UNPRECEDENTED BASE-PROMOTED OXIDATION OF IMIDAZO[1',5':1,2]PYRIDO[3,4-*b*]INDOLES

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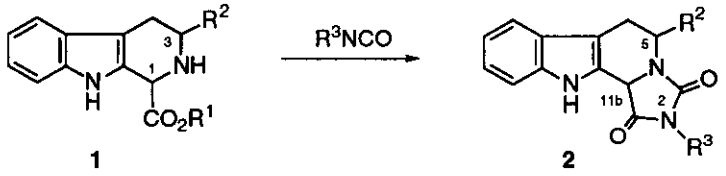
Abstract– 1,3-Dioxotetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole derivatives show a high tendency towards the oxidation at the 11b-bridgehead position in basic media. This oxidation, affording the corresponding 11b-hydroxy derivatives, is produced by reaction between atmospheric oxygen and the imidazopyrido derivative under the enol form and can be suppressed by working in inert atmosphere. In marked contrast, these imidazo[1',5':1,2]pyrido derivatives are completely stable in acidic conditions.

Our interest in exploring the versatility of tetrahydro-β-carboline derivatives as intermediates for the synthesis of highly restricted templates for use in the search of peptidemimics,[1] prompted us to undertake the preparation of 2-substituted imidazo[1',5':1,2]pyrido[3,4-*b*]indole-5-carboxylates (**2**; R^2= CO_2R) from the corresponding 1,3-disubstituted β-carbolines (**1**; R^2= CO_2R). With this aim, the methodology described for the synthesis of the 5-unsubstituted analogues (**2**[2,3]; R^2= H) from the tetrahydro-β-carbolines (**1**;R^1= R^2= H) was followed (Scheme 1). During the course of this undertaking, we found that our target imidazo[1',5':1,2]pyrido derivatives show an extraordinary tendency towards oxidation at the 11b-bridgehead position. The present paper deals with the factors influencing this unexpected oxidation.



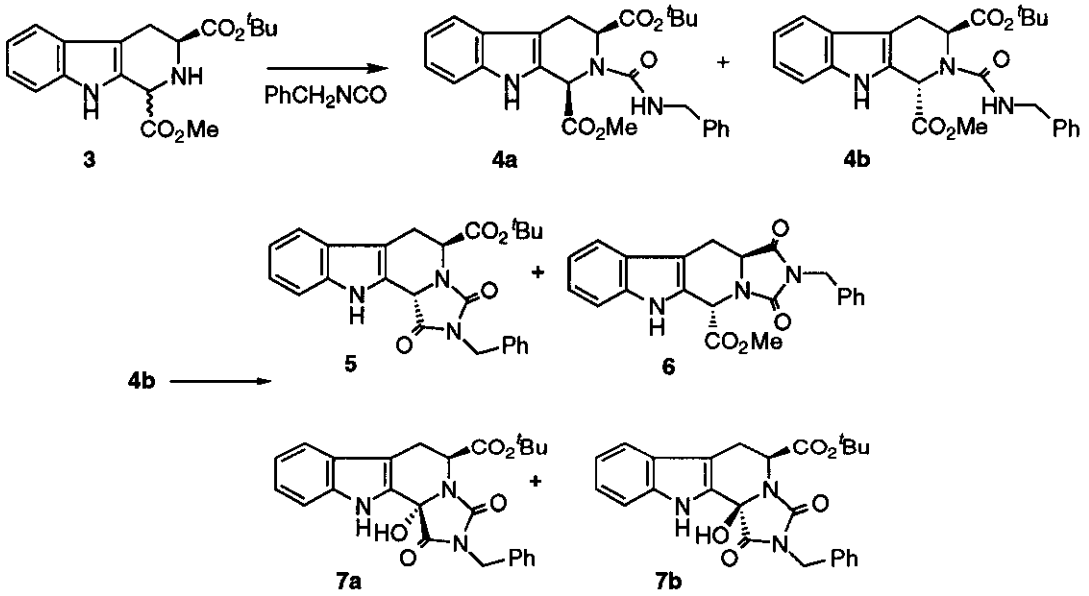
1 **2**

Scheme 1

RESULTS AND DISCUSSION

As indicated in Scheme 2, reaction of compounds (**3ab**), as a 1:4 mixture of *cis* and *trans* diastereomers, with benzyl isocyanate gave ureas (**4a**) and (**4b**), which were chromatographically separated in 9 and 76% yields, respectively. The ratio of *cis* to *trans* in which the ureas were formed indicated that, during the course of the

reaction, the starting *cis*-tetrahydro-β-carboline epimerized to the more stable *trans* stereoisomer, probably due to the acidity of the H-1 proton.



Scheme 2

Table 1.– Cyclization of Linear Urea Derivative (**4b**)

	Remaining	Final Compounds (Yield, %)			
Method[a]	**4b**	**5**	**6**	**7a**	**7b**
A	0	11	21	14	33
B	79	6	3	1	3
C	0	59	23	3	6
D	7	28	23	9	13

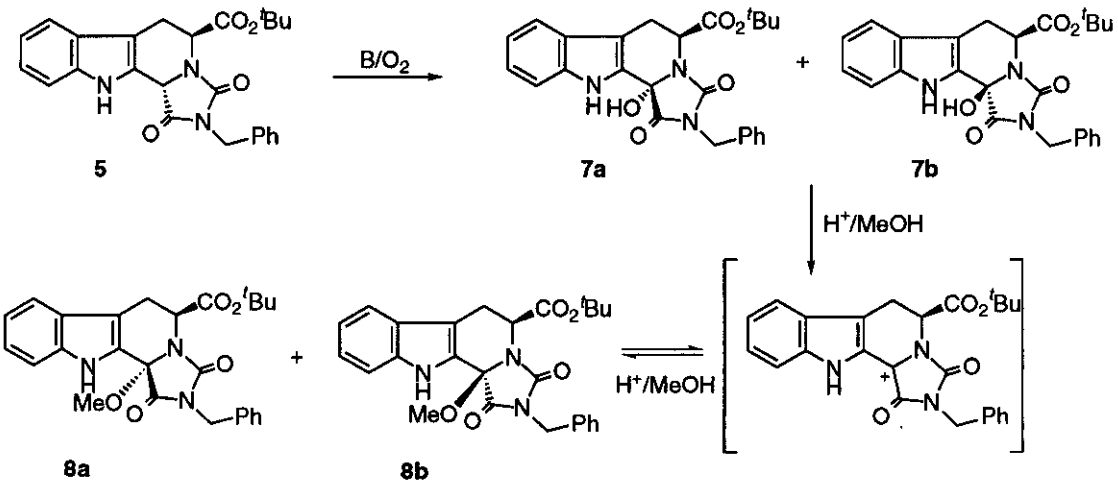
[a] A: NaH/THF/rt (30 min); B: THF/reflux (7 h); C: THF/Xylene(1:1)/reflux (5 h); D: THF+ Dibenzylurea(0.5 equiv)/reflux (7 h).

Cyclization of urea (**4b**) was induced by sodium hydride in THF at room temperature to produce the imidazo[1',5':1,2]pyrido derivative (**5**)[4] and its corresponding [1',5':1,6] regioisomer (**6**)[5] in 11 and 21% yield, respectively. However the overall yield of these regioisomers (33%) was lower than that of two additional and unexpected compounds (47%), which were identified as the 11b-hydroxy derivatives (**7a**) and (**7b**), as indicated afterwards. This result led us to perform the cyclization of urea (**4b**) under different conditions and to study the formation of hydroxylated compounds (**7**). Heat-mediated cyclizations required high temperatures to drive the reaction to complexion. Thus, as shown in Table 1, little cyclization occurred in refluxing THF while the reaction was completed in refluxing 1:1 THF/xylene after 5 h. Under these latter

conditions, the major regioisomer was the imidazo[1',5':1,2]pyrido derivative (**5**) and only traces of the hydroxylated analogues (**7**) were formed. Surprisingly, when crude (**4b**) contamined with dibenzylurea was used as starting material cyclization was almost completed in refluxing THF after 5 h. Moreover, in this case the hydroxy derivatives (**7**) resulted in higher ratio than in the other heat-mediated cyclizations. This fact suggests that the dibenzylurea not only induced the cyclization but also the formation of the hydroxylated products.

Oxidation of activated C-H bonds, specially tertiary centers adjacent to C=X groups, to the corresponding hydroxy derivatives has been described by direct enolate oxygenation[6-10] and by using selective oxidants.[11-14] Among these methods, aeration of lithio enolates of carboxylic acids, esters, amides and lactams is widely used for effecting α-hydroxylation. Similar hydroxylations of diketopiperazines and 1,3-dioxoperhydropyrrolo[1,2-*c*]imidazoles, structurally related to compound (**5**), utilizing radical initiator under oxygen atmosphere have also been reported.[15] According to this free-radical mechanism, the formation of the hydroxylated derivatives (**7**) could be due to the presence of peroxides in the THF used as solvent or cosolvent in the cyclizations.[16] However, the fact that compound (**5**) remained unchanged in refluxing THF or THF/xylene, even in the presence of the radical initiator azaisobutyronitrile (Table 2), discards this possibility. Furthermore, several experiments were made which confirmed that the formation of **7** occurred by the action of the atmospheric oxygen *via* enolization of the imidazo[1',5':1,2]pyrido system. As shown in Table 2, an approximately 50% of compound (**5**) was converted into the 11b-hydroxy analogues on heating in refluxing THF in the presence of dibenzylurea. This conversion increased up to complete disappearance of the starting compound by employing strong basic media. The hydroxylation rate was also dependent on the base strength. These facts demonstrate that the 11b-hydroxy derivatives (**7**) are formed by oxidation of compound (**5**) through the hydantoine enolate intermediate. Evidence for the involvement of the atmospheric oxygen in the oxidation of **5** comes from conducting the reaction under strong basic conditions (1 equiv. of 2N NaOH, rt, 10 min) and argon atmosphere. Under these conditions, only traces (3%) of the oxidized derivatives (**7**) were obtained, while the oxidation was complete when oxygen was not removed from the reaction. The formation of small amounts of compounds (**7**) during the heat-mediated cyclizations of pure urea (**4b**) (Methods B and C, Table 1) suggests that this starting material may function as base producing the enolization of the resulting imidazo[1',5':1,2]pyrido derivative (**5**). Support for this suggestion comes from the fact that the ratio of oxidized compounds (**7**) was higher in THF than in THF/xylene, in agreement with the cyclization reaction rate in each solvent.

Although we have demonstrated that compound (**5**) is really oxidized in the presence of bases, a certain oxidation of the starting linear urea (**4b**) could also contribute to the final ratio of the 11b-hydroxyimidazopyrido derivatives (**7**), since **4b** could be enolizable due to the acidity of the H-1 hydrogen. To test this possibility, the direct treatment of **4b** with base was not undertaken because the cyclization reaction of **4b** proceeds as fast as the oxidation of compound (**5**) does. However, this possibility does not seem plausible, since the imidazo[1',5':1,6]pyrido derivative (**6**), in which the acidity of the H-5 hydrogen must be similar to that of the H-1 hydrogen in **4b**, remained completely unaltered when treated in THF (5 h, rt) with NaH or DBU (1 equiv.). This indicates that the observed oxidation reaction is exclusive of the imidazo[1',5':1,2]pyrido regioisomer.[17]



Scheme 3

Table 2.– Oxidation of Compound (**5**)

Base (equiv)	Solvent	Temp.	Time	Remaining **5** (%)[a]	**7a** (%)[a]	**7b** (%)[a]
–	THF	rt	5 h	99	–	–
–	THF	reflux	5 h	96	–	–
	THF/xylene	reflux	5 h	97	–	–
–	THF/AIBN[b]	reflux	5h	93	–	–
Dibenzylurea (0.5)	THF	rt	5 h	97	–	–
Dibenzylurea (0.5)	THF	reflux	5 h	48	6	42
NaH (1)	THF	rt	30 min	2	28	64
2N NaOH (0.5)	THF	rt	10 min	39	9	47
2N NaOH (0.5)	THF	rt	30 min	20	23	55
2N NaOH (1)	THF	rt	10 min	36	10	49
2N NaOH (1)	THF	rt	30 min	6	27	63
DBU (1)	THF	rt	30 min	13	34	44
NEt_3 (1)	MeOH	rt	30 min	83	2	8
NH_3 (Saturated)	MeOH	rt	30 min	55	28	12
DBU (1)	MeOH	rt	30 min	5	58	25
NaOMe (1)	MeOH	rt	30 min	0	62	25
2N NaOH (0.5)	MeOH	rt	10 min	24	42	31
2N NaOH (0.5)	MeOH	rt	30 min	0	51	43
2N NaOH (1)	MeOH	rt	10 min	0	54	41
2N NaOH (1)	MeOH/Ar[c]	rt	10 min	86	2	1

[a] % conversion measured by HPLC [Analytical HPLC (MeCN/H_2O(0.05% TFA)= 50/50)]

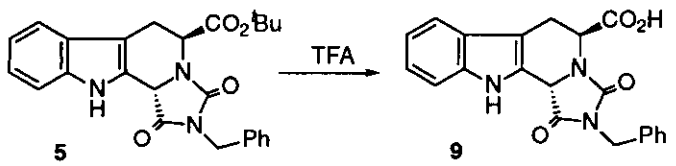
[b] Reaction in the presence of 0.5 equiv of azobisisobutyronitrile. [c] Reaction under argon atmosphere.

Concerning the stereoselectivity of the oxidation, it is interesting to note that, while in THF the more stable diastereoisomer (**7b**) is predominantly formed, in MeOH the major isomer (**7a**) is that resulting from attack of oxygen on the unhindered side of the intermediate enolate. Two main mechanistic rationales have been proposed for this kind of oxidation.[10] The first one implies the electrophilic addition of molecular oxygen to the enolate, activated by counterion complexation in a six-membered transition state. Alternatively, oxidation may proceed through a radical mechanism involving single-electron transfer from the enolate to oxygen generating an α-keto radical. A different participation of both mechanisms during the oxidation of compound (**5**) in THF and in MeOH could explain the differences found in the stereoselectivity.

The structural assignment of the 11b-hydroxy derivatives (**7a**) and (**7b**) was based on their ^{1}H NMR, ^{13}C NMR, IR, UV and MS spectral data. The ^{1}H NMR spectra of these derivatives were similar to that of compound (**5**), but the absence of the signal due to the H-11b proton and the appearance of a singlet that exchanges with D_2O were observed (Table 3). Additionally, the ^{13}C NMR spectra of **7a** and **7b** lack of the C-11b tertiary carbon present in **5** (54.88 ppm), while a new signal of quaternary carbon appeared at about 80 ppm in each case.[18] Comparison of the molecular peaks in the FAB MS spectra of **7a** (*m/z* 447.2109) and **7b** (*m/z* 447.2131) to that of **5** (*m/z* 431.1833) indicated a difference in 16 mass units and, therefore, the presence of an additional oxygen atom. Finally, the absorption band at about 3350 cm^{-1} in the IR spectra and the exchangeable singlets observed in ^{1}H NMR are in agreement with the additional oxygen taking part of an hydroxyl group.[19]

To facilitate the stereochemical assignment, compounds (**7a**) and (**7b**) were transformed into the corresponding 11b-methoxy analogues (**8**) by means of HCl/MeOH (Scheme 3).[20] As the formation of the methoxy derivatives is reversible, by way of the 11b-carbonium ions, the obtained 11b*S*/11b*R* ratio (**8a/8b** ≈ 1:2) is independent on the C-11b configuration of the starting alcohol. Compound (**8b**) showed strong dipolar exchange of magnetization (NOE) between the CH_3 protons of methoxy and *tert*-butyl groups, indicating that both groups are located on the same face of the molecule, while the protons of the MeO group in isomer (**8a**) only showed a weak, but significant, NOE with the H-5 proton. Therefore, compound (**8a**) has the absolute stereochemistry 5*S*,11b*S* and **8b** is 5*S*,11b*R*. Since no significant NOEs were found for the OH proton of **7a** and **7b**, the absolute configuration of these compounds was established by comparison of their ^{1}H and ^{13}C NMR data with those of the above indicated methoxy derivatives (**8**).

In marked contrast to the extreme propensity of the imidazo[1',5':1,2]pyrido skeleton to oxidation in basic media, no alteration was observed in acidic conditions. Thus, the carboxylic acid (**9**)[21] was obtained in quantitative yield by treatment of the corresponding 5-*tert*-butoxycarbonyl derivative (**5**) with TFA (Scheme 4).



Scheme 4

Table 3.– Significant ^{1}H NMR Chemical Shifts of Imidazo[1',5':1,2]pyrido[3,4-*b*]indole Derivatives (200 MHz, $CDCl_3$)

Compd	R^1	R^2	2-CH2	H-5	H-6	H-11b	R^1	R^2
5	O^{t}Bu	H	4.59	5.22	3.20	5.55	1.36 (^{t}Bu)	–
					2.56			
7a	O^{t}Bu	OH	4.53	3.95	3.01	–	1.56 (^{t}Bu)	6.32 (OH)
					2.56			
7b	O^{t}Bu	OH	4.67	5.48	3.22	–	1.39 (^{t}Bu)	6.46 (OH)
8a	O^{t}Bu	OMe	4.56	4.08	3.15	–	1.49 (^{t}Bu)	3.29 (Me)
					3.00			
8b	O^{t}Bu	OMe	4.45	5.02	3.32	–	1.17 (^{t}Bu)	3.06 (Me)
					2.76			
9	OH	H	4.57	5.35	3.30	5.43	6.47 (CO_2H)	–
					3.10			

Table 3.– Significant ^{13}C NMR Chemical Shifts of Imidazo[1',5':1,2]pyrido[3,4-*b*]indole Derivatives (50 MHz,$CDCl_3$)

Compd	R^1	R^2	C-1	C-3	C-5	C-6	C-11b	R^1	R^2
5	O^{t}Bu	H	169.35	155.74	52.51	25.54	54.88	79.42	–
								27.73	
7a	O^{t}Bu	OH	171.23	154.36	53.11	22.19	82.38	82.87	–
								27.86	
7b	O^{t}Bu	OH	172.55	155.75	52.55	24.63	79.31	84.34	–
								27.83	
8a	O^{t}Bu	OMe	169.15	154.65	53.13	22.34	86.75	82.35	52.08
								27.90	(Me)
8b	O^{t}Bu	OMe	169.11	156.18	50.97	21.52	84.78	82.38	52.06
								27.76	(Me)
9	OH	H	170.68	156.31	50.21	23.20	54.89	–	–

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded with a Varian Gemini 200 spectrometer operating at 200 MHz, 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). IR spectra were recorded with a Shimadsu IR435 spectrophotometer. UV absorption spectra were taken with a Perkin-Elmer 550 SE spectrophotometer using EtOH as sample solvent. HRMS spectra were registered in a VG autospec using m-nitrobenzyl alcohol as matrix. 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 0.05% TFA in H_2O (solvent B) were used as mobile phase. Tryptophan derivatives were purchased from Bachem. Compound (**3**) was prepared as described for the corresponding 3-unsubstituted analogues.[2,3]

2-Benzylcarbamoyl-3-*tert*-butoxycarbonyl-1-methoxycarbonyl-1,2,3,4-tetrahydro-β-carbolines (4a and 4b). A solution of the epimeric mixture of 1,3-disubstituted tetrahydro-β-carboline (**3ab**; **a/b**=1:4) (0.43 g, 1.3 mmol) in dry THF (10 mL) was treated with benzyl isocyanate (0.32 mL, 2.6 mmol). After 24 h of stirring at rt, the solvent was evaporated. The major isomer (**4b**; (1*S*,3*S*); 0.36 g, 60%) was obtained by precipitation with CH_2Cl_2. The minor diastereoisomer (**4a**) was obtained after purification on a silica gel column, using a gradient from 9 to 28% of EtOAc in hexane.

Isomer (1*R*,3*S*) (**4a**): (54 mg, 9%), foam; HPLC: t_R= 33.27 min (A/B= 40/60); ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.40 (s, 1H, H-11), 7.52-7.05 (m, 9H, Ar), 6.05 (t, 1H, H-9, J= 5.5), 5.88 (s, 1H, H-1), 5.17 (d, 1H, H-3, J= 6.23), 4.49 (m, 2H, C*H*$_2$Ph), 3.80 (s, 3H, CO_2Me), 3.26 (d, 1H, H-4, J= 15.7), 3.01 (ddd, 1H, H-4, J= 15.7, 6.2, 1.9), 1.21 (s, 9H, CH_3 Boc); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 170.42 and 169.10 (CO_2R), 158.97 (NCON), 107.69-139.12 (Ar), 82.23 (C, Boc), 53.51 (C-1), 52.97 (C-3), 52.84 (CO_2*Me*), 45.26 (*C*H$_2$Ph), 27.72 (*C*H$_3$, Boc), 23.34 (C-4). Anal. Calcd for $C_{26}H_{29}N_3O_5$: C, 67.37; H, 6.31; N, 9.06. Found: C, 67.11; H, 6.35; N 9.00.

Isomer (1*S*,3*S*) (**4b**): (458 mg, 76%), white solid, mp= 165-167 °C (CH_2Cl_2); HPLC: t_R= 63.33 min (A/B= 40/60); ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.47 (s, 1H, H-11), 7.2-7.6 (m, 9H, Ar), 5.80 (s, 1H, H-1), 5.29 (t, 1H, H-9, J= 5.8), 4.94 (dd, 1H, H-3, J= 5.6, 1.3), 4.65 (m, 2H, C*H*$_2$Ph), 3.87 (s, 3H, CO_2Me), 3.58 (dd, 1H, H-4, J= 15.4, 1.7), 3.39 (ddd, 1H, H-4, J= 15.4, 5.6 ,1.7), 1.38 (s, 9H, CH_3 Boc). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 170.99 and 170.79 (CO_2R), 158.48 (NCON), 107.06-139.07 (Ar), 82.24 [C, Boc), 55.78 (C-1), 55.68 (C-3), 52.78 (CO_2*Me*), 44.86 (*C*H$_2$Ph), 27.57 (*C*H$_3$, Boc), 24.10 (C-4). Anal. Calcd for $C_{26}H_{29}N_3O_5$: C, 67.37; H, 6.31; N, 9.06. Found: C, 67.16; H, 6.10; N 8.98.

Cyclization of the 2-benzylcarbamoyl derivative (4b)

Method A.– A solution of compound (**4b**) (0.2 g, 0.43 mmol) in dry THF (7 mL) was treated with NaH (60% suspension in mineral oil) (17 mg, 0.43 mmol). After 30 min of reaction at rt, the solution was

neutralized with 1N HCl and the solvents evaporated. The residue was extracted with CH_2Cl_2, and the extract was washed with H_2O and dried over Na_2SO_4. After evaporation of the solvent, the resulting residue was purified on a silica gel column, using a gradient from 8 to 50% of EtOAc in hexane, to give the products indicated in Table 1.

Method B.– A solution of compound (**4b**) (0.18 g, 0.4 mmol) in THF or THF/xylene (1:1) (10 mL) was refluxed for 5-7 h. Then, the solvents were evaporated and the resulting residue was purified on a silica gel column, using a gradient from 8 to 50% of EtOAc in hexane (Table 1).

(5*S*,11b*S*)-2-Benzyl-5-*tert*-butoxycarbonyl-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]-pyrido[3,4-*b*]indole-1,3(2*H*)-dione (5).– White solid, mp= 150 °C (EtOAc/hexane); HPLC: t_R= 15.33 min (A/B= 50/50). UV λ (nm)(EtOH): 278 (2410), 230 (2820). HRMS *m/z* calcd for $C_{25}H_{25}N_3O_4$ 431.1845, found 431.1833. Anal. Calcd for $C_{25}H_{25}N_3O_4$: C, 69.59; H, 5.84; N, 9.74. Found: C, 69.80; H, 5.82; N, 9.44.

(5*S*,11b*S*)-2-Benzyl-5-methoxycarbonyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,6]-pyrido[3,4-*b*]indole-1,3(2*H*)-dione (6).–Foam; HPLC: t_R= 16.73 min (A/B= 40/60); ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.46 (s, 1H, H-11), 7.00-7.50 (m, 9H, Ar), 5.81 (d, 1H, H-5, J= 2.1), 4.76 (m, 2H, C*H*$_2$Ph), 4.48 (dd, 1H, H-11a, J= 11.3, 5.5), 3.83 (s, 3H, CO_2Me), 3.40 (dd, 1H, H-11, J= 15.4, 5.5), 2.80 (ddd, 1H, H-11, J= 15.4, 11.3, 2.1). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 172.18 (C-1), 168.59 (CO_2Me), 154.92 (C-3), 107.79-136.49 (Ar), 54.39 (C-5), 53.29 (C-11a), 50.47 (CO_2*Me*), 42.41 (*C*H$_2$Ph), 22.75 (C-11). Anal. Calcd for $C_{22}H_{19}N_3O_4$: C, 67.86, H, 4.92; N, 10.79. Found: C, 68.01; H, 5.20; N, 10.52.

2-Benzyl-5-*tert*-butoxycarbonyl-11b-hydroxy-5,6,11,11a-tetrahydro-1*H*-imidazo[1',5':1,2]-pyrido[3,4-*b*]indole-1,3(2*H*)-diones (7a and 7b)

Isomer (5*S*,11b*S*) (**7a**): Foam; HPLC: t_R= 9.07 min (A/B= 50/50); IR (KBr) ν (cm^{-1}): 3360 (OH), 1725 (C=O); UV λ (nm)(EtOH): 288 (2300), 228 (2710); HRMS *m/z* calcd for $C_{25}H_{25}N_3O_5$ 447.1794, found 447.2109; Anal. Calcd for $C_{25}H_{25}N_3O_5$: C, 67.10; H, 5.63; N, 9.39. Found: C, 67.23; H, 5.80; N, 9.11.

Isomer (5*S*,11b*R*) (**7b**): Foam; HPLC: t_R= 12.07 min (A/B= 50/50); IR (KBr) ν (cm^{-1}): 3380 (OH), 1748 (C=O); UV λ (nm) (EtOH): 282 (2340), 224 (2760); HRMS *m/z* calcd for $C_{25}H_{25}N_3O_5$ 447.1794, found 447,2131. Anal. Calcd for $C_{25}H_{25}N_3O_5$: C, 67.10; H, 5.63; N, 9.39. Found: C, 67.32; H, 6.04; N, 9.06.

Studies on the oxidation of compound (5) in basic media

General procedure: To a solution of compound (**5**) (25 mg, 0.06 mmol) in MeOH or THF (1 mL) the corresponding base (0.03-0.06 mmol) was added. After 10-30 min of reaction at rt, the solution was neutralized with 0.1N HCl and the solvents evaporated. The crude reaction mixture was analyzed by HPLC (Table 2).

2-Benzyl-5-*tert*-butoxycarbonyl-11b-metoxy-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]-pyrido[3,4-b]indole-1,3(2*H*)-diones (8a and 8b).– A solution of the epimeric mixture (**7ab**) (0.2 g, 0.46 mmol) in MeOH (7 mL) was acidified to pH=3 with 1N HCl. After 4 h

of stirring at rt, the solution was neutralized with Et_3N and the solvents evaporated. The residue was extracted with EtOAc, and the extract was washed with H_2O and dried over Na_2SO_4. After evaporation of the solvent, the resulting residue was purified on a silica gel column using a gradient from 0.2 to 2% of Et_2O in CH_2Cl_2.
Isomer (5*S*,11b*S*) (**8a**): (29% , from **7ab**, **a/b**= 2.5:1; and 25%, from **7ab**, **a/b**= 1:2.3); Foam; HPLC: t_R= 21.20 min (A/B= 50/50); UV λ (nm)(EtOH): 289 (2410), 228 (2730); Anal. Calcd for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.10. Found: C, 67.42; H, 5.67; N, 8.85.
Isomer (5*S*,11b*R*) (**8b**): (58%, from **7ab**, **a/b**= 2.5:1; and 61%, from **7ab**, **a/b**= 1:2.3); Foam; HPLC: t_R= 17.33 min (A/B= 50/50); UV λ (nm)(EtOH): 288 (2190), 228 (2720); HRMS *m/z* calcd for $C_{26}H_{27}N_3O_5$ 461.1951, found 461.1932; Anal. Calcd for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.10. Found: C, 67.71; H, 5.96; N, 9.15.

(5*S*,11b*S*)-2-Benzyl-5-carboxy-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido-[3,4-*b*]indole-1,3(2*H*)-dione (9).– A solution of compound (**5**) (0.4 g, 0.92 mmol) in CH_2Cl_2 (4 mL) was treated with TFA (2 mL) under stirring at rt for 2 h. After evaporation of the solvents the product (0.34 g, 98%) was obtained as a syrup. HPLC: t_R= 3.00 min (A/B= 50/50). Anal. Calcd for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.56; N, 11.19. Found: C, 66.87; H, 4.80; N, 10.74.

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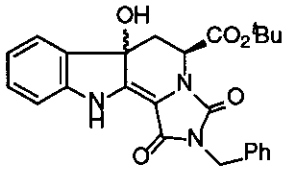
16. Anhydrous peroxide-free THF was obtained by passing commercial grade THF through a column of aluminum oxide (Fluka, 06290), followed by refuxing over $LiAlH_4$, destillation and storage over Na.
17. Other 1,3-dioxotetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole derivatives, synthesized by us, showed a similar behaviour in basic media to that of compound (**5**). Thus, derivative [**2**; R^2= CO_2Me, t_R= 16.93 min (A/B= 40/60)] was completely transformed into two new compounds of lower retention time (t_R= 10.07 and 12.40 min, A/B= 40/60) when treated with 2N NaOH (1 equiv.) in MeOH (rt, 10 min). Under these conditions, compound [**2**; R^2= $CONH_2$, t_R= 18.06 min (A/B= 30/70)] also afforded the corresponding 11b-hydroxy derivatives (t_R= 8.61 and 16.93 min, A/B= 30/70).
18. Compounds whose ^1H and ^{13}C NMR data are in concordance with those reported for the 11b-hydroxy derivatives (**7a**) and (**7b**) were obtained during basic treatments of related 5-unsubstituted imidazo[1',5':1,2]pyrido analogues (**2**; R^2= H, references 2 and 3). However, the absence of the signal due to the H-11b proton and the presence of a new quaternary carbon at ≈80 ppm in these derivatives were, in our opinion, erroneously interpreted as the enolic form of the 1,3-dioxoimidazole ring.
19. The ^1H and ^{13}C NMR data of compounds (**7a**) and (**7b**) could also fit to the 6a-hydroxy structure depicted below, but their UV spectra were similar to those of the starting compound (**5**) and different from those described for related 6a-hydroxy compounds. R. Güller, and H.J. Borschberg, *Helv. Chim. Acta*, 1993, **76**, 1847.



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21. BOP mediated couplings of carboxylic acid (**19**) with different phenylalanine derivatives afforded, in each case, a single diastereoisomeric compound (N. De la Figuera, unpublished results), indicating that no epimerization occurred at any of the asymmetric centers during the synthetic steps.

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