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Deoxygenation of Phenolic Alkaloids by a Modified Pd/C-Catalyzed Hydrogenolysis Method

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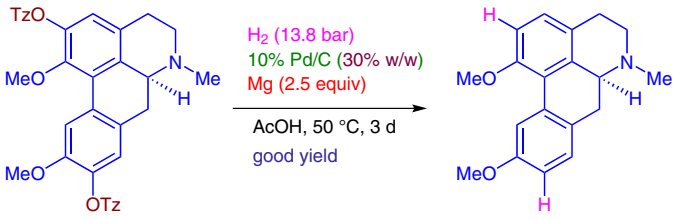

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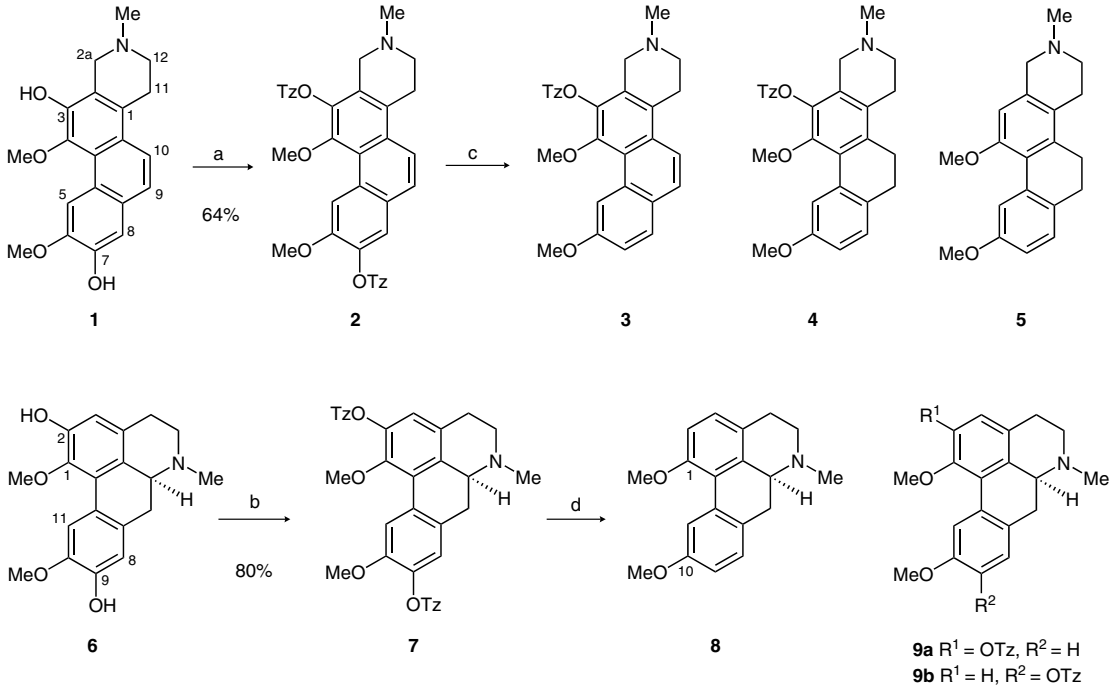
Abstract A modified palladium on carbon (Pd/C) catalyzed hydrogenolysis method for the removal of the phenolic-OH group in phenolic alkaloids as the 1-phenyl-1*H*-tetrazol-5-yl derivative by the addition of magnesium metal or ammonium acetate in acetic acid is described. Five different types of isoquinoline alkaloids, i.e., phenanthrene alkaloid, aporphine, pavine, protoberberine, and 1-benzyltetrahydroisoquinoline, were used as reactants. The results indicate that the addition of either magnesium metal or ammonium acetate has the advantage of decreasing the amount of Pd/C and the accelerating reaction rate over the simple Pd/C-catalyzed hydrogenolysis, thus it is practical for larger-scale preparation of de-phenolated alkaloids for pharmacological study.

Key words phenolic alkaloids, de-phenolation, 1-phenyl-1*H*-tetrazol-5-yl ether, ammonium acetate, magnesium

Phenolic alkaloids are widely present in several plant families and they are reported to possess a variety of pharmacological activity. For the study of structure-activity relationships (SARs), chemical modification of these bioactive compounds to obtain various derivatives is essential. Removal of the phenolic-OH groups is an important approach to clarify the role of this functional group in the pharmacological activity. Some direct methods, such as using reducing agents or Lewis acids, have been developed for this purpose.[1] However, they generally encounter the drawbacks of requiring large amounts of reagent and give low yields. Indirect methods, converting the phenolic-OH into electron-withdrawing groups, including sulfonate,[2,3] dimethyl thiocarbonate,[4] isourea,[4] aryl ether,[5] 1-phenyl-1*H*-tetrazol-5-yl ether,[6] and phosphate ester,[7] followed by reductive removal of these groups, are another approach. Among these, palladium on carbon (Pd/C) catalyzed hydrogenolysis of the 1-phenyl-1*H*-tetrazol-5-yl ether or triflate to give non-phenolic compounds is commonly used. However, these methods are sometimes unsatisfactory in alkaloid chemistry, presumably due to steric hindrance or amine chemistry. For example, the 1-phenyl-1*H*-tetrazol-5-yl ether method usually requires larger amounts of Pd/C than are generally used for catalytic hydrogenation (≥40% vs. 10%, w/w) to complete the reaction[8] and thus it is not practical for larger-scale preparations. The triflate ether method sometimes gives lower yields when preparing the phenolic triflate ether of alkaloids with the commonly used conditions (Tf_2NPh, base, r.t.) because of steric effects or solubility problems. For example, when litebamine (**1**) was converted into the bis(triflyl ether), the yield was lower than 30%,[9] making subsequent de-phenolation impractical. The reason for the lower yield could be due to the poor solubility of **1** that arises from the planar phenanthrene core structure.

Sajiki and co-workers have reported that the Pd/C-catalyzed deoxygenation of phenol triflates or mesylates can be undertaken efficiently with the aid of magnesium metal and methanol in the presence of ammonium acetate without the use of hydrogen gas.[3] Attempts to use this method to remove phenolic groups for phenolic alkaloids were made, but unfortunately, this approach was unsuccessful using boldine triflate, prepared from boldine (**6**), as the reactant. Thus this method might not be applicable to some substrates that have secondary or tertiary amine moieties within the molecules, such as alkaloids, due to the catalyst poisoning effect of the amine moiety. Since both 1-phenyl-1*H*-tetrazol-5-yloxy (TzO) and triflyl groups are electron-withdrawing, Sajiki's method was adopted using the *O*,*O*-bis(1-phenyl-1*H*-tetrazol-5-yl) derivative of **6**, i.e., **7**. However, removal of the 1-phenyl-1*H*-tetrazol-5-yloxy group this derivative did not occur under neutral (MeOH) or acidic (AcOH) conditions. While in the presence of hydrogen gas and either magnesium or ammonium acetate under acidic conditions (AcOH), we found that not only the reaction was successful, but also that the reaction rate increased dramat-



Scheme 1 *Reagents and conditions*: (a) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, DMF, 90 °C, 2 h; (b) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, KI, MeCN, 90 °C, 1 d; (c) see Table 1; (d) see Table 2.

ically. Accordingly, optimization and application of this modified Pd/C-catalyzed method on compounds of five-type isoquinoline alkaloids, the phenanthrene alkaloid litebamine (**1**), the aporphine boldine (**6**), 8/9-hydroxy-2,3-dimethoxypavine (**10**), 2,3-dihydroxy-9,10-dimethoxyprotoberberine (**13**), and the benzylisoquinoline reticuline (**16**), were undertaken.

Reaction of 3,7-*O*,*O*-bis(1-phenyl-1*H*-tetrazol-5-yl)litebamine (**2**), prepared from litebamine (**1**) by reaction with 5-chloro-1-phenyl-1-*H*-tetrazole with potassium carbonate as the base, with 50% w/w of 10% Pd/C and under 13.8 bar hydrogen hydrogenolyzed only the 7-OTz group to give 3-*O*-(1-phenyl-1*H*-tetrazol-5-yl)-7-dehydroxylitebamine (**3**), followed by hydrogenation of the C9–C10 double bond to yield 3-*O*-(1-phenyl-1*H*-tetrazol-5-yl)-7-dehydroxy-9,10-dihydrolitebamine (**4**) (Scheme 1). This reaction gave low yields of **3** and **4** together with the recovery of starting material **2** (Table 1, entry 1). The ^{1}H NMR spectrum of **3** showed an AMX system for H5, H7, and H8 at δ = 8.83, 7.26, and 7.83, respectively, and an AB system for H9 and H10 at δ = 7.80 and 7.78 (*J* = 9.1 Hz), while that of **4** showed a similar AMX system for H5, H7, and H8, but an A_2B_2 system for H9 and H10 at δ = 2.82 and 2.72, supporting their structures.

A similar result was also found when removing the 1-phenyl-1*H*-tetrazol-5-yloxy group from 2,9-*O*,*O*-bis(1-phenyl-1*H*-tetrazol-5-yl)boldine (**7**). Low yield (25%) with incomplete hydrogenolysis took place while reaction of **7** with 40% weight of 10% Pd/C (Table 2, entry 1). Increasing the amount of 10% Pd/C up to 70% w/w and prolonging the reaction time up to seven days did not improve the yield, instead more byproducts were produced. The problem of

Table 1 Effect of Ammonium Acetate on the Pd/C Assisted Hydrogenolysis of **2** in Acetic Acid at 50 °C

Entry	Reactant **2**	10% Pd/C (w/w)	NH_4OAc (equiv)	H_2 (bar)	Time (d)	Products [yield (%)]
1	105.1 mg	50%	–	13.8	3	**3** (16) + **4** (16) + **2**
2	51.7 mg	50%	3	13.8	1.5	**3** (5) + **4** (50) + **5** (35)
3	10.6 mg	50%	6	13.8	3	**4** + **5** (31:69)[a]
4	1.0 g	30%	10	13.8	4	**5** (64)
5	10.5 mg	30%	10	1	2	**3** major

[a] The ratio was determined by ^{1}H NMR (200 MHz) spectroscopic analysis of the mixture without purification.

Table 2 Effect of Magnesium and Hydrogen on the Pd/C Assisted Hydrogenolysis of **7** in Acetic Acid at 50 °C

Entry	Reactant (**7**)	10% Pd/C (w/w)	Mg (equiv)	H_2 (bar)	Time (d)	Products [yield (%)]
1	500.0 mg	40%	–	13.8	3	**8** (25) + **7**
2	19.3 mg	50%	3	13.8	3	**8** (~100)[a]
3	101.4 mg	30%	3	13.8	3	**8** (~100)[a]
4	6.8 g	30%	2.5	13.8	3	**8** (87)
5	20.4 mg	30%	2.5	6.9	3	**8** + **9a** + **9b** + **7** (22:19:48:11)[b]
6	20.3 mg	30%	2.5	4.8	3	**8** + **9a** + **9b** + **7** (13:19:32:36)[b]
7	20.8 mg	30%	2.5	1	3	no reaction

[a] The product without purification is ^{1}H NMR essentially pure.
[b] The ratio was determined by ^{1}H NMR (400 MHz) spectroscopic analysis.

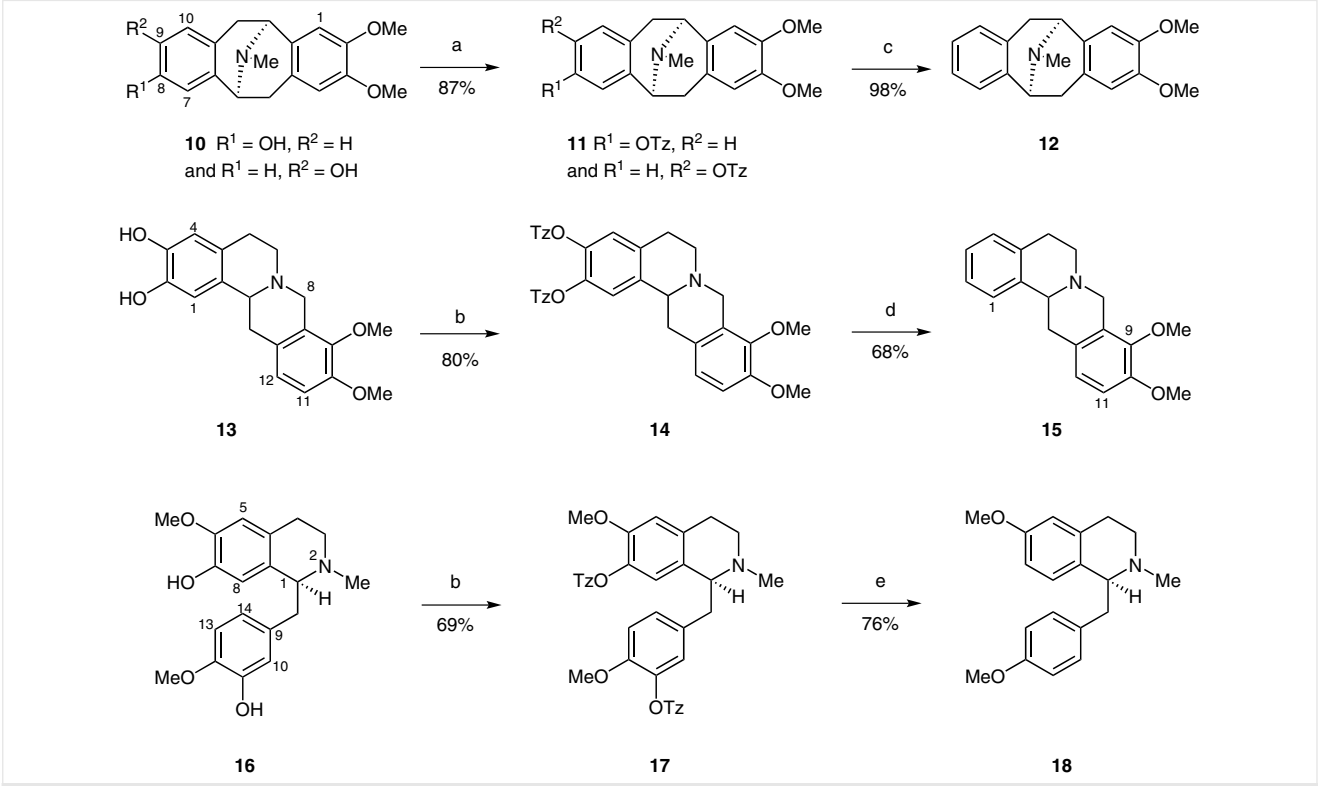
the incomplete reaction described above was solved by addition of ammonium acetate or magnesium metal. Under the optimized conditions, 10% Pd/C (30%, w/w), ammonium acetate (10 equiv), hydrogen (13.8 bar), acetic acid (50 °C, 4 d; Table 1, entry 4), exhaustive hydrogenolysis of **2** was achieved to give **5** exclusively in 64% isolated yield on 1.0 gram scale. The ^{1}H NMR spectrum of **5** showed signals for H5, H7, and H8 as an AMX system at δ = 7.86, 6.73, and 7.12, respectively, and a singlet for H3 (δ = 6.55), supporting its structure. Complete hydrogenolysis of **7** was achieved under the optimized conditions of 10% Pd/C (30%, w/w), magnesium (3 equiv), hydrogen (13.8 bar) (50 °C, 3 d; Table 2, entry 3) to afford **8** almost quantitatively on a 0.1 gram scale.

The ^{1}H NMR spectrum of **8** showed an AB system for H2 and H3 (δ = 6.88 and 7.04; J = 8.4 Hz) and an AMX system for H8, H9, and H11 at δ = 7.17, 6.78, and 7.90, respectively, supporting its structure.

The effect of the amount of ammonium acetate added on the Pd/C-assisted hydrogenolysis was evaluated. The reaction rate was found to be proportional to the amount of ammonium acetate added (Table 1). Complete hydrogenolysis on **2** cannot be achieved in the presence of 3–6 equivalents of ammonium acetate [H_2 (13.8 bar), 50 °C, 1.5–3 d] (Table 1, entries 2 and 3). Both *O*-(1-phenyl-1*H*-tetrazol-5-yl) groups at the C3 and C7 positions in **2** could be removed readily, accompanied by hydrogenation at the C9–C10 double bond, increasing the amount of ammonium acetate to 10 equivalents required a reaction time of four days (Table 1, entry 4). Under 1 bar hydrogen, the addition of 10 equivalents of ammonium acetate removed the 7-*O*-(1-phenyl-1*H*-tetrazol-5-yl) group readily to give **3** as the major product in two days without affecting the C9–C10 double bond (Table 1, entry 5). This study indicated that the addition of ammonium acetate could accelerate the reaction rate and reduce the amount of Pd/C used. The relative reaction rate of this modified method on the reactive sites in **2** was found to be 7-*O*-Tz >Δ^9 > 3-*O*-Tz.

The effect of magnesium metal and hydrogen pressure on the Pd/C-assisted hydrogenolysis was evaluated using 2,9-*O*,*O*-bis(1-phenyl-1*H*-tetrazol-5-yl)boldine (**7**) as the reactant (Table 2). Complete hydrogenolysis could be achieved to yield 1,10-dimethoxyaporphine (**8**) when magnesium metal was added. Addition of three equivalents of magnesium metal could reduce the amount of Pd/C from 70% to 30% w/w (H_2, 13.8 bar) (Table 2, entry 3). The amount of magnesium metal could be further reduced to 2.5 equivalents when the reaction was performed on a gram scale (Table 2, entry 4). Decreasing the pressure of hydrogen gave a lower reaction rate resulting in incomplete reaction and low yield (Table 2, entries 5–7). Although the amount of Pd/C used is up to 30% w/w, it has been reduced to some extent compared to the previous method (≥40% w/w). Pd/C-catalyzed reduction of aporphine triflates also used higher amounts of Pd/C (about 20% w/w).[10] This phenomenon could be attributed to alkaloids amine chemistry.

To explore the scope of this modified Pd/C assisted hydrogenolysis method, removal of the phenolic group on three isoquinoline alkaloids of different type were investigated (Scheme 2). 8/9-Hydroxy-2,3-dimethoxypavine (**10**),[11] prepared by sodium/liquid ammonia reductive cleavage of *O*-methylcaryachine, was converted into 2,3-dimethoxy-8/9-*O*-(1-phenyl-1*H*-tetrazol-5-yl)pavine **11** by a method similar to that described above. Without adding magnesium, complete hydrogenolysis on **11** to give **12** could not be reached (82% yield + **11**) using 50% (w/w) 10% Pd/C [H_2 (3.4 bar), AcOH, 50 °C, 3 d]. This reaction yielded 2,3-dimethoxypavine (**12**) in 98% isolated yield when 1.3 equivalents of magnesium were added to the reaction mixture, with the amount of 10% Pd/C reduced to 30% (w/w). The ^{1}H NMR spectrum of **12** showed signals for four aryl protons at δ = 7.11–7.04 (m, 3 H) and 6.95 (br d, J = 7.3 Hz, 1 H) and for H1 and H4 as two singlets at δ = 6.59 and 6.41, respectively, supporting its structure. 2,3-Dihydroxy-9,10-dimethoxyprotoberberine (**13**) and reticuline (**16**) were also converted into the corresponding *O*,*O*-bis(1-phenyl-1*H*-tetrazol-5-yl) derivatives **14** and **17**, respectively. Subsequent hydrogenolysis using this modified method with



Scheme 2 *Reagents and conditions*: (a) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, acetone, reflux, 1 d; (b) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, KI, MeCN, reflux, 1 d; (c) 10% Pd/C (30% w/w), Mg (1.3 equiv), H_2 (3.4 bar), AcOH, 50 °C, 3 d; (d) 10% Pd/C (30% w/w), Mg (2.5 equiv), H_2 (13.8 bar), AcOH, 50 °C, 2.5 d; (e) 10% Pd/C (35% w/w), Mg (4 equiv), H_2 (13.8 bar), AcOH, 50 °C 3 d.

similar reaction conditions gave 9,10-dimethoxyprotoberberine (**15**) and 7,11-didehydroxyreticuline (**18**) in 68% and 76% yields, respectively (Scheme 2). The ^{1}H NMR spectrum of **15** showed signals for six aryl protons, including four between δ = 7.30 and δ = 7.10 (m) and two as an AB system at δ = 6.86 and 6.79 (J = 8.4 Hz) for H11 and H12, supporting its structure. The ^{1}H NMR spectrum of **18** showed signals for seven aryl protons, including an AA′BB′ system for H10/H14 at δ = 6.98 and H11/H13 at δ = 6.77 (J = 8.6 Hz) and an overlapped three-proton signal at δ = 6.58 for H5, H7, and H8, supporting its structure.

Based on the mechanistic study of Pd/C-catalyzed reduction of aryl sulfonates proposed by Mori et al.,[12] ammonium acetate will dissociate to ammonia and acetic acid. The generated ammonia will coordinate to the Pd(0) center to enhance the electron density of palladium, speeding up palladium-mediated electron transfer to the aromatic ring. The magnesium metal, on the other hand, will reduce Pd(II) to the active Pd(0), accelerating the single-electron-transfer (SET) process.

In summary, a modified method for complete removal of the phenolic–OH group from phenolic alkaloids of various types involving conversion into the corresponding 1-phenyl-1*H*-tetrazol-5-yl ethers and reduction using Pd/C and either magnesium metal or ammonium acetate under moderate hydrogen pressure in acetic acid was developed. The reactivity, reaction rate, and yield are improved to a great extent by the addition of either magnesium or ammonium acetate. Moreover, the amount of Pd/C used in these conditions is significantly lower, making this modified method more practical for larger-scale preparations of the de-phenolated alkaloids.

IR spectra were obtained using a Jasco FT/IR-410. NMR spectra were recorded on a Bruker Avance 400 spectrometer (Bremen, Germany) using $CDCl_3$ as calculated standard. Mass spectra were measured on an Esquire 2000 ion trap mass spectrometer (ESIMS) and a microOTOF orthogonal ESI-TOF mass spectrometer (HRESIMS) (Bruker Daltonics, Bremen, Germany). Column chromatography was carried out on Silica gel 60 (40–63 μm) or alumina (neutral, 70–230 mesh), purchased from Merck. Litebamine (**1**) and 2,3-dihydroxy-9,10-dimethoxyprotoberberine (**13**) were prepared according to the reported procedure;[13,14] reticuline (**16**) was isolated from *Neolitsea konishii*.[15] All other reagents and solvents used are commercially available.

3,7-*O*,*O*-Bis(1-phenyl-1*H*-tetrazol-5-yl)litebamine (2); Typical Procedure

To a mixture of litebamine (**1**, 903 mg, 2.7 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (1.2 g, 6.7 mmol), and K_2CO_3 (2.2 g, 15.9 mmol) in DMF (40 mL) was stirred at 90 °C. After completion of the reaction (TLC), the solvent was removed in vacuo and the residue was suspended in $CHCl_3$ (80 mL), washed with water (3 × 80 mL), dried (anhyd Na_2SO_4), and evaporated to dryness. The residue was chromatographed (silica gel, 70 g, 0.5–10% MeOH–$CHCl_3$, saturated with 25% aq NH_3) to yield **2** (1.1 g, 64%) as a yellowish amorphous solid.

IR (KBr): 2936, 1541, 1523, 1507, 1457, 1375, 1295, 1255 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.02 (s, 1 H, H5), 7.92 (s, 1 H, H8), 7.90–7.87 (m, 4 H, Tz-H), 7.76 (d, *J* = 9.3 Hz, 1 H, H10), 7.75 (d, *J* = 9.3 Hz, 1 H, H9), 7.65–7.48 (m, 6 H, Tz-H), 4.18 (br s, 2 H, H2a), 3.90 (s, 3 H, 6-OMe), 3.63 (s, 3 H, 4-OMe), 3.51 (br s, 2 H, H12), 3.26 (br s, 2 H, H11), 2.78 (s, 3 H, NMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (Cq), 159.8 (Cq), 149.8 (Cq), 148.0 (Cq), 142.6 (Cq), 142.5 (Cq), 134.4 (Cq), 133.3 (Cq), 133.1 (Cq), 131.1 (Cq), 130.3 (Cq), 130.0 (CH), 129.8 (CH), 129.7 (CH), 129.4 (CH), 128.9 (Cq), 128.1 (CH), 127.4 (Cq), 123.1 (Cq), 122.2 (CH), 122.2 (CH), 120.2 (CH), 119.8 (CH), 110.0 (CH), 61.2 (CH_3), 56.1 (CH_3), 51.3 (CH_2), 50.9 (CH_2), 44.3 (CH_3), 24.9 (CH_2).

MS (ESI): *m*/*z* = 628 ($[M + H]^+$).

2,9-*O*,*O*-Bis(1-phenyl-1*H*-tetrazol-5-yl)boldine (7)

Prepared according to the typical procedure using boldine (**6**; 5.2 g, 14.3 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (6.5 g, 35.7 mmol), K_2CO_3 (10.0 g, 72.4 mmol), with addition of KI (129.2 mg, 0.8 mmol) with MeCN (250 mL) as the solvent at 90 °C for 1 d. Colorless amorphous solid; yield: 7.0 g (80%).

IR (KBr): 2957, 2839, 2806, 1619, 1537, 1502, 1452, 1, 1393, 1317, 1294, 1236, 1072, 1000, 759 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1 H, H11), 7.87–7.84 (m, 4 H, Tz-*H*), 7.58–7.54 (m, 4 H, Tz-H), 7.50–7.48 (m, 2 H, Tz-H), 7.31 (s, 1 H, H8), 7.19 (s, 1 H, H3), 3.77 (s, 3 H, 10-OMe), 3.48 (s, 3 H, 1-OMe), 3.17–3.03, 2.76–2.57, 2.54 (m, 7 H), 2.54 (s, 3 H, NMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (Cq), 159.9 (Cq), 149.2 (Cq), 146.4 (Cq), 146.1 (Cq), 141.6 (Cq), 134.8 (Cq), 133.3 (Cq), 133.2 (Cq), 130.6 (Cq), 130.4 (Cq), 129.8 (CH), 129.6 (CH), 129.5 (Cq), 129.5 (CH), 129.3 (CH), 127.6 (Cq), 122.1 (CH), 122.1 (CH), 120.8 (CH), 120.7 (CH), 112.9 (CH), 62.3 (CH), 61.1(CH_3), 56.3 (CH_3), 52.7 (CH_2), 43.8 (CH_3), 33.4 (CH_2), 28.8 (CH_2).

MS (ESI): *m*/*z* = 616 ($[M + H]^+$).

2,3-Dimethoxy-8-*O*-(1-phenyl-1*H*-tetrazol-5-yl)pavine (11a) and 2,3-Dimethoxy-9-*O*-(1-phenyl-1*H*-tetrazol-5-yl)pavine (11b)

Prepared according to the typical procedure using 8/9-hydroxy-2,3-dimethoxypavine (**10**; 780.0 mg, 2.5 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (500.0 mg, 2.8 mmol), K_2CO_3 (2.0 g, 14.5 mmol), with acetone (50 mL) as the solvent at reflux for 1 d. Colorless amorphous solid; yield: 992.0 mg (80%).

IR (KBr): 2905, 2832, 1596, 1541, 1497, 1450, 1239, 1214, 1126, 1109, 1095, 1019, 759 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.71 (m, 4 H, Tz-H), 7.23–7.02 (m, 6 H), 6.58 (s, 1 H), 6.57 (s, 1 H), 6.42 (s, 1 H), and 6.41 (s, 1 H) (H1, H4), 4.12 (d, 1 H), 4.10 (d, 1 H), 4.04 (d, 1 H), and 4.03 (d, 1 H) (H6, H12), 3.83 (s, 3 H) and 3.82 (s, 3 H) (2-OMe), 3.76 (s, 6 H, 3-OMe), 3.50–3.39 (m, 4 H, H5α, H11α), 2.73 (1 H), 2.71 (1 H), 2.62 (1 H), and 2.57 (1 H) (each d, *J* = 16.6 Hz) (H5β, H11β), 2.531 (3 H) and 2.525 (3 H) (each s, NMe).

MS (ESI): *m*/*z* = 456 ($[M + H]^+$).

9,10-Dimethoxy-2,3-*O*,*O*-bis(1-phenyl-1*H*-tetrazol-5-yl)protoberberine (14)

Prepared according to the typical procedure using 2,3-dihydroxy-9,10-dimethoxyprotoberberine (**13**; 83.7 mg, 0.2 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (128.9 mg, 3.0 mmol), K_2CO_3 (417.8 mg, 72.4 mmol), with addition of KI (6.4 mg, 0.1 mmol) with MeCN (4 mL) as the solvent at reflux for 1 d. Colorless amorphous solid; yield: 113.1 mg (80%).

IR (KBr): 2939, 2831, 1596, 1548, 1531, 1501, 1454, 1329, 1279, 1082, 759 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H) and 7.55 (s, 1 H) (H1, H4), 7.42–7.37 (m, 10 H, Tz-H), 6.87 (d, *J* = 8.4 Hz, 1 H, H11), 6.80 (d, *J* = 8.4 Hz, 1 H, H12), 4.37 (br d, 1 H), 4.09 (m, 1 H), 3.86 (s, 3 H) and 3.84 (s, 3 H) (9-OMe, 10-OMe), 3.73 (m, 1 H), 3.44–3.23 (m, 3 H) and 3.10–2.92 (m, 3 H) (H5, H6, H13).

^{13}C NMR (100 MHz, CD_3CN): δ = 160.1 (Cq), 159.9 (Cq), 151.4 (Cq), 145.7 (Cq), 143.0 (Cq), 142.8 (Cq), 135.3 (Cq), 133.4 (Cq), 133.3 (Cq), 130.7 (CH), 130.5 (CH), 130.5 (CH), 127.0 (Cq), 124.8 (CH), 123.3 (CH), 123.2 (CH), 122.8 (CH), 120.6 (CH), 112.6 (CH), 60.4 (CH_3), 59.5 (CH), 56.3 (CH_3), 53.3 (CH_2), 50.9 (CH_2), 35.1 (CH_2), 28.5 (CH_2).

MS (ESI): *m*/*z* = 616 ($[M + H]^+$).

7,11-*O*,*O*-Bis(1-phenyl-1*H*-tetrazol-5-yl)reticuline (17)

Prepared according to the typical procedure using reticuline (**16**; 100.9 mg, 0.3 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (171.6 mg, 0.9 mmol), K_2CO_3 (442.3 mg, 3.2 mmol), with addition of KI (10.9 mg, 0.1 mmol) with MeCN (5 mL) as the solvent at reflux for 1 d. Colorless amorphous solid; yield: 118.9 mg (63%).

IR (KBr): 2937, 2840, 1596, 1543, 1504, 1453, 1297, 1267, 1087, 1019, 758 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.80 (m, 4 H, Tz-H), 7.54–7.51 (m, 4 H, Tz-H), 7.46–7.43 (m, 2 H, Tz-H), 7.13 (d, *J* = 2.0 Hz, 1 H, H10), 6.96 (dd, *J* = 2.0, 8.4 Hz, 1 H, H14), 6.83 (d, *J* = 8.4 Hz, 1 H, H13), 6.75 (s, 1 H) and 6.68 (s, 1 H) (H5, H8), 3.71 (s, 3 H) and 3.68 (s, 3 H) (6-OMe, 12-OMe), 3.69 (m, 1 H, H1), 3.15–3.03 (m, 2 H), 2.89–2.72 (m, 4 H), 2.49 (s, 3 H, NMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1 (Cq), 160.0 (Cq), 148.6 (Cq), 148.4 (Cq), 141.9 (Cq), 140.1 (Cq), 134.3 (Cq), 133.3 (Cq), 133.2 (Cq), 132.2 (Cq), 129.7 (Cq), 129.5 (CH), 129.1 (CH), 129.1 (CH), 122.7 (CH), 122.3 (CH), 122.2 (CH), 120.7 (CH), 112.9 (CH), 112.6 (CH), 64.3 (CH), 55.8 (CH_3), 55.8 (CH_3), 47.0 (CH_2), 42.7 (CH_3), 39.9 (CH_2), 26.2 (CH_2).

MS (ESI): *m*/*z* = 618 ($[M + H]^+$).

3,7-Didehydroxy-9,10-dihydrolitebamine (5); Typical Procedure

To a solution of compound **2** (1.0 g, 1.6 mmol) in AcOH (50 mL) was added 10% Pd/C (326.6 mg, 30% w/w) and NH_4OAc (1.2 g). The mixture was stirred at 50 °C under 13.8 bar of H_2 for 4 d. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was suspended in H_2O (70 mL) and the pH of the solution was adjusted to 7–8 by 25% aq NH_3, extracted by $CHCl_3$ (3 × 70 mL). The combined organic layers were dried (anhyd Na_2SO_4) and evaporated under reduced pressure to give a residue which was chromatographed (alumina, 4.5 g, 3–20% EtOAc–hexanes) to give 3,7-didehydroxy-9,10-dihydrolitebamine (**5**, 317.9 mg, 64%) as a yellowish oil.

IR (KBr): 2932, 2833, 2779, 1602, 1462, 1313, 1117, 1098 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 2.6 Hz, 1 H, H5), 7.12 (d, *J* = 8.2 Hz, 1 H, H8), 6.73 (dd, *J* = 2.6, 8.2 Hz, 1 H, H7), 6.55 (s, 1 H, H3), 3.83 (s, 3 H, 6-OMe), 3.81 (s, 3 H, 4-OMe), 3.59 (br s, 2 H), 2.79–2.59 (m, 8 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}NO_2$: 310.1807; found: 310.1812.

3-*O*-(1-Phenyl-1*H*-tetrazol-5-yl)-7-dehydroxylitebamine (3) and 3-*O*-(1-phenyl-1*H*-tetrazol-5-yl)-7-dehydroxy-9,10-dihydrolitebamine (4)

Prepared according to the typical procedure using **2** (51.7 mg, 0.08 mmol), 10% Pd/C (25.9 mg, 50% w/w), and NH_4OAc (20.9 mg, 0.27 mmol) with AcOH (4 mL) as the solvent at 50 °C under 13.8 bar of H_2 for 1.5 d. Both **3** (2.3 mg, 6%) and **4** (20.4 mg, 50%) were obtained as yellowish oils.

3-*O*-(1-Phenyl-1*H*-tetrazol-5-yl)-7-dehydroxylitebamine (3)

^1H NMR (400 MHz, $CDCl_3$): δ = 8.83 (d, *J* = 2.4 Hz, 1 H, H-5), 7.98–7.96 (m, 2 H, Tz-H), 7.83 (d, *J* = 8.7 Hz, 1 H, H-8), 7.80 (d, *J* = 9.1 Hz, 1 H) and 7.78 (d, *J* = 9.1 Hz, 1 H) (H9, H10), 7.74–7.59 (m, 3 H, Tz-H), 7.26 (dd, *J* = 2.4, 8.7 Hz, 1 H, H-7), 4.15 (s, 2 H), 3.89 (s, 3 H) and 3.63 (s, 3 H) (4-OMe, 6-OMe), 3.41 (br s, 2 H), 3.21 (br s, 2 H), 2.74 (s, 3 H, NMe).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{26}N_5O_3$: 468.2036; found: 468.2049.

3-*O*-(1-Phenyl-1*H*-tetrazol-5-yl)-7-dehydroxy-9,10-dihydrolitebamine (4)

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.88 (m, 2 H, Tz-H), 7.79 (d, *J* = 2.5 Hz, 1 H, H-5), 7.74–7.59 (m, 3 H, Tz-H), 7.13 (d, *J* = 8.2 Hz, 1 H, H-8), 6.77 (dd, *J* = 2.5, 8.2 Hz, 1 H, H-7), 3.76 (s, 3 H) and 3.37 (s, 3 H) (4-OMe, 6-OMe), 3.59 (s, 2 H), 2.82 (t-like, 2 H), 2.72 (t-like, 2 H), 2.67 (m, 4 H), 2.43 (s, 3 H, NMe).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{28}N_5O_3$: 470.2192; found: 470.2194.

1,10-Dimethoxyaporphine (8)

Prepared according to the typical procedure using **7** (6.8 g, 11.1 mmol), 10% Pd/C (2.0 g, 30% w/w), and Mg (675.5 mg, 27.8 mmol) with AcOH (80 mL) as the solvent at 50 °C under 13.8 bar of H_2 for 3 d. Yellowish oil; yield: 2.8 g (87%).

IR (KBr): 2958, 1655, 1459, 1268, 1071, 1031 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 2.6 Hz, 1 H, H11), 7.17 (d, *J* = 8.2 Hz, 1 H, H8), 7.04 (d, *J* = 8.4 Hz, 1 H, H3), 6.88 (d, *J* = 8.4 Hz, 1 H, H2), 6.78 (dd, *J* = 2.6, 8.2 Hz, 1 H, H9), 3.85 (s, 3 H, 10-OMe), 3.83 (s, 3 H, 1-OMe), 3.13–3.00, 2.70–2.55, and 2.50–2.48 (7 H, m), 2.54 (s, 3 H, N-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0 (Cq), 154.9 (Cq), 136.6 (Cq), 133.0 (Cq), 128.6 (CH), 128.5 (Cq), 128.5 (CH), 125.5 (Cq), 121.9 (Cq), 114.7 (CH), 112.1 (CH), 110.8 (CH), 63.2 (CH), 55.7 (CH_3), 55.3 (CH_3), 53.2 (CH_2), 43.9 (CH_3), 33.8 (CH_2), 28.5 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_2$: 296.1645; found: 296.1655.

2,3-Dimethoxypavine (12)

Prepared according to the typical procedure using **11** (30.4 mg, 0.07 mmol), 10% Pd/C (10.0 mg, 30% w/w), and Mg (3.2 mg, 0.13 mmol) with AcOH (3 mL) as the solvent at 50 °C under 3.4 bar of H_2 for 3 d. Yellowish oil; yield: 19.4 mg (98%).

IR (KBr): 2996, 2918, 2892, 2851, 2832, 2804, 2779, 1607, 1515, 1455, 1373, 1352, 1337, 1261, 1241, 1212, 1109, 1076, 1009, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.11–7.04 (m, 3 H, H7–9), 6.95 (d, *J* = 7.3 Hz, 1 H, H10), 6.59 (s, 1 H, H1), 6.41 (s, 1 H, H4), 4.10 (d, *J* = 5.6 Hz, 1 H, H6), 4.04 (d, *J* = 5.6 Hz, 1 H, H12), 3.82 (s, 3 H, 2-OMe), 3.74 (s, 3 H, 3-OMe), 3.48 (dd, *J* = 5.6, 16.4 Hz, 1 H, H11α), 3.44 (dd, *J* = 5.6, 16.4 Hz, 1 H, H5α), 2.71 (d, *J* = 16.4 Hz, 1 H, H11β), 2.60 (d, *J* = 16.4 Hz, 1 H, H5β), 2.54 (s, 3 H, NMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8 (Cq), 147.5 (Cq), 138.1 (Cq), 132.0 (Cq), 129.5 (Cq), 129.1 (CH), 127.2 (CH), 126.6 (CH), 125.9 (CH), 123.6 (CH), 111.4 (CH), 109.9 (CH), 56.6 (CH_3), 56.4 (CH_3), 55.9 (CH), 55.6 (CH), 40.8 (CH_3), 34.2 (CH_2), 33.3 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_2$: 296.1645; found: 296.1660

9,10-Dimethoxyprotoberberine (15)

Prepared according to the typical procedure using **14** (20.0 mg, 0.03 mmol), 10% Pd/C (6.5 mg, 30% w/w), and Mg (2.1 mg, 0.08 mmol) with AcOH (1.5 mL) as the solvent at 50 °C under 13.8 bar of H_2 for 2.5 d. Yellowish oil; yield: 6.5 mg (68%).

IR (KBr): 2833, 1727, 1658, 1642, 1613, 1495, 1454, 1357, 1277, 1084, 1057, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.10 (m, 4 H, H1–4), 6.87 (d, *J* = 8.4 Hz, 1 H, H12), 6.79 (d, *J* = 8.4 Hz, 1 H, H11), 4.29 (d, *J* = 15.6 Hz, 1 H, H8), 3.84 (s, 3 H) and 3.83 (s, 3 H) (9-OMe, 10-OMe), 3.77–3.62 (m, 2 H), 3.36–3.28 (m, 3 H), 2.95–2.75 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4 (Cq), 145.1 (Cq), 133.9 (Cq), 129.7 (Cq), 128.9 (CH), 127.1 (Cq), 126.5 (CH), 126.2 (CH), 125.5 (CH), 123.9 (CH), 122.1 (Cq), 111.2 (CH), 60.2 (CH_3), 59.6 (CH), 55.9 (CH_3), 53.7 (CH_2), 51.1 (CH_2), 35.6 (CH_2), 28.8 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO_2$: 296.1645; found: 296.1634

7,11-Didehydroxyreticuline (18)

Prepared according to the typical procedure using **17** (30.6 mg, 0.05 mmol), 10% Pd/C (11.0 mg, 35% w/w), and Mg (4.8 mg, 0.20 mmol) with AcOH (3 mL) as the solvent at 50 °C under 13.8 bar of H_2 for 3 d. Yellowish oil; yield: 11.3 mg (76%).

IR (KBr): 2938, 2834, 1611, 1512, 1463, 1373, 1246, 1177, 1037, 821 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 8.6 Hz, 2 H, H10, H14) and 6.77 (d, *J* = 8.6 Hz, 2 H, H11, H13), 6.60–6.56 (m, 3 H, H5, H7, H8), 3.77 (s, 3 H) and 3.75 (s, 3 H) (6-OMe 12-OMe), 3.73 (m, 1 H, H1), 3.22–3.10 (m, 2 H), 2.89–2.73 (m, 3 H), 2.66 (dt, *J* = 16.2, 5.0 Hz, 1 H), 2.49 (s, 3 H, NMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9 (Cq), 157.7 (Cq), 135.1 (Cq), 131.5 (Cq), 130.6 (CH), 129.0 (CH), 113.5 (CH), 113.1 (CH), 111.7 (CH), 64.8 (CH), 55.2 (CH_3), 55.1 (CH_3), 46.8 (CH_2), 42.5 (CH_3), 40.5 (CH_2), 26.0 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{24}NO_2$: 298.1802; found: 298.1798.

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Supporting Information

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(9) Starting from litebamine (**1**) and following the procedure in ref. 10 gave poor yield of the bistriflate product, accompanied with unreacted **1** as the major component, while replacement of Et_3N with K_2CO_3 led to a better yield. The detailed procedure follows: A mixture of **1** (51.8 mg, 0.15 mmol), *N*-phenyl-bis(trifluoromethanesulfonimide) (140.5 mg, 0.40 mmol), and K_2CO_3 (76.5 mg, 0.55 mmol) in DMF (1 mL) was stirred at r.t. for 1 d. The mixture was diluted with $CHCl_3$ (10 mL), washed with H_2O (3 × 3 mL), and evaporated to dryness. The residue was chromatographed (silica gel, 3.6 g, 0–20% MeOH–$CHCl_3$, saturated with 25% aq NH_3) to yield 3,7-*O*,*O*-bistriflyl litebamine ether (14.8 mg, 16%) as a yellowish oil.

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(11) 8/9-Hydroxy-2,3-dimethoxypavine (**3**) was synthesized from *O*-methylcaryachine by reductive cleavage of methylenedioxy group with Na/liquid ammonia following the procedure: Lee, S. S.; Lin, C. Y.; Chen, C. H. *J. Chin. Chem. Soc.* **1991**, *38*, 389; ^{1}H NMR (80 MHz, $CDCl_3$): δ = 6.60–6.90 (m, 3 H, H7,8(9),10), 6.87 (d, *J* = 8.4 Hz, 1 H, H12), 6.57 (s, 1 H, H1), 6.38 (s, 1 H, H4), 3.80 (s, 3 H, 2-OMe), 3.83 (s, 3 H, 3-OMe), 2.46 (s, 3 H, NMe). MS (EI): *m*/*z* = 311 (70) ([M]$^+$), 310 (42), 204 (65), 160 (100)..

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