Stereocontrolled Elaboration of Quaternary Carbon Centers through the Asymmetric Michael-Type Alkylation of Chiral Imines/Secondary Enamines: Enantioselective Synthesis of (+)-Vincamine

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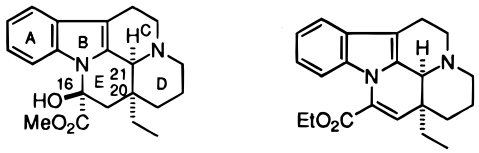
An enantioselective synthesis of (+)-vincamine (**1**) has been developed. The key strategic element was the stereocontrolled elaboration of a quaternary carbon center (future C-20 center of **1**) by using the asymmetric Michael reaction involving chiral imines/secondary enamines under neutral conditions. Thus, addition of enaminolactam (*S*)-**12**, derived from ketolactam **7** (itself prepared in four steps from commercially available tryptamine) and (*S*)-1-phenylethylamine, to methyl acrylate led, after hydrolytic workup, to adduct (*R*)-**6** with a 90% stereoselectivity. The critical removal of the additional keto group of **6** was then examined. After extensive experimentation, we finally established that the most efficient deoxygenation procedure was the Wolff−Kishner reduction of the corresponding keto acid, which proceeded with a 55% yield. The cornerstone [ABD]-tricyclic lactam ester **38** thus obtained was next cyclized under Bischler−Napieralski reaction conditions to afford, after catalytic hydrogenation of the intermediary iminium perchlorate salt, a mixture of the desired, known indoloquinolizidine **5** and its epimer **39**, in a ratio of 6:1, respectively. Basic treatment of **5** led to (+)-homoeburnamonine **4**, which was finally converted, according to a known procedure, into our goal (+)-vincamine (**1**). Thus, synthesis of (+)-vincamine (**1**) has been achieved by a linear sequence of 15 chemical operations, starting from tryptamine, with an overall yield of 1.2%.

Introduction

Vinca alkaloids comprise a large group of biologically active, naturally occurring bases, isolated from several plants of the *Vinca* species.[1] Among these bases, (+)-vincamine (**1**), the major alkaloid encountered in periwinkle (*Vinca minor* L., *Apocynaceae*), appears to be a particularly attractive synthetic target. In man, the best established pharmacological property of vincamine (**1**) and semisynthetic derivatives, such as ethyl apovincaminate (**2**) (vinpocetine, Cavinton),[2] is the cerebroprotective activity, caused by a dilation of brain arteries, improving the global cerebral blood flow. Thus, vinpocetine has been proposed for the treatment of certain vascular dementia, by enhancing oxygen release of hemoglobin,[3] of the sensorineural impairment of hearing,[4] in ophthalmological therapy.[5] Recent investigations have shown that pharmacon **2** also exhibits a protective effect against brain damage caused by ischemia,[6] a gastroprotective action,[7] and a remarkable promising activity in removing tumoral calcinosis,[8] effects possibly related to the powerful hydroxyl radical-scavenging capability of this molecule (close to that of vitamin E)[9] (Chart 1).

Chart 1



(+)-1 **2**

Several strategies for the synthesis of vincamine (**1**) (the "biogenetic" numbering system was used here)[10] and analogs have been developed. The common feature in these approaches was to establish first the [ABCD]-type octahydroindolo[2,3-*a*]quinolizine system of this alkaloid, starting from an indole subunit, and to achieve the synthesis by creating the fifth ring E. Thus, strategically, the elaboration of vincamine (**1**) and related alkaloids reduced to four main methodologies for establishing the requisite *gem*-disubstituted tetracyclic indoloquinolizidine moieties **3** bearing two controlled stereogenic carbon

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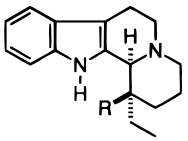
Chart 2



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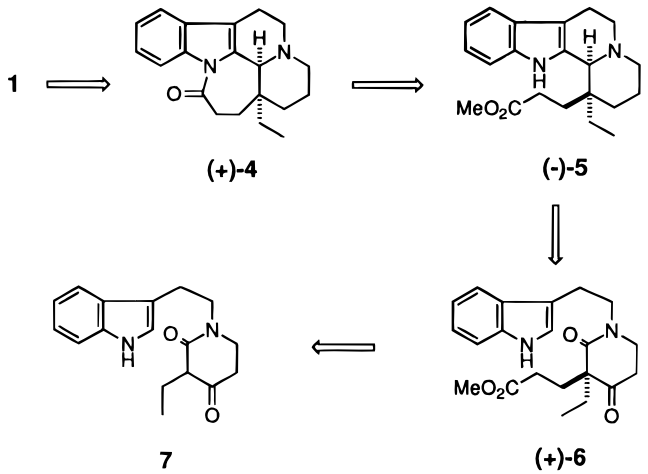
atoms, namely the crucial quaternary center at C-20 and the adjacent methine at C-21: the Pictet−Spengler cyclization,[11] the Bischler−Napieralski (B−N) cyclization,[12] the Michael-type alkylation of the so-called "Wenkert's enamine",[13] and the annulation reaction of a dihydro-β-carboline[14−17] (Chart 2).

Synthetic Plan, Results and Discussion

Our own strategy for the enantioselective synthesis of (+)-vincamine (**1**) is outlined in the retrosynthetic pathway depicted in Scheme 1.[18] The basic approach featured a general methodology for the stereocontrolled elaboration of quaternary carbon centers as key step in the construction of the [ABD]-type subunit **6** from keto lactam **7**. The latter compound was efficiently prepared in four steps, starting from tryptamine. Synthesis of the requisite tricycle **6**, in its desired *R* configuration, involved the asymmetric Michael addition of the chiral enaminolactam, prepared from **7** and (*S*)-1-phenylethylamine, to methyl acrylate. Wolff−Kishner (W−K) reduction of the additional keto group of **6**, followed by B−N cyclization, led to the indoloquinolizidine derivative **5**, having established during the events the correct stereochemical relationship between C-20 and C-21. Base-induced cyclization of **5** finally gave (+)-homoeburnamonine **4**, a direct, known precursor of (+)-vincamine (**1**). Alternatively, compound **5** can be converted into **1** by the efficient two-step procedure recently reported by Nemes.[13i]

Scheme 1



As mentioned above, the key step in the synthesis of our goal **1** was the stereocontrolled creation of a quaternary carbon center (step **7** → **6**) by using the asymmetric Michael reaction involving chiral imines/secondary enamines, derived from 1-phenylethylamine, which we reported a decade ago.[19] We were confident that this methodology might be applied to the peculiar β-keto lactam topology of **7**, having previously established that addition of a chiral enaminolactam, derived from a β-keto lactam model, to methyl acrylate, led to the expected adduct with a good yield and an excellent stereoselectivity (94%).[20] The requisite tricyclic ketolactam **7** was elaborated in four steps with an overall yield of 43%, as follows.[21] Conjugate addition of tryptamine to ethyl acrylate (THF, 12 h at 20 °C, 83%) gave adduct **8**, which was next condensed with ethylmalonic acid monoethyl ester (DCC, cat. DMAP, CH_2Cl_2, 18 h at 20 °C, 83%) to furnish diester **9**. Dieckmann cyclization of **9** (NaH, THF, 4 h at 20 °C, 79%) afforded **10**, which upon decarbethoxylation (LiBr, 2 equiv of water, 12 h at reflux in DMF, 79%), finally gave the desired keto lactam **7** (Scheme 2).

First Route: Use of Methyl 2-Acetoxyacrylate as Michael Acceptor. Strategically, it became apparent

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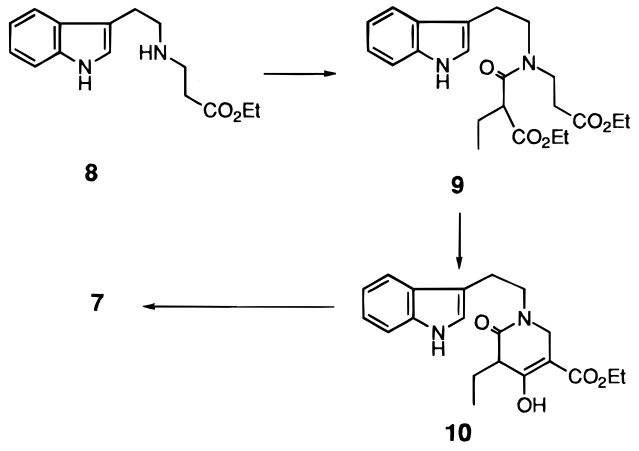
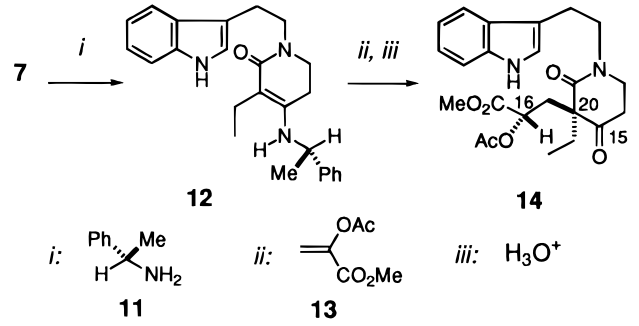
Scheme 2



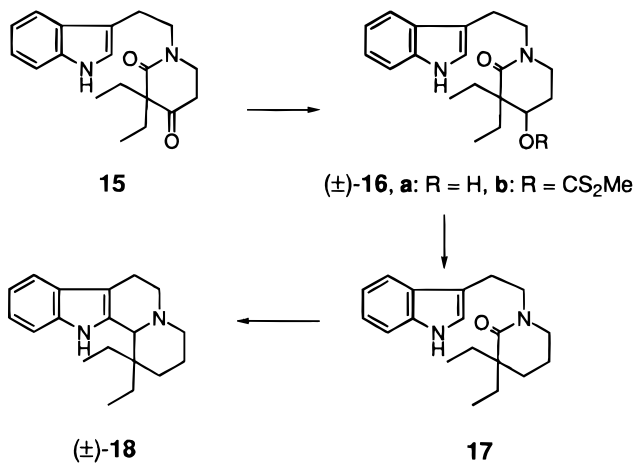
Scheme 3



that a concise, direct construction of the future ring E of vincamine **1** from the tricyclic precursor **7** should require the presence, at the subsequently created quaternary carbon center, of a "masked" pyruvic acid ester side chain. In this respect, the use of methyl 2-acetoxyacrylate (**13**)[13c,d] as electrophilic partner in the above-mentioned asymmetric Michael reaction would achieve two goals, namely the installation of a quaternary stereocenter with predictable configuration and simultaneous introduction of an α-acetoxypropanoate appendage, equivalent, through simple oxidation, to the desired pyruvic acid ester moiety. Thus, we began our investigation by condensing enamino lactam **12**, prepared from **7** and (*S*)-1-phenylethylamine (**11**) (of 96% ee) (12 h at reflux in toluene, with azeotropic removal of water, catalytic *p*-TsOH, quantitative), with methyl 2-acetoxyacrylate (**13**) (neat, hydroquinone, 24 h at 60 °C, then 20% aqueous AcOH, 24 h at 40 °C). Adduct (16*S*,20*R*)-**14** was thus obtained in 66% yield as a *single* diastereomer, as evidenced by ^{1}H and ^{13}C NMR spectroscopy, and with a 96 ± 1% ee [determined by ^{1}H NMR, having added Eu $(hfc)_3$ as chiral shift reagent]. Taking into account that the ee of the starting chiral auxiliary amine **11** was 96%, the efficiency of the asymmetric induction in the present Michael process was therefore 99 ± 1%. The relative configuration at the two newly created stereogenic centers C-16 and C-20 was determined at the level of the pentacyclic lactone derivative **21** (*vide infra*).[18] The portrayed absolute configuration of adduct **14**, although not definitely established, paralleled the stereochemical outcome observed in the condensation of acceptor **13** with the chiral imine derived from 2-methylcyclohexanone and amine **11** (Scheme 3).[22]

With the necessary adduct **14** in hand, we next envisaged the construction of a tetracyclic indoloquinolizidine of type **3**. However, all attempts at B−N cyclization of **14** ($POCl_3$, 24 h in MeCN at reflux and then $NaBH_3CN$; $POCl_3$, 24 h in toluene at reflux and then $NaBH_4$; or 24 h in neat $POCl_3$ at reflux and then H_2/Pd-C)[12] proved to be invariably unsuccessful. Having suspected the presence of the keto group at C-15 in compound **14** to be responsible for the failure, we then decided to examine the B−N cyclizations of model keto lactam **15**, and of its derivative **17**, lacking the interfering keto group. As anticipated, the attempted B−N cyclization of **15** (prepared in 62% yield by condensing **7** with EtI, Triton B, MeOH−CH_3CN, 4 days at 20 °C) was fruitless. Conversion of **15** into **17** was accomplished by using the Barton−McCombie radical-induced deoxygenation procedure.[23] For this purpose, keto lactam **15** was first reduced into alcohol **16a** ($NaBH_4$, MeOH, 1 h at 20 °C, 90%), which was converted into xanthate **16b** ((i) NaH in THF, 30 min at 20 °C; (ii) CS_2, 30 min at 20 °C; (iii) MeI, 15 min at 20 °C, 50%). Reduction of this xanthate (*n*-Bu_3SnH, AIBN, 4 h in toluene at reflux) finally gave the desired lactam **17** with a 73% yield. *B−N cyclization of this lactam now proceeded in a straightforward manner* ((i) 4 h in $POCl_3$ at reflux; (ii) anion exchange with aqueous $LiClO_4$; (iii) $NaBH_4$, MeOH, 12 h at 20 °C) to furnish the expected tetracyclic derivative **18**[17a] in 60% yield (Scheme 4).

Scheme 4



*The precedent series of experiments clearly established that the failure of the B−N cyclization of keto lactam **15** (and very likely **14**) was due to the presence of the keto group.* Removal of the interfering keto group of **14** was therefore examined. W−K reduction of the α-hydroxy acid, obtained by saponification of **14** ((i) LiOH in MeOH, 2 h at 20 °C; (ii) hydrazine hydrate, diethylene glycol, 30 min at 160 °C; (iii) KOH, 4 h, 220 °C) was first attempted.[11c] However, this reaction proved to be unsatisfactory, delivering the desired "deoxygenated" derivative in only very low yield (3%).[24] The above, alternative methodology involving the reduction of a xanthate was therefore tried next. The first step in this sequence required the chemoselective reduction of the keto group of **14**, a somewhat tricky problem due to the presence of four carbonyl functions in this molecule. This transformation was efficiently realized by using LiAlH(O-*t*-Bu)$_3$ as reducing agent (THF, 48 h, 20 °C, 85%).

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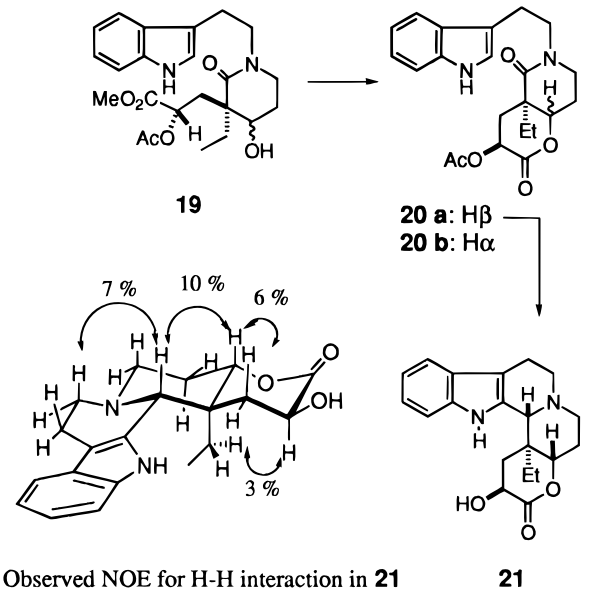
(24) Unexpectedly, compound **17** (6%) was also isolated in this reaction, along with unidentified indolic derivatives.

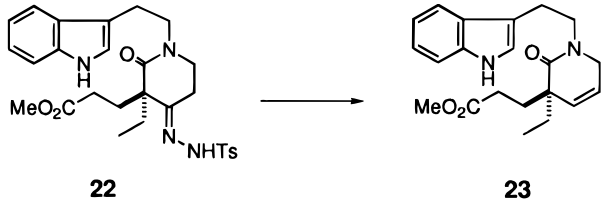
Scheme 5



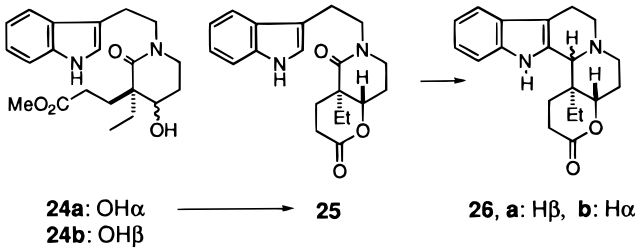
However, derivatization of the alcohols **19** thus obtained was thwarted by their propensity to cyclize into lactones **20** (this partial, spontaneous cyclization was ended by heating **19** for 24 h at reflux in benzene in the presence of amberlyst R15, 72%). Epimeric lactones **20** (3:1 mixture) were separated by chromatography over silica gel. Unfortunately, treatment of major *trans* isomer **20a** under B−N cyclization conditions ((i) $POCl_3$, 14 h in refluxing MeCN; (ii) 1 bar of H_2, Pd−C) gave with a low yield (20%) the pentacyclic derivative **21**, exhibiting the "unnatural" *trans* relationship between the ethyl substituent at C-20 and the H atom a C-21 (cleavage of the acetoxy group took place during this operation). The depicted relative stereochemistry in **21** was assigned by ^{1}H NMR spectroscopy, including NOE experiments (Scheme 5). In view of the above results, this route was abandoned.

Second Route: Use of Methyl Acrylate as a Michael Acceptor. Having thus been forcibly diverted from the "direct" route involving the introduction, in enaminolactam **12**, of an α-acetoxypropanoate side chain, equivalent to a pyruvic acid ester moiety, an alternative plan was devised, in which the key step was the Michael addition of **12** to methyl acrylate. Indeed, it was our hope that the propanoate appendage thus introduced in adduct **6** might be less prone to interfere with the subsequent synthetic steps than the α-acetoxypropanoate side chain of related adduct **14**. Addition of **12** of 96% ee to methyl acrylate proceeded smoothly (THF, hydroquinone, 48 h at 60 °C, then 20% aqueous AcOH, 3 days at 40 °C) to furnish adduct (*R*)-**6** with a 70% yield and an ee of 89 ± 1%, corresponding to an asymmetric induction of 92 ± 1%, after correction of the optical purity of the chiral auxiliary. The ee of adduct **6** was determined by ^{1}H NMR spectroscopy [after adding $Eu(hfc)_3$ as chiral shift reagent], and its absolute configuration was unambiguously established through the completion of the synthesis of natural (+)-vincamine (**1**) (*vide infra*). In view of the difficulties encountered in the first route, our next synthetic efforts were focused upon the removal of the keto group of adduct **6**. In this respect, the reduction of the corresponding *p*-tosylhydrazone **22** (prepared from **6**, $TsNHNH_2$, 10 days in MeOH at reflux, in 80% yield) seemed particularly attractive. However, attempted

Scheme 6



Scheme 7



reduction of **22** ($NaBH_4$ in AcOH, or catecholborane[25]) proved to be unsuccessful. By contrast, treatment of **22** with LiH (48 h in toluene at reflux)[26] gave the expected unsaturated lactam **23** in 55% yield. Unfortunately, all efforts at reducing selectively the hindered double bond of the lactam ring of **23** invariably failed because of the competitive reduction of the indole nucleus (Scheme 6).

An alternative way for reducing the keto group of **6** employed alcohols **24**, obtained as a 3:1 epimeric mixture by treating **6** with $LiAlH(O\text{-}t\text{-}Bu)_3$ (THF, 4 h at 20 °C, 74%). However, derivatization of these alcohols was again impeded by their marked propensity to cyclize into lactones. This cyclization was thus accomplished with a 78% yield by heating major alcohol **24a** for 3 h in benzene at reflux, in the presence of amberlyst R15. B−N cyclization of the resulting *trans* lactone **25** gave a 3:1 epimeric mixture of pentacyclic derivatives **26** ((i) $POCl_3$ at reflux 5 h; (ii) anion exchange with aqueous $LiClO_4$; (iii) 1 bar of H_2, 10% Pd-C, DMF, 40%). Unfortunately, examination of the ^{1}H NMR data of **26** revealed that, as observed for the conversion **20a** → **21**, the major isomer **26a** exhibited the undesired *trans* relationship between the ethyl substituent at C-20 and the H atom at C-21 (Scheme 7).

In view of these results, we decided to reduce first the interfering carbomethoxy group of **6**. For this purpose, **6** was saponified into acid **27** (LiOH, H_2O_2, 5 h at 20 °C, 76%), which was then transformed into diols **28a** ((i) *i*-BuOCOCl, Et_3N, 30 min at 0 °C; (ii) $NaBH_4$, MeOH, 24 h at 20 °C, 75%). Selective protection of the primary alcohol group of **28a** (*t*-$BuPh_2SiCl$, imidazole, DMF, 12 h at 20 °C, 68%) furnished the corresponding *tert*-butyldiphenylsilyl ether derivatives **28b**, which were next converted into xanthates **29** ((i) NaH, THF, 20 min at 20 °C; (ii) CS_2, 30 min; (iii) MeI, 15 min at 20 °C, 50%).[27] Reduction of these xanthates (*n*-Bu_3SnH, AIBN, 2 h in toluene at reflux, 85%) finally gave the pivotal derivative **30** (Scheme 8).

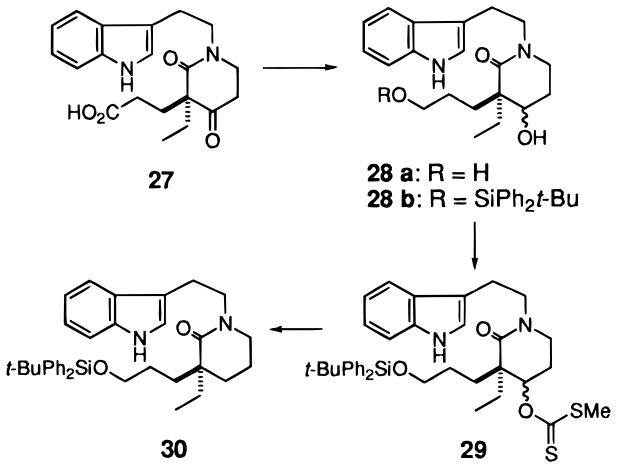
At this juncture, two strategies have evolved for the subsequent construction of an indolo[2,3-*a*]quinolizidine

(25) Kabalka, G. W.; Baker, J. D., Jr. *J. Org. Chem.* **1975**, *40*, 1834−1835.

(26) Caglioti, L.; Grasselli, P.; Selva, A. *Gazz. Chim. Ital.* **1964**, 537−551.

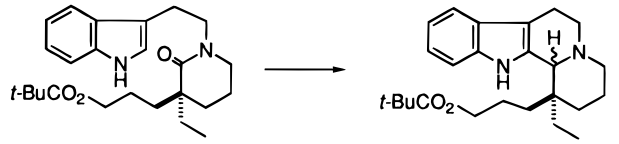
(27) The exact amount of HNa should be used in this reaction, in order to minimize the condensation of the indole nitrogen atom with CS_2.

Scheme 8



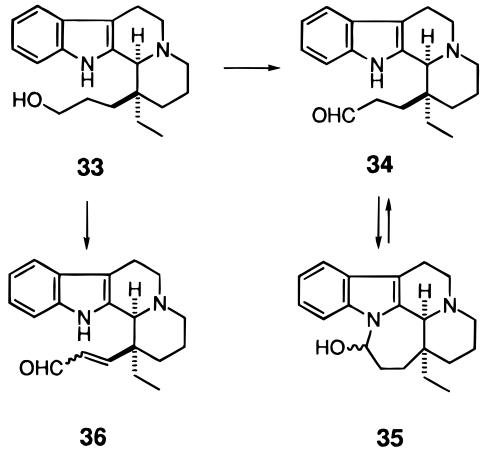
27 **28 a**: R = H; **28 b**: R = $SiPh_2t$-Bu; **29** **30**

Scheme 9



31 **32**, **a**: Hβ, **b**: Hα

Scheme 10



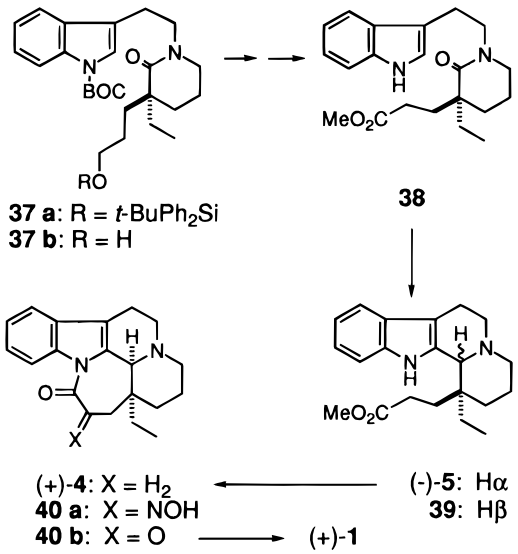
33 **34** **36** **35**

of type **3**: an approach in which compound **30** was subjected to B−N cyclization prior to the restoration of the correct oxidation state of the three-carbon appendage and an alternative one, in which the order of these two reactions was inverted. During the course of the first approach, it became apparent that the *tert*-butyldiphenylsilyl protecting group of **30** was too labile under the B−N cyclization conditions. The related transformation was therefore effected on the more robust pivaloate **31**, prepared from **30** ((i) *n*-Bu_4NF, THF, 2 h at 20 °C; (ii) *t*-$BuCO_2H$, DCC, catalytic DMAP, CH_2Cl_2, 24 h at 20 °C, 65%). When exposed to the B−N cyclization conditions ((i) $POCl_3$ at reflux, 6 h; (ii) anion exchange with $LiClO_4$; (iii) 1 bar of H_2, Pd−C, DMF), **31** gave a 3:1 epimeric mixture of tetracyclic derivatives **32** (45% yield), separated by flash chromatography over silica gel. To our delight, the major isomer **32b** exhibited the "natural" *cis* relationship between the ethyl appendage at C-20 and the H group at C-21, as evidenced through its correlation with authentic (+)-homoeburnamonine **4** (*vide infra*) (Scheme 9).

With the requisite tetracycle **32b** in hand, we next examined its conversion into our goal vincamine **1**. Removal of the pivaloyl group of **32b** (DIBAH, CH_2Cl_2, 2 h at −78 °C, 89%) furnished alcohol **33**[17n] of 90% enantiomeric purity, which proved to be identical in all respects with an authentic sample prepared by reduction of (+)-homoeburnamonine **4**, a correlation that definitely established the relative and absolute configuration of **33**. In other respects, since the transformation of **33** into homoeburnamonine **4** has been accomplished, its present preparation constitutes a formal synthesis of (+)-**4**, and therefore of (+)-vincamine (**1**). However, considering the modest yields reported for conversion **33**→ **4** (20−26%),[17n] we decided to reexamine this transformation. After extensive experimentation, we discovered that DMSO/SO_3−pyridine oxidation of **33** (Et_3N, 30 min at 20 °C)[14b] furnished with a 60% yield aldehyde **34**, in equilibrium with epimeric carbinolamines **35**.[17n] In view of the fact that compounds **34**/**35** have been efficiently oxidized into homoeburnamonine **4** by using pyridinium dichromate,[11h] this new access to these molecules constitutes a significant improvement for transforming **33** into **4**. Incidentally, an unexpected result was obtained in the Dess−Martin periodinane oxidation of alcohol **33** (CH_2Cl_2, 2 h at 20 °C): α,β-unsaturated aldehyde **36** (4:1 mixture of *E*/*Z* stereomers) was the only compound isolated, although with a modest yield (32%) (Scheme 10).

The alternative approach for converting **30** into vincamine **1** first involved the restoration of the propanoate appendage. Preliminary experiments having established that a "free" indole nucleus was not stable to the conditions required for the direct oxidation of a primary alcohol group into a carboxylic function (Jones reagent or pyridinium dichromate), the indole nitrogen atom of compound **30** was first protected as *tert*-butoxycarbonyl (BOC) derivative **37a** [NaH, $(t\text{-BuOCO})_2O$, THF, 3 h at 20 °C, 69%]. Selective deprotection of the *tert*-butyldiphenylsilyl group then gave primary alcohol **37b** (*n*-Bu_4NF, THF, 2 h at 20 °C, 77%), which was transformed into ester **38** ((i) pyridinium dichromate, DMF, 12 h at 20 °C; (ii) CH_2N_2, Et_2O; (iii) HCO_2H, 12 h at 20 °C, 46%). B−N cyclization of **38** next afforded the iminium perchlorate salt [13g] ((i) $POCl_3$ at reflux, 3 h; (ii) anion exchange with aqueous $LiClO_4$), which, upon catalytic hydrogenation (1 bar of H_2, 10% Pd−C, DMF), furnished with a 52% combined yield the cornerstone derivative (−)-**5**,[13g,h,14a] of 91% enantiomeric purity, along with its epimer **39**, in a ratio of 6:1, respectively, which were easily separated by chromatography over alumina. Compound **5** was then enantiomerically enriched to *ca*. 100% ee through the recrystallization of its (+)-dibenzoyl-D-tartarate salt derivative.[13g] Physical and spectroscopic data of upgraded **5** proved to be identical in all respects with those reported in the literature. Moreover, base-induced cyclization of **5** (NaHMDS, THF−toluene, 2 h at 20 °C, 70%)[14a] gave enantiomerically pure (+)-homoeburnamonine **4**, indistinguishable in all respects from an authentic sample. Finally, compound **4** has been transformed by using Oppolzer's protocol (NaHMDS, *t*-BuONO, toluene, 1 h at 50 °C, 65%)[14a] into a mixture of *syn*/*anti* oximes **40a**, which were next converted through the α-keto lactam intermediate **40b**, according to the Szantay procedure ((i) AcOH, *p*-TsOH, paraformaldehyde, 100 °C, 5 h; (ii) MeOH, *t*-BuOK, 2 h at 20 °C, 40% overall yield),[13g] into our goal (+)-vincamine (**1**). Our synthetic sample of (+)-**1** also proved to be identical in all respects with the natural material (Scheme 11).

Scheme 11



Epilog and Conclusion

Although the present enantioselective synthesis of (+)-**1** realizes our original objective, it nevertheless suffers from a vexing drawback, namely a poor overall yield (0.16%), reflecting a lenghty experimental endeavor (23 chemical steps from commercially available tryptamine). This was essentially due to the transient change of oxidation state of the ester group of adduct **6** (reduction, then reoxidation of the resulting alcohol into the requisite carboxyl function), dictated by its interference with the subsequent steps devoted to the removal of the keto group. With a view to simplify the above synthetic scheme, we recently sought an alternative route for the direct removal of the keto group of **6**, but preserving the oxidation state of the ester function. The W−K reduction of **6**, a methodology that was *a priori* postponed, considering the disappointing result obtained in the related reduction of adduct **14** (*vide supra*), was thus examined. To our delight, W−K reduction of keto acid **27**, derived from **6**, ((i) hydrazine hydrate, diethylene glycol, 30 min at 160 °C; (ii) KOH, 4 h at 220 °C; (iii) acidification with 12 *N* HCl; (iv) CH_2N_2) furnished the desired keto ester **38** with a satisfactory yield (55%). *Thus, this alternative constitutes a remarkable improvement of our synthetic scheme, since the removal of the keto group of adduct* ***6****, which was originally accomplished in 11 steps with a 5% yield, now proceeded in only three steps, with a 37% yield.*

A concise, direct approach for the total enantioselective synthesis of (+)-vincamine (**1**) has thus been developed. The key tactical element was the asymmetric Michael addition of chiral enamino lactam **12** to methyl acrylate to create stereoselectively the crucial quaternary carbon center at C-20. Thus, according to the strategy that was ultimately adopted, involving the W−K reduction of the keto group of adduct **6**, (+)-vincamine (**1**) has been synthesized by a linear sequence of 15 chemical operations, with an overall yield of 1.2% (mean yield per step: 74%), from commercially available tryptamine. In this respect, this approach constitutes an efficient enantioselective synthesis of (+)-**1**. Further extensions of the present strategy are currently under investigation in our laboratory.

Experimental Section

General Methods. Melting points were recorded on a capillary tube melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as neat films between NaCl plates or KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise stated. Recognition of methyl, methylene, methine, and quaternary carbon nuclei in ^{13}C NMR spectra rests on the *J*-modulated spin-echo sequence or 2D-HMQC spectroscopy. Mass spectra analyses were recorded by electron impact at 70 eV. Optical rotations were measured at 589 nm in a 1 dm cell at specified temperature. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). All liquid chromatography separations were performed using Merck silica gel 60 (230−400 mesh ASTM). Diethyl ether and tetrahydrofuran (THF) were distilled from Na−benzophenone ketyl. Methanol was dried over magnesium and distilled. Benzene and CH_2Cl_2 were distilled from calcium hydride, under a nitrogen atmosphere. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware that was flame-dried under a positive pressure of nitrogen. Organic layers were dried over anhydrous $MgSO_4$. Chemicals obtained from commercial suppliers were used without further purification. Elemental analyses were obtained from the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France.

3-[[2-(1*H*-Indol-3-yl)ethyl]amino]propanoic Acid Ethyl Ester (8). To a stirred solution of tryptamine (10 g, 62.5 mmol) in THF (20 mL) was added dropwise at 20 °C ethyl acrylate (6.25 g, 62.5 mmol). After being stirred for 12 h, the reaction mixture was concentrated under reduced pressure, and the residual oil was directly chromatographed on silica gel (CH_2Cl_2−MeOH, 9:1) to give adduct **8** (13.5 g, 83%) as a yellow oil: IR (neat) 3428, 1729, 1623 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.20 (t, J = 7.1 Hz, 3 H), 1.56 (broad s, 1H), 2.50 (t, J = 6.6 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H), 2.97 (s, 4H), 4.08 (q, J = 7.1 Hz, 2H), 7.01 (d, J = 2.3 Hz, 1H), 7.07−7.23 (m, 2H), 7.31 (d, J = 6.4 Hz, 1H), 7.62 (d, J = 6.4 Hz, 1H), 8.30 (broad s, 1H); ^{13}C NMR (50 MHz) δ 14.0 (CH_3), 25.4 (CH_2), 34.4 (CH_2), 44.7 (CH_2), 49.5 (CH_2), 60.3 (CH_2), 111.0 (CH), 113.2 (C), 118.6 (CH), 119.0 (CH), 121.8 (CH), 122.0 (CH), 127.2 (C), 136.4 (C), 172.5 (C); MS *m*/*e* (rel intensity) 261 [(M + 1)$^{\bullet+}$, 3], 260 (M$^{\bullet+}$, 3), 173 (9), 144, (16), 130 (100).

2-[[[3-(Ethoxycarbonyl)propyl][2-(1*H*-indol-3-yl)ethyl]amino]carbonyl]butanoic Acid Ethyl Ester (9). To a mixture of amino ester **8** (12 g, 46.1 mmol), ethylmalonic acid monoethyl ester (8.11 g, 50.7 mmol), and 1,4-bis(methylamino)pyridine (0.61 g, 5 mmol) in CH_2Cl_2 (100 mL) was added 1,3-dicyclohexylcarbodiimide (10.5 g, 51 mmol). The reaction mixture was stirred at 20 °C for 18 h, and then the solid was filtered off and washed with three 20 mL portions of CH_2Cl_2. The combined fitrates were evaporated, and the residue was chromatographed on silica gel (ethyl acetate−hexane, 1:1) to yield amido ester **9** as an oil (15.4 g, 83%): IR (neat) 3400, 3350, 1731, 1640 cm^{-1}; ^{1}H NMR (200 MHz) (due to amide resonance most signals are splitted into two sets in a 60:40 ratio) δ 0.69 and 0.98 (2 t, J = 7.4 Hz, 3H), 1.20−1.30 (m, 6H), 1.50−2.20 (m, 2H), 2.50−2.60 (m, 2H), 2.95−3.10 (m, 2H), 3.31 (t, J = 7.2 Hz, 1H), 3.40−3.90 (m, 4H), 3.95−4.20 (m, 4H), 6.99 (d, J = 1.9 Hz, 1H), 7.05−7.20 (m, 2H), 7.36 (t, J = 6.6 Hz, 1H), 7.58 and 7.69 (2 d, J = 7.3 Hz, 1H), 8.59 and 8.76 (2 broad s, 1H); MS *m*/*e* (rel intensity) 402 (M$^{\bullet+}$, 0.35), 357 (1.3), 260 (5), 214 (7), 144 (20), 143 (100), 130 (43).

5-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-4-hydroxy-6-oxo-1,2,5,6-tetrahydro-3-pyridinecarboxylic Acid Ethyl Ester (10). In a two-necked flask equipped with a magnetic stirrer, a dropping funnel, and a reflux condenser was placed sodium hydride (60% in mineral oil, 2.76 g, 69 mmol). The solid was washed with hexane under nitrogen (2 × 15 mL) and covered with THF (15 mL). A solution of amido ester **9** (14.5 g, 36.08 mmol) in THF (50 mL) was added dropwise at 20 °C, and the resulting mixture was stirred for 4 h. After the mixture was cooled to 0 °C, ethanol (20 mL) was cautiously added, and the reaction mixture was poured into water (50 mL), acidified to pH 5−6 with 2 N HCl, and extracted with CH_2Cl_2 (3 × 100

mL). The combined organic layers were dried and concentrated in vacuo. Chromatography (hexane−ethyl acetate, 40:60) gave lactam **10** (10.2 g, 79%) as a white solid: mp 140−142 °C (Et_2O); IR (neat) 3500, 3300, 1679, 1642 cm^{-1}; ^1H NMR (200 MHz) δ 0.86 (t, J = 7.4 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.80−2.20 (m, 2H), 3.08 (t, J = 7.6 Hz, 2H), 3.17 (m, 1H), 3.60−3.90 (m, 2H), 3.91 (dd, J = 15.4, 3.0 Hz, 1H), 4.02 (dd, J = 15.4, 2.5 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 7.04 (d, J = 2.2 Hz, 1H), 7.00−7.20 (m, 2H), 7.36 (dd, J = 7.0, 1.4 Hz, 1H), 7.69 (d, J = 7.0 Hz, 1H), 8.36 (broad s, 1H), 11.93 (s, 1H); ^{13}C NMR (50 MHz) δ 9.8 (CH_3), 14.2 (CH_3), 23.0 (CH_2), 23.9 (CH_2), 45.1 (CH_2), 46.2 (CH), 47.7 (CH_2), 60.9 (CH_2), 93.8 (C), 111.1 (CH), 112.6 (C), 118.7 (CH), 119.3 (CH), 122.0 (2 CH), 127.4 (C), 136.3 (C), 168.2 (C), 168.8 (C), 169.5 (C). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.41; H, 6.74; N, 7.86. Found: C, 67.35; H, 6.83; N, 7.89.

3-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2,4-piperidinedione (7). To a stirred solution of keto ester **10** (4.0 g, 11.2 mmol) in DMF (20 mL) were successively added LiBr (1.07 g, 12.3 mmol) and water (0.40 mL, 22.4 mmol). The reaction mixture was refluxed for 12 h. After cooling, the DMF was removed under reduced pressure (0.1 Torr), and the residue was suspended in water (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated. The crude residue was chromatographed on silica gel (hexane-ethyl acetate, 40:60) and further purified by recrystallization in Et_2O to give pure **7** (2.51 g, 79%) as white crystals: mp 132 °C; IR (KBr) 3320, 1720, 1650 cm^{-1}; ^1H NMR (300 MHz) δ 0.99 (t, J = 7.4 Hz, 3H), 1.85−2.15 (m, 2H), 2.23 (ddd, J = 17.4, 8.7, 5.8 Hz, 1H), 2.37 (dt, J = 17.4, 5.0 Hz, 1H), 3.00−3.10 (m, 2H), 3.21 (dt, J = 13.4, 5.5 Hz, 1H), 3.42 (ddd, J = 13.4, 8.8, 5.1 Hz, 1H), 3.70−3.92 (m, 2H), 7.01 (d, J = 2.2 Hz, 1H), 7.12 (td, J = 7.0, 1.2 Hz, 1H), 7.20 (td, J = 7.0, 1.1 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 8.28 (broad s, 1H); ^{13}C NMR (75 MHz) δ 11.8 (CH_3), 18.9 (CH_2), 23.7 (CH_2), 38.0 (CH_2), 43.5 (CH_2), 48.9 (CH_2), 58.7 (CH), 111.3 (CH), 112.7 (C), 118.5 (CH), 119.4 (CH), 122.1 (2 CH), 127.2 (C), 136.3 (C), 168.2 (C), 205.5 (C); MS *m/e* (rel intensity) 284 ($M^{\bullet+}$, 9), 144 (13), 143 (100), 130 (48). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.83; H, 7.04; N, 9.86. Found: C, 71.71; H, 7.07; N, 9.77.

(*S*)-3-Ethyl-4-[(1-phenylethyl)amino]-1-[2-(1*H*-indol-3-yl)ethyl]-5,6-dihydro-2(1*H*)-pyridinone (12). A solution of keto lactam **7** (3.60 g, 12.7 mmol) in toluene (20 mL) was placed in a round-bottom flask equipped with a Dean−Stark trap. (*S*)-(+)-1-Phenylethylamine (1.70 g, 14.0 mmol, $[\alpha]^{22}_D$ +39.1, neat, ee 96%) was added, followed by *p*-toluenesulfonic acid (0.05 g, 0.26 mmol). The reaction mixture was refluxed for 12 h with azeotropic removal of water. After cooling, the reaction mixture was concentrated under reduced pressure to give enamino lactam **12** as a pale yellow solid (4.90 g, quantitative). Recrystallization in EtOAc afforded an analytical sample of **12** as white crystals: mp 158 °C; $[\alpha]^{22}_D$ +16.0 (c = 1.3, $CHCl_3$); IR (KBr) 3425, 3190, 2969, 1614, 1591 cm^{-1}; ^1H NMR (300 MHz) δ 1.11 (t, J = 7.4 Hz, 3H), 1.50 (d, J = 6.7 Hz, 3H), 1.85−2.05 (m, 1H), 2.18−2.35 (m, 1H), 2.30−2.55 (m, 2H), 2.91−3.20 (m, 4H), 3.62 (t, J = 7.1 Hz, 2H), 4.23 (d, J = 6.9 Hz, 1H), 4.41−4.55 (m, 1H), 6.95 (d, J = 2.5 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.25−7.40 (m, 6H), 7.65 (d, J = 7.2 Hz, 1H), 8.40 (broad s, 1H); ^{13}C NMR (50 MHz) δ 12.9 (CH_3), 17.3 (CH_2), 24.0 (CH_2), 24.9 (CH_2), 25.0 (CH_3), 44.6 (CH_2), 47.9 (CH_2), 52.5 (CH), 103.9 (C), 111.7 (CH), 113.6 (C), 118.8 (CH), 119.0 (CH), 121.7 (CH), 122.1 (CH), 125.2 (2 CH), 127.1 (CH), 128.4 (C), 128.8 (2 CH), 136.3 (C), 145.1 (C), 149.5 (C), 167.5 (C); MS *m/e* (rel intensity) 387 ($M^{\bullet+}$, 42), 358 (6), 257 (60), 245 (59), 244 (94), 143 (52), 130 (30), 105 (100). Anal. Calcd for $C_{25}H_{29}N_3O$: C, 77.51; H, 7.49; N, 10.85. Found: C, 77.32; H, 7.68; N, 10.69.

[*R*-(*R,*S**)]-α-(Acetyloxy)-3-ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2,4-dioxo-3-piperidinepropanoic Acid Methyl Ester (14).** A mixture of enaminolactam **12** (1.36 g, 3.51 mmol), freshly distilled methyl 2-acetoxyacrylate **13** (1.01 g, 7.0 mmol), and hydroquinone (20 mg) in THF (10 mL) was stirred at 60 °C for 24 h. THF (20 mL) was added, followed by 20% aqueous acetic acid (10 mL). The mixture was stirred for 24 h at 40 °C. The solvent was removed under reduced pressure, and 1 N HCl (5 mL) was added to the residual oil. The mixture was extracted with CH_2Cl_2 (5 × 20 mL), and the collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (cyclohexane−ethyl acetate, 4:1) afforded keto ester **21** as a yellow gum (0.99 g, 66%): $[\alpha]^{22}_D$ −11.9 (c = 1.7; EtOH); IR (neat) 3420, 1747, 1710, 1635 cm^{-1}; ^1H NMR (400 MHz) δ 0.78 (t, J = 7.5 Hz, 3H), 1.81 (q, J = 7.5 Hz, 2H), 2.01(s, 3H), 2.37 (dd, J = 13.9, 8.9 Hz, 1H), 2.46−2.55 (m, 3H), 3.09 (t, J = 7.1 Hz, 2H), 3.28 (dt, J = 12.9, 6.2 Hz, 1H), 3.38 (ddd, J = 12.9, 7.8, 5.7 Hz, 1H), 3.71(s, 3H), 3.75 (dt, J = 13.3, 6.9 Hz, 1H), 3.93 (dt, J = 13.3, 7.1 Hz, 1H), 4.92 (dd, J = 13.9, 8.8 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 7.13 (td, J = 7.5, 1.1 Hz, 1H), 7.20 (td, J = 7.5, 1.2 Hz, 1H), 7.36 (d, J = 7.4 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 8.10 (broad s, 1H); ^{13}C NMR (100 MHz) δ 9.2 (CH_3), 20.6 (CH_3), 23.6 (CH_2), 32.6 (CH_2), 36.1 (CH_2), 38.9 (CH_2), 42.6 (CH_2), 48.7 (CH_2), 52.4 (CH_3), 58.5 (C), 70.2 (CH), 111.3 (CH), 112.6 (C), 118.6 (CH), 119.5 (CH), 122.2(CH), 122.3 (CH), 127.2 (C), 136.3 (C), 169.9 (C), 170.0 (C), 170.1 (C), 207.7 (C). No satisfactory microanalytical data could be obtained for that uncrystalline material.

[3*S*-(3*β*,4aα,8a*β*)]-3-Acetoxy-4a-ethyl-6-[2-(1*H*-indol-3-yl)ethyl]octahydro-2,5-pyrano[3,2-*c*]pyridinedione (20a). To a solution of keto lactam **14** (3.50 g, 8.18 mmol) in THF (70 mL) was added portionwise lithium tri-*tert*-butoxyaluminohydride (4.16 g, 16.4 mmol). After the solution was stirred for 48 h at 20 °C, 1 N HCl was added (70 mL), and the reaction mixture was extracted with ethyl acetate (5 × 30 mL). The collected organic phases were washed with brine, dried, and concentrated in vacuo to leave crude epimeric alcohols **19** (2.99 g, 85% yield) as a yellow viscous oil. The above mixture of alcohols was dissolved in benzene (30 mL) and placed in a round-bottom flask equipped with a Dean-Stark trap filled with 3 Å molecular sieves. Amberlyst R15 (2 g) was added, and the reaction mixture was refluxed for 12 h. After cooling, the reaction mixture was filtered, concentrated under reduced pressure, and chromatographed on silica gel. Elution with hexane−ethyl acetate (20:80) gave the less polar lactone **20a** (1.49 g, 54%); further elution afforded lactone **20b** (0.50 g, 18%). Only the major isomer **20a** is described: oil; IR (neat) 3426, 1747, 1640 cm^{-1}; ^1H NMR (400 MHz) δ 1.03 (t, J = 7.6 Hz, 3H), 1.50 (q, J = 7.6 Hz, 2 H), 1.92 (dd, J = 13.3, 11.7 Hz, 1H), 2.03 (m, 2H), 2.18 (s, 3H), 2.85 (dd, J = 13.3, 7.6 Hz, 1H), 2.95−3.10 (m, 2H), 3.15−3.30 (m, 2H), 3.44−3.50 (m, 1H), 3.75−3.82 (m, 1H), 4.57 (dd, J = 12.3, 5.1 Hz, 1H), 5.05 (dd, J = 11.6, 7.6 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 7.13 (td, J = 7.4, 1.1 Hz, 1H), 7.20 (td, J = 7.5, 1.0 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 8.05 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.2 (CH_3), 20.6 (CH_3), 21.4 (CH_2), 22.7 (2 CH_2), 31.7 (CH_2), 44.4 (2 CH_2), 47.9 (C), 67.0 (CH), 79.1 (CH), 111.3 (CH), 112.6 (C), 118.5 (CH), 119.4 (CH), 122.0 (CH), 122.1 (CH), 127.3 (C), 136.3 (C), 167.3 (C), 169.6 (C), 169.9 (C).

[2*S*-(2*β*,4a*β*,14b*β*,14cα)]-2-Hydroxy-14c-ethyl-2,3,4a,5,6,8,9,14,14b,14c-deca-hydro-3-1*H*-indolo[2,3-*a*]pyrano[2,3-*h*]quinolizinone (21). To a solution of lactam **20a** (100 mg, 0.25 mmol) in acetonitrile (7 mL) was added freshly distilled $POCl_3$ (1.10 g, 7.2 mmol), and the reaction mixture was heated at reflux for 14 h. After evaporation to dryness, the amorphous brown solid obtained was dissolved in ethyl acetate (10 mL) and DMF (1 mL). Pd/C (10%, 50 mg) was added, and the resulting suspension was stirred under hydrogen atmosphere (1 bar) for 12 h. The reaction mixture was filtered through Celite and the solid residue washed with ethyl acetate. The filtrate was evaporated, and the crude residue was treated with a 30% ammonia solution. The mixture was extracted with CH_2Cl_2, and the collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (cyclohexane−ethyl acetate, 1:1) gave indoloquinolizidine **21** (17 mg, 20%) as an amorphous solid: IR (neat) 3437, 2753, 1744 cm^{-1}; ^1H NMR (400 MHz) δ 0.44 (t, J = 7.6 Hz, 3H), 1.30 (m, 1H), 1.89 (m, 1H), 1.95 (dd, J = 11.6, 11.3 Hz, 1H), 2.10 (qd, J = 12.4, 5.0 Hz, 1H), 2.47 (m, 1H), 2.59 (m, 2H), 2.67 (ddd, J = 14.9, 1.0, 0.5 Hz, 1H), 2.90 (m, 1H), 3.02 (ddd, J = 10.4, 4.8, 1.4 Hz, 1H), 3.10 (dd, J = 11.6, 7.4 Hz, 1H), 3.15 (m, 1H), 3.19 (s, 1H), 3.25 (broad s, 1H), 4.23 (dd, J = 12.4, 4.7 Hz, 1H), 4.38 (dd, J = 11.3, 7.4

Hz, 1H), 7.11−7.22 (m, 2H), 7.34 (d, J = 7.3 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.78 (broad s, 1H).

3,3-Diethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2,4-piperidione (15). To a solution of keto lactam **7** (2.60 g, 9.15 mmol) in anhydrous CH_3CN (30 mL) were added dropwise at 0 °C benzyltrimethylammonium hydroxide (Triton B, 40% methanol solution, 9 mL, 20 mmol) and iodoethane (3.12 g, 20 mmol). The reaction mixture was stirred at 20 °C. After 2 days, additional portions of Triton B (2.25 mL, 5 mmol) and ethyl iodide (0.78 g, 5.0 mmol) were added, and the stirring was continued for 2 days. The reaction mixture was concentrated in vacuo, and the residue was taken up into CH_2Cl_2 (50 mL) and washed with 1 N HCl, sodium bicarbonate, and finally brine. The collected organic phases were dried and concentrated in vacuo. Chromatography on silica gel (cyclohexane−ethyl acetate, 1:1) afforded lactam **15** as a viscous oil (1.77 g, 62%): IR (neat) 3309, 1723, 1629 cm^{-1}; ^1H NMR (200 MHz) δ 0.74 (t, J = 7.4 Hz, 6H), 1.84 (q, J = 7.4 Hz, 4H), 2.46 (t, J = 6.4 Hz, 2H), 3.09 (t, J = 7.2 Hz, 2H), 3.32 (t, J = 6.4 Hz, 2H), 3.85 (t, J = 7.3 Hz, 2H), 7.04 (d, J = 2.3 Hz, 1H), 7.00−7.20 (m, 2H), 7.35 (d, J = 7.4 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR (50 MHz) δ 9.7 (2 CH_3), 23.6 (CH_2), 30.7 (2 CH_2), 40.0 (CH_2), 42.7 (CH_2), 49.0 (CH_2), 62.3 (C), 111.4 (CH), 112.2 (C), 118.5 (CH), 119.2 (CH), 121.9 (CH), 122.1 (CH), 127.1 (C), 136.4 (C), 171.8 (C), 209.9 (C). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 72.89; H, 7.76; N, 8.85.

(±)-3,3-Diethyl-1-[2-(1*H*-indol-3-yl)ethyl]-4-hydroxy-2-piperidinone (16a). To a solution of keto lactam **15** (1.76 g, 5.6 mmol) in ethanol (20 mL) was added portionwise 0.38 g (10 mmol) of sodium borohydride. The mixture was stirred at 20 °C for 1 h, poured into saturated aqueous ammonium chloride (20 mL), and extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were driedm and the solvents were removed under reduced pressure. The residue was chromatographed on silica gel (hexane−ethyl acetate, 1:4) to afford alcohol **16a** (1.59 g, 90%), which crystallized on standing: mp 65 °C (Et_2O); IR (neat) 3420−3250, 1610 cm^{-1}; ^1H NMR (200 MHz) δ 0.85 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H), 1.45 (m, 1H), 1.55−2.00 (m, 5H), 2.60 (broad s, 1H), 2.98 (t, J = 7.4 Hz, 2H), 3.07−3.40 (m, 2H), 3.42−3.70 (m, 2H), 3.92 (t, J = 5.8 Hz, 1H), 6.99 (d, J = 2.3 Hz, 1H), 7.05−7.20 (m, 2H), 7.33 (d, J = 7.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 8.70 (s, 1H); ^{13}C NMR (50 MHz) δ 8.9 (CH_3), 9.0 (CH_3), 23.0 (CH_2), 24.3 (CH_2), 26.5 (CH_2), 27.3 (CH_2), 44.0 (CH_2), 48.4 (CH_2), 49.7 (C), 69.0 (CH), 111.2 (CH), 113.1 (C), 118.7 (CH), 119.2 (CH), 121.9 (CH), 122.0 (CH), 127.4 (C), 136.3 (C), 172.9 (C). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.90. Found: C, 72.19; H, 8.36; N, 8.61.

3,3-Diethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2-piperidinone (17). In a 50 mL round-bottom flask was placed sodium hydride (80% in mineral oil, 0.50 g, 16.6 mmol). The solid was washed with hexane under nitrogen (2 × 5 mL) and covered with THF (7 mL). A solution of alcohol **16a** (1.0 g, 3.18 mmol) and imidazole (0. 05 g, 0.7 mmol) in THF (4 mL) was added dropwise at 20 °C. After the solution was stirred for 30 min at 20 °C, carbon disulfide (1.25 mL, 20.9 mmol) was added, the reaction mixture was stirred for 30 min, methyl iodide (0.76 mL, 12 mmol) was then added, and the mixture was stirred for a further 15 min period. The reaction mixture was poured into 1 N HCl, (10 mL), extracted with CH_2Cl_2 (3 × 30 mL), dried, and concentrated in vacuo. Chromatography on silica gel (hexane−ethyl acetate, 70:30) gave xanthate **16b** (0.62 g, 50%) as a pale yellow oil: IR (neat) 3426, 1626, 1226, 1057 (−OCS_2Me) cm^{-1}. To a solution of the above xanthate **16b** (0.62 g, 1.6 mmol) and AIBN (10 mg) in degassed toluene (15 mL), was added dropwise over 30 min tri-*n*-butyltin hydride (1.40 g, 4.8 mmol). The reaction mixture was heated at reflux for 4 h. After cooling, the solution was concentrated in vacuo and the residue partitioned between acetonitrile and petroleum ether. The separated acetonitrile layer was distilled, and the crude product was chromatographed on silica gel (cyclohexane−ethyl acetate, 70:30) to give lactam **17** (0.35 g, 73%): IR (neat) 3312, 1612 cm^{-1}; ^1H NMR (200 MHz) δ 0.85 (t, J = 7.4 Hz, 6H), 1.38−1.57 (m, 2H), 1.60−1.87 (m, 6H), 3.01 (t, J = 7.6 Hz, 2H), 3.22 (t, J = 5.7 Hz, 2H), 3.65 (t, J = 7.6 Hz, 2H), 7.03 (d, J = 2.3 Hz, 1H), 7.06−7.22 (m, 2H), 7.35 (dd, J = 7.2, 1.6 Hz, 1H), 7.68 (d, 1H, J = 6.8 Hz), 8.27 (broad s, 1H); MS m/e (rel intensity) 298 ($M^{\bullet+}$, 6), 269 (65), 213 (12), 168 (20), 143 (100); HRMS calcd for $C_{19}H_{26}N_2O$ 298.2045, obsd 298.2054.

(±)-1,1-Diethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (18). A mixture of lactam **17** (286 mg, 0.96 mmol) and freshly distilled $POCl_3$ (4 mL) was heated at reflux for 4 h. After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (15 mL) and treated by a 1 M aqueous solution of $LiClO_4$ (5 mL). After the mixture was stirred for 10 min, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The collected organic phases were washed with an aqueous solution of $LiClO_4$, dried, and concentrated in vacuo. The amorphous solid obtained was dissolved in MeOH (5 mL) and cooled to 0 °C, and sodium borohydride (400 mg, 10.6 mmol) was added portionwise. The reaction mixture was stirred for 12 h and quenched with aqueous sodium sulfate. The mixture was extracted with ethyl acetate (4 × 20 mL), and the combined organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (cyclohexane−ethyl acetate, 60:40) afforded indoloquinolizidine **18** (162 mg, 60%) as a viscous yellow oil: ^1H NMR (400 MHz) δ 0.69 (t, J = 7.7 Hz, 3H), 1.10 (m, 1H), 1.17 (t, J = 7.7 Hz, 3H), 1.40−1.59 (m, 3H), 1.76 (q, J = 7.7 Hz, 2H), 1.86 (m, 1H), 1.98 (dq, J = 14.4, 7.7 Hz, 1H), 2.35 (td, J = 11.9, 2.5 Hz, 1H), 2.59 (td, J = 11.2, 7.5 Hz, 1H), 2.61−2.66 (m, 1H), 2.95−3.10 (m, 3H), 3.34 (s, 1H), 7.08 (td, J = 7.4, 1.0 Hz, 1H), 7.14 (td, J = 7.5, 1.1 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.83 (broad s, 1H); ^{13}C NMR (50 MHz) δ 7.3 (CH_3), 8.0 (CH_3), 21.9 (CH_2), 22.1 (CH_2), 25.5 (CH_2), 29.9 (CH_2), 31.4 (CH_2), 39.4 (C), 54.2 (CH_2), 56.9 (CH_2), 66.5 (CH), 110.5 (CH), 111.4 (C), 117.8 (CH), 119.1 (CH), 121.3 (CH), 126.8 (C), 133.9 (C), 135.8 (C).

(*R*)-3-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2,4-dioxo-3-piperidinepropanoic Acid Methyl Ester (6). A mixture of enamino lactam **12** (4.8 g, 12.4 mmol), methyl acrylate (2.23 mL, 24.8 mmol), and hydroquinone (50 mg) in THF (10 mL) was heated at 60 °C for 2 days. After the mixture was cooled to 20 °C, 20% aqueous acetic acid (20 mL) and THF (50 mL) were added, and the mixture was stirred for 72 h at 40 °C. The solvents were removed under reduced pressure, and 1 N HCl (100 mL) was added to the residual oil. The mixture was extracted with CH_2Cl_2 (5 × 100 mL), and the collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (hexane−ethyl acetate, 4:1) gave keto lactam **6** (3.20 g, 70%) as a pale yellow oil: $[\alpha]^{22}_D$ +12.1 (EtOH, c = 2.5); IR (neat) 3320, 1730, 1635 cm^{-1}; ^1H NMR (200 MHz) δ 0.75 (t, J = 7.4 Hz, 3H), 1.84 (q, J = 7.4 Hz, 2H), 2.08−2.22 (m, 4H), 2.46 (t, J = 6.4 Hz, 2H), 3.08 (t, J = 7.1 Hz, 2H), 3.32 (t, J = 6.4 Hz, 2H), 3.63 (s, 3H), 3.73−3.91 (m, 2H), 7.08 (d, J = 2.3 Hz, 1H), 7.12 (td, J = 7.5, 1.0 Hz, 1H), 7.20 (td, J = 7.5, 1.0 Hz, 1H), 7.36 (dd, J = 7.4, 1.3 Hz, 1H), 7.68 (d, J = 7.4 Hz, 1H), 8.40 (broad s, 1H); ^{13}C NMR (50 MHz) δ 9.3 (CH_3), 23.4 (CH_2), 29.6 (CH_2), 30.1 (CH_2), 30.5 (CH_2), 39.1 (CH_2), 42.6 (CH_2), 48.8 (CH_2), 51.5 (CH_3), 60.5 (C), 111.3 (CH), 112.1 (C), 118.4 (CH), 119.2 (CH), 121.9 (CH), 122.2 (CH), 127.1 (C), 136.2 (C), 170.8 (C), 173.1 (C), 208.7 (C); MS m/e (rel intensity) 370 ($M^{\bullet+}$, 8), 339 (3), 199 (3), 196 (3), 144 (15) 143 (100), 130 (28). Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.91; H, 7.16; N, 7.55.

(*R*)-3-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2-oxo-4-[[(4-methylphenyl)sulfonyl]hydrazono]-3-piperidinepropanoic Acid Methyl Ester (22). A mixture of keto lactam **6** (2.00 g, 5.4 mmol) and (*p*-toluenesulfonyl)hydrazine (2.00 g, 10.8 mmol) in MeOH (10 mL) was heated at reflux. After the mixture was stirred for 2 days, an additional portion of (*p*-toluenesulfonyl)hydrazine (1.00 g, 5.4 mmol) in MeOH (2 mL) was added. The operation was repeated each 48 h during 10 days. The mixture was then concentrated under reduced pressure, and the residue was chromatographed on silica gel (hexane−ethyl acetate, 1:1) to give pure *p*-tosylhydrazone **22** (2.30 g, 80%) as a yellow amorphous solid: IR (neat) 3420, 1730, 1644, 1621 cm^{-1}; ^1H NMR (200 MHz) δ 0.57 (t, J = 7.1 Hz, 3H), 1.75 (q, J = 7.1 Hz, 2H), 1.96−2.08 (m, 4H), 2.21 (t, J = 6.1 Hz, 2H), 2.43 (s, 3H), 3.01 (t, J = 6.8 Hz, 2H), 3.14 (t, J = 5.9

Hz, 2H), 3.62 (s, 3H), 3.63−3.77 (m, 2H), 7.00 (d, J = 2.3 Hz, 1H), 7.04 (td, J = 7.6, 1.2 Hz 1H), 7.16 (td J = 7.5, 1.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.6 Hz, 1H), 7.39 (s, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 8.10 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.9 (CH_3), 21.6 (CH_3), 23.6 (CH_2), 25.3 (CH_2), 29.3 (CH_2), 31.1 (CH_2), 31.5 (CH_2), 43.2 (CH_2), 49.0 (CH_2), 51.5 (CH_3), 54.0 (C), 111.3 (CH), 112.7 (C), 118.6 (CH), 119.4 (CH), 122.1 (CH), 122.4 (CH), 127.3 (C), 128.1 (2 CH), 129.5 (2 CH), 135.0 (C), 136.4 (C), 144.3 (C), 157.9 (C), 170.9 (C), 173.7 (C); Anal. Calcd for $C_{28}H_{34}N_4O_5S$: C, 62.45; H, 6.31; N, 10.40. Found: C, 62.28; H, 6.50; N, 10.31.

(*R*)-3-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2-oxo-1,2,3,6-tetrahydro-3-pyridinepropanoic Acid Methyl Ester (23). To a suspension of LiH (70 mg, 8.80 mmol) in toluene (5 mL) was added *p*-tosylhydrazone **22** (1.0 g, 1.86 mmol). The mixture was heated at reflux for 48 h. After being cooled to 20 °C, the mixture was poured into crushed ice and extracted with CH_2Cl_2. The collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (hexane−ethyl acetate, 1:1) gave unsaturated lactam **23** (362 mg, 55%) as a pale yellow oil: IR (neat) 3410, 1731, 1619, 1494 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.80 (t, J = 7.4 Hz, 3H), 1.22−1.35 (m, 1H), 1.58−1.68 (m, 2H),1.95−2.07 (m, 1H), 2.15−2.32 (m, 3H), 3.06 (t, J = 7.8 Hz, 2H), 3.63 (s, 3H), 3.74 (dd J = 7.8, 7.3 Hz, 2H), 3.85 (s, 2H), 5.35 (dt, J = 10.2, 2.0 Hz, 1H), 5.79 (dt, J = 10.2, 3.0 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 7.12 (td, J = 7.6, 1.0 Hz, 1H), 7.19 (td, J = 7.8, 1.2 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 8.18 (broad s, 1H); ^{13}C NMR (75 MHz) δ 9.4 (CH_3), 23.0 (CH_2), 30.2 (CH_2), 33.3 (CH_2), 34.9 (CH_2), 47.2 (C), 47.7 (CH_2), 49.3 (CH_2), 51.5 (CH_3), 111.1 (CH), 113.0 (C), 118.8 (CH), 119.4 (CH), 122.0 (CH), 122.1 (CH), 122.2 (CH), 127.4 (C), 130.3 (CH), 136.3 (C), 171.1 (C), 173.8 (C).

[4a*R*-(4aα,8a*β*)]-4a-Ethyl-6-[2-(1*H*-indol-3-yl)ethyl]octahydro-2,5-pyrano[3,2-*c*]pyridinedione (25). To a solution of keto lactam **6** (1.10 g, 2.97 mmol) in THF (10 mL) was added portionwise lithium tri-*tert*-butoxyaluminohydride (1.51 g, 5.95 mmol). After the solution was stirred for 4 h at 20 °C, 1 N HCl was added (20 mL), and the reaction mixture was extracted with ethyl acetate (5 × 40 mL). The collected organic phases were washed with brine, dried, and concentrated in vacuo to leave crude epimeric alcohols **24a**,**b** (820 mg, 74% yield) as a colorless viscous oil. The pure α-isomer **24a** (610 mg, 1.64 mmol) obtained by chromatography on silica gel (ethyl acetate−MeOH 98:2) was dissolved in benzene (10 mL), Amberlyst R15 (0.1 g) was added, and the reaction mixture was refluxed for 12 h with azeotropic removal of water. After cooling, the mixture was filtered, concentrated under reduced pressure, and chromatographed on silica gel. Elution with ethyl acetate gave **25** (435 mg, 58%) as white crystals: mp 210 °C (ethyl acetate); IR (neat) 3440, 1741, 1640 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.95 (t, J = 7.5 Hz, 3H), 1.58 (q, J = 7.5 Hz, 2 H), 1.90 (dt, J = 14.1, 8.8 Hz, 1H), 2.00−2.20 (m, 2H), 2.25−2.50 (m, 1H), 2.50−2.80 (m, 2H), 2.90−3.10 (m, 2 H), 3.20−3.40 (m, 1H), 3.45 (dt, J = 6.4, 6.9 Hz, 1H), 3.80 (dt, J = 6.4, 6.9 Hz, 1H), 4.37 (dd, J = 12.0, 5.3 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 7.07−7.20 (m, 2H), 7.35 (d, J = 7.3 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (50 MHz) δ 8.3 (CH_3), 21.6 (CH_2), 22.7 (CH_2), 23.0 (CH_2), 24.7 (CH_2), 27.8 (CH_2), 42.9 (CH_2), 44.3 (CH_2), 47.9 (C), 78.3 (CH), 111.2 (CH), 112.5 (C), 118.4 (CH), 119.2 (CH), 121.9 (2 CH), 127.3 (CH), 136.2 (C), 170.7 (C), 171.3 (C);

[14b*S*-(14b*β*,14cα)]-14c-Ethyl-2,3,4a,5,6,8,9,14,14b,14c-decahydro-3−1*H*-indolo[2,3-*a*]pyrano[2,3-*h*]quinolizinone (26a). A mixture of lactam **25** (370 mg, 1.09 mmol) and freshly distilled $POCl_3$ (9 mL) was heated at reflux for 6 h. After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (15 mL) and treated by a 1 M aqueous solution of $LiClO_4$ (5 mL). After the solution was stirred for 10 min, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The collected organic phases were washed with an aqueous solution of $LiClO_4$, dried, and concentrated in vacuo. The amorphous solid obtained was taken up in DMF (3 mL), 10% Pd/C (200 mg) was added, and the resulting suspension was stirred under hydrogen atmosphere (1 bar) for 4 h. The reaction mixture was filtered through Celite and the solid residue washed with ethyl acetate. The filtrate was evaporated, and the crude residue was treated by a 30% ammonia solution. The mixture was extracted with CH_2Cl_2, and the collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (cyclohexane−ethyl acetate, 1:1) afforded indoloquinolizidine **26b** (35 mg, 10%); further elution gave indoloquinolizidine **26a** (105 mg, 30%). Only the major isomer **26a** is described: IR (neat) 3423, 2847, 2813, 1730 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.52 (t, J = 7.6 Hz, 3H), 1.60 (m, 1H), 1.80−2.30 (m, 4 H), 2.40−3.20 (m, 9H) 3.16 (s, 1H), 4.52 (dd J = 12.0, 4.8 Hz, 1H), 7.05−7.20 (m, 2H), 7.31 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.72 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.6 (CH_3), 19.5 (CH_2), 21.9 (CH_2), 27.0 (CH_2), 27.3 (CH_2), 27.4 (CH_2), 40.8 (C), 52.9 (CH_2), 53.9 (CH_2), 67.4 (CH), 84.0 (CH), 110.8 (CH), 111.9 (C), 118.0 (CH), 119.6 (CH), 121.9 (CH), 126.7 (C), 132.2 (C), 135.9 (C), 171.2 (C).

(*R*)-3-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2,4-dioxo-3-piperidinepropanoic Acid (27). To a solution of keto lactam **6** (5.45 g, 20 mmol) in methanol (100 mL) was added dropwise at 0 °C 680 mg (20 mmol) of lithium hydroxide in 30% hydrogen peroxide (20 mL). After being stirring for 5 h at 20 °C, the reaction mixture was cooled to 0 °C and acidified to pH 3 with 1 N HCl. The aqueous solution was extracted with ethyl acetate (3 × 100 mL). The combined extracts were cautiously washed with saturated aqueous sodium bisulfite, dried, and evaporated in vacuo. The residue was chromatographed on silica gel (CH_2Cl_2-MeOH, 9:1) to give acid **27** as a viscous yellow oil (4.10 g, 76%): IR (neat) 3500−2500, 1725, 1633 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.71 (t, J = 7.3 Hz, 3H), 1.80 (q, J = 7.3 Hz, 2H), 2.09 (broad s, 4H), 2.38 (t, J = 6.2 Hz, 2H), 3.04 (t, J = 6.7 Hz, 2H), 3.15−3.30 (m, 2H), 3.70 (dt, J = 13.3, 6.8 Hz, 1H), 3.90 (dt, J = 13.3, 6.8 Hz, 1H), 7.00 (s, 1H), 7.05−7.21 (m, 2H), 7.33 (d, J = 7.3 Hz, 1H), 7.61 (d, J = 7.1 Hz, 1H), 8.63 (broad s, 1H); ^{13}C NMR (50 MHz) δ 9.3 (CH_3), 23.3 (CH_2), 29.8 (CH_2), 30.1 (CH_2), 30.4 (CH_2), 39.0 (CH_2), 42.6 (CH_2), 48.8 (CH_2), 60.6 (C), 111.4 (CH), 112.0 (C), 118.3 (CH), 119.3 (CH), 121.9 (CH), 122.5 (CH), 127.1 (C), 136.3 (C), 171.2 (C), 176.5 (C), 208.7 (C). No satisfactory microanalytical data could be obtained for that uncrystalline material.

[3*R*-(3*R,4*R**)]- and [3*R*-(3*R**,4*S**)]-3-Ethyl-1-[[2-(1*H*-indol-3-yl)ethyl]-3-[[3-(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-4-hydroxy-2-piperidinones (28b).** To a solution of acid **27** (2.20 g, 6.18 mmol) in THF (20 mL) were added triethylamine (1.3 mL, 9.27 mmol) and isobutyl chloroformate (1.27 g, 9.27 mmol). After being stirred for 30 min at 0 °C, the solid was filtered off and washed with three 5 mL portions of THF. The combined fitrates were cooled to 0 °C, and $NaBH_4$ (4.00 g, 0.1 mol) was added portionwise, followed with 10 mL of methanol. After the mixture was stirred for 24 h at 20 °C, 3 N HCl (100 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (4 × 100 mL). The collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (CH_2Cl_2−MeOH, 9:1) gave diols **28a** (1.60 g, 75%) as a 3:1 mixture of diastereomers: HRMS calcd for $C_{20}H_{28}N_2O_3$ 344.209 99, found 344.209 69. The above mixture of diols (1.60 g, 4.65 mmol) was dissolved into DMF (6 mL), and imidazole (1.60 g, 4.64 mmol) was added, followed by *tert*-butyldiphenylsilyl chloride (1.40 mL, 4.80 mmol). The reaction mixture was stirred at 20 °C for 12 h, and then water was added and the mixture extracted with ethyl acetate (3 × 20 mL). The collected organic phases were dried and concentrated in vacuo. Chromatography on silica gel (hexane−ethyl acetate, 1:1) afforded silyl ethers **28b** (1.84 g, 68%, 3:1 mixture of diastereomers) as a pale yellow oil: IR (neat) 3435, 1618 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.90 (t, J = 7.5 Hz, 3H), 1.06 (s, 9H), 1.30−2.10 (m, 8H), 2.98 (t, J = 7.4 Hz, 2H), 3.12 (m, 1H), 3.32 (m, 1H), 3.50 (m, 1H), 3.65 (t, J = 5.8 Hz, 2H), 3.70 (m, 1H), 3.89 (dd, J = 7.0, 3.8 Hz, 1H), 6.95 (d, J = 2.3 Hz, 1H), 7.10−7.20 (m, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.35−7.45 (m, 7H), 7.60−7.75 (m, 5H), 8.13 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.6 (CH_3), 19.2 (C), 22.9 (CH_2), 24.1 (CH_2), 26.3 (CH_2), 26.9 (3 CH_3), 27.6 (CH_2), 29.9 (CH_2), 30.7 (CH_2), 43.9 (CH_2), 48.2 (CH_2), 49.0 (C), 64.4 (CH_2), 69.3 (CH), 111.1 (CH), 113.1 (C), 118.7 (CH), 119.2 (CH), 121.9 (CH), 122.1 (CH), 127.5 (C), 127.6 (4 CH), 129.6 (2 CH),

134.0 (2 C), 135.6 (4 CH), 136.3 (C), 172.9 (C); MS *m/e* (rel intensity) 582 ($M^{\bullet+}$, 3), 525 (24), 507 (2), 440 (4), 382 (3), 199 (35), 143 (100); HRMS calcd for $C_{36}H_{46}N_2O_3Si$ 582.327 62, found 582.327 77.

(*S*)-3-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-3-[3-[[1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-2-piperidinone (30). In a 50 mL round-bottom flask was placed sodium hydride (80% in mineral oil, 100 mg, 3.33 mmol). The solid was washed with hexane under nitrogen (2 × 5 mL) and covered with THF (7 mL). A solution of alcohols **28b** (1.30 g, 2.23 mmol) and imidazole (0.05 g, 0.7 mmol) in THF (10 mL) was added dropwise at 20 °C. After the solution was stirred for 30 min at 20 °C, carbon disulfide (0.4 mL, 6.65 mmol) was added, the reaction mixture was stirred for 30 min, iodomethane (0.54 g, 3.80 mmol) was then added, and the mixture was stirred for a further 15 min period. The reaction mixture was poured into 1 N HCl (10 mL), extracted with CH_2Cl_2 (3 × 30 mL), dried, and concentrated in vacuo. Chromatography (hexane−ethyl acetate, 60:40) gave epimeric xanthates **29** (0.75 g, 50%): IR (neat) 3447, 1627, 1217, 1060 (−OCS_2Me) cm^{-1}; MS *m/e* (rel intensity) 672 ($M^{\bullet+}$, 0.15), 657 (0.25), 615 (0.8), 564 (2), 549 (10), 535 (8), 507 (35), 344 (10), 143 (100). To a solution of xanthates **29** (0.75 g, 1.12 mmol) in degassed toluene (15 mL) containing AIBN (10 mg) was added dropwise over 30 min tri-*n*-butyltin hydride (1.62 g, 5.58 mmol). The reaction mixture was heated at reflux for 2 h. After cooling, the solution was concentrated in vacuo and the residue partitioned between acetonitrile and petroleum ether. The acetonitrile layer was evaporated, and the crude product was chromatographed on silica gel (cyclohexane−ethyl acetate, 80:20) to give lactam **30** (0.54 g, 85%) as a colorless oil: IR (neat) 3485, 1635, 1235 cm^{-1}; ^1H NMR (200 MHz) δ 0.86 (t, J = 7.4 Hz, 3H), 1.06 (s, 9H), 1.44−1.88 (m, 10H), 3.01 (t, J = 7.4 Hz, 2H), 3.28 (m, 2H), 3.50−3.80 (m, 4H), 6.95 (d, J = 2.3 Hz, 1H), 7.05−7.25 (m, 2H), 7.30−7.50 (m, 7H), 7.60−7.70 (m, 5H), 8.20 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.7 (CH_3), 19.2 (C), 20.0 (CH_2), 23.2 (CH_2), 26.9 (3 CH_3), 27.6 (CH_2), 29.3 (CH_2), 31.4 (CH_2), 34.8 (CH_2), 44.6 (CH_2), 48.6 (CH_2), 48.9 (C), 64.5 (CH_2), 111.1 (CH), 113.1 (C), 118.7 (CH), 119.1 (CH), 121.8 (CH), 122.1 (CH), 127.6 (C and 4 CH), 129.5 (2 CH), 134.1 (2 C), 135.5 (4 CH), 136.3 (C), 174.5 (C). No satisfactory microanalytical data could be obtained for that uncrystalline material.

(*S*)-2,2-Dimethylpropanoic Acid 3-[3-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2-oxopiperidine-3-yl]propyl Ester (31). To a solution of lactam **30** (3.22 g, 5.7 mmol) in dry THF (6 mL) was added dropwise a 1 M solution of tetra-*n*-butylammonium fluoride in THF (12 mL, 12 mmol). After the mixture was stirred for 4 h, saturated NaCl was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL), dried, and concentrated in vacuo. To the crude residue dissolved in CH_2Cl_2 (20 mL) were successively added pivalic acid (0.70 g, 6.9 mmol), 4-(dimethylamino)pyridine (0.12 g, 1.0 mmol), and 1,3-dicyclohexylcarbodiimide (1.42 g, 6.9 mmol). The reaction mixture was stirred at 20 °C for 24 h, and then the solid was filtered off and washed with three 20 mL portions of CH_2Cl_2. The combined filtrates were evaporated, and the residue was chromatographed on silica gel (ethyl acetate−hexane, 1:1) to yield amido ester **31** (1.52 g, 65% overall yield): $[\alpha]^{22}_D$ +30.9 (c = 0.8, EtOH); IR (neat) 3291, 1728, 1615 cm^{-1}; ^1H NMR (200 MHz) δ 0.86 (t, J = 7.4 Hz, 3H), 1.21 (s, 9H), 1.42−1.82 (m, 10H), 3.02 (t, J = 7.4 Hz, 2H), 3.22 (t, J = 5.6 Hz, 2H), 3.57−3.80 (m, 2H), 4.03 (t, J = 5.6 Hz, 2H), 7.04 (d, J = 2.3 Hz, 1H), 7.07−7.24 (m, 2H), 7.56 (d, J = 7.4 Hz, 1H), 7.68 (d, J = 7.4 Hz, 1H), 8.20 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.6 (CH_3), 20.0 (CH_2), 23.1 (CH_2), 23.8 (CH_2), 27.2 (3 CH_3), 29.4 (CH_2), 31.4 (CH_2), 34.7 (CH_2), 38.7 (C), 44.5 (CH_2), 48.4 (CH_2), 48.7 (C), 64.7 (CH_2), 111.1 (CH), 113.1 (C), 118.7 (CH), 119.2 (CH), 121.8 (CH), 122.1 (CH), 127.5 (C), 136.3 (C), 174.2 (C), 178.0 (C). Anal. Calcd for $C_{25}H_{36}N_2O_3$: C, 72.78; H, 8.79; N, 6.79. Found: C, 72.55; H, 8.68; N, 6.68.

(1*S*,*trans*)-2,2-Dimethylpropanoic Acid 3-[1-Ethyl-1-[1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine]]propyl Ester (32a) and (1*S*,*cis*)-2,2-dimethylpropanoic Acid 3-[1-Ethyl-1-[1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine]]propyl Ester (32b). A mixture of lactam **31** (500 mg, 1.21 mmol) and freshly distilled $POCl_3$ (10 mL) was heated at reflux for 6 h. After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (15 mL) and treated with a 1 M aqueous solution of $LiClO_4$ (5 mL). After the mixture was stirred for 10 min, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The collected organic phases were washed with an aqueous solution of $LiClO_4$, dried, and concentrated in vacuo to give a brown amorphous solid (560 mg, 93%). The crude iminium salt obtained was dissolved in DMF (5 mL), 10% Pd/C (250 mg) was added, and the resulting suspension was stirred under hydrogen atmosphere (1 bar) for 4 h. The reaction mixture was filtered through Celite and the solid residue washed with CH_2Cl_2. The filtrate was evaporated, and the crude residue was treated by a 30% ammonia solution. The mixture was extracted with CH_2Cl_2, and the collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (cyclohexane−ethyl acetate, 60:40) afforded *trans*-indoloquinolizidine **32a** (57 mg, 12% from lactam **31**) as a viscous oil: IR (neat) 3445, 2801, 2753, 1721 cm^{-1}; ^1H NMR (200 MHz) δ 0.67 (t, 3H, J = 7.6 Hz), 1.28 (s, 9H), 1.08−2.10 (m, 12H), 2.35 (ddd, J = 12.2, 12.0, 2.5 Hz, 1H), 2.40−2.80 (m, 2H), 2.85−3.10 (m, 3H), 3.29 (s, 1H), 4.21 (t, J = 6.0 Hz, 2H), 7.07−7.24 (m, 2H), 7.30 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 8.01 (s, 1H), ^{13}C NMR (50 MHz) δ 7.4 (CH_3), 22.1 (CH_2), 22.2 (CH_2), 23.3 (CH_2), 25.5 (CH_2), 27.4 (3 CH_3), 32.4 (CH_2) 35.2 (CH_2), 39.2 (C), 39.3 (CH_2), 54.1 (CH_2), 56.9 (CH_2), 65.2 (CH_2), 67.2 (CH), 110.7 (CH), 111.8 (C), 117.8 (CH), 119.2 (CH), 121.4 (CH), 126.8 (C), 134.0 (C), 135.9 (C), 178.5 (C). Further elution gave *cis*-indoloquinolizidine **32b** (160 mg, 33% from lactam **31**) as an oil: IR (neat) 3515, 3458, 2800, 2751, 1715 1467 cm^{-1}; ^1H NMR (400 MHz) δ 1.08 (s, 9H), 1.17 (t, J = 7.5 Hz, 3H), 1.35−1.65 (m, 4H), 1.65−2.05 (m, 6H), 2.34 (td, J = 12.4, 2.8 Hz, 1H), 2.45−2.80 (m, 2H), 2.80−3.10 (m, 3H), 3.32 (s, 1H), 3.88 (t, J = 6.8 Hz, 2H), 7.07−7.24 (m, 2H), 7.31 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.80 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.0 (CH_3), 21.9 (CH_2), 22.1 (CH_2), 22.5 (CH_2), 27.1 (3 CH_3), 29.0 (CH_2), 31.4 (CH_2), 32.2 (CH_2), 38.7 (C), 39.3 (CH_2), 54.1 (CH_2), 56.9 (CH_2), 65.0 (CH_2), 66.4 (CH), 110.6 (CH), 111.8 (C), 117.9 (CH), 119.2 (CH), 121.4 (CH), 126.8 (C), 133.6 (C), 135.9 (C), 178.5 (C). No satisfactory microanalytical data could be obtained for that uncrystalline material.

(1*S*,*cis*)-1-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propanol (33). To a solution of ester **32b** (110 mg, 0.28 mmol) in CH_2Cl_2 (3 mL) was added dropwise at −78 °C diisobutylaluminum hydride (1.25 mL, 1 M solution in CH_2Cl_2). After 2 h, ethyl acetate (1 mL) was added, followed by addition of saturated aqueous sodium/potassium tartrate solution. After being stirred for 0.5 h, the reaction mixture was filtered, and the aluminum salts collected were washed with several portions of CH_2Cl_2. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2. The combined extracts were dried and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 94/6) to give gave lactam **33** (75 mg, 89%) as a pale yellow oil: $[\alpha]^{22}_D$ −97.2 (EtOH, c = 1.7); IR (neat) 3515, 3380, 2947, 2805 cm^{-1}; ^1H NMR (200 MHz) δ 1.16 (t, J = 7.6 Hz, 3H), 1.20−1.50 (m, 2H), 1.51−1.62 (m, 3H), 1.64−2.0 (m, 6H), 2.36 (td J = 11.4, 2.6 Hz, 1H,), 2.50−2.70 (m, 2H), 2.80−3.10 (m, 3H), 3.60 (s, 1H), 3.46 (td, J = 6.8, 2.4 Hz, 2H), 7.06−7.20 (m, 2H), 7.32 (dd, J = 6.8, 1.8 Hz, 1H), 7.48 (dd, J = 6.6, 1.8 Hz, 1H), 7.94 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.0 (CH_3), 21.7 (CH_2), 22.0 (CH_2), 26.3 (CH_2), 29.2 (CH_2), 31.2 (CH_2), 32.0 (CH_2), 39.3 (C), 54.2 (CH_2), 56.5 (CH_2), 63.6 (CH_2), 66.4 (CH), 110.7 (CH), 111.5 (C), 117.8 (CH), 119.2 (CH), 121.3 (CH), 126.9 (C), 133.6 (C), 135.9 (C).

(*S*)-3-Ethyl-1-[2-[1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl-]ethyl]-3-(3-hydroxypropyl)-2-piperidinone (37b). Sodium hydride (80% in mineral oil, 90 mg, 3.00 mmol) was washed with hexane under nitrogen (2 × 5 mL) and covered with THF (2 mL). Lactam **30** (520 mg, 0.92 mmol) in THF (5 mL) was added dropwise at 20 °C. After the mixture was stirred for 10 min at 20 °C, di-*tert*-butyl dicarbonate (240 mg, 1.10 mmol) in THF (2 mL) was added, and the resulting mixture was stirred for 3 h. The mixture was poured into saturated ammonium chloride and extracted with ethyl acetate

(3 × 10 mL). The collected organic phases were dried and concentrated in vacuo to leave protected indole **37a** (422 mg, 69%) as a viscous oil that was used in the next step without further purification. To a solution of the above lactam **37a** (422 mg, 0.63 mmol) in dry THF (5 mL) was added dropwise at 0 °C a 1 M solution of tetra-*n*-butylammonium fluoride in THF (1.0 mL, 1.00 mmol). After the mixture was stirred for 4 h at 20 °C, saturated NaCl was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried, and concentrated in vacuo. The residue was chromatographed on silica gel (ethyl acetate−cyclohexane, 1:4) to give alcohol **37b** (208 mg, 77%) as a viscous oil: IR (neat) 3449, 1731, 1622 cm^{-1}; ^1H NMR (200 MHz) δ 0.85 (t, J = 7.4 Hz, 3H), 1.64 (s, 9H), 1.40−1.86 (m, 10H), 2.32 (s, 1H), 2.92 (t, J = 7.2 Hz, 2H), 3.21 (m, 2H), 3.45−3.70 (m, 4H), 7.23 (td, J = 7.4, 1.4 Hz, 1H), 7.30 (td, J = 7.4, 1.4 Hz, 1H), 7.40 (s, 1H), 7.62 (d, J = 7.4 Hz, 1H), 8.10 (d, J = 7.4 Hz, 1H); ^{13}C NMR (50 MHz) δ 8.6 (CH_3), 19.9 (CH_2), 22.8 (CH_2), 27.7 (CH_2), 28.2 (3 CH_3), 29.0 (CH_2), 31.8 (CH_2), 34.2 (CH_2), 44.6 (C), 48.1 (CH_2), 49.0 (CH_2), 62.8 (CH_2), 83.4 (C), 115.1 (CH), 117.8 (C), 119.0 (CH), 122.4 (CH), 123.2 (CH), 124.3 (CH), 130.4 (C), 135.4 (C), 149.9 (C), 175.0 (C).

(*S*)-3-Ethyl-1-[2-(1-*H*-indol-3-yl)ethyl]-2-oxo-3-piperidinepropanoic Acid Methyl Ester (38). From the Oxidation of Alcohol 37b. To a stirred solution of pyridinium dichromate (0.75 g, 2 mmol) in DMF (2 mL) was added rapidly at 20 °C alcohol **37b** (170 mg, 0.4 mmol) in DMF (1 mL). After 12 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and filtered through Florisil. The solid was washed twice with 10 mL portions of CH_2Cl_2. The combined filtrates were evaporated to leave a yellow oil that was used directly in the next step. To a cooled solution of the crude acid in a 1:3 mixture of CH_2Cl_2−Et_2O (10 mL), was added an etheral solution of diazomethane until no more nitrogen evolution was observed. The reaction mixture was then concentrated in vacuo. The residue was dissolved in formic acid (5 mL), and the reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was then concentrated in vacuo. The residue was taken into CH_2Cl_2 (20 mL), washed with sodium bicarbonate, dried, and concentrated. Purification by chromatograpy on silica gel (ethyl acetate−hexane, 30:70) gave ester **38** (65 mg, 46% overall yield from **37b**) as a viscous yellow oil: $[\alpha]^{22}_D$ +15.3 (c = 1.9, EtOH); IR (neat) 3283, 1738, 1616 cm^{-1}; ^1H NMR (400 MHz) δ 0.84 (t, J = 7.4 Hz, 3H), 1.45−1.60 (m, 1H), 1.65−1.95 (m, 6H), 2.28−2.40 (m, 2H), 3.00 (t, J = 7.4 Hz 2H), 3.19 (t, J = 5.7 Hz, 2H), 3.57−3.70 (m, 2H), 3.66 (s , 3H), 7.05 (s, 1H), 7.13 (t, J = 6.9 Hz, 1H), 7.16 (t, J = 7.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 8.10 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.4 (CH_3), 19.6 (CH_2), 23.0 (CH_2), 29.5 (CH_2), 30.8 (CH_2), 33.1 (CH_2), 44.0 (CH_2), 48.6 (CH_2), 48.7 (C), 51.4 (CH_3), 111.2 (CH), 112.5 (C), 118.5 (CH), 118.9 (CH), 121.6 (CH), 122.2 (CH), 127.3 (C), 136.3 (C), 173.6 (C), 174.2 (C); MS m/e (rel intensity) 356 ($M^{\bullet+}$, 6), 325 (2), 214 (4), 182 (11), 171 (6), 143 (100); HRMS calcd for $C_{21}H_{28}N_2O_3$ 356.20999, obsd 356.20975. Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.85. Found: C, 70.62; H, 7.99; N, 7.75. **From the Wolff−Kishner Reduction of Keto Acid 27.** To a degassed solution of acid **27** (3.56 g, 10 mmol) in diethylene glycol (75 mL) placed in a round flask equipped with a short distillation path was added hydrazine hydrate (12 mL, 0.38 mmol). The temperature of the reaction mixture was raised to 160 °C over a 1 h period, allowing the distillation of water and hydrazine excess. The reaction mixture was cooled to 20 °C, and crushed molten KOH (13 g, 0.23 mol) was added in one portion. The mixture was then heated to 220−225 °C until no nitrogen evolution could be observed. After 4 h, the reaction mixture was cooled to 150 °C, and the major part of the solvent was removed under reduced pressure (0.05 Torr). The residue was cooled to 0 °C, taken up into water (50 mL), and partially neutralized with concentrated HCl (30 mL). The mixture was extracted twice with CH_2Cl_2 (20 mL). The aqueous phase was then acidified to pH 2 with 3 N HCl. The mixture was extracted with CH_2Cl_2, and the collected organic phases were washed with brine, dried, and concentrated in vacuo. The residue was dissolved in Et_2O (10 mL) and cooled to 0 °C, and an etheral solution of diazomethane was added until no more nitrogen evolution was observed. The reaction mixture was then concentrated in vacuo, and chromatography on silica gel (ethyl acetate−hexane, 70:30) gave pure lactam **38** (1.90 g, 55%).

(1*S*,*trans*)-1-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propanoic Acid Methyl Ester (39) and (1*S*,*cis*)-1-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-propanoic Acid Methyl Ester (5). To a solution of lactam **38** (1.21 g, 3.4 mmol) in acetonitrile (4 mL) was added freshly distilled $POCl_3$ (8 mL). The mixture was heated at 100 °C until no more starting material could be detected by TLC (4 h). After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (15 mL), 1 M aqueous $LiClO_4$ (5 mL) was added, and stirring was continued for 10 min. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The collected organic phases were washed with an aqueous solution of $LiClO_4$, dried, and concentrated in vacuo to give a brown amorphous solid (1.39 g): IR (neat) 3600, 1742, 1630, 1540 cm^{-1}; ^1H NMR (200 MHz) δ 0.68 (t, J = 7.2 Hz, 3H), 1.50−2.60 (m, 10 H), 3.15 (m, 2H), 3.65 (s, 3H), 3.94 (m, 2H), 4.07 (m, 2H), 7.16 (t, J = 7.7 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 10.70 (broad s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 8.0 (CH_3), 17.3 (CH_2), 18.2 (CH_2), 25.7 (CH_2), 28.1 (CH_2), 29.5 (CH_2), 31.5 (CH_2), 43.1 (C), 51.5 (CH_3), 53.7 (CH_2), 54.5 (CH_2), 113.3 (CH), 121.3 (C and CH), 121.5 (CH), 122.8 (C), 124.8 (CH), 128.4 (C), 140.3 (C), 170.2 (C), 172.7 (C). The crude iminium salt obtained above was dissolved in DMF (10 mL). Pd/C (10%, 600 mg) was added, and the resulting suspension was stirred under hydrogen atmosphere (1 bar) for 5 h. The reaction mixture was filtered through Celite and the solid residue washed with CH_2Cl_2. The filtrate was evaporated, and the residue was treated by a 30% ammonia solution. The mixture was extracted with CH_2Cl_2, and the collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (cyclohexane−ethyl acetate, 60:40) afforded a 6:1 mixture of *cis*- and *trans*-indoloquinolizidine **5** and **39** (600 mg, 52%). Separation was achieved by chromatography on alumina (CH_2Cl_2−MeOH, 90:10) to give in the first fractions the *trans* isomer **39** (86 mg) [IR (neat) 3366, 2800, 2755, 1731 cm^{-1}; ^1H NMR (200 MHz) δ 0.69 (t, J = 7.4 Hz, 3H), 1.01−1.60 (m, 9H), 1.70−2.70 (m, 11H), 2.90−3.10 (m, 3H), 3.34 (s, 1H), 3.81 (s, 3H), 7.00−7.20 (m, 2H), 7.37 (d, 1H, J = 7.2 Hz), 7.55 (d, 1H, J = 6.9 Hz), 8.90 (broad s, 1H); ^{13}C NMR (50 MHz) δ 7.2 (CH_3), 21.9 (2 CH_2), 25.3 (CH_2), 28.2 (CH_2), 31.9 (CH_2), 33.0 (CH_2), 39.4 (C), 52.1(CH_3), 54.0 (CH_2), 56.9 (CH_2), 66.4 (CH), 110.9 (CH), 111.6 (C), 117.6 (CH), 119.0 (CH), 121.1 (CH), 126.6 (C), 133.0 (C), 136.2 (C), 175.8. (C)]; further elution gave *cis*-indoloquinolizidine **5** (514 mg) as a viscous oil: $[\alpha]^{22}_D$ −113 (c = 2, CH_2Cl_2). Recrystallization of the dibenzoyl-D-tartarate salt[13g] gave enantiomerically pure **5**: $[\alpha]^{22}_D$ −124 (c = 2, CH_2Cl_2) (lit.[13g] $[\alpha]^{22}_D$ −121 (c = 2.02, CH_2Cl_2)); IR (neat) 3511, 2801, 2753, 1730 cm^{-1}; ^1H NMR (400 MHz) δ 1.18 (t, J = 7.6 Hz, 3H), 1.40−1.60 (m, 4 H), 1.69 (dq, J = 15.7, 7.6, 1H), 1.81 (dq, J = 15.7, 7.6 Hz, 1H), 1.90 (m, 1H), 2.05−2.15 (m, 2H), 2.20 (m, 1H), 2.36 (ddd, J = 12.1, 12.0, 2.4 Hz, 1H), 2.55 (ddd, J = 11.0, 10.9, 3.6 Hz, 1H), 2.65 (m, 1H), 2.90 (m, 1H), 3.00 (m, 2H), 3.34 (s, 1H), 3.57 (s, 3H), 7.08 (td, J = 6.8, 1.5 Hz, 1H), 7.14 (td,J = 6.8, 1.5 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.81 (broad s, 1H); ^{13}C NMR (50 MHz) δ 8.1 (CH_3), 21.9 (2 CH_2), 28.6 (2 CH_2), 30.9 (CH_2), 32.2 (CH_2), 39.3 (C), 51.5 (CH_3), 54.1 (CH_2), 56.7 (CH_2), 66.2 (CH), 110.7 (CH), 111.8 (C), 117.8 (CH), 119.2 (CH), 121.4 (CH), 126.8 (C), 133.4 (C), 135.8 (C), 174.7 (C), MS (IC, CH_4) m/e (rel intensity) 341 ($(M + H)^{\cdot+}$, 100). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.22. Found: C, 73.86; H, 8.42; N, 8.04.

***D*-Homoeburnamenin-14(15*H*)-one (4).** To a stirred solution of enantiopure ester **5** (295 mg, 0.87 mmol) in anhydrous toluene (5 mL) was added dropwise at 0 °C a solution of sodium bis(trimethylsilyl)amide (2 M in THF, 1.5 mL, 3 mmol). After being stirred for 2 h at 20 °C, the reaction mixture was cooled to 0 °C, and saturated $NaHCO_3$ solution (4 mL) was added. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The collected organic phases were washed with brine, dried, and

concentrated in vacuo to leave a solid that was purified by chromatography (hexane−ethyl acetate, 50:50, R_f 0.43). Crystallization in methanol gave pure homoeburnamonine **4** (188 mg, 70%) as white crystals: mp 154−155 °C; $[\alpha]^{22}_D$ +20.3 (c = 1.4, DMF) (lit.[14a] mp 154−155 °C; $[\alpha]^{22}_D$ +20.7 (c = 1, DMF)); IR (KBr): 2934, 2860, 2805, 1699 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.89 (t, J = 7.5 Hz, 3H), 1.03 (td, J = 13.6, 3.7 Hz, 1H), 1.42 (dt, , J = 12.8, 3.1 Hz, 1H), 1.50−1.63 (m, 3H), 1.68 (dddd, J = 13.1, 12.8, 12.8, 3.8 Hz, 1 H), 2.05−2.20 (m, 2H), 2.46 (ddd, J = 16.0, 4.1, 2.3 Hz, 1H), 2.66 (m, 1H), 2.71 (m, 1H), 2.76 (m, 1H), 2.80 (m, 1H), 3.00 (ddd, J = 12.4, 12.4, 4.5 Hz, 1H), 3.11 (dddd, J = 16.0, 16.0, 5.0, 3.0 Hz, 1H), 3.32 (dd, J = 13.0, 5.3 Hz, 1H), 4.08 (s, 1H), 7.27−7.35 (m, 2H), 7.44 (d J = 6.9 Hz, 1H), 8.46 (d, J = 7.8 Hz, 1H); ^{13}C NMR (50 MHz) δ 7.6 (CH_3), 17.3 (CH_2), 21.2 (CH_2), 28.4 (CH_2), 31.9 (2 CH_2), 32.5 (CH_2), 37.6 (C), 46.3 (CH_2), 51.5 (CH_2), 62.4 (CH), 117.5 (2 CH and C), 123.5 (CH), 124.6 (CH), 130.1 (C), 133.1 (C), 136.1 (C), 173.2 (C). Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.66; H, 7.78; N, 9.06. The thus obtained (+)-lactam **4** was shown to be identical with an authentic sample provided by Roussel-Uclaf, on the basis of a mixed melting point and the specific rotation.

(+)-Vincamine (1). To a solution of D-homoeburnamonine **4** (130 mg, 0.42 mmol) in toluene (0.8 mL) were successively added *tert*-butyl nitrite (950 mg, 9.2 mmol) and sodium bis(trimethylsilyl)amide (2 M in THF, 0.6 mL, 1.2 mmol). The reaction mixture was stirred for 1.5 h at 50 °C. After cooling, the solution was poured into saturated ammonium chloride. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate. The collected organic phases were washed with brine, dried, and concentrated in vacuo. Purification by chromatography (hexane−ethyl acetate, 50:50) gave a mixture of isomeric oximes **40a** (92 mg, 65%) as an amorphous solid. To a solution of the above mixture of oximes (90 mg, 0.26 mmol) in glacial acetic acid (2 mL) were added dry *p*-TsOH (100 mg, 0.26 mmol) and paraformaldehyde (100 mg, 0.26 mmol). The reaction mixture was heated at 100−105 °C for 5 h under stirring. After cooling, the solution was poured into 10 mL of ice−water, treated with 25% NH_4OH to pH 9, and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried, filtered, and evaporated to dryness. The residue (**40b**) was dissolved in anhydrous methanol (2 mL), and potassium *tert*-butoxide (10 mg) was added. After being stirred at 20 °C for 2 h, the reaction mixture was poured into brine (4 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The collected organic phases were dried and concentrated in vacuo to leave a white solid. Crystallization in methanol gave pure (+)-vincamine (**1**) (39 mg, 40%) as white crystals: mp 230−232 °C; $[\alpha]^{22}_D$ +44.0 (c = 1.4, pyridine) (lit.[13i] mp 234−235 °C; $[\alpha]^{22}_D$ +44.5 (c = 1, pyridine)); IR (KBr) 3400−2400, 1748 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.91 (t, J = 7.5 Hz, 3H), 1.30−1.80 (m, 5H), 2.10 (d, J = 14.3, 1H), 2.24 (d, J = 14.2, 1H), 2.27 (m, 1H), 2.42−2.70 (m, 3H), 2.90−3.10 (m, 1H), 3.20−3.40 (m, 2H), 3.82 (s, 3H), 3.92 (s, 1H), 4.64 (s, 1H), 7.08−7.18 (m, 3H), 7.45−7.52 (m, 1H); ^{13}C NMR (50 MHz) δ 7.6 (CH_3), 16.8 (CH_2), 20.8 (CH_2), 25.1 (CH_2), 28.9 (CH_2), 35.1 (C), 44.4 (CH_2), 44.6 (CH_2), 50.9 (CH_2), 54.2 (CH_3), 59.1 (CH), 81.9 (C), 105.9 (C), 110.3 (CH), 118.4 (CH), 120.2 (CH), 121.6 (CH), 129.0 (C), 131.4 (C), 134.4 (C), 174.4 (C). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.33; N, 7.90. Found: C, 71.05; H, 7.40; N, 7.80. The obtained (+)-vincamine (**1**) was shown to be identical with an authentic sample provided by Pr. Jean Lévy (Faculté de Pharmacie de Reims, France), on the basis of a mixed melting point and the specific rotation.

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Supporting Information Available: Copies of ^{1}H or ^{13}C NMR spectra (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current mastehead page for ordering information.

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