

## Novel Synthesis of the Natural Protoberberine Alkaloids: Oxypalmatine and Oxypseudopalmatine

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Oxypalmatine and oxypseudopalmatine were synthesized in three steps from the benzonitrile **11** and toluamides **12a, b**. The lithiated cycloaddition reaction yielded 3-arylisquinolinone intermediates. A subsequent internal  $S_N2$  reaction produced the corresponding 8-oxoprotoberberines, oxypalmatine and oxypseudopalmatine.

**Key Words** : Oxypalmatine, Oxypseudopalmatine, 3-Arylisquinolinones

### Introduction

Protoberberines are the important group of natural isoquinoline alkaloids that possess a variety of biological activities.<sup>1-4</sup> These compounds mainly exist in nature as tetrahydroprotoberberines or quaternary salts but several oxoprotoberberines were isolated recently.<sup>5-9</sup> Oxypalmatine **1** was isolated from the stems of *Cocculus orbiculatus*<sup>5</sup> and *Cosciniium fenestratum*,<sup>8</sup> while oxypseudopalmatine **2** was found in *Stephania suberosa*.<sup>9</sup>

In cytostatic activity tests involving several protoberberines and MDA-MB-231 mammalian tumor cells, oxypseudopalmatine inhibited cell proliferation by 87% at a concentration of  $10^{-5}$  M.<sup>10</sup>

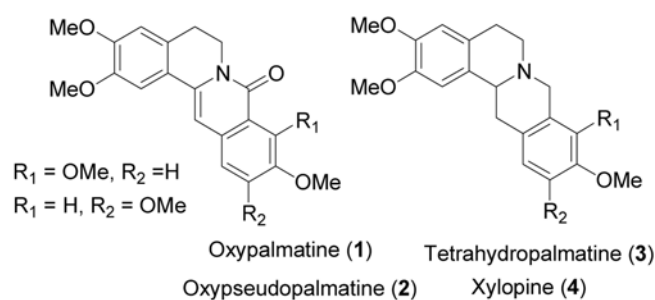
The transformation of oxypalmatine **1** and oxypseudo-

palmatine **2** to tetrahydropalmatine **3** and xylopine **4** has also been reported.<sup>11,12</sup> These alkaloids possess diverse biological activities, including anxiolytic<sup>13</sup> and analgesic effects,<sup>14</sup> as well as free radical and lipid peroxidation inhibitory activity.<sup>15</sup>

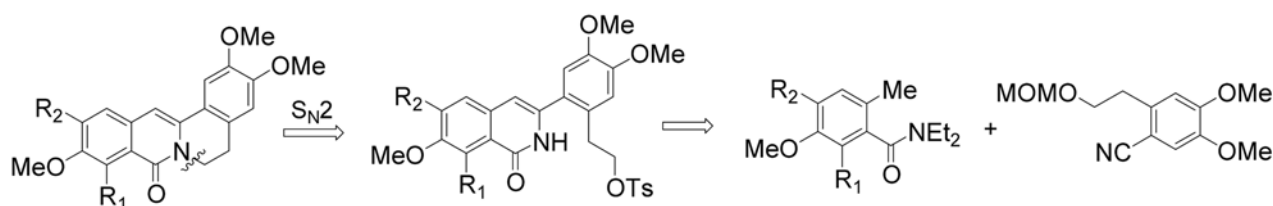
As a part of our ongoing efforts to synthesize all types of substitution patterns on the aromatic rings of protoberberines, we applied our procedure to oxypalmatine and oxypseudopalmatine. Our strategy is based on the formation of 3-arylisquinoline that can be converted to protoberberines *via* an intramolecular  $S_N2$  reaction as depicted in Scheme 1. Easy access to the starting materials and the one-pot reaction for constructing essential carbon atoms of desired protoberberines make this method simple and efficacious. Recently, we synthesized natural benzo[*c*]phenanthridines and protoberberines using the coupling reactions of *N,N*-diethyl-*o*-toluamides and benzonitriles.<sup>16-18</sup> 8-Oxoprotoberberine alkaloids, such as oxycoptisine, oxypseudocoptisine, oxypseudoberberine<sup>16</sup> and oxyberberine,<sup>18</sup> were prepared by ring closure of the two-carbon chain at position 2 (NH) of the 3-arylisquinolinone intermediates. In order to validate the generality of this lithiated cycloaddition reaction, we applied this method to the synthesis of oxypalmatine and oxypseudopalmatine.

### Results and Discussion

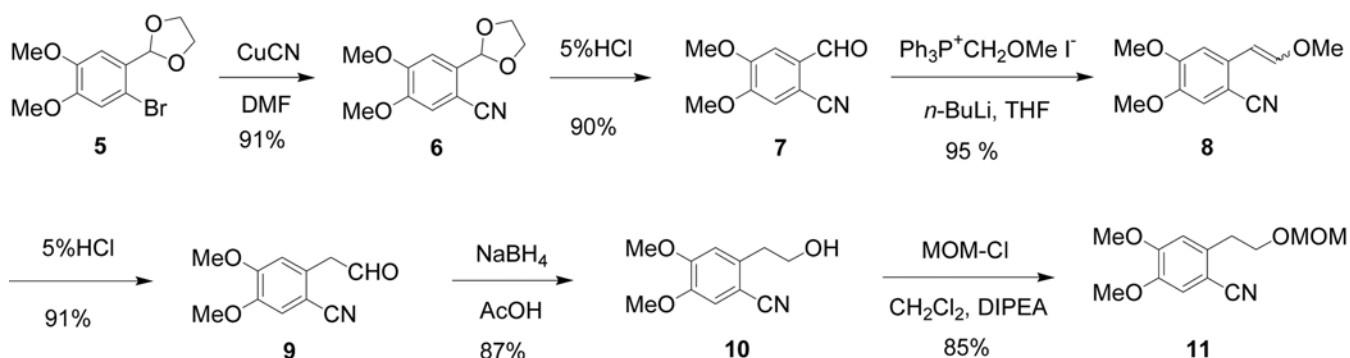
The benzonitrile **11** was prepared as previously reported (Scheme 2).<sup>16-17</sup> Bromoacetal **5** was synthesized from com-



**Figure 1.** Structure of Oxoprotoberberines and tetrahydroprotoberberines.



**Scheme 1.** Retrosynthesis of protoberberines.

Scheme 2. Synthesis of benzonitrile **11**.

mercially available veratraldehyde,<sup>19</sup> and **5** was then reacted with CuCN in DMF to yield 2-acetal benzonitrile **6** in 91% yield. After hydrolysis of the acetal group with 5% HCl, the aldehyde **7** was treated with  $\text{Ph}_3\text{P}^+\text{CH}_2\text{OMe I}^-/n\text{-BuLi}$  to produce the enol ethers **8** as an *E/Z* mixture (1:2) in 95% yield. The mixture was hydrolyzed with 5% HCl to give the homobenzaldehyde **9**, which was then reduced with  $\text{NaBH}_4$  to afford the alcohol **10** in 87% yield. The homobenzyl alcohol **10** was protected with methoxymethyl (MOM) chloride to yield benzonitrile **11** in 85% yield.

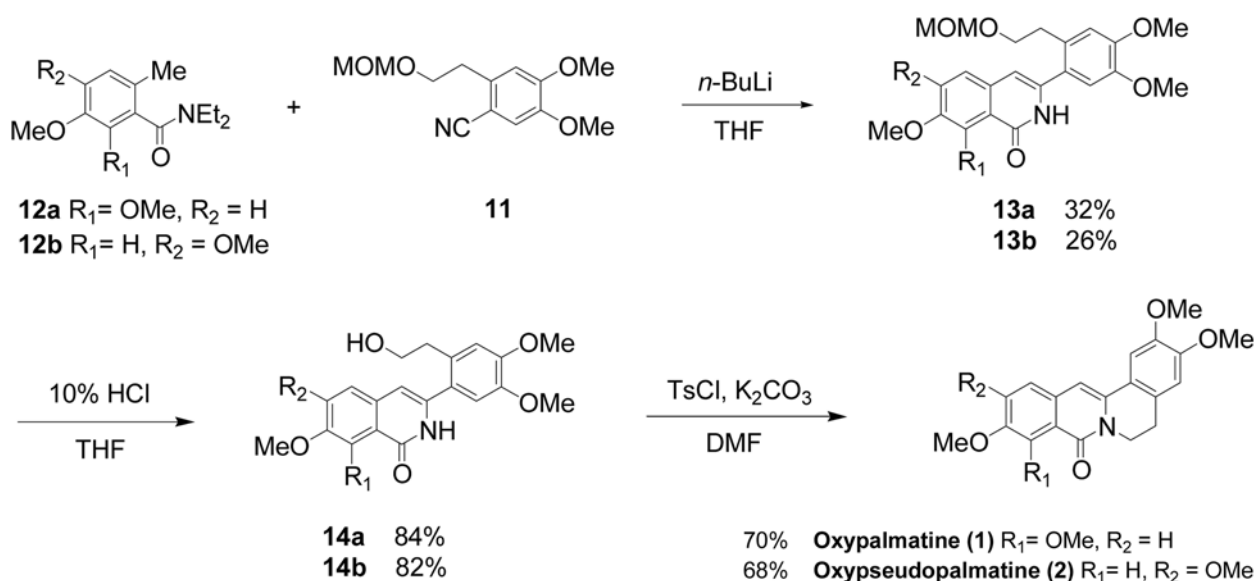
The toluamide-benzonitrile cycloaddition reaction and the synthesis of oxypalmatine and oxypseudopalmatine are depicted in Scheme 3. *N,N*-diethyl-*o*-toluamides **12a**, **b**<sup>16-18</sup> were deprotonated with *n*-BuLi to give carbanions,<sup>20</sup> which were then reacted with benzonitrile **11** at  $-70^\circ\text{C}$  in THF to afford the 3-arylisquinolin-1(2*H*)-ones **13a**, **b** in 32 and 26% yields, respectively. Considering the recovered starting materials of **12a**, **b** the yields were 67 and 65%, respectively. The MOM protecting group was removed with 10% HCl to give the alcohols **14a**, **b**. The Bois-Choussy group has also reported the low-yield synthesis of these alcohols through  $\text{S}_{\text{RN}}1$  reactions between *o*-iodobenzamides and the enolate anion from 2-acetyl homoveratric acid.<sup>20</sup> Compounds **14a**, **b**

were then reacted with *p*-TsCl in DMF in the presence of  $\text{K}_2\text{CO}_3$  to afford oxypalmatine and oxypseudopalmatine in 70 and 68% yields, respectively.

In conclusion, we synthesized oxypalmatine **1** and oxypseudopalmatine **2** in three steps from the benzonitrile **11** and toluamides **12a**, **b**. The formal synthesis of tetrahydropalmatine and xylopine has therefore also been accomplished, as the conversions of oxypalmatine and oxypseudopalmatine to tetrahydropalmatine and xylopine, respectively, were already established. The application of this toluamide-benzonitrile cycloaddition method to other substituted protoberberine alkaloids is currently under investigation.

### Experimental Section

Melting points were determined on an Electrothermal IA9200 melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra ( $^1\text{H-NMR}$ ) were recorded on a Varian 300 spectrometer, using TMS as the internal standard; chemical shifts are reported in parts per million and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). IR spectra were recorded on a Perkin-Elmer 783 spectrometer and a Nicolet instrument using KBr

Scheme 3. Synthesis of Oxypalmatine **1** and oxypseudopalmatine **2**.

pellets. Mass spectra were analyzed on Varian MS 1200. Solvents were routinely distilled prior to use. Anhydrous THF was distilled from sodium-benzophenone. Column chromatography was performed on Merck silica gel 60 (70-230 mesh). TLC was carried out using plates coated with silicagel 60F 254 purchased from Merck Co. Reagents were obtained from commercial suppliers and were used without purification.

**2-[1,3]Dioxolan-2-yl-4,5-dimethoxybenzonitrile (6).** A mixture of acetal **5** (14.5 g, 50 mmol), CuCN (5.34 g, 60 mmol) in DMF (40 mL) was refluxed for 3 hrs. The hot, dark reaction mixture was poured into a solution of sodium cyanide (15 g, 300 mmol) in water (200 mL). After the mixture was shaken well, the mixture was extracted with benzene. The combined extract was concentrated and purified by column chromatography with *n*-hexane-ethyl acetate (3:1) to give benzonitrile **6** as white needles (10.7 g, 91%). mp: 105.5-107.5 °C. IR (cm<sup>-1</sup>): 2221 (CN). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.10 (s, 2H), 5.95 (s, 1H), 4.26-4.08 (m, 4H), 3.95 (s, 3H), 3.91 (s, 3H). EIMS *m/z* (%): 235 (M<sup>+</sup>, 100).

**2-Formyl-4,5-dimethoxybenzonitrile (7).** The cyano acetal **6** (14.1 g, 60 mmol) in 5% HCl (10 mL) was warmed up at 50-60 °C for 15 min. The solid was collected, washed with water and dried giving aldehyde **7** as pale yellow solid (10.32 g, 90%). mp: 142-144 °C. IR: 2231 (CN), 1693 (CO). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 10.26 (s, 1H), 7.49 (s, 1H), 7.19 (s, 1H), 4.01 (s, 3H), 4.01 (s, 3H). EIMS *m/z* (%): 191 (M<sup>+</sup>, 100).

**4,5-Dimethoxy-2-(2-methoxyvinyl)benzonitrile (8).** To the solution of (methoxymethyl)triphenylphosphonium iodide (11.97 g, 35 mmol) in dry THF (50 mL) was added *n*-butyllithium (22 mL, 35.2 mmol) at 0 °C and the mixture was stirred for 1 h at 0 °C. The reaction mixture was added aldehyde **3** (4.78 g, 25 mmol) in THF (20 mL) at the same temperature. The reaction mixture was stirred for 30 min at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over sodium sulfate. After removing the solvent *in vacuo* the residue was purified by column chromatography with *n*-hexane-ethyl acetate (3:1) to afford to afford styrene **8** as a (*E/Z*) isomer mixture (1:2) as a yellow solid (5.2 g, 95%). δ (cis): 7.70 (s, 1H), 6.98 (s, 1H), 6.27 (d, *J* = 7.1 Hz, 1H), 5.57 (d, *J* = 7.1 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H). δ (trans): 7.14 (d, *J* = 12.8 Hz, 1H), 6.97 (s, 1H), 6.84 (s, 1H), 6.04 (d, *J* = 12.8 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 3.75 (s, 3H).

**4,5-Dimethoxy-2-(2-oxoethyl)benzonitrile (9).** A solution of The *E/Z* mixture of **8** (4.81 g, 22 mmol) in acetone (30 mL) and 10% HCl (10 mL) was refluxed for 2 hrs. The acetone was removed and reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, brine and dried over anhydrous sodium sulfate. After removing the solvent, the residue was purified by column chromatography on silica gel with *n*-hexane-ethyl acetate (1:1) to give aldehyde **9** as an oil (4.1 g, 91%). IR (cm<sup>-1</sup>): 2220 (CN), 1720 (C=O), 1300-1000 (C-O). <sup>1</sup>H

NMR (300 MHz, CDCl<sub>3</sub>) δ: 9.78 (s, 1H), 7.10 (s, 1H), 6.75 (s, 1H), 4.00 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H). EIMS *m/z* (%): 205 (M<sup>+</sup>, 85).

**2-(2-Hydroxyethyl)-4,5-dimethoxybenzonitrile (10).** To the mixture of aldehyde **9** (4.1 g, 20 mmol) in acetic acid (20 mL) was added NaBH<sub>4</sub> (1.52 g, 40 mmol). After the reaction was over, 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 alcohol **10** as yellow oil (3.59 g, 87%). IR (cm<sup>-1</sup>): 3480 (OH), 2220 (CN). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.00 (s, 1H), 6.95 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.91 (t, *J* = 6.5 Hz, 2H), 3.03 (t, *J* = 6.5 Hz, 2H). EIMS *m/z* (%): 207 (M<sup>+</sup>, 74).

**4,5-Dimethoxy-2-(2-methoxymethoxyethyl)benzonitrile (11).** To the mixture of alcohol **10** (3.59 g, 17.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added diisopropylethylamine (DIPEA) (4.55 g, 35 mmol) and chloromethylmethyl ether (2.8 g, 35 mmol) at 0 °C. After the reaction was over, CH<sub>2</sub>Cl<sub>2</sub> was removed *in vacuo* and the residue was purified by column chromatography with *n*-hexane-ethyl acetate (3:1) to give benzonitrile **11** as a yellow oil (3.69 g, 85%). IR (cm<sup>-1</sup>): 2230 (CN), 1300-1000 (C-O). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.03 (s, 1H), 6.86 (s, 1H), 4.61 (s, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.79 (t, *J* = 6.6 Hz, 2H), 3.29 (s, 3H), 3.07 (t, *J* = 6.6 Hz, 2H). EIMS *m/z* (%): 251 (M<sup>+</sup>, 100).

**3-[4,5-Dimethoxy-2-(2-methoxymethoxyethyl)phenyl]-7,8-dimethoxy-2H-isoquinolin-1-one (13a).** A solution of *N,N*-diethyl-*o*-toluamide **12a** (2.01 g, 8 mmol) and benzonitrile **11** (2.51 g, 10 mmol) in dry THF (30 mL) were added dropwise to the solution of *n*-BuLi (10 mL of 1.6 M in hexane, 16 mmol) in THF (40 mL) at -70 °C and then the reaction mixture was stirred at the same temperature for 6hs. The reaction was quenched with water and extracted with ethyl acetate and dried over sodium sulfate. After removing the solvent, the residue was purified by column chromatography with *n*-hexane-ethyl acetate (1:1) to afford isoquinoline **13a** as solid (1.1 g, 32%) with recovered starting material **12a** (1.05 g). mp: 142-145 °C. IR (cm<sup>-1</sup>): 3400 (NH), 1630 (C=O). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 10.14 (b, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 6.92 (s, 1H), 6.89 (s, 1H), 6.42 (s, 1H), 4.72 (s, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.88 (s, 3H), 3.88 (t, *J* = 5.7 Hz, 2H), 3.27 (s, 3H), 2.90 (t, *J* = 5.7 Hz, 2H). EIMS *m/z* (%): 429 (M<sup>+</sup>, 67).

**3-[4,5-Dimethoxy-2-(2-methoxymethoxyethyl)phenyl]-6,7-dimethoxy-2H-isoquinolin-1-one (13b).** The procedure described for the synthesis of compound **13a** was used with toluamide **12b** (2.5 g, 10 mmol) and benzonitrile **11** (2.05 g, 8 mmol) to afford compound **13b** as a yellow oil (1.1 g, 26%) with recovered starting material **12b** (1.5 g). IR (cm<sup>-1</sup>): 3400 (NH), 1665 (C=O). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 10.37 (b, 1H), 7.79 (s, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 6.45 (s, 1H), 4.72 (s, 2H), 4.01 (s, 3H), 4.01 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.92 (t, *J* = 5.7 Hz, 2H), 3.32 (s, 3H), 2.90 (t, *J* = 5.7 Hz, 2H). EIMS *m/z* (%): 429 (M<sup>+</sup>, 45).

**3-[2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl]-7,8-dimethoxy-2H-isoquinolin-1-one (14a).** To the mixture of compound **13a** (400 mg, 0.93 mmol) in THF (15 mL) was added 10% HCl (5 mL) and the reaction was refluxed for 2 hrs. The reaction mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extract was washed with water, brine and dried over anhydrous sodium sulfate. After removing the solvent, the residue was purified by column chromatography on silica gel with CH<sub>2</sub>Cl<sub>2</sub>: MeOH (20:1) to give alcohol **14a** as a yellow solid (300 mg, 84%). mp: 197-200 °C. IR (cm<sup>-1</sup>): 3337 (NH, OH), 1642 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO) δ: 11.43 (s, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 6.87 (s, 1H), 6.79 (s, 1H), 6.44 (s, 1H), 4.07 (t, *J* = 5.4 Hz, 2H), 3.95 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 2.83 (t, *J* = 5.4 Hz, 2H). EIMS *m/z* (%): 385 (M<sup>+</sup>, 100).

**3-[2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-2H-isoquinolin-1-one (14b).** The procedure described for compound **14a** was used with compound **13b** (300 mg, 0.7 mmol) and 10% HCl (5 mL) in THF (15 mL) to give alcohol **14b** as a yellow solid (220 mg, 82%). mp: 175-178 °C (lit.<sup>21</sup>: 130-133 °C). IR (cm<sup>-1</sup>): 3400, 3300 (NH, OH), 1642 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO) δ: 11.31 (b, 1H), 7.55 (s, 1H), 7.16 (s, 1H), 6.95 (s, 1H), 6.90 (s, 1H), 6.45 (s, 1H), 5.11 (t, *J* = 4.5 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.64 (m, 2H), 2.72 (t, *J* = 6.6 Hz, 2H). EIMS *m/z* (%): 385 (M<sup>+</sup>, 100).

**2,3,9,10-Tetramethoxy-5,6-dihydroisoquino[3,2-a]isoquinolin-8-one (oxypalmatine) (1).** The mixture of compound **14a** (260 mg, 0.67 mmol), tosyl chloride (250 mg, 1.3 mmol) and K<sub>2</sub>CO<sub>3</sub> (550 mg, 4 mmol) in DMF (10 mL) was stirred for 4 h at 100 °C. To this mixture water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. After removing the solvent, the residue was purified by column chromatography on silica gel with *n*-hexane-ethyl acetate (1:2) to give oxypalmatine **1** as a yellow solid (174 mg, 70%). mp: 181-183 °C (lit.<sup>22</sup>: 183-184 °C). IR (cm<sup>-1</sup>): 2960, 1640. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.34-7.31 (d, 2H), 7.23 (s, 1H), 6.76 (s, 1H), 6.72 (s, 1H), 4.32 (t, *J* = 6.0 Hz, 2H), 4.01 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H), 2.92 (t, *J* = 6.0 Hz, 2H). EIMS *m/z* (%): 367 (M<sup>+</sup>, 100).

**2,3,10,11-Tetramethoxy-5,6-dihydroisoquino[3,2-a]isoquinolin-8-one (oxypseudopalmatine) (2).** The procedure described for compound **1** was used with compound **10b** (190 mg, 0.5 mmol) and tosyl chloride (190 mg, 1 mmol)

and K<sub>2</sub>CO<sub>3</sub> (400 mg, 3 mmol) to give oxypseudopalmatine **2** as a yellow solid (126 mg, 68%). mp: 187-189 °C (lit.<sup>23</sup> 185-186 °C. lit.<sup>24</sup> 195-197 °C. lit.<sup>9</sup> 196-198 °C). IR (cm<sup>-1</sup>): 1640. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.78 (s, 1H), 7.33 (s, 1H), 6.96 (s, 1H), 6.85 (s, 1H), 6.76 (s, 1H), 4.36 (t, *J* = 6.0 Hz, 2H), 4.01 (s, 3H), 4.01 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 2.90 (t, *J* = 6.0 Hz, 2H). EIMS *m/z* (%): 367 (M<sup>+</sup>, 100).

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