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A Versatile Total Synthesis of Benzo[*c*]phenanthridine and Protoberberine Alkaloids Using Lithiated Toluamide−Benzonitrile Cycloaddition

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A new versatile synthesis of benzo[*c*]phenanthridine and protoberberine alkaloids using lithiated toluamide−benzonitrile cycloaddition was carried out. The coupling reaction between benzonitrile **6** with *o*-toluamides (**8a**−**c**) afforded 3-arylisoquinolines (**9a**−**c**) that were transformed to the protoberberines (**11a**−**c**) or benzo[*c*]phenanthridines (**14a**−**c**). These compounds were synthesized by ring closure of the two-carbon chain on either position 2 or 4 of the 3-arylisoquinolinone (**9a**−**c**). Several kinds of substituted benzo[*c*]phenanthridine alkaloids such as oxysanguinarine, oxyavicine, and oxynitidine as well as protoberberines such as 8-oxocoptisine, 8-oxopseudoberberine, and 8-oxopseudocoptisine were synthesized.

Introduction

Natural benzo[*c*]phenanthridine and protoberberine alkaloids have been attractive to synthetic organic chemists and biochemists over the last two decades since these compounds have shown interesting biological properties such as antitumor,[1−6] antiviral,[7,8] and antimicrobacterial activities.[9,10] Therefore, much attention has been focused on the efficient synthesis of these alkaloids.[11−13] Benzo[*c*]phenanthridine alkaloids have been considered to be biosynthesized from the corresponding protoberberine alkaloids presumably via a 3-arylisoquinoline intermediate.[14] We have reported the synthesis of 3-arylisoquinoline derivatives with biological evaluations.[15] For the model study of these alkaloids, the synthesis of a benzo[*c*]phenanthridine skeleton was performed.[16] The synthesis involved the cycloaddition of lithiated *o*-methyltoluamide with benzonitriles to prepare substituted 3-arylisoquinolinones.[17] To synthesize both of the natural alkaloids, the aforementioned synthetic method was applied. The advantages of this methodology were considered not only due to easy access to the staring materials but also because it is a one-pot procedure for construction of all carbon atoms for both alkaloids.

Results and Discussion

Retrosynthesis of these alkaloids indicates that the coupling of benzonitrile with *o*-toluamide might afford 3-arylisoquinolinone that would be a key intermediate in the synthesis of both alkaloids. Protoberberine or benzo[*c*]phenanthridine alkaloids could be synthesized through the ring closure of the two carbon chains, either on position 2 or 4, of the 3-arylisoquinolinone (Scheme 1).

For the lithiated toluamide−benzonitrile cycloaddition reaction, the starting benzonitrile **6** was synthesized as

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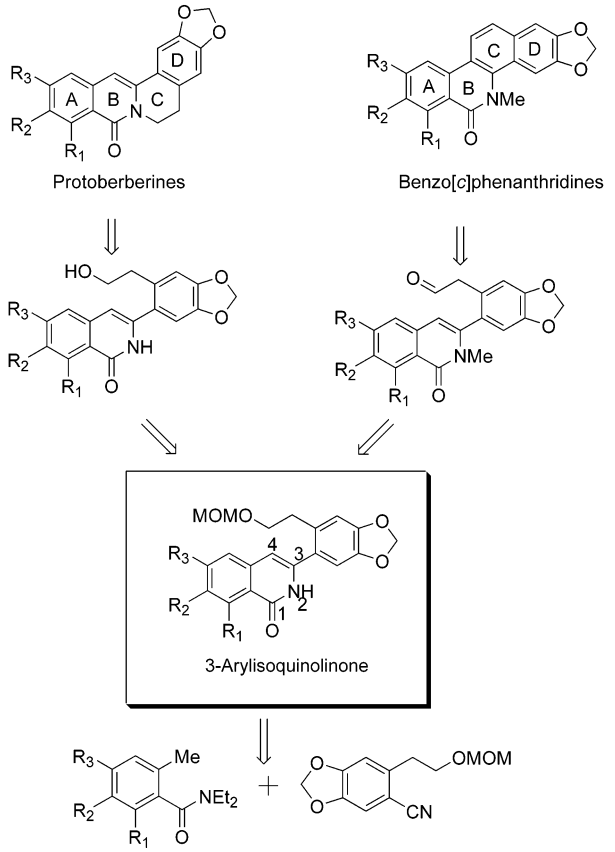
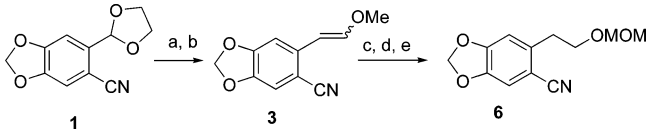
SCHEME 1. Retrosynthesis of Protoberberines and Benzo[*c*]phenanthridine Alkaloids



SCHEME 2. Synthesis of Benzonitrile Derivative 6[a]

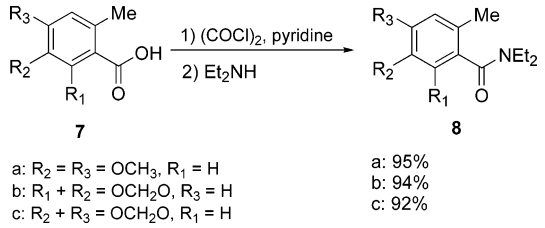


[a] Reagents and conditions: (a) 10% HCl, 100%; (b) $Ph_3P^+CH_2OMe\ I^-$, *n*-BuLi, THF, 62%; (c) 5% HCl, acetone, 97%; (d) $NaBH_4$, AcOH, 82%; (e) MOMCl, CH_2Cl_2, diisopropylethylamine, 96%.

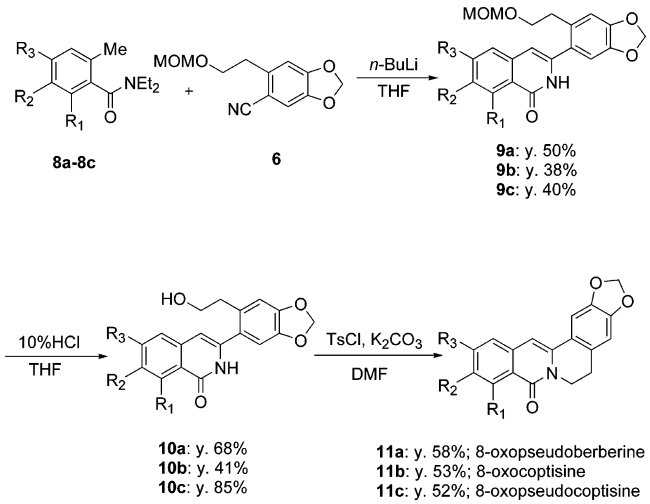
depicted in Scheme 2. Acetal **1**[18] was hydrolyzed with 10% hydrochloric acid to afford the aldehyde **2**, which was treated with $Ph_3P^+CH_2OMe\ I^-$/*n*-BuLi, providing the styrene **3**. The *E*/*Z* mixture of stereoisomers (*E*/*Z* = 1/2) was hydrolyzed without separating them to give the homobenzaldehyde **4**, which was then reduced with $NaBH_4$. The resultant alcohol **5** was then protected with methoxymethyl chloride to yield the MOM-protected benzonitrile **6**, in 96% yield.

N,*N*-Diethyl-*o*-toluamides **8a**, **8b**, and **8c** were synthesized from the corresponding substituted benzoic acids **7a**, **7b**, and **7c**[19−21] by treatment of oxalyl chloride followed by diethylamine. This resulted in a high overall yield of 92−95%, as shown in Scheme 3.

SCHEME 3. Synthesis of *N*,*N*-Diethyl-*o*-toluamide Derivatives 8a−c



SCHEME 4. Synthesis of Protoberberine Alkaloids 11a−c



The strategy used was based on the synthesis of 3-arylisoquinolinone **9a**−**c**, which are crucial intermediates in the formation of a C ring of protoberberine or benzo[*c*]phenanthridines. *N*,*N*-Diethyl-*o*-toluamide **8a**−**c** was deprotonated with *n*-butyllithium to give the anion, which was treated with benzonitrile **6** at −78 °C in THF to afford the 3-arylisoquinoline-1(2*H*)-one **9a**−**c**.[22] Deprotection of **9a**−**c** with 10% HCl resulted in the alcohols **10a**−**c**, which were then reacted with *p*-TsCl in DMF in the presence of K_2CO_3 to afford the desired protoberberine alkaloids.[23] There was a 52−58% yield of 8-oxopseudoberberine **11a**, 8-oxocoptisine **11b**, and 8-oxopseudocoptisine **11c** (Scheme 4).

MOM-protected alcohol **9a**−**c** was treated with MeI/K_2CO_3 providing the *N*-methylated products **12a**−**c** in a 62−90% yield without yielding any *o*-methylated compounds. The hydrolysis of the MOM group with 10% HCl gave the alcohols **13a**−**c**. The alcohols were then oxidized with PCC/NaOAc[24] to provide the desired benzo[*c*]-phenanthridine alkaloids oxynitidine **14a**, oxysanguinarine **14b**, and oxyavicine **14c** as shown in Scheme 5. In this reaction, it was assumed that the oxidation produced the aldehyde and the intramolecular enamide−aldehyde cyclization occurred so as to form a C ring of benzo[*c*]phenanthridine, and the consecutive dehydration process, resulting in the aromatized ring system.

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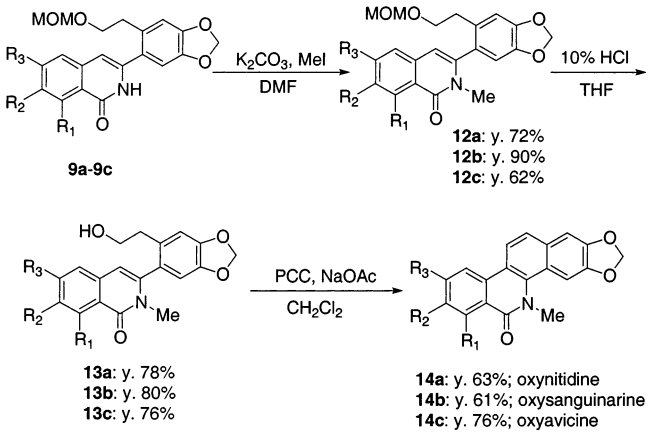
SCHEME 5. Synthesis of Benzo[*c*]phenanthridine Alkaloids 14a−c



In conclusion, the synthesis of natural protoberberine and benzo[*c*]phenanthridine alkaloids through the same intermediates **9a**−**c** in three or four steps, respectively, from the benzonitrile **6** and toluamde **8a**−**c** was successful. This methodology is considered to be a more direct route to benzo[*c*]phenanthridine or protoberberine synthesis than the previous reported condensation routes.[25−27] We believe that this synthetic application would broaden the utility of this methodology for preparation of the analogues on a multigram scale, which are necessary to define structure−activity relationships or to identify the biological target of these compounds.

Experimental Section

6-Formylbenzo[1,3]dioxole-5-carbonitrile (2). The acetal **1** (8.3 g, 37 mmol) in 10% HCl was warmed at 50−60 °C for 5 min. The resulting solid was collected, washed with water, and dried to give a pale yellow solid which was recrystallized with *n*-hexane to afford the aldehyde **2** (6.57 g, 100%). Mp = 162−164 °C. IR: 2230 (CN), 1690 (CO). ^{1}H NMR ($CDCl_3$) δ: 10.24 (s, 1H), 7.44 (s, 1H), 7.44 (s, 1H), 6.20 (s, 2H). EIMS: *m*/*z* 175 (M^+, 100). Anal. Calcd for $C_9H_5NO_3$: C, 61.72; H, 2.88; N, 8.00. Found: C, 61.83; H, 2.96; N, 8.06.

6-(2-Methoxyvinyl)benzo[1,3]dioxole-5-carbonitrile (3). To a solution of (methoxymethyl)triphenyl phosphonium chloride (9.58 g, 28 mmol) in dry THF (50 mL) was added *n*-butyllithium (18 mL, 28.8 mmol) at 0 °C, and the solution was stirred at 0 °C for 1 h. To this mixture was added the aldehyde (3.5 g, 20 mmol) in THF (20 mL) and the resulting mixture stirred at room temperature for 30 min. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were washed with water and brine and dried over sodium sulfate. After removal of the solvent in vacuo, the residue was purified by column chromatography with *n*-hexanes−ethyl acetate (3:1) to afford the *E*/*Z* isomers (1/2) of **3** as a yellow solid (2.5 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: (*Z* isomer) 7.66 (s, 1H), 6.94 (s, 1H), 6.02 (s, 2H), 6.26 (d, *J* = 7.1 Hz, 1H), 5.58 (d, *J* = 7.1 Hz, 1H), 3.82 (s, 3H); (*E* isomer) 7.10 (d, *J* = 12.8 Hz, 1H), 6.94 (s, 1H), 6.85 (s, 1H), 6.02 (s, 2H), 6.04. (d, *J* = 12.8 Hz, 1H), 3.73 (s, 3 H).

6-(2-Oxoethyl)benzo[1,3]dioxole-5-carbonitrile (4). The reaction mixture of *E*/*Z* isomer **3** (4.1 g, 20 mmol) in acetone (30 mL) and 5% HCl (10 mL) was refluxed for 5 h. The acetone was evaporated off, and water was poured into the residue and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with *n*-hexanes−ethyl acetate (1:1) to give the aldehyde **4** as a solid (3.84 g, 97%). Mp = 78−80 °C. IR (cm^{-1}): 2220 (CN), 1720 (C=O), 1300−1000 (CO). ^{1}H NMR ($CDCl_3$) δ: 9.78 (s, 1H), 7.06 (s, 1H), 6.75 (s, 1H), 6.10 (s, 2H), 3.93 (s, 2H). EIMS: *m*/*z* 189 (M^+, 100). Anal. Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.65; H, 3.78; N, 7.46.

6-(2-Hydroxyethyl)benzo[1,3]dioxole-5-carbonitrile (5). To a solution of aldehyde **4** (3.02 g, 16 mmol) in acetic acid (20 mL) was added $NaBH_4$ (1.14 g, 30 mmol). After the reaction was complete, acetic acid was removed in vacuo and the residue was poured into water and extracted with ethyl acetate. The organic solvent was evaporated off, and the residue was purified by column chromatography with *n*-hexane−ethyl acetate (1:1) to give the alcohol **5** as a yellow solid (2.51 g, 82%). Mp = 70.4−72.3 °C. IR (cm^{-1}): 3360 (OH), 2220 (CN), 1720 (C=O), 1300−1000 (C−O). ^{1}H NMR ($CDCl_3$) δ: 6.98 (s, 1H), 6.84 (s, 1H), 6.04 (s, 2H), 3.86 (t, *J* = 6.5 Hz, 2H), 2.99 (t, *J* = 6.5 Hz, 2H). EIMS: *m*/*z* 191 (M^+, 100). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.78; H, 4.69; N, 7.34.

6-(2-Methoxymethoxyethyl)benzo[1,3]dioxole-5-carbonitrile (6). To a solution of alcohol **5** (2.54 g, 13.3 mmol) in CH_2Cl_2 (25 mL) at 0 °C were added diisopropylethylamine (DIPEA) (3.25 g, 30 mmol) and chloromethylmethyl ether (2.02 g, 20 mmol). The reaction mixture was stirred overnight, and CH_2Cl_2 was evaporated off to give the residue, which was purified by column chromatography with *n*-hexanes−ethyl acetate (3:1) to give benzonitrile **6** as a yellow oil (3.01 g, 96%). IR (cm^{-1}): 2230 (CN), 1300−1000 (CO). ^{1}H NMR ($CDCl_3$) δ: 6.99 (s, 1H), 6.85 (s, 1H), 6.04 (s, 2H), 4.60 (s, 2H), 3.77 (t, *J* = 6.5 Hz, 2H), 3.30 (s, 3H), 3.05 (t, *J* = 6.5 Hz, 2H). EIMS: *m*/*z* 235 (M^+, 100). HRMS-EI (calcd for $C_{12}H_{13}NO_4$): 235.2354, found 235.2358.

2-Methyl-4, 5-dimethoxy-*N*,*N*-diethylbenzamide (8a). To a suspension of 2-methyl-4,5-dimethoxybenzoic acid **7a** (5 g, 19.9 mmol) in CH_2Cl_2 (50 mL) containing pyridine (3.23 g, 40.8 mmol) was slowly added oxalyl chloride (17.8 mL) with stirring. After an additional 2 h of stirring, the excess oxalyl chloride was removed in vacuo and the last traces of oxalyl chloride were removed by co-distillation with benzene. The acid chloride obtained was dissolved in CH_2Cl_2 (20 mL) and carefully treated with diethylamine (18.65 g, 255 mmol) at 0 °C. After the reaction mixture was diluted with water, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The organic portions were washed with water and brine, dried over anhydrous sodium sulfate, and then evaporated to give 2-methyl-4,5-dimethoxy-*N*,*N*-diethylbenzamide **8a** (6.07 g, 95%) as an oil. IR (cm^{-1}): 1631 (NCO). ^{1}H NMR ($CDCl_3$) 6.68 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 3,-75−2.90 (m, 4H), 2.23 (s, 3H), 1.50−0.85 (m, 6H). EIMS: *m*/*z* 251 (M^+, 24).

5-Methylbenzo[1,3]dioxole-4-carboxylic Acid Diethylamide (8b). The procedure described for compound **8a** was used with carboxylic acid **7b** (4.2 g, 23 mmol) to give *N*,*N*-diethyltoluamide **8b** (5.12 g, 94%). IR (cm^{-1}): 1642 (NCO). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.70 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 5.94 (m, 2H), 3.44−3.40 (m, 2H), 3.27−3.18 (m, 2H), 2.20 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). EIMS: *m*/*z* 235 (M^+, 93).

6-Methylbenzo[1,3]dioxole-5-carboxylic Acid Diethylamide (8c). The procedure described for compound **8a** was used with carboxylic acid **7c** (1.68 g, 9.2 mmol) to give *N*,*N*-diethyltoluamide **8c** (2 g, 92%). IR (cm^{-1}): 1651 (NCO). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.66 (s, 1H), 6.64 (s, 1H), 5.93 (s, 2H), 3.20−3.12 (m, 4H), 2.19 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). EIMS: *m*/*z* 235 (M^+, 86).

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6,7-Dimethoxy-3-[6-(2-methoxymethoxyethyl)benzo-[1,3]dioxol-5-yl]-2*H*-isoquinolin-1-one (9a). A solution of *N*,*N*-diethyltoluamide **8a** (2.01 g, 8 mmol) and benzonitrile **6** (1.41 g, 6 mmol) in THF (20 mL) was added dropwise to a solution of *n*-butyllithium (10 mL of 1.6 M in hexane, 16 mmol) in THF (15 mL) at −70 °C, and then the reaction mixture was stirred at the same temperature for 6 h. The reaction was quenched with water, extracted with ethyl acetate, and dried over sodium sulfate. After removal of the solvent, the residue was purified by column chromatography with *n*-hexanes−ethyl acetate (1:1) to afford the product **9a** as an orange solid (1.27 g, 50%). Mp = 180−183 °C. IR (cm^{-1}): 3400 (NH), 1630 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 10.3 (s, 1H), 7.79 (s, 1H), 6.90 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 6.39 (s, 1H), 6.02 (s, 2H), 4.72 (s, 2H), 4.01(s, 3H), 4.00(s, 3H), 3.87 (m, 2H), 3.36 (s, 3H), 2.85 (t, J = 5.7 Hz, 2H). EIMS: *m*/*z* 413 (M^+, 36). Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.69; H, 5.48; N, 3.40.

7-[6-(2-Methoxymethoxyethyl)benzo[1,3]dioxol-5-yl]-8*H*-[1,3]dioxolo[4,5-*h*]isoquinolin-9-one (9b). The procedure described for compound **9a** was used with toluamide **8b** (2.83 g, 12 mmol) and benzonitrile **6** (2.35 g, 10 mmol) to afford compound **9b** as an orange solid (1.48 g, 38%). Mp = 157−159 °C. IR (cm^{-1}): 3400 (NH), 1665 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 10.17 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.86 (s, 1H), 6.79 (s, 1H), 6.35 (s, 1H), 6.21 (s, 2H), 6.01 (s, 2H), 4.70 (s, 2H), 3.87 (t, J = 5.7 Hz, 2H), 3.39 (s, 3H), 2.85 (t, J = 5.7 Hz, 2H). EIMS: *m*/*z* 397 (M^+, 68). Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.56; H, 4.71; N, 3.59.

7-[6-(2-Methoxymethoxyethyl)benzo[1,3]dioxol-5-yl]-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (9c). The procedure described for compound **9a** was used with toluamide **8c** (1.39 g, 5.9 mmol) and benzonitrile **6** (1.15 g, 4.9 mmol) to afford compound **9c** as an orange solid (936 mg, 40%). Mp = 161.3−165.2 °C. IR (cm^{-1}): 3400 (NH), 1665 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 10.33 (s, 1H), 7.75 (s, 1H), 6.88 (s, 1H), 6.86 (s, 1H), 6.80 (s, 1H), 6.35 (s, 6.35), 6.08 (s, 2H), 6.01 (s, 2H), 4.72(s, 2H), 3.89 (t, J = 5.4 Hz, 2H), 3.32 (s, 3H), 2.84 (t, J = 5.7 Hz, 2H). EIMS: *m*/*z* 397 (M^+, 41%). Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.71; H, 4.78; N, 3.55.

3-[6-(2-Hydroxyethyl)benzo[1,3]dioxol-5-yl]-6,7-dimethoxy-2*H*-isoquinolin-1-one (10a). To a solution of compound **9a** (200 mg, 0.48 mmol) in THF (15 mL) was added 10% HCl (5 mL), and the reaction was refluxed for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (20:1) to give an alcohol **10a** as a yellow solid (122 mg, 68%). Mp = >250 °C. IR (cm^{-1}): 3400 (NH, OH), 1642 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 11.30 (s, 1H), 7.55 (s, 1H), 7.16 (s, 1H), 6.96 (s, 1H), 6.89 (s, 1H), 6.39 (s, 1H), 6.05 (s, 2H), 5.06 (t, J = 4.5 Hz, 1H), 3.87(s, 3H), 3.86 (s, 3H), 3.57 (m, 2H), 2.67 (t, J = 6.7 Hz, 2H). EIMS: *m*/*z* 369 (M^+, 67). Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.08; H, 5.20; N, 3.81.

7-[6-(2-Hydroxyethyl)benzo[1,3]dioxol-5-yl]-8*H*-[1,3]dioxolo[4,5-*h*]isoquinolin-9-one (10b). The procedure described for compound **8a** was used with compound **9b** (200 mg, 0.48 mmol) and 10% HCl (5 mL) to give alcohol **10b** as a yellow solid (70 mg, 41%). Mp = 237−239 °C. IR (cm^{-1}): 3400, 3300 (NH, OH), 1636 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 11.17 (s, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 6.95 (s, 1H), 6.89 (s, 1H), 6.37 (s, 1H), 6.19 (s, 2H), 6.04 (s, 2H), 5.06 (t, J = 4.5 Hz, 1H), 3.58 (m, 2H), 2.68 (t, J = 6.6 Hz, 2H). EIMS: *m*/*z* 353 (M^+, 71). Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.61; H, 4.30; N, 3.91.

7-[6-(2-Hydroxyethyl)benzo[1,3]dioxol-5-yl]-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (10c). The procedure described for the compound **10a** was used with compound **9c** (200 mg, 0.48 mmol) and 10% HCl (5 mL) to give alcohol **10c** as a yellow solid (150 mg, 85%). Mp = 198−201 °C. IR (cm^{-1}): 3400, 3300 (NH, OH), 1636 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 11.46 (s, 1H), 7.56 (s, 1H), 7,21 (s, 1H),7.02 (s, 1H), 6.96 (s, 1H), 6.22 (s, 2H), 6.11 (s, 2H), 5.17 (t, J = 4.5, 1H), 3.68−3.62 (m, 2H), 2.73 (t, 2H). EIMS: *m*/*z* 353 (M^+, 71). Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.51; H, 4.17; N, 3.85.

10,11-Dimethoxy-5,6-dihydro[1,3]dioxolo[4,5-*g*]isoquino-[3,2-*a*]isoquinolin-8-one (Oxypseudoberine, 11a). The mixture of compound **10a** (100 mg, 0.28 mmol), tosyl chloride (115 mg, 0.6 mmol), and K_2CO_3 (138 mg, 1 mmol) in DMF (8 mL) was stirred at 100 °C for 4 h. Water was added, and the reaction mixture was extracted with ethyl acetate. The ethyl acetate extracts were washed with water and brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with *n*-hexanes−ethyl acetate (1:2) to give 8-oxypseudoberine **11a** as a yellow solid (57 mg, 58%). Mp = 266−268 °C dec. IR (cm^{-1}): 1650 (amide). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.21 (s, 1H), 6.90 (s, 1H), 6.77 (s, 1H), 6.71 (s, 1H), 6.01 (s, 2H), 4.33 (t, J = 6.0 Hz, 2H), 4.01 (s, 3H), 4.00 (s, 3H), 2.88 (t, J = 6.0 Hz, 2H). EIMS: *m*/*z* 351 (M^+, 100). Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.17; H, 4.91; N, 3.91.

Oxycoptisine (11b). The procedure described for compound **11a** was used with compound **10b** (30 mg, 0.085 mmol), tosyl chloride (38 mg, 0.2 mmol), and K_2CO_3 (68 mg, 0.5 mmol) to give 8-oxycoptisine **11b** as an orange solid (15 mg, 53%). Mp = 289−291 °C (lit.[28] mp 282−284 °C). IR (cm^{-1}): 1645 (amide). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.20 (s, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.74 (s, 1H), 6.70 (s, 1H), 6.21 (s, 2H), 6.04 (s, 2H), 4.27 (t, J = 6.0 Hz, 2H), 2.88 (t, J = 6.0 Hz, 2 H). EIMS: *m*/*z* 335 (M^+, 100). Anal. Calcd for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18. Found: C, 68.32; H, 3.76; N, 4.21.

Oxypseudocoptisine (11c). The procedure described for compound **11a** was used with compound **10c** (80 mg, 0.23 mmol), tosyl chloride (115 mg, 0.6 mmol), and K_2CO_3 (130 mg, 0.92 mmol) to give 8-oxypseudoberine **11c** as a yellow solid (41 mg, 52%). Mp = 276−279 °C dec (lit.[29] HCl salt form mp 270 °C). IR (cm^{-1}): 1650 (amide). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.77(s, 1H), 7.22(s, 1H), 6.89(s, 1H), 6.73(s, 1H), 6.71 (s, 1H), 6.07 (s, 2H), 6.01(s, 2H), 4.32 (t, J = 6.1 Hz, 2H), 2.90(t, J = 6.4 Hz, 2H). EIMS: *m*/*z* 335 (M^+, 79). Anal. Calcd for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18. Found: C, 68.02; H, 3.85; N, 4.12.

6,7-Dimethoxy-3-[6-(2-methoxymethoxyethyl)benzo-[1,3]dioxol-5-yl]-2-methyl-2*H*-isoquinolin-1-one (12a). The mixture of compound **9a** (150 mg, 0.36 mmol), K_2CO_3 (275 mg, 2 mmol), and methyl iodide (141 mg, 1.0 mmol) in DMF (8 mL) was heated at 100 °C for 3 h. The reaction was quenched with water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water and brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with *n*-hexanes−ethyl acetate (1:1) to give compound **12a** as an oil (110 mg, 72%). IR (cm^{-1}): 1646 (C=O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 6.90 (s, 1H), 6.83 (s, 1H), 6.70 (s, 1H), 6.34 (s, 1H), 6.02 (s, 2H), 4.51 (s, 2H), 4.03 (s, 3H), 3.98 (s, 3H), 3.62 (m, 2H), 3.31 (s, 3H), 3.20(s, 3H), 2.77−2.57 (m, 2 H). EIMS: *m*/*z* 427 (M^+, 100). HRMS-EI (calcd for $C_{23}H_{25}NO_7$): 427.4461, found 427.4467.

7-[6-(2-Methoxymethoxyethyl)benzo[1,3]dioxol-5-yl]-8-methyl-8*H*-[1,3]dioxolo[4,5-*h*]isoquinolin-9-one (12b). The procedure described for the compound **12a** was used with compound **9b** (300 mg, 0.75 mmol), K_2CO_3 (550 mg, 4 mmol),

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and methyl iodide (280 mg, 2.0 mmol) to give compound **12b** as an oil (280 mg, 90%). IR (cm^{-1}): 1655 (C═O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.16 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.88 (s, 1H), 6.69 (s, 1H), 6.30 (s, 1H), 6.23 (m, 2H), 6.02 (m, 2H), 4.51 (s, 2H), 3.61 (m, 2H), 3.24 (s, 3H), 3.20 (s, 3H), 2.75−2.59 (m, 2H). EIMS: *m*/*z* 411 (M^+, 100). HRMS-EI (calcd for $C_{22}H_{21}NO_7$): 411.4038, found 411.4039.

7-[6-(2-Methoxymethoxyethyl)benzo[1,3]dioxol-5-yl]-6-methyl-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (12c). The procedure described for compound **12a** was used with compound **9c** (300 mg, 0.75 mmol), K_2CO_3 (520 mg, 3.75 mmol), and methyl iodide (270 mg, 1.9 mmol) to give the product **12c** as an oil (190 mg, 62%). IR (cm^{-1}): 1655 (C═O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.79 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 6.29 (s, 1H), 6.07 (s, 2H), 6.02 (s, 2H), 4.50 (s, 2H), 3.63−3.58 (m, 2H), 3.29 (s, 3H), 3.20 (s, 3H), 2,78−2.56 (m, 2H). EIMS: *m*/*z* 411 (M^+, 100). HRMS-EI (calcd for $C_{22}H_{21}NO_7$): 411.4038, found 411.4040.

3-[6-(2-Hydroxyethyl)benzo[1,3]dioxol-5-yl]-6,7-dimethoxy-2-methyl-2*H*-isoquinolin-1-one (13a). To a solution of compound **12a** (90 mg, 0.21 mmol) in THF (10 mL) was added 10% HCl (3 mL), and the mixture was refluxed for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel with with *n*-hexanes−ethyl acetate (1:2) to give alcohol **13a** as a solid (63 mg, 78%). Mp = 191−194 °C. IR (cm^{-1}): 3356 (OH), 1642 (C═O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 6.71 (s, 1H), 6.34 (s, 1H), 6.03 (s, 2H), 4.02(s, 3H), 4.01 (s, 3H), 3.73 (m, 2H), 3.30 (s, 3H), 2.71−2.62 (m, 2H). EIMS: *m*/*z* 383 (M^+, 100). Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.53; H, 5.82; N, 3.69.

7-[6-(2-Hydroxyethyl)benzo[1,3]dioxol-5-yl]-8-methyl-8*H*-[1,3]dioxolo[4,5-*h*]isoquinolin-9-one (13b). The procedure described for compound **13a** was used with compound **12b** (250 mg, 0.6 mmol) and 10% HCl (10 mL) to give alcohol **13b** as a solid (177 mg, 80%). Mp = 199−200.5 °C. IR (cm^{-1}): 3300 (OH), 1654 (C═O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.16 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.87 (s, 1H), 6.71 (s, 1H), 6.30 (s, 1H), 6.23 (q, J = 1.4 Hz, 2H), 6.02 (q, J = 1.4 Hz, 2H), 3.73 (m, 2H), 3.23 (s, 3H), 2.75−2.55 (m, 2H). EIMS: *m*/*z* 367 (M^+, 100). Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.43; H, 4.68; N, 3.71.

7-[6-(2-Hydroxyethyl)benzo[1,3]dioxol-5-yl]-6-methyl-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (13c). The procedure described for compound **13a** was used with compound **12c** (105 mg, 0.26 mmol) and 10% HCl (3 mL) to give alcohol **13c** as a solid (73 mg, 76%). Mp = 208.2−209.7 °C. IR (cm^{-1}): 3300 (OH), 1654 (C═O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75 (s, 1H), 6.87 (s, 1H), 6.80 (s, 1H), 6.70 (s, 1H), 6.29 (s, 1H), 6.08 (s, 2H), 6.02 (m, 2H), 3.73 (m, 2H), 3.28 (s, 3H), 2.75−2.56 (m, 2H), 1.60 (s, 1H). EIMS: *m*/*z* 367 (M^+, 100). Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.41; H, 4.79; N, 3.74.

Oxynitidine (14a). To a solution of alcohol **13a** (40 mg, 0.10 mmol) in CH_2Cl_2 (8 mL) were added PCC (45 mg, 0.21 mmol) and NaOAc (15 mg, 0.18 mmol) at room temperature. After being stirred for 6 h, the reaction mixture was filtered and washed with CH_2Cl_2. The solvent was evaporated off, and the residue was purified by column chromatography on silica gel with *n*-hexanes−ethyl acetate (1:1) to afford oxynitidine **14a** as a white solid (23 mg, 63%). Mp = 284−285 °C (lit.[30] mp 280−283 °C, lit.[31] mp 284−285 °C). IR (cm^{-1}): 1642 (C═O). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J = 9.0 Hz, 1H), 7.91 (s, 1H), 7.63 (s, 1H), 7.58 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.17 (s, 1H), 6.10 (s, 2H), 4.10 (s, 3H), 4.04 (s, 3H), 3.97 (s, 3 H). EIMS: *m*/*z* 363 (M^+, 100). Anal. Calcd for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.85. Found: C, 69.44; H, 4.62; N, 3.76.

Oxysanguinarine (14b). The procedure described for compound **14a** was used with compound **13b** (20 mg, 0.10 mmol), PCC (25 mg, 0.21 mmol), and NaOAc (8 mg, 0.18 mmol) to afford oxysanguinarine **14b** as a white solid (16 mg, 61%). Mp = 360−362 °C (lit.[32] mp 366−368 °C). IR (cm^{-1}): 1652 (C═O). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.53 (s, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 7.16 (s, 1H), 6.27 (s, 2H), 6.09 (s, 2H), 3.90 (s, 3H). EIMS: *m*/*z* 347 (M^+, 100). Anal. Calcd for $C_{20}H_{13}NO_5$: C, 69.16; H, 3.77; N, 4.03. Found: C, 69.36; H, 3.95; N, 4.13.

Oxyavicine (14c). The procedure described for compound **14a** was used with compound **13c** (50 mg, 0.136 mmol), PCC (87 mg, 0.21 mmol), and NaOAc (27 mg, 0.18 mmol) to afford oxyavicine **14c** as a white solid (36 mg, 76%). Mp = 279−282 °C (lit.[33] mp 276−277 °C, lit.[34] mp 278−283 °C). IR (cm^{-1}): 1631(CO). H NMR (300 MHz, $CDCl_3$) δ: 7.93 (d, J = 8.6 Hz, 1H), 7.89 (s, 1H), 7.63 (s, 1H), 7.61 (s, 1H), 7.56 (d, J = 8.6, 1H), 7.18 (s, 1H), 6.13 (s, 2H), 6.10 (s, 2H), 3.97 (s, 3H). EIMS: *m*/*z* 347 (M^+, 61). Anal. Calcd for $C_{20}H_{13}NO_5$: C, 69.16; H, 3.77; N, 4.03. Found: C, 69.24; H, 3.69; N, 4.14.

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Supporting Information Available: Copies of ^1H NMR and MS charts of compounds **9a**−**c**, **11a**−**c**, and **14a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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