A Concise Synthesis of 8-Oxoberberine and Oxychelerythrine, Natural Isoquinoline Alkaloids through Biomimetic Synthetic Way

Thanh Nguyen Le and Won-Jea Cho*

College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Gwangju 500-757, Korea
**E-mail: wjcho@jnu.ac.kr*
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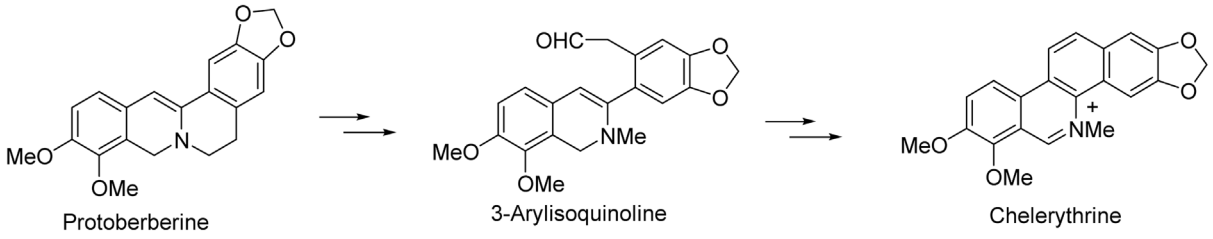
Natural isoquinoline alkaloids such as berberine and chelerythrine exhibit a variety of biological activities.[1,2] Berberine has been isolated from several medicinal herbs, such as *Hydrastis canadensis*, *Cortex phellodendri* and *Rhizoma coptidis* which are widely distributed in plants and used as the traditional oriental medicine. Recently it has been attracted by the unique biological activities such as antidiabetic,[3] anticancer[4,5] and antimicrobial activities.[6,7] One of the most interesting properties of berberine is that it exhibits cholesterol-lowering effect.[8,9] Oral administration of berberine in 32 hypercholesterolemic patients for 3 months reduced serum cholesterol by 29%, triglycerides by 35% and LDL-cholesterol by 25%.[9] Emerging of this compound as new cholesterol-lowering drug prompted us to develop new efficient synthesis of berberine.

Chelerythrine, a benzo[*c*]phenanthridine alkaloid, also has been investigated for its biological efficacy such as anti-tumor,[10] inhibition of protein kinase C,[11] induction of apoptosis through the generation of reactive oxygen and the stimulation of GSH transport.[12]

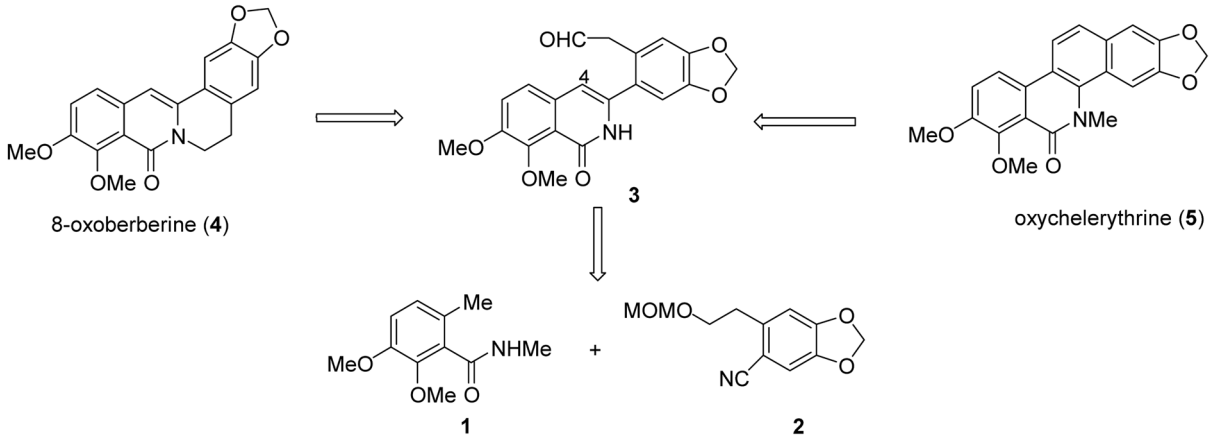
Due to the interesting biological activities, the synthesis of protoberberine and benzo[*c*]phenanthridines has been studied.[1,13,14] Recently, we have also reported a versatile synthetic pathways for these alkaloids using lithiated toluamide-bezonitrile cycloaddition.[15,16]

As depicted in Scheme 1, benzo[*c*]phenanthridine alkaloid, chelerythrine, was proposed to be biosynthesized from the corresponding protoberberine alkaloid.[17] In this pathway, the 3-arylisoquinolinone is a key intermediate for the cyclization step toward the benzo[*c*]phenanthridine skeleton.

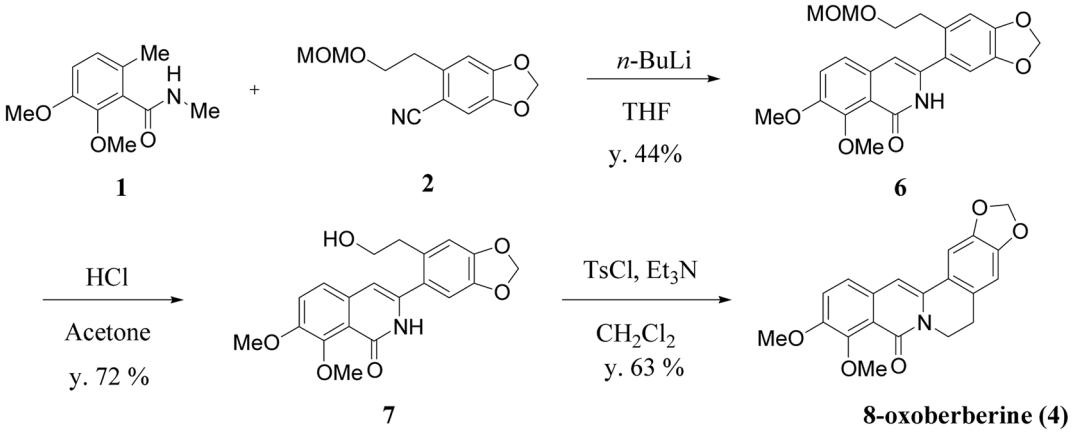
We have reported the synthesis and QSAR studies of 3-arylisoquinoline derivatives with antitumor activity.[17-20] The synthetic strategy involved in the coupling reaction of *N*-methyl-*o*-toluamide with benzonitrile derivatives.[21]



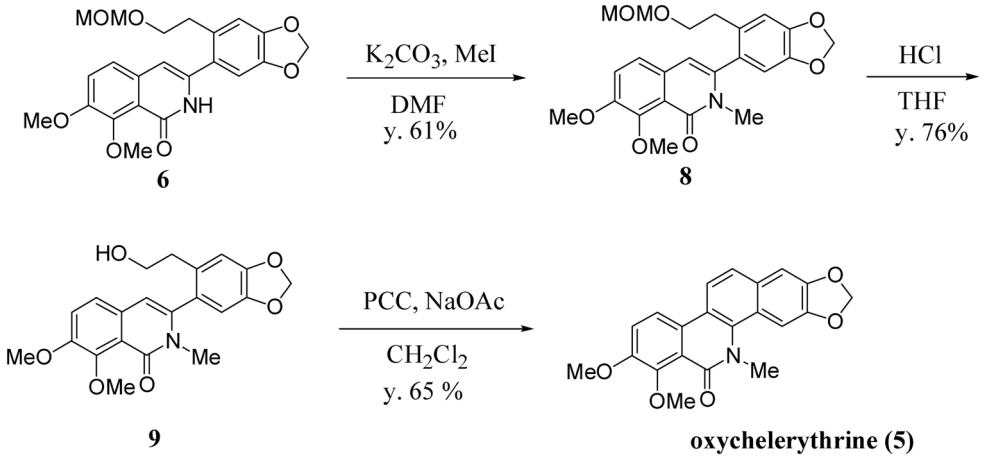
Scheme 1. Biosynthetic pathway of benzo[*c*]phenanthridine alkaloid from protoberberine.



Scheme 2. Retrosynthesis of 8-oxoberberine **4** and oxychelerythrine **5**.



Scheme 3. Synthesis of 8-oxoberberine **4**.



Scheme 4. Synthesis of oxychelerythrine **5**.

Retrosynthetic analysis of both alkaloids suggested that the coupling reaction of *o*-toluamide **1** with benzonitrile **2** affords 3-arylisoquinoline **3**, which could be converted to 8-oxoberberine **4** *via* S_N2 type cyclization of amide nitrogen. On the other hand, cyclization at C4 position could give oxychelerythrine **5** as shown in Scheme 2.

N-Methyl-*o*-toluamide **1**[22] was lithiated with *n*-butyl lithium to give the dianion, which was treated with benzonitrile **2**[15] at –50 °C in THF to afford the 3-arylisoquinoline-1(2*H*)-one **6**. Deprotection of MOM (methoxymethyl) with 10% HCl gave the alcohol **7**, which were then reacted with *p*-TsCl in DMF in the presence of triethylamine to afford the desired protoberberine alkaloid, oxyberberine **4** in 63% yield (Scheme 3).

The 3-arylisoquinoline intermediate **6** was treated with MeI/K_2CO_3 provided the *N*-methylated product **8** without yielding *O*-methylated compounds in 61% yield. Hydrolysis of MOM group with 10% HCl gave the alcohols **9** which was then oxidized with PCC/NaOAc to provide the desired benzo[*c*]phenanthridine alkaloid, oxychelerythrine **5** in 65% yield (Scheme 4).

In conclusion, we accomplished a biomimetic synthesis of 8-oxoberberine **4** and oxychelerythrine **5** in three and four steps, respectively. Efficiency and short synthetic step made this process possible to be used as a general method for multi gram scale preparation of these alkaloids.

Experimental Section

Melting points were determined by using the capillary method on Electrothermal IA9200 digital melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) data for ^{1}H NMR was taken on Varian Unity 300 plus spectrometer and were reported in ppm, downfield from the peak of tetramethylsilane as an internal standard. The data are reported as follows: chemical shift, number of proton, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). IR spectra were recorded on JASCO-FT IR spectrometer using $CHCl_3$ and KBr pellets. Mass spectra were obtained on JEOL JNS-DX 303 applying the electron-impact (EI) method. Column chromatography was performed on Merck silica gel 60 (70-230 mesh). TLC was carried out using plates coated with silica gel 60 F254 purchased from Merck. Chemical reagents were purchased from Aldrich Chemical Co. and used without further purification. Solvents were distilled prior to use: THF, ether were distilled from

sodium/ benzophenone.

7,8-Dimethoxy-3-[6-(2-methoxymethoxyethyl)benzo[1,3]-dioxol-5-yl]-2*H*-isoquinolin-1-one (6). To the solution of amide **1** (1.44 g, 6.8 mmol) in dry THF (20 mL) was added *n*-butyl lithium (5.6 mL of 2.5 M in hexane, 14 mmol) at −20 °C and maintained the reaction temperature never exceeding 20 °C. After the red orange solution was stirred at 0 °C for 1 h and cooled to -50 °C, benzonitrile **2** (1.35 g, 5.7 mmol) was added dropwise. The reaction mixture was stirred at the same temperature for 20 min and allowed to warm up to 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 (1 : 1) to afford 3-arylisoquinoline **6** as a sticky solid (1.05 g, 44 %). IR (cm^{-1}): 3400 (NH), 1630 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.30 (s, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 6.85 (s, 1H), 6.80 (s, 1H), 6.32 (s, 1H), 6.01 (s, 2H), 4.74 (s, 2H), 4.00 (s, 3H), 3.95 (s, 3H), 3.84 (m, 2H), 3.25 (s, 3H), 2.85 (m, 2H). MS, *m/e* (%): 413 (M^+, 10), 336 (14), 222 (59), 192 (94), 174 (100).

3-[6-(2-Hydroxyethyl)benzo[1,3]dioxol-5-yl]-7,8-dimethoxy-2*H*-isoquinolin-1-one (7). To a solution of compound **6** (450 mg, 1.09 mmol) in THF (15 mL) was added 10% HCl (5 mL) and then the reaction mixture was refluxed for 2 h. It 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_2Cl_2 : MeOH (20 : 1) to give an alcohol **7** as a yellow solid (290 mg, 72%). mp: 218-220 °C. IR (cm^{-1}): 3400 (NH, OH), 1642 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.0 (s, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.31 (d, J = 8.7 Hz, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 6.28 (s, 1H), 6.00 (s, 2H), 5.05 (s, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.55 (m, 2H), 2.61 (t, J = 6.5 Hz, 2 H). MS, *m/e* (%): 369 (M^+, 34), 322 (57), 221 (60), 174 (100).

9,10-Dimethoxy-5,6-dihydro[1,3]dioxolo[4,5-*g*]isoquino-[3,2-*a*]isoquinolin-8-one (8-oxoberberine) (4). The mixture of compound **7** (100 mg, 0.28 mmol), tosyl chloride (115 mg, 0.6 mmol), and triethylamine (60 mg, 0.6 mmol) in CH_2Cl_2 was stirred at room temperature for overnight. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was dried over anhydrous sodium sulfate. After evaporating off the solvent, the residue was purified by column chromatography with *n*-hexane-ethyl acetate (1 : 1) to give 8-oxoberberine **4** as a yellow solid (61 mg, 63%). mp: 191-193 °C (lit.[15] 191-193 °C). IR (cm^{-1}): 1642 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.7 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 7.21 (s, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 6.01 (s, 2H), 4.29 (t, J = 6.2 Hz, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 2.89 (t, J = 6.2 Hz, 2H). MS, *m/e* (%): 351 (M^+, 100), 336 (53), 322 (44), 308 (41).

7,8-Dimethoxy-3-[6-(2-methoxymethoxyethyl)benzo[1,3]-dioxol-5-yl]-2-methyl-2*H*-isoquinolin-1-one (8). The mixture of compound **6** (310 mg, 0.75 mmol), K_2CO_3 (517 mg, 3.75 mmol) and methyl iodide (210 mg, 1.5 mmol) in DMF (6 mL) was heated at 100 °C for 3 h. The reaction mixture was quenched by water and then extracted with ethyl acetate. The combined ethyl acetate extracts were 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 the compound **8** as an oil (196 mg, 61%). IR (cm^{-1}): 1645 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.7 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.89 (s, 1H), 6.69 (s, 1H), 6.27 (s, 1H), 6.02 (m, 2H), 4.50 (s, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 3.61 (m, 2H), 3.25 (s, 3H), 3.20 (s, 3H), 2.85 (m, 2 H). MS, *m/e* (%): 427 (M^+, 100), 358 (14), 221 (59), 198 (92), 172 (80).

3-[6-(2-Hydroxyethyl)benzo[1,3]dioxol-5-yl]-7,8-dimethoxy-2-methyl-2*H*-isoquinolin-1-one (9). To the mixture of compound **8** (162 mg, 0.38 mmol) in THF (15 mL) was added 10% HCl (5 mL) and then the reaction mixture was refluxed for 2 h. It was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were 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 with *n*-hexane-ethyl acetate (1 : 1) to give the alcohol **9** as a solid (110 mg, 76%). mp: 163-165 °C. IR (cm^{-1}): 3450 (OH), 1650 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.7 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.93 (s, 1H), 6.70 (s,1H), 6.28 (s, 1H), 6.01 (m, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 3.72 (m, 2H), 3.24 (s, 3H), 2.79-2.53 (m, 2 H). MS, *m/e* (%): 383 (M^+, 100), 368 (49), 354 (19), 206 (18).

1,2-Dimethoxy-12-methyl-12*H*-[1,3]dioxolo[4',5':4,5]-benzo[1,2-*c*]phenanthridin-13-one (5) (oxychelerythrine). The reaction mixture of alcohol **9** (70 mg, 0.18 mmol), PCC (80 mg, 0.37 mmol) and NaOAc (25 mg, 0.3 mmol) in CH_2Cl_2 (8 mL) was stirred for 5 h. The reaction mixture was filtered and the filtrate was washed with CH_2Cl_2. The combined solvents were evaporated off and the residue was purified by column chromatography on silica gel with *n*-hexane-ethyl acetate (1 : 1) to afford the oxychelerythrine **5** as a white solid (42 mg, 65%). mp 198-199 °C. (lit.[23] 197-198 °C). IR (KBr) (cm^{-1}): 1645 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H) 7.58 (d, J = 9.0 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 7.52 (s, 1H), 7.16 (s, 1H), 6.10 (s, 2H), 4.08 (s, 3H), 3.98 (s, 3H), 3.90 (s, 3H). MS, *m/e* (%): 363 (M, 35), 348 (15), 334 (14), 305 (18), 190 (20), 57 (100). *Anal*. Calc. for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.85. Found: C, 69.63; H, 4.69; N, 3.87.

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