the $^1H$ and $^{13}C$ NMR data (see Tables I and II).

In conclusion a rapid and simple procedure adaptable to large-scale work allows facile preparation of important bicyclic intermediates from naturally occurring compounds with appropriate chirality and functionalities to be further elaborated into prostanoids by known routes.

## Experimental Section

$^1H$ NMR spectra were recorded at 60 or 90 MHz with HDO as internal standard (at 4.70 ppm) for $D_2O$ solutions and $Me_4Si$ as internal standard for $CDCl_3$ solutions. $^{13}C$ NMR spectra were registered at 20 or 22.63 MHz with dioxane (67.4 ppm from $Me_4Si$) as internal standard for $D_2O$ solutions and $Me_4Si$ as internal standard for $CDCl_3$ solutions. Silica gel $SiF_{254}$ (Erba) plates were used for TLC and compounds were visualized by spraying with 2 N $H_2SO_4$ and heating at 120 °C. All new compounds described gave satisfactory elemental analyses.

**Isolation and Purification of the Iridoid Glucosides.** Aucubin (1) was isolated from *Eucommia ulmoides* (Eucommiaceae) and purified as already described (ref 2c). Isolation of scandoside and 10-deacetylasperulosidic acid from *Asperula odorosa* (Rubiaceae) and preparation of their Me esters **9** and **10** were carried out according to the procedures described in ref 11.

**General "One-Pot" Preparation of *cis*-2-Oxabicyclo[3.3.0]oct-7-enes.** A buffer solution (pH 5.4) of the iridoid glucoside and the β glucosidase (Fluka) in the molar ratio 10:1 was stored at 35 °C, and the reaction was checked by TLC ($CHCl_3$/MeOH (8:2) as eluent). Generally after 24 h the reaction was stopped, the solution was transferred to a large flask, and with vigorous magnetic stirring an excess of $NaBH_4$ was added during 1 h at room temperature. Then the solution was carefully bubbled with $CO_2$ until pH 8. To the neutralized solution was added dropwise 6 N HCl until the solution became 2 N in HCl. Checked periodically by TLC ($CHCl_3$/MeOH (9:1) as eluent), the reaction was stopped after 1 h by addition of 6 N NaOH until neutral. To the solution was added decolorizing charcoal to absorb all the organic products, and the suspension was then poured on a silica gel layer in a Gooch funnel. The inorganic salts were totally removed with water and finally the Gooch funnel was eluted with MeOH; evaporation in vacuo of the methanolic solution yielded a crude residue, generally purified by column chromatography (silica gel) with $CHCl_3$/MeOH (9:1) as eluent.

The overall yields of the described procedure for the different compounds were as follows: **7** from **1** (66%); **8** from **3** (47%); **15** from **9** (57%); and **15** from **10** (48%).

**Isolation of Cyclopentenepolyol 13.** A 140-mg (0.3 mmol) sample of **9** (ref 11) was treated as described above in the general "one-pot" procedure. After $CO_2$ bubbling, decolorizing charcoal (500 mg) was added to the solution. The suspension was then poured on a silica gel layer stratified in a Gooch funnel and eluted with water to eliminate the inorganic salts. The final elution with MeOH afforded, after evaporation in vacuo, 52 mg (69%) of almost pure **13** as an oil.

**Isolation of Cyclopentenepolyol 14.** A 340-mg (0.73 mmol) sample of **10** (ref 11) was worked up as described above for **9**. The final methanolic elution afforded, after evaporation, mg 130 of **14** (71%) as an oil.

**Oxidation of 16: Lactone 17.** A 20-mg (0.08 mmol) sample of **16** was stirred at 45 °C, in a dry apparatus with 10 mL of anhydrous $CH_2Cl_2$. Three portions of freshly prepared PCC (200 mg) were added in 2 h at room temperature to the mixture. After 48 h, the reaction, checked by TLC, was stopped and the brown suspension was poured on a silica gel column and eluted with ether. The evaporation of the ether solution afforded 20 mg of crude products. Column chromatography (silica gel, $CHCl_3$/MeOH (95:5) as eluent) yielded 10 mg of **17** (50%) and 8 mg of unreacted **16**. **17** (oil): IR ($CHCl_3$) 1780, 1750 $cm^{-1}$.

**Hydrogenation of 7: Compound 20.** 5% Rh on $Al_2O_3$ (Fluka) was added in catalytic amount to a solution of 30 mg (0.18 mmol) of **7** in 5 mL of MeOH. The heterogeneous solution was stirred, under a hydrogen atmosphere at normal pressure, for 8 h at room temperature. Filtration and concentration of the suspension gave a crude residue of 30 mg which was chromatographed on a silica gel column (MeOH/$CHCl_3$ (9:1) as eluent), affording 23 mg (73%) of pure **20** as a colorless oil.

**Ring Closure of 20: Compound 21.** To a solution of 23 mg (0.13 mmol) of **20** in 10 mL of dry benzene was added 10 mg of TsCl, and the mixture was refluxed for 8 h. After evaporation of benzene, the crude residue was chromatographed on silica gel ($CH_2Cl_2$), yielding 17 mg of **21** (85%) as a colorless oil.

**Monomesyl Derivative 18.** To a solution of 90 mg (0.53 mmol) of **7** in 0.5 mL of dry pyridine was carefully added, at 0 °C, 1 mL of MsCl (6 mmol). The temperature was then raised to room temperature during 1 h. After addition of $Et_2O$, the solution was acidified at 0 °C with 2 N HCl. The ethereal solution was extracted twice with water and then dried over $Na_2SO_4$. Evaporation of the ether solution afforded a residue of 88 mg which, chromatographed on a silica gel column (hexane/ether (3:7) as eluent), yielded 75 mg of pure **18** (54%) as an oil.

**Acetyl Derivative 19.** To a solution of 75 mg (0.30 mmol) of **18** in dry pyridine (0.5 mL) was added 1 mL of acetic anhydride (9 mmol) and 0.02 mL of $NEt_3$ (0.2 mmol). The reaction mixture was kept at 50 °C for 20 h and then was diluted with $Et_2O$ (20 mL) and extracted with 2 N $H_2SO_4$ and $H_2O$ until neutral. The organic layer, dried over $Na_2SO_4$, afforded after evaporation 73 mg of residue. Silica gel chromatography (hexane/ether (3:7) as eluent) yielded 58 mg of pure **19** (66%) as an oil.

**Registry No.** **1**, 479-98-1; **2**, 64274-28-8; **3**, 63879-67-4; **4**, 94707-62-7; **5**, 64274-29-9; **6**, 79307-50-9; **7**, 94707-63-8; **8**, 94707-64-9; **9**, 27530-67-2; **10**, 52613-28-2; **11**, 94799-03-8; **12**, 82345-54-8; **13**, 94707-65-0; **14**, 94799-04-9; **15**, 94707-66-1; **16**, 94707-67-2; **17**, 94707-68-3; **18**, 94707-69-4; **19**, 94707-70-7; **20**, 94707-71-8; **21**, 94707-72-9; β-glucosidase, 9001-22-3.

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# A New Efficient Total Synthesis of Vindorosine and Vindoline[1]

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*Received June 4, 1984*

Highly stereoselective total syntheses of indole alkaloids vindorosine (**1a**) and vindoline (**1b**) are described. An imino Diels–Alder reaction, a stereospecific alkylation, and a rearrangement induced by the Pummerer reaction are the key steps of these short and high overall yield sequences.

Aspidosperma alkaloid vindoline (**1b**)[2] is with catharanthine (**2a**)[3] the direct biogenetic precursor[4] of the antitumor alkaloids of *Catharanthus roseus* like vinblastine (**3**).[5] The discovery in our laboratory[6] of a hemisynthetic

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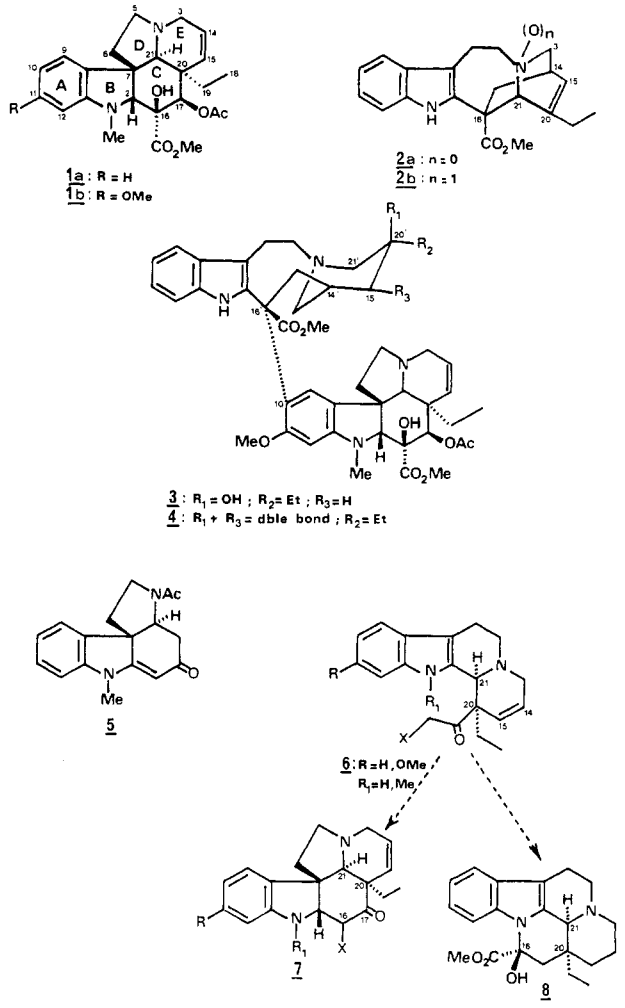
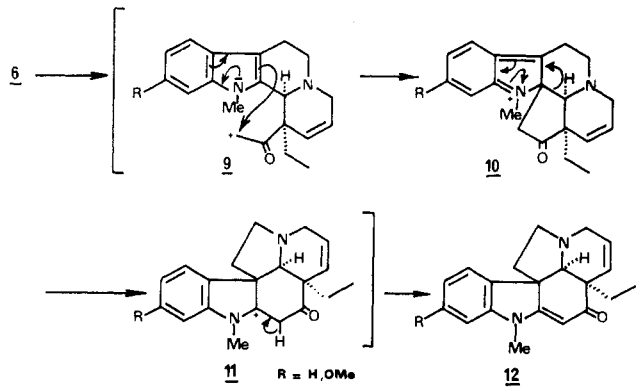
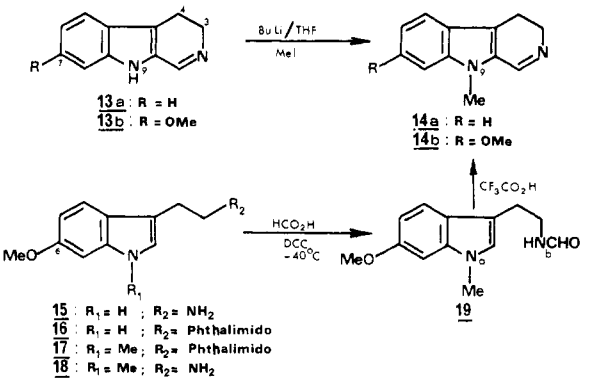
**Scheme I**



**Scheme II**



**Scheme III**



route affording anhydrovinblastine (**4**), and vinblastine (**3**) from vindoline (**1b**) and catharanthine $N_b$-oxide (**2b**), by a fragmentation induced by the modified Polonovski reaction,[7] increased the interest in the total syntheses of these alkaloids. We wish to disclose in the present paper a new efficient synthesis leading to vindorosine (11-desmethoxyvindoline) (**1a**) and vindoline (**1b**) by a route following a "retrobiomimetic" pathway.

Since the elegant total synthesis of vindorosine (**1a**)[8a] and vindoline (**1b**)[8b] by Büchi et al., several improvements directed toward the synthesis of Büchi's tetracyclic intermediate **5** appeared in the literature.[9-11] All these syntheses were characterized by the elaboration of the cycles A, B, C, and D either directly from an indole or an oxindole intermediate[9,10] or via a rearrangement induced by a carbocation intermediate.[11]

Our strategy for the construction of vindorosine (**1a**) and vindoline (**1b**) was first centered around the preparation of [2,3-*a*]indoloquinolizidine derivative **6** which could lead directly to an intermediate **7** bearing the complete aspidosperma framewosk, i.e., the cycles A, B, C, D, and E[12] (Scheme I).

In addition, these indoloquinolizidine synthons could be of interest in the total synthesis of several eburnane alkaloids like vincamine (**8**).[13] It is well-known that following Wenkert's hypothesis,[14] the aspidosperma alkaloids are the biogenetic precursors of eburna alkaloids.[15] Thus, it follows that the absolute configuration of the two carbons $C_{20}$ and $C_{21}$[16] are the same for these two families of indole

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(11) (a) Takano, S.; Shishido, K.; Sato, M.; Yuta, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1978**, 943. (b) Takano, S.; Shishido, K.; Matsuzaka, J.; Sato, M.; Ogasawara, K. *Heterocycles* **1979**, *13*, 307.

(12) For recent synthesis of aspidosperma alkaloids see: (a) Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443. (b) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. (c) Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335. (d) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 1118. (e) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2086. (f) Pearson, A. J.; Rees, D. C. *J. Am. Chem. Soc.* **1982**, *104*, 1118. (g) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685. (h) Wenkert, E.; Ortito, K.; Simmons, D. P.; Ardisson, J.; Kunesch, N.; Poisson, J. *J. Org. Chem.* **1983**, *48*, 5006.

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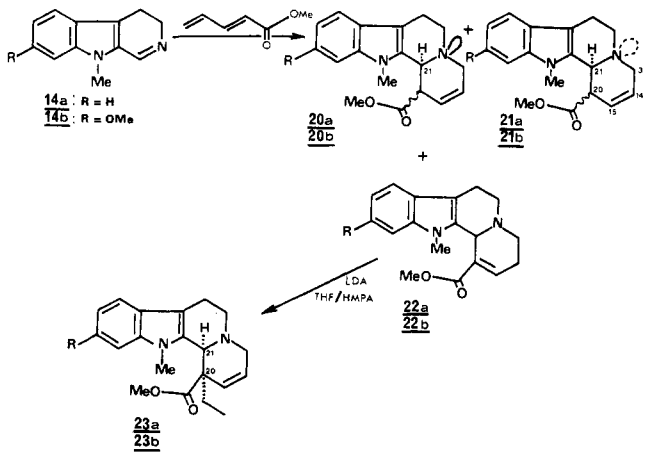
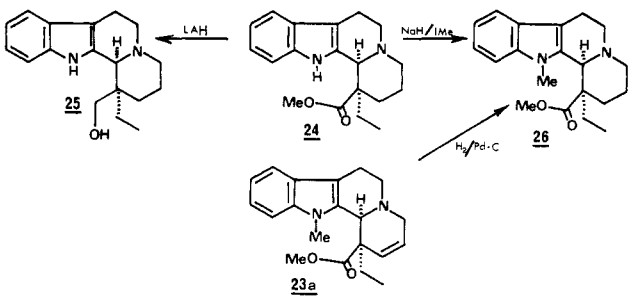
(16) The biogenetical numbering [Le Men, J.; Taylor, W. I. *Experientia* **1965**, *18*, 173] has been used in this paper for the indoloquinolizidines derivatives and subsequent compounds.

**Scheme IV**



**Scheme V**



alkaloids.

The second feature of this synthesis was the formation of a carbocation intermediate **9** which could induce a rearrangement[11,17] affording the aspidosperma skeleton by a process which should be the reverse of the biogenetic pathway[15] (Scheme II).

An imino Diels–Alder reaction[18] between 9-methyldihydro-β-carboline derivatives **14a** and **14b** and a diene conjugated with an electron-withdrawing group was chosen for the synthesis of the requisite indoloquinolizidine compounds **6**. By this way the $C_{14}$–$C_{15}$ double bond could be introduced at the first stage of the synthesis.

The classical preparation of 9-methyldihydro-β-carboline (**14a**)[19] has been improved by a direct N-methylation of the corresponding dihydro-β-carboline (**13a**) (BuLi, THF, MeI, 83%) (Scheme III). However the same methodology appeared to be inoperative in the case of 7-methoxydihydro-β-carboline (**13b**). Compound **14b** was prepared from the 6-methoxytryptamine (**15**) via the corresponding phthalimide derivative **16** which was alkylated and solvolyzed according to Kuehne's procedure.[20] Classical formylation ($Ac_2O$–$HCO_2H$) gave only a poor yield of the desired $N_b$-formyl-$N_a$-methyl-6-methoxytryptamine (**10**). However this compound has been prepared easily by treatment with formic anhydride ($HCO_2H$–DCC, –40 °C).[21] The resulting $N_b$-formyl derivative **19** in the presence of trifluoroacetic acid[22] gave rise to the anticipated dihydro-β-carboline **14b**, which could be used without further purification (yield ≃ 100%) (Scheme III).

*N*-Methyldihydro-β-carboline (**14a**) subjected to an imino Diels–Alder reaction in the presence of methyl pentadienoate led to a mixture of three products (total yield 71%): **20a**, **21a**, and **22a** (Scheme IV).

In the IR compound **20a** exhibited Wenkert–Bohlmann absorptions[23] characteristic of a *trans*-quinolizidine configuration. The chemical shift of $C_{21}H$, a broad singlet at 3.95 ppm, corroborates this attribution. In contrast compound **21a**, which is devoid of Wenkert–Bohlmann absorptions in the IR, is characterized in its $^1H$ NMR spectrum by a broad doublet ($\delta$ 4.5, $J$ = 9 Hz) attributed to $C_{21}H$. This chemical shift is typical of a *cis*-quinolizidine skeleton.[24]

The third compound **22a** is characterized by a lower frequency for the carbonyl ($\delta$ 1700 $cm^{-1}$) in the IR and by the presence of only one olefinic proton (broad singlet, $\delta$ 5.33) in its NMR spectrum. In addition the characteristic retro-Diels–Alder fragmentation at $m/z$ 184, which is present in the mass spectra of compounds **20a** and **21a**, is lacking in the spectrum of compound **22a**. All these observations are in agreement with the presence of a conjugated ester in this compound.

However, without further separation, the mixture of these three indoloquinolizidine derivatives was deprotonated with LDA in THF–HMPA[25] and alkylated with ethyl iodide, affording compound **23a** (98%) as a single diastereomer (Scheme IV). The relative configurations of the two carbons $C_{20}$ and $C_{21}$ in compound **23a** have been established by a chemical correlation. The indoloquinolizidine derivative **24**, which has been converted previously[26] to the known alcohol **25**,[27] was alkylated with methyl iodide. The resulting product **26** was identical with the product obtained by hydrogenation of **23a** (Scheme V).

The stereospecific alkylation of the mixture of indoloquinolizidines **20a**, **21a**, and **22a** can be rationalized in terms of steric interaction between $N_a$-methyl and the oxygen of the common ester enolate intermediate. This interaction which is strong for a *trans*-quinolizidine intermediate (A) is minimized for the corresponding *cis*-quinolizidine intermediate (B). Electrophilic attack of ethyl iodide on this intermediate on the less hindered face of the molecule led to the formation of the observed diastereomer.

In a similar way, 7-methoxy-9-methyldihydro-β-carboline (**14b**) afforded, after imino Diels–Alder reaction with methyl pentadienoate, three products **20b**, **21b**, and **22b** (total yield 88%) which were directly alkylated (LDA, THF–HMPA, EtI) to afford the indoloquinolizidine derivative **23b** (80%) as a single product (Scheme IV).

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(18) (a) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. (b) Bohlmann, F.; Habeck, D.; Poetsch, E.; Schumann, D. *Chem. Ber.* **1967**, *100*, 2742. (c) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
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(22) $POCl_3$, classical reagent for the Bischler Napieralsky cyclization, did not afford compound **14b**.
(23) (a) Wenkert, E.; Roychaudhuri, D. *J. Am. Chem. Soc.* **1956**, *78*, 6417. (b) Bohlmann, F. *Angew. Chem.* **1957**, *69*, 541. (c) Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109.
(24) (a) Gribble, G. W.; Nelson, R. B. *J. Org. Chem.* **1973**, *38*, 2831. (b) After double irradiation experiments at 400 MHz, it was not possible to determine the configuration at $C_{20}$ in indoloquinolizidines **20a** and **21a**. However deprotonation of the mixture of compounds **20a**, **21a**, and **22a** (LDA–THF–HMPA) led after quenching with $H_3O^+$ to indoloquinolizidine **20a** as the sole product. In comparison with the stereochemical result of the alkylation giving rise to indoloquinolizidine **23a**, cis relative configurations could be assigned for $C_{20}H$ and $C_{21}H$ in indoloquinolizidine **20a** and trans relative configurations in indoloquinolizidine **21a**.
(25) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.
(26) Langlois, Y.; Pouilhès, A.; Génin, D.; Andriamialisoa, R. Z.; Langlois, N. *Tetrahedron* **1983**, *39*, 3755.
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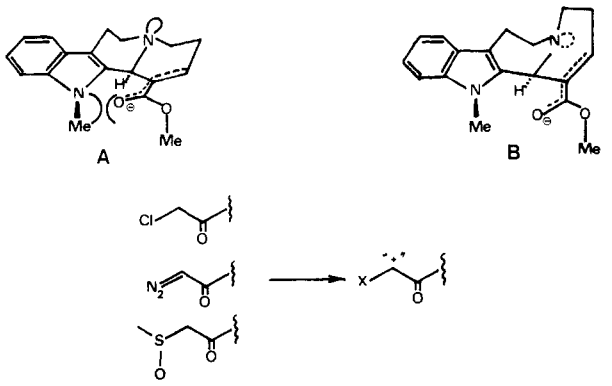


With the requisite indoloquinolizidines **23a** and **23b** in hand, we next examined the possibility of generation of a carbocationic species $\alpha$ to a carbonyl group which could be subjected to intramolecular nucleophilic attack from the indole nucleus. Three possibilities could be envisaged for such an intermediate: $\alpha$-chloro ketone,[28] $\alpha$-diazo ketone,[11,29] and $\beta$-keto sulfoxide.[30] After some disappointing results concerning the preparation of the diazo ketone **27**, we turned our attention toward the synthesis of the appropriate $\beta$-keto sulfoxide.

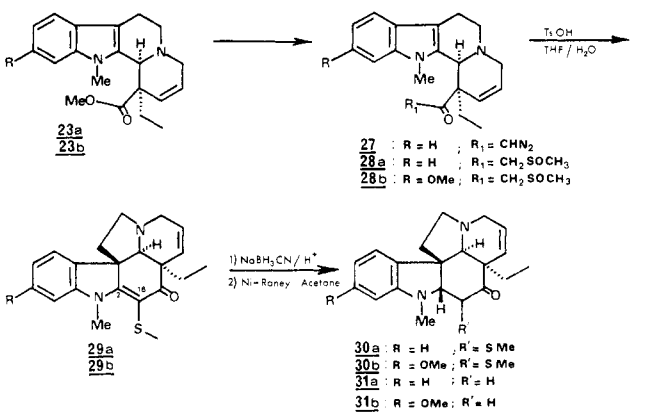
Thus indoloquinolizidines **23a** and **23b** were treated with dimsyllithium[31] in THF–$Me_2SO$ and led to the expected $\beta$-ketosulfoxides **28a** and **28b** (86% and 80%, respectively) as a mixture of diastereomers (Scheme VI). The $\beta$-keto sulfoxides **28a** and **28b** in the presence of tosylic acid in THF afforded readily the anticipated aspidosperma derivatives **29a** and **29b** (73% and 70%, respectively) after Pummerer reaction[32] and intramolecular nucleophilic attack of the indole nucleus (Scheme VI). This rearrangement, which proceeds in good yield, was facilitated by the position of the $\beta$-keto sulfoxide side chain just above the plane of the indole nucleus.

The two following steps, reduction of the double bond $C_2$–$C_{16}$ of the vinylogous lactams **29a** and **29b** with sodium cyanoborohydride[33] and subsequent hydrogenolysis[34] of the resulting thioethers **30a** and **30b**, gave rise to the two pentacyclic ketones **31a** and **31b** already prepared by Büchi.[8] These compounds were obtained in 36% and 26% overall yield from the dihydro-$\beta$-carbolines **13a** and **13b** (Scheme VI).

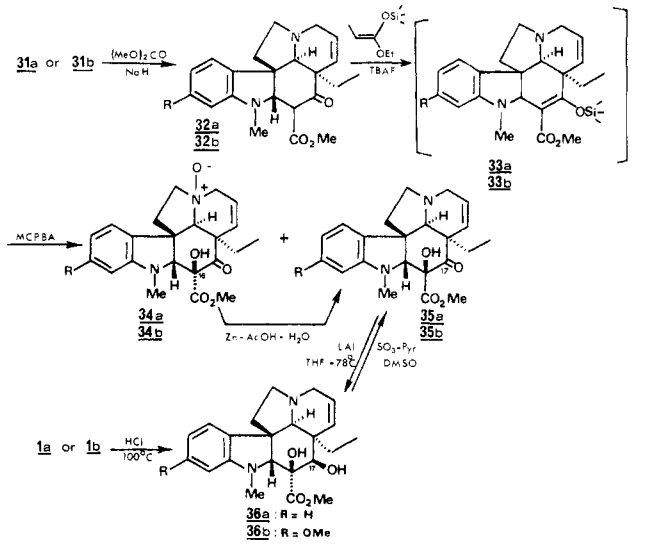
Carbomethoxylation of ketones **31a** and **31b** was performed according to Büchi's procedure ($(MeO)_2CO$, NaH, THF)[8,36] and afforded the $\beta$-keto esters **32a** and **32b** from the corresponding ketones **31a** and **31b** (80% and 79%).[37] The last difficult step of the synthesis, hydroxylation at $C_{16}$, was achieved via a trimethylsilyl enol ether. Thus the unstable trimethylsilyl enol ether **33a**, obtained by exchange with methylketene ethyl trimethylsilyl acetal in the presence of a catalytic amount of tetrabutylammonium fluoride,[38] was treated without isolation with MCPBA and led to the $N_b$-oxide **34a** hydroxylated at $C_{16}$ (88%). This compound after quantitative reduction with zinc in acetic acid[39] afforded the corresponding amine **35a** as a single diastereomer, which was identical with 17-oxo-17-desacetoxyvindorosine (**35a**) obtained by oxidation ($SO_3$–pyridine–$Me_2SO$)[40] of 17-desacetylvindorosine (**36a**) (Scheme VII). In a similar way $\beta$-keto ester **32b** after sequential treatment with methylketene ethyl trimethylsilyl acetal and MCPBA afforded a mixture of 17-oxo-17-desacetoxyvindoline (**35b**) and of the corresponding $N_b$-oxide **34b**. $N_b$-oxide **34b** was reduced quantitatively to the corresponding amine **35b** (total yield of **35b** from **32b**, 89%) and was identical with the product obtained by oxidation of 17-deacetylvindoline (**36b**).

The stereospecificity of the hydroxylation at $C_{16}$ of silyl enol ethers **33a** and **33b** is probably due to the presence

**Scheme VI**



**Scheme VII**



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of the α-ethyl side chain at $C_{20}$ which prevents electrophilic attack of the enolic double bond on the more hindered α side of ring C. It is also interesting to note that, as far as we know, this is the first example of hydroxylation of a relatively electron poor olefin in which a trimethylsilyl enol ether is conjugated to an ester group.

The reduction of the carbonyl group of compound **35b** ($LiAlH_4$–THF, –78 °C)[8a] afforded desacetylvindoline (**36b**) (52%) with some amount of starting material **35b** (≃12%). Acetylation of desacetylvindoline (**36b**) ($Ac_2O$–pyridine then EtOH–$H_2O$)[39] gave rise quantitatively to (±)-vindoline (**1b**).

The overall yield (≃10%) of the synthesis of (±)-vindoline (**1b**) prompts us to consider the coupling reaction of the enantiomeric mixture **1b** with catharanthine $N_b$-oxide (**2b**).[6] This reaction could be of interest for both a mechanistic and a structure–activity relationship point of view. On the other hand, an enantioselective approach to the total synthesis of aspidosperma and eburna alkaloids is in current development in our laboratory.

## Experimental Section

IR spectra ($\nu$ $cm^{-1}$, $CHCl_3$) were recorded on a Perkin Elmer 297 spectrometer and UV spectra [$CH_3OH$, $\lambda_{max}$, nm ($\epsilon$)] on a Jobin-Yvon Duospac 203 spectrometer. $^1H$ NMR spectra were obtained if not specified on an IEF 402 MHz spectrometer[44] ($\delta$ 0 ($Me_4Si$), $CDCl_3$). Coupling constants, $J$, are given in hertz; s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet, respectively. Mass spectra were measured on an MS 50. Preparative-layer chromatography (preparative TLC) was performed with Kieselgel HF 254 (Merck) and column chromatography on Kieselgel 60 (70–230 mesh) (Merck).

**Preparation of 9-Methyl-3,4-dihydro-β-carboline (14a).** To a solution of BuLi (40 mL, 64 mmol, 1.6 M in hexane) in THF (200 mL) at –10 °C was added dropwise a solution of 3,4-dihydro-β-carboline[41] (7.25 g, 42.6 mmol) in THF (100 mL). The reaction mixture was stirred for 2 h at –10 °C and methyl iodide (13 mL, 210 mmol) was added. The reaction was monitored by TLC. After 2 h, excess BuLi was carefully destroyed by $H_2O$–NaCl. THF was evaporated in vacuo and the residue was extracted with dichloromethane and washed with water. The organic layer was dried with magnesium sulfate, filtrated, and concentrated by rotary evaporation. The residue was purified by column chromatography (dichloromethane–methanol–aqueous ammonia 95:5:0.5) to give 9-methyl-3,4-dihydro-β-carboline (**14a**)[19b] (6.5 g, 83%).

**Preparation of $N_b$-Formyl-$N_a$-methyl-6-methoxytryptamine (19).** A solution of anhydrous formic acid (0.6 mL, 16 mmol) and triethylamine (1.2 mL, 8.6 mmol) in THF (20 mL) was added to a solution of dicyclohexylcarbodiimide (1.745 g, 8.5 mmol) in THF (10 mL) at –70 °C under argon. After being stirred 5 h at –40 °C, the reaction mixture was cooled to –70 °C and a solution of 6-methoxy-1-methyltryptamine (470 mg, 2.3 mmol) in THF (20 mL) was added. After 2 h the reaction mixture was extracted with dichloromethane and washed with water. The organic solution was concentrated, filtered through Celite, and afforded after evaporation **19** (534 mg, 100%): IR 3300, 2950, 1660; $^1H$ NMR 8.10 (s, 1 H, CHO), 7.37 (d, 1 H, $J$ = 10, $C_4H$), 6.75 (m, 3 H, aromatic + $C_2H$), 5.62 (m, 1 H, $N_bH$), 3.90 (s, 3 H) and 3.70 (s, 3 H) ($OCH_3$ and $NCH_3$), 3.62 (m, 2 H, $CH_2$), 2.95 (t, 2 H, $J$ = 8, $CH_2$); MS, $m/z$ 232 ($M^{+\cdot}$), 189, 173 (100%); $M_r$ 232.1211, calcd 232.1211 for $C_{13}H_{16}N_2O_2$.

**Preparation of 7-Methoxy-9-methyl-3,4-dihydro-β-carboline (14b).** A solution of **19** (534 mg, 2.3 mmol) in a mixture of dichloromethane and trifluoroacetic acid (50 mL, 60:40) was stirred at room temperature under argon for 1 h. The reaction mixture was concentrated and the residue was dissolved in dichloromethane, washed with water, dried over magnesium sulfate, and concentrated to give **14b** (433 mg, 88%): IR 3000, 1610; UV (MeOH) 264, 345; (MeOH–$H_3O^+$) 260, 386; $^1H$ NMR (60 MHz) 8.02 (broad, s, 1 H, $C_1H$), 3.61 (s, 3 H) and 3.50 (s, 3 H) ($OCH_3$ and $NCH_3$); MS, $m/z$ 214 ($M^{+\cdot}$, 100%), 213; $M_r$ 214.1108, calcd 214.1106 for $C_{13}H_{14}N_2O$.

**Imino Diels–Alder Reaction: Preparation of Indoloquinolizidines 20a, 21a, and 22a.** To a solution of imine **14a** (1.1 g, 5.97 mmol) in chlorobenzene (40 mL) was added 2,4-pentadienoic acid methyl ester[42] (1.5 g, 13.4 mmol). The mixture was heated and stirred at 120 °C under argon for 4 h. The resulting brown solution was evaporated under vacuum and the residue after purification by flash chromatography (dichloromethane–pentane 1:1) afforded 1.25 g (71%) of the mixture of **20a**, **21a**, and **22a**. Purification of this mixture by preparative TLC (dichloromethane–methanol 95:5) gave **20a** (20%) (less polar), **21a** (53%), and **22a** (more polar) (27%).

**20a**: IR 2810, 2790, 2740 (Wenkert–Bohlmann bands), 1720; UV 277, 285, 292; $^1H$ NMR $\delta$ 7.5–7 (4 H, aromatic), 6.01 and 5.83 (2 broad d, 1 H, $C_{14}$-H and $C_{15}$-H[16]), 3.95 (broad s, 1 H, $C_{21}H$), 3.73 (s, 3 H, $NCH_3$), 3.28 (s, 3 H, $CO_2CH_3$), MS, $m/z$ 296 ($M^{+\cdot}$), 265, 183 (100%); $M_r$ 296.1507, calcd 296.1524 for $C_{18}H_{20}N_2O_2$.

**21a**: IR 1720; UV 277, 285, 292; $^1H$ NMR $\delta$ 7.5–7 (4 H, aromatic), 5.97 and 5.70 (2 broad d, 1 H, $C_{14}H$ and $C_{15}H$), 4.5 (d, 1 H, $J$ = 9, $C_{21}H$), 3.95 (broad d, 1 H, $C_3$-Ha), 3.71 (s, 3 H, $NCH_3$), 3.48 (s + m, 4 H, $CO_2CH_3$ and $C_{20}H$); MS, $m/z$ 296 ($M^{+\cdot}$), 265, 183 (100%); $M_r$ 296.1522, calcd 296.1524 for $C_{18}H_{20}N_2O_2$.

**22a**: IR 1700; UV 280, 287, 294; $^1H$ NMR (60 MHz) 7.5–7 (4 H, aromatic), 5.33 (broad s, 1 H, $C_{15}H$), 3.81 and 3.57 (2 s, 3 H, $NCH_3$ and $CO_2CH_3$); MS, $m/z$ 296 ($M^{+\cdot}$), 280.

**Preparation of Indoloquinolizidine 23a.** To a solution of diisopropylamine (0.19 mL, 1.3 mmol) in THF (1 mL) was added $n$-butyllithium (1.6 M in hexane) (0.75 mL, 1.2 mmol) at –70 °C. The mixture was warmed to 20 °C for 10 min and cooled at –70 °C before addition of HMPA (0.3 mL). After 30 min, this solution of lithium diisopropylamide was added to a solution of the mixture of **20a**, **21a**, and **22a** (270 mg, 0.91 mmol) in THF (1 mL) at –70 °C under argon. The mixture was stirred for 10 min at –70 °C and warmed to 0 °C before addition of ethyl iodide (150 μL, 1.87 mmol). After being stirred at 0 °C for 10 min, the reaction medium was poured into brine and extracted with dichloromethane. After the usual workup, crude product was purified by preparative TLC (ethyl acetate–pentane 1:1 + ammonia) and afforded **23a** (289 mg, 98%): IR 2950, 1720; UV 276, 286, 292; $^1H$ NMR 7.42 (d, $J$ = 8) and 7.25 (d, 1 H, $J$ = 8) ($C_9H$ and $C_{12}H$), 7.10 (dd, 1 H, $J \simeq 8$) and 7.04 (dd, 1 H, $J \simeq 8$) ($C_{10}H$ and $C_{11}H$), 5.98 (2 H, $C_{14}H$ and $C_{15}H$), 4.06 (s, 1 H, $C_{21}H$), 3.68 (s, 3 H, $NCH_3$), 3.17 (s, 3 H, $CO_2CH_3$), 2.18 (m, 1 H, $C_{19}H_a$), 1.78 (m, 1 H, $C_{19}H_b$), 0.96 (t, 3 H, $J$ = 7, $C_{18}H_3$); MS, $m/z$ 324 ($M^{+\cdot}$), 184 (100%); $M_r$ 324.1830, calcd 324.1837 for $C_{20}H_{24}N_2O_2$; mp 104 °C (ether). Anal. Found: C, 74.09; H, 7.41; N, 8.63. Calcd: C, 74.04; H, 7.46; N, 8.64.

**Imino Diels–Alder Reaction: Preparation of Indoloquinolizidines 20b, 21b, and 22b.** A mixture of imine **14b** (450 mg, 2.1 mmol) and 2,4-pentadienoic acid methyl ester (650 mg, 5.8 mmol) in chlorobenzene (20 mL) was heated under argon at 120 °C for 8 h. Chlorobenzene was distilled off under vacuum and the residue purified by flash chromatography (dichloromethane–methanol 98:2) afforded a mixture of **20**, **21b**, and **22b** (599 mg, 87.5%). This mixture was directly alkylated without further purification to afford **23b**.

Purification of the mixture of compounds **20b**, **21b**, and **22b** (60 mg) by preparative TLC (dichloromethane–methanol 95:5) afforded **20b** (8 mg, 13.3%) (less polar), **21b** (40 mg, 66%), and **22b** (8 mg, 13.3%) (more polar).

**20b**: IR 2900, 2820, 2800, 2750 (Wenkert–Bohlmann bands), 1730; UV (MeOH) 233, 282, 300; $^1H$ NMR $\delta$ 7.33 (d, 1 H, $J$ = 10, $C_9H$), 6.73 (m, 2 H, $C_{10}H$ and $C_{12}H$), 6.03 (dd, 1 H, $J$ = 12, 4, $C_{14}H$), 5.83 (broad dd, 1 H, $C_{15}H$), 3.87 (s, 3 H, $OCH_3$), 3.72 (s, 3 H, $NCH_3$), and 3.31 (s, 3 H, $CO_2CH_3$); MS, $m/z$ 326, $M_r$ 326.1627, calcd 326.1630 for $C_{19}H_{22}N_2O_3$.

**21b**: IR 2900, 2850, 1720; UV (MeOH) 233, 282, 300; $^1H$ NMR $\delta$ 7.33 (d, 1 H, $J$ = 10, $C_9H$), 6.75 (dd, 1 H, $J$ = 10, 2, $C_{10}H$), 6.72 (d, 1 H, $J$ = 2, $C_{12}H$), 5.95 (broad d, 1 H, $C_{14}H$), 5.70 (d, 1 H, $J$ = 10, $C_{15}H$), 4.45 (d, 1 H, $J$ = 10, $C_{21}H$), 3.87 (s, 3 H, $OCH_3$), 3.73 (s, 3 H, $NCH_3$), 3.31 (s, 3 H, $CO_2CH_3$), MS, $m/z$ 326 ($M^{+\cdot}$) 214; $M_r$ 326.1630, calcd 326.1630 for $C_{19}H_{22}N_2O_3$.

**22b**: IR 2900, 2850, 2830, 1700; UV (MeOH) 232, 285, 300; $^1H$ NMR $\delta$ 7.33 (d, 1 H, $J$ = 10, $C_9H$), 7.13 (m, 1 H, $C_{10}H$), 6.70 (d, 1 H, $C_{12}H$), 6.74 (m, 1 H, $C_{15}H$), 5.30 (s, 1 H, $C_{21}H$), 3.87 (s, 3 H,

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$OCH_3$), 3.78 (s, 3 H, $NCH_3$), 3.50 (s, 3 H, $CO_2CH_3$); MS, $m/z$ 326; $M_r$ 326.1620, calcd 326.1630 for $C_{19}H_{22}N_2O_3$.

**Preparation of Indoloquinolizidine 23b.** To a solution of lithium diisopropylamide (5.47 mmol) in THF/HMPA, prepared as for **23a**, was added a solution of **20b**, **21b**, and **22b** (400 mg, 1.2 mmol) in THF (10 mL) at −50 °C under argon. The mixture was stirred for 15 min at −50 °C and warmed to 0 °C before addition of ethyl iodide (0.3 mL, 3.75 mmol). After being stirred for 10 min at 0 °C, the reaction medium was treated as for **23a**. Purification by column chromatography (ethyl acetate–methanol 99:1) afforded **23b** (347 mg, 80%): IR 2910, 1720; UV 233, 278, 296; $^1$H NMR 7.32 (d, 1 H, $J$ = 8, $C_{12}$H), 6.75 (m, 2 H, $C_9$H + $C_{10}$H), 5.97 (broad s, 2 H, $C_{14}$H + $C_{15}$H), 4.06 (s, 1 H, $C_{21}$H), 3.87 (s, 3 H, $OCH_3$), 3.62 (s, 3 H) and 3.16 (s, 3 H) ($CO_2CH_3$ and $NCH_3$), 0.94 (t, 3 H, $J \simeq 7$, $C_{18}H_3$); MS, $m/z$ 354 ($M^{+\cdot}$), 214 (100%); $M_r$ 354.1937, calcd 354.1943 for $C_{21}H_{26}N_2O_3$.

**Preparation of Indoloquinolizidine (26).** To a solution of compound **24**[26] (52 mg, 0.17 mmol) in dimethylformamide (2 mL) at 0 °C was added in one portion sodium hydride (13.5 mg, 0.57 mmol). The resulting mixture was stirred under argon at 0 °C for 15 min and warmed at 20 °C. After 15 min, methyl iodide (40 μL, 0.64 mmol) was added. The mixture was stirred for an additional 30 min. Excess of methyl iodide was evaporated under vacuum and the reaction medium extracted with dichloromethane, washed with water, dried over magnesium sulfate, filtrated, and concentrated. Purification by preparative TLC (hexane–ethyl acetate 20:80) afforded **26** (43 mg, 80%): IR 3420, 2920, 1720; UV 280, 287, 294; $^1$H NMR 7.5–7 (4 H aromatic), 3.78 (s, 1 H, $C_{21}$H), 3.67 (s, 3 H) and 3.42 (s, 3 H) ($CO_2CH_3$ and $NCH_3$), 0.79 (t, 3 H, $J$ = 7, $C_{18}H_3$); MS, $m/z$ 326 ($M^{+\cdot}$), 325 (100%), 311, 211, 184.

**Hydrogenation of Indoloquinolizidine 23a.** A solution of **23a** (23 mg, 0.07 mmol) in ethanol (3 mL) was stirred in the presence of 10% Pd-C (5 mg) under hydrogen for 20 h. Filtration and evaporation of the ethanolic solution afforded quantitatively a compound identical with compound **26**.

**Preparation of β-Keto Sulfoxide 28a.** To a solution of dimethyl sulfoxide (0.58 mL, 8.2 mmol) in THF (25 mL) at −20 °C under argon was added dropwise $n$-butyllithium (5 mL, 8 mmol, 1.6 M in hexane). The mixture was warmed to −10 °C for 10 min and cooled at −20 °C. To this solution of dimsyllithium was added sequentially dimethyl sulfoxide (6 mL) and dropwise a solution of **23a** (820 mg, 2.53 mmol) in THF (10 mL). After being stirred at room temperature for 1 h, the mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with dichloromethane. After the usual treatment, the residue was chromatographed (dichloromethane–methanol 92:8) to provide **28a** (746 mg, 80%) as a mixture of diastereomers. **28a**: IR 2950, 1690; UV (MeOH) 230, 275; $^1$H NMR (60 MHz) 7.5–7 (4 H aromatic), 5.9 (m, 2 H, $C_{15}$H and $C_{14}$H), 3.60 (s, 3 H) and 3.58 (s, 3 H) ($CO_2CH_3$ and $NCH_3$), 2.46 and 2.42 (2s, $S(O)CH_3$), 0.98 (t, 3 H, $J$ = 7, $C_{18}H_3$); MS, $m/z$ (370 ($M^{+\cdot}$) 307, 184 (100%).

**Preparation of β-Keto Sulfoxide 28b.** To a solution of dimethyl sulfoxide (0.105 mL, 14.8 mmol) in THF (25 mL) at −20 °C under argon was added dropwise $n$-butyllithium (0.88 mL, 1.41 mmol, 1.6 M in hexane). The mixture was warmed to −10 °C for 10 min and cooled at −20 °C. To this solution was added sequentially dimethyl sulfoxide (1.75 mL) and dropwise a solution of **23b** (140 mg, 0.39 mmol) in THF (1.5 mL). The mixture was treated as above and afforded after preparative TLC (ethyl acetate–ammonia) **28b** (136 mg, 86%) as a mixture of diastereomers. **28b**: IR 2920, 1695; UV (MeOH) 230, 310; $^1$H NMR 7.5 (d, 1 H, $C_{12}$H), 6.95 (m, 2 H, $C_9$H and $C_{10}$H), 6.0 (m, 2 H, $C_{14}$H and $C_{15}$H), 3.83 (s, 3 H, $OCH_3$), 3.51 (s, 6 H, $CO_2CH_3$ and $NCH_3$), 2.45 (s, 3 H, $S(O)CH_3$), 0.90 (t, 3 H, $J$ = 7, $C_{18}H_3$); MS, $m/z$ 400 ($M^{+\cdot}$), 292, 277, 214 (100%), 213, 187.

**Rearrangement of β-Keto Sulfoxide 28a to 29a.** To a solution of compound **28a** (130 mg, 0.35 mmol) in THF (10 mL) was added in one portion $p$-toluenesulfonic acid monohydrate (280 mg, 1.47 mmol). The mixture was refluxed under argon and monitored by TLC (ethyl acetate–methanol 90:10). After being evaporated under vacuum, the residue was dissolved in dichloromethane and the organic phase was washed twice with an aqueous solution of sodium bicarbonate (10%) and then with water. After the usual workup, the residue was purified by column chromatography (ethyl acetate–methanol 95:5) and provided **29a** (90 mg, 73%): IR 3100, 1640; UV ($CH_3OH$) 224 (15.500), 249 (18.300), 300 (9.000), 372 (20.500); ($CH_3OH$–$H_3O^+$) 222 (13.800), 248 (18.000), 296 (9.000), 378 (18.500); $^1$H NMR 7.24 (m, 2 H), 6.98 (dd, 1 H) and 6.87 (d, 1 H) (4 H aromatic), 6.00 (d, 1 H, $J_{14,15}$ = 10.5, $C_{15}$H), 5.85 (dd, 1 H, $J_{14,15}$ = 10.5 and $J_{3,14}$ = 4.5, $C_{14}$H), 3.80 (s, 3 H, $NCH_3$), 3.39 (dd, 1 H, $J_{3a,3b}$ = 16.5 and $J_{3a,14}$ = 4.5, $C_3H_a$), 3.08 (d, 1 H, $J_{3a,3b}$ = 16.5, $C_3H_b$), 2.97 (dd, 1 H, $C_5H_a$), 2.81 (s, 1 H, $C_{21}$H), 2.60 (m, 1 H, $C_5H_b$, $C_6H_a$), 2.12 (s, 3 H, $SCH_3$), 2.02 (m, 1 H, $C_6H_a$, $C_5H_b$), 1.77 (dd, 1 H, $J_{6a,6b}$ = 12 and $J_{5,6}$ = 4.5, $C_6H_b$), 1.07 (q, 2 H, $J$ = 7, $C_{19}H_2$), 0.6 (t, 3 H, $J$ = 7, $C_{18}H_3$); MS, $m/z$ 352 ($M^{+\cdot}$), 305, 265, 198, 134 (100%), 122, 107; $M_r$ 352.1607, calcd 352.1627 for $C_{21}H_{24}N_2OS$.

**29a** hydrochloride: mp 196 °C ($CH_3OH$). Anal. Found: C, 62.72; H, 6.70; N, 6.87. Calcd for $C_{21}H_{25}N_2OSCl$, $CH_3OH$: C, 62.76; H, 6.94; N, 6.65.

**Rearrangement of β-Keto Sulfoxide 28b to 29b.** In a similar way, to a solution of compound **28b** (120 mg, 0.3 mmol) in THF (9 mL) was added $p$-toluenesulfonic acid (240 mg, 1.26 mmol). After treatment as for β-keto sulfoxide **28a**, the crude product was purified by preparative TLC (ethyl acetate–ammonia) and provide aspidosperma derivative **29b** (80 mg, 70%): IR 2910, 1700, 1625; UV ($CH_3OH$) 228 (11 300), 265 (13 000), 303 (3.600), 370 (18.000); ($CH_3OH$–$H_3O^+$) 270 (13.300), 300 (3.300), 378 (13.500); $^1$H NMR 7.22 (d, 1 H, $C_9$H), 6.56 (dd, 1 H, $C_{10}$H), 6.52 (d, 1 H, $C_{12}$H), 6.09 (d, 1 H, $J_{14,15}$ = 10.5, $C_{15}$H), 5.92 (dd, 1 H, $J_{14,15}$ = 10.5, $J_{3,14}$ = 5, $C_{14}$H), 3.86 (2 s, 3 H, $OCH_3$ and $NCH_3$), 3.48 (dd, 1 H, $J_{3a,3b}$ = 16.5 and $J_{3,14}$ = 5, $C_3H_a$), 3.16 (d, 1 H, $J_{3a,3b}$ = 16.5, $C_3H_b$), 3.03 (dd, 1 H, $C_5H_a$), 2.87 (s, 1 H, $C_{21}$H), 2.67 (m, 1 H, $C_5H_b$), 2.20 (s, 1 H, $SCH_3$), 0.71 (t, 3 H, $J_{18,19}$ = 7, $C_{18}H_3$); MS, $m/z$ 382 ($M^{+\cdot}$), 335, (100%), 228, 188, 134, 122; $M_r$ 382.1722, calcd 382.1715 for $C_{22}H_{26}N_2O_2S$.

**Reduction of Compound 29a To Give 30a.** To a solution of compound **29a** (39 mg, 0.11 mmol) in methanol (2.5 mL) under argon was added trifluoroacetic acid (0.2 mL) and sodium cyanoborohydride (28 mg, 0.37 mmol). After 5 min, the mixture was treated with an excess of 10% aqueous solution of sodium bicarbonate and extracted with dichloromethane. The crude product was purified by preparative TLC (dichloromethane) and afforded **30a** (35 mg, 89%): IR 1705, 1600; UV ($CH_3OH$) 252, 305 ($CH_3OH$–$H_3O^+$), 248, 302; $^1$H NMR 7.11 (dd, 1 H), 7.10 (d, 1 H), 6.75 (dd, 1 H, $J$ = 8) and 6.45 (d, 1 H, $J$ = 8, $C_{10}$H, $C_{11}$H, $C_9$H, and $C_{12}$H), 5.82 (ddd, 1 H, $J_{14,15}$ = 10, $J_{3a,14}$ = 5 and $J_{3b,14}$ = 1.5, $C_{14}$H), 5.39 (d, 1 H, $J_{14,15}$ = 10, $C_{15}$H), 5.26 (d, 1 H, $J \simeq$ 2, $C_{16}$H), 3.62 (d, 1 H, $C_2$H), 2.89 (s, 3 H, $NCH_3$), 2.32 (s, 1 H, $C_{21}$H), 2.15 (s, 3 H, $SCH_3$), 1.55 and 1.28 (m, 2 H, $C_{19}H_2$), 0.36 (t, 3 H, $J_{18,19}$ = 7, $C_{18}H_3$); MS, $m/z$ 354 ($M^{+\cdot}$), 266 (100%), 158, 135, 122, 121, 107; $M_r$ 354.1770, calcd 354.1776 for $C_{21}H_{26}N_2OS$; mp 180 °C (ether). Anal. Found: C, 71.12; H, 7.37; N, 7.78. Calcd: C, 71.15; H, 7.39; N, 7.90.

**Reduction of Compound 29b To Give 30b.** A solution of compound **29b** (42 mg, 0.11 mmol) in methanol (2.5 mL) was treated as above with sodium cyanoborohydride (23 mg, 0.37 mmol) in the presence of trifluoroacetic acid (0.2 mL). After alcalinization and extraction with dichloromethane, preparative TLC (dichloromethane) afforded **30b** (40 mg, 95%): IR 1705, 1600; UV ($CH_3OH$) 252, 305; ($CH_3OH$–$H_2O^+$) 248, 302. $^1$H NMR 6.98 (d, 1 H, $J_{9,10}$ = 8.2, $C_9$–H), 6.29 (dd, 1 H, $J_{9,10}$ = 8.2 and $J_{10,12}$ = 2.2, $C_{10}$H), 6.02 (d, 1 H, $J_{10,12}$ = 2.2, $C_{12}$H), 5.82 (ddd, $J_{14,15}$ = 10, $J_{3a,14}$ = 5, and $J_{3b,14}$ = 1.5, $C_{14}$H), 5.40 (broad d, 1 H, $J_{14,15}$ = 10, $C_{15}$H), 5.29 (d, 1 H, $J$ = 2, $C_{16}$H), 3.77 (s, 3 H, $OCH_3$), 3.64 (d, 1 H, $J_{2,16}$ = 2, $C_2$H), 2.88 (s, 3 H, $NCH_3$), 2.14 (s, 3 H, $SCH_3$), 1.58 and 1.27 (m, 2 H, $C_{19}H_2$) 0.40 (t, 3 H, $J_{18,19}$ = 7, $C_{18}H_3$), MS, $m/z$ 384 ($M^{+\cdot}$), 296 (100%), 158, 135, 122, 121; mp 158 °C (ether). Anal. Found: C, 68.78; H, 7.31; N, 7.58. Calcd: C, 68.71; H, 7.34; N, 7.29 for $C_{22}H_{28}N_2O_2S$.

**Hydrogenolysis of Keto Thioether 30a To Give 31a.** To a suspension of Ni (Raney) in acetone (20 mL) and cyclohexene (2 mL), previously refluxed for 1 h, was added a solution of **30a** (300 mg, 0.85 mmol) in acetone (60 mL). After being refluxed for 4 h, dichloromethane (30 mL) was added and the resulting suspension filtered and evaporated. The residue after purification by column chromatography (hexane–dichloromethane 50:50) afforded ketone **31a** (240 mg, 92%): IR 2960, 2910, 2860, 2770, 1700; UV ($CH_3OH$) 252, 320; ($CH_3OH$–$H_3O^+$) 249, 313; $^1$H NMR 7.12 (d and dd, 2 H), 6.75 (dd, 1 H), 6.47 (d, 1 H, $C_9$H, $C_{10}$H, $C_{11}$H,

and $C_{12}H$), 5.78 (dd, 1 H, $C_{14}H$), 5.53 (d, 1 H, $C_{15}H$), 2.68 (s, 3 H, $NCH_3$), 0.38 (t, 3 H, $J_{18,19}$ = 7, $C_{18}H_3$); MS, $M_r$ 308.1885, calcd 308.1888 for $C_{20}H_{24}N_2O$; mp 155–156 °C (ether). Anal. Found: C, 77.85; H, 7.86; N, 9.00. Calcd: C, 77.88; H, 7.84; N, 9.08.

**Hydrogenolysis of Keto Thioether 30b To Give 31b.** The same procedure as above was used for compound **30b** (170 mg, 0.48 mmol). Ketone **31b** (140 mg, 94%) was isolated after preparative TLC (ether–pentane 50–50): IR 2900, 2800, 2700, 1700, 1620, 1600; UV ($CH_3OH$) 254, 315 ($CH_3OH$–$H_3O^+$) 253, 312; $^1H$ NMR 7.02 (d, 1 H, $J_{9,10}$ = 8, $J_{10,12}$ = 2, $C_{10}H$), 6.03 (d, 1 H, $J_{10,12}$ = 2, $C_{12}H$), 5.79 (ddd, 1 H, $J_{14,15}$ = 10, $J_{3a,14}$ = 5, $J_{3b,14}$ = 1.6, $C_{14}H$), 5.53 (broad d, 1 H, $J_{14,15}$ = 10, $C_{15}H$), 3.78 (s, 3 H, $OCH_3$), 2.67 (s, 3 H, $NCH_3$), 0.43 (t, 3 H, $J_{18,19}$ = 7, $C_{18}H_3$); MS, $m/z$ 338 ($M^+\cdot$), 296, 135, 124, 122, 121, 107; $M_r$ 338.4524, calcd. 338.4520 for $C_{21}H_{26}N_2O_2$; mp 176 °C (ether). Anal. Found: C, 74.26; H, 7.73; N, 8.31. Calcd: C, 74.52; H, 7.74; N, 8.28.

**Preparation of β-Keto Ester 32a.**[8,36] To a suspension of NaH (120 mg, 5 mmol) in THF (2 mL) under argon at room temperature was added dropwise ketone **31a** (150 mg, 0.49 mmol). The mixture was stirred 2 h and dimethyl carbonate (0.75 mL, 0.89 mmol) was added. After being refluxed for 30 h the reaction medium was diluted at 0 °C with an aqueous saturated solution of ammonium chloride (2 mL) and acetic acid–water 50:50 (6 mL). The aqueous solution was extracted with ether (100 mL × 4), and the organic layer washed with an aqueous solution of $Na_2CO_3$ until pH 9 and with brine. After rotatory evaporation the residue was purified by preparative TLC (dichloromethane–methanol 98:2) and afforded **32a** (140 mg, 79%) as a mixture of ketone and enol. **32a**: IR 2920, 2850, 2760, 1710, 1700; UV ($CH_3OH$) 252, 305, ($CH_3OH$–$H_3O^+$) 255, 305; $^1H$ NMR 7.10–6.40 (4 H, aromatic), 5.87 (broad s, 2 H, $C_{14}H$ and $C_{15}H$), 4.22 (s, 1 H, $C_{16}H$), 3.82 and 3.72 (2 s, 3 H, $CO_2CH_3$), 3.65 (s, 1 H, $C_2H$), 2.74 and 2.67 (2 s, 3 H, $NCH_3$), 2.73 (s, 1 H, $C_{21}H$), 0.54 and 0.42 (2 t, 3 H, $C_{18}H_3$); MS, $m/z$ 366 ($M^+\cdot$), 267, 266, 158, 135 (100%), 122, 121, 107; $M_r$ 366.1923, calcd 366.1943 for $C_{22}H_{26}N_2O_3$; mp 168 °C (ether). Anal. Found: C, 72.14; H, 7.18; N, 7.77. Calcd: C, 72.10; H, 7.15; N, 7.65.

**Preparation of β-Keto Ester 32b.** β-Keto ester **32b** was prepared in a similar way from ketone **31b** (yield, 80%). **32b**: IR 2920, 2860, 2800, 1730, 1705; UV ($CH_3OH$) 255, 308 ($CH_3OH$–$H_3O^+$) 252, 305; $^1H$ NMR 6.33 (d, 1 H, $C_9H$), 5.70 and 5.66 (2 d, 1 H, $C_{10}H$), 5.43 (broad s, 1 H, $C_{12}H$), 5.32 (broad s, 2 H, $C_{14}H$ and $C_{15}H$), 3.85 (s, 1 H, $C_{16}H$), 3.45 and 3.43 (2 s, 6 H, $CO_2CH_3$ and $OCH_3$), 3.29 (s, 1 H, $C_2H$), 2.45 and 2.40 (2 s, 3 H, $NCH_3$), 0.57 and 0.42 (2 t, 3 H, $C_{18}H_3$); MS, $m/z$ 396 ($M^+\cdot$), 188, 174, 135, (100%), 124, 122, 121, 107; $M_r$ 396.2038, calcd 396.2049 for $C_{23}H_{28}N_2O_4$; mp 148 °C (hexane).

**Hydroxylation of β-Keto Ester 32a To Give 34a.** To a solution of **32a** (210 mg, 0.57 mmol) in THF (12 mL) was added under argon tetrabutylammonium fluoride (0.5 mL, 1 M in THF) and a solution of methylketene ethyl trimethylsilyl acetal (420 mg, 2.41 mmol) in THF (10 mL). The mixture was stirred for 6 h at room temperature and concentrated by rotary evaporation. The residue was dissolved in anhydrous 1,2-dichloroethane (4 mL) and treated with *m*-chloroperbenzoic acid (240 mg, 1.39 mmol) at 0 °C under argon. After 30 min at 0 °C, the mixture was poured in dichloromethane (200 mL) and washed three times with an aqueous solution of sodium bicarbonate (10%) and with water. The residue obtained after the usual workup was purified by column chromatography (dichloromethane–methanol 95:5) to give compound **34a** (200 mg, 88%): IR 3300, 2950, 1715, 1700; UV ($CH_3OH$) 248, 302, ($CH_3OH$–$H_3O^+$) 248, 302; $^1H$ NMR 7.98, 7.88, 7.55 and 6.59 (d, t, t, d, 4 H, $C_9H$, $C_{10}H$, $C_{11}H$, and $C_{12}H$), 6.08 (d, 1 H, $C_{15}H$), 5.76 (dd, 1 H, $C_{14}H$), 3.85 (s, 1 H) and 3.80 (s, 1 H) ($C_2H$ and $C_{21}H$), 3.83 (s, 3 H, $CO_2CH_3$), 2.69 (s, 3 H, $NCH_3$), 0.37 (t, 3 H, $C_{18}H_3$); MS, $m/z$ 398 ($M^+\cdot$), 382, 265, 158, 144, 135, 122, 121; $M_r$ 382.1899, calcd 382.1892 for $C_{22}H_{26}N_2O_5$; mp 179–180 °C ($CH_3OH$–ether). Anal. Found: C, 69.01; H, 6.70; N, 7.20. Calcd: C, 69.09; H, 6.85; N, 7.33.

**Reduction of $N_b$-Oxide 34a To Give 17-Desacetoxy-17-oxovindorosine (35a).**[39] To a solution of $N_b$-oxide **34a** (20 mg, 0.05 mmol) in water–acetic acid (2 mL, 50:50) was added activated Zn. After being stirred for 1 h at room temperature under argon, the mixture was poured into dichloromethane and washed with an aqueous solution of sodium bicarbonate (10%) to leave **35a** (18.7 mg, 100%), which was identical with 17-desacetoxy-17-oxovindorosine prepared from vindorosine.

**Deacetylation of Vindorosine.** Vindorosine was desacetylated according to the procedure described by Trojanek.[43]

**Preparation of 17-Desacetoxy-17-oxovindorosine 35a from 17-Desacetylvindorosine (36a).** To a solution of 17-desacetylvindorosine (100 mg, 0.27 mmol) in $Me_2SO$ (0.3 mL) was added triethylamine (0.2 mL, 1.43 mmol) and sulfur trioxide–pyridine (110 mg, 0.79 mmol). After being stirred for 48 h at room temperature, the mixture was diluted with dichloromethane (50 mL) alcalinized with an aqueous solution of sodium bicarbonate (10%) and washed with water. The residue obtained after the usual workup was purified by preparative TLC (dichloromethane–methanol 94:6) and afforded 17-desacetoxy-17-oxovindorosine (20 mg, 20%) and 60 mg of starting material. 17-Desacetoxy-17-oxovindorosine: IR 3000–2800, 1735, 1700–1600; UV ($CH_3OH$) 255, 310 ($CH_3OH$ + $H_3O^+$) 252, 310; $^1H$ NMR 7.16, 7.11, 6.81, 6.55 (t, d, t, d, 4 H, $C_9H$, $C_{10}H$, $C_{11}H$, and $C_{12}H$), 5.78 (dd, 1 H, $J_{14,15}$ = 10, $J_{3,14}$ = 4, $C_{14}H$), 5.68 (d, 1 H, $J_{14,15}$ = 10, $C_{15}H$), 3.92 (s, 1 H, $C_2H$), 3.88 (s, 3 H, $CO_2CH_3$), 3.51 (m, $C_3H_a$), 2.86 (m, 1 H, $C_3H_b$), 2.71 (s, 1 H, $C_{21}H$), 2.70 (s, 3 H, $NCH_3$), 1.51 (m, 1 H, $C_{19}H_a$), 1.30 (m, 1 H, $C_{19}H_b$), 0.40 (t, 3 H, $J_{18,19}$ = 7, $C_{18}H_3$); MS, $m/z$ 382 ($M^+\cdot$), 350, 295, 266, 158, 144, 135 (100%), 122, 121, 107; $M_r$ 382.1899, calcd 382.1892 for $C_{22}H_{26}N_2O_4$.

**Hydroxylation of β-Keto Ester 32b To Give 34b and 35b.** To a solution of **32b** (70 mg, 0.18 mmol) in THF (4 mL) was added sequentially tetrabutylammonium fluoride (0.2 mL, 1 M in THF) and a solution of methylketene ethyl trimethylsilyl acetal (140 mg, 0.80 mmol) in THF (2 mL). The mixture was treated as for **32a**, dissolved in 1,2-dichloroethane and oxidized with *m*-chloroperbenzoic acid (70 mg, 0.40 mmol). The residue was purified by preparative TLC ($SiO_2$, dichloromethane–methanol 90:10) and afforded three products **35b** (27 mg, 37%), **34b** (40 mg, 52%), and **32b** $N_b$-oxide (2 mg, 2.7%). **34b** was directly reduced by zinc in acetic acid to afford **35b**.

**Reduction of $N_b$-Oxide 34b To Give 17-Desacetoxy-17-oxovindoline (35b).** $N_b$-Oxide **34b** (30 mg, 0.07 mmole) was reduced as for **34a** with zinc (300 mg) in acetic acid–water (10 mL, 50:50) and afforded **35b** (29 mg, 100%) (total yield of **35b** from **32b**, 89%). **35b** was identical with 17-desacetoxy-17-oxovindoline obtained by oxidation of 17-desacetylvindoline: $M_r$ 412.2024, calcd 412.2018 for $C_{23}H_{28}N_2O_5$; mp 140 °C. Anal. Found: C, 67.04; H, 6.85; N, 6.90. Calcd: C, 66.97; H, 6.84; N, 6.79.

**Preparation of 17-Desacetoxy-17-oxovindoline (35b) from 17-Desacetylvindoline (36b).** To a solution of desacetylvindoline (414 mg, 1 mmol) in $Me_2SO$ (1 mL) was added triethylamine (0.9 mL, 6.47 mmol) and a solution of sulfur trioxide–pyridine complex (478 mg, 3.44 mmol) in $Me_2SO$ (2 mL). After being stirred for 20 h at 20 °C and 6 h at 60 °C, the mixture was treated as for 17-desacetoxy-17-oxovindorosine. The residue purified by preparative TLC (dichloromethane–methanol 92:8) gave 17-desacetoxy-17-oxovindoline (300 mg, 73%): IR 3400, 2900, 2800, 2750, 1740, 1700, 1600; UV ($CH_3OH$) 245, 302 ($CH_3OH$–$H_3O^+$) 250, 308; $^1H$ NMR 6.98 (d, 1 H, $J_{9,10}$ = 9, $C_9H$), 6.36 (dd, 1 H, $J_{9,10}$ = 9, $J_{10,12}$ = 1.5, $C_{10}H$), 6.11 (d, 1 H, $J_{10,12}$ = 1.5, $C_{12}H$), 5.79 (dd, 1 H, $J_{14,15}$ = 10, $J_{3,14}$ = 4, $C_{14}H$), 5.69 (d, 1 H, $J_{14,15}$ = 10, $C_{15}H$), 3.92 (s, 1 H, $C_2H$), 3.77 and 3.87 (2 s, 3 H, × 2, $CO_2CH_3$ and $OCH_3$), 2.68 (s, 3 H, $NCH_3$), 2.51 (s, 1 H, $C_{21}H$), 1.53 (m, 1 H, $C_{19}H_a$), 1.30 (m, 1 H, $C_{19}H_b$), 0.46 (t, 3 H, $J$ = 7, $C_{18}H_3$); MS, $m/z$ 412, 310, 184, 183; $M_r$ 412.2024, calcd 412.2000 for $C_{23}H_{28}N_2O_5$.

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