtain **33** according to a one-pot reductive alkylation procedure. (1*S*)-1-amino-1-benzyl-prop-2-ene **15** was reacted with ferrocenecarboxaldehyde in the presence of acetic acid and sodium cyanoborohydride or of sodium triacetoxyborohydride in methanol. Unfortunately, and for reasons which we have not elucidated, no formation of *N*-Fcm derivative **33** was observed under such conditions.[‡]

Another possible candidate was the benzenesulfonyl group, easy to introduce by N-sulfonylation and whose cleavage[23] from nitrogen especially under reductive conditions (SmI_2, etc.) has been described in several papers.[31] However, we found that condensation between *N*-sulfonylallylamines and vinylacetyl chlorides bearing α-substituents invariably resulted, under a variety of conditions, in low yields and extensive reconjugation of the double bond of the vinylacetyl moiety.

The 2,4-dimethoxybenzyl (Dmb) group was finally selected. Probably as a result of the presence of the methoxy group at the ortho position of the phenyl ring,[32] acylation of *N*-Dmb derivatives of amino acids or amines in general has been shown to remain relatively easy (as compared to the corresponding unsubstituted *N*-benzyl derivatives). Condensation of 2,4-dimethoxybenzaldehyde with racemic 1-phenyl-prop-2-enylamine **19** in the presence of sodium triacetoxyborohydride in 1,2-dichloroethane[33] afforded the *N*-Dmb adduct **34** (Fig. 3) in 78% yield. *N*-trityl-(*S*)-1-benzyl-prop-2-enylamine **14** was detritylated in HCl/aqueous acetone[19] at reflux and directly reacted, without intermediate purification, with 2,4-dimethoxybenzaldehyde/sodium triacetoxyborohydride as before to lead to *N*-Dmb-(*S*)-1-benzyl-prop-2-enylamine **35** in 61% overall yield and without any racemisation. *N*-Dmb-(*R*)-1-benzyl-prop-2-enylamine ent-**35** was obtained in the same manner.

Acylation of **35** with (*R*)-2-benzyl-but-3-enoyl chloride **30**

‡ We are not aware of any examples in the litterature of direct conversion of ferrocecarboxaldehyde to ferrocenylamine through one-pot reductive amination with borohydrides. Eckert and Deidel[30] used dihydrogen gas in the presence of palladium catalyst to effect the reduction of ferrocenylimines to ferrocenylamines, a method that could not be applied to our case due to the presence of ethylenic bonds.

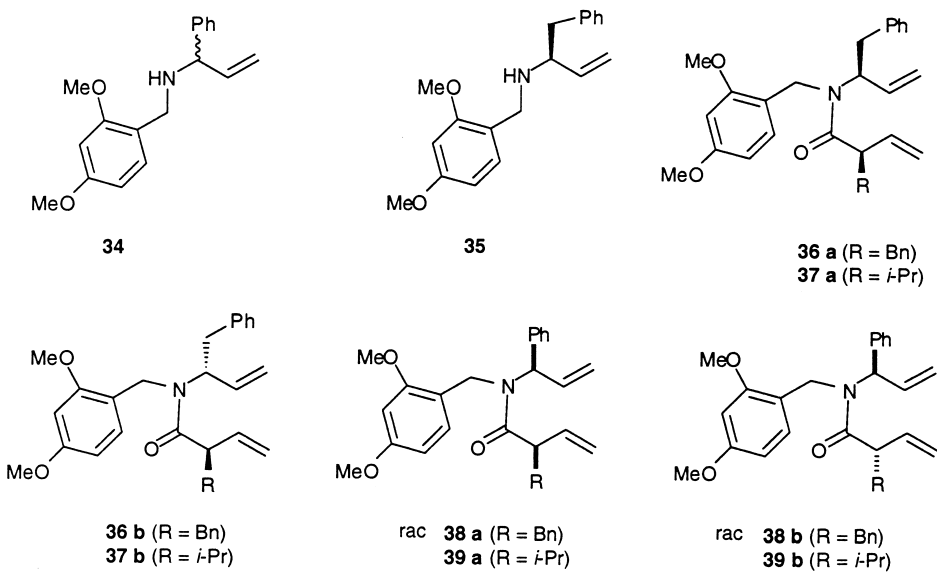


Figure 3.

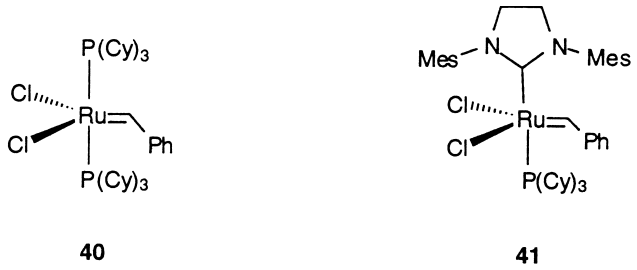


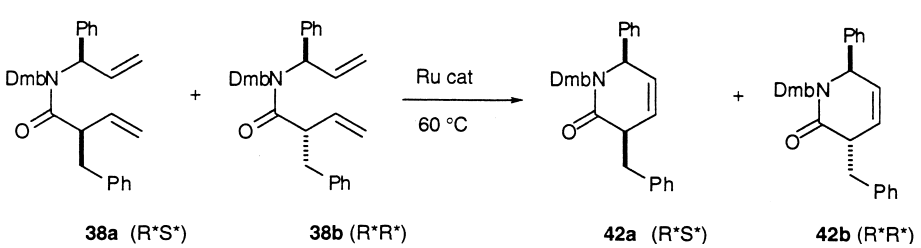
Figure 4.

under standard conditions (Et_3N, dichloromethane, 0°C then room temperature) gave poor results. 36% of the expected amide **36** was obtained, but contaminated with a side-product whose structure was not elucidated. Fortunately, by resorting to BSA-mediated acylation as described by Raucher and Jones,[34] satisfactory results were finally obtained and **36a** was isolated in 90% yield, with no detectable reconjugation of the double bond and in diasteroisomerically and enantiomerically pure form (de, ee>98%), as determined by chiral HPLC. Amides **37a** (80% yield), **36b** (59% yied) and **37b** (59% yield) were similarly obtained, in all cases with the same purity, by condensation of **35** or its enantiomer **ent-35** with (*R*)-2-benzyl-but-3-enoyl chloride **30** or (*R*)-2-isopropyl-but-3-enoyl chloride **31**. Coupling of racemic *N*-Dmb-1-phenyl-prop-2-enylamine **34** with racemic acyl chlorides **25** and **26** gave the corresponding amides, respectively, in 82 and 52% yield and as a ca. 1:1 mixture of diastereoisomers **38a/38b** and **39a/39b** which could not be separated by chromatography. For all amides **36**–**39** NMR showed the presence of two rotamers, but, due to peak overlapping, only in the case of **36a** and **36b** could their relative proportions (ca. 4:1) be properly estimated.

2.2. Ring-closing metathesis of *N*-Dmb-bis-olefinic amides to *N*-Dmb-dihydropyridones

RCM of bis-olefinic amides to the corresponding *N*-2,4-dimethoxybenzyl-dihydropyridones were carried out in benzene at 60°C at a 0.03 M concentration and with 10–20 mol% of Grubbs' first or second generation catalysts **40** or **41** (Fig. 4).

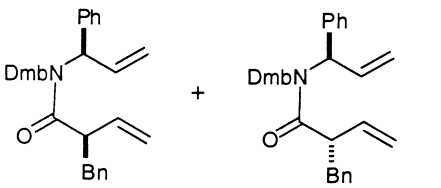
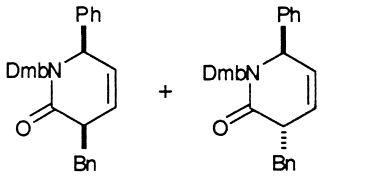
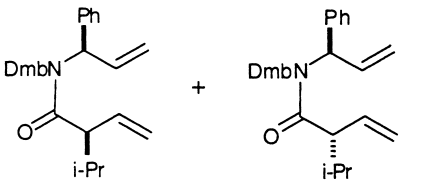
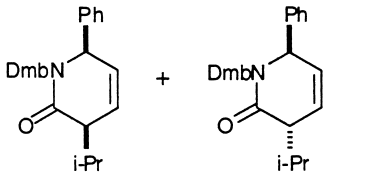
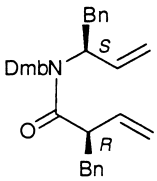
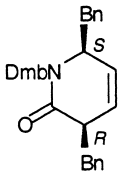
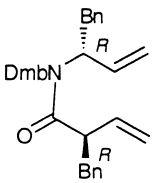
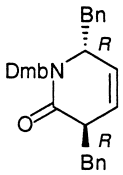
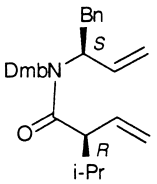
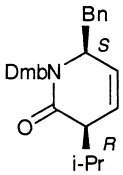
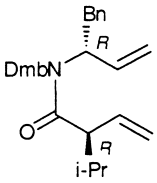
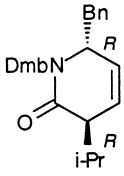
Table 1.



Catalyst (amount)	Reaction time (h)	Total yield (%)[a]	**42a/42b**[b]
40 (10 mol%+10 mol% after 12 h)	30	76	2:1
40 (4 mol%×4 every 6 h)	24	84	3:2
41 (10 mol%)	24	94	1:1

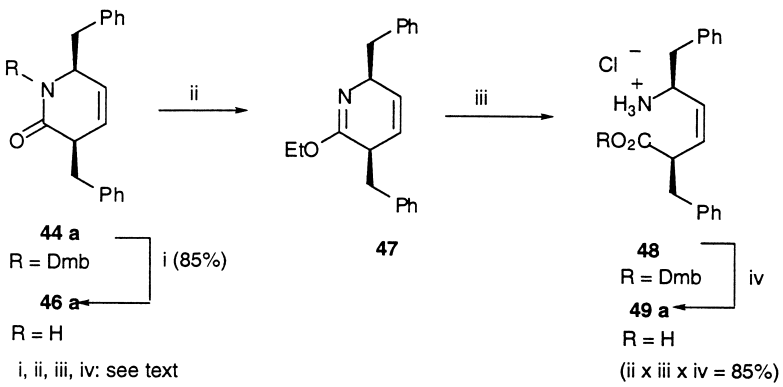
[a] Isolated yield (column chromatography).
[b] **42a** and **42b** were separately collected by chromatography.

Table 2. Ring-closing metathesis of bis-olefinic amides

Starting amides	Dihydrophridones	Yield (%)[a,b]
 **38 a** (rac) + **38 b** (rac)	 **42 a** (rac) + **42 b** (rac)	84
 **39 a** (rac) + **39 b** (rac)	 **43 a** (rac) + **43 b** (rac)	72
 **36 a**	 **44 a**	90
 **36 b**	 **44 b**	83
 **37 a**	 **45 a**	90
 **37 b**	 **45 b**	80

[a] After purification by chromatography.
[b] Reaction conditions: benzene solution 0.03 M in substrate, **41** (10 mol%), 60°C, 24–36 h.

The results reported in Table 1 concerns RCM of the diastereomeric mixture **38a**+**38b**. They show that, as it is generally the case,[15a,b] catalyst **41** proved more efficient than catalyst **40**. Due to its comparatively greater fragility, catalyst **40** had to be added in several portions to improve the yields. Even so, those remain lower than the 94% yield obtained with catalyst **41**. The diastereoisomeric *N*-Dmb-dihydropyridones **42a** and **42b** were separated by column chromatography and their respective relative stereochemistry (R^*S^* and R^*R^*) could later be



Scheme 6.

established by NMR studies on the corresponding N-deprotected dihydropyridones in racemic liquid crystalline solvent.[§] The results of Table 1 show that RCM of the R^*S^* amide **38a** leading to (R^*S^*) *cis* cyclised product **42a** occurs more readily than RCM of diastereoisomeric R^*R^* amide **38b** to the (R^*R^*) *trans* cyclic isomer **42b**. The reason for this difference in reactivity is not clearly understood.

The results concerning RCM of all *N*-Dmb-amides using 10 mol% of catalyst **41** are summarised in Table 2. Yields in cyclised products (from 72 to 94%) are quite satisfactory, given that both olefinic bonds taking part in the metathesis process bear rather bulky groups at the allylic position. In the enantioenriched series, (*S*,*R*) amides **36a**, **37a** and (*R*,*R*) amides **36b** and **37b** were found to lead, respectively, and exclusively (by NMR standards) to (3*R*,6*S*) **44a**, **45a** and (3*R*,6*R*) dihydropyridones **44b**, **45b**, showing the enantioconservative character of the metathesis reaction. Unlike **42a** and **42b**, the diastereoisomeric *N*-Dmb-dihydropyridones **43a** and **43b** obtained from RCM of the diastereoisomeric mixture of (R^*R^*) and (R^*S^*) amides **39a** and **39b** could not be separated by column chromatography.

2.3. Removal of Dmb group and hydrolysis of dihydropyridones to *Z*-ethylenic pseudodipeptides

Final conversion of *N*-Dmb pyridones to *Z*-ethylenic pseudopeptides was carried out as illustrated for the case of the (2*R*,6*S*)-dibenzylsubstituted compounds in Scheme 6.

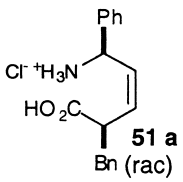
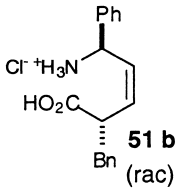
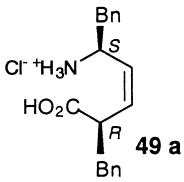
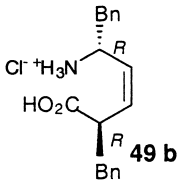
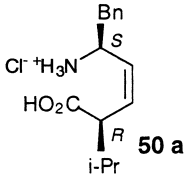
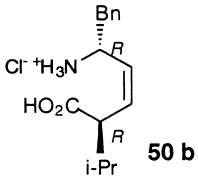
Removal of the Dmb group from diastereoisomerically and enantiomerically pure **44a**, **44b**, **45a**, **45b** and diastereoisomerically pure but racemic **42a** and **42b**[¶] was achieved in 80–88% yield in dependance of the substitution pattern of the dihydropyridone by treatment with *anhydrous* trifluoroacetic acid[35] in the presence of triethylsilane for carbocation scavenging. Due to the harsh conditions it requires, direct hydrolytic ring opening of the N-deprotected dihydropyridones proved unsatisfactory. Therefore, dihydropyridones were first converted to imidates by reaction with triethyloxonium tetrafluoroborate in dichloromethane at room temperature and under an argon atmosphere. Tetrafluoroboric acid and triethyloxonium tetrafluoroborate in excess were eliminated by extraction of the organic phase with pH 7 phosphate buffer. After drying and evaporation, crude imidates were obtained, contaminated (NMR in dry CD_2Cl_2) by a small amount (less than 10%) of starting dihydropyridones.[‖] They were directly hydrolysed to aminoester at room temperature under mild acidic conditions (0.3 M HCl in water/ethanol) similar to those used by Schöllkopf for cleavage of cyclic bis-lactim ethers.[36,37] We previously reported[16a] that the hydrolytic ring opening of the imidate derived from 6-benzyl-2,6-dihydropyridone (i.e. with no substituent on the carbon next to carbonyl) was followed by a slow (6 days) but complete hydrolysis of the aminoester to acid and this unexpected reaction had been tentatively explained by a general acid catalysis by the neighbouring NH_3^+ group. Disubstituted aminoesters however did not display such unusual sensitivity to acidic medium and conversions to amino acids had finally to be achieved under standard conditions in refluxing 6N HCl for

[§] An equimolecular mixture of poly-γ-benzyl-L-glutamate (PBLG) and poly-γ-benzyl-D-glutamate (PBDG) in $CDCl_3$ was used in this study (see for instance Canlet, C.; Merlet, D.; Lesot, P.; Meddour, A.; Loewenstein, A.; Courtieu, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1–5). The assignment of the relative stereochemistry at C(3) and C(6) for **42a** and **42b** is based on the measurement of the carbon–proton residual dipolar couplings D_{CH} of the heterocycle and subsequently on the calculation of ordering tensor for this part of the molecule, assuming a model geometry for the two diastereoisomers (Boucard, V., Aroulanda, C.; Merlet, D, to be published eslsewhere). Shortly: due to the planearity of the ethylenic and the amide bonds, **42a** and **42b** adopt a butterfly-like shape. Given the rapid equilibrium between the two possible conformers on the NMR time scale, the C(3)–H and C(6)–H bonds may be considered as almost anti-parallel in the (R^*,R^*) (*trans*) diasteroisomer but have different orientations in the (R^*,S^*) (*cis*) isomer. Therefore, in the first case similar, and in the second case different dipolar coupling constants are expected in an anisotropic medium. Compound **42b**, the first one to be eluted during column chromatography, exhibits the same value of +87 Hz for the two dipolar coupling constants $D_{C(3)-H}$ and $D_{C(6)-H}$. On the contrary, compound **42a** exhibits very different dipolar coupling constants: $D_{C(3)-H}$=−65 Hz and $D_{C(6)-H}$=+97 Hz. The (R^*,S^*) and (R^*,R^*) configurations may thus confidently be assigned, respectively, to **42a** and **42b**.

[¶] Conversion to *Z*-ethylenic pseudopeptides of (3R^*,6S^*) **43a** and (3R^*,6R^*) **43b** which could not be separated by chromatography was not undertaken.

[‖] This small amount of dihydropyridone is more likely the result of a partial rehydrolysis of the imidate ester during work-up than that of an uncomplete reaction with triethyloxonium tetrafluoroborate. Indeed under non acidic conditions imidate esters are known to be hydrolysed back to amides (Patai, S. *Chemistry of the Amidines and the Imidates*; John Wiley: NY, 1975; Vol. 1, Chapter 9, p 423).

Table 3. Conversion of *N*-Dmb-dihydropyridones to *Z*-ethylenic pseudopeptides

N-Dmb-digydropyridones	*Z*-ethylenic pseudopeptides	Corresponding aminoacid sequence	Overall yields	
			A (%)[a]	B (%)[b]
42a (rac)	 **51 a**	(Phenyl)Gly-Phe (LL+DD)	60	47
42b (rac)	 **51 b**	(Phenyl)Gly-Phe (LD+DL)	71	55
44a	 **49 a**	L-Phe-L-Phe	72	53
44b	 **49 b**	D-Phe-L-Phe	67	45
45a	 **50 a**	L-Phe-L-Val	66	40
45b	 **50 b**	D-Phe-L-Val	65	30

[a] From *N*-Dmb-dihydropyridone (four steps).
[b] From *N*-Dmb-allylic amines (six steps).

one to three hours. The crude aminoacids were purified by ion-exchange chromatography. They were obtained diastereoisomerically pure by NMR standard (de >95%). Overall yields from *N*-Dmb-dihydro-pyridones (60–76%) and from *N*-Dmb-amines (35–60%) are summarised in Table 3.

3. Conclusion

In conclusion, ring-closing metathesis of easily accessible enantiopure bis-olefinic amides leads, in good to excellent yields to dihydropyridones which in turn may in few steps be converted to otherwise difficult to obtained enantiopure *Z*-ethylenic pseudopeptides. We are now working at the incorporation of such entities in short polypeptidic units.

Aside from their own interest, *Z*-ethylenic isosteres are likely to be, by use of one of the many methods available for olefin inversion,[38] direct precursors of their *E*-congeners whose access, as already pointed out in footnote[†] of the introduction is rather difficult, and of various potentially interesting polyfunctional pseudopeptidic entities through stereospecific transformations of the double bond such as epoxidation, aziridination or dihydroxylation. These are under current investigation.

4. Experimental

Typical experimental procedures are given for the synthesis of the (*Z*)-alkene pseudopeptidic analog of L-Phe-L-Phe. Unless otherwise mentioned, similar protocols have been used in the synthesis of other pseudopeptidic analogs. The experimental procedures for the preparation of enantiomerically pure (*R*) and (*S*)-1-benzyl-prop-2-enylamine from D- and L- phenylalanine are essentially those of Albeck and Persky[19] and are not described here. Reduction of phenylalanine to phenylalaninol (step (i) in Scheme 3) was carried out according to Abiko and Masamune.[39] The preparation of racemic 1-phenyl-prop-2-enylamine from cinnamyl alcohol by the trichloroacetamidate method has been described by Overman.[20]

4.1. General information

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 200 or 250 MHz and ^{13}C NMR spectra at 63 MHz. $CDCl_3$ was used as solvent if not mentioned otherwise. Chemical shifts are quoted in ppm relative to TMS. When necessary, unambiguous ^{1}H NMR assignments were obtained by decoupling or COSY experiments. GC/MS analyses were carried out on a OK1 DP 125 gas chromatograph equipped with a CPSil quartz capillary column and connected to a Riber Mag R10-10 mass detector. High resolution mass spectra (HRMS) and electrospray mass spectra were obtained on a Finningan-MAT-95-S spectrometer. HPLC analyses were performed on a Spectra-Physics P100-UV100 HPLC system with detection at λ=254 nm and equipped with a chiral column Chiralcel OD-H from Daicel Chemical Industries Ltd. Mixtures of hexane and isopropanol were used for elution. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at room temperature (concentration in g/100 mL). All solvents were dried and freshly distilled under a nitrogen atmosphere. If not otherwise stated, reactions were performed under argon atmosphere using standard Schlenk techniques.

4.1.1. *N*-[(2*R*)-2-Benzyl-3-butenoyl]-(1*S*)-2,10-camphorsultam 28. To a solution in 30 mL of THF cooled at −78°C of 6.32 g (22.3 mmol) of (1*S*,5*R*)-*N*-but-3-enoyl-2,10-camphorsultam (prepared by acylation of the sodium salt of (1*S*,5*R*)-(−)-2,10-camphorsultam with 3-butenoyl chloride in toluene according to published procedures[40]) was added dropwise through a cannula and over a period of ca. 1 h a solution of 4.1 g of sodium hexamethyldisilazane (22.3 mmol) in 80 mL of THF. The solution, which became orange-coloured, was stirred for 1 h at − 78°C. 8 mL (66.9 mmol) of benzyl bromide diluted in 9.3 mL (66.9 mmol) of HMPA was then slowly added. The reaction mixture was stirred for 16 h at −40°C, upon which it was warmed above 0°C and quenched with 200 mL of water. The aqueous mixture was extracted several times with AcOEt. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The residual solid was recrystallised in MeOH to afford 5.16 g of **28** as white crystals. Yield: 62%. Mp: 167–168°C. $[\alpha]_D^{20}$=−47 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz): δ 7.25–7.1 (m, 5H, Ar–H); 6.0–5.85 (m, 1H, vinylic CH); 5.25–5.12 (m, 2H, vinylic CH_2); 4.1–4.0 (broad q, 1H, CH α to C=O); 3.82–3.75 (m, 1H, CH α to N); 3.42–3.29 (dd, AB system, $^2J_{AB}$=14 Hz, 2H, CH_2 α to SO_2); 3.18–3.08 and 2.92–2.82 (two dd, *AB*X system, $^2J_{AB}$=12 Hz, $^3J_{AX}$=8 Hz, $^3J_{BX}$=5 Hz, (1+1)H); 2.0–1.65 m, 5H); 1.38–1.22 (m, 2H); 0.87 (s, 3H); 0.63 (s, 3H). ^{13}C NMR: δ 172.5; 137.7; 134.7; 129.5; 128.2; 127.8; 126.5; 118.5; 65.15; 53.07; 51.35; 44.6; 40.1; 38.25; 32.8; 26.35; 20.4; 19.8. IR ($CHCl_3$): 1691 (C=O); 1639 (C=C) cm^{-1}. GC/MS (EI) *m*/*z*: (rel. int.): 282 [M$^+$] (0.5%), 159 (20%), 131 (55%), 91 (100%). Anal. Calcd for $C_{21}H_{27}NO_3S$: C, 67.56; H, 7.24; N, 3.75; S, 8.58. Found: C, 67.27; H, 7.21; N, 3.73; S, 8.59.

4.1.2. *N*-[(2*R*)-2-Isopropyl-3-butenoyl]-(1*S*)-2,10-camphorsultam 29. Yield 43%. White crystals. Mp: 152–153°C. $[\alpha]_D^{20}$=−95.9 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz): δ 5.90–5.66 (m, 1H); 5.3–5.1 (m, 2H); 3.9–3.8 (t, 1H, ^3J=5.5 Hz, CH α to C=O); 3.55–3.38 (dd, AB system, 2H, ^2J=13.5 Hz, CH_2 α to SO_2); 3.39–3.29 (t, 1H, ^3J=8 Hz, CH α to N); 2.15–2.0 (m, 3H); 1.95–1.80 (m, 3H); 1.45–1.28 (m, 2H); 1.16 (s, 3H); 0.97–0.85 (m (two d+one s), 9H). ^{13}C NMR: δ 172.5; 137.7; 134.3; 118.8; 65.4; 53.15; 50.5; 118.15; 44.6; 32.5; 32.8; 32.4; 26.3; 20.7; 20.4; 19.8; 19.45.

4.1.3. (2*R*)-2-Benzyl-3-butenoic acid. To a solution of 2.20 g (5.93 mmol) of **28** in a mixture of 40 mL of THF and 10 mL of water were successively added 1 g (23.7 mmol) of $LiOH{\cdot}H_2O$ and 4.15 mL (47.40 mmol) of 35% aqueous hydrogen peroxide. The reaction mixture was stirred first for 1 h at 0°C and then overnight at room temperature. After acidification to ca. pH 2 with 2N hydrochloric acid, the aqueous phase was extracted several times with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated by rotary evaporation. The residue was taken up in hexane and the resulting heterogeneous mixture was filtered. The precipitate was washed with hexane and discarded. Evaporation of the filtrates gave 1.12 g of crude acid as an oil contaminated with small amounts (<10%) of camphorsultam-derived by-products. Yield: ca. 90%. Oil. ^{1}H NMR (200 MHz): δ 11.65 (broad s, 1H); 7.38–7.18 (m, 5H, Ar–H); 5.98–5.80 (m, 1H, vinylic CH); 5.20 (d, $^3J_{cis}$=10 Hz, 1H, vinylic C*H*H); 5.14 (d, $^3J_{trans}$=17.3 Hz; 1H, vinylic CH*H*); 3.46–3.3 (broad q, *J*=7.6 Hz, 1H, CH α to C=O); 3.15–3.10 and 2.9–2.78 (two dd, *AB*X system, $^2J_{AB}$=13.5 Hz, $^3J_{AX}$=7.5 Hz, $^3J_{BX}$=7.5 Hz, (1+1)H). ^{13}C NMR: δ 179.6; 138.15; 134.55; 128.25; 128.1; 126.4; 118.15; 51.7; 37.9. IR (CCl_4): 3525–3065 (OH); 1708 (C=O); 1639 (C=C) cm^{-1}. GC/MS (EI) *m*/*z*: (rel. int.): 176 (M$^+$), 91 (100%).

4.1.4. (2*R*)-2-Isopropyl-3-butenoic acid. The crude product is distilled under reduced pressure. Bp: 125°C (1 mm). Oil. Yield 51%. ^{1}H NMR (250 MHz): δ 11.4 (broad s, 1H); 5.9–5.67 (m, 1H); 5.18–5.1 (m, 2H); 2.78–2.62 (broad t, ^3J=ca. 11 Hz, 1H); 2.07–1.87 (m, 1H); 0.94 (d, ^3J=8.5 Hz, 3H); 0.88 (d, ^3J=8.5 Hz, 3H). ^{13}C NMR: δ 180.4; 134.4; 128.65; 57.9; 30.4; 20.6; 19.5.

4.1.5. (2*R*)-2-Benzyl-3-butenoyl chloride 30. A solution of 1 g (5.68 mmol) of crude (2*R*)-2-benzyl-3-butenoic acid and 780 μL (8.60 mmol, 1.5 equiv.) of dichloromethyl methyl ether in 12 mL of dichloromethane was heated at reflux for 1 h. The solvent was evaporated and the residue

was purified by distillation to give 0.79 g of a colourless oil. Bp: 110°C (1 mm). Yield 72%. ^{1}H NMR (250 MHz): δ 7.35–7.1 (m, 5H); 5.9–5.7 (m, 1H); 5.28 (d, $^3J_{cis}$=10 Hz, 1H); 5.20 (d, $^3J_{trans}$=15 Hz, 1H); 3.7 (q, ^3J=8 Hz); 3.25–3.12 and 2.98–2.87 (two dd, *AB*X system, $^2J_{AB}$=14 Hz, $^3J_{AX}$=7.5 Hz, $^3J_{BX}$=7.5 Hz, (1+1)H). ^{13}C NMR: δ 179.6; 138.1; 134.5; 128.25; 128.1; 126.4; 118.15; 51.7; 37.9. IR (CCl_4): 1792 (C=O); 1638 (C=C) cm^{-1}. GC/MS *m/z*: (rel. int.): 159 [M$^+$−Cl], 131 (10%), 91 (100%).

4.1.6. 2*R*-2-Isopropyl-3-butenoyl chloride 31. The dichloromethane solution of the acid and dichloromethyl methyl ether was refluxed during 16 h. The solvent was then evaporated and the crude acyl chloride (yield 70%) was directly engaged in coupling reactions with the *N*-Dmb allylic amines. Oil. ^{1}H NMR (200 MHz): δ 5.9–5.7 (m, 1H); 5.35–5.18 (two overlapping d (app. t), $^3J_{cis}$=10 Hz, $^3J_{trans}$=18 Hz, 2H); 2.78–2.65 (broad t, ^3J=ca. 8–9 Hz, 1H); 2.12–1.88 (broad oct. ^3J=ca. 6–7 Hz, 1H); 1.01 (d, ^3J=6.5 Hz, 3H); 0.89 (d, ^3J=6.5 Hz, 3H). ^{13}C NMR: δ 207.1; 132.1; 121.1; 68.6; 30.6; 20.2; 19.0. IR (CCl_4): 1792 (C=O); 1639 (C=C) cm^{-1}.

4.1.7. But-3-enoic acid allyl ester 20. 16 g (0.186 mol) of vinylacetic acid and 38 mL (0.56 mol) of allyl alcohol were diluted in 100 mL of benzene. To this solution were added 10.66 g (0.056 mol) of *p*-toluene sulfonic acid monohydrate and the reaction mixture was refluxed for about 3 h with azeotropic elimination of water in a Dean–Stark separator. The reaction mixture was extracted with aqueous HCO_3Na and dried with $MgSO_4$. Benzene was eliminated through a Vigreux column at atmospheric pressure and the residue was distilled to give 13.8 g of **20** as a colourless liquid. Bp: 125°C (760 mm). Yield: 60%. ^{1}H NMR (200 MHz): δ 5.93–5.71 (m, 2H); 5.25–5.0 (m, 4H); 4.50–4.47 (d, ^3J=5 Hz); 3.02 (d, ^3J=7 Hz, 2H). ^{13}C NMR: δ 171.0; 131.9; 130.05; 121.1; 65.2; 38.9.

4.1.8. Racemic 2-benzyl-3-butenoic acid allyl ester 21. 3.72 mL of a 1.6 M solution of *n*-BuLi in hexane were added at 0°C to a solution of 834 μL (5.94 mmol) of dry diisopropylamine in 4.5 mL of THF. After 30 min, the solution was cooled to −78°C and 1.07 mL of HMPA (6.15 mmol) were added to it. The reaction mixture was stirred at −78°C for 1 h. 3 g (23.8 mmol) of 3-butenoic acid allyl ester diluted in 4.5 mL of THF were then added dropwise over a period of 30 min. The reaction mixture was stirred at −78°C for 1 h, upon which 0.71 mL of benzyl bromide (5.95 mmol) were added over a few minutes. Stirring at −78°C was continued for 1 h before quenching the reaction mixture by 10 mL of 5% aqueous HCl. The aqueous phase was extracted several times with ether and the organic phase was washed with 5% aqueous HCl and with brine and dried over $MgSO_4$. After evaporation, the residue was purified by column chromatography (silicagel, eluent heptane/AcOEt 95: 5) to give 1.06 g of **21** as a colourless oil. Yield (based on *n*-BuLi): 82%. ^{1}H NMR (250 MHz): δ 7.30–7.10 (m, 5H, Ar–H); 5.83–5.7 (m, 2H, two vinylic CH); 5.3–5.05 (m, 4H, two vinylic CH_2); 4.51 (d, ^3J=5.5 Hz, 2H, CH_2 α to O); 3.42–3.28 (q, ^3J=7.5 Hz, 1H, CH_2 α to C=O); 3.17–3.05 and 2.90–2.78 (two dd, *AB*X system, $^2J_{AB}$=13.5 Hz, $^3J_{AX}$=7.5 Hz, $^3J_{BX}$=7.5 Hz, (1+1)H). ^{13}C NMR: δ 172.75; 138.4; 135.2; 131.8; 128.9; 128.2; 126.3; 118.0; 117.6; 65.05; 51.9; 38.3. GC/MS (EI) 216 (M$^+$), 175 (M−41, 100%), 129 (98%), 115 (33%), 91 (88%).

4.1.9. Racemic 2-isopropyl-3-butenoic acid allyl ester 22. Same experimental procedure as above, except that 2 equiv. (based on *n*-BuLi) of alkylating agent (isopropyl iodide) was used. Yield: 46%. ^{1}H NMR (250 MHz): δ 5.97–5.72 (m, 2H); 5.32–5.05 (m, 4H); 4.51 (d, ^3J=5.5 Hz, 2H); 2.75–2.63 (t, ^3J=9 Hz, 2H); 2.1–1.9 (broad oct, ^3J=ca. 7 Hz, 1H); 0.90 (d, ^3J=7 Hz, 3H); 0.86 (d, ^3J=7 Hz, 3H). ^{13}C NMR: δ 173.45; 135.0; 132.2; 64.95; 58.15; 30.60; 20.7; 19.6.

4.2. Racemic 2-benzyl-3-butenoic and racemic 2-isopropyl-3-butenoic acids 23 and 24

In a Schlenk tube under an argon atmosphere 1 g (4.6 mmol) of 2-benzyl-3-butenoic acid allyl ester **21** was dissolved in 10 mL of degassed dichloromethane. 1.14 mL (9.2 mmol) of phenylsilane was then syringed into the solution followed by 26.5 mg (0.023 mmol) of palladium tetrakis(triphenylphosphine) rapidly added as a solid. A mildly exothermic reaction with gas evolution immediately ensued. After 30 min, the golden-yellow solution was twice treated for a few minutes with 10 mL of half-saturated aqueous HCO_3Na under vigorous stirring. The aqueous phases were then acidified with aqueous HCl and twice extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and evaporated to give 688 mg of racemic 2-benzyl-3-butenoic **23** as a colourless oil.

By the same procedure racemic 2-isopropyl-3-butenoic acid **24** was obtained from allyl ester **22**.

4.2.1. 1-[*N*-(1′*S*)-(1′-Benzyl-prop-2′-enyl)amino]methyl-2,4-dimethoxybenzene 35. 870.4 mg (2 mmol) of $NaBH(OAc)_3$ were added, as a solid, to a solution of 588 mg (2 mmol) of (*S*)-1-benzyl-prop-2-enylamine **15** and 680 mg (2 mmol) of 2,4-dimethoxybenzaldehyde in 200 mL of dichloroethane. The reaction mixture was stirred at room temperature for 16 h and then quenched with saturated aqueous Na_2CO_3. The organic phase was washed with brine and dried over $MgSO_4$. After evaporation, the residue was purified by column chromatography on silica gel (eluent heptane/AcOEt from 6:4 to 2:8 with 1% Et_3N). Yield 725 mg (61%). $[\alpha]_D^{20}$=−24.2 (*c* 1.75, $CHCl_3$). ^{1}H NMR (250 MHz): δ 7.3–7.08 (5H, benzyl Ar–H); 6.95 (d, ^3J=8 Hz, 1H, Dmb Ar–H); 6.4–6.3 (m, 2H, Dmb Ar–H); 5.85–5.62 (m, 1H); 5.18–5.02 (m, 2H); 3.75 (s, 3H); 3.47 (s, 3H); 3.66 and 3.46 (two d, AB system, $^2J_{AB}$=13 Hz, (1+1)H); 3.27–3.17 (m, 1H, CH α to N); 2.82–2.72 and 2.71–2.60 (two dd, *AB*X system $^2J_{AB}$=13 Hz, $^3J_{AX}$=5 Hz, $^3J_{BX}$=9 Hz, (1+1)H). ^{13}C NMR: δ 159.75; 158.5; 141.0; 138.5; 130.25; 129.15; 128.1; 126.0; 120.25; 115.95; 103.05; 98.1; 61.2; 55.1; 54.6; 46.7; 42.3. GC/MS *m/z*: (rel. int.): 297 [M$^+$], 151 (100%, M$^+$−$C_6H_3(MeO)_2$−CH_2); 206 (60%), 91 (35%). HRMS (EI) calcd for $C_{19}H_{23}NO_2$ [M$^+$] 297.1728, found 297.1727.

4.2.2. 1-[*N*-(1′*R*)-(1′-Benzyl-prop-2′-enyl)amino]methyl-2,4-dimethoxybenzene ent-35 and racemic 1-[*N*-(1′-phenyl-prop-2′-enyl)amino]methyl-2,4-dimethoxybenzene 34. Yields around 80% were obtained by the same

procedure. *1-[N-(1′-phenyl-prop-2′-enyl)amino]methyl-2,4-dimethoxybenzene* **34** (racemic): ^{1}H NMR (200 MHz): δ 7.4–7.2 (m, 5H); 7.05 (d, ^3J=8 Hz, 1H); 6.4–6.3 (m, 2H); 6.05–5.85 (m, 1H); 5.2 (d, 1H, $^3J_{trans}$=17 Hz); 5.1 (d, 1H, $^3J_{cis}$=10.5 Hz); 4.15 (d, ^3J=7.5 Hz, 1H; 3.8 (s, 3H). 3.75 (s, 3H); 3.65 (s, 2H); 1.95 (broad s, 1H, NH). ^{13}C NMR: δ 141.35; 130.54; 128.4; 127.4; 127.05; 114.9; 103.5; 98.5; 65.85; 55.35; 55.3; 46.6.

4.2.3. (2*R*,1′*S*)-*N*-(1′-Benzyl-prop-2′-enyl)-*N*-[(2,4-dimethoxyphenyl)methyl]-2-benzyl-but-3-enamide 36a. 646 μL (2.6 mmol) of BSA (*N*,*O*-bistrimethylsilylacetamide) were syringed at room temperature into a solution of 733 mg (2.46 mmol) of amine **35** in 2 mL of dichloromethane. The reaction was stirred for 1 h at room temperature before cooling to 0°C. A solution of 507.5 mg (2.6 mmol) of (*R*)-2-benzyl-but-3-enoyl chloride in 2 mL of dichloromethane was then added dropwise and the reaction was stirred for 2 h at 0°C and for 16 h at room temperature. The reaction was quenched with aqueous phosphate buffer (pH 7). After addition of Et_2O, the aqueous phase was decanted and reextracted with Et_2O. The organic phases were combined, washed with brine, dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica with heptane/diethyl ether 1:1 to give 921 mg of pure **36a** as a pale yellow oil. Yield: 82%. $[\alpha]_D^{20}$=−54.8 (*c* 0.90, $CHCl_3$). ^{1}H NMR (200 MHz, variable temperature and COSY experiments showed the presence of two rotamers in a ca. 4:1 ratio): δ 7.4–7.0 (m, 10H, benzyl Ar–H); 6.83 (d, *J*=8.5 Hz, ca. 0.2H (minor rotamer), Dmb Ar–H); 6.57 (d, *J*=8.5 Hz, ca. 0.8H (major rotamer), Dmb Ar–H); 6.43 (d, *J*=2 Hz, 1H, Dmb Ar–H); 6.36 (dd, *J*=8.5 Hz, 2.05 Hz, ca. 0.2H (minor rotamer), Dmb Ar–H); 6.23 (dd, *J*=8.5, 2.0 Hz, ca. 0.8H (major rotamer), Dmb Ar–H); 5.93–5.58 (m, 2H, two vinylic CH); 5.12–4.70 (m, 5H, two vinylic CH_2+CH α to N); 4.30 and 4.13 (two d, AB system, $^2J_{AB}$=18 Hz, (1+1)H); 3.77–3.75 (two s, 6H); 3.35–3.2 (broad q, 1H, CH α to C=O); 3.15–2.66 (m, 4H, two benzylic CH_2); coalescence of the peaks of the two rotamers was observed at 320 K. ^{13}C NMR (the presence of the two rotamers induces a splitting of most peaks; only the peaks of major rotamer are listed here): δ 173.4; 159.8; 157.1; 139.5; 138.1; 136.85; 135.7; 129.4; 129.3; 128.0; 126.05; 125.9; 117.4; 116.5; 103.6; 98.0; 59.2; 55.3; 55.1; 50.2; 42.9; 39.0; 38.5. IR ($CHCl_3$): 1668 (C=O); 1642 (C=C) cm^{-1}. HRMS (EI) calcd for $C_{30}H_{33}NO_3$ [M$^+$] 455.2460, found 455.2458.

4.2.4. (2*R*,1′*R*)-*N*-(1′-Benzyl-prop-2′-enyl)-*N*-[2,4-dimethoxyphenyl)methyl]-2-benzyl-but-3-enamide 36b. Oil. Yield 80%. ^{1}H NMR (200 MHz): two rotamers in a ca. 4:1 ratio: δ 7.3–7.1 (m, 10H, benzyl Ar–H); 6.95 (d, *J*=8.5 Hz, ca. 0.2H (minor rotamer), Dmb Ar–H); 6.50 (d, *J*=8.5 Hz, ca. 0.8H (major rotamer), Dmb Ar–H); 6.40 (d, *J*=2 Hz, 1H, Dmb Ar–H); 6.16 (dd, *J*=8.5 Hz, 2.5 Hz, ca. 0.8H, (major rotamer), Dmb Ar–H); 6.0–5.75 (m, 2H, two vinylic CH); 5.18–4.67 (m, 5H, two vinylic CH_2+CH α to N); 4.20 and 4.01 (two d, AB system, $^2J_{AB}$=17 Hz, (1+1)H); 3.80–3.70 (apparent s, 6H); 3.40–3.15 (broad q, 1H, CH α to C=O); 3.05–2.55 (m, 4H, two benzylic CH_2). HRMS (EI) calcd for $C_{30}H_{33}NO_3$ [M$^+$] 455.2460, found 455.2464.

4.2.5. (2*R*,1′*S*)-*N*-(1′-Benzyl-prop-2′-enyl)-*N*-[2,4-dimethoxyphenyl)methyl]-2-isopropyl-but-3-enamide 37a. Pale yellow oil. Yield 60%. $[\alpha]_D^{20}$=−91.2. (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz): δ 7.30–6.95 (m, 6H, benzyl Ar–H+1 Dmb Ar–H); 6.45–6.35 (m, 2H, Dmb Ar–H); 5.98–5.78 (m, 1H, vinylic CH); 5.72–5.57 (m, 1H, vinylic CH); 5.2–4.75 (m, 5H, two vinylic CH_2+CH α to N); 4.45 and 4.24 (two d, AB system, $^3J_{AB}$=18 Hz, (1+1)H); 3.8 (s, 3H); 3.77 (s, 3H); 3.05–2.8 (m, 2H, benzylic CH_2); 2.60 (t, ^3J=9 Hz, 1H, CH α to C=O); 2.12–1.90 (broad oct, 1H); 0.80 (d, ^3J=7.0 Hz, 3H); 0.73 (d, ^3J=7.0 Hz, 3H). ^{13}C NMR: δ 174.0; 159.8; 157.5; 137.2; 135.9; 129.45; 129.4; 128.55; 128.3; 128.1; 126.1; 118.5; 117.7; 103.35; 98.05; 59.4; 55.75; 55.35; 55.2; 43.1; 38.75; 30.35; 21.4; 19.85. HRMS (EI) calcd for $C_{26}H_{33}NO_3$ [M$^+$] 407.2460, found 407.2456.

4.2.6. (2*R*,1′*R*)-*N*-(1′-Benzyl-prop-2′-enyl)-*N*-[(2,4-dimethoxyphenyl)methyl]-2-isopropyl-but-3-enamide 37b. Pale yellow oil. Yield 58%. ^{1}H NMR (250 MHz): δ 7.3–7.15 (m, 5H, benzyl Ar–H); 6.88 (d, *J*=8 Hz, 1H, Dmb Ar–H); 6.45–6.38 (sharp m, 1H, Dmb Ar–H); 6.38–6.32 (dd, *J*=8 and 2 Hz, 1H, Dmb Ar–H); 6.0–5.7 (m, 2H, two vinylic CH); 5.1–4.70 (m, 5H, two vinylic CH_2+CH α to N); 4.40 and 4.18 (two d, AB system, $^3J_{AB}$=18 Hz, (1+1)H); 3.8 (s, 3H); 3.77 (s, 3H); 3.15–3.02 and 2.95–2.85 (two dd, *AB*X system, $^2J_{AB}$=14 Hz; $^3J_{AX}$=7.5 Hz; $^3J_{BX}$=8 Hz, (1+1)H); 2.68–2.58 (t, ^3J=9 Hz, 1H, CH α to C=O); 2.08–1.87 (broad oct, ^3J=7–8 Hz, 1H); 0.90–0.70 (m, 6H).

4.2.7. Mixture of (2*R,1′*S**)- and (2*R**,1′*R**)-*N*-(1′-phenyl-prop-2′-enyl)-*N*-[2,4-dimethoxyphenyl)methyl]-2-benzyl-but-3-enamide [38a+38b].** Off-white powder. Yield 82%. NMR spectra are too complex to be of diagnostic value. HRMS (EI) calcd for $C_{29}H_{31}NO_3$ [M$^+$] 441.2304, found 441.2302

4.2.8. Mixture of (2*R,1′*S**)- and (2*R**,1′*R**)-*N*-(1′-phenyl-prop-2′-enyl)-*N*-[2,4-dimethoxyphenyl)methyl]-2-isopropyl-but-3-enamide [39a+39b].** Yellow oil. Yield 52%. NMR spectra are too complex to be of diagnostic value. HRMS (EI) calcd for $C_{25}H_{31}NO_3$ [M$^+$] 393.2304, found 393.2300.

4.3. General procedure for ring-closing metathesis

The reaction are run under an argon atmosphere and in degassed solvent. 7.5 mL of freshly distilled benzene are syringed in a first Schlenk tube containing 42 mg (0.05 mmol) of catalyst **41**. The resulting solution is then transfered through a cannula into a second Schlenk tube containing 0.5 mmol of bis-olefinic amide dissolved in 10 mL of benzene. The reaction mixture is heated under magnetic stirring at 65–70°C for 24–36 h. The reaction may be conveniently monitored by ccm. After cooling at room temperature, the solvent is evaporated and the residue is directly purified by column chromatography on silica with heptane/AcOEt ca. 7:3 as the eluent.

4.3.1. (3*R*,6*S*)-*N*-[(2,4-Dimethoxyphenyl)methyl]-3,6-dibenzyl-3,6-dihydro-2-pyridone 44a. Oil. Yield 90%. $[\alpha]_D^{20}$=−72.8. (*c* 0.125, $CHCl_3$). ^{1}H NMR (250 MHz): δ

7.33–7.0 (m, 11H, benzyl Ar–H+1 Dmb Ar–H); 6.48–6.40 (m, 2H, Dmb Ar–H); 5.44 (very sharp m, 2H, olefinic H); 5.34 (d, ^2J=15 Hz, 1H, Dmb C*H*H); 4.26 (d, ^2J=15 Hz, 1H, Dmb CH*H*); 4.03–3.98 (m, 1H, CH α to N); 3.82 (s, 3H); 3.78 (s, 3H); 3.18–3.06 (m, 1H, CH α to C=O); 2.97–2.89 and 2.2–2.1 (two dd, *AB*X system, $^2J_{AB}$=13 Hz, $^3J_{AX}$=4 Hz, $^3J_{BX}$=8.5 Hz, (1+1)H); 2.85–2.76 and 2.06–1.93 (two dd, *AB*X system, $^2J_{AB}$=13 Hz, $^3J_{AX}$=3 Hz, $^3J_{BX}$=9 Hz, (1+1)H). ^{1}H NMR (250 MHz, toluene d^8): δ 7.46 (d, *J*=8 Hz) and 7.2–6.97 (m) (10H, Ar–H); 6.88 (d, 1H, *J*=10 Hz, Ar–H); 6.38–6.28 (m, 2H, Ar–H); 5.64 (d, ^2J=15 Hz, 1H, Dmb C*H*H); 5.29–5.1 (two dd, *J*=10.5 and 3.9 Hz, 2H, olefinic H); 4.33 (d, ^2J=15 Hz, 1H, Dmb CH*H*); 3.98–3.87 (m, 1H, CH α to N); 3.37 (s, 3H); 3.32 (s, 3H); 3.20–3.08 (m, 1H, CH α to C=O); 2.98–2.82 and 2.40–2.25 (two dd, *AB*X system, $^2J_{AB}$=15.0 Hz, $^3J_{AX}$=1.5 Hz, $^3J_{BX}$=5 Hz, (1+1)H); 2.70–2.56 and 1.90–1.78 (two dd, *AB*X system, $^2J_{AB}$=13.0 Hz, $^3J_{AX}$=1.5 Hz, $^3J_{BX}$=5 Hz, (1+1)H). ^{13}C NMR: δ 170.2; 160.1; 158.4; 138.6; 136.5; 130.7; 129.8; 129.5; 128.1; 128.0; 126.5; 126.2; 124.9; 117.5; 104.3; 98.2; 57.7; 55.24; 55.2; 43.7; 40.5; 39.8; 39.4. GC/MS (EI) 336 (25%, M^+-91); 151 (100%, $M^+-C_6H_3(MeO)_2-CH_2$); 91 (63%). HRMS (EI) calcd for $C_{28}H_{29}NO_3$ [M^+] 427.2153, found 427.2147.

4.3.2. (3*R*,6*R*)-*N*-[(2,4-Dimethoxyphenyl)methyl]-3,6-dibenzyl-3,6-dihydro-2-pyridone 44b. Oil. Yield 83%. ^{1}H NMR (250 MHz): δ 7.27–7.0 (m, 10H, benzyl Ar–H); 6.86 (d, 1H, *J*=8.5 Hz, Dmb ArH); 6.47–6.35 (m, 2H, Dmb Ar–H); 5.54 (very sharp m, 2H, olefinic H); 5.32 (d, ^2J=15 Hz, 1H, Dmb C*H*H); 4.26 (d, 1H, ^2J=15 Hz, Dmb CH*H*); 4.05–3.85 (m, 1H, CH α to N); 3.81 (s, 3H); 3.79 (s, 3H); 3.21–3.13 (dd, part of *AB*X system, $^2J_{AB}$=14 Hz; $^3J_{AB}$=4.5 Hz, 1H); 2.93–2.78 (m, 3H, two benzylic H and CH α to C=O); 2.46–2.36 (m, 1H, benzylic H). ^{13}C NMR: δ 170.55; 160.0; 158.45; 139.20; 136.2; 130.0; 129.8; 129.55; 128.1; 127.2; 126.55; 126.0; 125.2; 117.45; 104.35; 98.25; 57.8; 55.35; 41.5; 40.8; 39.35; 37.3.

4.3.3. (3*R*,6*S*)-*N*-[(2,4-Dimethoxyphenyl)methyl]-3-isopropyl-6-benzyl-3,6-dihydro-2-pyridone 45a. Oil. Yield 90%. $[\alpha]_D^{20}=-20.0$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz): δ 7.30–7.12 (m, 5H, benzyl ArH); 7.07 (d, 1H, *J*=6.5 Hz, Dmb Ar–H); 6.5–6.4 (sharp m, 2H, Dmb Ar–H); 5.68–5.6 (dd, ^3J=10.5 and 4 Hz, 1H, olefinic H); 5.54–5.47 (dd, ^3J=10.5 and 4 Hz, 1H, olefinic H); 5.28 (d, ^2J=15 Hz, 1H, Dmb C*H*H); 4.34 (d, ^2J=15 Hz, 1H, Dmb CH*H*); 4.08–3.97 (m, 1H, CH α to N); 3.83 (s, 3H); 3.77 (s, 3H); 3.4–3.27 and 2.63–2.53 (two dd, *AB*X system, $^2J_{AB}$=13.0 Hz, $^3J_{AX}$=4.0 Hz, $^3J_{BX}$=10.0 Hz, (1+1)H); 2.9–2.8 (m, 1H, CH α to C=O); 2.30–2.17 (broad oct, 1H); 1.00 (d, ^3J=7.0 Hz, 3H); 0.82 (d, ^3J=7.0 Hz, 3H). ^{13}C NMR: δ 170.7; 160.1; 158.45; 137.25; 130.85; 129.41; 129.39; 126.5; 125.95; 123.45; 117.95; 104.35; 98.25; 58.45; 55.35; 55.3; 47.95; 42.05; 40.7; 31.25; 20.6; 18.95. HRMS (EI) calcd for $C_{24}H_{29}NO_3$ [M^+] 379.2148, found 379.2152.

4.3.4. (3*R*,6*R*)-*N*-[(2,4-Dimethoxyphenyl)methyl]-3-isopropyl-6-benzyl-3,6-dihydro-2-pyridone 45b. Oil. Yield 80%. $[\alpha]_D^{20}=-78.8$ (*c* 0.78, $CHCl_3$). ^{1}H NMR (250 MHz): δ 7.3–7.0 (m, 6H, benzyl Ar–H+1 Dmb Ar–H); 6.5–6.4 (m, 2H, Dmb Ar–H); 5.21–5.06 (m, 2H, olefinic H); 5.41 (d, ^2J=15 Hz, 1H, Dmb C*H*H); 4.22 (d, ^2J=15 Hz, 1H, Dmb CH*H*); 4.09–3.98 (m, 1H, CH α to N); 3.80 (s, 3H); 3.77 (s, 3H); 3.0–2.77 (one m, 1H, CH α to C=O, and two dd, *AB*X system, $^2J_{AB}$=ca. 12–13 Hz; $^3J_{AX}$=ca. 4.0 Hz, $^3J_{BX}$=7.5 Hz, (1+1)H); 2.6–2.45 (m, 1H, isopropyl CH); 0.87 (d, ^3J=7.0 Hz, 3H); 0.66 (d, ^3J=7.0 Hz, 3H). ^{13}C NMR: δ 170.7; 160.1; 158.45; 136.5; 130.2; 129.9; 128.1; 126.5; 126.2; 124.05; 117.5; 104.3; 98.35; 57.35; 55.3; 45.95; 40.8; 39.7; 28.9; 20.05; 17.6.

4.3.5. (3*R,6*S**)-*N*-[(2,4-Dimethoxyphenyl)methyl]-3-benzyl-6-phenyl-3,6-dihydro-2-pyridone 42a.** R_f (SiO_2, heptane/AcOEt 7:3): 0.24. Solid. Mp: 82°C. Yield 42% (theoretical yield 50%). ^{1}H NMR (200 MHz): δ 7.32–7.16 (m, 9H, Ar–H); 6.68–6.6 (m, 2H, Ar–H); 6.58–6.48 (m, 2H, Ar–H); 5.62–5.50 (sharp m, 2H, olefinic H); 5.10 (d, ^2J=14 Hz, 1H, Dmb C*H*H); 4.95–4.88 (m, 1H, CH α to N); 3.79 (s, 3H); 3.70 (s, 3H); 3.58 (d, ^2J=14 Hz, 1H, Dmb CH*H*); 3.47–3.35 (m, 1H, CH α to C=O); 3.35–3.12 (two dd, *AB*X system, $^2J_{AB}$=13.0 Hz, $^3J_{AX}$=5.0 Hz, $^3J_{BX}$=ca. 7 Hz, (1+1)H). ^{13}C NMR: δ 169.35; 160.1; 158.5; 139.95; 138.3; 131.0; 129.95; 128.55; 128.45; 128.35; 128.3; 127.55; 126.95; 126.4; 126.15; 123.5; 117.45; 104.0; 98.15; 62.35; 55.25; 55.05; 43.0; 41.55; 39.65. HRMS (EI) calcd for $C_{27}H_{28}NO_3$ [M^+] 413.1991, found 413.1997.

4.3.6. (3*R,6*R**)-*N*-[(2,4-Dimethoxyphenyl)methyl]-3-benzyl-6-phenyl-3,6-dihydro-2-pyridone 42b.** R_f (SiO_2, heptane/AcOEt 7:3): 0.34. Solid. Mp: 85°C. Yield 42% (theoretical yield 50%). ^{1}H NMR (200 MHz): δ 7.38–7.08 (m, 10H, benzyl Ar–H); 6.83 (d, *J*=8 Hz, 1H, Dmb Ar–H); 6.41–6.31 (m, 2H, Dmb Ar–H); 5.63–5.56 (sharp m, 2H, olefinic H); 5.19 (d, $^2J_{AB}$=15 Hz, 1H, Dmb C*H*H); 4.81–4.72 (m, 1H, CH α to N); 3.79 (s, 3H); 3.69 (s, 3H); 3.64 (partially masked d, 1H, Dmb CH*H*); 3.55–3.42 (m, 1H, CH α to C=O); 3.4–3.3 and 3.18–3.06 (two dd, *AB*X system, $^2J_{AB}$=13.5 Hz, $^3J_{AX}$=4.5 Hz, $^3J_{BX}$=8 Hz, (1+1)H). ^{13}C NMR: δ 169.75; 160.05; 158.5: 140.6; 138.7; 130.15; 129.7; 128.75; 128.15; 127.82; 126.9: 126.3; 126.15; 124.05; 117.25; 104.1; 98.15; 62.1; 55.35; 55.05; 42.15; 41.45; 38.8. HRMS (EI) calcd for $C_{27}H_{28}NO_3$ [M^+] 413.1991, found 413.1993.

4.3.7. Mixture of (3*R,6*S**)- and (3*R**,6*R**)-*N*-[(2,4-dimethoxyphenyl)methyl]-3-isopropyl-6-phenyl-3,6-dihydro-2-pyridone [43a+43b].** Oil. Yield 72%. ^{1}H NMR (250 MHz): δ 7.38–7.05 (m, 6H+6H, Ar–H); 6.48–6.3 (m, 2H+2H, Ar–H); 5.80–5.6 (m, 2H+2H, olefinic H); 5.31 (d, ^2J=14.5 Hz, 1H, Dmb C*H*H); 5.18 (d, ^2J=14.5 Hz, 1H, Dmb CH*H*); 5.06–4.98 (m, 1H CH α to N); 4.9–4.82 (m, 1H, CH α to N); 3.82–3.68 (four s+one d (?), 13H); 3.55 (d, $^2J_{AB}$=14.5 Hz, Dmb CH*H*); 3.1–3.02 (m, 1H, CH α to C=O); 3.0–2.9 (m, 1H, CH α to C=O); 2.80–2.58 (m (two overlapping oct), 1H+1H); 1.06 (d, ^3J=7 Hz, 3H); 1.02 (d, ^3J=7 Hz, 3H); 0.95 (d, ^3J=7 Hz, 3H); 0.75 (d, ^3J=7 Hz, 3H). ^{13}C NMR: δ 170.35; 170.3; 160.20; 160.1; 158.65; 158.6; 140.9; 140.7; 131.05; 130.95; 128.8; 128.7; 127.9; 127.75; 127.6; 127.15; 126.95; 121.30; 121.05; 117.7; 117.5; 104.05; 103.85; 98.7; 98.2; 62.25; 61.8; 55.35; 55.10; 55.05; 46.85; 46.4; 41.85; 41.55; 30.55; 20.6; 20.2; 19.05; 17.55. HRMS (EI) calcd for $C_{23}H_{27}NO_3$ [M^+] 393.2304, found 393.2300.

4.3.8. (3*R*,6*S*)-3,6-Dibenzyl-3,6-dihydro-2-pyridone 46a. 155 mg (0.36 mmol) of (3*R*,6*S*)-*N*-[(2,4-dimethoxyphenyl)-

methyl]-3,6-dibenzyl-3,6-dihydro-2-pyridone **44a** were dissolved in 40 mL of trifluoracetic acid (freshly distilled over a small amount of P_2O_5) containing 115.5 μL (0.72 mmol) of triethylsilane. The reaction mixture was heated at reflux for 30 min and then allowed to cool to room temperature. Trifluoroacetic acid was removed by rotary evaporation and the residue was directly purified by column chromatography on silica using a gradient of heptane/AcOEt from 7:3 to 2:8, 86 mg of **46a** were collected as a white solid: Yield: 85%. Mp: 120–123°C. $[\alpha]_D^{20}=-221$ (*c* 0.2, $CHCl_3$). ^{1}H NMR (200 MHz): δ 7.40–6.93 (m, 10H, Ar–H); 6.15 (broad s, 1H, NH); 5.7–5.55 (sharp m, 2H, olefinic H); 4.1–3.98 (m, 1H, CH α to N); 3.27–3.13 (m, 1H, CH α to C=O); 3.09–2.95 and 2.90–2.78 (two dd, *AB*X system, $^2J_{AB}$=13 Hz, $^3J_{AX}$=4 Hz, $^3J_{BX}$=7.5 Hz, (1+1)H); 2.48–2.35 and 1.90–1.72 (two dd, *AB*X system, $^2J_{AB}$=13.5 Hz, $^3J_{AX}$=5 Hz, $^3J_{BX}$=8.5 Hz, (1+1)H). ^{13}C NMR: δ 171.3; 137.8; 136.4; 129.9; 129.45; 128.5; 128.1; 126.7; 126.4; 125.6; 124.8; 55.0; 43.7; 43.4; 38.7. IR ($CHCl_3$): 1678 (C=O); 1654 (C=C) cm^{-1}. GC/MS (EI) *m/z*: (rel. int.): 277 [M$^+$] (0.5%), 186 (18%), 91 (100%).

4.3.9. (3*R*,6*R*)-3,6-Dibenzyl-3,6-dihydro-2-pyridone. White solid. Yield: 80%. Mp: 102–103°C. ^{1}H NMR (250 MHz): δ 7.35–7.05 (m, 10H, Ar–H); 6.08 (broad s, 1H, NH); 5.70–5.52 (sharp m (two dd), 2H, olefinic H); 3.98–3.85 (m, 1H, CH α to N); 3.22–3.12 (dd, part of *AB*X system, $^2J_{AB}$=13 Hz, $^3J_{AX}$=4 Hz, 1H); 3.10–3.01 (m, 1H, CH α to C=O); 2.98–2.80 (m, parts of *AB*X system, 2H); 2.68–2.5 (dd, part of *AB*X system, $^2J_{AB}$=13.5 Hz, $^3J_{AX}$=8.5 Hz, 1H). ^{13}C NMR: δ 171.7; 138.05; 136.15; 129.45; 129.35; 128.7; 128.15; 126.95; 126.3; 125.75; 125.05; 54.55; 43.4; 42.1; 34.5.

4.3.10. (3*R*,6*S*)-3-Isopropyl-6-benzyl-3,6-dihydro-2-pyridone. White solid. Yield: 88%. Mp: 102–104°C. $[\alpha]_D^{20}=-38.7$ (*c* 1.26, $CHCl_3$). ^{1}H NMR (250 MHz): δ 7.35–7.1 (m, 5H, Ar–H); 6.32 (broad s, 1H, NH); 5.85–5.72 (broad d, ^3J=10.5 Hz, 1H, olefinic H); 5.70–5.61 (broad d, ^3J=10.5 Hz, 1H, olefinic H); 4.25–4.12 (m, 1H, CH α to N); 2.98–2.85 and 2.72–2.60 (two dd, *AB*X system, $^2J_{AB}$=13 Hz, $^3J_{AX}$=5.5 Hz, $^3J_{BX}$=8.5 Hz, (1+1) H); 2.9–2.8 (m, 1H, CH α to C=O); 2.47–2.28 (broad oct, 1H); 0.99 (d, ^3J=7 Hz, 3H); 0.77 (d, ^3J=7 Hz, 3H). ^{13}C NMR: δ 171.7; 136.85; 129.35; 128.95; 127.2; 125.7; 123.2; 55.2; 46.4; 38.75; 27.05; 19.75; 17.3.

4.3.11. (3*R*,6*R*)-3-Isopropyl-6-benzyl-3,6-dihydro-2-pyridone. Viscous oil. Yield 85%. $[\alpha]_D^{20}=-47$ (*c* 0.77, $CHCl_3$). ^{1}H NMR (200 MHz): δ 7.4–7.1 (m, 5H, Ar–H); 6.75 (broad s, 1H, NH); 5.9–5.79 (broad d, ^3J=10 Hz, 1H, olefinic H); 5.79–5.65 (broad d, ^3J=10 Hz, 1H, olefinic H); 4.3–4.16 (m, 1H, CH α to N); 2.99–2.75 and 2.78–2.65 (two dd, *AB*X system, $^2J_{AB}$=13.5 Hz, $^3J_{AX}$=5.5 Hz, $^3J_{BX}$=8 Hz, (1+1)H); 2.8–2.7 (m, 1H, CH α to C=O); 2.48–2.28 (m, 1H, isopropyl CH); 0.96 (d, ^3J=7 Hz, 3H); 0.79 (d, ^3J=7 Hz, 3H). ^{13}C NMR: δ 172.0; 136.2; 129.4; 128.8; 127.1; 125.9; 122.7; 55.9; 46.1; 43.4; 30.9; 19.75; 17.3.

4.3.12. (3*R,6*S**)-3-Benzyl-6-phenyl-3,6-dihydro-2-pyridone.** White solid. Yield 80%. Mp: 119–120°C. ^{1}H NMR (400 MHz): δ 7.22–7.17 (m, 8H, Ar–H); 6.61 (dd, ^3J=7 and 1.5 Hz, 2H, Ar–H); 6.07 (broad s, 1H, NH); 5.7–5.64 (dt, ^3J=10 and 2 Hz, 1H, olefinic H); 5.63–5.57 (broad d, ^3J=10 Hz, 1H, olefinic H); 5.01–4.97 (m, 1H, CH α to N); 3.36–3.30 (m, 1H, CH α to C=O); 3.27–3.22 and 3.16–3.10 (two dd, *AB*X system, $^2J_{AB}$=13 Hz, $^3J_{AX}$=7 Hz, $^3J_{BX}$=4 Hz, (1+1)H). ^{13}C NMR: δ 170.3; 140.6; 137.85; 130.05; 128.8; 128.4; 127.95; 126.7; 126.5; 125.3; 124.65; 58.8; 41.65; 38.6. HRMS (EI) calcd for $C_{18}H_{17}NO$ [M$^+$] 263.1310, found 263.1305.

4.3.13. (3*R,6*R**)-3-Benzyl-6-phenyl-3,6-dihydro-2-pyridone.** White solid. Yield 85%. Mp: 121–123°C. ^{1}H NMR (400 MHz): δ 7.35–7.12 (m, 10H, Ar–H); 5.93 (broad s, 1H, NH); 5.65 (sharp m, 2H, olefinic H); 4.73 (d, ^3J=4.5 Hz, 1H, CH α to N); 3.35–3.30 (m, 1H, CH α to C=O); 3.27–3.21 and 3.07–3.0 (two dd, *AB*X system, $^2J_{AB}$=13 Hz, $^3J_{AX}$=4 Hz, $^3J_{BX}$=8.5 Hz, (1+1)H). ^{13}C NMR: δ 171.1; 145.6; 141.1; 138.0; 129.6; 129.0; 128.27; 128.25; 128.23; 126.5; 125.85; 124.8; 58.35; 41.9; 38.8. HRMS (EI) calcd for $C_{18}H_{17}NO$ [M$^+$] 263.1310, found 263.1309.

4.4. (3*R*,6*S*)-3,6-Dibenzyl-2-ethoxy-3,6-dihydropyridine 47

100 mg (0.36 mmol)) of (3*R*,6*S*)-3,6-dibenzyl-3,6-dihydro-2-pyridone **46a** were introduced into a Schlenk tube and put in solution into 3 mL of degassed dichloromethane under an argon atmosphere. A solution of 82.2 mg (0.43 mmol) of freshly recrystallised (pentane/CH_2Cl_2) triethyloxonium tetrafluoroborate in 3 mL of dichloromethane contained in another Schlenk tube was added through a cannula to the reaction mixture which gradually turned purple. After stirring at room temperature for 2 h, the reaction was quenched by adding 8 equiv. of degassed 1 M aqueous phosphate buffer (pH 7). The organic phase was transferred through a cannula into a third Schlenk tube containing $MgSO_4$. The remaining aqueous phase was extracted by 5 mL of additional degassed CH_2Cl_2 and the new CH_2Cl_2 phase was also transferred by a cannula into the third Schlenk tube. After drying, the joined organic phases were transferred via a cannula in a fourth Schlenk and the solvent was evaporated on a vacuum line. The crude imidate which could be contaminated by ca. 5–10% of starting pyridone was not stored, but directly engaged in the subsequent hydrolytic step.

4.4.1. (3*R*,6*S*)-3,6-Dibenzyl-2-ethoxy-3,6-dihydropyridine 47. Oil. ^{1}H NMR (200 MHz, CD_2Cl_2): δ 7.36–7.0 (m, 10H, Ar–H); 5.71–5.62 (dd, ^3J=10 and 1 Hz, 1H, olefinic H); 5.59–5.48 (dd, ^3J=10 and 2.5 Hz, 1H, olefinic H); 4.28–4.0 (m, 3H, ethyl CH_2+CH α to N); 3.10–2.95 (m, 1H, CH α to C=N); 2.85–2.75 (dd, part of *AB*X system, $^2J_{AB}$=13 Hz, $^3J_{AX}$=4.5 Hz, 1H); 2.45–2.3 (m (apparent quint.), parts of *AB*X system, 2H); 2.18–2.05 (dd, part of *AB*X system, $^2J_{AB}$=13 Hz, $^2J_{AX}$=7 Hz, 1H); 1.32 (t, ^3J=7 Hz).

4.4.2. (3*R*,6*R*)-3,6-Dibenzyl-2-ethoxy-3,6-dihydropyridine. Oil. ^{1}H NMR (250 MHz, CD_2Cl_2): δ 7.32–7.05 (m, 10H, Ar–H); 5.8–5.7 (broad d, ^3J=11 Hz, 1H, olefinic H); 5.65–5.54 (dd, ^3J=11 and 1 Hz, 1H, olefinic H); 4.4–4.18 (m, 2H, ethyl CH_2); 4.2–4.08 (m, 1H, CH α to N); 3.12–2.75 (m, 5H, two benzylic CH_2+CH α to C=N); 1.35 (t, ^3J=7 Hz, 3H).

4.4.3. (3*R*,6*S*)-3-Isopropyl-6-benzyl-2-ethoxy-3,6-dihydropyridine. Oil. ^{1}H NMR (250 MHz, CD_2Cl_2): δ 7.35–7.18 (m, 5H, Ar–H); 5.87–5.75 (dd, ^3J=10 and 1 Hz, 1H, olefinic H); 5.73–5.6 (dd, ^3J=10 and 2 Hz, 1H, olefinic H); 4.55–4.48 (m, 1H, CH α to N); 4.48–4.2 (q, ^3J=7 Hz, 2H, ethyl CH_2); 3.2–3.05 and 2.88–2.73 (two dd, *AB* X system, $^2J_{AB}$=13 Hz, $^3J_{AX}$=8 Hz, $^3J_{BX}$=8 Hz, (1+1) H); ca. 2.85 (m, partially masked, 1H, CH α to C=N); 2.18–2.0 (m, 1H); 1.35 (t, ^3J=7 Hz, 3H); 0.95 (d, ^3J=7 Hz, 3H); 0.63 (d, ^3J=7 Hz, 3H).

4.4.4. (3*R*,6*R*)-3-Isopropyl-6-benzyl-2-ethoxy-3,6-dihydropyridine. ^{1}H NMR (250 MHz, CD_2Cl_2): δ 7.4–7.18 (m, 5H); 6.0–5.92 (broad d, ^3J=10 Hz, 1H, olefinic H); 5.76–5.65 (m, 1H, olefinic H); 4.86–4.75 (m, 1H, CH α to N); 4.68–4.47 (m, 2H, ethyl CH_2); 3.34–3.26 and 3.14–3.04 (two dd, *AB* X system, $^2J_{AB}$=13.5 Hz, $^3J_{AX}$=4 Hz, $^3J_{BX}$=8 Hz, (1+1)H); 2.75–2.62 (m, 1H, CH α to C=N); 2.40–2.30 (m, 1H, isopropyl CH); 1.54 (t, ^3J=7 Hz, 3H); 0.98 (d, ^3J=7 Hz, 3H); 0.86 (d, ^3J=7 Hz, 3H).

4.4.5. (3*R,6*S**)-3-Benzyl-6-phenyl-2-ethoxy-3,6-dihydropyridine.** ^{1}H NMR (200 MHz, CD_2Cl_2): δ 7.3–7.11 (m, 8H, Ar–H); 6.68–6.52 (m, 2H, Ar–H); 5.78–5.6 (m, 2H, olefinic H); 5.15–5.05 (broad d, *J*=ca. 6.5 Hz, 1H, CH α to N); 4.15 (q, ^3J=7 Hz, 2H, ethyl CH_2); 3.28–3.0 (m, 3H, benzylic CH_2+CH α to C=N); 1.32 (t, ^3J=7 Hz, 3H).

4.4.6. (3*R,6*R**)-3-Benzyl-6-phenyl-2-ethoxy-3,6-dihydropyridine.** ^{1}H NMR (200 MHz, CD_2Cl_2): δ 7.27–7.02 (m, 10H, Ar–H); 5.78–5.55 (m, 2H, olefinic H); 4.70–4.64 (m, 1H, CH α to N); 4.1–3.97 (q, ^3J=7 Hz, 2H, ethyl CH_2); 3.25–2.8 (m, 3H, benzylic CH_2+CH α to C=N); 1.23 (t, ^3J=7 Hz, 3H).

4.4.7. Ethyl (2*R*,5*S*)-2-benzyl-5-amino-6-phenyl-3-hexenoate hydrochloride 48 and (2*R*,5*S*)-2-benzyl-5-amino-6-phenyl-3-hexenoic acid hydrochloride 49a. To the crude imidate **47** (0.36 mmol) contained in a Schlenk tube under an argon atmosphere was added 0.75 mL of EtOH. To this ethanolic solution were added 5 mL of aqueous 0.3N HCl. The reaction mixture which was first cloudy and then after a while limpid again was stirred under an argon atmosphere and at room temperature for 24 h. After extraction with Et_2O (for the elimination of the small amount of dihydropyridone **46a** possibly present in starting crude imidate), the aqueous phase was evaporated under vacuum to give a white powder which could be identified by NMR as the amino ester hydrochloride **48**. ^{1}H NMR (200 MHz, D_2O): δ 7.2–6.7 (m, 10H, Ar–H); 5.6–5.4 (m, 1H, olefinic H); 5.42–5.22 (m, 1H, olefinic H); 4.08–3.9 (broad q, 1H, CH α to N); 3.88–3.72 (q, *J*=7.0 Hz, 2H, ethyl CH_2); 3.22–3.05 (m, 1H, CH α to C=O); 2.75–2.58 (dd, part of *AB* X system, $^2J_{AB}$=ca. 13 Hz, $^3J_{AX}$=ca. 4.5 Hz, 1H); 2.4–2.1 (m, parts of *AB* X system, 2H); 1.86–1.7 (dd, part of *AB* X system, $^2J_{AB}$=ca. 13 Hz, $^3J_{AX}$=ca. 5.5 Hz, 1H); 0.88 (t, ^3J=7 Hz, 3H).

The above amino ester hydrochloride salt was taken up in 4 mL of 20% aqueous HCl and the solution was heated at reflux for 2 h. Once cooled to room temperature, the solution was evaporated under vacuum. The residue was dissolved in water and loaded onto a column of Dowex 50W-X8 (H^+ form) cation exchange resin. The column was eluted first with water and then with 1N NH_4OH. The fractions containing the amino acid were combined, concentrated by rotary evaporation and finally pumped out on a vacuum line. The residual aminoacid was converted back to its hydrochloride salt **49a**. 107 mg of a white powder were thus collected. Yield: 85% (based on dihydropyridone **46a**, three steps). $[\alpha]_D^{20}$=−69.3 (*c* 0.07, H_2O). ^{1}H NMR (200 MHz, D_2O): δ 7.2–6.8 (m, 10H, Ar–H); 5.55 (t, ^3J=11.5 Hz, 1H, olefinic H); 5.30 (t, ^3J=10.6 Hz, 1H, olefinic H); 4.0 (broad q, ^3J=9 Hz, 1H, CH α to N); 3.22 (broad q, ^3J=9 Hz, 1H, CH α to C=O); 2.62–2.40 (m, 2H, parts of *AB* X sysems); 2.20–2.06 (dd, part of *AB* X system, $^2J_{AB}$=13.5 Hz, $^3J_{AX}$=8 Hz, 1H); 2.05–1.92 (dd, part of *AB* X system, $^2J_{AB}$=13.5 Hz, $^3J_{AX}$=6.0 Hz, 1H). ^{13}C NMR (D_2O): δ 177.0; 134.9; 133.1; 129.6; 129.1; 128.9; 128.5; 127.4; 126.6; 49.8; 46.4; 38.5; 37.4. Anal. Calcd for $C_{19}H_{22}NO_2Cl$. 2.2 H_2O: C, 61.47; H, 7.16; N, 3.77. Found: C, 61.47; H, 7.05; N, 3.76.

(2*R*,5*S*)-2-benzyl-5-amino-6-phenyl-3-hexenoic acid: HRMS (ESI negative mode): calcd for $C_{19}H_{21}NO_2$ $[M-H]^-$ 294.1494, found 294.1490.

Others pseudopeptidic analogs were obtained in a similar way. They were characterised by high resolution mass spectroscopy on the zwitterion and NMR spectroscopy on the hydrochloride salt.

4.4.8. Ethyl (2*R*,5*R*)-2-benzyl-5-amino-6-phenyl-3-hexenoate hydrochloride. White powder. ^{1}H NMR (200 MHz, D_2O): δ 7.2–6.85 (m, 10H, Ar–H); 5.58–5.48 (t, ^3J=11 Hz, 1H, olefinic H); 5.38–5.25 (t, ^3J=10 Hz, 1H, olefinic H); 3.88–3.7 (m, 1H, CH α to N); 3.7–3.52 (q, ^3J=7 Hz, 2H, ethyl CH_2); 3.0–2.45 (m, 5H, two benzylic CH_2+CH α to C=O); 0.84 (t, ^3J=7 Hz, 3H).

4.4.9. (2*R*,5*R*)-2-Benzyl-5-amino-6-phenyl-3-hexenoic acid hydrochloride 49b. White powder. Yield based on dihydropyridone (three steps): 84%; $[\alpha]_D^{20}$=−245 (*c* 0.22, H_2O). ^{1}H NMR (200 MHz, D_2O): δ 7.15–6.90 (m, 10H); 5.48 (t, ^3J=10.5 Hz, 1H, olefinic H); 5.20 (t, ^3J=10.5 Hz, 1H, olefinic H); 3.95–3.88 (broad q, ^3J=8 Hz, 1H, CH α to N); 3.20–3.05 (broad q, ^3J=8 Hz, 1H, CH α to C=O); 2.5–2.38 (m, 3H, parts of *AB* X system); 2.18–2.05 (dd, part of *AB* X system, $^2J_{AB}$=14.5 Hz, $^3J_{AX}$=8.0 Hz, 1H). ^{13}C NMR (D_2O): δ 176.4; 135.23; 132.85; 129.95; 129.75; 129.5; 129.2; 128.9; 127.7; 127.25; 126.65; 50.7; 46.05; 39.0; 38.5.

(2*R*,5*R*)-2-benzyl-5-amino-6-phenyl-3-hexenoic acid: HRMS (ESI negative mode): calcd for $C_{19}H_{21}NO_2$ $[M-H]^-$ 294.1494, found 294.1492.

4.4.10. Ethyl (2*R*,5*S*)-2-isopropyl-5-amino-6-phenyl-3-hexenoate hydrochloride. White powder. ^{1}H NMR (250 MHz, D_2O): δ 7.18–6.92 (m, 5H, Ar–H); 5.75–5.68 (dd, ^3J=11 Hz and ca. 1–2 Hz, 1H, olefinic H); 5.58–5.48 (dd, ^3J=11 Hz and ca. 2 Hz, 1H, olefinic H); 4.55–4.42 (m, 1H, CH α to N); 4.27–4.1 (q, ^3J=7 Hz, 2H, ethyl CH_2); 3.0–2.8 (m, 3H, benzylic CH_2+CH α to C=O); 1.70–1.57 (oct, ^3J=ca. 7 Hz, 1H); 1.18 (t, ^3J=7 Hz, 3H); 0.62 (d, ^3J=7 Hz, 3H); 0.22 (d, ^3J=7 Hz, 3H).

4.4.11. (2*R*,5*S*)-2-Isopropyl-5-amino-6-phenyl-3-hexenoic acid hydrochloride 50a. Yield based on dihydropyridone (three steps): 75%. $[\alpha]_D^{20}=-13.3$ (*c* 0.33, H_2O). ^1H NMR (250 MHz, D_2O): δ 7.15–6.97 (m, 5H, Ar–H); 5.55 (t, $^3J=10$ Hz, 1H, olefinic H); 5.44 (t, $^3J=10$ Hz, 1H, olefinic H); 4.20–4.05 (broad q, 1H, CH α to N); 2.95–2.6 (m, 3H, benzylic CH_2+CH α to C=O); 1.48–1.3 (oct, $^3J=7$ Hz, 1H); 0.46 (d, $^3J=7$ Hz, 3H); 0.23 (d, $^3J=7$ Hz, 3H). ^{13}C NMR (D_2O): δ 177.2; 134.5; 130.5; 129.2; 127.5; 126.7; 125.9; 55.1; 48.6; 44.0; 29.8; 18.5; 16.45.

(2R,5S)-2-Isopropyl-5-amino-6-phenyl-3-hexenoic acid: HRMS electrospray: calcd for $C_{15}H_{21}NO_2$ $[M-H]^-$ 246.1494, found 246.1495.

4.4.12. Ethyl (2*R*,5*R*)-2-isopropyl-5-amino-6-phenyl-3-hexenoate hydrochloride. White powder. *(2R,5R)*-2-isopropyl-5-amino-6-phenyl-3-hexenoic acid hydrochloride **50b**: White powder. Yield based on dihydropyridone (three steps): 77%. $[\alpha]_D^{20}=+25.7$ (*c* 0.17, H_2O). ^1H NMR (250 MHz, D_2O): δ 7.15–6.95 (m, 5H, ArH); 5.60–5.40 (m, 2H, olefinic H); 4.12–4.40 (broad q, $^3J=8$ Hz, 1H, CH α to N); 3.3–2.8 (m, 3H, two benzylic H+CH α to C=O); 1.40–1.27 (oct, $^3J=7$ Hz, 1H); 0.48 (d, $^3J=7$ Hz, 3H); 0.28 (d, $^3J=7$ Hz, 3H). ^{13}C NMR (D_2O): δ 177.0; 135.2; 129.5; 127.9; 127.7; 126.5; 124.3; 55.7; 48.7; 43.1; 29.7; 18.5; 16.8.

(2R,5R)-2-Isopropyl-5-amino-6-phenyl-3-hexenoic acid: HRMS electrospray: calcd for $C_{15}H_{21}NO_2$ $[M-H]^-$ 246.1494, found: 246.1492.

4.4.13. Ethyl (2*R,5*S**)-2-benzyl-5-amino-5-phenyl-3-pentenoate hydrochloride.** White powder. ^1H NMR (250 MHz, D_2O): δ 7.2–7.08; 6.93–6.78; 6.78–6.68 (three m, 10H, Ar–H); 5.73–5.54 (m (apparent.quint.); 2H, olefinic H); 4.84 (d, $^3J=8.5$ Hz, 1 Hz, CH α to N); 3.9–3.8 (q, $^3J=7$ Hz, 2H, ethyl CH_2); 3.52–3.4 (broad q, $^3J=$ca. 6.5 Hz, 1H, CH α to C=O): 2.78–2.68 and 2.42–2.3 (two dd, *AB*X system, $^2J_{AB}=14$ Hz, $^3J_{AX}=7$ Hz, $^3J_{BX}=8.5$ Hz, (1+1)H); 0.90 (t, $^3J=7$ Hz).

4.4.14. (2*R,5*S**)-2-Benzyl-5-amino-5-phenyl-3-pentenoic acid hydrochloride 51a.** White powder. Yield based on dihydropyridone (three steps): 85%. ^1H NMR (250 MHz, D_2O): 7.28–7.03; 7.0–6.85; 6.85–6.78 (three m, 10H, Ar–H); 5.78–5.58 (m (apparent.quint.), 2H, olefinic H); 4.92 (d, $^3J=8$ Hz, 1H, CH α to N); 3.58–3.46 (broad q, $^3J=$ca. 7–8 Hz, 1H, CH α to C=O); 2.90–2.77 and 2.52–2.4 (two dd, *AB*X system, $^2J_{AB}=13$ Hz, $^3J_{AX}=5$ Hz, $^3J_{BX}=8$ Hz, (1+1)H). ^{13}C NMR (D_2O): δ 177.2; 133.8; 132.3; 131.8; 131.35; 131.1; 130.8; 130.5; 130.1; 129.5; 129.2; 55.0; 49.05; 39.5.

(2R,5S*)*-2-Benzyl-5-amino-5-phenyl-3-pentenoic acid: HRMS (ESI negative mode): calcd for $C_{18}H_{19}NO_2$ $[M-H]^-$ 280.1337, found 280.1340.

4.4.15. Ethyl (2*R,5*R**)-2-benzyl-5-amino-5-phenyl-3-pentenoate hydrochloride.** White powder. ^1H NMR (250 MHz, D_2O): δ 7.25–7.0 (m, 10H, Ar–H); 5.88–5.58 (m, 2H, olefinic H); 4.80 (d, $^3J=8$ Hz, 1H, CH α to N); 3.62–3.38 (m, 3H, ethyl CH_2+CH α to C=O); 2.95–2.80 and 2.79–2.65 (two dd, ABX system, $J_{AB}=13$ Hz, $J_{AX}=6.5$ Hz, $J_{BX}=8$ Hz, (1+1)H); 0.68 (t, $^3J=$Hz).

4.4.16. (2*R,5*R**)-2-Benzyl-5-amino-5-phenyl-3-pentenoic acid hydrochloride 51b.** White powder. Yield based on dihydropyridone (three steps): 80%. ^1H NMR (250 MHz, D_2O): δ 7.21–7.0 (m, 10H); 5.9–5.6 (m, 2H, olefinic H); 3.48–3.32 (q, $^3J=8.5$ Hz, 1H, CH α to C=O); 3.02–2.88 and 2.82–2.7 (two dd, *AB*X system, $J_{AB}=13.5$ Hz, $J_{AX}=6.5$ Hz, $J_{BX}=8$ Hz, (1+1)H); CH α to N probably masked by water band. ^{13}C NMR (D_2O): δ 177.0; 134.75; 132.1; 131.95; 131.85; 131.45; 130.64; 130.45; 130.15; 130.07; 129.7; 54.95; 49.15; 40.5.

(2R,5R*)*-2-Benzyl-5-amino-5-phenyl-3-pentenoic acid: HRMS (ESI negative mode): calcd for $C_{19}H_{21}NO_2$ $[M-H]^-$ 280.1337; found 280.1333.

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