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Protecting-Group-Free Total Synthesis of Isoquinoline Alkaloids by Nickel-Catalyzed Annulation of *o*-Halobenzaldimine with an Alkyne as the Key Step

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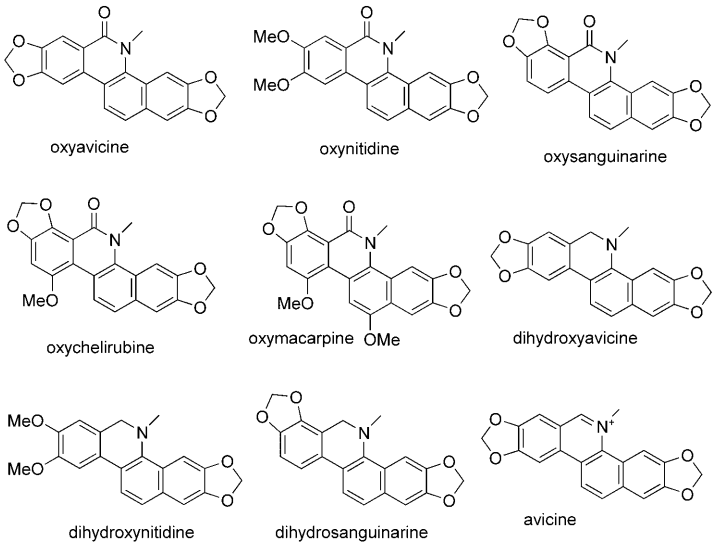
Abstract: An efficient short total synthesis of benzo[*c*]phenanthridine alkaloids including oxyavicine, oxynitidine, and oxysanguinarine is described. Thus, *N*-methyl-*o*-bromobenzaldimines **1b–d** undergo regioselective cyclization with 4-(benzo[*d*][1,3]dioxol-5-yl)but-3-yn-1-ol (**2b**) in the presence of $[Ni(cod)_2]$ (cod = 1,5-cyclooctadiene). In situ oxidation of the resultant isoquinolinium salts gives isoquinolinone derivatives **5b–d** with benzo[*d*][1,3]dioxol-5-yl substitution at the C_3 atom and a $(CH_2)_2OH$ group at the C_4 atom. Later, oxidation of the alcohol group in **5b–d** to the aldehyde moiety followed by acid-catalyzed cyclization and dehydration completes the total syntheses to give oxyavicine, oxynitidine, and oxysanguinarine in 67, 65, and 60% yields, respectively. The synthesis requires four steps from *o*-bromobenzaldehyde derivatives. Transformations of these alkaloids to the other alkaloids in this family are also discussed herein.

Keywords: alkaloids · isoquinolines · nickel · ring-closing reactions · total synthesis

Introduction

Efficient syntheses of natural products are important as these products and their derivatives have been the basis for new drug development.[1,2] Among the isoquinoline alkaloids, over 80 types of benzo[*c*]phenanthridine alkaloids have been characterized.[3] The structures of some of these alkaloids are shown below. For example, oxyavicine isolated from *Zanthoxylum avicennae* root bark,[4a] *Broussonetia papyrifera* fruits,[4b] and *Zanthoxylum nitidum* root,[4c] can be used to treat ophthalmic disorders.[4b] In addition, it exhibits analgesic and anti-inflammatory effects.[4c] On the other hand, oxynitidine, isolated from *Zanthoxylum rhoifolium,*[5a] *Zanthoxylum nitidum* root,[5b] and *Fagara macrophylla* bark,[5c] exhibited potent inhibitory activity toward the hepatitis B virus.[5d] Recently oxysangunarine was also isolated from the Ranunculaceae (seeds of *Coptis*).[6a] One of the important crude drugs in both China and Japan were rhizomes of *Coptis* spp.; oxysanguinarine was one of the constituents in the drug.



Despite the numerous reports on benzo[*c*]phenanthridine alkaloids, to date, highly efficient synthesis remains a challenge. A Robinson–Bailey synthesis[7a] and enamide photocyclization[7b] methods as key steps for the total synthesis were reported by Bailey et al. and Ninomiya et al., respectively. Diels–Alder cycloaddition reactions[7c] with arynes by using pyrrolinediones and α-pyrones as aza diene equivalents are known. Condensation of the homophthalic ester[6b] with Schiff base and a 3,4-(methylenedioxy)homophthalic anhydride[7d] reaction with Schiff base in benzene solution

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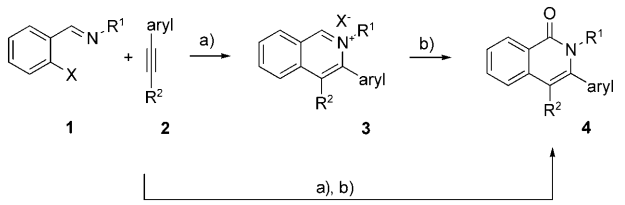
followed by diazo ketone cyclization were devised for the total synthesis of benzophenanthridines. Most of these syntheses require complex starting materials: an eight-step sequence to the homophthalic ester and seven-step sequence to the 3,4-(methylenedioxy)homophthalic anhydride were reported.[7e] Clark described the synthesis of oxynitidine by a cycloaddition reaction of lithiated toluamide with imine.[8a] Recently Cho et al. reported syntheses[8b,c] of oxyavicine, oxynitidine, and oxysanguinarine from benzonitriles derived from *o*-bromobenzaldehydes. Both of these syntheses required multistep procedures with a large number of reagents and needed protection and deprotection techniques.

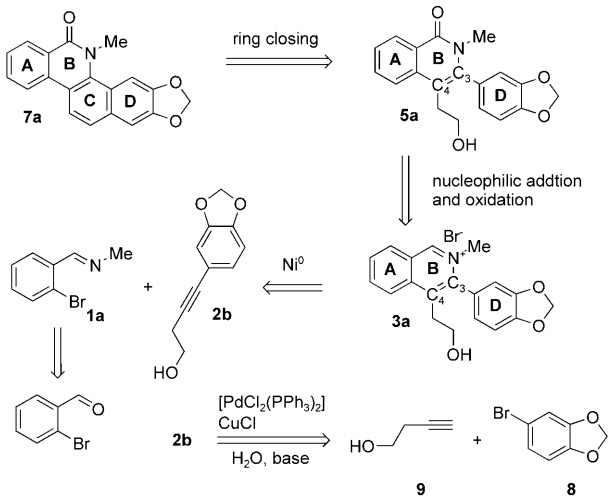
Our recent method of nickel-catalyzed regioselective cyclization of *o*-halobenzaldimine with an alkyne has provided an efficient access to isoquinolinium salts and isoquinolinones with multiple substitutions.[9a] For aryl alkyl alkynes **2** used in the reaction, the reaction always yields the corresponding isoquinolinium salts **3** with the aryl substitution on the alkynes at the C_3 position (Scheme 1). The observed regiochemical preference[9b] of the alkyne moiety in product **3** and the facile conversion of the isoquinolinium salt to the corresponding amide prompted us to explore the application of the present method to the total syntheses[9c,d] of isoquinolinone alkaloids. Herein, we provide a full report of our approach to the total syntheses of three isoquinolinone (belonging to benzo[*c*]phenanthridine) alkaloids including oxyavicine, oxynitidine, oxysanguinarine, and 9-demethoxy-10-methoxy oxynitidine by using this new regioselective strategy to construct the key isoquinolinone intermediates. The syntheses of the three natural products were completed in much higher yields and with shorter steps than the previously reported procedures.



Scheme 1. Nickel-catalyzed synthesis of isoquinolinium and isoquinolinone derivatives. a) Ni^0; b) $K_3[Fe(CN)_6]$, CsOH.

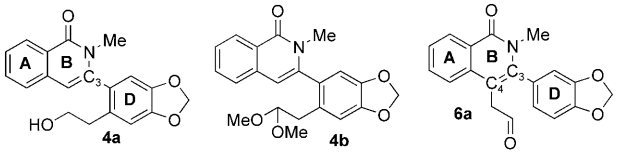
Results and Discussion

First, we set about the synthesis of compound **7a** (Scheme 2), which aimed at developing an efficient route flexible enough to provide access to various members of the benzo[*c*]phenanthridine alkaloids. From a retrosynthetic viewpoint, isoquinolinone **7a** could be easily obtained from isoquinolinone **5a** (Scheme 2). The C ring could be constructed by oxidation of the $(CH_2)_2OH$ group over the B ring in **5a**, followed by an acid-catalyzed cyclization and dehydration reaction. The isoquinolinone derivative **5a** could be obtained from the corresponding isoquinolinium derivative **3a** by a nucleophilic addition of a OH^- group to the C_1 carbon atom of **3a** and oxidation of the resultant derivative. Isoquinolinium salt **3a** could be ultimately synthesized from an intermolecular Ni-catalyzed[9e–g] cyclization reaction between imine **1a** and alkyne **2b** (Scheme 2). Imine **1a** could be readily obtained from *o*-bromobenzaldehyde and methylamine,[9e–j] whereas internal alkyne **2b** could be easily prepared by a Sonogashira reaction from 5-bromobenzo[*d*]-[1,3]dioxole and but-1-yn-4-ol. An attractive feature of this sequence is that all the carbon atoms of the complex natural product could be all obtained in the nickel-catalyzed annulation step.



Scheme 2. Retrosynthetic analysis for isoquinolinone **7a**.

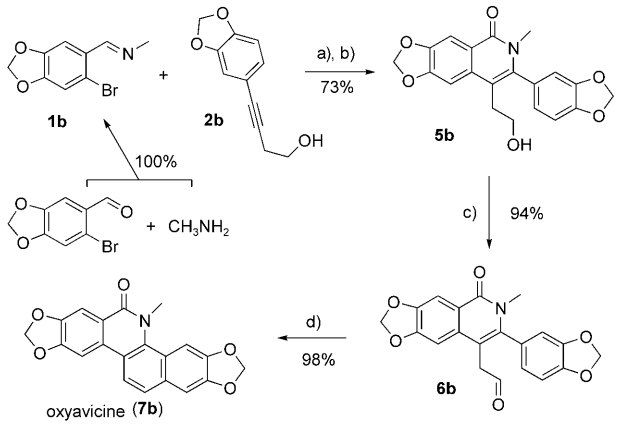
Alternatively, isoquinolinone **7a** might also be obtained from isoquinolinone **4a** or **4b**. Similar strategies have been employed to construct the C ring of isoquinolinones.[8b–d,10] With suitable terminal alkynes, amides **4a** and **4b** can be synthesized from our nickel-catalyzed reaction described above. However, since multiple steps are required for the preparation of these terminal alkyne substrates, we eliminated these two strategies from our synthetic plan.



The requisite alkyne **2b** was prepared by Sonogashira coupling starting from commercially available 5-bromobenzo[*d*][1,3]dioxole (**8**) and 3-butyn-1-ol (**9**) in 83% yield. *N*-Methyl-*o*-bromobenzaldimine (**1a**) was readily prepared in essentially quantitative yield from commercially available 2-bromobenzaldehyde by condensation with aqueous methylamine by using methanol as the solvent. Treatment of **1a** with alkyne **2b** in the presence of $[Ni(cod)_2]$

(5 mol%; cod = 1,5-cyclooctadiene) and 10 mol% of P(*o*-Tol)$_3$ in acetonitrile for 3.0 h at 80°C, followed by the addition of $K_3[Fe(CN)_6]$ and CsOH,[11a] in a mixture of H_2O and MeOH gave **5a** in 71% yield. In this reaction, isoquinolinium salt **3a** was first obtained from the nickel-catalyzed step and was then transformed to **5a** (Scheme 2). Pyridinium chlorochromate (PCC) oxidation of the primary alcohol group in **5a** afforded the corresponding aldehyde derivative **6a** in 91% yield. Under Swern oxidation conditions,[11b] by using Et_3N as the base, nearly the same yield of **6a** was obtained. As expected, **6a** underwent subsequent acid-catalyzed cyclization and dehydration smoothly to afford the final product **7a** in 96% yield.

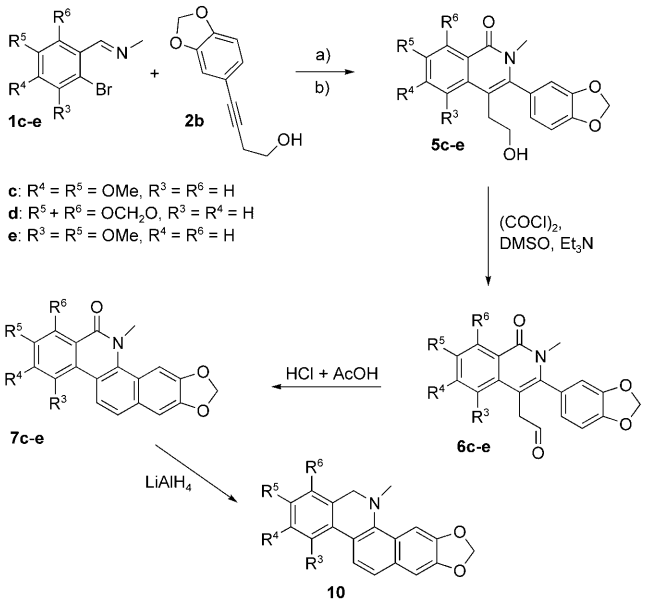
The success of the synthesis of **7a** prompted us to undertake the total synthesis of oxyavicine (**7b**, Scheme 3)[4] by using the nickel-catalyzed methodology. The required imine



Scheme 3. Total synthesis of oxyavicine (**7b**) from *o*-bromopiperonal. a) $[Ni(cod)_2]$/P(*o*-Tol)$_3$; b) CsOH, $K_3[Fe(CN)_6]$; c) $(COCl)_2$, DMSO, Et_3N; d) HCl, AcOH.

1b was synthesized from commercially available 2-bromopiperonal and methylamine. Annulation of imine **1b** with alkyne **2b** catalyzed by $[Ni(cod)_2]$/P(*o*-Tol)$_3$ and subsequent nucleophilic addition and oxidation procedures gave amide **5b** in 73% yield. We then converted this intermediate to the corresponding aldehyde derivative **6b** in 94% yield by Swern oxidation. After a successful acid-catalyzed ring-closing and dehydration reaction, we obtained oxyavicine (**7b**) in 98% yield. Thus, oxyavicine was synthesized in four steps in 67% overall yield from the commercially available 2-bromopipernal. Recent synthesis of this compound by cycloaddition of lithiated toluamide with a benzonitrile derivative required ten steps from 2-bromopiperonal (7% overall yield).[8b–d]

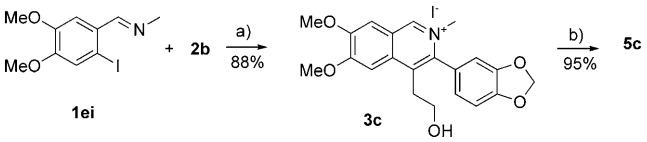
The achievement of the synthesis of oxyavicine (**7b**) further encouraged us to pursue the total syntheses of oxynitidine[5] and oxysanguinarine as matter of course (Scheme 4). With the key alkyne **2b** in hand, we next synthesized imines **1c** and **1d** from commercially available 6-bromoveratraldehyde and 5-bromo-1,3-benzodioxole-4-carboxaldehyde with methylamine in quantitative yields. The standard nickel-cat-



Scheme 4. Total synthesis of isoquinolinone alkaloids. a) $[Ni(cod)_2]$, P(*o*-Tol)$_3$; b) CsOH, $K_3[Fe(CN)_6]$.

alyzed cyclization of imines **1c** and **1d** with alkyne **2b** led to the corresponding isoquinolinium salts; subsequent oxidation procedures provided amides **5c** and **5d** in 78 and 69% yields, respectively. Oxidation of the alcohol functionality in **5c** and **5d** yields the corresponding aldehyde derivatives **6c** and **6d** in 89 and 93%, respectively. These were then cyclized under acidic conditions by using HCl (aq) and acetic acid to complete the total synthesis[5,6] of oxynitidine (**7c**)[5] and oxysanguinarine (**7d**).[6] The overall yields of **7c** and **7d** were 65 and 60%, respectively.

An alternative route to compound **5c** was from *N*-methyliodoveratraldehyde imine (**1ei**) and alkyne **2b** via first the isolation of isoquinolinium salt **3c** and then the oxidation of the salt (Scheme 5). The combined yield of the two steps



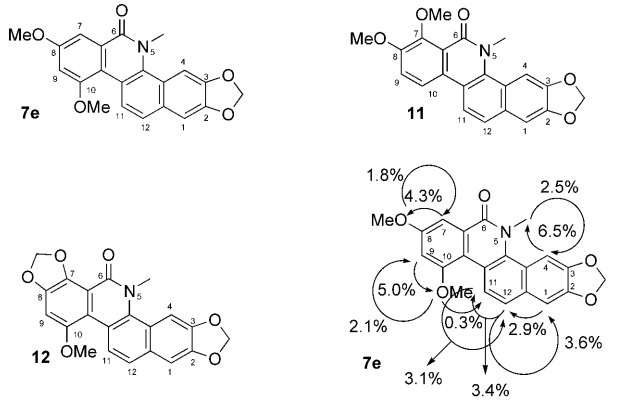
Scheme 5. An alternative route to isoquinolinone **5c**. a) $[Ni(cod)_2]$, P(*o*-Tol)$_3$; b) CsOH, $K_3[Fe(CN)_6]$.

was 84% yield. The spectral data of these final products are in agreement with those reported previously.[8,10] Oxynitidine is known to show significant activity of anti-HBV DNA replication.[5] Previously, oxynitidine was synthesized in seven steps with an overall yield of 15% from 2-methyl-4,5-dimethoxybenzoic acid[8a] and in 10% overall yield from 2-bromopiperonal.[8b–d] Oxysanguinarine was synthesized from piperonal[6b] in less than 1% overall yield (16 steps) and in 11% overall yield from *o*-bromopiperonal.[8b–d]

Recently, an alkaloid named as turraeanthin B was isolated from the stem bark of *Turraeanthin africanus* and its structure was assigned as 9-demethoxy-10-methoxy oxynitidine **7e**.[12a] Based on the isoquinolinium salt approach, we started the synthesis of this alkaloid. The required aldehyde derivative was synthesized from bromination of the corresponding aldehyde derivative according to a literature procedure.[12b] This was then converted to the corresponding imine **1e**. With the standard procedures described in Scheme 4, 9-demethoxy-10-methoxy oxynitidine (**7e**) was synthesized from **1e** and **2b** in 59% overall yield. The nickel-catalyzed annulation of **1e** with **2b** followed by treatment with CsOH and $K_3[Fe(CN)_6]$ gave isoquinolinone **5e** in 65% yield. The acid-catalyzed cyclization reaction of aldehyde **6e**, prepared in 94% yield from the oxidation of the primary alcohol group in **5e** (Scheme 4), in the presence of aqueous HCl and acetic acid, produced **7e** in 97% yield.

Unfortunately, we have found that the NMR spectroscopic data of the synthesized compound **7e** is different from the compound isolated from the bark of *Turraeanthus africanus*. The structure of intermediate compound **5e** was thoroughly verified by its NOE and X-ray crystallographic data. In addition, the chemical shift of the C_{11} proton of **7e** is in agreement with similar OMe-substituted compound **12** (entries 3 and 5, Table 1).[12c] The C_{11} proton of the OMe-substituted compound **12** was shifted much more downfield relative to the C_{11} proton of compound **11** (entries 4 and 5, Table 1). This is likely due to the hydrogen-bonding interaction between the C_{11} proton and the OMe group at the C_{10} atom of compound **12**. The coupling constant[12c] for the C_{11} and C_{12} protons is at around 9.0 Hz for compound **12** and 8.0 Hz for compound **11**. Compound **7e** shows a similar coupling constant to that of compound **12** (Table 1). Also, the structure of compound **7e** was thoroughly verified by NOE experiments. These results strongly indicate that the structure of the isolated compound from the stem bark of *Turraeanthin africanus* is different from molecule **7e** and needs to be revised.

Table 1. Selected ^{1}H NMR spectroscopic data for turraeanthin B and compounds **7e**, **11**, and **12**.



Entry	Compound	δ H_{11} [ppm]	δ H_{12} [ppm]	$J(H_{11}–H_{12})$ [Hz]
1	turraeanthin B ([D_5]pyridine)[a]	7.70	8.35	8.5
2	**7e** ([D_5]pyridine)[a]	9.39	7.79	9.0
3	**7e** ($CDCl_3$)[a]	9.01	7.47	9.0
4	**11** ($CDCl_3$)[a]	7.97	7.51	8.0
5	**12** ($CDCl_3$)[a]	9.00	7.48	9.0

[a] The solvent used to acquire the NMR spectra.

All of these alkaloids **7** can be conveniently transformed[12c] into the corresponding dihydro derivatives, which are also natural products, by reduction with $LiAlH_4$ (Scheme 4). Dihydro derivatives **10** can be converted to isoquinolinium salts, avicine, nitidine,[7c,10c] and sanguinarine,[13a] by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone oxidation, followed by treatment with concentrated hydrochloric acid.[13] The benzo[*c*]phenanthridine alkaloids containing the 12-methoxy group can be obtained by conversion of the corresponding alkaloids containing a hydrogen atom at C_{12}. For example, oxychelirubine was iodinated with *N*-iodosuccinimide to give the corresponding C_{12}-iodo derivative, and oxymacarpine[13] was obtained by displacement of the iodine atom with sodium methoxide. Most benzo[c]phenanthridine alkaloids have multiple substituents on the A and D rings.[3a] The present methodology constructs all carbon atoms of the alkaloid in one step by the nickel-catalyzed cyclization of *o*-halobenzaldimine and alkyne containing the necessary substitution over the A and D rings. Hence, a large number of alkaloids can be prepared as these starting materials, with desired substitutions on A and D rings, can be easily obtained.

Conclusions

We have developed a distinctive strategy for the total synthesis of benzo[*c*]phenanthridine alkaloids without using protecting groups, which have recently attracted great attention from various researchers around the world.[14] The present protocol is the shortest total synthesis procedure described up to now and gives the highest yields of the natural products synthesized including oxyavicine, oxynitidine,[5] and oxysanguinarine with readily available starting materials for benzo[*c*]phenanthridine alkaloids. This protocol may find widespread use for other isoquinoline alkaloid syntheses as well. Studies in this direction are underway.

Experimental Section

General information: Infrared (IR) spectra were recorded on a Horiba FT-720 spectrophotometer using KBr as a matrix for the pellet. ^{1}H NMR spectra were measured on a Varian Mercury-400 (400 MHz), a Varian Unity INOVA-500 (500 MHz) or a Bruker Avance-600 (600 MHz) in $CDCl_3$ or [D_5]pyridine, while ^{13}C NMR spectra were recorded on a Mercury-400 (100 MHz) or a Varian Unity INOVA-500 (125 MHz) in $CDCl_3$ using TMS as an internal standard. High-resolution mass (HR-MS) spectra were obtained on a Finnigan MAT-95XL. Melting points are uncorrected and were measured with a Fargo MP-2D melting point apparatus.

***N*-Methyl-*o*-bromoveratraldimine (1c)**: Aqueous methylamine solution (100 mg, 35% in water, 1.13 mmol) was added to a solution of 6-bromoveratraldehyde (245 mg, 1 mmol) in methanol (2 mL), and the resultant solution was stirred at room temperature for 12 h. After removal of sol-

vents by a rotary evaporator, **1c** solidified and was further dried under vacuum for 12 h (nearly quantitative yield). The compound was pure as shown by its ^{1}H NMR spectrum and was used for further synthesis.

Synthesis of 4-(benzo[*d*][1,3]dioxol-5-yl)but-3-yn-1-ol (2b): A round-bottomed flask (100 mL) equipped with a condenser was charged with [Pd(PPh_3)$_4$] (347 mg, 0.3 mmol) and CuI (114 mg, 0.6 mmol). Degassed distilled water (60 mL), but-1-yn-4-ol (1.05 g, 15 mmol), and pyrrolidine (45 mmol) were added to the flask under nitrogen. 5-Bromobenzo[*d*]-[1,3]dioxole (2.81 g, 14 mmol) was added by a syringe and the stirring was continued at room temperature for 30 min and at 60 °C for 3.0 h. The mixture was extracted with ether and the solvents were removed by vacuum. The residue was separated on a silica-gel column by using a mixture of hexanes and ethyl acetate (30:70) as the eluent to afford the desired pure product **2b** in 83% yield.

Synthesis of 3-(benzo[*d*][1,3]dioxol-5-yl)-4-(2-hydroxyethyl)-6,7-dimethoxy-2-methylisoquinolin-1(2*H*)one (5c): A screw-cap seal tube containing *N*-methyl-6-bromoveratraldimine **1c** (129 mg, 0.5 mmol) was charged with [Ni(cod)$_2$] (7 mg, 0.025 mmol) and P(*o*-Tol)$_3$ (16 mg, 0.05 mmol) inside a glove box and was then fitted with a septum. Alkyne **2b** (114 mg, 0.6 mmol) and freshly distilled MeCN (4 mL) were added to the seal tube under a nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 3 h. Then, water (5 mL), MeOH (5 mL), K_3[Fe(CN)$_6$] (1.65 g), and CsOH (aq) (0.9 mL, 50% w/w in H_2O) were added and the mixture was stirred vigorously at 70 °C for 12 h. The solvents were removed by vacuum and the resultant residue was extracted with dichloromethane. Separation on a short column of silica gel by using hexane/EtOAc as the eluent gave pure isoquinolinone derivative **5c** in 78% yield. White solid; m.p. 238 °C; R_f = 0.18 (75% ethyl acetate in hexanes); IR (KBr): $\tilde{\nu}$ = 1033, 1239, 1491, 1584, 1635, 2917 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.71–2.78 (m, 2H), 3.23 (s, 3H), 3.70 (t, J = 7.5 Hz, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6.03 (s, 2H), 6.70–6.71 (m, 2H), 6.90 (d, J = 8.5 Hz, 1H), 7.10 (s, 1H), 7.87 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 32.0, 34.0, 56.1, 56.2, 62.5, 101.5, 103.9, 108.4, 108.8, 109.8, 111.0, 119.8, 123.1, 129.0, 131.7, 140.2, 148.1, 148.3, 149.2, 153.5, 161.8 ppm; HRMS (EI$^+$): m/z: calcd for $C_{21}H_{21}NO_6$: 383.1369; found: 383.1368.

Synthesis of 6,7-dimethoxy-3-(benzo[*d*][1,3]dioxol-5-yl)-4-(2-hydroxyethyl)-2-methyl-isoquinolinium iodide (3c): A screw-cap seal tube containing *N*-methyl-6-iodoveratraldimine (153 mg, 0.5 mmol) was evacuated and purged with nitrogen gas three times. Later, the tube was charged with [Ni(cod)$_2$] (7 mg, 0.025 mmol) and P(*o*-Tol)$_3$ (16 mg, 0.05 mmol) inside a glove box. Alkyne **2b** (114 mg, 0.6 mmol) and freshly distilled MeCN (3 mL) were added to the system. The reaction mixture was stirred at 80 °C for 3.0 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane. The mixture was filtered through a silica-gel pad (0.5 cm) and washed with a small amount of methanol. The filtrate was concentrated in a rotary evaporator and the residue was washed with ethyl acetate and hexane to afford the desired pure product **3c** in 88% yield. Yellow solid; m.p. 216 °C; IR (KBr): $\tilde{\nu}$ = 1218, 1249, 1427, 1504, 3617 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.08–3.15 (m, 2H), 3.77 (m, 2H), 4.04 (s, 6H), 4.14 (s, 3H), 6.10 (s, 2H), 6.98 (m, 3H), 7.53 (s, 1H), 7.81 (s, 1H), 9.91 ppm (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 32.7, 47.5, 57.1, 57.6, 61.2, 102.0, 104.0, 107.6, 109.3, 109.9, 124.0, 124.5, 133.5, 136.5, 143.0, 144.9, 148.7, 149.5, 152.7, 158.1, 176.7 ppm; HRMS (FAB$^+$): m/z: calcd for $C_{21}H_{22}NO_5^+$: 368.1498; found: 368.1494.

Synthesis of 2-(3-(benzo[*d*][1,3]dioxol-5-yl)-1,2-dihydro-6,7-dimethoxy-2-methyl-1-oxoisoquinolin-4-yl)acetaldehyde (6c): DMSO (0.72 mmol) was added dropwise to a precooled solution of $(COCl)_2$ (0.36 mmol) in dry CH_2Cl_2 (5 mL) at −60 °C. Then, isoquinolinone **5c** (0.3 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise. After 15 min, Et_3N (1.5 mmol) was also added dropwise. The mixture was then brought to room temperature and stirred for a further 15 min. The mixture was extracted with CH_2Cl_2 and the solvent was removed under vacuum to give the crude product. Further purification on a short silica-gel column (10 cm) by using hexane and ethyl acetate (30:70) as the eluent gave the desired pure product **6c** in 89% yield. Pale-yellow solid; m.p. 233 °C; R_f = 0.31 (50% ethyl acetate in hexanes); IR (KBr): $\tilde{\nu}$ = 1037, 1244, 1491, 1635, 1712, 2921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.30 (s, 3H), 3.47–3.51 (m, 2H), 3.93 (s, 3H), 4.00 (s, 3H), 6.05 (m, 2H), 6.70–6.71 (m, 2H), 6.76 (s, 1H), 6.91 (d, J = 7.8 Hz, 1H), 7.88 (s, 1H), 9.56 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 34.3, 44.5, 56.0, 56.2, 101.6, 103.4, 106.0, 108.4, 109.0, 109.4, 119.5, 122.9, 128.4, 131.4, 141.7, 148.4, 148.5, 149.3, 153.6, 161.8, 199.6 ppm; HRMS (EI$^+$): m/z: calcd for $C_{21}H_{19}NO_6$: 381.1212; found: 381.1212.

Synthesis of oxynitidine (7a): Isoquinoline derivative **6c** (95 mg, 0.25 mmol) was placed in a 25 mL round-bottomed flask. Acetic acid (1 mL) was added slowly to the flask followed by aqueous HCl (30%, 0.1 mL). The flask was kept over a water bath at room temperature and was stirred for 20 min. Then KOH in water was added slowly to neutralize the solution and the mixture was extracted with dichloromethane. The solvent was removed under vacuum to give the crude product (the NMR spectra of the crude product showed they were pure). Further purification on a short silica-gel column (10 cm) by using hexane and ethyl acetate (30:70) as the eluent gave 85.0 mg of the desired product **7c** in 94% yield. White solid; m.p. 278 °C; R_f = 0.59 (70% ethyl acetate in hexanes); IR (KBr): $\tilde{\nu}$ = 1038, 1263, 1476, 1643, 2923 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.95 (s, 3H), 4.03 (s, 3H), 4.07 (s, 3H), 6.07 (s, 2H), 7.14 (s, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.55 (s, 1H), 7.60 (s, 1H), 7.89 (s, 1H), 7.95 ppm (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 41.2, 56.1, 56.2, 101.5, 102.6, 102.8, 104.7, 108.6, 116.6, 118.3, 119.1, 121.0, 123.2, 128.9, 131.8, 135.9, 147.0, 147.4, 149.7, 153.5, 164.3 ppm; HRMS (EI$^+$): m/z: calcd for $C_{21}H_{17}NO_5$: 363.1107; found: 363.1104.

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