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2-Amino-3-oxohexahydroindolizino[8,7-*b*]indole-5-carboxylate Derivatives as New Scaffolds for Mimicking β–Turn Secondary Structures. Molecular Dynamics and Stereoselective Synthesis

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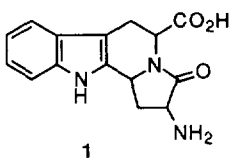
Abstract: Highly constrained 2-amino-3-oxohexahydroindolizino[8-7-*b*]indole-5-carboxylate derivatives of general formula **1** have been developed as novel β–turn mimetics. Molecular dynamics studies on model structures **2a** and **2b** have revealed that both indolizinoindole derivatives are able to adopt conformations close to those of ideal type II' β–turn. The asymmetric synthesis of this heterocyclic system was accomplished from 1,3-di- and 1,2,3-trisubstituted tetrahydro-β–carbolines, which were prepared in stereoselective or stereospecific way by application of the Pictet-Spengler reaction.

INTRODUCTION

An important feature of peptide and protein secondary structure is the case in which the amino acid chain reverses direction.[1] The reverse turns, as a consequence of their frequent appearance on the external surface of the molecule, are postulated as loci for receptor binding, antibody recognition and posttranslational modifications.[1-3] However, most of the biologically active peptides are highly flexible molecules and the number of their possible conformations complicates attempts to relate structural parameters and activities. For all these reasons, in recent years, major efforts have been devoted to the development of templates or scaffolds that mimic or stabilize these secondary structural features, specially β–turns.[4] Several non-peptide systems, including heterocyclic, aromatic and lactam derivatives, have been designed to mimic the different types of β–turns.[5] Although the incorporation of some of these scaffolds into bioactive peptides has led to peptidomimetics with enhanced activity or metabolic stability,[6] most of them lack an appendage for the corner residue side chains and can only be obtained by a lengthy synthesis.[5]

Taking into account these facts, we designed the 2-amino-3-oxohexahydroindolizino[8,7-*b*]indole-5-carboxylate system (**1**) as a potential β–turn dipeptide mimetic. The particular interest in this heterocyclic system was supported by two main reasons: *a)* the known ability of certain bicyclic lactams, structurally related to the hexahydroindolizino moiety, to mimic the central dipeptide core of β–turns,[5] and *b)* the presence of the indole ring, that can be considered as the side chain of the i+2 residue, could represent an additional advantage in the case of β–turns having aromatic or hydrophobic amino acids in the third residue.



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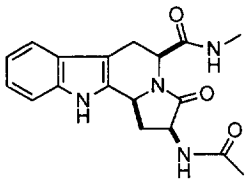
In order to determine the ability of the hexahydroindolizino[8,7-*b*]indole system **1** to induce β–turn-like conformations, computer molecular modeling studies were first undertaken. This paper, describes the results of these studies along with stereoselective systhetic routes for the preparation of conveniently protected derivatives of **1**. A preliminary communication of this work has been reported.[7]

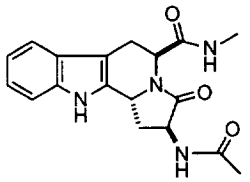
RESULTS AND DISCUSSION

Molecular dynamics.

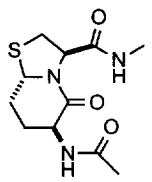
N-Acetyl-*N'*-methylamide model compounds **2a** and **2b**, having *S* configuration at C_2 and C_5 positions, were selected for this study. The low-energy conformations of 2- and 5-substituents of derivatives **2a** and **2b** were previously explored by systematic rotation of ϕ_2 and ψ_3 torsion angles.[7] In the preliminary approach, the spatial disposition of the 5-*N*-methylcarboxamide group was fixed as equatorial and axial for **2a** and **2b**, respectively, in agreement with published X-Ray and ^{1}H NMR data for related compounds.[8] The results of this conformational search, in which only isomer **2b** is able to adopt β–turn (type II') like conformations, suggested a possible participation of the 5-CONHMe group disposition on the conformational behaviour of compounds **2a** and **2b**. To clarify this point, an alternate molecular modeling strategy that allowed free mobility of the 6-membered saturated ring seemed to us more appropriate. We have used molecular dynamics at high temperature followed by energy minimization. Since the 1-thioindolizidine derivative BTD is a competent type-II' β–turn mimetic, the conformational behaviour of Ac-BTD-NHMe has also been studied for comparative purposes.



2a



2b



Ac-BTD-NHMe

The conformational parameters found for structures **2a**, **2b** and Ac-BTD-NHMe are listed in tables 1, 2 and 3, respectively. As deduced from these tables, 35, 28 and 57% of the obtained minima for **2a**, **2b** and the BTD derivative, respectively, have αC_1-αC_4 distances within the standard value defined for any β–turn conformation ($D\alpha C_1$-$\alpha C_4 \leq 7$ Å).[9]

Regarding the torsion angles, it can be noted that both the hexahydroindolizino[8,7-*b*]indole derivatives and the BTD structure showed ψ_2 values close to those observed in an ideal type-II' β–turn (ϕ_2=60°, ψ_2=-120°, ϕ_3=-80°, ψ_3=0°). In a similar way, all minima of BTD derivative have ϕ_3 dihedral angles within the standard values predicted for this type of reverse turn. However, for structure **2a** two main conformational families can be found as a consequence of the greater variability of the ϕ_3 parameters. The first set of conformations (10 minima), characterized by positive ϕ_3 values and hence by equatorial dispositions of the C_5-substituent, is incompatible with β–turn conformation of type-II'. In the second conformational family of **2a** the 5-CONHMe group mainly adopts axial disposition (negative ϕ_3 values) and 5 out of 7 conformers showed ϕ_3 values in good agreement with those predicted for the classical type-II' β–turn. The fact that

compound **2b**, having 11b*R* configuration, showed small variations of ϕ_3 and a conformational behaviour more similar to that of BTD than to that of the 11b*S*-stereoisomer **2a**, indicated that the ability of the hexahydroindolizino ring to fix the ϕ_3 torsion angle is clearly dependent on the C_{11b} stereochemistry.

Table 1. Conformational Parameters of Conformers Found for Structure **2a**

		Torsion angles (°)				
	ΔE					DαC1-αC4
Conf.	(Kcal/mol)	ϕ_2	ψ_2	ϕ_3	ψ_3	(Å)
1	0.00	-173.2	-159.3	27.2	67.4	8.74
2	0.04	-173.0	-161.4	35.5	-13.9	8.87
3	0.73	-172.6	-153.9	-59.3	85.6	6.86
4	0.98	-176.2	-109.9	61.8	-19.2	9.11
5	1.26	-174.3	-155.3	-50.9	-58.6	7.10
6	1.56	-173.9	-156.9	13.5	-82.2	8.57
7	1.58	51.5	-137.0	-17.9	-53.0	5.29
8	1.70	-176.7	-109.8	57.8	44.6	9.30
9	1.84	59.1	-150.6	-56.8	-12.6	5.52
10	2.07	-94.5	-104.6	61.4	-20.0	8.38
11	2.15	61.3	-156.5	-62.5	75.9	5.48
12	2.35	-88.2	-160.6	36.1	-11.1	7.99
13	2.68	-96.6	-158.8	27.2	65.5	7.96
14	2.72	-89.2	-151.3	-60.0	82.9	6.44
15	2.73	60.4	-160.7	35.4	-15.7	8.11
16	3.39	61.1	-159.0	28.0	66.5	8.15
17	5.66	-171.7	-94.7	-29.4	127.3	6.26

Table 2. Conformational Parameters of Conformers Found for Structure **2b**

		Torsion angles (°)				
	ΔE					DαC1-αC4
Conf.	(Kcal/mol)	ϕ_2	ψ_2	ϕ_3	ψ_3	(Å)
1	0.00	49.5	-115.6	-112.6	26.7	5.76
2	0.10	-172.8	-102.3	-102.2	78.2	6.87
3	1.14	-172.1	-149.5	-143.1	74.5	9.60
4	1.42	-89.2	-99.9	-100.7	74.2	5.98
5	1.63	-174.1	-97.3	-114.7	-88.7	7.74
6	2.46	57.9	-145.2	-135.9	67.7	7.82
7	2.79	-171.9	-148.5	-146.8	-93.6	10.33
8	3.65	-97.7	-148.5	-142.5	75.2	9.53
9	4.05	-175.2	-94.5	-71.5	-40.5	7.89
10	4.21	-171.5	-150.3	-95.5	67.7	8.75
11	4.37	-173.9	-92.8	-72.6	139.1	9.11
12	4.65	69.0	-119.3	-113.4	-83.1	7.31
13	5.83	-87.5	-91.4	-71.2	-27.8	6.87
14	6.45	-91.7	-148.5	-94.4	67.4	8.20

Considering the topographical parameters as a whole, it can be remarked that for Ac-BTD-NHMe the lowest energy conformer has bond angles and interatomic distances within that expected for an hydrogen-

bonded type-II' β-turn. In this case, conformers 2 (ΔE=1.49 Kcal/mol) and 14 (ΔE=6.76 Kcal/mol) also fit these requirements. For the hexahydroindolizino[8,7-*b*]indole derivatives **2a** and **2b** only one conformer, in each case, fulfils all conformational parameters defined for this type of reverse turn. Similarly to BTD, this conformer is the absolute minimum for structure **2b**, while for isomer **2a** it is conformer 9 (ΔE=1.84 Kcal/mol). Therefore, it is expected that BTD and derivative **2b** will be more effective replacements for the (i+1) and (i+2) residues of a type-II' β-turn than analogue **2a**.

Table 3. Conformational Parameters of Conformers Found for Ac-BTD-NHMe

		Torsion angles (°)				
Conf.	ΔE (Kcal/mol)	ϕ_2	ψ_2	ϕ_3	ψ_3	$D\alpha C_1$-αC_4 (Å)
1	0.00	54.8	-124.1	-67.3	-14.6	5.08
2	1.49	55.3	-130.9	-95.6	21.2	5.54
3	1.59	58.2	-146.0	-88.1	70.0	5.66
4	2.31	-155.8	-157.9	-87.2	76.3	7.95
5	3.20	59.0	-129.4	-76.8	63.5	5.40
6	3.98	-156.0	-132.9	-77.5	76.8	7.36
7	4.40	-156.4	-137.6	-65.6	151.4	8.91
8	4.80	-158.0	-138.1	-68.1	-28.9	7.78
9	5.55	-66.4	-75.1	-83.8	69.7	4.59
10	5.65	-163.0	-80.1	-85.2	74.9	6.53
11	5.98	-45.5	-61.4	-60.9	-8.0	5.47
12	6.23	-159.4	-85.3	-89.4	70.8	7.23
13	6.73	-155.9	-148.6	-94.9	-87.4	9.36
14	6.76	41.1	-103.8	-84.8	-4.6	5.56
15	6.96	-85.3	-83.3	-88.9	67.0	6.11
16	8.19	-164.0	-80.8	-81.6	160.9	7.88
17	8.44	-163.0	-82.2	-82.1	156.4	8.87
18	8.47	49.4	-108.6	-90.3	63.6	6.05
19	8.51	118.3	-87.7	-84.2	74.6	5.88
20	9.15	-159.9	-71.0	-62.2	-29.5	7.19
21	9.54	-164.8	-76.5	-91.7	-71.3	6.88

The folded conformers ($D\alpha C_1$-$\alpha C_4 \leq 7$ Å) of structures **2a**, **2b** and Ac-BTD-NHMe were compared to standard β-turns[1] (Table 4). For the indolizinoindole derivatives **2a** and **2b** the best superimpositions were always found with type-II' β-turn (Figure 1).

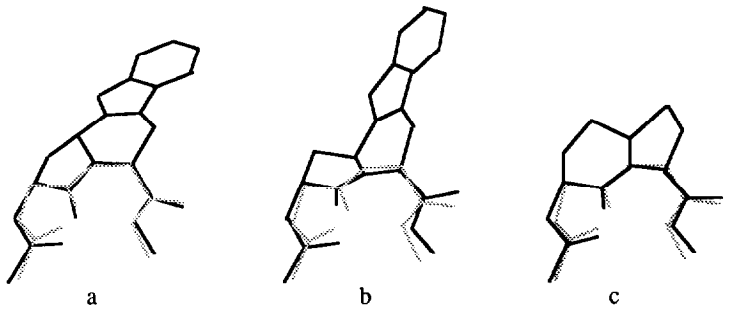


Figure 1.– *Superimposition of a type-II' β-turn (grey) with (a) conformer **2a**:9, (b:) conformer **2b**:1 and (c) conformer **BTD**:1*

As expected, conformers **2a**:9 and **2b**:1 gave the lowest rms values. Minima, **2a**:7 and **2a**:11, which shown comparable rms values to conformer **2a**:9, have, at least, one torsion angle that differs more than 40° from the definition of a β-turn type-II'. These conformers could fall into the category of distorted β-turn (type IV) conformations.[9] Similar results were found for the BTD derivative, obtaining the best rms values for those conformers having torsion angles within the standard parameters described for a classical type-II' β-turn. In this case, conformers 9 and 11 showed a good fit with ideal β-turn of type I or III. However, the probability that BTD acted as a mimetic of these types of β-turns should be considerably reduced as a consequence of the high relative energy of these conformers. According to these molecular modeling results, the ability of the studied structures to induce type-II' β-turn-like conformations can be ordered as BTD ≥ **2b** > **2a**.

Table 4. Comparison of Folded Conformers of Structures **2a, 2b** and Ac-BTD-NHMe with Different Standard β-Turns[1]

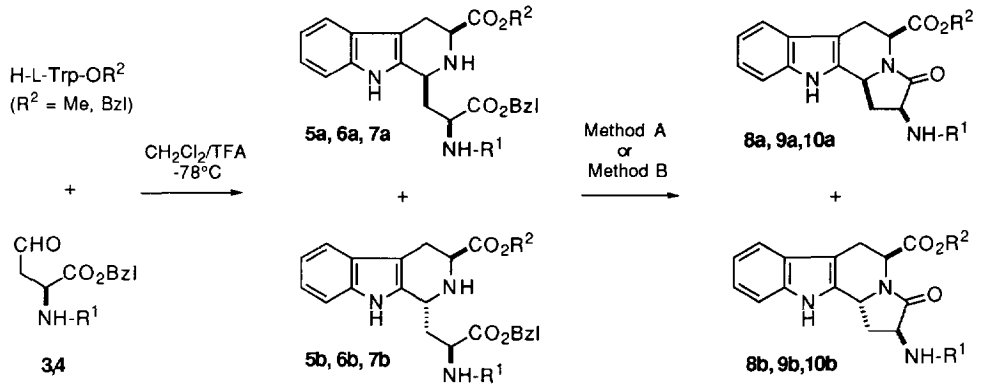
		β-Turn (rms, Å)[a]					
	Conf.	I	I'	II	II'	III	III'
2a	3	1.08	1.20	0.94	0.85	1.05	1.18
	7	0.56	0.89	0.56	0.27	0.62	1.01
	9	0.78	0.72	0.51	0.27	0.88	0.80
	11	0.76	0.84	0.53	0.39	0.84	0.90
	14	1.07	1.04	0.79	0.79	1.11	0.99
	17	0.78	1.33	0.99	0.89	0.73	1.39
2b	1	0.74	0.69	0.53	0.34	0.85	0.75
	2	0.93	1.20	0.91	0.80	0.90	1.21
	4	0.79	0.96	0.64	0.60	0.86	0.98
	13	0.84	1.12	0.82	0.73	0.80	1.12
BTD	1	0.61	0.76	0.51	0.14	0.72	0.89
	2	0.79	0.64	0.51	0.29	0.90	0.72
	3	0.77	0.77	0.52	0.35	0.86	0.82
	5	0.59	0.90	0.56	0.34	0.67	1.00
	9	0.38	1.00	0.57	0.50	0.56	1.12
	10	0.78	1.27	0.89	0.80	0.74	1.30
	11	0.22	1.12	0.72	0.58	0.24	1.24
	14	0.54	0.84	0.56	0.27	0.62	0.95
	15	0.61	1.08	0.67	0.61	0.63	1.13
	18	0.59	1.05	0.70	0.52	0.58	1.12
	19	0.63	1.22	0.87	0.71	0.59	1.31
	21	0.98	1.09	0.92	0.78	0.97	1.11

[a] Fits were carried out by superposition of the ten atoms of the amide backbone.

Chemistry.

Conveniently protected 1,3-disubstituted tetrahydro-β-carbolines were initially selected as intermediates for the preparation of the hexahydroindolizino[8,7-*b*]indole derivatives. As shown in scheme 1, compounds **5-7** were synthesized *via* the Pictet-Spengler reaction under conditions of kinetic control.[10] Accordingly, γ-aldehydes **3** and **4** were condensed with H-L-Trp-OR^2 (R^2=Me, Bzl) to generate the corresponding imine intermediates, which were treated at -78°C with TFA to induce cyclization. The desired tetrahydro-β-carbolines **5ab** (**a**/**b**=10:1), **6ab** (**a**/**b**=6:1) and **7ab** (**a**/**b**=8:1) were isolated in 91, 75 and 84% yield,

respectively. The predominantly formed *cis*-carbolines could be isolated by simple precipitation from EtOAc-hexane (5:1), while minor stereoisomers were always obtained unpurified with the corresponding major compounds. The diastereomeric *cis*/*trans* ratio was determined from the crude reaction mixtures by HPLC or ^{1}H NMR spectroscopy. From these data, it seems that the diastereoselectivity of the Pictet-Spengler reactions is particularly influenced by the character of the aldehyde *N*-protecting group and, in a minor extent, by the size of the *C*-protecting group of Trp. Thus, interactions between phenyl moieties of the Z group and the indole, that might contribute to the stabilization of the intermediates governing the formation of *cis*-stereoisomers, could explain the improvement in selectivities observed for the Z-substituted carbolines when compared to the corresponding Boc-derivatives.[11] On other hand, the slight increase in *trans*-stereoselectivity found for the OBzl derivative **7ab** when compared to the OMe analogue **5ab** is in agreement with previously reported data on the influence of substituents at C-3 position.[12]



3: R^1= Z; **4**: R^1= Boc; **5, 8**: R^1= Z, R^2= Me; **6, 9**: R^1= Boc, R^2= Me; **7, 10**: R^1=Z, R^2= Bzl

Scheme 1

The hexahydroindolizino[8,7-*b*]indole derivatives **8-10** were easily obtained by intramolecular γ-lactamization of carbolines **5-7** in refluxing xylene (Method A). Similar **a**/**b** ratio to that of the starting tetrahydro-β-carbolines was found following this method (Table 5). Compounds **8a**, **9a** and **10a**, having 11b*S* stereochemistry, were stereospecifically prepared from isolated *cis*-tetrahydro-β-carbolines using the above indicated conditions. However, when the optically pure *cis*-products **5a** and **7a** were refluxed in the presence of a large excess of acid [TFA(10 eq.)] both the 11b*S*- (**8a** and **10a**) and 11b*R*- (**8b** and **10b**) isomers were formed (Method B, Table 5). This alternate method allowed the stereoselective preparation of the 11b*R*-hexahydroindolizino[8,7-*b*]indole derivatives in an approximately 60% diastereomeric excess.

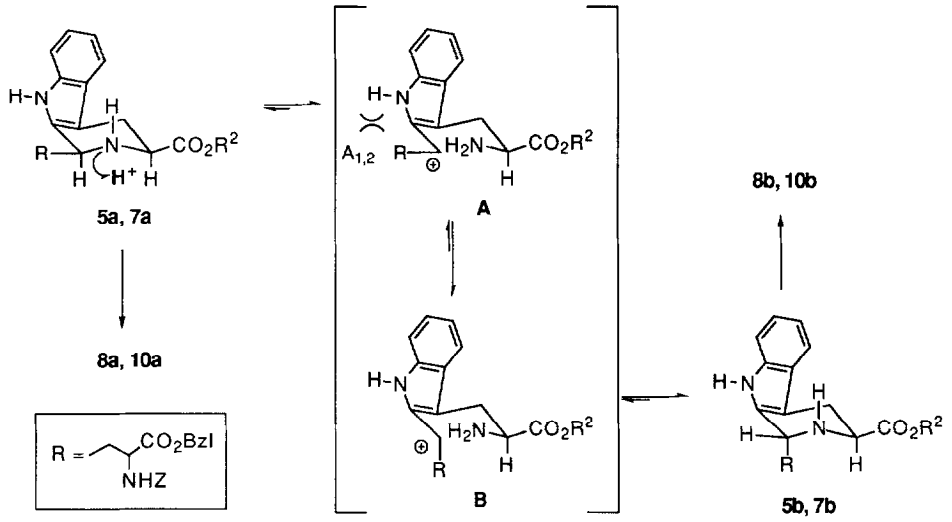
The formation of compounds **8b** and **10b** from **5a** and **7a**, respectively, can be explained by the mechanism depicted in Scheme 2. Assuming that *cis*-carbolines mainly exist as the 1,3-diequatorial conformers,[10] the 2-NH group of **5a** or **7a** is protonated, under conditions of heat and acid, to furnish the carbocation A after ring cleavage across the 1,2(C-N) bond. Bond rotation around position-1 of cation A results in the relief of $A_{1,2}$-strain to provide the sterically more favoured cation B, which then cyclizes to give the *trans*-isomer **5b** or **7b**.[10,13] A faster intramolecular γ-lactamization of these latter tetrahydro-β-carbolines,

when compared to their *cis*-counterparts, may also contribute to the displacement of the equilibrium towards the preferential formation of the 11b*R* derivatives.

Table 5. Preparation of Hexahydroindolizino[8,7-*b*]indole Derivatives from 1,3-Disubstituted Tetrahydro-β-carbolines. Influence of the γ-Lactamization Method on the Stereochemistry

Starting β-carboline	R^1	R^2	**a/b** ratio	Method[a]	Final compd.	Yield[b] %	**a/b** ratio
5ab	Z	Me	2:1	A	**8ab**	72	2:1
5a	Z	Me	—	A	**8a**	75	—
5a	Z	Me	—	B	**8ab**	89	1:4
6ab	Boc	Me	2.5:1	A	**9ab**	58	2.5:1
6a	Boc	Me	—	A	**9a**	78	—
7a	Z	Bzl	—	A	**10a**	95	—
7a	Z	Bzl	—	B	**10ab**	76	1:5

[a] Method A: xylene/reflux, 15-24 h. Method B: toluene/TFA (10 eq.)/reflux, 4 h. [b] From isolated compounds.

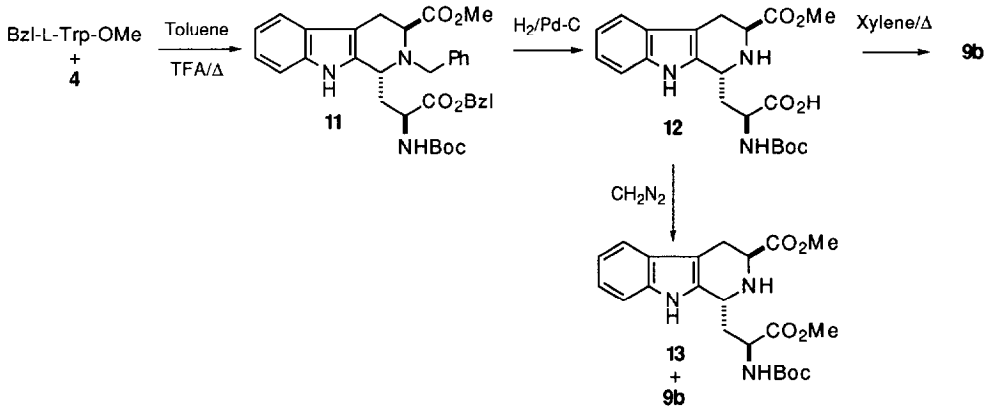


Scheme 2

The absolute stereochemistry at the C_{11b} stereocentre in compounds **10a** and **10b** was assigned on the basis of NOE studies. Thus, strong exchanges of magnetization among the H_2-H_{11b} and H_5-H_{11b} protons in compound **10a** indicated that these three protons are located on the same face of the heterocyclic ring. As the absolute configuration at C_2 and C_5 is *S*, since the synthesis started with L-Asp and L-Trp, compound **10a** have 11b*S* configuration. On the contrary, these NOE's were not observed in the diastereoisomer **10b**, in which the H_{11b} proton has a *trans*-relationship with respect to the H_2 and H_5 protons. The stereochemical assignment of each diastereomeric pair of compounds **8** and **9** was made by correlation of their ^1H and ^{13}C NMR spectra with those of **10a** and **10b**.

In the ^1H NMR spectra, the main differences between 11b*S*- and 11b*R*-diastereoisomers were found for the chemical shifts of the H-5 protons and the $J_{5,6}$ coupling constant values (Table 6). Thus, the signal corresponding to the downfield H_6 proton in the 11b*R* stereoisomers always appears as a doublet with a large geminal coupling constant, indicating that no coupling exists with vecinal H_5 proton ($J_{5,6}$=0 Hz). This result is only consistent with an equatorial disposition of the H-5 proton. However, the observed $J_{5,6}$ values for the 11b*S* analogues are in concordance with the preferent adoption of an axial disposition of the mentioned proton. In agreement to that, the H_5 resonance in compounds having 11b*S* configuration appeared considerably shielded (~1 ppm) when compared to the same proton in the 11b*R*-isomers. Consistently, the C_5 and C_{11b} resonances in the 11b*R* derivatives appear at higher field than the corresponding carbons of the 11b*S* isomers (Table 6). This shift, presumably due to the steric interactions of the 5-axial substituent and the C-H bond at the C_{11b} centre in the 11b*R*-stereoisomers, is similar to that reported for related tetrahydro-β-carbolines.[14,15]

It is known that *trans*-tetrahydro-β-carbolines can be obtained with excellent diastereocontrol, and in high optical purity, by Pictet-Spengler reaction between N^{α}-benzyl tryptophan esters and aldehydes, under conditions of kinetic and thermodynamic control.[13] Taking into account that the *trans*-tetrahydro-β-carboline **11** is the precursor of the 11b*R* hexahydroindolizino[8,7-*b*]indole derivative **9b**, the more promising compound as β–turn mimetic in this series, we decided to investigate this alternate route for its preparation. In fact, condensation of Bzl-L-Trp-OMe and aldehyde **4** stereospecifically afforded the 1,2,3-trisubstituted derivative **11**, which was exclusively transformed into the desired tetracyclic analogue **9b** by *N*- and *O*-debenzylation and subsequent cyclization of the resulting compound **12** (Scheme 3). In order to facilitate the cyclization step, the carboxylic acid **12** was reacted with diazomethane to provide **13**. The fact that compound **9b** was directly formed during the esterification reaction indicates that lactamization of the *trans*-tetrahydro-β-carbolines is faster than that of the corresponding *cis*-isomers, which required more drastic cyclization conditions.



Scheme 3

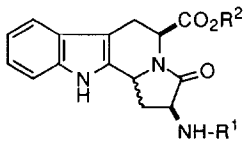
Finally, for incorporation of these indolizidinoindole derivatives into peptide sequences, the selective removal of the *C*- and *N*-protecting groups was carried out. Thus, saponification of **8a, 8b, 9a** and **9b**

Table 6. Selected NMR Data for the Hexahydroindolizino[8,7-*b*]indole Derivatives

	^{1}H NMR[a]								^{13}C NMR[b]				
Compd.	1-H	2-H	5-H	6-H	11-H	11b-H	2-NH	$J_{5,6}$	C-1	C-2	C-5	C-6	C-11b
8a	1.77 2.89	4.53	4.21	2.85	11.07	5.06	7.59	6.5 9.0	32.59	51.71	53.70	23.52	51.29
8b	2.38	4.16	5.21	2.97 3.23	11.11	5.21	8.04	7.3 0.0	31.80	51.57	50.11	23.05	49.91
9a	1.74 2.90	4.46	4.19	2.98	11.06	5.01	7.44	6.2 8.4	32.72	51.89	53.72	23.58	51.26
9b	2.34	4.08	5.18	3.00 3.21	11.08	5.18	7.56	7.1 0.0	31.73	50.91	49.92	22.85	49.60
10a[c]	1.90 3.17	4.53	4.33	3.00 3.31	7.99	4.90	5.37	4.7 7.3	32.69	51.84	53.73	23.51	51.20
10b[c]	2.39	4.26	5.32	3.36	8.27	5.25	5.46	7.7 0.0	31.81	51.49	50.25	23.22	49.93
14a	1.65 2.85	4.45	4.68	2.75 3.32	11.01	5.08	7.58	7.8 0.0	33.60	52.86	49.34	23.47	48.67
14b	2.37	4.15	5.08	2.92 3.23	11.08	5.25	8.03	7.2 0.0	31.76	51.60	50.16	23.29	49.89
15a	1.72 2.85	4.45	5.07	2.92 3.31	11.05	4.96	7.12	7.0 0.0	33.55	52.31	49.09	23.34	48.48
15b	2.32	4.03	5.05	2.82 3.30	10.97	5.34	7.36	7.4 0.0	32.22	51.60	50.64	23.66	50.18
16a	1.81 3.05	4.35	4.35	2.98	11.21	5.15	8.47	[d]	31.40	52.45	50.11	23.54	48.74
16b	2.54	4.04	5.29	3.02 3.27	11.22	5.28	8.70	7.3 0.0	28.91	50.36	50.10	22.94	49.78
17a[e]	1.90 3.12	4.41	5.20	3.00 3.35	—	5.17	—	7.1 0.0					
17b[c]	2.35 2.62	3.96	5.14	2.88 3.24	—	5.23	—	7.2 0.0					

[a] Registered at 300 MHz in DMSO-d_6. [b] Registered at 50 MHz in DMSO-d_6. [c] ^{1}H NMR in $CDCl_3$. [d] Not determined. [e] Registered in D_2O.

derivatives with NaOH in methanol gave the free carboxylic acids **14a, 14b, 15a** and **15b** in excellent yield. Compounds **15a** and **15b** were also obtained from **10a** and **10b** by catalytic hydrogenation in the presence of Boc_2O. Using this method, about a 20% of the fully deprotected derivatives **17a** and **17b** were also obtained. Removal of Z and Boc groups by catalytic hydrogenation and treatment with TFA, respectively, afforded the corresponding amino derivatives **16a** and **16b**.



Compd.	R^1	R^2	C_{11b}
14a	Z	H	*S*
14b	Z	H	*R*
15a	Boc	H	*S*
15b	Boc	H	*R*
16a	H	Me	*S*
16b	H	Me	*R*
17a	H	H	*S*
17b	H	H	*R*

In the ^1H NMR spectra of the carboxylic acid derivatives it can be observed that both the chemical shifts and the $J_{5,6}$ coupling constants of the 11b*S* stereoisomers are rather different from those obtained for the corresponding protected analogues. However, for the 11b*R* isomers these parameters were very similar to those of their precursor derivatives. Thus, compound **14a**, **15a** and **17a** exhibited $J_{5,6}$ values (0 and ~7 Hz) and H_5 chemical shifts (~5 ppm) close to those found for the 11b*R*-stereoisomers. These data demonstrated an equatorial disposition for the H_5 proton in **14a**, **15a** and **17a**, as it was always observed for the indolizinoindole derivatives of *R* configuration at C_{11b}, and, opposite to the axial disposition of this proton in the fully protected 11b*S* derivatives. The existence of both axial and equatorial dispositions for the C_5 substituent in the 11b*S* model compound **2a**, evidenced from the molecular modeling study here described, is in good agreement with these observations. Thus, the 11b*S* and 11b*R* derivatives are able to display an axial disposition of the 5-CO_2R group, but the possibility of find this conformation is higher in the second ones. As the capacity to mimic β-turn (II') conformation depends on this disposition, it is expected that both of these stereoisomeric scaffolds could act as mimetics of this turn in solution.

Due to the presence of the aromatic indole ring, the bicyclic lactams here reported could constitute and interesting complement to the well established BTD for mimicking β–turn type II' conformations in peptides of biological significance.

EXPERIMENTAL SECTION

Starting amino acid derivatives were obtained from Bachem and used without further purification. Analytical TLC was performed on aluminium sheets coated with 0.2 mm layer of silica gel 60 F_{254} (Merck). Silica gel 60 (230-400 mesh, Merck) was used for column chromatography. Compounds were detected with UV light, Erlich's reagent or ninhydrin. Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. ^1H NMR spectra were recorded with a Varian XL-300 operating at 300 MHz using Me_4Si as internal standard. NOESY spectra were recorded at 600 ms and, 1.5-second relaxation delay was used.

^{13}C NMR spectra were recorded with a Varian Gemini 200 (50 MHz). Carbon assignments were performed by heteronuclear (C-H) correlations (HETCOR). Elemental analyses were obtained on a CHN-O-RAPID apparatus. Analytical HPLC was performed on a Water chromatograph using a Nova-Pak C_{18} (3.9 × 150 mm, 4 μm) column with CH_3CN(A)/H_2O (0.05% TFA) (B) system as eluent (flow rate, 1 mL/min) with UV detection (214 nm). Z-L-Asp(H)-OBzl[16] and Boc-L-Asp(H)-OBzl[16] were prepared from the corresponding alcohols[17] by Swern's oxidation.[18] Bzl-L-Trp-OMe was prepared as described.[19]

Molecular Dynamics.

Model compounds **2a, 2b** and Ac-BTD-NHMe were built using the library of fragments available in the molecular modeling program Insight II (version 2.2.0, Biosym Tech., San Diego, CA, USA) and minimized with the cvff91 force field.[20] These conformations were used as starting point in the molecular dynamics calculations. They were heated to 1500 K, increasing the temperature 10 K each 0.15 ps., and equilibrated during 20 ps. Finally, 75 ps. of simulation were done, during which 300 structures were stored at equal intervals. All these structures were optimized using the above mentioned force field during 500 cycles of steepest descents followed by Conjugate Gradients minimization until the gradient was below 0.001 Kcal/Å. The molecular dynamics simulation and the minimization process was repeated twice, starting from different conformations. The minima obtained were compared to eliminate those previously encountered. The unique minima found for all compounds were superimposed (from αC_1 to αC_4) with model β-turns and the root mean square (rms) deviations were calculated.

Synthesis of Tetrahydro-β-Carbolines

General Procedure: To a solution of aldehyde **3** or **4** (5.2 mmol) in dry CH_2Cl_2 (28 mL) were added H-L-Trp-OR[2] (5.2 mmol) and Et_3N (5.2 mmol). After stirring for 1 h at rt, the reaction mixture was cooled to –78°C. A solution of TFA (11.5 mmol) in dry CH_2Cl_2 (3 mL) was then added dropwise. The reaction content was stirred at –78°C for 1 h and then was allowed to warm to rt. The resulting solution was neutralized with saturated $NaHCO_3$, the organic layer was separated, washed with brine, dried over $MgSO_4$ and evaporated. The corresponding *cis*-tetrahydro-β-carboline was precipitated by treatment of the crude residue with EtOAc/hexane (5:1). A second portion of the *cis*- and *trans*-tetrahydro-β-carboline mixture was obtained by evaporation of the mother liquors and purification on a silica gel column using EtOAc/hexane (1:2) as eluent.

(1S,3S,2'S)- and (1R,3S,2'S)-1-[2'-Benzyloxycarbonyl-2'-(benzyloxycarbonyl)amino]ethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (5a and 5b).

Isomer **5a**: 1.86 g, 66%. White solid, mp 147-150°C (EtOAc). HPLC: t_R=10.9 min (A/B=50/50). ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H, NH^i), 7.41-6.98 [m, 14H, In and C_6H_5 (Bzl, Z)], 6.11 (d, 1H, 2'-NH, J=6.9), 5.12-5.03 [m, 4H, CH_2 (Bzl, Z)], 4.52 (m, 1H, H-2'), 4.19 (m, 1H, H-1), 3.72 (s, 3H, CO_2CH_3), 3.63 (dd, 1H, H-3, J=11.0, 4.3), 3.03 (m, 1H, H-4, J=15.1, 4.3, 1.8), 2.74 (m, 1H, H-4, J=15.1, 11.0, 2.3), 2.25 (m, 2H, H-1'). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.24, 172.18, 156.29 (CO), 136.21-108.28 (18C, Ar), 67.44 and 67.02 [CH_2 (Bzl, Z)], 56.27 (C-3), 52.11 (OCH_3), 52.03 (C-2'), 50.21 (C-1), 36.67 (C-1'), 25.53 (C-4). Anal. Calcd for $C_{31}H_{31}N_3O_6$: C, 68.75; H, 5.77; N, 7.76. Found: C, 68.57; H, 5.81; N, 7.56. Mixture **5a+5b**: 0.71 g, 25% (**a**/**b** ratio, 2:1). HPLC **5b**: t_R=13.7 min (A/B=50/50). ^1H NMR **5b** (300 MHz, $CDCl_3$, from the **5a+5b** mixture): δ 9.32 (s, 1H, NH^i), 7.41-6.98 [m, 14H, In and C_6H_5 (Bzl, Z)], 5.85 (d, 1H, 2'-NH, J=8.3), 4.61 (m,

1H, H-2'), 4.19 (m, 1H, H-1), 3.81 (dd, 1H, H-3, J=9.7, 4.2), 3.68 (s, 3H, CO_2CH_3), 3.03 and 2.74 (m, 2H, H-4), 2.25 and 2.02 (m, 2H, H-1').

(1S,3S,2'S)- and (1R,3S,2'S)-1-[2'-Benzyloxycarbonyl-2'-(tert-butoxycarbonyl)amino]ethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (6a and 6b).

Isomer **6a**: 0.95 g, 36%. White solid, mp 178-180°C (EtOAc). HPLC: t_R=6.7 min (A/B=50/50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 1H, NH^i), 7.47-7.06 [m, 9H, In and C_6H_5 (Bzl)], 5.81 (d, 1H, 2'-NH, J=7.8), 5.19 [m, 2H, CH_2 (Bzl)], 4.56 (m, 1H, H-2'), 4.28 (m, 1H, H-1), 3.82 (s, 3H, CO_2CH_3), 3.73 (dd, 1H, H-3, J=11.0, 4.2), 3.11 (m, 1H, H-4, J=14.9, 4.2, 1.7), 2.83 (m, 1H, H-4, J=14.9, 11.0, 2.4), 2.35 and 2.18 (m, 2H, H-1'), 1.41 [s, 9H, CH_3 (Boc)]. ^{13}C NMR (50 MHz, DMSO-d_6): δ 173.12, 172.57, 155.51 (CO), 135.97-106.64 (12C, Ar), 78.38 [C (Boc)], 65.89 [CH_2 (Bzl)], 55.88 (C-3), 51.63 (OCH_3), 51.17 (C-2'), 49.50 (C-1), 35.06 (C-1'), 28.09 [CH_3 (Boc)], 25.35 (C-4). Anal. Calcd for $C_{28}H_{33}N_3O_6$: C, 66.25; H, 6.55; N, 8.28. Found: C, 66.08; H, 6.84; N, 8.27. Mixture **6a+6b**: 1.03 g, 39% (**a/b** ratio, 2.5:1). HPLC **6b**: t_R=8.9 min (A/B=50/50). ^{1}H NMR **6b** (300 MHz, $CDCl_3$, from the **6a+6b** mixture): δ 9.22 (s, 1H, NH^i), 7.47-7.06 [m, 9H, In and C_6H_5 (Bzl)], 5.51 (d, 1H, 2'-NH, J=8.5), 4.56 (m, 1H, H-2'), 4.28 (m, 1H, H-1), 3.85 (m, 1H, H-3), 3.76 (s, 3H, CO_2CH_3), 3.10 (m, 2H, H-4), 2.15 (m, 2H, H-2'), 1.39 [s, 9H, CH_3 (Boc)].

(1S,3S,2'S)- and (1R,3S,2'S)-3-Benzyloxycarbonyl-1-[2'-benzyloxycarbonyl-2'-(benzyloxycarbonyl)-amino]ethyl-1,2,3,4-tetrahydro-β-carboline (7a and 7b).

Isomer **7a**: 1.89 g, 59%. White solid, mp 107-110°C (EtOAc). HPLC: t_R=17.86 min (A/B=50/50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H, NH^i), 7.40-6.97 [m, 19H, In and C_6H_5 (Bzl, Z)], 6.11 (d, 1H, 2'-NH, J=7.6), 5.17-4.87 [m, 6H, CH_2 (Bzl, Z)], 4.52 (m, 1H, H-2'), 4.19 (m, 1H, H-1), 3.66 (dd, 1H, H-3, J=11.1, 3.9), 3.05 (m, 1H, H-4, J=15.1, 3.9), 2.66 (m, 1H, H-4, J=15.1, 11.1, 2.4), 2.25 (m, 2H, H-1'). ^{13}C NMR (50 MHz, DMSO-d_6): δ 172.64, 172.50, 156.20 (CO), 136.86-105.92 (26C, Ar), 66.12, 65.75, 65.67 [CH_2 (Bzl, Z)], 56.06 (C-3), 51.44 (C-2'), 49.46 (C-1), 34.95 (C-1'), 25.49 (C-4). Anal. Calcd for $C_{37}H_{35}N_3O_6$: C, 71.94; H, 5.71; N, 6.80. Found: C, 71.66; H, 5.67; N, 6.91. Mixture **7a+7b**: 0.81 g, 25% (**a/b** ratio, 2:1). HPLC **7b**: t_R=20.72 min (A/B=50/50). ^{1}H NMR **7b** (300 MHz, $CDCl_3$, from the **7a+7b** mixture): δ 9.28 (s, 1H, NH^i), 7.40-6.97 [m, 19H, In and C_6H_5 (Bzl, Z)], 5.88 (d, 1H, 2'-NH, J=8.2), 5.17-4.87 (m, 6H, CH_2 (Bzl, Z)], 4.60, (m, 1H, H-2'), 4.19 (m, 1H, H-1), 3.87 (dd, 1H, H-3, J=10.4, 4.3), 3.05 and 2.66 (m, 2H, H-4), 2.25 and 2.04 (m, 2H, H-1').

(1R,3S,2'S)-2-Benzyl-1-[2'-Benzyloxycarbonyl-2'-(tert-butoxycarbonyl)amino]ethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (11).

To a solution of aldehyde **4** (1.53 g, 4.5 mmol) and Bzl-L-Trp-OMe (1.55 g, 5 mmol) in toluene (15 mL) was added TFA (0.39 mL, 5 mmol) and molecular sieve (4Å). After refluxing for 4 h, the molecular sieve was filtered and the filtrate evaporated to dryness. The resulting residue was purified on a silica gel column, using EtOAc/hexane (1:5) as eluent, to give 1.4 g (58%) of the title compound as a syrup. HPLC: t_R=7.19 min (A/B=70/30). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.35 (s, 1H, NH^i), 7.58-7.08 [m, 14H, In and C_6H_5 (Bzl)], 5.24 (d, 1H, 2'-NH, J=7.3), 5.10 [m, CH_2 (Bzl)], 4.41 (m, 1H, H-2'), 4.10 (dd, 1H, H-3, J=10.1, 5.9), 3.82 (m, 5H CO_2CH_3, 2-CH_2, H-1), 3.44 (d, 1H, 2-CH_2, J=13.5), 3.08 (m, 2H, H-4), 2.19 (m, 2H, H-1'), 1.35 [s, 9H, CH_3 (Boc)]. ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.06, 171.71, 156.12 (CO), 138.89-106.85 (20C, Ar), 80.32 [C (Boc)], 67.37 [CH_2 (Bzl)], 57.12 (OCH_3), 52.93 (2-CH_2), 52.75 (C-2'), 52.69 (C-3), 52.25 (C-1), 38.64 (C-1'), 28.17 [CH_3 (Boc)], 20.19 (C-4). Anal. Calcd for $C_{35}H_{39}N_3O_6$: C, 70.33; H, 6.57; N, 7.03. Found: C, 69.98; H, 6.30; N, 7.22.

(1R,3S,2'S)-1-[2'-(tert-Butoxycarbonyl)amino-2'-carboxy]ethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (12).

Compound **11** (0.8 g, 1.33 mmol) was dissolved in MeOH (60 mL) and hydrogenated at rt and 30 psi of pressure for 2 h in the presence of Pd-C. After filtration of the catalyst the solvent was evaporated to provide 0.45 g (81%) of the title product as a foam. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.17 (s, 1H, NH^i), 7.49-7.02 (m, 5H, In and 2'-NH), 4.80 (m, 1H, H-2'), 3,79 (s, 3H, CO_2CH_3), 3.60 (m, 2H, H-1 and H-3), 3.33 (dd, 1H, H-4, J=15.2, 5.1), 3.04 (dd, 1H, H-4, J=15.2, 9.5), 2.39 (m, 2H, H-1'), 1.40 [s, 9H, CH_3 (Boc)]. Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.06. Found: C, 60.23; H, 6.36; N, 9.91.

(1R,3S,2'S)-1-[2'-(tert-Butoxycarbonyl)amino-2'-methoxycarbonyl]ethyl-3-methoxy-carbonyl-1,2,3,4-tetrahydro-β-carboline (13).

To a solution of compound **12** (0.3 g, 0.72 mmol) in MeOH (10 mL) was added, at 0°C, an ethereal solution of diazomethane, freshly prepared from *N*-nitroso-*N*-methylurea (0.5 g, 4.2 mmol). After 1 h of reaction, the solvents were evaporated to dryness and the residue purified on a silica gel column, using EtOAc/hexane (1:4) as eluent, to provide 0.124 g (40%) of compound **13** and 0.132 g (46%) of a product identified as derivative **9b**. **13**: Syrup HPLC: t_R=8.85 min (A/B=40/60). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (s, 1H, NH^i), 7.55-7.08 (m, 4H, In), 5.59 (d, 1H, 2'-NH, J=7.5), 4.60 (m, 1H, H-2'), 3.97 (dd, 1H, H-3, J=10.5, 5.3), 3.80 (m, 1H, H-1), 3.79 and 3.68 (s, 6H, CO_2CH_3), 3.13 (dd, 1H, H-4, J=16.2, 10.5), 3.97 (dd, 1H, H-4, J=16.2, 5.3), 2.35 and 2.31 (m, 2H, H-1'), 1.48 [s, 9H, CH_3 (Boc)]. ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.83, 172.39, 156.48 (CO), 136.20-106.06 (8C, Ar), 80.75 [C (Boc)], 57.26 and 57.20 (OCH_3), 52.45 (C-3), 52.08 (C-1), 51.70 (C-2'), 37.72 (C-1'), 28.25 [CH_3 (Boc)], 19.41 (C-4). Anal. Calcd for $C_{22}H_{29}N_3O_6$: C, 61.24; H, 6.77; N, 9.74. Found: C, 61.63; H, 7.09; N, 9.44.

Synthesis of Hexahydroindolizino[8,7-b]indole Derivatives

Method A: A solution of the corresponding tetrahydro-β-carboline (2 mmol) in xylene (40 mL) was refluxed for 15-24 h. After evaporation of the solvent the resulting residue was purified on a silica gel column using EtOAc/hexane (1:2) as eluent.

Method B: To a solution of the corresponding Z-protected *cis*-tetrahydro-β-carboline (1 mmol) in toluene (5 mL) was added TFA (10 mmol). After refluxing the reaction mixture for 4 h, the solvents were evaporated and the residue purified as indicated in Method A.

(2S,5S,11bS)-2-(Benzyloxycarbonyl)amino-5-methoxycarbonyl-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (8a).

Obtained in 48 and 75% yield from **5ab** (**a**/**b**=2:1) and **5a**, respectively, using method A and, in 19% yield, from **5a** using method B. White solid, mp 212-215°C (EtOAc). HPLC: t_R=9.47 min (A/B=40/60). Anal. Calcd for $C_{24}H_{23}N_3O_5$: C, 66.50; H, 5.35; N, 9.69. Found: C, 66.80; H, 5.12; N, 9.75.

(2S,5S,11bR)-2-(Benzyloxycarbonyl)amino-5-methoxycarbonyl-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (8b).

Obtained in 24% yield from **5ab** (**a**/**b**=2:1) using method A and in 70% yield from **5a** using method B. Light yellow solid, mp 208-211°C (EtOAc). HPLC: t_R=10.49 min (A/B=40/60). Anal. Calcd for $C_{24}H_{23}N_3O_5$: C, 66.50; H, 5.35; N, 9.69. Found: C, 66.25; H, 4.99; N, 9.39.

(2S,5S,11bS)-2-(tert-Butoxycarbonyl)amino-5-methoxycarbonyl-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (9a).

Obtained in 42 and 78% yield from **6ab** (**a**/**b**=2.5:1) and **6a**, respectively, using method A. White solid, mp 233-235°C (EtOAc). HPLC: t_R=33.00 min (A/B=28/72). Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 63.18; H, 6.60; N, 10.21.

(2S,5S,11bR)-2-[2'-(tert-Butoxycarbonyl)amino-5-methoxycarbonyl-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (9b).

Obtained in 16 and 48% yield from **6ab** (**a**/**b** ratio, 2.5:1) and **12**, respectively, using method A. White solid, mp 118-120°C (EtOAc/hexane). HPLC: t_R=34.76 min (A/B=28/72). Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.31; N, 10.52. Found: C, 62.89; H, 6.56; N, 10.25.

(2S,5S,11bS)-5-Benzyloxycarbonyl-2-(benzyloxycarbonyl)amino-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (10a).

Obtained in 95 and 13% yield from **7a** using methods A and B, respectively. White solid, mp 155-156°C (EtOAc/hexane). HPLC: t_R=46.33 min (A/B=39/61). Anal. Calcd for $C_{30}H_{27}N_3O_5$: C, 70.71; H, 5.34; N, 8.25. Found: C, 70.63; H, 5.55; N, 7.97.

(2S,5S,11bR)-5-Benzyloxycarbonyl-2-(benzyloxycarbonyl)amino-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (10b).

Obtained in 63% yield from **7a** using method B. White solid, mp 200-202°C (EtOAc/hexane). HPLC: t_R=46.33 min (A/B=39/61). Anal. Calcd for $C_{30}H_{27}N_3O_5$: C, 70.71; H, 5.34; N, 8.25. Found: C, 70.51; H, 5.09; N, 8.13.

Removal of C-Terminal Protecting Groups

Method A: A solution of the corresponding 5-methoxycarbonylhexahydroindolizino[8,7-*b*]indole derivative (0.44 mmol) in MeOH (7 mL) was treated with 2N NaOH (0.66 mmol) and the mixture was stirred at rt for 18 h. After evaporation of the MeOH the remaining aqueous mixture was diluted with H_2O (5 mL), acidified with 1N HCl to pH 3, and extracted with CH_2Cl_2 (50 mL). The extract was dried (Na_2SO_4) and evaporated. The residue was purified on a silica gel column using CH_2Cl_2/MeOH (5:1).

Method B: A solution of compound **10a** or **10b** (2.35 mmol) and Boc_2O (4.7 mmol) in MeOH (50 mL) was hydrogenated at rt and 45 psi of pressure for 2.5 h in the presence of 10% Pd-C. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was treated with warm EtOAc and the precipitate, corresponding to compound **17a** or **17b** filtered. The mother liquors were evaporated and the residue purified as in method A.

(2S,5S,11bS)-2-(Benzyloxycarbonyl)amino-5-carboxy-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino-[8,7-b]indole (14a).

Obtained in 97% yield as a foam from **8a** using method A. HPLC: t_R=14.26 min (A/B=30/70). Anal. Calcd for $C_{23}H_{21}N_3O_5$: C, 65.86; H, 5.04; N, 10.02. Found: C, 65.57; H, 4.81; N, 9.86.

(2S,5S,11bR)-2-(Benzyloxycarbonyl)amino-5-carboxy-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino-[8,7-b]indole (14b).

Obtained in 94% yield from **8b** using method A. White solid, mp 135-137°C. HPLC: t_R=16.23 min (A/B=30/70). Anal. Calcd for $C_{23}H_{21}N_3O_5$: C, 65.86; H, 5.04; N, 10.02. Found: C, 65.67; H, 5.35; N, 10.27.

(2S,5S,11bS)-2-(tert-Butoxycarbonyl)amino-5-carboxy-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino-[8,7-b]indole (15a).

Obtained in 91 and 72% from **9a** and **10a** using methods A and B, respectively. White solid, mp 210-212°C (dec.) (EtOAc). HPLC: t_R=9.12 min (A/B=30/70). Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.01; N, 10.90. Found: C, 62.55; H, 6.35; N, 10.54.

(2S,5S,11bR)-2-(tert-Butoxycarbonyl)amino-5-carboxy-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino-[8,7-b]indole (15b).

Obtained in 90 and 73% from **9b** and **10b** using methods A and B, respectively. White solid, mp 140-143°C (EtOAc). HPLC: t_R=10.39 min (A/B=30/70). Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.01; N, 10.90. Found: C, 62.74; H, 6.43; N, 10.55.

(2S,5S,11bS)-2-Amino-5-carboxy-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (17a). Obtained, after lyophilization, in 22% yield from **10a** using method B. HPLC: t_R=8.44 min (A/B=15/85).

(2S,5S,11bR)-2-Amino-5-carboxy-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole (17b).

Obtained, after lyophilization, in 20% yield from **10b** using method B. HPLC: t_R=15.20 min (A/B=15/85).

Removal of* N-*Terminal Protecting Groups

Method A: A solution of the corresponding Z-protected indolizino[8,7-*b*]indole derivative (0.52 mmol) and TFA (0.52 mmol) in MeOH (40 mL) was hydrogenated at rt and 20 psi of pressure for 1.5 h in the presence of 10% Pd-C. The catalyst was filtered and the solvent evaporated to dryness.

Method B: A solution of the corresponding Boc-protected indolizino[8,7-*b*]indole derivative (0.5 mmol) and TFA (10 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 1 h and the solvents were evaporated to dryness.

(2S,5S,11bS)-2-Amino-5-methoxycarbonyl-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole. Trifluoracetate salt (16a).

Obtained as a foam in 94 and 93% yield from **8a** and **9a** using methods A and B, respectively. HPLC: t_R=4.56 min (A/B=25/75). Anal. Calcd for $C_{16}H_{17}N_3O_3.CF_3CO_2H$: C, 52.30; H, 4.39; N, 10.16. Found: C, 52.17; H, 4.54; N, 10.23.

(2S,5S,11bR)-2-Amino-5-methoxycarbonyl-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole. Trifluoracetate salt (16b).

Obtained as a syrup in 88 and 97% yield from **8b** and **9b** using methods A and B, respectively. HPLC: t_R=5.78 min (A/B=25/75). Anal. Calcd for $C_{16}H_{17}N_3O_3.CF_3CO_2H$: C, 52.30; H, 4.39; N, 10.16. Found: C, 52.38; H, 4.62; N, 9.83.

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