Total Synthesis of Oxyfagaronine, Phenolic Benzo[*c*]phenanthridine and General Synthetic Way of 2,3,7,8- and 2,3,8,9-Tetrasubstituted Benzo[*c*]phenanthridine Alkaloids

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Benzo[*c*]phenanthridine alkaloids such as oxynitidine, oxysanguinarine, oxyavicine and phenolic oxyfagaronine were synthesized from easily available starting benzonitriles 5 and toluamides 6 using a lithiated toluamide-benzonitrile cycloaddition reaction. The coupling reaction provided 3-arylisoquinolinones that were transformed to the benzo[*c*]phenanthridones. This method is highly efficient and could be useful for preparing diverse substituted aromatic benzo[*c*]phenanthridine compounds on a multi gram scale.

Key words oxyfagaronine; oxynitidine; oxysanguinarine; oxyavicine; benzo[*c*]phenanthridine; cycloaddition

Benzo[*c*]phenanthridines are isoquinoline alkaloids, many of which have various biological activities.[1—4] Sanguinarine displays antibacterial[5,6] and antifungal[7] activities while nitidine and fagaronine have been investigated as potential antitumor and antiviral agents.[8—12] Hence, much attention has been focused on the development of facile synthetic methodology of benzo[*c*]phenanthridines.[3,13—16] The approaches to these alkaloids *via* 3-arylisoquinoline intermediates such as homophthalic ester and homophthalic-imine condensation,[17] phenyl ethyl isocyanate cyclization[18] and imine-toluamide[19] condensation were reported. However, the limited application of diverse substitutions on the aromatic rings of benzo[*c*]-phenanthridine is a barrier for broadening the utility of these methods.

We have synthesized the benzo[*c*]phenanthridine skeleton[20,21] and recently reported the preliminary synthesis of benzo[*c*]phenanthridine alkaloids, including oxynitidine, oxysanguinarine[22] and oxychelerythrine.[23] An alternative method to benzo[*c*]phenanthridine and protoberberine alkaloids was also documented.[24] Both syntheses involved the cycloaddition reaction of lithiated *o*-toluamides with benzonitriles to prepare substituted 3-arylisoquinolinones, which could be transformed to benzo[*c*]phenanthridine alkaloids *via* an intramolecular enamide ring formation reaction. The advantage of this our strategy is easy access to the starting materials, which will be useful for preparing alkaloids with various substituents. Here we report our progress in synthesizing oxynitidine, oxysanguinarine, oxyavicine, and phenolic oxyfagaronine using the former procedure (Fig. 1).

Retrosynthetic consideration of benzo[*c*]phenanthridine shows that the coupling of benzonitrile with *o*-toluamide might produce 3-arylisoquinolinone, which could be converted to an aldehyde. One more C extension can be introduced by the Wittig reaction and the B ring of benzo[*c*]-phenanthridine could be constructed by an intramolecular ring closure as shown in Chart 1.

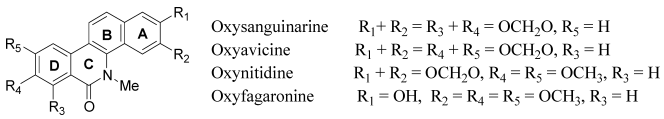

Fig. 1. Structure of Benzo[*c*]phenanthridine Alkaloids

Results and Discussion

The benzonitriles **5a**, **b** were easily prepared from the acetal bromides in four steps. For the synthesis of oxyfagaronine, the hydroxyl group at ring A was protected by benzyl group. The bromides **1a**, **b** were converted to benzonitriles **2a**, **b** in 67% and 81% yield, respectively. The Resenmund-von Braun reaction was performed using DMF instead of pyridine as a solvent.[25] The acetal groups of **2a**, **b** were removed by 5% HCl to afford aldehydes **3a**, **b**, which were then reduced with $NaBH_4$. Alcohol groups were protected by MOM group to provide the desired benzonitriles **5a**, **b** in excellent yields as outlined in Chart 2.

For the synthesis of oxysanguinarine, oxyavicine, and oxynitidine, the substituted *N*,*N*-diethyl *o*-toluamides **6a**—**c**[24] were deprotonated with *n*-BuLi and then treated with benzonitrile **5a**. In this cycloaddition reaction, the starting *N*-methyl *o*-toluamide was modified to *N*,*N*-diethyl toluamides because the coupling reaction with benzonitriles that were protected with benzyl or methoxybenzyl gave lower yields due to a weak solubility in THF. The cycloaddition reaction between *N*,*N*-diethyl toluamides **6a**—**c** and MOM-protected

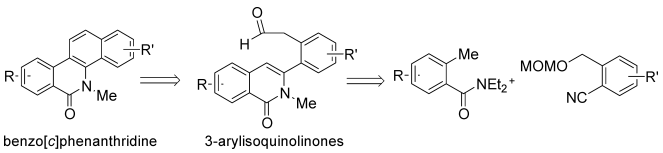

Chart 1. Retrosynthetic Pathway of Benzo[*c*]phenanthridines

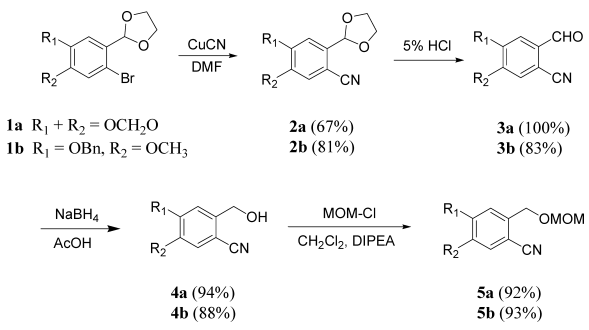

Chart 2. Synthesis of Benzonitriles **5a**, **b**

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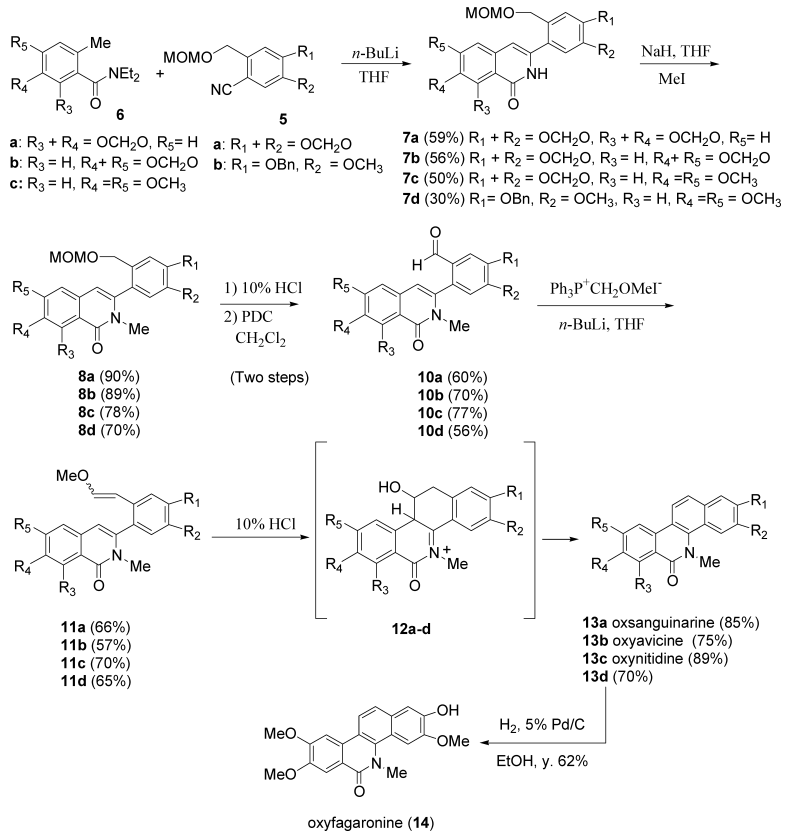

Chart 3. Synthesis of Oxysanguinarine, Oxyavicine, Oxynitidine, and Oxyfagaronine

benzonitrile **5a** produced 3-arylisoquinolinones **7a**—**c** in 50—59% yield. These compounds were treated with MeI in the presence of 60% NaH to give compounds **8a**—**c**. The MOM group was removed by reflux with 10% HCl and the obtained alcohols were oxidized with PDC to afford aldehydes **10a**—**c**. The Wittig reactions were carried out with these aldehydes to yield mixture of *cis*/*trans* isomers. Without separating the *cis*/*trans* mixture of **11a**—**c**, they were hydrolyzed with 10% HCl to give natural benzo[*c*]phenanthridines: oxysanguinarine (**13a**), oxyavicine (**13b**) and oxynitidine (**13c**) in 75—89% yield. We postulated that acidic hydrolysis of the terminal methoxy vinyl group yielded the aldehyde and the consecutive intramolecular enamide-aldehyde cyclization also occurred to form the B ring of benzo[*c*]phenanthridones as shown in Chart 3.[26,27] The consecutive dehydration and deprotonation reaction of intermediates **12a**—**c** would easily occur thus producing a fully aromatized ring system of benzo[*c*]phenanthridines **13a**—**c**. Oxysanguinarine (**13a**), which is a 2,3,7,8-tetraoxygenated alkaloid was prepared in 20.7% overall yield and the 2,3,8,9-tetraoxygenated alkaloids, oxyavicine (**13b**) and oxynitidine (**13c**), were obtained in 20.5% and 19.6% overall yield, respectively.

We chose phenolic benzo[*c*]phenanthridine, fagaronine, as a next target to determine the generality of our method. Fagaronine contains a hydroxyl group at ring A, which made the total synthesis of this alkaloids more difficult because a suitable protective group was needed.[28] In our approach, the phenol was protected with a conventional benzyl group[29] and benzonitrile **5b** was obtained from the starting material **1b** in 55% overall yield.

For the synthesis of fagaronine, the coupling reaction between toluamide **6c** and benzonitrile **5b** was carried out to give 3-arylisoquinolinone **7d** in 30% yield. The consecutive *N*-methylation, deprotection with 10% HCl, oxidation with PDC, and the Wittig reaction followed by hydrolysis produced the benzo[*c*]phenanthridine compound **13d**. Since compound **13d** was converted to fagaronine[29] we have accomplished the formal synthesis of fagaronine. The oxyfagaronine **14** was easily prepared from compound **13d** by a hydrogenation reaction in the presence of 5% Pd/C, which was identical with the authentic sample provided by Prof. T. Ishikawa.[30]

Conclusion

In conclusion, we succeeded in synthesizing four natural benzo[*c*]phenanthridine alkaloids with diverse substituted patterns. The present synthesis shows that our method could be applied for the synthesis of both 2,3,7,8- and 2,3,8,9-substituted alkaloids including phenolic alkaloid. This methodology could be applied to the synthesis of other substituted aromatized benzo[*c*]phenanthridines and would provide simple multi-gram scale preparation of these compounds.

Experimental

Melting points were determined on an Electrothermal IA9200 melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^{1}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 pellets. Mass spectra were analyzed on Varian MS 1200. Elemental analyses were performed on a CaHo Erba elemental analyzer. Solvents were routinely distilled prior to use. Anhydrous THF was distilled from sodium-benzophenone. Column chromatography was per-

formed 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.

6-[1,3]Dioxolan-2-yl-benzo[1,3]dioxole-5-carbonitrile (2a) A mixture of 6-bromopiperonal ethylene acetal[25] (15 g, 55 mmol), CuCN (5.91 g, 66 mmol) in DMF (20 ml) was refluxed for 3 h. The hot and dark reaction mixture was poured into a warm solution of sodium cyanide (10 g) in water. After the mixture was shaken well, the mixture was extracted with benzene (60 ml). The combined extract was concentrated and purified by column chromatography to give benzonitrile compound **2a** as a white needles (8.3 g, 67%). mp 92—93 °C. IR (cm^{-1}): 2220 (CN). ^{1}H-NMR ($CDCl_3$) δ: 7.07 (s, 1H); 7.05 (s, 1H); 6.08 (s, 2H); 5.92 (s, 1H); 4.23—4.05 (m, 4H).

4-Benzyloxy-2-[1,3]dioxolan-2-yl-5-methoxybenzonitrile (2b) The procedure described for compound **2a** was used with acetal **1b** (9.1 g, 25 mmol), CuCN (2.7 g, 30 mmol) in DMF (20 ml) to afford compound **5b** as a bright yellow solid (6.3 g, 81%). mp 142—144 °C. IR (cm^{-1}): 2220 (CN). ^{1}H-NMR ($CDCl_3$) δ 7.43—7.33 (m, 5H), 7.13 (s, 3H), 7.12 (s, 1H); 5.92 (s, 1H), 5.19 (s, 2H), 4.19—4.05 (m, 4H), 3.90 (s, 3H). EI-MS: *m/z* 311 (M^+, 100). *Anal.* Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.74; H, 5.30; N, 4.55.

6-Formylbenzo[1,3]dioxole-5-carbonitrile (3a) The cyano acetal **2a** (8.3 g, 37 mmol) in 5% HCl (25 ml) was warmed at 50—60 °C for 15 min. The solid was collected, washed with water and dried to give aldehyde **3a** as a pale yellow solid (6.57 g, 100%). mp 160—162 °C. IR (cm^{-1}): 2230 (CN). ^{1}H-NMR ($CDCl_3$) δ: 10.24 (s, 1H), 7.44 (s, 1H), 7.44 (s, 1H), 6.20 (s, 2H).

4-Benzyloxy-2-formyl-5-methoxybenzonitrile (3b) The procedure described for aldehyde **3a** was used with acetal **2b** (5.6 g, 18 mmol) in 5% HCl (25 ml) to give aldehyde **3b** as a pale yellow solid (4 g, 83%). mp 153—156 °C. IR (cm^{-1}): 2230 (CN). ^{1}H-NMR ($CDCl_3$) δ: 10.23 (s, 1H), 7.54 (s, 1H), 7.46—7.36 (m, 5H), 7.19 (s, 1H); 5.24 (s, 2H), 3.99 (s, 3H). EI-MS: *m/z* 267 (M^+, 100). *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.70; H, 4.64; N, 5.35.

6-Hydroxymethylbenzo[1,3]dioxole-5-carbonitrile (4a) To a solution of aldehyde **3a** (4.02 g, 23 mmol) in acetic acid (30 ml) was added $NaBH_4$ (1.71 g, 45 mmol) at room temperature. After stirring the reaction for 2 h, acetic acid was removed *in vacuo* to give the residue which was poured into water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over sodium sulfate. The solvent was evaporated off and the residue was purified by column chromatography with *n*-hexane–ethyl acetate (2 : 1) to give the alcohol **4a** as a white solid (3.81 g, 94%). mp 152—154 °C. IR (KBr) cm^{-1}: 3400 (OH), 2230 (CN). ^{1}H-NMR ($CDCl_3$): δ 7.21 (s, 1H), 6.85 (s, 1H), 6.13 (s, 2H), 5.19 (s, 2H). EI-MS: *m/z* 177 (M^+, 100). *Anal.* Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 61.22; H, 3.89; N, 7.82.

4-Benzyloxy-2-hydroxymethyl-5-methoxybenzonitrile (4b) The procedure described for compound **4a** was used with aldehyde **3b** (4.02 g, 15 mmol) in acetic acid (20 ml) and $NaBH_4$ (1.14 g, 30 mmol) to give alcohol **4b** as a yellow solid (3.57 g, 88%). mp 139—141 °C. IR (cm^{-1}): 2230 (CN). ^{1}H-NMR ($CDCl_3$) δ: 7.45—7.33 (m, 5H), 7.13 (s, 1H), 7.06 (s, 1H); 5.20 (s, 2H), 4.79 (s, 2H), 3.89 (s, 3H). EI-MS *m/z* 269 (M^+, 100). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20; O, 17.82.

6-Methoxymethoxymethylbenzo[1,3]dioxole-5-carbonitrile (5a) To a solution of **4a** (4.3 g, 24 mmol) in CH_2Cl_2 (30 ml) were added diisopropylethylamine (DIPEA) (6.46 g, 50 mmol) and chloromethyl methyl ether (4.02 g, 50 mmol) at 0 °C. The reaction mixture was stirred over night, and CH_2Cl_2 was evaporated off to give the residue, which was purified by column chromatography with *n*-hexane–ethyl acetate (4 : 1) to give benzonitrile **5a** as a yellow oil (4.88 g, 92%). IR (neat) cm^{-1}: 2230 (CN), 1300—1000 (C–O). ^{1}H-NMR ($CDCl_3$) δ: 7.02 (s, 1H), 7.01 (s, 1H), 6.07 (s, 2H), 4.74 (s, 2H), 4.67 (s, 2H), 3.43 (s, 3H). EI-MS: *m/z* 221 (M^+, 30). *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.78; H, 5.06; N, 6.13.

4-Benzyloxy-5-methoxy-2-methoxymethoxymethylbenzonitrile (5b) The procedure described for compound **5a** was used with alcohol **4b** (4.4 g, 16 mmol), diisopropylethylamine (DIPEA) (3.9 g, 30 mmol) and chloromethyl methyl ether (2.5 g, 30 mmol) to give benzonitrile **5b** as a yellow solid (4.75 g, 93%). mp 75.5—76.5 °C; IR (cm^{-1}): 2230 (CN), 1300—1000 (C–O). ^{1}H-NMR ($CDCl_3$) δ: 7.42—7.38 (m, 5H), 7.08 (s, 1H), 7.05 (s, 1H); 5.21 (s, 2H), 4.73 (s, 2H), 4.69 (s, 2H), 3.89 (s, 3H), 3.38 (s, 3H). EI-MS *m/z* 313 (M^+, 60). *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.68; H, 6.35; N, 4.20.

General Procedure for the Preparation of 7a—d Dry THF (10 ml) was added *n*-BuLi (7.5 mmol) at −40 °C. After the addition was completed, the solution was stirred till the temperature fell at −70 °C and the solution of *o*-toluamide **6** (4.7 mmol) and benzonitrile **5** (5.4 mmol) in dry THF (10 ml) were added drop-wise. The reaction mixture was stirred at the same temperature for 4 h. The reaction solution was quenched with water and extracted and dried over sodium sulfate. After removing the solvent, the residue was separated by column chromatography with *n*-hexane–ethyl acetate (1 : 1) to afford compound **7**.

7-(6-Methoxymethoxymethylbenzo[1,3]dioxol-5-yl)-8*H*-[1,3]dioxolo[4,5-*h*]isoquinolin-9-one (7a) Yellow solid (59%). mp 151—153 °C; IR (KBr) cm^{-1}: 3400 (NH), 1665 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.38 (s, 1H), 7.18 (d, *J*=8.2 Hz, 1H), 7.04 (d, *J*=8.2 Hz, 1H), 6.94 (s, 1H), 6.93 (s, 1H), 6.39 (s, 1H), 6.23 (s, 2H), 6.04 (s, 2H), 4.77 (s, 2H), 4.45 (s, 2H), 3.51 (s, 3H). EI-MS: *m/z* 383 (M^+, 17). *Anal.* Calcd for $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.36; H, 4.46; N, 3.68.

7-(6-Methoxymethoxymethylbenzo[1,3]dioxol-5-yl)-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (7b) Solid (56%). mp 183—185 °C. IR (KBr) cm^{-1}: 3400 (NH), 1657 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 7.75 (s, 1H), 6.96 (s, 1H), 6.95 (s, 1H), 6.89 (s, 1H), 6.41 (s, 1H), 6.09 (s, 2H), 6.04 (s, 2H), 4.78 (s, 2H), 4.46 (s, 2H), 3.42 (s, 3H). EI-MS: *m/z* 383 (M^+, 12). *Anal.* Calcd for $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.78; H, 4.37; N, 3.78.

6,7-Dimethoxy-3-(6-methoxymethoxymethylbenzo[1,3]dioxol-5-yl)-2*H*-isoquinolin-1-one (7c) Yellow solid (50%). mp 151—154.5 °C. IR (KBr) cm^{-1}: 3400 (NH), 1657 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.62 (s, 1H), 7.78 (s, 1H), 6.97 (s, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 6.44 (s, 1H), 6.06 (s, 2H), 4.80 (s, 2H), 4.46 (s, 2H), 4.02 (s, 3H), 4.01 (s, 3H), 3.44 (s, 3H). EI-MS: *m/z* 399 (M^+, 75). *Anal.* Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.35; H, 5.25; N, 3.43.

3-(4-Benzyloxy-5-methoxy-2-methoxymethoxymethylphenyl)-6,7-dimethoxy-2*H*-isoquinolin-1-one (7d) Yellow oil (30%). IR (cm^{-1}): 3400 (NH), 1657 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 7.77 (s, 1H), 7.48—7.32 (m, 5H), 7.00 (s, 1H), 6.93 (s, 1H), 6.86 (s, 1H), 6.50 (s, 1H), 5.22 (s, 2H), 4.73 (s, 2H), 4.47 (s, 2H), 4.02 (s, 3H), 4.00 (s, 3H), 3.87 (s, 3H), 3.38 (s, 3H). EI-MS: *m/z* 491 (M^+, 4). HR-MS-EI (Calcd for $C_{28}H_{29}NO_7$): 491.1904. Found: 491.1906.

General Procedure for the Preparation of 8a—d To the solution of compound **7** (3.9 mmol) in THF (20 ml) at 0 °C under nitrogen was added NaH dispersion 60% (10 mmol). The resulting mixture was stirred at the same temperature for 1 h. After the ice bath was removed, the reaction mixture was added methyl iodide (10 mmol) in THF (5 ml) and warmed up to 60 °C. The reaction was quenched with water and 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 separated by column chromatography on silica gel with *n*-hexane–ethyl acetate (2 : 1) to give compound **8**.

7-(6-Methoxymethoxymethylbenzo[1,3]dioxol-5-yl)-8-methyl-8*H*-[1,3]dioxolo[4,5-*h*]isoquinolin-9-one (8a) Oil (90 %). IR (cm^{-1}): 1655 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.17 (d, *J*=8.2 Hz, 1H), 7.03 (s, 1H), 6.95 (d, *J*=8.2 Hz, 1H), 6.72 (s, 1H), 6.31 (s, 1H), 6.24 (m, 2H), 6.04 (m, 2H), 4.57 (s, 2H), 4.35 (q, 2H), 3.25 (s, 3H), 3.24 (s, 3H). EI-MS: *m/z* 397 (M^+, 23). HR-MS-EI (Calcd for $C_{21}H_{19}NO_7$): 397.1204. Found: 397.1205.

7-(6-Methoxymethoxymethylbenzo[1,3]dioxol-5-yl)-6-methyl-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (8b) Oil (89%). IR (cm^{-1}): 1650 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.79 (s, 1H), 7.03 (s, 1H), 6.80 (s, 1H), 6.72 (s, 1H), 6.30 (s, 1H), 6.08 (s, 2H), 6.04 (s, 2H), 4.55 (d, 2H), 4.31 (q, 2H), 3.29 (s, 3H), 3.24 (s, 3H). EI-MS: *m/z* 397 (M^+, 23). HR-MS-EI (Calcd for $C_{21}H_{19}NO_7$): 397.1204. Found: 397.1202.

6,7-Dimethoxy-3-(6-methoxymethoxymethylbenzo[1,3]dioxol-5-yl)-2-methyl-2*H*-isoquinolin-1-one (8c) Solid (78%). mp 58.2—62.3 °C. IR (KBr) cm^{-1}: 1650 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 7.04 (s, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 6.34 (s, 1H), 6.06 (s, 2H), 4.55 (m, 2H), 4.34 (m, 2H), 4.03 (s, 3H), 3.98 (s, 3H), 3.31 (s, 3H), 3.24 (s, 3H). EI-MS: *m/z* 413 (M^+, 80). *Anal.* Calcd for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.99; H, 5.55; N, 3.40.

3-(4-Benzyloxy-5-methoxy-2-methoxymethoxymethylphenyl)-6,7-dimethoxy-2-methyl-2*H*-isoquinolin-1-one (8d) Oil (70%). IR (cm^{-1}): 1650 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.83 (s, 1H), 7.50—7.32 (m, 5H), 7.12 (s, 1H), 6.83 (s, 1H), 6.79 (s, 1H), 6.37 (s, 1H), 5.22 (s, 2H), 4.73 (s, 2H), 4.47 (s, 2H), 4.02 (s, 3H), 3.97 (s, 3H), 3.88 (s, 3H), 3.33 (s, 3H), 3.19 (s, 3H). EI-MS: *m/z* 505 (M^+, 24). HR-MS-EI (Calcd for $C_{29}H_{31}NO_7$): 505.2107. Found: 505.2108.

General Procedure for the Preparation of 9a—d To the solution of compound **8** (3.5 mmol) in THF (15 ml) was added 10% HCl (10 ml) and the reaction was refluxed for 3 h. The reaction mixture 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 separated by column chromatography on silica gel with *n*-hexane–ethyl acetate (1 : 2) to give an alcohol **9**.

7-(6-Hydroxymethyl-benzo[1,3]dioxol-5-yl)-8-methyl-8*H*-[1,3]dioxolo[4,5-*h*]-isoquinolin-9-one (9a) Yellow solid (80%). mp 227—230 °C. IR (cm^{-1}): 3300 (OH), 1654 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.16 (d, J=8.2 Hz, 1H), 7.10 (s, 1H), 6.95 (d, J=8.2 Hz, 1H), 6.70 (s, 1H), 6.31 (s, 1H), 6.22 (m, 2H), 6.04 (m, 2H), 4.44 (s, 2H), 3.22 (s, 3H); EI-MS: *m/z* 353 (M^+, 25). *Anal.* Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.68; H, 4.45; N, 3.94.

7-(6-Hydroxymethylbenzo[1,3]dioxol-5-yl)-6-methyl-6*H*-[1,3]dioxolo[4,5-*g*]-isoquinolin-5-one (9b) Solid (65%). mp 217—219 °C. IR (KBr) cm^{-1}: 3300 (OH), 1641 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.09 (s, 1H), 6.78 (s, 1H), 6.69 (s, 1H), 6.30 (s, 1H), 6.07 (s, 2H), 6.04 (s, 2H), 4.43 (s, 2H), 3.25 (s, 3H), 2.49 (s, 1H). EI-MS: *m/z* 353 (M^+, 24). *Anal.* Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.78; H, 4.27; N, 3.86.

3-(6-Hydroxymethylbenzo[1,3]dioxol-5-yl)-6,7-dimethoxy-2-methyl-2*H*-isoquinolin-1-one (9c) White solid (86%). mp 171.5—173.5 °C. IR (KBr) cm^{-1}: 3300 (OH), 1641 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.10 (s, 1H), 6.81 (s, 1H), 6.71 (s, 1H), 6.35 (s, 1H), 6.05 (s, 2H), 4.45 (m, 2H), 4.01 (s, 3H), 3.97 (s, 3H), 3.29 (s, 3H). EI-MS: *m/z* 369 (M^+, 74). *Anal.* Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.23; H, 5.16; N, 3.77.

3-(4-Benzyloxy-2-hydroxymethyl-5-methoxyphenyl)-6,7-dimethoxy-2-methyl-2*H*-isoquinolin-1-one (9d) Yellow solid (65%). mp 181—183.5 °C. IR (cm^{-1}): 3300 (OH), 1641 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.81 (s, 1H), 7.48—7.40 (m, 5H), 7.17 (s, 1H), 6.82 (s, 1H), 6.77 (s, 1H), 6.37 (s, 1H), 5.22 (s, 2H), 4.46 (s, 2H), 4.02 (s, 3H), 3.97 (s, 3H), 3.88 (s, 3H), 3.29 (s, 3H). EI-MS: *m/z* 461 (M^+, 54). *Anal.* Calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.04. Found: C, 70.47; H, 5.64; N, 3.00.

General Procedure for the Preparation of 10a—d Reaction mixture of alcohol **9** (2.1 mmol) and PDC (4.2 mmol) in CH_2Cl_2 (30 ml) was stirred for 2 h. Reaction mixture was filtered and washed with CH_2Cl_2. The solvent was evaporated off and the residue was separated by column chromatography on silica gel with *n*-hexane–ethyl acetate (2 : 1) to afford the aldehyde **10**.

6-(8-Methyl-9-oxo-8,9-dihydro-[1,3]dioxolo[4,5-*h*]isoquinolin-7-yl)benzo[1,3]dioxole-5-carbaldehyde (10a) Solid (68%). mp 234—236 °C. IR (cm^{-1}): 1700, 1654 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.79 (s, 1H), 7.46 (s, 1H), 7.18 (d, J=8.2 Hz, 1H), 6.95 (d, J=8.2 Hz, 1H), 6.85 (s, 1H), 6.35 (s, 1H), 6.25 (s, 2H), 6.15 (s, 2H), 3.28 (s, 3H). EI-MS: *m/z* 351 (M^+, 100). *Anal.* Calcd for $C_{19}H_{13}NO_6$: C, 64.96; H, 3.73; N, 3.99. Found: C, 64.88; H, 3.76; N, 3.89.

6-(6-Methyl-5-oxo-5,6-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-7-yl)benzo[1,3]dioxole-5-carbaldehyde (10b) Solid (79%). mp >300 °C. IR (cm^{-1}): 1700, 1640 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.75 (s, 1H), 7.80 (s, 1H), 7.47 (s, 1H), 6.83 (s, 1H), 6.82 (s, 1H), 6.34 (s, 1H), 6.17 (s, 2H), 6.10 (s, 2H), 3.34 (s, 3H). EI-MS: *m/z* 351 (M^+, 100). *Anal.* Calcd for $C_{19}H_{13}NO_6$: C, 64.96; H, 3.73; N, 3.99. Found: C, 64.98; H, 3.77; N, 3.95.

6-(6,7-Dimethoxy-2-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)benzo[1,3]dioxole-5-carbaldehyde (10c) Solid (99%). mp 209.5—212 °C. IR (cm^{-1}): 1700, 1640 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.83 (s, 1H), 7.48 (s, 1H), 6.84 (s, 1H), 6.84 (s, 1H), 6.39 (s, 1H), 6.17 (s, 2H), 4.04 (s, 3H), 3.99 (s, 3H), 3.37 (s, 3H). EI-MS: *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, 65.58; H, 4.67; N, 3.80.

5-Benzyloxy-2-(6,7-dimethoxy-2-methyl-1-oxo-1,2-dihydroisoquinolin-3-yl)-4-methoxybenzaldehyde (10d) Solid (86%). mp 205—207 °C. IR (cm^{-1}): 1700, 1640 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.80 (s, 1H, CHO), 7.84 (s, 1H), 7.60 (s, 1H), 7.51—7.35 (m, 5H), 6.86 (s, 1H), 6.84 (s, 1H), 6.41 (s, 1H), 5.25 (s, 2H), 4.04 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.35 (s, 3H). EI-MS: *m/z* 459 (M^+, 11), 91 (100). *Anal.* Calcd for $C_{27}H_{25}NO_6$: C, 70.58; H, 5.48; N, 3.05. Found: C, 70.88; H, 5.38; N, 3.25.

General Procedure for the Preparation of 11a—d To the solution of (methoxymethyl)triphenylphosphonium chloride (3 mmol) in dry THF (15 ml) was added *n*-BuLi (3.2 mmol) at 0 °C and solution was stirred at 0 °C for 1 h. The reaction mixture was added aldehyde **10** (0.60 mmol) in THF (10 ml) and was stirred at room temperature for 3 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were washed with water, brine and dried over sodium sulfate. After removing the solvent, the residue was separated by column chromatography with *n*-hexane–ethyl acetate (3 : 1) to afford mixture of *cis*/*trans* isomer **11**.

7-[6-(2-Methoxyvinyl)benzo[1,3]dioxol-5-yl]-8-methyl-8*H*-[1,3]dioxolo[4,5-*h*]isoquinolin-9-one (11a) *cis*/*trans* (1 : 1). Brown oil (66%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (*cis*): 7.70 (s, 1H), 7.18 (d, J=8.2 Hz, 1 H), 6.95 (d, J=8.2 Hz, 1H), 6.70 (s, 1H), 6.31 (s, 1H), 6.23 (s, 2H), 6.01 (s, 2H), 5.98 (d, J=7.1 Hz, 1H), 4.85 (d, J=7.1 Hz, 1H), 3.75 (s, 3H), 3.23 (s, 3H). δ (*trans*): 7.18 (d, J=8.2 Hz, 1H), 6.95 (d, J=8.2 Hz, 1H), 6.92 (d, J=12.8 Hz, 1H), 6.89 (s, 1H), 6.70 (s, 1H), 6.30 (s, 1H), 6.23 (s, 2H), 6.01 (s, 2H), 5.47 (d, J=12.8 Hz, 1H), 3.48 (s, 3H), 3.23 (s, 3H).

7-[6-(2-Methoxyvinyl)benzo[1,3]dioxol-5-yl]-6-methyl-6*H*-[1,3]dioxolo[4,5-*g*]isoquinolin-5-one (11b) *cis*/*trans* (1 : 2). Brown oil (57%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (*cis*): 7.80 (s, 1H), 7.71 (s, 1H), 6.81 (s, 1H), 6.69 (s, 1H), 6.30 (s, 1H), 6.08 (s, 2H), 6.01 (s, 2H), 5.97 (d, J=7.1 Hz, 1H), 4.81 (d, J=7.1 Hz, 1H), 3.75 (s, 3H), 3.29 (s, 3H). δ (*trans*): 7.80 (s, 1H), 6.90 (s, 1H), 6.88 (d, J=12.8 Hz, 1H), 6.82 (s, 1H), 6.69 (s, 1H), 6.30 (s, 1H), 6.09 (s, 2H), 6.01 (s, 2H), 5.44 (d, J=12.8 Hz, 1H), 3.47 (s, 3H), 3.29 (s, 3H).

6,7-Dimethoxy-3-[6-(2-methoxyvinyl)benzo[1,3]dioxol-5-yl]-2-methyl-2*H*-isoquinolin-1-one (11c) *cis*/*trans* (1.5 : 1). Brown oil (70%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (*cis*): 7.80 (s, 1H), 7.71 (s, 1H), 6.83 (s, 1H), 6.70 (s, 1H), 6.34 (s, 1H), 6.01 (s, 2H), 5.97 (d, J=7.2 Hz, 1H), 4.83 (d, J=7.2 Hz, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.75 (s, 3H), 3.29 (s, 3H). δ (*trans*): 7.80 (s, 1H), 6.91 (s, 1H), 6.90 (d, J=12.8 Hz, 1H), 6.86 (s, 1H), 6.70 (s, 1H), 6.35 (s, 1H), 6.01 (s, 2H), 5.45 (d, J=12.8 Hz, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.46 (s, 3H), 3.29 (s, 3H).

3-[4-Benzyloxy-5-methoxy-2-(2-methoxyvinyl)phenyl]-6,7-dimethoxy-2-methyl-2*H*-isoquinolin-1-one (11d) *cis*/*trans* (1 : 1). Brown oil (65%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (*cis*): 7.83 (s, 1H), 7.60 (s, 1H), 7.51—7.35 (m, 5H), 6.85 (s, 1H), 6.74 (s, 1H), 6.36 (s, 1H), 5.96 (d, J=7.1 Hz, 1H), 5.25 (s, 2H), 4.81 (d, J=7.1 Hz, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 3.69 (s, 3H), 3.30 (s, 3H). δ (*trans*): 7.83 (s, 1H), 7.60 (s, 1H), 7.51—7.35 (m, 5H), 6.94 (s, 1H), 6.85 (s, 1H), 6.78 (d, J=12.8 Hz, 1H), 6.74 (s, 1H), 6.36 (s, 1H), 5.44 (d, J=12.8 Hz, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 3.45 (s, 3H), 3.30 (s, 3H).

General Procedure for the Preparation of 13a—d The reaction mixture of *cis*/*trans* isomers **11** (0.4 mmol) in methanol (20 ml) and 10% HCl (5 ml) was refluxed for 3 h. The methanol was removed by evaporation, reaction mixture 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 separated by column chromatography on silica gel with *n*-hexane–ethyl acetate (1 : 2) to give **13**.

Oxysanguinarine (13a) White solid (85%). mp 360—362 °C (lit.[31] mp 366—368 °C). IR (cm^{-1}): 1652 (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, J=8.6 Hz, 1H), 7.76 (d, J=9.6 Hz, 1H), 7.56 (s, 1H), 7.52 (d, J=8.6 Hz, 1H), 7.23 (d, J=9.6 Hz, 1H), 7.16 (s, 1H), 6.27 (s, 2H), 6.10 (s, 2H), 3.90 (s, 3H). EI-MS *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 (13b) Solid (75%). mp 279—282 °C (lit.[32] mp 276—277 °C, lit.[33] mp 278—283 °C). IR (cm^{-1}): 1631 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.92 (d, J=8.6 Hz, 1H), 7.89 (s, 1H), 7.63 (s, 1H), 7.61 (s, 1H), 7.56 (d, J=8.6 Hz, 1H), 7.18 (s, 1H), 6.13 (s, 2H), 6.10 (s, 2H), 3.97 (s, 3H). EI-MS *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.

Oxynitidine (13c) Solid (88%). mp 284—285 °C (lit.[17] mp 280—283 °C, lit.[26,27] mp 284—285 °C). IR (cm^{-1}): 1642 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J=9.0 Hz, 1H), 7.93 (s, 1H), 7.65 (s, 1H), 7.60 (s, 1H), 7.57 (d, J=8.8 Hz, 1H), 7.19 (s, 1H), 6.11 (s, 2H), 4.11 (s, 3H), 4.04 (s, 3H), 3.99 (s, 3H). EI-MS *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.

2-Benzyloxy-3,8,9-trimethoxy-5-methyl-5*H*-benzo[*c*]phenanthridin-6-one (13d) Solid (70%). mp 219—221 °C (lit.[28] mp 227—229 °C). IR (cm^{-1}): 1649 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J=9.0 Hz, 1H), 7.93 (s, 1H), 7.63 (s, 1H), 7.59 (s, 1H), 7.56—7.36 (m, 5H), 7.50 (d, J=9.0 Hz, 1H), 7.23 (s, 1H), 5.31 (s, 2H), 4.10 (s, 3H); 4.06 (s, 3H), 4.05 (s, 3H), 4.04 (s, 3H). EI-MS, *m/z* 455 (M^+, 22). *Anal.* Calcd for $C_{28}H_{25}NO_5$: C, 73.83; H, 5.53; N, 3.08. Found: C, 73.65; H, 5.67; N, 3.34.

Oxyfagaronine (14) The mixture of compound **13d** (40 mg, 0.088 mmol) and 5% Pd/C (20 mg) in EtOH (10 ml) was treated with hydrogen gas at 70 psi for 5 h using Parr apparatus. The reaction mixture was filtered off and the filtrate was evaporated to give the residue which was purified by column chromatography to give **14** (oxyfagaronine) as a white solid (20 mg, 62%). mp 273—275 °C (lit.[30] mp 273—275 °C). IR (cm^{-1}): 1649 (CO). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J=9.0 Hz, 1H), 7.93 (s, 1H), 7.63 (s, 1H), 7.62 (s, 1H), 7.56 (d, J=9.0 Hz, 1H), 7.33 (s, 1H), 4.11 (s, 3H), 4.06 (s, 3H), 4.05 (s, 3H), 4.05 (s, 3H). EI-MS, *m/z* 365 (M^+, 85). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.25; H, 5.45; N, 3.58.

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