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SYNTHESIS OF HYDROXYETHYL DERIVATIVES OF 1-ARYLTETRAHYDROISOQUINOLINE ALKALOIDS

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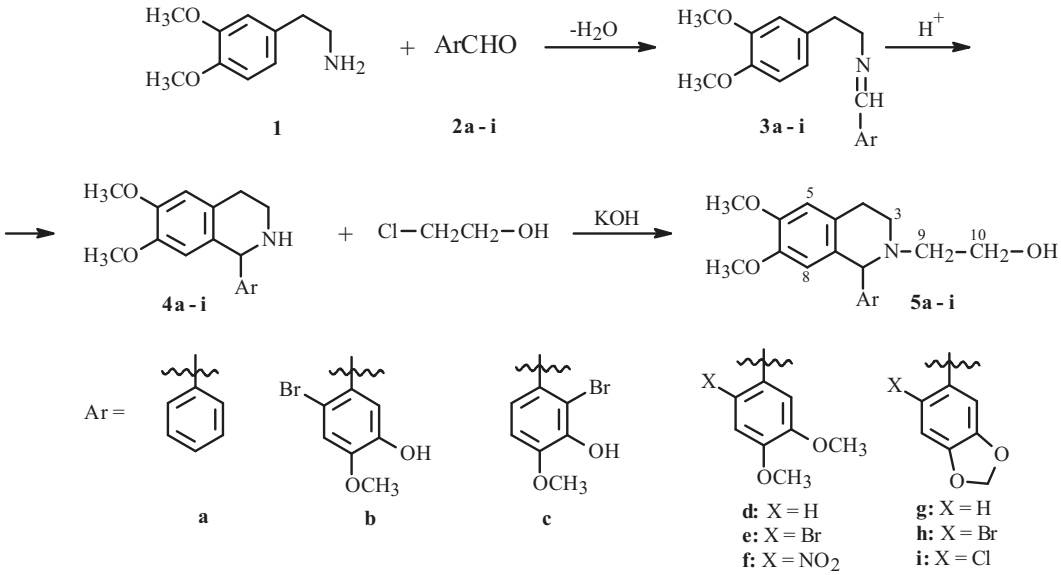
New hydroxyethyl derivatives of 1-aryltetrahydroisoquinoline alkaloids and diisoquinoline were prepared using a Pictet–Spengler reaction.

Keywords: Pictet–Spengler reaction, hydroxyethyl derivatives of 1-aryltetrahydroisoquinoline alkaloids.

The activity spectrum of known biologically active isoquinoline alkaloids and their analogs (papaverine, morphine, codeine, berberine, palmatine, emetine, glaucine, sanguinarine, α,β-bicuculine) is unusually broad [1]. Also, 1,2,3,4-tetrahydroisoquinoline derivatives include compounds exhibiting CNS depressant [2], NMDA receptor blocker [3], and other properties.

It is well known that over 4,000 compounds are synthesized in order to identify one active drug. Therefore, knowledge of the structure–activity relationships and the mechanism of action of drugs at the molecular level forms a foundation for predicting the biological properties of new compounds and their targeted synthesis. An example of an effective approach to the synthesis of new potentially biologically active structures is the PASS computer prediction of the biological activity of 1-(4′-methoxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. A preliminary pharmacological study showed that this compound at a dose of 5 mg/kg decreased the number of pain writhings in mice by an average of 56% and prolonged to 60 min the manifestation time of a reaction (hot-plate test) at a dose of 10 mg/kg. This surpassed significantly the analgesic activity of analgin in this test [4]. The results prompted the synthesis of a series of compounds of this class.

For this, homoveratrylamine (**1**) was condensed with aldehydes **2a**–**i**, producing in high yield the corresponding imines **3a**–**i**, which cyclized in acidic solution to racemic 1-phenyltetrahydroisoquinolines **4a**–**i** [5]. We used the previously developed method for synthesizing *N*-(β-hydroxyethyl)cytisine [6] in order to prepare the hydroxyethyl amine derivatives. Use of KOH and 70% EtOH instead of K_2CO_3 and EtOH increased the yields of **5a**, **5d**, and **7**.



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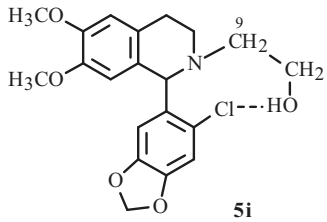
The structures of the obtained compounds were proved using IR and PMR spectra.

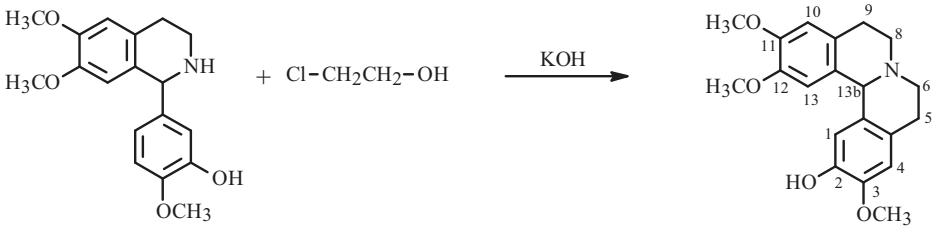
A comparison of the chemical shifts and the nature of the H-9 resonances of the 10 synthesized compounds showed that the hydroxyethyl protons appeared differently in **5a**–**i**. These protons in PMR spectra of **5b**, **c**, **e**, **f**, **h**, and **i** formed four independent resonances characteristic of a cyclic moiety instead of the expected two triplets. This was observed when the 1-phenyl radical had a halide or nitro group in the *o*-position. These compounds featured an intramolecular H-bond (e.g., an absorption band for **5i** at 3159 cm^{-1} in the IR spectrum) that formed a new ring and hindered free rotation of the hydroxyethyl group.



5i

Proton resonances in PMR spectra of **5a-i** were assigned based on COSY and NOESY NMR spectra using **5i** as an example.

It was expected that the reaction of 1-(3′-hydroxy-4′-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6**) and ethylenechlorohydrin would give 1-(3′-hydroxy-4′methoxyphenyl)-2-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. However, intramolecular alkylation under the conditions described above (methods A and B) led to the new tetracyclic diisoquinoline **7**.



6 **7**

The ring closure was proved rather convincingly based on PMR spectral data. Methine proton H-13b resonated at δ 5.046 ppm in the PMR spectrum of **7**. The Overhauser effect upon suppressing this resonance enabled the resonances of aromatic protons H-10 and H-13 to be found. Resonances of two aromatic protons (δ 7.064 and 6.569 ppm), three methoxy groups, and equatorial methylene protons H-9e and H-5e were also assigned using mutual Overhauser effects. Resonances of the methylene systems were assigned unambiguously in double-resonance experiments with sequential suppression of the aforementioned resonances.

The geminal pair H-8 appeared as a common 2H multiplet at δ 3.581 ppm; their vicinal partners H-9, as a separate resonance (br.dt) at δ 2.557 ppm and a component in a 3H multiplet at δ 2.73 ppm. The two other components of this multiplet belonged to axial protons H-5a and H-6a. The equatorial protons of this methylene system resonated at δ 3.248 ppm (multiplet H-5e overlapped with the MeOH resonance) and δ 2.992 ppm as a ddd for H-6e (see Experimental).

In contrast with **6**, **4d**, which had a methoxy instead of a hydroxy in the phenyl ring, did not cyclize. This was consistent with the presence of a hydroxyl band at 3265 cm^{-1} in the IR spectrum of **5d** and five resonances for aromatic protons in the PMR spectrum.

EXPERIMENTAL

IR spectra were recorded in KBr pellets and vaseline oil on an FTIR system 2000 instrument (PerkinElmer). PMR spectra of **5a**–**i** and **7** as the bases were recorded in $CDCl_3$ or MeOH-d_4 with HMDS internal standard on a Unity-400+ spectrometer (Varian). The R_f values were determined on silica gel LS 5/40 plates using $CHCl_3$–MeOH (4:1, 1; 6:1, 2; 12:1, 3). Melting points of all synthesized compounds were determined on a Boetius microstage. 1-(Aryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **4a**–**i** were prepared by a Pictet–Spengler reaction [5].

Preparation of Hydroxyethyl Derivatives of 1-(Aryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 5a–i. *Method A*. A solution of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydrosioquinoline (**4a**, **4d**, **8**, 2.0 g, 0.007 mol) in EtOH (20 mL)

was treated with ethylenechlorohydrin (1.5 mL, 0.021 mol) and a solution of KOH (0.43 g, 0.007 mol) in H_2O (10 mL) and refluxed for 3 h (TLC monitoring). The solvent was distilled off. The residue was dissolved in H_2O and extracted exhaustively with $CHCl_3$. The $CHCl_3$ was distilled off. The product was crystallized or converted to the hydrochloride.

Method B. A solution of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4a**–**i**, 2.0 g, 0.007 mol) in EtOH (30 mL) was treated with ethylenechlorohydrin (1.5 mL, 0.021 mol) and K_2CO_3 (2 g, 0.014 mol) and refluxed for 4–6 h (TLC monitoring). The mixture was worked up analogously as described above.

1-Phenyl-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5a). $C_{19}H_{23}NO_3$. Prepared by *method A* as the hydrochloride from **4a** (2.0 g, 0.007 mol), ethylenechlorohydrin (1.5 mL, 0.021 mol), and KOH (0.43 g, 0.007 mol). Yield 2.19 g (94%).

Prepared by *method B* as the hydrochloride from **4a** (1.0 g, 0.003 mol), ethylenechlorohydrin (0.7 mL, 0.009 mol), and K_2CO_3 (0.8 g). Yield 0.65 g (50%), mp of the hydrochloride 182–184°C (Me_2CO), R_f 0.86 (system 2).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.85–3.00 (2H, m, H-9), 3.15 (2H, m, H-4), 3.40 (2H, m, H-3), 3.55 (3H, s, 7-OCH_3), 3.60, 3.78 (each 1H, m, H-10), 3.79 (3H, s, 6-OCH_3), 4.91 (1H, s, H-1), 6.14 (1H, s, H-8), 6.59 (1H, s, H-5), 7.27 (5H, m, Ar-H).

1-(6′-Bromo-3′-hydroxy-4′-methoxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5b). $C_{20}H_{24}BrNO_5$. *Method B.* Prepared as the hydrochloride from **4b** (1.0 g, 0.0025 mol), ethylenechlorohydrin (0.5 mL, 0.0076 mol), and K_2CO_3 (0.78 g, 0.0056 mol). Yield 0.61 g (55%), mp of hydrochloride 179–182°C, R_f 0.74 (system 1).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.66 (1H, dt, J = 3.4, 3.4, 13.5, H_e-9), 2.78 (1H, m, H_a-3), 2.89 (1H, ddd, J = 3.9, 9.1, 12.9, H_e-4), 3.11 (1H, m, H_a-9), 3.34 (1H, m, H_a-4), 3.54 (1H, dt, J = 4.5, 8.5, 12.1, H_e-3), 3.66 (3H, s, 7-OCH_3), 3.75 (1H, m, H_e-10), 3.86* (3H, s, 6-OCH_3), 3.89* (3H, s, 4′-OCH_3), 3.99 (1H, m H_a-10), 5.10 (1H, s, H-1), 6.19 (1H, s, H-8), 6.60 (1H, s, H-5), 6.72 (1H, s, H-2′), 7.03 (1H, s, H-5′).

1-(2′-Bromo-3′-hydroxy-4′-methoxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5c). $C_{20}H_{24}BrNO_5$. *Method B.* Prepared as the hydrochloride from **4c** (1.0 g, 0.0025 mol), ethylenechlorohydrin (0.5 mL, 0.0076 mol), and K_2CO_3 (0.88 g, 0.006 mol). Yield 0.77 g (69%), mp of hydrochloride 168–169°C (Me_2CO), R_f 0.8 (system 3).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.53 (1H, dt, J = 3.5, 3.5, 12.7, H_e-9), 2.61 (1H, ddd, J = 4.4, 8.3, 12.5, H_a-3), 2.73 (1H, ddd, J = 5.1, 8.35, 13.0, H_e-4), 2.84 (1H, ddd, J = 4.6, 7.9, 12.7, H_a-9), 2.85 (1H, m, H_a-4), 3.13 (1H, dt, J = 5.3, 5.3, 12.5, H_e-3), 3.58 (1H, s, 7-OCH_3), 3.62 (1H, dt, J = 4.4, 7.9, 11.0, H_e-10), 3.69 (1H, ddd, J = 3.5, 7.5, 11.0, H_a-10), 3.80* (3H, s, 6-OCH_3), 3.81* (3H, s, 4′-OCH_3), 5.01 (1H, s, H-1), 6.16 (1H, s, H-8), 6.52 (1H, d, J = 8.5, H-5′), 6.54 (1H, s, H-5), 6.66 (1H, d, J = 8.5, H-6′).

1-(3′,4′-Dimethoxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5d). $C_{21}H_{27}NO_5$. *Method A*. Prepared as the hydrochloride from **4d** (1.98 g, 0.006 mol), ethylenechlorohydrin (1.1 mL, 0.016 mol), and KOH (0.68 g, 0.012 mol). Yield 2.04 g (91%).

Method B. Prepared as the hydrochloride from **4d** (0.5 g, 0.0015 mol) and ethylenechlorohydrin (0.3 mL, 0.0045 mol). Yield 0.35 g (62%), mp of hydrochloride 201–203°C (Me_2CO), R_f 0.57 (system 3). IR spectrum (KBr, ν_{max}, cm^{-1}): 3265 (OH), 2944, 2585, 1609 (C=C), 1523 (Ar–H), 1466 (CH_2), 1264, 1241 (C–O) 1162 (C–N).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.63 (1H, m, H-9), 2.71 (3H, m, H-4, 9), 3.11 and 3.34 (each 1H, m, H-3), 3.57 (1H, s, 7-OCH_3), 3.55 and 3.70 (each 1H, m, H-10), 3.77* (3H, s, 3′-OCH_3), 3.80* (3H, s, 6-OCH_3), 3.81* (3H, s, 4′-OCH_3), 4.69 (1H, s, H-1), 6.17 (1H, s, H-8), 6.57 (1H, s, H-5), 6.72 (1H, dd, J = 2, 8, H-6′), 6.75 (1H, d, J = 8, H-5′), 6.84 (1H, br. signal, H-2′).

1-(6′-Bromo-3′,4′-dimethoxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5e). $C_{21}H_{26}BrNO_5$. *Method B.* Prepared from **4e** (1.0 g, 0.0024 mol), ethylenechlorohydrin (0.32 mL, 0.005 mol), and K_2CO_3 (1.8 g, 0.013 mol). Yield 0.62 g (56%), mp 166–168°C (Me_2CO), R_f 0.77 (system 1).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.6 (OH), 2.52 (1H, dt, J = 3.2, 3.2, 13.4, H_e-9), 2.66 (1H, m, H_a-3), 2.79 (2H m, H_e-4, H_a-9), 3.04 (1H, ddd, J = 5.44, 10.5, 15.72, H_a-4), 3.26 (1H, dt, J = 4.4, 4.4, 11.5, H_e-3), 3.44 (1H, m, H_e-10), 3.65 (3H, s, 7-OCH_3), 3.69* (3H, s, 3′-OCH_3), 3.69 (1H, m, H_e-10), 3.86* (3H, s, 6-OCH_3), 3.88* (3H, s, 4′-OCH_3), 5.03 (1H, s, H-1), 6.21 (1H, s, H-8), 6.61 (2H, s, H-5, 2′), 7.03 (1H, s, H-5′).

1-(6′-Nitro-3′,4′-dimethoxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5f). $C_{21}H_{26}N_2O_7$. *Method B.* Prepared from **4f** (1.0 g, 0.0027 mol), ethylenechlorohydrin (0.54 mL, 0.008 mol), and K_2CO_3 (0.8 g, 0.006 mol). Yield 0.88 g (79%), mp 158–161°C (Me_2CO), R_f 0.62 (system 2).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.6 (OH), 2.53 (1H, dt, J = 3.4, 13.0, H_e-9), 2.66 (1H, ddd, J = 4.2, 9.0, 12.7, H_a-3), 2.74 (2H, m, H_e-4, H_a-9), 2.96 (1H, ddd, J = 5.3, 8.5, 15.3, H_a-4), 3.16 (1H, dt, J = 4.9, 4.9, 11.99, H_e-3), 3.46

(1H, m, H_e-10), 3.67 (3H, s, 7-OCH_3), 3.65–3.70 (1H, m, H_a-10), 3.74* (3H, s, 3′-OCH_3), 3.87* (3H, s, 6-OCH_3), 3.94* (3H, s, 4′-OCH_3), 5.4 (1H, s, H-1), 6.33 (1H, s, H-8), 6.62 (1H, s, H-5), 6.69 (1H, s, H-2′), 7.37 (1H, s, H-5′).

1-(3′,4′-Methylenedioxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5g). $C_{20}H_{23}NO_5$. *Method B.* Prepared as the hydrochloride from **4g** (1.5 g, 0.005 mol), ethylenechlorohydrin (0.9 mL, 0.013 mol), and K_2CO_3 (0.8 g, 0.006 mol). Yield 1.34 g (78%), mp of hydrochloride 149–152°C (Me_2CO), R_f 0.71 (system 3).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.56 (1H, dt, J = 4.4, 4.4, 12.9, H_e-9), 2.67 (1H, ddd, J = 4.6, 9.0, 12.0, H_a-3), 2.77 (1H, ddd, J = 5.4, 9.0, 16.0, H_e-4), 2.90 (1H, ddd, J = 4.4, 8.3, 12.9, H_a-9), 2.96 (1H, dt, J = 5.3, 5.3, 16.0, H_a-4), 3.19 (1H, dt, J = 5.5, 5.5, 12.0, H_e-3), 3.48 (1H, ddd, J = 4.4, 9.4, 11.1, H_e-10), 3.58 (3H, s, 7-OCH_3), 3.64 (1H, ddd, J = 4.4, 8.3, 11.1, H_a-10), 3.78 (3H, s, 6-OCH_3), 4.57 (1H, s, H-1), 5.85, 5.86 (each 1H, d, J = 1.5, 3′-OCH_2O-4′), 6.17 (1H, s, H-8), 6.55 (1H, s, H-5), 6.63 (1H, s, H-6′), 6.67 (1H, s, H-5′), 6.67 (1H, s, H-2′).

1-(6′-Bromo-3′,4′-methylenedioxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5h). $C_{20}H_{22}BrNO_5$. *Method B.* Prepared from **4h** (1.5 g, 0.004 mol), ethylenechlorohydrin (0.78 mL, 0.012 mol), and K_2CO_3 (0.8 g, 0.006 mol). Yield 1.17 g (77%), mp 143–144°C (MeOH), R_f 0.87 (system 2). IR spectrum (KBr, ν_{max}, cm^{-1}): 3425 (OH), 1610 (C=C), 1515 (Ar–H), 1476 (CH_2), 1251, 1225 (C–O), 1131 (C–N), 1040 (C–Br), 939, 928 (O–CH_2–O), 859, 804.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.47 (1H, dt, J = 3.5, 3.5, 12.7, H_e-9), 2.58 (1H, ddd, J = 4.0, 9.5, 12,0, H_a-3), 2.69 (1H, dt, J = 4.6, 4.2, 16.0, H_e-4), 2.76 (1H, ddd, J = 4.8, 9.8, 12.8, H_a-9), 2.92 (1H, ddd, J = 4.6, 9.5, 15.5, H_a-4), 3.16 (1H, dt, J = 4.5, 4.5, 11.8, H_e-3), 3.39 (1H, ddd, J = 3.6, 4.8, 11.0, H_e-10), 3.61 (3H, s, 7-OCH_3), 3.64 (1H, ddd, J = 3.5, 9.8, 11.0, H_a-10), 3.79 (3H, s, 6-OCH_3), 4.99 (1H, s, H-1), 5.86 (2H, s, 3′-OCH_2O-4′), 6.16 (1H, s, H-8), 6.50 (1H, s, H-2′), 6.54 (1H, s, H-5), 6.95 (1H, s, H-5′).

1-(6′-Chloro-3′,4′-methylenedioxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5i). $C_{20}H_{22}ClNO_5$. *Method B.* Prepared from **4i** (1.5 g, 0.004 mol), ethylenechlorohydrin (0.9 mL, 0.013 mol), and K_2CO_3 (0.8 g, 0.006 mol). Yield 1.46 g (87%), mp 157–159°C (MeOH), R_f 0.92 (system 2). IR spectrum (KBr, ν_{max}, cm^{-1}): 3503 (OH), 1613 (C=C), 1505 (Ar–H), 1474 (CH_2), 1248, 1225 (C–O), 1128 (C–N), 1033 (C–Cl), 929 (O–CH_2–O), 877, 859.

IR spectrum in vaseline oil (ν_{max}, cm^{-1}): 3501 (OH free), 3159 (intramolecular H-bond), 1611 (C=C), 1499 (Ar–H), 1306, 1222 (C–O), 1127 (C–N), 1032 (C–Cl), 928 (O–CH_2–O).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.49 (1H, dt, J = 3.7, 13.0, H_e-9), 2.58 (1H, ddd, J = 4.1, 9.3, 12,1, H_a-3), 2.70 (1H, dt, J = 4.1, 5.1, 15.7, H_e-4), 2.73 (1H, ddd, J = 4.9, 9.6, 13.0, H_a-9), 2.89 (1H, ddd, J = 5.1, 9.3, 15.7, H_a-4), 3.15 (1H, dt, J = 5.1, 5.1, 12.1, H_e-3), 3.41 (1H, ddd, J = 3.7, 4.9, 11.1, H_e-10), 3.61 (3H, s, 7-OCH_3), 3.63 (1H, ddd, J = 3.7, 9.6, 11.1, H_a-10), 3.79 (3H, s, 6-OCH_3), 5.02 (1H, s, H-1), 5.86 (2H, s, 3′-OCH_2O-4′), 6.14 (1H, s, H-8), 6.47 (1H, s, H-2′), 6.54 (1H, s, H-5), 6.78 (1H, s, H-5′).

3,11,12-Trimethoxy-6,8,9,13b-tetrahydro-5*H*-isoquinolino[1,2-*a*]isoquinolin-2-ol (7). $C_{20}H_{23}NO_4$. *Method A.* Prepared as the hydrochloride from **6** (2.0 g, 0.006 mol), ethylenechlorohydrin (1 mL, 0.015 mol), and KOH (0.37 g). Yield 1.93 g (85%).

Method B. Prepared from **6** (1.0 g, 0.003 mol), ethylenechlorohydrin (0.7 mL, 0.01 mol), and K_2CO_3 (1.85 g, 0.013 mol) as the hydrochloride. Yield 0.6 g (53%), mp of hydrochloride 188–191°C, R_f 0.59 (system 2).

PMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 2.557 (1H, br.td, J = 13.2, 6.5, H-9*a*), 2.68–2.78 (3H, m, H-9e, 6*a*, 5*a*), 2.992 (1H, ddd, J = 15.7, 10.2, 6.2, H-6e), 3.248 (1H, d, H-5e), 3.508 (3H, s, 12-OCH_3), 3.581 (2H, m, H-8), 3.731* (3H, s, 11-OCH_3), 3.788 (3H, s, 3-OCH_3), 5.046 (1H, br.s, H-13b), 6.163 (1H, s, H-13), 6.569 (1H, s, H-1), 6.653 (1H, s, H-10), 7.064 (1H, s, H-4).

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