NEW SCAFFOLDS FOR PEPTIDOMIMETICS. SYNTHETIC APPROACHES TOWARDS 2,4-DIOXOOCTAHYDROPYRIMIDO[1',6':1,2]PYRIDO[3,4-*b*]-INDOLE-6-CARBOXYLIC ACID DERIVATIVES

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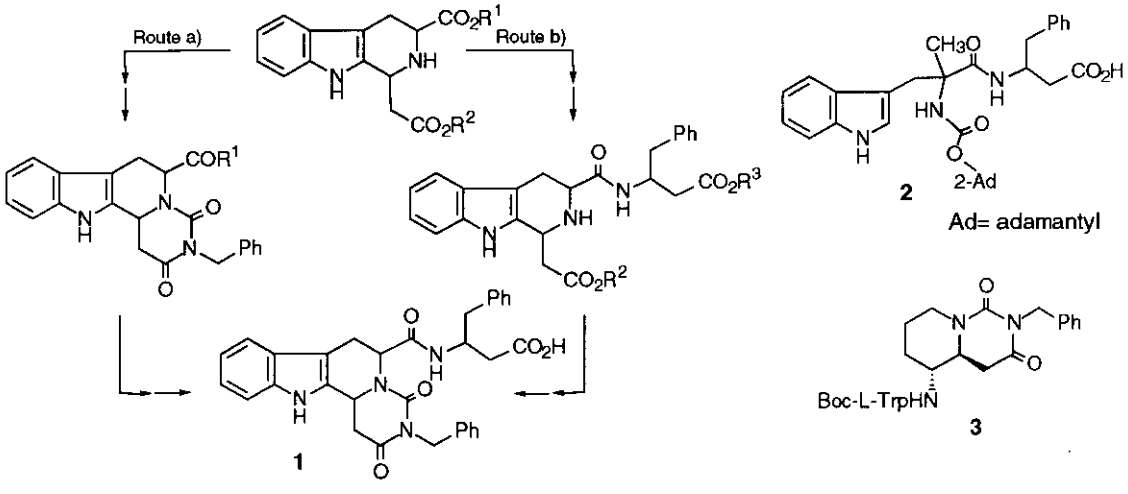
Abstract– The synthesis of 6-substituted 2,4-dioxooctahydropyrimido[1',6':1,2]pyrido-[2,3-*b*]indole derivatives from 1-(alkyloxycarbonyl)methyltetrahydro-β-carboline-3-carboxylic acid derivatives is described. The construction of the pyrimidine ring competes with that of the imidazole, to provide imidazo[1',5':1,6]pyrido[2,3-*b*]indole derivatives, when an alkyloxycarbonyl group is placed in position 3 of the tetrahydro-β-carboline, but not when there is a carboxamide function in such position.

Besides the broad screening and the rational design, a useful approach in the search of new peptidomimetics for a given receptor is the combination of pharmacophoric groups of two different series of ligands for that receptor.[1] In the cholecystokinin (CCK) field, this tactic led to the discovery of potent and selective CCK-A and CCK-B antagonists[2,3] as well as to the first examples of non-peptide CCK agonists.[4] Following this approach, and with the aim of developing new non-peptide ligands for CCK receptors, we designed compounds (**1**) as hybrid molecules combining key structural features of the dipeptoid CCK antagonists (**2**) and compound (**3**), as prototype of a novel series of highly potent and selective CCK-A antagonists containing the 2-benzyl-1,3-dioxoperhydropyrido[1,2-*c*]pyrimidine ring (Scheme 1).[5,6]



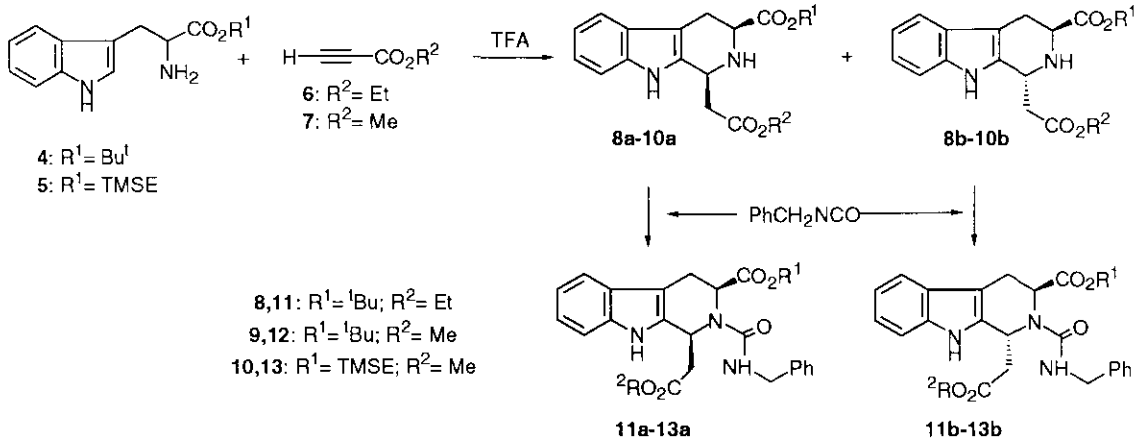
Scheme 1

It is known that conformational restrictions of the key tryptophan residue in the series of dipeptoids, such as α-methylation in compounds (**2**), lead to increased receptor-selective binding and potency. Based on these facts, compounds (**1**) incorporate a highly restricted Trp moiety together with the 2,4-dioxopyrimidopyrido skeleton, closely related to the nitrogen bridged bicyclic ring of compound (**3**), embedded within its structure.

As depicted in Scheme 1, two alternative strategies were envisaged for the synthesis of the target compounds (**1**) from suitably protected tetrahydro-β-carboline derivatives as common starting materials. In route a) the pyrimido[1',6':1,2]pyrido[2,3-*b*]indole skeleton is elaborated prior to the incorporation of the β-Phe residue present in dipeptoids (**2**), while this sequence of reactions is reversed in route b). This paper deals with the comparative study on the synthesis of compounds (**1**) by application of these synthetic routes.

RESULTS AND DISCUSSION

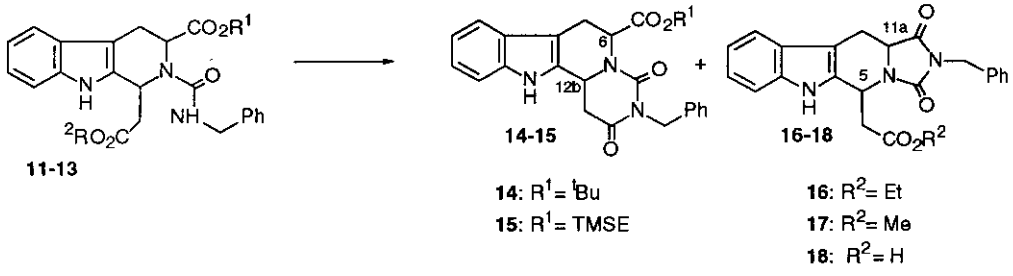
The starting 1-alkyloxycarbonylmethyl substituted tetrahydro-β-carbolines (**8-10**) were prepared by modified Pictet-Spengler reaction between the Trp derivatives (**4**) and (**5**) and the alkyl propiolates (**6**) and (**7**) (Scheme 2).[7] Although a moderate selectivity was observed in the formation of the *cis*-isomers (**8a-10a**) (**a/b** from 1.5:1 to 2.9:1) the diastereomeric pair was always obtained. Tetrahydro-β-carbolines (**9ab**) and (**10ab**) were chromatographically separated into its corresponding *cis*- **9a** and **10a** and *trans*-diatereomers (**9b**) and (**10b**), while the **8ab** analogues were used as diastereomeric mixture in the following step. The absolute configuration at C-1 in compounds (**9**) and (**10**) was established by the presence of a significant NOE between H-1 and H-3 protons in the *cis*-derivatives (**9a**) and (**10a**).



Scheme 2

Reaction of the tetrahydro-β-carbolines (**8-10**) with benzyl isocyanate afforded the corresponding 2-benzylcarbamoyl derivatives (**11-13**) in good yield (Scheme 2). The *cis*- and *trans*-isomers (**11a**) and (**11b**), obtained from the mixture (**8ab**), were easily separated by column chromatography. Although the *tert*-butyl and trimethylsilylethyl (TMSE) esters were used to minimize cyclization through the 3-

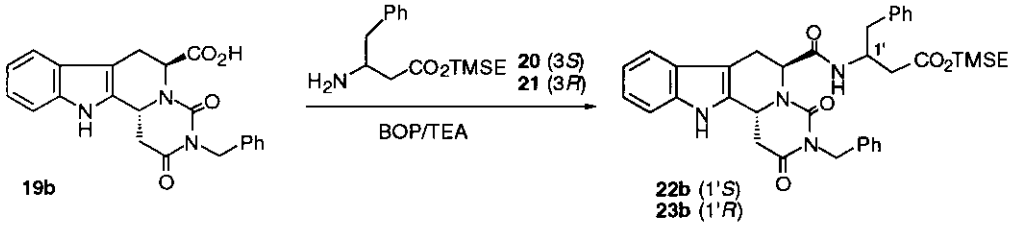
carboxylate group, the base-induced cyclization of ureas (**11-13**) provided, in all cases, a mixture of the pyrimido[1',6':1,2]pyrido[2,3-*b*]indole derivatives (**14**) and (**15**) and the imidazo[1',5':1,6]pyrido-[2,3-*b*]indoles (**16-18**), which were separated chromatographically (Scheme 3).[9] As shown in Table 1, the predominant formation of the six- or five-membered ring in compounds (**14**) and (**15**) or (**16-18**) was clearly dependent on the 3-carboxylate protecting group of the starting tetrahydro-β-carbolines, being the 3-trimethylsilylethyl esters (**13**) those leading to the desired pyrimidopyrido derivatives as major products. It is interesting to note that in the cyclization of the *trans*-tetrahydro-β-carboline (**13b**), the expected pyrimido[1',6':1,2]pyrido derivative (**15b**) was obtained along with its 6*R*,12b*R* diastereoisomer (**15c**), resulting from the epimerization of **15b** at the C-6 center. This epimerization was not observed either in the cyclization of the *tert*-butyl protected analogues (**11b**) and (**12b**) or in that of the *cis* -isomers (**11a-13a**). The formation of 5*S*,11a*R* imidazo[1',5':1,6]pyrido[2,3-*b*]indoles (**16c**) and (**17c**), from 1*S*,3*S cis* tetrahydro-β-carbolines (**11a-13a**), can be explained by epimerization at C-11a of the initially formed 5S,11aS-diastereoisomers, as previously described for related compounds.[8]



Scheme 3

Attempts to obtain the pyrimido[1',6':1,2]pyrido[2,3-*b*]indole derivatives by heating the 2-carbamoyl tertahydro-β-carbolines in refluxing THF were unsuccessful. Under these conditions, only the slow cyclization to the imidazo[1',5':1,6]pyrido[2,3-*b*]indole derivatives was observed.

To incorporate the β-Phe residue into the pyrimido[1',6':1,2]pyrido[2,3-*b*]indole skeleton, the carboxylic derivative (**19b**), quantitatively obtained by treatment of **14b** or **15b** with TFA, was coupled with trimethylsilylethyl (3*S*)- and (3*R*)-3-(benzyloxycarbonyl)amino-4-phenylbutanoate (**20**) and (**21**), using BOP,[9] to provide hybrid dipeptoid derivatives (**22b**) (48%) and (**23b**) (55%), respectively (Scheme 4). In envisioning possible epimerizations at the asymmetric centers of the pyrimidopyrido ring, the trimethylsilylethyl group, cleavable under mild conditions, namely TFA or fluoride ions,[10] was selected as *C*-protector of the β-Phe residue.



Scheme 4

Table 1.– Results of the NaH-Induced Cyclization of 2-Carbamoyl-tetrahydro-β-carbolines

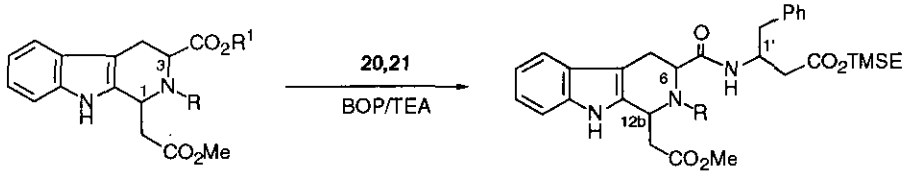
Starting Compd	Config. 1,3	R^1	R^2	Final Compd	Config. 6,12b	Config. 5,11a	R^1	R^2	Yield (%)
11a	*S,S*	Bu^t	Et	**14a**	*S,S*	–	Bu^t	–	3
				+					
				16c	–	*S,R*	_	Et	30
12a	*S;S*	Bu^t	Me	**14a**	*S,S*	–	Bu^t	–	3
				+					
				17c	–	*S,R*	_	Me	65
13a	*S,S*	TMSE	Me	**15a**	*S,S*	–	TMSE	–	56
				+					
				17c	–	*S,R*	–	Me	38
11b	*R,S*	Bu^t	Et	**14b**	*S,R*	–	Bu^t	–	13
				+					
				16b	–	*R,S*	_	Et	30
12b	*R,S*	Bu^t	Me	**14b**	*S,R*	–	Bu^t	–	31
				+	–				
				17b		*R,S*	_	Me	18
				+	–				
				18b		*R,S*	_	H	25
13b	*R,S*	TMSE	Me	**15b**	*S,R*	–	TMSE	–	20
				+					
				15c	*R,R*	–	TMSE	–	31
				+					
				17b	–	*R,S*	–	Me	42

In order to obtain the target hybrid dipeptoids following the alternative route b (Scheme 1), tetrahydro-β-carbolines (**9a**) and (**9b**) were transformed into the 2-benzyloxycarbonyl-substituted 3-carboxylic acid derivatives (**25a**) and (**25b**) (Scheme 5). These latter compounds were then condensed with the β-Phe derivatives (**20**) and/or (**21**), using BOP as coupling agent, to provide compounds (**26a**, **27a** and **27b**) in low or moderate yield. Removal of the Z group by catalytic hydrogenation yielded derivatives (**28a**, **29a** and **29b**), that were transformed into the desired pyrimido[1',6':1,2]pyrido[2,3-*b*]indole derivatives by treatment with benzyl isocyanate followed by NaH-induced cyclization. During this cyclization reaction, the pyrimido[1',6':1,2]pyrido[2,3-*b*]indole derivatives (**30a**) (59%), (**32a**) (45%) and (**23b**) (39%) were formed along with the corresponding methyl ester analogues (**31a**) (24%), (**33a**) (23%) and (**34b**) (27%), respectively. This transesterification of the trimethylsilylethyl ester by the NaOMe, generated *in situ*, was avoided by using DBU to promote the cyclization. Using this base, compound (**23b**) was obtained in 89% overall yield from **29b**. The formation of imidazo[1',5':1,6]pyrido[2,3-*b*]indole derivatives was never observed in this second synthetic strategy, indicating that the existence of a carboxamide group at C-3 of the tetrahydro-β-carbolines prevents the cyclization through this position.

Comparing the synthesis of the target compound (**23b**) from the tetrahydro-β-carboline (**9b**) by the two synthetic routes, it must be noted that, in spite of the smaller number of steps, route a) involving the formation of the 2,4-dioxopyrimido[1',6':1,2]pyrido skeleton and subsequent incorporation of the β-Phe moiety resulted in lower overall yield (14% from **9b**) than the alternative route b) (21%). The fact that, in this second pathway, the formation of the pyrimido compounds does not compete with that of the

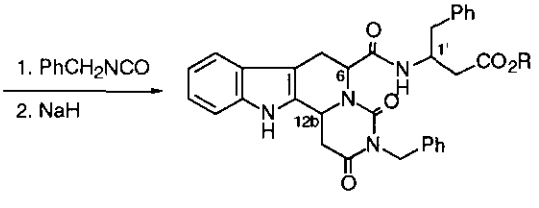
imidazo[1',5':1,6]pyrido[2,3-*b*]indole derivatives, as it occurs in the first route, takes account for the difference in the overall yield obtained in these two alternative approaches.

Finally, treatment of the (6*S*,11b*R*)-derivatives (**22b**) and (**23b**) with TFA, to remove the trimethylsilylethyl protecting group, afforded the corresponding carboxylic acids (**35b**) and (**36b**) along with the 1,12b-unsaturated compounds (**37**) and (**38**), respectively (Scheme 6, Table 2). These unsaturated compounds were predominantly obtained from *C*-deprotection of the (6*S*,12b*S*)-diatereoisomers (**30a**) and (**32a**), respectively, under similar conditions (Table 2). Surprisingly, in both cases the expected (6*S*,12b*S*) diastereoisomers were not found but their 12b*R* epimers (**35b**) and (**36b**) were isolated.



9a: R^1= Bu^t, R= H (1*S*,3*S*)
24a: R^1= Bu^t, R= Z (1*S*,3*S*)
25a: R^1= H, R=Z (1*S*,3*S*)
9b: R^1= Bu^t, R= H (1*R*,3*S*)
24b: R^1= Bu^t, R=Z (1*R*,3*S*)
25b: R^1=H, R=Z (1*R*,3*S*)

26a: R=Z (1*S*,3*S*,1'*S*)
27a: R= Z (1*S*,3*S*,1'*R*)
27b: R= Z (1*R*,3*S*,1'*R*)
28a: R= H (1*S*,3*S*,1'*S*)
29a: R= H (1*S*,3*S*,1'*R*)
29b: R= H (1*R*,3*S*,1'*R*)

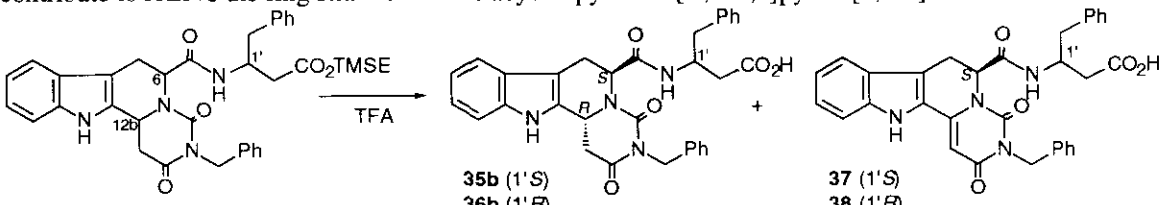


30a: R=TMSE (6*S*,12b*S*,1'*S*)
31a: R= Me (6*S*,12b*S*,1'*S*)
32a: R= TMSE (6*S*,12b*S*,1'*R*)
33a: R=Me (6*S*,12b*S*,1'*R*)
23b: R=TMSE (6*S*,12b*R*,1'*R*)
34b: R= Me (6*S*,12b*R*,1'*R*)

Scheme 5

Alternative removal of the trimethylsilylethyl protecting group by using tetrabutylammonium fluoride resulted in complex mixtures of decomposition products. Attempts to remove the *C*-protecting group from the β-Phe moiety by saponification of the corresponding methyl ester derivatives (**31a**, **33a** and **34b**) were also unsuccessful. Thus, saponification of **34b** afforded a complex mixture of products from which the oxidized compound (**38**) (11%) and the imidazo[1',5':1,6]pyrido[2,3-*b*]indole derivative (**18b**) (23%) were isolated. The formation of this latter compound could be due to the opening of the pyrimidine ring, followed by cyclization to a more stable 5-membered imidazole ring. From the deprotection reaction results, it appears that the pyrimido[1',6':1,2]pyrido[2,3-*b*]indole derivatives show a high tendency towards the oxidation in both acidic and basic media. This oxidation, specially favored for the 6*S*,12b*S*

diastereoisomers, seems to indicate that the appearance of a double bond between 1 and 12b positions may contribute to relieve the ring strain of the tetracyclic pyrimido[1',6':1,2]pyrido[2,3-*b*]indole skeleton.[11]



22b (6*S*,12b*R*,1'*S*)
23b (6*S*,12b*R*,1'*R*)
30a (6*S*,12b*S*,1'*S*)
32a (6*S*,12b*S*,1'*R*)

Scheme 6

Table 2.– Results of the *C*-Terminal Deprotection

Starting Compd	Config. 6,12b,1'	Method[a]	Final Compd (%)				
			35b	**36b**	**37**	**38**	**18b**
22b	*S,R,S*	A	40		20		
23b	*S,R,R*	A		51		32	
30a	*S,S,S*	A	18		58		
32a	*S,S,R*	A		7		71	
34b	*S,R,R*	B				11	23

[a] A: TFA; B: NaOH.

In spite of the synthetic efforts, none of the synthetic compounds, here reported, were able to bind to CCK-A or CCK-B receptors at concentrations up to 10^{-5} M. This fact could indicate that, in the dipeptoid series, only a certain degree of conformational constraint at the Trp moiety is tolerated to access both the CCK-A and CCK-B receptor binding sites. However, we have recently found that replacement of the α-Me-Trp residue of dipeptoids by a 2-amino-3-oxohexahydroindolizino[8,7-*b*]indole-5-carboxylate skeleton leads to CCK-A antagonists with nanomolar binding affinities and better selectivity for this receptor subtype than the parent dipeptoid.[12] These results suggest that the differences in conformational features between all these closely related rigid skeletons derived from Trp are critical for binding to CCK-A receptors. Therefore, a study on these differences could provide useful information about the optimal spatial arrangement of dipeptoid analogues containing restricted Trp moieties for high affinity and selectivity for CCK-A receptors.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded with a Varian Gemini 200 or a Varian XL-300 spectrometers operating at 200 and 300 MHz, respectively, using TMS as internal standard. ^{13}C NMR spectra were registered on a Varian Gemini 200 (50 MHz). The ^{13}C NMR assignations were performed by means of heteronuclear H-C

correlations (HETCOR). Elemental analyses were obtained on a CHN-O-RAPID instrument. Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F254 (Merck). Silica gel 60 (230-400 mesh, Merck) was used for column chromatography. Analytical HPLC was performed on a Waters Nova-pak C_{18} (3.9 x 150 mm, 4 μm) column, with a flow rate of 1 mL/min, using a tuneable UV detector set at 214 nm. Mixtures of MeCN (solvent A) and H_2O (solvent B) or MeCN (solvent A) and 0.05% TFA in H_2O (solvent C) were used as mobile phases. Amino acid derivatives (**5**, **20** and **21**) were prepared as described.[13]

*Synthesis of 3-Alkyloxycarbonyl-1-(alkyloxycarbonyl)methyltetrahydro-β-carbolines (**8-10**)*

A solution of the H-Trp-O^{t}Bu or H-Trp-OTMSE (**4** or **5**) (10 mmol) in $CHCl_3$ (20 mL) was treated, at 0°C, with the corresponding alkyl propiolate (**6** or **7**, 20 mmol). The reaction mixture was stirred overnight at rt and then TFA (10 mmol) was added and the stirring continued for 15 min. The obtained solution was neutralized with saturated $NaCO_3H$ solution and the organic layer was separated, dried over Na_2SO_4 and evaporated. The resulting residue was purified on a silica gel column as specified in each case.

(1*RS*,3*S*)-3-*tert*-Butoxycarbonyl-1-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carbolines (8ab).– Chromatographic solvent system: gradient from 1 to 16% Et_2O in CH_2Cl_2; 13% (from **4** and **6**; **a/b** ratio 1.6:1, measured by ^{1}H-NMR); syrup; Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.81. Found: C, 66.79; H, 7.38; N, 7.78.

3-*tert*-Butoxycarbonyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carbolines (9a and 9b).– Chromatographic solvent system: gradient from 1 to 33% Et_2O in CH_2Cl_2; Isomer (1*S*,3*S*) **9a**: 31% (from **4** and **7**); syrup; t_R= 11.0 min (A/C, 45/55); Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 65.89; H, 6.81; N, 7.96. Isomer (1*R*,3*S*) **9b**: 20% (from **4** and **7**); syrup; t_R= 9.6 min (A/C, 45/55); Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 65.93; H, 6.96; N, 7.97.

1-(Methoxycarbonyl)methyl-3-(2'-trimethylsilyl)ethoxycarbonyl-1,2,3,4-tetrahydro-β-carbolines (10a and 10b).– Chromatographic solvent system: gradient from 1 to 11% Et_2O in CH_2Cl_2; Isomer (1*S*,3*S*) **10a**: 32% (from **5** and **7**); syrup; t_R= 14.3 min (A/C, 54/46); Anal. Calcd for $C_{20}H_{28}N_2O_4Si$: C, 61.83; H, 7.26; N, 7.21. Found: C, 61.56; H, 7.18; N, 7.05. Isomer (1*R*,3*S*) **10b**: 11% (from **5** and **7**); syrup; t_R= 12.7 min (A/C, 54/46); Anal. Calcd for $C_{20}H_{28}N_2O_4Si$: C, 61.83; H, 7.26; N, 7.21. Found: C, 61.51; H, 6.99; N, 6.89.

*Synthesis of 2-Benzylcarbamoyl-1,2,3,4-tetrahydro-β-carboline Derivatives (**11-13**)*

A solution of the corresponding 2-unsubstituted tetrahydro-β-carboline (**8-10**) (1.7 mmol) in dry THF (12 mL) was treated with benzyl isocyanate (0.43 mL, 3.5 mmol) and stirred at rt for 24 h. After evaporation of the solvent the residue was purified on a silica gel column as specified in each case.

2-Benzylcarbamoyl-3-*tert*-butoxycarbonyl-1-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carbolines (11a and 11b).– Chromatographic solvent system: gradient from 25 to 65% Et_2O in hexane; Isomer (1*S*,3*S*) **11a**: 46% (from **8ab**); syrup; t_R= 17.9 min (A/B, 50/50); Anal. Calcd for $C_{28}H_{33}N_3O_5$: C, 68.41; H, 6.77; N, 8.55. Found: C, 68.19; H, 6.85; N, 8.30. Isomer (1*R*,3*S*) **11b**:

22% (from **8ab**); syrup; t_R= 17.9 min (A/B, 50/50); Anal. Calcd for $C_{28}H_{33}N_3O_5$: C, 68.41; H, 6.77; N, 8.55. Found: C, 68.07; H, 6.97; N, 8.22.

(1*S*,3*S*)-2-Benzylcarbamoyl-3-*tert*-butoxycarbonyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (12a).– Chromatographic solvent system: gradient from 1 to 3% Et_2O in CH_2Cl_2; foam, 84% (from **9a**); t_R= 12.7 min (A/B, 50/50); Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.88; H, 6.73; N, 8.65.

(1*R*,3*S*)-2-Benzylcarbamoyl-3-*tert*-butoxycarbonyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (12b).– Chromatographic solvent system: gradient from 1 to 3% Et_2O in CH_2Cl_2; 83% (from **9b**); white solid, mp= 130-132°C (Et_2O); t_R= 9.9 min (A/B, 50/50); Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.74; H, 6.50; N, 8.91.

(1*S*,3*S*)-2-Benzylcarbamoyl-3-(2'-trimethylsilyl)ethoxycarbonyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (13a).–Chromatographic solvent system: gradient from 9 to 20% EtOAc in hexane; foam, 71% (from **10a**); t_R= 11.2 min (A/B, 60/40); Anal. Calcd for $C_{28}H_{35}N_3O_5Si$: C, 64.47; H, 6.76; N, 8.05. Found: C, 64.28; H, 6.70; N, 7.73.

(1*R*,3*S*)-2-Benzylcarbamoyl-3-(2'-trimethylsilyl)ethoxycarbonyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (13b).– Chromatographic solvent system: gradient from 1 to 5% Et_2O in CH_2Cl_2; 60% (from **10b**); white solid, mp= 155-157°C (Et_2O); t_R= 8.8 min (A/B, 60/40); Anal. Calcd for $C_{28}H_{35}N_3O_5Si$: C, 64.47; H, 6.76; N, 8.05. Found: C, 64.52; H, 6.57; N, 8.15.

Table 3. Significant ^{1}H NMR Chemical Shifts (δ, ppm) of Tetrahydro-β-carboline Derivatives

Compd	Config. C-1	H-1[a]	1-CH_2[a]	H-3[b]	H-4[a,b]	^{i}NH[c]	NH(Bzl)	CH_2(Z)	$J_{3,4}$
8a[d]	*S*	4.55	2.85	3.65	2.70	8.85 (s)			10.9 4.0
8b[d]	*R*	4.66	2.85	3.75	2.80	8.61 (s)			8.8 4.8
9a[d]	*S*	4.52	2.85	3.68	2.75	8.80			11.0 4.0
9b[d]	*R*	4.66	2.87	3.74	2.80	8.56			7.9 2.2
10a[e]	*S*	4.49	2.78	3.69	2.76	8.72			11.2 4.1
10b[e]	*R*	4.66	2.83	3.80	2.87	8.54			8.5 5.0
11a[d]	*S*	5.44	3.27 2.80	5.11	3.43 3.02	8.77	5.35		6.7 1.7
11b[d]	*R*	5.48	3.28 2.68	4.28	3.41 3.04	8.36	5.64		4.7 6.7
12a[d]	*S*	5.47	3.26 2.99	5.30	3.42 3.01	8.79	5.30		6.9 1.5
12b[d]	*R*	5.47	3.27 2.71	4.24	3.38 3.02	8.42	5.67		4.4 7.0
13a[d]	*S*	5.50	3.31 3.04	5.39	3.49 3.05	8.76	5.39		7.1 1.5
13b[e]	*R*	5.48	3.21 2.78	4.24	3.45 3.10	8.30	5.95		4.4 7.8
24a[f]	*S*	5.60	3.00	5.15	3.29 3.03	10.28		5.20	7.9 2.7
24b[f]	*R*	5.43	2.90	4.78	3.25 2.90	10.56		5.17	9.8 3.8
25a[f]	*S*	5.60	3.12 2.89	5.27	3.12 3.00	10.24		5.20	7.1 2.1
25b[f]	*R*	5.45	3.05 2.98	4.85	3.29 2.98	10.57		5.17	9.9 3.6

[a] Multiplet. [b] Double doublet. [c] Singlet. [d] 200 MHz ($CDCl_3$). [e] 300 MHz ($CDCl_3$). [f] 300 MHz (DMSO-d_6, 90°C).

*Cyclization of 2-Carbamoyl-1,2,3,4-tetrahydro-β-carboline Derivatives (**11-13**)*

Method A.– A solution of the corresponding 2-carbamoyl-1,2,3,4-tetrahydro-β-carboline derivative (**11-13**) (0.3 mmol) in dry THF (5 mL) was treated with NaH (60% dispersion in mineral oil) (0.12 g, 0.3 mmol) and stirred at rt for 30 min. Then, the solution was neutralized with 1N HCl, and EtOAc and H_2O were added. The organic layer was separated, dried over Na_2SO_4 and evaporated to dryness. The resulting residue was purified on a silica gel column, as specified in each case, to provide a mixture of the pyrimido[1',6':1,2]pyrido[2,3-*b*]indole derivatives (**14** and **15**) and the imidazo[1',5':1,6]pyrido[2,3-*b*]indoles (**16-18**) (Table 1).

Method B.– A solution of the corresponding 2-carbamoyl-1,2,3,4-tetrahydro-β-carboline derivative (**12**) or (**13**) (0.2 mmol) in dry THF (10 mL) was refluxed for 15 days. After evaporation of the solvent the residue was purified on a silica gel column, as specified in each case, to provide the corresponding imidazo[1',5':1,6]pyrido[2,3-*b*]indole derivative.

(6*S*,12b*S*)-3-Benzyl-6-*tert*-butoxycarbonyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (14a).– Chromatographic solvent system: gradient from 10 to 20% EtOAc in hexane; 3% (from both **11a** and **12a**, method A); foam; $[\alpha]_D$ +75.8° (*c* 0.5 in $CHCl_3$); t_R= 26.2 min (A/B, 45/55); Anal. Calcd for $C_{26}H_{27}N_3O_4$: C, 70.09; H, 6.11; N, 9.43. Found: C, 69.75; H, 5.98; N, 9.37.

(6*S*,12b*R*)-3-Benzyl-6-*tert*-butoxycarbonyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (14b).– Chromatographic solvent system: gradient from 10 to 20% EtOAc in hexane; 13 and 31% (from **11b** and **12b**, respectively, method A); white solid, mp= 170-172°C (EtOAc/hexane); $[\alpha]_D$ +135.4° (*c* 0.5 in $CHCl_3$); t_R= 28.8 min (A/B, 45/55); Anal. Calcd for $C_{26}H_{27}N_3O_4$: C, 70.09; H, 6.11; N, 9.43. Found: C, 69.83; H, 6.02; N, 9.40.

(6*S*,12b*S*)-3-Benzyl-6-(2'-trimethylsilyl)ethoxycarbonyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (15a).– Chromatographic solvent system: gradient from 5 to 20% Et_2O in CH_2Cl_2; 56% (from **13a**, method A); foam; $[\alpha]_D$ +182.0° (*c* 0.5 in $CHCl_3$); t_R= 11.1 min (A/B, 60/40); Anal. Calcd for $C_{27}H_{31}N_3O_4Si$: C, 66.23; H, 6.38; N, 8.58. Found: C, 66.45; H, 6.25; N, 8.49.

(6*S*,12b*R*)-3-Benzyl-6-(2'-trimethylsilyl)ethoxycarbonyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (15b).– Chromatographic solvent system: gradient from 5 to 50% Et_2O in hexane; 20% (from **13b**, method A); white solid, mp= 150°C (Et_2O/hexane); $[\alpha]_D$ +134.0° (*c* 0.5 in $CHCl_3$); t_R= 13.9 min (A/B, 60/40); Anal. Calcd for $C_{27}H_{31}N_3O_4Si$: C, 66.23; H, 6.38; N, 8.58. Found: C, 65.97; H, 6.00; N, 8.61.

(6*R*,12b*R*)-3-Benzyl-6-(2'-trimethylsilyl)ethoxycarbonyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (15c).– Chromatographic solvent system: gradient from 10 to 20% EtOAc in hexane; 31% (from **13b**, method A); foam; $[\alpha]_D$ -180.0° (*c* 0.5 in $CHCl_3$); t_R= 11.1 min (A/B, 60/40); Anal. Calcd for $C_{27}H_{31}N_3O_4Si$: C, 66.23; H, 6.38; N, 8.58. Found: C, 66.21; H, 6.44; N, 8.63.

(5*R*,11a*S*)-2-Benzyl-5-ethoxycarbonylmethyl-1,3-dioxo-2,3,4,6,11,11a-hexahydroimidazo[1',5':1,6]pyrido[3,4-*b*]indole (16b).– Chromatographic solvent system: gradient from

10 to 20% EtOAc in hexane; 30% (from **11b**, method A); syrup; t_R= 6.7 min (A/B, 50/50); Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.06. Found: C, 68.83; H, 5.40; N, 9.70.

(5*S*,11a*R*)-2-Benzyl-5-ethoxycarbonylmethyl-1,3-dioxo-2,3,4,6,11,11a-hexahydroimidazo[1',5':1,6]pyrido[3,4-*b*]indole (16c).– Chromatographic solvent system: gradient from 10 to 20% EtOAc in hexane; 30% (from **11a**, method A); syrup; t_R= 6.7 min (A/B, 50/50); Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.06. Found: C, 69.12; H, 5.33; N, 10.16.

(5*S*,11a*S*)-2-Benzyl-5-methoxycarbonylmethyl-1,3-dioxo-2,3,4,6,11,11a-hexahydroimidazo[1',5':1,6]pyrido[3,4-*b*]indole (17a).– Chromatographic solvent system: gradient from 10 to 20% EtOAc in hexane; 17% (from both **12a** and **13a**, method B); $[\alpha]_D$ -3.1° (*c* 0.6 in $CHCl_3$); syrup; t_R= 15.7 min (A/B, 40/60); Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.41. Found: C, 68.63; H, 5.14; N, 10.35.

(5*R*,11a*S*)-2-Benzyl-5-methoxycarbonylmethyl-1,3-dioxo-2,3,4,6,11,11a-hexahydroimidazo[1',5':1,6]pyrido[3,4-*b*]indole (17b).– Chromatographic solvent system: gradient from 10 to 30% EtOAc in hexane; 18 and 42% (from **12b** and **13b**, respectively, method A) and 46% (from **12b**, method B); syrup; $[\alpha]_D$ -256.8° (*c* 1 in $CHCl_3$); t_R= 15.7 min (A/B, 40/60); Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.41. Found: C, 68.25; H, 5.07; N, 10.29.

(5*S*,11a*R*)-2-Benzyl-5-methoxycarbonylmethyl-1,3-dioxo-2,3,4,6,11,11a-hexahydroimidazo[1',5':1,6]pyrido[3,4-b]indole (17c).– Chromatographic solvent system: gradient from 10 to 50% EtOAc in hexane; 65 and 38% (from **12a** and **13a**, respectively, method A); syrup; $[\alpha]_D$ +254.5° (*c* 0.6 in $CHCl_3$); t_R= 15.7 min (A/B, 40/60); Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.41. Found: C, 68.51; H, 5.36; N, 10.27.

(5*R*,11a*S*)-2-Benzyl-5-carboxymethyl-1,3-dioxo-2,3,4,6,11,11a-hexahydroimidazo-[1',5':1,6]pyrido[3,4-*b*]indole (18b).– Chromatographic solvent system: MeOH; 25% (from **12b**, method A); white solid, mp 273-275°C (MeOH/H_2O); t_R= 3.0 min (A/B, 50/50).

Table 4. Significant ^1H and ^{13}C NMR Chemical Shifts (δ, ppm) of Pyrimido[1',6':1,2]pyrido[3,4-*b*]indole Derivatives ($CDCl_3$)

Compd	Config. 6,12b	H-1[a]	3-CH_2[b]	H-6[a,c]	H-7[a,c]	H-12b[b]	^{i}NH[d]	$J_{6,7}$	C-1	C-4	C-6	C-12b
14a	*S,S*	3.37 3.21	5.07	5.29	3.57 3.08	5.00	8.52	5.7 2.7	36.37	154.39	55.86	46.66
14b	*S,R*	2.72 3.46	5.06	5.47	3.46 3.20	5.21	7.98	6.4 0.0	38.76	154.54	53.56	46.63
15a (15c)	*S,S* (*R,R*)	2.97 2.77	4.67	4.20	3.34 2.70	5.55	9.02	5.5 3.0	40.31	154.47	53.71	44.50
15b	*S,R*	3.22 2.76	5.10	5.59	3.55 3.18	5.26	8.16	5.2 0.0	38.67	154.66	52.97	46.58
19b	*S,R*	3.39 2.68	4.97	5.58	3.53 3.19	5.10	8.87	5.9 0.0				

[a] Double doublet. [b] Multiplet. [c] Doublet. [d] Singlet

(6*S*,12b*R*)-3-Benzyl-6-carboxy-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido-[1',6':1,2]-pyrido[3,4-*b*]indole (19b).– A solution of compound (**14b**) (93 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) was treated with TFA (0.5 mL) and stirred at room temperature for 3 h. The solvents were

evaporated to dryness yielding the title compound (79 mg, 97%) as a white foam, that was used without further purification. t_R= 32.4 min (A/B, 30/70). ^{1}H NMR data recorded in Table 4.

Table 5. Significant ^{1}H and ^{13}C NMR Chemical Shifts (δ, ppm) of Imidazo[1',5':1,6]pyrido[3,4-*b*]indole Derivatives

Compd	5,11a	H-5[a]	5-CH_2[a]	2-CH_2[a]	H-11[b]	H-11a[b]	^{i}NH[c]	$J_{11,11a}$	C-1	C-3	C-5	C-11a
16b[d] (**16c**)	*R,S* (*S,R*)	5.52	2.94 2.76	4.64	3.31 2.70	4.10	8.98	11.1 5.6	172.34	154.49	44.56	53.63
17a[d]	*S,S*	5.33	4.20 2.62	4.71	3.41 2.81	4.20	8.80	11.4 4.2	173.08	155.21	48.62	58.30
17b[d] (**17c**)	*R,S* (*S,R*)	5.53	2.96 2.78	4.65	3.31 2.70	4.21	8.92	11.1 5.6	172.41	154.48	44.63	53.57
18b[e]	*R,S*	5.47	2.92 2.84	4.63	3.23 2.73	4.69	11.04	11.2 5.4	172.87	153.99	53.31	62.83

[a] Multiplet. [b] Double doublet. [c] Singlet. [d] $CDCl_3$. [e] DMSO-d_6.

(6*S*,12b*R*,1'*S*)-3-Benzyl-6-[1'-benzyl-2'-(2-trimethylsilylethoxycarbonyl)ethyl]-carbamoyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]-indole (22b).– A solution of the carboxylic acid derivative (**19b**) (40 mg, 0.1 mmol) and the β-Phe derivative (**20**) (32 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) was successively treated with BOP (50 mg, 0.1 mmol) and TEA (0.157 mL, 0.1 mmol). After stirring overnight at rt, CH_2Cl_2 and H_2O were added. The organic layer was separated, dried over Na_2SO_4 and evaporated. The resulting residue was purified on a silica gel column using a gradient from 10 to 20% EtOAc in hexane as eluent to give the title compound (27 mg, 48%) as a syrup; t_R= 53.1 min (A/B, 53/47); Anal. Calcd for $C_{37}H_{42}N_4O_5Si$: C, 68.28; H, 6.50; N, 8.61. Found: C, 68.45; H, 6.50; N, 8.34. ^{1}H NMR data recorded in Table 7.

(6*S*,12b*R*,1'*R*)-3-Benzyl-6-[1'-benzyl-2'-(2-trimethylsilylethoxycarbonyl)ethyl]-carbamoyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]-indole (23b).– This compound (30 mg, 55%) was obtained as a syrup from **19b** (39 mg, 0.1 mmol) and **21** (32 mg, 0.11 mmol), following the above described procedure for the preparation of compound **22b**; t_R= 50.5 min (A/B, 53/47); Anal. Calcd for $C_{37}H_{42}N_4O_5Si$: C, 68.28; H, 6.50; N, 8.61. Found: C, 68.25; H, 6.73; N, 8.23. ^{1}H NMR data recorded in Table 7.

(1*S*,3*S*)-2-Benzyloxycarbonyl-3-*tert*-butoxycarbonyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (24a).– A solution of tetrahydro-β-carboline (**9a**) (0.93 g, 2.7 mmol) and propylene oxide (2.8 mL, 40 mmol) in CH_2Cl_2 (20 mL) was cooled to -20°C and treated with benzyl chloroformate (0.36 mL, 3.2 mmol). After stirring at rt for 18 h, the solvents were evaporated to dryness and the resulting residue was purified on a silica gel column using AcOEt/hexane (1:10) as eluent. The title compound (1.06 g, 82%) was obtained as a syrup; t_R= 34.9 min (A/B, 50/50); Anal. Calcd for $C_{27}H_{30}N_2O_6$: C, 67.77; H, 6.32; N, 5.85. Found: C, 67.65; H, 6.31; N, 5.63. ^{1}H NMR data recorded in Table 3.

(1*R*,3*S*)-2-Benzyloxycarbonyl-3-*tert*-butoxycarbonyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (24b).– This compound (0.93 g, 72%) was obtained as an oil from **9b** (2.7 mmol) following the above described procedure. Purification was performed on a silica gel column

using AcOEt/hexane (1:5) as eluent; t_R= 23.0 min (A/B, 50/50); Anal. Calcd for $C_{27}H_{30}N_2O_6$: C, 67.77; H, 6.32; N, 5.85. Found: C, 67.80; H, 6.25; N, 5.60. ^{1}H NMR data recorded in Table 3.

(1*S*,3*S*)-2-Benzyloxycarbonyl-3-carboxy-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (25a).– A solution of compound (**24a**) (0.96 g, 2 mmol) in CH_2Cl_2 (3 mL) was treated with TFA (1.5 mL, 20 mmol). After stirring at rt for 7 h, the solvents were evaporated to dryness to give the title compound (0.81 g, 96%) as a foam, that was used without further purification; t_R= 16.1 min (A/B, 40/60). ^{1}H NMR data recorded in Table 3.

(1*R*,3*S*)-2-Benzyloxycarbonyl-3-carboxy-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (25b).– This compound (0.61 g, 97%) was obtained as a foam from **24b** (1.5 mmol) following the above described procedure; t_R= 10.3 min (A/B, 40/60). ^{1}H NMR data recorded in Table 3.

(1*S*,3*S*,1'*S*)-2-Benzyloxycarbonyl-3-[1'-benzyl-2'-[2-trimethylsilylethoxycarbonyl]-ethyl]carbamoyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (26a).– A solution of tetrahydro-β-carboline (**24a**) (0.5 g, 1.2 mmol) and the β-Phe derivative (**20**) (0.33 g, 1.2 mmol) in CH_2Cl_2 (18 mL) was treated with BOP (0.53 g, 1.2 mmol) and TEA (0.17 mL, 1,2 mmol) and stirred overnight at rt. After evaporation of the solvent, the residue was dissolved in EtOAc and washed with citric acid (10%), $NaHCO_3$ (10%) and brine. The organic layer was dried over Na_2SO_4 and evaporated leaving a residue which was purified on a silica gel column using a gradient from 10 to 20% EtOAc in hexane. The title compound (0.28 g, 35%) was obtained as a syrup; t_R= 9.8 min (A/B, 70/30); Anal. Calcd for $C_{38}H_{45}N_3O_7Si$: C, 66.74; H, 6.63; N, 6.14. Found: C, 66.63; H, 6.50; N, 6.11.

(1*S*,3*S*,1'*R*)-2-Benzyloxycarbonyl-3-[1'-benzyl-2'-[2-trimethylsilylethoxycarbonyl]-ethyl]carbamoyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (27a).– This compound (43%, syrup) was obtained from **24a** and **21** following the procedure described for the preparation of compound (**26a**). Purification was done on a silica gel column using a gradient from 10 to 25% EtOAc in hexane; t_R= 9.7 min (A/B, 70/30); Anal. Calcd for $C_{38}H_{45}N_3O_7Si$: C, 66.74; H, 6.63; N, 6.14. Found: C, 66.49; H, 6.71; N, 6.15.

(1*R*,3*S*,1'*R*)-2-Benzyloxycarbonyl-3-[1'-benzyl-2'-[2-trimethylsilylethoxycarbonyl]-ethyl]carbamoyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (27b).– This compound (40%, syrup) was obtained from **24b** and **21** following the procedure described for the preparation of compound (**26a**). Purification was done on a silica gel column using a gradient from 10 to 30% EtOAc in hexane; t_R= 6.7 min (A/B, 70/30); Anal. Calcd for $C_{38}H_{45}N_3O_7Si$: C, 66.74; H, 6.63; N, 6.14. Found: C, 66.72; H, 6.65; N, 5.92.

(1*S*,3*S*,1'*S*)-3-[1'-Benzyl-2'-[2-trimethylsilylethoxycarbonyl]ethyl]carbamoyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (28a).– A solution of the Z-protected tertahydro-β-carboline (**26a**) (0.27 g, 0.4 mmol) in MeOH (15 mL) was hydrogenated at rt and 35 psi of pressure for 2 h, in the presence of 10% Pd-C (30 mg) as catalyst. Filtration of the catalyst and evaporation give the title compound (0.16 g, 76%) as a syrup; t_R= 13.9 min (A/B, 50/50); Anal. Calcd for $C_{30}H_{39}N_3O_5Si$: C, 65.54; H, 7.15; N, 7.64. Found: C, 65.36; H, 7.28; N, 7.40.

(1*S*,3*S*,1'*R*)-3-[1'-Benzyl-2'-[2-trimethylsilylethoxycarbonyl]ethyl]carbamoyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (29a).– This compound (64%, syrup) was obtained as a syrup from **27a** following the above described procedure; t_R= 15.5 min (A/B, 50/50); Anal. Calcd for $C_{30}H_{39}N_3O_5Si$: C, 65.54; H, 7.15; N, 7.64. Found: C, 65.63; H, 7.02; N, 7.38.

(1*R*,3*S*,1'*R*)-3-[1'-Benzyl-2'-[2-trimethylsilylethoxycarbonyl]ethyl]carbamoyl-1-methoxycarbonylmethyl-1,2,3,4-tetrahydro-β-carboline (29b).– This compound (83%, syrup) was obtained from **27b** following the above described procedure for the synthesis of compound (**28a**); t_R= 13.5 min (A/B, 50/50); Anal. Calcd for $C_{30}H_{39}N_3O_5Si$: C, 65.54; H, 7.15; N, 7.64. Found: C, 65.55; H, 7.01; N, 7.42.

Table 6. Significant ^{1}H NMR Chemical Shifts (δ, ppm) and Coupling Constants (Hz) of Compounds **26-29**

Compd.	1,1'	H-1[a]	1-CH_2[b]	H-3[a]	H-4[a]	^{i}NH[c]	H-1'[b]	1'-CH_2[b]	H-2'[b]	OMe[c]	CH_2 (Z)[b]	$J_{3,4}$
26a[d]	*S,S*	5.59	2.88	5.05	3.17 3.00	10.32	2.39	2,77	4.27	3.05	5.17	6.8 3.3
27a[d]	*S,R*	5.56	2.93 2.83	5.02	3.14 3.00	10.11	2.42	2.75	4.25	3.62	5.16	– 2.9
27b[d]	*R,R*	5.48	2.96	4.70	3.10 3.04	10.49	2.23	2.60	4.10	3.52	5.11	– –
28a[e]	*S,S*	4.50	2.85	3.54	3.20 2.50	8.75	2.56	2.95	4.50	3.81	–	11.6 4.1
29a[f]	*S,R*	4.50	2.88	3.53	3.19 2.65	8.75	2.54	2.95	4.50	3.81	–	11.2 4.2
29b[f]	*R,R*	4.54	2.87	3.55	3.21 2.68	8.50	2.52	3.01	4.50	3.77	–	10.2 4.6

[a] Double doublet. [b] Multiplet. [c] Singlet. [d] 300 MHz (DMSO-d_6). [e] 200 MHz ($CDCl_3$). [f] 300 MHz ($CDCl_3$).

(6*S*,12b*S*,1'*S*)-3-Benzyl-6-[1'-benzyl-2'-[2-trimethylsilylethoxycarbonyl]ethyl]-carbamoyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]-indole (30a).– A solution of the tetrahydro-β-carboline (**28a**) (126 mg, 0.23 mmol) in dry THF (3 mL) was treated with benzyl isocyanate (0.042 mL, 0.34 mmol), stirred overnight at rt and evaporated. The residue was dissolved in EtOAc and washed with H_2O. The organic layer was separated, dried over Na_2SO_4 and evaporated. The resulting residue was dissolved in THF (4 mL) and treated with NaH (60% suspension in mineral oil) (9.2 mg, 0.23 mmol). After 10 min of reaction the solution was neutralized with 1N HCl and EtOAc and H_2O were added. The organic layer was separated, dried over Na_2SO_4 and evaporated leaving a residue which was purified on a silica gel column using a gradient from 10 to 60% EtOAc in hexane as eluent to give the title compound (88 mg, 59%) as a foam, along with the corresponding methyl ester derivative (**31a**) (31 mg, 24%); **30a**: t_R= 30.5 min (A/B, 53/47); Anal. Calcd for $C_{37}H_{42}N_4O_5Si$: C, 68.28; H, 6.50; N, 8.61. Found: C, 68.25; H, 6.63; N, 8.52. **31a**: t_R= 18.2 min (A/B, 42/58); Anal. Calcd for $C_{33}H_{32}N_4O_5$: C, 70.20; H, 5.71; N, 9.92. Found: C, 70.03; H, 5.84; N, 10.00.

(6*S*,12b*S*,1'*R*)-3-Benzyl-6-[1'-benzyl-2'-[2-trimethylsilylethoxycarbonyl]ethyl]-carbamoyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]-indole (32a).–This compound was obtained (45%, foam) from derivative (**29a**) following the above

described procedure. Using this method the corresponding methyl ester derivative (**33a**) (23%, foam) was also formed; **32a**: t_R= 31.2 min (A/B, 53/47); Anal. Calcd for $C_{37}H_{42}N_4O_5Si$: C, 68.28; H, 6.50; N, 8.61. Found: C, 68.10; H, 6.41; N, 8.57. **33a**: Anal. Calcd for $C_{33}H_{32}N_4O_5$: C, 70.20; H, 5.71; N, 9.92. Found: C, 69.87; H, 5.95; N, 9.66.

(6*S*,12b*R*,1'*R*)-3-Benzyl-6-[1'-benzyl-2'-methoxycarbonylethyl]carbamoyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (34b).– This compound was obtained (27%, syrup) along with the expected derivative (**23b**) (39%) from **29b**, following the above described procedure for the synthesis of **30a**. t_R= 22.7 min (A/B, 42/58); Anal. Calcd for $C_{33}H_{32}N_4O_5$: C, 70.20; H, 5.71; N, 9.92. Found: C, 70.17; H, 5.61; N, 9.75.

*Removal of C-Terminal Trimethylsilylethyl Group from **22b**, **23b**, **30a** and **32a***

A solution of the corresponding trimethylsilyl-protected derivative (50 mg, 0.08 mmol) in CH_2Cl_2/TFA (2:1, 1.5 mL) was stirred at rt for 4 h. After evaporation of the solvents, the resulting residue was purified on a silica gel column using a gradient from 1 to 25% MeOH in CH_2Cl_2.

(6*S*,12b*R*,1'*S*)-3-Benzyl-6-[1'-benzyl-2'-carboxyethyl]carbamoyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (35b).– White foam, 18 and 40% (from **30a** and **22b**, respectively); $[\alpha]_D$ +67.0° (*c* 0.1 in MeOH); t_R= 11.9 min (A/B, 40/60); Anal. Calcd for $C_{32}H_{30}N_4O_5$: C, 69.80; H, 5.49; N, 10.17. Found: C, 69.58; H, 5.62; N, 10.03.

(6*S*,12b*R*,1'*R*)-3-Benzyl-6-[1'-benzyl-2'-carboxyethyl]carbamoyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (36b).– White foam, 7 and 51% (from **32a** and **23b**, respectively); $[\alpha]_D$ +46.1° (*c* 0.5 in MeOH); t_R= 12.7 min (A/B, 40/60); Anal. Calcd for $C_{32}H_{30}N_4O_5$: C, 69.80; H, 5.49; N, 10.17. Found: C, 69.73; H, 5.29; N, 9.83.

(6*S*,1'*S*)-3-Benzyl-6-[1'-benzyl-2'-carboxyethyl]carbamoyl-2,4-dioxo-2,3,4,6,7,12,-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (37).– White foam, 58 and 20% (from **30a** and **22b**, respectively); $[\alpha]_D$ -32.0° (*c* 0.5 in MeOH); t_R= 27.1 min (A/B, 34/66); Anal. Calcd for $C_{32}H_{28}N_4O_5$: C, 70.06; H, 5.14; N, 10.21. Found: C, 69.77; H, 5.32; N, 10.25.

(6*S*,1'*R*)-3-Benzyl-6-[1'-benzyl-2'-carboxyethyl]carbamoyl-2,4-dioxo-2,3,4,6,7,12-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indole (38).– White foam, 71 and 32% (from **32a** and **23b**, respectively); $[\alpha]_D$ -57.0° (*c* 0.8 in MeOH); t_R= 30.3 min (A/B, 34/66); Anal. Calcd for $C_{32}H_{28}N_4O_5$: C, 70.06; H, 5.14; N, 10.21. Found: C, 69.91; H, 5.20; N, 9.98.

*Removal of C-Terminal Methyl Group from **34b***

A solution of the methyl-protected derivative (**34b**) (22 mg, 0.04 mmol) in MeOH (1 mL) was treated with 2N NaOH (0.08 mmol) and stirred overnight at rt. After evaporation of the MeOH, the remaining aqueous mixture was diluted with H_2O and acidified with 1N HCl to pH 3, and extracted with EtOAc. The extract was dried over Na_2SO_4 and evaporated. The resulting residue was purified on a silica gel column using a gradient from 1 to 25% MeOH in CH_2Cl_2, to give compounds (**38**) (2.5 mg, 11%) and (**18b**) (4 mg, 23%).

Table 7. Significant ^{1}H NMR Chemical Shifts (δ, ppm) and Coupling Constants (Hz) of Compounds (**22, 23** and **30-38**)

Compd.	12b,1'	H-1[a]	3-CH_2[a]	H-6[b,c]	6-CONH[b]	H-7[b,c]	H-12b[a]	^{i}NH[d]	H-1'[a]	1'-CH_2[a]	H-2'[a]	$J_{6,7}$
22b[e]	*R,S*	2.52 2.96	5.05	5.39	6.61	2.96 3.30	4.29	7.95	2.38	2.69	4.29	– 0.0
23b[e]	*R,R*	2.65 3.11	5.02	5.40	6.62	3.11 3.24	5.16	8.02	2.34	2.65	4.29	6.1 –
30a[e]	*S,S*	3.26	5.02	5.00	[g]	3.09 3.44	4.86	8.86	2.30	2.70	4.30	5.4 3.6
31a[e]	*S,S*	3.25	5.00	5.00	6.58	2.98 3.32	4.80	9.02	2.31	2.65	4.27	5.3 3.2
32a[e]	*S,R*	3.32 3.38	4.99	5.00	6.85	3.11 3.26	4.85	8.60	2.35	2.72	4.30	5.2 3.9
33a[e]	*S,R*	3.20	4.91	4.85	6.73	3.00 3.15	4.85	8.76	2.29	2.66	4.25	5.8 –
34b[e]	*R,R*	2.70 3.15	5.04	5.40	6.54	3.06 3.15	5.11	8.25	2.35	2.65	4.30	6.2 0.0
35b[f]	*R,S*	2.80	5.06	5.50	[g]	3.10 3.46	5.05	10.14	2.50	2.80	4.34	6.3 0.0
36b[f]	*R,R*	2.75 3.35	4.98	5.43	[g]	3.10 3.41	5.36	c	2.43	2.72	4.29	6.6 0.0
37[f]	–,*S*	6.24	5.18	5.72	[g]	3.44 3.74	–	10.94	2.46	2.83	4.32	7.1 0.0
38[f]	–,*R*	6.21	5.12	5.66	[g]	3.38 3.62	–	10.73	2.45	2.75	4.30	6.8 0.0

[a] Multiplet. [b] Doublet. [c] Double doublet. [d] Singlet. [e] 300 MHz, $CDCl_3$. [f] 300 MHz, $(CD_3)_2CO$. [g] Included within the Aromatic proton signals.

ACKNOWLEDGEMENTS

We thank the Comisión Interministerial de Ciencia y Tecnología (SAF 97 0030) and Fundación La Caixa (97/022-01) for financial support.

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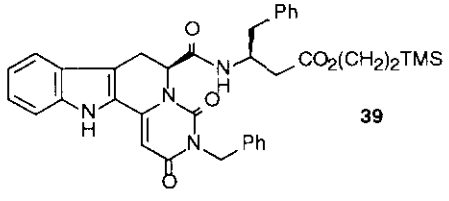
11. Compound (**30a**) was transformed itself into the 1,12b-unsaturated derivative (**39**) in $CDCl_3$ solution (half life, 90 days).^{1}H NMR (300 MHz, $CDCl_3$): δ 10.01 (s, 1H, NH^i), 7.50-6.90 (m, 15H, H-Ar, 6-CONH), 6.22 (s, 1H, H-1), 5.58 (d, 1H, H-6, J= 6.9), 5.15 (m, 2H, 3-CH_2), 4.29 (m, 1H, H-1'), 4.04 (m, 2H, CO_2CH_2), 3.60 (d, 1H, H-7, J= 16.7), 3.23 (dd, 1H, H-7, J= 16.7, 10.9), 2.67 (m, 2H, 1'-CH_2), 2.31 (m, 2H, 1'-CH_2), 0.90 (m, 2H, CH_2TMS), 0.0 (s, 9H, TMS). Anal. Calcd for $C_{37}H_{40}N_4O_5Si$: C, 68.49; H, 6.21; N, 8.64. Found: C, 68.40; H, 6.33; N, 8.37.



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Received, 22nd September, 1998