# A NEW REGIOSELECTIVE SYNTHESIS OF ISOPAVINE AND PAVINE ALKALOIDS *VIA* DOUBLE CYCLIZATION OF *N*-(1,2-DIARYLETHYL)-*N*-(2-PHENYLSULFINYLETHYL)FORMAMIDE

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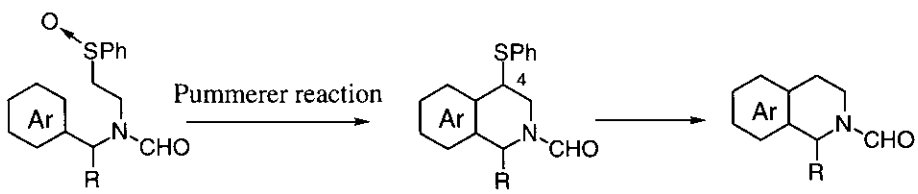
***Abstract*** —— Pummerer reaction of *N*-[1,2-(3,4-dimethoxyphenyl)ethyl]-*N*-(2-phenylsulfinylethyl)formamide (**9**) using trifluoroacetic anhydride and boron trifluoride etherate caused double cyclization to give *N*-formylisopavine (**21**). Acid catalyzed cyclization of the 1,2-dihydroisoquinoline (**23**) prepared from 4-phenylthio-1,2,3,4-tetrahydroisoquinoline (**11**) gave *N*-formylpavine (**26**). $LiAlH_4$ reduction of the *N*-formates (**21** and **26**) gave (±)-*O*-methylthalisopavine (**4**) and (±)-argemonine (**5**), respectively.

Recently, we have developed a highly efficient synthesis of 1,2,3,4-tetrahydroisoquinolines (TIQs) utilizing Pummerer reaction as a key step.[1] The cyclization of the sulfoxides (**1**) produces 4-phenylthio substituted *N*-formyl-TIQs (**2**) whose reductive elimination of the phenylthio group gives *N*-formyl-TIQs (**3**).

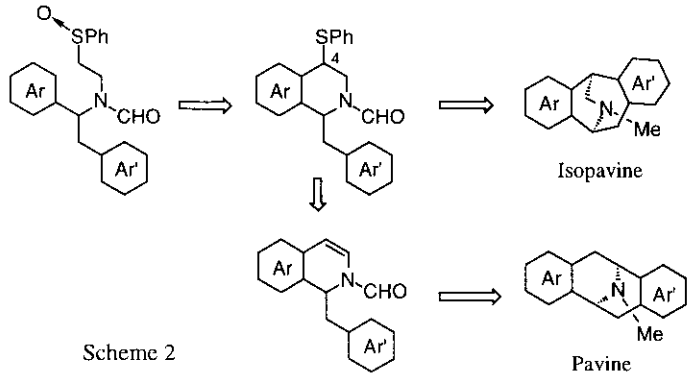



**1** **2** **3**

Scheme 1

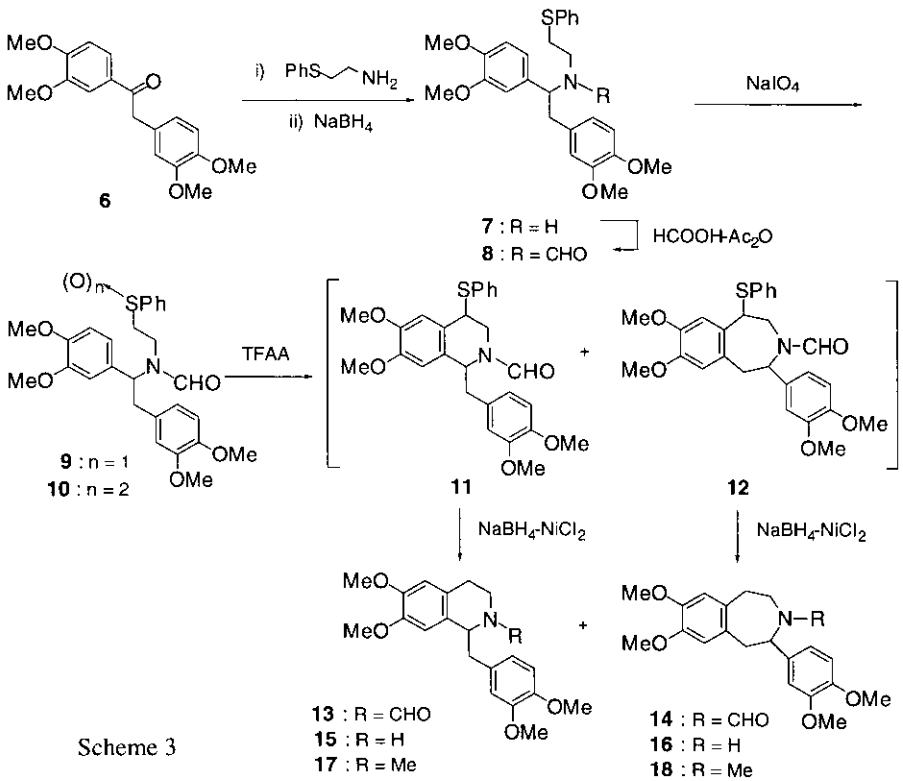
In order to expand the utility of this TIQ synthetic method we designed the route constructing isopavine and pavine alkaloids from 1-arylmethyl-4-phenylthio-TIQs as shown in Scheme 2. In this paper we describe a regioselective synthesis of (±)-*O*-methylthalisopavine (**4**), an isopavine alkaloid,[2,3] and (±)-argemonine (**5**),

a pavine alkaloid.[2,4]




Scheme 2

The sulfoxide (**9**) was prepared from 3,4,3'4'-tetramethoxydeoxybenzoin (**6**)[5] in 85% overall yield as follows. Condensation of **6** with 2-phenylthioethylamine[6] in the presence of titanium tetraisopropoxide followed by $NaBH_4$ reduction of the resulting imine gave the amine (**7**) in 93% yield. Formylation of **7** with formic acid-acetic anhydride gave the formamide (**8**) in 97% yield. Oxidation of **8** with sodium metaperiodate in aqueous MeOH gave the sulfoxide (**9**) in 94% yield together with the sulfone (**10**) (5% yield).

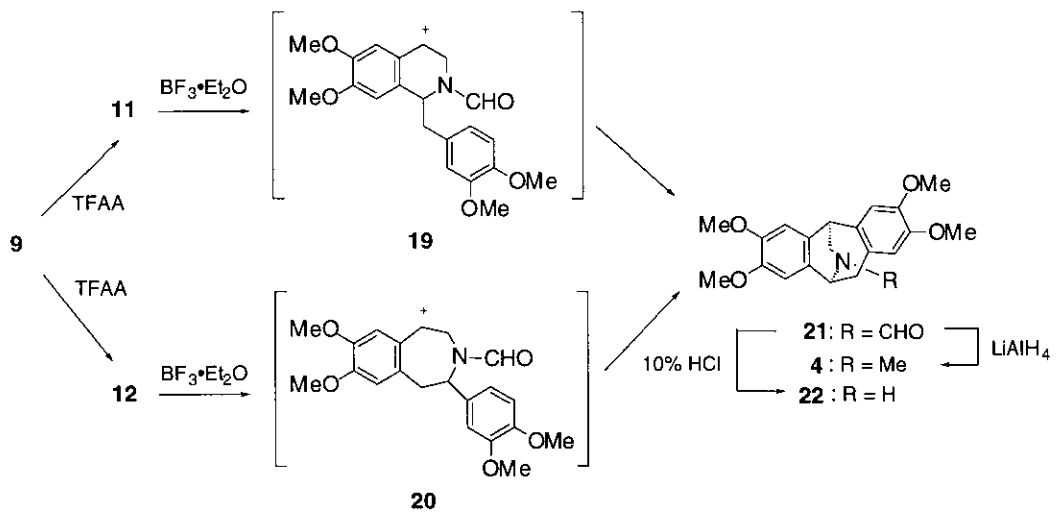



Scheme 3

Treatment of the sulfoxide (**9**) with trifluoroacetic anhydride (TFAA) in benzene at room temperature for 3 h caused a cyclization to give an inseparable mixture of 4-phenylthio-TIQ (**11**) and 5-phenylthiotetrahydrobenzazepine (**12**) in 82% yield.[7] The product was proved to be a 3:1 mixture of **11** and **12** as follows. Reductive desulfurization of the mixture with $NaBH_4$-$NiCl_2$ gave an inseparable mixture of **13** and **14** in 77% yield. Hydrolysis of the desulfurized products with 10% HCl gave (±)-tetrahydropapaverine (**15**)[8]

and tetrahydrobenzazepine (**16**) in 46% and 18% yields, respectively. $LiAlH_4$ reduction of the mixture (**13** and **14**) gave (±)-laudanosine (**17**)[9] and *N*-methyltetrahydrobenzazepine (**18**)[10] in 76 and 22% yields, respectively. Thus, the cyclization of the sulfoxide (**9**) occurred competitively at the nucleophilic centers of either benzene ring; that is, one formed a six-membered ring and the other formed a seven membered ring with preference of the former process.

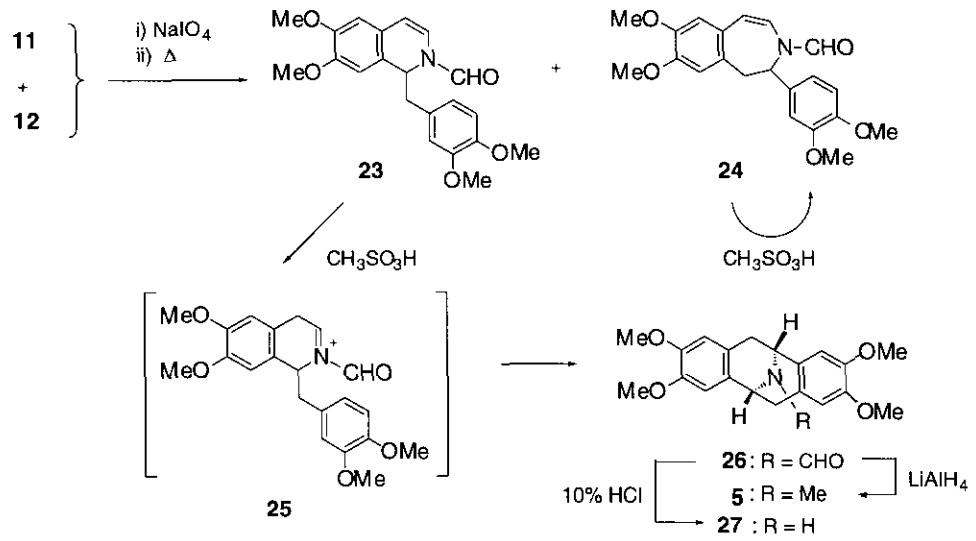
The sulfoxide (**9**), when treated with TFAA in benzene at room temperature for 1 h and then with $BF_3$•$Et_2O$ for 16 h, gave an *N*-formylisopavine (**21**) as a single product in 54% yield (Scheme 4). The formation of isopavine was readily deduced from MS and $^1$H-NMR spectra which indicated the loss of phenylthio group and of two aromatic protons. The formation of **21** as a sole product suggested that not only the 4-phenylthio-TIQ (**11**) but also the 5-phenylthiobenzazepine (**12**) underwent the second cyclization *via* the carbocations (**19** and **20**) generated by elimination of phenylthio group. In fact, the mixture of **11** and **12** on treatment with $BF_3$•$Et_2O$ in benzene at room temperature for 20 h or under reflux for 2 h gave the *N*-formylisopavine (**21**) as a sole product in 90 and 92% yields, respectively.[11]




Scheme 4

This $BF_3$•$Et_2O$ mediated cyclization was found to be solvent-dependent. Thus, the reaction in acetonitrile under reflux for 2 h gave **21** in 94% yield, but refluxing in THF resulted in recovery of the starting material. $LiAlH_4$ reduction of **21** gave (±)-*O*-methylthalisopavine (**4**)[12] in 85% yield. Hydrolysis of **21** with 10% HCl in EtOH under reflux for 8 h gave (±)-2,3,7,8-tetramethoxyisopavine (**22**)[13] in 99% yield.

Oxidation of the phenylthio group of the mixture (**11** and **12**) with $NaIO_4$ in aqueous MeOH followed by pyrolysis of the resulting sulfoxides under refluxing toluene gave a mixture of the dihydroisoquinoline (**23**) and the dihydrobenzazepine (**24**) in 68% yield. The mixture was then treated with methanesulfonic acid to give the *N*-formylpavine (**26**) in 68% yield along with the unchanged dihydrobenzazepine (**24**) (30%). The selective formation of **26** clearly indicated that the protonation on the double bond of **23** selectively formed the nitrenium ion (**25**). $LiAlH_4$ reduction of **26** or hydrolysis of **26** with 10% HCl gave (±)-argemonine (**5**)[14] in 86% yield or (±)-*N*-desmethylargemonine (**27**) in 85% yield, respectively.




Scheme 5

Thus, we revealed a highly effective and regioselective synthesis of isopavine and pavine alkaloids using Pummerer reaction as a key step. The method offers a useful alternative to the classical one which consists in an acid-catalyzed double cyclization of benzylaminoacetaldehyde dialkyl acetals.[12a-b, 13a-b, 15]

## EXPERIMENTAL

**General Notes.** Unless otherwise noted, the following procedures were adopted. Melting points were taken on a Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were obtained as KBr disks with a JASCO FT/IR-5000 or a Horiba FT-170 spectrophotometer, and are given in $cm^{-1}$. NMR spectra were measured on a JEOL JNM-EX 90 ($^1H$, 90 MHz) or a JEOL JNM-α 500 ($^1H$, 500 MHz $^{13}C$, 125 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard, and the chemical shifts are given in δ values. The following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddd = double double doublet, m = multiplet. $^1H$-$^1H$, $^1H$-$^{13}C$ COSY spectra were obtained with the usual pulse sequence. The $^1H$-NMR and $^{13}C$-NMR spectra indicated that all *N*-formyl derivatives are present in $CDCl_3$ as pairs of peaks due to the anisotropy of the *N*-formyl group.

LRMS and HRMS were taken on a JEOL JMS-AX 505H spectrometer at 70 eV [electron ionization MS (EIMS)] or at 270 eV [chemical ionization MS (CIMS, reactant gas: *iso*-butane)] using direct or GC/MS inlet system, and figures in parentheses indicate the relative intensities. The elemental analyses were recorded on a Yanagimoto CHN coder MT-3. TLC was performed on Merck precoated Silica gel 60 $F_{254}$ plates (Merck). Unless otherwise stated, column chromatography was carried out with silica gel (Wakogel C-200). The organic extract from each reaction mixture was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo* to dryness.

***N*-[1,2-(3,4-Dimethoxyphenyl)ethyl]-2-phenylsulfanylethylamine (7).** A mixture of 3,4,3'4'-tetramethoxydesoxybenzoin (**6**)[5] (10 g, 31.65 mmol), 2-phenylthioethylamine[6] (5.8 g, 37.91 mmol), and titanium tetraisopropoxide (13.5 g, 47.54 mmol) was heated at 80℃ for 3 h. After cooling, the reaction mixture was diluted with MeOH (200 mL). To this solution, $NaBH_4$ (1.45 g, 38.36 mmol) was added in small portions under ice-cooling. The reaction mixture was stirred at rt for 1 h and concentrated *in vacuo*. Water (*ca* .50 mL) was added to the residue, and the mixture was diluted with MeOH (*ca.* 600 mL). After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was suspended in water and extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt-hexane (1:1) to give **7** (13.5 g, 93%) as pale yellow gum. IR: 1606, 1591, 1516, 1464, 1417, 1261, 1236, 1155, 1138, 1028. $^1$H-NMR (90 MHz): 2.40-3.10 (6H, m, -$SCH_2CH_2N$=, $ArCH_2$-), 3.68 (1H, dd, $J$ = 2.0, 5.5 Hz), Ar<u>C</u>H($CH_2$Ar)N=), 3.81 (3H, s, -$OCH_3$), 3.86 (9H, s, 3 x -$OCH_3$), 6.56-7.75 (6H, m, Ar-H), 7.17 (5H, s, Ar-H). EIMS *m/z*: 302 (M-151, base peak), 285 (3), 192 (6), 151 (7), 137 (61), 109 (11). CIMS *m/z*: 454 ($MH^+$, 34), 344 (7), 301 (base peak), 192 (4), 154 (18), 137 (17).

***N*-[1,2-(3,4-Dimethoxyphenyl)ethyl]-*N*-(2-phenylsulfanylethyl)formamide (8).** A mixture of **7** (12 g, 26.49 mmol), 98% formic acid (36.5 g, 793 mmol) and acetic anhydride (27 g, 265 mmol) was heated at 70℃ for 1 h, then concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt-hexane (2:1) to give **8** (12.3 g, 97%) as pale yellow gum. IR: 1664 (=NCO-), 1591, 1516, 1464, 1417, 1267, 1238, 1155, 1142, 1026. $^1$H-NMR (90 MHz): 2.20-6.65, 2.90-3.70 (total 6H, -$SCH_2CH_2N$=, $ArCH_2$-), 3.81, 3.83, 3.84, 3.86, 3.91 (total 12H, 4 x -$OCH_3$), 4.58, 5.67 (total 1H, dd, $J$ = 6.3, 9.0 Hz and t, $J$ = 9.0 Hz, Ar<u>C</u>H($CH_2$Ar)N=), 6.50-7.00 (6H, m, Ar-H), 7.10-7.35 (5H, m, Ar-H), 7.93, 8.03 (total 1H, each s, =NCHO). EIMS *m/z*: 330 (M-151, 64), 302 (71), 300 (67), 285 (8), 151 (13), 137 (base peak), 109 (22). CIMS *m/z*: 482 ($MH^+$, 8), 303 (4), 301 (base peak), 182 (48).

***N*-[1,2-(3,4-Dimethoxyphenyl)ethyl]-*N*-(2-phenylsulfinylethyl)formamide (9).** A solution of sodium metaperiodate (7.48 g, 34.97 mmol) in $H_2O$ (100 mL) was added to a solution of **8** (11.22 g, 23.33 mmol) in MeOH (500 mL), and the mixture was stirred at rt for 16 h. After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo* and extracted with $CHCl_3$. The crude material was purified by column chromatography with AcOEt. The first eluate gave *N*-[1,2-(3,4-dimethoxyphenyl)ethyl]-*N*-(2-phenylsulfonylethyl)formamide (**10**) (0.54 g, 4.5%) as colorless plates

(from AcOEt-$CHCl_3$). mp 180-181℃. IR: 1664 (=NCO-), 1593, 1518, 1466, 1446, 1417, 1302, 1269, 1246, 1149, 1082, 1026. $^1$H-NMR (90 MHz): 2.40-2.85, 3.10-4.20 (6H, m, -$SCH_2CH_2N$=, $ArCH_2$-), 3.82, 3.84, 3.88, 3.91 (each 3H, s, 4 x -$OCH_3$), 4.70, 5.70 (total 1H, each t, $J$ = 7.0 Hz, Ar$\underline{C}$H($CH_2$Ar)N=), 6.55-7.00 (6H, m, Ar-H), 7.40-8.10 (6H, m, Ar-H, =NCHO). EIMS *m/z*: 361 (24), 333 (base peak), 300 (44), 285 (5), 253 (15), 192 (10), 151 (11). CIMS *m/z*: 514 ($MH^+$, 2), 243 (5), 301 (base peak), 214 (52), 186 (6), 169 (10), 151 (6). *Anal.* Calcd for $C_{27}H_{31}NO_7S$: C, 63.14; H, 6.08; N, 2.73. Found: C, 62.94; H, 6.12; N, 2.69.

The second eluate gave **9** (10.9 g, 94%) as pale yellow plates (from $Et_2O$-hexane). mp 134-136℃. IR: 1664 (=NCO-), 1591, 1581, 1464, 1444, 1417, 1267, 1142, 1086, 1026. $^1$H-NMR (90 MHz): 2.0-3.70 (6H, m, -$SCH_2CH_2N$=, $ArCH_2$-), 3.77, 3.83, 3.85, 3.89, 3.91 (total 6H, each s, 4 x-$OCH_3$), 4.70, 4.73 and 5.55-5.80 (total 1H, each t, $J$ = 7.7 Hz and m, Ar$\underline{C}$H($CH_2$Ar)N=), 6.55-7.05 (6H, m, Ar-H), 7.45, 7.50 (total 5H, each s, Ar-H), 7.99, 8.03, 8.06, 8.15 (total 1H, each s, =NCHO). EIMS *m/z*: 300 (61), 285 (8), 220 (base peak), 192 (35), 167 (47), 151 (21), 139 (7). CIMS *m/z*: 498 ($MH^+$, 10), 482 (17), 372 (79), 301 (base peak), 287 (26), 220 (15), 182 (63), 167 (31), 153 (29), 141 (63). *Anal.* Calcd for $C_{27}H_{31}NO_6S$: C, 65.17; H, 6.28; N, 2.81. Found: C, 64.93; H, 6.58; N, 2.80.

**Pummerer Cyclization of 9 with TFAA.** TFAA (546 mg, 2.60 mmol) was added to a solution of **9** (1.15 g, 5.48 mmol) in dry benzene (20 mL) at rt, and the mixture was stirred for 3 h. The reaction mixture was concentrated and the residue was purified by column chromatography with AcOEt-hexane (2:1) to give a mixture of 2-formyl-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline (**11**) and 3-formyl-2-(3,4-dimethoxyphenyl)-7,8-dimethoxy-5-phenylsulfanyl-2,3,4,5-tetrahydro-*1H*-benzo[*d*]azepine (**12**) (429 mg, 82%) as yellow gum.

**Reductive Desulfurization of a Mixture of 11 and 12 with $NaBH_4$-$NiCl_2$.** $NaBH_4$ (760 mg, 20.10 mmol) was added in small portions to a stirred solution of a mixture of **11** and **12** (917 mg, 1.91 mmol) containing $NiCl_2$• $6H_2O$ (1.59g, 6.69 mmol) in MeOH-THF (3:1) (60 mL) under ice-cooling. Stirring was continued for 30 min at rt. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was suspended in water, acidified with 5% HCl, and extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt-hexane (2:1). The first eluate gave a mixture of 2-formyl-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2-dihydroisoquinoline (**23**) and 3-formyl-2-(3,4-dimethoxyphenyl)-7,8-dimethoxy-2,3-dihydro-*1H*-benzo[*d*]azepine (**24**) (58 mg, 8%) as yellow gum. The second eluate gave a mixture of 2-formyl-1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**13**) and 3-formyl-2-(3,4-dimethoxyphenyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-*1H*-benzo-[*d*]azepine (**14**) (549 mg, 77%) as pale yellow gum.

**Hydrolysis of a Mixture of Tetrahydroisoquinoline (13) and Tetrahydrobenzazepine (14).** A solution of a mixture of **13** and **14** (800 mg, 2.16 mmol) in EtOH (20 mL)-10% HCl (10 mL) was refluxed for 20 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water, basified with 10% NaOH, and extracted with $CHCl_3$. The products were purified by $Al_2O_3$ (Merck

aluminium oxide 90, 90-230 mesh) column chromatography with AcOEt. The first eluate gave 2-(3,4-dimethoxyphenyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-*1H*-benzo[*d*]azepine (**16**) (135 mg, 18%) as pale yellow gum. HCl salt (from EtOH-$Et_2O$): mp 246-249℃. IR: 1606, 1560, 1518, 1464, 1340, 1266, 1229, 1111, 1029. $^1$H-NMR (500 MHz): 2.76 (1H, ddd, $J$ = 0.9, 6.0, 14.7 Hz, H-5), 2.77 (1H, d, $J$ = 14.5 Hz, H-1), 2.84 (1H, ddd, $J$ = 0.9, 11.3, 12.2 Hz, H-4), 3.13 (1H, ddd, $J$ = 1.5, 11.3, 14.7 Hz, H-5), 3.31 (1H, dd, $J$ = 9.8, 14.5 Hz, H-1), 3.32 (1H, ddd, $J$ = 1.8, 6.0, 12.2 Hz, H-4), 3.65 (1H, d, $J$ = 9.8 Hz, H-2), 3.84 (3H, s, 8-$OCH_3$), 3.87 (3H, s, 7-$OCH_3$), 3.88 (3H, s, 4'-$OCH_3$), 3.92 (3H, s, 3'-$OCH_3$), 6.64 (1H, s, H-9), 6.68 (1H, s, H-6), 6.84 (1H, d, $J$ = 8.0 Hz, H-5'), 6.93 (1H, dd, $J$ = 2.2, 8.0 Hz, H-6'), 6.99 (1H, d, $J$ = 2.2 Hz, H-2'). $^{13}$C-NMR: 38.43 (t, C-5), 46.73 (t, C-1), 49.07 (t, C-4), 55.88 (q, 8-$OCH_3$), 55.90 (q, 7-$OCH_3$), 55.95 (q, 4'-$OCH_3$), 55.97 (q, 3'-$OCH_3$ ), 63.80 (d, C-2), 109.56 (d, C-2'), 111.03 (d, C-5'), 113.20 (d, C-6), 113.63 (d, C-9), 118.47 (d, C-6'), 132.88 (s, C-9a), 134.44 (s, C-5a), 139.10 (s, C-1'), 146.63 (s, C-8), 146.75 (s, C-7), 148.06 (s, C-4'), 148.98 (s, C-3'). EIMS m/z: 343 ($M^+$, 43), 341 (14), 326 (10), 301 (8), 192 (3), 178 (base peak), 165 (45), 151 (36), 147 (10), 136 (9). HRMS: Calcd for $C_{20}H_{25}NO_4$: 343.1783. Found: 343.1777.

The second eluate gave 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**15**) (337 mg, 46%) as pale yellow gum (lit.,[8a] oil). HCl salt (from EtOH-$Et_2O$): mp 218-222℃ (lit.,[8b] mp 215-220℃; lit.,[8c] mp 216-216.5℃). IR: 1608, 1589, 1516, 1464, 1261, 1234, 1113, 1028. $^1$H-NMR (500 MHz): 2.68 (1H, ddd, $J$ = 5.0, 5.0, 16.0 Hz, H-4), 2.76 (1H, ddd, $J$ = 5.0, 7.3, 16.0 Hz, H-4), 2.86 (1H, dd, $J$ = 9.5, 13.7 Hz, H-α), 2.91 ( 1H, ddd, $J$ = 5.0, 7.3, 11.3 Hz, H-3), 3.17 (1H, dd, $J$ = 4.3, 13.7 Hz, H-a), 3.21 (1H, dd, $J$ = 5.0, 11.3 Hz, H-3), 3.83 (3H, s, 7-$OCH_3$), 3.85 (3H, s, 3'-$OCH_3$), 3.86, 3.87 (each 3H, s, each one of 6-, 4'-$OCH_3$), 4.13 (1H, dd, $J$ = 4.3, 9.5 Hz, H-1), 6.60 (1H, s, H-8), 6.67 (1H, s, H-5), 6.76 (1H, d, $J$ = 1.8 Hz, H-2'), 6.80 (1H, dd, $J$ = 1.8, 8.3 Hz, H-6'), 6.83 (1H, d, $J$ = 8.3 Hz, H-5'). $^{13}$C-NMR: 29.45 (t, C-4), 40.88 (t, C-3), 42.17 (t, C-α), 55.77 (q, 7-$OCH_3$), 55.83 (q, 3'-$OCH_3$), 55.91 (q x 2, 6-, 4'-$OCH_3$), 56.78 (d, C-1), 109.31 (d, C-5'), 111.24 (d, C-5 or C-8), 111.76 (d, C-5 or C-8), 112.33 (d, C-2'), 121.33 (d, C-6'), 127.39 (s, C-4a), 130.37 (s, C-8a), 131.37 (s, C-1'), 146.92 (s, C-7), 147.36 (s, C-3'), 147.58 (s, C-6), 148.86 (s, C-4'). EIMS *m/z*: 340 (16), 326 (7), 324 (7), 310 (6), 192 (base peak), 176 (9). CIMS *m/z*: 433 ($MH^+$, base peak), 342 (28), 192 (73), 153 (15).

**$LiAlH_4$ Reduction of a Mixture of Tetrahydroisoquinoline (13) and Tetrahydrobenzazepine (14).** $LiAlH_4$ (112 mg, 2.95 mmol) was added to a solution of a mixture of **13** and **14** (550 mg, 1.48 mmol) in dry THF (20 mL) under ice cooling, and the mixture was refluxed for 2 h. Wet $Et_2O$ was added to the reaction mixture and insoluble material was filtered off. The product was purified by column chromatography with AcOEt-MeOH (8:2). The first eluate gave 2-(3,4-dimethoxyphenyl)-7,8-dimethoxy-3-methyl-2,3,4,5-tetrahydro-*1H*-benzo [*d*]azepine (**18**) (117 mg, 22%) as pale yellow gum. HCl salt (from EtOH-$Et_2O$): mp 240-245℃ [lit.,[10] mp 255-260℃ (HCl salt)]. IR: 1608, 1593, 1514, 1464, 1452, 1263, 1230, 1138, 1109, 1028. $^1$H-NMR (500 MHz): 2.08 (3H, s, =$NCH_3$), 2.40 (1H, ddd, $J$ = 0.9, 10.5, 12.5 Hz, H-4), 2.73 (1H, d, $J$ = 14.8 Hz, H-1), 2.80 (1H, ddd, $J$ = 0.9, 7.3, 15.3 Hz, H-5), 3.06 (1H, d, $J$ =9.5 Hz, H-2), 3.21 (1H, ddd, $J$ = 1.5, 10.5, 15.3 Hz, H-5), 3.24 (1H, ddd, $J$ = 1.5, 7.3, 12.5 Hz, H-4), 3.33 (1H, dd, $J$ = 9.5, 14.8 Hz, H-1), 3.82 (3H, s, 8-$OCH_3$), 3.87 (3H, s, 7-$OCH_3$), 3.88 (3H, s, 4'-

$OCH_3$), 3.89 (3H, s, 3'-$OCH_3$), 6.59 (1H, s, H-9), 6.68 (1H, s, H-6), 6.82 (2H, s, H-5' and H-6'), 6.89 (1H, s, H-2'). $^{13}$C-NMR: 35.23 (t, C-5), 44.31 (t, C-1), 45.60 (q, =$NCH_3$), 55.89 (q, 8-$OCH_3$), 55.93 (q, 7-$OCH_3$), 56.01 (q, 4'-$OCH_3$), 56.05 (q, 3'-$OCH_3$), 57.67 (t, C-4), 70.59 (d, C-2), 109.85 (d, C-2'), 110.88 (d, C-5'), 112.35 (d, C-6), 113.36 (d, C-9), 119.30 (d, C-6'), 132.37 (s, C-9a), 134.09 (s, C-5a), 138.45 (s, C-1'), 146.84 (s, C-8), 147.08 (s, C-7), 147.95 (s, C-4'), 149.17 (s, C-3'). EIMS *m/z*: 357 ($M^+$, base peak), 342 (27), 326 (11), 314(32), 301 (87), 283 (12), 268 (8), 252 (4), 220 (5), 206 (22), 192 (54), 178 (54), 176 (60), 165 (48), 161 (26), 151 (94), 133 (7). HRMS: Calcd for $C_{21}H_{27}NO_4$, 357.1940. Found: 357.1924.

The second eluate gave 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**17**) (403 mg, 76%) as colorless needles (from EtOH). mp 117-119℃ (lit.,[8a] mp 110-112℃; lit.,[9a] mp 116-117℃; lit.,[9b] mp 114-115℃). IR: 1606, 1589, 1516, 1452, 1375, 1265, 1228, 1142, 1105, 1030, 1018. $^1$H-NMR (500 MHz): 2.55 (3H, s, =$NCH_3$), 2.60 (1H, ddd, $J$ = 4.0, 4.3, 15.7 Hz, H-4), 2.78 (1H, dd, $J$ = 7.6, 13.5 Hz, H-α), 2.78 (1H, ddd, $J$ = 4.0, 5.5, 12.5 Hz, H-3), 2.84 (1H, ddd, $J$ = 5.5, 8.3, 15.7 Hz, H-4), 3.17 (1H, dd, $J$ = 5.0, 13.5 Hz, H-α), 3.19 (1H, ddd, $J$ = 4.3, 8.3, 12.5 Hz, H-3), 3.72 (1H, dd, $J$ = 5.0, 7.6 Hz, H-1), 3.57 (3H, s, 7-$OCH_3$), 3.79 (3H, s, 3'-$OCH_3$), 3.83, 3.84 (each 3H, s, each one of 6-, 4'-$OCH_3$), 6.06 (1H, s, H-8), 6.56 (1H, s, H-5), 6.61 (1H, d, $J$ = 2.0 Hz, H-2'), 6.64 (1H, dd, $J$ = 2.0, 8.2 Hz, H-6'), 6.76 (1H, d, $J$ = 8.2 Hz, H-5'). $^{13}$C-NMR: 25.39 (t, C-4), 40.82 (t, C-α), 42.58 (q, =$NCH_3$), 46.89 (t, C-3), 55.55 (q, 7-$OCH_3$), 55.76 (q, 3'-$OCH_3$), 55.81, 55.91 (each q, each one of 6-, 4'-$OCH_3$), 64.86 (d, C-1), 111.01 (d, C-5'), 111.10 (d, C-5 or C-8), 111.19 (d, C-5 or C-8), 113.03 (d, C-2'), 121.90 (d, C-6'), 125.84 (s, C-4a), 128.94 (s, C-8a), 132.33 (s, C-1'), 146.34 (s, C-7), 147.33 (s, C-3'), 147.35 (s, C-6), 148.56 (s, C-4'). EIMS *m/z*: 355 (5), 340 (6), 206 (M-151, base peak), 190 (13), 162 (4). CIMS *m/z*: 358 ($MH^+$, base peak), 206 (31), 153 (8).

**Pummerer Cyclization of 9 with TFAA-$BF_3$•$Et_2O$.** TFAA (1.15 g, 5.47 mmol) was added to a solution of **9** (540 mg, 1.09 mmol) in dry benzene (20 mL) at rt, and the mixture was stirred for 0.5 h. $BF_3$•$Et_2O$ (450 mg, 3.17 mmol) was added and stirring was continued at the same temperature for 16 h. The reaction mixture was washed with 5% NaOH, brine, and extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt-MeOH (95:5) to give *N*-formylisopavine (**21**) (215 mg, 54%) as pale yellow plates (from MeOH). mp 234-236℃ (lit.,[12] mp 232.5-234℃). IR: 1660 (=NCO-), 1610, 1514, 1464, 1425, 1401, 1344, 1284, 1248, 1120, 1112, 1018. $^1$H-NMR (500 MHz): 2.98, 3.20 (total 1H, each dd, $J$ = 2.3, 17.0 Hz, H-11), 3.36, 3.53 (total 1H, each dd, $J$ = 4.7, 17.0 Hz, H-11), 3.59, 4.09 (total 1H, each ddd, $J$ = 0.9, 4.3, 12.5 Hz and $J$ = 0.9, 0.9, 12.5 Hz, H-13), 3.74, 3.87 (total 1H, each dd, $J$ = 3.2, 10.0 Hz and $J$ = 2.0, 10.0 Hz, H-13), 3.78, 3.86, 3.87, 3.88, 3.90 (total 12H, each s, 4 x -$OCH_3$), 3.85-3.93 (1H, m, H-5), 4.96, 5.59 (total 1H, each dd, $J$ = 2.5, 4.3 Hz, H-10), 6.50, 6.51; 6.71, 6.72; 6.78, 6.80; 6.81, 6.82 (each total 1H, each s, H-1, H-4, H-6, H-9), 8.22, 8.42 (total 1H, each s, =NCHO). $^{13}$C-NMR: 38.70, 41.66 (total 1C, each t, C-11), 44.74, 45.73 (total 1C, each d, C-5), 49.01, 51.37 (total 1C, each t, C-13), 50.93, 56.19 (total 1C, each d, C-10), 55.90, 55.93, 56.08, 56.10, 56.26 (total 4C, each q, 4 x -$OCH_3$), 108.73, 108.97; 109.07, 109.59; 111.68, 111.90; 114.20, 114.38 (total 4C, each d, C-1, C-4, C-6, C-9), 125.00, 126.51, 127.83, 127.99, 131.37, 133.08, 133.87, 133.92 (total 4C,

each s, C-4a, C-5a, C-9a, C-11a), 146.98, 147.12, 148.06, 148.23, 148.25, 148.39, 148.45, 148.65 (total 4C, each s, C-2, C-3, C-7, C-8).161.76, 162.12 (total 1C, each d, =NCHO). EIMS *m/z*: 369 ($M^+$, 9), 340 (5), 324 (4), 311 (base peak), 295 (4), 269 (10), 218 (7), 190 (6), 155 (5). HRMS: Calcd for $C_{21}H_{22}NO_5$: 369.1576. Found: 369.1581. *Anal.* Calcd for $C_{21}H_{22}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.03; H, 6.32; N, 3.75.

**Treatment of a Mixture of 11 and 12 with $BF_3$•$Et_2O$.** i) $BF_3$•$Et_2O$ (1.5 g, 10.56 mmol, 10 molar eq) was added a solution of a mixture of **11** and **12** (500 mg, 1.04 mmol) in dry benzene (20 mL) at rt and the mixture was stirred for 20 h. The reaction mixture was worked up as described above to give *N*-formylisopavine (**21**) (348 mg, 90%). ii) A solution of a mixture of **11** and **12** (500 mg, 1.04 mmol) in dry benzene or acetonitrile (each 20 mL) containing $BF_3$•$Et_2O$ (445 mg, 3.13 mmol, 3 molar eq) was refluxed for 2 h, and worked up as the same manner as that above to give **21** (352 mg, 91%, in benzene) or (361 mg, 94%, in acetonitrile).

**(±)-*O*-Methylthalisopavine (4).** $LiAlH_4$ (165 mg, 4.34 mmol) was added to a solution of **21** (800 mg, 2.17 mmol) in dry THF (40 mL) under ice cooling, and the mixture was refluxed for 3 h. Wet $Et_2O$ was added to the reaction mixture and insoluble material was filtered off. The product was purified by column chromatography with $CHCl_3$-MeOH (9:1) to give **4** (738 mg, 96%) as colorless plates (from EtOH). mp 169-171℃ (*lit.*,[12a] *mp 165-166*℃; *lit.*,[12b] *mp 91-92*℃; *lit.*,[12c] *mp 163-165*℃; *lit.*,[12d] mp 164-166.5℃; lit.,[12e] mp 164.5-166.5℃). IR: 1608, 1510, 1464, 1335, 1246, 1234, 1204, 1113, 1011. $^1$H-NMR (500 MHz): 2.50 (3H, s, $=NCH_3$), 2.85 (1H, dd, $J$ = 4.0, 10.5 Hz, H-13), 2.93 (1H, dd, $J$ = 3.0, 17.5 Hz, H-11), 3.52 (1H, dd, $J$ = 4.0, 17.5 Hz, H-11), 3.56 (1H, dd, $J$ = 1.5, 10.5 Hz, H-13), 3.64 (1H, dd, $J$ = 1.0, 4.0 Hz, H-5), 3.77 (3H, s, 2-$OCH_3$), 3.86, 3.87, 3.88 (each 3H, s, 3- or 7- or 8-$OCH_3$), 3.86 (1H, dd, $J$ = 4.0, 17.5 Hz, H-10), 6.53 (s, H-1), 6.65 (s, H-6), 6.76 (s, H-4), 6.77 (s, H-9). $^{13}$C-NMR: 38.22 (t, C-11), 45.25 (q, $=NCH_3$), 45.84 (d, C-5), 55.88 (q, 2-$OCH_3$), 56.03 (q x 2), 56.16 (q) (3- or 7- or 8-$OCH_3$), 59.99 (t, C-13), 62.24 (d, C-10), 108.80 (d, C-4), 110.17 (d, C-9), 111.26 (d, C-6), 114.34 (d, C-1), 126.63 (s, C-9a), 129.99 (s, C-11a), 133.94 (s, C-5a), 134.61 (s, C-4a), 146.61 (s, C-3), 147.61 (s, C-8), 147.74 (s, C-2), 147.95 (s, C-7). EIMS *m/z*: 355 ($M^+$, 25), 338 (9), 312 (39), 297(5), 281(5), 269 (12), 254 (3), 204 (base peak), 188 (6), 156 (5). HRMS: Calcd for $C_{21}H_{25}NO_4$: 355.1783. Found: 355.1829. *Anal.* Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.79; H, 7.20; N, 3.89.

**(±)-*N*-Desmethyl-*O*-methylthalisopavine (22).** A solution of *N*-formylisopavine (**21**) (800 mg, 2.17 mmol) in EtOH (20 mL)-10% HCl (10 mL) was refluxed for 8 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water, basified with 10% NaOH, and extracted with $CHCl_3$. The products were purified by column chromatography with $CHCl_3$-MeOH (9:1) to give **22** (732 mg, 99%), as colorless needles (from EtOH). mp 162-163℃ (lit.,[13a] mp 153.5-155℃; lit.,[13b] mp 149-151℃). IR: 1608, 1512, 1464, 1347, 1248, 1203, 1117, 1021. $^1$H-NMR (500 MHz): 3.12 (1H, dd, $J$ = 3.5, 17.0, H-11), 3.25 (1H, dd, $J$ = 4.5, 11.0 Hz, H-13), 3.35 (1H, dd, $J$ = 4.0, 17.0 Hz, H-11), 3.60 (1H, dd, $J$ = 1.0, 11.0 Hz, H-13), 3.71 (1H, dd, $J$ = 1.0, 4.5 Hz, H-5), 3.78 (3H, s, 2-$OCH_3$), 3.86,

3.87, 3.88 (each 3H, s, 3- or 7- or 8-$OCH_3$), 4.25 (1H, t, $J$ = 3.5 Hz, H-10), 6.53 (s, H-1), 6.68 (s, H-6), 6.75 (s, H-4), 6.76 (s, H-9). $^{13}$C-NMR: 41.63 (t, C-11), 45.93 (d, C-5), 51.00 (t, C-13), 54.48 (d, C-10), 55.79 (s, 2-$OCH_3$), 55.94 (s x 2), 56.07 (s) (3- or 7- or 8-$OCH_3$), 109.03 (d, C-4), 109.09 (d, C-9), 111.30 (d, C-6), 114.32 (d, C-1), 126.73 (s, C-9a), 131.82 (s, C-11a), 134.07 (s, C-4a), 135.07 (s, C-5a), 146.56 (s, C-3), 147.56 (s, C-8), 147.52 (s, C-2), 147.75 (s, C-7). EIMS *m/z*: 341 ($M^+$, 33), 340 (33), 324 (12), 312 (base peak), 297 (9), 281 (11), 269 (26), 254 (6), 238 (3), 190 (54). HRMS: Calcd for $C_{20}H_{23}NO_4$: 341.1627. Found: 341.1633. *Anal.* Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.06; H, 6.85; N, 4.04.

**Preparation of Dihydroisoquinoline (23) and Dihydrobenzazepine (24).** A solution of sodium metaperiodate (1.0 g, 4.67 mmol) in $H_2O$ (5 mL) was added to a solution of a mixture of **11** and **12** (1.5 g, 3.31 mmol) in MeOH (50 mL), and the mixture was stirred at rt for 16 h. After removal of precipitated inorganic materials by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$. The residue was purified by column chromatography with AcOEt. The first eluate gave a mixture of sulfones of **11** and **12** (136 mg, 8.5%) as pale brown gum. The second eluate gave a mixture of sulfoxides of **11** and **12** (1.10 g, 71%) as yellow gum. A solution of a mixture of sulfoxides (**11** and **12**) (3.0 g, 6.06 mmol) in dry toluene (60 mL) was refluxed for 1 h, and the mixture was concentrated *in vacuo*. The residue was dissolved in small portion of $CHCl_3$ and subjected to column chromatography with AcOEt to give a mixture of **23** and **24** (2.15 g, 96%) as yellow gum.

**(±)-*N*-Formylpavine (26).** Methanesulfonic acid (1.10 g, 13.75 mmol) was added to a solution of a mixture of **23** and **24** (2.13 g, 5.77 mmol) in acetonitrile (50 mL) and stirred for 4 h at rt. The reaction mixture was basified with 28% $NH_4OH$, and the insoluble material was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography with AcOEt. The first eluate gave **24** (643 mg, 30%) as pale yellow needles (from AcOEt-hexane). mp 141-143℃. IR: 1691, 1641, 1606, 1518, 1464, 1360, 1265, 1225, 1144, 1105, 1026. $^1$H-NMR (500 MHz): 3.21, 3.31 (total 1H, each dd, $J$ = 2.0, 15.0 Hz, H-1), 3.28, 3.41 (total 1H, each dd, $J$ = 6.0, 15.0 Hz, H-2), 3.66, 3.69, 3.73, 3.75, 3.76, 3.78, 3.81, 3.82 (total 12H, each s, 7-, 8-, 3'-, 4'-$OCH_3$), 5.31, 6.12 (total 1H, each dd, $J$ = 2.0, 6.0 Hz, H-2), 5.71, 5.80 (total 1H, d and dd, $J$ = 11.0 Hz and 1.0, 11.0 Hz, H-5), 6.36, 6.41 (total 1H, each s, H-6 or H-9), 6.48, 6.59 (total 1H, each d, $J$ = 2.0 Hz, H-2'), 6.54, 6.55 (total 1H, each dd, $J$ = 2.0, 8.0 Hz, H-6'), 6.60, 6.65 (total 1H, each d, $J$ = 8.0 Hz, H-5'), 6.62, 6.65 (total 1H, each s, H-6 or H-9), 6.64, 7.30 (total 1H, each d, $J$ = 11.0 Hz, H-4), 8.23, 8.49 (total 1H, each s, =NCHO). LRMS *m/z*: 369 ($M^+$, base peak), 324 (78), 309 (31), 293 (8), 277 (9), 266 (6), 231 (9), 218 (10), 190 (10), 162 (14), 151 (126). HRMS: Calcd for $C_{21}H_{23}NO_5$: 369.1576. Found: 369.1562. *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.21; H, 6.39; N, 3.71.

The second eluate gave **26** (1.45 g, 68%) as pale yellow columns (from EtOH). mp 146-149℃ (lit.,[14] mp 146-149℃. IR: 1664 (=NCO-), 1610, 1518, 1439, 1354, 1252, 1117, 1016. $^1$H-NMR (500 MHz): 2.78, 2.91 (total 2H, each d, $J$ = 16.0 Hz, H-6, H-12), 3.38, 3.40 (total 2H, each dd, $J$ = 6.0, 16.0 Hz, H-6, H-12), 3.78, 3.79 (total 6H, each s, 3-, 9-$OCH_3$), 3.86, 3.87 (total 6H, each s, 2-, 8-$OCH_3$), 4.95, 5.73

(total 2H, each d, $J$ = 6.0 Hz, H-5, H-11), 6.46, 6.48 (total 2H, each s, H-1, H-7), 6.66, 6.68 (total 2H, each s, H-4, H-10), 8.28 (1H, s, =NCHO). $^{13}$C-NMR: 36.14, 38.11 (total 1C, each t, C-6, C-12), 46.34, 52.18 (total 1C, each d, C-5, C-11), 55.68 (2C, q x 2, 3-, 9-$OCH_3$), 55.92, 55.96 (total 2C, each q x 2, 2-, 8-$OCH_3$), 108.71, 109.26 (total 1C, each d, C-1, C-7), 111.46, 111.79 (total 1C, each d, C-4, C-10), 123.38, 124.29 (total 1C, each s, C-6a, C-12a), 127.91, 128.09 (total 1C, each s, C-4a, C-10a), 147.67, 147.91 (total 1C, each s, C-3, C-9), 148.26, 148.45 (total 1C, each s, C-2, C-8), 159.08 (d, =NCHO). EIMS *m/z*: 369 ($M^+$, base peak), 354 (5), 340 (37), 324 (13), 309 (16), 293 (6), 266 (4), 250 (4), 218 (72), 190 (58). HRMS: Calcd for $C_{21}H_{23}NO_5$: 369.1576. Found: 369.1570. *Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.45; H, 6.53; N, 3.61.

**(±)-Argemonine (5).** $LiAlH_4$ (76 mg, 2.0 mmol) was added to a solution of *N*-formylpavine (**26**) (370 mg, 1.0 mmol) in dry THF (20 mL) under ice cooling, and the mixture was refluxed for 2 h. The reaction mixture was worked up as described above, and the crude material was purified by column chromatography with AcOEt-MeOH (8:2) to give **5** (304 mg, 85%) as pale yellow gum. HCl salt (from EtOH-$Et_2O$): mp 224-227℃ (decomp) (lit.,[12e] mp 138-140℃; lit.,[14] 109-110℃ (each free base)]. IR: 1610, 1513, 1463, 1367, 1255, 1213, 1171, 1111. $^1$H-NMR (500 MHz): 2.53 (3H, s, =$NCH_3$), 2.61 (2H, d, $J$ = 16.0 Hz, H-6, H-12), 3.40 (2H, dd, $J$ = 5.5, 16.0 Hz, H-6, H-12), 3.77 (6H, s, 3-, 9-$OCH_3$), 3.85 (6H, s, 2-, 8-$OCH_3$), 4.01 (2H, d, $J$ = 5.5 Hz, H-5, H-11), 6.45 (2H, s, H-4, H-10), 6.61 (2H, s, H-1, H-7). $^{13}$C-NMR: 33.50 (t x 2, C-6, C-12), 40.82 (q, =$NCH_3$), 55.62 (q x 2, 3-, 9-$OCH_3$), 55.87 (q x 2, 2-, 8-$OCH_3$), 56.34 (d x 2, C-5, C-11), 109.94 (d x 2, C-1, C-7), 111.42 (d x 2, C-4, C-10), 123.85 (s x 2, C-6a, C-12a), 129.88 (s x 2, C-4a, C-10a), 147.40 (s x 2, C-3, C-9), 147.77 (s x 2, C-2, C-8). EIMS *m/z*: 355 ($M^+$, 21), 338 (5), 308 (4), 264 (4), 240 (3), 226 (2), 204 (base peak), 177 (3), 160 (3), 139 (5). HRMS: Calcd for $C_{21}H_{25}NO_4$: 355.1783. Found: 355.1761.

**(±)-*N*-Desmethylargemonine (27).** A solution of *N*-formylpavine (**26**) (500 mg, 1.36 mmol) in EtOH (20 mL)-10% HCl (10 mL) was refluxed for 8 h. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water, basified with 10% NaOH, and extracted with $CHCl_3$. The products were purified by column chromatography with $CHCl_3$-MeOH (9:1) to give **27** (394 mg, 85%) as colorless prisms (from EtOH). mp 205-208℃. IR: 1610, 1512, 1464, 1350, 1338, 1263, 1240, 1119, 1016. $^1$H-NMR (500 MHz): 2.72 (2H, d, $J$ = 16.0 Hz, H-6, H-12), 3.31 (2H, dd, $J$ = 6.0, 16.0 Hz, H-6, H-12), 3.77 (6H, s, 3-, 9-$OCH_3$), 3.85 (6H, s, 2-, 8-$OCH_3$), 4.38 (2H, d, $J$ = 6.0 Hz, H-5, H-11), 6.45 (2H, s, H-4, H-10), 6.63 (2H, s, H-1, H-7). $^{13}$C-NMR: 37.34 (t x 2, C-6, C-12), 50.02 (d x 2, C-5, C-11), 55.62 (q x 2, 3-, 9-$OCH_3$), 55.89 (q x 2, 2-, 8-$OCH_3$), 109.44 (d x 2, C-1, C-7), 111.72 (d x 2, C-4, C-10), 124.59 (s x 2, C-6a, C-12a), 131.00 (s x 2, C-4a, C-10a), 147.25 (s x 2, C-3, C-9), 147.78 (C-2, C-8). EIMS *m/z*: 341 ($M^+$, 39), 340 (37), 324 (9), 310 (3), 280 (2), 190 (base peak), 170 (s), 152 (9). HRMS: Calcd for $C_{20}H_{23}NO_4$: 341.1627. Found: 341.1642. *Anal.* Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.23; H, 6.90; N, 4.00.

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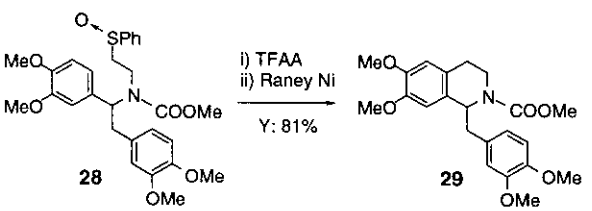


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