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SYNTHESIS OF 1-ARYLTETRAHYDROISOQUINOLINE ALKALOIDS AND THEIR ANALOGS

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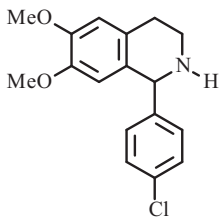
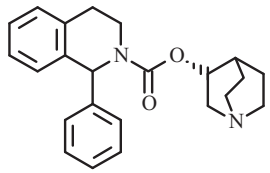
Three alkaloids of the cryptostylin series and 20 monomolecular and 3 bimolecular 1-aryltetrahydroisoquinoline derivatives were prepared using the Picte–Spengler reaction.

Keywords: 1-aryltetrahydroisoquinoline alkaloids, analogs, Pictet–Spengler reaction.

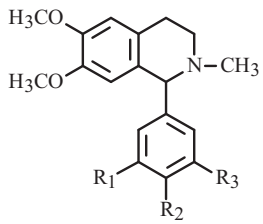
The synthesis of condensed *N*-containing heterocycles has recently been attracting more and more attention. 1-Aryltetrahydroisoquinolines are interesting because of their valuable pharmacological properties. In addition to natural alkaloids of this type [1], including cryptostylins I, II, and III (**2**–**5**) [2], synthetic 1-aryltetrahydroisoquinolines, e.g., antiepileptic agent **1A** [3] or muscarinic acetylcholine receptor antagonist **1B** (solifenacin agent) are interesting [4].



1A



1B



2 - 5

2: $R_1 = H$, $R_2 = R_3 = OCH_2O$; **3:** $R_1 = H$, $R_2 = R_3 = OCH_3$
4: $R_1 = R_2 = R_3 = OCH_3$; **5:** $R_1 = R_2 = R_3 = H$

1-Phenyltetrahydroisoquinoline alkaloids **2**–**5** were isolated previously only from two species of the genus *Cryptostylus* [5]. Isolation of **5** from *Adhatoda vasica* Nees has now also been reported [6].

This group of compounds was synthesized using the Pictet–Spengler reaction [5] starting from homoveratrylamine (**6**) and substituted aldehydes (**7a**–**t**). This turned out to be more effective than Bischler–Napieralski cyclization [7].

Condensation of amine **6** with aldehydes **7a**–**t** occurred in two steps. Schiff bases **8a**–**t** were easily obtained for all aldehydes upon refluxing in C_6H_6 for 1–1.5 h. The condensing agent in the second step was CF_3CO_2H. The yields of the target isoquinolines **9** were lower if HCl was used.

Racemates of alkaloids **2**, **3**, and **5** and *N*-methyl derivative **9r** were obtained by methylation of **9a**, **n**, **q**, and **r** [8].

Having developed a synthetic method for isoquinolines **9**, we extended it to the preparation of bimolecular compounds **10**–**12** by using vanillin oxidation to synthesize dehydrodivanillin [9].

The majority of the products were characterized by IR and NMR spectroscopy. The spectral properties of compounds **9**, namely the lack of an absorption band for the imine in the IR spectra and the presence of singlets for aromatic protons (H-5 and H-8 at δ 6.14–6.67 ppm) in PMR spectra in addition to a singlet for methine proton H-1 at δ 4.80–5.15 ppm, confirmed that substituted 1-phenyltetrahydroisoquinolines had formed.

A feature of mass spectra of compounds **9** was a base peak for the molecular ion. The principal fragmentation pathway of the 1-phenyltetrahydroisoquinoline bases was due to cleavage of C1-Ph bonds to form fragments with *m*/*z* 192 (stable 6,7-dimethoxy-3,4-dihydroisoquinoline ion) and a phenyl moiety.

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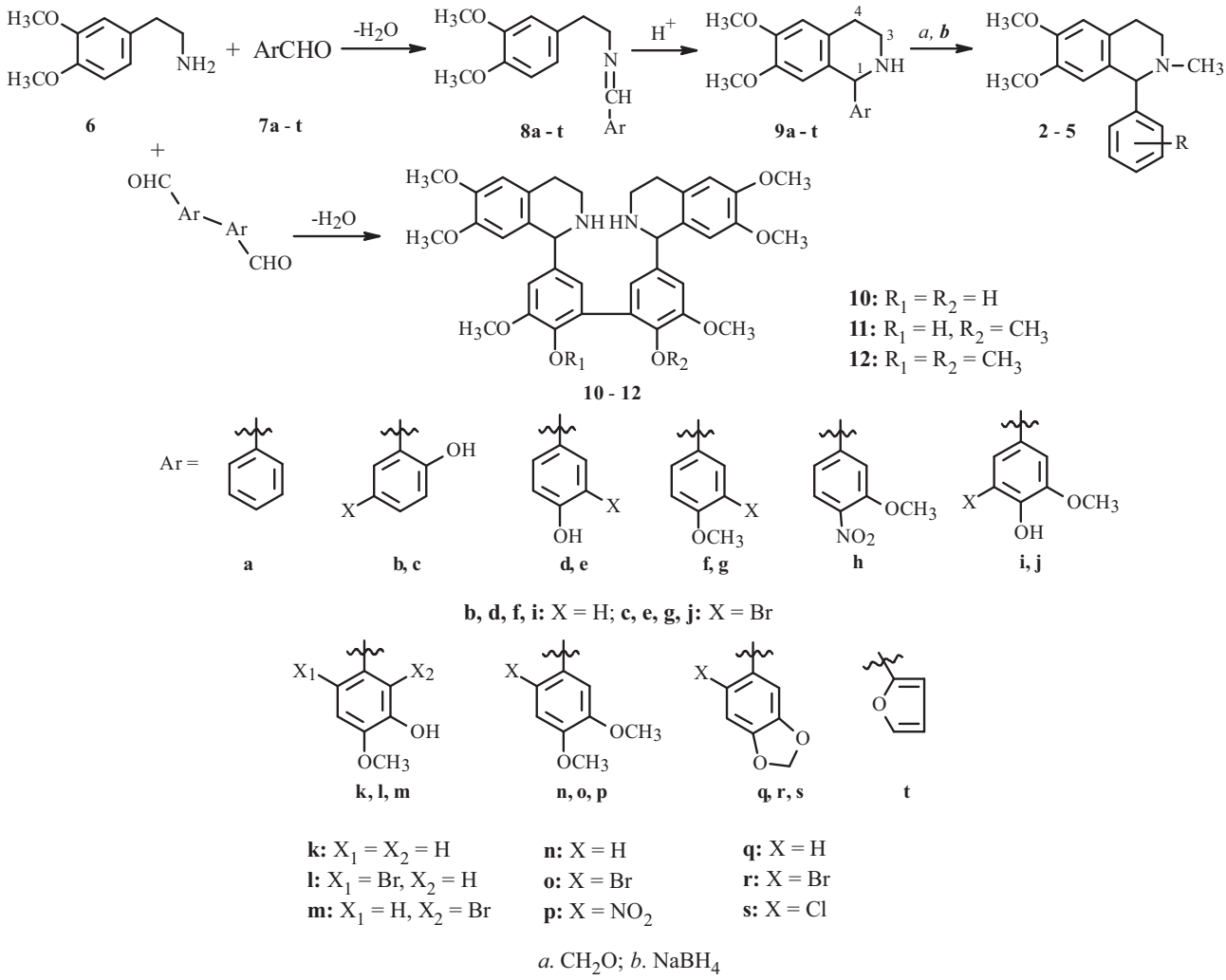

a. CH_2O; *b.* $NaBH_4$

Decomposition of alkaloids **2**, **3**, and **5** and methyl derivative **9r** by electron impact began with loss of a methyl radical and subsequent elimination of the C-6 methoxyl to form peaks for ions with *m*/*z* $[M]^+$ (100%), $[M - 15]^+$, and $[M - 15 - 31]^+$. Loss of the methyl radical and methoxyl favored formation of a stable ion.

EXPERIMENTAL

IR spectra were recorded from KBr pellets on a System 2000 FTIR instrument (Perkin-Elmer); mass spectra, on a Kratos M90; PMR spectra, on Tesla BS-567A (100 MHz) and Varian Unity-400+ spectrometers ($CDCl_3$, Py, DMSO-d_6 solvents, HMDS internal standard). R_f values were determined on LS 5/40 silica gel plates (Czech. SSR) using $CHCl_3$:MeOH (4:1). Melting points of all synthesized compounds were measured on a Boetius microstage.

General Method for Preparing Substituted 1-Phenyltetrahydroisoquinolines. A solution of 3,4-dimethoxyphenylethylamine (1.81 g, 0.01 mol) in C_6H_6 (30 mL) was treated with substituted benzaldehyde (0.01 mol) and refluxed with a Dean–Stark trap until water separation was complete (1–2 h). The solvent was distilled off. The resulting imine was treated with CF_3CO_2H (10 mL), heated on a water bath for ~2 h, cooled, and made basic with NH_3 to pH 9–10. The amine was extracted exhaustively with $CHCl_3$. The crude product was purified by preparing the hydrochloride or by column chromatography over silica gel using $CHCl_3$:MeOH (100:1→100:10). The resulting product was crystallized from Me_2CO.

1-(Phenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9a). $C_{17}H_{19}O_2N$. Prepared from **6** (1.81 g, 0.01 mol) and benzaldehyde (**7a**, 1.06 g, 0.01 mol). Yield 2.17 g (81%), mp 118–121°C (Me_2CO), mp 102–103°C [10], R_f 0.47. PMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 2.68 (1H, m, H-4), 2.85 (2H, m, H-3, 4), 3.25 (1H, m, H-3), 3.42* (3H, s, 7-OCH_3), 3.67* (3H, s, 6-OCH_3), 4.85 (1H, s, H-1), 6.14 (1H, s, H-8), 6.67 (1H, s, H-5), 7.20 (5H, m, Ar-H).

1-(2′-Hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9b). $C_{17}H_{18}O_3N$. Prepared from **6** (1.9 g, 0.01 mol) and 2-hydroxybenzaldehyde (1.33 g, 0.01 mol). Yield 2.11 g (70%), mp 159–162°C (Me_2CO), R_f 0.58. PMR

spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.73 (2H, m, H-4), 2.87 (2H, m, H-3), 3.46* (3H, s, 7-OCH_3), 3.66* (3H, s, 6-OCH_3), 5.05 (1H, s, H-1), 6.31 (1H, s, H-8), 6.64 (1H, d, J = 7, H-3′), 6.68 (1H, s, H-5), 6.72 (1H, d, J = 7, H-6′), 6.99 (2H, m, H-4′, 5′).

1-(5′-Bromo-2′-hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9c). $C_{17}H_{18}O_3NBr$. Prepared from **6** (1.52 g, 0.008 mol) and 5-bromo-2-hydroxybenzaldehyde (1.66 g, 0.008 mol). Yield 2.5 g (82%), mp of hydrochloride 189–192°C (Me_2CO), R_f 0.51. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.70 (2H, m, H-4), 2.86 (2H, m, H-3), 3.51* (3H, s, 7-OCH_3), 3.67* (3H, s, 6-OCH_3), 5.08 (1H, s, H-1), 6.37 (1H, s, H-8), 6.62 (1H, d, J = 8.5, H-3′), 6.67 (1H, s, H-5), 7.18 (1H, dd, J = 8.5, 2.3, H-4′), 7.05 (1H, d, J = 2.3, H-6′).

1-(4′-Hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9d). $C_{17}H_{19}O_3N$. Prepared from **6** (1.9 g, 0.01 mol) and 4-hydroxybenzaldehyde (1.28 g, 0.01 mol). Yield 1.22 g (41%), mp of hydrochloride 216–218°C (Me_2CO), R_f 0.35. PMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 2.77 and 2.96 (1H each, m, H-4), 2.95–3.15 (1H each, m, H-3), 3.56* (3H, s, 7-OCH_3), 3.79* (3H, s, 6-OCH_3), 4.92 (1H, s, H-1), 6.26 (1H, s, H-8), 6.71 (1H, s, H-5), 6.73 (2H, d, J = 8.5, H-3′, 5′), 7.03 (2H, d, J = 8.5, H-2′, 6′).

1-(3′-Bromo-4′-hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9e). $C_{17}H_{18}O_3NBr$. Prepared from **6** and 4-hydroxy-3-bromobenzaldehyde. Yield 40%, mp of hydrochloride 205–207°C (Me_2CO), R_f 0.9. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.64 and 2.80 (1H each, m, H-4), 3.26 (2H, m, H-3), 3.44* (3H, s, 7-OCH_3), 3.66* (3H, s, 6-OCH_3), 4.78 (1H, s, H-1), 6.15 (1H, s, H-8), 6.62 (1H, s, H-5), 6.80 (1H, d, J = 8, H-5′), 6.94 (1H, dd, J = 1.8, 8, H-6′), 7.22 (1H, d, J = 1.8, H-2′).

1-(4′-Methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9f). $C_{18}H_{21}O_3N$. Prepared from **6** (2.39 g, 0.013 mol) and 4-methoxybenzaldehyde (1.79 g, 0.013 mol). Yield 2.4 g (62%), mp 265–267°C (Me_2CO), R_f 0.52. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.70 (1H, m, H-4), 2.85 (2H, m, H-3, 4), 3.27 (1H, m, H-3), 3.42* (3H, s, 7-OCH_3), 3.66* (6H, s, 6, 4′-OCH_3), 4.82 (1H, s, H-1), 6.13 (1H, s, H-8), 6.63 (1H, s, H-5) 6.79 (2H, d, J = 8.9, H-3′, 5′), 7.09 (2H, d, J = 8.9, H-2′, 6′).

1-(3′-Bromo-4′-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9g). $C_{18}H_{20}O_3NBr$. Prepared from **6** and 3-bromo-4-methoxybenzaldehyde. Yield 59%, mp 262–264°C (Me_2CO), R_f 0.9. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.69 (2H, m, H-4), 2.83 (1H, m, H-3), 3.20 (1H, m, H-3), 3.46* (3H, s, 7-OCH_3), 3.69* (3H, s, 6-OCH_3), 3.78* (3H, s, 4′-OCH_3), 4.85 (1H, s, H-1), 6.17 (1H, s, H-8), 6.64 (1H, s, H-5), 6.95 (1H, d, J = 8.5, H-5′), 7.13 (1H, dd, J = 8.5, 2, H-6′), 7.37 (1H, d, J = 2, H-2′).

1-(3′-Methoxy-4′-nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9h). $C_{18}H_{20}O_5N_2$. Prepared from **6** and 3-methoxy-4-nitrobenzaldehyde. Yield 64%, mp 181–183°C (Me_2CO), R_f 0.44. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.71 (2H, m, H-4), 2.88 and 3.22 (2H, m, H-3), 3.49* (3H, s, 7-OCH_3), 3.70* (3H, s, 6-OCH_3), 3.81* (3H, s, 3′-OCH_3), 5.0 (1H, s, H-1), 6.25 (1H, s, H-8), 6.68 (1H, s, H-5), 6.87 (1H, dd, J = 8, 1.2, H-6′), 7.30 (1H, d, J = 1.2, H-2′), 7.77 (1H, d, J = 8, H-5′).

1-(4′-Hydroxy-3′-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9i). $C_{18}H_{21}O_4N$. Prepared from **6** (1.91 g, 0.01 mol) and vanillin (1.52 g, 0.01 mol). Yield 2.73 g (82%), mp of hydrochloride 199–203°C (Me_2CO), R_f 0.55. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.66 (1H, m, H-4), 2.80 (1H, m, H-3, 4), 3.29 (1H, m, H-3), 3.45* (3H, s, 7-OCH_3), 3.74* (3H, s, 6-OCH_3), 3.75* (3H, s, 3′-OCH_3), 4.72 (1H, s, H-1), 6.14 (1H, s, H-8), 6.59 (1H, s, H-5), 6.56 (1H, d, J = 1.8, H-2′), 6.57 (1H, dd, J = 1.8, 8, H-6′), 6.82 (1H, d, J = 8, H-5′).

1-(5′-Bromo-4′-hydroxy-3′-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9j). $C_{18}H_{20}O_4NBr$. Prepared from **6** and 5-bromovanillin. Yield 38%, mp 193°C, R_f 0.84. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.68 (2H, m, H-4), 2.81 and 3.28 (1H each, m, H-3), 3.47* (3H, s, 7-OCH_3), 3.68* (3H, s, 6-OCH_3), 3.72* (3H, s, 3′-OCH_3), 4.75 (1H, s, H-1), 6.21 (1H, s, H-8), 6.64 (1H, s, H-5), 6.81* (1H, d, J = 1.2, H-6′), 6.82* (1H, d, J = 1.2, H-2′).

1-(3′-Hydroxy-4′-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9k). $C_{18}H_{21}O_4N$. Prepared from **6** (1.81 g, 0.01 mol) and isovanillin (1.52 g, 0.01 mol) [11]. Yield 1.64 g (52%), mp 183–184°C (Me_2CO), R_f 0.52. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.5–3.15 (4H, 2m, H-3, 4), 3.45* (3H, s, 7-OCH_3), 3.67* (6H, s, 6, 4′-OCH_3), 4.73 (1H, s, H-1), 6.19 (1H, s, H-8), 6.57 (1H, d, J = 9, H-5′), 6.61 (2H, s, H-5, 2′), 6.76 (1H, d, J = 9, H-6′).

1-(6′-Bromo-3′-hydroxy-4′-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9l). $C_{18}H_{20}O_4NBr$. Prepared from **6** (1.33 g, 0.007 mol) and 6-bromoisovanillin (1.69 g, 0.007 mol) [12]. Yield 1.88 g (64%), mp 181–183°C (Me_2CO), R_f 0.44. Mass spectrum: *m/z* 394 (M^+ + 1, Br-79), 396 (M^+ + 1, Br-81), 216 (80, Br-81), 214 (51, Br-79), 201 (56, Br-81), 199 (34, Br-79), 174 (20, Br-81), 172 (13, Br-79), 161 (49), 146 (100), 121 (35). PMR spectrum (100 MHz,

DMSO-d_6, δ, ppm): 2.8–3.2 (4H, m, H-3, 4), 3.48* (3H, s, 7-OCH_3), 3.72* (3H, s, 6-OCH_3), 3.75* (3H, s, 4′-OCH_3), 5.48 (1H, s, H-1), 6.15 (1H, s, H-8), 6.48* (1H, s, H-5), 6.76* (1H, s, H-2′), 7.15 (1H, s, H-5′).

1-(2′-Bromo-3′-hydroxy-4′-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9m). $C_{18}H_{20}O_4NBr$. Prepared from **6** (1.52 g, 0.008 mol) and 2-bromo-3-hydroxy-4-methoxybenzaldehyde (1.92 g, 0.008 mol) [13]. Yield 2.15 g (66%), mp 199–200°C (Me_2CO), R_f 0.54. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.65 (2H, m, H-4), 2.78 (2H, m, H-3), 3.44* (3H, s, 7-OCH_3), 3.66* (3H, s, 6-OCH_3), 3.70 (3H, s, 4′-OCH_3), 5.22 (1H, s, H-1), 6.18 (1H, s, H-8), 6.27 (1H, d, J = 8, H-5′), 6.64 (1H, s, H-5), 6.76 (1H, d, J = 8, H-6′).

1-(3′,4′-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9n). $C_{19}H_{23}O_4N$. Prepared from **6** (1.81 g, 0.01 mol) and veratrylaldehyde (1.66 g, 0.01 mol). Yield 2.38 g (72%), mp 72–74°C (Me_2CO), R_f 0.58. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 2.65 and 2.80 (3H, 2m, 2H-4, H-3), 3.24 (1H, m, H-4), 3.44* (3H, s, 7-OCH_3), 3.62* (3H, s, 3′-OCH_3), 3.66* (6H, s, 6, 4′-OCH_3), 4.78 (1H, s, H-1), 6.18 (1H, s, H-8), 6.77 (1H, s, H-5), 6.62, 6.68, 6.82 (1H each, br.d, H-2′, 5′, 6′).

1-(6′-Bromo-3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9o). $C_{19}H_{22}O_4NBr$. Prepared from **6** (2.82 g, 0.015 mol) and 6-bromo-3,4-dimethoxybenzaldehdye (3.82 g, 0.015 mol). Yield 3.9 g (61%), mp 144°C (Me_2CO), R_f 0.50. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 2.56–2.76 (2H, m, H-4), 2.86–3.04 (2H, m, H-3), 3.43* (3H, s, 7-OCH_3), 3.68* (3H, s, 6-OCH_3), 3.51* (3H, s, 4′-OCH_3), 3.73* (3H, s, 3′-OCH_3), 5.14 (1H, s, H-1), 6.12 (1H, s, H-8), 6.65 (2H, s, H-5, H-2′), 7.11 (1H, s, H-5′).

1-(3′,4′-Dimethoxy-6′-nitrophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9p). $C_{19}H_{22}O_6N_2$. Prepared from **6** (2.24 g, 0.012 mol) and 4,5-dimethoxy-2-nitrobenzaldehyde (2.73 g, 0.012 mol) [14]. Yield 3.28 g (71%), mp 224–225°C (Me_2CO), R_f 0.53. Mass spectrum (+ESI) (*m/z*, I_{rel},%): 375 (M^+ + 1) 326 (20), 312 (38), 296 (100), 281 (35), 269 (17), 252 (43). PMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 2.80 (2H, m, H-4), 2.92, 3.4 (2H, m, H-3), 3.46* (3H, s, 7-OCH_3), 3.59* (3H, s, 3′-OCH_3), 3.68* (3H, s, 6-OCH_3), 3.80* (3H, s, 4′-OCH_3), 5.51 (1H, s, H-1), 6.27 (1H, s, H-8), 6.65* (1H, s, H-5), 6.69* (1H, s, H-2′), 7.51 (1H, s, H-5′).

1-(3′,4′-Methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9q). $C_{18}H_{19}O_4N$. Prepared from **6** (1.66 g, 0.009 mol) and 3,4-methylenedioxybenzaldehyde (1.37 g, 0.009 mol) [14]. Yield 2.06 g (72%), mp 254–257°C (Me_2CO), R_f 0.5. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 2.5–3.0 (4H, H-3, 4), 3.45* (3H, s, 7-OCH_3), 3.66* (3H, s, 6-OCH_3), 4.86 (1H, s, H-1), 5.92* (2H, s, 3′, 4′-OCH_2O), 6.17 (1H, s, H-8), 6.62–6.87 (4H, m, H-5, Ar-H).

1-(6′-Bromo-3′,4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9r). $C_{18}H_{18}O_4NBr$. Prepared from **6** (2.54 g, 0.014 mol) and 6-bromo-3,4-methylenedioxybenzaldehyde (3.21 g, 0.014 mol). Yield 4.95 g (90%), mp 201–203°C (Me_2CO), R_f 0.52. Mass spectrum (70 eV): *m/z* 393/391 (M^+ 100, Br-79/81), 379/377 (24, Br-79/81), 363/361 (14/13, Br-79/81), 193 (22), 192 (65). PMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 2.98 and 3.05 (2H, m, H-4), 3.31 and 3.43 (2H, m, H-3), 3.53* (3H, s, 7-OCH_3), 3.73* (3H, s, 6-OCH_3), 5.78 (1H, s, H-1), 6.07* (2H, s, 3′, 4′-OCH_2O), 6.15 (1H, s, H-8), 6.65 (1H, s, H-5), 6.82 (1H, s, H-2′), 7.30 (1H, s, H-5′).

1-(6′-Bromo-3′,4′-methylenedioxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*N*-methyl 9r). Mass spectrum (70 eV): *m/z* 407/405, 392/390 $(M - 15)^+$, 361/359 $(M - 15 - OCH_3)^+$, 283 (31), 252, 207 (43), 206 (34), 191, 190 (24.8), 163 (22).

1-(6′-Chloro-3′,4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9s). $C_{18}H_{18}O_4NCl$. Prepared from **6** (2.2 g, 0.012 mol) and 6-chloro-3,4-methylenedioxybenzaldehyde (2.24 g, 0.012 mol). Yield 1.79 g (42%), mp 107–108°C (Me_2CO), R_f 0.55. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.8–2.85 (2H, ddd, J = 16.4, 6.2, 5.5, H-4), 3.03–3.11 (2H, dt, J = 12.1, 6.2, 6.2, H-3), 3.71* (3H, s, 7-OCH_3), 3.88* (3H, s, 6-OCH_3), 5.48 (1H, s, H-1), 5.92* (1H, d, J = 0.4, OCH_2O-3′, 4′), 5.93* (1H, d, J = 1.6, OCH_2O-3′, 4′), 6.27 (1H, s, H-8), 6.44 (1H, s, H-5), 6.63 (1H, s, H-2′), 6.88 (1H, s, H-5′).

1-(2′-Furanyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9t). $C_{15}H_{17}O_3N$. Prepared from **6** (1.56 g, 0.0086 mol) and furfurol (0.83 g, 0.0086 mol). Yield 0.78 g (35%), mp of hydrochloride 221–224°C (Me_2CO), R_f 0.55. PMR spectrum (100 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.5–3.0 (2H, m, H-4), 3.16 (2H, m, H-3), 3.54* (3H, s, 7-OCH_3), 3.65* (3H, s, 6-OCH_3), 4.97 (1H, s, H-1), 6.45 (1H, s, H-8), 6.61 (1H, s, H-5), 5.94 (d, J = 3, H-4′), 6.28 (dd, J = 3, 1, H-3′), 7.49 (d, J = 1, H-5′).

1,1′-Bis-[(4″,4‴-dihydroxy-5″,5‴-dimethoxyphenyl-3″,3‴-di)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline] (10). $C_{36}H_{40}N_2O_8$. Prepared from **6** (1.1 g, 0.0061 mol) and 2,2′-dihydroxy-3,3′-dimethoxy-5,5′-diformyldiphenyl (dehydrodivanillin) (1.0 g, 0.0033 mol). Yield 0.78 g (35%), mp of hydrochloride 178–185°C (Me_2CO), R_f 0.75 ($CHCl_3$:MeOH 2:1). PMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 2.0 (2H, s, H-2, 2′), 2.78 and 2.99 (8H, m, H-3, 3′, 4, 4′), 3.45* (3H, s,

7-OCH_3), 3.49* (3H, s, 6-OCH_3), 3.65* (6H, s, 6′, 7′-OCH_3), 3.69* (6H, s, 5″, 5‴-OCH_3), 5.03 (2H, s, H-1, 1′), 6.27 (2H, s, H-8, 8′), 6.54 (2H, s, H-5, 5′), 6.63 and 6.74 (4H, 2s, H-2″, 2‴, 6″, 6‴).

1,1′-Bis-[(4″-hydroxy-4‴,5″,5‴-trimethoxyphenyl-3″,3‴-di)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline] (11). $C_{37}H_{42}N_2O_8$. Prepared from **6** (0.65 g, 0.0036 mol) and 2-hydroxy-2′,3,3′-trimethoxy-5,5′-diformyldiphenyl (0.6 g, 0.0018 mol). Yield 0.87 g (71%), mp 198–203°C (Me_2CO), R_f 0.57 ($CHCl_3$:MeOH 2:1).

1,1′-Bis-(4″,4‴,5″,5‴-tetramethoxyphenyl-3″,3‴-di)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline] (12). $C_{38}H_{44}N_2O_8$. Prepared from **6** (1.68 g, 0.009 mol) and 2,2′,3,3′-tetramethoxy-5,5′-diformyldiphenyl (1.54 g, 0.0046 mol). Yield 2.41 g (79%), mp of hydrochloride 242–245°C (Me_2CO), R_f 0.5 ($CHCl_3$:MeOH 2:1). PMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 2.03 (2H, s, H-2, 2′), 3.33* (9H, s, 7, 6, 7′-OCH_3), 3.46* (6H, s, 6′, 5‴-OCH_3), 3.71* (6H, s, 4″, 4‴-OCH_3), 3.81* (3H, s, 5″-OCH_3), 5.59 (2H, s, H-1, 1′), 6.29 (1H, s, H-5), 6.31 (1H, s, H-5′), 6.45 (1H, s, H-8), 6.51 (1H, s, H-8′), 6.79 (2H, s, H-6″, 6‴), 7.3 (2H, s, H-2″, 2‴).

General Method for Preparing Alkaloids 2, 3, and 5 and the Methyl Derivative of 9r. A solution of 1-(3′,4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.7 g, 0.002 mol) in MeOH (20 mL) was treated with formalin (0.06 mL, 0.002 mol, 27%), refluxed for 1.5 h (TLC monitoring), cooled in ice, and reduced by $NaBH_4$ (1 g). The solvent was distilled off. The solid was dissolved in H_2O (10 mL) and extracted exhaustively with $CHCl_3$. The crude product was purified by producing the hydrochloride or by chromatography over SiO_2 using $CHCl_3$:MeOH (100:1→100:10). The product was crystallized from Me_2CO or MeOH.

1-(3′,4′-Methylenedioxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2). $C_{19}H_{21}O_4N$. Prepared from 1-(3′,4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.7 g, 0.002 mol) and formalin (0.06 mL, 0.002 mol, 27%). Yield 0.47 g (64%), mp 115–117°C (Me_2CO), R_f 0.82. NMR spectral data corresponded to those for cryptostylin [2].

1-(3′,4′-Dimethoxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3). $C_{20}H_{22}O_4N$. Prepared from 1-(3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1.0 g, 0.003 mol) and formalin (0.08 mL, 0.003 mol, 27%). Yield 0.84 g (81%), mp of hydrochloride 206–209°C (Me_2CO), R_f 0.81. NMR spectral data corresponded to those for cryptostylin II [2].

1-Phenyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5). $C_{18}H_{24}O_2N$. Prepared from 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.5 g, 0.0018 mol) and formalin (0.05 mL, 0.0018 mol, 27%). Yield 0.4 g (76%), mp of hydrochloride 234–239°C (Me_2CO), R_f 0.84. NMR spectral data corresponded to those for the natural alkaloid (unnamed) [6].

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