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PREPARATION OF 6-PHENYL- AND 8-PHENYL TETRAHYDRO-ISOQUINOLINES FROM BOLDINE

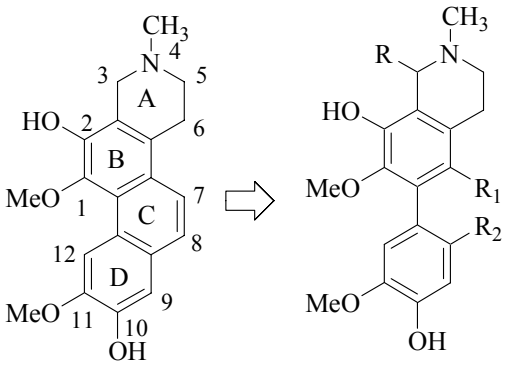
Wei-Jan Huang, Chung-Hsiung Chen, and Shoei-Sheng Lee*

School of Pharmacy, College of Medicine, National Taiwan University, 1 Jen-Ai Road, Sec. 1, Taipei, Taiwan 100, Republic of China, shoeilee@ha.mc.ntu.edu.tw

Abstract-Four 6-phenyl- and 8-phenyltetrahydroisoquinolines were prepared by structural modifications of boldine nucleus. These involved four major reaction steps, including solvolysis of 2-hydroxyaporphine, ozonolysis of the C-9,10 double bond of phenanthrene nucleus leading to the key intermediate, and final Pictet-Spengler cyclization to respective target products.

Previous study in our laboratory has demonstrated that the phenanthrene alkaloid, litebamine (**1**) and its *N*-homologues possess anti-acetylcholinesterase activity.[1] Among these, **1** showed an IC_{50} value of 22 μM. These compounds had been prepared *via* a facile semi-synthetic method starting from boldine (**3**) with the key solvolysis of 2-hydroxyaporphine by a pull-push mechanism.[2] Molecular modeling study revealed that the distance between N^4 and O^2 of **1** is close to corresponding atoms in the extended-conformation of acetylcholine (4.28 Å vs. 3.82 Å). Hence, the substitutions around these two atoms could serve as the key pharmacophore determinant for their biological activity. The effect of *N*-substitutions has been studied and the best activity was displayed by the *N*-butyl homologue.[1] However further application of these analogues was limited by their poor solubility in organic solvents, arising from strong intermolecular π-electron bonding and hydrogen bonding due to coplanar aryl structure and the attached heteroatoms. To overcome this limitation, this study focused on the breakdown of the coplanar phenanthrene moiety, which led to the preparation of 6- and 8-phenyltetrahydroisoquinolines after appropriate chemical

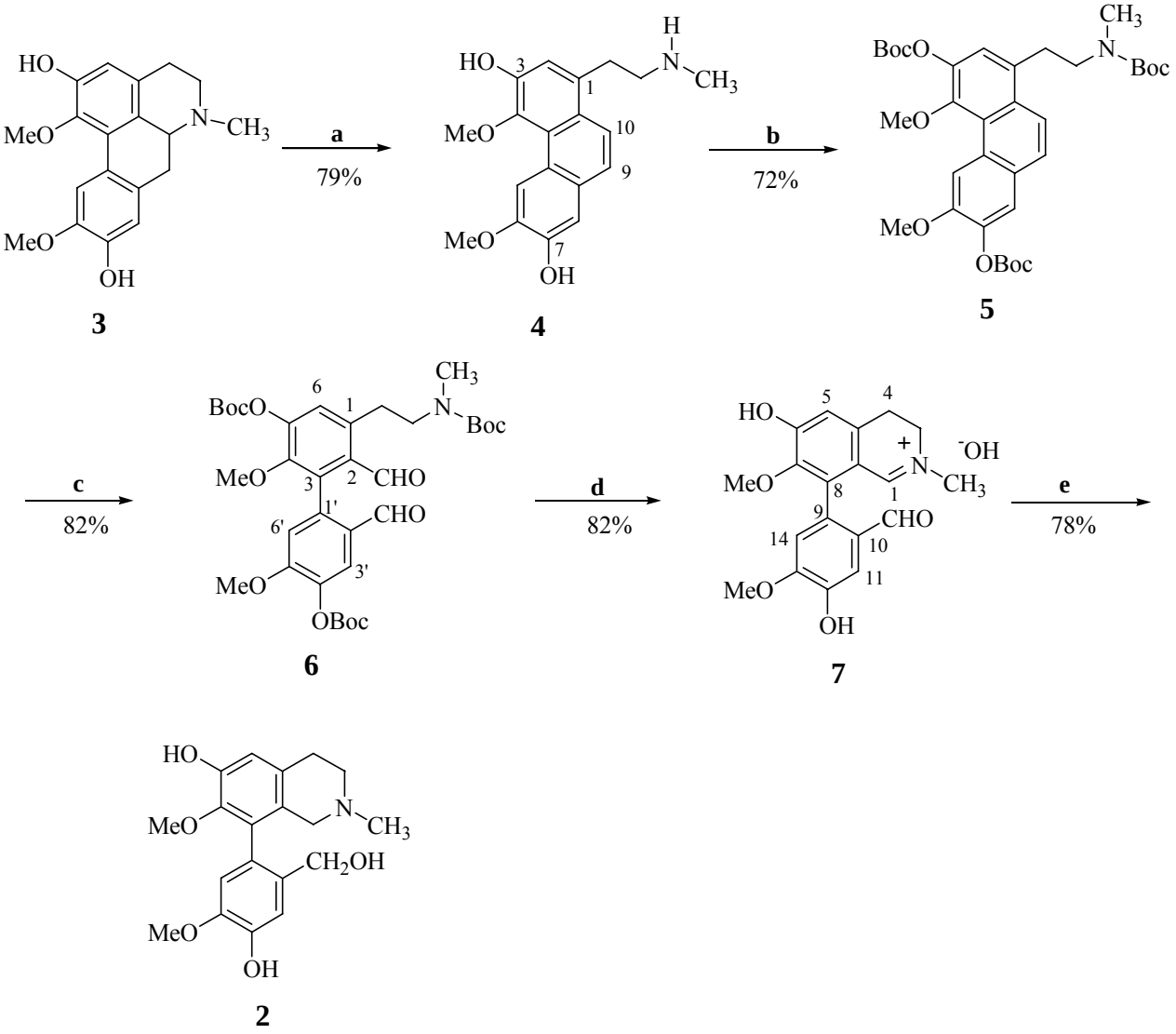
procedures. The following describes our efforts in this aspect.



1

RESULTS AND DISCUSSION

8-Phenyltetrahydroisoquinoline (**2**) was prepared as shown in Scheme 1. Solvolysis of boldine (**3**) gave secoboldine (**4**).[2,3] Protection of the secondary amine and two hydroxy groups (3- and 7-OH) of **4** with various groups including acetyl, 2,2,2-trichloroethylcarbonyl (Troc), *t*-butoxycarbonyl (Boc) and formyl was attempted and the Boc group was found to be the best one. Thus, reaction of **4** with $(Boc)_2O$ gave **5** in 72% yield. The ^1H NMR spectrum of **5** showed two sets of signals due to the existence of s-*trans*- and s-*cis*-forms of carbamate, which was converted into almost single set upon elevation of NMR probe temperature, $\delta_{Boc\text{-}Me}$ at 1.54, 1.52 and 1.25, each 9H. Ozonolysis[4] of **5** followed by reductive work-up gave a dialdehyde (**6**) in 82% yield, δ 9.79 and 9.52 (CHO x 2). Treatment of **6** with TFA under room temperature to remove the Boc protecting group yielded an aminoaldehyde, which cyclized to **7** spontaneously under the reaction condition in 82% yield, $\delta_{H\text{-}1}$ δ 7.94 and $\delta_{2\text{-}Me}$ 3.37 ($\delta_{2\text{-}Me}$ 2.77 in **6**) and $\delta_{10\text{-}C\underline{H}O}$ 9.43. HRFABMS spectrum of **7** showed the molecular ion at *m/z* 342.1346, consistent with that calculated for $C_{19}H_{20}NO_5$. Sodium borohydride reduction of **7** gave 8-aryltetrahydroisoquinoline (**2**) in 78% yield, δ_{H-1} 3.13 and 2.99 (each 1H, d, J = 15.2 Hz), $\delta_{2\text{-}Me}$ 2.30 and $\delta_{10\text{-}CH2OH}$ 4.13 and 4.09 (each d, J = 11.9 Hz). The HRFABMS spectrum of **2** showed a quasi-molecular ion $(M+H)^+$ at *m/z* 346.1650, consistent with the expected formula $C_{19}H_{24}NO_5$. It is also noted that **2** is not stable at basic conditions. Hence, during work-up, the reaction mixture must be neutralized first to avoid any decomposition.

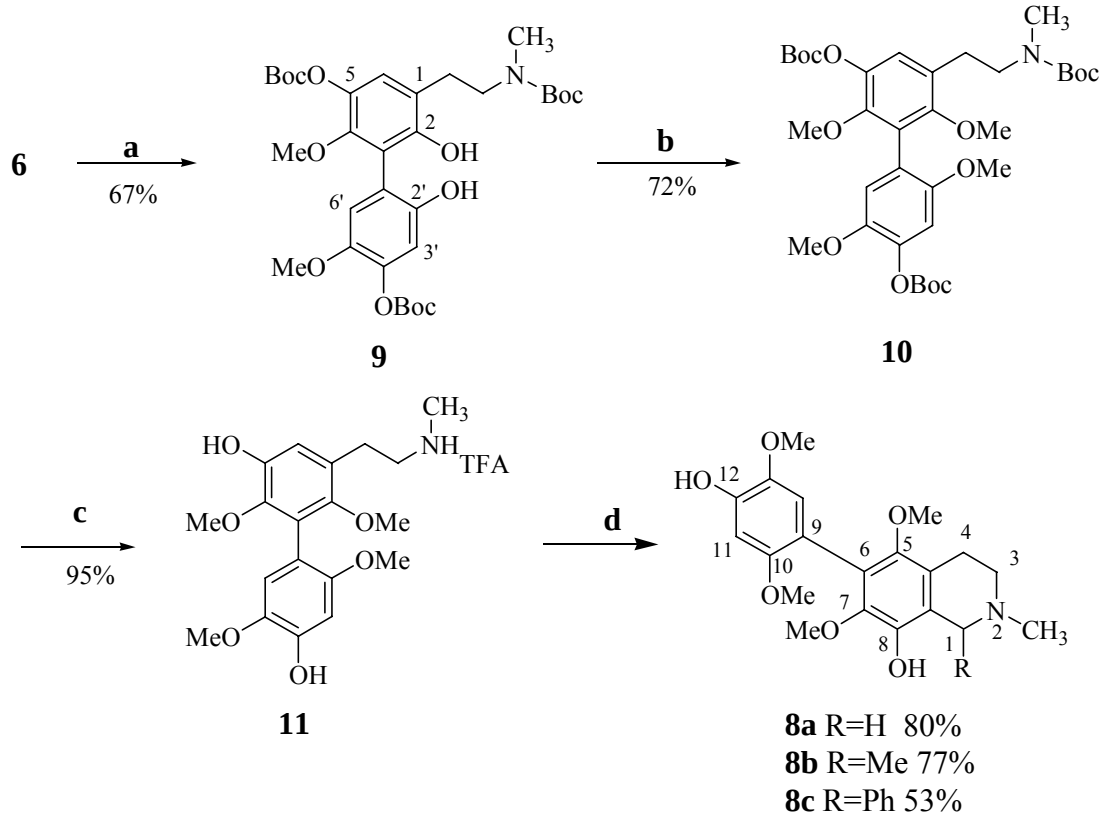


Reagents: a) 1N NH_4OAc-EtOH (1:1), Δ, 24 h; b) $(Boc)_2O$, NaOH, MeOH, rt; c) (1) O_3, CH_2Cl_2-MeOH, -78 °C, (2) $(NH_2)_2CS$, rt; d) TFA-CH_2Cl_2 (4:1), rt, 2.5 h; e) $NaBH_4$, MeOH, rt.

Scheme 1

6-Phenyltetrahydroisoquinolines (**8a-c**) were prepared, following the approach as depicted in Scheme *2*. Baeyer-Villiger reaction of the dialdehyde (**6**) and subsequent alkaline hydrolysis[5] of the resultant diformate ester gave the biphenol product (**9**) in 67% yield. The ESIMS spectrum of **9** showed $(M+Na)^+$ at *m/z* 658 and its ^1H NMR spectrum showed the absence of signals for two aldehydic protons. *O*-Methylation of **9** by reacting with dimethyl sulfate and potassium carbonate under reflux gave **10** in 72% yield, δ 3.24 and 3.66 (2 x OMe). Treatment of **10** with TFA in dichloromethane afforded the TFA salt of a diphenolic 3-arylphenethylamine (**11.**TFA), which was purified by a Sephadex LH-20 column.

The free base of **11** is not stable in the air and thus was characterized as TFA salt, δ_{NMe} 2.72. HRFABMS spectrum showed a quasi- molecular ion $(M+H)^+$ at *m/z* 364.1762, consistent with that calculated for $C_{19}H_{26}NO_6$.

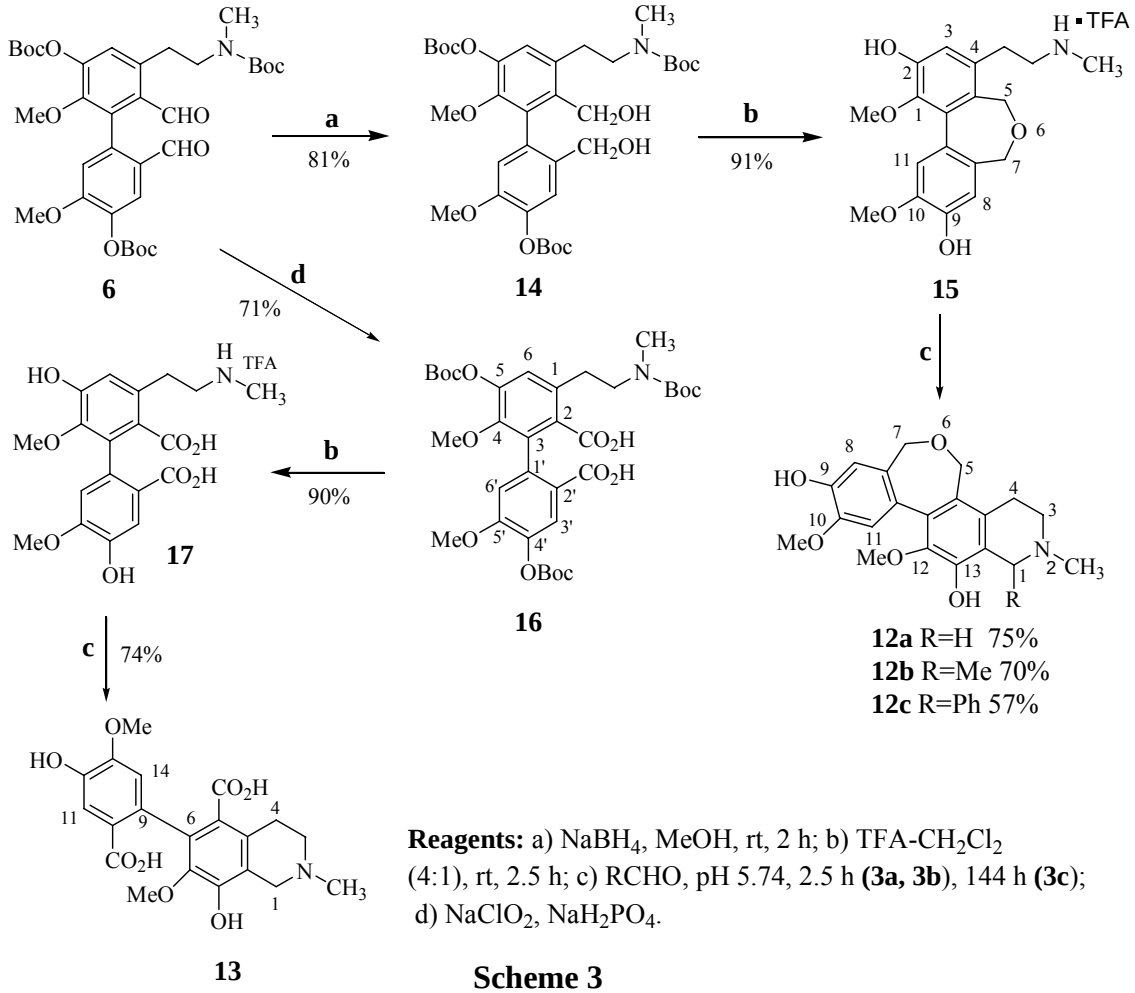


Reagents: a) (1) MCPBA, CH_2Cl_2, rt; (2) NaOH, MeOH, rt; b) Me_2SO_4/K_2CO_3, EtOH, ¡µ, 24 h; c) TFA-CH_2Cl_2 (4:1), rt, 2.5 h; d) RCHO, pH 5.74, 2.5 h (**8a, 8b**) or 6 days (**8c)**

Scheme 2

Pictet-Spengler reaction of **11** with varieties of aldehydes (HCHO, MeCHO, PhCHO) under the acetate buffer conditions (pH 5.74) yielded the respective products (**8a-c**) (80%, 77%, 53%). The production of **8c** required longer reaction time (144 h) due to the steric and electronic effect caused by the 1-phenyl and 2-OH groups. Comparing to that of **11**, the ^{1}H NMR spectrum of **8a** lacked an aromatic signal but showed an additional AB system ($\delta_{H\text{-}1}$ 3.62 and 3.57, each d, J_{AB} = 15.8 Hz). This structure was further supported by nuclear Overhauser effect difference (NOED) experiments, showing the following correlations: H-11 (δ 6.63). 10-OMe (δ 3.64) (10.9%), 13-OMe (δ 3.80). H-14 (δ 6.72) (10.5%), 7-OMe (δ 3.36). H-14

(2.3%), and 5-OMe (δ 3.31)→ H-4 (δ 2.86) (4.3%). The HREIMS spectrum of **8a** displayed a molecular ion $(M)^+$ at *m/z* 375.1680, confirming the expected formula of $C_{20}H_{25}NO_6$. Both compounds (**8b**) and (**8c**) contain two chiral centers, one at C-1 and the other formed by the biphenyl moiety, giving rise to four stereo-isomers for each compound. This fact is reflected by their ^{1}H NMR spectra displaying two sets of signals for the diastereomeric pair. Attempts to separate these two diastereomers by conventional chromatographic techniques were made but all failed.



Scheme 3

Compounds (**12a-c**) and (**13**) were prepared as shown in Scheme 3. Reduction of **6** with $NaBH_4$ yielded **14** (81%), whose ^{1}H NMR spectrum showed two ABX systems for protons of benzylic hydroxy group, one at δ 5.02 (t, *J* = 4.8 Hz, 2'-CH_2OH), 4.17 (dd) and 4.07 (dd) (each *J* = 4.8, 11.2 Hz, 2'-CH_2OH), the other at δ 4.75 (t, *J* = 4.6 Hz, 2-CH_2OH), 4.10 (dd) and 3.98 (dd) (each *J* = 4.6, 13.1 Hz, 2-CH_2OH). Removal of Boc groups from **14** by treating with TFA in CH_2Cl_2 afforded **15** in 91% yield, whose ^{1}H

NMR spectrum displayed the absence of signals from Boc groups and the presence of two AX systems (δ_{H-5} 4.61 and 3.75, J_{AX} = 12.1 Hz; δ_{H-7} 4.36 and 3.99, J_{AX} = 11.1 Hz) instead of two ABX systems in the spectrum of **14**. The latter could indicate the formation of a dibenzo[*c*,*e*]oxepine moiety from two benzylic alcohols by losing one molecule of water under a relatively strong acidic condition. This is the case since the HRFABMS spectral analysis provided a molecular formula $C_{19}H_{23}NO_5$ for **15**, short of a H_2O unit as predicted simply for a Boc-deprotected product. This suggestion was confirmed by analysis of an HMBC plot (Figure 1), which displayed three-bond couplings of H-5 (α and β) to C-7, and H-7 (α and β) to C-5.

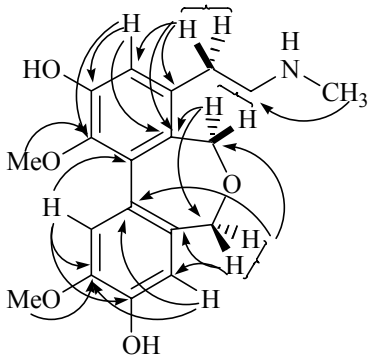


Figure 1. HMBC (right) data of **15**

Pictet-Spengler cyclization of **15** with varieties of aldehyde under the similar condition as described for **8a-c** yielded the product (**12a-c**) (75%, 70%, 57%), respectively. The ^{1}H NMR spectrum of **12a** showed the absence of one aryl proton signal but the presence of an additional AB system (H-1's, δ 3.81 and 3.53, each d, J = 15.8 Hz) relative to that of **15**. HRFABMS spectrum indicated a molecular formula $C_{20}H_{23}NO_5$ for **15**, consistent with that for the predicted tetrahydroisoquinoline product. Similar to that discussed for **8b-c**, both compounds (**12b**) and (**12c**) possess two chiral centers and their ^{1}H NMR spectra revealed two sets of signals. The identities of **12b-c** were also confirmed by analysis of their ^{1}H NMR, ^{13}C NMR and HRFABM spectral data as listed in EXPERIMENTAL. Oxidation of the benzylic alcohols in **6** by sodium chlorite[6] gave the dibenzoic acid (**16**) in 71% yield. The ESIMS spectrum of **16** showed a quasi-molecular ion $(M+H)^+$ at *m/z* 692 and its ^{1}H NMR spectrum showed the absence of signals for two formyl protons. Boc deprotection of **16** by TFA in CH_2Cl_2 afforded **17** in 90% yield, whose ^{1}H NMR spectrum showed the absence of signals for three Boc groups. Pictet-Spengler reaction of **17** with

formaldehyde yielded **13** (74%), which was purified by passing through an Amberlite XAD-2 column. The structure of **13** was confirmed by its ^{1}H NMR spectrum, $\delta_{H\text{-}1}$ 4.02 (2H, s), ^{13}C NMR, δ_{COOH} 171.7 (s) and 171.2 (s), and HRFABMS spectrum, providing a molecular formula $C_{20}H_{22}NO_8$.

To the best of our knowledge, this study provides a facile preparation of four tetrahydroisoquinolines from boldine. The anti-AChE activity of these compounds was evaluated by colorimetric method.[7] This result indicated that **8a-c**, **12a-c**, **13** are all inactive against AChE. This might be due to the destruction of coplanar structure of phenanthrene moiety in the active **1**. The replacement by a biphenyl structure, whose torsion angle is 110^o based on a molecular modeling study, might give rise to a steric hindrance for binding to AChE. In a previous study it was reported that 8-phenyltetrahydroisoquinoline possessed anti-psychotic effect[8] which provides an additional biological aspect for **2a**.

EXPERIMENTAL

The physical and spectral data of prepared compounds were obtained from the following instruments: Fisher-Johns melting point apparatus (uncorrected); JEOL JMX-HX110 (HREIMS and HRFABMS), JMS-SX102A (EIMS and FABMS) and Finnigan Mat TSQ-7000 (ESIMS) mass spectrometers; Bruker AMX-400 spectrometers using solvent peak as reference standard.

Secoboldine (4). The mixture of boldine (**3**) (32.00 g, 97.86 mmol), EtOH (700 mL) and 1M NH_4OAc (700 mL) was heated under reflux overnight and cooled to rt. The pure crystalline product (**4**) (25.00 g, 79%), mp 123-124 °C (lit., 120-121 ^{o}C),[3] was collected by suction.

***O,O,N*-Tri-*t*-butoxycarbonylsecoboldine (5):** $(Boc)_2O$ (65 mL, 274.16 mmol) was added dropwise to the mixture of **4** (20.00 g, 61.16 mmol), NaOH (7.34 g, 183.48 mmol) and MeOH (650 mL) under nitrogen. The reaction mixture was stirred at rt for 24 h. The white precipitate formed was collected by filtration and was washed with H_2O, and finally recrystallized from MeOH to afford **5** (27.61 g, 72%): R_f 0.5 ($CHCl_3$); mp 150-152 °C (MeOH); IR ν: 2979, 1764, 1701, 1464, 1249 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 333 K) δ 9.12 (1H, s, H-5), 7.96 (1H, d, *J*= 9.1 Hz, H-10), 7.82 (1H, d, *J*= 9.1 Hz, H-9), 7.81 (1H, s, H-8), 7.38 (1H, s, H-2), 3.99 (3H, s, 6-OMe), 3.88 (3H, s, 4-OMe), 3.49 (2H, t, *J*=7.2 Hz, H-11), 3.25 (2H, t, *J*=7.2 Hz, H-12), 2.78 (3H, s, N-CH_3), 1.54 and 1.52 (each 9H, s, OBoc-Me), 1.25 (9H, s,

NBoc-Me); ESIMS *m/z* $(M+Na)^+$ 650 (30), 572 (100), 516 (22), 288 (15).

5-*t*-Butoxycarbonyloxy-3-(4-*t*-butoxycarbonyloxy-2-formyl-5-methoxyphenyl)-*N*-*t*-butoxycarbonyl-2-formyl-4-methoxy-*N*-methylphenethylamine (6): The mixture of **5** (12.00 g, 19.14 mmol), CH_2Cl_2 (160 mL) and MeOH (160 mL) was cooled to –78 °C and then treated with ozone until all the starting material were gone. After addition of $(NH_2)_2CS$ (3.00 g, 39.41 mmol) to the above solution, the reaction mixture was warmed to rt for 30 min, washed with 1% $NaHCO_3$ (50 mL x 3) and dried over Na_2SO_4. The organic solvents were then removed under reduced pressure and the concentrate was purified by a silica gel column (20% EtOAc/*n*-Hexane) to give pure oil (**6**, 10.34 g, 82%): R_f 0.24 ($CHCl_3$); IR ν: 2931, 1763, 1695, 1508, 1473, 1274 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 333 K) δ 9.79 (1H, s, -CHO), 9.52 (1H, s, CHO), 7.71 (1H, s, H-3'), 7.29 (1H, s, H-6'), 7.09 (1H, s, H-6), 3.87 (3H, s, 5'-OMe), 3.45-3.42 (2H, m, 1-$CH_2C\underline{H}_2$-N), 3.38 (3H, s, 4-OMe), 3.21-3.12 (2H, m, 1-$C\underline{H}_2CH_2$), 2.77 (3H, s, N-$C\underline{H}_3$), 1.50 and1.48 (each 9H, s, OBoc-Me), 1.35 (9H, s, NBoc-Me); ESIMS *m/z* $(M+Na)^+$ 682 (100), $(M+H)^+$ 660 (18), 560 (40).

8-(2-Formyl-4-hydroxy-5-methoxyphenyl)-6-Hydroxy-7-methoxy-2-methyl-3,4-dihydroisoquinolinium hydroxide (7): To a solution of **6** (1.00 g, 3.30 mmol) in CH_2Cl_2 (20 mL) was added TFA (5 mL) and the reaction solution was stirred at rt for 3.5 h. After removal of the organic solvent, the residue was basified with 37% NH_4OH, followed by extracted with isopropanol-$CHCl_3$ (1:3, 50 mL x 4). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to afford essentially pure **7** (926 mg, 82%). R_f: 0.32 (20% MeOH/$CHCl_3$); mp: 210-212 °C (MeOH); IR ν: 2360, 1673, 1572, 1406, 1323, 1290, 1168 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.43 (1H, s, 10-CHO), 7.94 (1H, s, H-1), 7.35 (1H, s, H-11), 6.82 (1H, s, H-14), 6.77 (1H, s, H-5), 3.84 (3H, s, 13-OMe), 3.78 (2H, t-like, *J*= 8.0 Hz, H-3), 3.37 (3H, s, NCH_3), 3.38 (3H, s, 7-OMe), 3.12 (2H, t-like, *J*= 8.0 Hz, H-4); ^{13}C-NMR (50 MHz, DMSO-d_6) δ 190.3 (s, 2'-CHO), 163.5 (s), 160.4 (d), 152.7 (s), 147.4 (s), 145.9 (s), 136.1 (s), 135.9 (s), 129.2 (s), 127.9 (s), 117.7 (d), 115.2 (d), 114.0 (d), 113.4 (s), 59.8 (q), 56.4 (q), 48.7 (t, C-3), 46.3 (q, 2-Me), 25.8 (C-4, t); HRFABS Calcd for $C_{19}H_{20}NO_5$ (M-OH) 342.1341, Found 342.1346.

8-(4-Hydroxy-2-hydroxymethyl-5-methoxyphenyl)-6-Hydroxy-7-methoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (2): To a solution of **7** (500 mg, 1.39 mmol) in MeOH (10 mL) was added $NaBH_4$ (131 mg, 3.48 mmol). The reaction mixture was stirred at rt for 2 h, neutralized with 2N HCl and extracted with $CHCl_3$ (50 mL x 3). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give a residue, which was purified by a silica gel column (1-5% MeOH/$CHCl_3$) to give pure oil (**2**, 373 mg, 78%): R_f : 0.18 (20% MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (1H, d, *J*= 3.4 Hz, H-11), 6.68 (1H, s, H-14), 6.63 (1H, s, H-5), 4.13 and 4.09 (2H, d, *J*= 11.9 Hz, 10-C$\underline{H_2}$OH), 3.82 (3H, s, 13-OMe), 3.36 (3H, s, 7-OMe), 3.13 (1H, d, *J*= 15.2 Hz, H-1_a), 2.99 (1H, d, *J*= 15.2 Hz, H-1_b), 2.93-2.90 (1H, m, H-4), 2.84-2.78 (1H, m, H-4), 2.76-2.72 (1H, m, H-3), 2.57-2.52 (1H, m, H-3), 2.30 (3H, s, N-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3 (s), 146.3 (s), 145.6 (s), 142.8 (s), 132.4 (s), 131.4 (s), 130.8 (s), 125.6 (s), 124.8 (s), 116.0 (d), 115.2 (d), 112.2 (d), 62.9 (t, 10-CH_2OH), 61.1 (q, 7-OMe), 56.1 (q, 13-OMe), 55.9 (t, C-1), 52.4 (t, C-3), 45.9 (q, 2-Me), 28.9 (t, C-4); HRFABMS Calcd for $C_{19}H_{24}NO_5$ (M+H) 346.1655, Found 346.1650.

5-*t*-Butyoxycarbonyloxy-3-(4-*t*-butoxycarbonyloxy-2-hydroxy-5-methoxyphenyl)-2-hydroxy-4-methoxy-*N*-*t*-butoxycarbonyl-*N*-methylphenethylamine (9): To a solution of **6** (10.00 g, 15.17 mmol) in dry CH_2Cl_2 (200 mL) was added MCPBA (70%**,**14.96 g, 60.67 mmol) and the resulting solution was stirred at rt under nitrogen for 24 h. An excessive amount of saturated $NaHSO_3$ was added the reaction mixture until no remains of MCPBA checked by potassium iodide-starch paper. After an addition of 2M NaOH (70 mL) and MeOH (70 mL), the mixture was stirred for 0.5 h and adjusted to pH about 7 with 1M HCl, and then extracted with $CHCl_3$ (100 mL x 3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue obtained was purified by a silica gel column ($CHCl_3$) to give pure **9** (6.46 g, 67%): R_f 0.69 (1.5% MeOH/$CHCl_3$); mp 80-83 °C (MeOH); IR ν: 2979 (s), 1762 (s), 1668 (s), 1478 (s), 1249 (s), 1145 (s) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 333 K) δ 7.23 (1H, s, H-6'), 7.05 (1H, s, H-3'), 6.90 (1H, s, H-6), 3.76 (3H, s, 5'-OMe), 3.43 (2H, t, *J*= 7.3 Hz, 1-C$\underline{H_2}$-CH_2), 3.35 (3H, s, 4-OMe), 2.93 (2H, t, *J*= 7.3 Hz, CH_2-C$\underline{H_2}$-N), 2.77 (3H, s, N-CH_3), 1.50 and 1.48 (each 9H, s, OBoc-Me), 1.39 (9H, s, NBoc-Me; ESIMS: *m/z* $(M+Na)^+$ 658 (50), 630 (35), 580 (100).

5-*t*-Butoxycarbonyloxy-3-(4-*t*-butoxycarbonyloxy-2,5-dimethoxyphenyl)-2,4-dimethoxy-*N*-butoxycarbonyl-*N*-methylphenethylamine (10): To the mixture of **9** (2.80 g, 4.41 mmol), K_2CO_3 (1.52 g, 11.03 mmol) and acetone (50 mL) was added Me_2SO_4 (2.5 mL, 26.36 mmol) and the resulting solution was heated to reflux under nitrogen for 24 h. After removal of the organic solvent, the residue was dissolved in H_2O (50 mL) and extracted with $CHCl_3$ (50 mL x 3). The combined $CHCl_3$ layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue obtained was purified by a silica gel column (22% EtOAc/*n*-Hexane) to give **10** (2.10 g, 72%): R_f 0.73 (1.5% MeOH/$CHCl_3$); mp 56-58 °C (MeOH); IR ν: 2977, 1760, 1696, 1510, 1474, 1420, 1393 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 313 K) δ 7.02 (1H, s, H-6'), 6.98 (1H, s, H-3'), 6.88 (1H, s, H-6), 3.71 (3H, s, 5'-OMe), 3.66 (3H, s, OMe), 3.42 (3H, s, OMe), 3.38 (2H, t, *J*=6.2 Hz, 1-C$\underline{H}_2$-CH_2), 3.24 (3H, s, 2-OMe), 2.78 (3H, s, N-CH_3), 2.93 (2H, t, *J*=6.2 Hz, 1-CH_2-C$\underline{H}_2$-N) 1.49 and 1.48 (each 9H, s, OBoc-Me), 1.35 (9H, s, NBoc-Me); ESIMS *m/z* $(M+Na)^+$ 686 (50), 608 (100), 552 (30).

2,4-Dimethoxy-5-hydroxy-3-(4-hydroxy-2,5-dimethoxyphenyl)-*N*-methylphenethylamine TFA salt (11): The mixture of **10** (2.10 g, 3.16 mmol), TFA (8 mL) and CH_2Cl_2 (32 mL) were stirred at rt for 2.5 h. After removal of the organic solvent, the residue was purified by a Sephadex LH-20 column (50% MeOH/H_2O) to give oil (**11**, 1.43 g, 95%): R_f 0.26 (10% MeOH/$CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 6.75 (1H, s, H-6'), 6.74 (1H, s, H-3'), 6.63 (1H, s, H-6), 3.79 (3H, s, 5'-OMe), 3.69 (3H, s, 2'-OMe), 3.45 (3H, s, 4-OMe), 3.33 (3H, s, 2-OMe), 3.22 (2H, t, *J*=7.0 Hz, 1-CH_2-C$\underline{H}_2$-N), 2.92 (2H, t, *J*=7.0 Hz, 1-C$\underline{H}_2$-CH_2), 2.72 (3H, s, N-CH_3); HRFAB Calcd for $C_{19}H_{26}NO_6$ (M-TFA+H) 364.1760, Found 364.1762.

8-Hydroxy-6-(4-hydroxy-2,5-dimethoxyphenyl)-5,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (8a): The mixture of **11** (200 mg, 0.42 mmol), MeOH (15 mL), 0.1N AcOH (6 mL), 1N NaOAc (6 mL) and 37% HCHO (3 mL, 39.96 mmol) in a 50 mL round bottom flask was stirred at rt for 2.5 h. After removal of MeOH, the aqueous residue was neutralized with 25% NH_4OH and extracted with $CHCl_3$ (30 mL x 3) .The combined $CHCl_3$ layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue obtained was purified by a silica gel column (5% MeOH/$CHCl_3$) to give amorphous solid (**8a**, 120 mg, 80%): R_f 0.55 (10% MeOH/$CHCl_3$); mp 88-90 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.72

(1H, s, H-14), 6.63 (1H, s, H-11), 3.80 (3H, s, 13-OMe), 3.64 (3H, s, 10-OMe), 3.62 (1H, d, *J*= 15.8 Hz, H-1a), 3.57 (1H, *J*= 15.8 Hz, H-1b), 3.36 (3H, s, 7-OMe), 3.31 (3H, s, 5-OMe), 2.86 (2H, t, *J*= 5.7 Hz, H-4), 2.66 (2H, t, *J*= 5.7 Hz, H-3), 2.49 (3H, s, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9 (s), 148.8 (s), 146.2 (s), 142.7 (s), 141.1 (s), 140.6 (s), 123.1 (s), 122.6 (s), 121.1 (s), 114.5 (d), 113.4 (s), 99.8 (d), 60.6 (q), 60.0 (q), 56.5 (q), 56.2 (q), 52.6 (t), 52.0 (t), 45.9 (q, 2-Me), 23.9 (t, C-3); HREIMS Calcd for $C_{20}H_{25}NO_6$ (M) 375.1682, Found 375.1680.

8-Hydroxy-6-(4-hydroxy-2,5-dimethoxyphenyl)-5,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydro-isoquinoline (8b): The mixture of **11** (132 mg, 0.28 mmol), 0.1N AcOH (4.5 mL), 1N NaOAc (4.5 mL) and acetaldehyde (15 mL, 265.91 mmol) in a 50 mL round bottom flask was stirred at rt for 2.5 h. Following the work-up and separation similar to that described for **8a** gave amorphous solid (**8b**, 83 mg, 77%): R_f 0.31 (10% MeOH/$CHCl_3$); mp 80-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 and 6.72 (1H, s, H-14), 6.66 (s) and 6.65 (s) (1H, H-11), 4.06 (1H, q, *J*= 6.4 Hz, H-1), 3.80 (3H, s, 13-OMe), 3.72 (s) and 3.37 (s) (3H, 10-OMe), 3.37 (s) and 3.36 (s) (3H, 7-OMe), 3.31 (3H, s, 5-OMe), 3.08-3.06 (1H, m, H-4), 2.87-2.84 (1H, m, H-4), 2.82-2.54 (2H, m, H-3), 2.54 (s) and 2.53 (s) (3H, 2-Me), 1.42 (d) and 1.40 (d) (3H, *J*=6.7 Hz, 1-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9 (s) and 151.8 (s), 148.7 (s), 146.3 (s), 143.5 (s), 141.7 (s), 140.5 (s) and 140.4 (s), 123.4 (s), 122.6 (s), 122.3 (s), 120.5 (s) and 120.4 (s), 114.4 (d) and114.2 (d), 113.0 (s), 99.8 (d), 60.6 (q), 59.8 (q), 56.5 (q), 56.3 (q) and 56.2 (q), 54.2 (q), 43.6 (t), 40.4 (q) and 40.3 (q), 22.8 (q), 19.3 (t) and 19.2 (t), 16.4 (q) and 16.3 (q); HREIMS Calcd for $C_{21}H_{27}NO_6$ (M) 389.1838, Found 389.1832.

8-Hydroxy-6-(4-hydroxy-2,5-dimethoxyphenyl)-5,7-dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetra-hydroisoquinoline (8c): The mixture of **11** (156 mg, 0.33 mmol), MeOH (20 mL), 0.1N AcOH (6 mL), 1N NaOAc (6 mL) and benzaldehyde (1 mL, 9.23 mmol) in a 50 mL round bottom flask was stirred at rt for 144 h. Following the work-up and separation similar to that described for **8a** gave amorphous solid (**8c**, 100 mg, 53%): R_f 0.55 (3% MeOH/$CHCl_3$); mp 90-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (5H, m, 1-C_6H_5), 6.77 (s) and 6.73 (s) (1H, H-14), 6.66 (s) and 6.65 (s) (1H, H-11), 4.80 (s) and 4.78 (s) (1H, H-1), 3.83 (s) and 3.81 (s) (3H, 13-OMe), 3.71 (s) and 3.69 (3H, 10-OMe), 3.41 (s) and 3.38 (s) (3H,

7-OMe), 3.29 and 3.28 (3H, s, 5-OMe), 2.95-2.93 (2H, m, H-4), 2.92-2.89 (1H, m, H-3), 2.65-2.63 (1H, m, H-3), 2.37 (s) and 2.36 (s) (3H, 2-Me); ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.4 (s) and 152.3 (s), 149.1 (s) and 149.0 (s), 146.6 (s), 143.6 (s), 142.3 (s), 140.9 (s) and 140.8 (s), 140.2 (s) and 139.8 (s), 130.4 (d) and 130.3 (d), 130.0 (d), 128.3 (d) and 128.2 (d), 127.9 (d) and 127.8 (d), 123.9 (s) and 123.8 (s), 123.7 (s) and 123.6 (s), 123.4 (s), 122.9 (s), 115.0 (d) and 114.8 (d), 114.0 (s), 100.3 (d) and 100.2 (d), 63.6 (q), 61.1 (q) and 61.1 (q), 60.7 (q) and 60.6 (q), 57.1 (q), 56.8 (q) and 56.7 (q), 46.4 (t), 56.8 (q) and 56.7 (q), 46.2 (t), 42.7 (q) and 42.6 (q), 22.5 (t) and 22.4 (t); HREIMS Calcd for $C_{21}H_{27}NO_6$ (M) 451.1995, Found 451.1997.

5-*t*-Butoxycarbonyloxy-3-(4-*t*-butoxycarbonyloxy-2-hydroxymethyl-5-methoxyphenyl)-2-hydroxymethyl-4-methoxy-*N*-*t*-butoxycarbonyl-*N*-methylphenethylamine (14): To a solution of **6** (3.00 g, 4.55 mmol) in MeOH (45 mL) was added $NaBH_4$ (344 mg, 9.09 mmol) portionwise and the resulting solution was stirred at rt under nitrogen for 2 h. After removal of organic solvent, the reaction mixture was partitioned between $CHCl_3$ (100 mL) and water (50 mL x 3). The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a residue, which was purified by a silica gel column (50% EtOAc/ *n*-Hexane) to give **14** (2.44 g, 81%): R_f 0.51 (3% MeOH/$CHCl_3$); mp 80-84 °C (MeOH); IR ν: 3410, 2978, 1762, 1687, 1473, 1274, 1151 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 333 K) δ 7.23 (1H, s, H-6'), 7.05 (1H, s, H-3'), 6.90 (1H, s, H-6), 5.02 (1H, t, *J*= 4.8 Hz, 2'-CH_2O<u>H</u>), 4.75 (1H, t, *J*= 4.6 Hz, 2-CH_2O<u>H</u>), 4.17 (1H, dd, *J*= 4.8, 11.2 Hz, 2'-C<u>H</u>$_2$OH), 4.10 (1H, dd, *J*= 4.6, 13.1 Hz, 2-C<u>H</u>$_2$OH), 4.07 (1H, dd, *J*= 4.8, 11.2 Hz, 2'-C<u>H</u>$_2$OH), 3.98 (1H, dd, *J*= 4.6, 13.1 Hz, 2-C<u>H</u>$_2$OH), 3.76 (3H, s, 5'-OMe), 3.41 (2H, t, *J*= 7.6 Hz, 1-C<u>H</u>$_2$CH$_2$), 3.34 (3H, s, 4-OMe), 2.92 (2H, t, *J*= 7.6 Hz, 1-CH$_2$C<u>H</u>$_2$N), 2.76 (3H, s, N-CH_3), 1.49 and 1.48 (each 9H, s, OBoc-Me), 1.38 (9H, s, NBoc-Me); ESIMS *m/z* $(M+Na)^+$ 686 (30), 546 (100).

2,9-Dihydroxy-1,10-dimethoxy-4-[2-(methylamino)ethyl]-5,7-dihydrodibenzo[*c*,*e*]oxepine TFA salt (15): The mixture of **14** (1.40 g, 2.11 mmol), TFA (4 mL) and CH_2Cl_2 (16 mL) was stirred at rt for 2.5 h. Following the separation procedure similar to **11** gave oil (**15**, 880 mg, 91%): R_f 0.24 (3% MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 7.31 (1H, s, H-11), 6.89 (1H, s, H-8), 6.86 (1H, s, H-3), 4.61 (1H, d, *J*=

12.1 Hz, H-5_a), 4.36 (1H, d, *J*= 11.1 Hz, H-7_a), 3.99 (1H, d, *J*= 11.1 Hz, H-7_b), 3.88 (3H, s, 10-OMe), 3.75 (1H, d, *J*= 12.1 Hz, H-5_b), 3.41 (3H, s, 1-OMe), 3.27-3.25 (1H, m) and 3.18-3.17 (1H, m) (4-$CH_2C\underline{H}_2N$), 3.15-3.13 (1H, m) and 2.96-2.94 (1H, m) (4-$C\underline{H}_2CH_2$), 2.72 (3H, s, 2-CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 151.8 (s), 148.8 (s), 147.9 (s), 144.7 (s), 136.6 (s), 132.4 (s), 129.7 (s), 129.4 (s), 126.5 (s), 118.4 (d), 117.0 (d), 113.9 (d), 67.7 (t), 62.7 (t), 60.3 (q), 56.6 (q), 51.4 (t), 33.7 (q), 30.9 (t); HRFABS Calcd for $C_{19}H_{24}NO_5$ (M-TFA+H) 346.1654, Found 346.1658.

9,13-Dihydroxy-10,12-dimethoxy-2-methyl-1,2,3,4,5,7-hexahydrobenzoxepino[*12a,5a,f*]isoquinoline (12a): The mixture of **15** (150 mg, 0.33 mmol), MeOH (20 mL), 0.1N AcOH (6 mL), 1N NaOAc (6 mL) and 37% HCHO (3 mL, 39.96mmol) in a 50 mL round bottom flask was stirred at rt for 2.5 h. Following the work-up and purification similar to that described for **8a** gave amorphous solid (**12a**, 88 mg, 75%): R_f 0.41 (10% MeOH/$CHCl_3$); mp 140-146 °C; ^{1}H NMR (400 MHz, CD_3OD,) δ 7.34 (1H, s, H-11), 6.88 (1H, s, H-8), 4.66 (1H, d) and 3.68 (1H, d) (*J*= 11.9 Hz, H-5), 4.33 (1H, d) and 3.96 (1H, d) (*J*= 11.0 Hz, H-7), 3.89 (3H, s, 10-OMe), 3.81 (1H, d, *J*= 15.8 Hz, H-1_a), 3.53 (1H, d, *J*= 15.8 Hz, H-1_b), 3.32 (3H, s, 1-OMe), 3.00-2.98 (2H, m, H-4), 2.94-2.92 (1H, m) and 2.70-2.69 (1H, m) (H-3), 2.53 (3H, s, 2-CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 148.9 (s), 147.9 (s), 147.8 (s), 143.2 (s), 134.2 (s), 129.6 (s), 129.5 (s), 128.1 (s), 125.7 (s), 120.5 (s), 117.1 (d), 113.7 (d), 74.4 (t), 67.8 (t), 62.2 (t), 60.4 (q), 56.6 (q), 53.4 (t), 53.0 (t), 44.9 (q), 26.1 (t); HRFABS Calcd for $C_{20}H_{24}NO_5$ (M+H) 358.1655, Found 358.1663.

9,13-Dihydroxy-10,12-dimethoxy-1,2-dimethyl-1,2,3,4,5,7-hexahydrobenzoxepino[*12a,5a,f*]isoquinoline (12b): The mixture of **15** (140 mg, 0.31 mmol), 0.1N AcOH (4.5 mL), 1N NaOAc (4.5 mL) and acetaldehyde (15 mL, 265.91 mmol) in a 50 mL round bottom flask was stirred at rt for 2.5 h. Following the work-up and purification similar to that described for **8a** gave amorphous solid (**12b**, 79 mg, 70%): R_f 0.44 (10% MeOH/$CHCl_3$); mp 226-230 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (s) and 7.36 (s) (1H, H-11), 6.94 (1H, s, H-8), 4.75 (d) and 4.73 (d) (1H, *J*= 11.8 Hz, H-5_a), 4.39 (d) and 4.38 (d) (1H, *J*= 11.0 Hz, H-7_a), 4.22 (q) and 4.17 (q) (1H, *J*= 6.5 Hz, H-1), 4.03 and 4.00 (1H, *J*= 11.0 Hz, H-7_b), 3.94 (3H, s, 10-OMe), 3.81 and 3.72 (1H, d, *J*= 11.8 Hz, H-5_b), 3.39 (3H, s, 1-OMe), 3.22-3.19 (1H, m, 1H, H-4a), 3.05-3.02 (1H, m, H-4_b), 2.94-2.91 (2H, m, H-3), 2.55 (s) and 2.53 (s) (3H, 2-Me), 1.44 (d) and 1.43 (d)

(3H, *J*= 6.5 Hz, 1-Me); ^{13}C NMR (100 MHz, DMSO-d_6); δ 147.2 (s), 146.4 (s), 141.6 (s), 131.4 (s), 128.2 (s), 127.7 (s), 124.3 (s), 124.1 (s), 116.4 (s), 116.3 (d), 112.9 (d), 112.8 (d), 66.1 (t), 60.9 (t) and 60.8 (t), 59.9 (q) and 59.8 (q), 53.9 (q) and 53.3 (q), 45.7 (t), 43.8 (t), 42.3 (d) and 41.6 (d), 24.4 (t) and 23.4 (t), 15.6 and 15.0 (q); HRFABS *m/z* Calcd for $C_{21}H_{26}NO_5$ (M+H) 372.1811, Found 372.1809.

9,13-Dihydroxy-10,12-dimethoxy-2-methyl-1-phenyl-1,2,3,4,5,7-hexahydrobenzoxepino[*12a,5a,f*]-isoquinoline (12c). The mixture of **15** (113 mg, 0.25 mmol), MeOH (13 mL), 0.1N AcOH (4 mL), 1N NaOAc (4 mL) and benzaldehyde (1.5 mL, 13.85 mmol) in a 25 mL round bottom flask was stirred at rt for 144 h. Following the work-up and purification similar to that described for **8a** gave amorphous solid (**12c**, 61 mg, 57%): R_f 0.49 (10% MeOH/$CHCl_3$); mp 240-245 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.42-7.21 (5H, m, 1-C_6H_5), 7.20 (s) and 7.18 (s) (1H, H-11), 6.97 (s) and 6.96 (s) (1H, H-9), 5.17 (s) and 5.01 (s) (1H, s, H-1), 4.84 (d) and 4.83 (d) (1H, *J*= 11.9 Hz, H-5_a), 4.46 (d) and 4.42 (d) (1H, *J*= 11.0 Hz, H-7_a), 4.39 (d) and 4.38 (d) (1H, *J*= 11.0 Hz, H-7_b), 3.99 and 3.91 (3H, s, 10-OMe), 3.84 (d) and 3.78 (d) (1H, *J*= 11.9 Hz, H-5_b), 3.35 (s) and 3.31 (s) (3H, 1-OMe), 3.26-3.13 (1H, m, H-4_a), 3.03-2.99 (1H, m, H-4_b), 2.76-2.74 (2H, m, H-3), 2.40 (3H, s, 2-Me); ^{13}C NMR (50 MHz, DMSO-d_6) δ 147.7 (s), 147.1 (s), 146.8 (s), 142.3 (s), 141.9 (s), 141.2 (s), 132.3 (s), 130.2 (d), 129.9 (d), 129.4 (s), 128.6 (d), 127.8 (d), 126.9 (s), 126.0 (s), 124.4 (s), 124.2 (s), 116.8 (d), 113.2 (d), 66.6 (t), 64.3 (q) and 62.4 (q), 61.5 (t) and 61.2 (t), 60.4 (q) and 60.2 (q), 56.2 (d), 47.5 (t) and 44.8 (t), 43.0 (q) and 42.4 (q), 25.7 (t) and 24.0 (t); HRFABS Calcd for $C_{26}H_{28}NO_5$ (M+H) 434.1968, Found 434.1958.

5-*t*-Butoxycarbonyloxy-3-(4-*t*-butoxycarbonyloxy-2-carboxyl-5-methoxyphenyl)-2-carboxy-4-methoxy-*N*-butoxycarbonyl-*N*-methylphenethylamine (16): To a solution of **6** (1.50 g, 2.28 mmol) in *t*-BuOH (75 mL) was added 2-methyl-2-butene (13.5 mL). A 30 mL aqueous solution of $NaClO_2$ (2.51 g, 29.22 mmol) and NaH_2PO_4-H_2O (2.51 g, 7.26 mmol) was added dropwise to the above solution over a period of 20 min and the mixture was stirred at rt for overnight. The *t*-BuOH was removed under reduced pressure and then the residue was partitioned between $CHCl_3$ (50 mL) and water (30 mL x 3). The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated to give a residue, which was purified by a silica gel column (5% MeOH/$CHCl_3$) to give **16** (1.12 g, 71%): R_f 0.18 (10% MeOH/$CHCl_3$); mp 190-194 °C (MeOH); IR

ν: 3445, 2979, 2935, 1763, 1662, 1591, 1456, 1369, 1274 cm^{-1}; ^1H NMR (CD_3OD) δ 7.48 (1H, s, H-3'), 6.94 (1H, s, H-6'), 6.82 (1H, s, H-6), 3.82 (3H, s, 5'-OMe), 3.47 (3H, s, 4-OMe), 3.07 (2H, t, *J*= 7.6 Hz, 1-C$\underline{H_2}$-CH_2), 3.00 (3H, s, N-CH_3), 2.80 (2H, t, *J*= 7.6 Hz, 1-CH_2-C$\underline{H_2}$-N), 1.53 and 1.51 (each 9H, s, OBoc-Me), 1.39 (9H, s, NBoc-Me); ESIMS *m/z* $(M+H)^+$ 692 (100), 367 (40), 136 (60).

2-Carboxy-3-(2-carboxy-4-hydroxy-5-methoxyphenyl)-5-hydroxy-4-methoxy-*N*-methylphenethylamine TFA salt (17): The mixture of **16** (680 mg, 0.98 mmol), TFA (4 mL) and CH_2Cl_2 (16 mL) was stirred at rt for 2.5 h. Following the work-up and purification similar to that described for **11** yielded pure oil (**17**, 431 mg, 90%): R_f 0.19 (50% MeOH/$CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 7.48 (1H, s, H-3'), 6.83 (1H, s, H-6'), 6.74 (1H, s, H-6), 3.85 (3H, s, 5'-OMe), 3.43 (3H, s, 4-OMe), 3.28-3.25 (2H, m, 1-CH_2C$\underline{H_2}$-N), 3.04-2.91 (2H, m, 1-C$\underline{H_2}CH_2$), 2.69 (3H, s, N-CH_3); HRFABS Calcd for $C_{19}H_{22}NO_8$ (M–TFA+H) 392.1346, Found 392.1353.

5-Carboxy-6-(2-carboxy-4-hydroxy-5-methoxyphenyl)-8-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (13): The mixture of **17** (150 mg, 0.33 mmol), MeOH (10 mL), 0.1N AcOH (4 mL), 1N NaOAc (4 mL) and 37% HCHO (1 mL, 13.32 mmol) in a 25 mL round bottom flask was stirred at rt for 2.5 h. After removal of MeOH, the aqueous residue was passed through an Amberlite XAD-2 column (30 g), washed with water (150 mL) to remove inorganic salt, then eluted with MeOH (100 mL) to give pure **13** (71 mg, 74%): R_f 0.12 (50% MeOH/$CHCl_3$); mp 270-274 °C (MeOH); ^1H NMR (400 MHz, DMSO-d_6) δ 6.98 (1H, s, H-11), 6.44 (1H, s, H-14), 4.02 (2H, s, H-1), 3.68 (3H, s, 13-OMe), 3.18-3.16 (2H, m, H-4), 3.16 (3H, s, 7-OMe), 2.79 (3H, s, 2-Me), 2.68-2.50 (1H, m, H-3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.7 (s), 171.2 (s), 148.8 (s), 146.5 (s), 146.4 (s), 144.0 (s), 132.9 (s), 130.7 (s), 130.6 (s), 127.0 (s), 124.5 (s), 118.9 (s), 116.5 (d), 114.8 (d), 61.4 (q), 56.7 (q), 52.1 (t), 51.7 (t), 44.4 (q, 2-Me), 25.6 (t, C-4); HRFABMS Calcd for $C_{20}H_{22}NO_8$ (M+H) 404.1346, Found 404.1435.

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