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SYNTHESIS OF (±)-ANNONELLIPTINE AND (±)-ANOMOLINE

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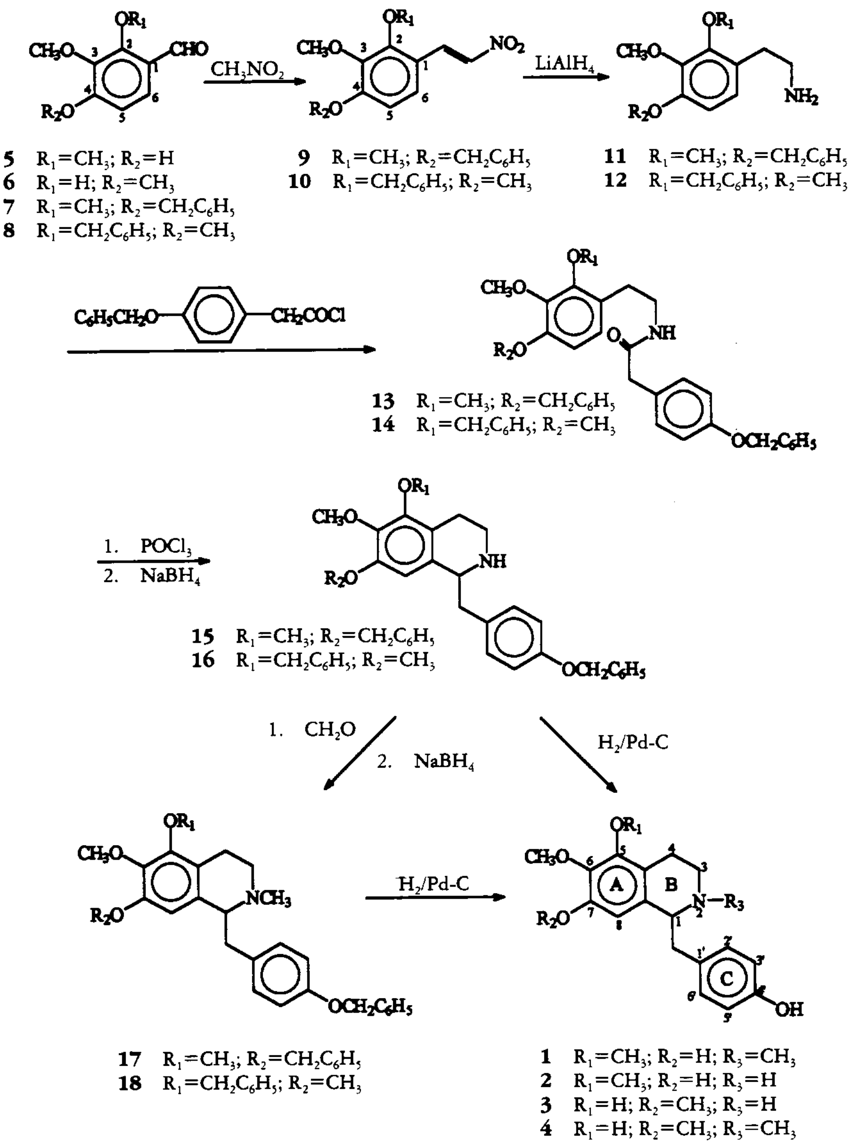
ABSTRACT.—In order to confirm the structures of annonelliptine [**1**] and anomoline [**2**], chemical synthesis of (±)-**1** and (±)-**2** has been achieved. Two isomeric alkaloids, (±)-*N*-northalmeline [**3**] and (±)-thalmeline [**4**] were also prepared by a similar approach. The structures of **1** and **2** were confirmed unequivocally by comparison with the synthetic samples. COLOC and nOe nmr spectra were also used to study the structures of these compounds.

Two novel tetraoxygenated benzylisoquinoline alkaloids, annonelliptine [**1**] from *Annona elliptica* (1) and anomoline [**2**] from *Annona cherimola* (2), were reported recently. The structures of these two naturally occurring alkaloids were elucidated entirely by spectroscopic methods and assigned as (*R*)-1-(4′-hydroxybenzyl)-2-methyl-5,6-dimethoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline [**1**] and its des-*N*-methyl base [**2**]. The substitution patterns in ring A of **1** and **2** were assigned by correlation with nmr measurements of related alkaloids (1,2). However, the possibility of hydroxy substitution at C-5 in ring A was not excluded completely. Herein, the chemical syntheses of (±)-**1** and (±)-**2**, along with their isomeric benzylisoquinolines, (±)-*N*-northalmeline [**3**] and (±)-thalmeline [**4**], are reported as confirmation of their structures.

The syntheses of alkaloids **1**–**4** are illustrated in Scheme 1. The major step in the formation of the benzylisoquinoline ring was carried out by Bischler-Napieralski cyclization in the presence of $POCl_3$ (3). Substituted benzaldehydes **5** and **6** were prepared as described previously (4,5), and were differentiated by their ^{1}H-nmr spectra. The chemical shift of the aldehyde proton in **6** was lower than that of **5** by about 1.12 ppm due to the intramolecular hydrogen bonding of the OH to the aldehyde moiety at the ortho position. In addition, irradiation of the methoxy signal of **5** at δ 3.93 enhanced the aromatic H signal at δ 7.27 by 7.6%, but no nOe effect was detected when the methoxy signal of **6** was irradiated. Isoquinolines **15** and **16** were prepared from aldehydes **5** and **6** as shown in Scheme 1. *N*-Methylation of **15** and **16** by reaction with formalin followed by $NaBH_4$ reduction yielded the *N*-methyl isoquinolines **17** and **18**. Catalytic hydrogenation of **15**–**18** on Pd-charcoal to remove the protecting benzyl group yielded **2**, **3**, **1**, and **4**, respectively. The spectral and other physical data of **1** and **2** were identical to those of natural **1** and **2**, establishing their structures. ^{1}H-Nmr studies on these alkaloids revealed that the C-7 methoxy signal of **3** or **4** shifted to a slightly lower field than other methoxy signals within these molecules. The chemical shift of the aromatic proton at C-8 may be used to distinguish between **1** and **2** or **3** and **4**. The aromatic proton at C-8 was shifted to a significantly lower field in isomers in which the OH was substituted at C-5 (**3** and **4**) compared with isomers in which it was at C-7 (**1** and **2**). Enhancement of the aromatic proton signal at C-8 by 2.4% and 4.7% in an nOe difference spectrum was observed when the methoxy signal at C-7 of **3** or **4** was irradiated, respectively. Moreover, the structure of **2** was also characterized by analysis of its ^{1}H-^{13}C COSY and COLOC nmr spectra to confirm that two methoxy groups are substituted at the C-5 and C-6 positions, and that the hydroxy substituent was located at the C-7 position. Assignments of the results from the COLOC spectrum are summarized in



SCHEME 1

Figure 1. Compound **4** (thalmeline) was originally isolated from *Thalictrum minus* by Nikola *et al.* (6) in 1970, but neither the isolation from a natural source nor the synthesis of *N*-northalmeline [**3**] has been reported in the literature.

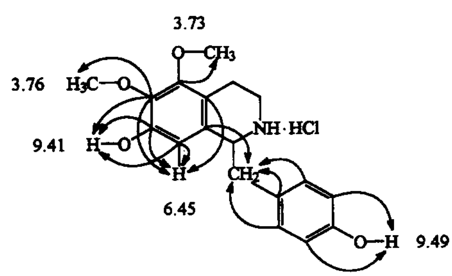


FIGURE 1. Correlation observed in the COLOC nmr spectrum of anomoline·HCl [**2**].

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mps were measured on a Laboratory Devices melting point apparatus and are reported uncorrected. Uv spectra were obtained on a Jasco 7800 uv-vis spectrophotometer. Ir spectra were taken on a

Jasco A-100 grating ir or a Nicolet MX-1 Ft-ir spectrophotometer as KBr disks. The nmr spectra were recorded using a Varian EM-360 nmr or a Bruker AM-300 nmr spectrometer in $CDCl_3$ unless otherwise stated. Mass spectra were determined with a JEOL TMS-D-300 gc/ms instrument. Elemental analysis was carried out with a Perkin-Elmer 2400 elemental analyzer.

2-Benzyloxy-3,4-dimethoxybenzaldehyde [**8**].—A mixture of 2-hydroxy-3,4-dimethoxybenzaldehyde [**6**] (5) (10 g, 54.9 mmol), 10 ml (78.9 mmol) of benzyl chloride, and 5.4 g anhydrous K_2CO_3 in 50 ml of EtOH was refluxed for 5 h to yield the crude product **8**. After purification by Si gel cc using $CHCl_3$ as eluent, 10.99 g (73.6%) of **8** were obtained as a pale yellow oil; ir ν max (neat) 2750, 1680 (CHO) cm^{-1}; ^{1}H nmr δ 3.77 (6H, s, 2×OMe), 5.07 (2H, s, -OCH_2Ph), 6.61 (1H, d, J=9 Hz, H-5), 7.25 (5H, s, -OCH$_2$*Ph*), 7.45 (1H, d, J=9 Hz, H-6), 10.05 (1H, s, CHO).

4-Benzyloxy-2,3-dimethoxy-β-nitrostyrene [**9**].—A mixture of 4-benzyloxy-2,3-dimethoxybenzaldehyde [**7**] (3) (6.4 g, 23.5 mmol), nitromethane (4.5 ml, 73.8 mmol) and NH_4OAc (4.6 g) in 70 ml of AcOH was refluxed for 4 h. After cooling, the mixture was poured into 500 ml of ice-H_2O. Yellow needles were obtained after crystallization from EtOH to give 5.55 g (74.88%) of **9**; mp 83–84°; ir ν max 1628 (s, NO_2), 1500, 1340 (s, NO_2) cm^{-1}; ^{1}H nmr δ 3.77 (3H, s, OMe-2), 3.92 (3H, s, OMe-3), 5.04 (2H, s, -OCH_2Ph), 6.61 (1H, d, J=9 Hz, H-5), 7.02 (1H, d, J=9 Hz, H-6), 7.28 (5H, s, -OCH$_2$*Ph*), 7.58 (1H, d, J=13.5 Hz, α-H), 7.98 (1H, d, J=13.5 Hz, β-H).

2-Benzyloxy-3,4-dimethoxy-β-nitrostyrene [**10**].—A mixture of **8** (13.5 g, 44.9 mmol), nitromethane (10 ml, 164 mmol), and NH_4OAc (10 g) in 180 ml of AcOH yielded 12 g (76.8%) of **10** as yellow needles; mp 86–87°; ir ν max 1610 (s, NO_2), 1490, 1330 (s, NO_2) cm^{-1}; ^{1}H nmr δ 3.87 (6H, s, 2×OMe), 5.09 (2H, s, -OCH_2Ph), 6.66 (1H, d, J=9 Hz, H-5), 7.13 (1H, d, J=9 Hz, H-6), 7.33 (5H, s, -OCH$_2$*Ph*), 7.54 (1H, d, J=13.5 Hz, α-H), 8.01 (1H, d, J=13.5 Hz, β-H).

β-(2,3-Dimethoxy-4-benzyloxy)phenylethylamine [**11**].—A solution of **9** (7.1 g, 22.5 mmol) in 80 ml of anhydrous THF was added dropwise to a well-stirred suspension of $LiAlH_4$ (3 g, 79.4 mmol) in 120 ml of anhydrous Et_2O, and the mixture was refluxed for 4 h. Excess $LiAlH_4$ was destroyed by dropwise addition of 3 ml of H_2O, 3 ml of 15% NaOH solution, and 3 ml of H_2O. The combined filtrate was concentrated to dryness under reduced pressure, and an oily amine **11** was obtained. It was converted to the HCl salt to yield **11**·HCl (4.3 g, 59.1%) as white crystals; mp 141–142°; ir ν max 3350, 3330 (m, NH_2) cm^{-1}; ^{1}H nmr δ 1.48 (2H, s, NH_2, D_2O exchangeable), 2.50–3.05 (4H, m, methylenes), 3.77 (6H, s, 2×OMe), 4.93 (2H, s, -OCH_2Ph), 6.48 (1H, d, J=9 Hz, H-6), 6.67 (1H, d, J=9 Hz, H-5), 7.25 (5H, s, -OCH$_2$*Ph*).

β-(2-Benzyloxy-3,4-dimethoxy)phenylethylamine [**12**].—A solution of **10** (15 g, 47.6 mmol) in 150 ml of anhydrous THF was reduced with $LiAlH_4$ (6.5 g, 171 mmol) to afford 9.94 g (64.53%) of **12**·HCl as white crystals; mp 141–142°; ir ν max 3350, 3330 (m, NH_2) cm^{-1}; ^{1}H nmr δ 1.63 (2H, s, NH_2, D_2O exchangeable), 2.45–3.00 (4H, m, α,β-CH_2), 3.69 (3H, s, OMe-4), 3.73 (3H, s, OMe-3), 4.90 (2H, s, -OCH_2Ph), 6.44 (1H, d, J=9 Hz, H-6), 6.68 (1H, d, J=9 Hz, H-5), 7.23 (5H, s, -OCH$_2$*Ph*).

N-*(2,3-Dimethoxy-4-benzyloxyphenylethyl)-4'-benzyloxyphenacetamide* [**13**].—A mixture of *p*-benzyloxyphenylacetic acid (7 g, 28.9 mmol) and $SOCl_2$ (11 ml, 152 mmol) in 45 ml of anhydrous C_6H_6 was refluxed for 1.5 h. After cooling, the solvent was removed to give a crude pale yellow residue of the acid chloride. A solution of this acid chloride in CH_2Cl_2 was added dropwise to a solution of **11** (7.1 g, 24.7 mmol) in 100 ml of CH_2Cl_2 and 50 ml of 5% NaOH solution in a cooling bath. After stirring at room temperature for 1 h, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O, and then with dilute HCl three times, and then dried over anhydrous $MgSO_4$. The solution was evaporated to give a yellow oil which was recrystallized from EtOH to afford 11.19 g (88.47%) of **13** as white crystals; mp 91–92°; ir ν max 3300 (s, NH_2), 1625 (s, amide I), 1505 (s, amide II) cm^{-1}; ^{1}H nmr δ 2.54 (2H, t, J=6 Hz, Ar-CH_2), 3.1 (2H, t, J=6 Hz, NH-CH_2), 3.3 (2H, s, -COCH_2Ph), 3.65 (3H, s, OMe-2), 3.71 (3H, s, OMe-3), 4.91 (4H, s, 2×OCH_2Ph), 5.5 (1H, br s, NH), 6.37 (1H, d, J=9 Hz, H-6), 6.52 (1H, d, J=9 Hz, H-5), 6.73 (2H, d, J=9 Hz, H-2', H-6'), 7.02 (2H, d, J=9 Hz, H-3', H-5'), 7.21 (10H, s, 2×-OCH$_2$*Ph*); eims *m/z* $[M]^+$ 511 (1), 271 (11), 270 (58), 180 (13), 179 (15), 167 (14), 91 (100).

N-*(2-Benzyloxy-3,4-dimethoxyphenylethyl)-4'-benzyloxyphenacetamide* [**14**].—The acetyl chloride prepared from *p*-benzyloxyphenylacetic acid (7.3 g, 30.1 mmol) and $SOCl_2$ (4.4 ml, 61.8 mmol) was reacted with amine **12** (8.6 g, 30 mmol) in the presence of NaOH solution. After workup, 12.2 g (79.7%) of **14** as white crystals were obtained from EtOH; mp 77–78°; ir ν max 3250 (NH, s), 1620 (s, amide I), 1490 (s, amide II) cm^{-1}; ^{1}H nmr δ 2.62 (2H, t, J=6 Hz, Ar-CH_2), 3.26 (2H, t, J=6 Hz, NHCH_2), 3.35 (2H, s, COCH_2Ph), 3.85 (6H, s, 2×OMe), 5.1 (4H, s, 2×-OCH_2Ph), 5.62 (1H, br s, NH), 6.53 (1H, d, J=9 Hz, H-6), 6.71 (1H, d, J=9 Hz, H-5), 6.85 (2H, d, J=9 Hz, H-2', H-6'), 7.05 (2H, d, J=9 Hz, H-3', H-5'), 7.37 (10H, s, 2×-OCH$_2$*Ph*); eims *m/z* $[M]^+$ 511 (4), 270 (29), 180 (49), 167 (23), 91 (100).

1-(4'-Benzyloxybenzyl)-5,6-dimethoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline [**15**].—A mixture of **13** (5 g, 9.78 mmol) and $POCl_3$ (4.6 ml, 28.2 mmol) in 40 ml of $CHCl_3$ was refluxed for 2 h. After cooling, excess reagents were removed *in vacuo* to give a brown residue of a dihydroisoquinoline. $NaBH_4$ (2.2 g, 58 mmol) was added to this residue in 40 ml of MeOH over 20 min and was then stirred for 30 min at room temperature. The mixture was evaporated to dryness and the residue was dissolved in H_2O and extracted with 100 ml of CH_2Cl_2 three times. The extract was washed well with H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. The oily residue was treated with 1 M HCl in Et_2O and 3.97 g (76.5%) of **15**·HCl was obtained. The crude HCl salt was recrystallized from EtOH to give white crystals of **15**·HCl; mp 210–211°; ir ν max 3320 (w, NH) cm^{-1}; uv λ max (MeOH) (log ϵ) 284 (3.24), 225 (4.54) nm; λ min (MeOH) (log ϵ) 254 (2.81) nm; ^1H nmr δ 1.87 (1H, s, NH), 2.38–2.83 (6H, br m, methylenes), 3.68, 3.7 (6H, d, 2×OMe), 4.0 (1H, m, H-1), 4.85 (4H, s, 2×-OCH_2Ph), 6.34 (1H, s, H-8), 6.74 (2H, d, J=9 Hz, H-2′, H-6′), 6.98 (2H, d, J=9 Hz, H-3′, H-5′), 7.21 (10H, s, 2×-OCH_2*Ph*); eims *m/z* 299 (21), 298 (100), 192 (23), 91 (20).

1-(4′-Benzyloxybenzyl)-5-benzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [**16**].—A solution of **14** (5 g, 4.8 mmol) was treated with $POCl_3$ (4.6 ml, 28.2 mmol) in $CHCl_3$ and then reduced with 2.2 g (58 mmol) of $NaBH_4$ in MeOH to yield 14 g (79.7%) of **16**·HCl; mp 164–164°; ir ν max 3340 (w, NH) cm^{-1}; uv λ max (MeOH) (log ϵ) 282 (3.76), 228 (4.30) nm; λ min (MeOH) (log ϵ) 254 (3.18)nm; ^1H nmr δ 2.13 (1H, s, NH), 2.43–3.14 (6H, br m, methylenes), 3.77 (3H, s, OMe-7), 3.83 (3H, s, OMe-6), 4.1 (1H, m, H-1), 5.01 (4H, s, 2×-OCH_2Ph), 6.44 (1H, s, H-8), 6.89 (2H, d, J=9 Hz, H-2′, H-6′), 7.09 (2H, d, J=9 Hz, H-3′, H-5′), 7.36 (10H, s, 2×-OCH_2*Ph*); eims *m/z* $[M+1]^+$ 496 (1), 312 (20), 299 (29), 298 (100), 207 (13), 206 (11), 192 (25), 178 (22), 91 (56).

1-(4′-Benzyloxybenzyl)-2-methyl-5,6-dimethoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline [**17**].—A MeOH solution of **15** (1.86 g, 3.8 mmol) was stirred with HCHO (5.5 ml, 64 mmol) for 30 min at room temperature and then $NaBH_4$ (1.2 g, 40 mmol) was added. The solution was evaporated and the residue was partitioned between H_2O (100 ml) and $CHCl_3$ (100 ml). The organic layer was dried over anhydrous $MgSO_4$ and evaporated, and then 1 M HCl in Et_2O was added. The *N*-methylisoquinoline **17**·HCl (1.8 g, 86.8%) was crystallized as white needles; mp 193–194°; uv λ max (MeOH) (log ϵ) 279 (3.72), 220 (4.66) nm; λ min (MeOH) (log ϵ) 253 (3.29) nm; ^1H nmr δ 2.4 (3H, s, Me-N), 2.53–3.17 (6H, m, methylenes), 3.75 (6H, s, 2×OMe), 4.68, 4.89 (4H, d, 2×-OCH_2Ph), 5.84 (1H, s, H-8), 6.83 (4H, s, J=9 Hz, AB q), 7.24 (10H, s, 2×-OCH_2*Ph*); eims *m/z* $[M+1]^+$ 510 (0.2), 313 (19), 312 (100), 298 (26), 178 (4), 91 (16).

1-(4′-Benzyloxybenzyl)-2-methyl-5-benzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [**18**].—A solution of **16** (1.86 g, 3.8 mmol) in 25 ml of MeOH was *N*-methylated with HCHO (5.5 ml, 64 mmol) and then reduced with $NaBH_4$ (12 g, 40 mmol). Workup gave 1.85 g (90.85%) of **18**·HCl; mp 92–93°; uv λ max (MeOH) (log ϵ) 280 (3.35), 225 (4.38) nm; λ min (MeOH) (log ϵ) 255 (2.75) nm; ^1H nmr δ 2.36 (3H, s, Me-N), 2.46, 2.30 (6H, m, methylenes), 3.42 (3H, s, OMe-7), 3.74 (3H, s, OMe-6), 4.71 (4H, s, 2×-OCH_2Ph), 5.78 (1H, s, H-8), 6.76 (2H, d, J=9 Hz, H-2′, H-6′), 6.9 (2H, d, J=9 Hz, H-3′, H-5′), 7.27 (10H, s, 2×-OCH_2*Ph*); eims *m/z* 313 (21), 312 (100), 206 (23), 192 (15), 91 (14).

1-(4′-Hydroxybenzyl)-5,6-dimethoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline HCl [(±)-anomoline HCl] [**2**].—A solution of **15** (0.5 g, 0.9 mmol) in 30 ml of EtOH was shaken with H_2 at 25 psi in the presence of 10% Pd/C (100 mg) for 2 h. The filtrate was concentrated to dryness under reduced pressure and 1 M HCl in Et_2O was added to yield 210 mg (63.3%) of **2**·HCl as white crystals from EtOH; mp 238.5–240°; [lit. (2) 193–194.5° (free base)]; ir ν max 3330 (OH, s), 2800–2400 (w, $>NH_2^+$) cm^{-1}; uv λ max (MeOH) (log ϵ) 280 (3.58), 227 (4.2) nm; λ min (MeOH) (log ϵ) 252.5 (2.79) nm; ^1H nmr (DMSO-d_6) δ 2.75–3.31 (6H, m, methylenes), 3.73 (3H, s, OMe-5), 3.76 (3H, s, OMe-6), 4.49 (1H, s, H-1), 6.45 (1H, s, H-8), 6.76 (2H, d, J=8.8 Hz, H-3′, H-5′), 7.16 (2H, d, J=8.8 Hz, H-2′, H-6′), 9.29 (2H, s br, $>NH_2^+$, D_2O exchangeable), 9.41 (1H, s, OH, D_2O exchangeable), 9.49 (1H, s, OH, D_2O exchangeable); ^{13}C nmr (DMSO-d_6) δ 18.7 (C-4), 37.8 (C-3), 54.3 (C-1), 59.4 (OMe), 109.0 (C-8), 114.8 (C-3′, C-5′), 115.7 (C-4a), 129.9 (C-2′, C-6′), 127.3 (C-1′), 125.3 (C-8a), 139.3 (C-6), 149.6 (C-7), 148.8 (C-5), 155.8 (C-4′); eims *m/z* $[M+1]^+$ 316 (0.3), 209 (15), 208 (100), 192 (18); *anal.*, calcd for $C_{18}H_{21}NO_4$·HCl, C 61.45, H 6.30, N 3.98, found C 61.20, H 6.21, N 3.95.

1-(4′-Hydroxybenzyl)-5-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline HCl [(±)-N-northalmeline HCl] [**3**].—A mixture of **16** (1 g, 1.8 mmol) and 10% Pd/C (250 mg) in 100 ml of EtOH under H_2 was shaken for 2 h and treated with HCl to afford 400 mg (60.54%) of **3**·HCl as crystals from EtOH; mp 220–222° (free base, mp 207–208°); ir ν max 3240 (s, OH), 2800–2400 (w, $>NH_2^+$) cm^{-1}; uv λ max (MeOH) (log ϵ) 278.5 (3.54), 224 (4.34) nm; λ min (MeOH) (log ϵ) 255 (2.96) nm; ^1H nmr (DMSO-d_6) δ 2.72–3.36 (6H, m, methylenes), 3.57 (3H, s, OMe-7), 3.64 (3H, s, OMe-6), 4.47 (1H, s, H-1), 6.09 (1H, s, H-8), 6.75 (2H, d, J=8.2 Hz, H-3′, H-5′), 7.13 (2H, d,

J=8.2 Hz, H-2′, H-6′), 9.10 (1H, s, OH, D_2O exchangeable), 9.42 (2H, br s, >NH_2^+, D_2O exchangeable), 9.47 (1H, s, OH, D_2O exchangeable), ^{13}C nmr (DMSO-d_6) δ 19.5 (C-4), 38.5 (C-3), 55.4 (C-1), 55.5, 60.3 (OMe), 101.6 (C-8), 112.9 (C-4a), 115.4 (C-3′, C-5′), 126.3 (C-8a), 127.8 (C-1′), 130.8 (C-2′, C-6′), 135.1 (C-6), 147.4 (C-7), 150.9 (C-5), 156.5 (C-4′); eims *m/z* $[M+1]^+$ 316 (0.3), 209 (14), 208 (100), 192 (10); *anal.*, calcd for $C_{18}H_{21}NO_4$·HCl, C 61.45, H 6.30, N 3.98, found C 61.12, H 6.34, N 3.95.

1-(4′-Hydroxybenzyl)-2-methyl-5,6-dimethoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline HCl [(±)-annonelliptine HCl] [**1**].—A mixture of **17** (500 mg, 0.9 mmol) and 10% Pd/C (250 mg) in 30 ml of EtOH was shaken under H_2 for 4 h and treated with HCl to afford 200 mg (60.79%) of **1**·HCl as crystals from EtOH; mp 230–231°; free base: mp 182.5–184° [lit. (1) mp 198–200° (free base)]; ir ν max 3224 (s, OH), 2800–2400 (w, >NH_2^+) cm^{-1}; uv λ max (MeOH) (log ε) 281 (3.87), 225 (4.54) nm; λ min (MeOH) (log ε) 252.5 (3.09) nm; ^{1}H nmr (DMSO-d_6) δ 2.48–3.07 (6H, m, methylenes), 2.27 (3H, s, Me-N), 3.70 (3H, s, OMe-5), 3.70 (3H, s, OMe-6), 4.43 (1H, s, H-1), 6.27 (1H, s, H-8), 6.91 (2H, d, J=8.8 Hz, H-2′, H-6′), 6.62 (2H, d, J=8.3 Hz, H-3′, H-5′), 8.92 (1H, s, OH, D_2O exchangeable), 9.06 (1H, s, OH, D_2O exchangeable); ^{13}C nmr (DMSO-d_6) δ 16.3 (C-4), 43.9 (Me-N), 54.9 (C-3), 60.1 (OMe), 63.7 (C-1), 111 (C-8), 113.8 (C-3′, C-5′), 113.8 (C-4a), 125.5 (C-8a), 126.0 (C-1′), 130.5 (C-2′, C-6′), 140.2 (C-6), 149.3 (C-7), 150.5 (C-5), 156.4 (C-4′); eims *m/z* 223 (13), 222 (100), 206 (16); *anal.*, calcd for $C_{19}H_{23}NO_4$·HCl·1/2H_2O, C 60.88, H 6.72, N 3.73, found C 61.20, H 6.65, N 3.70.

1-(4′-Hydroxybenzyl)-2-methyl-5-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline HCl [(±)-thalmeline HCl] [**4**].—A mixture of **18** (2 g, 3.6 mmol) and 10% Pd/C (500 mg) in 150 ml of EtOH was shaken under H_2 for 4 h and treated with HCl to afford 800 mg (60.79%) of **4**·HCl as crystals from EtOH; mp 160–162° [lit. (6) 214–216° (dec) (oxalate)]; ir ν max 3330 (OH, s), 2800–2400 (w, >NH_2^+) cm^{-1}; uv λ max (MeOH) (log ε) 280.5 (3.51), 224 (4.31) nm; λ min (MeOH) (log ε) 253 (2.92) nm; ^{1}H nmr (DMSO-d_6) δ 2.74 (3H, s, Me-N), 2.80–3.34 (6H, m, methylenes), 3.37 (3H, s, OMe-7), 3.63 (3H, s, OMe-6), 4.43 (1H, s, H-1), 5.47 (1H, s, H-8), 6.73 (2H, d, J=7.8 Hz, H-3′, H-5′), 6.98 (2H, d, J=8.8 Hz, H-2′, H-6′), 9.23 (1H, s, OH, D_2O exchangeable), 9.50 (1H, s, OH, D_2O exchangeable), 11.0 (1H, s, NH^+, D_2O exchangeable); ^{13}C nmr (DMSO-d_6) δ 16.4 (C-4), 38.5 (C-3), 55.1, 43.6 (Me-N), 55.1 (C-1), 60.4 (OMe), 102.9 (C-8), 110.5 (C-4a), 115.3 (C-3′, C-5′), 125.1 (C-8a), 126.3 (C-1′), 131.0 (C-2′, C-6′), 135.3 (C-6), 147.6 (C-7), 150.5 (C-5), 156.5 (C-4′); eims *m/z* 223 (13), 222 (100), 206 (10); *anal.*, calcd for $C_{19}H_{23}NO_4$·HCl·H_2O, C 59.45, H 6.83, N 3.65, found C 59.89, H 6.95, N 3.56.

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