General Access to Tacamine and Vinca-Eburna Alkaloids through Tandem *Non-Biomimetic* Oxidation of Dihydropyridines/Zn-Mediated Radical Addition Processes − Unexpected Facial Selectivity of Flattened Cyclohexyl-Type Radicals

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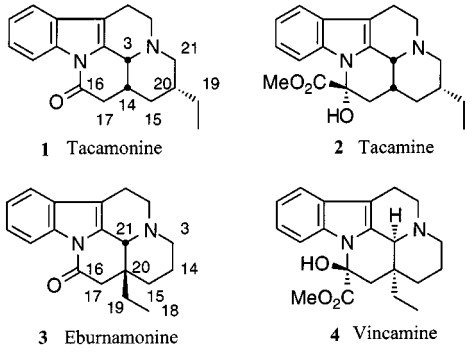
A general route to the eburnamine-vincamine and tacamine indole alkaloid groups has been developed. The key features of the synthetic strategy are the halocyclization of a dihydropyridine (a *non-biomimetic* oxidation of these compounds) and the radical addition of the resulting halo derivative to activated alkenes. The latter process shows an unusual stereoselectivity, favouring the generation of a *cis* stereochemistry in a 1,2-disubstituted 6-membered ring. Theoretical calculations suggest conformational control at the intermediate radical level, and a preferential face selectivity producing the observed products.

Introduction

The development of general methods for the synthesis of natural products is a key field in ongoing research in organic chemistry. Pursuing our interests in the chemistry of dihydropyridines,[1] we have been focusing our attention on exploitation of the recently described *non-biomimetic* oxidation processes of these versatile compounds.[2] In these reactions, the oxidative transformation takes place through bonding with electronegative atoms instead of the well-known electron transfer that produces pyridinium salts [the usual NAD(P)H → NAD(P)$^+$ metabolic conversion]. Although the *conventional* use of dihydropyridines in alkaloid synthesis (mainly involving oxidation, reduction and electrophilic additions upon these substrates) constitutes a well-established methodology;[3] the *non-biomimetic* oxidation approach opens up new and interesting possibilities in this field. To test this hypothesis, we chose indole alkaloids belonging to the tacamine[4] and vinca-eburna[5] groups as synthetic targets. These two biogenetically related types share the same pentacyclic skeleton, bearing a two-carbon chain located at different positions, and include tacamonine (**1**), tacamine (**2**), eburnamonine (**3**) and vincamine (**4**) among their prototypical members (Scheme 1). The interesting pharmacological properties of some of these alkaloids has stimulated systematic therapeutic and synthetic studies.[6,7]



Scheme 1. Representative tacamine and vinca-eburna alkaloids

Results and Discussion

Synthesis of Tacamonine

In the retrosynthetic analysis of tacamonine (Scheme 2), the final ring-closure to the pentacyclic system would take place through the interaction of the indole nitrogen atom with a suitable functional group located on the side-chain of a substituted indolo[2,3-*a*]quinolizidine precursor. This compound could be prepared by radical addition of an appropriate alkyl halide (**6**, for instance) to an electron-deficient olefin. A stereoselective route to the iodo derivative **6** has already been reported,[2c] as the result of the *non-biomimetic* oxidative halocyclization of the 1,4-dihydropyridine **5**, which in turn is the product of the sodium dithionite reduction of the pyridinium salt obtained by quaternization of 3-acetylpyridine with tryptophyl bromide.[8]

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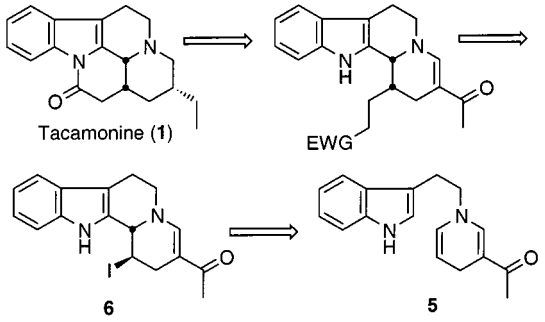
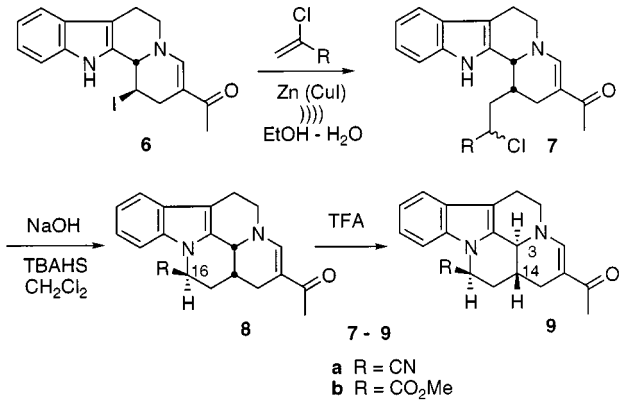


Scheme 2. Retrosynthetic analysis of tacamonine



Scheme 3. Radical addition based route to pentacyclic systems **8** and **9**

The outlined approach presents a priori the challenge of achieving a *cis* configuration from an addition of an α-substituted, six-membered cyclic radical. In the cyclohexyl series, *trans*-1,2-disubstituted cyclohexanes are usually the major products.[9,10] On the other hand, though, the precursor of the ethyl group is electronically and sterically well placed through the synthetic scheme; the acetyl residue, forming part of a vinylogous amide, should stabilize the piperidine nitrogen atom at the earlier stages, and afterwards should promote an all-*cis* stereochemistry on catalytic hydrogenation of the tetrahydropyridine moiety. This proposal is, in principle, flexible enough to be applicable after minor modification to the synthesis of the rest of the tacamine and eburna-vinca alkaloids (see below).

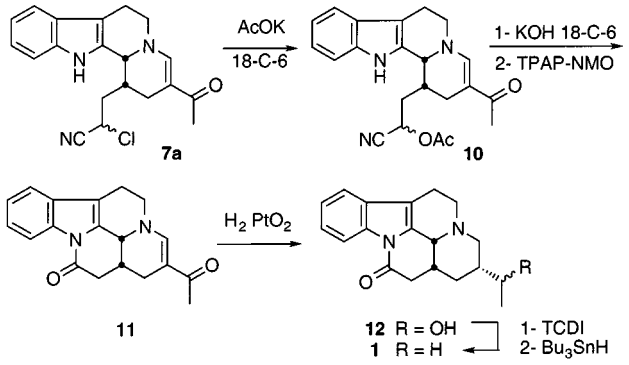
The first experiments involved interaction between the halo derivative **6** and ethyl acrylate in the presence of AIBN and Bu_3SnH or TTMSS; these were unsuccessful as we could only isolate the addition product in very low yields (< 5%). We then turned our attention to Zn-mediated conjugate additions of alkyl halides in aqueous media under sonochemical activation conditions.[11] Thus, when an EtOH/H_2O solution of **6** and α-chloroacrylonitrile was sonicated in the presence of Zn(CuI), the addition compound **7a** was obtained in a reasonable (57%) yield, as an epimeric mixture (1:1) at C-16.[12] In an analogous fashion, indoloquinolizidine **7b** was produced (56%) from the reaction with methyl α-chloroacrylate (Scheme 3). However, the moderately deactivated methyl α-acetoxyacrylate[13] failed to give the desired addition compounds in acceptable yields (ca. 10%).

Contrary to expectations, the stereogenic centre generated in the process was found to be in a *cis* relationship with the adjacent one. This unusual stereochemical outcome for a radical reaction implies a clean inversion of configuration at the proradical centre, resulting in a *cis*-1,2-disubstituted six-membered ring (arising from a *syn* addition). The base-promoted cyclization of the α-chloronitriles **7a** was achieved under phase-transfer catalysis conditions, yielding pentacycle **8a** (75%) as a single stereoisomer, while **7b** was converted into **8b** (59%) under the same conditions. Theoretical calculations showed that thermodynamic control, established through the base-catalysed epimerization at the α-position (C-16) of the cyclized nitriles and esters **8**, is the most plausible cause of this stereochemical preference (see Supporting Information). The stereochemical assignments were confirmed by spectroscopic analysis of the cyclic derivatives **8** (NOEs and coupling constants of the diagnostic signals). Further evidence was provided by the acid-catalysed epimerization, which enabled the *trans*-indoloquinolizidines **9a** (89%) and **9b** (97%) to be prepared from the corresponding *cis* isomers **8**. The *trans* stereochemistry of compounds **9** were clearly recognizable from the large H^3-H^{14} coupling constant ($J \approx 10$ Hz).

All attempts to attach a hydroxy group at C-16 in **8b** failed.[14] On treatment of chloronitrile **7a** with potassium acetate in dry acetonitrile under phase-transfer catalysis (18-C-6) conditions, acetoxynitrile **10** (64%) was obtained as an epimeric mixture (Scheme 4). Further hydrolysis resulted in the formation of the corresponding aldehyde, which spontaneously cyclized onto the indole ring to afford a mixture of C-16 hydroxy epimers. Without being purified, the mixture was oxidized with TPAP to yield acylindole **11** (32% overall yield). Catalytic hydrogenation of **11** brought about the simultaneous reduction of the olefin and carbonyl moieties, and took place with stereocontrol to yield alcohol **12** (43%, epimeric mixture at C-19), together with a small amount of tacamonine (**1**, 12%) arising from the subsequent hydrogenolysis of **12** in the acidic medium. Finally, the Barton−McCombie deoxygenation[15] of the corresponding thioimidazolide (obtained by reaction between **12** and TCDI) afforded tacamonine (**1**) in 57% overall yield over the two steps. The spectroscopic characteristics of the material obtained matched perfectly with those reported in the literature.[4a,6a] This also constitutes a formal synthesis of (16*R*)- and (16*S*)-de(methoxycarbonyl)tacamine.[6a]

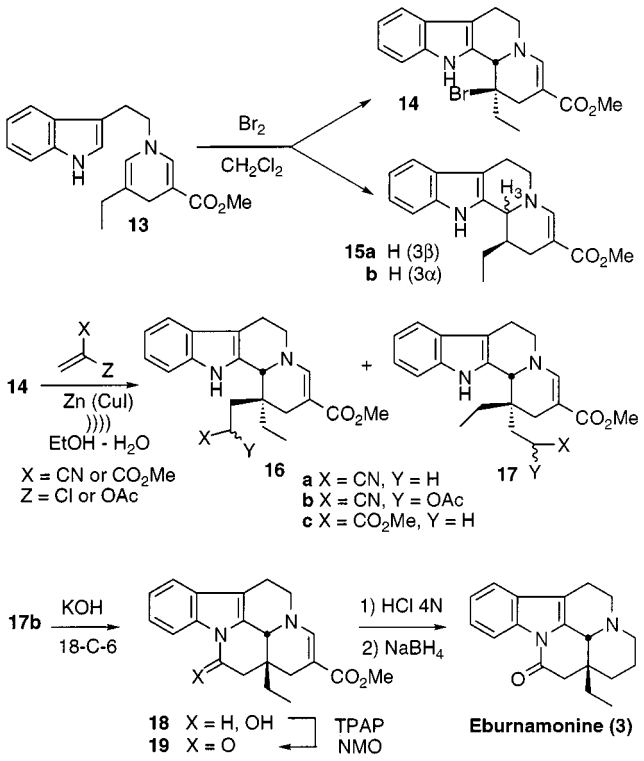
Synthesis of Eburnamonine and Vincamine

A similar approach was devised for the preparation of eburna-vinca alkaloids. The starting material was dihydropyridine **13**,[16] itself the product of the sodium dithionite reduction of the corresponding pyridinium salt.[17] Although iodine or NIS reaction with dihydropyridine **13** were not successful, bromocyclization of **13** in THF solution at low temperature afforded the expected bromoquinolizidine **14** stereoselectively (34%, Scheme 5), together with



Scheme 4. Total synthesis of tacamonine (**1**)

trans-indoloquinolizidine **15a**[16,18] (15%), probably the result of the acid-promoted cyclization of the starting material.

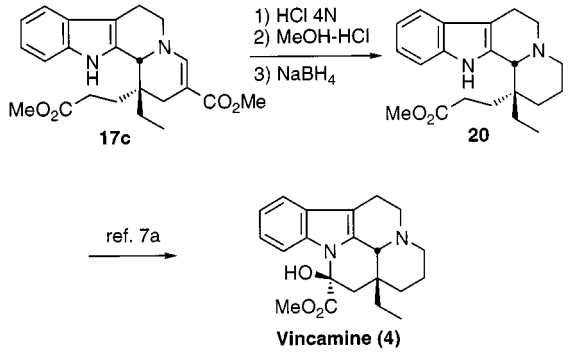


Scheme 5. Total synthesis of eburnamonine (**3**)

The Zn-promoted radical addition of this halo derivative onto electron-deficient olefins was conducted under the conditions previously used for iodoquinolizidine **6**, and on treatment with chloroacrylonitrile, a nearly equimolar mixture of tetracyclic derivatives **16a** and **17a** was obtained in 76% yield. The differences from the similar reactions described above concerned the stereoselectivity of the process and the reductive dechlorination observed here, which could not be avoided by shortening the reaction time. Once again a strong, but not exclusive, tendency to form the *disfavoured* compound **17a** (arising from *syn* addition) was observed. The relative stereochemistry of the reaction products was determined by a series of diagnostic NOEs.

Although this result had demonstrated the feasibility of constructing the crucial C-20 quaternary stereogenic centre in eburna-vinca alkaloids, the unexpected reduction of the C−Cl bond imposed a change in the synthetic plan. The difference in reactivity between the bromo derivative **14** and the iodoquinolizidine **6** prompted us to examine the reaction between **14** and α-acetoxyacrylonitrile,[19] in an attempt to ensure the proper degree of oxidation at C-16. We were pleased to observe that this reaction, under the usual conditions, afforded the desired acetoxynitrile **17b** (32%, mixture of epimers at C-16), although with only moderate stereoselectivity, with the corresponding C-20 diastereomers (**16b**, 10%) also being isolated. Only minor quantities (4%) of the reduction product **15b** were formed. Chemoselective hydrolysis of **17b** with solid KOH under phase-transfer catalysis conditions afforded the pentacyclic alcohol **18** (88%, mixture of epimers at C-16), which on TPAP oxidation gave indololactam **19** (84%). The removal of the vinylogous urethane moiety involved an acid-promoted hydrolysis, decarboxylation and reduction sequence in a one-pot operation,[20] to furnish (±)-eburnamonine (**3**, 60%),[21] which was identical with a commercial sample.

The synthesis of vincamine (**4**) was tackled by similar means and, on addition of methyl α-chloroacrylate to bromo derivative **14** under sonochemical conditions, an epimeric mixture of *cis*-**17c** (21%) and *trans*-**16c** (27%) was obtained (Schemes 5 and 6). The stereochemical outcome of this reaction shows trends similar to those observed in the above **a** series, producing a nearly equimolar amount of each stereoisomer. The hydrolytic-reductive *deprotection* of the vinylogous urethane in **17c** (including a reesterification step) afforded the known indoloquinolizidine **20** (40%, traces of the epimer also detected), which has previously been converted into vincamine (**4**),[7a][7f] which constitutes a formal synthesis of this alkaloid.



Scheme 6. Formal synthesis of vincamine (**4**)

Explanation of the Observed Sstereoselectivity

The clean inversion of configuration observed in the radical addition to generate indoloquinolizidines **7** and the tendency to undergo additions *syn* to the substituent adjacent to the radical centre were puzzling questions. The accepted mechanism for the Luche process[22] involves the generation of radical species from the alkyl halide and their subsequent addition to the olefin (racemization of optically

active alkyl iodides has been reported for these reactions).[23,24] We tried to interpret the reaction mechanism with the help of Density Functional calculations (see Methods), performed for model pyrroloquinolizidines (Figure 1), to examine the stability of the starting halo derivatives, radical intermediates, and products.

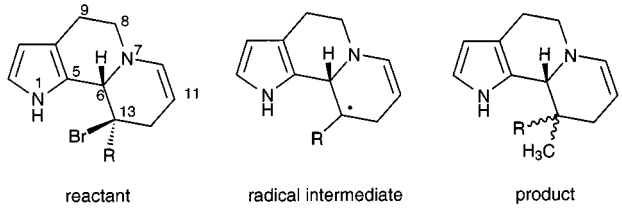


Figure 1. Schematic representation of the reactant, radical intermediate and product (R = H or CH_3) in the reactive process for the model compound used in calculations; the atom numbering is arbitrary

The calculations showed the existence of two distinct conformations, denoted here as extended (E) and folded (F), differing in their terminal six-membered rings (Figure 2). In addition, the E conformation allows the central six-membered ring some flexibility in the arrangement of atoms C-8 and C-9 relative to the plane formed by the aromatic ring (the two arrangements here are denoted up and down). A detailed analysis of the reaction mechanism should consider all these conformational degrees of freedom.

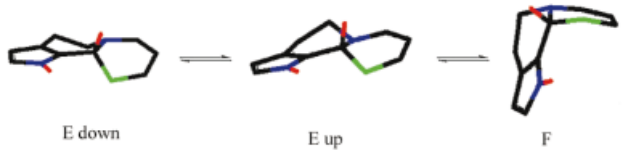


Figure 2. Schematic representation of the extended (E) and folded (F) conformations of the model pyrroloquinolizidines considered in calculations; the (pro)stereogenic centre is labelled in green; most hydrogen atoms are omitted for clarity

In the reactant (R = H) in the gas phase, the E conformation is clearly more stable than the F conformation (see Table 1). The source of this preference can be attributed to the repulsive contact between the hydrogen atoms attached to N-1 and C-13. The F conformer is nevertheless better hydrated than the E conformers, which can be explained by the difference in the dipole moments [F: 2.97 Debyes; E: 1.48 (up) and 1.33 (down) Debyes]. Overall, the calculations suggest that both the E and the F conformers of the reactant are populated in aqueous solution. Replacement of R = H by R = CH_3 increases the steric hindrance between the (N1)H and CH_3(C-13) groups in the F conformer [(N1)H···C(C-13) distance: 2.58 Å], which is now destabilized by around 27 kJ/mol relative to the E form. The intrinsic gas phase difference in stability between E and F conformations is not compensated for by the better hydration of the F conformer. Accordingly, the reactant with R = CH_3 should exist in water only in the E conformation.

Table 1. Relative stabilities [kJ/mol] of the *cis* and *trans* isomers in the gas phase and in aqueous solution, determined by theoretical calculations

Structures		ΔG_{gas} [a]	$\Delta\Delta G_{sol}$	ΔG_{wat}
Reactants				
R = H	E up	0.0	0.0	0.0
	E down	2.9	0.0	2.9
	F	14.2	−13.3	0.9
R = CH_3	E up	0.0	0.0	0.0
	E down	6.7	−1.2	5.5
	F	27.2	−13.7	13.5
Radical intermediate				
R = H	E up	0.0	0.0	0.0
	E down	4.2	−1.1	3.1
	F	2.9	−0.4	2.5
R = CH_3[b]	E up (ax)	0.0	0.0	0.0
	E up (eq)	0.4	−0.4	0.0
	E down	2.5	0.4	2.9
	F	−3.4	1.6	−5.0
Product				
R = H[c]	E up (*trans*)	0.0	0.0	0.0
	E up (*cis*)	−3.3	0.7	−2.6
	E down (*trans*)	4.2	−2.0	f2.2
	E down (*cis*)	4.6	−0.4	4.2
	F (*trans*)	2.6	−0.8	f1.8
	F (*cis*)	7.6	−1.7	5.9
R = CH_3	E up	0.0	0.0	0.0
	E down	9.3	−0.8	8.5
	F	11.3	−0.4	10.9

[a] The free energy difference in the gas phase (ΔG_{gas}) was determined from B3LYP calculations using the 6−31G(d) basis set. The free energy difference in water (ΔG_{wat}) was determined by adding the relative free energy of solvation ($\Delta\Delta G_{sol}$), computed from MST-HF/6−31G(d) calculations, to the gas phase free energy difference. Calculations were performed using a model compound in which the indole ring and the $COCH_3$ group in **8** were replaced by a pyrrole ring and a hydrogen atom (see Methods). R denotes the substituent at C13 (Figure 1). − [b] Two energy minima, with the methyl group placed in either pseudo-equatorial or pseudo-axial positions, were found for the E up conformer (see text). − [c] *cis* and *trans* denote the position of the methyl group, which simulates the nitrile-containing alkyl chain, with respect to the pyrrole ring.

The formation of both *syn* and *anti* products from treatment of **14** suggests that the radical intermediate should be relatively stable, in order to permit the approach of the conjugated nitrile to one of the faces of the six-membered ring. It is therefore necessary to examine the conformational preferences of the radical intermediate.

When R = H, the radical intermediate has a preference for the E conformation (Table 1 and Figure 3), but such a preference (2.9 kJ/mol) is nonetheless lower than that found for the reactant. The relative stability between conformers in the gas phase is little affected upon hydration, as is to be expected from the close similarity between the dipole moments of the different conformers (ranging between 1.29 and 1.51 Debyes).

The conformational preference of the radical intermediate changes when R = CH_3, with the F conformer now being more stable than the E form by 3.4 kJ/mol. Test calculations performed for the radical intermediates bearing

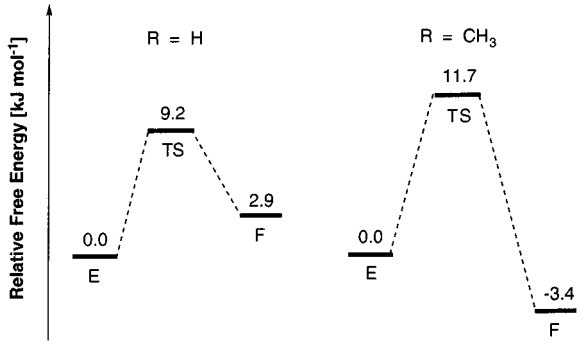


Figure 3. Schematic free energy profiles [kJ/mol] for the E → F conversion in the gas phase

an aldehyde group in position C-11, simulating the $COCH_3$ and CO_2CH_3 groups present in compounds **6** and **14**, indicate that the F conformer is destabilized (4.9 kJ/mol) relative to the E form when R = H, but is more stable (−3.1 kJ/mol) than the E conformer when R = CH_3, thus confirming the change in the conformational preference induced by attachment of the methyl group at position 13.

These data suggest that the stereochemical attack by the conjugated nitrile onto the indoloquinolizidine should be modulated by the reactive pathways of either the pro-*syn* and pro-*anti* faces of the E conformer (when R = H) or those of the F conformer (when R = CH_3) in the radical intermediates. For the latter, however, the conversion of the E conformer − i.e., the preferred one in the reactant (see above) − to the F conformer should be fast enough to allow thermodynamic equilibrium to be reached. The calculated free energies of activation for the E → F transition in the radical intermediate (see Figure 3) are 9.2 and 11.7 kJ/mol for the compounds with R = H and with R = CH_3, respectively, which emphasizes that the relative population of E and F conformers is determined by thermodynamic equilibrium.[25]

To investigate the pro-*syn*/pro-*anti* addition to the stereocenter for the E (R = H) and F (R = CH_3) conformers of the radical intermediate, we examined the spin density distributions. No significant difference in their distributions between the two faces was found, however (data not shown). Owing to the lack of evidence supporting an orbital-based preference in the reactive pathway, we examined the role of steric factors using MIP calculations (see Methods). For the E conformer (R = H), there is a clear preference for the approach of the probe at the pro-*syn* face (Figure 4), which stems from steric hindrance with the hydrogen atoms located at positions vicinal to the pro-stereocentre. In contrast, two sterically permitted regions appear above and below the six-membered ring in the F conformation (R = CH_3), thus permitting the approach of the probe to the pro-stereocentre both at the pro-*syn* and at the pro-*anti* faces (Figure 4). These results therefore suggest that the stereoselectivity of the addition reaction is modulated by steric factors.

Figure 4. Representation of the sterically accessible regions for the E (R = H, top) and F (R = CH_3, bottom) conformers of the radical intermediates; the radical carbon atom is marked in green; regions in red correspond to an isoenergy surface of −4 kJ/mol

The difference between the reactive pathways for the pro-*syn*/pro-*anti* approach to the E conformer of **6** is reflected in the relative stability of the products (modelled mimicking the nitrile-containing alkyl chain by a methyl group; see Figure 1). Thus, the *cis* product (arising from a *syn* addition) is around 3 kJ/mol more stable than the *trans* isomer (from an *anti* addition), both in the gas phase and in aqueous solution (Table 1). Note also that the most stable product of **14** adopts the E conformation.

In summary, the calculations allow us to conclude that the differences between the stereochemical addition of conjugated nitriles to **6** and **14** arise from three factors. Firstly, the preference for an extended (E) conformation in the radical intermediate formed from the indoloquinolizidine structure **6** is altered upon alkylation of the prostereogenic carbon atom, the most stable form then being the folded (F) conformation. Secondly, the lack of kinetic control in the E → F conversion in the alkylated radical permits a thermodynamic equilibrium between E and F conformations to become established.[26] Thirdly, the approach of the conjugated nitrile to either of the two faces of the ring is sterically feasible in the folded conformation (R = CH_3), while there is a preferred route in the extended conforma-

tion (R = H).[27] Overall, the subtle balance between these factors provides an explanation for the stereoselective addition observed experimentally.

Conclusion

Halocyclization of *N*-tryptophyl-1,4-dihydropyridines affords the corresponding iodo(bromo)indoloquinolizidines. These flexible systems contain flattened tetrahydropyridine frameworks, which provide unique platforms in which radical additions proceed with altered stereoselectivities. This allows for reversal of the reactivity patterns of six-membered cyclic radicals, to favour *syn* selectivity. In this way, short syntheses of the racemic forms of indole alkaloids tacamonine, eburnamonine and vincamine have been accomplished.[28]

Experimental Section

General: All solvents were purified and dried by standard methods. All reagents were of commercial quality, from freshly opened containers. Organic extracts were dried with anhydrous sodium sulfate. − TLC and column chromatography were carried out using SiO_2. − Melting points were determined in a capillary tube and are uncorrected. − Microanalyses and HRMS were performed by the Centro de Investigación y Desarrollo (CSIC), Barcelona. − Unless otherwise specified, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference at 200, 300, or 500 MHz (^1H); 50.3 or 75 MHz (^{13}C). − Only noteworthy IR absorptions are listed. − UV spectra were measured in MeOH solution.

Theoretical Calculations: Calculations were performed at the Density Functional Theory (DFT) level using the B3LYP functional,[29] which includes Becke's three-parameter exchange-correlation operator and the Lee−Yang−Parr correlation operator. The 6−31G(d) basis[30] was used for all atoms but bromine, which was treated using an effective core potential and the LANL2DZ basis.[31] UHF calculations were performed for all radical species. Calculations were performed using a model compound for the indoloquinolizidine structures **6** and **14** (Figure 1), and for the final product **8**. In the model compound the indole unit was replaced by a pyrrole unit, and the $COCH_3$/$COOCH_3$ group attached to C-11 was replaced by a hydrogen atom.

The geometries of reactants, radical intermediates, transition states, and products were fully optimized at the B3LYP/6−31G(d) level. The nature of minimum energy or transition state of the stationary points was confirmed from inspection of the vibrational frequencies. The calculated frequencies were used to compute the zero-point energy correction and the thermal and entropic (determined at 298 K and 1 atm) corrections in order to examine the differences in stability using the standard procedures implemented in Gaussian 94.[32] Using frontier orbital theory, the stereochemical preference of the addition reaction was investigated considering the role of both orbital-based and steric factors. To this end, we examined the spin density distribution and performed Molecular Interaction Potential (MIP) calculations[33] using a classical neutral point particle with van der Waals hardness and radius of 0.5 kJ/mol and 0.2 nm. MIP calculations were performed using the MOPETE computer program.[34] The influence of solvation on the stability of the chemical species involved in the reactive process was examined from self-consistent reaction field calculations using the MST continuum model.[35] Calculations were performed using the MST HF/6−31G(d) parameterized version for solvation in water. MST calculations were performed using a locally modified version of MonsterGauss.[36]

General Method for the Sonochemically Promoted Addition of Iodoindoloquinolizidine 6 to Electron-Deficient Olefins: A suspension of Zn (90 mg, 1.38 mmol) and CuI (78 mg, 0.4 mmol) in a mixture of EtOH/H_2O (7: 3, 3 mL, previously degassed) was sonicated (cleaning bath) under an inert gas at room temperature for 5 min. The olefin (10 mmol) and a solution of iodoquinolizidine **6**[2c] (200 mg, 0.51 mmol) in THF (3 mL) were added, and the resulting mixture was sonicated for 8 h. Dilution with ethyl acetate (50 mL) and filtration through a short pad of Celite gave a solution, which was washed with saturated aqueous NaCl solution (3 × 30 mL), dried, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with hexanes/ethyl acetate gave the addition compounds.

Indoloquinolizidine 7a: This compound was obtained according to the general procedure, using α-chloroacrylonitrile. Compound **7a** (1:1 mixture of epimers, 57%) was obtained after chromatography (elution with hexanes/ethyl acetate, 2:3) as an orange solid, m.p. 150−151 °C (CH_2Cl_2). − ^1H NMR ($CDCl_3$ + [D_6]DMSO): δ = 10.15 and 10.2 (2 s, 1 H), 7.50 (d, *J* = 7.4 Hz, 1 H), 7.46 (s, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.22−7.10 (m, 2 H), 4.74 (br. s, 1 H), 4.23 (*J* = 9.1 and 7.1 Hz) and 4.16 (*J* = 9.9 and 5.6 Hz) (2 dd, 1 H), 3.67 (m, 2 H), 2.98−2.80 (m, 3 H), 2.73 (m, *J* = 16.6 and 1.5 Hz, 1 H), 2.51 (m, 1 H), 2.23 (s, 3 H), 1.78−1.58 (m, 2 H). − ^{13}C NMR ($CDCl_3$ + [D_6]DMSO): δ = 193.6, 148.0, 136.5 and 136.4, 129.8 and 129.7, 125.9, 121.6, 119.0, 117.6, 117.0 and 116.6, 111.2, 109.1, 105.1 and 105.0, 55.3 and 55.1, 51.1, 41.0 and 40.8, 33.9 and 33.5, 31.9 and 31.2, 24.1, 23.6, 21.5. − IR (KBr): $\tilde{\nu}$ = 3250, 2250, 1575 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 307 nm (4.60), 220 (4.64). − MS (EI): *m*/*z* (%) = 353 (1) [M^+], 318 (12), 83 (100). − HRMS (EI): calcd. for $C_{20}H_{20}ClN_3O$ 353.1284; found 353.1294. − $C_{20}H_{20}ClN_3O$: calcd. C 67.95, H 5.70, N 11.8; found C 67.78, H 5.76, N 11.62.

Indoloquinolizidine 7b: This compound was obtained according to the general procedure, using methyl α-chloroacrylate. Compound **7b** (3:2 mixture of epimers, 56%) was obtained after chromatography (elution with hexanes/ethyl acetate, 2:3) as an orange solid, m.p. 137−138 °C (CH_2Cl_2). − ^1H NMR: δ = 8.30 and 8.10 (2 s, 1 H), 7.55 (d, *J* = 7.3 Hz, 1 H), 7.42 (s, 1 H), 7.38 (d, *J* = 8.2 Hz, 1 H), 7.24−7.10 (m, 2 H), 4.71 and 4.62 (2 br. s, 1 H), 4.25 (dd, *J* = 11.3 and 3.4 Hz, 1 H, an epimer) and 4.10 (dd, *J* = 9.0 and 5.8 Hz, 1 H, second epimer), 3.70 and 3.64 (2 s, 3 H), 3.68−3.65 (m, 2 H), 3.00−2.80 (m, 2 H), 2.75−2.60 (m, 3 H), 2.43 (m, 1 H), 2.23 (s, 3 H), 1.68 (m, 1 H). − ^{13}C NMR: δ = 194.2, 170.0 and 169.9, 148.4 and 148.3, 136.7 and 136.6, 130.5 and 130.1, 126.5 and 126.4, 122.2, 119.6, 118.0, 111.4, 109.9, 106.2 and 106.1, 56.0 and 55.8, 55.3, 53.0 and 52.9, 51.4, 32.8 and 31.4, 31.9 and 31.7, 24.9 and 23.4, 23.9, 21.8. − IR (KBr): $\tilde{\nu}$ = 3227, 1737, 1574 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 308 nm (4.94), 221 (4.97). − MS (EI): *m*/*z* (%) = 386 (1) [M^+], 352 (89), 351 (78). − HRMS (EI): calcd. for $C_{21}H_{23}ClN_2O_3$ 386.1392; found 386.1397; − $C_{21}H_{23}ClN_2O_3$: calcd. C 65.20, H 5.99, N 7.24; found C 65.04, H 6.13, N 6.98.

Pentacyclic Derivatives 8: Powdered NaOH (68 mg, 1.70 mmol) and tetrabutylammonium hydrogen sulfate (23 mg, 68 μmol) were added to a solution of chloro derivative **7** (0.7 mmol) in anhydrous CH_2Cl_2 (30 mL), and the resulting suspension was stirred at room temperature under N_2 for 12 h. Ethyl acetate (100 mL) and water

(100 mL) were added, the phases were separated, and the organic layer was washed with brine (5 × 50 mL), dried and filtered. The solvent was removed under reduced pressure to give a residue, which was chromatographed on silica gel. Elution with hexanes/ethyl acetate afforded the corresponding pentacyclic derivative **8**.

Nitrile 8a: Obtained after chromatography (elution with hexanes/ethyl acetate, 2:3) as an orange gum (75%). − ^{1}H NMR: δ = 7.63 (d, *J* = 8.5 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.27 (m, 1 H), 7.19 (d, *J* = 2.0 Hz, 1 H), 7.17 (m, 1 H), 4.94 (dd, *J* = 10.5 and 6.0 Hz, 1 H), 4.59 (m, *J* = 7.5, 2.0 and 2.0 Hz, 1 H), 3.80 (dd, *J* = 13.5 and 5.5 Hz, 1 H), 3.69 (m, 1 H), 2.90 (m, 1 H), 2.81 (m, 1 H), 2.70 (m, 2 H), 2.62 (m, 1 H), 2.50 (m, *J* = 16.6 and 1.5 Hz, 1 H), 2.10 (s, 3 H), 1.40 (m, *J* = 16.6, 12.0 and 2.2 Hz, 1 H). − ^{13}C NMR: δ = 194.0, 146.1, 137.4, 130.8, 128.4, 122.9, 121.4, 118.6, 117.4, 111.5, 110.5, 108.6, 51.7, 50.5, 40.8, 31.8, 27.8, 24.0, 22.6, 18.4. − IR (KBr): $\tilde{\nu}$ = 2241, 1645, 1571 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 303 nm (4.22), 222 (4.36). − MS (EI): *m*/*z* (%) = 317 (63) [M$^+$], 274 (11), 207 (100). − HRMS (EI): mass calcd. for $C_{20}H_{19}N_3O$ 317.1528; found 317.1524.

Ester 8b: Obtained after chromatography (elution with hexanes/ethyl acetate, 2:3) as an orange solid (59%), m.p. 118−119 °C (CH_2Cl_2). − ^{1}H NMR: δ = 7.37 (d, *J* = 8.0 Hz, 1 H), 7.16 (d, *J* = 2.0 Hz, 1 H), 7.10−7.04 (m, 2 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 4.71 (dd, *J* = 11.5 and 5.0 Hz, 1 H), 4.55 (m, *J* = 6.5, 2.0 and 2.0 Hz, 1 H), 3.80 (s, 3 H), 3.74 (dd, *J* = 13.5 and 6.0 Hz, 1 H), 3.65 (m, *J* = 13.5, 8.5 and 5.5 Hz, 1 H), 2.89 (m, 2 H), 2.50 (m, 3 H), 2.30 (m, *J* = 13.5, 11.0 and 3.5 Hz, 1 H), 2.05 (s, 3 H), 1.45 (m, *J* = 14.5, 11.0 and 2.0 Hz, 1 H). − ^{13}C NMR: δ = 194.0, 172.4, 146.4, 136.7, 131.0. 128.0, 121.9, 120.3, 118.3, 111.5, 110.0, 106.0, 52.9, 52.5, 52.0, 50.5, 30.8, 27.8, 24.1, 22.8, 18.7. − IR (KBr): $\tilde{\nu}$ =1751, 1587 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 304 nm (4.66), 225 (4.75). − MS (EI): *m*/*z* (%) = 350 (47) [M$^+$], 291 (15), 264 (55), 180 (100); − $C_{21}H_{22}N_2O_3$: C 71.98, H 6.33, N 7.99; found C 71.75, H 6.58, N 7.72.

Acid-Catalysed Isomerization of *cis*-Indoloquinolizidines 8: A solution of indoloquinolizidine **8** (0.1 mmol) in TFA (5 mL) was stirred at room temperature under N_2 until no starting material could be detected by TLC (17 h for **8a**, 2 h for **8b**). The mixture was poured into a saturated aqueous Na_2CO_3 solution (100 mL), and the resulting mixture was extracted with ethyl acetate (4 × 25 mL).The organic extracts were dried, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with hexanes/ethyl acetate gave the corresponding *trans*-indoloquinolizidine **9**.

***trans*-Indoloquinolizidine 9a:** Obtained after chromatography (elution with hexanes/ethyl acetate, 2:3) as an orange gum (89%). − ^{1}H NMR: δ = 7.50 (d, *J* = 8.0 Hz, 1 H), 7.39 (s, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.30 (m, 1 H), 7.21 (m, 1 H), 5.35 (dd, *J* = 5.0 and 2.0 Hz, 1 H), 3.86 (d, *J* = 9.5 Hz, 1 H), 3.71 (m, 1 H), 3.64 (m, 1 H), 3.00 (m, 1 H), 2.86 (m, 2 H), 2.58 (d, *J* = 14.0 Hz, 1 H), 2.25 (m, 1 H), 2.21 (s, 3 H), 2.09 (m, 2 H). − ^{13}C NMR: δ = 194.2, 147.2, 138.4, 131.7, 129.3, 123.2, 121.9, 119.5, 116.5, 110.8, 109.7, 109.2, 54.0, 49.3, 44.8, 32.6, 31.2, 25.3, 24.1, 21.4. − IR (KBr): $\tilde{\nu}$ = 2240, 1640, 1584 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 306 nm (4.31). − MS (EI): *m*/*z* (%) = 317 (81) [M$^+$], 274 (100). − HRMS (EI): calcd. for $C_{20}H_{19}N_3O$ 317.1528; found 317.1515.

***trans*-Indoloquinolizidine 9b:** Obtained after chromatography (elution with hexanes/ethyl acetate, 2:3) as an orange solid (97%), m.p. 124−125 °C (CH_2Cl_2). − ^{1}H NMR: δ = 7.48 (d, *J* = 8.0 Hz, 1 H), 7.40 (br. s, 1 H), 7.18−7.10 (m, 3 H), 5.12 (d, *J* = 6.0 Hz, 1 H), 3.88 (bd, *J* = 10.5 Hz, 1 H), 3.68 (m, 2 H), 3.57 (s, 3 H), 3.07 (m, 1 H), 2.85 (m, 1 H), 2.76 (m, *J* = 15.0 and 3.0 Hz, 1 H), 2.44 (d, *J* = 14.0 Hz, 1 H), 2.21 (m, 1 H), 2.19 (s, 3 H), 2.02 (m, 1 H), 1.98 (m, 1 H). − ^{13}C NMR: δ = 194.0, 171.2, 147.5, 138.5, 132.3, 128.3, 122.1, 120.4, 118.7, 109.6, 109.5, 105.9, 55.5, 54.3, 52.4, 49.5, 32.0, 29.5, 25.3, 24.1, 21.4. − IR (KBr): $\tilde{\nu}$ =1737, 1578 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 308 nm (4.32), 222 (4.46). − MS (EI): *m*/*z* (%) = 350 (85) [M$^+$], 307 (100); − $C_{21}H_{22}N_2O_3$: C 71.98, H 6.33, N 7.99; found C 71.67, H 6.49, N 7.65.

Acetoxynitrile 10: Potassium acetate (373 mg, 3.8 mmol) and 18-C-6 (80 mg, 0.3 mmol) were added to a solution of α-chloronitrile **7a** (536 mg, 1.52 mmol) in dry acetonitrile (25 mL). The resulting suspension was stirred at reflux for 9 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (100 mL) and washed with brine (5 × 50 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with hexanes/ethyl acetate (45:55) afforded **10** (366 mg, 64% as a 1:1 mixture of epimers) as an orange solid, m.p. 124−125 °C (CH_2Cl_2). − ^{1}H NMR: δ = 8.81 and 8.73 (2 s, 1 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.44 (s, 1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.25−7.13 (m, 2 H), 5.13 (*J* = 9.4 and 6.3 Hz) and 5.07 (*J* = 7.3 and 5.2 Hz) (2 dd, 1 H), 4.71 (br. s, 1 H), 3.67 (dd, *J* = 7.4 and 3.2 Hz, 2 H), 2.95−2.67 (m, 4 H), 2.49 (m, *J* = 16.2 and 4.8 Hz, 1 H), 2.24 (s, 3 H), 2.06 and 1.99 (2 s, 3 H). − 1.70−1.40 (m, 2 H). − ^{13}C NMR: δ = 194.2 and 194.1, 169, 148.1 and 148.0, 136.7 and 136.6, 129.9 and 129.8, 126.4, 122.5, 119.9, 118.1, 116.9, 111.5 and 111.4, 110.4, 105.9 and 105.8, 60.5 and 60.1, 55.7 and 55.6, 51.3, 31.7 and 31.5, 29.8 and 29.7, 25.1 and 24.7, 24.0, 21.8, 20.4 and 20.2. − IR (KBr): $\tilde{\nu}$ = 3232, 2250, 1752, 1574 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 308 nm (4.67), 221 (4.68). − MS (EI): *m*/*z* (%) = 377 (78) [M$^+$], 334 (100). − HRMS (EI): calcd. for $C_{22}H_{23}N_3O_3$ 377.1721; found 377.1739.

Indololactam 11: Powdered KOH (33 mg, 0.5 mmol) and 18-C-6 (11 mg, 40 μmol) were added to a solution of acetoxynitrile **10** (75 mg, 0.2 mmol) in dry acetonitrile (6 mL). The resulting suspension was stirred at room temp. for 5 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (100 mL) and washed with brine (5 × 50 mL). The organic phase was dried, filtered and concentrated under reduced pressure. The residue (57 mg) was dissolved in dry acetonitrile (5 mL), and TPAP (4 mg, 11 μmol), 4-methylmorpholine *N*-oxide (33 mg, 0.28 mmol) and powdered 4-Å molecular sieves (95 mg) were added. The resulting suspension was stirred at room temp. for 24 h, and the mixture was eluted through a short pad of SiO_2 with EtOAc. The eluates were concentrated under reduced pressure, and the residue was chromatographed on silica gel. Elution with hexanes/ethyl acetate (1:1) afforded **11** (20 mg, 32%) as a yellow, amorphous solid. − ^{1}H NMR: δ = 8.28 (d, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 7.5 Hz, 1 H), 7.29−7.19 (m, 2 H), 7.18 (d, *J* = 2.0 Hz, 1 H), 4.57 (br. s, 1 H), 3.80 (m, *J* = 13.5, 5.0 and 1.5 Hz, 1 H), 3.63 (m, *J* = 13.5, 10.0 and 6.0 Hz, 1 H), 3.03 (dd, *J* = 17.1 and 4.3 Hz, 1 H), 2.80 (dd, *J* = 17.1 and 2.0 Hz, 1 H), 2.73 (m, 2 H), 2.59 (m, 2 H), 2.07 (s, 3 H), 1.55 (m, *J* = 17.5, 13.5 and 2.0 Hz, 1 H). − ^{13}C NMR: δ = 194.3, 166.2, 145.5, 135.9, 131.6, 129.1, 125.0, 124.1, 118.1, 116.5, 112.8, 112.7, 51.1, 50.3, 38.5, 30.2, 24.3, 22.1, 21.4. − IR (KBr): $\tilde{\nu}$ = 1700, 1591 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 302 nm (4.60), 224 (4.52). − MS (EI): *m*/*z* (%) = 306 (56) [M$^+$], 263 (41), 168 (100). − HRMS (EI): mass calcd. for $C_{19}H_{18}N_2O_2$ 306.1361; found 306.1368.

Hydroxylactam 12: PtO_2 (5 mg) was added to a solution of ester lactam **11** (25 mg, 82 μmol) in acetic acid (10 mL), and the resulting suspension was hydrogenated (1 atm.) at room temp. for 9 h. The

catalyst was filtered, the filtrate was concentrated under reduced pressure, and the residue was dissolved in EtOAc (50 mL) and washed with a saturated aqueous Na_2CO_3 solution (3 × 25 mL) and brine (3 × 25 mL). The organic extracts were dried and filtered, and the solvents were evaporated to give a residue that was chromatographed on Al_2O_3. Elution with CH_2Cl_2 afforded a small amount of tacamonine (**1**) (3 mg, 12%,). Elution with CH_2Cl_2/MeOH (99:1) gave hydroxylactam **12** (11 mg, 43% as a 2:1 mixture of epimers at C-19) as an oil. − Data for the major epimer: ^{1}H NMR: δ = 8.35 (d, *J* = 7.5 Hz, 1 H), 7.42 (d, *J* = 7.5 Hz, 1 H), 7.33−7.25 (m, 2 H), 4.36 (m, 1 H), 3.38−3.33 (m, 2 H), 3.47 (m, *J* = 6.5 Hz, 1 H), 3.00 (dd, *J* = 17.0 and 5.0 Hz, 1 H), 2.88 (m, 1 H), 2.69 (dd, *J* = 17.0 and 2.0 Hz, 1 H), 2.61 (m, *J* = 11.0, 3.0 and 1.5 Hz, 1 H), 2.51 (m, 1 H), 2.46 (m, 1 H) 2.23 (dd, *J* = 11.0 Hz, 1 H), 1.84 (bd, *J* = 13.0 Hz, 1 H), 1.66 (m, 1 H), 1.10 (d, *J* = 6.5 Hz, 3 H), 0.80 (br. s, 1 H), 0.71 (m, *J* = 13.0, 12.5 and 12.5 Hz, 1 H). − ^{13}C NMR: δ = 167.2, 134.4, 131.1, 129.8, 124.4, 123.9, 118.1, 116.5, 112.8, 69.7, 53.2, 50.4, 47.3, 43.4, 39.6, 34.1, 27.4, 21.2, 16.3. − Data for the minor epimer: ^{1}H NMR: δ = 8.35 (d, *J* = 7.5 Hz, 1 H), 7.42 (d, *J* = 7.5 Hz, 1 H), 7.33−7.25 (m, 2 H), 4.36 (m, 1 H), 3.38−3.33 (m, 2 H), 3.40 (m, *J* = 6.5 Hz, 1 H), 3.00 (dd, *J* = 17.0 and 5.0 Hz, 1 H), 2.92 (m, *J* = 11.0, 3.0 and 1.5 Hz, 1 H), 2.88 (m, 1 H), 2.67 (dd, *J* = 17.0 and 2.0 Hz, 1 H), 2.51 (m, 1 H), 2.46 (m, 1 H), 2.18 (dd, *J* = 11.0 Hz, 1 H), 1.66 (m, 1 H), 1.60 (bd, *J* = 13.0 Hz, 1 H), 1.12 (d, *J* = 6.5 Hz, 3 H), 0.80 (br. s, 1 H), 0.70 (m, *J* = 13.0, 12.5 and 12.5 Hz, 1 H). − ^{13}C NMR: δ = 167.1, 134.4, 131.1, 129.8, 124.4, 123.9, 118.1, 116.3, 112.4, 70.0, 53.1, 50.4, 47.0, 43.7, 39.6, 34.1, 28.5, 21.4, 16.3. − IR (NaCl): $\tilde{\nu}$ = 3400, 1710 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 242 nm (4.21). − MS (EI): *m*/*z* (%) = 310 (93) [M$^+$], 309 (100), 209 (43), 167 (36). − HRMS (EI): mass calcd. for $C_{19}H_{22}N_2O_2$ 310.1672; found 310.1681.

Tacamonine (1): TCDI (16 mg, 90 μmol) was added to a solution of hydroxylactam **12** (14 mg, 45 μmol) in benzene/THF (1:1, 3 mL). The resulting solution was stirred at reflux under Ar for 3 h. The solvent was removed under reduced pressure, and the residue was purified by filtration through a short pad of Al_2O_3 (elution with EtOAc). The eluate was concentrated under reduced pressure, and the resulting imidazolide (10 mg) was dissolved in toluene/THF (1:1, 2 mL) and stirred at reflux temp. under Ar. A solution of Bu_3SnH (10 μL, 36 μmol) in toluene (0.5 mL) was added over 30 min, and stirring at reflux was continued for 3 h. The solvent was removed under reduced pressure, the residue was dissolved in acetonitrile (10 mL) and the resulting solution was washed with pentane (10 × 10 mL). The acetonitrile solution was concentrated and the residue was filtered through a short pad of SiO_2 (elution with CH_2Cl_2) to yield pure tacamonine (**1**, 4 mg, 57%), the ^{1}H and ^{13}C NMR spectra of which match those of an authentic sample.[4a,6a]

Bromocyclization of Dihydropyridine 13: A solution of bromine (67 mg, 0.42 mmol) in anhydrous THF (1 mL) was added to a solution of dihydropyridine **13**[16] (139 mg, 0.42 mmol) in dry CH_2Cl_2 (10 mL) maintained at −78 °C under Ar, and the resulting solution was stirred for 15 min at this temperature. CH_2Cl_2 (40 mL) was added and the solution was extracted with aqueous $Na_2S_2O_3$ (0.1 M, 3 × 25 mL) and brine (5 × 25 mL). The organic phase was dried, filtered and concentrated to give a residue, which was chromatographed on silica gel. Elution with hexanes/CH_2Cl_2 (1:1) afforded bromoquinolizidine **14** (55 mg, 34%) as a slightly unstable, yellow, amorphous solid. − ^{1}H NMR: δ = 9.15 (s, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.49 (d. *J* = 1.5 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.22 (m, 1 H), 7.13 (m, 1 H), 5.25 (s, 1 H), 3.71 (s, 3 H),3.66 (m, 1 H), 3.57 (m, *J* = 11.5, 11.0 and 4.0 Hz, 1 H), 3.38 (d, *J* = 16.0 Hz, 1 H), 3.03 (d, *J* = 16.0 Hz, 1 H), 2.89 (m, 1 H), 2.81 (m, 1 H), 1.57 (m, 1 H), 1.46 (m, 1 H), 0.94 (t, *J* = 7.5 Hz, 3 H). − ^{13}C NMR: δ = 167.6, 145.7, 135.7, 128.6, 125.9, 122.5, 119.6, 118.0, 112.1, 111.2, 91.9, 73.4, 62.7, 52.1, 50.9, 36.0, 27.6, 22.0, 9.3. − IR (KBr): $\tilde{\nu}$ = 3476, 1670, 1617cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 291 nm (4.39), 220 (4.66). − MS (EI): *m*/*z* (%) = 309 (41) [M$^+$ −Br], 308 (100), 249 (84). − Elution with hexanes/CH_2Cl_2 (4:6) afforded quinolizidine **15a** (20 mg, 15%) as a solid. M.p. 81−83 °C (MeOH, ref.[16] 80−82 °C). − ^{1}H NMR: δ = 7.84 (br. s, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.39 (s, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.17 (m, 1 H), 7.10 (m, 1 H), 4.39 (br. s, 1 H), 3.73 (dd, *J* = 13.5 and 5.0 Hz, 1 H), 3.64 (s, 3 H), 3.45 (m, *J* = 13.5, 13.0 and 4.5 Hz, 1 H), 2.92 (m, 1 H), 2.77 (m, *J* = 15.0 and 4.5 Hz, 1 H), 2.21 (d, *J* = 5.0 Hz, 1 H), 2.11 (m, 1 H), 1.68 (m, 1 H), 1.54 (m, 1 H), 1.06 (t, *J* = 7.5 Hz, 3 H). − ^{13}C NMR: δ = 169.5, 145.2, 135.8, 133.0, 127.2, 122.0, 119.8, 118.1, 110.9, 109.5, 97.4, 56.3, 51.4, 50.7, 36.9, 25.3, 22.6, 22.4, 11.9. − IR (NaCl): $\tilde{\nu}$ = 3314, 1658, 1617 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 291 nm (4.50), 223 (4.62). − MS (EI): *m*/*z* (%) = 310 (46) [M$^+$], 281 (29), 251 (30).

Sonochemical Addition of Bromoindoloquinolizidine 14 to α-Chloroacrylonitrile: This was done according to the general procedure for the sonochemical additions, using bromo derivative **14** (114 mg, 0.29 mmol), α-chloroacrylonitrile (0.5 mL, 6.28 mmol), Zn (52 mg, 0.79 mmol) and CuI (45 mg, 0.23 mmol), in a mixture of EtOH/H_2O (sonication time 1 h). Indoloquinolizidine **17a** (40 mg, 38%) was obtained after chromatography (SiO_2; elution with hexanes/CH_2Cl_2, 1:3) as a solid, m.p. 144−145 °C (CH_2Cl_2). − ^{1}H NMR: δ = 7.97 (br. s, 1 H), 7.51 (s, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.21 (m, 1 H), 7.15 (m, 1 H), 4.49 (s, 1 H), 3.71 (s, 3 H), 3.65 (m, 1 H), 3.51 (m, *J* = 11.5, 11.5 and 4.0 Hz, 1 H), 2.86 (m, 2 H), 2.40 (d, *J* = 17.0 Hz, 1 H), 2.24 (d, *J* = 17.0 Hz, 1 H), 2.03 (m, 2 H), 1.89 (m, 1 H), 1.81 (m, 1 H), 1.63 (m, 1 H), 1.45 (m, 1 H), 1.20 (t, *J* = 7.5 Hz, 3 H). − ^{13}C NMR: δ = 168.6, 145.9, 136.1, 129.5, 126.2, 122.7, 120.1, 120.0, 118.2, 112.4, 111.0, 92.7, 58.6, 52.1, 50.8, 37.4, 29.5, 29.0, 28.5, 22.2, 11.9, 7.8. − IR (KBr): $\tilde{\nu}$ = 3429, 2250, 1676, 1627 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 291 nm (4.53), 221 (4.54). − MS (EI): *m*/*z* (%) = 363 (48) [M$^+$], 323 (100). − HRMS (EI): calcd. for $C_{22}H_{25}N_3O_2$ 363.1947; found 363.1946. − $C_{22}H_{25}N_3O_2$: calcd. C 72.70, H 7.33, N 11.56; found C72.51, H 7.69, N 11.27. − On elution with hexanes/CH_2Cl_2 (1:4), **16a** (40 mg, 38%) was obtained as a solid. − ^{1}H NMR: δ = 8.28 (br. s, 1 H), 7.44 (s, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.13 (m, 1 H), 7.05 (m, 1 H), 4.29 (s, 1 H), 3.63 (s, 3 H), 3.56 (dd, *J* = 12.0 and 3.0 Hz, 1 H), 3.42 (m, *J* = 12.0, 12.0 and 4.O Hz, 1 H), 2.77 (m, 2 H), 2.51 (m, 1 H), 2.39 (m, 1 H), 2.31 (m, 1 H), 2.24 (d, *J* = 16.0 Hz, 1 H), 2.10 (d, *J* = 16.0 Hz, 1 H), 1.94 (m, 1 H), 1.21 (m, 2 H), 0.56 (t, *J* = 7.5 Hz, 3 H). − ^{13}C NMR: δ = 168.7, 146.0, 136.3, 129.8, 126.2, 122.3, 120.1, 119.8, 117.9, 112.2, 111.2, 92.7, 60.2, 52.2, 50.8, 37.8, 32.5, 30.3, 24.3, 22.3, 12.3, 8.3. − IR (KBr): $\tilde{\nu}$ = 3415, 2250, 1676, 1623 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 292 nm (4.50), 221 (4.53). − MS (EI): *m*/*z* (%) = 363 (46) [M$^+$], 323 (100). − HRMS (EI): calcd. for $C_{22}H_{25}N_3O_2$ 363.1947; found 363.1936.

Sonochemical Addition of Bromoindoloquinolizidine 14 to α-Acetoxyacrylonitrile: This was done according to the general procedure for the sonochemical additions, using bromo derivative **14** (300 mg, 0.77 mmol), α-acetoxyoacrylonitrile[19] (1.28 g, 11.53 mmol), Zn (137 mg, 2.10 mmol) and CuI (120 mg, 0.63 mmol), in a mixture of EtOH/H_2O (sonication time 1 h). *cis*-Indoloquinolizidine **15b** (10 mg, 4%) was obtained after chromatography (SiO_2; elution with hexanes/CH_2Cl_2, 6:4). On elution with hexanes/CH_2Cl_2 (1:1), acetoxynitrile **16b** (33 mg, 10%, mixture of epimers at C-16) was ob-

tained as an amorphous solid. − ^{1}H NMR (data for the major epimer): δ = 8.61 (br. s, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.49 (s, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.21 (m, 1 H), 7.15 (m, 1 H), 5.60 (dd, *J* = 9.9 and 3.9 Hz, 1 H), 4.48 (s, 1 H), 3.70 (s, 3 H), 3.65 (m, 1 H), 3.43 (m, 1 H), 2.84 (m, 2 H), 2.59 (dd, *J* = 15.6 and 9.9 Hz, 1 H), 2.40 (br. s, 2 H), 2.33 (dd, *J* = 15.6 and 3.9 Hz, 1 H), 1.45 (m, 1 H), 0.98 (m, 1 H), 0.71 (t, *J* = 7.2 Hz, 3 H); NOE between H-3 (4.48) and H-17 (2.33). − ^{13}C NMR (data for the major epimer): δ = 168.6, 168.4, 145.8, 136.1, 129.3, 126.4, 122.6, 120.0, 118.1, 116.9, 113.0, 111.4, 92.2, 58.6, 58.0, 52.4, 50.8, 38.0, 35.7, 28.0, 24.7, 22.4, 20.7, 7.5. − IR (KBr): $\tilde{\nu}$ = 3400, 2250, 1733, 1684, 1638 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 292 nm (4.48), 222 (4.57). − MS (EI): *m*/*z* (%) = 421 (36) [M$^+$], 362 (39), 323 (100). − On elution with hexanes/CH_2Cl_2 (1:4), **17b** (105 mg, 32%, mixture of epimers at C-16) was obtained as an amorphous solid. − ^{1}H NMR (data for the major epimer): δ = 8.01 (br. s, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.45 (s, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.21−7.08 (m, 2 H), 5.20 (dd, *J* = 8.5 and 4.5 Hz, 1 H), 4.43 (s, 1 H), 3.65 (s, 3 H), 3.60 (m, 1 H), 3.44 (m, 1 H), 2.87 (m, 1 H), 2.78 (m, 1 H), 2.34 (d, *J* = 18.0 Hz, 1 H), 2.23 (d, *J* = 18.0 Hz, 1 H), 2.00−1.80 (m, 3 H), 1.94 (s, 3 H), 1.60 (m, 1 H), 1.18 (t, *J* = 7.2 Hz, 3 H); NOE between 3-H (4.43) and 18-H (1.18). − ^{13}C NMR (data for the major epimer): δ = 169.0, 168.5, 145.8, 136.2, 128.2, 126.2, 122.7, 120.0, 118.2, 117.3, 112.7, 111.0, 93.3, 58.8, 58.0, 52.0, 50.9, 37.2, 35.1, 29.9, 29.5, 22.2, 20.3, 7.9. − IR (NaCl): $\tilde{\nu}$ = 3400, 2250, 1754, 1675, 1621 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 293 nm (4.44), 222 (4.55). − MS (EI): *m*/*z* (%) = 421 (20) [M$^+$], 362 (11), 337 (29), 323 (100). − HRMS (EI): calcd. for $C_{24}H_{27}N_3O_4$ 421.2002; found 421.1992.

Pentacyclic Alcohol 18: Powdered KOH (85%, 23 mg, 0.35 mmol) and 18-C-6 (6 mg, 22 μmol) were added to a solution of acetoxynitrile **17b** (49 mg, 0.11 mmol) in dry acetonitrile (4 mL). The resulting suspension was stirred at room temp for 2.5 h. The solvent was removed under reduced pressure, and the residue was taken up in EtOAc (50 mL) and washed with brine (5 × 25 mL). The organic phase was dried, filtered and concentrated under reduced pressure to afford hydroxy derivative **18** (36 mg, 88%, mixture of epimers at C-16) as an amorphous solid. − ^{1}H NMR (data for the major epimer): δ = 7.60 (m, 1 H), 7.40 (m, 1 H), 7.25 (s, 1 H), 7.19−7.06 (m, 2 H), 5.68 (dd, *J* = 9.2 and 5.8 Hz, 1 H), 4.10 (br. s, 1 H), 3.80 (m, 1 H), 3.61 (s, 3 H), 3.58 (m, 1 H), 2.80 (m, 2 H), 2.45−1.30 (m, 7 H), 0.95 (t, *J* = 7.4 Hz, 3 H). − ^{13}C NMR (data for the major epimer): δ = 168.5, 142.3, 137.8, 133.3, 128.1, 123.6, 120.5, 118.9, 112.6, 109.2, 101.6, 77.2, 56.2, 50.8, 48.6, 41.8, 39.8, 30.1, 23.4, 21.4, 8.0. − IR (NaCl): $\tilde{\nu}$ = 3330, 1665, 1611 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 286 nm (4.61), 249 (3.9), 226 (4.79). − MS (EI): *m*/*z* (%) = 352 (16) [M$^+$], 334 (15), 208 (100). − HRMS (EI): calcd. for $C_{21}H_{24}N_2O_3$ 352.1786; found 352.1783.

Indololactam 19: Alcohol **18** (24 mg, 68 μmol) was dissolved in dry acetonitrile (3 mL), and TPAP (3 mg, 82 μmol), 4-methylmorpholine *N*-oxide (16 mg, 0.14 mmol) and powdered 4-Å molecular sieves (60 mg) were added. The resulting suspension was stirred at room temp. for 24 h, and the mixture was eluted through a short pad of SiO_2 with EtOAc. The eluates were concentrated under reduced pressure, and the residue was chromatographed on silica gel. Elution with hexanes/CH_2Cl_2 (1:1) afforded lactam **19** (20 mg, 84%) as a solid. − ^{1}H NMR: δ = 8.32 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.31 (m, 1 H), 7.28 (s, 1 H), 7.26 (m, 1 H), 4.18 (m, *J* = 2.5 Hz, 1 H), 3.81 (dd, *J* = 13.5 and 6.0 Hz, 1 H), 3.60 (s, 3 H), 3.54(m, 1 H), 2.79 (d, *J* = 17.5 Hz, 1 H), 2.77 (m, 1 H), 2.72 (m, 1 H), 2.71 (d, *J* = 17.5 Hz, 1 H), 2.26 (dd, *J* = 17.0 and 2.5 Hz, 1 H), 1.75 (dm, *J* = 17.0 Hz, 1 H), 1.61 (m, 1 H), 1.50 (m, 1 H), 0.95 (t, *J* = 7.5 Hz, 3 H); NOE between 3-H (4.18) and 17β-H (2.79), 19-H (1.61 and 1.50), and 18-H (0.95). − ^{13}C NMR: δ = 168.2, 166.8, 143.4, 134.4, 132.6, 129.5, 124.8, 124.0, 118.2, 116.4, 113.1, 100.4, 55.1, 50.9, 50.2, 42.9, 37.4, 29.6, 25.6, 22.0, 7.8. − IR (KBr): $\tilde{\nu}$ = 1704, 1619 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 279 nm (4.51), 240 (4.37). − MS (EI): *m*/*z* (%) = 350 (51) [M$^+$], 319 (14), 224 (100). − HRMS (EI): calcd. for $C_{21}H_{22}N_2O_3$ 350.1630; found 350.1614.

Eburnamonine (3): A suspension of lactam **19** (18 mg, 51 μmol) in hydrochloric acid solution (4 M, 5 mL) was stirred at reflux for 2.5 h. The resulting solution was concentrated to dryness, and the residue was diluted with MeOH (3 mL). The resulting solution was cooled to 0 °C and $NaBH_4$ (6 mg, 0.15 mmol) was added. Stirring at this temp. was continued for 1 h. The mixture was poured into saturated aqueous Na_2CO_3 solution (25 mL) and extracted with EtOAc (4 × 15 mL). The organic extract was washed with brine (2 × 10 mL), dried, filtered and concentrated to give a residue, which was chromatographed on silica gel. Elution with hexanes/CH_2Cl_2 (1:1) afforded (±)-eburnamonine (**3**) (9 mg, 60%), identical (^{1}H and ^{13}C NMR, IR, TLC) to a commercial sample.

Sonochemical Addition of Bromoindoloquinolizidine 14 to Methyl α-Chloroacrylate: This was done according to the general procedure for the sonochemical additions, using bromo derivative **14** (175 mg, 0.45 mmol), methyl α-chloroacrylate (0.69 mL, 6.75 mmol), Zn (79 mg, 1.21 mmol) and CuI (68 mg, 0.36 mmol), in a mixture of EtOH/H_2O (sonication time 8 h). After chromatography (SiO_2; hexanes/CH_2Cl_2, 1:1), indoloquinolizidine **16c** (48 mg, 27%) was obtained as a gum. − ^{1}H NMR: δ = 7.95 (br. s, 1 H), 7.51 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 7.8 Hz, 1 H), 7.22−7.10 (m, 2 H), 4.47 (br. s, 1 H), 3.70 (s, 3 H); 3.65 (m, 1 H), 3.53 (s, 3 H), 3.45 (m, 1 H), 2.91 (m, 1 H), 2.79 (m, 1 H), 2.36 (d, *J* = 16.8 Hz, 1 H), 2.24 (d, *J* = 16.8 Hz, 1 H), 2.15- 1.55 (m, 5 H), 1.17 (t, *J* = 7.8 Hz, 3 H), 0.85 (m, 1 H). − ^{13}C NMR: δ = 174.1, 168.8, 146.0, 135.9, 130.2, 126.3, 122.2, 119.7, 118.0, 112.1, 110.9, 93.2, 58.9, 52.1, 51.5, 50.7, 37.4, 29.4, 29.2, 28.7, 27.7, 22.2, 8.0. − IR (KBr): $\tilde{\nu}$ = 3348, 1735, 1667, 1624 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 292 nm (4.50), 223 (4.61). − MS (EI): *m*/*z* (%) = 396 (100) [M$^+$], 323 (65), 169 (56). − On elution with hexanes/CH_2Cl_2 (1:3), **17c** (39 mg, 21%) was obtained as a gum. − ^{1}H NMR: δ = 9.4 (br. s, 1 H), 7.51 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.21−7.09 (m, 2 H), 4.54 (br. s, 1 H), 3.81 (s, 3 H), 3.70 (s, 3 H), 3.65 (m, 2 H), 2.83 (m, 2 H), 2.57 (m, 2 H), 2.35 (d, *J* = 16.2 Hz, 1 H), 2.15 (m, 2 H), 1.25 (m, 2 H), 0.90 (m, 1 H), 0.64 (t, *J* = 7.5 Hz, 3 H). − ^{13}C NMR: δ = 176.1, 168.8, 146.0, 136.3, 129.9, 126.0, 121.9, 119.4, 117.7, 111.8, 111.1, 92.5, 58.4, 52.4, 52.3, 50.7, 37.5, 30.5, 28.2, 28.1, 24.3, 22.3, 7.7. − IR (KBr): $\tilde{\nu}$ = 3345, 1731, 1667, 1629 cm^{-1}. − UV (MeOH): λ_{max} (log ε) = 292 nm (4.51), 222 (4.58). − MS (EI): *m*/*z* (%) = 396 (100) [M$^+$], 323 (57), 169 (58). − HRMS (EI): calcd. for $C_{23}H_{28}N_2O_4$ 396.2049; found 396.2056.

Indoloquinolizidine Carboxylic Ester 20: A suspension of diester **17c** (18 mg, 51 μmol) in hydrochloric acid solution (4 M, 5 mL) was stirred at reflux for 3 h. The resulting solution was concentrated to dryness, and the residue was diluted with MeOH/HCl (2 M, 3 mL) and stirred at room temp for 14 h. The solvent was removed under reduced pressure, the residue was dissolved in MeOH (5 mL), and the resulting solution was cooled to 0 °C. $NaBH_4$ (43 mg, 1.14 mmol) was added, and stirring at this temp. was continued for 1 h. The mixture was poured into saturated aqueous Na_2CO_3 solution (25 mL) and extracted with EtOAc (4 × 15 mL). The organic extract was washed with brine (2 × 10 mL), dried, filtered and concentrated to give a residue, which was chromatographed on

silica gel. Elution with hexanes/CH_2Cl_2 (1:1) afforded ester **20** (11 mg, 40%), the spectroscopic data of which match those reported in the literature.[7a][7f]

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