TOTAL SYNTHESIS OF SINOMENDINE AND ITS ANALOGS

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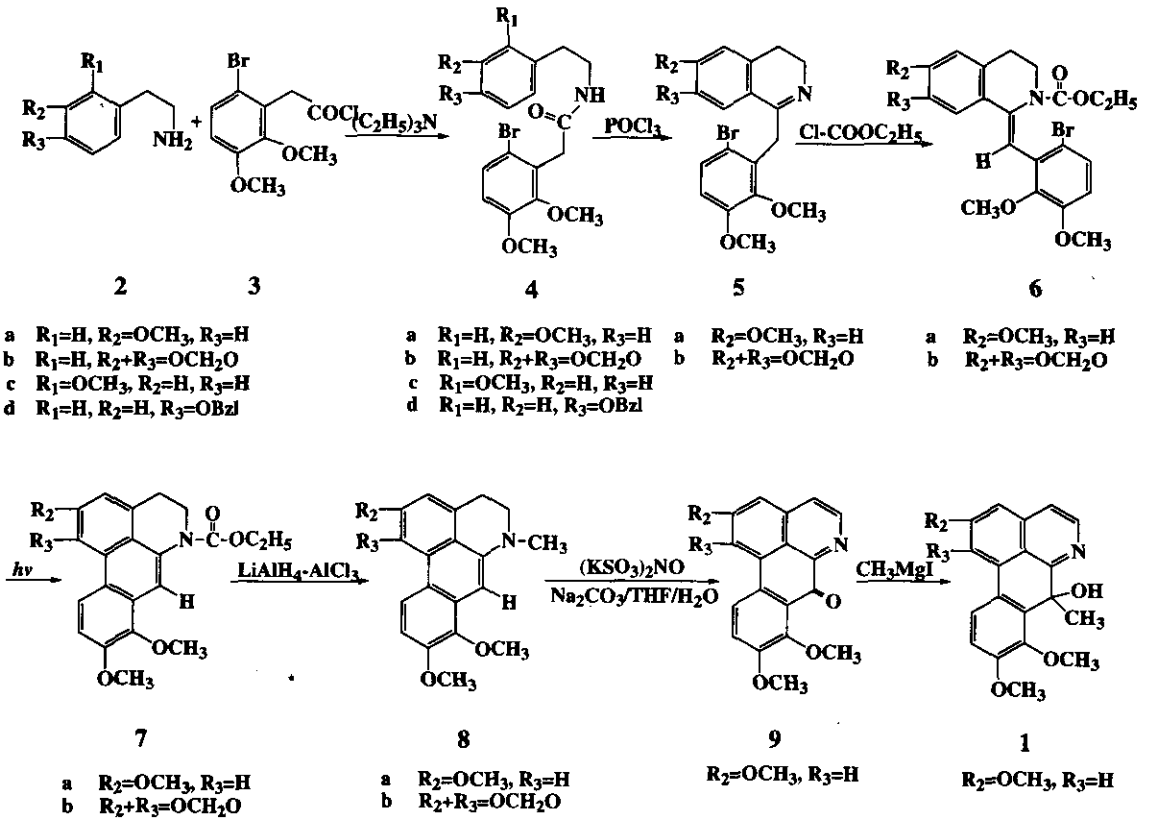
Abstract - Sinomendine (**1**), a good receptor antagonist of angiotensin II and rare oxoaporphine alkaloid isolated from traditional Chinese drug *Sinomenium acutum* (Thunb.) Rehd. *et* Wils, was synthesized from a bromobenzylidenetetrahydroisoquinolineenamide precursor (**6**). Photocyclization of this enamide led to a protected aporphine (**7**), which could be converted into oxoaporphine (**9**) and (±)-sinomendine (**1**) by Fremy's salt oxidation followed an available Grignard reaction.

Sinomendine (**1**), a minor alkaloid isolated from the rhizome of *Sinomenium acutum* (Thunb.) Rehd. *et* Wils,[1] a traditional Chinese drug (Chinese name *Qingfengteng*), showed apparent activity of angiotensin II antagonist by binding the angiotensin II receptor.[1] However, the rare amount in *Sinomenium acutum* (Thunb.) Rehd. *et* Wils precluded further development of this interesting compound. To overcome this problem and optimum its structure-effect relation, a synthetic program was outlined (Scheme 1).

The first step in the synthesis involved a *Bischler-Napieralski* cyclization of *N*-phenylethylphenylacetamides (**4**), which were prepared by condensation of phenylethylamines (**2**) with 6-bromophenylacetyl chloride (**3**) as previously described,[2] with phosphorus oxychloride in anhydrous acetonitrile. Only acetamides (**4a**) and (**4b**) were smoothly cyclized.

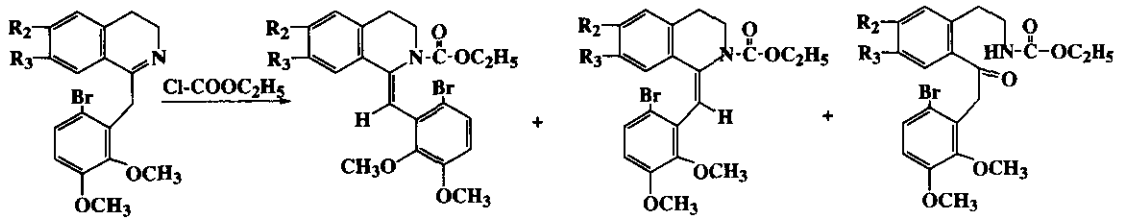
Scheme 1



Condensation of the 3,4-dihydroisoquinoline compound (**5**) with ethyl chloroformate afforded *cis*- (**6**) and *trans*-isomer (**6'**) of benzylidenecarbethoxytetrahydroisoquinoline (Scheme 2a). The configuration of *cis*- or *trans*-isomer was assigned on the basis of its ^1H nmr spectrums,[3] wherein the isomer with methyl and methylene protons of the ethoxycarbonyl function resonating unusually upfield at ~ 0.9 ppm and ~ 3.7 ppm was the *cis*-isomer because of the shielding effect of the aromatic ring D, and the isomer with methyl and methylene protons at 1.4 ppm and 4.2 ppm was *trans*- configuration because the aromatic ring D was remote from them. The large steric repulsion between the aromatic rings A and D in the *trans*-isomer (**6'**) made it unstable and the main product was the *cis*-isomer (**6**). Moreover, the steric group of R_3 made this result more apparently. For example, when R3 was a hydrogen, the ratio of *cis*- and *trans*-isomer was about 9:1; in the

case of -OCH_2O-, only the *trans*-isomer was detected (Scheme 2a). In apart from the target *trans*- and *cis*-isomer of benzylidenecarbethoxytetrahydroisoquinolines afforded, a side-product (**10**) was also generated (Scheme 2a). The carbon-nitrogen bond of the 3,4-dihydroisoquinoline (**5**) was hydrolyzed easily as the nitrogen atom was acetylated in basic conditions (Scheme 2b), even hydrolyzed completely if in more longer time and more basic solvent.

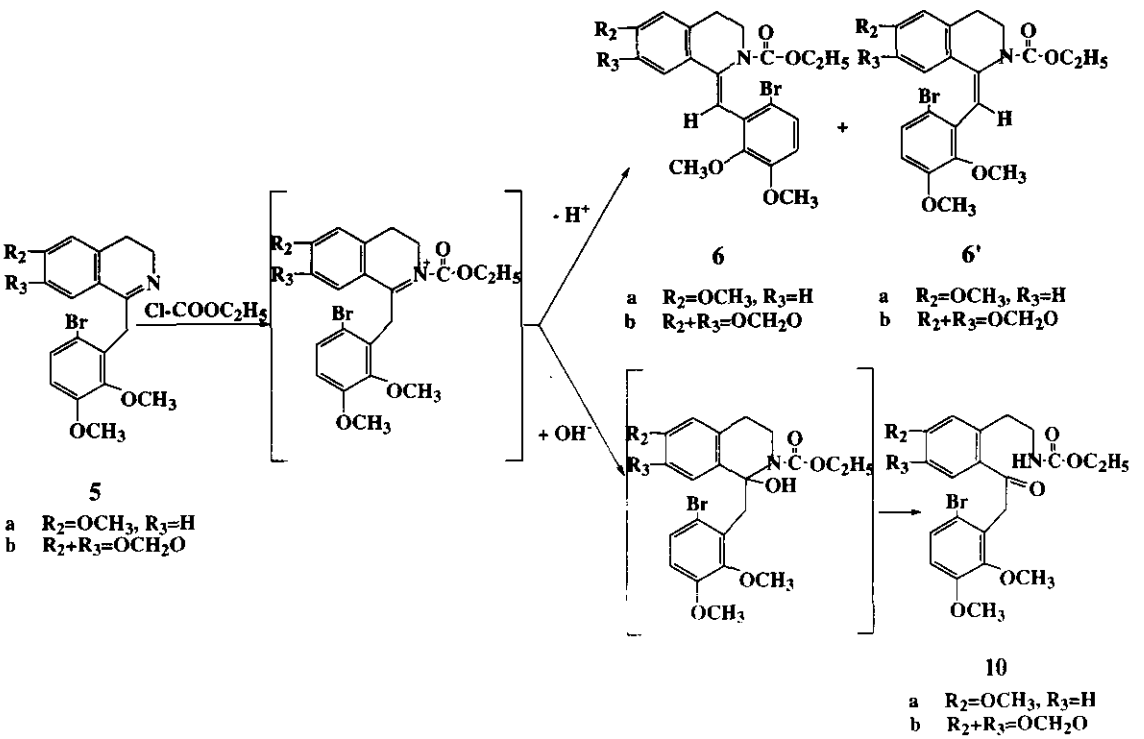
Scheme 2a



a R_2=OCH_3, R_3=H
b R_2+R_3=OCH_2O

0.9 1 0.1 0

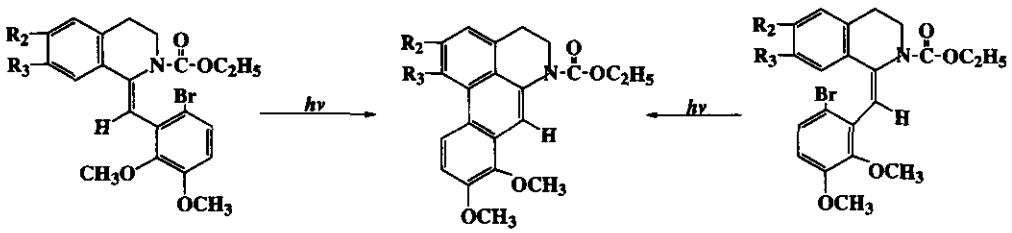
Scheme 2b



a R_2=OCH_3, R_3=H
b R_2+R_3=OCH_2O

Irradiation of *cis*- or *trans*-isomer of benzylidenecarbethoxytetrahydroisoquinoline (**6** or **6'**) in the dry toluene/*tert*-butyl alcohol under nitrogen atmosphere in the presence of *tert*-BuOK as acid scavenger gave the desired compound (**7**) with yield higher than 70% (Scheme 3). Both *cis*- and *trans*-isomer under irradiation condition could be cyclized, that may support the possible radical mechanism rather than the concerted mechanism in *Pschorr* cyclization procedure.[4]

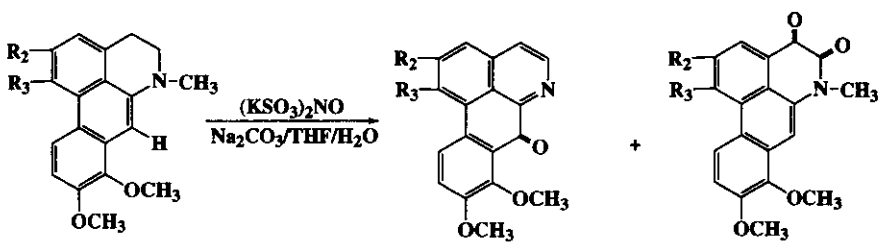
Scheme 3



Mild oxidation of the aporphine (**8**), which was readily obtained by reduction of the 6-ethoxycarbonylnoraporphine (**7**) with $LiAlH_4$, by Fremy's salt[5] in aqueous THF gave a mixture of the corresponding oxoaporphine (**9**) and 4,5-dioxoaporphine (**11**) (Scheme 4). The occurrence of side product of 4,5-dioxoaporphine (**11**) may be due to the steric effect of 8-methoxyl group that prevented the methene from being oxidized to form the target compound (**9**). When compound (**8**) was oxidized in water solvent, in spite of its low-solubility, the reaction could complete in 3 days and the main product was 4,5-dioxoaporphine (**11**); however, when performed the oxidation reaction in organic solvent (THF), it would take long time even more than one week to consume the material and the main product was the desired oxoaporphine (**9**), which could be readily converted into (±)-

sinomendine (**1**) by reacting with MeMgI.

Scheme 4



8 R_2=OCH_3, R_3=H

9 R_2=OCH_3, R_3=H

11 R_2=OCH_3, R_3=H

EXPERIMENTAL

General experimental procedures: Melting points were taken on a hot-stage microscope and are uncorrected. Infrared spectra were in potassium bromide on a Perkin-Elmer model 240C spectrophotometer. Mass spectra were obtained with model VG-ZAB-2F spectrometer. The ^{1}H nmr spectra were determined on a JEOL FX-90MHz or Varian-VXR-300MHz spectrometer in $CDCl_3$ with TMS as internal standard and chemical shifts reported in δ ppm units. Photolysises were carried out using medium-pressure mercury as lamps (250 watts).

N-(Substituted phenylethyl)-6-bromo-2,3-dimethoxyphenylacetamides (4)

A solution of 6-bromo-2,3-dimethoxyphenylacetyl chloride (**3**) (1.26 g, 4.3 mmol) in 5 ml of chloroform was added dropwise over 20 min to a stirred solution of substituted phenylethylamine (**2**) (4.3 mmol) and triethylamine (1.0 g, 10 mmol) in 5 ml of chloroform. The solution was stirred for 0.5~1 h at room temperature, then washed with equal volume of water, 2.5% hydrochloric acid, 2.5% sodium carbonate and water, respectively. The chloroform layer was dried over magnesium sulfate, and evaporated to give a solid residue. The solid residue was recrystallized from methanol to give the corresponding acetamide (**4**) in high yield.

Acetamide (**4a**), ***N*-(3'-methoxyphenethyl)-6-bromo-2,3-dimethoxyphenylacetamide**, as a white crystal in 81% yield. mp 114-115 °C; ^{1}H nmr ($CDCl_3$) δ: 2.73 (t, 2H, Ar**CH$_2$**CH$_2$-, J=6.9 Hz), 3.47 (m, 2H, ArCH$_2$**CH$_2$**-), 3.75 (s, 2H, Ar**CH$_2$**CO-), 3.78, 3.80, 3.85 (3s, 9H, 3 x O**CH$_3$**), 5.52 (br, 1H, N**H**), 6.69-7.16 (m, 4H, **H-2', H-4', H-5', H-6'**), 6.74 (d, 1H, **H-4**, J=9.6 Hz), 7.27 (d, 1H, **H-5**, J=9.6 Hz). Anal. Calcd for $C_{19}H_{22}NO_4Br$: C, 55.89; H, 5.43; N, 3.43. Found: C, 55.90; H, 5.19; N, 3.32.

Acetamide(**4b**), ***N*-(3',4'-methylenedioxyphenethyl)-6-bromo-2,3-dimethoxyphenylacetamide**, as a white crystal in 83% yield. mp 148-149 °C; ^{1}H nmr ($CDCl_3$) δ: 2.65 (t, 2H, Ar**CH$_2$**CH$_2$-, J=7.1 Hz), 3.41 (m, 2H, ArCH$_2$**CH$_2$**-), 3.76 (s, 2H, Ar**CH$_2$**CO-), 3.80, 3.86 (2s, 6H, 2 x O**CH$_3$**), 5.50 (br, 1H, N**H**), 5.91 (s, 2H, O**CH$_2$**O), 6.51(dd, 1H, **H-6'**, J_1=7.8 Hz, J_2=2.4 Hz), 6.57 (d, 1H, **H-2'**, J=2.4 Hz), 6.65 (d, 1H, **H-5'**, J=7.8 Hz), 6.76 (d, 1H, **H-4**, J=9.6 Hz), 7.30 (d, 1H, **H-5**, J=9.6 Hz). Anal. Calcd for $C_{19}H_{20}NO_5Br$: C, 54.04; H, 4.77; N, 3.32. Found: C, 54.05; H, 4.76; N, 3.41.

Acetamide (**4c**), ***N*-(2'-methoxyphenethyl)-6-bromo-2,3-dimethoxyphenylacetamide**, as a white crystal in 80% yield. mp 150-152 °C; ^{1}H nmr ($CDCl_3$) δ: 2.80 (t, 2H, Ar**CH$_2$**CH$_2$-, J=6.6 Hz), 3.48 (m, 2H, ArCH$_2$**CH$_2$**-), 3.78~3.88 (m, 11H, 3 x O**CH$_3$** and Ar**CH$_2$**CO-), 5.69 (br, 1H, N**H**), 6.76~7.30 (m, 4H, **H-3'**, **H-4'**, **H-5'**, **H-6'**), 6.81 (d, 1H, **H-4**, J=9.0 Hz), 7.30 (d, 1H, **H-5**, J=9.0 Hz). Anal. Calcd for $C_{19}H_{22}NO_4Br$: C, 55.89; H, 5.43; N, 3.43. Found: C, 55.95; H, 5.45; N, 3.42.

Acetamide (**4d**), ***N*-(4'-benzyloxyphenethyl)-6-bromo-2,3-dimethoxyphenylacetamide**, as a white crystal in 92% yield. mp 144-146 °C; ^{1}H nmr ($CDCl_3$) δ: 2.68 (t, 2H, Ar**CH$_2$**CH$_2$-, J= 6.3 Hz), 3.42 (m, 2H, ArCH$_2$**CH$_2$**-), 3.75 (s, 2H, Ar**CH$_2$**CO-), 3.78, 3.85 (2s, 6H, 2 x O**CH$_3$**), 5.03 (s, 2H, Ar**CH$_2$**O-), 5.50 (br, 1H, -N**H**-), 6.74 (d, 1H, **H-4**, J=8.7 Hz), 6.83 (d, 2H, **H-2'**, J=9.0 Hz), 6.70 (d, 2H, **H-3'**, J=9.0 Hz), 7.26 (d, 1H, **H-5**, J=8.7 Hz), 7.30~7.50 (m, 5H, Ar**H**). Anal. Calcd for $C_{25}H_{26}NO_4Br$: C, 61.99; H, 5.41; N, 2.89. Found: C, 61.91; H, 5.11; N, 2.72.

1-(6'-Bromo-2',3'-dimethoxybenzyl)-3,4-dihydroisoquinolines (5)

A solution of the amide (**4**) (1.2 mmol) and phosphorus oxychloride (1.30 g, 8.5 mmol) in

dry acetonitrile (20 ml) was refluxed for 2-5 h. Only amides (**4a**) and (**4b**) could be converted into 3,4-dihydroisoquinoline (**5**). The excess reagent and solvent were removed under vacuum and the residue was poured into 5% sodium hydroxide, and then extracted with methylene chloride. The extraction was dried over magnesium sulfate and evaporated to give a white crystal (**5**).

Dihydroisoquinoline (**5a**), **1-(6'-bromo-2',3'-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline**, in 91% yield. mp 130-132 °C (from ethanol); ^{1}H nmr ($CDCl_3$) δ: 3.07 (t, 2H, ArC**H$_2$**CH$_2$, J=7.2 Hz), 3.92 (m, 2H, ArCH$_2$C**H$_2$**N-), 3.79, 3.84, 3.93 (3s, 9H, 3 x OCH_3), 4.81 (s, 2H, ArC**H$_2$**-), 6.70 (d, 1H, **H-5**, J=2.4 Hz), 6.74 (d, 1H, **H-4'**, J=8.7 Hz), 6.78 (m, 1H, **H-7**), 7.31 (d, 1H, **H-5'**, J=8.7 Hz), 7.38 (d, 1H, **H-8**, J=8.7 Hz). The above compound was dissolved in methylene chloride and through which was passed hydrogen chloride gas, affording the hydrochloride salt, mp 152-153 °C (from ethanol); ms 426 (M). Anal. Calcd for $C_{19}H_{21}NO_3BrCl$: C, 53.48; H, 4.96; N, 3.28. Found: C, 54.13; H, 4.37; N, 3.24.

Dihydroisoquinoline (**5b**), **1-(6'-bromo-2',3'-dimethoxybenzyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline**, in 77% yield without further purification. ^{1}H nmr ($CDCl_3$) δ: 3.01 (t, 2H, ArC**H$_2$**CH$_2$N, J=7.5 Hz), 3.80, 3.92 (2s, 6H, 2 x OC**H$_3$**), 3.89(m, 2H, ArCH$_2$C**H$_2$**N-), 4.83 (s, 2H, ArC**H$_2$**-), 6.01 (s, 2H, OC**H$_2$**O), 6.74 (d, 1H, **H-4'**, J=8.7 Hz), 6.74 (s, 1H, **H-5**), 6.84 (s, 1H, **H-8**), 7.32 (d, 1H, **H-5'**, J=8.7 Hz).

Ethyl 1-(6'-bromo-2',3'-dimethoxybenzylidene)-1,2,3,4-tetrahydroisoquinoline-2-carboxylates (**6** and **6'**) and **2-phenylacetyl-*N*-carbethoxyphenethylamines** (**10**):

A solution of ethyl chloroformate (2.0 g, 18 mmol) in methylene chloride (12 ml) was added dropwise over 5 min to a stirred mixture of the dihydroisoquinoline (**5**) (2.8 mmol) in 30 ml of methylene chloride and 20 ml of 10% sodium carbonate at 0-5 °C. The mixture was stirred at room temperature for 30 min. The methylene chloride layer was washed with water, dried over magnesium sulfate, and evaporated. The residue from **5a** was chromatographed on silica gel with petroleum ether/ethyl acetate (4:1) as eluent, giving three compositions. The first fraction afforded **6'a**, the ***trans*-isomer** of **ethyl 6-**

methoxy-1-(6'-bromo-2',3'-dimethoxybenzylidene)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate, as a white crystal in 8.0% yield. mp 74-75 °C (from petroleum ether 60-90 °C); ms 462 (M); ^{1}H nmr ($CDCl_3$) δ: 1.37 (t, 3H, CH_3, J=6.6 Hz), 2.94 (t, 2H, $ArCH_2CH_2$, J=5.7 Hz), 3.68, 3.75, 3.83 (3s, 9H, 3 x OCH_3), 3.90 (m, 2H, $ArCH_2CH_2$), 4.30 (q, 3H, CH_2CH_3, J=6.6 Hz), 6.44 (m, 1H, **H-7**), 6.68 (d, 1H, **H-5**, J=2.4 Hz), 6.69 (s, 1H, HC=), 6.74 (d, 1H, **H-4'**, J=9.0 Hz), 6.82 (d, 1H, **H-8**, J=8.1 Hz), 7.27 (d, 1H, **H-5'**, J=9.0 Hz). Anal. Calcd for $C_{22}H_{24}NO_5Br$: C, 57.15; H, 5.23; N, 3.03. Found: C, 56.81; H, 5.37; N, 2.83.

The second fraction gave **6a**, the ***cis*-isomer** of **ethyl 6-methoxy-1-(6'-bromo-2',3'-dimethoxybenzylidene)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate**, as a white crystal in 71% yield. mp 138-139 °C (from petroleum ether 60-90 °C); ms 462 (M); ^{1}H nmr ($CDCl_3$) δ: 0.91 (t, 3H, -CH_3, J=6.9 Hz), 2.91 (t, 2H, $ArCH_2CH_2$, J=5.7 Hz), 3.73, 3.82, 3.83 (3s, 9H, 3 x OCH_3), 3.80 (m, 2H, $ArCH_2CH_2$), 3.95 (m, 2H, CH_2CH_3), 6.67 (s, 1H, HC=), 6.69 (d, 1H, **H-5**, J=3.0 Hz), 6.74 (d, 1H, **H-4'**, J=9.0 Hz), 7.27 (d, 1H, **H-8**, J=8.7 Hz), 7.80 (d, 1H, **H-5'**, J=9.0 Hz). Anal. Calcd for $C_{22}H_{24}NO_5Br$: C, 57.15; H, 5.23; N, 3.03. Found: C, 56.98; H, 5.43; N, 2.85.

The third fraction was **10a**, **2-(6'-bromo-2',3'-dimethoxyphenylacetyl)-*N*-carbethoxy-5-methoxyphenethylamine**, as a white crystal in 14% yield. mp 109-111 °C (from petroleum ether 60-90 °C); ms 480 (M); ir: 3310 (-NH-), 1694 (C=O); ^{1}H nmr ($CDCl_3$) δ: 1.18 (t, 3H, -CH_3, J=6.9 Hz), 3.40 (t, 2H, $ArCH_2CH_2$, J=6.6 Hz), 3.73 (m, 2H, $ArCH_2CH_2$), 3.81, 3.85, 3.85 (3s, 9H, 3 x OCH_3), 4.05 (q, 2H,CH_2CH_3, J=6.9 Hz), 4.26 (s, 2H, $ArCH_2CO$), 5.22 (br, 1H, -NH), 6.77 (d, 1H, H_3, J=9.6 Hz), 6.83 (m, 1H, H_4), 6.87 (d, 1H, H_6, J=2.4 Hz), 7.29 (d, 1H, $H_{4'}$, J=9.0 Hz), 7.94 (d, 1H, $H_{5'}$, J=9.0 Hz). Anal. Calcd for $C_{22}H_{26}NO_6Br$: C, 55.01; H, 5.46; N, 2.92. Found: C, 55.32; H, 5.75; N, 2.75.

Two compositions from **5b**, chromatographed on silica gel with petroleum ether/ethyl acetate (4:1) as eluent, were afforded as following: the first fraction was **6b**, the ***cis*-isomer** of **ethyl 6,7-methylenedioxy-1-(6'-bromo-2',3'-dimethoxybenzylidene)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate**, as a white crystal in 56% yield. mp 109-111 °C (from petroleum ether 60-90 °C); ms 477 (M); ^{1}H nmr ($CDCl_3$) δ: 0.89 (t, 3H, -CH_3,

J=6.6 Hz), 2.84 (t, 2H, ArC**H**$_2$CH$_2$, J=6.0 Hz), 3.67(m, 2H, C**H**$_2$CH$_3$), 4.40 (m, 2H, ArCH$_2$C**H**$_2$), 3.79, 3.82, (2s, 6H, 2 x OC**H**$_3$), 5.96 (s, 2H, OC**H**$_2$O), 6.04 (s, 1H, **H**C=), 6.60 (s, 1H, **H-5**), 6.67 (s, 1H, **H-8**), 6.69 (d,1H, **H-4'**, J=9.0 Hz), 7.28 (d, 1H, **H-5'**, J=9.0 Hz). Anal. Calcd for $C_{22}H_{22}NO_6Br$: C, 55.47; H, 4.66; N, 2.99. Found: C, 55.78; H, 4.65; N, 2.99.

The second fraction was **10b**, **2-(6'-bromo-2',3'-dimethoxyphenylacetyl)-*N*-carbethoxy-4,5-methylenedioxyphenethylamine**, as a white crystal in 11% yield. mp 109-111 °C (from petroleum ether 60-90 °C); ir: 3310 (-NH-), 1694 (C=O); ^{1}H nmr $CDCl_3$) δ: 1.16 (t, 3H, -C**H**$_3$, J=7.5 Hz), 2.92 (t, 2H, ArC**H**$_2$CH$_2$, J=6.9 Hz), 3.38 (m, 2H, ArCH$_2$C**H**$_2$), 3.80, 3.83 (2s, 6H, 2 x OC**H**$_3$), 3.93 (q, 2H, OC**H**$_2$CH$_3$, J=7.5 Hz), 4.37 (s, 2H, ArC**H**$_2$CO), 5.30 (br, 1H, N**H**), 6.00 (s, 2H, OC**H**$_2$O), 6.75 (d, 1H, J=9.0 Hz, **H4'**), 6.77 (s, 1H, **H$_6$**), 7.26 (d, 1H, J=9.0 Hz, **H$_{5'}$**), 7.35 (s, 1H, **H$_3$**). Anal. Calcd for $C_{22}H_{24}NO_7Br$: C, 53.45; H, 4.89; N, 2.83. Found: C, 53.33; H, 5.11; N, 2.64.

Ethyl 8,9-dimethoxy-6a,7-dehydronoraporphine-6-carboxylates (7)

A solution of stilbene (**6**) (0.9 mmol) in *tert*-butyl alcohol (50 ml) and toluene (600 ml) was mixed with potassium *tert*-butoxide (0.50 g, 4.4 mmol), and then stirred under nitrogen atmosphere at room temperature while being irradiated with a 250 W high pressure mercury lamp for 4h. The pale yellow reaction mixture was then evaporated under vacuum and the residue was mixed with chloroform (20 ml) and 5% dilute hydrochloride (20 ml). The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated. The yellow oil was chromatographed on silica gel with petroleum ether/ethyl acetate (4:1) as eluent, giving dehydroaporphine (**7**).

Ethyl 2,8,9-trimethoxy-6a,7-dehydronoraporphine-6-carboxylate (7a), as oil in 88% yield. Ms 381 (M); ^{1}H nmr ($CDCl_3$) δ: 1.36 (t, 3H, -C**H**$_3$, J=7.5 Hz), 3.20 (t, 2H, ArC**H**$_2$C H$_2$, J=6.0 Hz), 3.99, 4.01, 4.02 (3s, 9H, 3 x OC**H**$_3$), 4.12 (t, 2H, ArCH$_2$C**H**$_2$,J=6.0 Hz), 4.32 (q, 2H, C**H**$_2$CH$_3$, J=7.5 Hz), 6.97 (d, 1H, **H$_3$**, J=2.0 Hz), 7.25 (d, 1H, **H$_{10}$**, J=9.3 Hz), 7.83 (d, 1H, **H$_1$**, J=2.0 Hz), 8.12 (s, 1H, **H$_7$**), 8.25 (d, 1H, **H$_{11}$**, J=9.3 Hz). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.49; H,

6.21; N, 3.82.

Ethyl 1,2-methylenedioxy-8,9-dimethoxy-6a,7-dehydronoraporphine-6-carboxylate (**7b**), as oil in 73% yield. ^{1}H Nmr ($CDCl_3$) δ: 1.35 (t, 3H, -C**H$_3$**, J=7.5 Hz), 3.16 (t, 2H, ArC**H$_2$**CH_2, J=5.7 Hz), 3.99, 4.00 (2s, 6H, 2 x OC**H$_3$**), 4.09 (t, 2H, $ArCH_2$C**H$_2$**, J=5.7 Hz), 4.30 (q, 2H, C**H$_2$**CH_3, J=7.5 Hz), 6.21 (s, 2H, OC**H$_2$**O), 6.97 (s, 1H, **H$_3$**), 7.22 (d, 1H, **H$_{10}$**, J=9.3 Hz), 8.05 (s, 1H, **H$_7$**), 8.75 (d, 1H, **H$_{11}$**, J=9.3 Hz).

6a,7-Dehydroaporphines (8)

A solution of the ester (**7**) (0.26 mmol) in 6 ml of dried tetrahydrofuran was added to suspension of lithium aluminum hydride (35 mg, 0.95 mmol) and aluminum chloride (45 mg, 0.33 mmol) in 6 ml of dried tetrahydrofuran, and refluxed for 1.5 h. The solvent was evaporated and the residue was treated with 5% ammonium hydroxide (5 ml), and then extracted with chloroform (5 ml). The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated to give a yellow crystal, which was recrystallized from methanol to give pale yellowish needles (**8**).

2,8,9-Trimethoxy-6a,7-dehydroaporphine (**8a**) in 89% yield. mp 144-146 °C; ms 323 (M); ^{1}H nmr ($CDCl_3$) δ: 3.14 (s, 3H, NC**H$_3$**), 3.26 (t, 2H, ArC**H$_2$**CH_2, J=6.2 Hz), 3.40 (t, 2H, $ArCH_2$C**H$_2$**, J=6.2 Hz), 3.99, 4.00, 4.02 (3s, 9H, 3 x OC**H$_3$**), 6.90 (s, 1H, **H$_7$**), 6.90 (d, 1H, **H$_3$**, J=2.7 Hz), 7.05 (d, 1H, **H$_{10}$**, J=8.4 Hz), 7.79 (d, 1H, **H$_1$**, J=2.7 Hz), 8.15 (d, 1H, **H$_{11}$**, J=8.4 Hz). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.26; H, 6.37; N, 4.18.

1,2-Methylenedioxy-8,9-dimethoxy-6a,7-dehydroaporphine (**8b**) in 90% yield. mp 140-141 °C; ^{1}H nmr ($CDCl_3$) δ: 3.02 (s, 3H, NC**H$_3$**), 3.18 (t, 2H, ArC**H$_2$**CH_2, J=7.2 Hz), 3.24 (t, 2H, $ArCH_2$C**H$_2$**, J=7.2 Hz), 3.84, 3.85 (2s, 6H, 2 x OC**H$_3$**), 6.10(s, 2H, OC**H$_2$**O), 6.81 (s, 1H, **H$_3$**), 6.86 (s, 1H, **H$_7$**), 7.20 (d, 1H, **H$_{10}$**, J=9.0 Hz), 8.60 (d, 1H, **H$_{11}$**, J=9.0 Hz) Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.67; N, 4.15. Found: C, 71.15; H, 5.90; N, 4.13.

7-Oxoaporphine (9) and 4,5-dioxoaporphine (11)

To a mixture of compound (**8a**) (150 mg, 0.46 mmol), THF (30 ml) and 5% sodium carbonate (30 ml) was added freshly prepared Fremy's salt (1.0 g, 3.7 mmol). The suspension was stirred at room temperature. After one week, the solvent was evaporated and the residue was extracted with chloroform. The extraction was washed with water, dried over magnesium sulfate, and evaporated to give a red gum. The red gum was purified by silica gel column eluted with chloroform/methanol (10:1), affording two products. The first product was **2,8,9-trimethoxy-6a,7-dehydro-4,5-dioxoaporphine** (**11**), a red solid in 22% yield (35.2 mg). mp 263-265 °C (from methanol-chloroform); ms 352 (M+1); ir 1660(-CO-CO-); ^{1}H nmr ($CDCl_3$) δ: 3.89 (s, 3H, NC**H$_3$**), 4.05, 4.06, 4.08 (3s, 9H. 3 x OC**H$_3$**), 7.35 (d, 1H, **H$_{10}$**, J=9.3 Hz), 7.82 (s, 1H, **H$_7$**), 8.12 (d, 1H, **H$_3$**, J=2.1 Hz), 8.25 (d, 1H, **H$_{11}$**, J=9.3 Hz), 8.38 (d, 1H, **H$_1$**, J=2.1 Hz). Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.87; N, 3.99. Found: C, 68.26; H, 4.83; N, 3.75.

The second fraction was a yellow crystal, **2,8,9-trimethoxy-7-oxoaporphine** (**9**) in 36% yield. mp 179-180 °C (from methanol-chloroform); ms 320 (M-1); ir 1640 (C=O); ^{1}H nmr ($CDCl_3$) δ 3.83, 3.93, 3.99 (3s, 9H, 3 x OC**H$_3$**), 7.49 (d,1H, **H$_3$**, J=1.8 Hz), 7.51 (d, 1H, **H$_{10}$**, J=8.8 Hz), 8.05 (d, 1H, **H$_4$**, J=5.5 Hz), 8.22 (d,1H, **H$_1$**, J=1.8 Hz), 8.34 (d, 1H, **H$_{11}$**, J=8.8 Hz), 8.81 (d, 1H, **H$_5$**, J=5.5 Hz). Anal. Calcd for $C_{19}H_{15}NO_4 1/2H_2O$: C, 69.15; H, 4.85; N, 4.24. Found: C, 69.66; H, 4.95; N, 3.84.

2,8,9-Trimethoxy-7-hydroxy-7-methylaporphine ((±)-sinomendine, 1)

To a suspension of freshly prepared methylmagnisium iodide (170 mg, 1 mmol) in 5 ml of dried THF was slowly added dropwise oxoaporphine (**9**) (150 mg, 0.46 mmol) in 5 ml of dried THF. The reaction mixture was refluxed for 1 h. After evaporation the residue was dissolved in 20 ml of ether, then treated with the same volume of aqueous saturated solution of ammonium chloride. The ether layer was washed with water, dried over magnesium sulfate, and evaporated. The residue was purified on silica gel eluted with methanol/chloroform (1:10) to give a red solid, **2,8,9-trimethoxy-7-hydroxy-7-methylaporphine** (**1**), in 64% yield. mp 141-142 °C (from methanol-chloroform); ms 338 (M+1), 320 (M-OH); ^{1}H nmr ($CDCl_3$) δ: 1.24 (s, 3H, C**H$_3$**), 3.95, 3.97, 4.08 (3s, 9H, 3 x

OC**H3**), 6.99 (d, 1H, **H3**, J=1.8 Hz), 7.03 (d, 1H, **H10**, J=8.7 Hz), 7.51 (d, 1H, **H4**, J=5.7 Hz), 7.64 (d, 1H, **H1**, J=1.8 Hz), 7.80 (d, 1H, **H11**, J=8.7 Hz), 8.54 (d, 1H, **H5**, J=5.7 Hz). EIms (m/z) for $C_{20}H_{19}NO_4$ (**I**), Calcd 337.1314. Found 337.1311.

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