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NEW APPROACHES TO THE SYNTHESIS OF EBURNANE ALKALOIDS

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Abstract—Aldehyde **12** which is a key precursor of the Eburnane alkaloid vincamine **1** has been prepared in two ways. The first one involves a photochemical rearrangement of a spiro oxaziridine intermediate and the second is based on an imino Diels–Alder reaction followed by a stereo and regioselective alkylation.

The noteworthy pharmacological properties of several compounds of the Eburnane type alkaloids and especially of vincamine **1**[1] account for important work oriented towards their total synthesis.[2–6]

We have tested two new routes to vincamine and its analogues. The first one involves the photolysis of oxaziridines, following a scheme which can be applied to an asymmetric synthesis. The second one involves imino Diels–Alder reactions followed by a regio and stereoselective alkylation.

I. *Photolysis of oxaziridines*

The general Scheme 1 was retained for the synthesis of several precursors of vincamine **1**. This scheme can be extended to an enantioselective synthesis if the chirality required for C 20 of Eburnane compounds is introduced in the starting cyclopentanones **2a** or **2b**.

The target molecules are either the aldehyde **12**, intermediate in the synthesis of vincamine **1** by Oppolzer *et al.*[3b] (which can be obtained *via* the ester **8a** and the chloro derivative **8b**[3a]) or compound **8c**[4a,b] which can lead to **1** by a process improved according to an industrial patent.[4c]

The disubstituted cyclopentanone **2a** was prepared as described[7] and led by a classical sequence to the cyclopentanone **2b**. On the other hand, the decarboxylation of the acid obtained from **2a** followed by the Michael addition of methyl acrylate afforded **2c**.[8] The preparation of imines **3** from the 2,2'-disubstituted cyclopentanones **2** was complicated by the presence of the nucleophilic indole ring. Several methods using Lewis acid catalysts, such as $TiCl_4$[9] or dibutyl tin dichloride,[10] which are known to be efficient in the case of hindered ketones, were useless for the preparation of imines **3**. Best results were obtained by heating at 40° in toluene for three days tryptamine and ketones **2** in the presence of 4 Å molecular sieve. The resulting unstable imines **3** were directly oxidized rapidly at 0° with MCPBA. The imine **3a** led to two diastereoisomeric oxaziridines **4a**$_1$ and **4a**$_2$ (ratio 1/8) but compounds **3b** and **3c** apparently afforded only one diastereoisomeric oxaziridine **4b** and **4c** respectively.

†To simplify, the numbering according to Le Men and Taylor[23] has been introduced for compounds **4** and the followers.

The photochemical rearrangement of spiro-oxaziridines has been studied especially by Lattes *et al.*[11] who showed that N-substituted spiro-oxaziridines obtained from unsymmetrical cyclanones as **A**, irradiated in aprotic medium, rearrange with good yields to lactams **B** bearing the substituent in the α position to the CO group.

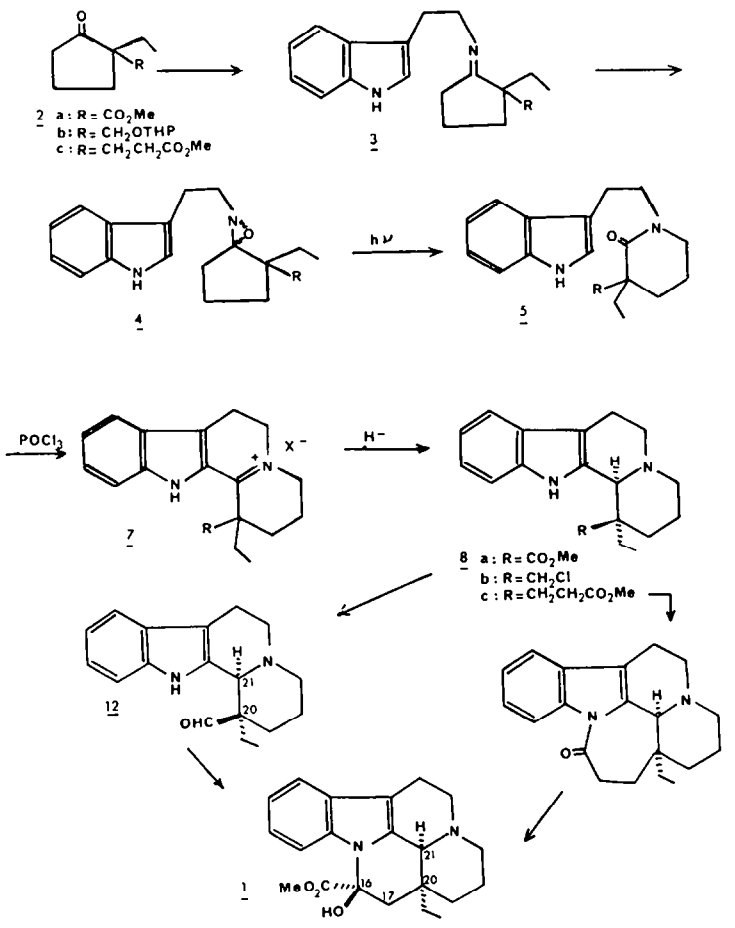
The regioselectivity can be explained by steric considerations: the C–C bond which is broken during the photochemical process is antiparallel to the N lone pair of electrons.[11b]

The oxaziridines **4** were irradiated with a medium pressure lamp (100 W) at room temperature without oxygen (the solutions were degassed by argon for 30 min before irradiations). A comparative study with several solvents (dioxane, benzene, acetonitrile) showed that the best results were obtained in anhydrous acetonitrile with high dilutions. As expected, the diastereoisomeric compounds **4a**$_1$ and **4a**$_2$ afforded by irradiation the same rearranged product **5a** (55% yield). The lactam **5b** was obtained in the same way from the compound **4b** but starting from the oxaziridine **4c**, the formation of a small quantity of the isomer **6** was observed in addition to the lactam **5c** (Scheme 2). Compared with the results of Lattes[11] the irradiation times were shorter and the lower yields could be explained by the absorption of the indolic chromophore or by the photosensitivity of the resulting lactams **5**.

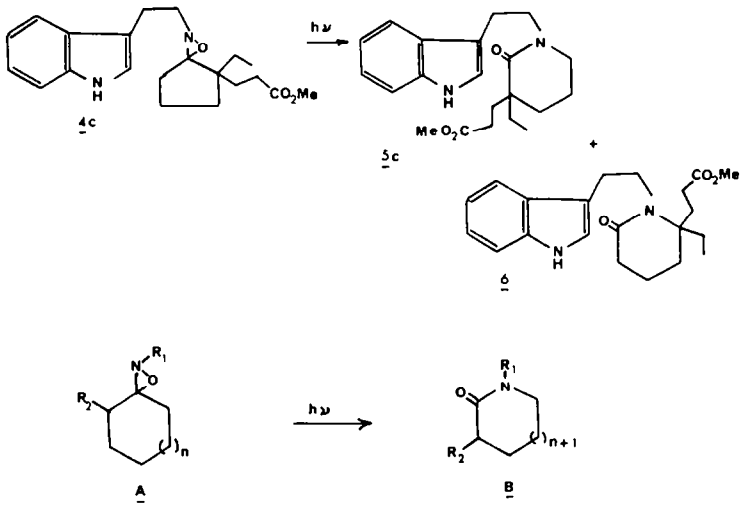
The Bischler–Napieralski cyclization of the lactam **5a** ($POCl_3$, CH_3CN) led to the immonium salt **7a** reduction of which by means of sodium borohydride at −70° afforded the two isomers **8a** (*cis*) and **9** (*trans*) in the ratio 1/1.5. According to the work of Wenkert[12] the ratio of the isomers *cis*/*trans* was raised to 7/1 by reduction of the immonium salt **7a** with H_2 (Pd/C). The relative configurations at centers 20 and 21† were assigned after reduction of these esters with $LiAlH_4$ into the alcohols **10** and **11**, previously obtained by Oppolzer[3] (Scheme 3).

The reduction of the ester **8a** (*cis*) by Dibal was not easy to control and led in toluene at −78°, not only to the aldehyde **12** but also to the alcohol **10**.

The Swern oxidation (oxalyl chloride—DMSO)[13] was used in order to transform this primary alcohol into aldehyde **12**, a precursor of vincamine **1**.[3b] The only isolated product (80%) exhibited a UV spectrum of an indolenine chromophore. Structure **14** was



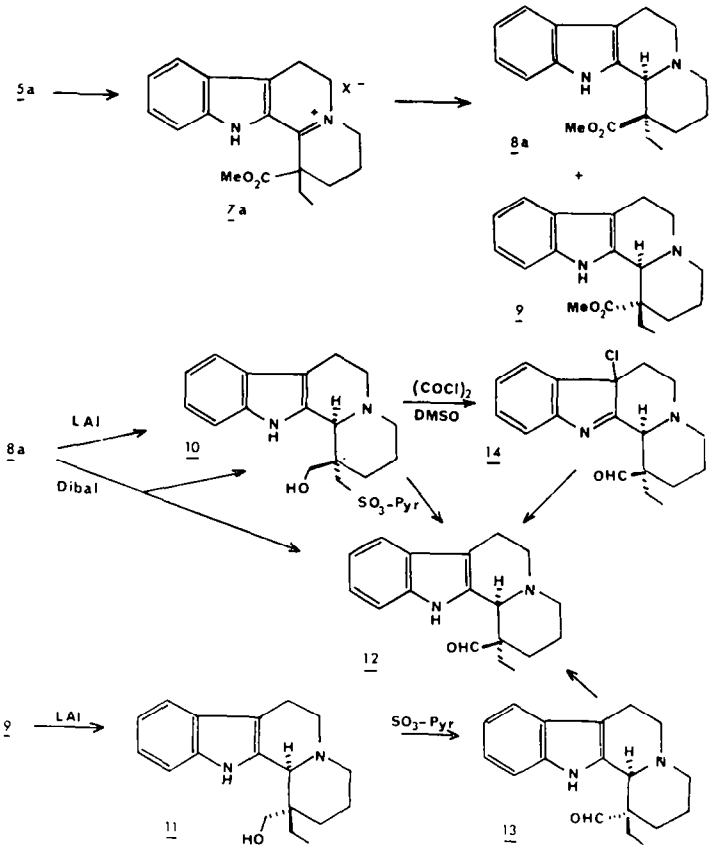
Scheme 1.



Scheme 2.

attributed to this compound which was identical with the product obtained by treatment of aldehyde **12** with N-chlorobenzotriazole. This was confirmed by the formation of the aldehyde **12** in the reaction of **14** with sodium iodide in acetic acid[14] (Scheme 3). It is noteworthy that Swern oxidation applied to the epimeric alcohol **11** led according to Danieli[15] directly to the epimeric aldehyde **13** (83%) without formation of the corresponding 7-chloro indolenine.

However the desired aldehyde **12** can be prepared more efficiently by oxidation of the primary alcohol **10** with the sulfur trioxide-pyridine complex, in the

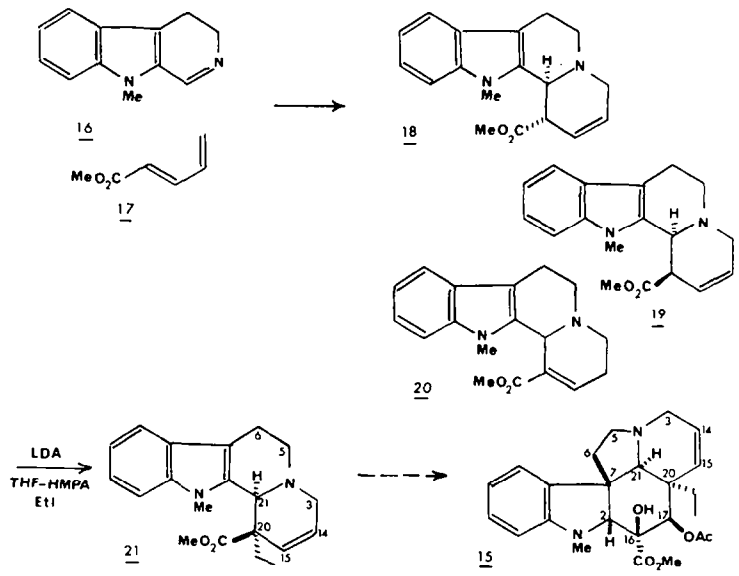


Scheme 3.

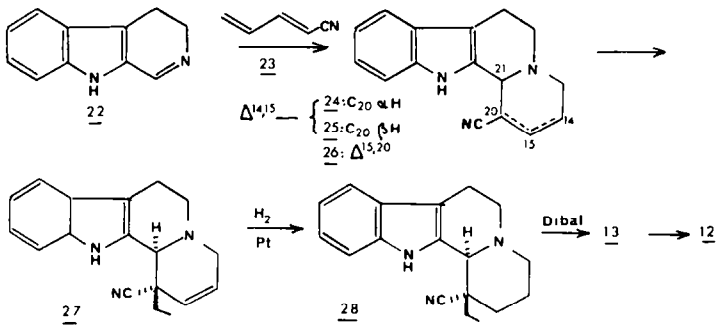
presence of triethylamine in DMSO (80% yield). Similarly the alcohol *trans* **11** can be oxidized to the aldehyde *trans* **13** (50%) which can be equilibrated into the aldehyde *cis* **12** (Scheme 3) according to the method of Oppolzer.[3b]

II. *Imino Diels–Alder reactions*

We have shown recently in the total synthesis of vindorosine **15**[17] that the hetero Diels–Alder reaction[18] between 9-methyl-4,9 dihydro-3H-pyrido [3, 4-b] indole **16** and methyl pentadienoate **17** led to a mixture of three isomers (**18**, **19** and **20**). The alkylation of this mixture (LDA, THF-HMPA, EtI) afforded a single diastereoisomer **21** in which the relative configurations of C_{20} and C_{21} are as in the Eburnane alkaloids (Scheme 4).



Scheme 4.



Scheme 5.

This result led us to undertake by this method a synthesis of alkaloids of this group and especially of vincamine **1**.

The first experiment of a Diels–Alder reaction with 4,9 dihydro-3H pyrido [3, 4-b] indole **22** and methyl pentadienoate **17** followed by alkylation employing the conditions used for the N-Me derivative **16** did not give the expected result. With 1-cyano-1,3 butadiene **23** as diene, the Diels–Alder reaction led to the three isomers **24**, **25** and **26** (in approximate ratios of 1/1/3). Alkylation of this mixture was stereoselective and afforded the diastereoisomer **27** (80% yield). The *trans* relative configurations of the hydrogen at C_{21} and the Et chain at C_{20} in **27** was established through its hydrogenation (PtO_2) into the previously described dihydro derivative **28**,[6] followed by a reduction with DIBAL, thus affording the *trans* aldehyde **13**, which can lead to the *cis*isomer **12** (Scheme 5).[3b] There is a striking difference in stereoselectivity during the alkylation step between the N_a-Me compounds (**18**, **19**, **20**) and the unsubstituted compounds **24**–**26**; this could be due in part, in the case of the latter compounds, to the lack of steric interaction which can be observed between the N_a-Me and the intermediate enolate ester in compounds **18**–**20**.

Starting from imine **29**, a Diels–Alder reaction with 1-cyano-1,3-butadiene **23**, afforded in good yield (86%) principally two diastereoisomers **30** and **31**. The alkylation of the mixture of these compounds led to the *cis* diastereoisomer **32** (55% yield). The latter was hydrogenated (Pd/C) and the N of the indole nucleus was deprotected quantitatively by means of sodium in ammonia, affording the *cis* compound **34**.[6] The cyano group of this derivative was partially reduced with DIBAL to the known *cis* aldehyde **12**, a precursor of vincamine **1** (Scheme 6).

Although some yields have to be increased, these preliminary studies show that the photochemical rearrangement of spiro-oxaziridines and the imino Diels–Alder reaction, followed by a regio and stereoselective alkylation, lead to indoloquinolizidines, which are direct precursors of Eburnane alkaloids.

EXPERIMENTAL

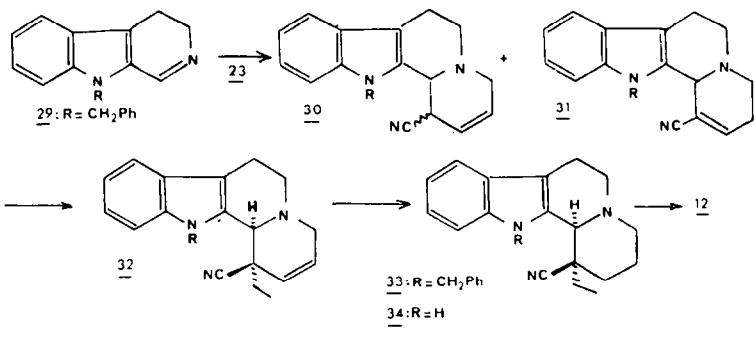
IR spectra (νcm^{-1}, $CHCl_3$) were recorded on a Perkin–Elmer 257; UV spectra (EtOH, λ_{max}, nm) on a Bausch and Lomb Spectronic 505 or a Jobin–Yvon Duospac 203 ^1H NMR spectra were obtained ($CDCl_3$, Me_4Si, $\delta = 0$ ppm) on a Varian T 601 EM 360, Brukër WP 80 spectrometer or on an IEF 400 prototype;[22] coupling constants, *J*, are given in hertz; s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet, respectively. Mass spectra were measured on an MS 50. Preparative TLC was performed with Kieselgel HF 254 (Merck).

Cyclopentanone **2a**—*1-ethyl-2-oxocyclopentane carboxylic acid methyl ester*

This was prepared following the method described in 73% yield. BP_4: 81°. IR: 1750, 1720. ^1H NMR (60 MHz): 3.70 (s, 3H, CO_2CH_3); 2.7–1.5 (m, 8H, $4CH_2$); 0.90 (t, 3H, CH_3).

Cyclopentanone **2b**—*2-ethyl-2-(2 tetrahydro 2H-pyranyl-oxymethyl) cyclopentanone*

(a) *Protection of the carbonyl group—spiro (1',3' dioxolane-2,2') cyclopentane-1-carboxylic acid methyl ester.* Ethylene glycol (0.5 ml, 9 mmol) and *p*-toluenesulfonic acid (3 mg) were added to a soln of **2a** (500 mg, 2.9 mmol) in benzene (50 ml). The mixture was heated at 120° for 19 hr with elimination of the water. After neutralization, extraction with $CHCl_3$ and usual work up, the corresponding ethylene ketal was obtained with 92% yield: IR: 1720. ^1H NMR (60 MHz): 3.8 (m, 4H, O–CH_2–CH_2–O); 3.60 (s, 3H, CO_2CH_3); 2.4–1.4 (m, 8H); 0.75 (t, 3H, CH_3).



Scheme 6.

(b) *Reduction of the methoxy carbonyl group—spiro-(1,3-dioxolane-2,1′) 2′-hydroxymethylcyclopentane.* A soln of 2-ethyl-2-methoxycarbonyl cyclopentanone ethylene ketal (575 mg, 2.7 mmol) in dry THF (5 ml) was added to a soln of $LiAlH_4$ (149 mg, 3.9 mmol) in THF (9 ml). The mixture was heated under reflux for 30 min, then the excess of $LiAlH_4$ was destroyed and the primary alcohol was extracted with $CHCl_3$ (95%): IR: 3550–3200. ^1H NMR: 3.8 (4H, OCH_2–CH_2–O); 3.5 (2H, CH_2OH); 2.9 (1H, OH); 2.0–1.2 (8H); 0.80 (t, 3H, CH_3).

(c) *Deprotection of the carbonyl group—2-ethyl-2-hydroxymethylcyclopentanone.* A saturated aqueous soln of tartaric acid (2 ml) was added to a soln of the ketal (230 mg, 1.2 mmol) in ether and the mixture was stirred at room temp for 12 hr. Then Na_2CO_3 aq was added and the corresponding ketone 2-ethyl 2-hydroxymethyl cyclopentanone) was extracted with $CHCl_3$ (158 mg, 90%): IR: 3550–3200, 1715. ^1H NMR (60 MHz): 3.5 (2H, CH_2OH); 2.4 (1H, OH); 2.3–1.2 (8H); 0.85 (t, 3H, CH_3).

(d) *Cyclopentanone* **2b**—*2-ethyl-2-(2-tetrahydro 2H-pyranyloxymethyl) cyclopentanone.* A soln of dihydropyran (0.6 ml, 6.6 mmol) in dry THF (1 ml) and a soln of *p*-toluenesulfonic acid (7 mg, 0.04 mmol) in THF (1 ml) were added to a soln of 2-ethyl 2-hydroxy-methyl cyclopentanone (590 mg, 4.2 mmol) in THF. The mixture was stirred at room temp for 2 hr, neutralized and extracted with $CHCl_3$. **2b** was obtained in 100% yield after usual work up. IR: 1725, MS: *m/z* 226 (M^+), 198, 142, 125, 112, 85 (100%), 84, 67, 55. ^1H NMR (60 MHz): 4.50 (1H, pseudo-anomeric); 0.85 (t, 3H, CH_3).

Cyclopentanone **2c**

2-ethylcyclopentanone (1.6 g, 14 mmol) was prepared as described.[7] $BP_{24} = 50°$. IR: 1720. NMR (60 MHz): 2.4–1.1 (8 H); 0.90 (t, 3H, J = 7, CH_3) was treated with methyl acrylate (1.26 ml, 14 mmol) in presence of t-BuOK following the described method,[8] affording **2c** which was distilled *in vacuo* (50% yield): BP_5 121°. IR: 1735, 1720. MS: 198 (M^+), 167, 148, 111, 110 (100%), 80, 74, 69, 55. ^1H NMR (60 MHz): 3.60 (s, 3H, CO_2CH_3); 2.5–1.2 (12H); 0.80 (t, 3H, CH_3).

Oxaziridines $\mathbf{4a_1}$ *and* $\mathbf{4a_2}$

Tryptamine (188 mg, 1.2 mmol) and molecular sieve 4 Å (500 mg) were added to a soln of **2a** (200 mg, 1.2 mmol) in toluene (10 ml) and the mixture was heated at 40° for 3 days under argon. Molecular sieve was renewed every day. The imine **3a** was not isolated (IR: 3350, 1725, 1660). After elimination of molecular sieve by filtration, *m*-chloroperbenzoic acid (150 mg, 0.87 mmole) was added at 0° under argon and the mixture was stirred at 0° for 45 min before neutralization with Na_2CO_3 aq and extraction with $CHCl_3$.

The residue obtained after usual work up was purified by preparative TLC (AcOEt:Hexane, 1:1), yielding **2a** (33 mg) and a mixture of $\mathbf{4a_1}$ and $\mathbf{4a_2}$ (135 mg) which gave $\mathbf{4a_1}$ (10 mg) and $\mathbf{4a_2}$ (79 mg) by preparative TLC (AcOEt:hexane, 3:7).

Compound $\mathbf{4a_1}$. IR: 3350, 1720, 1620, UV: 225, 267, 283 and 292. MS *m/z*: 328 (M^+), 262, 198, 170, 143, 110. ^1H NMR (400 MHz)[C23] 8.0 (s, 1H, NH); 7.58 (d, 1H); 7.35 (d, 1H); 7.18 (dd, 1H); 7.12 (dd, 1H); aromatic; 7.05 (s, 1H, C_2-H); 3.66 (s, 3H, CO_2CH_3); 1.47 (dq, 2H, J = 7, C_{19}-H); 0.90 (t, 3H, J = 7, C_{18}-H).

Compound $\mathbf{4a_2}$. IR: 3400, 1720, 1630. UV: 225, 284 and 293. MS *m/z*: 328 (M^+), 269, 198, 170, 169, 143, 142, 130. ^1H NMR (400 MHz): 8.0 (s, 1H, NH); 7.58 (d, 1H); 7.36 (d, 1H); 7.18 (dd, 1H); 7.11 (dd, 1H): aromatic; 7.05 (s, 1H, C_2-H); 3.70 (s, 3H, CO_2CH_3); 1.42 (dq, 2H, J = 6.7, C_{19}-H); 0.87 (t, 3H, J = 6.7, C_{18}-H).

Oxaziridine **4b**

The imine **3b** was prepared from tryptamine and **2b** (940 mg, 4.1 mmol) as described but the condensation was performed at 80°. After oxidation and usual treatment, the separation of the products by preparative TLC (AcOEt:hexane, 3:7) gave **2b** (320 mg) and **4b** (200 mg (24% corr. yield)): UV: 225, 276, 283 and 292. MS *m/z*: 384 (M^+), 300, 227, 170, 158, 144, 143 (100%), 130, 85. ^1H NMR (400 MHz): 8.0 (s, 1H, NH); 7.61 (d, 1H); 7.35 (d, 1H); 7.18 (dd, 1H); 7.11 (dd, 1H) aromatic; 7.06 (s, 1H, C_2-H); 4.57 (m, 1H, pseudoanomeric); 0.86 (t, 3H, J = 7, C_{18}-H).

Oxaziridine **4c**

Starting from **2c** (342 mg, 1.7 mmol) and tryptamine, the corresponding imine **3c** and **4c** were prepared as described previously. Preparative TLC (AcOEt:hexane, 4:6) of the residue obtained in the usual way afforded **2c** (157 mg) and **4c** (67 mg, corr. yield 20%): IR: 3375, 1725. UV: 221, 272, 282, 291. MS *m/z*: 356 (M^+), 247, 226, 197, 165, 143, 139 (100%), 130, 111. ^1H NMR (400 MHz): 8.05 (s, 1H, NH); 7.59 (d, 1H); 7.37 (d, 1H); 7.22 (dd, 1H); 7.13 (dd, 1H): aromatic; 7.01 (s, 1H, C_2-H); 3.66 (s, 3H, CO_2CH_3); 0.93 (t, 3H, J = 6.6, C_{18}-H).

Irradiation of oxaziridines **4**

General method. A soln of the oxaziridine in dry acetonitrile was previously degassed during 30 min under argon in a quartz tube and was irradiated with a medium pressure lamp (100 W). The medium was monitored by TLC and the solvent was distilled off *in vacuo* before purification.

Lactam **5a**

After irradiation of $\mathbf{4a_1}$ and $\mathbf{4a_2}$ (900 mg, 2.7 mmol) during 1 hr, the products were separated by flash column chromatography on SiO_2 (AcOEt–hexane) affording $\mathbf{4a_1}$ and $\mathbf{4a_2}$ (154 mg) and **5a** (corr. yield 55%): IR: 3375, 1725, 1620. UV: 225, 276, 284, 292. Ms *m/z*: 328 (M^+), 269, 243, 196, 186, 170, 144, 143, 130. ^1H NMR (400 MHz): 8.09 (s, 1H, N_a-H); 7.67 (d, 1H); 7.36 (d, 1H); 7.18 (dd, 1H); 7.11 (dd, 1H); aromatic; 7.05 (s, 1H, C_2-H); 3.73 (s, 3H, CO_2CH_3); 3.67 (m, 2H); 3.05 (m, 2H): C_5-H and C_6-H; 3.21 (m, 2H, C_3-H); 2.0 (m, 2H, J = 7, C_{19} – H); 0.92 (t, 3H, J = 7, C_{18} – H). (Found: C, 69.7 H, 7.32; N, 8.34; O, 14.70. Calc. for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53; O, 14.62%.)

Lactam **5b**

The irradiation of **4b** (223 mg, 0.58 mmol) during 1 hr. 45 and purification by preparative TLC (AcOEt:hexane, 1:1) afforded the starting **4b** (20 mg) and **5b** (80 mg, corr. yield 39%): IR: 3250, 1610. UV: 224, 274, 284, 291. MS *m/z*: 384 (M^+), 299, 242, 227, 158, 143 (100%), 130, 85. ^1H NMR (400 MHz): 8.1 (s, 1H, N_a-H); 7.67 (d, 1H, 7.35 (d, 1H), 7.17 (dd, 1H); 7.11 (dd, 1H): aromatic; 7.05 (s, 1H, C_2-H); 4.6 (dt, 1H, pseudoanomeric); 4.05 (d, 1H, J = 9) and 3.21 (d, 1H, J = 9): C_{20}-H; 0.87 (t, 3H, J = 7, C_{18}-H).

Lactams **5c** *and* **6**

The oxaziridine **4c** (69 mg, 0.35 mmol) was irradiated during 1 hr. Preparative TLC of the residue (AcOEt:hexane, 1:1) afforded starting material (25 mg), **5c** (16 mg, corr. yield 36%) and the isomer **6** (3 mg, corr. yield 7%):

Lactam **5c**. IR: 3250, 1730, 1610. UV: 223, 275, 282 and 291. SM *m/z*: 356 (M^+), 325, 267, 226, 214, 198, 182, 144, 143 (100%), 130. ^1H NMR (400 MHz): 8.06 (s, 1H, N_a-H); 7.67 (d, 1H); 7.36 (d, 1H); 7.18 (dd, 1H); 7.12 (dd, 1H): aromatic; 7.05 (s, 1H, C_2-H); 3.65 (s, 1H, CO_2CH_3): 3.63 (m, 2H) and 3.0 (2H, C_5-H and C_6-H); 3.18 (2H, C_3-H); 1.52 (m, 2H, C_{19}-H); 0.83 (t, 3H, J = 7, C_{18}-H). (Found: C, 70.51; H, 8.05; N, 7.76; O, 13.64. Calc. for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86; O, 13.47).

Lactam **6**. IR: 3250, 1730, 1610. UV: 223, 275, 282, 290. Ms *m/z*: 356 (M^+), 325, 226, 214, 197, 196, 182, 165, 144, 143 (100%), 130. ^1H NMR (400 MHz): 8.03 (s, 1H, N_a-H); 7.84 (d, 1H); 7.37 (d, 1H); 7.21 (dd, 1H); 7.16 (dd, 1H); aromatic; 7.09 (s, 1H, C_2-H); 3.67 (s, 3H, CO_2CH_3); 3.48 (2H) and 3.08 (m, 2H), C_5-H and C_6-H; 2.44 (2H, C_{14}-H); 0.91 (t, 3H, J = 7.5, C_{18}-H).

Esters **8a** (cis) *and* **9** (trans)

$POCl_3$ (7.5 ml, 81 mmol) was added to a stirred soln of **5a** (1.73 g, 5.2 mmol) in dry MeCN (85 ml) and the mixture was heated under reflux for 18 hr. After evaporation of the solvent and the reagent, the residue was dissolved in MeOH (30 ml) and reduced by excess of $NaBH_4$ at $-70°$. The medium was poured into brine and extracted with CH_2Cl_2. A standard work up and flash chromatography (SiO_2, hexane, AcOEt) afforded **8a** (541 mg, 33%) and **9** (807 mg, 49%).

Ester **8a**. IR: 3400, 1720. UV: 228, 277, 286, 293. MS *m/z*: 312 (M^+), 297, 253, 197, 170, 169. ^1H NMR (400 MHz): 7.85 (s, 1H, N_a-H); 7.49 (d, 1H); 7.34 (d, 1H); 7.17 (dd, 1H); 7.12 (dd, 1H): aromatic; 3.72 (s, 3H, CO_2CH_3); 0.90 (t, 3H, J = 7, C_{18}-H).

Ester **9**. IR: 3400, 1710. UV: 227, 276, 284, 293. MS *m/z*: 312 (M^+), 296, 280, 252, 196, 170. ^1H NMR (400 MHz): 8.46 (s, 1H, N_a-H); 7.47 (d, 1H); 7.28 (d, 1H); 7.13 (dd, 1H); 7.07 (dd, 1H): aromatic; 3.86 (s, 3H, CO_2CH_3); 0.70 (t, 3H, J = 7, C_{18}-H). m.p. 148–150° (AcOEt–Et_2O).

Alcohol **10**

A soln of **8a** (200 mg, 0.64 mmol) in dry THF (2 ml) was added slowly under argon to a soln of $LiAlH_4$ (73 mg, 1.92 mmol) in THF (4 ml) and the medium was heated under reflux for 15 min. After usual work up, **10** previously described[3b] was isolated in quantitative yield.

Alcohol **11**

The ester **9** was reduced with $LiAlH_4$ as described and **11**[3b] was isolated with 100% yield, m.p. 236° (MeOH) lit.[15]: 222° (MeOH).

Chloroindolenine **14**

(a) DMSO (0.1 ml, 1.6 mmol) was added under argon at $-60°$ to a soln of oxalyl chloride (0.07 ml, 0.8 mmol) in dry CH_2Cl_2 (1 ml). After 5 min, a soln of **10** (9 mg, 0.032 mmol) in CH_2Cl_2 was added and the mixture was stirred for 45 min at -60 to $-40°$. An excess of Et_3N was added before extraction with CH_2Cl_2. A standard workup afforded **14** (80%): IR: 1710. UV: 227, 252, 264, 280, 289. EtOH + H^+: 248, 283. Ms *m/z*: 281, 252, 251, 238, 223, 197, 196, 187, 170. ^1H NMR (400 MHz): 10.26 (s, 1H, CHO); 7.57 (d, 1H); 7.46 (d, 1H); 7.39 (dd, 1H); 7.28 (dd, 1H): aromatic; 3.71 (s, 1H, C_{21}-H); 0.88 (t, 3H, J = 7.5, C_{18}-H).

(b) N-Chlorobenzotriazol (21.6 mg, 0.14 mmole) was added under argon at 0° to a soln of **12** (33.8 mg, 0.12 mmol) in CH_2Cl_2 (0.35 ml). After 15 min, the solvent was evaporated under vacuum at 0° and **14** (29 mg, 79%) was isolated by preparative TLC (AcOEt:Pentane, 2:8). IR, UV, MS, ^1H NMR (400 MHz) spectra were identical to those of the compound described above.

Aldehyde **12**

(a) *From the chloroindolenine* **14**. NaI (7 mg, 0.047 mmol) was added to a soln of **14** (5 mg, 0.016 mmol) in AcOH (0.5 ml) under argon. After stirring 2 hr at room temp, the medium was neutralized ($NaHCO_3$–H_2O) and extracted with CH_2Cl_2. Purification of the residue by TLC (AcOEt:hexane, 3:7) gave the known **12**.[3]

(b) *From the alcohol* **10**. A soln of the complex SO_3-pyridine (83 mg, 0.52 mmol) in dry DMSO (0.5 ml) was added under argon at room temp to a soln of **10** (50 mg, 0.18 mmol) in DMSO (1 ml) and Et_3N (1 ml, 7 mmol). The mixture was stirred at room temp for 1 hr before extraction with CH_2Cl_2. After usual work up and preparative TLC (AcOEt:hexane, 4:6), aldehydes **12** (40 mg, 80%) and **13** (2 mg, 4%) were obtained.

Aldehyde **13** *from the alcohol* **11**

A soln of **11** (110 mg, 0.39 mmol) in dry DMSO (3 ml) and Et_3N (3 ml) was added to a soln of the complex SO_3-pyridine (183 mg, 1.15 mmol) in dry DMSO (1 ml). The mixture was heated under stirring at 60° for 12 hr. After extraction with CH_2Cl_2 and usual workup, aldehydes **13** (54 mg, 50%) and **12** (10 mg, 9%) were isolated by preparative TLC.

trans-*Nitrile* **27**

(a) Diels–Alder between **22**[20] and **23** (compounds **24**, **25** and **26**): 1-Cyano-1,3-butadiene (1.12 g, 0.014 mol) and hydroquinone (50 mg) were added under argon to a stirred suspension of **22** (2.0 g, 0.018 mol) in chlorobenzene (10 ml). The mixture was heated at 120° for 2 hr. After filtration, washing with CH_2Cl_2 and evaporation, the residue (3.0 g) was purified by chromatography (SiO_2, AcOEt). The isomers **24** (0.434 g), **25** (0.324 g) and **26** (1.184 g) were obtained in ratios of 1.3/1/3.6.

Compound **24**. IR: 3350 N-H, 2240, 1650. UV: 285, 292; EtOH + H^+: 275, 283, 292. MS *m/z*: 249 (M^+), 170, 169. ^1H NMR (400 MHz): 8.47 (s, 1H, N–H); 7.50 (d, 1H, J = 8.4) and 7.37 (d, 1H, J = 8.4), C_9-H and C_{12}-H; 7.19 (dd, 1H, J = J′ = 8.4) and 7.11 (dd, 1H, J = J′ = 8.4): C_{10}-H and C_{11}-H; 6.02 (m, 1H) and 5.71 (dq, 1H, $J_{14,15}$ = 10, C_{14}-H and C_{15}-H); 3.83 (br d, 1H, C_{21}-H).

Compound **25**. IR: 3370, 2240. UV: 282, 292. MS *m/z*: 249 (M^+), 170, 169. ^1H NMR (400 MHz): 7.98 (s, 1H, N-H); 7.49 (d, 1H, J = 8.4) and 7.25 (d, 1H, J = 8.4): C_9-H and C_{12}-H; 7.16–7.06 (m, 2H, C_{10}-H and C_{11}-H); 6.0 (m, 1H) and 5.66 (m, 1H; C_{14}-H and C_{15}-H); 3.61 (br.s, 1H, C_{21}-H).

Compound **26**. IR: 3350, 2200. UV: 285, 292. MS *m/z*: 249 (M^+), 248. ^1H NMR (400 MHz): 8.48 (s, 1H, N-H); 7.50 (d, 1H, J = 8) and 7.35 (d, 1H, J = 8) C_9-H and C_{12}-H; 7.16 (dd, 1H, J = 8) and 7.09 (dd, 1H, J = 8): C_{10}-H and C_{11}-H; 6.82 (m, 1H, C_{15}-H); 4.69 (d, 1H, $J_{15,21}$ = 1.5, C_{21}-H).

(b) *Alkylation of the mixture of compounds* **24**, **25** *and* **26**. BuLi (1.6 M in hexane, 6.85 ml, 11 mmol) was added under argon at $-50°$ to a stirred soln of diisopropylamine (1.75 ml, 12.4 mmol) in dry THF (10 ml). After 5 min at $-50°$ and 10 min at $-30°$, the medium was coolded at $-78°$ before the addition of HMPA (1.85 ml, 11 mmol) and the mixture was stirred at this temp for 1 hr. A soln of the isomers **24**, **25**, **26** (0.762 g, 3 mmol) in THF (65 ml) was added slowly and the soln was stirred 5 min at $-70°$ and 10 min at 0° before the addition of EtI (1.04 ml, 13 mmol). After 5 min of reaction, addition of brine and extraction with ether, **27** (0.67 g, 80%) was separated by filtration on SiO_2 (AcOEt:hexane, 1:1): IR: 3400, 2850–2750, 2220. UV: 225, 280, 290. MS *m/z*: 277 (M^-), 170, 169. ^1H NMR (80 MHz): 8.4 (br.s, 1H, N_a-H); 7.48–6.97 (4H, aromatic); 5.82 (2H, C_{14}-H and C_{15}-H): 4.05 (s, 1H, C_{21}-H); 1.00 (t, 3H, $J_{18,19}$ = 7, C_{18}-H).

Compound **28**. Compound **27** (21 mg, 0.18 mmol) in EtOH (10 ml) was hydrogenated at atmosheric pressure with PtO_2 as catalyst affording quantitatively the known *trans* cyano derivative **28**.[6]

Aldehyde **13** from cyano compound **28**

A soln of Dibal (20% in toluene, 0.152 ml, 0.19 mmol) was added to a stirred soln of **28** (55 mg, 0.19 mmol) in dry toluene (2 ml) under argon at $-70°$. The medium was hydrolyzed at $-70°$ with aqueous MeOH (20%, 3 ml) and HCl aq (20%, 3 ml), alkalinized with Na_2CO_3 aq and extracted with ether. The aldehyde **13**[3] (30 mg) was isolated after usual workup.

9-*Benzyl*-4,9-*dihydro*-3*H*-*pyrido* [3,4-*b*]*indole* **29**

A soln of **22**[20] (1.82 g, 11.66 mmol) in DMF (30 ml) was added slowly under argon to a suspension of NaH (0.76 g, 55% in oil, 17.4 mmol) in DMF (15 ml) at $-16°$. The mixture was stirred for 30 min at $-10°$ and cooled at $-70°$ before the addition of a soln of benzyl bromide (3.64 g, 21.3 mmol) in DMF (2 ml). After 45 min the medium was acidified (HCl 0.1 N) and extracted with ether. The aqueous layer was made alkaline (Na_2CO_3/H_2O) and extracted with CH_2Cl_2. The residue (2.3 g) isolated after usual workup was filtered through SiO_2 (hexane:AcOEt:MeOH:NH_4OH, 6.5:3:3:0.04) giving **29** (1.44 g, 50%)[21b,24]: m.p. 138–139°;

lit. 138°[21b]. ^{1}H NMR (60 MHz): 8.36 (br.s, 1H, C_1-H); 7.6–7.0 (9H, aromatic); 5.3 (2H, CH_2-Ph).

Preparation of compound **32**

(a) Diels–Alder reaction with **29** and **23**: compounds **30** and **31**:

Compound **23** (0.567 g, 7.1 mmol) stabilized with hydroquinone, was added to a stirred soln of **29** (1.655 g, 6.36 mmol) in chlorobenzene (15 ml). The medium was heated at 120° for 22 hr. After evaporation of the solvent, the residue (2.3 g) was purified by chromatography (SiO_2, AcOEt:hexane, 6:4). The diastereoisomers **30** (1.626 g) and **31** (0.232 g) were isolated in 86% total yield.

Compound **30**. IR: 2230. UV: 286. EtOH + H^+: 270. MS *m/z*: 339 (M^+), 260, 91. ^{1}H NMR (60 MHz): 7.5–6.7 (m, 9H, aromatic); 5.8 (m, 1H) and 5.4 (m, 1H, C_{14}-H and C_{15}-H): 5.06 (s, 2H, CH_2–Ph).

Compound **31**. IR: 2200. UV: 286. EtOH + H^+: 270. MS *m/z*: 339 (M^+), 91. ^{1}H NMR (60 MHz): 7.0–6.6 (9H, aromatic); 6.7 (m, 1H, C_{15}-H); 5.5 (s, 2H, CH_2Ph); 4.6 (m, 1H, C_{21}-H).

(b) *Alkylation of the compounds* **30** and **31**. The alkylation was performed as described for the preparation of **27**. After extraction with ether, the major compound **32** (1.03 g, 55%) was separated by filtration through SiO_2 (hexane:AcOEt, 1:1). IR: 2200, 730–700. UV: 287. MS *m/z*: 367 (M^+, 260, 91 ^{1}H NMR (60 MHz): 7.6–6.6 (9H, aromatic); 5.8 (2H, C_{14}-H and C_{15}-H); 5.0 (s, 2H, CH_2Ph); 3.80 (s, 1H, C_{21}-H); 1.00 (t, 3H, $J_{18,19} = 7$, C_{18}-H).

Compound **33**. The compound **32** (30 mg, 0.08 mmol) in EtOH (3 ml) was hydrogenated at atmospheric pressure, in presence of Pd/C (6 mg) as catalyst. The dihydro derivative **33** was obtained in quantitative yield. IR: 2200, 730–700. MS *m/z*: 369 (M^+), 368, 287, 260, 91. ^{1}H NMR (80 MHz): 7.5–6.57 (9H aromatic); 5.15 (s, 2H, CH_2Ph); 3.60 (s, 1H, C_{21}-H); 0.95 (t, 3H, $J_{18,19} = 7$, C_{18}-H).

Compound **34**. A soln of **33** (60 mg, 0.16 mmol) in THF (2 ml) was added to a soln of Na (8 mg, 0.33 mmol) in ammonia (80 ml). The mixture was stirred for 2 hr before the addition of MeOH (2 ml). H_2O (20 ml) was added after the evaporation of NH_3 and the product was extracted with ether. The **34** previously described[6] was isolated in 93% yield after usual work up, m.p.: 238° (CH_2Cl_2–$PhCH_3$). Lit.: 231–3° (MeOH).[6]

Aldehyde **12** *from* **34**. A soln of Dibal (20% in toluene, 0.103 ml, 0.15 mmol) was added under argon to a stirred soln of the **34** (44 mg, 0.158 mmol) in dry CH_2Cl_2 (4 ml) at −70°. The mixture was stirred 4 hr at −70°, hydrolyzed with an aqueous soln of MeOH then with HCl aq (20%, 3 ml) alkalinized with Na_2CO_3/H_2O and extracted with ether. The residue obtained in the usual way was purified by preparative TLC (AcOEt:hexane, 1:1) affording **12** (7 mg, 16%) and the starting **34**.

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