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A Synthesis of Seco-mesembrane Alkaloids, (±)-Joubertiamine, (±)-Joubertinamine, and (±)-Epijoubertinamine

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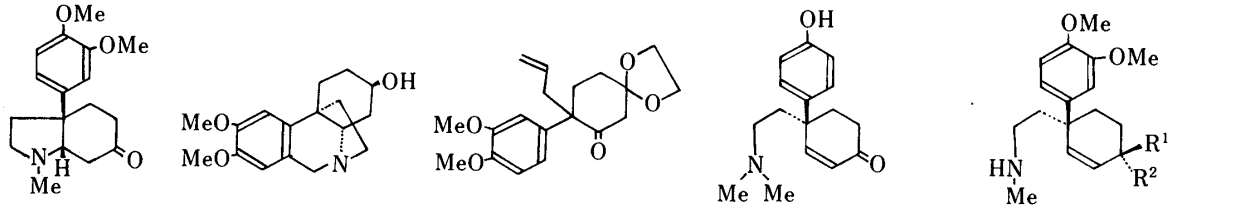
A synthesis of seco-mesembrane alkaloids, (±)-joubertiamine (**4**), (±)-joubertinamine (**5**), and (±)-epijoubertinamine (**6**), was accomplished starting with 2-allyl-2-aryl-5,5-ethylenedioxycyclohexanones (**10** and **3**), which are readily available by allylation of 2-aryl-5,5-ethylenedioxycyclohexanones (**9** and **16**) with allyl bromide and 50% aqueous sodium hydroxide in the presence of 18-crown-6.

Keywords——(±)-joubertiamine; (±)-joubertinamine; (±)-epijoubertinamine; seco-mesembrane alkaloid; 2-allyl-2-aryl-5,5-ethylenedioxycyclohexanone; allylation; 18-crown-6; sodium borohydride–cerium trichloride; oxidation

Previously,[2] we have reported a synthesis of Sceletium and Amaryllidaceae alkaloids, (±)-mesembrine (**1**) and (±)-dihydromaritidine (**2**) starting with a 2-allyl-2-arylcyclohexanone derivative (**3**), which is readily prepared by allylation of the 2-arylcyclohexanone derivative (**16**) with allyl bromide and 50% aqueous sodium hydroxide (NaOH) in the presence of a phase-transfer catalyst (18-crown-6). In order to extend the methodology, a synthesis of seco-mesembrane alkaloids (a subgroup of Sceletium alkaloids[3]), (±)-joubertiamine (**4**),[4] (±)-joubertinamine (**5**),[5] and (±)-epijoubertinamine (**6**),[5b] which are of pharmaceutical interest,[3] was carried out. The present paper presents details of our synthesis of the title alkaloids.

A key compound (**10**) for a synthesis of **4** was prepared starting with 2-(4′-phenylmethoxyphenyl)acetaldehyde[6] in the same manner as reported previously.[2] Namely, Robinson annelation of the aldehyde with methyl vinyl ketone (MVK) followed by ketalization gave 2-aryl-5,5-ethylenedioxycyclohexene (**7**) in 25% overall yield (based on the aldehyde). Hydroboration-oxidation of **7** afforded a cyclohexanol (**8**), which was oxidized with chromic anhydride–pyridine complex[7] in dichloromethane to furnish a 2-arylcyclohexanone (**9**) in 51% overall yield (based on **7**).



1 2 3 4

joubertinamine (**5**): R^1=OH, R^2=H

epijoubertinamine (**6**): R^1=H, R^2=OH

Chart 1

As reported previously,[2] allylation of **9** with allyl bromide and 50% aqueous NaOH in the presence of 18-crown-6 in benzene gave a 2-allyl-2-arylcyclohexanone (**10**) (68%) accompanied with an undesired fission product (**11**) (3.5%). The structure of the former (**10**) was determined to be 2-allyl-5,5-ethylenedioxy-2-(4′-phenylmethoxyphenyl)cyclohexanone on the basis of the proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra and elemental analysis. Sodium borohydride ($NaBH_4$) reduction of **10** followed by acetylation with acetic anhydride–pyridine afforded a cyclohexyl acetate (**12**) as a sole product, which was oxidized in the reported manner[2] to give the (1*RS*,2*SR*)-2-formylmethylcyclohexyl acetate (**13**) in 54% overall yield (based on **10**). The ^{1}H-NMR spectrum of **13** showed a one-proton triple ($J=7$ Hz) due to a hydrogen at the 1-position at δ 5.17, indicating that the formylmethyl and acetoxyl groups in **13** were *trans*-oriented.

Reductive amination[8] of **13** with dimethylamine hydrochloride in the presence of sodium cyanoborohydride gave a 2-dimethylaminomethylcyclohexyl acetate as an oil, which was heated at 100 °C with 10% hydrochloric acid (HCl) to give (±)-joubertiamine (**4**) in 71% yield (based on **13**). Spectral data of (±)-**4** were identical with those reported.[4]

Next, we tried to synthesize (±)-joubertinamine (**5**) and (±)-epijoubertinamine (**6**) in an analogous manner.

Compound **16**[2] was prepared by an improved method. Namely, annelation of 3,4-dimethoxyphenylpyruvic acid[9] with MVK gave a hydroxy acid (**14**) in 89% yield, ketalization of which with 2-ethyl-2-methyl-1,3-dioxolane afforded a 5,5-ethylenedioxy acid (**15**) in 94% yield. Oxidation of **15** with lead tetraacetate in benzene–chloroform gave **16** in 84% overall

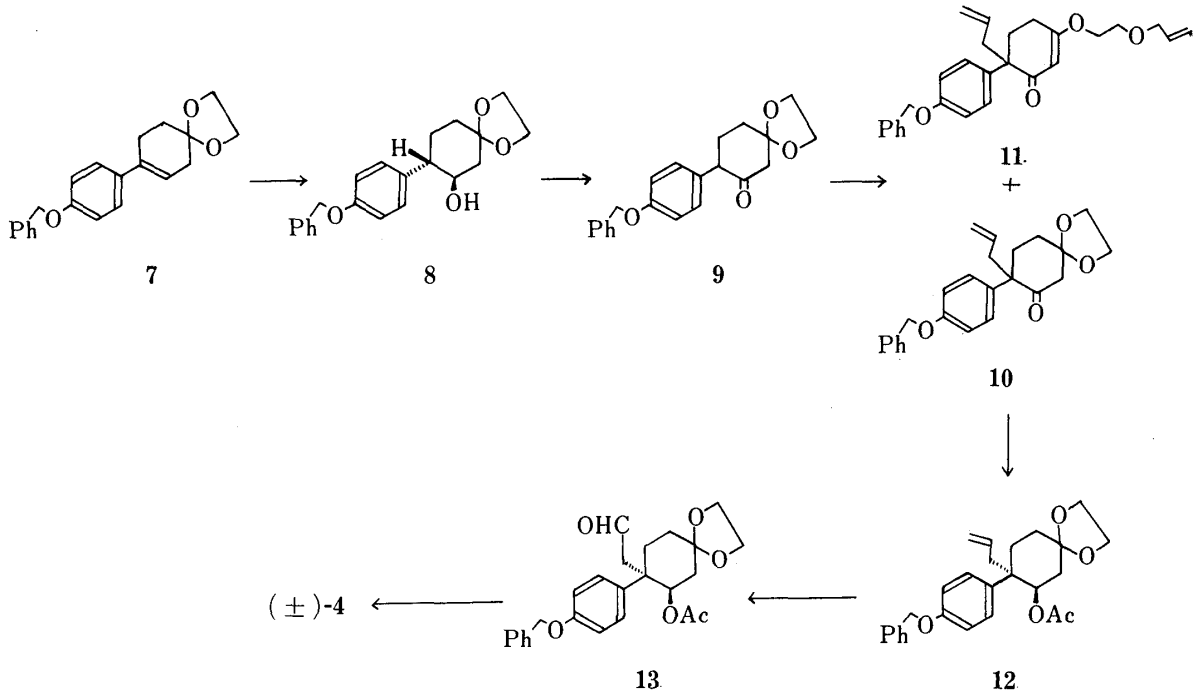


Chart 2

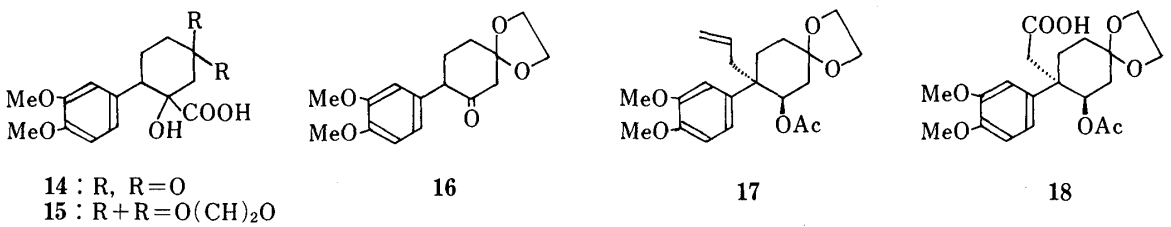


Chart 3

yield (based on the pyruvic acid). Furthermore, **16** was converted into **17** in a manner similar to that reported previously.[2)]

Oxidation of **17**[2)] according to the method of Sharpless *et al.*[10)] unexpectedly gave an aldehyde,[2)] which was oxidized with 1% aqueous potassium permanganate solution in acetone to afford an acetoxy acid (**18**) in 71% yield.

Conversion of **18** into the key compounds **25** and **27** for a synthesis of (±)-**5** and (±)-**6** was carried out by the following two routes (routes A and B).

In route A, the (1*RS*,4*SR*)- and (1*SR*,4*SR*)-amido alcohols (**25**) and (**26**) were prepared *via* an enone amide (**21**). *N*-Methylamidation of **18** was performed by the mixed anhydride method to give **19**, which was treated with 6 N HCl in methanol, giving **20**[11)] and **21** in a product ratio of 1 : 3.8, while heating of **19** with 6 M HCl in methanol afforded **20** (95.6%) as a sole product. Reduction of **21** with $NaBH_4$ in the presence of cerium trichloride[12)] gave the amido alcohols (**25**) (64%) and (**26**) (20.8%). In route B, **25** and **26** were synthesized through an enone ester (**23**). Esterification of **18** with diazomethane–ether solution gave an acetoxy ester (**22**), which was treated with 6 N HCl in methanol to yield an enone ester (**23**)[13)] and γ-lactone (**24**) in a product ratio of 10 : 1. The former (**23**) was reduced with the same reagent as noted for **21** to give a diastereomeric mixture of 2-cyclohexenols, which was treated with 40% aqueous methylamine solution to give the amido alcohols (**25**) (33.3%) and (**26**) (12.6%) and diastereomeric mixtures of unchanged 2-cyclohexenols (7.5%) and 4-aryl-4-carboxymethyl-2-cyclohexenols (37.8%). Spectral data of the amido alcohols (**25**) and (**26**) were identical with those of samples obtained by route A.

The amido alcohols (**25** and **26**) thus obtained were reduced with sodium bis(2-methoxyethoxy)aluminum hydride-toluene in tetrahydrofuran to give (±)-joubertinamine (**5**) and (±)-epijoubertinamine (**6**) in 54 and 53% yields, respectively; the spectral data were identical with those of the natural[14)] and synthetic[5b)] alkaloids described in the literature.

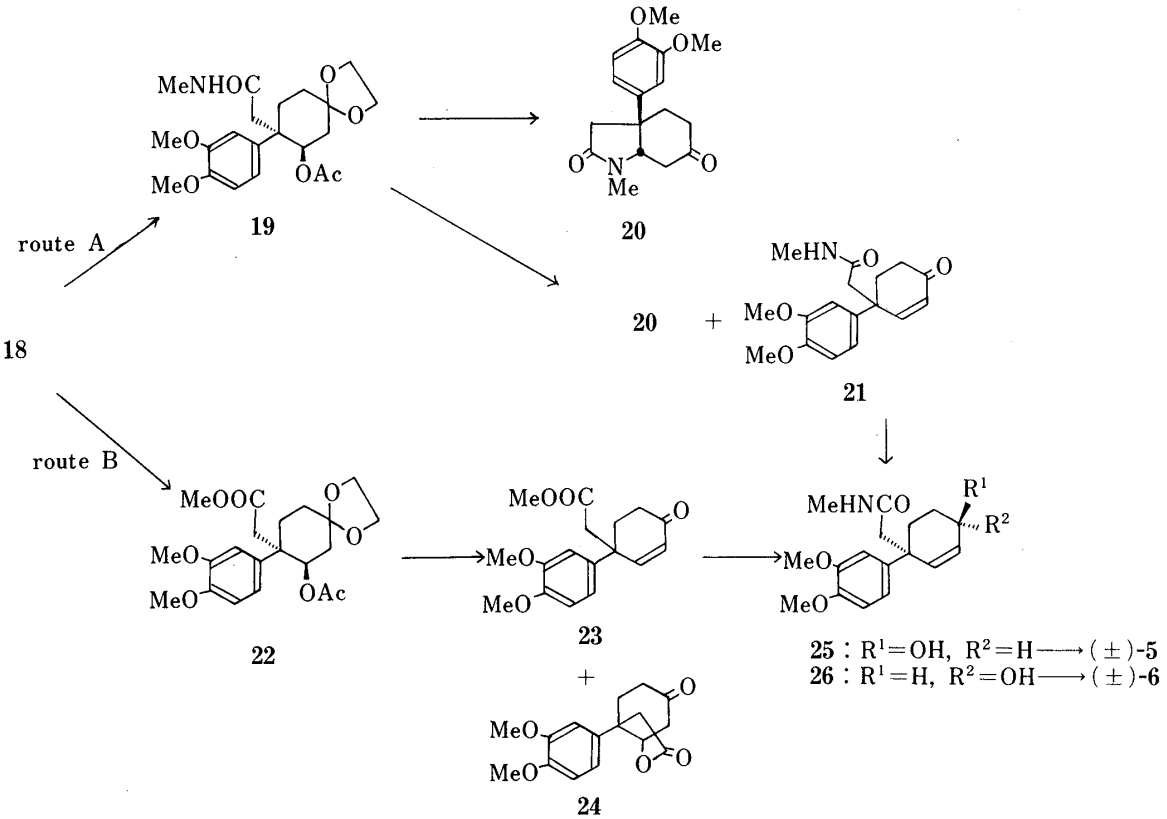


Chart 4

Thus, a synthesis of seco-mesembrane alkaloids, (±)-joubertiamine (**4**), (±)-joubertinamine (**5**), and (±)-epijoubertinamine (**6**) was achieved through allylation of the 2-aryl-5,5-ethylenedioxycyclohexanones (**9** and **16**) with allyl bromide and 50% aqueous NaOH in the presence of 18-crown-6.

Experimental

Melting points were measured on a Büchi melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a Hitachi 215 or 260-10 infrared spectrophotometer in $CHCl_3$ solution, unless otherwise noted. ^{1}H- and ^{13}C-NMR spectra were taken with a Hitachi 24B (60 MHz) or JEOL JNM-FX-100 (100 MHz) spectrometer in $CDCl_3$ solution using $(CH_3)_4Si$ as an internal standard, unless otherwise noted. Mass spectra (MS) were measured with a Hitachi RMU-7M mass spectrometer (70 eV). Column chromatography was performed on silica gel (Kanto Chemical Co., Ltd.) and preparative thin layer chromatography (TLC) on Kiesel gel HF_{254} (Merck), unless otherwise noted.

4,4-Ethylenedioxy-1-(4′-phenylmethoxyphenyl)cyclohexene (7)——A cyclohexene derivative (**7**) was prepared in 25% overall yield starting from 4-phenylmethoxyphenylacetaldehyde[6] though a procedure similar to that reported previously.[2] Colorless plates, mp 138—139 °C (MeOH). IR (KBr): 1615, 1520 cm^{-1}. ^{1}H-NMR (100 MHz) δ: 1.87 (2H, br t, J=6 Hz, 5-H), 2.28—2.77 (4H, m, 3- and 4-H_2), 3.93 (4H, s, OCH_2CH_2O), 4.99 (2H, s, OCH_2Ar), 7.12—7.38 (9H, m, 4×ArH and C_6H_5). *Anal.* Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.38; H, 6.86.

5,5-Ethylenedioxy-2-(4′-phenylmethoxyphenyl)cyclohexanol (8)——Hydroboration-oxidation of **7** (200 mg) as noted previously[2] gave a cyclohexanol derivative (**8**) (185 mg, 88%) as colorless needles, mp 119.5—121 °C (MeOH–H_2O). IR (KBr): 3530 (OH), 1615, 1520 cm^{-1}. ^{1}H-NMR (100 MHz) δ: 3.92 (4H, s, OCH_2CH_2O), 4.99 (2H, s, OCH_2Ar), 6.87, 7.12 (each 2H, d, J=9 Hz, 4×ArH), 7.28 (5H, s, C_6H_5). *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.13; H, 7.12.

5,5-Ethylenedioxy-2-(4′-phenylmethoxyphenyl)cyclohexanone (9)——A solution of the cyclohexanol derivative (**8**) (11 g, 0.032 mol) in CH_2Cl_2 (100 ml) was added dropwise to a stirred, ice-cooled solution of Collins reagent[7] in CH_2Cl_2 (prepared from CrO_3 (19.4 g, 0.194 mol) and pyridine (30.7 g, 0.338 mol) in CH_2Cl_2 (250 ml)) and stirring was continued at room temperature for 1 h. Then 5% aqueous NaOH (1000 ml) and CH_2Cl_2 (100 ml) were added to the reaction mixture and the whole was stirred at room temperature for 5 min. The CH_2Cl_2 layer was separated. Usual work-up of the CH_2Cl_2 layer gave an oil (12.8 g), which was crystallized by trituration in ether to give a cyclohexanone derivative (**9**) (6.1 g, 56%) as colorless plates, mp 111.5—112.5 °C (MeOH). IR (KBr): 1725 (C=O) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.71 (2H, br s, 6-H_2), 3.97 (4H, s, OCH_2CH_2O), 5.00 (2H, s, OCH_2Ar), 6.94, 7.03 (each 2H, d, J=9 Hz, 4×ArH), 7.12—7.46 (5H, m, C_6H_5). *Anal.* Calcd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.60; H, 6.55.

2-Allyl-5,5-ethylenedioxy-2-(4′-phenylmethoxyphenyl)cyclohexanone (10) and 3-(2-Allyloxyethoxy)-6-allyl-6-(4′-phenylmethoxyphenyl)cyclohex-2-en-1-one (11)——Reaction of the cyclohexanone derivative (**9**) (450 mg) as reported previously[2] gave a 2-allylcyclohexanone (**10**) (346 mg, 69%) as colorless prisms, mp 94.5—95.5 °C (MeOH) and a 6-allylcyclohex-2-en-1-one (**11**) (19.5 mg, 3.5%), mp 82—83 °C (MeOH) by crystallization (MeOH) and preparative TLC (developing solvent; benzene : AcOEt : MeOH = 100 : 10 : 1). **10**: IR: 1710 (C=O) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 3.84 (4H, s, OCH_2CH_2O), 4.60—5.80 (3H, m, $-CH=CH_2$), 4.95 (2H, s, OCH_2Ar), 6.88, 7.00 (each 2H, d, J=9 Hz, 4×ArH), 7.30 (5H, s, C_6H_5). ^{13}C-NMR (25 MHz) δ: 28.239 (t), 31.468 (t), 44.267 (t), 49.493 (t), 54.776 (s), 64.522 (t), 64.640 (t), 69.982 (t), 110.432 (s), 115.072 (d), 117.712 (t), 127.401 (d), 127.636 (d), 127.928 (d), 128.515 (d), 131.450 (s), 134.095 (d), 136.795 (s), 157.692 (s), 207.892 (s). *Anal.* Calcd for $C_{24}H_{26}O_4$: C, 76.16; H, 6.93. Found: C, 76.14; H, 6.86. **11**: IR: 1640, 1610 (CH=CHC=O) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 3.65, 3.86 (each 2H, t, J= 3.7 Hz, OCH_2CH_2O), 3.98 (2H, dt, J=5.7, 1.4 Hz, $OCH_2CH=CH_2$), 5.00 (2H, s, OCH_2Ar), 5.34 (1H, s, 2-H), 6.87, 7.14 (each 2H, d, J=8.5 Hz, 4×ArH), 7.00—7.49 (5H, m, C_6H_5). ^{13}C-NMR (25 MHz) δ: 26.360 (t), 29.883 (t), 44.561 (t), 51.019 (s), 67.458 (t), 67.752 (t), 69.924 (t), 72.213 (t), 102.861 (d), 114.603 (d), 128.458 (d), 132.216 (s), 134.151 (d), 134.738 (d), 136.969 (s), 157.579 (s), 176.066 (s), 200.433 (s). *Anal.* Calcd for $C_{27}H_{30}O_4$: C, 77.48; H, 7.23. Found: C, 77.54; H, 7.11.

2-Allyl-5,5-ethylenedioxy-2-(4′-phenylmethoxyphenyl)cyclohexyl Acetate (12)——A solution of the 2-allylcyclohexanone derivative (**10**) (400 mg, 0.79 mmol) in MeOH (20 ml) was reduced with $NaBH_4$ (90 mg, 2.77 mmol) at room temperature for 3 h. Usual work-up of the reaction mixture gave an oil (304 mg), which was crystallized by trituration in MeOH to give the 2-allylcyclohexanol derivative (296 mg, 98%) as colorless plates, mp 99.5—101 °C (MeOH–H_2O). IR: 3520 (OH) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 3.03 (1H, d, J=6.3 Hz, OH; disappeared on addition of D_2O), 3.96 (4H, s, OCH_2CH_2O), 4.12 (1H, m, $W_{1/2}$=12.5 Hz, 1-H), 5.00 (2H, s, OCH_2Ar), 6.89, 7.24 (each 2H, d, J= 8 Hz, 4×ArH), 7.20—7.40 (5H, m, C_6H_5). *Anal.* Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.95; H, 7.30. Acetylation (Ac_2O–pyridine) of the 2-allylcyclohexanol derivative gave the corresponding acetate (**12**) as colorless prisms (69%), 112—113 °C (MeOH). IR: 1730 ($OCOCH_3$) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 1.98 (3H, s, $OCOCH_3$), 2.38 (2H, d, J=6.8 Hz, $-CH_2CH=$), 3.90 (4H, m, $W_{1/2}$=5.4 Hz, OCH_2CH_2O), 5.03 (2H, s, OCH_2Ar), 4.76—5.60

(4H, m, $-CH=CH_2$ and 1-H), 6.88, 7.27 (each 2H, d, $J=8$ Hz, 4 × ArH), 7.20—7.48 (5H, m, C_6H_5). *Anal.* Calcd for $C_{26}H_{30}O_5$: C, 73.91; H, 7.16. Found: C, 73.98; H, 7.10.

(1*RS*,2*SR*)-5,5-Ethylenedioxy-2-formylmethyl-2-(4′-phenylmethoxyphenyl)cyclohexyl Acetate (13)——Oxidation of the 2-allylcyclohexyl acetate derivative (**12**) (1.57 g, 3.72 mmol) as reported previously[2] gave a 2-formylmethylcyclohexyl acetate (**13**) (1.45 g, 92%) as colorless prisms, mp 128.5—130 °C (AcOEt–hexane). IR: 1740 ($OCOCH_3$), 1720 (CHO) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.01 (3H, s, $OCOCH_3$), 2.58 (2H, d, $J=2.9$ Hz, $-CH_2CHO$), 3.57—4.14 (4H, br s, $W_{1/2}=5.4$ Hz, OCH_2CH_2O), 5.03 (2H, s, OCH_2Ar), 5.17 (1H, t, $J=7$ Hz, 1-H), 6.92, 7.46 (each 2H, d, $J=$ 8.5 Hz, 4 × ArH), 7.11—7.56 (5H, m, C_6H_5), 9.24 (1H, t, $J=2.9$ Hz, $-CH_2CHO$). *Anal.* Calcd for $C_{25}H_{28}O_6$: C, 70.89; H, 6.56. Found: C, 70.94; H, 6.67.

(±)-Joubertiamine (4)——A mixture of the aldehyde (**13**) (306.8 mg, 0.72 mmol), $Me_2NH \cdot HCl$ (54.7 mg, 0.87 mmol), and $NaBH_3CN$ (353.8 mg, 4.3 mmol) in anhydrous MeOH (10 ml) was stirred at room temperature for 41 h. Removal of the solvent *in vacuo* gave an oily residue, which was dissolved in CH_2Cl_2. Usual work-up of the CH_2Cl_2 solution gave an oil (317 mg), which was subjected to silica gel column chromatography. Elution with CH_2Cl_2 : MeOH = 100 : 5 gave a colorless oil (247 mg, 84%). IR: 1735 ($OCOCH_3$) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 1.98 (3H, s, $OCOCH_3$), 2.40 (6H, s, NMe_2), 3.88 (4H, br s, OCH_2CH_2O), 5.00 (2H, s, OCH_2Ar), 5.16 (1H, dd, $J=4$, 6 Hz, 1-H), 6.88 (2H, d, $J=8.5$ Hz, 2 × ArH), 7.00—7.55 (7H, m, 2 × ArH, C_6H_5). A solution of the amine (156.8 mg, 0.35 mmol) and 20% HCl (5 ml) in MeOH (7 ml) was heated at 100 °C (bath temperature) under N_2 for 4 h. The ice-cooled reaction mixture was made alkaline with 10% aqueous NaOH and the product was taken up in ether. Usual work-up of the ether extract gave (±)-joubertiamine (**4**) (76.5 mg, 85.3%), mp 162.5—164 °C (CH_3CN) (lit.[4] 126—130 °C (dec.)). IR: 1680 (α,β-unsaturated C=O) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 1.80—2.50 (8H, m, 4 × CH_2), 2.26 (6H, s, NMe_2), 6.68 (1H, d, $J=10$ Hz, 6-H), 6.45, 7.00 (each 2H, d, $J=8.5$ Hz, 4 × ArH), 7.03 (1H, d, $J=10$ Hz, 1-H). MS *m/z* (%): 259 (M^+, 10.5), 73 (4.0), 72 (2.4), 71 (3.2), 58 (100). *Anal.* Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.14; H, 8.07; N, 5.50. The spectral data of (±)-**4** were identical with those reported for the synthetic alkaloid.[4]

5,5-Ethylenedioxy-2-(3′,4′-dimethoxyphenyl)cyclohexanone (16)——A solution of MVK (8.4 g, 0.12 mol) in MeOH (20 ml) was added dropwise to a stirred, ice-cooled solution of 3,4-dimethoxyphenylpyruvic acid[9] (22.4 g, 0.1 mol) in 5% aqueous NaOH (115 ml) over a period of 15 min and the whole was stirred at room temperature for 5 h. The residue obtained on removal of the solvent *in vacuo* was acidified carefully with concentrated HCl to afford 1-carboxy-2-(3′,4′-dimethoxyphenyl)-5-oxocyclohexanol (**14**) (26.2 g, 89.1%), mp 176—177 °C (MeOH–H_2O). IR (KBr): 3700—2700 (COOH, OH), 1705 (C=O) cm^{-1}. ^{1}H-NMR (100 MHz) (acetone-d_6) δ: 3.12 (1H, dd, $J=4$, 12 Hz, 2-H), 3.76, 3.77 (each 3H, s, 2 × OCH_3), 6.77 (1H, dd, $J=2$, 12 Hz, 6′-H), 6.86 (1H, d, $J=12$ Hz, 5′-H), 6.97 (1H, d, $J=2$ Hz, 2′-H). *Anal.* Calcd for $C_{15}H_{18}O_6$: C, 61.20; H, 6.12. Found: C, 61.37; H, 6.20. A mixture of keto acid (**14**) (5.88 g, 0.02 mol) in $CHCl_3$ (300 ml), 2-ethyl-2-methyl-1,3-dioxolane (4.72 g, 0.042 mol), and *p*-TsOH · H_2O (0.19 g, 0.001 mol) was refluxed with removal of H_2O formed through a Dean-Stark apparatus for 0.5 h. Usual work-up of the $CHCl_3$ layer gave **15** (6.34 g, 94%), mp 149.5—151 °C ($CHCl_3$–benzene). IR (KBr): 3570—2700 (COOH, OH), 1700 (C=O) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 3.83, 3.84 (each 3H, s, 2 × OCH_3), 4.03 (4H, s, OCH_2CH_2O), 6.60—6.90 (3H, m, 3 × ArH). *Anal.* Calcd for $C_{17}H_{22}O_7$: C, 60.36; H, 6.51. Found: C, 60.44; H, 6.75.

$Pb(OAc)_4$ (59 g, 0.12 mol) was added to a solution of **15** (37.4 g, 0.11 mol) in a mixture of benzene (1000 ml) and $CHCl_3$ (200 ml) and stirring was continued at room temperature for 5 min. The reaction mixture was basified carefully with saturated aqueous $NaHCO_3$ and the precipitate was filtered off through a celite bed. The celite bed was washed well with $CHCl_3$. Usual work-up of the combined organic layers gave a cyclohexanone (**16**) (30.2 g, 93.3%), mp 105—109 °C, spectral data of which were identical with those of an authentic sample.[2]

2-Carboxymethyl-5,5-ethylenedioxy-2-(3′,4′-dimethoxyphenyl)cyclohexyl Acetate (18)——A solution of the 2-allylcyclohexyl acetate derivative (**17**)[2] (4.62 g, 12.3 mmol) in CCl_4 (30 ml) was added to a stirred mixture[10] of $NaIO_4$ (12.0 g, 56.1 mmol), $RuCl_3(H_2O)_n$ (105 mg, 0.46 mmol), H_2O (40 ml) and CCl_4 (25 ml) and stirring was continued at room temperature for 2 h. The reaction mixture was filtered through a celite bed and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* afforded an oil, which was subjected to column chromatography. Elution with $CHCl_3$: ether = 1 : 1 gave an oil (3.75 g, 80.8%). It was identical with an authentic sample[2] of the aldehyde on the basis of a comparison of their spectral data.

A solution of 1% aqueous $KMnO_4$ was added dropwise to a stirred solution of the aldehyde[2] (847.6 mg, 2.2 mmol) in acetone (20 ml) at room temperature over a period of 1 h until the color of permanganate ion remained (20 ml of 1% aqueous $KMnO_4$ was required). H_2O was added to the reaction mixture and the precipitate was filtered off. The filtrate was acidified carefully with 10% HCl and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an oil, which was crystallized by trituration in ether to give an acid (**18**) (685 mg, 71.4%), mp 163—164 °C (ether). IR: 2800—2400 (COOH), 1725 ($OCOCH_3$), 1710 (C=O) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.00 (3H, s, $OCOCH_3$), 3.84, 3.85 (each 3H, s, 2 × OCH_3), 3.84—3.98 (4H, m, OCH_2CH_2O), 5.24 (1H, dd, $J=6$, 7 Hz, 1-H), 6.75 (1H, d, $J=2$ Hz, 5′-H), 7.00 (1H, dd, $J=2$, 8 Hz, 6′-H), 7.07 (1H, d, $J=2$ Hz, 2′-H). *Anal.* Calcd for $C_{20}H_{26}O_6$: C, 60.90; H, 6.67. Found: C, 61.01; H, 6.78.

(1*RS*,2*SR*)-5,5-Ethylenedioxy-2-(*N*-methylamidomethyl)-2-(3′,4′-dimethoxyphenyl)cyclohexyl Acetate (19)——A

solution of $ClCOOC_2H_5$ (570 mg, 5.3 mmol) in $CHCl_3$ (5 ml) was added dropwise to a stirred, ice-cooled solution of the acid (**18**) (1.26 g, 3.2 mmol) and Et_3N (5 ml) in $CHCl_3$ (10 ml) and the whole was stirred at room temperature for 45 min. Then 40% aqueous $MeNH_2$ (6 ml) was added to the stirred reaction mixture and stirring was continued at room temperature for 1 h. The reaction mixture was acidified carefully with 10% HCl and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an amido acetate (**19**) (955.8 mg, 73.4%), mp 169—171 °C (ether). IR: 3450 (CONH), 1730 ($OCOCH_3$), 1665 (CONH) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.00 (3H, s, $OCOCH_3$), 2.47 (2H, br s, CH_2CO), 2.52 (3H, d, J=5.8 Hz, $CONHCH_3$), 3.86, 3.88 (each 3H, s, 2×OCH_3), 3.84—3.96 (4H, m, OCH_2CH_2O), 4.65 (1H, br s, $W_{1/2}$=11.6 Hz, CONH), 5.30 (1H, dd, J=5, 6 Hz, 1-H), 6.70—7.10 (3H, m, 3×ArH). *Anal.* Calcd for $C_{21}H_{29}NO_7$: C, 61.81; H, 7.09; N, 3.44. Found: C, 61.90; H, 7.17; N, 3.32.

***cis*-3a-(3′,4′-Dimethoxyphenyl)-1-methyloctahydroindole-2,6-dione (20)**——A solution of the amido acetate (**19**) (288 mg, 0.71 mmol) and 3 M HCl (12 ml) in MeOH (12 ml) was refluxed for 3.5 h. The reaction mixture was basified with 10% aqueous NaOH and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an oil, which was subjected to preparative TLC (developing solvent; $CHCl_3$: MeOH = 20 : 1) to give **20** as an oil (210 mg, 95.6%). IR: 1725 ($OCOCH_3$), 1680 (γ-lactam) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.85 (3H, s, $CONCH_3$), 3.87, 3.88 (each 3H, s, 2×OCH_3), 4.31 (1H, t, J=4.3 Hz, 7a-H), 6.75 (1H, d, J=2 Hz, 2′-H), 6.82 (1H, s, 5′-H), 6.83 (1H, d, J=2 Hz, 6′-H). MS m/z: 303 (M^+). Although attempts to crystallize the oil failed, the spectral data were identical with those of a reported sample.[1)]

4-(3′,4′-Dimethoxyphenyl)-4-(*N*-methylcarbonyl)-2-cyclohexenone (21)——A solution of the amido acetate (**19**) (60 mg, 0.147 mmol) and 6 N HCl (2 ml) in MeOH (2 ml) was stirred at room temperature for 50 min. The reaction mixture was basified with saturated aqueous $NaHCO_3$ and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an oil, which was subjected to preparative TLC (developing solvent : $CHCl_3$: MeOH = 20 : 1) to give **20** (8.5 mg, 19%) and a cyclohexanone derivative (**21**) as an oil (34 mg, 76.1%) (mobility; **20** > **21**). The former was identical with the sample obtained above by comparison of their spectral data.

21: IR: 1680, (CH=CHCO), 1670 (CONH) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.30 (4H, br s, 5-, 6-H_2), 2.62 (3H, d, J=5.8 Hz, $CONHCH_3$), 2.65 (2H, s, CH_2CONH), 3.85 (6H, s, 2×OCH_3), 5.14 (1H, br s, $W_{1/2}$=11.6 Hz, CONH), 6.13 (1H, d, J=10 Hz, 2-H), 6.80 (3H, br s, 3×ArH), 7.42 (1H, d, J=10 Hz, 3-H). High resolution MS Calcd for $C_{17}H_{21}NO_4$: m/z (M^+): 303.1471. Found: 303.1472.

4-(3′,4′-Dimethoxyphenyl)-4-methoxycarbonylmethyl-2-cyclohexenone (23)——A diazomethane-ether solution was added to a solution of the acid (**18**) (109 mg, 0.28 mmol) in ether (10 ml) until a yellow color remained, and the whole was allowed to stand at room temperature for 45 min. Usual work-up of the reaction mixture gave an oil (**22**) (109.7 mg, 96.9%). IR: 1740, 1730 ($COOCH_3$, $OCOCH_3$) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.04 (3H, s, $OCOCH_3$), 2.62 (2H, s, CH_2CO), 3.46 (3H, s, $COOCH_3$), 3.86 (6H, s, 2×OCH_3), 3.90 (4H, m, OCH_2CH_2O), 5.24 (1H, dd, J=6, 8 Hz, 1-H), 6.70—7.10 (3H, m, 3×ArH). MS m/z: 408 (M^+). A solution of the ester (**22**) (28.7 mg, 0.17 mmol) and 6 N HCl (2.5 ml) in MeOH (2.5 ml) was heated at 50 °C (bath temperature) for 20 min. The reaction mixture was basified with saturated aqueous $NaHCO_3$ and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an oil, which was subjected to preparative TLC (developing solvent: benzene : EtOAc = 2 : 1) to give the 2-cyclohexenone derivative (**23**) as an oil (42.5 mg, 83%) and the γ-lactone (**24**) as an oil (3.6 mg, 7.4%) (mobility: **23** > **24**). **23**: IR: 1730 ($COOCH_3$), 1670 (CH=CHCO) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.29 (4H, s, 5-, 6-H_2), 2.78, 2.95 (each 1H, d, J=15 Hz, CH_2CO), 3.57 (3H, s, $COOCH_3$), 3.87 (6H, s, 2×OCH_3), 6.17 (1H, d, J=10 Hz, 2-H), 6.79 (3H, s, 3×ArH), 7.37 (1H, d, J=10 Hz, 3-H). High-resolution MS Calcd for $C_{17}H_{20}O_5$ m/z: (M^+): 304.1311. Found: 304.1303. **24**: IR: 1780 (γ-lactone), 1720 (CO) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 3.90 (6H, s, 2×OCH_3), 4.23 (1H, t, J=3 Hz, 7a-H), 5.57—6.00 (3H, m, 3×ArH).

(1*RS*,4*SR*)- and (1*SR*,4*SR*)-4-(3′,4′-Dimethoxyphenyl)-4-(*N*-methylcarbamoylmethyl)-2-cyclohexenols (25 and 26)——i) From **21**: $NaBH_4$ (0.198 g, 5.23 mmol) was added to a stirred solution of the enone amide (**21**) (1.67 g, 5.51 mmol) and $CeCl_3 \cdot 7H_2O$ (2.07 g, 5.56 mmol) in MeOH (60 ml) and the whole was stirred at room temperature for 10 min. H_2O (50 ml) was added to the mixture and the product was taken up in $CHCl_3$. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave an oil, which was subjected to column chromatography over Al_2O_3 (Wako Chemical Industries Ltd.). Elution with $CHCl_3$: MeOH = 300 : 1 afforded the (1*RS*,4*SR*)-amido alcohol (**25**) (1.08 g, 64%) and the (1*SR*,4*SR*)-amido alcohol (**26**) (0.35 g, 20.8%) successively. **25**: mp 143 °C (AcOEt). IR (KBr): 3700—3150 (NH, OH), 1640 (CONH) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.54 (3H, d, J=5.2 Hz, $CONHCH_3$), 2.55 (2H, s, CH_2CO), 3.84, 3.86 (each 3H, s, 2×OCH_3), 4.06—4.36 (1H, m, $W_{1/2}$=18 Hz, 1-H), 5.08 (1H, br s, $W_{1/2}$=14.5 Hz, CONH), 5.80—6.12 (2H, m, 2-, 3-H), 6.64—6.92 (3H, m, 3×ArH). *Anal.* Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.80; H, 7.78; N, 4.76. **26**: mp 108.5—110 °C (AcOEt–hexane). IR (KBr): 3700—3150 (NH, OH), 1640 (CONH) cm^{-1}. ^{1}H-NMR (100 MHz) δ: 2.61 (2H, s, CH_2CO), 2.62 (3H, d, J=5.2 Hz, $CONHCH_3$), 3.84, 3.85 (each 3H, s, 2×OCH_3), 4.00—4.16 (1H, m, $W_{1/2}$=10 Hz, 1-H), 5.32 (1H, br s, $W_{1/2}$=14.5 Hz, CONH), 5.88—6.16 (2H, m, 2-, 3-H), 6.80 (3H, s, 3×ArH). *Anal.* Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.87; H, 7.66; N, 4.84.

ii) From **23**: $NaBH_4$ (79 mg, 2.1 mmol) was added in one portion to a stirred, ice-cooled solution of the enone ester (**23**) (424 mg, 1.4 mmol) and $CeCl_3 \cdot 7H_2O$ (823 mg, 2.2 mmol) in MeOH (30 ml) and stirring was continued at room temperature for 30 min. H_2O (20 ml) was added to the reaction mixture and treatment as described in i) gave a

diastereomeric mixture of 2-cyclohexenol derivatives as an oil (419 mg, 98%). IR: 3600—3200 (OH), 1720 ($COOCH_3$) cm^{-1}. ^1H-NMR (100 MHz) δ: 1.78 (1H, s, OH), 2.60—2.80 (2H, m, CH_2CO), 3.53, 3.54 (2:1) (3H, each s, $COOCH_3$), 3.85, 3.87 (each 3H, s, $2\times OCH_3$), 4.00—4.36 (1H, m, 1-H), 5.80—6.28 (2H, m, 2-, 3-H), 6.64—6.92 (3H, m, $3\times$ ArH). High-resolution MS Calcd for $C_{17}H_{22}O_5$ *m/z* (M^+): 306.1468. Found: 306.1487.

A solution of the resultant 2-cyclohexenols (57 mg, 0.19 mmol) and 40% aqueous CH_3NH_2 (3.2 ml) in MeOH (2 ml) was stirred at room temperature for 5 d. The product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and dried over anhydrous Na_2SO_4. Removal of the solvent gave an oil, which was subjected to preparative TLC (Al_2O_3 plate; Aluminumoxyd F_{254}, Merck; developing solvent, $CHCl_3$: MeOH = 100 : 1) to give the (1*RS*,4*SR*)-amido alcohol (**25**) (19 mg, 33.3%) the (1*SR*,4*SR*)-amido alcohol (**26**) (7 mg, 12.6%), and unchanged 2-cyclohexenols (4 mg, 7.5%). The aqueous layer was acidified with 6 N HCl and the acidic product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave a diastereomeric mixture of 4-carboxymethyl-4-(3′,4′-dimethoxyphenyl)-2-cyclohexenols, mp 164 °C (acetone) (21 mg, 37.8%). IR (KBr): 3450 (OH), 2870—2400 (COOH), 1720 (C=O) cm^{-1}. ^1H-NMR (100 MHz) ($CDCl_3$–CD_3OD) δ: 2.54—2.86 (2H, m, CH_2CO), 3.83, 3.85 (each 3H, s, $2\times OCH_3$), 4.00—4.32 (1H, m, 1-H), 5.80—6.32 (2H, m, 2-, 3-H), 6.70—6.96 (3H, m, $3\times$ ArH). High-resolution MS Calcd for $C_{16}H_{20}O_5$ *m/z* (M^+): 292.1309. Found: 292.1300. Spectral data for **25**, **26**, and 2-cyclohexenols were identical with those of the samples obtained above.

(±)-Joubertinamine (5) and (±)-Epijoubertinamine (6)——(±)-**5**: A solution of the (1*RS*,4*SR*)-amido alcohol (**25**) (60 mg, 0.2 mmol) in anhydrous tetrahydrofuran (THF) (2 ml) was refluxed with NaAl $(OCH_2CH_2OCH_3)_2H_2$–toluene (0.3 ml) for 2 h under Ar. Then 1 M NaOH (3 ml) was added to the ice-cooled reaction mixture and the product was taken up in AcOEt. Usual work-up of the AcOEt extract gave an oil, which was separated by preparative TLC on an Al_2O_3 plate (Aluminumoxyd F_{254}, Merck) (developing solvent, $CHCl_3$: MeOH = 150 : 1) to afford (±)-joubertinamine (**5**) as an oil (31 mg, 54%). IR: 3600—3100 (NH, OH) cm^{-1}. ^1H-NMR (100 MHz) δ: 2.32 (3H, s, $NHCH_3$), 2.36 (2H, s, OH, NH), 3.84, 3.85 (each 3H, s, $2\times OCH_3$), 4.19 (1H, dd, J = 5.5, 9 Hz, 1-H), 5.85 (2H, s, 2-, 3-H), 6.64—6.88 (3H, m, $3\times$ ArH). High-resolution MS Calcd for $C_{17}H_{25}NO_3$ *m/z* (M^+): 291.1836. Found: 291.1831. Acetylation of (±)-**5** with Ac_2O–pyridine afforded (±)-*N*,*O*-diacetyljoubertinamine as an oil. IR (neat): 1725 ($OCOCH_3$), 1630 ($NCOCH_3$) cm^{-1}. ^1H-NMR (100 MHz) δ: 1.92, 1.99 (7:8) (3H, each s, $NCOCH_3$), 2.03 (3H, s, $OCOCH_3$), 2.84, 2.91 (7:8) (3H, each s, NCH_3), 3.84, 3.85, 3.87, 3.89 (6H, each s, $2\times OCH_3$), 5.27 (1H, m, $W_{1/2}$ = 16 Hz, 1-H), 5.72—6.10 (2H, m, 2-, 3-H), 6.64—6.92 (3H, m, $3\times$ ArH). High-resolution MS Calcd for $C_{21}H_{29}NO_5$ *m/z* (M^+): 357.2047. Found: 357.2036. The spectral data for (±)-**5** and the *N*,*O*-diacetyl derivative were identical with those of the natural alkaloid.[14]

(±)-**6**: Reduction of the (1*SR*,4*SR*)-amido alcohol (**26**) (57 mg, 0.19 mmol) in the same manner as noted for **25** gave (±)-epijoubertinamine (**6**) as an oil (34 mg, 53%). IR: 3600—3100 (NH, OH) cm^{-1}. ^1H-NMR (100 MHz) δ: 2.06 (2H, s, OH, NH), 2.34 (3H, s, NCH_3), 3.84, 3.86 (each 3H, s, $2\times OCH_3$), 3.96—4.18 (1H, m, $W_{1/2}$ = 10 Hz, 1-H), 5.97 (2H, s, 2-, 3-H), 6.76 (3H, s, $3\times$ ArH). High-resolution MS Calcd for $C_{17}H_{25}NO_3$ *m/z* (M^+): 291.1836. Found: 291.1864. Acetylation of (±)-**6** in the same manner as noted above gave (±)-*N*,*O*-diacetyljoubertinamine as an oil. IR (neat): 1720 ($OCOCH_3$), 1630 ($NCOCH_3$) cm^{-1}. ^1H-NMR (100 MHz) δ: 1.92, 1.99 (1:1.1) (3H, each s, $NCOCH_3$), 2.04, 2.06 (1.1:1) (3H, each s, $OCOCH_3$), 2.84, 2.87 (1:1.1) (3H, each, s, NCH_3), 3.84, 3.85, 3.87 (6H, each s, $2\times OCH_3$), 5.04—5.22 (1H, m, $W_{1/2}$ = 10 Hz, 1-H), 5.84—6.20 (2H, m, 2-H, 3-H), 6.60—6.88 (3H, m, $3\times$ ArH). High-resolution MS Calcd for $C_{21}H_{29}NO_5$ *m/z* (M^+): 375.2047. Found: 375.2044. The spectral data for (±)-**6** was identical with those reported for the synthetic alkaloid.[5b]

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