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TETRAHEDRON

New Entries Into the Indolizino[8,7-*b*]Indole Ring System

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Abstract: Tetrahydro-β-carbolines **2** and **3** possessing a proton on nitrogen N-2 react with one molecule of activated alkyne to give, depending on the solvent, either enamines or heterocyclic derivatives of indolizino[8,7-*b*]indole skeleton. The enamines obtained can be quantitatively transformed into the same skeleton. The application of acidic or basic catalysis determines the position of the double bond in the pyrrole ring as well as the nature of the substituents in positions 1,2,3 and 11b.

Keywords : Enamines; Cyclization; Indolizine; X-Ray crystal structures.

INTRODUCTION

The main synthetic routes to tetrahydro-β-carbolines make use of the Pictet-Spengler[1] and Bischler-Napieralski[2] reactions. The scope of these transformations was enlarged by introducing activated alkynes instead of the usual aldehyde or ketone partners[3]. The reaction proceeds *via* a tryptaminic enamine which can be isolated or intramolecularly trapped depending on the conditions to give high yields of tetrahydro-β-carbolines. For these carbolines, a secondary character of nitrogen N-2 as in **2** and **3** allows a new condensation with a second equivalent of alkyne. This leads to a new and efficient synthesis of the title compounds, which is outlined here. The reactivity of the enamines **5** is studied in both acidic and basic conditions.

RESULTS and DISCUSSION

Reactions of carbolines 2 and 3 with acetylenic esters (Scheme 1)

Reactions of carbolines **2** and **3** with dimethyl acetylenedicarboxylate (DMAD) or methyl propynoate (MP) led to the results summarized in Table 1.

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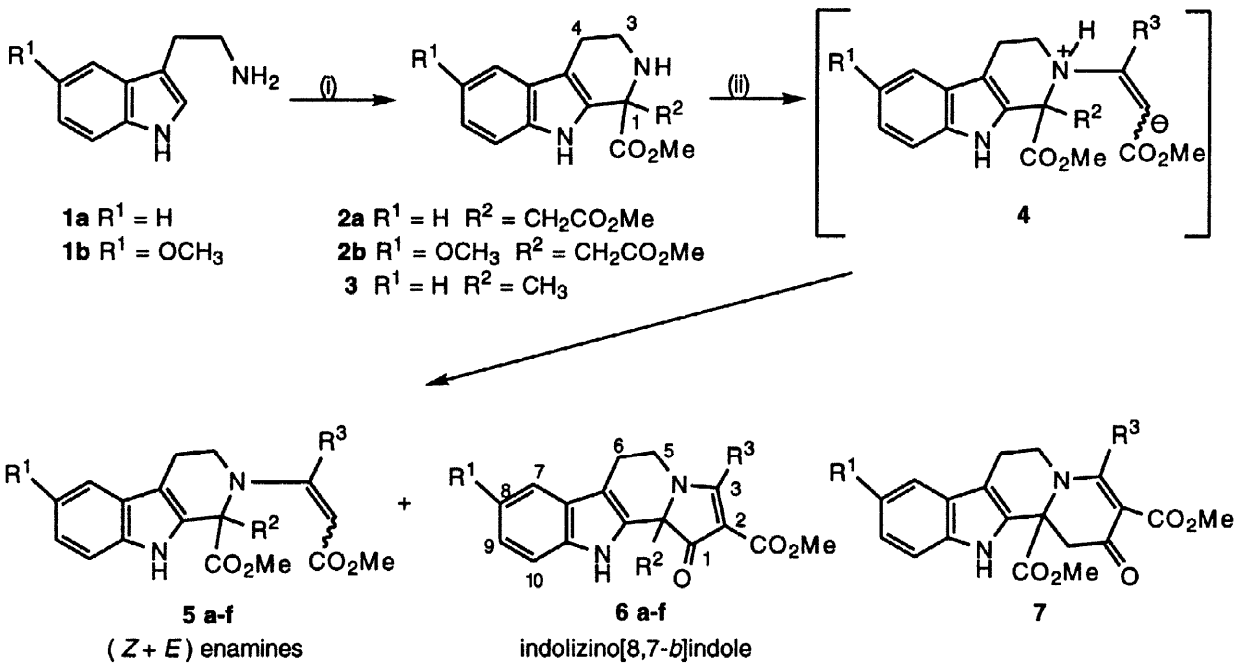
In methanol, at room temperature (Condition A) the reaction yielded the expected 1,4-adducts **5** and a minor product of structure **6**. The (*Z*) or (*E*) configuration of the enamines **5a, 5b** and **5e** was etablished on the basis of the ^{1}H NMR chemical shift of the β-enaminic proton. Resonance at low field (6.52, 5.82 ppm respectively for **5a** and **5e**) occurs in the (*Z*) form, which is caused by the deshielding effect induced by the ester group R^3.

The geometry of the enaminic double bond in **5c** and **5f** (R = H) is (*E*) as proved by the coupling constant value of the ethylenic protons (J = 14 Hz).

The minor product **6** issued from the cyclization of the enamine on the carboxylate group at position 1 of the carboline ring system. The alternative six-membered structure **7** corresponding to the cyclization of the enamine on the carbomethoxymethyl group R^2 was ruled out by mass spectrometry, which showed loss of 73 mass units (CH_2CO_2Me) in **6a** instead of 59 (CO_2Me) for structure **7a**.



(i) DMAD/MeOH then $CF_3CO_2H/CHCl_3$ (ref 3 for **2a**, **2b**), CH_3CO_2Me/EtOH/reflux (ref 4 for **3**)
(ii) see Table 1. R^3—≡—CO_2Me MP : R^3 = H; DMAD : R^3 = CO_2Me

	R^1	R^2	R^3		R^1	R^2	R^3
5a, 6a	H	CH_2CO_2Me	CO_2Me	**6d**	OCH_3	CH_2CO_2Me	H
5b, 6b	OCH_3	CH_2CO_2Me	CO_2Me	**5e, 6e**	H	CH_3	CO_2Me
5c, 6c	H	CH_2CO_2Me	H	**5f, 6f**	H	CH_3	H

Scheme 1

Regioselectivity of the cyclization cannot be explained by means of the Baldwin rules [5] for cyclization, since both 5-*exo*-trig and 6-*exo*-trig are allowed processes. Cyclization to a five-membered ring may simply be a consequence of the higher stability of a carbonyl group in a five rather than in a six-membered ring.

Table 1. Reaction of carbolines **2** and **3** with activated alkynes

entries	S.M	Products	conditions (a) time and yields (b)							
			A		B		C		D	
1	**2a** + DMAD	**(*Z*)- 5a**	(0.5h)	68.5	(1.5h)	-----	(6.5h)	----	(0.5h)	----
		(*E*)- 5a		20		90.1		----		----
		6a		7		7.5		92.8		96.1
2	**2b** + DMAD	**(*E*)-5b**	(12h)	60		----		----	(16h)	-----
		6b		3		----		----		57
3	**2a** + MP	**(*E*)-5c**	(64h)	78.7	(19h)	63.7	(66h)	36.2	(68h)	----
		6c		2.5		5		50		96.4
4	**2b** + MP	**6d**				----			(24h)	72
5	**3** + DMAD	**(*Z*)-5e**	(0.5h)	74.7	(1h)	57	(3h)	----	(1h)	----
		(*E*)-5e		3.8		22		----		----
		6e		13.4		13		98.2		90.5
6	**3** + MP	**(*E*)-5f**	(17h)	84	(24h)	89	(17h)	40	(12h)	----
		6f		10.4		8.6		42		97.8

(a) - conditions : 2 eq. of alkyne / 1 eq. of carboline. A : Methanol, RT ; B : Methanol, reflux ; C : Toluene, reflux ; D : Toluene, acetic acid (10 eq.), reflux.

(b) - yields of isolated and purified compounds.

Reactivity of the enamines 5 in neutral or acidic medium

The difference in the observed results when using conditions A-D may be rationalized by examination of the mechanism implied in the condensation and of the reactivity of the intermediate enamine **5** in neutral or acidic medium (Table 2).

Table 2. Heterocyclisation of enamines **5** in acidic medium (a)

SM	(*Z*)-5a	(*E*)-5a	(*E*)-5c	(*Z*)-5e	(*E*)-5e	(*E*)-5f
Time (min)	45	30	60	60	45	240
Products	**6a**	**6a**	**6c**	**6e**	**6e**	**6f**
Yield (%)	98	96	94	95.2	96	98

(a) : the enamine was refluxed in toluene in presence of 10 equivalents of acetic acid.

The first step of the reaction corresponds to the 1,4-addition of the amine function of the carboline to the activated alkyne leading to a zwitterionic species **4**. Two pathways are compatible with the observed cyclization of **4** into **6**. The zwitterionic species **4** may either react directly in its anionic form or give the enamines **5**, which leads subsequently to cyclized products **6**. In neutral methanol, abstraction of a proton by the anionic carbon atom produces rapidly the enamine, which is stable under these conditions, therefore, only a minor

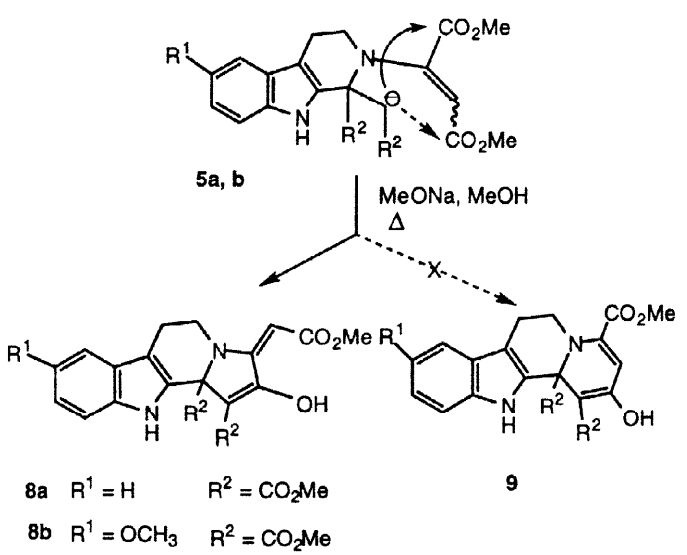
amount of **6** is produced. In toluene, cyclization takes place predominantly, because proton abstraction from the solvent is not possible, and prototropy is not the most efficient reaction mechanism. The cyclization reaction is catalyzed under acidic conditions. This effect can be explained by the activation of the reacting carbonyl group.

Reactivity of enamines 5 in basic medium

In order to prepare the indolizino[8,7-*b*]indole skeleton in another way, the enamines **5a** and **5b** were submitted to basic conditions (Table 3): the same preference for five membered ring formation was observed, and compounds **8a** and **8b** were isolated (Scheme 2). The ester enolate may react either at the olefinic carbon (1,4-addition) or at an ester carbonyl (Dieckmann condensation).

The first 5-*endo*-trig process was not observed, while the second one occured at the ester group following a 5-*exo*-trig process leading to the β-keto ester isolated as a single compound in its enolic form. Compound **9** originating from a 6-*exo*-trig cyclization process was not produced.

The enamines **5c** and **5e** do not bear carbomethoxy groups in the positions that reacted in the Dieckmann cyclization of **5a** and **5b**. The only observed reaction is the isomerisation of (*E*)-**5e** into (*Z*)-**5e** (see Table 3). No transformation was observed from the enamine **5f**, which does not possess any activated methylene group. There is no conclusive spectroscopic argument to discern the possible compounds **8** from **9**. All NMR and MS observations are compatible with both structures, including the detection of long range C-H chemical shift correlations (HMBC). The structure **8a** was thus established using X-ray crystallography.



Scheme 2. Dieckmann reaction on enamines **5a, 5b**.

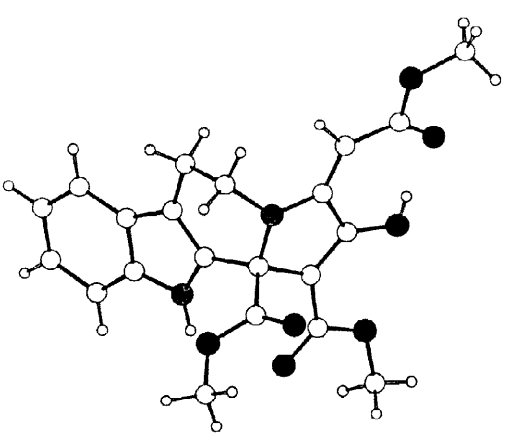


Figure 1. ORTEP drawing of **8a**

Table 3. Dieckmann reaction on enamines **5** (a)

Entries	S.M.	time (h)	Isolated products (yield %)	Method of purification (b)(solvent)
1	(*Z*)-**5a**	0.5	**8a** (74) + (*E*)-**5a** (24)	C.C. : **8a** CH_2Cl_2/acetone (99/1), (*E*)-**5a** (8/2)
2	(*Z*)-**5a**	22	**8a** (85)	C (MeOH)
3	(*E*)-**5a**	1	**8a** (90)	C (MeOH)
4	(*E*)-**5b**	3	**8b** (66.2)	C (EtOH)
5	(*E*)-**5c**	12	SM (90)	C.C. ($CHCl_3$/MeOH, 99/1)
6	(*Z*)-**5e**	17	SM (80)	C.C. ($CHCl_3$/MeOH, 99/1)
7	(*E*)-**5e**	2.5	(**Z**)-**5e** (66.5)	C.C.P.C. (CH_2Cl_2/MeOH, 99/1)
8	(*E*)-**5f**	20	SM (88)	C.C. ($CHCl_3$/MeOH, 99/1)

(a) : the enamine was refluxed in methanol in presence of 2 equivalents of sodium methoxide.

(b) : C. = crystallization; C.C. = column chromatography; C.C.P.C. = centrifugal circular preparative chromatography.

Crystallographic data for **8a** : $C_{21}H_{20}N_2O_7$, CH_3OH, M= 412.4, triclinic, P^{-1}, Z= 2, with a= 13.876(6), b= 8.860(4), c= 8.559(4) Å, a= 100.88(5), b= 95.99(4), c= 96.08(4)°, V= 1019(3) $Å^3$, d_X= 1.34 gcm^{-3}. The intensities of 3709 reflections were measured with a Philips PW1100 4-circle diffractometer using monochromatized CuKa radiation (speed 0.05°S^{-1}, width 2.2°, mode w/2q). No absorption correction was applied (m= 0.81 mm^{-1}). The 3289 independent and significant [I<3s(I)] reflections were used to solve (SHELXS 86)[6] and refine (SHELX 76)[7] the structure. Anisotropic thermal parameters were used for C, N, O atoms. Hydrogen atoms were calculated at theoretical positions and introduced in structure factor calculations with isotropic temperature factors. One disordered molecule of methanol was located near a center of symmetry. The final R index is 0.076 (R_W = 0.086). The list of atomic coordinates, bond lengths and angles have been deposited at the Cambridge Data Centre.

CONCLUSION

Many compounds having the indolizino[8,7-b]indole skeleton exhibit pharmacological properties[8] and are useful intermediates in industry as exemplified by the preparation of various indolic alkaloids[9]. Methods of access to the indolizino[8,7-b]indole were reviewed many years ago[10] reviewed while the synthesis of the indolizine core has been more recently[11]. The preparation of the former involved mostly a condensation between an α-keto acid or ester and a tryptophan [12] or tryptamine[13] derivative. Another method used a [1,3] dipolar cycloaddition reaction of a β-carboline azomethine ylide with acetylenic[9,14] or olefinic[9,15] derivatives. To the best of our knowledge, neither the presently described one-pot heterocyclization in acidic medium nor the two step procedure *via* a Dieckmann reaction have been reported.

Work is in progress to apply this methodology to the synthesis of other heterocyclic systems.

EXPERIMENTAL SECTION

General methods and materials.

All melting points (mp) were determined on a Kofler hot stage apparatus. IR spectra were taken in KBr pellets with a Philips Pye Unicam SP3-200 or an FT-IR BOMEM spectrometer. UV spectra were obtained on a Philips PU 8720 UV/VIS spectrophotometer. Low and high resolution mass spectra were recorded on a Jeol JMSD 300 mass spectrometer operating at 70 eV. NMR spectra were recorded on a Bruker AC300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C with TMS as internal standard (δ=0). Coupling constants *J* are given in Hz (s, d, t, dd and m indicate singlet, doublet, triplet, doublet of doublets and multiplet respectively). Elemental analyses were performed by the Microanalysis Service of the University of Reims. Analytical thin layer chromatography (T.L.C.) was carried out on commercial Merck 60 PF_{254} silica gel plates. The components were visualized with UV light (254 nm) and cerium sulfate spray. All column chromatography (C.C.) was conducted on Merck 60 silical gel (70-20 mesh) or (230-400 mesh) for flash chromatography. Centrifugal circular preparative chromatography (C.C.P.C.) was performed in a Chromatotron ^{R} (Harrison Research) with Merck 60 PF_{254} silica gel.

Compounds **2a**[3b], **2b**[3b], **3**[4] were preparated according to the reported methods.

Condensation of carbolines 2 and 3 with acetylenic esters.

General procedure : To a solution of the carboline (1 mmole) in 5 mL of the solvent (methanol or toluene depending on the chosen procedure), was added, under magnetic stirring, the acetylenic ester (2 mmoles) and acetic acid (10 mmoles) in procedure D. The resulting mixture was either stirred at room temperature (procedure A) or refluxed (procedures B, C, D). After completion of the reaction as indicated by T.L.C. (eluent : ether), the mixture was evaporated to dryness and constituents separated by C.C. or C.C.P.C. Yields are reported in Table 1.

Condensation of 2a with DMAD

Compounds **(*Z*)-5a**, **(*E*)-5a**, **6a** were separated by flash-chromatography.

Eluents: **(*Z*)-5a**: CH_2Cl_2/acetone (99.5/0.5); **(*E*)-5a**: CH_2Cl_2/acetone (98/2); **6a** : CH_2Cl_2/acetone (92/8).

Dimethyl(*Z*)-2-(1-carbomethoxy-1-carbomethoxymethyl-1,2,3,4-tetrahydro-β-carbolin-2-yl)-butenedioate 5a.

mp: 155°C (EtOH); IR (KBr) 3420, 1740 (sh), 1710, 1640 cm^{-1}; UV (MeOH) 225, 286, 322 nm; MS (EI), m/z (%) 444 (M^+, 25), 387 (58), 385 (M^+ - CO_2Me, 98), 371 (19), 353 (19),171 (100); ^{1}H NMR ($CDCl_3$) δ : 9.06 (s, 1H, NH), 7.47 (d, J = 7Hz, 1H, ArH), 7.3 (d, J = 7Hz, 1H, ArH), 7.12 (t, J = 7Hz, 1H, ArH), 7.05 (t, J = 7Hz, 1H, ArH), 6.52 (s, 1H, C<u>H</u>-CO_2CH_3), 3.71, 3.64, 3.62, 3.61 (s, 3H) (4 x OCH_3), 3.41 and 2.9 (d, J = 16 Hz, 2H, C<u>H</u>$_2$-CO_2Me), 3.4 to 3.3 (m, 2H, H-4), 2.97 to 2.67 (m , 2H, H-3); ^{13}C NMR ($CDCl_3$) δ : 172.9, 170.5, 166.2, 165 (4 x <u>C</u>O_2Me), 145.9 (N-<u>C</u>-CO_2Me), 135.8 (C-8a), 131.3 (C-9a), 126.2(C-4b), 122.3 (<u>C</u>H-CO_2Me), 122.1 (C-6), 119.2 (C-7), 118.4 (C-5), 111.2 (C-8), 110.7 (C-4a), 63.6 (C-1),52.5, 52, 51.7 (4 x

$CO_2\underline{C}H_3$), 50.6 ($\underline{C}H_2$-CO_2Me), 41.9 (C-3), 22.2 (C-4). Anal.calcd. for $C_{22}H_{24}N_2O_8$: C, 59.45; H, 5.44; N, 6.30. Found: C, 59.50; H, 5.66; N, 6.27.

Dimethyl(*E*)-2-(1-carbomethoxy-1-carbomethoxymethyl-1,2,3,4-tetrahydro-β-carbolin-2-yl)-butenedioate 5a.

mp: 178°C (EtOH); IR (KBr) 3350, 1740, 1690 cm^{-1}; UV (MeOH) 222, 286 nm; MS (EI), m/z (%) 444 (M^+, 8), 386 (25), 385 (M^+ - CO_2Me, 100); ^1H NMR ($CDCl_3$) δ : 8.87 (s, 1H, NH), 7.45 (d, J = 7 Hz, 1H, ArH), 7.26 (d, J = 7 Hz, 1H, ArH), 7.15 (d, J = 7Hz, 1H, ArH), 7.06 (d, J = 7Hz, 1H, ArH), 4.62 (s, 1H, C$\underline{H}$-CO_2Me), 3.9 (s, 3H), 3.6 (s, 6H), 3.56 (s, 3H) (4 x OCH_3), 3.46 (d, J = 15Hz, 1H) and 3.36 (d, J = 15Hz, 1H) ($C\underline{H}_2$-CO_2Me), 3.65 to 3.5 (m, 2H, H-3), 2.95 to 2.75 (m, 2H, H-4); ^{13}C NMR ($CDCl_3$) δ : 171.1, 170, 167.1, 165.7 (4 x $\underline{C}O_2Me$), 152 (N-$\underline{C}$-CO_2Me), 136.6 (C-8a), 128.8 (C-9a), 125.7 (C-4b), 123 (C-6), 119.9 (C-7), 118.6 (C-5), 11.6 (C-8), 111.1 (C-4a), 89.9 ($\underline{C}$H-CO_2Me), 64.4 (C-1), 53.9, 53.1, 52.2, 51.0 (4 x $CO_2\underline{C}H_3$), 47.2 ($\underline{C}H_2$-CO_2Me), 38.7 (C-3), 21.3 (C-4). Anal. calcd. for $C_{22}H_{24}N_2O_8$: C, 59.45; H, 5.44; N, 6.30. Found: C, 59.60; H, 5.55; N, 6.34.

2,3-dicarbomethoxy-11b-carbomethoxymethyl-1-oxo-1,5,6,11b-tetrahydroindolizino[8,7-*b*] indole 6a.

mp: 191°C (EtOH); IR (KBr) 3340, 1760 (sh), 1750, 1710 (sh), 1690 cm^{-1}; UV (MeOH) 223, 242 (sh), 285, 292 (sh), 313 nm; MS (EI), m/z (%) 413 (M^+ + 1, 25), 412 (M^+, 96), 381 (27), 380 (27), 339 (M^+ - CH_2CO_2Me, 40), 226 (17), 225 (77), 308 (19), 307 (25), 294 (21), 293 (100), 267 (19), 266 (52), 154 (25); ^{1}HNMR ($CDCl_3$) δ : 8.92 (s, 1H, NH), 7.45 (s, 1H, ArH), 7.37 (s, 1H, ArH), 7.21 (t, J = 7 Hz, 1H, ArH), 7.11(t, J = 7Hz, 1H, ArH), 4.06, 3.74, 3.64 (s, 3H, 3 x OCH_3), 3.53 (d, J = 15Hz, 1H) and 3.10 (d, J = 15Hz, 1H) ($C\underline{H}_2$-CO_2Me), 4.0 to 3.6 (m, 2H, H-6), 3.05 to 2.92 (m, 2H, H-5); ^{13}C NMR ($CDCl_3$) δ : 193.4 (C-1), 171, 169, 168 (3 x $\underline{C}O_2Me$), 162.3 (C-3), 161.3 (C-2), 136.9 (C-10a), 127.4 (C-11a), 125.7 (C-6b), 122.9 (C-8), 119.8 (C-9), 118.3 (C-7), 111.6 (C-10), 107.4 (C-6a), 69.2 (C-11b), 53.7, 52.1, 51.4 (3 x $CO_2\underline{C}H_3$), 43 ($\underline{C}H_2$-CO_2Me), 40.8 (C-5), 22.9 (C-6). Anal. calcd. for $C_{21}H_{20}N_2O_7$: C, 61.16; H, 4.89; N, 6.79. Found: C, 61.05; H, 4.64; N, 6.67. HRMS (EI): calcd. for $C_{21}H_{20}N_2O_7$: 412,1269. Found: 412,1261.

Condensation of 2b with DMAD

Compounds (*E*)-**5b** and **6b** were separated by C.C. ($CHCl_3$).

Dimethyl (*E*)-2-(1-carbomethoxy-1-carbomethoxymethyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-2-yl)-butenedioate 5b.

mp: 195°C (EtOH); IR (KBr) 3283, 1740, 1693 cm^{-1}; UV(MeOH) 221, 284 nm; MS (EI), m/z (%) 474 (M^+, 3), 416 (25), 415 (M^+ - CO_2Me, 100); ^1H NMR ($CDCl_3$) δ : 8.86 (s, 1H, NH), 7.23 (d, J = 8Hz, 1H, ArH), 6.95 (d, J = 4Hz, 1H, ArH), 6.83 (dd, J = 8Hz, J = 4Hz, 1H, ArH), 4.68 (s, 1H, C$\underline{H}CO_2Me$), 3.97 (s, 3H, ArOC$\underline{H}_3$), 3.84 , 3.67, 3.65 , 3.62 (s, 3H, 4 x CO_2CH_3), 3.74 to 3.4 (m, 2H, H-4), 3.52 (d, J = 15 Hz, 1H) and 3.45 (d, J = 15Hz, 1H)($C\underline{H}_2CO_2Me$), 2.98 to 2.79 (m, 2H, H-3); ^{13}C NMR ($CDCl_3$) δ : 171.1, 169.9, 167.1, 165. 7 (4 x $\underline{C}O_2Me$), 154.2 (C-6), 152 (N-$\underline{C}$-CO_2Me), 131.7 (C-9a), 129.3 (C-8a), 126.1 (C-4b), 113.1 (C-7), 112.4 (C-8), 110.7 (C-4a), 100.3 (C-5), 89.6 ($\underline{C}$H-CO_2Me), 64.3 (C-1), 55.8 (Ar-O$\underline{C}H_3$), 53.8, 53.1, 52.1, 51

(4 x $CO_2\underline{C}H_3$), 47.3 (C-3), 36.4 ($\underline{C}H_2$-CO_2Me), 23.1 (C-3). Anal. calcd. for $C_{23}H_{26}N_2O_9$: C, 58.22; H, 5.52; N, 5.90. Found: C, 58.09; H, 5.51; N, 5.82.

2,3-dicarbomethoxy-11b-carbomethoxymethyl-8-methoxy-1-oxo-1,5,6,11b-tetrahydro indolizino[8,7-*b*]indole 6b.

mp: 210°C (MeOH); IR (KBr) 3335, 1743, 1686, 1612 cm^{-1}; UV (MeOH) 221, 242, 280, 311 nm; MS (EI), m/z (%) 443 (M^+ + 1, 21), 442 (100), 369 (38), 356 (17), 355 (75), 338 (21), 337 (35), 324 (19), 323 (90), 297 (21), 296 (57); ^1H NMR ($CDCl_3$) δ : 8.8 (s, 1H, NH), 7.25 (d, J = 8Hz, 1H, H-10), 6.86 (d, J = 2Hz, 1H, H-7), 6.84 (dd, J = 8Hz, J = 2Hz, 1H, H-9), 3.82 (s, 3H, Ar$O\underline{C}H_3$), 4.06 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H) (3 x $CO_2\underline{C}H_3$), 4.0 (dd, J = 6Hz, J = 13Hz, H-5), 3.8 to 3.7 (m, 1H, H'-5), 3.5 (d, J = 15Hz, 1H) and 3.1 (d, J = 15Hz, 1H) ($\underline{C}H_2$-CO_2Me), 3.3 to 2.85 (m, 2H, H-6); ^{13}C NMR ($CDCl_3$) δ : 206.1 (C-1), 193.4 (C-3), 171.1, 168, 161.4 (3 x $\underline{C}O_2$Me), 162.4 (C-2), 154.4 (C-8), 132 (C-10a), 128.2 (C-11a), 126.4 (C-6b), 113.2 (C-7), 112.6 (C-9), 107.4 (C-6a), 100.5 (C-10), 69.2 (C-11b), 55.9 (Ar$O\underline{C}H_3$), 53.8, 52.2, 51.5 (3 x $CO_2\underline{C}H_3$), 43.1 (C-5), 41 ($\underline{C}H_2$-CO_2Me), 23.1 (C-6); Anal. calcd. for $C_{22}H_{22}N_2O_8$: C, 59.72; H, 5.01, N; 6.33. Found: C, 59.56; H, 4.98; N, 6.40.

Condensation of 2a with MP

Compounds (*E*)-**5c** and **6c** were separated by C.C.P.C. (eluent : $CHCl_3$).

Methyl (*E*)-3-(1-carbomethoxy-1-carbomethoxymethyl-1,2,3,4-tetrahydro-β-carbolin-2-yl)-propenoate 5c.

mp:168°C (EtOH); IR (KBr) 3400,1740,1670,1600 cm^{-1}; UV (MeOH) 221, 280 nm; MS (EI), m/z(%) 386 (M^+, 5), 355 (5), 328 (21), 327 (M^+ - CO_2Me, 100); ^1H NMR ($CDCl_3$) δ : 8.95 (s, 1H, NH), 7.78 (d, J = 14Hz, 1H, N-C$\underline{H}$), 7.54 (d, J = 7Hz, 1H, ArH), 7.39 (d, J = 7Hz, 1H, ArH), 7.24(t, J = 7Hz, 1H, ArH), 7.16 (t, J = 7Hz, 1H, ArH), 4.98 (d, J = 14Hz, 1H, C$\underline{H}$-CO_2Me), 3.73, 3.72, 3.65 (s, 3H, 3 x CO_2CH_3), 3.51 (d, J = 14Hz, 1H) and 3.34 (d, J = 14Hz, 1H) ($\underline{C}H_2CO_2$Me), 3.7 to 3.55 (m, 2H, H-4), 2.95 to 2.85 (m, 2H, H-3); ^{13}C NMR ($CDCl_3$) δ : 170.7, 170.2, 169.5 (3 x $\underline{C}O_2$Me), 148.6 (N-$\underline{C}$H-CO_2Me), 136.5 (C-8a), 128.8 (C-9a), 125.6 (C-4b), 122.9 (C-6), 119.6 (C-7), 116.5 (C-5), 111.4 (C-8), 111(C-4a), 89.3 ($\underline{C}$H-CO_2Me), 64.6 (C-1), 55.6, 52.2, 50.8 (3 x $CO_2\underline{C}H_3$), 44.6 ($\underline{C}H_2$-CO_2Me), 40.6 (C-3), 20.3 (C-4). Anal. calcd. for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.12; H, 5.80; N, 7.31.

2-carbomethoxy-11b-carbomethoxymethyl-1-oxo-5,6,11,11b-tetrahydroindolizino[8,7-*b*] indole 6c.

mp: 251°C (EtOH); IR (KBr) 3390, 1730, 1710, 1650 cm^{-1}; UV (MeOH) 222, 245, 285, 294 (sh), 310 nm; MS (EI), m/z (%) 355(M^+ + 1, 29), 354 (M^+, 100), 323 (31), 322 (50), 281 (M^+ - CH_2CO_2Me, 73), 267 (57), 249 (25), 235 (44), 208 (48); ^{1}HNMR ($CDCl_3$) δ : 8.22 (s, 1H, NH), 8.13(s, 1H, H-3), 7.44 (d, J = 7Hz, 1H, ArH), 7.39 (d, J = 7Hz, 1H, ArH), 7.2 (t, J = 7Hz, 1H, ArH), 7.1 (t, J = 7Hz, 1H, ArH), 4.51 to 4.05 and 3.85 to 3.65 (m, 2H, H-5), 3.48 (d, J = 15Hz, 1H) and 3.06 (d, J = 15Hz, 1H) ($\underline{C}H_2CO_2$Me), 3.07 to 2.82 (m, 2H, H-6); ^{13}C NMR ($CDCl_3$) δ : 193.9 (C-1), 169.6 (C-3), 168.2, 163.1 (2 x $\underline{C}O_2$Me), 136.7 (C-10a), 128.1 (C-11a), 126 (C-6b), 123.1(C-9), 120 (C-8), 118.4 (C-7), 111.7 (C-10), 107.2 (C-6a), 106.7 (C-2), 69.0(C-11b),

52.1 and 51.2 (2 x $CO_2\underline{C}H_3$), 44.9 ($CH_2CO_2\underline{C}H_3$), 40.9 (C-5), 23.6 (C-6). Anal. calcd. for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 63.93; H, 4.92; N,7.77. HRMS (EI): calcd. for $C_{19}H_{18}N_2O_5$: 354.1214; found: 354.1212.

Condensation of 2b with MP

Only method D was used.

2-carbomethoxy-11b-carbomethoxymethyl-8-methoxy-1-oxo-1,5,6,11b-tetrahydro indolizino[8,7-*b*] indole 6d.

mp: 210°C (MeOH); IR (KBr) 3306, 1746, 1717, 1641 cm^{-1}; UV (MeOH) 220, 243, 281, 306 nm; MS (EI) m/z (%) 385 (M^+ + 1, 21), 384 (M^+, 100), 353 (23), 352 (71), 312 (19), 311 (M^+ - CH_2CO_2Me, 98), 297 (73), 280 (19), 279 (44), 256 (15), 255 (59), 239 (15), 238 (79), 237 (23); ^1H NMR ($CDCl_3$) δ : 9.02 (s, 1H, NH), 8.75 (s, 1H, H-3), 7.35 (d, J = 7Hz, 1H, ArH), 6.85 (d, J = 7Hz, 2H, 2 x ArH), 3.8, 3.75, 3.6 (s, 3H, 3 x OCH_3), 4.12 to 4.05, 3.87 to 3.7 and 3.04 to 2.85 (m, 4H, H-5 and H-6), 3.48 (d, J = 15Hz, 1H) and 3.07 (d, J = 15Hz, 1H)($C\underline{H}_2CO_2Me$); ^{13}C NMR ($CDCl_3$) δ : 193.6 (C-1), 169.9 (C-3), 166.6, 163.2 (2 x $\underline{C}O_2Me$), 154.2 (C-8), 131.9 (C-10a), 128.7 (C-11a), 126.3 (C-6b), 112.7 and 112.6 (C-9 and C-10), 106.8 (C-6a), 106.6 (C-2), 100.4 (C-7), 69.2 (C-11b), 55.8 ($ArO\underline{C}H_3$), 51.9 and 51.1 (2 x $CO_2\underline{C}H_3$), 44.9 (C-5), 40.8 ($\underline{C}H_2CO_2Me$), 23.7 (C-6). Anal. calcd. for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found ; C, 62.07; H, 5.11; N, 7.12.

Condensation of 3 with DMAD

(*Z*)-5e was filtered off the reaction mixture. The filtrate was evaporated to dryness and the mixture of **(*E*)-5e, 6e** was separated by C.C.P.C. (eluent : CH_2Cl_2).

dimethyl(*Z*)-2-(1-carbomethoxy-1-methyl-1,2,3,4-tetrahydro-β-carbolin-2-yl)-butenedioate 5e.

mp: 195°C (EtOH), IR (KBr) 3350, 1720, 1700, 1590 cm^{-1}; UV (MeOH) 224, 285, 293, 330 nm; MS (EI), m/z (%) 386 (M^+, 1), 328 (19), 327 (M^+ - CH_2CO_2Me, 100), 269 (15), 235 (12), 209 (38), 184 (29), 183 (40), 171 (19), 168 (34), 167 (19), 156 (21), 155 (21), 154 (27), 140 (13), 128 (11), 115 (13), 101 (25); ^1H NMR ($CDCl_3$) δ : 9.17 (s, 1H, NH), 7.44 (d, J = 7Hz ,1H, ArH), 7.28 (d, J = 7Hz, 1H, ArH), 7.1 (t, J = 7Hz, 1H, ArH), 7.03 (t, J = 7Hz, 1H, ArH), 5.82 (s, 1H, $C\underline{H}$-CO_2Me), 3.74 (s, 3H), 3.64 (s, 3H) and 3.63 (s, 3H) (3 x CO_2CH_3), 4.35 to 4.0, 3.9 to 3.2, 2.75 to 2.67 (m, 4H, H-3 and H-4), 1.68 (s, 3H, C1-CH_3); ^{13}C NMR ($CDCl_3$) δ : 173.7, 167.3, 165.6 (3 x $\underline{C}O_2Me$), 147.7 (N- $\underline{C}$-CO_2Me), 136.2 (C-8a), 132.3 (C-9a), 126.3 (C-4b), 121.8 ($\underline{C}H$-CO_2Me), 118.9 (C-7), 116.1 (C-6), 110.8 (C-8), 109.4 (C-4a), 107.6 (C-5), 62.4(C-1), 52.6, 52.1, 50.8 (3 x $CO_2\underline{C}H_3$), 51.3 (C-4), 24 (CH_3), 21.2 (C-3). Anal. calcd. for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.13; H, 5.82; N, 7.12.

dimethyl(*E*)-2-(1-carbomethoxy-1-methyl-1,2,3,4-tetrahydro-β-carbolin-2-yl)-butenedioate 5e.

amorphous solid; IR (KBr) 3376, 1738, 1732, 1703 cm^{-1}, UV (MeOH) 222, 285, 292 (sh) nm; MS (EI), m/z (%) 386 (M^+, 1), 328 (21), 327 (M^+ - CO_2Me, 100); ^1H NMR ($CDCl_3$) δ : 8.17 (s, 1H, NH), 7.52 (d, J = 7Hz, 1H, ArH), 7.36 (d, J = 7Hz, 1H, ArH), 7.24 (t, J = 7Hz, 1H, ArH), 7.15 (t, J = 7Hz, 1H, ArH), 4.69 (s,

1H, C<u>H</u>-CO_2Me), 3.97 (s, 3H), 3.71 (s, 3H) and 3.67 (s, 3H) (3 x CO_2CH_3), 3.7 to 3.45 and 3.0 to 2.8 (m, 4H, H-3 and H-4); ^{13}C NMR ($CDCl_3$) δ : 172.5, 167.2, 166 (3 x <u>C</u>O_2Me), 152.3 (N-<u>C</u>-CO_2Me), 136.2 (C-8a), 131.5 (C-9a), 126 (C-4b), 122.7 (C-7), 119.7 (C-6), 116.5 (C-8), 111.2 (C-5), 109 (C-4a), 90.2 (<u>C</u>H-CO_2Me), 63.3 (C-1), 53.4, 53, 50.9 (3 x CO_2<u>C</u>H_3), 46.6 (C-3), 21.4 (C-4), 20.6 (CH_3). Anal. calcd. for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.74; N, 7.25. Found : C, 61.87, H, 5.45 , N, 7.07.

2,3-dicarbomethoxy-11b-methyl-1-oxo-1,5,6,11b-tetrahydroindolizino[8,7-*b*]indole 6e.

mp: 212°C (EtOH), IR (KBr) 3387, 1753, 1690 (sh) cm^{-1}, UV (MeOH) 222, 240, 285, 291, 314 nm; MS (EI), m/z (%) 355 (M^+ + 1, 21), 354 (M^+, 98), 339 (11), 323 (14), 296 (10), 268 (35), 267 (100), 235 (17), 209 (40), 208 (29), 207 (13), 183 (19); ^1H NMR ($CDCl_3$) δ : 9.0 (s,1H, NH), 7.43 (d, J = 7Hz, 1H, ArH), 7.39 (d, J = 7Hz, 1H, ArH), 7.2 (t, J = 7Hz, 1H, ArH), 7.1 (t, J = 7Hz, 1H, ArH), 4.08 (s, 3H, $ArOCH_3$), 3.77 (s, 3H, CO_2CH_3), 4.05 to 3.92, 3.8 to 3.65, 3.09 to 2.92 (m, 4H, H-5 and H-6), 1.78 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ : 194.8 (C-1), 169.4 (C-3), 162.7, 161.4 (2 x <u>C</u>O_2Me), 136.7 (C-10a), 129.7 (C-11a), 125.9 (C-6b), 122.6 (C-9), 119.9 (C-8), 118.3 (C-7), 111.7 (C-10), 106.5 (C-6a), 69.3 (C-11b), 53.8 and 51.5 (2 x CO_2<u>C</u>H_3), 47.7 (C-5), 23.2 (C-6), 22.8 (CH_3). Anal. calcd. for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found : C, 64.43; H, 4.86; N, 7.73.

Condensation of 3 with MP

Compounds (***E*)-5f** and **6f** were separated by C.C.P.C: (***E*)-5f** ($CHCl_3$), **6f** ($CHCl_3$/MeOH, 98/2).

methyl(*E*)-3-(1-carbomethoxy-1-methyl-1,2,3,4-tetrahydro-β-carbolin-2-yl)-propenoate 5f.

mp: 175°C (EtOH); IR (KBr) 3340, 1730, 1680, 1610 cm^{-1}; UV (MeOH) 222, 284 nm; MS (EI), m/z (%) 328 (M^+, 2), 297 (4), 270 (19), 269 (100); ^1H NMR ($CDCl_3$) δ : 8.56 (s, 1H, NH), 7.73 (d, J = 14Hz, 1H, N-C<u>H</u>), 7.5 (d, J = 7Hz, 1H, ArH), 7.35 (d, J = 7Hz, 1H, ArH), 7.2 (t, J = 7Hz, 1H, ArH), 7.12 (t, J = 7Hz, 1H, ArH), 5.0 (d, J = 14Hz, 1H, C<u>H</u>-CO_2Me), 3.71 (s, 3H, CO_2CH_3), 3.82 to 3.73, 3.55 to 3.39 and 2.95 to 2.82 (m, 4H, H-3 and H-4), 1.95 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ : 172.4, 170 (2 x <u>C</u>O_2Me), 148.7 (N-<u>C</u>H), 136.4 (C-8a), 131.1 (C-9a), 126 (C-5), 111.2(C-8), 109.8 (C-4a), 88 (<u>C</u>H-CO_2Me), 63.6 (C-1), 53.2, 50.7 (2 x CO_2<u>C</u>H_3), 43.8 (C-3), 24.5 (CH_3), 20.4 (C-4). Anal. calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found : C, 65.90; H, 6.10; N, 8.45.

2-carbomethoxy-11b-methyl-5,6,11,11b-tetrahydro-1-oxo indolizino[8,7-*b*]indole 6f.

mp: 245°C (EtOH); IR (KBr) 3345, 3256, 1726 (sh), 1670 (br.) cm^{-1}; UV (MeOH) 222, 244, 285, 292, 306 nm; MS (EI), m/z (%) 297 (M^+ + 1, 20), 296 (M^+, 100), 266 (20), 265 (16), 264 (37), 237 (11), 210 (34), 209 (98), 208 (19), 207 (24), 183 (28), 182 (10), 168 (11), 167 (15), 155 (16), 154 (19), 128 (10), 115 (15); ^1H NMR ($CDCl_3$) δ : 9.3 (s, 1H, NH), 8.68 (s, 1H, H-3), 7.43 (s, 1H, ArH), 7.4 (s, 1H, ArH), 7.17 (t, J = 7Hz, 1H, ArH), 7.08 (t, J = 7Hz, 1H, ArH), 3.76 (s, 3H, CO_2CH_3), 4.1 to 4.0, 3.8 to 3.65 and 3.05 to 2.82 (m, 4H, H-5 and H-6), 1.92 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ : 195.4 (C-1), 168.0 (C-3), 163.5 (<u>C</u>O_2Me), 136.6 (C-10a), 130.2 (C-11a), 125.8 (C-6b), 122.5 (C-9), 119.6 (C-8), 118.3 (C-7), 111.7 (C-10), 106.0 (C-6a), 103.9 (C-2), 69.1 (C-11b), 51.2 (CO_2<u>C</u>H_3), 44.5 (C-5), 23.7 (C-6), 22.8 (CH_3). Anal. calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found : C, 68.60; H, 5.04; N, 9.21.

Heterocyclization of the enamines 5 in acidic medium.

General procedure : Acetic acid (10 mmol.) was added to a solution of the enamine (1 mmol.) in toluene (10 mL). The mixture was refluxed and the reaction monitored by TLC eluent: [ether-MeOH, 99/1]. After disappearance of the starting material, the reaction was stopped by cooling, the mixture concentrated under vacuum and the residue extracted by $CHCl_3$ (50 ml). The organic layer was washed with $NaHCO_3$ and after evaporation of the solvent, compounds **8** were isolated by crystallization. Yields and reaction times are reported in Table 2.

Dieckmann reaction on the enamines 5a, 5b, 5c, 5e, 5f.

General procedure: MeONa (108 mg, 2 mmol.) was added to a solution of the studied enamine (1 mmol.) in methanol (20 mL). The resulting mixture was refluxed and reaction was monitored by T.L.C. (eluent : ether). After the reaction time indicated for each case in Table 3, the reaction mixture was acidified by 1N HCl and extracted by $CHCl_3$ (3 x 50 ml). The organic layer, after evaporation of the solvent, was purified (see Table 3).

(*E*)-3-carbomethoxymethylidene-1,11b,-dicarbomethoxy-2-hydroxy-3,5,6,11b-tetrahydro indolizino[8,7-*b*]indole 8a.

mp: 205°C (MeOH); IR (KBr) 3380 (broad), 1750, 1670, 1605 cm^{-1}; UV (MeOH), 222, 279, 337 nm; MS (EI), m/z (%) 412 (M^+, 6), 353 (50), 322 (21), 321 (100); ^1H NMR ($CDCl_3$) δ : 15.3 (s, 1H, OH), 9.45 (s, 1H, NH), 7.47 (d, J = 7Hz, 1H, ArH), 7.36 (d, J = 7Hz, 1H, ArH), 7.2 (t, J = 7Hz, 1H, ArH), 7.07 (t, J = 7Hz, 1H, ArH), 5.13 (s, 1H, C<u>H</u>-CO_2Me), 3.93 (s, 3H, $ArOCH_3$), 3.79, 3.78 (s, 3H, 2 x CO_2CH_3), 4.02 (dd, J = 5Hz, J = 15Hz, 1H) and 2.7 (dd, J = 5Hz, J = 15Hz, 1H) (H-5), 3.5 to 3.4 and 3.05 to 2.95 (m, 2H, H-6); ^{13}C NMR ($CDCl_3$) δ : 173.5, 168.6, 165.8 (3 x <u>C</u>O_2Me), 160 (C-2), 158.6 (C-3), 135.9 (C-11a), 130.8 (C-10a), 125.8 (C-6b), 122.6 (C-9), 119.5 (C-7), 118.5 (C-8), 111.5 (C-10), 109.2 (C-1), 108 (C-6a), 83.9 (<u>C</u>H-CO_2Me), 72.2 (C-11b), 53.5, 52.4, 52.2 (3 x CO_2<u>C</u>H_3), 40.7 (C-5), 15.2 (C-6). Anal. calcd. for $C_{21}H_{20}N_2O_7$, 1/2 CH_3OH : C, 60.27; H, 5.17; N, 6.54. Found : C, 60.26; H, 5.17; N, 6.47.

(*E*)-3-carbomethoxymethylidene-1,11b-dicarbomethoxy-2-hydroxy-8-methoxy-3,5,6,11b-tetrahydro indolizino[8,7-*b*]indole 8b.

mp: 211°C (EtOH), IR (KBr) 3380 (broad), 1746, 1666 cm^{-1}; UV (MeOH), 222 (sh), 278, 337 nm; MS (EI), m/z (%) 442 (M^+, 1), 373 (36), 352 (23), 351 (96), 147 (100); ^1H NMR ($CDCl_3$) δ : 15.2 (s, 1H, OH), 9.33 (s, 1H, NH), 7.27 (d, J = 8Hz, 1H, H-10), 6.91 (d, J = 2Hz, 1H, H-7), 6.87 (dd, J = 2Hz, J = 8.8Hz, H-9), 5.13 (s, 1H, C<u>H</u>-CO_2Me), 4.03 (dd, 1H, J = 5Hz, J = 14 Hz, H-5), 3.95, 3.76, 3.75 (s, 3H, 3 x CO_2CH_3), 3.84 (s, 3H, $ArOCH_3$), 3.52 to 3.46 (m, 1H, H'-5), 2.99 (ddd, 1H, J = 15Hz, J = 12Hz, J = 5Hz, H-6), 2.76 (dd, 1H, J = 15Hz, J = 4Hz, H'-6); ^{13}C NMR ($CDCl_3$) δ : 173.6, 168.5, 165.8 (3 x <u>C</u>O_2Me), 160 (C-2), 158.7 (C-3), 154.1 (C-8), 131.5 (C-11a), 131.2 (C-10a), 126.1 (C-6b), 112.9 (C-9), 112.3 (C-10), 109.3 (C-1), 107.7 (C-6a), 100.7 (C-7), 83.9 (<u>C</u>H-CO_2Me), 72.2 (C-11b), 56 (ArO<u>C</u>H_3), 53.5 , 52.4, 52.2 (3 x CO_2<u>C</u>H_3), 40.8 (C-5), 19.9 (C-6); Anal. calcd. for $C_{22}H_{22}N_2O_8$: C, 59.72; H, 5.01; N, 6.33 . Found : C, 59.58; H, 4.72; N, 6.36.

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