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Stereoselective synthesis of vinylogous peptides

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Abstract—A *trans* or *cis* ethenyl group has been inserted between the α-carbon and the carboxyl group of α-aminoacids by Horner stereoselective olefination of α-aminoaldehydes. Numerous pure *cis* and *trans* vinylogous α-aminoacids have been obtained thus and coupled with aminopartners by classical methods. The versatility of the method was illustrated by the preparation of a [*trans* vinylogous-Gly^3]Leu-enkephalin.

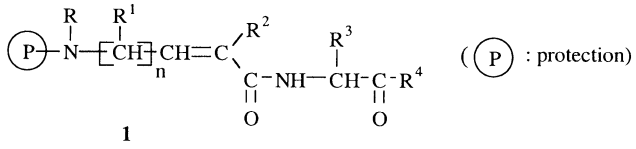
1. Introduction

During the last few decades, there has been an increasing effort to rationally design new neuroactive peptides with controlled conformations and defined biological functions. The principal reason is that the therapeutic applications of endogenous peptides have been limited severely. They are subject to poor bioavailibility, rapid proteolytic degradation, and interact competitively with different receptors. The example of enkephalins is now well known.[1]

Numerous investigations are directed towards the synthesis of peptide analogs that are protected against proteolytic attack and specific for analgesic receptor. Introduction of conformational restraint has become a standard strategy for increasing the receptor selectivity and the duration action of peptide ligands. A major approach in the development of conformationaly restricted aminoacids and peptides is the synthesis of head-to-fail cyclic peptides.[1g,2] Vinylogous amino acids have hitherto been little explored. A sole example of *trans* ethylenic bond has been proposed by Schreiber as a rigid extension of a peptide residue by inclusion between the α-carbon and the carbonyl, resulting in vinylogous aminoacid.[3]

We have recently shown in a short communication that the insertion of an ethenyl CH=CMe group between the α-carbon and the carboxyl group of Proline can be used to control the structure of a peptide.[4] The *trans* CH=CMe group leads to an open conformer in which the amide groups are exposed to solvation in solution or engaged in intermolecular hydrogen bonds in the solid state. Conversely, the *cis* CH=CMe group induces the formation of a very stable intramolecular hydrogen bond closing a nine-membered pseudocycle that involved an excellent mimic of the natural β-turn.[4] As a consequence, these vinylogous aminoacids represent an attractive approach for the construction of new peptide materials.

In this paper, we present a more detailed study of the stereoselective syntheses of *trans* and *cis* vinylogous dipeptides **1** (a *trans* vinylgous dipeptide is a dipeptide where R^2 and H present a *trans* relationship on the double bond, a *cis* vinylogous dipeptide is a dipeptide where R^2 and H present a *cis* relationship):



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The strategy is based on stereoselective Horner reactions applied to α-aminoaldehydes with the stereochemical control of the olefination determined by the choice of the Horner reagent. Previous results with the lithiated anions derived from *N*-substituted (diethyl-β-ketophosphono)-α-aminoacids or from 2-diethylphosphono alcanoic acids and aliphatic, aromatic and glucidic aldehydes have shown a preference for the formation of the *trans* olefins.[5] Analogously the direct generation of unsaturated peptides by reaction between the lithiated anions derived from *N*-(diethyl-β-ketophosphono)-α-aminoacids and aminoaldehydes was considered, but failed, leading to the decomposition of the aminoaldehydes.

On the basis of these observations and other previous works,[6] a stereoselective synthesis of *trans* vinylogous aminoacids **4** was then realized using the convenient reaction between the lithiated dianions **3** derived from

Keywords: vinylogous peptides; Horner stereoselective olefination; neuroactive peptides.

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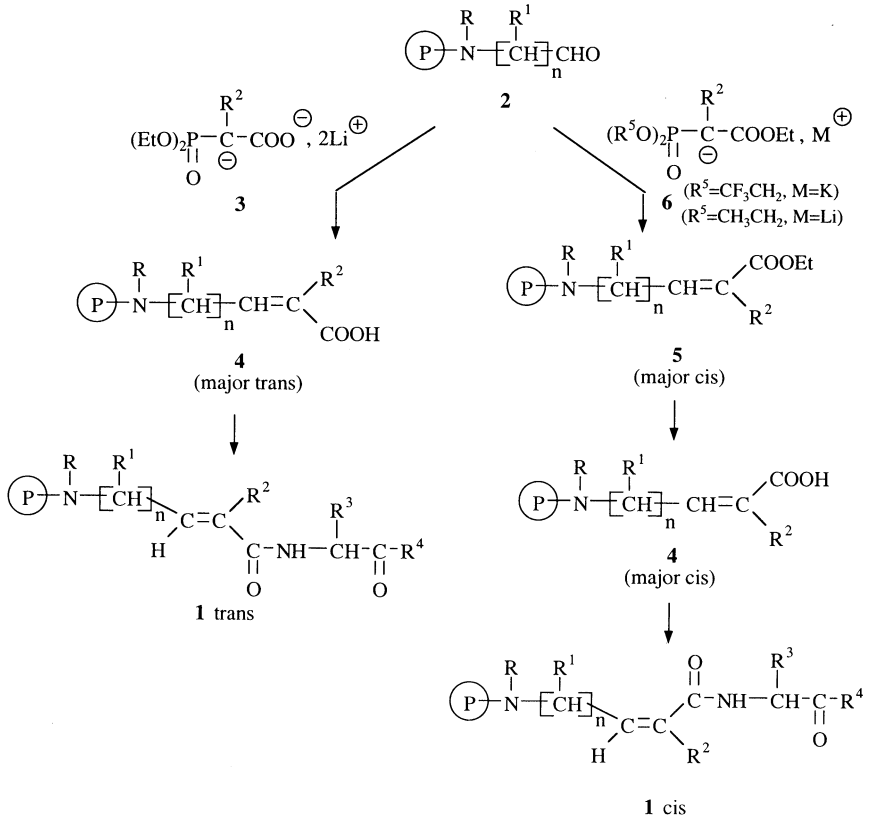


Scheme 1.

2-diethylphosphono alcanoic acids and α-aminoaldehydes **2** that gave major *trans* stereomer (Scheme 1).

The preparation of *cis* vinylogous aminoacids **4** needed another stereoselective synthesis, based on the use of two systems, either KH/ethyl 2-bis(trifluoroethyl)phosphono alcanoate or BuLi/ethyl 2-diethylphosphono alcanoate. With α-aminoaldehydes **2** these reagents led to major or exclusive *cis* vinylogous amino esters **5**. Basic hydrolysis of these α,β-ethylenic esters **5** led to *cis* vinylogous amino acids **4** (Scheme 1).

The target **1** *trans* or **1** *cis* vinylogous peptides were respectively obtained by a classical coupling between the so obtained *trans* or *cis* vinylogous aminoacids **4** and an aminoacid or a peptide fragment.

2. Results and discussion

2.1. Preparation of the *trans* vinylogous aminoacids 4

The dilithiated dianions **3** were prepared from 2-diethylphosphono alcanoic acids by treatment with *n*-butyllithium in a mixture of hexane–tetrahydrofuran at −60°C in the cases where R^2=H, CH_3, C_5H_{11}, C_6H_5 or at −78°C for R^2=F, Cl. For R^2=OC_2H_5, the acid was converted into the corresponding dianion with LDA at −78°C in the same solvent.

After addition of the aminoaldehyde **2** at the metallation temperature and stirring for 60 min at this temperature, the mixture was allowed to warm to room temperature. After 3 h stirring at 25°C, the mixture was then hydrolysed. Subsequent acidification of the aqueous solution at pH=4 with 6 M HCl, followed by extraction with diethylether led to the expected vinylogous aminoacids **4**.

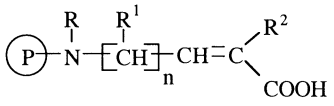
The crude products **4** may be used without purification. Nevertheless a chromatographic purification on a silica gel column was possible in the cases where R^2=H, alkyl or aryl. When R^2 was a halogen or an ethoxy, the acids **4** presented a low stability and degraded on the chromatographic column.

First, the Horner reaction was tested with *N*-*Z*-protected alaninal. The expected olefination product **4a** was obtained in a low yield with R^2=CH_3 (Table 1).

The replacement of the *Z*-moiety by Boc led to increasing yields (compare **4d** and **4a**, **4h** and **4b**). The strategy allowed the obtention of the double bond with a wide range of carbon and heteroatom-containing substituents (R^2=CH_3, C_5H_{11}, Ph, F, Cl, OC_2H_5). The ethoxy group was of particular interest for further possible synthetic transformation into α-keto acid. Equally different structures of aminoaldehydes **4**, alaninal (**4a**–**4i**), valinal (**4j**), glycinal (**4k**, **4l**), phenylanalinal (**4m**, **4n**), prolinal (**4o**–**4s**), β-alaninal (**4t**), have been easily converted into alkenoic acids. The bulkiness of the substituents decreased the reactivity either of the aminoaldehyde (phenylanalinal (**4m**, **4n**)) or the dianion (R^2=C_5H_{11}(**4e**), Ph (**4f**)).

In the cases where R^2=CH_3 (**4a**, **4d**, **4j**, **4l**, **4n**, **4p**, **4t**), C_5H_{11} (**4e**), Ph (**4f**, **4o**) the preferential configuration of the formed

Table 1. Preparation of the vinylogous aminoacids **4** by Horner reaction between *N*-protected aminoaldehydes **2** and dianions **3**



4

4	(P)	*n*	R	R^1	R^2	Yield (%)	*trans*/*cis*[a]
4a	Z	1	H	CH_3	CH_3	25	65:35
4b	Z	1	H	CH_3	Cl	80	40:60
4c	Boc	1	H	CH_3	H	71	>98:2[b]
4d	Boc	1	H	CH_3	CH_3	79	60:40
4e	Boc	1	H	CH_3	C_5H_{11}	12	95:5
4f	Boc	1	H	CH_3	C_6H_5	38.5	60:40
4g	Boc	1	H	CH_3	OC_2H_5	71	45:55
4h	Boc	1	H	CH_3	Cl	92.5	30:70
4i	Boc	1	H	CH_3	F	82	35:65
4j	Boc	1	H	i-C_3H_7	CH_3	79	82:18
4k	Boc	1	H	H	H	77	>98:2[b]
4l	Boc	1	H	H	CH_3	77	75:25
4m	Boc	1	H	CH_2Ph	H	52	>98:2[b]
4n	Boc	1	H	CH_2Ph	CH_3	35.5	75:25
4o	Boc	1	$-(CH_2)_3-$		C_6H_5	72	82:18
4p	Boc	1	$-(CH_2)_3-$		CH_3	80	80:20
4q	Boc	1	$-(CH_2)_3-$		OC_2H_5	45	30:70
4r	Boc	1	$-(CH_2)_3-$		Cl	68	35:65
4s	Boc	1	$-(CH_2)_3-$		F	62	30:70
4t	Boc	2	H	H	CH_3	70	98:2

[a] *trans*/*cis* ratio was determinated by ^{1}H NMR of the crude product.
[b] Only one isomer was observed by ^{1}H- and ^{13}C NMR.

double bond is that where the carboxylic acid and the amino group are *trans*.

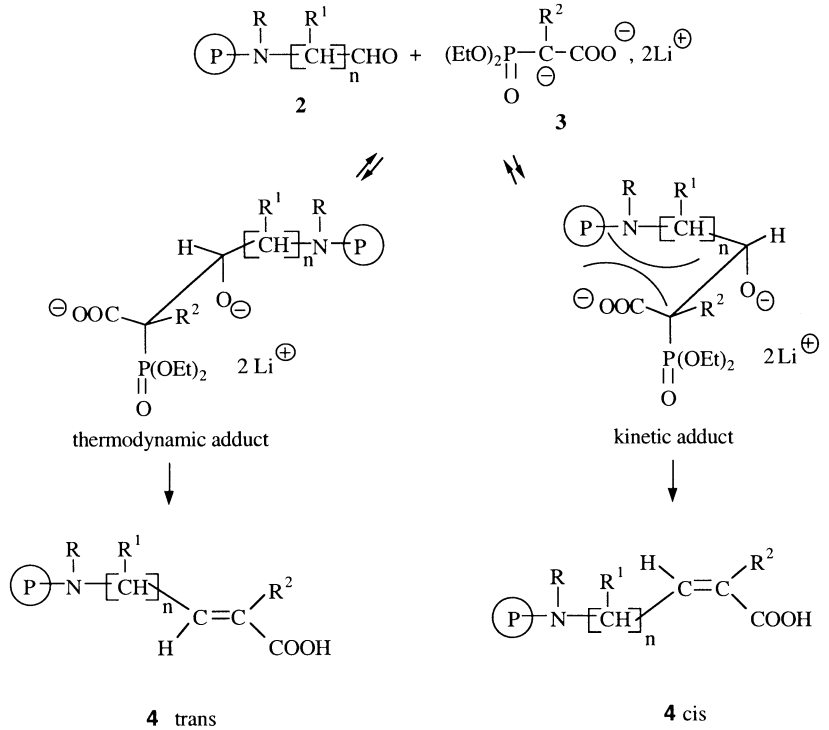
When R^2=H (**4c**, **4k**, **4m**), the reaction was completely stereoselective and gave only the *trans* isomer. This result is typical of the dianion derived of the diethylphosphonoacetic acid in the Horner reaction.[6] The reaction of this dianion onto an aldehyde is under thermodynamic control. The more stable intermediate adduct where the carboxylic group moved away from the amino group, was exclusively formed and led to the *trans* olefin. With a bulky R^2 (CH_3, C_5H_{11}, Ph), the difference of stability between the two intermediates decreased as well as the stereoselectivity (Scheme 2).

The electron withdrawing groups (R^2=F (**4i**, **4s**), Cl (**4h**, **4r**), OC_2H_5 (**4g**, **4q**)) promoted a faster addition of the dianion onto the carbonyl compound, involving a kinetic control of the reaction. As a result, the preferred adduct was this where the carboxylic acid eclipsed the amino group. In this case, the decomposition of the kinetic intermediate gave a double bond containing a *cis* arrangement of the carboxylic acid and the amino group (Scheme 2).

A further column chromatographic purification on silica gel could give pure *trans* isomers of the acids **4** if R^2 is an electron donating group or an hydrogen. In the case of **4l**, the *trans* and *cis* stereomers could be easily separated by selective precipitation in ether. Only the acid **4l** with a *trans* configuration precipitated in ether. The conversion of the acids **4** into corresponding *N*-isopropyl amides **4′** was an attractive alternative when the acids **4** are unstable (R^2=F, Cl, OEt), because the *trans* and *cis* amides can be easily separated by chromatography without decomposition. The purity of the ethylenic stereomers was evaluated by ^{1}H- and ^{13}C NMR analysis of the acids.

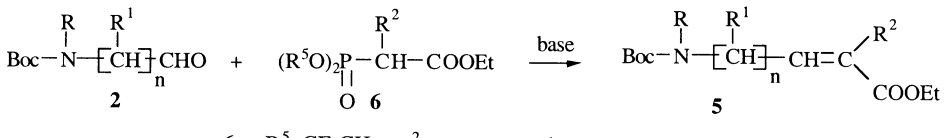
2.2. Preparation of the *cis* vinylogous aminoacids 4

It is known that the electronic effects influence the stereoselectivity of the Horner reaction. The formation of *cis*



Scheme 2.

Table 2. Results of the Horner reaction with **6a** or **6b** and a range of aminoaldehydes **2**



6a R^5=CF_3CH_2 R^2=H, Me base: KH

6b R^5=CH_3CH_2 R^2= Cl, F, Me base: BuLi

5	*n*	R	R^1	R^2	6	5 (Yield %)	*trans*/*cis*[a]
5c	1	H	CH_3	H	**6a**	72	25:75
5d	1	H	CH_3	CH_3	**6a**	79	7:93
5d	1	H	CH_3	CH_3	**6b**	82	10:90
5h	1	H	CH_3	Cl	**6b**	88	2:98
5i	1	H	CH_3	F	**6b**	95	<2:98[b]
5j	1	H	*i*-C_3H_7	CH_3	**6a**	87	10:90
5j	1	H	*i*-C_3H_7	CH_3	**6b**	80	80:20
5l	1	H	H	CH_3	**6a**	85	35:65
5l	1	H	H	CH_3	**6b**	63	14:86
5p	1		$-(CH_2)_3-$	CH_3	**6a**	79	10:90
5p	1		$-(CH_2)_3-$	CH_3	**6b**	71	70:30
5r	1		$-(CH_2)_3-$	Cl	**6b**	95	33:67
5s	1		$-(CH_2)_3-$	F	**6b**	92	<2:98[b]
5w	1		$-(CH_2)_3-$	H	**6a**	77	16:84
5t	2	H	H	CH_3	**6a**	91	40:60
5t	2	H	H	CH_3	**6b**	60	40:60
5u	2	H	H	Cl	**6b**	90	16:84
5v	2	H	H	F	**6b**	97	<2:98[b]

[a] *trans*/*cis* ratio determinated by ^{1}H NMR of the crude product.
[b] Only one isomer observed by ^{1}H and ^{13}C NMR.

olefins can also be favoured when the phosphorus atom electrophilicity is increased. Thus, an efficient method has been reported to produce *cis*-unsaturated esters using bis(trifluoroethyl)phosphonoesters.[7] Some particular examples of *cis*-vinylogous aminoesters have been prepared with bis(trifluoroethyl)phosphonoesters,[8] but the method lacked generality and the transformation of *cis*-vinylogous aminoesters into vinylogous peptides was not described.[8] The optimal *cis* stereoselection could be obtained with the use of a base having minimally complexing counterions to decrease the factor reversibility and to facilitate the elimination. KH was therefore a good candidate for the synthesis of *cis*-unsaturated esters. In light of these results, we investigated the formation of *cis* vinylogous aminoacids **4** from KH/bis(trifluoroethyl) phosphonoesters and aminoaldehydes **2** in the cases where the previous procedure could not allowed to obtain sufficient amounts of *cis* acids **4** (R^2=H, Me).

In a second time, we decided to reinvestigate with the same purpose the selectivity of the Horner reaction using the lithium anions derived of **6b** because it has been previously observed in particular cases by us[6] as others[9] that lithium ethyl 2-diethylphosphono propanoate (**6b**, R^2=Me) could lead to *cis* unsaturated esters whereas the general behaviour of this last anion was known to give major *trans* unsaturated compounds. Analogously, we have noticed during our precedent investigations using dianions **3** the great capacity of the lithiated anions derived from ethyl diethylphosphono halogenoacetic acids (**6b**, R^2=Cl, F) to preferably lead to *cis* double bond (see Table 1).

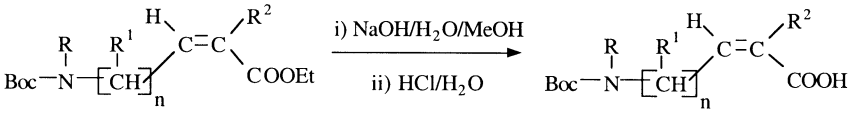
The reactions were run in THF using 1 equiv. of aminoaldehyde **2**, 1.2 equiv. of Horner reagent and 1.2 equiv. of base (KH when R^5=CF_3CH_2 or Buli when R^5=CH_3CH_2). An excess of phosphonate **6** was required to obtain an optimum *cis*/*trans* product ratio. In the case of **6a**, the following sequence of operations was realized: addition of the phosphonate at 0°C onto KH/THF; stirring for 15 min at 0°C, addition of the aminoaldehyde at −78°C onto the potassium anion; stirring for 3 h at −78°C; addition of a solution of 2% hydrochloric acid at −78°C; extractive work-up; column chromatography. With the reagents **6b**, the procedure was similar except for the metallation that was effected at −78°C with BuLi 1.6 M in hexane/THF (Table 2).

As it can be observed from the results of Table 2, the Horner reaction afforded in all cases the vinylogous amino esters **5** in good yields. With reagent **6a**, the formation of esters **5** proceeded with a good *cis*-stereoselectivity, which was not affected by the size of R^1 and the nature of R^2.

On the other hand, it appeared that the behaviour of **6b** was more specific, the stereoselectivity depended much on the nature of the aminoaldehyde except when R^2=F where pure *cis* esters could be obtained in very good yields whatever is the nature of the aminoaldehyde (**5i**, **5s**, **5v**). When R^2=CH_3, the size of R^1 had a marked effect on the stereoselectivity: with a feebly hindered R^1 (Me, H), a high *cis* stereoselectivity was observed (**5d**, **5l**, **5t**), while a bulky R^1 involved the *trans* preference (**5j**, **5p**). The same trend was verified in the case R^2=Cl where the best *cis* stereoselectivity was established with the L-alanine moiety (R^1=Me, **5h**) or with the β-alanine moiety (**5u**).

The stereochemical course of these reactions could be explained on the basis of the previously proposed mechanism in the case of the dianions **3** (Scheme 2). In the case of **6a**, the phosphorus electrophilicity combined with the

Table 3. Hydrolysis of *cis*-vinylogous ester **5** into *cis*-vinylogous acids **4**



5 **4**

4	*n*	R	R^1	R^2	Yield (%)
4d	1	H	CH_3	CH_3	88
4j	1	H	i-C_3H_7	CH_3	89
4l	1	H	H	CH_3	90
4p	1		$-(CH_2)_3-$	CH_3	80
4w	1		$-(CH_2)_3-$	H	80
4t	2	H	H	CH_3	96

potassium ion effect and the low temperature promoted the decomposition of the kinetic adduct to give the *cis* alkene. With the lithiated ethyl 2-diethylphosphono propanoate carbanion **6b**, the decrease of the phosphorus electrophilicity and the use of the cation Li^+ decelerated the elimination of $(EtO)_2P(O)OLi$. Combined with the increase of the bulkiness of R^1 these different factors retarded the decomposition of the kinetic intermediate and permitted the equilibration with the thermodynamic adduct. The direct consequence was the reversibility of this first step that involved the decrease of the *cis* stereoselectivity (**5j**, **5p**). However, with small R^1, the decomposition of the kinetic adduct remained faster than the interconversion with the thermodynamic adduct and the *cis* stereoselectivity was conserved, as exemplified with **5d**, **5l**, **5t**. In these cases, it was noteworthy that the observed *cis* stereoselectivity was either practically identical to the one obtained with **6a** (**5d**, **5t**) or even better (**5l**). These results were remarkable considering the difficulty to obtain the Horner reagent **6a** compared to the accessibility of **6b**.

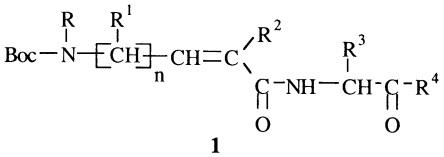
From a practical point of view, it was important to note that the pure *cis* isomers could be easily obtained after a chromatographic separation in all the cases where the *trans*/*cis* ratio was <40:60.

The basic hydrolysis of pure *cis*-vinylogous *N*-protected amino esters **5** was effected with 1N solution of NaOH (2.5 equiv.) in H_2O/EtOH (1:2) for 2 h at 20°C except for the ester **5t** that exhibited a particular resistance to hydrolysis. It was observed that this compound was completely hydrolysed only after 48 h at room temperature. Subsequent acidification at pH=2 with 1N HCl aqueous solution, followed by extraction with AcOEt led to the pure *cis*-vinylogous *N*-protected amino acids **4** (Table 3).

2.3. Coupling of *N*-protected vinylogous aminoacids 4 with aminoacid derivatives

Pure *cis* or pure *trans* or mixture of *cis*/*trans* vinylogous aminoacids **4** were coupled with different aminoacid derivatives in the presence of BOP as coupling reagent and led to the desired peptides **1** in good yields and with a total stereospecificity (Table 4). The reaction occurred at room

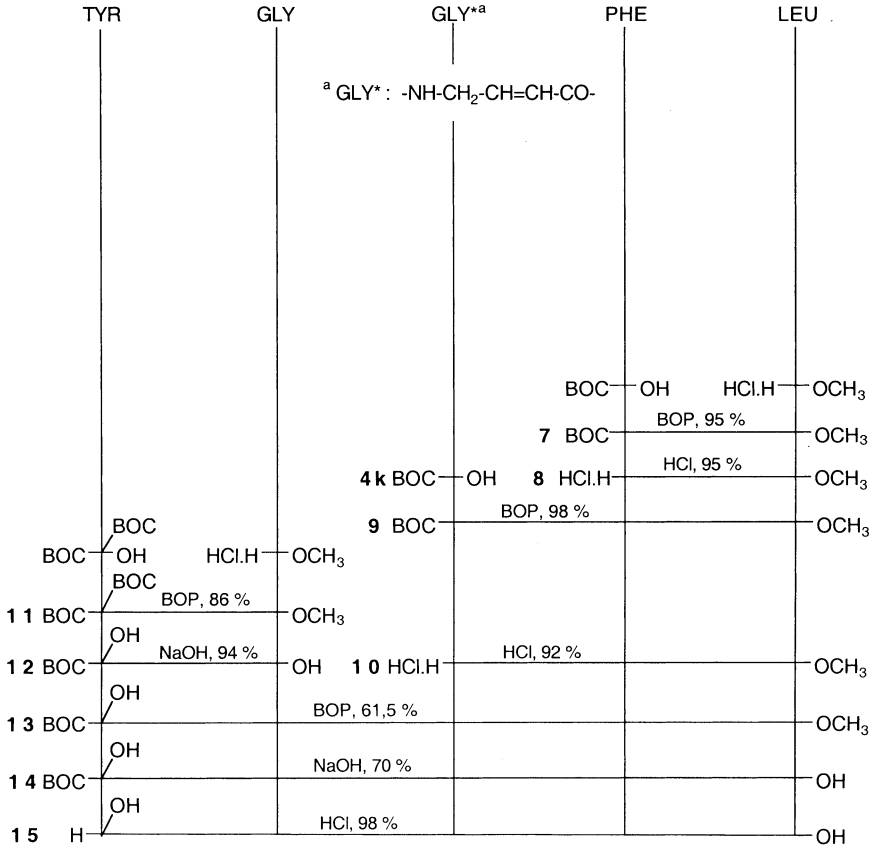
Table 4. Results of the coupling between vinylogous aminoacids **4** and aminoacid derivatives



1

1	*n*	R	R^1	R^2	R^3	R^4	Yield (%)	*trans*/*cis*[a]
1ca	1	H	CH_3	H	$CH(CH_3)_2$	OCH_3	76	>98:2[b]
1cb	1	H	CH_3	H	H	OCH_3	92	>98:2[b]
1ia	1	H	CH_3	F	H	OCH_3	93	35:65
1ga	1	H	CH_3	OC_2H_5	H	OCH_3	80	45:55
1da	1	H	CH_3	CH_3	CH_3	OCH_3	55	60:40
1db	1	H	CH_3	CH_3	CH_2COOMe	OCH_3	70	60:40
1ka	1	H	H	H	H	OCH_3	78	>98:2[b]
1ma	1	H	CH_2Ph	H	H	OCH_3	82	>98:2[b]
1pa	1		$-(CH_2)_3-$	CH_3	CH_3	$NHCH(CH_3)_2$	84	<2:98
1pa	1		$-(CH_2)_3-$	CH_3	CH_3	$NHCH(CH_3)_2$	76	>98:2[b]
1pb	1		$-(CH_2)_3-$	CH_3	CH_3	O–CH_3	82	<2:98
1pb	1		$-(CH_2)_3-$	CH_3	CH_3	OCH_3	80	>98:2[b]
1pc	1		$-(CH_2)_3-$	CH_3	CH_2COOMe	OCH_3	87	<2:98
1pc	1		$-(CH_2)_3-$	CH_3	CH_2COOMe	OCH_3	85	>98:2[b]
1wd	1		$-(CH_2)_3-$	H	CH_3	$NHCH_3$	70	25:75

[a] *trans*/*cis* ratio determinated by ^1H NMR on the crude product **1** and identical to this of the starting reagent **4**.
[b] Only one isomer observed by ^1H- and ^{13}C NMR.



Scheme 3.

temperature with one equivalent of triethylamine in dichloromethane and was complete after stirring for two hours. The formed HMPT was easily removed by chromatography on silica gel. When a mixture of geometrical isomers of **4** was used as starting compound the *cis*/*trans* ratio was conserved into the product **1**. A further column chromatographic purification using graduated elution gave pure *cis* or pure *trans* isomer of **1** easily. The separation of **1** *cis* and **1** *trans* was often easier than acid **4** or ester **5**. As a consequence, it could be more convenient to use a mixture of *cis*/*trans* acid **4** as starting reagent than to proceed to a purification into pure **4** *cis* or pure **4** *trans* after the initial Horner reaction that produced **4**. A large number of acid **4** was tested (R^2=H, CH_3, F, Cl, EtO) with different aminoacids derivatives (val-OMe, gly-OMe, asp(OMe)-OMe, ala-NH*i*Pr, ala-NHMe, ala-OMe). All the yields were high and the reaction was relatively insensitive to changes in amino partner or R^2 substituent.

Although in all cases only two stereomers were observed and assigned to *cis* and *trans* double bond isomers, the configurational stability of the all chiral centres was also studied. A first source of possible epimerisation was the Horner reaction, although few examples of the literature indicate that Boc-protected amino aldehydes may partially racemise under the C–C bond forming reaction conditions in which they are employed.[10] The other source of possible epimerisation was the coupling reaction. To study these eventualities, parallel couplings of pure *trans* vinylogous *N*-Boc-L-alanine-OH with both L-valine-OMe and DL-valine-OMe were realised. ^{1}H- and ^{13}C NMR analyses of the so-obtained pure diastereoisomer vinylogous aminoacid *trans* **1ca** LL compared to the racemic *trans* **1ca** LL, LD unambiguously demonstrated the configurational integrity of all chiral carbons in the successive reactions used to obtain **1**.

2.4. Synthesis of a Leu-enkephalin analogue including the vinylogous glycine residue –NH–CH_2–CH=CH–CO– at position 3

Encouraged by the precedent results, the total synthesis of a modified Leu-enkephalin was carried out with the aim to both reduce the flexibility of the peptide and increase its resistance towards endopeptidase.

According to the site of enzymatic degradation of Leu-enkephalin by the corresponding enkephalinase,[11] the replacement of Gly^3 by the vinylogous glycine residue –NH–CH_2–CH=CH–CO– should increase the stability of the peptide towards this metallopeptidase strongly. The synthetic scheme is presented in Scheme 3.

The strategy involved the initial preparation of the vinylogous *trans*-*N*-Boc-glycine **4k** according to the Table 1. The synthesis of this aminoacid required careful attention to the selection of protecting group so that final deprotection would not cause unwanted chemical transformations of the double bond. For example, the *N*-*Z*-moiety could not be selectively deprotected with HBr/AcOH or with catalytic hydrogenation because the addition reactions on the double bond are faster than the deprotection. The *N*-Boc moiety was once more the best protection.

The best activation method was attained with BOP as coupling reagent. The tripeptide **9** was obtained in excellent yield (98%). Removal of the N-terminal *t*-butoxycarbonyl protecting group into the unsaturated peptide with anhydrous HCl in ether (better than trifluoroacetic acid) yielded the corresponding chlorhydrate salt **10** (92%).

Coupling of the fragment Boc-Tyr-Gly-OH **12** with the unsaturated tripeptide **10** was achieved in the presence of BOP reagent in DMF. No special problem was encountered during the coupling and the purification of the pentapeptide **13**. The presence of the double bond facilitated the solubility of the peptide in usual organic solvent greatly. No side chain protecting group was necessary. The unsaturated pentapeptide **13** was easily purified on a silica gel chromatographic column with ethylacetate/acetone: 4:1 as solvent.

The hydrolysis of the methyl ester group was achieved with a 1N solution of NaOH in methanol with stirring for 2 h at 20°C. After concentration the residue was acidified at pH 4 with 1N HCl aqueous solution and extracted with ethyl acetate leading to **14**.

Final removal of the *N*-Boc group with anhydrous HCl in THF gave the desired fully deprotected Leu-enkephalin analogue **15** which was fully characterised (^{1}H NMR, ^{13}C NMR, FAB MS). This synthesis confirmed the excellent feasibility of the introduction of a vinylogous aminoacid into a peptide chain.

3. Conclusions

New *cis*- and *trans*-vinylogous aminoacids including a bi- or a tri-substituted double bond were prepared using a judicious choice of Horner reactions between suitable phosphonate anions and *N*-protected aminoaldehydes. Mainly *trans* vinylogous aminoacids were easily obtained with the lithium dianions derived from 2-diethylphosphono alcanoic acids whereas *cis* were mainly obtained from Still reagent ethyl 2-bis(trifluoroethyl)phosphono alcanoate. For certain *cis* vinylogous acids a complete reinvestigation of the behaviour of lithium ethyl 2-diethylphosphono alcanoate led to a very interesting alternative to the Still reagent, not easily available. These vinylogous aminoacids could be easily introduced into a peptide as illustrated with a total synthesis of the Leu-enkephalin analogue that included the *trans*-vinylogous glycine moiety in replacement of the 3 glycine residue. As a consequence a lot of combinations using *cis* and *trans* vinylogous aminoacids and aminoacids was now possible leading to a various new library of peptide analogues. Works concerning this last point and applications in the solid phase peptide synthesis are under investigation.

4. Experimental

4.1. General

Melting Points were determined in a capillary tube in an Electrothermal apparatus and were uncorrected. Thin layer chromatography (TLC) were carried out on aluminium-backed silica gel-coated plates (Kieselgel 60-F_{254}, Merck or Alugram®Sil G/UV_{254}, Macherey-Nagel), spots were identified under an UV lamp (λ=254 nm) or developed using iodine. Column chromatographies were performed on silicagel 60 or 70–230 mesh with the indicated eluent, dried and distilled shortly before use. IR spectra of solids were recorded as KBr pellets, and IR spectra of liquids were recorded as thin films on KBr plates with a Nicolet 210 FT-IR spectrophotometer. All NMR experiments were recorded on a Brucker AC spectrometer [250 MHz (^{1}H), 235.36 MHz (^{19}F) and 62.896 MHz (^{13}C)]. Chemical shifts were given as δ ppm values and *J* values were given in Hertz (Hz). Isomer ratios were determined by ^{1}H NMR on the crude products. Optical rotations were measured with a Bellingham and Stanley ADP 220 automatic polarimeter, in chloroform or methanol solution with 1 or 2 dm cells at the designate concentration in g/100 mL at room temperature. Mass spectra (EI, 70 eV and CI) were obtained on a Fison Trio 1000 spectrometer and Mass Spectra (FAB) were measured on an Autospec Fited Cesium Gun (Micromass, Manchester). Solvents were purified by standard procedures just before use.

4.2. Typical procedure for the preparation of the aminoaldehyde 2

Boc-L-Alaninal, Boc-L-valinal and Boc-L-phenylalaninal were easily prepared from Boc-amino acids according to Fehrentz and Castro.[12] The Boc-L-prolinal was synthesised similarly.[13] Some modifications were employed in order to obtain the Boc-glycinal.

4.2.1. *N*-(*t*-Butoxycarbonyl)-glycine *N*-methoxy-*N*-methylamide. Yield: 85%, white solid; mp 102°C; R_f=0.55 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3290, 1715 and 1660; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.40 [s, 9H, $C(CH_3)_3$], 3.15 (s, 3H, $N-CH_3$), 3.67 (s, 3H, $O-CH_3$), 3.93–4.06 (m, 2H, $NH-CH_2$), 5.27 (m, 1H, $NH-CH_2$); ^{13}C NMR (62.696 MHz, $CDCl_3$): δ_C=28.2 [3C, $C(CH_3)_3$], 32.3 ($N-CH_3$), 41.6 ($NH-CH_2$), 61.3 ($O-CH_3$), 79.5 [$C(CH_3)_3$], 155.8 (*C*O Boc), 170.1 (*C*O).

4.2.2. *N*-(*t*-Butoxycarbonyl)-glycinal. Lithium aluminium hydride (8.6 mL, 1 M in ether, 5 equiv.) was added to a stirred solution of a *N*-(*t*-butoxycarbonyl)-glycine *N*-methoxy-*N*-methylamide (6.9 mmol) in THF (80 mL). Reduction was complete within 15–20 min. The mixture was hydrolysed with a solution of potassium hydrogen sulfate (1.41 g, 10.35 mmol) in water (10 mL). Then the mixture was evaporated and extracted with dichloromethane (3× 60 mL). The organic phases were combined, washed successively with 3N HCl (3×20 mL), with a saturated aqueous NaCl solution (1×20 mL), with an aqueous $NaHCO_3$ solution (3×20 mL) and with a saturated NaCl solution (3×20 mL), and finally dried with magnesium sulfate. The solvent was evaporated to leave the crude glycinal which was further used without purification. Yield: 85% as a colourless oil; R_f=0.37 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3370 and 1695; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.42 [s, 9H, $C(CH_3)_3$], 3.95–4.11 (m, 2H, $NH-CH_2$), 5.37 (m, 1H, $NH-CH_2$), 9.62 (s, 1H, –*C*HO); ^{13}C NMR (62.696 MHz, $CDCl_3$): δ_C=28.1 [3C, $C(CH_3)_3$],

51.2 (NH–CH_2), 79.9 [$C(CH_3)_3$], 155.7 (*C*O Boc), 197.5 (*C*HO).

4.3. Typical procedure for the preparation of the *trans* vinylogous aminoacids 4

To a solution of *n*-butyllithium (9.22 mL, 14 mmol, 1.56 M in hexane) in 20 mL THF, was added dropwise at −60°C in the cases where R^2=H, CH_3, C_5H_{11}, C_6H_5 or at −78°C for R^2=F, Cl a solution of 2-diethylphosphono-alcanoic acid (6.8 mmol, 1 equiv.) in THF (10 mL). For R^2=OC_2H_5, the acid was converted into the corresponding dianion **3** with LDA at −78°C in the same solvent. In all cases, after 30 min stirring at the metallation temperature, the aminoaldehyde **2** (6.8 mmol) in THF (5 mL) was added dropwise at this temperature. The reaction medium was allowed to warm to −60°C for 1 h, then to room temperature. After stirring for 3 h, it was hydrolysed with water (20 mL). The organic layer was separated and washed with 10% aqueous $NaHCO_3$ (2×15 mL). The aqueous phases were combined and acidified to pH=3.5 with 12N HCl and extracted with ether (2×30 mL). After drying over $MgSO_4$, the solvent was removed under vacuum to leave the crude product, which was purified by column chromatography.

4.3.1. [L-(*trans*)]/[L-(*cis*)]-4-[(Benzyloxycarbonyl)amino]-2-methyl-2-pentenoic acid 4a. Yield: 290 mg (25%), white solid, (*trans*/*cis*: 65:35), R_f=0.48 (ethyl acetate/hexane: 1:1) IR (KBr plate)/cm^{-1}: ν_{max}=3320, 3025, 1720, 1700 and 1650. MS (FAB^-) *m*/*z* calculated for $C_{14}H_{16}NO_4$ $[M-H]^-$ 262.1, found 262.1 (100%). *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.24 (d, $^3J_{H-H}$= 6.5 Hz, 3H, CH–C*H*$_3$), 1.92 [s, 3H, CH=C(C*H*$_3$)–CO], 4.56 (m, 1H, C*H*–CH_3), 4.96–5.26 (m, 3H, Ph–C*H*$_2$ and N*H*–CH), 6.66 [dd, $^3J_{H-H}$=9.0 Hz and $^4J_{H-H}$=1.2 Hz, 1H, C*H*=C(CH_3)–CO], 7.35 (br s, 5H, *Ph*), 9.00 (br s, 1H, O*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.2 [CH=C(*C*H$_3$)–CO], 20.3 (CH–*C*H$_3$), 45.4 (*C*H–CH_3), 67.8 (*C*H$_2$-Ph), 127.1, 128.1 (2C), 128.5 (2C), 136.2 (*Ph*), 141.0 [CH=*C*(CH_3)–CO], 144.2 [*C*H=C(CH_3)–CO], 155.5 (*C*O Boc), 172.7 (*C*OOH). *cis* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.24 (d, $^3J_{H-H}$=6.5 Hz, 3H, CH–C*H*$_3$), 1.92 [s, 3H, CH=C(C*H*$_3$)–CO], 4.86 (m, 1H, C*H*–CH_3), 4.96–5.26 (m, 3H, Ph–C*H*$_2$ and N*H*–CH), 5.73 [d, $^3J_{H-H}$=8.0 Hz, 1H, C*H*=C(CH_3)–CO], 7.35 (br s, 5H, *Ph*), 9.00 (br s, 1H, –O*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=10.8 [CH=C(C*H*$_3$)–CO], 18.2 (CH–*C*H$_3$), 45.4 (CH–*C*H$_3$), 66.9 (*C*H$_2$-Ph), 127.1, 128.1 (2C), 128.5 (2C), 136.2 (*Ph*), 141.0 [CH=*C*(CH_3)–CO], 144.2 [*C*H=C(CH_3)–CO], 155.7 (*C*O Boc), 172.7 (*C*OOH).

4.3.2. [L-(*trans*)]/[L-(*cis*)]-4-[(Benzyloxycarbonyl)amino]-2-chloro-2-pentenoic acid 4b. Yield: 530 mg (80%), colourless oil, (*trans*/*cis*: 40:60), R_f=0.37 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3345, 3025, 1735, 1730, 1700 and 1630; MS (FAB^-) *m*/*z* calculated for $C_{13}H_{13}NO_4Cl$ $[M-H]^-$ 282.5, found 282.0 (100%). *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.35 (d, $^3J_{H-H}$=7.5 Hz, 3H, CH–C*H*$_3$), 4.50–5.10 (m, 2×1H, C*H*–CH_3 and N*H*–CH), 5.10 (s, 2H, Ph-C*H*$_2$), 6.10 (d, $^3J_{H-H}$= 11.0 Hz, 1H, C*H*=CCl–CO), 7.35 (s, 5H, *Ph*), 11.5 (br s, 1H, –O*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=18.6 (CH–*C*H$_3$), 45.1 (*C*H–CH_3), 66.7 (Ph-*C*H$_2$), 123.6 (CH=*C*Cl–CO), 127.7, 128.1 (2C), 128.6 (2C), 135.8 (*Ph*), 144.2 (*C*H=CCl–CO), 156.1 (*C*O Boc), 171.2 (*C*OOH); *cis* isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H= 1.35 (d, $^3J_{H-H}$=7.5 Hz, 3H, CH–C*H*$_3$), 4.50–5.10 (m, 2×1H, C*H*–CH_3 and N*H*–CH), 5.10 (s, 2H, Ph–C*H*$_2$), 7.05 (d, $^3J_{H-H}$=11.5 Hz, 1H, C*H*=CCl–CO), 7.35 (s, 5H, *Ph*), 11.5 (br s, 1H, –O*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=17.8 (CH–*C*H$_3$), 46.5 (*C*H–CH_3), 67.9 (Ph-*C*H$_2$), 123.6 (CH=*C*–Cl–CO), 126.6, 127.7 (2C), 128.1, 128.6, 135.8 (*Ph*), 145.7 (*C*H=CCl–CO), 155.5 (*C*O Boc), 171.8 (*C*OOH).

4.3.3. [L-(*trans*)]-4-[(*t*-Butoxycarbonyl)amino]-2-pentenoic acid 4c. Yield: 220 mg (71%), white solid, mp 78°C, R_f=0.56 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3430, 3050, 2975, 1710 and 1650; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.28 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–C*H*$_3$), 1.45 [s, 9H, C(C*H*$_3$)$_3$], 4.42 (m, 1H, C*H*–CH_3), 4.61 (br s, 1H, N*H*), 6.11 (dd, $^3J_{H-H}$=15.5 Hz and $^4J_{H-H}$=1.5 Hz, 1H, CH=C*H*–CO), 6.97 (dd, $^3J_{H-H}$=15.5 Hz and $^3J_{H-H}$= 4.0 Hz, 1H, C*H*=CH–COOH), 9.50 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.2 (CH–*C*H$_3$), 28.4 [3C, C(*C*H$_3$)$_3$], 47.1 (*C*H–CH_3), 80.0 [*C*(CH_3)$_3$], 119.6 (CH=*C*H–CO), 151.8 (*C*H=CH–CO), 154.9 (*C*O Boc), 171.0 (*C*OOH); $[\alpha]_D$=+13° (*c*=0.3, $HCCl_3$); MS (EI^+) *m*/*z* calculated for $C_{10}H_{17}NO_4Cl$ $[M]^+$ 215.6, found 215.6 (<2%), 142.9 [$[M-t\text{BuO}]^+$, 17%], 158.0 [$[M-t\text{Bu}]^+$, 37%], 96.0 [$[M-t\text{BuOCO–OH}]^+$, 70%], 113.2 [$[M-t\text{BuOCO}]^+$, 76%], 68.7 [$[M-t\text{BuOCO–COOH}]^+$, 100%].

4.3.4. [L-(*trans*)]-4-[(*t*-Butoxycarbonyl)amino]-2-methyl-2-pentenoic acid 4d. Yield: 640 mg of a white solid obtained after a separation on a chromatographic silicagel column from 1.693 g (79%) of a (*trans*/*cis*: 60:40) mixture; mp 136°C; R_f=0.39 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3320, 1700, 1695 and 1645; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.22 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–C*H*$_3$), 1.44 [s, 9H, C(C*H*$_3$)$_3$], 1.91 [s, 3H, CH=C(C*H*$_3$)–CO], 4.49 (m, 1H, C*H*–CH_3), 4.74 (br s, 1H, N*H*), 6.65 [dd, $^3J_{H-H}$=8.15 Hz and $^4J_{H-H}$=1.2 Hz, 1H, C*H*=C(CH_3)–CO], 7.45 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=11.9 [CH=C(*C*H$_3$)–CO], 20.1 (CH–*C*H$_3$), 28.0 [3C, C(*C*H$_3$)$_3$], 44.6 (*C*H–CH_3), 80.1 [*C*(CH_3)$_3$], 127.4 [CH=*C*(CH_3)–CO], 144.3 [*C*H=C(CH_3)–CO], 155.1 (*C*O Boc), 171.8 (*C*OOH); $[\alpha]_D$=+19° (*c*=0.25, $HCCl_3$) MS (EI^+) *m*/*z* calculated for $C_{11}H_{19}NO_4$ $[M]^+$ 229.13, found 230.5 [$[M+1]^+$, 10%], 173.6 [$[M+1-t\text{Bu}]^+$, 35%], 129.3 [$[M+1-t\text{BuOCO}]^+$, 27%], 112.2 [$[M+1-t\text{BuOCO–OH}]^+$, 100%].

4.3.5. [L-(*trans*)]-4-[(*t*-Butoxycarbonyl)amino]-2-pentyl-2-pentenoic acid 4e. Yield: 71 mg (12%), colourless oil (*trans*/*cis*: 95:5); R_f=0.62 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3310, 1720, 1715 and 1700; ^{1}H NMR (250 MHz, CD_3CN): δ_H=1.18 (d, $^3J_{H-H}$=5.0 Hz, 3H, CH–C*H*$_3$), 1.30–1.41 (m, 9H, *CH*$_2$–C*H*$_2$–C*H*$_2$–C*H*$_3$), 1.41 [s, 9H, C(C*H*$_3$)$_3$], 2.28–2.40 [m, 2H, CH=C(C*H*$_2$–C_4H_9)–CO], 4.44 (ddq, $^3J_{H-H}$=9.0, 7.0, 5.0 Hz, 1H, C*H*–CH_3), 5.28 (d, $^3J_{H-H}$=7.0 Hz, 1H, N*H*–CH), 6.49 [d, $^3J_{H-H}$= 9.0 Hz, 1H, C*H*=C(CH_2–C_4H_9)–CO], 11.0 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=16.3 (CH_2–*C*H$_3$), 18.3 (CH–*C*H$_3$), 26.9 (*C*H$_2$–CH_3), 27.9 and

28.1 (2C, 2×CH_2), 28.4 [3C, C(CH_3)$_3$], 31.3 [CH=C(CH_2–C_4H_9)–CO], 46.7 (CH–CH_3), 78.3 [C(CH_3)$_3$], 125.5 [CH=C(C_5H_{11})–CO], 145.0 [CH=C(C_5H_{11})–CO], 155.6 (*C*O Boc), 171.4 (*C*OOH); MS (FAB$^-$) *m/z* calculated for $C_{15}H_{23}NO_4$ [M−H]$^-$ 284.2, found 284.1 (100%).

4.3.6. [L-(*trans*)]/[L-(*cis*)]-4-[(*t*-Butoxycarbonyl)amino]-2-phenyl-2-pentenoic acid 4f. Yield: 193 mg (38.5%); white solid (*trans*/*cis*: 60:40); R_f=0.51 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3330, 1685 and 1645; MS (FAB$^-$) *m/z* calculated for $C_{16}H_{21}NO_4$ [M−H]$^-$ 290.2, found 290.1 (100%). *trans* Isomer: ^{1}H NMR (250 MHz, CD_3COCD_3): δ_H=1.16 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.38 [s, 9H, C(CH_3)$_3$], 4.24 (ddq, $^3J_{H-H}$=9.5, 7.0, 7.0 Hz, 1H, CH–CH_3), 6.18 (d, $^3J_{H-H}$=7.0 Hz, 1H, NH–CH), 6.94 [d, $^3J_{H-H}$=9.5 Hz, 1H, CH=C(Ph)–CO], 7.23–7.45 (m, 5H, *Ph*), 11.0 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.8 (CH–CH_3), 28.2 [3C, C(CH_3)$_3$], 45.7 (CH–CH_3), 79.6 [C(CH_3)$_3$], 128.0, 128.3 (2C), 129.5 (2C), 133.9 [CH=C(Ph)–CO], 144.7 (*Ph*), 147.5 [CH=C(Ph)–CO], 154.8 (*C*O Boc), 171.3 (*C*OOH). *cis* Isomer: ^{1}H NMR (250 MHz, CD_3COCD_3): δ_H=1.16 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.38 [s, 9H, C(CH_3)$_3$], 4.24 (ddq, $^3J_{H-H}$=9.5, 7.0, 7.0 Hz, 1H, CH–CH_3), 6.08 [d, $^3J_{H-H}$=9.5 Hz, 1H, CH=C(Ph)–CO], 6.18 (d, $^3J_{H-H}$=7.0 Hz, 1H, NH–CH), 7.23–7.45 (m, 5H, *Ph*), 11.0 (br s, 1H, COO*H*).

4.3.7. [L-(*trans*)]/[L-(*cis*)]-4-[(*t*-Butoxycarbonyl)amino]-2-ethoxy-2-pentenoic acid 4g. Yield: 320 mg (71%), colourless oil (*trans*/*cis*: 45:55); R_f=0.66 (acetone); IR (KBr film)/cm^{-1}: ν_{max}=3345, 1770, 1700 and 1645; MS (FAB$^-$) *m/z* calculated for $C_{12}H_{20}NO_5$ [M−H]$^-$ 258.1, found 258.1 (100%). *cis* Isomer: ^{1}H NMR (250 MHz, CD_3COCD_3): δ_H=1.20–1.34 (m, 2×3H, CH–CH_3 and O–CH_2–CH_3), 1.39 [s, 9H, C(CH_3)$_3$], 3.95 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 4.89 (m, 1H, CH–CH_3), 5.15 [d, $^3J_{H-H}$=9.5 Hz, 1H, CH=C(OEt)–CO], 6.10 (br s, 1H, NH–CH), 11.0 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.2 (O–CH_2–*C*H_3), 19.6 (CH–*C*H_3), 28.2 [3C, C(*C*H_3)$_3$], 52.9 (*C*H–CH_3), 68.3 (O–*C*H_2–CH_3), 79.8 [*C*(CH_3)$_3$], 113.7 [*C*H=C(OEt)–CO], 148.5 [CH=*C*(OEt)–CO], 155.6 (*C*O Boc), 166.9 (*C*OOH). *trans* Isomer: ^{1}H NMR (250 MHz, CD_3COCD_3): δ_H=1.20–1.34 (m, 2×3H, CH–CH_3 and O–CH_2–CH_3), 1.39 [s, 9H, C(CH_3)$_3$], 3.79 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 4.68 (m, 1H, CH–CH_3), 6.10 (br s, 1H, NH–CH), 6.20 [d, $^3J_{H-H}$=9.0 Hz, 1H, CH=C(OEt)–CO], 11.0 (br s, 1H, COO*H*).

4.3.8. [L-(*trans*)]/[L-(*cis*)]-4-[(*t*-Butoxycarbonyl)amino]-2-chloro-2-pentenoic acid 4h. Yield: 400 mg (92.5%), colourless oil (*trans*/*cis*: 30:70); R_f=0.68 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3315, 1700 and 1650. *cis* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.31 (d, $^3J_{H-H}$=8.8 Hz, 3H, CH–CH_3), 1.46 [s, 9H, C(CH_3)$_3$], 4.62 (m, 1H, CH–CH_3), 4.84 (br s, 1H, NH–CH), 6.05 (m, 1H, CH=CCl–CO), 7.90 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=18.6 (CH–*C*H_3), 27.9 [3C, C(*C*H_3)$_3$], 45.5 (*C*H–CH_3), 81.7 [*C*(CH_3)$_3$], 124.5 (*C*H=CCl–CO), 151.4 (CH=*C*Cl–CO), 156.2 (*C*O Boc), 165.2 (*C*OOH). *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.31 (d, $^3J_{H-H}$=8.8 Hz, 3H, CH–CH_3), 1.46 [s, 9H, C(CH_3)$_3$], 4.62 (m, 1H, CH–CH_3), 4.84 (br s, 1H, NH–CH), 7.05 (d, $^3J_{H-H}$=8.2 Hz, 1H, CH=CCl–CO), 7.90 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=19.9 (CH–*C*H_3), 28.2 [3C, C(*C*H_3)$_3$], 45.7 (*C*H–CH_3), 81.4 [*C*(CH_3)$_3$], 124.5 (*C*H=CCl–CO), 144.2 (CH=*C*Cl–CO), 156.9 (*C*O Boc), 164.0 (*C*OOH).

4.3.9. [L-(*trans*)]/[L-(*cis*)]-4-[(*t*-Butoxycarbonyl)amino]-2-fluoro-2-pentenoic acid 4i. Yield: 514 mg (82%), colourless oil (*trans*/*cis*: 35:65); R_f=0.58 (acetone); IR (KBr film)/cm^{-1}: ν_{max}=3330, 3115, 1805, 1700, and 1620; MS (FAB$^-$) *m/z* calculated for $C_{10}H_{16}NO_4F$ [M−H]$^-$ 232.11, found 232.1 (100%). *cis* Isomer: ^{1}H NMR (250 MHz, CD_3COCD_3): δ_H=1.30 (d, $^3J_{H-H}$=5.5 Hz, 3H, CH–CH_3), 1.39 [s, 9H, C(CH_3)$_3$], 4.63 (m, 1H, CH–CH_3), 6.17 (dd, $^3J_{H-F}$=32 Hz and $^3J_{H-H}$=8.0 Hz, 1H, CH=CF–CO), 6.05–6.55 (m, 2×1H, NH–CH and COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.8 (CH–*C*H_3), 28.3 [3C, C(*C*H_3)$_3$], 43.3 (*C*H–CH_3), 79.3 [*C*(CH_3)$_3$], 122.9 (d, $^2J_{C-F}$=9.0 Hz, 1C, *C*H=CF–CO), 147.1 (d, $^1J_{C-F}$=244 Hz, 1C, CH=*C*F–CO), 156.7 (*C*O Boc), 163.9 (d, $^2J_{C-F}$=37 Hz, 1C, *C*OOH); ^{19}F NMR (235.35 MHz, CD_3COCD_3): δ_F=−124.18 (d, $^3J_{F-H}$=32 Hz). *trans* Isomer: ^{1}H NMR (250 MHz, CD_3COCD_3): δ_H=1.30 (d, $^3J_{H-H}$=5.5 Hz, 3H, CH–CH_3), 1.39 [s, 9H, C(CH_3)$_3$], 5.09 (m, 1H, CH–CH_3), 5.93 (dd, $^3J_{H-F}$=15 Hz and $^3J_{H-H}$=9.5 Hz, 1H, CH=CF–CO), 6.05–6.55 (m, 2×1H, NH–CH and COOH; ^{19}F NMR (235.35 MHz, CD_3COCD_3): δ_F=−177.9 (d, $^3J_{F-H}$=15 Hz).

4.3.10. [L-(*trans*)]-4-[(*t*-Butoxycarbonyl)amino]-2,5-dimethyl-2-hexenoic acid 4j. 275 mg of a colourless oil obtained after a chromatographic separation on a silicagel column of 430 mg (79%) of a (*trans*/*cis*: 82:18) mixture; R_f=0.41 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3325, 1710, 1695 and 1650; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=0.92 (d, $^3J_{H-H}$=6.8 Hz, 3H, CH–CH_3), 0.96 (d, $^3J_{H-H}$=6.6 Hz, 3H, CH–CH_3), 1.44 [s, 9H, C(CH_3)$_3$], 1.78 [m, 1H, CH(CH_3)$_2$], 1.89 [d, $^4J_{H-H}$=1.1 Hz, 3H, CH=C(CH_3)–CO], 4.26 (m, 1H, NH–CH), 4.57 (br s, 1H, NH–CH), 6.63 [dd, $^3J_{H-H}$=9.8 Hz and $^4J_{H-H}$=1.1 Hz, 1H, CH=C(CH_3)–CO], 11.0 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.8 [CH=C(*C*H_3)–CO], 18.4 and 18.5 [2C, CH(*C*H_3)$_2$], 28.3 [3C, C(*C*H_3)$_3$], 32.8 [*C*H(CH_3)$_2$], 54.0 (NH–*C*H–CH=), 78.7 [*C*(CH_3)$_3$], 129.1 [CH=*C*(CH_3)–CO], 142.3 [*C*H=C(CH_3)–CO], 155.3 (*C*O Boc), 172.7 (*C*OOH); MS (FAB$^-$) *m/z* calculated for $C_{13}H_{22}NO_4$ [M−H]$^-$ 256.2, found 256.0 (100%). [α]$_D$=+30° (*c*=0.20, $HCCl_3$).

4.3.11. (*trans*)-4-[(*t*-Butoxycarbonyl)amino]-2-butenoic acid 4k. Yield: 584 mg (77%), white solid, mp 115°C, R_f=0.58 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3325, 1710, 1690 and 1655; ^{1}H NMR (250 MHz, CD_3COCD_3): δ_H=1.43 [s, 9H, C(CH_3)$_3$], 3.89 (dd, $^3J_{H-H}$=4.8 Hz and $^4J_{H-H}$=2.0 Hz, 2H, CH_2), 5.91 (dt, $^3J_{H-H}$=15.5 Hz and $^4J_{H-H}$=2.0 Hz, 1H, CH=CH–CO), 6.31 (br s, 1H, NH), 6.91 (dd, $^3J_{H-H}$=15.5, 4.8 Hz, 1H, CH=CH–CO), 11.0 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=28.3 [3C, C(*C*H_3)$_3$], 41.3 (NH–*C*H_2), 80.1 [*C*(CH_3)], 120.6 (CH=*C*H–CO), 147.3 (*C*H=CH–CO), 155.6 (*C*O Boc), 170.6 (*C*OOH); MS (FAB$^-$) *m/z* calculated for $C_9H_{14}NO_4$ [M−H]$^-$ 200.1, found 200.1 (100%).

4.3.12. (*trans*)-4-[(*t*-Butoxy)carbonyl)amino]-2-methyl-2-butenoic acid 4l. 410 mg, white solid obtained by precipitation with diethyl ether from 828 mg (77%) of a (*trans*/*cis*: 75:25) mixture; mp 117°C, R_f=0.66 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3370, 1685 and 1650; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.56 [s, 9H, C(CH_3)$_3$], 1.99 [d, $^4J_{H-H}$=1.0 Hz, 3H, CH=C(CH_3)–CO], 4.01 (t, $^3J_{H-H}$=6.5 Hz, 2H, NH–CH_2), 6.42 (br s, 1H, NH–CH$_2$), 6.85 [dt, $^3J_{H-H}$=6.5 Hz and $^4J_{H-H}$=1.0 Hz, 1H, CH=C(CH$_3$)–CO], 9.47 (br s, 1H, COOH); ^{13}C NMR (62.896 MHz, CD_3COCD_3): δ_C=12.9 [CH=C(*C*H$_3$)–CO], 29.0 [3C, C(*C*H$_3$)$_3$], 39.8 (NH–*C*H$_2$), 79.3 [*C*(CH$_3$)$_3$], 129.4 [CH=*C*(CH$_3$)–CO], 140.8 [*C*H=C(CH$_3$)–CO], 157.1 (*C*O Boc), 169.3 (*C*OOH). *cis* Isomer: IR (KBr film)/cm^{-1}: ν_{max}=3330, 1685, 1660 and 1520; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.43 [s, 9H, C(CH_3)$_3$], 1.91 [s, 3H, CH=C(CH_3)–CO], 4.05 (t, $^3J_{H-H}$=6.0 Hz, 2H, NH–CH_2), 5.09 (br s, 1H, NH–CH$_2$), 6.05 [m, 1H, CH=C(CH$_3$)–CO], 9.47 (br s, 1H, COOH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.0 [CH=C(*C*H$_3$)–CO], 28.3 [3C, C(*C*H$_3$)$_3$], 39.7 (NH–*C*H$_2$), 79.9 [*C*(CH$_3$)$_3$], 129.4 [CH=*C*(CH$_3$)–CO], 140.9 [*C*H=C(CH$_3$)–CO], 156.6 (*C*O Boc), 171.5 (*C*OOH); MS (CI$^-$) *m*/*z* calculated for $C_{10}H_{16}NO_4$ [M−H]$^-$ 214.12, found 214.0 (7%), 157.8 [[M−H−*t*BuO]$^-$, 37%], 114.2 [[M−H−*t*BuOCO]$^-$, 37%], 56.9 [[*t*Bu-H]$^-$, 87%], 40.9 [[C_3H_5–H]$^-$, 100%].

4.3.13. [L-(*trans*)]-4-[(*t*-Butoxycarbonyl)amino]-5-phenyl-2-pentenoic acid 4m. Yield: 674 mg (52%), white solid, mp 165°C, R_f=0.41 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3285, 3060, 1700, 1660 and 1640; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.40 [s, 9H, C(CH_3)$_3$], 2.73–3.04 (m, 2H, CH–CH_2), 4.37–4.75 (m, 2×1H, NH–CH), 5.86 (dd, $^3J_{H-H}$=15.5, 4.0 Hz, 1H, CH=CH–CO), 7.01 (dd, $^3J_{H-H}$=15.5, 4.7 Hz, 1H, CH=CH–CO), 7.15–7.36 (m, 5H, *Ph*), 10.4 (br s, 1H, COOH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=28.2 [3C, C(*C*H$_3$)$_3$], 40.7 (CH–*C*H$_2$), 52.3 (NH–*C*H), 80.1 [*C*(CH$_3$)$_3$], 120.5 (CH=*C*H–CO), 126.9, 128.6, 128.8, 129.1, 129.4 and 136.2 (*Ph*), 150.0 (*C*H=CH–CO), 155.0 (*C*O Boc), 170.9 (*C*OOH); [α]$_D$=+30° (*c*=0.2, $HCCl_3$); MS (EI$^+$) *m*/*z* calculated for $C_{16}H_{21}NO_4$ [M]$^+$ 291.2, found 291.8 (6%), 191.3 [[M+1−*t*BuOCO]$^+$, 38%], 89.8 [[C_7H_6]$^+$, 100%].

4.3.14. [L-(*trans*)]/[L-(*cis*)]-4-[(*t*-Butoxycarbonyl)amino]-2-methyl-5-phenyl-2-pentenoic acid 4n. Yield: 210 mg (35.5%), white solid (*trans*/*cis*: 75:25). R_f=0.61 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3065, 1720, 1715 and 1690; MS (EI$^+$) *m*/*z* calculated for $C_{17}H_{23}NO_4$ [M]$^+$ 305.16, found 306.2 [[M+1]$^+$, 2%], 249.6 [[M+1−*t*Bu]$^+$, 20%], 187.0 [[M−*t*BuOCO–OH]$^+$, 21%], 112.9 [[M+1−*t*BuOCO–OH–Ph]$^+$, 72%], 89.8 [[C_7H_6]$^+$, 100%]. *trans* Isomer: ^{1}H NMR (250 MHz, CD_3COCD_3): δ_H=1.36 [s, 9H, C(CH_3)$_3$], 1.65 [d, $^4J_{H-H}$=1.5 Hz, 3H, CH=C(CH_3)–CO], 2.80 and 2.99 (2dd, $^3J_{H-H}$=13.5, 7.5 Hz, 2×1H, CH–CH_2), 4.65 (ddt, $^3J_{H-H}$=9.25, 7.5, 5.0 Hz, 1H, NH–CH), 6.28 (d, $^3J_{H-H}$=5.0 Hz, 1H, NH–CH), 6.69 [dd, $^3J_{H-H}$=9.25 Hz and $^4J_{H-H}$=1.5 Hz, 1H, CH=C(CH$_3$)–CO], 7.12–7.35 (m, 5H, *Ph*), 11.0 (br s, 1H, COOH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.2 [CH=C(*C*H$_3$)–CO], 28.8 [3C, C(*C*H$_3$)$_3$], 41.0 (CH–*C*H$_2$), 50.8 (*C*H–CH$_2$), 80.4 [*C*(CH$_3$)$_3$], 128.5 [CH=*C*(CH$_3$)–CO], 129.0 (3C), 129.5 (2C) and 136.2 (*Ph*), 142.5 [*C*H=C(CH$_3$)–CO], 155.1 (*C*O Boc), 172.6 (*C*OOH). *cis* Isomer: ^{1}H NMR (250 MHz, CD_3COCD_3) δ_H=1.36 [s, 9H, C(CH_3)$_3$], 1.96 [d, $^4J_{H-H}$=1.5 Hz, 3H, CH=C(CH_3)–CO], 2.80 and 2.99 (2dd, $^3J_{H-H}$=13.5, 7.5 Hz, 2×1H, CH–CH_2), 5.13 (ddt, $^3J_{H-H}$=9.0, 7.5, 5.0 Hz, 1H, CH–CH$_2$), 5.96 [dd, $^3J_{H-H}$=9.0 Hz and $^4J_{H-H}$=1.5 Hz, 1H, CH=C(CH$_3$)–CO], 6.16 (d, $^3J_{H-H}$=5.0 Hz, 1H, NH–CH), 7.12–7.38 (m, 5H, *Ph*), 11.0 (br s, 1H, COOH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.5 [CH=C(*C*H$_3$)–CO], 28.9 [3C, C(*C*H$_3$)$_3$], 40.7 (CH–*C*H$_2$), 51.3 (*C*H–CH$_2$), 80.3 [*C*(CH$_3$)$_3$], 128.5 [CH=*C*(CH$_3$)–CO], 129.4 (3C), 129.8 (2C) and 136.5 (*Ph*), 142.7 [*C*H=C(CH$_3$)–CO], 156.3 (*C*O Boc), 172.4 (*C*OOH).

4.3.15. [L-(*trans*)]/[L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[2′-carboxy-2′-phenyl-1′-ethenyl] pyrrolidine 4o. Yield: 498 mg (72%), colourless oil (*trans*/*cis*: 82:18). R_f=0.43 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=1670 and 1650. *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.43 [s, 9H, C(CH_3)$_3$], 1.58–2.37 (m, 2×2H, CH–CH_2–CH_2), 3.32–4.01 (m, 2H, N–CH_2), 4.63 (m, 1H, N–CH), 7.09 [d, $^3J_{H-H}$=9.0 Hz, 1H, CH=C(Ph)–CO], 7.20–7.53 (m, 5H, *Ph*), 11.0 (br s, 1H, COOH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=24.0 (CH–CH$_2$–*C*H$_2$), 28.3 [3C, C(*C*H$_3$)$_3$], 32.4 (CH–*C*H$_2$), 47.2 (N–*C*H$_2$), 56.2 (N–*C*H), 81.9 [*C*(CH$_3$)$_3$], 127.2, 128.3, 128.4 (2C), 130.8 (2C), 137.1 and 138.9 [*C*H=*C*(*Ph*)–CO], 156.1 (*C*O Boc), 169.2 (*C*OOH). *cis* isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H= 1.46 [s, 9H, C(CH_3)$_3$], 1.58–2.37 (m, 2×2H, CH–CH_2–CH_2), 3.32–4.01 (m, 2H, N–CH_2), 4.63 (m, 1H, N–CH), 5.81 [d, $^3J_{H-H}$=10.5 Hz, 1H, CH=C(Ph)–CO], 7.20–7.53 (m, 5H, *Ph*), 11.0 (br s, 1H, COOH).

4.3.16. [L-(*trans*)]-*N*-(*t*-Butoxycarbonyl)-2-[2′-carboxy-2′-methyl-1′-ethenyl]pyrrolidine 4p. Yield: 498 mg, colourless oil obtained after a chromatographic separation on a silicagel column from 973 mg (80%) of a (*trans*/*cis*: 80:20) mixture; R_f=0.35 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3070, 1705, 1695 and 1650; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.37 [s, 9H, C(CH_3)$_3$], 1.57–2.26 (m, 2×2H, CH–CH_2–CH_2), 1.85 [s, 3H, CH=C(CH_3)–CO], 3.30–3.57 (m, 2H, N–CH_2), 4.46 (m, 1H, N–CH), 6.71 [d, $^3J_{H-H}$=8.8 Hz, 1H, CH=C(CH$_3$)–CO], 11.0 (br s, 1H, COOH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=11.9 [CH=C(*C*H$_3$)–CO], 23.7 and 24.3 (CH–CH$_2$–*C*H$_2$), 28.2 [3C, C(*C*H$_3$)$_3$], 31.7 and 32.1 (CH–*C*H$_2$), 46.3 and 46.8 (N–*C*H$_2$), 55.1 (N–*C*H), 79.6 [*C*(CH$_3$)$_3$], 125.7 [CH=*C*(CH$_3$)–CO], 145.2 [*C*H=C(CH$_3$)–CO], 154.4 (*C*O Boc), 172.5 (*C*OOH); MS (EI$^+$) *m*/*z* calculated for $C_{13}H_{21}NO_4$ [M]$^+$ 255.2, found 256.2 [[M+1]$^+$, 41%], 154.1 [[M−*t*BuOCO]$^+$, 48%], 200.0 [[M+1−*t*Bu]$^+$, 52%], 109.9 [[M+1−*t*BuOCO–COOH]$^+$, 77%], 137.9 [[M+1−*t*BuOCO–OH]$^+$, 78%], 56.9 [[*t*Bu]$^+$, 100%].

4.3.17. [L-(*trans*)]/[L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[2′-carboxy-2′-ethoxy-1′-ethenyl] pyrrolidine 4q. Yield: 967 mg (45%), colourless oil (*trans*/*cis*: 30:70); IR (KBr film)/cm^{-1}: ν_{max}=1710, 1690 and 1645. *trans* Isomer: R_f=0.19 (ethyl acetate/hexane: 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.37 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH$_2$–CH_3), 1.44 [s, 9H, C(CH_3)$_3$], 1.65–2.30 (m, 2×2H, CH–CH_2–CH_2), 3.22–3.53 (m, 2H, N–CH_2), 3.94–4.83 (m, 2H, O–CH_2–CH$_3$), 4.61 (m,

1H, N–C*H*), 6.13 [m, 1H, C*H*═C(OEt)–CO], 11.0 (br s, 1H, COO*H*). *cis* Isomer: R_f=0.38 (ethyl acetate/hexane: 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.37 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.47 [s, 9H, C(CH_3)$_3$], 1.65–2.30 (m, 2×2H, CH–CH_2–CH_2), 3.70–3.88 (m, 2H, N–CH_2), 3.94–4.83 (m, 2H, O–CH_2–CH_3), 4.61 (m, 1H, N–C*H*), 4.76 [m, 1H, C*H*═C(OEt)–CO], 11.0 (br s, 1H, COO*H*).

4.3.18. [L-(*trans*)]/[L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[2′-carboxy-2′-chloro-1′-ethenyl] pyrrolidine 4r. Yield: 385 mg (68%), colourless oil (*trans*/*cis*: 35:65). R_f=0.32 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=1695 and 1650. *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.48 [s, 9H, C(CH_3)$_3$], 1.65–2.39 (m, 2×2H, CH–CH_2–CH_2), 3.33–3.60 (m, 2H, N–CH_2), 4.67 (m, 1H, N–C*H*), 7.09 (m, 1H, C*H*═CCl–CO), 8.99 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=23.7 and 23.8 (CH–CH_2–CH_2), 28.2 [3C, C(CH_3)$_3$], 31.4 and 31.8 (CH–CH_2), 46.4 and 46.9 (N–CH_2), 56.3 (N–*C*H), 80.5 [*C*(CH_3)$_3$], 122.8 (*C*H═CCl–CO), 145.0 (CH═*C*Cl–CO), 154.6 (*C*O Boc), 165.1 (*C*OOH); *cis* isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.48 [s, 9H, C(CH_3)$_3$], 1.65–2.39 (m, 2×2H, CH–CH_2–CH_2), 3.33–3.60 (m, 2H, N–CH_2), 4.67 (m, 1H, N–C*H*), 6.04 (d, $^3J_{H-H}$=10.4 Hz, 1H, C*H*═CCl–CO), 8.99 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=24.7 (CH–CH_2–*C*H_2), 28.7 [3C, C(*C*H_3)$_3$], 30.6 (CH–*C*H_2), 46.4 (N–*C*H_2), 55.4 (N–*C*H), 81.9 [*C*(CH_3)$_3$], 126.0 (*C*H═CCl–CO), 137.1 (CH═*C*Cl–CO), 156.0 (*C*O Boc), 163.9 (*C*OOH); MS (FAB$^-$): *m*/*z* calculated for $C_{12}H_{17}NO_4Cl$ [M−H]$^-$ 274.6, found 274.1 (100%).

4.3.19. [L-(*trans*)]/[L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[2′-carboxy-2′-fluoro-1′-ethenyl] pyrrolidine 4s. Yield: 147 mg (62%), colourless oil (*trans*/*cis*: 30:70); IR (KBr film)/cm^{-1}: ν_{max}=1735, 1695, 1670, 1650 and 1635; MS (FAB$^-$) *m*/*z* calculated for $C_{12}H_{17}NO_4F$ [M−H]$^-$ 258.1, found 258.1 (100%). *trans* Isomer: R_f=0.19 (ethyl acetate/hexane: 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.46 [s, 9H, C(CH_3)$_3$], 1.67–2.35 (m, 2×2H, CH–CH_2–CH_2), 3.31–3.55 (m, 2H, N–CH_2), 4.69 (m, 1H, N–C*H*), 6.13 (dd, $^3J_{H-F}$=35 Hz and $^3J_{H-H}$=8.6 Hz, 1H, C*H*═CF–CO), 9.30 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=23.6 (CH–CH_2–*C*H_2), 28.1 [3C, C(*C*H_3)$_3$], 31.9 (CH–*C*H_2), 46.5 (N–*C*H_2), 52.0 (N–*C*H), 80.5 [*C*(CH_3)$_3$], 120.8 (d, $^2J_{C-F}$=14 Hz, 1C, *C*H═CF–CO), 146.7 (d, $^1J_{C-F}$=271 Hz, 1C, CH═*C*F–CO), 154.7 (*C*O Boc), 162.7 (d, $^2J_{C-F}$=35 Hz, 1C, *C*OOH); ^{19}F NMR (235.35 MHz, $CDCl_3$): δ_F=−130.5 (d, $^3J_{F-H}$=35 Hz). *cis* Isomer: R_f=0.38 (ethyl acetate/hexane: 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.43 [s, 9H, C(CH_3)$_3$], 1.67–2.35 (m, 2×2H, CH–CH_2–CH_2), 3.31–3.55 (m, 2H, N–CH_2), 4.81 (m, 1H, N–C*H*), 5.65 (dd, $^3J_{H-F}$=34 Hz and $^3J_{H-H}$=9.9 Hz, 1H, C*H*═CF–CO), 9.30 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=24.1 (CH–CH_2–*C*H_2), 28.1 [3C, C(*C*H_3)$_3$], 31.4 and 32.8 (CH–*C*H_2), 46.4 and 46.5 (N–*C*H_2), 53.0 (d, $^3J_{C-F}$=8.0 Hz, 1C, N–*C*H), 81.4 [*C*(CH_3)$_3$], 122.1 (d, $^2J_{C-F}$=13.5 Hz, 1C, *C*H═CF–CO), 148.3 (d, $^1J_{C-F}$=258 Hz, 1C, CH═*C*F–CO), 155.5 (*C*O Boc), 162.4 (d, $^2J_{C-F}$=34 Hz, 1C, *C*OOH); ^{19}F NMR (235.35 MHz, $CDCl_3$): δ_F=−128.9 (d, $^3J_{F-H}$=34 Hz).

4.3.20. (*trans*)-5-[(*t*-Butoxycarbonyl)amino]-2-methyl-2-pentenoic acid 4t. Yield: 170 mg (70%), colourless oil, R_f=0.45 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3345, 3075, 1715, 1695 and 1645; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.46 [s, 9H, C(CH_3)$_3$], 1.86 [d, $^4J_{H-H}$=1.0 Hz, 3H, CH═C(*C*H_3)–CO], 2.37–3.61 (m, 2H, *C*H_2–CH═), 3.26 (q, $^3J_{H-H}$=6.7 Hz, 2H, NH–*C*H_2), 4.63 (br s, 1H, N*H*–CH_2), 6.85 [t, $^3J_{H-H}$=6.4 Hz, 1H, *C*H═C(CH_3)–CO], 10.5 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.1 [CH═C(*C*H_3)–CO], 28.3 [3C, C(*C*H_3)$_3$], 29.4 (*C*H_2–CH═), 39.3 (N–*C*H_2), 80.1 [*C*(CH_3)$_3$], 129.5 [CH═*C*(CH_3)–CO], 140.6 [*C*H═C(CH_3)–CO], 155.5 (*C*O Boc), 172.6 (*C*OOH); MS (EI$^+$) *m*/*z* calculated for $C_{11}H_{19}NO_4$ [M]$^+$ 229.1, found 230.0 [[M+1]$^+$, 6%], 130.0 [[M−*t*BuOCO]$^+$, 30%], 173.9 [[M+H−*t*Bu]$^+$, 44%], 112.0 [[M+H−*t*BuOCO–OH]$^+$, 68%], 56.9 [[*t*Bu]$^+$, 100%].

4.4. Typical procedure for the preparation of *N*-isopropyl vinylogous aminoamides 4′

Triethylamine (71 mg, 1 equiv.) was added to a stirred solution of Boc *N*-protected vinylogous amino acid **4** (0.705 mmol) in dichloromethane (10 mL). Then, benzotriazol-1-yloxytris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), (312 mg, 1 equiv.) was added, followed after a few minutes by amine hydrochloride (1 equiv.) and triethylamine (80 mg, 1.5 equiv.). The mixture was stirred at room temperature until TLC analysis indicated the total consumption of the amino component (90–20 min, depending to the substrate). The mixture was then diluted with dichloromethane (25 mL) and washed successively with 3N aqueous HCl (3×5 mL), saturated NaCl aqueous solution (5 mL), saturated $NaHCO_3$ solution (3×5 mL) and saturated NaCl solution (3×5 mL). The organic layer was dried over magnesium sulfate and the solvent evaporated. The crude product was purified by column chromatography on silica gel.

4.4.1. [L-(*trans*)] or [L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[(*N*-isopropyl)-2′-carboxamide-2′-ethoxy-1′-ethenyl]-pyrrolidine 4′q. Yield: 145 mg (78%), colourless oil (*trans*/*cis*: 30:70); IR (KBr film)/cm^{-1}: ν_{max}=3330, 1690, 1680 and 1640. *cis* Isomer: R_f=0.58 (ethyl acetate/hexane: 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.17 [d, $^3J_{H-H}$=6.5 Hz, 2×3H, CH(CH_3)$_2$], 1.32 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.40 [s, 9H, C(CH_3)$_3$], 1.55–2.41 (m, 2×2H, CH–CH_2–CH_2), 3.63–3.78 (m, 2H, N–CH_2), 4.08 [m, 1H, CH(CH_3)$_2$], 4.62–4.83 (m, 2H, O–CH_2–CH_3), 4.93 (m, 1H, N–C*H*), 5.39 [m, 1H, C*H*═C(OEt)–CO], 8.25 (m, 1H, *i*Pr-N*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=15.5 (O–CH_2–*C*H_3), 22.4 [2C, CH(*C*H_3)$_2$], 23.8 (CH–CH_2–*C*H_2), 28.4 [3C, C(*C*H_3)$_3$], 34.0 (CH–*C*H_2), 41.1 [*C*H(CH$_3$)$_2$], 46.7 (N–*C*H_2), 52.6 (N–*C*H), 69.2 (O–*C*H_2–CH_3), 78.6 [*C*(CH_3)$_3$], 115.6 [*C*H═C(OEt)–CO], 149.1 [CH═*C*(OEt)–CO], 154.2 (*C*O Boc), 162.3 (*C*ONH*i*Pr); $[\alpha]_D$=+89.2° (*c*=0.5, $HCCl_3$). *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.21 [d, $^3J_{H-H}$=6.5 Hz, 2×3H, CH(CH_3)$_2$], 1.40 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.50 [s, 9H, C(CH_3)$_3$], 1.49–2.18 (m, 2×2H, CH–CH_2–CH_2), 3.17–3.41 (m, 2H, N–CH_2), 3.76 [m, 1H, CH(CH_3)$_2$], 3.85–4.08 (m, 2H, O–CH_2–CH_3), 4.56 (m, 1H, N–C*H*), 5.90 [m, 1H, C*H*═C(OEt)–CO], 6.91 (m, 1H, *i*Pr-N*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.4 (O–CH_2–*C*H_3), 22.7 [2C, CH(*C*H_3)$_2$], 23.7 (CH–CH_2–*C*H_2),

28.4 [3C, C(CH_3)$_3$], 34.0 (CH–CH_2), 41.1 [CH(CH$_3$)$_2$], 46.2 (N–CH_2), 54.7 (N–CH), 63.4 (O–CH_2–CH$_3$), 79.4 [C(CH$_3$)$_3$], 108.1 [CH=C(OEt)–CO], 146.9 [CH=C(OEt)–CO], 154.8 (CO Boc), 162.8 (CONH*i*Pr).

4.4.2. [L-(*trans*)]- or [L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[(*N*-isopropyl)-2′-carboxamide-2′-chloro-1′-ethenyl]-pyrrolidine 4′r. Yield: 365 mg (84%), colourless oil (*trans*/*cis*: 30:70); IR (KBr film)/cm^{-1}: ν_{max}=3350, 1700, 1685 and 1650. *cis* Isomer: R_f=0.73 (ethyl acetate/hexane: 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.22 [d, $^3J_{H-H}$=6.5 Hz, 2×3H, CH(CH_3)$_2$], 1.46 [s, 9H, C(CH_3)$_3$], 1.54–2.23 (m, 2×2H, CH–CH_2–CH_2), 3.31–3.46 (m, 2H, N–CH_2), 4.09 [m, 1H, CH(CH_3)$_2$], 4.64 (m, 1H, N–CH), 5.81 (m, 1H, CH=CCl–CO), 8.88 (m, 1H, *i*Pr-NH). *trans* Isomer: R_f=0.64 (ethyl acetate/hexane: 1:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.21 [d, $^3J_{H-H}$=6.5 Hz, 2×3H, CH(CH_3)$_2$], 1.41 [s, 9H, C(CH_3)$_3$], 1.61–2.29 (m, 2×2H, CH–CH_2–CH_2), 3.38–3.61 (m, 2H, N–CH_2), 4.09 [m, 1H, CH(CH_3)$_2$], 4.61 (m, 1H, N–CH), 6.39 (m, 1H, CH=CCl–CO), 7.05 (m, 1H, *i*Pr-NH).

4.4.3. [L-(*trans*)]- or [L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[(*N*-isopropyl)-2′-carboxamide-2′-fluoro-1′-ethenyl]-pyrrolidine 4′s. Yield: 255 mg (85%), white solid (*trans*/*cis*: 35:65); IR (KBr film)/cm^{-1}: ν_{max}=3310, 1695, 1680, 1665, 1660, 1650 and 1640. *cis* Isomer: R_f=0.6 (ethyl acetate/hexane: 1:1); mp 73°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.21 [d, $^3J_{H-H}$=7.3 Hz, 2×3H, CH(CH_3)$_2$], 1.43 [s, 9H, C(CH_3)$_3$], 1.61–2.34 (m, 2×2H, CH–CH_2–CH_2), 3.23–3.51 (m, 2H, N–CH_2), 4.12 [m, 1H, CH(CH_3)$_2$], 4.79 (m, 1H, N–CH), 5.50 (m, 1H, CH=CF–CO), 8.19 (m, 1H, *i*Pr-NH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=21.9 and 22.3 [2C, CH(CH_3)$_2$], 23.8 (CH–CH_2–CH_2), 28.3 [3C, C(CH_3)$_3$], 32.8 (CH–CH_2), 40.1 [CH(CH$_3$)$_2$], 46.7 (N–CH_2), 53.1 (d, $^3J_{C-F}$=8.0 Hz, 1C, N–CH), 79.9 [C(CH$_3$)$_3$], 122.5 (d, $^2J_{C-F}$=31.6 Hz, 1C, CH=CF–CO), 148.4 (d, $^1J_{C-H}$=258 Hz, 1C, CH=CF–CO), 154.8 (CO Boc), 159.3 (d, $^2J_{C-F}$=31.8 Hz, 1C, CONH*i*Pr); ^{19}F NMR (235.36 MHz, CD_3COCD_3): δ_F=−123.5 (d, $^3J_{F-H}$=19 Hz, 1F); $[\alpha]_D$=+83° (c=0.4, $HCCl_3$). *trans* Isomer: R_f=0.4 (ethyl acetate/hexane: 1:1); mp 106°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.21 [d, $^3J_{H-H}$=6.5 Hz, 2×3H, CH(CH_3)$_2$], 1.43 [s, 9H, C(CH_3)$_3$], 1.69–2.24 (m, 2×2H, CH–CH_2–CH_2), 3.29–3.57 (m, 2H, N–CH_2), 4.13 [m, 1H, CH(CH_3)$_2$], 4.69 (m, 1H, N–CH), 6.00 (dd, $^3J_{H-F}$=36 Hz and $^3J_{H-H}$=9.2 Hz, 1H, CH=CF–CO), 6.05 (m, 1H, *i*Pr-NH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=22.3 [2C, CH(CH_3)$_2$], 23.3 and 24.1 (CH–CH_2–CH_2), 28.3 [3C, C(CH_3)$_3$], 31.8 and 32.1 (CH–CH_2), 41.4 [CH(CH$_3$)$_2$], 46.1 (N–CH_2), 53.9 (N–CH), 79.5 [C(CH$_3$)$_3$], 116.8 (d, $^2J_{C-F}$=33 Hz, 1C, CH=CF–CO), 150.0 (d, $^1J_{C-H}$=269 Hz, 1C, CH=CF–CO), 154.1 (CO Boc), 159.3 (d, $^2J_{C-F}$=27 Hz, 1C, CONH*i*Pr); ^{19}F NMR (235.36 MHz, CD_3COCD_3): δ_F=−129.8 (d, $^3J_{F-H}$=36 Hz, 1F);); $[\alpha]_D$=−6.1° (c=0.25, $HCCl_3$).

4.5. Typical procedure for the preparation of the *cis* vinylogous aminoesters 5

The bis(trifluoroethyl) phosphonoesters **6a** were prepared according to the Savignac method.[14] The ethyl 2-diethylphosphonopropanoate **6b** was commercially available (R^2=CH_3). It was synthesized with the appropriate method when R^2=Cl[15] or F[16].

With the ethyl bis(trifluoroethyl)phosphonoalcanoates 6a. The phosphonate **6a** (1.08 g, 3.12 mmol) was added to a slurry of oil-free potassium hydride (125 mg, 3.12 mmol) in THF (10 mL) at 0°C. The solution was stirred for 15 min at this temperature followed by cooling to −78°C. Aminoaldehyde **2** (520 mg, 2.6 mmol) in THF (5 mL) was added over 15 min. The reaction mixture was stirred at −78°C for 3 h and then quenched with 2% aqueous HCl (15 mL). The aqueous phase was extracted with dichloromethane (3×50 mL). The organic layers were combined and dried with $MgSO_4$. After filtration the solvent was evaporated and the so-obtained crude product was purified by column chromatography on silica gel.

With the ethyl 2-diethylphosphonoalcanoates 6b. 1.6 mL of *n*-butyllithium (2.37 mmol, 1.54 M in hexane) were added dropwise to the phosphonate **6b** (550 mg, 2.37 mmol) in THF (10 mL) with stirring at room temperature. After 20 min, the mixture was cooled to −78°C with stirring and aminoaldehyde **2** (360 mg, 2.26 mmol) in THF (10 mL) was added dropwise. After 3 h stirring, the reaction was quenched with an aqueous saturated ammonium chloride solution (12 mL) at −78°C. The aqueous phase was extracted with diethyl ether (3×30 mL) and the combined organic phases were washed with water (2×5 mL). Then the organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude product, which was purified by column chromatography on silica gel.

4.5.1. Ethyl [L-(*trans*)]/[L-(*cis*)]-4-[(*t*-butoxycarbonyl)-amino]-2-pentenoate 5c. Yield: 360 mg (72%) of a (*trans*/*cis*: 25:75) mixture obtained with phosphonate **6a** (R^2=H); colourless oil; R_f=0.57 (acetone/ethyl acetate/hexane: 1:1/1); IR (KBr film)/cm^{-1}: ν_{max}=3355, 1720, 1715, 1705, 1695, 1660 and 1650. *cis* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.17 (d, $^3J_{H-H}$=7.25 Hz, 3H, CH–CH_3), 1.29 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.45 [s, 9H, C(CH_3)$_3$], 4.18 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 4.78 (br s, 1H, NH), 5.16 (m, 1H, NH–CH), 5.74 (dd, $^3J_{H-H}$=11.6 Hz and $^4J_{H-H}$=0.75 Hz, 1H, CH=CH–CO), 6.11 (m 1H, CH=CH–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.2 (O–CH_2–CH_3), 20.2 (CH–CH_3), 28.3 [3C, C(CH_3)$_3$], 45.4 (NH–CH), 60.2 (O–CH_2–CH_3), 79.5 [C(CH$_3$)$_3$], 119.5 (CH=CH–CO), 151.9 (CH=CH–CO), 155.2 (CO Boc), 165.7 (COOEt). *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.27 (d, $^3J_{H-H}$=7.25 Hz, 3H, CH–CH_3), 1.29 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.45 [s, 9H, C(CH_3)$_3$], 4.19 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 4.31–4.59 (m, 2×1H, NH and NH–CH), 5.91 (dd, $^3J_{H-H}$=15.75 Hz and $^4J_{H-H}$=1.3 Hz, 1H, CH=CH–CO), 6.88 (dd, $^3J_{H-H}$=15.75 Hz and $^3J_{H-H}$=4.85 Hz, 1H, CH=CH–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.2 (O–CH_2–CH_3), 20.3 (CH–CH_3), 28.5 [3C, C(CH_3)$_3$], 45.5 (NH–CH), 60.4 (O–CH_2–CH_3), 79.5 [C(CH$_3$)$_3$], 118.9 (CH=CH–CO), 149.3 (CH=CH–CO), 155.2 (CO Boc), 165.7 (COOEt).

4.5.2. Ethyl [L-(*trans*)]- or [L-(*cis*)]-4-[(*t*-butoxycarbonyl)-amino]-2-methyl-2-pentenoate 5d. Yield: 983 mg (79%);

colourless oil (*trans*/*cis*: 7:93) obtained with phosphonate **6a** and 1.05 g (82%); colourless oil (*trans*/*cis*: 10:90) obtained with phosphonate **6b**. *cis* Isomer: colourless oil; R_f=0.54 (ethyl acetate/hexane: 1:4); IR (KBr film)/cm^{-1}: ν_{max}=3360, 1715, 1695 and 1650; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.25 (d, $^3J_{H-H}$=6.8 Hz, 3H, CH–CH_3), 1.32 (t, $^3J_{H-H}$=7.1 Hz, 3H, O–CH$_2$–CH_3), 1.43 [s, 9H, C(CH_3)$_3$], 1.90 [d, $^4J_{H-H}$=1 Hz, 3H, CH=C(CH_3)–CO], 4.22 (q, $^3J_{H-H}$=7.1 Hz, 2H, O–CH_2–CH$_3$), 4.53 (m, 1H, N*H*), 4.94 (m, 1H, NH–C*H*), 5.79 [d, $^3J_{H-H}$=8.6 Hz, 1H, C*H*=C(CH$_3$)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.0 (O–CH$_2$–*C*H$_3$), 20.1 [CH=C(*C*H$_3$)–CO], 20.6 (CH–*C*H$_3$), 28.2 [3C, C(*C*H$_3$)$_3$], 45.7 (NH–*C*H), 60.2 (O–*C*H$_2$–CH$_3$), 78.9 [*C*(CH$_3$)$_3$], 126.7 [CH=*C*(CH$_3$)–CO], 144.5 [*C*H=C(CH$_3$)–CO], 154.9 (*C*O Boc), 167.1 (*C*OOEt); $[\alpha]_D$=+47° (*c*=1.0, $HCCl_3$). MS (FAB$^+$): *m*/*z* calculated for $C_{13}H_{23}NO_4$ [M]$^+$ 257.2, found 258.2 [[M+1]$^+$, 76%], 202.2 [[M−*t*Bu]$^+$, 100%]. *trans* Isomer: colourless oil; R_f=0.5 (ethyl acetate/hexane: 1:4); IR (KBr film)/cm^{-1}: ν_{max}=3360, 1700, 1680 and 1655; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.17 (d, $^3J_{H-H}$=6.8 Hz, 3H, CH–CH_3), 1.24 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH$_2$–CH_3), 1.34 [s, 9H, C(CH_3)$_3$], 1.86 [s, 3H, CH=C(CH_3)–CO], 4.14 (q, $^3J_{H-H}$=6.8 Hz, 2H, O–CH_2–CH$_3$), 4.46 (m, 1H, N*H*), 4.72 (m, 1H, NH–C*H*), 6.49 [dd, $^3J_{H-H}$=8.9 Hz and $^4J_{H-H}$=1.3 Hz, 1H, C*H*=C(CH$_3$)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.4 [CH=C(*C*H$_3$)–CO], 14.0 (O–CH$_2$–*C*H$_3$), 20.5 (CH–*C*H$_3$), 28.3 [3C, C(*C*H$_3$)$_3$], 44.8 (NH–*C*H), 60.5 (O–*C*H$_2$–CH$_3$), 78.3 [*C*(CH$_3$)$_3$], 128.0 [CH=*C*(CH$_3$)–CO], 142.7 [*C*H=C(CH$_3$)–CO], 154.9 (*C*O Boc), 167.9 (*C*OOEt); $[\alpha]_D$=−12° (*c*=0.8, $HCCl_3$).

4.5.3. Ethyl [L-(*cis*)]-4-[(*t*-butoxycarbonyl)amino]-2-chloro-2-pentenoate 5h. Yield: 489 mg (88%); colourless oil obtained with phosphonate **6b**; R_f=0.62 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3340, 1715, 1700 and 1690; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.29 (d, $^3J_{H-H}$=7.15 Hz, 3H, CH–CH_3), 1.36 (t, $^3J_{H-H}$=7.15 Hz, 3H, O–CH$_2$–CH_3), 1.36 [s, 9H, C(CH_3)$_3$], 4.28 (q, $^3J_{H-H}$=7.15 Hz, 2H, O–CH_2–CH$_3$), 4.69 (m, 1H, N*H*), 5.00 (m, 1H, NH–C*H*), 6.30 (d, $^3J_{H-H}$=8.65 Hz, 1H, C*H*=C*Cl*–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=13.8 (O–CH$_2$–*C*H$_3$), 19.9 (CH–*C*H$_3$), 28.1 [3C, C(*C*H$_3$)$_3$], 45.7 (NH–*C*H), 62.2 (O–*C*H$_2$–CH$_3$), 79.4 [*C*(CH$_3$)$_3$], 122.2 (*C*H=CCl–CO), 146.2 (CH=*C*Cl–CO), 154.8 (*C*O Boc), 161.9 (*C*OOEt).

4.5.4. Ethyl [L-(*cis*)]-4-[(*t*-butoxycarbonyl)amino]-2-fluoro-2-pentenoate 5i. Yield: 261 mg (95%); white solid obtained with phosphonate **6b**; mp 64–65°C; R_f=0.57 (ethyl acetate/hexane: 1:3); IR (KBr film)/cm^{-1}: ν_{max}=3360, 1725, 1685 and 1665; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.25 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.30 (t, $^3J_{H-H}$=7.5 Hz, 3H, O–CH$_2$–CH_3), 1.37 [s, 9H, C(CH_3)$_3$], 4.26 (q, $^3J_{H-H}$=7.5 Hz, 2H, O–CH_2–CH$_3$), 4.88 (m, 1H, N*H*), 5.01 (m, 1H, NH–C*H*), 5.79 (dd, $^3J_{H-H}$=8.9 Hz and $^3J_{H-F}$=20 Hz, 1H, C*H*=C*F*–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.0 (O–CH$_2$–*C*H$_3$), 20.8 (CH–*C*H$_3$), 28.2 [3C, C(*C*H$_3$)$_3$], 43.0 (d, $^4J_{C-F}$=4.0 Hz, 1C, NH–*C*H), 61.6 (O–*C*H$_2$–CH$_3$), 79.4 [*C*(CH$_3$)$_3$], 125.7 (d, $^2J_{C-F}$=17 Hz, 1C, *C*H=CF–CO), 146.5 (d, $^1J_{C-F}$=256 Hz, 1C, CH=*C*F–CO), 154.9 (*C*O Boc), 160.3 (d, $^3J_{C-F}$=8.9 Hz, 1C, *C*OOEt); ^{19}F NMR (235.35 MHz, $CDCl_3$): δ_F=−123.6 (d, $^3J_{F-H}$=20 Hz).

4.5.5. Ethyl [L-(*trans*)]- or [L-(*cis*)]-4-[(*t*-butoxycarbonyl)-amino]-2,5-dimethyl-2-hexenoate 5j. Yield: 740 mg (63%) of pure *cis* isomer obtained after a separation on a silicagel chromatographic column from 1.015 g (87%) of a (*trans*/*cis:* 10:90) mixture obtained with the phosphonate **6a** and 590 mg (80%) of a (*trans*/*cis*: 80:20) mixture obtained with the phosphonate **6b**. *cis* Isomer: colourless oil; R_f=0.59 (ethyl acetate/hexane: 1:2); IR (KBr film)/cm^{-1}: ν_{max}=3370, 1710, 1695 and 1655; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=0.91 and 0.93 [2d, $^3J_{H-H}$=6.7 Hz, 2×3H, CH(CH_3)$_2$], 1.32 (t, $^3J_{H-H}$=7.1 Hz, 3H, O–CH$_2$–CH_3), 1.43 [s, 9H, C(CH_3)$_3$], 1.87 [m, 1H, C*H*(CH$_3$)$_2$], 1.93 [d, $^4J_{H-H}$=1.0 Hz, 3H, CH=C(CH_3)–CO], 4.22 (q, $^3J_{H-H}$=7.1 Hz, 2H, O–CH_2–CH$_3$), 4.60 (m, 1H, N*H*), 4.74 (m, 1H, NH–C*H*), 5.74 [dd, $^3J_{H-H}$=9.5 Hz and $^4J_{H-H}$=0.5 Hz, 1H, C*H*=C(CH$_3$)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=13.9 (O–CH$_2$–*C*H$_3$), 17.7 and 18.8 [2C, CH(*C*H$_3$)$_2$], 20.4 [CH=C(*C*H$_3$)–CO], 28.1 [3C, C(*C*H$_3$)$_3$], 32.6 [*C*H(CH$_3$)$_2$], 53.9 (NH–*C*H), 60.1 (O–*C*H$_2$–CH$_3$), 78.5 [*C*(CH$_3$)$_3$], 128.2 [CH=*C*(CH$_3$)–CO], 140.9 [*C*H=C(CH$_3$)–CO], 155.2 (*C*O Boc), 167.2 (*C*OOEt). *trans* Isomer: colourless oil; R_f=0.51 (ethyl acetate/hexane: 1:2); IR (KBr film)/cm^{-1}: ν_{max}=3370, 1700, 1695 and 1655; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=0.89 [d, $^3J_{H-H}$=6.8 Hz, 2×3H, CH(CH_3)$_2$], 1.28 (t, $^3J_{H-H}$=7.1 Hz, 3H, O–CH$_2$–CH_3), 1.41 [s, 9H, C(CH_3)$_3$], 1.79 [m, 1H, C*H*(CH$_3$)$_2$], 1.90 [d, $^4J_{H-H}$=0.5 Hz, 3H, CH=C(CH_3)–CO], 4.22 (q, $^3J_{H-H}$=7.1 Hz, 2H, O–CH_2–CH$_3$), 4.51 (m, 1H, N*H*), 4.79 (m, 1H, NH–C*H*), 6.49 [dd, $^3J_{H-H}$=9.5 Hz and $^4J_{H-H}$=0.5 Hz, 1H, C*H*=C(CH$_3$)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=13.0 [CH=C(*C*H$_3$)–CO], 13.8 (O–CH$_2$–*C*H$_3$), 18.5 and 19.1 [2C, CH(*C*H$_3$)$_2$], 28.0 [3C, C(*C*H$_3$)$_3$], 32.9 [*C*H(CH$_3$)$_2$], 55.4 (NH–*C*H), 60.6 (O–*C*H$_2$–CH$_3$), 79.3 [*C*(CH$_3$)$_3$], 128.4 [CH=*C*(CH$_3$)–CO], 139.9 [*C*H=C(CH$_3$)–CO], 155.3 (*C*O Boc), 167.7 (*C*OOEt).

4.5.6. Ethyl (*trans*)- or (*cis*)-4-[(*t*-butoxycarbonyl)amino]-2-methyl-2-butenoate 5l. Yield: 1.14 g (41%) of pure *cis* isomer obtained after a separation on a silicagel chromatographic column from 2.37 g (85%) of a (*trans*/*cis:*35:65) mixture obtained with the phosphonate **6a** and 345 mg (63%) of a (*trans*/*cis*: 14:86) mixture obtained with the phosphonate **6b**. *cis* Isomer: colourless oil; R_f=0.35 (ethyl acetate/hexane: 1:4); IR (KBr film)/cm^{-1}: ν_{max}=3370, 1715, 1695 and 1645; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.23 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH$_2$–CH_3), 1.37 [s, 9H, C(CH_3)$_3$], 1.82 [d, $^4J_{H-H}$=1.0 Hz, 3H, CH=C(CH_3)–CO], 3.93–4.07 (m, 2H, NH–CH_2), 4.13 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH$_3$), 5.07 (m, 1H, N*H*–CH$_2$), 5.93 [m, 1H, C*H*=C(CH$_3$)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.0 (O–CH$_2$–*C*H$_3$), 19.9 [CH=C(*C*H$_3$)–CO], 28.2 [3C, C(*C*H$_3$)$_3$], 39.4 (NH–*C*H$_2$), 60.3 (O–*C*H$_2$–CH$_3$), 79.1 [*C*(CH$_3$)$_3$], 128.7 [CH=*C*(CH$_3$)–CO], 140.2 [*C*H=C(CH$_3$)–CO], 155.8 (*C*O Boc), 167.2 (*C*OOEt). *trans* Isomer: colourless oil; R_f=0.29 (ethyl acetate/hexane: 1:4); IR (KBr film)/cm^{-1}: ν_{max}=3370, 1715, 1695 and 1655; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.28 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH$_2$–CH_3), 1.44 [s, 9H, C(CH_3)$_3$], 1.86 [d, $^4J_{H-H}$=1.0 Hz, 3H, CH=C(CH_3)–CO], 3.82–3.96 (m, 2H, NH–CH_2), 4.19 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH$_3$), 4.73 (m, 1H, N*H*–CH$_2$), 6.64 [dt, $^3J_{H-H}$=6.5 Hz and $^4J_{H-H}$=1.0 Hz, 1H, C*H*=C(CH$_3$)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.5 [CH=C(*C*H$_3$)–CO], 14.2 (O–CH$_2$–*C*H$_3$),

28.3 [3C, C(CH_3)$_3$], 38.8 (NH–CH_2), 60.7 (O–CH_2–CH_3), 79.7 [$C(CH_3)_3$], 129.5 [CH=$C(CH_3)$–CO], 137.9 [CH=C(CH_3)–CO], 155.3 (*C*O Boc), 167.5 (*C*OOEt); MS (EI^+): *m/z* calculated for $C_{12}H_{21}NO_4$ $[M]^+$ 243.2, found 244.2 $[[M+1]^+$ 100%].

4.5.7. [L-(*trans*)]- or [L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[1′-ethenyl-2′-methyl-2′-ethoxy carbonyl]-pyrrolidine 5p. Yield: 1.09 g (50%) of pure *cis* isomer obtained after a separation on a silicagel chromatographic column from 1.73 g (79%) of a (*trans*/*cis:*10:90) mixture obtained with the phosphonate **6a** and 872 mg (71%) of a (*trans*/*cis:*70:30) mixture obtained with the phosphonate **6b**. *cis* Isomer: colourless oil; R_f=0.78 (ethyl acetate/hexane: 1:4); IR (KBr film)/cm^{-1}: ν_{max}=1710, 1695 and 1620; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.30 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.39 [s, 9H, C(CH_3)$_3$], 1.61–2.35 (m, 2×2H, CH–CH_2–CH_2), 1.90 [CH=C(CH_3)–CO], 3.32–3.57 (m, 2H, N–CH_2), 4.19 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 5.02 (m, 1H, N–C*H*), 5.86 [d, $^3J_{H-H}$=6.5 Hz, 1H, C*H*=C(CH_3)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C= 14.1 (O–CH_2–CH_3), 20.0 [CH=C(CH_3)–CO], 23.8 (CH–CH_2–CH_2), 28.3 [3C, C(CH_3)$_3$], 33.0 (CH–CH_2–CH_2), 46.4 (N–CH_2), 56.1 (N–*C*H), 60.1 (O–CH_2–CH_3), 77.3 [$C(CH_3)_3$], 134.2 [CH=$C(CH_3)$–CO], 145.1 [*C*H=C(CH_3)–CO], 155.4 (*C*O Boc), 167.0 (*C*OOEt). *trans* Isomer: colourless oil; R_f=0.65 (ethyl acetate/hexane: 1:4); IR (KBr film)/cm^{-1}: ν_{max}=1710, 1695 and 1620; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.29 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.40 [s, 9H, C(CH_3)$_3$], 1.57–2.36 (m, 2×2H, CH–CH_2–CH_2), 1.89 [CH=C(CH_3)–CO], 3.28–3.54 (m, 2H, N–CH_2), 4.20 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 5.01 (m, 1H, N–C*H*), 6.57 [d, $^3J_{H-H}$=6.5 Hz, 1H, C*H*=C(CH_3)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C= 12.7 [CH=C(CH_3)–CO], 14.3 (O–CH_2–CH_3), 23.1 (CH–CH_2–CH_2), 28.0 [3C, C(CH_3)$_3$], 32.5 (CH–CH_2–CH_2), 45.8 (N–CH_2), 57.0 (N–*C*H), 61.1 (O–CH_2–CH_3), 77.1 [$C(CH_3)_3$], 129.7 [CH=$C(CH_3)$–CO], 137.1 [*C*H=C(CH_3)–CO], 154.4 (*C*O Boc), 169.2 (*C*OOEt).

4.5.8. [L-(*trans*)]-/[L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[1′-ethenyl-2′-chloro-2′-ethoxycarbonyl]-pyrrolidine 5r. Yield: 520 mg (95%); colourless oil (*trans*/*cis*: 33:67) obtained with phosphonate **6b**; R_f=0.65 (ethyl acetate/hexane: 1:4); IR (KBr film)/cm^{-1}: ν_{max}=1710, 1695 and 1620. *cis* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.35 (t, $^3J_{H-H}$=7.2 Hz, 3H, O–CH_2–CH_3), 1.41 [s, 9H, C(CH_3)$_3$], 1.64–2.91 (m, 2×2H, CH–CH_2–CH_2), 3.22–3.51 (m, 2H, N–CH_2), 4.46 (q, $^3J_{H-H}$=7.2 Hz, 2H, O–CH_2–CH_3), 5.55 (m, 1H, N–C*H*), 6.34 (d, $^3J_{H-H}$=8.3 Hz, 1H, C*H*=CCl–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=13.6 (O–CH_2–CH_3), 23.7 (CH–CH_2–CH_2), 28.0 [3C, C(CH_3)$_3$], 32.2 (CH–CH_2–CH_2), 46.2 (N–CH_2), 55.9 (N–*C*H), 61.7 (O–CH_2–CH_3), 79.3 [$C(CH_3)_3$], 121.1 (CH=*C*Cl–CO), 146.9 (*C*H=CCl–CO), 153.9 (*C*O Boc), 161.9 (*C*OOEt). *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.34 (t, $^3J_{H-H}$=7.2 Hz, 3H, O–CH_2–CH_3), 1.41 [s, 9H, C(CH_3)$_3$], 1.64–2.91 (m, 2×2H, CH–CH_2–CH_2), 3.22–3.51 (m, 2H, N–CH_2), 4.46 (q, $^3J_{H-H}$=7.2 Hz, 2H, O–CH_2–CH_3), 4.68 (m, 1H, N–C*H*), 6.97 (d, $^3J_{H-H}$=8.3 Hz, 1H, C*H*=CCl–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C= 13.6 (O–CH_2–CH_3), 24.2 (CH–CH_2–CH_2), 28.0 [3C, C(CH_3)$_3$], 31.5 (CH–CH_2–CH_2), 46.6 (N–CH_2), 55.9 (N–*C*H), 61.9 (O–CH_2–CH_3), 79.5 [$C(CH_3)_3$], 123.3 (*C*H=CCl–CO), 143.3 (CH=*C*Cl–CO), 155.1 (*C*O Boc), 163.0 (*C*OOEt).

4.5.9. [L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[1′-ethenyl-2′-fluoro-2′-ethoxycarbonyl]-pyrrolidine 5s. Yield: 261 mg (92%) of pure *cis* isomer obtained with phosphonate **6b**; colourless oil; R_f=0.61 (ethyl acetate/hexane: 1:2); IR (KBr film)/cm^{-1}: ν_{max}=1730, 1700 and 1670; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.35 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.40 [s, 9H, C(CH_3)$_3$], 1.64–2.37 (m, 2×2H, CH–CH_2–CH_2), 3.34–3.60 (m, 2H, N–CH_2), 4.32 (q, $^3J_{H-H}$=7.2 Hz, 2H, O–CH_2–CH_3), 5.13 (dt, $^3J_{H-H}$=8.5, 5.0 Hz, 1H, N–C*H*), 5.85 (dd, $^3J_{H-H}$=8.5 Hz and $^3J_{H-F}$= 20.25 Hz, 1H, C*H*=CF–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=13.6 (O–CH_2–CH_3), 23.9 and 23.2 (CH–CH_2–CH_2), 27.8 [3C, C(CH_3)$_3$], 32.5 (CH–CH_2–CH_2), 45.9 and 46.3 (N–CH_2), 52.6 (d, $^4J_{C-F}$=4.0 Hz, 1C, N–*C*H), 61.0 (O–CH_2–CH_3), 78.9 [$C(CH_3)_3$], 125.4 (d, $^2J_{C-F}$=7.0 Hz, 1C, *C*H=CF–CO), 146.1 (d, $^1J_{C-F}$= 237 Hz, 1C, CH=*C*F–CO), 153.9 (*C*O Boc), 160.2 (d, $^2J_{C-F}$=35 Hz, 1C, *C*OOEt); ^{19}F NMR (235.35 MHz, $CDCl_3$): δ_F=−124.5 (d, $^3J_{F-H}$=20.2 Hz).

4.5.10. [L-(*trans*)]- or [L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[1′-ethenyl-2′-ethoxycarbonyl]-pyrrolidine 5w. Yield: 434 mg (77%); colourless oil (*trans*/*cis*: 16:84); obtained with phosphonate **6a** *cis* isomer: colourless oil; R_f=0.61 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=1735, 1695 and 1650; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.24 (t, $^3J_{H-H}$=7.1 Hz, 3H, O–CH_2–CH_3), 1.37 [s, 9H, C(CH_3)$_3$], 1.58–2.40 (m, 2×2H, CH–CH_2–CH_2), 3.33–3.61 (m, 2H, N–CH_2), 4.14 (q, $^3J_{H-H}$=7.1 Hz, 2H, O–CH_2–CH_3), 5.25 (m, 1H, N–C*H*), 5.69 (d, $^3J_{H-H}$=11.5 Hz, 1H, CH=C*H*–CO), 6.18 (m, 1H, C*H*=CH–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.2 (O–CH_2–CH_3), 24.7 (CH–CH_2–CH_2), 28.3 [3C, C(CH_3)$_3$], 32.8 (CH–CH_2–CH_2), 46.9 (N–CH_2), 55.3 (N–*C*H), 59.9 (O–CH_2–CH_3), 79.3 [$C(CH_3)_3$], 118.0 (CH=*C*H–CO), 152.4 (*C*H=CH–CO), 154.6 (*C*O Boc), 165.9 (*C*OOEt) *trans* isomer: colourless oil; R_f=0.44 (ethyl acetate/hexane: 1:3); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.21 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.46 [s, 9H, C(CH_3)$_3$], 1.60–2.41 (m, 2×2H, CH–CH_2–CH_2), 3.30–3.52 (m, 2H, N–CH_2), 4.21 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 4.46 (m, 1H, N–C*H*), 5.82 (d, $^3J_{H-H}$= 16.2 Hz, 1H, CH=C*H*–CO), 6.80 (m, 1H, C*H*=CH–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.2 (O–CH_2–CH_3), 24.0 (CH–CH_2–CH_2), 28.4 [3C, C(CH_3)$_3$], 31.7 (CH–CH_2–CH_2), 46.3 (N–CH_2), 55.4 (N–*C*H), 60.3 (O–CH_2–CH_3), 79.4 [$C(CH_3)_3$], 120.5 (CH=*C*H–CO), 153.4 (*C*H=CH–CO], 154.6 (*C*O Boc), 165.9 (*C*OOEt); MS (FAB^+): *m/z* calculated for $C_{12}H_{21}NO_4$ $[M]^+$ 269.2, found 270.2 $[[M+1]^+$, 60%], 214.2 $[[M+1-t$Bu$]^+$, 84%], 170.1 $[[M-CH=CH-COOEt]^+$, 100%].

4.5.11. Ethyl (*trans*)- or (*cis*)-5-[(*t*-butoxycarbonyl)amino]-2-methyl-2-pentenoate 5t. Yield: 756 mg (50%) of pure *cis* isomer obtained after a separation on a silicagel chromatographic column from 1.750 g (91%) of a (*trans*/*cis:*40:60) mixture obtained with the phosphonate **6a** and 175 mg (60%) of a (*trans*/*cis:*40:60) mixture obtained with the phosphonate **6b**. *cis* Isomer: colourless oil; R_f=0.49 (ethyl acetate/hexane: 1:5); IR (KBr film)/cm^{-1}: ν_{max}=3375,

1715, 1695 and 1625; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H= 1.32 (t, $^3J_{H-H}$=7.1 Hz, 3H, O–CH_2–CH_3), 1.45 [s, 9H, C(CH_3)$_3$], 1.92 [CH=C(CH_3)–CO], 2.51–2.73 (m, 2H, N–CH_2–CH_2), 3.11–3.34 (m, 2H, N–CH_2–CH_2), 4.21 (q, $^3J_{H-H}$=7.1 Hz, 2H, O–CH_2–CH_3), 4.75 (m, 1H, N*H*–CH_2), 5.90 [t, $^3J_{H-H}$=8.0 Hz, 1H, C*H*=C(CH_3)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.2 (O–CH_2–*C*H_3), 20.5 [CH=C(*C*H_3)–CO], 28.3 [3C, C(*C*H_3)$_3$], 29.7 (NH–CH_2–*C*H_2), 40.0 (NH–*C*H_2–CH_2), 60.3 (O–*C*H_2–CH_3), 79.0 [*C*(CH_3)$_3$], 129.7 [CH=*C*(CH_3)–CO], 138.6 [*C*H=C(CH_3)–CO], 156.0 (*C*O Boc), 167.0 (*C*OOEt); MS (EI$^+$): *m*/*z* calculated for $C_{13}H_{23}NO_4$ [M]$^+$ 257.2, found 258.1 [[M+1]$^+$, 47%], 202.0 [[M+1−*t*Bu]$^+$, 56%], [[M+1−*t*BuOCO]$^+$, 100%]. *trans* Isomer: colourless oil; R_f=0.43 (ethyl acetate/hexane: 1:5); IR (KBr film)/cm^{-1}: ν_{max}=3365, 1710 and 1625; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.13 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.28 [s, 9H, C(CH_3)$_3$], 1.69 [CH=C(CH_3)–CO], 2.15–2.33 (m, 2H, N–CH_2–CH_2), 3.01–3.16 (m, 2H, N–CH_2–CH_2), 4.02 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 5.01 (m, 1H, N*H*–CH_2), 5.57 [t, $^3J_{H-H}$=6.5 Hz, 1H, C*H*=C(CH_3)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.1 [CH=C(*C*H_3)–CO], 13.9 (O–CH_2–*C*H_3), 28.0 [3C, C(*C*H_3)$_3$], 29.0 (NH–CH_2–*C*H_2), 39.0 (NH–*C*H_2–CH_2), 60.1 (O–*C*H_2–CH_3), 78.6 [*C*(CH_3)$_3$], 129.5 [CH=*C*(CH_3)–CO], 138.0 [*C*H=C(CH_3)–CO], 155.6 (*C*O Boc), 167.5 (*C*OOEt).

4.5.12. Ethyl (*trans*)/(*cis*)-5-[(*t*-butoxycarbonyl)amino]-2-chloro-2-pentenoate 5u. Yield: 243 mg (90%); yellow oil (*trans*/*cis*: 16:84) obtained with phosphonate **6b**; R_f=0.41 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3365, 1715, 1700 and 1690. *cis* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.23 (t, $^3J_{H-H}$=7.11 Hz, 3H, O–CH_2–CH_3), 1.32 [s, 9H, C(CH_3)$_3$], 2.59–2.71 (m, 2H, N–CH_2–CH_2), 3.09–3.21 (m, 2H, N–CH_2–CH_2), 4.16 (q, $^3J_{H-H}$=7.11 Hz, 2H, O–CH_2–CH_3), 4.96 (m, 1H, N*H*–CH_2), 6.34 (t, $^3J_{H-H}$=7.9 Hz, 1H, C*H*=CCl–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=13.8 (O–CH_2–*C*H_3), 28.1 [3C, C(*C*H_3)$_3$], 30.3 (NH–CH_2–*C*H_2), 39.2 (NH–*C*H_2–CH_2), 61.8 (O–*C*H_2–CH_3), 78.9 [*C*(CH_3)$_3$], 123.6 (CH=*C*Cl–CO), 140.9 (*C*H=CCl–CO), 155.7 (*C*O Boc), 162.3 (*C*OOEt). *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.14 (t, $^3J_{H-H}$=7.14 Hz, 3H, O–CH_2–CH_3), 1.36 [s, 9H, C(CH_3)$_3$], 2.42–2.53 (m, 2H, N–CH_2–CH_2), 3.21–3.32 (m, 2H, N–CH_2–CH_2), 3.99 (q, $^3J_{H-H}$=7.14 Hz, 2H, O–CH_2–CH_3), 4.97 (m, 1H, N*H*–CH_2), 6.97 (t, $^3J_{H-H}$=7.22 Hz, 1H, C*H*=CCl–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=13.9 (O–CH_2–*C*H_3), 28.1 [3C, C(*C*H_3)$_3$], 30.3 (NH–CH_2–*C*H_2), 39.3 (NH–*C*H_2–CH_2), 62.0 (O–*C*H_2–CH_3), 79.9 [*C*(CH_3)$_3$], 121.9 (*C*H=CCl–CO), 138.8 (CH=*C*Cl–CO), 155.7 (*C*O Boc), 162.3 (*C*OOEt).

4.5.13. Ethyl (*cis*)-5-[(*t*-butoxycarbonyl)amino]-2-fluoro-2-pentenoate 5v. Yield: 310 mg (97%) yellow oil obtained with phosphonate **6b**; R_f=0.47 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3360, 1730, 1715 and 1695; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.36 (t, $^3J_{H-H}$=7.2 Hz, 3H, O–CH_2–CH_3), 1.44 [s, 9H, C(CH_3)$_3$], 2.53–2.78 (m, 2H, N–CH_2–CH_2), 3.14–3.32 (m, 2H, N–CH_2–CH_2), 4.31 (q, $^3J_{H-H}$=7.2 Hz, 2H, O–CH_2–CH_3), 4.64 (m, 1H, N*H*–CH_2), 5.90 (dt, $^3J_{H-H}$=8.0 Hz and $^3J_{H-F}$=21.2 Hz, 1H, C*H*=CF–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=14.0 (O–CH_2–*C*H_3), 26.2 (NH–CH_2–*C*H_2), 28.2 [3C, C(*C*H_3)$_3$], 39.7 (NH–*C*H_2–CH_2), 61.4 (O–*C*H_2–CH_3), 79.2 [*C*(CH_3)$_3$], 119.9 (d, $^3J_{C-F}$=19 Hz, 1C, *C*H=CF–CO), 148.0 (d, $^1J_{C-F}$=254 Hz, 1C, CH=*C*F–CO), 155.9 (*C*O Boc), 160.5 (d, $^3J_{H-H}$=50 Hz, 1C, *C*OOEt); ^{19}F NMR (235.36 MHz, CD_3COCD_3): δ_F=−120.3 (d, $^3J_{F-H}$=19 Hz, 1F).

4.6. Typical procedure for the hydrolysis of *cis*-vinylogous aminoesters 5 into *cis*-aminoacids 4

To a solution of pure *cis*-vinylogous aminoester **5** (1.20 mmol) in ethanol (6 mL) was added dropwise 2.5 equiv. (3 mL) of a 1N NaOH aqueous solution. The mixture was stirred at room temperature until TLC analysis indicated that all aminoester was reacted (2–3 h). Then 1 equiv. of a 1N HCl aqueous solution was added (1.2 mL) before the mixture was evaporated to eliminate ethanol. Then, 1.6 equiv. of a 1N HCl aqueous solution was added again (1.6 mL), keeping up the temperature below 25°C, before the aqueous layer was extracted with ethyl acetate (3×15 mL). The organic layers were combined and dried over magnesium sulfate before the solvent was removed under vacuum to leave the crude product *cis*-aminoacid **4**.

4.6.1. [L-(*cis*)]-4-[(*t*-Butoxycarbonyl)amino]-2-methyl-2-pentenoic acid 4d. Yield: 218 mg (88%); colourless oil obtained from *cis*-ester **5d**; R_f=0.42 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3360, 1700, 1680 and 1640; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.22 (d, $^3J_{H-H}$= 6.0 Hz, 3H, CH–CH_3), 1.44 [s, 9H, C(CH_3)$_3$], 1.96 [d, $^4J_{H-H}$=1.3 Hz, 3H, CH=C(CH_3)–CO], 4.52 (m, 1H, C*H*–CH_3), 4.81 (br s, 1H, N*H*–CH), 5.47 [d, $^3J_{H-H}$=10.2 Hz, 1H, C*H*=C(CH_3)–CO], 7.90 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.3 and 20.5 [CH–*C*H_3 and CH=C(*C*H_3)–CO], 28.2 [3C, C(*C*H_3)$_3$], 45.8 (*C*H–CH_3), 80.9 [*C*(CH_3)], 130.1 [CH=*C*(CH_3)–CO], 138.3 [*C*H=C(CH_3)–CO], 156.6 (*C*O Boc), 170.5 (*C*OOH); $[\alpha]_D$=+31° (*c*=1.1, $HCCl_3$); MS (EI$^+$) *m*/*z* calculated for $C_{11}H_{19}NO_4$ [M]$^+$ 229.13, found 230.1 [[M+1]$^+$, 12%], 173.6 [[M+1−*t*Bu]$^+$, 39%], 129.3 [[M+1−*t*BuOCO]$^+$, 34%], 112.2 [[M+1−*t*BuOCO–OH]$^+$, 100%].

4.6.2. [L-(*cis*)]-4-[(*t*-Butoxycarbonyl)amino]-2,5-dimethyl-2-hexenoic acid 4j. Yield: 240 mg (90%) colourless oil obtained from *cis*-ester **5j**; R_f=0.48 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3325, 1710, 1695 and 1645; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=0.90 (d, $^3J_{H-H}$= 6.75 Hz, 3H, CH–CH_3), 0.95 (d, $^3J_{H-H}$=6.7 Hz, 3H, CH–CH_3), 1.42 [s, 9H, C(CH_3)$_3$], 1.71 [m, 1H, C*H*(CH_3)$_2$], 1.97 [s, 3H, CH=C(CH_3)–CO], 4.14 (m, 1H, NH–C*H*–CH=), 4.81 (br s, 1H, N*H*), 5.47 [d, $^3J_{H-H}$=10 Hz, 1H, C*H*=C(CH_3)–CO], 9.71 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=18.5 and 18.8 [2C, CH(*C*H_3)$_2$], 20.8 [CH=C(*C*H_3)–CO], 28.3 [3C, C(*C*H_3)$_3$], 31.9 [*C*H(CH_3)$_2$], 55.7 (NH–*C*H–CH=), 81.1 [*C*(CH_3)$_3$], 132.3 [CH=*C*(CH_3)–CO], 134.4 [*C*H=C(CH_3)–CO], 157.1 (*C*O Boc), 170.4 (*C*OOH); MS (FAB$^-$) *m*/*z* calculated for $C_{13}H_{22}NO_4$ [M−H]$^-$ 256.2, found 256.1 (100%). $[\alpha]_D$= +42° (*c*=1.0, $HCCl_3$).

4.6.3. (*cis*)-4-[(*t*-Butoxycarbonyl)amino]-2-methyl-2-butenoic acid 4l. Yield: 189 mg (90%); colourless oil from *cis*-ester **5l**; R_f=0.55 (ethyl acetate); IR (KBr film)/

cm^{-1}: ν_{max}=3330, 1685, 1660 and 1520; ^1H NMR (250 MHz, $CDCl_3$): δ_H=1.43 [s, 9H, C(CH_3)$_3$], 1.91 [s, 3H, CH=C(CH_3)–CO], 4.05 (t, $^3J_{H-H}$=6.0 Hz, 2H, NH–CH_2), 5.09 (br s, 1H, NH–CH_2), 6.05 [m, 1H, CH=C(CH_3)–CO], 9.47 (br s, 1H, COOH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.0 [CH=C(*C*H_3)–CO], 28.3 [3C, C(*C*H_3)$_3$], 39.7 (NH–*C*H_2), 79.9 [*C*(CH_3)$_3$], 129.4 [CH=*C*(CH_3)–CO], 140.9 [*C*H=C(CH_3)–CO], 156.6 (*C*O Boc), 171.5 (*C*OOH); MS (CI^-) *m*/*z* calculated for $C_{10}H_{16}NO_4$ $[M-H]^-$ 214.12, found 214.2 (7%), 157.6 [[M−H–*t*BuO]$^-$, 35%], 114.3 [[M−H–*t*BuOCO]$^-$, 39%], 56.9 [[tBu−H]$^-$, 85%], 40.7 [[C_3H_5–H]$^-$, 100%].

4.6.4. [L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[1′-ethenyl-2′-methyl-2′-carboxy]-pyrrolidine 4p. Yield: 617 mg (80%) colourless oil from *cis*-ester 5p; R_f=0.48 (ethyl acetate/hexane: 1:1) IR (KBr film)/cm^{-1}: ν_{max}=3030, 1715, 1695 and 1640; ^1H NMR (250 MHz, $CDCl_3$): δ_H=1.47 [s, 9H, C(CH_3)$_3$], 1.62–2.19 (m, 2×2H, CH–CH_2–CH_2), 1.99 [s, 3H, CH=C(CH_3)–CO], 3.23–3.57 (m, 2H, N–CH_2), 4.55 (m, 1H, N–C*H*), 5.42 [d, *J*=11.0 Hz, 1H, C*H*=C(CH_3)–CO], 11.31 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=21.2 [CH=C(*C*H_3)–CO], 24.4 (CH–CH_2–*C*H_2), 28.9 [3C, C(*C*H_3)$_3$], 32.8 (CH–*C*H_2), 47.5 (N–*C*H_2), 56.2 (N–*C*H), 81.9 [*C*(CH_3)$_3$], 132.6 [CH=*C*(CH_3)–CO], 134.5 [*C*H=C(CH_3)–CO], 156.5 (*C*O Boc), 171.0 (*C*OOH); MS (EI^+) *m*/*z* calculated for $C_{13}H_{21}NO_4$ $[M]^+$ 255.2, found 256.2 [[M+1]$^+$, 39%], 154.1 [[M−*t*BuOCO]$^+$, 49%], 200.0 [[M+1−*t*Bu]$^+$, 55%], 109.9 [[M+1−*t*BuOCO–COOH]$^+$, 75%], 137.9 [[M+1−*t*BuOCO–OH]$^+$, 80%], 56.9 [[*t*Bu]$^+$, 100%]; $[\alpha]_D$=+25° (*c*=1.4, $HCCl_3$).

4.6.5. [L-(*cis*)]-*N*-(*t*-Butoxycarbonyl)-2-[1′-ethenyl-2′-carboxy]-pyrrolidine 4w. Yield: 920 mg (80%) as an oil obtained from *cis*-ester **5w**; R_f=0.10 (ethyl acetate/hexane: 4:1); IR (KBr film)/cm^{-1}: ν_{max}=1720, 1695 and 1650; ^1H NMR (250 MHz, $CDCl_3$): δ_H=1.41 [s, 9H, C(CH_3)$_3$], 1.63–2.39 (m, 2×2H, CH–CH_2–CH_2), 3.34–3.52 (m, 2H, N–CH_2), 4.84 (m, 1H, N–C*H*), 5.31 (m, 1H, C*H*=CH–CO), 5.80 (m, 1H, CH=C*H*–CO), 9.45 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=24.2 (CH–CH_2–*C*H_2), 28.7 [3C, C(*C*H_3)$_3$], 31.4 (CH–*C*H_2), 45.3 (N–*C*H_2), 55.7 (N–*C*H), 79.8 [*C*(CH_3)$_3$], 127.6 (CH=*C*H–CO), 129.5 (*C*H=CH–CO), 154.3 (*C*O Boc), 169.0 (*C*OOH); $[\alpha]_D$=+30° (*c*=1.3, $HCCl_3$).

4.6.6. (*cis*)-5-[(*t*-Butoxycarbonyl)amino]-2-methyl-2-pentenoic acid 4t. Yield: 68 mg (96%); colourless oil from *cis*-ester **5t**; R_f=0.57 (ethyl acetate); IR (KBr film)/cm^{-1}: ν_{max}=3370, 1695 and 1645; ^1H NMR (250 MHz, $CDCl_3$): δ_H=1.42 [s, 9H, C(CH_3)$_3$], 2.02 [d, $^4J_{H-H}$=1.0 Hz, 3H, CH=C(CH_3)–CO], 2.67 (dt, $^3J_{H-H}$=6.9 Hz, $^3J_{H-H}$=6.9 Hz, 2H, CH_2–CH=), 3.08–3.32 (m, 2H, NH–CH_2), 4.80 (br s, 1H, NH–CH_2), 6.01 [m, 1H, CH=C(CH_3)–CO], 10.6 (br s, 1H, COO*H*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.5 [CH=C(*C*H_3)–CO], 28.4 [3C, C(*C*H_3)$_3$], 30.1 (*C*H_2–CH=), 39.9 (N–*C*H_2), 79.2 [*C*(CH_3)$_3$], 128.9 [CH=*C*(CH_3)–CO], 141.7 [*C*H=C(CH_3)–CO], 156.2 (*C*O Boc), 172.8 (*C*OOH); MS (EI^+) *m*/*z* calculated for $C_{11}H_{19}NO_4$ $[M]^+$ 229.1, found 230.2 [[M+1]$^+$, 10%], 130.0 [[M−*t*BuOCO]$^+$, 40%], 173.9 [[M+H−*t*Bu]$^+$, 45%], 112.0 [[M+H–*t*BuOCO–OH]$^+$, 63%], 56.9 [[*t*Bu]$^+$, 100%].

4.7. Coupling of *N*-protected vinylogous aminoacids 4 with aminoacid derivatives

The procedure was similar to that employed above to synthesize the vinylogous aminoamides **4′**. The crude products **1** were purified on a silica gel chromatographic column.

4.7.1. (*trans*)-*N*-[4(*S*)-4-[*N*-(*t*-Butoxycarbonylamino)]-1-oxo-2-pentenyl]-L-valine methyl ester 1ca. Yield: 140 mg (76%); white solid obtained from **4c** (*trans*/*cis* >98:2); mp 118°C; R_f=0.47 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3440, 3350, 1735, 1700, 1685 and 1635; ^1H NMR (250 MHz, $CDCl_3$): δ_H=0.92 and 0.95 [2d, $^3J_{H-H}$=6.75 Hz, 2×3H, CH(CH_3)$_2$], 1.26 (d, $^3J_{H-H}$=6.75 Hz, 3H, CH–CH_3), 1.45 [s, 9H, C(CH_3)$_3$], 2.20 [m, 1H, C*H*(CH_3)$_2$], 3.74 (s, 3H, O–CH_3), 4.39 (m, 1H, C*H*–CH_3), 4.58 (m, 1H, N*H*–CH–CH_3), 4.64 [dd, $^3J_{H-H}$=8.75, 4.75 Hz, 1H, C*H*–CH(CH_3)$_2$], 5.94 (dd, $^3J_{H-H}$=15.3, 5.25 Hz, 1H, CH=C*H*–CO), 6.05 (d, $^3J_{H-H}$=8.75 Hz, 1H, N*H*–CH), 6.75 (dd, $^3J_{H-H}$=15.3, 5.25 Hz, 1H, C*H*=CH–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=17.8 (CH–*C*H_3), 18.9 and 20.2 [2C, CH(*C*H_3)$_2$], 28.3 [3C, C(*C*H_3)$_3$], 31.2 [*C*H(CH_3)$_2$], 47.0 [*C*H–CH(CH_3)$_2$], 52.1 (*C*H–CH=), 57.1 (O–*C*H_3), 79.4 [*C*(CH_3)$_3$], 122.7 (CH=*C*H–CO), 145.8 (*C*H=CH–CO), 155.1 (*C*O Boc), 166.2 (*C*O–NH), 172.5 (*C*OOCH$_3$); $[\alpha]_D$=+6.7° (*c*=1.1, $HCCl_3$); MS (EI^+): *m*/*z* calculated for $C_{16}H_{28}N_2O_5$ $[M]^+$ 328.2, found 329.3 [[M+1]$^+$,100%].

4.7.2. (*trans*)-*N*-[4(*S*)-4-[*N*-(*t*-Butoxycarbonylamino)]-1-oxo-2-pentenyl]-glycine methyl ester 1cb. Yield: 365 mg (92%); white solid obtained from **4c** (*trans*/*cis* > 98:2); mp 92°C; R_f=0.48 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3435, 3320, 3050, 1750, 1715, 1680 and 1635. *trans* Isomer: ^1H NMR (250 MHz, $CDCl_3$): δ_H=1.26 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.44 [s, 9H, C(CH_3)$_3$], 3.77 (s, 3H, O–CH_3), 4.11 (d, $^3J_{H-H}$=5.0 Hz, 2H, CH_2), 4.40 (m, 1H, C*H*–CH_3), 4.61 (m, 1H, N*H*–CH–CH_3), 5.96 (d, $^3J_{H-H}$=15.5 Hz, 1H, CH=C*H*–CO), 6.31 (d, $^3J_{H-H}$=5.0 Hz, 1H, N*H*–CH_2), 6.78 (dd, $^3J_{H-H}$=15.5, 5.0 Hz, 1H, C*H*=CH–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.0 (CH–*C*H_3), 28.1 [3C, C(*C*H_3)$_3$], 40.8 (*C*H_2), 46.7 (*C*H–CH_3), 51.9 (O–*C*H_3), 79.5 [*C*(CH_3)$_3$], 121.7 (CH=*C*H–CO), 145.5 (*C*H=CH–CO), 154.9 (*C*O Boc), 165.8 (*C*O–NH), 170.3 (*C*OOCH$_3$); $[\alpha]_D$=+2.2° (*c*=1.2, $HCCl_3$); MS (EI^+): *m*/*z* calculated for $C_{13}H_{22}N_2O_5$ $[M]^+$ 286.2, found 287.2 [[M+1]$^+$, 50%], 97.1 [[M−*t*BuOCONH–l CH_2COOCH_3]$^+$, 83%], 231.1 [[M+1−*t*Bu]$^+$, 83%].

4.7.3. (*trans*)/(*cis*)-*N*-[4(*S*)-4-[*N*-(*t*-Butoxycarbonylamino)]-2-fluoro-1-oxo-2-pentenyl]-glycine methyl ester 1ia. Yield: 242 mg (93%); white solid (*trans*/*cis*: 35:65); obtained from **4i** (*trans*/*cis*: 35:65); R_f=0.45 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3355, 3000, 1755, 1695 and 1660; MS (CI^-): *m*/*z* calculated for $C_{13}H_{20}N_2O_5$ $[M-H]^-$ 303.1, found 303.2 (100%). *trans* Isomer: ^1H NMR (250 MHz, CD_3COCD_3): δ_H=1.28 (d, $^3J_{H-H}$=6.25 Hz, 3H, CH–CH_3), 1.39 [s, 9H, C(CH_3)$_3$], 3.71 (s, 3H, O–CH_3), 4.38 (m, 1H, C*H*–CH_3), 4.61 (m, 1H, N*H*–CH–CH_3), 6.01 (dd, $^3J_{H-F}$=35 Hz and $^3J_{H-H}$=9.0 Hz, 1H, C*H*=CF–CO), 6.21 (d, $^3J_{H-H}$=7.5 Hz, 1H, N*H*–CH), 7.95 (d, $^3J_{H-H}$=6.0 Hz, 1H, N*H*–CH_2); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.7

(CH–CH_3), 28.3 [3C, C(CH_3)$_3$], 40.7 (CH_2), 41.8 (CH–CH_3), 53.4 (O–CH_3), 79.8 [$C(CH_3)_3$], 118.4 (d, $^2J_{C-F}$=8.5 Hz, 1C, CH=CF–CO), 149.5 (d, $^1J_{C-F}$=268 Hz, 1C, CH=CF–CO), 155.4 (CO Boc), 159.9 (d, $^2J_{C-F}$=5.8 Hz, 1C, CO–NH), 169.6 ($COOCH_3$); ^{19}F NMR (235.36 MHz, CD_3COCD_3): δ_F=−127.8 (d, $^3J_{F-H}$=35 Hz, 1F). *cis* Isomer: ^{1}H NMR (250 MHz, CD_3COCD_3): δ_H=1.28 (d, $^3J_{H-H}$=6.25 Hz, 3H, CH–CH_3), 1.39 [s, 9H, C(CH_3)$_3$], 3.71 (s, 3H, O–CH_3), 4.07 (d, $^3J_{H-H}$=6.0 Hz, 2H, CH_2), 5.21 (m, 1H, CH–CH_3), 5.78 (dd, $^3J_{H-F}$=15 Hz and $^3J_{H-H}$=9.0 Hz, 1H, CH=CF–CO), 6.25 (br s, 1H, NH–CH), 8.28 (d, $^3J_{H-H}$=6.0 Hz, 1H, NH–CH_2); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.7 (CH–CH_3), 28.3 [3C, C(CH_3)$_3$], 41.0 (CH_2), 41.8 (CH–CH_3), 52.5 (O–CH_3), 79.8 [$C(CH_3)_3$], 118.4 (d, $^2J_{C-F}$=8.5 Hz, 1C, CH=CF–CO), 149.5 (d, $^1J_{C-F}$=268 Hz, 1C, CH=CF–CO), 154.8 (CO Boc), 159.9 (d, $^2J_{C-F}$=5.8 Hz, 1C, CO–NH), 169.6 ($COOCH_3$); ^{19}F NMR (235.36 MHz, CD_3COCD_3): δ_F=−119.8 (d, $^3J_{F-H}$=15 Hz, 1F).

4.7.4. (*trans*)/(*cis*)-*N*-[4(*S*)-4-[*N*-(*t*-Butoxycarbonylamino)]-2-ethoxy-1-oxo-2-pentenyl]-glycine methyl ester 1ga. Yield: 221 mg (80%); colourless oil (*trans*/*cis*: 45:55); obtained from **4g** (*trans*/*cis*: 45:55); R_f=0.55 (ethyl acetate/hexane: 4:1); IR (KBr plate)/cm^{-1}: ν_{max}=3460, 1750, 1700, 1675 and 1645 *trans* isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.18 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.32 (t, $^3J_{H-H}$=7.0 Hz, 3H, O–CH_2–CH_3), 1.39 [s, 9H, C(CH_3)$_3$], 3.69 (s, 3H, O–CH_3), 3.89 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 3.94 (d, $^3J_{H-H}$=6.0 Hz, 2H, CH_2), 4.55 (m, 1H, CH–CH_3), 5.36 (d, $^3J_{H-H}$=7.0 Hz, 1H, NH–CH–CH_3), 5.93 [d, $^3J_{H-H}$=9.0 Hz, 1H, CH=C(OEt)–CO], 7.21 (d, $^3J_{H-H}$=6.0 Hz, 1H, NH–CH_2). *cis* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.18 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.32 (t, $^3J_{H-H}$=7.3 Hz, 3H, O–CH_2–CH_3), 1.39 [s, 9H, C(CH_3)$_3$], 3.69 (s, 3H, O–CH_3), 3.85 (q, $^3J_{H-H}$=7.0 Hz, 2H, O–CH_2–CH_3), 3.94 (d, $^3J_{H-H}$=6.0 Hz, 2H, CH_2), 4.96 [d, 1H, CH=C(OEt)–CO], 5.08 (m, 1H, CH–CH_3), 5.36 (d, $^3J_{H-H}$=7.0 Hz, 1H, NH–CH), 7.71 (br s, 1H, NH–CH_2).

4.7.5. (*trans*)/(*cis*)-*N*-[4(*S*)-4-[*N*-(*t*-Butoxycarbonylamino)]-2-methyl-1-oxo-2-pentenyl]-L-alanine methyl ester 1da. Yield: 128 mg (55%); colourless oil (*trans*/*cis*: 60:40) obtained from **4d** (*trans*/*cis*: 60:40); R_f=0.72 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3355, 1760, 1715, 1680 and 1625; MS (EI$^+$): *m*/*z* calculated for $C_{15}H_{25}N_2O_5$ [M]$^+$ 314.2, found 315.2 [[M+1]$^+$, 14%], 138.0 [[M+1−*t*BuO–HAlaOCH$_3$]$^+$or [M+1−*t*BuOCONH–$COOCH_3$]$^+$, 19%], 83.0 [[M−*t*BuOCO–CONHCH(CH$_3$)OCH$_3$]$^+$, 21%], 104.0 [[HAlaOCH$_3$]$^+$, 40%], 259.1 [[M−*t*Bu]$^+$, 50%], 111.1 [[M−*t*BuOCO–CONHCH(CH$_3$)OCH$_3$]$^+$, 100%]. *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.24 (d, $^3J_{H-H}$=6.5 Hz, 3H, CH–CH_3), 1.45 [s, 9H, C(CH_3)$_3$], 1.46 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.97 [s, 3H, CH=C(CH_3)–CO], 3.78 (s, 3H, O–CH_3), 4.41–4.64 (m, 2H, CH–CH_3 and NH–CH–CH_3), 4.65 (m, 1H, CH–CH_3), 6.22 (m, 1H, NH), 6.35 (d, $^3J_{H-H}$=7.5 Hz, 1H, CH=C(CH$_3$)–CO); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.7 [CH=C(*C*H$_3$)–CO], 18.3 (CH–*C*H$_3$), 20.9 [CH(*C*H$_3$)–CH=], 28.3 [3C, C(*C*H$_3$)$_3$], 45.1 [*C*H(CH$_3$)–CH=], 48.1 (*C*H–CH$_3$), 52.5 (O–*C*H$_3$), 79.5 [*C*(CH$_3$)$_3$], 130.5 [CH=*C*(CH$_3$)–CO], 138.1 [*C*H=C(CH$_3$)–CO], 155.0 (*C*O Boc), 168.1 (*C*O–NH), 173.7 (*C*OOCH$_3$); *cis* isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.21 (d, $^3J_{H-H}$=6.8 Hz, 3H, CH–CH_3), 1.45 [s, 9H, C(CH_3)$_3$], 1.46 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.92 [s, 3H, CH=C(CH_3)–CO], 3.74 (s, 3H, O–CH_3), 4.41–4.64 (m, 2H, CH–CH_3 and NH–CH–CH_3), 4.85 (m, 1H, CH–CH_3), 5.25 (d, $^3J_{H-H}$=11 Hz, 1H, CH=C(CH$_3$)–CO), 9.27 (br s, 1H, NH–CH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=18.2 (CH–*C*H$_3$), 20.7 and 21.1 [CH=C(*C*H$_3$)–CO and CH(*C*H$_3$)–CH=], 28.1 [3C, C(*C*H$_3$)$_3$], 44.6 [*C*H(CH$_3$)–CH=], 48.1 (*C*H–CH$_3$), 52.5 (O–*C*H$_3$), 79.7 [*C*(CH$_3$)$_3$], 130.5 [CH=*C*(CH$_3$)–CO], 144.8 [*C*H=C(CH$_3$)–CO], 156.4 (*C*O Boc), 168.1 (*C*O–NH), 173.7 (*C*OOCH$_3$).

4.7.6. (*trans*)/(*cis*)-*N*-[4(*S*)-4-[*N*-(*t*-Butoxycarbonylamino)]-2-methyl-1-oxo-2-pentenyl]-L-aspartic acid dimethyl ester 1db. Yield: 194 mg (70%) colourless oil (*trans*/*cis*: 60:40) obtained from **4d** (*trans*/*cis*: 60:40); R_f=0.70 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3345, 1750, 1710, 1665 and 1630; MS [EI$^+$]: *m*/*z* calculated for $C_{17}H_{28}N_2O_7$ [M]$^+$ 372.2, found 373.3 [[M+1]$^+$, 72%], 111.0 [[M−tBuOCO–HAsp(OCH$_3$)OCH$_3$]$^+$, 100%]. *trans* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.19 (d, $^3J_{H-H}$=6.7 Hz, 3H, CH–CH_3), 1.40 [s, 9H, C(CH_3)$_3$], 1.92 [s, 3H, CH=C(CH_3)–CO], 2.98 (AB part of an ABX system, ν_A=2.94, ν_B=2.96, $^3J_{AB}$=17.2 Hz, $^3J_{AX}$=4.5 Hz and $^3J_{BX}$=4.3 Hz, 2H, CH_2–$COOCH_3$), 3.67 and 3.74 (2s, 6H, O–CH_3), 4.46 [m, 1H, CH(CH$_3$)–CH=], 4.62 (m, 1H, NH–CH–CH_3), 4.87 (ddd, $^3J_{H-H}$=7.75, 4.5, 4.3 Hz, 1H, CH–CH_2), 6.20 [d, $^3J_{H-H}$=8.3 Hz, 1H, CH=C(CH$_3$)–CO], 6.82 (d, $^3J_{H-H}$=7.75 Hz, 1H, NH–CH–CH_2); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.6 [CH=C(*C*H$_3$)–CO], 18.2 (CH–*C*H$_3$), 28.3 [3C, C(*C*H$_3$)$_3$], 35.9 (*C*H$_2$), 45.1 [*C*H(CH$_3$)–CH=], 48.6 (*C*H–CH_2), 52.0 and 52.7 (2C, 2×O–*C*H$_3$), 79.9 [*C*(CH$_3$)$_3$], 130.2 [CH=*C*(CH$_3$)–CO], 138.6 [*C*H=C(CH$_3$)–CO], 155.0 (*C*O Boc), 168.2 (*C*O–NH), 171.2 and 171.6 (2C, 2×*C*OOCH$_3$). *cis* Isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.25 (d, $^3J_{H-H}$=6.7 Hz, 3H, CH–CH_3), 1.44 [s, 9H, C(CH_3)$_3$], 1.88 [s, 3H, CH=C(CH_3)–CO], 2.88 (d, $^3J_{AB}$=6.61 Hz, 2H, CH_2–$COOCH_3$), 3.67 and 3.71 (2s, 6H, O–CH_3), 4.36–4.95 [m, 3H, NH–CH–CH_2 and NH–CH–CH_3), 5.25 [d, $^3J_{H-H}$=9.25 Hz, 1H, CH=C(CH$_3$)–CO], 9.22 (br s, 1H, NH–CH–CH_2); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=19.9 and 20.9 [CH–*C*H$_3$ and CH=C(*C*H$_3$)–CO], 28.1 [3C, C(*C*H$_3$)$_3$], 44.4 [*C*H(CH$_3$)–CH=], 48.9 (*C*H–CH_2), 51.9 and 52.4 (2C, 2×O–*C*H$_3$), 79.7 [*C*(CH$_3$)$_3$], 130.5 [CH=*C*(CH$_3$)–CO], 144.7 [*C*H=C(CH$_3$)–CO], 156.4 (*C*O Boc), 168.2 (*C*O–NH), 171.2 and 171.6 (2C, 2×*C*OOCH$_3$).

4.7.7. (*trans*)-*N*-[4-[*N*-(*t*-Butoxycarbonylamino)]-1-oxo-2-butenyl]-glycine methyl ester 1ka. Yield: 377 mg (78%); colourless oil; R_f=0.40 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3310, 1750, 1685, 1680 and 1635; MS (EI$^+$): *m*/*z* calculated for $C_{12}H_{20}N_2O_5$ [M]$^+$ 272.1, found 273.1 [[M+1]$^+$, 8%], 126.9 [[M+1−*t*Bu–$NH_2CH_2COOCH_3$]$^+$, 17%], 156.1 [[M−*t*BuOCONH]$^+$, 23%], 217.1 [[M+1−*t*Bu]$^+$, 44%], 83.1 [[M−*t*BuO-CONH–CH_2COOCH_3]$^+$, 100%].^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.42 [s, 9H, C(CH_3)$_3$], 3.67 (s, 3H, O–CH_3), 3.76–3.85 (m, 2H, CH_2–CH=), 4.02 (d, $^3J_{H-H}$=6.0 Hz, 2H, NH–CH_2), 6.12 (dt, $^3J_{H-H}$=15.3 Hz and $^4J_{H-H}$=1.5 Hz, 1H, CH=CH–CO), 6.21 (br s, 1H, NH–CH_2–CH=), 6.75 (dt,

$^3J_{H-H}$=15.3, 4.25 Hz, 1H, CH_2–C*H*=CH), 7.62 (br s, 1H, N*H*–CH_2); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=28.1 [3C, C(CH_3)$_3$], 40.9 (2C, *C*H_2), 52.1 (O–*C*H_3), 79.4 [*C*(CH_3)$_3$], 122.9 (CH=*C*H–CO), 141.3 (*C*H=CH–CO), 155.7 (*C*O Boc), 165.7 (*C*O–NH), 170.5 (*C*OOCH$_3$).

4.7.8. (*trans*)-*N*-[4(*S*)-4-[*N*-(*t*-Butoxycarbonylamino)]-1-oxo-5-phenyl-2-pentenyl]-glycine methyl ester 1ma. Yield: 328 mg (82%); white solid; mp 130°C; R_f=0.52 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3430, 3315, 3035, 1750, 1715, 1685 and 1635; MS (CI$^-$): *m/z* calculated for $C_{19}H_{25}N_2O_5$ [M−H]$^-$ 361.2, found 361.3 (100%). ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.39 [s, 9H, C(CH_3)$_3$], 2.88 (d, $^3J_{H-H}$=5.7 Hz, 2H, CH_2-Ph), 3.77 (s, 3H, O–CH_3), 4.10 (d, $^3J_{H-H}$=5.1 Hz, 2H, CH_2), 4.38–4.71 (m, 2×1H, N*H*–C*H*–CH=), 5.86 (d, $^3J_{H-H}$=15.1 Hz, 1H, CH=C*H*–CO), 6.03 (br s, 1H, N*H*–CH_2), 6.83 (dd, $^3J_{H-H}$=15.1, 4.5 Hz, 1H, C*H*=CH–CO), 7.09–7.35 (m, 5H, *Ph*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=28.3 [3C, C(*C*H_3)$_3$], 41.0 and 41.3 (2C, *C*H_2 and *C*H_2-Ph), 52.4 (O–*C*H_3), 79.9 [*C*(CH_3)$_3$], 122.7 (CH=*C*H–CO), 126.8, 128.5 (2C), 129.4 (2C) and 136.5 (*Ph*), 144.3 (*C*H=CH–CO), 155.0 (*C*O Boc), 165.2 (*C*O–NH), 170.4 (*C*OOCH$_3$).

4.7.9. 2(*S*)-(*trans*)- or 2(*S*)-(*cis*)-*N*-(*t*-Butoxycarbonyl)-2-[2′-methyl-3′-oxo-1′-propenyl-3′-(*N*-isopropyl-L-alaninyl-amido)]pyrrolidine 1pa. *Trans* isomer: yield: 178 mg (84%) white solid obtained from pure *trans*-**4p**; mp 114°C; R_f=0.42 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3330, 1695, 1660 and 1620; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.12 [d, $^3J_{H-H}$=8.5 Hz, 6H, CH(CH_3)$_2$], 1.36 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.37 [s, 9H, C(CH_3)$_3$], 1.88 [s, 3H, CH=C(CH_3)–CO], 1.53–2.18 (m, 2×2H, CH–CH_2–CH_2), 3.27–3.57 (m, 2H, N–CH_2), 4.01 [m, 1H, C*H*(CH$_3$)$_2$], 4.47 (m, 1H, C*H*–CH$_3$), 4.60 (m, 1H, N–C*H*), 6.25 (m, 1H, N*H*–CH–CH$_3$), 6.76 [d, $^3J_{H-H}$=7.5 Hz, 1H, C*H*=C(CH$_3$)–CO], 7.01 (d, $^3J_{H-H}$=7.0 Hz, 1H, N*H*-*i*Pr); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.7 (CH–*C*H$_3$), 19.4 [CH=C(*C*H$_3$)–CO], 22.5 [CH(*C*H$_3$)$_2$], 23.6 (CH–CH$_2$–*C*H$_2$), 28.4 [3C, C(*C*H$_3$)$_3$], 32.6 (CH–*C*H$_2$–CH$_2$), 41.3 [*C*H(CH$_3$)$_2$], 46.4 (N–*C*H$_2$), 49.0 (*C*H–CH$_3$), 55.0 (N–*C*H), 79.3 [*C*(CH$_3$)$_3$], 129.2 [CH=*C*(CH$_3$)–CO], 138.0 [*C*H=C(CH$_3$)–CO], 154.2 (*C*O Boc), 168.2 (*C*O–NH), 171.5 (*C*ONH*i*Pr); [α]$_D$=−29.6° (*c*=0.4, $HCCl_3$); MS (FAB$^+$): *m/z* calculated for $C_{19}H_{33}N_3O_4$ [M]$^+$ 367.2, found 368.2 [[M+H]$^+$, 30%], 735.5 [[M+H+M]$^+$, 28%], 500.1 [[M+H+NHCH(CH$_3$)CONH*i*Pr]$^+$, 40%], 312.2 [[M+H−*t*Bu]$^+$, 44%], 138.1 [[M+H−*t*BuOCO–NHCH(CH$_3$)CONH*i*Pr]$^+$, 100%]. *cis* Isomer: yield: 69 mg (76%); white solid obtained from pure *cis*-**4p**; mp 99°C; R_f=0.47 (ethyl acetate); IR (KBr plate)/cm^{-1}: ν_{max}=3400, 3305, 1695, 1660 and 1620; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.01 [d, $^3J_{H-H}$=6.5 Hz, 2×3H, CH(CH_3)$_2$], 1.39 (d, $^3J_{H-H}$=6.0 Hz, 3H, CH–CH_3), 1.46 [s, 9H, C(CH_3)$_3$], 1.93 [d, $^4J_{H-H}$=1.0 Hz, 3H, CH=C(CH_3)–CO], 1.57–2.12 (m, 2×2H, CH–CH_2–CH_2), 3.27–3.46 (m, 2H, N–CH_2), 4.06 [m, 1H, C*H*(CH$_3$)$_2$], 4.40 (m, 1H, C*H*–CH$_3$), 4.57 (m, 1H, N–C*H*), 5.29 [d, $^3J_{H-H}$=10.5 Hz, 1H, C*H*=C(CH$_3$)–CO], 6.73 (d, $^3J_{H-H}$=7.0 Hz, 1H, N*H*-*i*Pr), 9.45 (d, $^3J_{H-H}$=7.0 Hz, 1H, N*H*–CH–CH$_3$); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=16.2 (CH–*C*H$_3$), 21.0 [CH=C(*C*H$_3$)–CO], 22.8 and 23.0 [2C, CH(*C*H$_3$)$_2$], 24.1 (CH–CH$_2$–*C*H$_2$), 28.7 [3C, C(*C*H$_3$)$_3$], 32.9 (CH–*C*H$_2$–CH$_2$), 41.3 [*C*H(CH$_3$)$_2$], 47.1 (N–*C*H$_2$), 49.2 (*C*H–CH$_3$), 55.5 (N–*C*H), 78.1 [*C*(CH$_3$)$_3$], 130.5 [*C*H=C(CH$_3$)–CO], 134.0 [CH=*C*(CH$_3$)–CO], 155.7 (*C*O Boc), 170.2 (*C*O–NH), 172.2 (*C*ONH*i*Pr); [α]$_D$=0.0° (*c*=0.9, $HCCl_3$); MS (EI$^+$): *m/z* calculated for $C_{19}H_{33}N_3O_5$ [M]$^+$ 367.2, found 368 [[M+1]$^+$, 9%], 238 [[M−NHCH(CH$_3$)CONH*i*Pr]$^+$, 22%], 181 [[M−*t*BuOCO–CONH*i*Pr]$^+$, 61%], 138 [[M−*t*BuOCO–NHCH(CH$_3$)CONH*i*Pr]$^+$, 85%], 57 [[M−*t*Bu]$^+$, 100%].

4.7.10. 2(*S*)-(*trans*)- or 2(*S*)-(*cis*)-*N*-(*t*-Butoxycarbonyl)-2-[2′-methyl-3′-oxo-1′-propenyl-3′-L-(*O*-methyl-alaninyl)]-pyrrolidine 1pb. *Trans* isomer: yield: 68 mg (80%); colourless oil obtained from pure *trans*-**4p**; R_f=0.24 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3325, 1745, 1695, 1675 and 1630; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.43 [s, 9H, C(CH_3)$_3$], 1.44 (d, $^3J_{H-H}$=6.7 Hz, 3H, CH–CH_3), 1.94 [s, 3H, CH=C(CH_3)–CO], 1.61–2.25 (m, 2×2H, CH–CH_2–CH_2), 3.35–3.57 (m, 2H, N–CH_2), 3.77 (s, 3H, O–CH_3), 4.58 (m, 1H, N–C*H*–CH$_2$), 4.64 (m, 1H, C*H*–CH$_3$), 6.09–6.47 [m, 2×1H, N*H*–CH–CH$_3$ and C*H*=C(CH$_3$)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.6 [CH=C(*C*H$_3$)–CO], 18.4 (CH–*C*H$_3$), 23.7 and 24.7 (CH–CH$_2$–*C*H$_2$), 28.3 [3C, C(*C*H$_3$)$_3$], 31.9 and 32.5 (CH–*C*H$_2$–CH$_2$), 46.4 (N–*C*H$_2$), 48.1 (*C*H–CH$_3$), 52.4 (O–*C*H$_3$), 55.0 (N–*C*H), 79.6 [*C*(CH$_3$)$_3$], 129.4 [CH=*C*(CH$_3$)–CO], 137.9 [*C*H=C(CH$_3$)–CO], 154.6 (*C*O Boc), 168.2 (*C*O–NH), 173.6 (*C*OOCH$_3$); [α]$_D$=−19° (*c*=0.82, $HCCl_3$); MS (EI$^+$): *m/z* calculated for $C_{17}H_{28}N_2O_5$ [M]$^+$ 340.2, found 341.4 [[M+1]$^+$, 12%], 240.4 [[M−*t*BuOCO]$^+$, 14%], 239.3 [[M+1−HAlaOCH$_3$]$^+$, 22%], 285.1 [[M+1−*t*Bu]$^+$, 79%], 137.3 [[M−*t*BuOCO–HAlaOCH$_3$]$^+$, 98%]. *cis* Isomer: yield: 46 mg (82%); white solid obtained from pure *cis*-**4p**; mp 146°C; R_f=0.50 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3245, 3050, 1670 and 1645; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.45 [s, 9H, C(CH_3)$_3$], 1.46 (d, $^3J_{H-H}$=7.2 Hz, 3H, CH–CH_3), 1.92 [d, $^4J_{H-H}$=1.3 Hz, 3H, CH=C(CH_3)–CO], 1.57–2.20 (m, 2×2H, CH–CH_2–CH_2), 3.38 (pt, $^3J_{H-H}$=6.5 Hz, 2H, N–CH_2), 3.73 (s, 3H, O–CH_3), 4.50 (dq, $^3J_{H-H}$=6.5 , 6.3 Hz, 1H, C*H*–CH$_3$), 5.04 (m, 1H, N–C*H*–CH$_2$), 5.34 [dd, $^3J_{H-H}$=10.8 Hz and $^4J_{H-H}$=1.3 Hz, 1H, C*H*=C(CH$_3$)–CO], 9.72 (d, $^3J_{H-H}$=6.3 Hz, 1H, N*H*–CH–CH$_3$); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=16.7 (CH–*C*H$_3$), 20.7 [CH=C(*C*H$_3$)–CO], 23.8 (CH–CH$_2$–*C*H$_2$), 28.4 [3C, C(*C*H$_3$)$_3$], 33.6 (CH–*C*H$_2$–CH$_2$), 47.0 (N–*C*H$_2$), 48.2 (*C*H–CH$_3$), 52.0 (O–*C*H$_3$), 55.0 (N–*C*H), 79.8 [*C*(CH$_3$)$_3$], 130.7 [*C*H=C(CH$_3$)–CO], 133.6 [CH=*C*(CH$_3$)–CO], 155.3 (*C*O Boc), 169.5 (*C*O–NH), 174.0 (*C*OOCH$_3$); [α]$_D$=+146° (*c*=0.55, $HCCl_3$); MS (EI$^+$): *m/z* calculated for $C_{17}H_{28}N_2O_5$ [M]$^+$ 340.2, found 341.1 [[M+1]$^+$, 70%], 241.0 [[M+1−*t*BuOCO]$^+$, 80%], 137.3 [[M−*t*BuOCO–HAlaOCH$_3$]$^+$, 100%].

4.7.11. 2(*S*)-(*trans*)- or 2(*S*)-(*cis*)-*N*-(*t*-Butoxycarbonyl)-2-[2′-methyl-3′-oxo-1′-propenyl-3′-L-(*O*,*O*-dimethylaspartyl)]-pyrrolidine 1pc. *Trans* isomer: yield: 45 mg (87%); colourless oil obtained from pure *trans*-**4p**; R_f=0.32 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3345, 1745, 1695, 1680 and 1635; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.40 [s, 9H, C(CH_3)$_3$], 1.91 [s, 3H, CH=C(CH_3)–CO], 1.57–2.19 (m, 2×2H, CH–CH_2–CH_2), 2.94 (AB part of an ABX pattern, ν_A=2.93, ν_B=2.95, $^3J_{AB}$=17.2 Hz, $^3J_{AX}$=4.6 Hz and $^3J_{BX}$=4.3 Hz, 2H, CH_2–COOCH$_3$), 3.32–3.58

(m, 2H, N–CH_2), 3.67 and 3.74 (2s, 2×3H, 2×O–CH_3), 4.48 (m, 1H, N–CH–CH_2), 4.87 (ddd, $^3J_{H-H}$=7.8, 4.5, 4.3 Hz, 1H, NH–CH–CH_2), 6.29 (br s, 1H, NH–CH–CH_2), 6.82 [m, 1H, CH=C(CH_3)–CO]; ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=12.4 [CH=C(*C*H_3)–CO], 24.1 (CH–CH_2–*C*H_2), 28.4 [3C, C(*C*H_3)$_3$], 32.5 (CH–*C*H_2–CH_2), 36.0 (*C*H_2–$COOCH_3$), 46.5 (N–*C*H_2), 48.6 (*C*H–CH_3), 51.9 and 52.7 (2C, 2×O–*C*H_3), 55.0 (N–*C*H), 79.4 [*C*(CH_3)$_3$], 129.1 [CH=*C*(CH_3)–CO], 138.1 [*C*H=C(CH_3)–CO], 154.3 (*C*O Boc), 168.3 (*C*O–NH), 171.2 and 171.6 (2C, 2×*C*$OOCH_3$); $[\alpha]_D$=+11° (*c*=0.45, $HCCl_3$); MS (EI^+): *m*/*z* calculated for $C_{19}H_{30}N_2O_7$ $[M]^+$ 398.2, found 399.6 (< 2%), 324.6 [$[M+1-t$BuO$]^+$, 3%], 279.8 [$[M+1-t$Bu-2×$OCH_3]^+$or $[M-2\times COOCH_3]^+$, 4%], 297.5 [$[M-t$BuOCO$]^+$, 5%], 237.0 [$[M+1-t$BuOCO–2×$OCH_3]^+$, 5%], 267.1 [$[M+1-t$Bu–$OCH_3]^+$, 6%], 343.6 [$[M+1-t$Bu$]^+$, 10%], 181.0 [$[M+1-t$BuOCO–2×$COOCH_3]^+$, 11%], 136.4 [$[M+1-t$BuOCO–HAsp(OCH$_3$)OCH$_3$$]^+$, 100%]. *cis* Isomer: Yield: 46 mg (85%) colourless oil obtained from pure *cis*-**4p**; R_f=0.38 (ethyl acetate/hexane: 1:1); IR (KBr film)/cm^{-1}: ν_{max}=3340, 3050, 1745, 1670 and 1645; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.45 [s, 9H, C(CH_3)$_3$], 1.92 [s, 3H, CH=C(CH_3)–CO], 1.57–2.19 (m, 2×2H, CH–CH_2–CH_2), 2.88 (d, $^3J_{H-H}$=6.6 Hz, 2H, CH_2–$COOCH_3$), 3.37 (pt, $^3J_{H-H}$=6.75 Hz, 2H, N–CH_2), 3.70 and 3.73 (2s, 2×3H, 2×O–CH_3), 4.87–5.03 (m, 2×1H, N–CH–CH_2 and NH–CH–CH_2), 5.33 [d, $^3J_{H-H}$=10.7 Hz, 1H, CH=C(CH_3)–CO], 976 (d, $^3J_{H-H}$=7.4 Hz, 1H, NH–CH–CH_2); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=20.8 [CH=C(*C*H_3)–CO], 23.8 (CH–CH_2–*C*H_2), 28.3 [3C, C(*C*H_3)$_3$], 32.6 (CH–*C*H_2–CH_2), 36.0 (*C*H_2–$COOCH_3$), 46.9 (N–*C*H_2), 48.9 (*C*H–CH_3), 51.8 and 52.2 (2C, 2×O*C*H_3), 54.9 (N–*C*H), 79.8 [*C*(CH_3)$_3$], 131.0 [*C*H=C(CH$_3$)–CO], 133.3 [CH=*C*(CH$_3$)–CO], 155.2 (*C*O Boc), 169.4 (*C*O–NH), 170.4 and 171.7 (2C, 2×*C*$OOCH_3$); $[\alpha_D]$=+189° (*c*=1.05, $HCCl_3$); MS (EI^+): *m*/*z* calculated for $C_{19}H_{30}N_2O_7$ $[M]^+$ 398.2, found 398.5 (< 6%), 237.0 [$[M+1-t$BuOCO–2×$OCH_3]^+$, 9%], 267.1 [$[M+1-t$BuOCO–$OCH_3]^+$, 10%], 279.6 [$[M+1-t$Bu–2×$OCH_3]^+$ or $[M-2\times COOCH_3]^+$, 18%], 181.0 [$[M+1-t$BuOCO–2×$COOCH_3]^+$, 18%], 136.4 [$[M+1-t$BuOCO–HAsp(OCH$_3$)OCH$_3$$]^+$, 94%].

4.7.12. 2(*S*)-(*trans*)/2(*S*)-(*cis*)-*N*-(*t*-Butoxycarbonyl)-2-[3′-oxo-1′-propenyl-3′-L-(*N*-methyl alaninylamido)]-pyrrolidine 1wd. Yield: 90 mg (70%); colourless oil (*trans*/*cis*: 25:75); *cis* isomer: R_f=0.18 (ethyl acetate/hexane: 3:1); IR (KBr plate)/cm^{-1}: ν_{max}=3330, 1695, 1680, 1665 and 1630; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.34 (d, $^3J_{H-H}$=7.0 Hz, 3H, CH–CH_3), 1.38 [s, 3×3, C(CH_3)$_3$], 1.52–2.19 (m, 2×2H, CH–CH_2–CH_2), 2.71 (d, $^3J_{H-H}$=5.0 Hz, 3H, NH–CH_3), 3.22–3.40 (m, 2H, N–CH_2), 4.39 (m, 1H, CH–CH_3), 4.76 (m, 1H, N–C*H*), 5.61 (dd, $^3J_{H-H}$=11.6 Hz and 10.3 Hz, 1H, CH=CH–CO), 5.76 (d, $^3J_{H-H}$=11.6 Hz, 1H, CH=C*H*–CO), 6.85 (m, 1H, N*H*-Me), 8.97 (pd, $^3J_{H-H}$=6.5 Hz, 1H, NH–CH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=16.6 (CH–*C*H_3), 23.9 (CH–CH_2–*C*H_2), 26.2 (NH–*C*H_3), 28.4 [3C, C(*C*H_3)$_3$], 32.2 (CH–*C*H_2–CH_2), 46.9 (N–*C*H_2), 49.2 (*C*H–CH_3), 54.9 (N–*C*H), 80.2 [*C*(CH_3)$_3$], 124.5 [CH=*C*H–CO], 138.5 [*C*H=CH–CO], 155.2 (*C*O Boc), 167.1 (*C*O–NH), 173.2 (*C*ONHiPr); MS (CI^-): *m*/*z* calculated for $C_{16}H_{26}N_3O_4$ $[M-H]^-$ 325.2, found 325.3 (100%).

4.8. Synthesis of a leu-enkephalin analogue

After the preparation of the essential synthon, *trans*-*N*-Boc vinylogous glycine **4k** as described above, three kinds of reactions were used: (i) BOP-coupling reaction as also described above excepted in the use of DMF instead of dichloromethane as solvent; (ii) in a manner similar to that used for the preparation of **4v**, the hydrolysis of the ester protection was realized with a sodium hydroxide solution 1 M in alcohol; (iii) the hydrolytic cleavage of the Boc group was performed with an hydrochloride acid gaseous barbotage in diethyl ether.

4.8.1. *N*-*t*-Butoxycarbonyl-L-phenylalanyl-L-leucine methyl ester 7. Yield: 1.136 g (95%); white solid; mp 108°C; R_f=0.85 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3500–3100, 1740, 1695, 1650; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=0.89 [d, $^3J_{H-H}$=5.0 Hz, 3H, CH(CH_3)$_2$], 0.91 [d, $^3J_{H-H}$=5.0 Hz, 3H, CH(CH_3)$_2$], 1.41 [s, 9H, C(CH_3)$_3$], 1.46–1.68 [m, 3H, CH_2–CH(CH$_3$)$_2$], 3.07 (d, $^3J_{H-H}$=6.5 Hz, 2H, CH_2-Ph), 3.69 (s, 3H, O–CH_3), 4.34 (dt, $^3J_{H-H}$=8.25 Hz, $^3J_{H-H}$=6.5 Hz, 1H, CH–CH_2-Ph)), 4.45–4.65 [m, 1H, CH–CH_2–CH(CH$_3$)$_2$], 4.99 (d, $^3J_{H-H}$=8.25 Hz, 1H, NHBoc), 6.27 (d, $^3J_{H-H}$=8.00 Hz, 1H, NH–CH–$COOCH_3$), 7.15–7.35 (m, 5H, *Ph*).

4.8.2. L-Phenylalanyl-L-leucine methyl ester hydrochloride 8. Yield: 945 mg (95%); white solid; ^{1}H NMR (250 MHz, CD_3OD): δ_H=0.94 [d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 0.97 [d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 1.50–1.80 [m, 3H, CH_2–CH(CH$_3$)$_2$], 2.97 (d, $^3J_{H-H}$=8.5 Hz, 1H, CH_2-Ph), 3.03 (d, $^3J_{H-H}$=8.5 Hz, 1H, CH_2-Ph), 3.71 (s, 3H, O–CH_3), 4.11 (dd, $^3J_{H-H}$=8.5 Hz, $^3J_{H-H}$=5.25 Hz, 1H, CH–CH_2-Ph), 4.50 [t, $^3J_{H-H}$=7.0 Hz, 1H, CH–CH_2–CH(CH$_3$)$_2$], 7.20–7.40 (m, 5H, *Ph*).

4.8.3. (*trans*)-*N*-[4-*N*-(*t*-Butoxycarbonylamino)-1-oxo-2-butenyl)]-phenylalanyl-leucine methyl ester 9. Yield: 645 mg (99%); white solid; mp 72°C; R_f=0.50 (ethyl acetate/hexane: 1:1); IR (KBr plate)/cm^{-1}: ν_{max}=3400, 3305, 1735, 1700, 1680 and 1640; ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=0.87 [d, $^3J_{H-H}$=5.5 Hz, 2×3H, CH(CH_3)$_2$], 1.45 [s, 9H, C(CH_3)$_3$], 1.48–1.60 [m, 3H, CH_2–CH(CH$_3$)$_2$], 3.04 (dd, $^3J_{H-H}$=13.5, 7.5 Hz, 1H, C*H*-Ph), 3.15 (dd, $^3J_{H-H}$=13.5, 6.0 Hz, 1H, C*H*-Ph), 3.70 (s, 3H, O–CH_3), 3.81–3.94 (m, 2H, NH–CH_2), 4.48 [m, 1H, CH–CH_2–CH(CH$_3$)$_2$], 4.62 (m, 1H, CH–CH_2-Ph), 4.75 (d, $^3J_{H-H}$=4.5 Hz, 1H, NH–CH_2), 5.92 (d, $^3J_{H-H}$=15.5 Hz, 1H, CH=C*H*–CO), 6.10 (d, $^3J_{H-H}$=8.0 Hz, 1H, NH–CH–$COOCH_3$), 6.20 (d, $^3J_{H-H}$=7.5 Hz, 1H, NH–CH=), 6.55 (dt, $^3J_{H-H}$=15.5, 5.0 Hz, 1H, CH=CH–CO), 7.15–7.35 (m, 5H, *Ph*); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=21.9 and 22.7 [2C, CH(*C*H$_3$)$_2$], 24.7 [*C*H(CH$_3$)$_2$], 28.0 [3C, C(*C*H$_3$)$_3$], 38.3 (*C*H$_2$-Ph), 41.3 [*C*H$_2$–CH(CH$_3$)$_2$], 50.9 [*C*H–CH_2–CH(CH$_3$)$_2$], 52.3 (O–*C*H$_3$), 54.3 (*C*H–CH_2-Ph), 79.9 [*C*(CH$_3$)], 123.1 (CH=*C*H–CO), 127.0, 128.6 (2C), 129.3 (2C) and 136.3 (*Ph*), 141.5 (*C*H=CH–CO), 155.6 (*C*O Boc), 165.0 (CH=CH–*C*O), 170.6 (*C*ONH), 172.7 (*C*$OOCH_3$); $[\alpha]_D$=−16° (*c*=0.6, $HCCl_3$); MS (FAB^+) *m*/*z* calculated for $C_{25}H_{37}N_3O_6$ $[M]^+$ 475.3, found 476.0 $[[M+1]^+$, 100%].

4.8.4. (*trans*)-*N*-(4-Amino-1-oxo-2-butenyl)-phenylalanyl-leucine methyl ester hydrochloride 10. Yield: 500 mg

(92%, crude); white solid; IR (KBr plate)/cm^{-1}: ν_{max}= 3270, 3055, 1740, 1710, 1665 and 1630; ^1H NMR (250 MHz, CD_3OD): δ_H=0.80 [d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 0.85 [d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 1.47–1.65 [m, 3H, CH_2–CH(CH$_3$)$_2$], 2.79 (dd, $^2J_{H-H}$=14.5 Hz, $^3J_{H-H}$=9.5 Hz, 1H, CH-Ph), 3.10 (dd, $^2J_{H-H}$=14.5 Hz, $^3J_{H-H}$=5.25 Hz, 1H, CH-Ph), 3.56–3.60 (m, 5H, O–CH_3 and NH–CH_2), 4.26 [t, $^3J_{H-H}$=7.25 Hz, 1H, CH–CH$_2$–CH(CH$_3$)$_2$], 4.68 (m, 1H, CH–CH$_2$-Ph), 6.14 (d, $^3J_{H-H}$=15.5 Hz, 1H, CH=CH–CO), 6.57 (dt, $^3J_{H-H}$= 15.5 Hz, $^3J_{H-H}$=6.3 Hz, 1H, CH=CH–CO), 7.02–7.21 (m, 5H, *Ph*); ^{13}C NMR (62.896 MHz, CD_3OD): δ_C=19.8 and 21.3 [2C, CH(CH_3)$_2$], 23.9 [CH(CH$_3$)$_2$], 37.0 (CH_2-Ph), 39.1 (NH–CH_2–CH=), 39.5 [CH_2–CH(CH$_3$)$_2$], 50.2 [CH–CH$_2$–CH(CH$_3$)$_2$], 50.7 (O–CH_3), 53.8 (CH–CH$_2$-Ph), 125.8 (CH=CH–CO), 127.0, 127.4 (2C), 128.3 (2C) and 136.3 (*Ph*), 140.5 (CH=CH–CO), 162.1 and 163.5 (2C, CH=CH–CO and CONH), 171.8 (COOCH$_3$).

4.8.5. *N*,*O*-di-*t*-Butoxycarbonyl-L-tyrosylglycine methyl ester 11. Yield: 810 mg (86%); white solid; mp 45° C; R_f=0.66 (ethyl acetate/hexane: 3:1); IR (KBr plate)/cm^{-1}: ν_{max}=3500–3150, 1740–1660; ^1H NMR (250 MHz, $CDCl_3$): δ_H=1.41 [s, 9H, C(CH_3)$_3$], 1.55 [s, 9H, C(CH_3)$_3$], 3.08 (d, $^3J_{H-H}$=6.25 Hz, 2H, CH_2-Ph), 3.74 (s, 3H, O–CH_3), 3.95 (dd, $^2J_{H-H}$=18.0 Hz, $^3J_{H-H}$=6.25 Hz, 1H, CH_2–COOCH$_3$), 4.03 (dd, $^2J_{H-H}$=18.0 Hz, $^3J_{H-H}$=5.25 Hz, 1H, CH_2–COOCH$_3$), 4.39 [dt, $^3J_{H-H}$=7.0 Hz, $^3J_{H-H}$=6.25 Hz, 1H, CH–CH$_2$-Ph], 5.00 (d, $^3J_{H-H}$=7.0 Hz, 1H, NH CH–CH$_2$-Ph), 6.49 (dd, $^3J_{H-H}$=5.25 Hz, $^3J_{H-H}$=6.25, 1H, NH–CH$_2$–COOCH$_3$), 7.10 (d, $^3J_{H-H}$=8.5 Hz, 2H, *Ph*), 7.22 (d, $^3J_{H-H}$=8.5 Hz, 2H, *Ph*) $[\alpha]_D$=−1.1° (*c*=0.9, $HCCl_3$).

4.8.6. *N*-*t*-Butoxycarbonyl-L-tyrosylglycine 12. Yield: 381 mg (94%); white solid; mp 80°C; R_f=0.46 (methanol); IR (KBr plate)/cm^{-1}: ν_{max}=3100–2800, 1710–1630; ^1H NMR (250 MHz, CD_3CO CD_3): δ_H=1.21 [s, 9H, C(CH_3)$_3$], 2.70 (dd, $^3J_{H-H}$=8.75 Hz, $^2J_{H-H}$=14.0 Hz, 1H, CH_2-Ph), 2.97 (dd, $^3J_{H-H}$=5.00 Hz, $^2J_{H-H}$=14.0 Hz, 1H, CH_2-Ph), 3.85 (d, $^3J_{H-H}$=5.75 Hz, 2H, CH_2–COOH), 4.22 (ddd, $^3J_{H-H}$=8.00 Hz, $^3J_{H-H}$=5.00 Hz, $^3J_{H-H}$=5.75 Hz, 1H, CH–CH$_2$-Ph), 5.88 (d, $^3J_{H-H}$=8.0 Hz, 1H, NH Boc), 6.61 (d, $^3J_{H-H}$=8.5 Hz, 2H, *Ph*), 6.98 (d, $^3J_{H-H}$=8.5 Hz, 2H, *Ph*), 7.41 (dd, $^3J_{H-H}$=5.75 Hz, 1H, NHCH$_2$COOH), 8.01 (s, 1H, PhOH), 12.0 (s, 1H, COOH) $[\alpha]_D$=−1.1° (*c*=0.9, $HCCl_3$).

4.8.7. (*trans*)-*N*-(*t*-Butoxycarbonyl)-L-tyrosylglycyl-*N*-(4-amino-1-oxo-2-butenyl)-phenyl alanyl-leucine methyl ester 13. Yield: 207 mg (61.5%); white solid; mp 110°C; R_f=0.42 (ethyl acetate/acetone 4:1); IR (KBr plate)/cm^{-1}: ν_{max}=3410, 3290, 1745, 1710, 1665 and 1615; ^1H NMR (250 MHz, CD_3COCD_3): δ_H=0.90 [d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 0.91 [d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 1.36 [s, 9H, C(CH_3)$_3$], 1.50–1.70 [m, 3H, CH_2–CH(CH$_3$)$_2$], 2.80–3.24 (m, 4H, CH_2-Ph–OH and CH_2-Ph), 3.69 (s, 3H, O–CH_3), 3.80–3.94 (m, 4H, NH–CH_2 and NH–CH_2–CH=), 4.37 (m, 1H, CH–CH$_2$-Ph–OH), 4.54 (dd, $^3J_{H-H}$= 7.5 Hz, $^3J_{H-H}$=7.5 Hz, 1H, CH–CH$_2$-Ph), 4.85 [dd, $^3J_{H-H}$= 5.0 Hz, $^3J_{H-H}$=8.0 Hz, 1H, CH–CH$_2$–CH(CH$_3$)$_2$], 6.00 (d, $^3J_{H-H}$=15.5 Hz, 1H, CH=CH–CO), 6.27 (d, $^3J_{H-H}$=7.0 Hz, 1H, NH–CH–CH$_2$-Ph–OH), 6.63 (dt, $^3J_{H-H}$=15.5 Hz, $^3J_{H-H}$=4.8 Hz, 1H, CH=CH–CO), 6.78 (d, $^3J_{H-H}$=8.5 Hz, 2H, *Ph*–OH), 7.10–7.30 (m, 5H, *Ph*), 7.31(d, $^3J_{H-H}$= 8.5 Hz, 2H, *Ph*-OH), 7.64 (d, $^3J_{H-H}$=8.0 Hz, 1H, NH–CH–CH$_2$-Ph), 7.70–7.85 [m, 3H, NH–CH$_2$, NH–CH$_2$–CH= and NH–CH–CH$_2$–CH(CH$_3$)$_2$], 8.25 (br s, 1H, Ph-OH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=22.0 and 22.6 [2C, CH(CH_3)$_2$], 24.7 [CH(CH$_3$)$_2$], 28.4 [3C, C(CH_3)$_3$], 38.3 (2C, CH_2-Ph and CH_2-Ph–OH), 39.7 (NH–CH_2), 40.7 (NH–CH_2–CH=), 42.9 [CH_2–CH(CH$_3$)$_2$], 51.4 [CH–CH$_2$–CH(CH$_3$)$_2$], 52.3 (O–CH_3), 55.3 (CH–CH$_2$-Ph), 56.4 (CH–CH$_2$-Ph–OH), 80.5 [C(CH$_3$)], 115.7 (2C, *Ph*-OH), 123.8 (CH=CH–CO), 127.0, 127.2 (C–OH), 128.6 (2C), 129.3 (2C), 130.4 (2C) and 136.7 (*Ph*), 139.6 (CH=CH–CO), 155.6 (CO Boc), 165.9 (CH=CH–CO), 169.1, 172.3 and 172.6 (3C, CONH), 172.9 (COOCH$_3$); MS (FAB^+): *m*/*z* calculated for $C_{36}H_{48}N_5O_9$ $[M]^+$ 695.4, found 696.3 $[[M+1]^+$, 56%], 1391.0 $[[M+1+M]^+$, 73%], 596.2 $[[M+1-t$BuOCO$]^+$, 100%].

4.8.8. (*trans*)-*N*-(*t*-Butoxycarbonyl)-L-tyrosylglycyl-*N*-(4-amino-1-oxo-2-butenyl)-phenyl alanyl-leucine 14. Yield: 101 mg (70%); white solid; mp 119°C; R_f=0.2 (methanol); IR (KBr plate)/cm^{-1}: ν_{max}=3280, 1770, 1645 and 1590; ^1H NMR (250 MHz, CD_3COCD_3): δ_H=0.90 [d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 0.91 [d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 1.36 [s, 9H, C(CH_3)$_3$], 1.50–1.70 [m, 3H, CH_2–CH(CH$_3$)$_2$], 2.80–3.24 (m, 4H, CH_2-Ph–OH and CH_2-Ph), 3.80–3.94 (m, 4H, NH–CH_2 and NH–CH_2–CH=), 4.37 (dd, $^3J_{H-H}$=7.0 Hz, $^3J_{H-H}$=7.0 Hz, 1H, CH–CH$_2$-Ph–OH), 4.54 [m, 1H, CH–CH$_2$–CH(CH$_3$)$_2$], 4.85 (m, 1H, CH–CH$_2$-Ph), 6.00 (d, $^3J_{H-H}$=15.5 Hz, 1H, CH=CH–CO), 6.27 (m, 1H, NH–CH–CH$_2$-Ph–OH), 6.63 (dt, $^3J_{H-H}$=15.5, 4.8 Hz, 1H, CH=CH–CO), 6.78 (d, $^3J_{H-H}$=8.5 Hz, 2H, *Ph*-OH), 7.10–7.30 (m, 5H, *Ph*), 7.31 (d, $^3J_{H-H}$=8.5 Hz, 2H, *Ph*-OH), 7.64 (m, 1H, NH–CH–CH$_2$-Ph), 7.70–7.85 [m, 3H, NH–CH$_2$, NH–CH$_2$–CH= and NH–CH–CH$_2$–CH(CH$_3$)$_2$], 8.25 (br s, 1H, Ph-OH), 11.5 (br s, 1H, COOH); ^{13}C NMR (62.896 MHz, $CDCl_3$): δ_C=21.0 and 22.1 [2C, CH(CH_3)$_2$], 24.3 [CH(CH$_3$)$_2$], 27.4 [3C, C(CH_3)$_3$], 37.8 (2C, CH_2-Ph and CH_2-Ph–OH), 39.0 (NH–CH_2), 40.4 (NH–CH_2–CH=), 42.2 [CH_2–CH(CH$_3$)$_2$], 50.2 [CH–CH$_2$–CH(CH$_3$)$_2$], 56.3 (CH–CH$_2$-Ph), 57.4 (CH–CH$_2$-Ph–OH), 78.6 [C(CH$_3$)], 114.8 (2C, *Ph*–OH), 123.4 (CH=CH–CO), 126.1, 127.9 (C–OH), 129.1 (2C), 130.1 (2C), 130.7 (2C) and 137.4 (*Ph*), 139.4 (CH=CH–CO), 155.8 (CO Boc), 168.2 (CH=CH–CO), 169.3, 170.1 and 170.4 (3C, CONH); MS (FAB^+): *m*/*z* calculated for $C_{35}H_{47}N_5O_9$ $[M]^+$ 681.3, found 682.3 $[[M+1]^+$, 100%].

4.8.9. (*trans*)-L-Tyrosylglycyl-*N*-(4-amino-1-oxo-2-butenyl)-phenylalanyl-leucine 15. Yield: 76 mg (98%); white solid; IR (KBr plate)/cm^{-1}: ν_{max}=3265, 3065, 1690, 1680, 1670, 1660, 1650 and 1645; ^1H NMR (250 MHz, CD_3OD): δ_H=0.90 [2d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 0.94 [2d, $^3J_{H-H}$=6.0 Hz, 3H, CH(CH_3)$_2$], 1.60–1.72 [m, 3H, CH_2–CH(CH$_3$)$_2$], 2.86–3.22 (m, 4H, CH_2-Ph–OH and CH_2-Ph), 3.52–3.63 (m, 2H, NH–CH_2), 3.85–4.11 (m, 3H, NH–CH_2–CH= and CH–CH$_2$-Ph–OH), 4.43 [m, 1H, CH–CH$_2$–CH(CH$_3$)$_2$], 4.78 (m, 1H, CH–CH$_2$-Ph), 6.08 (d, $^3J_{H-H}$=15.5 Hz, 1H, CH=CH–CO), 6.64 (dt, $^3J_{H-H}$=15.5, 5.0 Hz, 1H, CH=CH–CO), 6.78 (d, $^3J_{H-H}$=8.5 Hz, 2H, *Ph*-OH), 7.12–7.33 (m, 5H, *Ph*), 7.31 (d, $^3J_{H-H}$=8.5 Hz, 2H, *Ph*-OH); ^{13}C NMR (62.896 MHz, CD_3OD): δ_C=21.0

and 22.1 [2C, CH(CH_3)$_2$], 24.2 [CH(CH$_3$)$_2$], 28.9 [CH_2–CH(CH$_3$)$_2$], 35.9 and 37.1 (2C, CH_2-Ph and CH_2-Ph═OH), 42.5 (NH–CH_2), 46.7 (NH–CH_2–CH═), 50.2 [CH–CH_2–CH(CH$_3$)$_2$], 53.6 (2C, CH–CH_2-Ph and CH–CH_2-Ph–OH), 115.2 (2C, *Ph*-OH), 124.7 (CH═CH–CO), 125.7 (C–OH), 126.1, 127.9 (2C), 129.0 (2C), 130.0 and 137.9 (*Ph*), 138.1 (CH═CH–CO), 164.0, 167.9, 168.4, 171.4 and 173.8 (5C, CO).

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