# Partial Synthesis of *Rauwolfia* Alkaloids, Vomilenine and (19*Z*)-Vomilenine, and Their Relative Thermodynamic Stability as Revealed by Their Transformation into Perakine

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**The geometry of the ethylidene side chain in vomilenine (1) was proven to be (19*E*) by the spectroscopic analysis of the synthetic intermediates from ajmaline (2) to vomilenine (1). The relative thermodynamic stability of vomilenine (1) and (19*Z*)-vomilenine (19), as revealed by their transformation into perakine (9), is discussed.**

**Keywords** *Rauwolfia* alkaloid; indole alkaloid; ajmaline; vomilenine; (19*Z*)-vomilenine; perakine; partial synthesis; structure elucidation; differential NOE experiment; thermodynamic stability

Vomilenine (**1**) was first isolated from *Rauwolfia vomitoria* as a minor constituent[1] and later it was found in some New Caledonian *Rauwolfia* species.[2] Recently, the important role of vomilenine (**1**) in the biogenesis of some *Rauwolfia* alkaloids, such as ajmaline (**2**), raucaffricine (**8**), raucaffrinoline (**10**), *etc.*, has been revealed, as summarized in Chart 1.[3] The structure of **1** was determined by Taylor *et al.*[4] through the chemical correlation with ajmaline (**2**), as illustrated in Chart 2. The structure of **1** then proposed had a (19*Z*) ethylidene side chain, but later, without any chemical evidence, the geometry of the C-19 position was revised to (19*E*),[5] as in the common sarpagine class of indole alkaloids. However, several sarpagine-type indole alkaloids having a (19*Z*) ethylidene moiety were found in *Gardneria* and *Gelsemium* species.[6] Consequently, careful confirmation of the ethylidene configuration is needed. Meanwhile one of the *Rauwolfia* alkaloids, perakine (**9**), is considered to be an artifact derived from vomilenine (**1**) based on the fact that treatment of **1** with hot acetic acid gave perakine (**9**).[4] We were interested in the effect of the

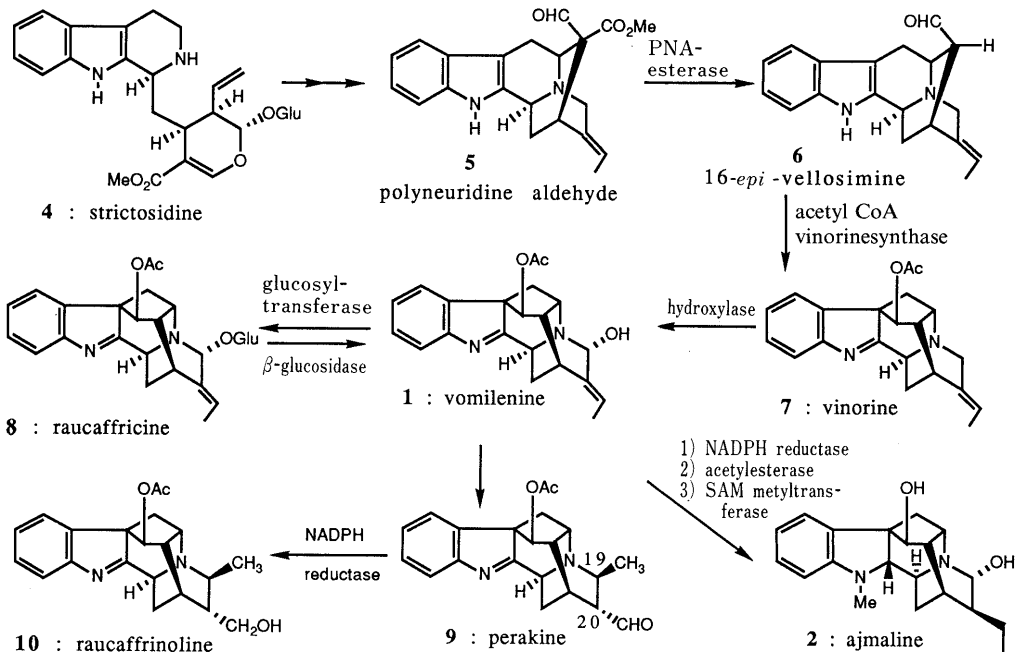



Chart 1. Proposed Biosynthetic Pathways of Sarpagine/Ajmaline Alkaloids[3]

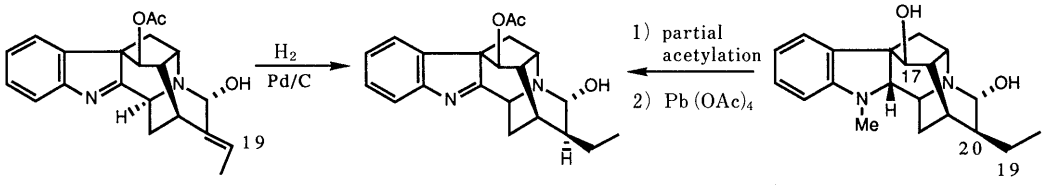
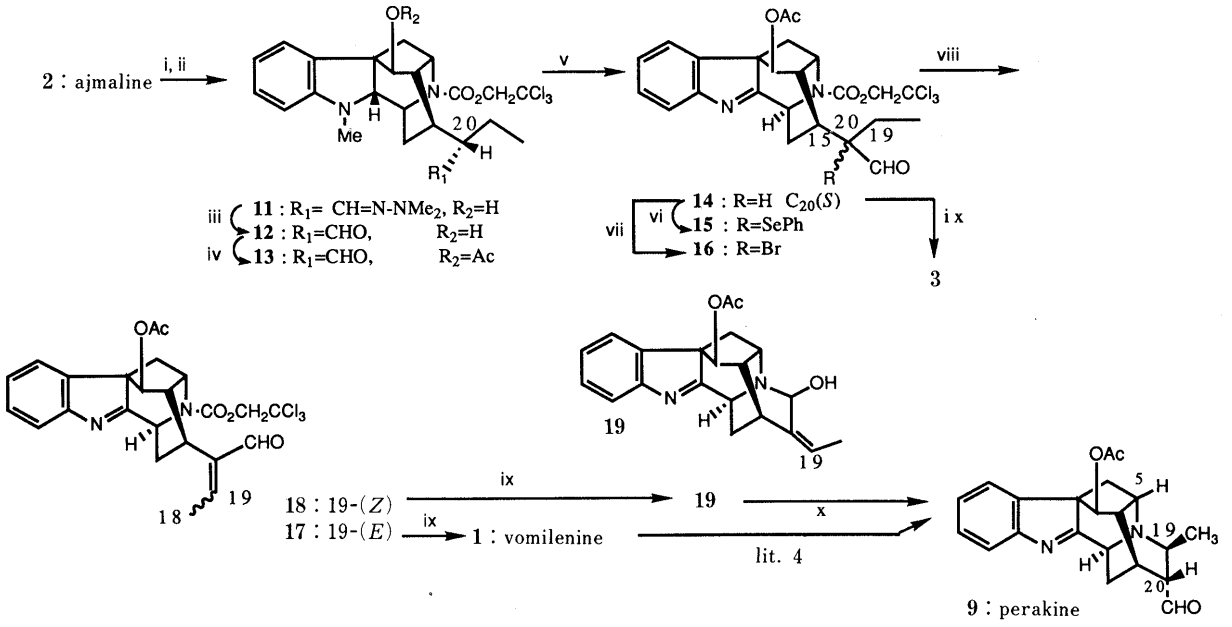



Chart 2

configuration of the ethylidene side chain on the facility of the transformation into perakine (**9**). In order to obtain chemical evidence of the configuration of the ethylidene side chain in **1** and to compare the thermodynamic stability of **1** and (19*Z*)-vomilenine (**19**), we planned the synthesis of vomilenine (**1**) and **19** from ajmaline (**2**).

Initially, ajmaline (**2**) was treated with *N*,*N*-dimethylhydrazine and a catalytic amount of $H_2SO_4$ to afford the secondary amine, that was directly converted to the carbamate (**11**) by using $\beta\beta\beta$-trichloroethyl chloroformate under Schotten–Baumann conditions in 70% overall yield. On hydrolysis of the hydrazone function in **11** with cupric chloride ($CuCl_2$) in aqueous tetrahydrofuran (THF) at pH 7,[7] the aldehyde (**12**) was obtained in 86% yield. After acetylation of the C-17 hydroxy group with acetic anhydride in pyridine, the $N_a$-methylindoline moiety was oxidized with lead tetraacetate [$Pb(OAc)_4$] in dry $CH_2Cl_2$ at $-70\,^{\circ}C$ to furnish the indolenine (**14**) in 88% yield. Compound **14** showed the characteristic ultraviolet (UV) absorption peaks at 210, 220, and 249 nm due to the indolenine chromophore. At this stage, we cleaved the protecting group on $N_b$ in **14** with zinc (Zn) in AcOH at room temperature to afford 1-demethyl-$\Delta'$-17-acetylajmaline (**3**) (mp 238—242 °C); its spectral properties [mass spectrum (MS), proton ($^1$H-) and carbon-13 nuclear magnetic resonance ($^{13}$C-NMR) spectra] were in accord with those of natural **3**.[2,8] This fact indicates that the configuration at the C-20 position did not epimerize under the reaction conditions of transformation from **2** to **3** *via* the hydrazone derivative. To introduce the double bond at the 19–20 position, a bromine atom or phenylselenyl group were introduced at the C-19 position through the silyl enol ether of the aldehyde function. Thus, **14** was treated successively with *tert*-butyldimethylsilyltriflate (TBSOTf) and triethylamine ($Et_3N$) in dry $CH_2Cl_2$ and then with phenylselenenyl chloride (PhSeCl) or *N*-bromosuccinimide (NBS) to provide the $\alpha$-substituted aldehydes (**15** or **16**) in 53% and 71% yields, respectively. Oxidation of **15** using *m*-chloroperbenzoic acid (*m*CPBA) or sodium periodate ($NaIO_4$) resulted in the exclusive formation of the tetrasubstituted olefins, but dehydrobromination of **16** with lithium carbonate ($Li_2CO_3$) in dimethylformamide (DMF) at 80°C afforded the desired *E*-olefin (**17**) in 26% yield accompanied with the *Z*-olefin (**18**) (21%) and tetrasubstituted olefins (total 18%). The geometry of the olefins (**17** and **18**) was unambiguously determined by nuclear Overhauser effect (NOE) experiments. Thus, irradiation of the C-21 aldehyde proton ($\delta$ 9.39, 9.37)[9] in **17** led to enhancement (22.7%) of the C-19 olefinic proton signal ($\delta$ 6.62), while 9.5% enhancement was observed between the aldehyde proton ($\delta$ 10.21, 10.16) and C-18 methyl protons ($\delta$ 2.16, 2.17) in **18**. Finally, the protecting group on $N_b$ in **17** was removed with Zn in AcOH at room temperature to give rise to vomilenine (**1**) in 68% yield. The $^1$H- and $^{13}$C-NMR spectra, infrared (IR) spectrum, MS and mp (189—191 °C) were identical with those of natural vomilenine (**1**). Therefore, the structure of vomilenine was concluded to be **1**. The *Z*-isomer (**18**) was also converted to the vomilenine-type compound (**19**) in 75% yield by removal of the carbamate group under the same reaction conditions.

Next, we compared the facility of the transformation of vomilenine (**1**) and (19*Z*)-vomilenine (**19**) into perakine (**9**). On standing of **19** in acetic acid at room temperature, 25% of the starting material had changed to perakine (**9**) after 17 h, and two weeks later **19** was completely converted to **9**. The synthetic compound (mp 179—183 °C) exhibited




reagents and conditions : i, $H_2N$-$NMe_2$, cat. $H_2SO_4$, 3A-MS, EtOH, reflux, 2.5 h; ii, $ClCO_2CH_2CCl_3$, 1N NaOH/$CH_2Cl_2$, 0°C to r.t., 40 min; iii, $CuCl_2$, aq. THF, phosphate buffer (pH 7); iv, $Ac_2O$, pyridine, r.t., overnight; v, $Pb(OAc)_4$, dry $CH_2Cl_2$, $-70$°C to 0°C, 4 h; vi, TBSOTf, $Et_3N$, dry $CH_2Cl_2$, 0°C to r.t., then PhSeCl in dry $CH_2Cl_2$, r.t.; vii, TBSOTf, $Et_3N$, dry $CH_2Cl_2$, 0°C to r.t., then NBS, 0°C; viii, $Li_2CO_3$, DMF, 80°C, 4.5 h; ix, activated Zn, AcOH, r.t., 1.5—3.5 h; x, AcOH, r.t., 2 weeks

Chart 3

spectral properties ($^1$H- and $^{13}$C-NMR, IR, and MS) in accord with those of authentic perakine (**9**). In contrast to the results obtained with **19**, **1** was quite stable in acetic acid at room temperature. For the conversion of vomilenine (**1**) to perakine (**9**), relatively severe conditions (reflux in AcOH)[4] were required. Interestingly, the two geometric isomers, vomilenine (**1**) and (19*Z*)-vomilenine (**19**), gave the same product, perakine (**9**). In the $^{13}$C-NMR spectra, the signal of C-21 in **19** was observed at 1.5 ppm upfield from the corresponding signal of **1**. Therefore, probably due to the steric repulsion between the hydroxy group and/or the hydrogen on C-21 and the $C_{18}$-methyl group in **19**, cleavage of the amino-acetal function in **19** could proceed more readily than that of **1** and subsequent Michael-type ring closure between $N_b$ and C-19 would furnish the thermodynamically controlled product, perakine (**9**), through epimerization at the C-20 position.

## Experimental

All melting points were determined on a Yamato MP-21 apparatus and are uncorrected. The instruments used in this study were as follows; UV spectra, Hitachi U3400 spectrophotometer; IR spectra, Hitachi 260 spectrophotometer; MS, Hitachi RMU-6E and RMU-7M spectrometers; $^1$H- and $^{13}$C-NMR spectra, JEOL JNM GX270, JEOL GSX400, and JEOL GSX500 instruments (in $CDCl_3$ with tetramethylsilane as an internal standard; chemical shifts are recorded in $\delta$ values); optical rotation, JASCO DIP-140 polarimeter. Thin-layer chromatography was performed on Merck precoated Silicagel 60 $F_{254}$ plates. Column chromatography was carried out on Merck Silica gel 60 (230—400 mesh for flash chromatography) and pre-packed columns [Kusano CPS-HS-221-05 (for medium-pressure column chromatography)].

**Preparation of the Hydrazone (11) from Ajmaline (2)** Concentrated $H_2SO_4$ (1 ml), *N,N*-dimethylhydrazine (6.8 ml, 89.5 mmol) and molecular sieves (3 Å, 12 g) were added to a stirred suspension of ajmaline (**2**) (6.0 g, 18.38 mmol) in dry ethanol (100 ml), and the mixture was heated under reflux for 2.5 h. After evaporation of the ethanol, the reaction mixture was poured into cold 10% aqueous $Na_2CO_3$ solution and the whole was extracted with $CHCl_3$. The organic extract was dried over $MgSO_4$ and evaporated to give 7.5 g of residue. The resulting crude hydrazone was dissolved in $CH_2Cl_2$ (240 ml) and 1 N NaOH solution (60 ml). Then $ClCO_2CH_2CCl_3$ (3.7 ml, 26.88 mmol) was added to the vigorously stirred solution during 2 min at 0 °C and the mixture was stirred at room temperature for 40 min. The reaction mixture was diluted with water (100 ml) and the organic layer was separated. The aqueous layer was extracted with $CH_2Cl_2$. The combined organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (AcOEt–hexane, 2 : 1) to give the carbamate (**11**) (7.00 g, 70%) as an amorphous powder. UV $\lambda_{max}^{EtOH}$ nm: 247, 293. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3350, 2950, 1750, 1300. $^1$H-NMR (270 MHz) $\delta$: 6.45, 6.40[9] (1H, each d, $J$=7.0 Hz, N=CH), 4.82, 4.79 (1H, each d, $J$=11.9 Hz, $CH_aH_bCCl_3$), 4.73, 4.69 (1H, each d, $J$=11.9 Hz, $CH_aH_bCCl_3$), 4.48, 4.40 (1H, each dd, $J$=7.3, 4.0 Hz, 5-H), 4.08, 4.07 (1H, each s, 17-H), 2.76, 2.75 [9H, each s, $N_a$-$CH_3$, $N(CH_3)_2$], 0.86, 0.84 (3H, each t, $J$=7.3 Hz, 18-$CH_3$). MS *m/z* (%): 544 ($M^+$+2, 24), 542 ($M^+$, 25), 144 (100), 113 (76).

**The Aldehyde (12)** $CuCl_2$ (139 mg, 0.103 mmol) was added to a solution of **11** (187 mg, 0.034 mmol) in THF (4.6 ml), phosphate buffer (pH 7, 0.24 ml) and water (2.2 ml). The mixture was stirred at room temperature for 36 h and then diluted with water (10 ml) and concentrated ammonia (5 ml). The whole was extracted with $CHCl_3$ and the organic layer was washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave a residue (214 mg), which was separated by flash column chromatography (AcOEt–hexane, 2 : 1) to afford the aldehyde (**12**) (149 mg, 86%) as an amorphous powder. UV $\lambda_{max}^{EtOH}$ nm: 247, 291. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 3300, 2950, 1710, 1430, 1120. $^1$H-NMR (270 MHz) $\delta$: 9.64 (1H, d, $J$=3.7 Hz, CHO), 4.90, 4.76 (1H, each d, $J$=11.9 Hz) and 4.83, 4.65 (1H, each d, $J$=12.2 Hz) ($CH_2CCl_3$), 4.68 (1H, d, $J$=8.6 Hz, 3-H), 4.48—4.40 (1H, m, 5-H), 4.13 (1H, s, 17-H), 2.77, 2.76 (3H, each s, $N_a$-$CH_3$), 0.86 (3H, t, $J$=7.3 Hz, 18-$CH_3$). MS *m/z* (%): 502 ($M^+$+2, 17), 500 ($M^+$, 18), 144 (100).

**The 17-*O*-Acetate (13)** A solution of **12** (618 mg, 1.23 mmol) in dry pyridine (10 ml) and acetic anhydride (4 ml) was stirred at room temperature overnight. After evaporation of the solvents, 5% aqueous $Na_2CO_3$ solution was added to the residue and the whole was extracted with $CHCl_3$. The organic extract was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified with flash column chromatography (AcOEt–hexane, 2 : 1) to give the acetate (**13**) (623 mg, 93%) as an amorphous powder. UV $\lambda_{max}^{EtOH}$ nm: 247, 293. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 2960, 1710, 1430, 1240, 1120. $^1$H-NMR (270 MHz) $\delta$: 9.51, 9.49 (1H, each d, $J$=3.4 Hz, CHO), 4.89 (1H, s, 17-H), 4.85, 4.70 (1H, each d, $J$=11.9 Hz) and 4.80 (1H, s) ($CH_2CCl_3$), 4.72 (1H, d, $J$=8.6 Hz, 3-H), 4.46—4.39 (1H, m, 5-H), 2.774, 2.768 (3H, each s, $N_a$-$CH_3$), 2.21, 2.19 (3H, each s, $OCOCH_3$), 0.87 (3H, t, $J$=7.4 Hz, 18-$CH_3$). MS *m/z* (%): 544 ($M^+$+2, 20), 542 ($M^+$, 20), 144 (100).

**Lead Tetraacetate Oxidation of the Indoline (13)** $Pb(OAc)_4$ was added to a stirred solution of **13** (915 mg, 1.68 mmol) in dry $CH_2Cl_2$ (20 ml) at −70 °C in the following manner: 0 min, 746 mg (1.68 mmol); 60 min, 840 mg (1.89 mmol); 135 min, 650 mg (1.47 mmol). During this period, stirring was continued at the same temperature, and after the final addition of $Pb(OAc)_4$ the reaction temperature was gradually raised to 0 °C over 1 h. The reaction mixture was diluted with $CH_2Cl_2$ and washed successively with 5% aqueous $Na_2CO_3$ solution and water. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was purified by flash column chromatography (AcOEt–hexane, 1 : 2) to yield the indolenine (**14**) (788 mg, 88%) as an amorphous powder. UV $\lambda_{max}^{MeOH}$ nm: 210, 220, 249. IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 2950, 1720, 1420, 1220, 1120. $^1$H-NMR (270 MHz) $\delta$: 9.544, 9.540 (1H, each d, $J$=4.4 Hz, CHO), 5.46, 5.43 (1H, each d, $J$=7.1 Hz, 3-H), 5.01, 4.84 (1H, each d, $J$=12.0 Hz, $CH_aH_bCCl_3$), 4.76, 4.57 (1H, each d, $J$=12.0 Hz, $CH_aH_bCCl_3$), 2.15, 2.14 (3H, each s, $COCH_3$), 0.88, 0.86 (3H, each t, $J$=7.2 Hz, 18-$CH_3$). MS *m/z* (%): 499 ($M^+$+2−CHO, 11), 497 ($M^+$−CHO, 12), 167 (100).

**1-Desmethyl-$\Delta'$-17-acetylajmaline (3)** Zinc dust (99 mg) was added to a solution of **14** (49 mg, 0.093 mmol) in acetic acid (1 ml), and the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* and then basified by the addition of chilled 5% aqueous $NaHCO_3$ solution. The whole was extracted with $CHCl_3$. The organic extract was washed with water, and dried over $MgSO_4$. Removal of the solvent gave a residue, which was subjected to medium-pressure liquid column chromatography (MPLC) (5% MeOH–$CHCl_3$) to afford 17 mg (52%) of **3** as colorless prisms, mp 238—242 °C (lit[8], 240—242 °C). UV $\lambda_{max}^{MeOH}$ nm: 219, 257. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3300—3000, 2960, 1740, 1240. $^1$H-NMR (500 MHz) $\delta$: 5.37 (1H, br s, OH), 5.00 (1H, s, 17-H), 4.33 (1H, d-like, $J\approx$11 Hz, 3-H), 4.31 (1H, s, 21-H), 3.33 (1H, t, $J$=5.7 Hz, 5-H), 2.78 (1H, dd, $J$=12.0, 5.0 Hz, 6-H$_\beta$), 2.42 (1H, m, 15-H), 2.26 (1H, t, $J$=6.0 Hz, 16-H), 2.17 (3H, s, $COCH_3$), 1.89 (1H, dd, $J$=14.0, 10.1 Hz, 14-H$_\alpha$), 1.74 (1H, dd, $J$=14.0, 5.0 Hz, 14-H$_\beta$), 1.64 (1H, d, $J$=12.0 Hz, 6-H$_\alpha$), 1.50—1.40 (2H, m, 19-$H_2$), 0.98 (3H, t, $J$=6.6 Hz, 18-$CH_3$). $^{13}$C-NMR (67.8 MHz) $\delta$: 183.2 (C2), 54.8 (C3), 49.8 (C5)*, 37.7 (C6), 65.1 (C7), 136.5 (C8), 123.8 (C9), 125.5 (C10), 128.8 (C11), 121.1 (C12), 156.4 (C13), 27.8 (C14), 27.6 (C15), 47.0 (C16)*, 78.7 (C17), 11.9 (C18), 26.0 (C19), 42.0 (C20), 87.5 (C21), 169.9 (CO), 21.1 ($CO\underline{C}H_3$) (The assignments having a superscript may be interchanged). MS *m/z* (%): 352 ($M^+$, 100), 324 (24), 323 (26), 169 (95). Exact MS Calcd for $C_{21}H_{24}N_2O_3$: 352.1788. Found: 352.1787.

**Preparation of the α-Phenylselenoaldehyde (15)** $Et_3N$ and TBSOTf were added to a stirred solution of **14** (318 mg, 0.60 mmol) in dry $CH_2Cl_2$ (5 ml) at 0 °C as follows: 0 min, $Et_3N$ (125 μl, 0.90 mmol) and TBSOTf (200 μl, 0.87 mmol); 45 min, $Et_3N$ (125 μl, 0.90 mmol) and TBSOTf (200 μl, 0.87 mmol); 180 min, TBSOTf (150 μl, 0.65 mmol). Stirring was continued at the same temperature for 4 h. To this reaction mixture containing silyl enol ether, a solution of PhSeCl (116 mg, 0.60 mmol) in dry $CH_2Cl_2$ (2 ml) was added at −20 °C. After 2 h, a solution of PhSeCl (89 mg, 0.46 mmol) in dry $CH_2Cl_2$ (0.6 ml) was added at −20 °C and then the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with $CH_2Cl_2$ and washed with 5% aqueous $Na_2CO_3$ solution. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by flash column chromatography (AcOEt–hexane, 2 : 1) and then by MPLC (1% MeOH–$CHCl_3$) to give oily **15** (220 mg, 53%) as a diastereomeric mixture and the starting material **14** (31 mg, 10%). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 2970, 1720, 1420, 1320, 1220. $^1$H-NMR (400 MHz) $\delta$: 7.70—7.20 (9H, m, arm-H). MS *m/z* (%): 655 ($M^+$+2−CO, 4), 653 ($M^+$−CO, 4), 345 (58), 343 (59), 169 (70), 168 (100), 167 (96).

**Preparation of the α-Bromoaldehyde (16)** $Et_3N$ and TBSOTf were added to a stirred solution of **14** (92 mg, 0.174 mmol) in dry $CH_2Cl_2$ (1.5 ml) at 0 °C as follows: 0 min, $Et_3N$ (37 ml, 0.27 mmol) and TBSOTf (58 ml, 0.25 mmol); 75 min, $Et_3N$ (37 ml, 0.27 mmol) and TBSOTf (58 ml,

0.25 mmol); 180 min, TBSOTf (29 ml, 0.13 mmol). After the final addition of the reagent, the mixture was stirred at room temperature for 5 h. To this reaction mixture containing silyl enol ether, a solution of NBS (36 mg, 0.202 mmol) in dry $CH_2Cl_2$ (1.5 ml) was added at 0 °C, and the whole was stirred at the same temperature for 10 min. The reaction mixture was diluted with $CH_2Cl_2$ and washed with 5% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (AcOEt–hexane, 1 : 2) to afford 75 mg (71%) of oily **16** as a diastereomeric mixture. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 2950, 1720, 1700, 1220. $^1$H-NMR (500 MHz) $\delta$: 9.47, 9.45, 9.42 (1H, each s, CHO), 2.19, 2.18, 2.17, 2.16 (3H, each s, $COCH_3$). MS *m/z* (%): 525 ($M^+ + 2 - HBr$, 15), 523 ($M^+ - HBr$, 17), 345 (63), 343 (65), 169 (77), 168 (90), 167 (100), 156 (63).

**Dehydrobromination of 16 with $Li_2CO_3$** A mixture of **16** (134 mg, 0.22 mmol) and $Li_2CO_3$ (50 mg, 0.68 mmol) in dry DMF (4 ml) was stirred at 80 °C for 4.5 h under an argon atmosphere. Then 5% aqueous $NaHCO_3$ solution was added to the reaction mixture and the whole was extracted with $CHCl_3$. The organic extract was washed with brine, dried over $MgSO_4$ and evaporated. DMF was removed in a Kugelrohr apparatus and the residue was purified by MPLC (AcOEt–hexane, 1 : 2) to give oily **17** (30 mg, 26%), oily **18** (25 mg, 21%), a more polar tetrasubstituted olefin (8 mg, 7%), and a less polar tetrasubstituted olefin (13 mg, 11%). **17**; UV $\lambda_{max}^{EtOH}$ nm: 220.2. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3000, 1710, 1430, 1220, 1130, 1040. $^1$H-NMR (500 MHz) $\delta$: 9.39, 9.37 (1H, each s, CHO), 6.62 (1H, q, $J$=7.2 Hz, 19-H), 5.52, 5.49 (1H, each d, $J$=8.5 Hz, 3-H), 5.06, 4.98 (1H, each m, 5-H), 4.85, 4.81 (1H, each d, $J$=11.8 Hz, $C\underline{H}_aH_bCCl_3$), 4.76, 4.63 (1H, each d, $J$=11.8 Hz $CH_a\underline{H}_bCCl_3$), 4.60, 4.59 (1H, each s, 17-H), 2.17, 2.16 (3H, each s, $COCH_3$), 2.05 (3H, d, $J$=6.9 Hz, 18-$CH_3$). MS *m/z* (%): 526 ($M^+ + 2$, 25), 524 ($M^+$, 24), 498 (13), 496 (13), 345 (54), 343 (53), 169 (69), 168 (76), 167 (100). **18**; UV $\lambda_{max}^{EtOH}$ nm: 220.5. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 2940, 1715, 1680, 1430, 1220, 1130, 1040. $^1$H-NMR (400 MHz) $\delta$: 10.21, 10.16 (1H, each s, CHO), 6.79 (1H, qt, $J$=7.5, 1.3 Hz, 19-H), 5.46, 5.44 (1H, each d, $J$=8.5 Hz, 3-H), 4.96, 4.73 (1H, each d, $J$=11.9 Hz, $C\underline{H}_aH_bCCl_3$), 4.91, 4.80 (1H, each m, 5-H), 4.80 (1H, s, 17-H), 4.70, 4.53 (1H, each d, $J$=11.9 Hz, $CH_a\underline{H}_bCCl_3$), 2.17, 2.16 (3H, each s, $COCH_3$), 2.16, 2.14 (3H, each dd, $J$=7.5, 1.6 Hz, 18-$CH_3$). MS *m/z* (%): 526 ($M^+ + 2$, 24), 524 ($M^+$, 23), 498 (13), 496 (13), 168 (82), 167 (100).

**Preparation of Vomilenine (1)** Zinc dust (450 mg) was added to a solution of **17** (124 mg, 0.24 mmol) in acetic acid (4 ml), and the mixture was stirred at room temperature for 3 h, then filtered. The filtrate was concentrated and then basified with chilled 5% aqueous $NaHCO_3$ solution. The whole was extracted with $CHCl_3$ and the organic extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave the residue, which was purified by MPLC (5% MeOH–$CHCl_3$) to afford 58 mg (68%) of vomilenine (**1**) as colorless prisms from AcOEt. mp 189—191 °C. $[\alpha]_D^{19}$ −71.6° ($c$=0.45, pyridine). UV $\lambda_{max}^{MeOH}$ nm: 219, 260. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3300—3000, 2950, 1740, 1600, 1450, 1230. $^1$H-NMR (500 MHz) $\delta$: 6.06 (1H, br s, OH), 5.75 (1H, q, $J$=6.6 Hz, 19-H), 5.03 (1H, br s, 21-H), 4.98 (1H, s, 17-H), 4.31 (1H, dd, $J$=7.1, 2.8 Hz, 3-H), 3.92 (1H, t, $J$=5.8 Hz, 5-H), 3.28 (1H, m, 15-H), 2.77 (1H, dd, $J$=12.1, 4.7 Hz, 6-$H_\beta$), 2.17 (3H, s, $COCH_3$), 1.68 (3H, d, $J$=6.6 Hz, 18-$CH_3$). $^{13}$C-NMR (67.8 MHz) $\delta$: 182.3 ($C_2$), 54.4 (C3)*, 50.9 (C5)*, 36.4 (C6), 65.2 (C7), 136.3 (C8), 123.8 (C9), 125.7 (C10), 128.8 (C11), 121.1 (C12), 156.4 (C13), 26.4 (C14), 28.4 (C15), 49.2 (C16)*, 77.6 (C17), 13.0 (C18), 119.6 (C19), 139.2 (C20),[10] 82.4 (C21), 169.9 (CO), 21.1 ($COCH_3$) (The assignments having a superscript may be interchanged). MS *m/z* (%): 350 ($M^+$, 29), 169 (100), 43 (15). *Anal.* Calcd for $C_{21}H_{22}N_2O_3 \cdot 1/4H_2O$: C, 71.07; H, 6.39; N, 7.89. Found: C, 70.96; H, 6.27; N, 7.82. Exact MS Calcd for $C_{21}H_{22}N_2O_3$: 350.1629. Found: 350.1627.

**Preparation of (19*Z*)-Vomilenine (19)** Zinc dust (99 mg) was added to a solution of **18** (42 mg, 0.08 mmol) in acetic acid (2 ml), and the mixture was stirred at room temperature for 1.5 h. A residue obtained by work-up as described above was purified by MPLC (iso-PrOH–$CHCl_3$–hexane, 7 : 63 : 30) to give 21 mg (75%) of **19** as an amorphous solid and 3 mg (7%) of the starting material **18**. UV $\lambda_{max}^{EtOH}$ nm: 219, 258. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3600—3100, 2970, 1740, 1230. $^1$H-NMR (500 MHz) $\delta$: 7.65—7.20 (4H, m, arm-H), 5.54 (1H, q like, 19-H), 5.19 (1H, s, 21-H), 4.99 (1H, s, 17-H), 2.16 (3H, s, $COCH_3$), 1.8—1.6 (3H, 18-$CH_3$). $^{13}$C-NMR (100 MHz) $\delta$: 182.9 (C2), 55.5 (C3), 50.6 (C5), 37.0 (C6), 64.3 (C7), 136.3 (C8), 123.8 (C9), 125.5 (C10), 128.7 (C11), 121.1 (C12), 156.4 (C13), 26.4 (C14), 34.4 (C15), 48.6 (C16), 77.8 (C17), 13.0 (C18), 122.1 (C19), 139.4 (C20), 80.9 (C21), 169.9 (CO), 21.0 ($OCH_3$. MS *m/z* (%): 350 ($M^+$, 100), 321 (20), 196 (32), 169 (56), 168 (80), 43 (42). Exact MS Calcd for $C_{21}H_{22}N_2O_3$: 350.1629. Found: 350.1621.

**Preparation of Perakine (9) from (19*Z*)-Vomilenine (19)** A solution of **9** (6 mg, 0.017 mmol) in acetic acid (0.5 ml) was stirred at room temperature under an argon atmosphere. After 17 h, a small portion of the reaction mixture was neutralized with chilled ammonia water and extracted with $CHCl_3$. The organic extract was dried over $MgSO_4$ and evaporated. The crude residue was subjected to $^1$H-NMR measurement. The ratio of (19*Z*)-vomilenine (**19**) and perakine (**9**) was calculated from the integrals of the signals of the olefinic proton (19-H) of **19** and the aldehyde proton (21-H) of **9**. The reaction mixture after 17 h contained 25% perakine (**9**) and 75% starting material **19**. The remaining reaction mixture was stirred at the same temperature for two weeks. The $^1$H-NMR spectrum of the crude residue obtained by the same work-up procedure as above showed the exclusive presence of perakine (**9**). The residue was crystallized from acetone–hexane to give 4 mg of colorless prisms. mp 179—182 °C (lit.[4] 185 °C). The chromatographic behavior on TLC, as well as the IR, MS, Exact MS (Calcd for $C_{21}H_{22}N_2O_3$: 350.1629. Found: 350.1622), and $^1$H- and $^{13}$C-NMR spectra of the semisynthetic compound were identical with those of authentic perakine (**9**). The stereochemistry at the C-19 and C-20 positions was further confirmed by the differential NOE spectrum. Irradiation of 18-$H_3$ ($\delta$ 1.30) in **9** led to enhancement of the 5-H (16%) and H-20 (15%) signals.

**Acknowledgment** We thank Professor J. Poisson, Centre d'Etudes Pharmaceutiques-F, for providing a sample of natural vomilenine. Thanks are also due to Mrs. H. Seki, Miss R. Hara and Mr. T. Kuramochi in the Analytical Center of our University for measurements of spectral data (NMR and MS). Support of this research by the Ministry of Education, Science and Culture, Japan (International Scientific Research Program, Joint Research; No. 01044025) is gratefully acknowledged.

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9) Carbamate derivatives of ajmaline were often found from the $^1$H-NMR spectra to occur as a mixture of rotational isomers in the ratio of approximately 1 : 1.
10) The chemical shift value at $C_{20}$ ($\delta$ 131.0) of vomilenine in the literature[2] should be revised to $\delta$ 139.2 (personal correspondence with Professor J. Poisson).