First Total Syntheses of (±)-Isopiline, (±)-Preocoteine, (±)-Oureguattidine and (±)-3-Methoxynordomesticine and the Biological Activities of (±)-3-Methoxynordomesticine

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A convenient and economical synthesis of 4-hydroxy-2,3-dimethoxybenzaldehyde has been developed. This was used as the starting material for the first total syntheses of (±)-isopiline, (±)-preocoteine, (±)-oureguattidine and (±)-3-methoxynordomesticine in which the key step involved formation of ring C of the aporphines by a radical-initiated cyclisation. Although (±)-3-methoxynordomesticine possesses weak antimicrobial activity, it inhibits the production of nitric oxide (NO), prostaglandin (PG)E_2, tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 and the expression of inducible nitric oxide synthase (iNOS) and cycloxygenase (COX)-2 in macrophages stimulated with LPS *in vitro*.

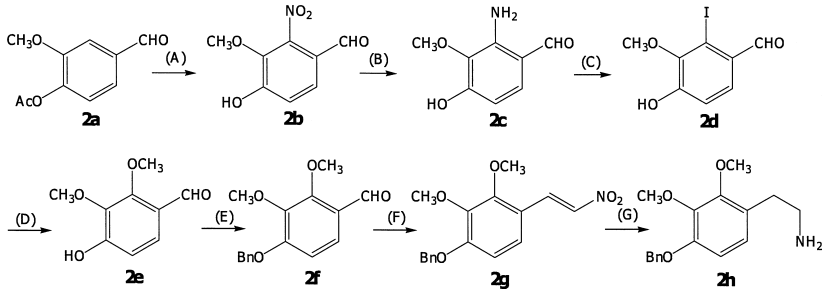
Key words alkaloid; aporphine; isoquinoline; synthesis; antimicrobial; anti-inflammatory activity

The aporphine alkaloids constitute a large group in the family of isoquinoline alkaloids and occur in a large number of plant families. They also exhibit a large variety of oxygenation patterns and biological activities. Aporphines with a 1-hydroxy-2,3-dimethoxy-substituted ring A are rather rare and occur in a restricted number of species.[1)] The structures of all these alkaloids were proposed based on spectroscopic analysis and conversion to known aporphines. No total synthesis of any member of the aporphines in this group has ever been reported and the minute quantities of the natural alkaloids isolated from plant sources make it impossible to carry out any biological activity evaluation of these alkaloids. In view of this limitation, it was therefore highly desirable to carry out the total syntheses of a number of these alkaloids to confirm their structures and to evaluate their biological activities.

Results and Discussion

Total Syntheses of Aporphine Alkaloids The lack of synthesis of this group of aporphine alkaloids may be partly due to the difficult access to 4-hydroxy-2,3-dimethoxybenzaldehyde (**2e**), the key starting compound necessary for the conversion to the key intermediate, 4-benzyloxy-2,3-dimethoxyphenethyl amine (**2h**). At the beginning of this work, only one synthesis of aldehyde (**2e**) had been reported. The synthesis, involving a Reimer–Tiemann formylation on 2,3-dimethoxyphenol, was extremely tedious and inefficient,[2)] making laboratory scale preparation of this aldehyde by this route not an attractive undertaking. We therefore sought to develop a more attractive and economical synthesis of **2e**. Thus, nitration of vanillin acetate with fuming nitric acid followed by hydrolysis gave **2b**[3)] which was reduced with iron powder and iron(II) sulfate to **2c**. This was converted to **2d** under standard diazotization and iodination conditions. Treatment of **2d** with sodium methoxide in the presence of copper(II) chloride gave **2e** in good yield. Benzylation then afforded the desired **2f**. This was converted into nitrostyrene (**2g**) which was reduced with lithium aluminium hydride to the desired amine (**2h**). All steps in the above synthesis can be carried out safely on a laboratory scale. With the desired amine (**2h**) available in ample quantity, it was decided to carry out total syntheses of the racemic forms of (−)-isopiline (**1a**),[4)] (+)-preocoteine (**1b**),[5)] (−)-oureguattidine (**1c**)[6)] and (+)-3-methoxynordomesticine (**1d**).[7)]

The strategy employed was based on the construction of the ring C by a radical-initiated cylisation.[8)] Such a cyclisation on a 7-benzyloxyisoquinoline precursor has not hitherto been reported. It was anticipated from the outset that due to



Reaction conditions: (A) (i) fuming HNO_3, dry ice/acetone; (ii) 10% NaOH; (B) $Fe(II)SO_4 \cdot 7H_2O$, iron power/ethanol–water; (C) (i) $NaNO_2$/20% HCl; (ii) KI; (D) $CuCl_2$/DMF, $NaOCH_3$/methanol; (E) BnCl, anh. K_2CO_3/ethanol; (F) CH_3NO_2, NH_4OAc/acetic acid; (G) LAH/THF.

Chart 1. Synthesis of 4-Benzyloxy-2,3-dimethoxyphenethylamine (**2h**)

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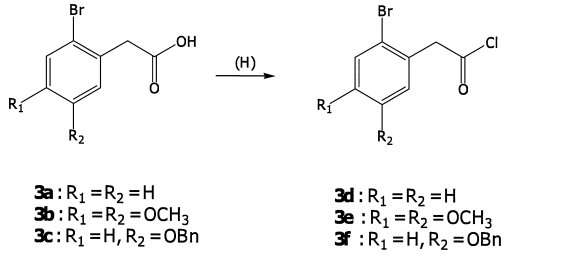
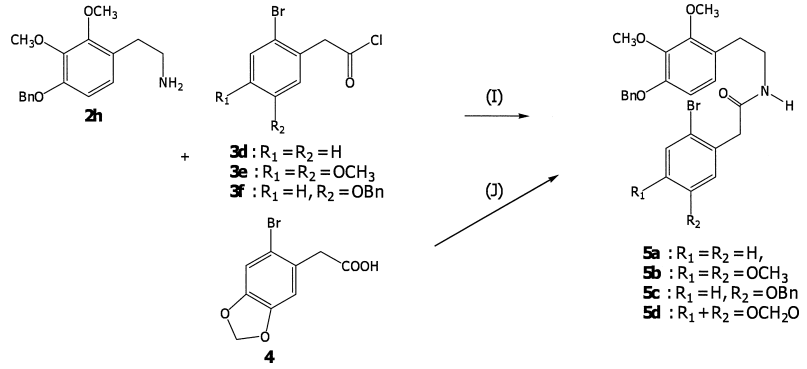
steric hindrance of the benzyloxy group at that position, the yields of the cyclisation step would be quite low. Condensation of amine (**2h**) with acid chlorides (**3d**—**f**) afforded in good yields amides (**5a**—**c**) respectively. Due to its poor solubility, acid (**4**) cannot be converted into the corresponding acid chloride. Condensation of amine (**2h**) and acid (**4**) was carried out in boiling xylene with water removal to give amide (**5d**). By a Bischler–Napieralski reaction, amides (**5a**—**d**) were converted respectively to dihydroisoquinolines (**6a**—**d**) which were substances of extremely low stability. These were quickly reduced with sodium borohydride to give tetrahydroisoquinolines (**7a**—**d**). (**7a**), (**7c**) and (**7d**) were converted into the trifluoroacetyl derivatives (**8a**), (**8c**) and (**8d**) while **7b** was converted into urethane (**8b**). Treatment of **8a**, **8b**, **8c** and **8d** with tributyltin hydride in the presence of azobis(isobutyronitrile) gave noraporphines (**9a**), (**9b**), (**9c**) and (**9d**) respectively in 8.3—10.9% yields. In all cases, cyclisation took place with concurrent loss of the benzyl protecting group at C-1 of the aporphine nucleus and the formation of the corresponding hydrogenolysis products (**8e**—**h**) in 13.1—41.6% yields. The structure of **9a** was supported by the presence of a doublet at δ_H 8.39, characteristic of the proton present at C-11 of the aporphine nucleus. Similarly, the ^{1}H-NMR spectra of **9b**, **9c** and **9d** also exhibited such low-field proton signals. Removal of the trifluoroacetyl groups from **9a** and **9d** gave (±)-isopiline (**1a**) and (±)-3-methoxynordomesticine (**1d**) respectively. On the other hand, reduction of **9b** with lithium aluminium hydride gave (±)-



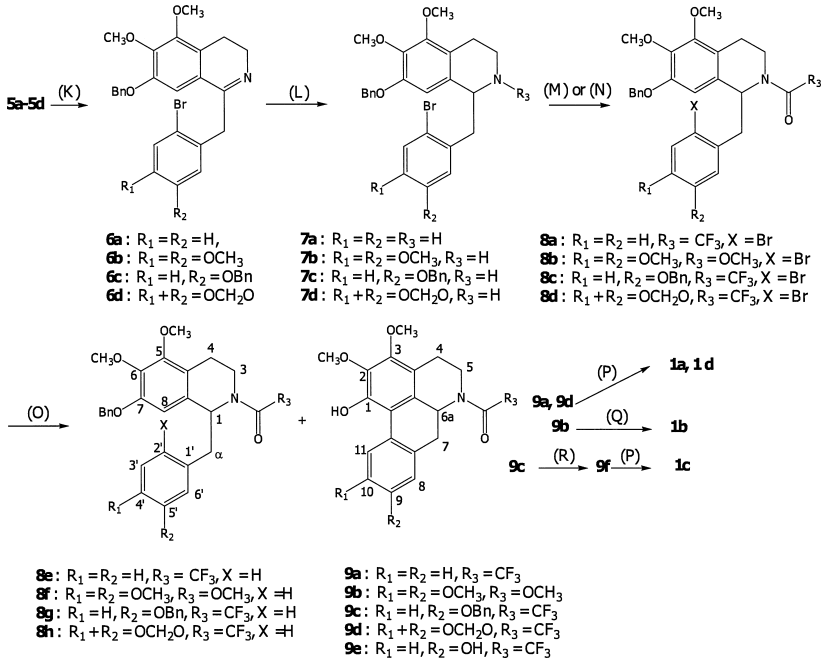
Reaction condition: (H) $SOCl_2$/benzene.

Chart 2. Syntheses of Acid Chlorides **3d**—**3f**



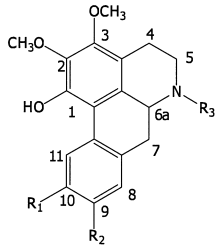
Reaction conditions: (I) 10% $NaHCO_3$/chloroform; (J) reflux/xylene.

Chart 3. Syntheses of Amides **5a—5d**



Reaction conditions: (K) $POCl_3$/acetonitrile; (L) $NaBH_4$/ethanol; (M) $(CF_3CO)_2O$, Et_3N/chloroform (**7a**, **7c**, **7d**→**8a**, **8c**, **8d**); (N) $ClCOOCH_3$, Et_3N/chloroform (**7b**→**8b**); (O) Bu_3SnH, AIBN/dry toluene; (P) K_2CO_3/methanol–water; (Q) LAH/THF; (R) H_2, Pd/C/ethanol.

Chart 4. Syntheses of Aporphine Alkaloids **1a**—**1d**



(±)-Isopiline (**1a**): R_1=R_2=R_3=H
(±)-Preocoteine (**1b**): R_1=R_2=OCH_3, R_3=CH_3
(±)-Oureguattidine (**1c**): R_1=R_3=H, R_2=OH
(±)-3-Methoxynordomesticine (**1d**): R_1+R_2=OCH_2O, R_3=H

Fig. 1. Structures of (±)-Isopiline (**1a**), (±)-Preocoteine (**1b**), (±)-Oureguattidine (**1c**) and (±)-3-Methoxynordomesticine (**1d**)

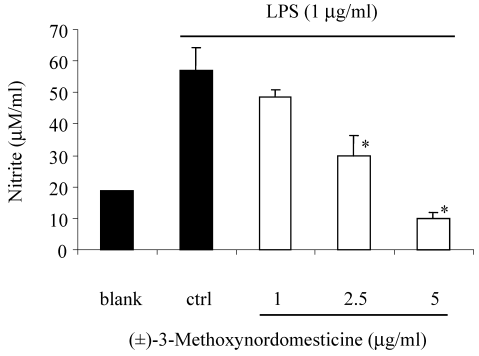


Fig. 2. Evaluation of Nitrite Production by RAW 264.7 Cells Stimulated for 24 h with LPS Alone or Combination with Increasing Concentrations (1—5 μg/ml) of (±)-3-Methoxynordomesticine

The values are the means of at least 3 determinations±S.D. Probability levels (Student's *t*-test): $*p<0.05$ *vs.* LPS-treated group.

preocoteine (**1b**) while catalytic removal of the benzyl group of (**9c**) at C-9 followed by removal of the trifluoroacetyl group gave (±)-oureguattidine (**1c**). The ^{1}H- and ^{13}C-NMR spectral data of synthetic (±)-isopiline (**1a**), (±)-preocoteine (**1b**), (±)-oureguattidine (**1c**) and (±)-3-methoxynordomesticine (**1d**) were identical in all respects with those of the respective natural alkaloids.

Biological Activities of (±)-3-Methoxynordomesticine (±)-3-Methoxynordomesticine was more effective against Gram-negative *Escherichia coli* ATCC10536 than Gram-positive *Staphylococcus aureus* ATCC25932 and budding yeast *Candida albicans* ATCC90028. The MIC value of 256 μg/ml was obtained for *E. coli* ATCC10536, whereas the MIC values lower or equal to 512 μg/ml were obtained for *S. aureus* ATCC25932 and *C. albicans* ATCC90028. The MMC value lower or equal to 512 μg/ml were obtained in all tested microorganisms. In the course of our studies on anti-inflammatory, we have found that (±)-3-methoxynordomesticine inhibits nitric oxide (NO) production in murine macrophage RAW 264.7 cells stimulated with lipopolysaccharide (LPS) (Fig. 2), we then investigated the effect of (±)-3-methoxynordomesticine on the release of prostaglandin E_2 (PGE_2). Compared with the untreated control, LPS (1 μg/ml) induced a great production of PGE_2 in RAW 264.7 cells. (±)-3-Methoxynordomesticine (1—5 mg/ml) inhibited the production of PEG_2 in RAW 264.7 cells stimulated with LPS in a concentration-dependent manner (Fig. 3). To elucidate the mechanism of the inhibitory effect of (±)-3-methoxynordomesticine on NO and PGE_2 production, we investigated their effects on inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 expression levels, respectively. In response to LPS, the iNOS and COX-2 inductions were markedly increased, and (±)-3-methoxynordomesticine significantly decreased the iNOS and COX-2 protein expression in a concentration-dependent manner (Figs. 4, 5). In contrast to iNOS and COX-2, (±)-3-methoxynordomesticine had no effect on the expression of β-actin and COX-1 (data not shown). This finding indicates that (±)-3-methoxynordomesticine could suppress NO and PGE_2 production in LPS-stimulated RAW 264.7 cells by inhibiting iNOS and COX-2 protein expression, respectively. It has been reported that cytokines such as tumor necrosis factor (TNF)-α, interleukin

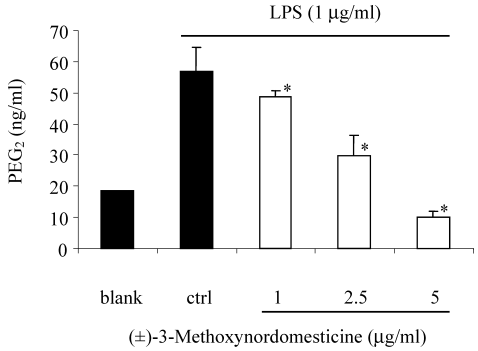


Fig. 3. Effect of (±)-3-Methoxynordomesticine on PEG_2 Production in LPS-Induced RAW 264.7 Macrophage for 24 h

The values are the means of at least 3 determinations±S.D. Probability level (Student's *t*-test): $*p<0.05$ *vs.* LPS-treated group.

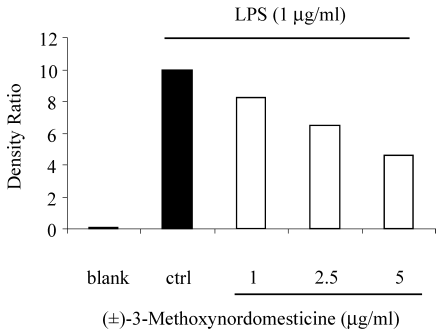


Fig. 4. Effect of (±)-3-Methoxynordomesticine on iNOS Protein Production by LPS-Induced RAW 264.7 Macrophage for 24 h

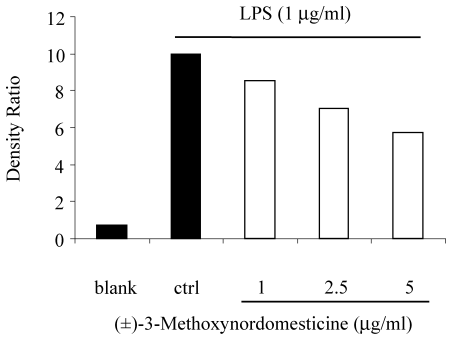


Fig. 5. Effect of (±)-3-Methoxynordomesticine and LPS-Induced COX-2 Protein Expression in RAW 264.7 Cells

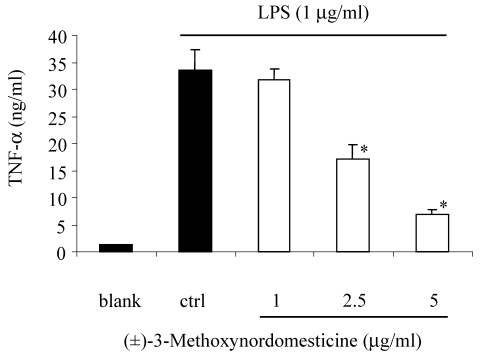


Fig. 6. Effect of (±)-3-Methoxynordomesticine on LPS-Induced TNF-α Production by RAW 264.7 Cells

The values are the means of at least 3 determinations±S.D. Probability level (Student's *t*-test): $*p<0.05$ *vs.* LPS-treated group.

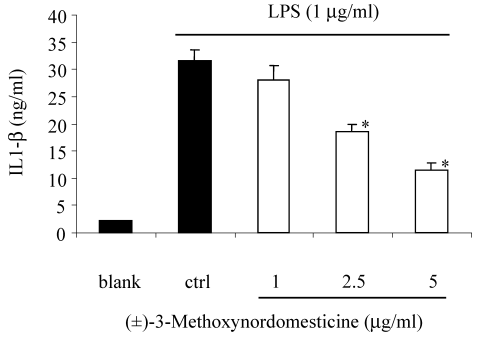


Fig. 7. Effect of (±)-3-Methoxynordomesticine on IL1-β Production by RAW 264.7 Cells

The values are the means of at least 3 determinations±S.D. Probability level (Student's *t*-test): $*p<0.05$ *vs.* LPS-treated group.

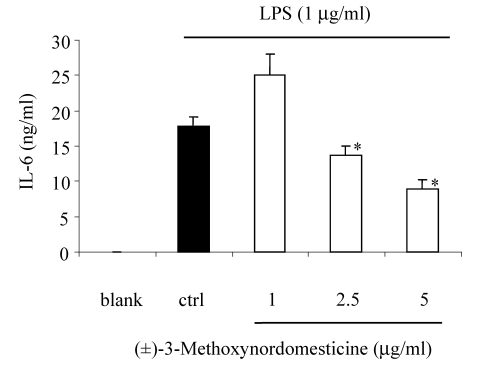


Fig. 8. Effect of (±)-3-Methoxynordomesticine on LPS Induced IL-6 Production by RAW 264.7 Cells

The values are the means of at least 3 determinations±S.D. Probability level (Student's *t*-test): $*p<0.05$ *vs.* LPS-treated group.

(IL)-1β and IL-6 are pro-inflammatory *in vitro* as well as *in vivo*.[9] The present study also demonstrated that (±)-3-methoxynordomesticine has inhibitory effects on the production of TNF-α, IL-1β and IL-6 in LPS-stimulated RAW 264.7 cells. As shown in Figs. 6—8, LPS-induced productions of TNF-α, IL-1β and IL-6 were significantly inhibited by (±)-3-methoxynordomesticine in a concentration-dependent manner. In addition, the cytotoxic effect of (±)-3-methoxynordomesticine was evaluated in the absence or presence of LPS (more than 95% cell viability). There is no significant difference on cell viability when treated with (±)-3-methoxynordomesticine at all concentrations used (1—5 μg/ml) in the absence or presence of LPS.

In conclusion, we found that (±)-3-methoxynordomesticine not only possesses antibacterial activity agaianst *E. coli* but also possesses anti-inflammatory activity. It inhibits the production of NO, PGE_2, TNF-α, IL-1β and IL-6 and the expression of iNOS and COX-2 in macrophages stimulated with LPS *in vitro*. From these results it is expected that (±)-3-methoxynordomesticine could be potentially useful for the treatment of inflammatory diseases.

Experimental

Melting points were determined on a Stuart Scientific SMP 2 melting point apparatus and are uncorrected. Infrared spectra were recorded on CH_2Cl_2-films with a Perkin Elmer Spectrum GX FT-IR spectrophotometer. Ultraviolet spectra were recorded on methanol solutions with a Perkin-Elmer Lambda 35 UV–VIS spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on (D) chloroform solutions at 300 MHz for ^{1}H and 75 MHz for ^{13}C with a Bruker AVANCE 300 spectrometer. Tetramethylsilane was used as the internal standard. Mass spectra were recorded on a POLARIS Q or HEWLETT PACKARD 5973 mass spectrometer. Elemental analyses were performed on a Perkin Elmer 2400 Elemental Analyser.

4-Hydroxy-2-nitro-3-methoxybenzaldehyde (2b) Vanillin acetate (**2a**) (50.0 g, 257.7 mmol) was slowly added with stirring to fuming nitric acid (200 ml) at −10—5 °C and stirring continued for 10 min. The mixture was poured into ice-water (800.0 g). The yellow precipitate was filtered, washed with some water and heated with stirring to boiling in 10% NaOH (400 ml). After cooling to room temperature, the mixture was acidified with conc. HCl and the crude product was filtered and recrystallized from water to give **2b** as a pale yellow solid (44.9 g, 88.6%), mp 136—138 °C [lit.[3] mp 136 °C]. ^{1}H-NMR δ: 3.92 (3H, s, O–CH_3), 7.19 (1H, d, J=8.5 Hz, Ar–H), 7.52 (1H, d, J=8.5 Hz, Ar–H), 9.72 (1H, s, CHO). ^{13}C-NMR δ: 66.00 (q), 122.29 (d), 123.08 (s), 133.74 (d), 144.04 (s), 148.55 (s), 162.07 (s), 190.82 (d).

2-Amino-4-hydroxy-3-methoxybenzaldehyde (2c) A mixture of **2b** (16.0 g, 81.2 mmol), iron(II) sulfate heptahydrate (4.0 g), iron powder (40.0 g), ethanol (150 ml) and water (50 ml) was refluxed for 4 h. The iron was filtered and the solvent removed under vacuum and the residue recrystallized from water (about 100 ml) to give **2c** as a pale brown solid (11.5 g, 84.8%), mp 137—138 °C [lit.[10] mp 138—139 °C]. ^{1}H-NMR δ: 3.81 (3H, s, O–CH_3), 6.39 (1H, d, J=8.6 Hz, Ar–H), 7.20 (1H, d, J=8.6 Hz, Ar–H), 9.71 (1H, s, CHO). ^{13}C-NMR δ: 58.81 (q), 105.72 (d), 113.01 (s), 131.77 (d), 132.17 (s), 144.96 (s), 154.87 (s), 191.05 (d).

2-Iodo-4-hydroxy-3-methoxybenzaldehyde (2d) A solution of sodium nitrite (9.5 g) in water (80 ml) was added to a stirred solution of **2c** (21.0 g, 125.7 mmol) in 20% HCl (250 ml) at 0—5 °C and stirring continued for 15 min. A solution of potassium iodide (100 g) in water (300 ml) was slowly added to the diazonium solution and stirring continued overnight. Chloroform (600 ml) and excess sodium thiosulfate were added and the chloroform layer was separated, washed with brine, then dried over anh. Na_2SO_4. Removal of the solvent under vacuum followed by recrystallization from ethanol–water gave **2d** as yellow needles (30.6 g, 87.5%), mp 154—156 °C [lit.[11] mp 155—156 °C]. ^{1}H-NMR δ: 3.92 (3H, s, O–CH_3), 7.03 (1H, d, J=8.5 Hz, Ar–H), 7.70 (1H, d, J=8.5 Hz, Ar–H), 9.97 (1H, s, CHO). ^{13}C-NMR δ: 64.40 (q), 105.13 (s), 121.32 (d), 131.69 (d), 132.03 (s), 151.84 (s), 160.86 (s), 198.87 (d).

4-Hydroxy-2,3-dimethoxybenzaldehyde (2e) A mixture of **2d** (4.2 g, 15.1 mmol), $CuCl_2$ (1.0 g) in *N*,*N*-dimethylformamide (60 ml) was added to sodium methoxide (9.7 g) in methanol (60 ml) and the mixture heated in an oil bath (≈160 °C) for 2 h. Water (100 ml) was added and the mixture acidified with 6 N HCl. The mixture was filtered and the filtrate extracted with ethyl acetate (1×100 ml, 2×50 ml). The extract was washed with water (5×100 ml) then dried over anh. Na_2SO_4. Removal of the solvent under vacuum gave a yellow oil which was chromatograped over silica gel using benzene as eluent to give aldehyde (**2e**) as pale yellow prisms (2.2 g, 78.0%), mp 72—73 °C [lit.[12] mp 75 °C]. ^{1}H-NMR δ: 3.96 (3H, s, O–CH_3), 4.01 (3H, s, O–CH_3), 6.81 (1H, d, J=8.7 Hz, Ar–H), 7.57 (1H, d, J=8.7 Hz, Ar–H), 10.20 (1H, s, CHO). ^{13}C-NMR δ: 61.05 (q), 62.05 (q), 111.54 (d), 122.95 (s), 124.97 (d), 139.25 (s), 156.05 (s), 156.34 (s), 188.67 (d).

4-Benzyloxy-2,3-dimethoxybenzaldehyde (2f) A mixture of **2e** (5.0 g, 27.5 mmol), benzyl chloride (3.8 g), anhydrous potassium carbonate (4.2 g) in ethanol (30 ml) was refluxed for 5 h. The potassium carbonate was filtered, and the filtrate cooled to room temperature to give **2f** as pale yellow

prisms (6.9 g, 92.4%), mp 63—64 °C [lit.[12] liquid]. ^{1}H-NMR δ: 3.90 (3H, s, O–CH_3), 4.02 (3H, s, O–CH_3), 5.17 (2H, s, Ph–CH_2), 6.79 (1H, d, J=8.8 Hz, Ar–H), 7.23—7.50 (5H, m, Ph–H), 7.55 (1H, d, J=8.8 Hz, Ar–H), 10.24 (1H, s, CHO). ^{13}C-NMR δ: 60.98 (q), 62.35 (q), 70.83 (t), 108.93 (d), 123.48 (s), 124.00 (d), 127.28 (d), 128.25 (d), 128.70 (d), 136.02 (s), 141.98 (s), 157.07 (s), 158.43 (s), 188.77 (d).

4-Benzyloxy-2,3-dimethoxy-β-nitrostyrene (2g) A mixture of **2f** (39.7 g, 145.9 mmol), ammonium acetate (29.2 g) and nitromethane (29.2 g) in acetic acid (440 ml) was refluxed for 2 h, then cooled to room temperature. Ice-water (2 l) was added to the mixture and the yellow precipitate was filtered. Drying of the solid in air gave **2g** as yellow needles (36.4 g, 79.2%), mp 80—81 °C [lit.[12] mp 83—84 °C]. ^{1}H-NMR δ: 3.90 (3H, s, O–CH_3), 4.00 (3H, s, O–CH_3), 5.18 (2H, s, Ph–CH_2), 6.76 (1H, d, J=8.8 Hz, Ar–H), 7.15 (1H, d, J=8.8 Hz, Ar–H), 7.30—7.49 (5H, m, Ph–H), 7.75 (1H, d, J=13.6 Hz, CH), 8.08 (1H, d, J=13.6 Hz, CH). ^{13}C-NMR δ: 60.99 (q), 61.26 (q), 70.93 (t), 109.28 (d), 117.26 (s), 126.40 (d), 127.26 (d), 128.29 (d), 128.74 (d), 135.28 (d), 136.04 (s), 136.63 (d), 142.81 (s), 154.42 (s), 156.44 (s).

4-Benzyloxy-2,3-dimethoxyphenethylamine (2h) A solution of **2g** (28.0 g, 88.9 mmol) in dry tetrahydrofuran (350 ml) was slowly added to a stirred and cooled suspension of lithium aluminium hydride (11.2 g) in dry tetrahydrofuran (140 ml) and stirring continued for 3 h. Diethyl ether (280 ml) was added and with continued cooling and vigorous stirring, water (15 ml), 15% NaOH (15 ml) and water (45 ml) were added in succession. The pale yellow granular residue was filtered and washed with ether. The combined organic phase was extracted with 12% HCl (1×100 ml, 2×60 ml). The extract was basified with conc. ammonia to litmus. The oil was separated and the aqueous layer was extracted with chloroform (2×100 ml). The oil and chloroform layer were combined, then dried over anh. Na_2CO_3. Removal of the solvent under vacuum gave **2h** as a yellow viscous oil (22.1 g, 86.6%) [lit.[12] oil]. ^{1}H-NMR δ: 2.69 (2H, t, J=6.9 Hz, CH_2), 2.89 (2H, t, J=6.9 Hz, CH_2), 3.90 (6H, s, O–CH_3×2), 5.09 (2H, s, Ph–CH_2), 6.65 (1H, d, J=8.5 Hz, Ar–H), 6.79 (1H, d, J=8.5 Hz, Ar–H), 7.28—7.45 (5H, m, Ph–H). ^{13}C-NMR δ: 33.89 (t), 42.80 (t), 60.79 (q), 61.02 (q), 70.97 (t), 109.29 (d), 124.32 (d), 125.91 (s), 127.25 (d), 127.85 (d), 128.53 (d), 137.15 (s), 142.91 (s), 151.48 (s), 152.20 (s).

2-(2-Bromophenyl)-*N*-(4-benzyloxy-2,3-dimethoxyphenethyl)acetamide (5a) A mixture of 2-bromophenylacetic acid (3.8 g, 17.6 mmol) and thionyl chloride (6.2 g) in benzene (100 ml) was refluxed for 1 h, then the solvent and excess thionyl chloride were removed under vacuum. The resulting crude acid chloride (**3a**) was dissolved in ethanol-free chloroform (50 ml) and added portionwise to a mixture of amine (**2h**) (5.0 g, 17.42 mmol) in chloroform (50 ml) and 10% $NaHCO_3$ (100 ml). The mixture was stirred at room temperature for 3 h. The chloroform layer was washed with 10% $NaHCO_3$ (3×50 ml), water (2×100 ml), 5% HCl (3×50 ml), water (100 ml), then dried over anh. Na_2SO_4. Removal of the solvent under vacuum gave a pale yellow solid which was recrystallized from benzene–hexane to give amide (**5a**) as a pale yellow solid (3.6 g, 42.8%), mp 101—103 °C. UV λ_{max} (MeOH) nm (log ε): 209 (4.72), 223 sh (4.35), 271 (3.16). IR (CH_2Cl_2-film) cm^{-1}: 3301, 2926, 1648, 1601, 1542, 1535, 1491, 1467, 1439, 1417, 1379, 1279, 1258, 1200, 1096, 1058, 1026. ^{1}H-NMR δ: 2.69 (2H, t, J=6.6 Hz, Ar–CH_2), 3.42 (2H, apparent q, J=6.5 Hz, N–CH_2), 3.67 (2H, s, CO–CH_2), 3.80 (3H, s, O–CH_3), 3.87 (3H, s, O–CH_3), 5.09 (2H, s, Ph–CH_2), 5.79 (1H, br s, NH), 6.58 (1H, d, J=8.5 Hz, Ar–H), 6.66 (1H, d, J=8.5 Hz, Ar–H), 7.10—7.50 (8H, m, Ar–H), 7.54 (1H, d, J=7.8 Hz, Ar–H). ^{13}C-NMR δ: 29.49 (t), 40.86 (t), 44.02 (t), 60.84 (q), 61.00 (q), 70.98 (t), 109.46 (d), 124.40 (d), 125.10 (s), 127.24 (d), 127.89 (d), 127.93 (d), 128.58 (d), 128.98 (d), 131.78 (d), 133.05 (d), 134.85 (s), 137.09 (s), 142.76 (s), 143.64 (s), 151.73 (s), 151.8 4 (s), 169.64 (s). EI-MS m/z (%): 483 [M]$^+$ (1), 270 (34), 179 (9), 91 (100). *Anal.* Calcd for $C_{25}H_{26}BrNO_4$: C, 61.99; H, 5.41; N, 2.89, Found: C, 61.75; H, 5.60; N, 3.02.

2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(4-benzyloxy-2,3-dimethoxyphenethyl)acetamide (5b) In a similar manner, **5b** was obtained as a pale yellow solid from benzene–hexane in 65.8% yield, mp 114—116 °C. UV λ_{max} (MeOH) nm (log ε): 207 (4.89), 230 sh (4.26), 282 (3.51), 294 sh (3.30). IR (CH_2Cl_2-film) cm^{-1}: 3307, 2935, 2843, 1652, 1603, 1506, 1466, 1439, 1417, 1386, 1260, 1219, 1193, 1166, 1096, 1058, 1029, 969. ^{1}H-NMR δ: 2.70 (2H, t, J=6.6 Hz, Ar–CH_2), 3.42 (2H, apparent q, J=6.5 Hz, N–CH_2), 3.60 (2H, s, CO–CH_2), 3.82 (3H, s, O–CH_3), 3.83 (3H, s, O–CH_3), 3.85 (3H, s, O–CH_3), 3.87 (3H, s, O–CH_3), 5.09 (2H, s, Ph–CH_2), 5.85 (1H, br s, NH), 6.59 (1H, d, J=8.5 Hz, Ar–H), 6.67 (1H, d, J=8.5 Hz, Ar–H), 6.81 (1H, s, Ar–H), 7.01 (1H, s, Ar–H), 7.32—7.43 (5H, m, Ph–H). ^{13}C-NMR δ: 29.48 (t), 40.89 (t), 43.50 (t), 56.09 (q), 56.20 (q), 60.80 (q), 61.02 (q), 70.97 (t), 109.40 (d), 113.89 (d), 114.87 (s), 115.57 (d), 124.39 (d), 125.02 (s), 126.58 (s), 127.25 (d), 127.93 (d), 128.57 (d), 137.05 (s), 142.77 (s), 148.70 (s), 148.93 (s), 151.78 (s), 151.84 (s), 170.14 (s). EI-MS m/z (%): 544 [M]$^+$ (3), 270 (8), 179 (17), 91 (100). *Anal.* Calcd for $C_{27}H_{30}BrNO_6$: C, 59.56; H, 5.55; N, 2.57, Found: C, 59.31; H, 5.72; N, 2.68.

2-(5-Benzyloxy-2-bromophenyl)-*N*-(4-benzyloxy-2,3-dimethoxyphenethyl)acetamide (5c) In a similar manner, **5c** was obtained as a pale yellow solid from ethanol in 72.9% yield, mp 127—128 °C. UV λ_{max} (MeOH) nm (log ε): 206 (4.87), 227 (4.33), 280 (3.22). IR (CH_2Cl_2-film) cm^{-1}: 3300, 3065, 3033, 2934, 2873, 2827, 1652, 1595, 1571, 1533, 1492, 1467, 1417, 1380, 1280, 1241, 1194, 1171, 1096, 1057, 1016, 910. ^{1}H-NMR δ: 2.69 (2H, t, J=6.6 Hz, Ar–CH_2), 3.41 (2H, apparent q, J=6.6 Hz, N–CH_2), 3.61 (2H, s, CO–CH_2), 3.81 (3H, s, O–CH_3), 3.86 (3H, s, O–CH_3), 5.02 (2H, s, Ph–CH_2), 5.06 (2H, s, Ph–CH_2), 5.81 (1H, br s, NH), 6.57 (1H, d, J=8.5 Hz, Ar–H), 6.66 (1H, d, J=8.5 Hz, Ar–H), 6.78 (1H, dd, J=3.0, 8.8 Hz, Ar–H), 6.95 (1H, d, J=3.0 Hz, Ar–H), 7.30—7.45 (11H, m, Ph–H×10 and Ar–H). ^{13}C-NMR δ: 29.52 (t), 40.84 (t), 44.25 (t), 60.83 (q), 61.01 (q), 70.24 (t), 70.98 (t), 109.46 (d), 115.62 (s), 115.84 (d), 117.94 (d), 124.40 (d), 125.12 (s), 127.25 (d), 127.49 (d), 127.91 (d), 128.17 (d), 128.56 (d), 128.65 (d), 133.61 (d), 135.80 (s), 136.34 (s), 137.08 (s), 142.78 (s), 151.74 (s), 151.86 (s), 158.32 (s), 169.44 (s). EI-MS m/z (%): 498 (9), 179 (25), 91 (70). *Anal.* Calcd for $C_{32}H_{32}BrNO_5$: C, 65.09; H, 5.46; N, 2.37, Found: C, 64.91; H, 5.62; N, 2.48.

2-(2-Bromo-4,5-methylenedioxyphenyl)-*N*-(4-benzyloxy-2,3-dimethoxyphenethyl)acetamide (5d) A solution of acid (**4**) (11.3 g, 43.6 mmol) and amine (**2h**) (12.5 g, 43.6 mmol) in xylene (150 ml) was refluxed for 24 h with water removal with a Dean-Stark trap. The xylene was then removed under vacuum to yield a brown sticky residue which was dissolved in chloroform (100 ml). The chloroform layer was washed with 5% HCl (3×100 ml), water (150 ml), 10% $NaCO_3$ (3×150 ml) and then dried over anh. Na_2SO_4. Removal of the solvent under vacuum gave a residue which was recrystallized with ethanol to give **5d** as white prisms (8.3 g, 36.1%), mp 139—141 °C. UV λ_{max} (MeOH) nm (log ε): 212 (4.48), 228 sh (4.23), 247 sh (3.99), 282 sh (3.97), 295 (4.01). IR (CH_2Cl_2-film) cm^{-1}: 3296, 2921, 1638, 1603, 1500, 1480, 1417, 1380, 1256, 1234, 1196, 1163, 1096, 1056, 1037, 971, 938, 926. ^{1}H-NMR δ: 2.70 (2H, t, J=6.6 Hz, Ar–CH_2), 3.42 (2H, apparent q, J=6.4 Hz, N–CH_2), 3.55 (2H, s, CO–CH_2), 3.83 (3H, s, O–CH_3), 3.87 (3H, s, O–CH_3), 5.08 (2H, s, Ph–CH_2), 5.85 (1H, br s, NH), 5.95 (2H, s, O–CH_2–O), 6.61 (1H, d, J=8.5 Hz, Ar–H), 6.69 (1H, d, J=8.5 Hz, Ar–H), 6.75 (1H, s, Ar–H), 6.98 (1H, s, Ar–H), 7.29—7.50 (5H, m, Ph–H). ^{13}C-NMR δ: 29.49 (t), 40.81 (t), 43.77 (t), 60.81 (q), 61.02 (q), 70.97 (t), 101.91 (t), 109.45 (d), 111.08 (d), 112.84 (d), 115.40 (s), 124.46 (d), 125.09 (s), 127.25 (d), 127.67 (s), 127.93 (d), 128.58 (d), 137.07 (s), 142.78 (s), 147.64 (s), 147.80 (s), 151.76 (s), 151.85 (s), 169.77 (s). EI-MS m/z (%): 527 [M]$^+$ (1), 257 (9), 179 (30), 91 (6). *Anal.* Calcd for $C_{26}H_{26}BrNO_6$: C, 59.10; H, 4.96; N, 2.65, Found: C, 59.28; H, 4.81; N, 2.40.

1-(2-Bromobenzyl)-7-benzyloxy-5,6-dimethoxy-3,4-dihydroisoquinoline (6a) A solution of **5a** (3.0 g, 6.2 mmol) and phosphorus oxychloride (10.0 g) in acetonitrile (80 ml) was refluxed for 3 h. The excess reagent and solvent were removed under vacuum. The residue was shaken with chloroform (50 ml) and dilute ammonium hydroxide (50 ml). The chloroform layer was washed with water (50 ml), then dried over anh. Na_2CO_3. Removal of the solvent under vacuum gave **6a** as a pale brown viscous oil (2.8 g) which was unstable and decomposed on standing. It was immediately used in the next step without further purification. ^{1}H-NMR δ: 2.69 and 2.73 (total 2H, 2t, J=7.6 Hz, CH_2 of both conformers), 3.71and 3.82 (total 2H, 2t, J=7.6 Hz, CH_2 of both conformers), 3.85, 3.88, 3.90 and 3.96 (total 6.7H, 4 s, O–CH_3×2 of both conformers and CH_2 of one conformer), 4.15 (1.30H, s, CH_2 of another conformer), 5.01 and 5.12 (total 2H, 2 s, Ph–CH_2 of both conformers), 6.85 (0.6H, s, Ar–H of one conformer), 7.04—7.65 (9.4H, m, Ph–H×5 of both conformers and Ar–H×4.4 of both conformer). ^{13}C-NMR δ: (both conformers) 18.53 (t), 19.04 (t), 24.85 (t), 42.38 (t), 46.79 (t), 48.04 (t), 60.97 (q), 61.00 (q), 61.04 (q), 61.08 (q), 71.12 (t), 71.20 (t), 107.94 (d), 109.21 (d), 120.66 (d), 121.53 (s), 123.90 (s), 124.54 (s), 124.85 (s), 124.92 (s), 127.38 (d), 127.50 (d), 127.60 (d), 127.64 (d), 128.00 (d), 128.02 (d), 128.15 (d), 128.24 (d), 128.57 (d), 129.69 (d), 129.88 (d), 130.20 (d), 131.02 (d), 132.49 (d), 132.85 (d), 133.07 (d), 136.63 (s), 137.45 (s), 140.19 (s), 145.09 (s), 150.04 (s), 150.09 (s), 150.79 (s), 150.88 (s), 163.64 (s), 165.08 (s).

1-(2-Bromo-4,5-dimethoxybenzyl)-7-benzyloxy-5,6-dimethoxy-3,4-dihydroisoquinoline (6b) In a similar manner, the unstable **6b** was obtained in 42.1% yield from benzene–hexane as a pale yellow solid, mp 148—150 °C. ^{1}H-NMR δ: 2.67 (2H, t, J=7.3 Hz, CH_2), 3.70 (2H, t, J=7.3 Hz, CH_2), 3.73 (3H, s, O–CH_3), 3.79 (3H, s, O–CH_3), 3.83 (3H, s, O–CH_3), 3.89 (3H, s, O–CH_3), 4.13 (2H, s, CH_2), 5.07 (2H, s, Ph–CH_2), 6.80 (1H, s,

Ar–H), 6.93 (1H, s, Ar–H), 7.01 (1H, s, Ar–H), 7.24—7.45 (5H, m, Ph–H). ^{13}C-NMR δ: 19.13 (t), 42.16 (t), 47.04 (t), 55.81 (q), 56.00 (q), 60.86 (q), 60.90 (q), 71.09 (t), 107.71 (d), 112.34 (d), 114.07 (s), 115.30 (d), 123.96 (s), 124.72 (s), 127.40 (d), 127.93 (d), 128.47 (d), 129.36 (s), 136.67 (s), 144.81 (s), 148.29 (s), 148.48 (s), 149.96 (s), 150.77 (s), 165.08 (s).

1-(5-Benzyloxy-2-bromobenzyl)-7-benzyloxy-5,6-dimethoxy-3,4-dihydroisoquinoline (6c) In a similar manner, **6c** was obtained in almost quantitative yield as an unstable pale brown viscous oil which decomposed quickly on standing. It was immediately used in the next step without further purification. ^{1}H-NMR δ: 2.63 (2H, t, J=7.5 Hz, CH_2), 3.68 (2H, t, J=7.5 Hz, CH_2), 3.84 (3H, s, O–CH_3), 3.90 (3H, s, O–CH_3), 4.07 (2H, s, CH_2), 4.94 (2H, s, Ph–CH_2), 5.01 (2H, s, Ph–CH_2), 6.71 (1H, dd, J=8.8, 2.8 Hz, Ar–H), 6.82 (1H, s, Ar–H), 6.88 (1H, d, J=2.8 Hz, Ar–H), 7.27—7.40 (10H, m, Ph–H), 7.44 (1H, d, J=8.8 Hz, Ar–H). ^{13}C-NMR δ: 19.03 (t), 42.80 (t), 47.09 (t), 60.96 (q), 61.00 (q), 70.13 (t), 71.14 (t), 107.78 (d), 115.20 (d), 116.45 (d), 124.00 (s), 124.81 (s), 127.40 (d), 127.42 (d), 127.97 (d), 128.05 (d), 128.56 (d), 133.35 (d), 136.50 (s), 136.72 (s), 138.65 (s), 144.85 (s), 150.01 (s), 150.77 (s), 158.17 (s), 164.69 (s).

1-(2-Bromo-4,5-methylenedioxybenzyl)-7-benzyloxy-5,6-dimethoxy-3,4-dihydro isoquinoline (6d) In a similar manner, **6d** was obtained in almost quantitative yield as an unstable pale brown viscous oil which decomposed quickly on standing. It was immediately used in the next step without further purification. ^{1}H-NMR δ: 2.67 (2H, t, J=7.5 Hz, CH_2), 3.70 (2H, t, J=7.5 Hz, CH_2), 3.85 (3H, s, O–CH_3), 3.91 (3H, s, O–CH_3), 4.02 (2H, s, CH_2), 5.06 (2H, s, Ph–CH_2), 5.93 (2H, s, O–CH_2–O), 6.73 (1H, s, Ar–H), 6.85 (1H, s, Ar–H), 7.01 (1H, s, Ar–H), 7.30—7.42 (5H, m, Ph–H). ^{13}C-NMR δ: 19.05 (t), 42.34 (t), 46.94 (t), 60.94 (q), 60.96 (q), 71.11 (t), 101.71 (t), 107.70 (d), 109.55 (d), 112.56 (d), 114.41 (s), 123.89 (s), 124.84 (s), 127.32 (d), 127.95 (d), 128.55 (d), 130.45 (s), 136.61 (s), 144.93 (s), 147.03 (s), 147.56 (s), 150.06 (s), 150.80 (s), 164.89 (s).

1-(2-Bromobenzyl)-7-benzyloxy-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7a) Sodium borohydride (0.4 g, 10.0 mmol) was added portionwise to a stirred solution of **6a** (2.8 g, 6.0 mmol) in ethanol (80 ml) and the mixture was refluxed for 1 h. Removal of the ethanol under vacuum gave a residue which was shaken with water (50 ml) and chloroform (50 ml). The chloroform layer was dried. Removal of the solvent gave a crude yellow viscous oil which was chromatograped over alumina using benzene as eluent to give tetrahydroisoquinoline (**7a**) as a pale yellow viscous oil (2.4 g, 85.4%). UV λ_{max} (MeOH) nm (log ε): 207 (4.44), 224 sh (4.05), 276 (2.94). IR (CH_2Cl_2-film) cm^{-1}: 3332, 2935, 2829, 1601, 1491, 1456, 1437, 1413, 1377, 1342, 1322, 1274, 1240, 1200, 1110, 1026, 916, 751, 697. ^{1}H-NMR δ: 2.58—2.78 (2H, m, CH_2), 2.84—2.94 (2H, m, CH_2), 3.10—3.29 (2H, m, CH_2), 3.86 (3H, s, O–CH_3), 3.89 (3H, s, O–CH_3), 4.16 (1H, dd, J=3.3, 10.2 Hz, H-1), 5.06 (2H, s, Ph–CH_2), 6.64 (1H, s, Ar–H), 7.00—7.45 (8H, m, Ph–H×5 and Ar–H×3), 7.55 (1H, d, J=7.8 Hz, Ar–H). ^{13}C-NMR δ: 23.79 (t), 39.53 (t), 42.81 (t), 54.94 (d), 60.39 (q), 60.86 (q), 71.02 (t), 107.97 (d), 121.99 (s), 124.88 (s), 127.25 (d), 127.36 (d), 127.79 (d), 128.21 (d), 128.49 (d), 131.95 (d), 132.99 (d), 133.98 (s), 137.21 (s), 138.67 (s), 141.04 (s), 150.40 (s), 151.19 (s). *Anal.* Calcd for $C_{25}H_{26}BrNO_3$: C, 64.11; H, 5.59; N, 2.99, Found: C, 64.29; H, 5.42; N, 2.81.

1-(2-Bromo-4,5-dimethoxybenzyl)-7-benzyloxy-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7b) In a similar manner, **7b** was obtained in 98.0% yield as a pale yellow viscous oil. UV λ_{max} (MeOH) nm (log ε): 210 (4.80), 229 sh (4.42), 284 sh (3.79), 295 sh (3.57). IR (CH_2Cl_2-film) cm^{-1}: 3429, 2935, 2839, 1602, 1506, 1456, 1438, 1413, 1380, 1322, 1259, 1219, 1164, 1109, 1029, 959. ^{1}H-NMR δ: 2.60—2.95 (4H, m, CH_2×2), 3.15—3.27 (2H, m, CH_2), 3.82 (3H, s, O–CH_3), 3.83 (3H, s, O–CH_3), 3.87 (3H, s, O–CH_3), 3.89 (3H, s, O–CH_3), 4.15 (1H, dd, J=3.2, 9.8 Hz, H-1), 5.07 (2H, s, Ph–CH_2), 6.62 (1H, s, Ar–H), 6.74 (1H, s, Ar–H), 7.04 (1H, s, Ar–H), 7.24—7.47 (5H, m, Ph-H). ^{13}C-NMR δ: 23.86 (t), 40.12 (t), 42.45 (t), 55.40 (d), 56.12 (q), 56.16 (q), 60.47 (q), 60.93 (q), 71.15 (t), 107.99 (d), 114.40 (d), 114.71 (s), 115.75 (d), 122.11 (s), 127.34 (d), 127.87 (d), 128.55 (d), 130.45 (s), 133.85 (s), 137.24 (s), 141.10 (s), 148.28 (s), 148.37 (s), 150.47 (s), 151.26 (s). *Anal.* Calcd for $C_{27}H_{30}BrNO_5$: C, 61.37; H, 5.72; N, 2.65, Found: C, 61.15; H, 5.88; N, 2.78.

1-(5-Benzyloxy-2-bromobenzyl)-7-benzyloxy-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7c) In a similar manner, **7c** was obtained in 92.1% yield as a pale yellow solid, mp 93—96 °C. UV λ_{max} (MeOH) nm (log ε): 206 (4.77), 229 (4.31), 282 (3.43). IR (CH_2Cl_2-film) cm^{-1}: 3335, 3089, 3064, 3032, 2935, 2829, 1592, 1570, 1492, 1456, 1435, 1413, 1342, 1321, 1277, 1240, 1201, 1169, 1111, 1028, 1015, 913. ^{1}H-NMR δ: 2.65—2.94 (4H, m, CH_2×2), 3.10—3.25 (2H, m, CH_2), 3.87 (3H, s, O–CH_3), 3.89 (3H, s, O–CH_3), 4.14 (1H, dd, J=3.3, 9.8 Hz, H-1), 5.02 (2H, s, Ph–CH_2), 5.08 (2H, s, Ph–CH_2), 6.65 (1H, s, Ar–H), 6.76 (1H, dd, J=3.0, 8.8 Hz, Ar–H), 6.87 (1H, d, J=3.0 Hz, Ar–H), 7.26—7.49 (11H, m, Ph–H×10 and Ar–H). ^{13}C-NMR δ: 23.78 (t), 39.53 (t), 42.93 (t), 54.97 (d), 60.46 (q), 60.93 (q), 70.19 (t), 71.11 (t), 108.03 (d), 114.76 (d), 115.58 (s), 118.51 (d), 122.02 (s), 127.31 (d), 127.45 (d), 127.84 (d), 128.10 (d), 128.53 (d), 128.63 (d), 133.57 (d), 133.88 (s), 136.49 (s), 137.22 (s), 139.64 (s), 141.09 (s), 150.45 (s), 151.22 (s), 157.93 (s). *Anal.* Calcd for $C_{32}H_{32}BrNO_4$: C, 66.90; H, 5.61; N, 2.44, Found: C, 66.74; H, 5.80; N, 2.58.

1-(2-Bromo-4,5-methylenedioxybenzyl)-7-benzyloxy-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7d) In a similar manner, **7d** was obtained in 64.0% yield from ethanol as a pale yellow solid, mp 105—106 °C. UV λ_{max} (MeOH) nm (log ε): 213 (4.34), 230 sh (4.09), 276 sh (3.83), 293 (3.88). IR (CH_2Cl_2-film) cm^{-1}: 3336, 2935, 1602, 1585, 1500, 1478, 1456, 1436, 1412, 1378, 1343, 1322, 1273, 1231, 1201, 1163, 1112, 1037, 964, 932. ^{1}H-NMR δ: 2.62—3.02 (4H, m, CH_2×2), 3.12—3.26 (2H, m, CH_2), 3.88 (3H, s, O–CH_3), 3.90 (3H, s, O–CH_3), 4.13 (1H, dd, J=3.6, 10.1 Hz, H-1), 5.09 (2H, s, Ph–CH_2), 5.95 (2H, s, O–CH_2–O), 6.62 (1H, s, Ar–H), 6.76 (1H, s, Ar–H), 7.03 (1H, s, Ar–H), 7.27—7.48 (5H, m, Ph–H). ^{13}C-NMR δ: 23.59 (t), 39.57 (t), 42.52 (t), 55.22 (d), 60.50 (q), 60.95 (q), 71.16 (t), 101.72 (t), 108.02 (d), 111.38(d), 112.91 (d), 114.95 (s), 121.89 (s), 127.29 (d), 127.87 (d), 128.56 (d), 131.45 (s), 133.58 (s), 137.21 (s), 141.15 (s), 147.22 (s), 147.31 (s), 150.52 (s), 151.22 (s). *Anal.* Calcd for $C_{26}H_{26}BrNO_5$: C, 60.95; H, 5.11; N, 2.73, Found: C, 60.80; H, 5.28; N, 2.90.

2-Trifluoroacetyl-1-(2-bromobenzyl)-7-benzyloxy-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8a) Trifluoroacetic anhydride (7.8 g) was added dropwise to a stirred mixture of **7a** (2.8 g, 6.0 mmol) and triethylamine (5.0 g) in chloroform (50 ml) at 0—10 °C. Stirring was continued at room temperature for 3 h. Chloroform (50 ml) was added and the chloroform layer was washed with 10% $NaHCO_3$ (5×60 ml), water (50 ml), 5% HCl (5×60 ml) and brine (50 ml), then dried over anh. Na_2SO_4. Removal of the solvent under vacuum gave a yellow viscous oil which was chromatographed over alumina using benzene as eluent to gave **8a** as a pale yellow solid (2.7 g, 78.3%), mp 106—108 °C. UV λ_{max} (MeOH) nm (log ε): 206 (4.87), 224 (4.49), 275 (3.52), 283 (3.50). IR (CH_2Cl_2-film) cm^{-1}: 2938, 1694, 1603, 1587, 1492, 1459, 1438, 1417, 1375, 1350, 1325, 1265, 1244, 1198, 1171, 1142, 1119, 1094, 1046, 1027, 905. ^{1}H-NMR δ: 2.70—3.36 (5H, m, H-3β, CH_2×2), 3.89 (6H, s, O–CH_3), 4.00—4.13 (1H, m, H-3α), 5.00 (2H, s, Ph–CH_2), 5.69—5.74 (1H, m, H-1), 6.43 (1H, s, Ar–H), 7.06—7.50 (8H, m, Ph–H×5 and Ar–H×3), 7.54 (1H, d, J=7.5 Hz, Ar–H). ^{13}C-NMR δ: (both conformers) 21.87 (t), 23.47 (t), 37.10 (t), 39.61 (t), 41.50 (t), 53.66 (d), 60.67 (q), 60.98 (q), 71.02 (t), 107.84 (d), 108.22 (d), 114.47 (s), 118.29 (s), 119.67 (s), 125.41 (s), 127.25 (d), 127.31 (d), 127.71 (d), 128.04 (d), 128.61 (d), 128.64 (d), 128.74 (d), 128.90 (d), 129.88 (s), 130.09 (s), 131.28 (d), 131.46 (d), 132.85 (d), 136.39 (s), 136.81 (s), 141.61 (s), 150.91 (s), 151.30 (s), 155.68 (s). *Anal.* Calcd for $C_{27}H_{25}BrF_3NO_4$: C, 57.46; H, 4.46; N, 2.48, Found: C, 57.30; H, 4.60; N, 2.62.

1-(2-Bromo-4,5-dimethoxybenzyl)-7-benzyloxy-2-carbomethoxy-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8b) Methyl chloroformate (4.1 g) was slowly added dropwise to a stirred mixture of **7b** (3.8 g, 7.2 mmol) and triethylamine (4.4 g) in chloroform (30 ml) at 0—10 °C. Stirring was continued at room temperature for 3 h. Chloroform (50 ml) and water (50 ml) were added and the chloroform layer was washed with 10% HCl (6×100 ml), water (50 ml), then dried over anh. Na_2SO_4. Removal of the solvent under vacuum gave a pale yellow viscous oil. The viscous oil was chromatograped over alumina using benzene as eluent to give **8b** as a white solid (3.2 g, 76.2%), mp 113—114 °C. UV λ_{max} (MeOH) nm (log ε): 207 (4.60), 233 sh (3.94), 284 (3.28). IR (CH_2Cl_2-film) cm^{-1}: 2936, 2843, 1698, 1603, 1509, 1452, 1409, 1382, 1342, 1258, 1220, 1165, 1106, 1088, 1029, 986. ^{1}H-NMR δ: 2.51—3.50 (5H, m, H-3β, CH_2×2), 3.43 and 3.65 (total 3H, 2 s, COO–CH_3 of both conformers), 3.78, 3.83, 3.85, 3.87, 3.88 and 3.89 (total 12H, 6 s, O–CH_3×4 of both conformers), 3.86—3.98 and 4.22—4.35 (total 1H, m, H-3α), 4.93 and 5.05 (total 2H, 2 s, Ph–CH_2 of both conformers), 5.18—5.35 (1H, m, H-1), 6.26, 6.46, 6.50, 6.59, 7.02 and 7.04 (total 3H, 6 s, Ar–H of both conformers), 7.30—7.50 (5H, m, Ph–H). ^{13}C-NMR δ: (both conformers) 22.24 (t), 22.42 (t), 37.12 (t), 38.44 (t), 41.17 (t), 42.02 (t), 52.27 (q), 52.61 (q), 53.32 (d), 54.90 (d), 56.03 (q), 56.12 (q), 56.23 (q), 60.62 (q), 60.69 (q), 60.97 (q), 71.04 (t), 71.14 (t), 108.27 (d), 108.59 (d), 113.76 (d), 114.10 (d), 115.14 (d), 115.29 (d), 121.07 (s), 121.27 (s), 127.15 (d), 127.26 (d), 127.82 (d), 127.96 (d), 128.40 (d), 128.60 (d), 129.59 (s), 129.76 (s), 131.55 (s), 131.66 (s), 137.02 (s), 141.42 (s), 148.10 (s), 148.16 (s), 148.20 (s), 148.33 (s),150.72 (s), 150.85 (s), 151.14 (s), 155.84 (s). 155.98 (s). *Anal.* Calcd for $C_{29}H_{32}BrNO_7$: C, 59.39; H, 5.50; N, 2.39, Found: C, 59.54; H, 5.37; N, 2.10.

2-Trifluoroacetyl-1-(5-benzyloxy-2-bromobenzyl)-7-benzyloxy-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8c) In a similar manner to

8a, **8c** was obtained in 62.1% yield from ethanol as a white solid, mp 108—110 °C. UV λ_{max} (MeOH) nm (log ε): 215 (4.66), 227 sh (4.52), 283 (4.12). IR (CH_2Cl_2-film) cm^{-1}: 2936, 1691, 1592, 1571, 1492, 1459, 1437, 1416, 1376, 1350, 1324, 1283, 1265, 1243, 1196, 1169, 1141, 1117, 1093, 1019, 905. ^{1}H-NMR δ: 2.70—3.08 (4H, m, $CH_2\times2$), 3.57—3.69 (1H, m, H-3β), 3.88 (6H, s, O–$CH_3\times2$), 3.99—4.09 (1H, m, H-3α), 4.97 (2H, s, Ph–CH_2), 4.98 (2H, s, Ph–CH_2), 5.69 (1H, dd, J=5.4, 8.9 Hz, H-1), 6.41 (1H, s, Ar–H), 6.70—6.78 (2H, m, Ar–H), 7.28—7.45 (11H, m, Ph–H×10 and Ar–H). ^{13}C-NMR δ: 23.42 (t), 39.68 (t), 41.66 (t), 53.74 (d), 60.68 (q), 60.99 (q), 70.23 (t), 71.03 (t), 108.19 (d), 115.22 (d), 116.12 (s), 117.88 (d), 118.24 (s), 119.68 (s), 127.24 (d), 127.47 (d), 128.03 (d), 128.13 (d), 128.65 (d), 130.01 (s), 133.33 (d), 136.47 (s), 136.81 (s), 137.38 (s), 141.63 (s), 150.90 (s), 151.32 (s), 155.51 (s), 157.97 (s). *Anal.* Calcd for $C_{34}H_{31}BrF_3NO_5$: C, 60.90; H, 4.66; N, 2.09, Found: C, 60.80; H, 4.8; N, 2.17.

2-Trifluoroacetyl-1-(2-bromo-4,5-methylenedioxybenzyl)-7-benzyloxy-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8d) In a similar manner to **8a**, **8d** was obtained in 65.7% yield from ethanol as a pale yellow solid, mp 152—154 °C. UV λ_{max} (MeOH) nm (log ε): 212 (4.70), 226 sh (4.43), 285 (4.08), 294 (4.09). IR (CH_2Cl_2-film) cm^{-1}: 2938, 1690, 1604, 1587, 1502, 1478, 1460, 1438, 1416, 1374, 1350, 1325, 1267, 1232, 1199, 1169, 1142, 1115, 1093, 1037, 933, 905. ^{1}H-NMR δ: 2.70—3.26 (4H, m, $CH_2\times2$), 3.57—3.70 (1H, m, H-3β), 3.88 (3H, s, O–CH_3), 3.89 (3H, s, O–CH_3), 4.00—4.11 (1H, m, H-3α), 5.04 (2H, s, Ph–CH_2), 5.64 (1H, dd, J=5.4, 9.0 Hz, H-1), 5.93—5.97 (2H, m, O–CH_2–O), 6.45 (1H, s, Ar–H), 6.56 (1H, s, Ar–H), 6.98 (1H, s, Ar–H), 7.28—7.45 (5H, m, Ph–H). ^{13}C-NMR δ: (both conformers) 21.86 (t), 23.48 (t), 39.67 (t), 39.72 (t), 41.40 (t), 42.29 (t), 53.93 (d), 60.69 (q), 61.00 (q), 71.15 (t), 101.77 (t), 108.29 (d), 110.53 (d), 112.75 (d), 115.56 (s), 118.34 (s), 119.74 (s), 127.20 (d), 128.06 (d), 128.67 (d), 129.33 (s), 130.05 (s), 136.83 (s), 141.65 (s), 147.33 (s), 147.47 (s), 150.92 (s), 151.35 (s), 155.79 (s). *Anal.* Calcd for $C_{28}H_{25}Br\ F_3NO_6$: C, 55.27; H, 4.14; N, 2.30, Found: C, 55.02; H, 4.31; N, 2.47.

1-Hydroxy-2,3-dimethoxy-6-trifluoroacetylnoraporphine (9a) A solution of azobis (isobutyronitrile) (0.6 g, 3.6 mmol) and tributyltin hydride (4.1 g, 14.0 mmol) in toluene (40 ml) was added dropwise in four equal portions over 3 h to a refluxing solution of **8a** (2.0 g, 3.6 mmol) in toluene (40 ml) and the resulting mixture was then refluxed for another 24 h. The solvent was then removed under vacuum and the residue was dissolved in acetonitrile (50 ml) and washed with hexane (3×50 ml), then dried over anh. Na_2SO_4. Removal of the solvent gave the crude noraporphine (1.1 g) as a brown viscous oil which was chromatograped over silica gel using hexane–ethyl acetate as eluent. The earlier fractions gave the hydrogenolysis product (**8e**) as a white solid (317.7 mg, 18.5%), mp 115—116 °C. ^{1}H-NMR δ: 2.71—2.78 (2H, m, H-4 of both conformers), 3.08 (2H, apparent d, J=6.8 Hz, Ar–CH_2), 3.38—3.50 (1H, m, H-3β of both conformers), 3.86, 3.87, 3.88 and 3.89 (total 6H, 4 s, O–$CH_3\times2$ of both conformers), 3.90—3.98 (1H, m, H-3α), 4.87 (2H, s, Ph–CH_2), 5.55 (1H, apparent t, J=6.8 Hz, H-1), 6.17 (1H, s, Ar–H), 7.04—7.12 (2H, m, Ar–H of both conformers), 7.22—7.41 (8H, m, Ph–H×5 and Ar–H×3 of both conformers). ^{13}C-NMR δ: (both conformers) 21.83 (t), 23.22 (t), 39.98 (t), 40.02 (t), 41.78 (t), 55.30 (d), 60.71 (q), 60.97 (q), 70.78 (t), 108.33 (d), 114.58 (s), 118.40 (s), 119.69 (s), 122.21 (s), 126.95 (d), 127.25 (d), 128.02 (d), 128.46 (d), 128.61 (d), 129.74 (d), 136.78 (s), 136.87 (s), 141.46 (s), 150.88 (s), 150.98 (s), 155.74 (s). The latter fractions gave pure noraporphine (**9a**) as a pale brown solid (151.6 mg, 10.9%), mp 205—206 °C. UV λ_{max} (MeOH) nm (log ε): 215 (4.51), 274 (4.22), 292 sh (4.07), 309 (4.02). IR (CH_2Cl_2-film) cm^{-1}: 3393, 2921, 2850, 1682, 1589, 1456, 1440, 1420, 1377, 1300, 1277, 1186, 1173, 1147, 1127, 1079, 1046, 1019, 952, 926. ^{1}H-NMR δ: 2.57—3.34 (5H, m, H-5β, $CH_2\times2$), 3.89 (3H, s, O–CH_3), 3.97 (3H, s, O–CH_3), 4.19—4.28 (1H, m, H-5α), 5.08 (1H, dd, J=4.2, 13.7 Hz, H-6a), 6.41 (1H, s, OH), 7.19—7.38 (3H, m, Ar–H), 8.39 (1H, d, J=7.9 Hz, H-11). ^{13}C-NMR δ: 23.93 (t), 33.19 (t), 41.09 (t), 52.33 (d), 60.55 (q), 61.03 (q), 114.48 (s), 116.43 (s), 118.26 (s), 122.11 (s), 127.06 (d), 127.29 (d), 128.12 (d), 128.49 (d), 131.36 (s), 134.86 (s), 138.80 (s), 146.13 (s), 148.32 (s), 155.81 (s). EI-MS *m*/*z* (%): 393 $[M]^+$ (43), 361 (6), 267 (100), 126 (2). *Anal.* Calcd for $C_{20}H_{18}F_3NO_4$: C, 61.07; H, 4.61; N, 3.56, Found: C, 61.24; H, 4.48; N, 3.40.

1-Hydroxy-6-carbomethoxy-2,3,9,10-tetramethoxynoraporphine (9b) In a similar manner, **8f** was obtained in 41.6% yield as a pale yellow solid, mp 121—122 °C. ^{1}H-NMR δ: 2.53—2.84 (2H, m, H-4 of both conformers), 2.84—3.10 (2H, m, Ar–CH_2 of both conformers), 3.10—3.30 (1H, m, H-3β), 3.52, 3.68, 3.71, 3.81, 3.84, 3.85, 3.87 and 3.88 (total 15H, 8 s, O–$CH_3\times4$ of both conformers), 4.05—4.22 (1H, m, H-3α), 4.85 (1.06H, ABq, J=12.1 Hz, Ph–CH_2 of one conformer), 4.96 (0.94H, s, Ph–CH_2 of another conformer), 5.05—5.15 and 5.15—5.25 (total 1H, apparent 2m, H-1 of both conformers), 6.11 and 6.28 (total 1H, 2 s, Ar–H of both conformers), 6.52—6.65 (2H, m, Ar–H of both conformers), 6.76 (1H, apparent t, J=8.5 Hz, Ar–H of both conformers), 7.26—7.44 (5H, m, Ph–H of both conformers). ^{13}C-NMR δ: (both conformers) 22.21 (t), 37.53 (t), 38.69 (t), 41.98 (t), 42.43 (t), 52.45 (q), 52.58 (q), 55.75 (q), 55.84 (q), 55.90 (q), 56.02 (d), 56.12 (d), 60.62 (q), 60.69 (q), 60.92 (q), 70.79 (t), 71.04 (t), 108.44 (d), 108.72 (d), 110.85 (d), 111.01 (d), 112.73 (d), 120.89 (s), 121.32 (s), 121.79 (d), 121.9 1(d), 127.11 (d), 127.21 (d), 127.86 (d), 127.91 (d), 128.53 (d), 130.63 (s), 131.71 (s), 136.96 (s), 141.13 (s), 141.32 (s), 147.65 (s), 147.73 (s), 148.61 (s), 150.34 (s), 150.58 (s), 150.77 (s), 151.11 (s), 155.89 (s), 156.00 (s). Noraporphine (**9b**) was obtained in 8.3% yield as a pale yellow solid, mp 212—213 °C. UV λ_{max} (MeOH) nm (log ε): 222 (4.54), 271 sh (3.91), 280 (4.00), 304 (4.12), 315 (4.12). IR (CH_2Cl_2-film) cm^{-1}: 3383, 2936, 2849, 1686, 1609, 1592, 1513, 1459, 1448, 1396, 1342, 1250, 1197, 1167, 1126, 1111, 1078, 1049, 1021, 974. ^{1}H-NMR δ: 2.47—2.98 (5H, m, H-5β, $CH_2\times2$), 3.77, 3.86, 3.91, 3.93 and 3.97 (total 15H, 5 s, O–$CH_3\times5$), 4.38—4.50 (total 1H, m, H-5α), 4.72—4.82 (total 1H, m, H-6a), 6.39 (1H, br s, OH), 6.78 (1H, s, H-8), 8.05 (1H, s, H-11). ^{13}C-NMR δ: 23.57 (t), 34.25 (t), 38.78 (t), 52.08 (d), 52.68 (q), 55.84 (q), 55.98 (q), 60.45 (q), 60.98 (q), 111.25 (d), 111.92 (d), 116.43 (s), 119.57 (s), 124.35 (s), 128.75 (s), 128.95 (s), 138.53 (s), 144.80 (s), 147.26 (s), 147.70 (s), 147.90 (s), 155.09 (s). EI-MS *m*/*z* (%): 415 $[M]^+$ (34), 383 (36), 327 (100), 88 (4). *Anal.* Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37, Found: C, 63.42; H, 6.21; N, 3.50.

9-Benzyloxy-1-hydroxy-2,3-dimethoxy-6-trifluoroacetylnoraporphine (9c) In a similar manner, **8g** was obtained in 38.6% yield as a yellow oil. ^{1}H-NMR δ: 2.70—2.77 (2H, m, H-4 of both conformers), 3.04 (2H, apparent d, J=6.8 Hz, Ar–CH_2), 3.34—3.47 (1H, m, H-3β), 3.84, 3.85 and 3.86 (total 6H, 3 s, O–$CH_3\times2$ of both conformers), 3.88—3.98 (1H, m, H-3α), 4.65 (0.2H, ABq, J=11.7 Hz, Ph–CH_2 of one conformer), 4.85 (1.8H, ABq, J=12.1 Hz, Ph–CH_2 of another conformer), 4.96 and 4.98 (total 2H, 2 s, Ph–CH_2 of both conformers), 5.56 (1H, apparent t, J=6.7 Hz, H-1), 6.17 (1H, s, Ar–H), 6.64—6.75 (2H, m, Ar–H of both conformers), 6.81—6.91 (1H, m, Ar–H of both conformers), 7.12—7.21 (1H, m, Ar–H of both conformers), 7.23—7.41 (total 10H, m, Ph–H of both conformers). ^{13}C-NMR δ: (both conformers) 23.18 (t), 39.99 (t), 40.03 (t), 41.80 (t), 55.23 (d), 60.65 (q), 60.92 (q), 69.87 (t), 70.76 (t), 108.31 (d), 113.50 (d), 114.62 (s), 116.10 (d), 118.44 (s), 119.66 (d), 122.40 (d), 127.25 (d), 127.47 (d), 127.92 (d), 127.98 (d), 128.54 (d), 128.58 (d), 129.45 (d), 129.73 (d), 129.97 (s), 136.77 (s), 136.91 (s), 138.48 (s), 141.45 (s), 150.85 (s), 150.99 (s), 155.71 (s), 158.86 (s). Noraporphine (**9c**) was obtained in 9.7% yield as a pale yellow solid, mp 183—184 °C. UV λ_{max} (MeOH) nm (log ε): 213 (4.67), 231 sh (4.43), 274 (4.28), 283 (4.31), 299 (4.19), 312 (4.11). IR (CH_2Cl_2-film) cm^{-1}: 3583, 3411, 2942, 1686, 1609, 1501, 1459, 1414, 1378, 1342, 1310, 1281, 1233, 1201, 1175, 1153, 1083, 1049, 1016, 974. ^{1}H-NMR δ: 2.57—3.10 (5H, m, CH, $CH_2\times2$), 3.21—3.33 (1H, m, H-5β), 3.87 (3H, s, O–CH_3), 3.97 (3H, s, O–CH_3), 4.18—4.28 (1H, m, H-5α), 5.10 (2H, s, Ph–CH_2), 6.35 (1H, s, OH), 6.90 (1H, d, J=2.4 Hz, H-8), 6.95 (1H, dd, J=2.4, 8.7 Hz, H-10), 7.30—7.50 (5H, m, Ph–H), 8.32 (1H, d, J=8.7 Hz, H-11). ^{13}C-NMR δ: 23.92 (t), 33.55 (t), 41.12 (t), 52.31 (d), 60.54 (q), 60.99 (q), 69.95 (t), 113.28 (d), 114.76 (d), 116.45 (s), 118.20 (s), 118.29 (s), 124.43 (s), 127.28 (s), 127.51 (d), 127.97 (d), 128.61 (d), 129.48 (d), 136.68 (s), 136.99 (s), 138.80 (s), 145.49 (s), 147.69 (s), 155.80 (s), 157.75 (s). EI-MS *m*/*z* (%): 499 $[M]^+$ (10), 373 (16), 91 (23), 32 (100). *Anal.* Calcd for $C_{27}H_{24}F_3NO_5$: C, 64.93; H, 4.84; N, 2.80, Found: C, 64.76; H, 4.98; N, 2.97.

1-Hydroxy-2,3-dimethoxy-9,10-methylenedioxy-6-trifluoroacetylnoraporphine (9d) In a similar manner, **8h** was obtained in 13.1% yield as a pale yellow solid, mp 129—130 °C. ^{1}H-NMR δ: 2.71—2.78 (2H, m, H-4 of both conformers), 2.99 (2H, apparent d, J=6.7 Hz, Ar–CH_2), 3.36—3.48 (1H, m, H-3β), 3.87 (3H, s, O–CH_3), 3.89 (3H, s, O–CH_3), 3.91—4.00 (1H, m, H-3α), 4.95 (2H, s, Ph–CH_2), 5.49 (1H, apparent t, J=6.7 Hz, H-1), 5.89—5.95 (2H, m, O–CH_2–O of both conformers), 6.24 (1H, s, Ar–H), 6.51 (1H, dd, J=1.4, 7.8 Hz, Ar–H), 6.54 and 6.56 (total 1H, 2d, J=1.4 Hz, Ar–H of both conformers), 6.70 and 6.75 (total 1H, 2d, J=7.8 Hz, Ar–H of both conformers), 7.28—7.42 (5H, m, Ph–H of both conformers). ^{13}C-NMR δ: (both conformers) 23.23 (t), 39.98 (t), 40.02 (t), 41.41 (t), 55.33 (d), 58.28 (d), 60.69 (q), 60.96 (q), 70.95 (t), 100.95 (t), 108.17 (d), 108.38 (d), 109.97 (d), 114.57 (s), 118.39 (s), 119.77 (s), 122.69 (d), 127.19 (d), 128.02 (d), 128.62 (d), 129.97 (s), 130.52 (s), 136.76 (s), 141.50 (s), 146.52 (s), 147.63 (s), 150.87 (s), 151.04 (s), 155.75 (s). Noraporphine (**9d**) was obtained in 10.4% as a pale yellow solid, mp 251—252 °C. UV λ_{max} (MeOH) nm (log ε): 220 (4.60), 235 sh (4.40), 274 sh (4.03), 283 (4.09), 309 (4.27), 320 (4.28). IR (CH_2Cl_2-film) cm^{-1}: 3402, 2919, 2850, 1686, 1506, 1488, 1459, 1431, 1414, 1373, 1354, 1305, 1281, 1239, 1225, 1186, 1146, 1094,

1045, 971, 940, 924. ^{1}H-NMR δ: 2.54—3.09 (4H, m, CH_2×2), 3.19—3.20 (1H, m, H-5β), 3.87 (3H, s, O–CH_3), 3.97 (3H, s, O–CH_3), 4.17—4.27 (1H, m, H-5α), 5.02 (1H, dd, J=4.2, 13.8 Hz, H-6a), 5.97 (2H, s, O–CH_2–O), 6.40 (1H, s, OH), 6.74 (1H, s, H-8), 7.95 (1H, s, H-11). ^{13}C-NMR δ: 23.88 (t), 33.18 (t), 41.09 (t), 52.48 (d), 60.54 (q), 61.01 (q), 101.01 (t), 108.80 (d), 108.82 (d), 114.47 (s), 116.54 (s), 118.17 (s), 124.93 (s), 127.38 (s), 129.17 (s), 138.77 (s), 145.42 (s), 146.26 (s), 146.56 (s), 147.80 (s), 155.83 (s). EI-MS *m/z* (%): 437 $[M]^+$ (38), 405 (3), 311 (100), 126 (9). *Anal.* Calcd for $C_{21}H_{18}F_3NO_6$: C, 57.67; H, 4.15; N, 3.20, Found: C, 57.48; H, 4.30; N, 3.37.

(±)-Isopiline (1a) A mixture of **9a** (60.0 mg, 15.3 mmol), potassium carbonate (1.0 g), methanol (20 ml) and water (5 ml) was refluxed for 3 h. The solvent was then removed under vacuum and water (20 ml) and 10% sodium bicarbonate (20 ml) were added to the residue followed by extraction with chloroform (2×20 ml). Removal of the solvent gave a brown solid which was triturated with ethanol to give (±)-isopiline (**1a**) as a pale grey solid (29.3 mg, 64.7%), mp 170—171 °C. UV λ_{max} (MeOH) nm (log ε): 214 (4.45), 220 sh (4.42), 232 sh (4.19), 274 (4.20), 291 sh (4.00), 309 (3.89). IR (CH_2Cl_2-film) cm^{-1}: 3583, 3305, 2931, 2849, 1587, 1490, 1463, 1445, 1418, 1380, 1338, 1305, 1267, 1226, 1196, 1152, 1110, 1086, 1052, 1025, 991, 960. ^{1}H-NMR δ: 2.72—3.25 (5H, m, H-5β, CH_2×2), 3.39—3.49 (1H, m, H-5α), 3.83—3.94 (1H, m, H-6a), 3.88 (3H, s, O–CH_3), 3.95 (3H, s, O–CH_3), 7.14—7.34 (3H, m, Ar–H), 8.32 (1H, d, J=7.2 Hz, H-11). ^{13}C-NMR δ: 23.12 (t), 36.82 (t), 42.82 (t), 53.80 (d), 59.95 (q), 60.83 (q), 115.39 (s), 118.32 (s), 126.69 (d), 126.82 (d), 127.73 (d), 127.84 (d), 131.59 (s), 132.18 (s), 134.90 (s), 138.75 (s), 145.31 (s), 149.09 (s). EI-MS *m/z* (%): 297 $[M]^+$ (73), 296 (100), 266 (18). *Anal.* Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71, Found: C, 72.60; H, 6.54; N, 4.86.

(±)-Preocoteine (1b) A mixture of **9b** (100.0 mg, 0.24 mmol) and lithium aluminium hydride (2.0 g) in dry tetrahydrofuran (40 ml) was refluxed for 3 h. Water (10 ml) was added dropwise followed by dilute ammonium hydroxide (25 ml). The pale yellow granular residue was filtered and washed with chloroform. The organic phase was separated and then dried over anh. Na_2SO_4. Removal of the solvent under vacuum gave a pale yellow-white solid which was recrystallized from benzene to give (±)-preocoteine (**1b**) as a pale yellow solid (66.6 mg, 74.5%), mp 179—180 °C. UV λ_{max} (MeOH) nm (log ε): 219 (4.38), 271sh (3.71), 281 (3.82), 308 (4.00), 319 (3.99). IR (CH_2Cl_2-film) cm^{-1}: 3400, 2937, 2846, 1609, 1593, 1515, 1463, 1430, 1397, 1375, 1347, 1310, 1284, 1253, 1226, 1215, 1195, 1115, 1082, 1058, 1036, 1014, 990, 971. ^{1}H-NMR δ: 2.70 (3H, s, N–CH_3), 2.68—3.36 (7H, m, CH, CH_2×3), 3.87, 3.91 and 3.96 (12H, 3 s, O–CH_3×4), 6.77 (1H, s, H-8), 7.96 (1H, s, H-11). ^{13}C-NMR δ: 21.72 (t), 30.34 (q), 33.06 (t), 52.60 (t), 55.91 (q), 56.03 (q), 60.08 (q), 60.87 (q), 62.24 (d), 111.03 (d), 111.73 (d), 115.92 (s), 117.28 (s), 124.31 (s), 126.93 (s), 135.80 (s), 139.06 (s), 145.01 (s), 147.52 (s), 147.69 (s), 148.07 (s). EI-MS *m/z* (%): 371 $[M]^+$ (100), 339 (35), 326 (17). *Anal.* Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77, Found: C, 67.80; H, 6.85; N, 3.90.

1,9-Dihydroxy-2,3-dimethoxy-6-trifluoroacetylnoraporphine (9e) A solution of **9c** (115.0 mg, 0.23 mmol) in ethanol (30 ml) was hydrogenolysed over 10% Pd/C (10.0 mg) at atmospheric pressure for 48 h. The catalyst was filtered and the solvent removed under vacuum. The resulting white residue was recrystallized from ethanol to give **9e** as a pale brown solid (84.3 mg, 89.4%), mp 274—275 °C. UV λ_{max} (MeOH) nm (log ε): 214 (4.64), 232 sh (4.39), 274 sh (4.25), 282 (4.28), 299 (4.16), 312 (4.08). IR (CH_2Cl_2-film) cm^{-1}: 3502, 3347, 2920, 2850, 1671, 1619, 1587, 1506, 1459, 1378, 1343, 1302, 1280, 1264, 1234, 1201, 1190, 1176, 1144, 1081, 1049, 1020, 973. ^{1}H-NMR (acetone-d_6) δ: 2.57—3.13 (4H, m, CH_2×2), 3.26—3.38 (1H, m, H-5β), 3.88 (3H, s, O–CH_3), 3.94 (3H, s, O–CH_3), 4.17—4.28 (1H, m, H-5α), 5.02 (1H, dd, J=5.1, 12.9 Hz, H-6a), 6.76—6.85 (2H, m, Ar–H), 8.31 (1H, d, J=8.4 Hz, H-11). ^{13}C-NMR (acetone-d_6) δ: 24.10 (t), 33.70 (t), 41.32 (t), 52.69 (d), 60.53 (q), 60.92 (q), 113.95 (d), 115.24 (d), 117.02 (s), 118.00 (s), 118.60 (s), 123.72 (s), 127.20 (s), 130.06 (d), 136.95 (s), 139.46 (s), 146.20 (s), 148.15 (s), 155.73 (s), 156.16 (s). EI-MS *m/z* (%): 409 $[M]^+$ (29), 377 (7), 283 (100), 126 (3). *Anal.* Calcd for $C_{20}H_{18}F_3NO_5$: C, 58.68; H, 4.43; N, 3.42, Found: C, 58.45; H, 4.60; N, 3.55.

(±)-Oureguattidine (1c) In a similar manner to **1a**, (±)-oureguattidine (**1c**) was obtained in 86.5% yield as a brown solid, mp 228—229 °C. UV λ_{max} (MeOH) nm (log ε): 209 sh (4.40), 221 (4.53), 269 sh (3.96), 303 (4.14), 314 (4.13). IR (CH_2Cl_2-film) cm^{-1}: 3412, 2922, 2850, 1610, 1463, 1420, 1380, 1341, 1298, 1227, 1195, 1154, 1112, 1085, 1048, 1026, 992. ^{1}H-NMR (pyridine-d_5) δ: 2.81—3.06 (5H, m, H-5β, CH_2×2), 3.39—3.49 (1H, m, H-5α), 3.86 (3H, s, O–CH_3), 3.88 (3H, s, O–CH_3), 4.00—4.15 (1H, m, H-6a), 7.21 (1H, d, J=2.6 Hz, H-8), 7.27 (1H, dd, J=2.6, 8.6 Hz, H-10), 9.03 (1H, d, J=8.6 Hz, H-11). ^{13}C-NMR (pyridine-d_5) δ: 23.97 (t), 38.03 (t), 43.42 (t), 54.85 (d), 60.01 (q), 60.56 (q), 114.37 (d), 115.67 (d), 117.70 (s), 118.28 (s), 125.23 (s), 130.69 (d), 132.05 (s), 138.02 (s), 140.77 (s), 147.25 (s), 149.74 (s), 157.52 (s). EI-MS *m/z* (%): 313 $[M]^+$ (88), 312 (100), 282 (23). *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47, Found: C, 68.78; H, 6.30; N, 4.58.

(±)-3-Methoxynordomesticine (1d) In a similar manner to **1a**, (±)-3-methoxynordomesticine (**1d**) was obtained in 78.6% yield as a pale brown solid, mp 206—208 °C. UV λ_{max} (MeOH) nm (log ε): 213 (4.73), 234 sh (4.40), 271 sh (4.41), 281 (4.45), 295 (4.29), 310sh (4.15). IR (CH_2Cl_2-film) cm^{-1}: 3437, 2919, 2850, 1620, 1542, 1502, 1463, 1430, 1413, 1381, 1357, 1303, 1292, 1255, 1228, 1196, 1148, 1126, 1096, 1039, 982, 932. ^{1}H-NMR δ: 2.58—3.00 (6H, m, CH_2×3), 3.35—3.44 (1H, m, H-6a), 3.87 (3H, s, O–CH_3), 3.94 (3H, s, O–CH_3), 5.95 (2H, ABq, J=1.4 Hz, O–CH_2–O), 6.72 (1H, s, H-8), 7.90 (1H, s, H-11). ^{13}C-NMR δ: 23.51 (t), 37.29 (t), 42.99 (t), 54.02 (d), 59.93 (q), 60.81 (q), 100.78 (t), 108.14 (d), 108.66 (d), 115.53 (s), 118.63 (s), 125.74 (s), 129.49 (s), 131.87 (s), 138.58 (s), 144.48 (s), 145.69 (s), 146.21 (s), 148.61 (s). EI-MS *m/z* (%): 341 $[M]^+$ (87), 340 (100), 310 (22). *Anal.* Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10, Found: C, 66.68; H, 5.84; N, 4.03.

Minimum Inhibitory Concentration (MIC) MIC of (±)-3-methoxynordomesticine was determined by NCCLS microbroth dilution methods.[13] (±)-3-Methoxynordomesticine was weighed and dissolved in DMSO to make a solution of concentration 2.56 mg/ml. From this stock solution two-fold serial dilution has been carried out to give a series of solutions from 256 to 0.50 μg/ml with culture medium in 96-well microplates (100 μl of total volume). Three different microorganisms were selected *viz. Staphylotcoccus aureus* ATCC25932, *Escherichia coli* ATCC10536 and *Candida albicans* ATCC90028. They were subcultured on nutrient broth supplemented with 10% glucose (NBG) (for bacteria) or Sabouraud glucose broth (for yeast) and incubated at 37 °C for 24 h. A final concentration of 1×10^5 cfu/ml of test bacteria or yeast was added to each dilution. The plates were incubated at 37 °C for 48 h. MIC was defined as the lowest concentration of the test agent that inhibited bacterial or yeast growth, as indicated by the absence of turbidity. Test agent-free broth containing 5% DMSO was incubated as the growth control. Minimum microbicidal concentration (MMC) was determined by inoculating onto nutrient agar plates (for bacteria) or Sabouraud agar plates (for yeast) a 100 μl of medium from each of the wells from the MIC test which showed no turbidity. MMCs were defined as the lowest concentration of the test agent where there was no microbial growth on the plates.

Anti-inflammatory Activity Murine macrophage RAW 264.7 cell line obtained from American Type Culture Collection (ATCC, Maryland, U.S.A.), was maintained in DMEM supplemented with 10% heat inactivated FBS, penicillin G (100 IU/ml), streptomycin (100 mg/ml), and L-glutamine (2 mM) and incubated at 37 °C in a humidified atmosphere containing 5% CO_2. Cells (1×10^6/ml) were pre-incubated 2 h with (±)-3-methoxynordomesticine (1, 2.5, 5 μg/ml) and further cultured 24 h with LPS (1 μg/ml) in 24-well plates. Supernatants were removed at the allotted times and NO, PGE_2, TNF-α, IL-1β and IL-6 levels were quantified by immunoassay kits according to the manufacture's protocols (Assay Designs' Correlate-EIA™, Stressgen, U.S.A.), respectively.

Western blot Cellular proteins were extracted from the control and (±)-3-methoxynordomesticine-treated RAW 264.7 cells. The washed cell pellets were resuspended in lysis buffer buffer (50 mM HEPES pH 7.0, 250 mM NaCl, 5 mM EDTA, 0.1% Nonidet P-40, 1 mM phenylmethylsulfonyl fluoride, 0.5 mM dithiothreitol, 5 mM NaF, 0.5 mM Na orthovanadate) containing 5 μg/ml each of leupeptin and aprotinin and incubated for 15 min at 4 °C. Cell debris was removed by microcentrifugation, followed by quick freezing of the supernatants. Protein concentration was determined by BioRad protein assay reagent according to the manufactures instruction, 40—50 μg of cellular proteins from treated and untreated cell extracts were electroblotted onto nitrocellulose membrane following separation on a 10% SDS-polyacrylamide gel electrophoresis. The immunoblot was incubated overnight with the blocking solution (5% skim milk) at 4 °C, followed by incubation for 4 h with a 1 : 500 dilution of monoclonal anti-iNOS and COX-2 antibody (Santacruz, CA, U.S.A.). Blots were washed 2 times with PBS and incubated with a 1 : 1000 dilution of horseradish peroxidase-conjugated goat anti-mouse IgG secondary antibody (Santacruz, CA, U.S.A.) for 1 h at room temperature. Blots were again washed three times in Tween 20/Tris-buffered saline (TTBS) and then developed by enhanced chemiluminescence (Amersham Life Science, Arlington Heights, IL, U.S.A.). Cytotoxicity assay. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cytotoxicity assay was performed according to the method previously described.[14] MTT solution was added at a concentration of 50 μg/ml into each well, which also contain 1, 2.5 and 5 μg/ml of (±)-3-methoxynordomes-

ticine. After 4 h of incubation at 37 °C, the medium was discarded and the formazan blue, which formed in the cells, was dissolved in 50 μl DMSO. The optical density at 540 nm was determined with a microplate reader. The optical density of formazan formed in control (untreated) cells was taken as 100% of viability.

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