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Synthesis of tetrahydroisoquinoline-based pseudopeptides and their characterization as suitable reverse turn mimetics

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Abstract—New peptidomimetics containing the Tic moiety were synthesized in enantiomerically pure form and their conformational features were studied by NMR, IR, and molecular modeling techniques. The presence of a reverse turn conformation was observed in all the structures, suggesting the key role of the scaffold as reverse turn inducer. In particular, all the analyses led to the conclusion that a β-turn conformation is mostly stabilized in tetrapeptide mimetic **4b** and in hexapeptide mimetics **5a**,**b**. In the case of **5a**,**b**, the C1 stereochemistry plays a central role in determining stable conformations, supporting the formation of a β-hairpin arrangement with a 14-membered intramolecular hydrogen bond ring only in **5b**.

1. Introduction

The design, synthesis, and application of peptidomimetic compounds have been for many years a focal point of a research aimed to develop new therapeutics with peptide-like activity and enhanced resistance toward proteases.[1]

The structural transition from a bioactive peptide to a non-peptidic compound involves the identification of the crucial amino acid side chains, the establishment of their spatial relationship, and the selection of an organic template, which is able to reproduce the geometry of the pharmacophoric model. Among the different strategies adopted to connect the peptide with the 'non-peptide world', of particular interest and success has been the replacement of a dipeptide substructure in a natural substrate with a constrained rigid analogue, capable to induce a folding in the peptide chain.[2] Reverse turns are structural motifs commonly found in bioactive peptides that, besides being fundamental in protein folding, play a central role as molecular recognition elements.[3] Therefore, they are very important as starting points in the design of reverse turn mimics, that is, to say scaffolds that restrict the conformational freedom of the peptide chain, thus providing structural stabilization when incorporated in oligopeptides. In addition, these pseudopeptide scaffolds may have on the molecular framework additional functionalities, suitable for the attachment of potential pharmacophoric groups. During the past decade, a large array of highly functionalized nitrogen heterocycles, mainly fused bicyclic lactams, have been synthesized and employed as reverse turn mimics, thereby providing a great variety of peptidomimetics as a tool for medicinal chemistry.[4]

In search of new small peptidomimetics that combine the structural rigidity with the ease of synthetic access, we focused on the 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) moiety, a core structure, which is known to exhibit affinity toward a wide range of receptors. In fact, the strategy of replacing individual amino acids such as tyrosine or phenylalanine with Tic derived frameworks has been used extensively to prepare conformationally constrained analogues of bioactive peptides. For instance, based on this approach, a number of δ- and κ-selective opioid receptor agonists and antagonists have been prepared,[5] by systematic modification of endogenous ligands, such as enkephalin, endomorphin, and dynorphin, thus allowing a better understanding of how opioid receptors function at molecular level. Constrained analogues of tyrosine have also been employed in the total synthesis of mimics of didemnin B,[6] the lead member of a class of marine natural peptides, and in the preparation of the first non-peptidic selective antagonist of the neuropeptide orexin.[7]

Compounds **1a**,**b** (Scheme 1) were recently reported by Grieco et al.[8] as new potential β-turn dipeptide mimics, arising from a key Pictet–Spengler reaction of the precursor **2**, derived from L-Dopa, with the aldehyde **3**, which can in

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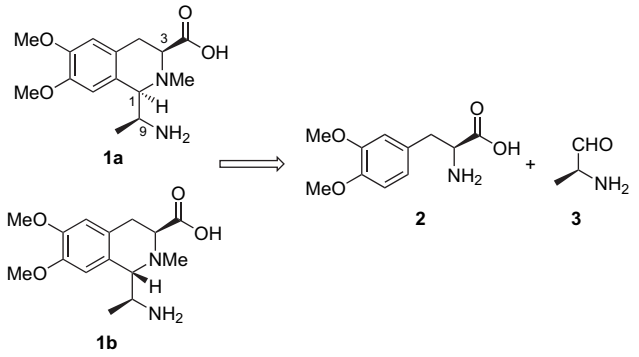
turn be prepared by reduction of L-Ala. Actually, **1a**,**b** can be envisaged as Tyr-Ala dipeptide mimics rigidified through the formation of the Tic core. Comparison of the structure of Tyr-Ala dipeptide with that of compounds **1a**,**b**, indicates an equal number of linkages between the terminal C and N atoms. On the other hand, the isosteric substitution occurs at the level of the peptide bond, with the oxo group of Ala being now replaced by the sp^3-hybridized stereogenic carbon atom C1.



Scheme 1. Retrosynthetic analysis for dipeptide mimics **1a**,**b**.

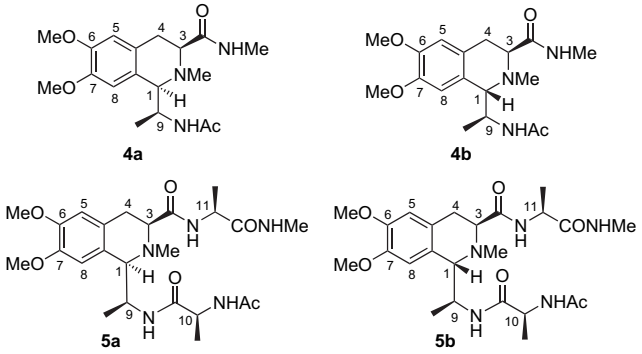


Figure 1. Atom labeling as used in the NMR interpretation.

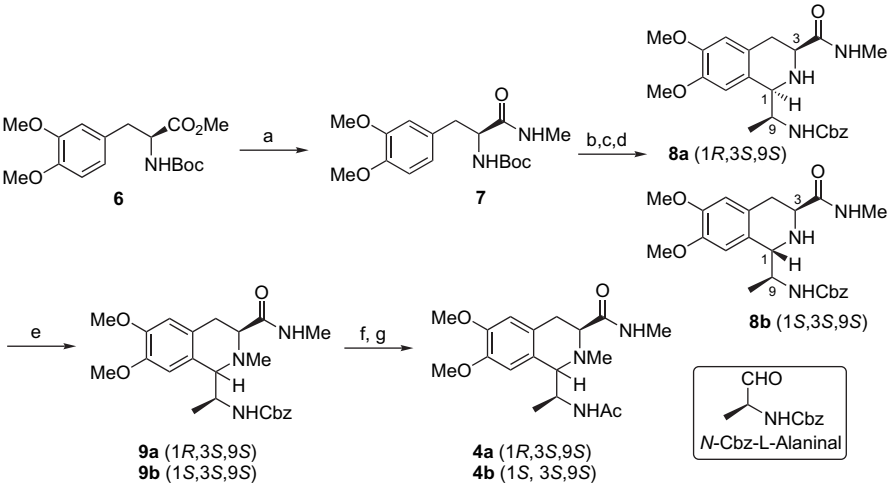
Herein we report the synthesis of enantiopure tetrapeptide mimics **4a**,**b** (Ac–AETIC–NHMe, AETIC=1-(1-aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) and hexapeptide mimics **5a**,**b** (Ac–(*S*)-Ala–AETIC–(*S*)-Ala–NHMe), and their conformational analysis by molecular modeling calculations,[9] ^{1}H NMR[10] and FTIR[11] (Fig. 1). This study indicated that both the diastereomeric Ac–AETIC–NHMe **4a**,**b** and Ac–(*S*)-Ala–AETIC–(*S*)-Ala–NHMe **5a**,**b** have a good propensity to adopt a reverse turn-like conformation. In particular, the structure **5b** shows a strong preference to form a β-hairpin.

2. Results and discussion

2.1. Synthesis

Scheme 2 outlines the synthesis of **4a**,**b** starting from the L-Dopa derivative **6**[12] and *N*-Cbz-L-alaninal.[13] We decided to employ the temporary benzyloxycarbonyl (Cbz) protecting group in the aldehyde component, since we have encountered many difficulties in handling *N*-acetyl-L-alaninal, because of its sensitivity toward racemization.[14]

Conversion ($MeNH_2$, rt) of methyl ester **6** into methylamide **7** occurred almost quantitatively. *N*-Boc removal (30% TFA, CH_2Cl_2) was followed by Pictet–Spengler condensation (*N*-Cbz-L-alaninal, 5% TFA, CH_2Cl_2), thus affording cleanly tetrahydroisoquinolines **8**, as an isomeric mixture (1:3, **8a** and **8b**, after chromatographic separation) at C1. Since in the preliminary investigation of these new peptidomimetic scaffolds, both diastereoisomers at the newly created C1 stereogenic center are in principle necessary, no attempt was made to control the stereogenic outcome of the Pictet–Spengler condensation. Detailed inspection of 1D and 2D NMR spectra permitted the chemical shift complete assignment for all protons and carbons in both the diastereoisomers. The determination of the configuration at the new stereogenic center C1 was deduced by 2D ^{1}H NOESY NMR, on the basis of the NOE interaction between H-1 and H-3, which was present in compound **8a** and absent in



Scheme 2. Reagents and conditions: (a) $MeNH_2$, methanol (98%). (b) TFA 30% in dichloromethane. (c) *N*-Cbz-L-alaninal, TFA 5% in dichloromethane. (d) Chromatographic separation (**8a**: 20%; **8b**: 60%, from step b). (e) CH_2O, $NaCNBH_3$, 1 M AcOH in methanol (**9a**: 91%; **9b**: 93%). (f) H_2, Pd/C, methanol. (g) Ac_2O, pyridine (**4a**: 70%; **4b**: 68%, from step f).

the case of compound **8b**. Thus, the absolute configuration at C1 was assigned as *R* in **8a** and *S* in **8b**. In order to avoid undesirable interactions of the tetrahydroisoquinoline ring N–H group, as a possible competitor on intramolecular hydrogen bond formation with carbonyl oxygen atoms, amines **8a** and **8b** were converted to the corresponding *N*-methyl derivatives **9a** and **9b**, via reductive amination with formaldehyde (CH_2O, 1 M AcOH in MeOH). Finally, removal of the Cbz protecting group (H_2, Pd/C 5%) and subsequent acetylation of the primary amine (Ac_2O, Py) afforded the targets Ac–AETIC–NHMe **4a** and **4b**.

The synthesis of hexapeptide mimics **5a**,**b** is reported in Scheme 3, starting from the same L-Dopa derivative **6**. Hydrolysis of methyl ester **6** (LiOH, THF/H_2O) was followed by coupling with (*S*)-Ala-methyl ester (IBCF, 4-methylmorpholine) to give **10**. Conversion of methyl ester into methylamide ($MeNH_2$, rt), provided tripeptide **11** in almost quantitative yield. Boc removal (30% TFA, CH_2Cl_2) and subsequent Pictet–Spengler condensation (*N*-Cbz-L-alaninal, 5% TFA, CH_2Cl_2) afforded cleanly tetrahydroisoquinolines **12**. As for **8a**,**b**, the isomeric mixture (2:3, **12a** and **12b**) at C1 was separated by flash chromatography and the distinct diastereoisomers were fully characterized by means of 1D and 2D NMR spectra. By 2D ^1H NOESY NMR, the configuration at the new stereogenic center C1 was deduced to be *R* in **12a** and *S* in **12b**. Methylation of the tetrahydroisoquinoline ring N–H group on both the diastereoisomers **12a** and **12b** furnished **13a**,**b** quantitatively. The final products **5a** and **5b** were obtained by hydrogenolysis of the Cbz protecting group, followed by coupling (IBCF, 4-methylmorpholine) with *N*-acetyl-L-alanine.

2.2. Conformational analysis

In order to evaluate the ability of the AETIC scaffolds to induce reverse turn conformations, computational studies were performed on **4a**,**b** and **5a**,**b** using the Spartan'06 software package.[15] The reverse turn mimicry of the different structures was evaluated by computing and analyzing different geometric parameters[3] (Fig. 2).

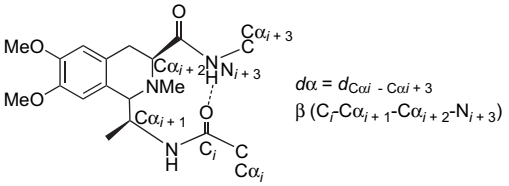
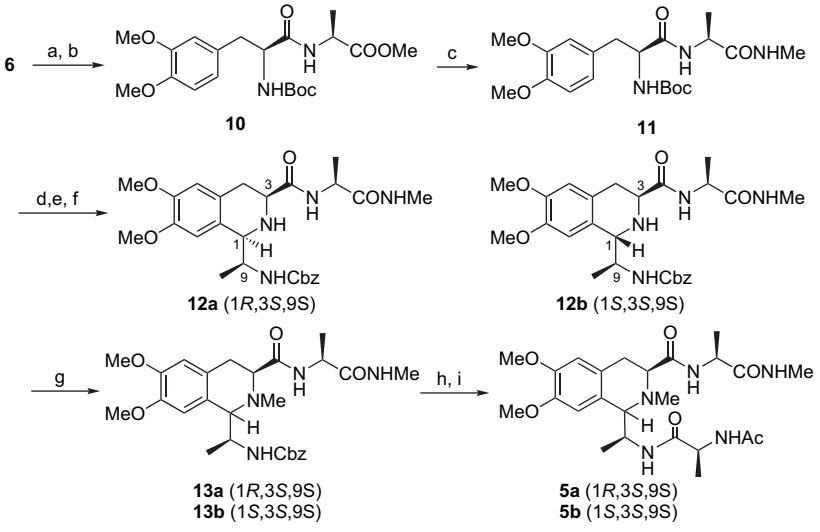


Figure 2. Definition of parameters to characterize β-turn propensity of AETIC systems.

Evaluation of the $C\alpha_i$–$C\alpha_{i+3}$ interatomic distance ($d\alpha$), which should be less than 7 Å to mimic a reverse turn, is a well established procedure.[3a] The virtual torsion angle β, defined by C_i–$C\alpha_{i+1}$–$C\alpha_{i+2}$–N_{i+3}, is another element, which has to be evaluated.[3,16] A measure of $|\beta|<30°$ is associated with a tight reverse turn, while $|\beta|<60°$ is usually referred to an open reverse turn.[17] An important feature of β-turns is the presence of a 10-membered ring hydrogen bond between the carbonyl oxygen at C_i and the hydrogen on N_{i+3}. This was evaluated by means of the 'hydrogen bonds' function implemented in the software, according to which hydrogen bonds are defined as non-bonded contacts between a nitrogen or oxygen and an hydrogen attached to nitrogen or oxygen, separated by a distance ranging from 1.6 Å to 2.1 Å and making an X–H···Y (X,Y=N,O) angle >120°. The computational procedure consisted of an unconstrained Monte Carlo/energy minimization conformational search using the molecular mechanics MMFF94 force field[18] in vacuo. For compounds **4a**,**b** and **5a**,**b**, respectively, 441 and 1089 conformers were generated. Only conformations within 6 kcal/mol of the global minimum were kept. Results are reported in Table 1 as percentage of conformers, which meet the cited requirements for a reverse turn.

Compounds **4a** and **4b** show moderate percentage of conformers satisfying the β-turn requirements. Compound **4b**,



Scheme 3. Reagents and conditions: (a) LiOH, THF/water 1:1. (b) L-Alanine-OMe, isobutyl chloroformate, 4-methylmorpholine, DMF (80%, from step a). (c) $MeNH_2$, methanol (95%). (d) TFA 30% in dichloromethane. (e) *N*-Cbz-L-alaninal, TFA 5% in dichloromethane. (f) Chromatographic separation (**12a**: 26%; **12b**: 39%, from step d). (g) CH_2O, $NaCNBH_3$, 1 M AcOH in methanol (**13a**: 88%; **13b**: 86%). (h) H_2, Pd/C, methanol; (i) *N*-acetyl-L-alanine, isobutyl chloroformate, 4-methylmorpholine, DMF (**5a**: 72%; **5b**: 68%, from step h).

Table 1. MC/EM conformational analysis for AETIC structures

Compound	No. of conf.<6 kcal/mol	% $d\alpha$<7 Å[a]	% $\|\beta\|$<30°[b]	% $\|\beta\|$<60°[b]	% Hydrogen bond (10-membered ring)[c]	% Hydrogen bond (14-membered ring β-hairpin conformation)[d]
4a	64	45 (29)	20 (13)	53 (34)	17 (11)	—
4b	58	62 (36)	60 (35)	62 (36)	28 (16)	—
5a	47	89 (42)	25.5 (12)	74 (35)	34 (16)	32 (15)
5b	55	98 (54)	67 (37)	83 (46)	20 (11)	43 (24)

[a] Percentage of conformers for which the distance between $C\alpha_i$ and $C\alpha_{i+3}$ is <7 Å. The occurrence numbers are given in parenthesis.
[b] Percentage of conformers in which the virtual torsion angle β (absolute value) is <30° (or 60°). The occurrence numbers are given in parenthesis.
[c] Percentage of conformers for which a 10-membered ring hydrogen bond between the carbonyl oxygen at C_i and the hydrogen on N_{i+3} is present. The occurrence numbers are given in parenthesis. Hydrogen bonds are evaluated by mean of the software 'hydrogen bonds' function.
[d] Percentage of conformers for which a 14-membered ring hydrogen bond between the carbonyl oxygen at C_4 and the hydrogen on N_{i-1} is present. This parameter is associated to a β-hairpin 2:2.[19] The occurrence numbers are given in parenthesis. Hydrogen bonds are evaluated by mean of the software 'hydrogen bonds' function.

bearing a 1,3-trans relative configuration, seems to be slightly favored in assuming a reverse turn conformation, with 62% of conformers having $d\alpha$<7 Å and $|\beta|$<60°. Characteristic intramolecular hydrogen bond is present in 28% of conformers for **4b** and in 17% of conformers for **4a**. On the contrary, structures **5a** and **5b** are predicted to easily assume a β-turn conformation (Fig. 3). In particular **5b**, with a 1,3-trans relative configuration, produced 98% of conformers with $d\alpha$<7 Å, 83% with $|\beta|$<60° (67% with $|\beta|$<30°), and 20% forming a 10-membered intramolecular hydrogen bond ring. Structures **5a**,**b** can also exhibit a further hydrogen bond involving carbonyl oxygen at C_4 and the hydrogen on N_{i-1}, thus leading to the formation of a 14-membered ring. The existence of these conformations demonstrates that the AETIC scaffolds **5a**,**b** have the proper requirements to induce an antiparallel alignment of the two peptide chains in a 2:2 type β-hairpin[19] arrangement.

Geometric parameters for the lowest energy conformations of **4a**,**b** and **5a**,**b** are reported in Table 2, where $d\alpha$ and β values are reported together with data characterizing the C_i═O···HN_{i+3} hydrogen bond. In geometrical definition[10] of hydrogen bond, it is assumed that the optimum bond distance for O···H is approximately 1.9 Å. The related N–H···O angle should be around 160°, while a C═O···H angle greater than 90° is considered as a favorable condition. Non-planarity about the N–C═O···H torsion angle is energetically unfavorable.

The lowest energy conformation of **4a** is not a β-turn mimic. The first β-turn inducing conformer for **4a** is calculated to lie 0.47 kcal/mol above the minimum, suggesting that **4a** can easily adopt the β-turn conformation. Results from the same analyses for structures **4b**, **5a**, and **5b**, clearly show that in these cases a β-turn conformation is stabilized.

2.3. Spectroscopic NMR and IR analyses

To validate the predictions from modeling, we investigated some structural features of the tetrapeptide mimics Ac–AETIC–NHMe **4a**,**b** and of the hexapeptide mimics Ac–(*S*)-Ala–AETIC–(*S*)-Ala–NHMe **5a**,**b**. In particular, the presence of an intramolecular hydrogen bond between the termini of the turn region was investigated by ^{1}H NMR[10] and FTIR[11] spectroscopies.

^{1}H NMR spectra were recorded in a relatively nonpolar solvent (i.e., $CDCl_3$)[20,21] that doesn't provide strong hydrogen bonding competition. As NH chemical shift values δ proved to be independent of concentration below 4.0 mM at 295 K,

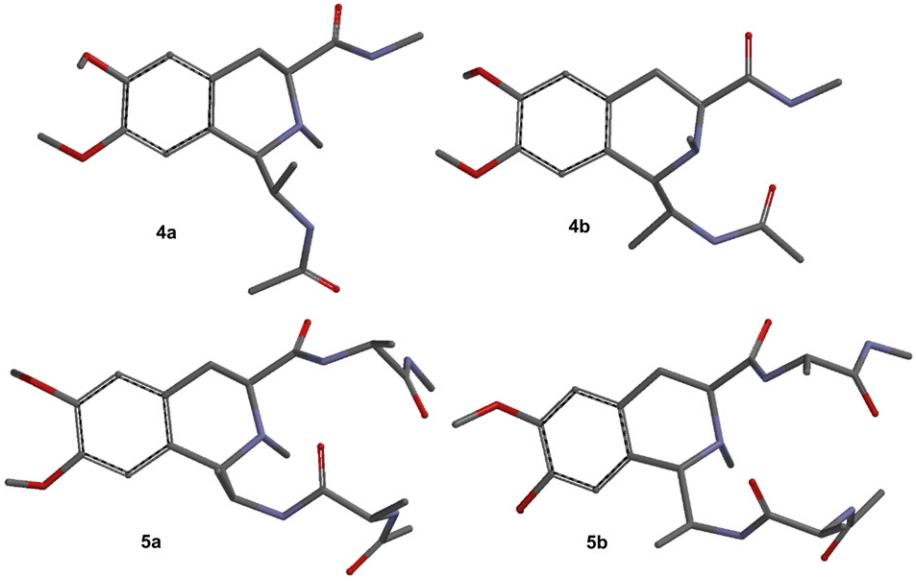


Figure 3. 3D representation of the lowest-energy conformers.

Table 2. Geometric parameters for lowest energy conformers

	4a	**4b**	**5a**		**5b**	
$d\alpha$ [Å]	8.359	4.992	4.931		5.252	
β[°]	−86.22	1.87	−20.48		−21.65	
d(C═O–HN) [Å]	5.572	1.819	1.821[a]	1.815[b]	2.008[a]	1.768[b]
NHO angle [°]	148.92	172.55	161.58[a]	167.24[b]	160.13[a]	170.99[b]
C═O–H angle [°]	66.73	117.54	125.80[a]	141.36[b]	102.62[a]	134.83[b]
N–C═O–H dihedral angle [°]	4.62	3.02	6.96[a]	3.47[b]	5.22[a]	2.10[b]
Energy [kcal/mol]	85.17	80.44	90.97		96.40	
ΔE of first β-turn [kcal/mol][c]	0.47 (85.64)	0	0		0	

[a] Geometric measurements for 10-membered ring hydrogen bond.
[b] Geometric measurements for 14-membered ring hydrogen bond.
[c] ΔE is referred to the lowest energy conformer. Absolute energy value is given in parenthesis.

all analyses were performed on 3.0 mM $CDCl_3$ solutions, that is, in the absence of a significant aggregation. To ascertain which amide protons are involved in intramolecular hydrogen bonds, the ^{1}H NMR chemical shifts of the amide protons and their temperature dependence ($\Delta\delta/\Delta T$) have been evaluated. In general, chemical shift values of the carboxamide hydrogens higher than 7 ppm in $CDCl_3$, and a low temperature coefficient (−2.6 ppb/K or smaller in absolute value) are indicative of NH involved in strong hydrogen bonds. A low chemical shift value (δ<7.0) and a low temperature coefficient (−2.6 ppb/K or smaller in absolute value) are significant of non-hydrogen-bonded amide protons. A temperature dependence larger than 2.6–3.0 ppb/K in absolute value implies an equilibrium between a hydrogen-bonded and a non-hydrogen-bonded state, apart from the chemical shift value.[22]

Compounds **4a**,**b** possess the minimal structural elements to form the characteristic intramolecular hydrogen bond that is a good indication to prove the formation of a reverse turn. In $CDCl_3$ solution, the N*H*Me resonates at 7.35 ppm in **4a** and at 7.75 ppm in **4b** that is at lower fields with respect to N*H*Ac, appearing at 5.40 ppm in **4a** and 6.32 ppm in **4b** (Table 3).

Temperature-dependent chemical shift changes suggest that N*H*Me is probably involved in an equilibrium between a hydrogen-bonded and a non-hydrogen-bonded state, both in **4a** and **4b**. Indeed, $\Delta\delta$ (N*H*Me)/ΔT values of −5.1 ppb/K (for **4a**) and −4.0 ppb/K (for **4b**) were observed. As expected, the non-hydrogen-bonded N*H*Ac showed low temperature coefficients, both in **4a** and **4b**.

These data are in good agreement with modeling predictions, according to which both the Ac–AETIC–NHMe **4a** and **4b** show a good propensity to adopt a β-turn conformation, in which the N*H*Me would be involved in a 10-membered intramolecular hydrogen bonding. In particular, this tendency seems to be more pronounced in Ac–AETIC–NHMe **4b**.

Table 3. Spectroscopic data of tetrapeptide mimics Ac–AETIC–NHMe **4a**,**b**

		δ ($CDCl_3$)	($\Delta\delta/\Delta T$)[a]	IR absorption bands
Ac–AETIC–NHMe **4a**	N*H*Me	7.35	−5.1	3342, 3428
	N*H*Ac	5.40	−1.1	
Ac–AETIC–NHMe **4b**	N*H*Me	7.75	−4.0	3326, 3432
	N*H*Ac	6.32	−1.2	

[a] ppb/K.

The IR spectroscopy permits the observation of distinct N–H stretching absorptions for hydrogen-bonded and non-hydrogen-bonded states. The IR spectrum of a 3 mM solution of **4a** exhibited two bands of almost equal intensity in the region of NH stretch, at 3342 cm^{-1} (hydrogen-bonded state) and at 3428 cm^{-1} (non-hydrogen-bonded state). On the other hand, the IR spectrum of a 3 mM solution of **4b** showed an extensive absorption band at 3326 cm^{-1} for an hydrogen-bonded NH stretch and a narrower band at 3432 cm^{-1} for a non-hydrogen-bonded NH stretch, thus attesting the presence of a more stable secondary structure for **4b**.

Similar conformational studies by NMR and IR were also performed on hexapeptide mimics (Ac–(*S*)-Ala–AETIC–(*S*)-Ala–NHMe) **5a**,**b**. In this case, investigation of both sequential and long-range NOEs in NOESY spectra would provide evidence of preferred conformations and give insight into stable β-hairpin-like conformations (Fig. 4).

From NOESY spectrum of **5a**, amide NH_A was found to be located internally to the potential reverse turn, in accordance with the cross-strand NOE cross-peak between NH_A and Me_9 that confirms that a tight reverse turn may occur. In addition, the cross-strand NOEs between NH_DAc and H_{11} and between NH_DAc and NH_BMe suggest the formation of a minimal hairpin.

In diastereoisomer **5a** the ^{1}H NMR data show the predominance of a hydrogen-bonded state for NH_A (δ ($CDCl_3$) 8.21 ppb/K, ($\Delta\delta/\Delta T$) −3.3 ppb/K), thus confirming the existence of the classical β-turn hydrogen-bonded 10-membered ring. The value of chemical shift for amide protons NH_BMe and NH_DAc indicated that these H atoms essentially don't participate to stable hydrogen bonds. On the other hand, the NH_C chemical shift over 7 ppm, together with the high value of $\Delta\delta/\Delta T$, are consistent with this atom being involved in an equilibrium between non-hydrogen-bonded and hydrogen-bonded states, at room temperature. This is in accordance with what was predicted from conformational analysis, that is, to say the presence of stabilized γ-turn conformers involving NH_C and the Ac terminal group.

The diastereoisomer **5b**, having a 1,3-trans relative configuration, seems to have a more organized structure. The NOESY spectrum showed sequential NOEs indicating that

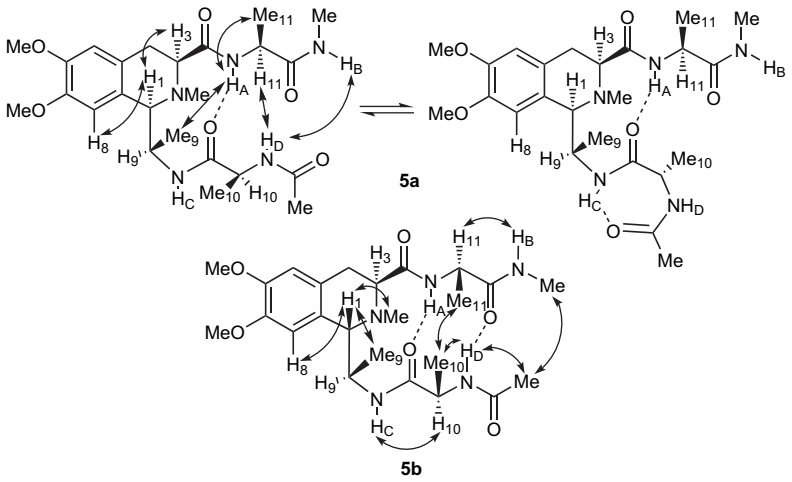


Figure 4. Schematic representation of the proposed structures for (Ac–(*S*)-Ala–AETIC–(*S*)-Ala–NHMe) **5a**,**b**. The expected hydrogen bonds are shown by dashed lines. Selected observed NOEs are highlighted by double-edged arrows.

Table 4. Spectroscopic data of hexapeptide mimics (Ac–(*S*)-Ala–AETIC–(*S*)-Ala–NHMe) **5a**,**b**

		δ ($CDCl_3$)	($\Delta\delta/\Delta T$)	IR absorption bands
(Ac–(*S*)-Ala–AETIC–(*S*)-Ala–NHMe) **5a**	NH_A	8.21	−3.3	3332, 3438
	NH_BMe	6.45	−2.7	
	NH_C	7.07	−13.9	
	NH_DAc	6.56	−5.0	
(Ac–(*S*)-Ala–AETIC–(*S*)-Ala–NHMe) **5b**	NH_A	8.20	−2.0	3308, 3441
	NH_BMe	6.34	−2.4	
	NH_C	6.64	−1.3	
	NH_DAc	8.09	−5.0	

the two arms are organized into β-strands. The presence of cross-strand NOEs between Me_{10} and Me_{11} and between the NMe and Ac groups fully supports the formation of a β-hairpin conformation. The hydrogen bonding studies showed the small magnitude of the temperature coefficient for NH_A (δ ($CDCl_3$) 8.20 ppb/K, ($\Delta\delta/\Delta T$) −2.0 ppb/K), clearly indicating participation of this atom in a strong intramolecular 10-membered ring hydrogen-bonding. The high chemical shift of NH_DAc, together with the large temperature dependence (δ ($CDCl_3$) 8.09 ppb/K, ($\Delta\delta/\Delta T$) −5.0 ppb/K), is in accord with the presence of a weakly hydrogen-bonded state for this proton. It participates with a 14-membered intramolecular hydrogen bond ring, while NH_BMe and NH_C are essentially non-hydrogen-bonded (Table 4).

Further evidence of the presence of a stable secondary structure for **5b** was given by the IR spectrum, which exhibited a broad absorption band at 3308 cm^{-1} for a hydrogen-bonded NH stretch and a weak band at 3441 cm^{-1} for a non-hydrogen-bonded NH stretch. In the IR spectrum of **5a**, we assigned the hydrogen-bonded NH stretching vibrations at 3332 cm^{-1} while the free NH appears at 3438 cm^{-1} (Table 4).

3. Conclusion

In this paper, we have described the synthesis of new enantiomerically pure tetrapeptide and hexapeptide mimics. Both MM calculations and spectroscopic NMR and IR investigations support the conclusion that the TIC-based scaffold **1b** is a better turn inducer than **1a**. In fact, in the case of the tetrapeptide mimics Ac–AETIC–NHMe, a β-turn conformation can be induced more easily in **4b** than in **4a**. In hexapeptide mimics (Ac–(*S*)-Ala–AETIC–(*S*)-Ala–NHMe), the propensity to adopt a reverse turn conformation is greatly enhanced, regardless at the stereochemistry at C1. In fact, the 1,3-cis and 1,3-trans relative configurations, in **5a** and **5b**, both allow the formation of a classical β-turn hydrogen-bonded 10-membered ring. In addition, a β-hairpin-like conformation can be postulated for **5b** in its lowest energy state, based on an additional hydrogen bond involving a 14-membered intramolecular ring.

In order to incorporate these AETIC scaffolds into selected linear or cyclic peptides, we are currently accomplishing their synthesis in a suitably protected form. Choosing appropriate protecting groups may also enable the introduction of these templates into SPPS, giving rise to larger peptides bearing the Tic constraint.

4. Experimental section

4.1. General

All solvents were distilled and properly dried (CaH_2), when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (Merck); spots were visualized with UV light or by treatment with

1% aq $KMnO_4$ solution. Products were purified by flash chromatography on Merck silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded with Bruker AC 300 (^1H, 300 MHz; ^{13}C, 75.4 MHz) and 400 MHz Avance (^1H, 400 MHz; ^{13}C, 100 MHz) NMR spectrometers. NOESY spectra were recorded with a mixing time of 700 ms. Chemical shifts are reported in parts per million downfield from $SiMe_4$ (δ=0.0). The temperature study was performed on 3 mM $CDCl_3$ solutions, with a temperature increment of 5 K between 297 K and 327 K. For the atom labeling in the NMR spectra: see Figure 1. HR-EI mass spectra were measured on VG 70–70 EQ–HF instrument equipped with its standard sources. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Jasco FTIR 300-E spectrometer.

Molecular modeling: The calculations were carried out using Spartan '06 for Windows.[14] The MMFF94[17] force field was used in vacuo for the energy minimization of **4a**,**b** and **5a**,**b**. The conformational analyses were carried out with unconstrained Monte Carlo method. The algorithm was a standard simulated annealing algorithm. Conformations were weighted via the normalized Boltzmann criteria. For compounds **4a**,**b** and **5a**,**b**, respectively, 441 and 1089 conformers were generated. Only conformations within 6 kcal/mol of the global minimum were kept. Structures were minimized using a gradient convergence criterion of 4.5×10^{-4} hartrees/bohr.

4.1.1. (*S*)-2-*tert*-Butoxycarbonylamino-3-(3,4-dimethoxyphenyl)propionic acid methyl ester (6). Compound **6** was prepared according to Ref. 12.

4.1.2. [(*S*)-2-(3,4-Dimethoxyphenyl)-1-methylcarbamoylethyl]carbamic acid *tert*-butyl ester (7). To a solution of **6** (1 g, 2.95 mmol) in dry methanol (10 mL) under nitrogen atmosphere, methylamine 40% aq solution (10 mL) was added dropwise. The mixture was stirred for 4 h at room temperature then the solvent was removed under reduced pressure affording pure **7** as a foam (977 mg, 98% yield). R_f=0.27 (hexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ +27.4 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.78 (d, *J*=6.8 Hz, 1H, 8a-H), 6.70 (d, *J*=6.8 Hz, 1H, 8-H), 6.68 (s, 1H, 5-H), 5.78 (br s, 1H, N*H*Me), 5.06 (br s, 1H, N*H*Boc), 4.22 (br m, 1H, 3-H), 3.85 (s, 3H, ArOCH_3), 3.81 (s, 3H, ArOCH_3), 3.04 (dd, *J*=13.1, 6.1 Hz, 1H, 4-H), 2.91 (dd, *J*=13.1, 6.7 Hz, 1H, 4-H), 2.70 (d, *J*=5.9 Hz, 3H, NHCH_3), 1.44 (s, 9H, Boc). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.2, 154.6, 148.3, 147.5, 128.1, 120.9, 111.8, 110.7, 79.2, 55.3, 55.2, 54.1, 37.2, 27.8, 26.2. HRMS-EI *m*/*z* calcd 338.1842, found 338.1849. Anal. Calcd for $C_{17}H_{26}N_2O_5$: C, 60.34%; H, 7.74%; N, 8.28%; O, 23.64%. Found: C, 60.69%; H, 7.51%; N, 8.12%.

N-Cbz-L-Alaninal was prepared according to Ref. 13.

4.1.3. [(*S*)-1-((1*R*,3*S*)-6,7-Dimethoxy-3-methylcarbamoyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl]carbamic acid benzyl ester (8a) and [(*S*)-1-((1*S*,3*S*)-6,7-dimethoxy-3-methylcarbamoyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl]carbamic acid benzyl ester (8b). Product **7** (500 mg, 1.48 mmol) was dissolved in 30% TFA/CH_2Cl_2 solution (15 mL) under nitrogen atmosphere, at 0 °C. After stirring for 3 h at 0 °C, the solvent was evaporated and the residue oil was treated with saturated $NaHCO_3$ aq solution, until pH 8 (10 mL). The aqueous phase was extracted with dichloromethane (3×15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure, thus affording the *N*-Boc deprotected product (*S*)-2-amino-3-(3,4-dimethoxyphenyl)-*N*-methyl-propionamide as an oil (335 mg). R_f=0.10 (methanol/ethyl acetate, 1:9). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.81 (d, *J*=8.0 Hz, 1H, 8a-H), 6.77 (s, 1H, 5-H), 6.75 (d, *J*=8.0 Hz, 1H, 8-H), 5.31 (s, 1H, N*H*Me), 3.87 (s, 3H, ArOCH_3), 3.84 (s, 3H, ArOCH_3), 3.59 (dd, *J*=8.8, 4.0 Hz, 1H, 3-H), 3.19 (dd, *J*=14.0, 4.0 Hz, 1H, 4-H), 2.83 (d, *J*=4.8 Hz, 3H, NHCH_3), 2.67 (dd, *J*=14.0, 8.8 Hz, 1H, 4-H), 2.51 (br s, 2H, NH_2).

Under nitrogen atmosphere, (*S*)-2-amino-3-(3,4-dimethoxyphenyl)-*N*-methyl-propionamide (300 mg, 1.26 mmol) was dissolved in 5% TFA/CH_2Cl_2 solution (10 mL) and cooled to 0 °C with an ice bath. A solution of *N*-Cbz-L-alaninal (260 mg, 1.26 mmol) in 5% TFA/CH_2Cl_2 solution (5 mL) was slowly added to the amine solution. After the addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, the residue oil was rinsed with saturated $NaHCO_3$ aq solution until pH 8 and the aqueous phase was extracted with dichloromethane (3×15 mL). The organic phase was then dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography over silica gel (ethyl acetate/methanol, 98:2) affording 126 mg (20% yield, from **7**) of **8a** as an oil and 377 mg (60% yield, from **7**) of **8b** as an oil.

Compound **8a**: R_f=0.40 (methanol/ethyl acetate, 1:9). $[\alpha]_D^{25}$ −64.5 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36 (m, 5H, Cbz aromatics), 6.96 (br m, 1H, N*H*Me), 6.67 (s, 1H, 8-H), 6.62 (s, 1H, 5-H), 5.34 (d, *J*=6.8 Hz, 1H, N*H*Cbz), 5.17 (s, 2H, Cbz-CH_2), 4.35 (m, 1H, 9-H), 4.28 (m, 1H, 1-H), 3.86 (s, 3H, ArOCH_3), 3.81 (s, 3H, ArOCH_3), 3.49 (dd, *J*=8.2, 3.6 Hz, 1H, 3-H), 3.07 (dd, *J*=15.0, 3.6 Hz, 1H, 4-H), 2.87 (d, *J*=5.2 Hz, 3H, NHCH_3), 2.68 (dd, *J*=15.0, 8.2, 1H, 4-H), 2.24 (br s, 1H, N*H*), 0.99 (d, *J*=6.4 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2, 156.2, 148.5, 148.1, 136.8, 128.7–127.8 (5C), 126.5, 126.1, 112.4, 109.1, 67.6, 59.7, 57.4, 55.5, 51.0, 33.0, 26.2, 18.1, 14.8. HRMS-EI *m*/*z* calcd 427.2107, found 427.2101. Anal. Calcd for $C_{23}H_{29}N_3O_5$: C, 64.62%; H, 6.84%; N, 9.83%; O, 18.71%. Found: C, 64.69%; H, 6.79%; N, 9.76%.

Compound **8b**: R_f=0.27 (methanol/ethyl acetate, 1:9). $[\alpha]_D^{25}$ −81.8 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (m, 5H, Cbz aromatics), 6.79 (br m, 1H, N*H*Me), 6.71 (s, 1H, 8-H), 6.56 (s, 1H, 5-H), 5.18 (d, *J*=6.7 Hz, 1H, N*H*Cbz), 5.00 (s, 2H, Cbz-CH_2), 4.30 (m, 1H, 9-H), 4.08 (m, 1H, 1-H), 3.85 (s, 3H, ArOCH_3), 3.77 (s, 3H, ArOCH_3), 3.56 (dd, *J*=11.2, 3.6 Hz, 1H, 3-H), 2.93 (dd, *J*=15.2, 3.6 Hz, 1H, 4-H), 2.86 (d, *J*=5.6 Hz, 3H, NHCH_3), 2.73 (dd, *J*=15.2, 11.2, 1H, 4-H), 2.18 (br s, 1H, N*H*), 1.30 (d, *J*=6.8 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.0, 156.0, 147.9, 147.7, 136.6, 128.6–127.7 (5C), 126.8, 126.6, 111.7, 109.0, 66.5, 59.7, 57.2, 55.9, 50.4, 33.1, 25.9, 18.6, 14.2. HRMS-EI *m*/*z* calcd 427.2107, found 427.2116. Anal. Calcd

for $C_{23}H_{29}N_3O_5$: C, 64.62%; H, 6.84%; N, 9.83%; O, 18.71%. Found: C, 64.53%; H, 6.77%; N, 9.88%.

4.1.4. [(*S*)-1-((1*R*,3*S*)-6,7-Dimethoxy-2-methyl-3-methylcarbamoyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl]carbamic acid benzyl ester (9a). Under nitrogen atmosphere, **8a** (200 mg, 0.47 mmol) was dissolved in 1 M AcOH in MeOH (8 mL), then a 40% formaldehyde aq solution (65 μL, 0.94 mmol) was added. After 30 min, $NaCNBH_3$ (58 mg, 0.94 mmol) was added in portions and the reaction was stirred at room temperature for 3 h. Then, a saturated $NaHCO_3$ aq solution (10 mL) was added and the mixture was stirred for 30 min. The reaction was extracted with dichloromethane (3×15 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent afforded pure product **9a** as a pale yellow oil (188 mg, 91% yield). R_f=0.21 (ethyl acetate). $[\alpha]_D^{25}$ −124.9 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (m, 5H, Cbz aromatics), 7.30 (br m, 1H, N*H*Me), 6.65 (s, 1H, 8-H), 6.55 (s, 1H, 5-H), 5.09 (d, *J*=12.1 Hz, 1H, CH_2Cbz), 5.03 (d, *J*=12.1 Hz, 1H, CH_2Cbz), 4.49 (d, *J*=8.6 Hz, 1H, N*H*Cbz), 4.17 (m, 1H, 9-H), 3.87 (s, 3H, ArOCH_3), 3.85 (s, 3H, ArOCH_3), 3.64 (d, *J*=3.8 Hz, 1H, 1-H), 2.99 (dd, *J*=12.5, 3.6 Hz, 1H, 3-H), 2.90 (dd, *J*=15.0, 3.6 Hz, 1H, 4-H), 2.85 (d, *J*=5.2 Hz, 3H, CONHCH_3), 2.64 (dd, *J*=15.0, 12.5, 1H, 4-H), 2.50 (s, 3H, NCH_3), 1.17 (d, *J*=6.7 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.98, 156.37, 148.09, 147.25, 136.29, 128.63–127.97 (5C), 127.54, 124.85, 111.42, 110.79, 68.98, 66.78, 66.28, 56.08, 55.96, 52.96, 45.48, 34.14, 25.93, 18.15. HRMS-EI *m*/*z* calcd 441.2264, found 441.2269. Anal. Calcd for $C_{24}H_{31}N_3O_5$: C, 65.29%; H, 7.08%; N, 9.52%; O, 18.12%. Found: C, 65.18%; H, 6.99%; N, 9.61%.

4.1.5. [(*S*)-1-((1*S*,3*S*)-6,7-Dimethoxy-2-methyl-3-methylcarbamoyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethyl]carbamic acid benzyl ester (9b). The same procedure for the preparation of **9a** was followed (pale yellow oil, 93% yield). R_f=0.42 (ethyl acetate/methanol, 9:1). $[\alpha]_D^{25}$ −78.1 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (br s, 1H, N*H*Me), 7.37 (m, 5H, Cbz aromatics), 6.69 (s, 1H, 8-H), 6.56 (s, 1H, 5-H), 5.27 (d, *J*=12.3 Hz, 1H, CH_2Cbz), 5.11 (d, *J*=12.3 Hz, 1H, CH_2Cbz), 4.75 (d, *J*=9.5 Hz, 1H, N*H*Cbz), 3.88 (s, 3H, ArOCH_3), 3.84 (s, 3H, ArOCH_3), 3.79 (m, 1H, 9-H), 3.31 (d, *J*=8.4 Hz, 1H, 1-H), 2.92 (dd, *J*=13.8, 2.6 Hz, 1H, 4-H), 2.86 (m, 2H, 4-H, 3-H), 2.75 (d, *J*=4.5 Hz, 3H, CONHCH_3), 2.44 (s, 3H, NCH_3), 0.96 (d, *J*=6.8 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1, 156.3, 147.9, 147.5, 136.3, 128.6–127.8 (5C), 126.7, 126.5, 111.5, 109.8, 67.0, 66.5, 65.9, 56.7, 55.9, 51.4, 46.8, 33.5, 25.9, 18.6. HRMS-EI *m*/*z* calcd 441.2264, found 441.2260. Anal. Calcd for $C_{24}H_{31}N_3O_5$: C, 65.29%; H, 7.08%; N, 9.52%; O, 18.12%. Found: C, 65.34%; H, 7.16%; N, 9.60%.

4.1.6. (1*R*,3*S*)-1-((*S*)-1-Acetylaminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylamide (4a). Product **9a** (150 mg, 0.34 mmol) was dissolved in methanol (10 mL) and 10% Pd/C (15 mg, 10% w/w) was added. The reaction mixture was then placed under a hydrogen atmosphere (1 bar) and stirred at room temperature overnight. The mixture was filtered through Celite and the solvent was evaporated under reduced pressure to afford the *N*-Cbz deprotected product (1*R*,3*S*)-1-((*S*)-1-aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methylamide as an oil (100 mg). R_f=0.10 (methanol/ethyl acetate/NH_3, 18:80:2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.02 (d, *J*=7.2 Hz, 1H, CON*H*Me), 6.68 (s, 1H, 8-H), 6.59 (s, 1H, 5-H), 4.05 (m, 1H, 1-H), 3.83 (s, 3H, ArOCH_3), 3.80 (s, 3H, ArOCH_3), 3.79 (m, 1H, 3-H), 3.06 (m, 2H, 9-H, 4-H), 2.88 (d, *J*=4.9 Hz, 3H, CONHCH_3), 2.65 (dd, *J*=14.8, 3.6 Hz, 1H, 4-H), 2.48 (br s, 2H, NH_2), 2.44 (s, 3H, NCH_3), 1.18 (d, *J*=7.0 Hz, 3H, 9-CH_3).

Under nitrogen atmosphere, (1*R*,3*S*)-1-((*S*)-1-aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylamide (90 mg, 0.29 mmol) and 4-(dimethylamino)pyridine (35 mg, 0.29 mmol) were dissolved in dry pyridine (4 mL). The solution was cooled to 0 °C with an ice bath and acetic anhydride (55 μL, 0.58 mmol) was added dropwise. The ice bath was removed and the reaction mixture was stirred overnight at room temperature. HCl 6 N was added slowly until pH 5 and then the solution was extracted with dichloromethane (3×10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography over silica gel (ethyl acetate/methanol, 93:7) affording **4a** as an oil (82 mg, 70% yield, from **9a**).

Compound **4a**: R_f=0.27 (ethyl acetate). $[\alpha]_D^{25}$ −105.1 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (br m, 1H, N*H*Me), 6.69 (s, 1H, 8-H), 6.61 (s, 1H, 5-H), 5.40 (d, *J*=6.9 Hz, 1H, N*H*Ac), 4.27 (m, 1H, 9-H), 4.11 (m, 1H, 1-H), 3.86 (s, 3H, ArOCH_3), 3.84 (s, 3H, ArOCH_3), 3.49 (dd, *J*=7.6, 3.0 Hz, 1H, 3-H), 3.07 (dd, *J*=15.0, 3.0 Hz, 1H, 4-H), 2.87 (d, *J*=5.2 Hz, 3H, NHCH_3), 2.68 (dd, *J*=15.0, 7.6, 1H, 4-H), 2.40 (s, 3H, NCH_3), 2.05 (s, 3H, NCOCH_3), 1.11 (d, *J*=6.4 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.2, 170.4, 147.5, 147.1, 127.5, 123.8, 111.3, 109.4, 67.6, 66.9, 57.6, 56.8, 48.2, 44.3, 34.0, 26.4, 23.5, 18.1. IR (3 mM $CHCl_3$ solution): 3428, 3342, 3002, 1662, 1517, 1245, 1055, 755 cm^{-1}. HRMS-EI *m*/*z* calcd 349.2002, found 349.2007. Anal. Calcd for $C_{18}H_{27}N_3O_4$: C, 61.87%; H, 7.79%; N, 12.03%; O, 18.32%. Found: C, 61.94%; H, 7.83%; N, 12.08%.

4.1.7. (1*S*,3*S*)-1-((*S*)-1-Acetylaminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylamide (4b). The same procedure for the preparation of **4a** was followed (oil, 68% yield, from **9b**).

4.1.8. (1*S*,3*S*)-1-((*S*)-1-Aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylamide. Pale yellow oil, R_f=0.15 (methanol/ethyl acetate/NH_3, 18:80:2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96 (d, *J*=7.4 Hz, 1H, CON*H*Me), 6.75 (s, 1H, 8-H), 6.58 (s, 1H, 5-H), 3.83 (s, 3H, ArOCH_3), 3.80 (s, 3H, ArOCH_3), 3.58 (d, *J*=9.2 Hz, 1H, 1-H), 3.11 (m, 2H, 4-H), 2.87 (d, *J*=5.2 Hz, 3H, CONHCH_3), 3.81 (m, 1H, 3-H), 2.65 (m, 1H, 9-H), 2.47 (s, 3H, NCH_3), 2.01 (br s, 2H, NH_2), 1.23 (d, *J*=7.6 Hz, 3H, 9-CH_3).

Compound **4b**: Pale yellow oil, R_f=0.18 (ethyl acetate). $[\alpha]_D^{25}$ −57.5 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (br d, *J*=4.6 Hz, 1H, CON*H*Me), 6.73 (s, 1H, 8-H), 6.66 (s, 1H, 5-H), 6.32 (d, *J*=8.9 Hz, 1H, N*H*Ac), 5.38 (d,

J=10.6 Hz, 1H, 1-H), 4.27 (m, 1H, 9-H), 4.13 (m, 1H, 3-H), 3.89 (s, 3H, ArOCH_3), 3.86 (s, 3H, ArOCH_3), 3.21 (dd, J=14.2, 5.3 Hz, 1H, 4-H), 3.10 (dd, J=14.2, 8.2 Hz, 1H, 4-H), 2.87 (d, J=4.6 Hz, 3H, CONHCH_3), 2.18 (s, 3H, NCH_3), 2.05 (s, 3H, NCOCH_3), 1.05 (d, J=6.4 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 170.0, 148.1, 147.9, 127.0, 124.2, 112.1, 110.0, 67.0, 65.7, 57.5, 56.5, 51.3, 42.8, 34.4, 26.4, 23.5, 18.1. IR (3 mM $CHCl_3$ solution): 3432, 3326, 2998, 2949, 1657, 1511, 1254, 805 cm^{-1}. HRMS-EI m/z calcd 349.2002, found 349.1998. Anal. Calcd for $C_{18}H_{27}N_3O_4$: C, 61.87%; H, 7.79%; N, 12.03%; O, 18.32%. Found: C, 61.79%; H, 7.84%; N, 12.09%.

4.1.9. (*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(3,4-dimethoxyphenyl)propionylamino]propionic acid methyl ester (10). To a THF/water 1:1 solution (50 mL) of **6** (2 g, 5.90 mmol), LiOH (354 mg, 14.75 mmol) was added. After 1 h, the solvent was concentrated in vacuo and 5% H_3PO_4 aq solution was added until the solution was at pH 3. The aqueous phase was extracted with ethyl acetate (2×30 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure affording pure (*S*)-2-*tert*-butoxycarbonylamino-3-(3,4-dimethoxyphenyl)propionic acid as a foam (1.86 g). R_f=0.36 (ethyl acetate/methanol, 7:3). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.11 (br s, 1H, COO*H*), 7.25 (d, J=2.6 Hz, 1H, 5-H), 6.83 (d, J=8.4 Hz, 1H, 8-H), 6.65 (dd, J=8.4, 2.6 Hz, 1H, 8a-H), 5.06 (d, J=5.8 Hz, 1H, N*H*Boc), 4.52 (br m, 1H, 3-H), 3.89 (s, 3H, ArOCH_3), 3.81 (s, 3H, ArOCH_3), 3.06 (m, 2H, 4-H), 1.44 (s, 9H, Boc).

Under nitrogen atmosphere, (*S*)-2-*tert*-butoxycarbonylamino-3-(3,4-dimethoxyphenyl)propionic acid (1.70 g, 5.23 mmol) was dissolved in dry DMF (12 mL). The solution was cooled to −20 °C and 4-methylmorpholine (1.15 mL, 10.46 mmol) and isobutyl chloroformate (681 μL, 5.23 mmol) were added. After 30 min, a solution of L-alanine-OMe hydrochloride (730 mg, 5.23 mmol) in dry DMF (5 mL) was added dropwise. The mixture was stirred at room temperature overnight. A 5% $NaHCO_3$ aq solution (25 mL) was added and the mixture was extracted with dichloromethane (3×15 mL). The organic phase was washed with brine, then with 20 mL of H_3PO_4 5% aq solution, dried over Na_2SO_4, and concentrated under reduced pressure to give pure **10** as an oil (1.93 g, 80% yield). R_f=0.27 (ethyl acetate/hexane, 1:1). $[\alpha]_D^{25}$ −50.1 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81 (d, J=7.9 Hz, 1H, 8-H), 6.77 (dd, J=7.9, 1.5 Hz, 1H, 8a-H), 6.75 (d, J=1.5 Hz, 1H, 5-H), 6.43 (d, J=7.1 Hz, 1H, H_A), 5.03 (br d, 1H, N*H*Boc), 4.52 (m, 1H, 3-H), 4.34 (br q, J=7.1 Hz, 1H, 11-H), 3.87 (s, 3H, ArOCH_3), 3.87 (s, 3H, ArOCH_3), 3.73 (s, 3H, COOCH_3), 3.07 (dd, J=13.8, 6.3 Hz, 1H, 4-H), 2.99 (dd, J=13.8, 6.8 Hz, 1H, 4-H), 1.44 (s, 9H, Boc), 1.36 (d, J=7.1 Hz, 3H, 11-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.5, 171.5, 156.0, 149.9, 148.9, 129.8, 122.2, 113.4, 112.3, 80.9, 56.7, 56.6, 54.1, 53.1, 48.9, 38.7, 29.0, 18.4. HRMS-EI m/z calcd 410.2053, found 410.2044. Anal. Calcd for $C_{20}H_{30}N_2O_7$: C, 58.52%; H, 7.37%; N, 6.82%; O, 27.29%. Found: C, 58.42%; H, 7.45%; N, 6.75%.

4.1.10. [(*S*)-2-(3,4-Dimethoxyphenyl)-1-((*S*)-1-methylcarbamoylethylcarbamoyl)ethyl]carbamic acid *tert*-butyl ester (11). To a solution of **10** (1.5 g, 3.66 mmol) in dry methanol (20 mL) under nitrogen atmosphere, a methylamine 40% aq solution (30 mL) was added dropwise. The mixture was stirred for 6 h at room temperature, and then the solvent was removed under reduced pressure affording pure **11** as an oil (1.42 g, 95% yield). R_f=0.27 (ethyl acetate/hexane, 1:1). $[\alpha]_D^{25}$ −50.1 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.82 (d, J=8.0 Hz, 1H, 8-H), 6.70 (dd, J=8.0, 2.0 Hz, 1H, 8a-H), 6.68 (d, J=2.0 Hz, 1H, 5-H), 6.58 (d, J=7.0 Hz, 1H, H_A), 6.40 (d, J=6.7 Hz, 1H, H_B), 5.05 (d, J=7.0 Hz, 1H, N*H*Boc), 4.44 (m, 1H, 3-H), 4.25 (br q, J=7.1 Hz, 1H, 11-H), 3.85 (s, 3H, ArOCH_3), 3.83 (s, 3H, ArOCH_3), 3.00 (m, 2H, 4-H), 2.68 (d, J=6.7, 3H, CONHCH_3), 1.44 (s, 9H, Boc), 1.31 (d, J=7.1 Hz, 3H, 11-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.8, 170.2, 156.4, 149.1, 147.9, 129.8, 121.5, 111.8, 110.5, 81.0 56.8, 56.4, 53.8, 52.5, 48.6, 36.4, 25.8, 18.0. HRMS-EI m/z calcd 409.2213, found 409.2219. Anal. Calcd for $C_{20}H_{31}N_3O_6$: C, 58.66%; H, 7.63%; N, 10.26%; O, 23.44%. Found: C, 58.60%; H, 7.58%; N, 10.31%.

4.1.11. {(*S*)-1-[(1*R*,3*S*)-6,7-Dimethoxy-3-((*S*)-1-methylcarbamoylethylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]ethyl}carbamic acid benzyl ester (12a) and {(*S*)-1-[(1*S*,3*S*)-6,7-dimethoxy-3-((*S*)-1-methylcarbamoylethylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]ethyl}carbamic acid benzyl ester (12b). Product **11** (1.25 g, 3.06 mmol) was dissolved in 30% TFA/CH_2Cl_2 solution (15 mL) under nitrogen atmosphere, at 0 °C. The reaction mixture was stirred for 5 h at 0 °C, then the solvent was evaporated and the residue oil was treated with saturated $NaHCO_3$ aq solution (20 mL) until pH 8. The aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The *N*-Boc deprotected product (*S*)-2-amino-3-(3,4-dimethoxyphenyl)-*N*-((*S*)-1-methylcarbamoylethyl)propionamide (908 mg) was obtained as an oil without further purification. R_f=0.08 (methanol/ethyl acetate, 1:9). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.66 (d, J=7.2 Hz, 1H, H_A), 6.78 (d, J=8.1 Hz, 1H, 8-H), 6.72 (dd, J=8.2, 2.4 Hz, 1H, 8a-H), 6.70 (d, J=2.4 Hz, 1H, 5-H), 6.45 (d, J=6.2 Hz, 1H, H_B), 4.40 (m, 1H, 11-H), 3.85 (s, 3H, ArOCH_3), 3.83 (s, 3H, ArOCH_3), 3.58 (dd, J=9.8, 3.4 Hz, 1H, 3-H), 3.15 (dd, J=11.4, 3.4 Hz, 1H, 4-H), 2.68 (d, J=6.2 Hz, 3H, CONHCH_3), 2.63 (dd, J=11.4, 9.8 Hz, 1H, 4-H), 1.56 (s, 2H, NH_2), 1.34 (d, J=7.1 Hz, 3H, 11-CH_3).

Under nitrogen atmosphere, (*S*)-2-amino-3-(3,4-dimethoxyphenyl)-*N*-((*S*)-1-methylcarbamoylethyl)propionamide (900 mg, 2.91 mmol) was dissolved in 5% TFA/CH_2Cl_2 solution (20 mL) and cooled to 0 °C with an ice bath. A solution of *N*-Cbz-L-alaninal (602 mg, 2.91 mmol) in 5% TFA/CH_2Cl_2 solution (8 mL) was slowly added to the amine solution. After the addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue oil was rinsed with saturated $NaHCO_3$ aq solution (20 mL) until pH 8 and the aqueous phase was extracted with dichloromethane (3×20 mL). The organic phase was then dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography over silica gel (ethyl acetate/methanol, 98:2) affording 337 mg (26% yield) of **12a** as an oil and 505 mg (39% yield) of **12b** as an oil.

Compound **12a**: R_f=0.18 (methanol/ethyl acetate, 1:9). $[\alpha]_D^{25}$ −84.5 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, *J*=7.7 Hz, 1H, H_A), 7.38 (m, 5H, Cbz aromatics), 6.69 (s, 1H, 8-H), 6.61 (s, 1H, 5-H), 6.51 (d, *J*=4.8 Hz, 1H, H_B), 5.63 (d, *J*=8.3 Hz, 1H, N*H*Cbz), 5.16 (d, *J*=12.0 Hz, 1H, Cbz-CH_2), 5.11 (d, *J*=12.0 Hz, 1H, Cbz-CH_2), 4.49 (m, 1H, 11-H), 4.30 (m, 2H, 1-H+9-H), 3.87 (s, 3H, ArOCH_3), 3.84 (s, 3H, ArOCH_3), 3.53 (dd, *J*=11.6, 3.7 Hz, 1H, 3-H), 3.00 (dd, *J*=15.5, 3.7 Hz, 1H, 4-H), 2.82 (d, *J*=4.8 Hz, 3H, CONHCH_3), 2.69 (dd, *J*=15.5, 11.6 Hz, 1H, 4-H), 2.38 (s, 1H, N*H*), 1.41 (d, *J*=7.0 Hz, 3H, 11-CH_3), 0.99 (d, *J*=6.6 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.2, 173.5, 156.6, 148.7, 148.6, 137.2, 129.3–128.7 (5C), 127.6, 127.5, 112.5, 109.6, 67.5, 59.8, 57.4, 56.9, 56.6, 52.0, 49.2, 33.8, 27.0, 18.6, 15.0. HRMS-EI *m*/*z* calcd 498.2478, found 498.2477. Anal. Calcd for $C_{26}H_{34}N_4O_6$: C, 62.63%; H, 6.87%; N, 11.24%; O, 19.25%. Found: C, 62.68%; H, 6.91%; N, 11.27%.

Compound **12b**: R_f=0.12 (methanol/ethyl acetate, 1:9). $[\alpha]_D^{25}$ −101.8 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (q, *J*=2.9 Hz, 1H, H_A), 7.31 (m, 5H, Cbz aromatics), 6.75 (s, 1H, 8-H), 6.59 (s, 1H, 5-H), 6.32 (d, *J*=4.7 Hz, 1H, H_B), 5.24 (br m, 1H, N*H*Cbz), 5.02 (s, 2H, Cbz-CH_2), 4.48 (m, 1H, 11-Ala), 4.35 (br m, 1H, 9-H), 4.09 (m, 1H, 1-H), 3.87 (s, 3H, ArOCH_3), 3.82 (s, 3H, ArOCH_3), 3.60 (dd, *J*=10.6, 3.8 Hz, 1H, 3-H), 2.94 (dd, *J*=15.1, 3.8 Hz, 1H, 4-H), 2.83 (d, *J*=4.7 Hz, 3H. NHCH_3), 2.77 (dd, *J*=15.1, 10.6 Hz, 1H, 4-H), 2.23 (s, 1H, N*H*), 1.39 (d, *J*=7.0 Hz, 3H, 11-CH_3), 1.32 (d, *J*=7.0 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.0, 173.3, 156.8, 148.7, 148.6, 137.4, 129.3–128.5 (5C), 127.5, 127.3, 112.1, 110.0, 67.2, 60.3, 57.6, 56.7, 56.6, 50.9, 49.3, 33.6, 27.0, 19.4, 18.7. HRMS-EI *m*/*z* calcd 498.2478, found 498.2480. Anal. Calcd for $C_{26}H_{34}N_4O_6$: C, 62.63%; H, 6.87%; N, 11.24%; O, 19.25%. Found: C, 62.69%; H, 6.81%; N, 11.30%.

4.1.12. {(*S*)-1-[(1*R*,3*S*)-6,7-Dimethoxy-2-methyl-3-((*S*)-1-methylcarbamoylethylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]ethyl}carbamic acid benzyl ester (13a). Under nitrogen atmosphere, **12a** (500 mg, 1.00 mmol) was dissolved in 1 M AcOH in MeOH (10 mL), then a 40% formaldehyde aq solution (138 μL, 2.00 mmol) was added. After 30 min, $NaCNBH_3$ (126 mg, 2.00 mmol) was added in portions and the reaction was stirred at room temperature for 4 h. Saturated $NaHCO_3$ aq solution (10 mL) was added and the mixture was stirred for 30 min. The reaction was extracted with dichloromethane (3×15 mL) and the combined organic layers were dried over Na_2SO_4. Evaporation of the solvent afforded pure product **13a** as an oil (451 mg, 88% yield). R_f=0.24 (methanol/ethyl acetate, 1:9). $[\alpha]_D^{25}$ −104.9 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, *J*=7.8 Hz, 1H, H_A), 7.32 (m, 5H, Cbz aromatics), 6.64 (s, 1H, 8-H), 6.61 (s, 1H, 5-H), 6.54 (br q, *J*=4.7 Hz, 1H, H_B), 5.18 (d, *J*=8.2 Hz, 1H, N*H*Cbz), 5.12 (d, *J*=12.0 Hz, 1H, Cbz-CH_2), 5.09 (d, *J*=12.0 Hz, 1H, Cbz-CH_2), 4.46 (m, 1H, 11-H), 4.08 (br m, 1H, 9-H), 3.86 (s, 3H, ArOCH_3), 3.83 (s, 3H, ArOCH_3), 3.71 (br m, 1H, 1-H), 2.97 (dd, *J*=12.3, 3.5 Hz, 1H, 3-H), 2.90 (dd, *J*=15.0, 3.5 Hz, 1H, 4-H), 2.82 (d, *J*=4.7 Hz, 3H, CONHCH_3), 2.67 (dd, *J*=15.0, 12.3 Hz, 1H, 4-H), 2.49 (s, 3H, NCH_3), 1.44 (d, *J*=7.0 Hz, 3H, 11-CH_3), 1.17 (d, *J*=6.8 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.2, 173.6, 156.6, 148.9, 148.4, 137.2, 129.2–128.7 (5C), 127.6, 126.9, 112.2, 111.6, 69.6, 68.2, 67.4, 56.8, 56.7, 54.2, 49.3, 47.0, 34.1, 26.9, 18.6, 17.9. HRMS-EI *m*/*z* calcd 512.2635, found 512.2639. Anal. Calcd for $C_{27}H_{36}N_4O_6$: C, 63.26; H, 7.08%; N, 10.93%; O, 18.73%. Found: C, 63.21; H, 7.11%; N, 10.88%.

4.1.13. {(*S*)-1-[(1*S*,3*S*)-6,7-Dimethoxy-2-methyl-3-((*S*)-1-methylcarbamoylethylcarbamoyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]ethyl}carbamic acid benzyl ester (13b). The same procedure for the preparation of **13a** as an oil was followed (86% yield). R_f=0.22 (methanol/ethyl acetate, 1:9). $[\alpha]_D^{25}$ −58.1 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.31 (d, *J*=7.7 Hz, 1H, H_A), 7.39 (m, 5H, Cbz aromatics), 6.68 (s, 1H, 8-H), 6.56 (s, 1H, 5-H), 6.43 (br q, *J*=5.2 Hz, 1H, H_B), 5.24 (d, *J*=12.0 Hz, 1H, Cbz-CH_2), 5.13 (d, *J*=12.0 Hz, 1H, Cbz-CH_2), 4.89 (d, *J*=8.0 Hz, 1H, N*H*Cbz), 4.50 (m, 1H, 11-H), 3.88 (s, 3H, ArOCH_3), 3.84 (br m, 1H, 9-H), 3.82 (s, 3H, ArOCH_3), 3.71 (br d, *J*=8.4 Hz, 1H, 1-H), 2.90 (dd, *J*=12.0, 3.2 Hz, 1H, 3-H), 2.83 (m, 2H, 4-H), 2.81 (d, *J*=5.2 Hz, 3H, CONHCH_3), 2.49 (s, 3H, NCH_3), 1.50 (d, *J*=6.8 Hz, 3H, 11-CH_3), 0.96 (d, *J*=6.8 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.0, 173.1, 156.7, 148.2, 147.3, 136.4, 129.2–128.7 (5C), 127.4, 126.5, 112.0, 110.6, 70.8, 67.9, 67.0, 56.0, 55.9, 53.35, 48.5, 46.1, 33.3, 26.3, 18.3, 16.8. HRMS-EI *m*/*z* calcd 512.2635, found 512.2637. Anal. Calcd for $C_{27}H_{36}N_4O_6$: C, 63.26; H, 7.08%; N, 10.93%; O, 18.73%. Found: C, 63.28; H, 7.10%; N, 10.96%.

4.1.14. (1*R*,3*S*)-1-[(*S*)-1-((*S*)-2-Acetylaminopropionylamino)ethyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((*S*)-1-methylcarbamoylethyl)amide (5a). Product **13a** (400 mg, 0.78 mmol) was dissolved in methanol (10 mL) and 10% Pd/C (40 mg, 10% w/w) was added. The reaction mixture was then placed under a hydrogen atmosphere (1 bar) and stirred at room temperature overnight. The mixture was filtered through Celite and the solvent was evaporated under reduced pressure to afford the *N*-Cbz deprotected product (1*R*,3*S*)-1-((*S*)-1-aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((*S*)-1-methylcarbamoylethyl)amide as an oil (283 mg). R_f=0.14 (methanol/ethyl acetate/NH_3, 18:80:2). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.11 (d, *J*=7.8 Hz, 1H, H_A), 6.68 (br q, *J*=5.0 Hz, 1H, H_B), 6.57 (s, 1H, 8-H), 6.41 (s, 1H, 5-H), 4.48 (m, 1H, 11-H), 4.08 (br m, 1H, 1-H), 3.81 (s, 3H, ArOCH_3), 3.78 (s, 3H, ArOCH_3), 3.61 (m, 1H, 9-H), 3.45 (m, 1H, 3-H), 3.12 (dd, *J*=14.8, 3.8 Hz, 1H, 4-H), 2.92 (m, 1H, 4-H), 2.81 (d, *J*=5.0 Hz, 3H, CONHCH_3), 2.51 (s, 3H, NCH_3), 2.46 (br s, 2H, NH_2), 1.51 (d, *J*=7.0 Hz, 3H, 11-CH_3), 1.05 (d, *J*=7.0 Hz, 3H, 9-CH_3).

Under nitrogen atmosphere, L-alanine-OMe hydrochloride (91 mg, 0.66 mmol) was dissolved in dry DMF (4 mL). The solution was cooled to −20 °C and 4-methylmorpholine (144 μL, 1.32 mmol) and isobutyl chloroformate (86 μL, 0.66 mmol) were added. After 30 min, a solution of (1*R*,3*S*)-1-((*S*)-1-aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((*S*)-1-methylcarbamoylethyl)amide (250 mg, 0.66 mmol) in dry DMF (2 mL) was added dropwise. The mixture was stirred at room temperature overnight. Then 5% $NaHCO_3$ aq solution (12 mL)

was added and the mixture was extracted with dichloromethane (3×10 mL). The organic phase was washed with brine (2×20 mL), then with 20 mL of H_3PO_4 5% aq solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (dichloromethane/methanol, 97:3) affording **5a** (276 mg, 72%, from **13a**), as a foam. R_f=0.24 (methanol/ethyl acetate, 1:9). $[\alpha]_D^{25}$ −121.9 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, *J*=7.6 Hz, 1H, H_A), 7.07 (d, *J*=8.6 Hz, 1H, H_C), 6.63 (s, 1H, 5-H), 6.56 (d, *J*=7.4 Hz, 1H, H_D), 6.49 (s, 1H, 8-H), 6.45 (br q, *J*=8.7 Hz, 1H, H_B), 4.51 (dq, *J*=7.4, 3.5 Hz, 1H, 10-H), 4.47 (br q, *J*=7.1 Hz, 1H, 11-H), 4.17 (dq, *J*=6.7, 4.5 Hz, 1H, 9-H), 3.88 (s, 3H, ArOCH_3), 3.84 (s, 3H, ArOCH_3), 3.64 (m, 2H, 3-H+1-H), 3.22 (dd, *J*=17.1, 6.8 Hz, 1H, 4-H), 2.87 (m, 4H, 4-H+NHCH_3), 2.52 (s, 3H, NCH_3), 2.00 (s, 3H, COCH_3), 1.39 (d, *J*=7.0 Hz, 3H, 11-CH_3), 1.34 (d, *J*=7.0 Hz, 3H, 10-CH_3), 1.08 (d, *J*=4.5 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1, 173.2, 172.4, 171.7, 148.7, 146.9, 125.4, 121.3, 112.8, 111.4, 60.1, 58.6, 56.1, 55.9, 51.3, 49.2, 48.3, 39.9, 27.3, 26.4, 23.1, 18.9, 18.3, 18.2. IR (3 mM $CHCl_3$ solution): 3332, 3438, 2995, 1665, 1518, 1450, 1256, 910, 704 cm^{-1}. HRMS-EI *m/z* calcd 491.2744, found 491.2749. Anal. Calcd for $C_{24}H_{37}N_5O_6$: C, 58.64; H, 7.59%; N, 14.25%; O, 19.53%. Found: C, 58.69; H, 7.63%; N, 14.20%.

4.1.15. (1*S*,3*S*)-1-[(*S*)-1-((*S*)-2-Acetylaminopropionylamino)ethyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((*S*)-1-methylcarbamoylethyl)amide (5b). The same procedure for the preparation of **5a** was followed (foam, 68% yield, from **13b**).

4.1.16. (1*R*,3*S*)-1-((*S*)-1-Amino-ethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid ((*S*)-1-methylcarbamoylethyl)amide. Oil, R_f=0.11 (methanol/ethyl acetate/NH_3, 18:80:2). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.01 (d, *J*=7.4 Hz, 1H, H_A), 6.81 (br q, *J*=5.2 Hz, 1H, H_B), 6.55 (s, 1H, 8-H), 6.48 (s, 1H, 5-H), 4.39 (m, 1H, 11-H), 3.81 (s, 3H, ArOCH_3), 3.79 (s, 3H, ArOCH_3), 3.65 (br m, 1H, 1-H), 3.28 (m, 1H, 3-H), 3.24 (m, 1H, 9-H), 3.04 (dd, *J*=13.5, 4.2 Hz, 1H, 4-H), 2.80 (d, *J*=5.2 Hz, 3H, CONHCH_3), 2.71 (m, 1H, 4-H), 2.45 (s, 3H, NCH_3), 2.15 (br s, 2H, NH_2), 1.50 (d, *J*=6.7 Hz, 3H, 11-CH_3), 1.15 (d, *J*=6.8 Hz, 3H, 9-CH_3).

Compound **5b**: oil, R_f=0.22 (methanol/ethyl acetate, 1:9). $[\alpha]_D^{25}$ −85.1 (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, *J*=9.1 Hz, 1H, H_A), 8.09 (d, *J*=8.8 Hz, 1H, H_D), 6.69 (s, 1H, 5-H), 6.64 (d, *J*=9.7 Hz, 1H, H_C), 6.57 (s, 1H, 8-H), 6.34 (q, *J*=4.8 Hz, 1H, H_B), 4.70 (m, 1H, 10-H), 4.59 (m, 1H, 11-H), 3.98 (m, 1H, 9-H), 3.88 (s, 3H, ArOCH_3), 3.87 (s, 3H, ArOCH_3), 3.14 (d, *J*=10.2 Hz, 1H, 1-H), 2.91 (dd, *J*=12.4, 3.2 Hz, 1H, 4-H), 2.81 (d, *J*=4.8 Hz, 3H, NHCH_3), 2.79 (dd, *J*=3.2, 2.2 Hz, 1H, 3-H), 2.74 (dd, *J*=12.4, 2.2 Hz, 1H, 4-H), 2.25 (s, 3H, NCH_3), 2.02 (s, 3H, COCH_3), 1.55 (d, *J*=7.1 Hz, 3H, 11-CH_3), 1.44 (d, *J*=6.9 Hz, 3H, 10-CH_3), 0.97 (d, *J*=6.7 Hz, 3H, 9-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.0, 173.9, 172.7, 171.2, 149.5, 147.8, 128.1, 127.1, 112.5, 110.7, 71.5, 69.3, 56.2, 56.0, 51.2, 48.2, 48.1, 45.8, 33.2, 26.2, 23.0, 18.8, 16.8, 15.8. IR (3 mM $CHCl_3$ solution): 3441, 3308, 2994, 1660, 1514, 1455, 1246, 794, 775 cm^{-1}. HRMS-EI *m/z* calcd 491.2744, found 491.2741. Anal. Calcd for $C_{24}H_{37}N_5O_6$: C, 58.64%; H, 7.59%; N, 14.25%; O, 19.53%. Found: C, 58.60%; H, 7.55%; N, 14.22%.

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